Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 3933–3935

TETRAHEDRON: *ASYMMETRY*

Polyhydroxylated pyrrolizidines. Part 3: A new and short enantiospecific synthesis of (+)-hyacinthacine A_2 ☆

Isidoro Izquierdo,* María T. Plaza and Francisco Franco

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

Received 2 September 2003; accepted 22 September 2003

Abstract—(1*R*,2*R*,3*R*,7a*R*)-1,2-Dihydroxy-3-hydroxymethylpyrrolizidine (+)-Hyacinthacine A_2 **1** has been synthesized by Wittig's methodology using [(2′*S*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]carbaldehyde **3**, prepared from a partially protected DMDP **2**, and the appropriated ylide, followed by cyclization by an internal reductive amination process of the resulting unsaturated aldehyde **4** and total deprotection.

1. Introduction

Hyacinthacine A_2 **1** was isolated for the first time by Asano et al.[2] from the bulbs of *Muscari armeniacum* (Hyacinthaceae), and was shown to be a potent and selective inhibitor of amyloglucosidase (*Aspergillus niger*).[2,3] Only two synthetic approaches have been recently reported for **1**, those by Martin et al.[4] and by Goti,[5] both from commercial 2,3,5-tri-*O*-benzyl-D-arabinofuranose, but unfortunately lacking in high stereoselectivity.

Retrosynthesis of **1** in Figure 1, clearly shows that functionalization and stereochemistry of this molecule exactly match that of the homochiral starting material, (2*R*,3*R*,4*R*,5*R*)-3,4-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)-pyrrolidine,[6] protected DMDP **2**. With this material in hand, only the following steps are necessary for achieving the synthesis of **1**: elongation at C(5′) of the carbon-chain of the pyrrolidine skeleton by two more carbon atoms with the appropriate functionalization (formyl group) and cyclization to the pyrrolizidine skeleton by an internal reductive amination process, and finally total deprotection.

According to Scheme 1, the actual homochiral starting material was [(2′*S*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-*tert* - butyloxycarbonyl - 5′ - *tert* - butyldiphenylsilyloxy-methylpyrrolidin-2′-yl] carbaldehyde **3**, prepared from **2** by a previously described procedure,[1] which was treated with triphenylphosphoranylideneacetaldehyde

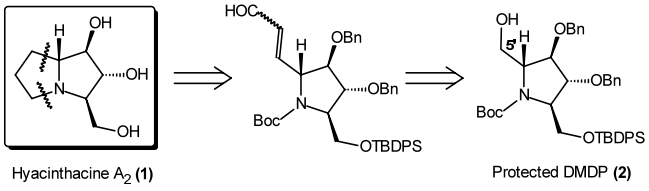
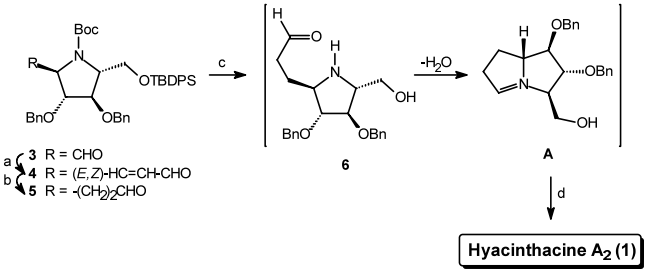


Figure 1. Retrosynthesis of hyacinthacine A_2 (**1**).



Scheme 1. *Reagents and conditions*: (a) Ph_3P=CHCHO/MePh/Δ; (b) H_2/10% Pd–C; (c) HCl, then Amberlite IRA-400 (OH^- form); (d) 10% Pd–C/HCl then Amberlite IRA-400 (OH^- form).

☆ For Part 2 of the series, see Ref. 1.

* Corresponding author. Tel.: +34-958-243847; fax: +34-958-2433845; e-mail: isidoro@ugr.es

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.09.042

to afford (*E*,*Z*)-3-[(2′*R*,3′*R*,4′*R*, 5′*R*)-3′,4′-dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethyl pyrrolidin-2′-yl]prop-2-enal **4**.

The structure of **4**, which exists as a mixture of rotamers,[1] was determined on the basis of its ^{1}H NMR data, where complex signals between δ 9.58–9.43 (H-1) and δ 7.10–6.00 (H-2,3) were observed.

Catalytic hydrogenation (10% Pd–C) of **4** afforded the protected saturated aldehyde **5**, according to the ^{1}H NMR spectra of an aliquot, which also showed the absence of rotameric forms (H-1 as a triplet at δ 9.52). Addition of hydrochloric acid to the above hydrogenation reaction mixture caused the total *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 new catalytic hydrogenation of **6**, as above, afforded a complex mixture, probably the intermediate Δ^5-pyrrolizine **A** together with some debenzylation products. Continuing the hydrogenation process, but in acid medium, the required (+)-hyacinthacine A_2 **1**, (1*R*,2*R*,3*R*,7a*R*)-1,2-dihydroxy-3-hydroxymethylpyrrolizidine, was finally achieved, after neutralization. The physical and spectroscopic data of **1** (see Fig. 2) closely matched those previously reported for a natural[2] and synthetic sample.[4]

2. Experimental

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). Mass spectra ware 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} 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).

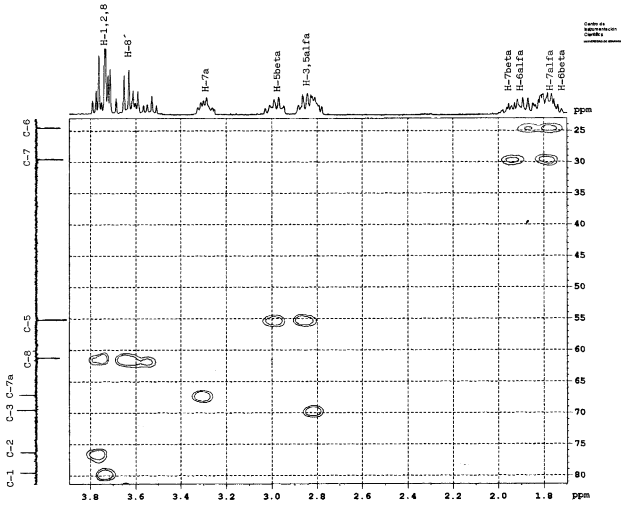


Figure 2. HMQC (D_2O) spectrum for (+)-Hyacinthacine A_2.

2.1. (*E*,*Z*)-3-[(2′*R*,3′*R*,4′*R*,5′*R*)-3′,4′-Dibenzyloxy-*N*-*tert*-butyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethyl pyrrolidin-2′-yl]prop-2-enal 4

A solution of **3**[1] (1.26 g, 1.86 mmol) in dry toluene (20 mL) was added triphenylphosphoranilydeneacetaldehyde (0.8 g, 2.51 mmol) and the mixture was heated at 100°C for 12 h. 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 (1:2) as eluent to give pure **4** (0.8 g, 57%) as a pale yellow syrup that was not investigated but used in the next step. ^{1}H NMR (300 MHz) inter alia: δ = 9.58–9.43 (m, 1H, H-1), 7.10–6.70 (2m, H-3 for *E*,*Z* isomers), 6.40–6.00 (m, H-2 for *E*,*Z* isomers), 1.25 and 1.35 (2s, CMe_3, *N*-Boc), 1.09 and 1.08 (2s, CMe_3, OTBDPS).

2.2. (1*R*,2*R*,3*R*,7a*R*)-1,2-Dihydroxy-3-hydroxymethylpyrrolizidine (+)-Hyacinthacine A_2, 1

Compound **4** (0.8 g, 1.13 mmol) in methanol (20 mL) was hydrogenated at 60 psi over 10% Pd–C (280 mg) for 30 min. TLC (ether/hexane 2:1) then showed the presence of a new compound **5** of slightly lower mobility. An aliquot was concentrated and showed the following ^{1}H NMR (300 MHz): δ = 9.52 (t, H-1), 7.70–7.10 (m, Ph), 4.80–3.50 (m, H-2′,3′,4′,5′,5″a,5″b and PhC*H*$_2$), 2.50–1.50 (m, H-2a,2b,3a,3b), 1.29 (s, $OCMe_3$) and 1.07 (s, $SiCMe_3$).

The reaction mixture was acidified with a few drops of conc. HCl and left at rt for 24 h, this caused the removal of the Boc and TBDPS protecting groups [TLC (ether/hexane 2:1) revealing a non mobile compound]. The catalyst was filtered off, washed with methanol and the filtrate and washings neutralized with Amberlite IRA-400 (OH^- form). A new hydrogenation as above under the presence of acid medium over 10% Pd–C (200 mg) for 12 h, gave a slightly mobile compound [TLC (ether/methanol/triethylamine 1:1:0.1)]. Finally pure **1** (50 mg, 26% from **4**) was isolated after neutralization and column chromatography (ether/methanol/TEA 2:1:0.1→ether/methanol/TEA 1:1:0.1), which had $[\alpha]_D^{25}$ = +10.5 (*c* 0.6, H_2O) [lit.[2] $[\alpha]_D^{25}$ = +20.1 (*c* 0.44, H_2O); lit.[4] $[\alpha]_D^{25}$ = +12.5 (*c* 0.6, H_2O); lit.[5] $[\alpha]_D^{25}$ = +12.7 (*c* 0.13, H_2O). NMR data (400 MHz, D_2O): ^{1}H, δ 3.79–3.71 (m, 3H, H-1,3,8), 3.63 (dd, 1H, $J_{3,8'}$ 6, $J_{8,8'}$ 12.1 Hz, H-8′), 3.37 (m, 1H, H-7a), 3.04 (broad dt, 1H, $J_{5\alpha,5\beta}$ 11.7, $J_{5\beta,6\alpha} = J_{5\beta,6\beta}$ = 6.5 Hz, H-5β), 2.93–2.85 (m, 2H, H-3,5α), 1.96–1.72 (m, 4H, H-6α,6β,7α,7β); ^{13}C, δ 81.09 (C-1), 77.72 (C-2), 71.47 (C-3), 69.42 (C-7a), 62.24 (C-8), 57.05 (C-5), 31.19 (C-7), and 26.32 (C-6).

Acknowledgements

The authors are deeply grateful to Ministerio de Ciencia y Tecnología (Spain) for financial support (Project PPQ2002-01303) as well as for a grant (F. Franco).

References

1. Izquierdo, I.; Plaza, M.-T.; Franco, F. *Tetrahedron: Asymmetry* **2002**, *13*, 1581–1585.
2. Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1–8.
3. (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265–295.
4. Rambaud, L.; Compain, P.; Martin, O. R. *Tetrahedron: Asymmetry* **2001**, *12*, 1807–1809.
5. Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett*. **2003**, *44*, 2315–2318.
6. Izquierdo, I.; Plaza, M.-T.; Franco, F. *Tetrahedron: Asymmetry* **2002**, *13*, 1503–1508.