Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1581–1585

TETRAHEDRON: *ASYMMETRY*

Polyhydroxylated pyrrolizidines. Part 2: The first total synthesis of (+)-hyacinthacine A_3†

Isidoro Izquierdo,* María T. Plaza and Francisco Franco

Department of Medicinal and Organic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain

Received 11 July 2002; accepted 17 July 2002

Abstract—The first total synthesis for the (+)-hyacinthacine A_3 **1** in a highly stereocontrolled manner, is reported herein. An appropriately protected polyhydroxylated pyrrolidine, such as (2*R*,3*R*,4*R*,5*R*)-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine **2**, (DMDP protected), readily available from D-fructose, was chosen as the homochiral starting material. The absolute configuration of natural **1** is also unambiguously established.

1. Introduction

The polyhydroxylated pyrrolizidine skeleton [1-azabicyclo[3.3.0]octane] is the basic framework of a diverse group of sugar mimic alkaloids isolated from natural sources. Among them, those recently isolated[1] bearing one carbon branch both at C(3) and C(5) are known as hyacinthacines. Most of these natural compounds show inhibitory activity against different kinds of glycoprotein processing glycosidases and hence their potentiality as new chemotherapeutic agents.[2] As a consequence of this bioactivity, a great deal of effort has been devoted over the last two decades in order to achieve either the isolation of new polyhydroxylated pyrrolizidine alkaloids from nature or to design stereocontrolled synthetic routes[2d,3] leading to these compounds, or to their unnatural isomers, which could be of interest for SAR studies.

The first synthesis for a hyacinthacine was that reported by Yoda's group[4] on the (+)-7a-*epi*-hyacinthacine A_2 (7-deoxyalexine), using a methodology previously applied to the synthesis of (+)-alexine.[3d] At the same time White et al.[3f] described the synthesis of its 2-*O*-benzyl derivative starting from 2,3-*O*-isopropylidene-D-glyceraldehyde, via a tandem ring-closing metathesis (RCM) and a transannular cyclization the key steps for the construction of pyrrolizidine skeleton. However, both methodologies are lacking in conciseness as well as in stereoselectivity. Subsequently, Martin et al.[5] reported on the first total synthesis of (+)-hyacinthacine A_2 from a suitably functionalized *N*,2-diallyl-pyrrolidine, prepared from a derivative of D-arabinose, in which a RCM reaction was the synthetic key step for building up the bicyclic pyrrolizidine skeleton. Simultaneously, our group reported[6] on the short and highly stereocontrolled syntheses of the already mentioned (+)-7-deoxyalexine and, for the first time, (+)-5,7a-di*epi*-hyacinthacine A_3, from a partially protected 2,5-dideoxy-2,5-imino-D-glucitol (DGDP).[7] To the best of our knowledge no other synthesis of the natural (+)-hyacinthacine A_3 has been communicated to date. Herein, we report on the first total enantiosynthesis of such a compound using an adequately protected 2,5-dideoxy-2,5-imino-D-mannitol (DMDP, **2**),[8] prepared from D-fructose, as the homochiral starting material.

Retrosynthesis for **1** (Scheme 1) indicates that protected DMDP could be considered an excellent starting chiral template for its enantiosynthesis, since carbon-chain lengthening at C(5′) (the original C-6 of D-fructose) with a suitably functionalized three more carbon atoms fragment, followed by a further cyclization, could lead to the pyrrolizidine skeleton with the stereochemistry at C(7a) correct for the target molecule.

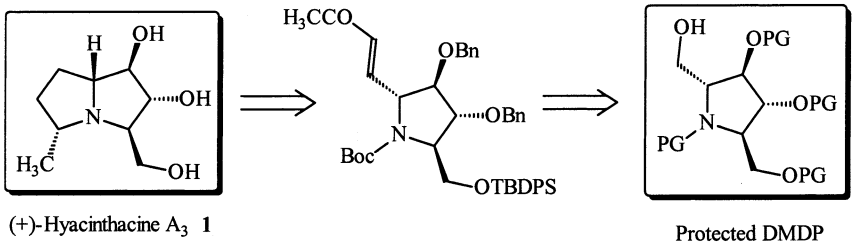
2. Results and discussion

According to Scheme 2, oxidation of (2*R*,3*R*,4*R*,5*R*)-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine[8a]

* Corresponding author. E-mail: isidoro@platon.ugr.es

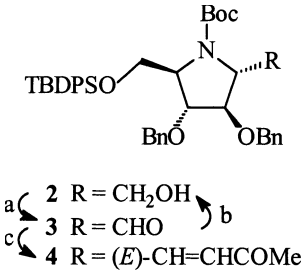
† For Part 1 of the series, see: Ref. 6.

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00408-1



(+)-Hyacinthacine A_3 **1** Protected DMDP

Scheme 1. Retrosynthesis of (+)-hyacinthacine A_3.



Scheme 2. Synthesis of α,β-unsaturated pyrrolidinic ketone **4**. *Reagents and conditions*: (a) TPAP/NMO/Cl_2CH_2/4 Å MS; (b) $NaBH_4$/MeOH; (c) Ph_3P=CHCOMe/PhMe/Δ.

2 with *N*-methylmorpholine *N*-oxide catalyzed by tetra-*n*-propylammonium perruthenate (TPAP)[9] yielded the aldehyde **3** according to its NMR spectra, where two rotameric forms for **3** could clearly be observed [signals for formyl group at δ 9.51d (J 1.3 Hz) and 9.43d (J 2.3 Hz)]. That rotamers of **3**, which are expected for *N*-acyl pyrrolidines,[10] and not epimers at C (5), actually exist could be demonstrated by its sodium borohydride reduction to starting **2**. Subsequent treatment of **3** with 1-triphenylphosphoranylidene-2-propanone afforded (*E*)-4-[(2′*R*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]but-3-en-2-one **4** in a highly stereoselective manner. The structure of **4**, which also exists as a mixture of rotamers, was determined on the basis of its analytical and spectroscopic data, where the *E* configuration was established from the $J_{3,4}$ value (16.2 Hz).

Catalytic hydrogenation (10% Pd–C) of **4** afforded the protected saturated ketone **5**, according to the ^{1}H and ^{13}C NMR spectra of an aliquot, which showed the absence of rotameric forms. Addition of hydrochloric acid to the above hydrogenation reaction mixture achieved the complete *N*- and *O*-deprotection of **5** to **6**, in order to promote the required cyclization to the pyrrolizidine skeleton. Thus, neutralization [Amberlite IRA-400 (OH^- form)], followed by a second catalytic hydrogenation of **6**, as above, afforded (+)-hyacinthacine A_3 **1**, [(1*R*,2*R*,3*R*,5*R*,7a*R*)-1,2-dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine] in only one step, which physical and spectroscopic data (see Figs. 1 and 2) closely matching those previously reported[1b] for the natural compound. Formation of **1** must take place, according to Scheme 3, by a subsequent internal condensation to the intermediate Δ^5-pyrrolizine **A**, not isolated but observed by TLC analysis, and final hydrogenation to **1**.

The configuration of the new C(5) stereogenic center was determined from the results of extensive NOE experiments. The definite NOE effects (see Fig. 3) between C(3)H and C(5)Me and between C(2)H and C(7a)H indicated that the formers are in the α-face, whereas the latter are in the β-face.

The high stereoselectivity found in the hydrogenation of intermediate Δ^5-pyrrolizine **A**, where **1** was the only detected and isolated pyrrolizidine merits comment. Formation of **1** can be attributed, according to our previous results[6] and to Fig. 3, to the particular shape of this kind of molecule,[1b] where that the β-face is less hindered for hydrogen attack that the α-face is, preferentially affording compound **1**.

3. Conclusions

Finally, two important conclusions can be drawn 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 (1*R*,2*R*,3*R*,5*R*,7a*R*) is the actual configuration for the natural (+)-hyacinthacine A_3.

4. Experimental

4.1. General

Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^{1}H 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 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 E. Merck silica gel 60 F_{254} aluminum sheets with 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 (E. Merck, 7734). All the compounds were shown to be homogeneous by

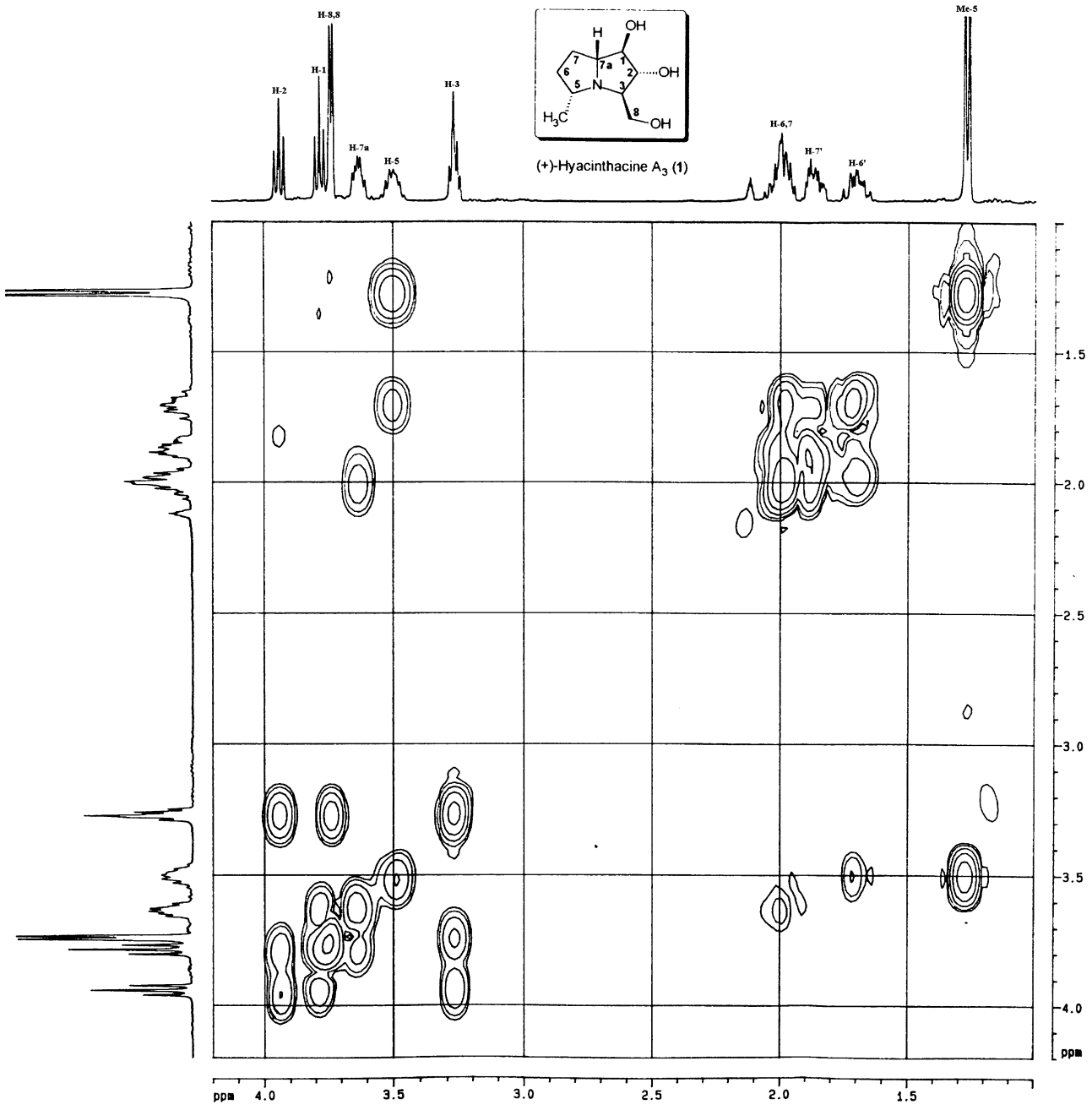


Figure 1. 2D ^{1}H–^{1}H COSY for (+)-hyacinthacine A_3.

chromatography and characterized by NMR spectroscopy and FAB-HRMS with thioglycerol matrix.

4.2. (*E*)-4-[(2′*R*,3′*R*,4′*R*,5′*R*)-3′,4′-Dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5′-*tert*-butyldiphenylsilyl oxymethylpyrrolidin-2′-yl]but-3-en-2-one 4

To a stirred solution of (2*R*,3*R*,4*R*,5*R*)-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-2′-*O*-*tert*-butyldiphenyl silyl-2,5-bis(hydroxymethyl)pyrrolidine[8a] **2** (360 mg, 0.53 mmol) in dry dichloromethane (5 mL), were added activated 4 Å molecular sieve (270 mg), *N*-methylmorpholine *N*-oxide (92 mg, 0.79 mmol) and TPAP (19 mg) and the reaction mixture kept at room temperature for 2 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 (Scharlau, 230–400 mesh) and thoroughly washed with dichloromethane. The combined filtrate and washings were concentrated to a residue, presumably [(2′*S*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]carbaldehyde **3** as a syrup. NMR (300 MHz) data (inter alia), δ: 9.51 (d, $J_{2',CHO}$ 1.3 Hz) and 9.43 (d, $J_{2',CHO}$ 2.3 Hz); ^{13}C NMR, δ: 200.47 and 200.26 (CHO). Compound **3** was dissolved in toluene (10 mL) and 1-triphenylphosphoranylidene-2-propanone (460 mg, 1.44 mmol) was added and the mixture refluxed for 24 h. TLC (ether/hexane, 1:2) then revealed the presence of a slightly slower-running com-

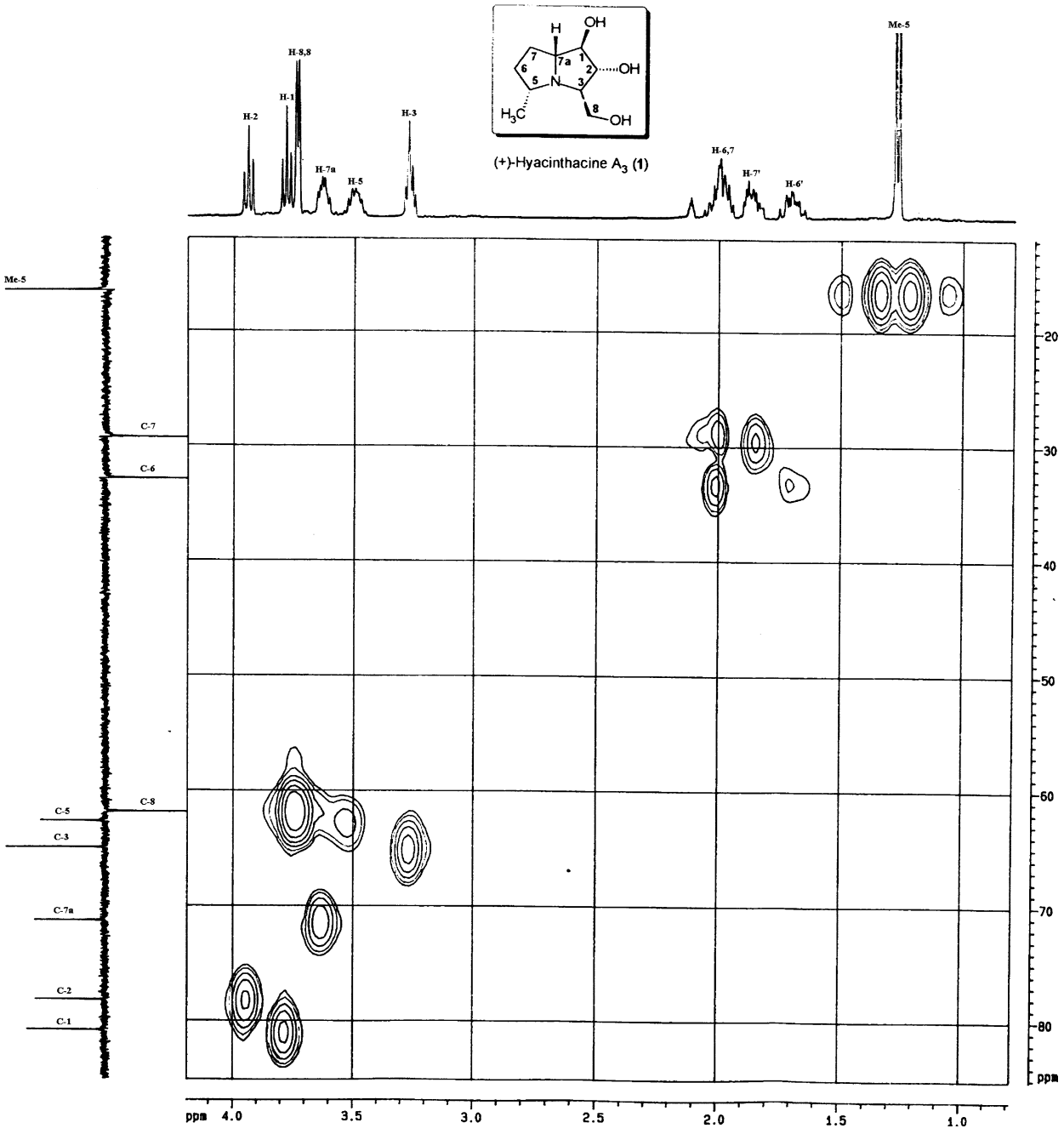
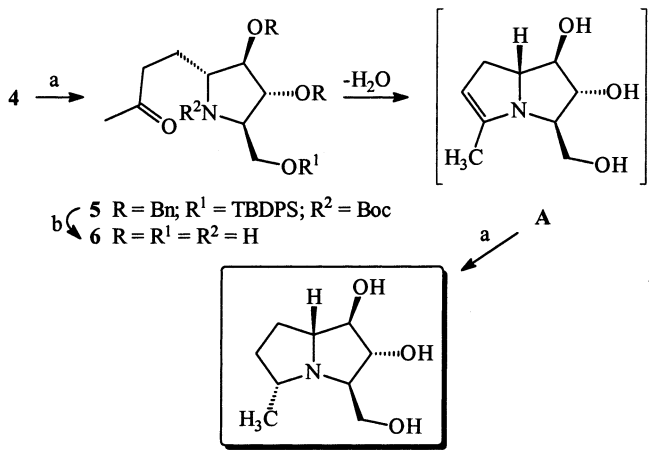


Figure 2. 2D ^{1}H–^{13}C COSY for (+)-hyacinthacine A_3.

pound. The reaction mixture was filtered and supported on silica gel, then chromatographed (ether/hexane, 1:1) to afford **4** (380 mg, quantitative) as a thick syrup: $[\alpha]_D^{26}$ +16 (*c* 1); ν_{max}^{film} 3067 and 3033 (aromatic), 1697, 1679 and 1632 (C=O, conjugated ketone, Boc, and C=C conjugated), 739 and 700 cm^{-1} (aromatic). ^{1}H NMR (300 MHz) data (inter alia): 6.70 and 6.68 (2dd, 1H, $J_{2',4}$ 7.6 and 8.7 Hz, H-4 for the two rotamers), 6.10 and 6.00 (2d, 1H, $J_{3,4}$ 16.2 Hz, H-3 for the two rotamers), 2.17 and 2.13 (2s, 3H, H-1,1,1 for the two rotamers), 1.33 and 1.27 (2s, 9H, Me_3CO for the two rotamers), 1.06 and 1.04 (2s, 9H, Me_3CSi for two rotamers). Mass spectrum (LSIMS): *m/z*: 742.3537 [M^++Na] for $C_{44}H_{53}NO_6NaSi$ 742.3540 (deviation +0.3 ppm).

4.3. (+)-Hyacinthacine A_3 [1 (1*R*,2*R*,3*R*,5*R*,7a*R*)-1,2-dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine]

Compound **4** (380 mg, 0.52 mmol) in dry methanol (20 mL) was hydrogenated at 4 atm over 10% Pd–C (142 g) for 12 h. TLC (ether/hexane, 2:1) then showed a compound, presumably **5**, with the same mobility. An aliquot was concentrated and showed the following NMR data: ^{1}H NMR, δ: 7.68–7.20 (2m, 20H, 5 Ph), 4.68 and 4.58 (2d, 2H, *J* 12.2 Hz, CH_2Ph), 4.45 and 4.42 (2d, 2H, *J* 12.6 Hz, CH_2Ph), 4.40 (s, 1H, H-4′), 4.26 (d, 1H, $J_{2',3'}$ 6.3 Hz, H-3′), 4.07 (dd, 1H, $J_{5',5''a}$ 4.7, $J_{5''a,5''b}$ 10.5 Hz, H-5″a), 4.00 (dd, 1H, $J_{5',5''b}$ 8.8 Hz, H-5′), 3.78 (m, 1H, H-2′), 3.64 (bt, 1H, H-5″b), 2.45



Scheme 3. Synthesis of (+)-hyacinthacine A_3 from **4**. *Reagents and conditions*: (a) 10% Pd–C/H_2; (b) 10% Pd–C/H_2/ClH, 1 atm, rt, 34 h, then Amberlite IRA-400 (OH^-, form).

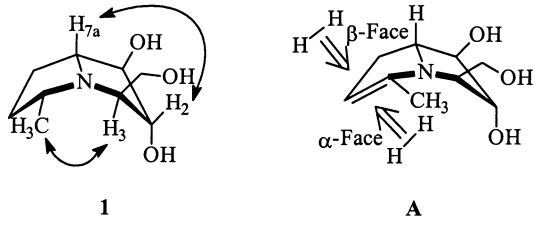


Figure 3. NOE interactions in **1** and hydrogenation pathway of intermediate Δ^5-pyrrolizine **A**.

(ddd, 1H, *J* 6.0, *J* 9.5, *J* 16.0 Hz, H-3a), 2.35–2.17 (2 m, 2H, H-3b,4a), 2.10 (s, 3H, H-1,1,1), 2.01–1.89 (m, 1H, H-4b), 1.27 (s, 9H, $OCMe_3$) and 1.05 (s, 9H, $SiCMe_3$); ^{13}C NMR (inter alia), 208.02 (C-2), 154.15 (C=O, Boc), 83.70 and 83.92 (C-3′,4′), 71.48 and 71.04 (2 $PhCH_2$), 64.89 and 63.90 (C-2′,5′), 62.21 (C-5″), 41.05 (C-4), 29.69 (C-1), 28.35 ($OCMe_3$), 26.93 ($SiCMe_3$), 25.38 ($OCMe_3$), and 19.25 ($SiCMe_3$). The reaction mixture was acidified with conc. hydrochloric acid and left at room temperature for 34 h. TLC (ether) then showed a non mobile compound. The catalyst was filtered off, washed with methanol and the filtrate and washings neutralized with Amberlite IRA-400 (OH-form) and then hydrogenated again with 10% Pd–C (100 mg) at 4 atm for 12 h. TLC (ether–methanol–triethylamine, 1:1:0.1) then revealed a slightly mobile compound. Removal of the catalyst as above, followed by column chromatography (ether–methanol–triethylamine, 1:1:0.1) yielded pure syrupy **1** (68 mg, 70% from **4**): $[\alpha]_D^{25}$ +14, $[\alpha]_{405}^{26}$ +42 (*c* 0.55, water) [lit.[1b] $[\alpha]_D^{25}$ +19.2 (*c* 0.43, water)]. NMR data (400 MHz, D_2O): δ: 3.91 (bt, 1H, $J_{1,2}=J_{2,3}=7.5$ Hz, H-2), 3.76 (bt, 1H, $J_{1,7a}$ 7.2 Hz, H-1) 3.71 (d, 2H, $J_{3,8}$ 4.5 Hz, H-8,8), 3.59 (dt, 1H, $J_{7,7a}=J_{7',7a}=4$ Hz, H-7a), 3.46 (m, 1H, H-5), 3.24 (m, 1H, H-3), 2.03–1.92 (m, 2H, H-6,7), 1.88–1.80 (m, 1H, H-7′), 1.73–1.63 (m, 1H, H-6′), 1.24 (d, 3H, $J_{5,Me}$ 6.8 Hz, Me-5); ^{13}C NMR, 80.86 (C-1), 78.21 (C-2), 71.26 (C-7a), 64.96 (C-3), 62.65 (C-5), 61.82 (C-8), 32.87 (C-6), 29.26 (C-7), and 16.49 (Me-5). Mass spectrum (LSIMS): *m*/*z*: 188.1292 $[M^+ + H]$ for $C_9H_{18}NO_3$ 188.1287 (deviation −2.7 ppm).

Acknowledgements

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

References

1. (a) Kato, A; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95–103; (b) Asano, N.; Kuroi, H.; Ikeda, H.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1–8.
2. (a) Ostrander, G. K.; Scribner, N. K.; Rohrschneider, L. R. *Cancer Res.* **1988**, *48*, 1091–1094; (b) Ratner, L. *AIDS Res. Hum. Retroviruses* **1992**, *8*, 165–173; (c) Vlietinck, A. J.; De Bruyne, T.; Apers, S.; Pieters, L. A. *Planta Med.* **1998**, *64*, 97–109; (d) For recent reviews: Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **2000**, *11*, 1645–1680, Compain, P.; Martin, O. R. *Bioorg. Med. Chem.*, **2001**, *9*, 3077–3092 and Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry*, **2001**, *56*, 265–295.
3. (a) Casiraghi, G.; Zanardi, F.; Rassu, G.; Pinna, L. *Org. Prep. Proc. Int.* **1996**, *28*, 643–682; (b) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875–2886; (c) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887–2896; (d) Yoda, H.; Katoh, H.; Takabe, K. *Tetrahedron Lett.* **2000**, *41*, 7661–7665; (e) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785–5793; (f) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129–9142; (g) Gallos, J. K.; Sarli, W. C.; Koftis, Y. V.; Argyropoulous, E. C. *Tetrahedron Lett.* **2000**, *41*, 4819–4822; (h) Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276–4284.
4. Yoda, H.; Asai, F.; Takabe, K. *Synlett* **2000**, 1001–1003.
5. Rambaud, L.; Compain, P.; Martin, O. R. *Tetrahedron: Asymmetry* **2001**, *12*, 1807–1809.
6. Izquierdo, I.; Plaza, M.-T.; Robles, R.; Franco, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2481–2487.
7. Izquierdo, I.; Plaza, M.-T.; Robles, R.; Franco, F. *Carbohydr. Res.* **2001**, *330*, 401–408.
8. (a) Izquierdo, I.; Plaza, M.-T.; Franco, F. *Tetrahedron: Asymmetry* **2002**, *13*, 1503–1508; (b) For a recent review on DMDP, see: Wrodnigg, T. M. *Monatsh. Chem.* **2002**, *133*, 393–426.
9. Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13–19.
10. Aamlid, K. H.; Hough, L.; Richardson, A. C. *Carbohydr. Res.* **1990**, *202*, 117–129.