Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1807–1809

TETRAHEDRON: *ASYMMETRY*

# First total synthesis of (+)-hyacinthacine $A_2$

Lauriane Rambaud, Philippe Compain and Olivier R. Martin*

*Institut de Chimie Organique et Analytique, CNRS-Université d'Orléans, BP 6759, 45067 Orléans, France*

Received 20 June 2001; accepted 15 July 2001

**Abstract**—The first synthesis of (+)-hyacinthacine $A_2$ has been achieved in six steps from 2,3,5-tri-*O*-benzyl-D-arabinofuranose in an overall yield of 11%. The structure of this natural product was thus unambiguously established as (1*R*,2*R*,3*R*,7a*R*)-1,2-dihydroxy-3-hydroxymethylpyrrolizidine. 

Owing to their remarkable biological properties as glycosidase[1] and glycosyltransferase[2] inhibitors, iminosugars promise a new generation of carbohydrate-based therapeutics for the control of various diseases including diabetes, cancer and viral infection.[3] The discovery and biological evaluation of new natural polyhydroxylated alkaloids is therefore a crucial task.[4] Very recently new pyrrolizidines, hyacinthacines $A_1$–$A_3$, have been isolated from an extract (60% aqueous-EtOH) of the bulbs of *Muscari armeniacum* (Hyacinthaceae) (Fig. 1).[5] The $A_2$ epimer was found to be a selective inhibitor of amyloglucosidase (*Aspergillus niger*) with an $IC_{50}$ value in the μM range. It is noteworthy that australine, a close analog of hyacinthacine $A_2$ (i.e. 7-deoxyaustraline), is also an inhibitor of amyloglucosidase[6] and was found to display antiviral and anti-HIV activity.[7]

In order to facilitate the study of this family of natural products as well as to establish the absolute configuration of the hyacinthacines, we have designed a general strategy for the synthesis of these and related pyrrolizidines based on a concise synthetic sequence. The retrosynthesis is outlined in Scheme 1.

It was envisaged that the polyhydroxylated 1-azabicyclo[3.3.0]octane ring system could arise from a substituted pyrrolidine carrying two ethenyl groups by way of a ring-closing metathesis (RCM) reaction. The required precursor **B** would be generated from the δ-keto benzoate (**C**, prepared from a D-arabinofuranose derivative) by a reductive amination using allylamine followed by an intramolecular displacement of the benzoate group.[8] The unsaturated bicyclic system **A** resulting from the RCM reaction, with a double bond tactically positioned at C(7)–C(6), is an advanced intermediate in the synthesis of various polyhydroxy–pyrrolizidines such as hyacinthacine $A_2$, australine[9] or casuarine.[10]

The synthesis began with the highly stereoselective addition of divinylzinc to commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose to afford the heptenitol **1** in 95% yield (Scheme 2).[11] Regioselective benzoyla-

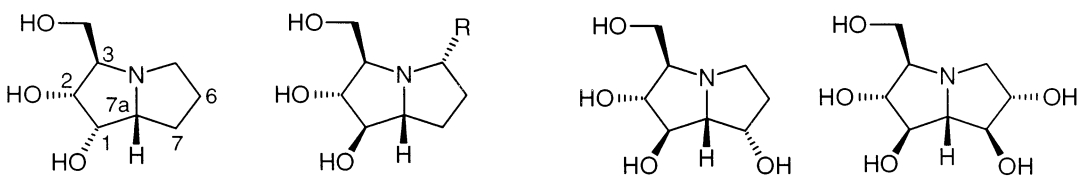
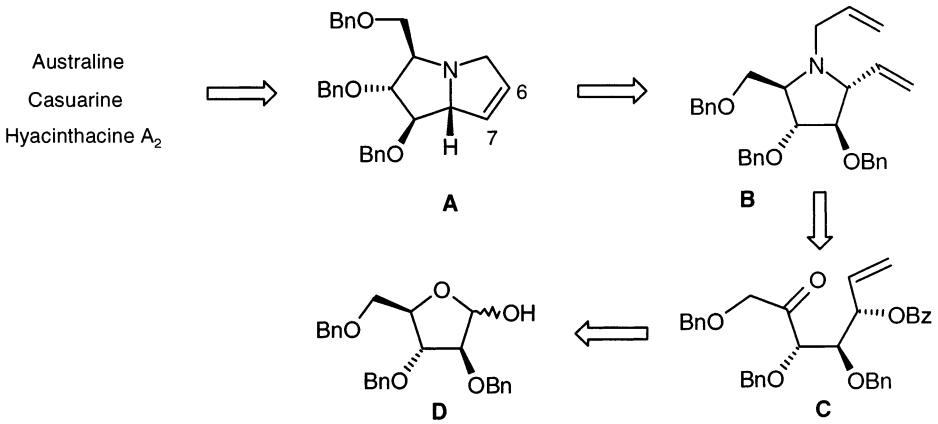


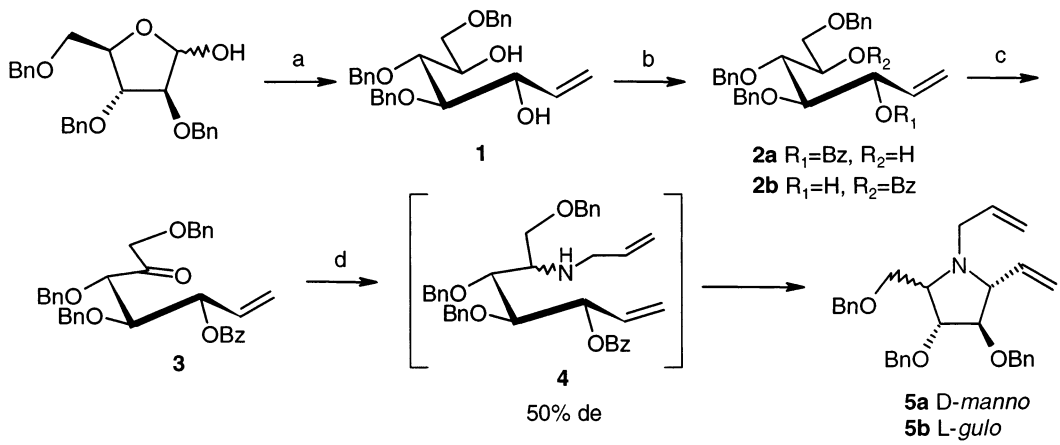

**Figure 1.**

* Corresponding author. Fax: +33 2 38 41 72 81; e-mail: olivier.martin@univ-orleans.fr

0957-4166/01/$ - see front matter 
PII: S0957-4166(01)00324-X




**Scheme 1.**

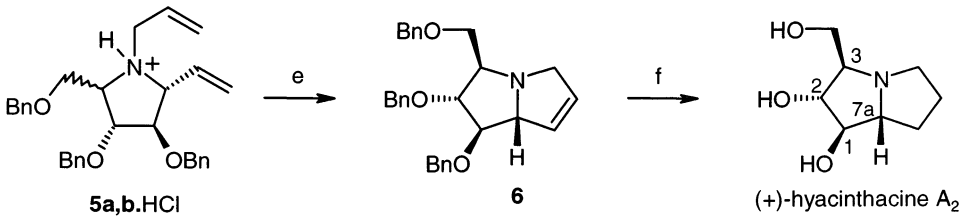



**Scheme 2.** *Reagents and conditions*: (a) $(CH_2{=}CH)_2Zn$, Ref. 11a; 95%; (b) BzCl (1 equiv.), $n$Bu$_4$NI (0.05 equiv.), $CH_2Cl_2$/NaOH 1N (1/1), 0°C, 3 h; (c) TFAA (3 equiv.), DMSO (4 equiv.), $Et_3N$ (5 equiv.), $CH_2Cl_2$, −78°C to rt; 63% (2 steps); (d) allylamine (10 equiv.), AcOH (5 equiv.), $NaBH_3CN$ (5 equiv.), molecular sieves 3 Å, MeOH, 0–40°C, 6 days; 78%.

tion of the allylic hydroxyl group was achieved using benzoyl chloride in a two-phase system ($CH_2Cl_2$/NaOH 1N) in the presence of a catalytic amount of tetrabutylammonium iodide at 0°C (ratio 3.5/1 in favor of the desired allylic benzoate **2a**). Swern oxidation of the mixture of the two unseparable monobenzoates with trifluoroacetic anhydride and DMSO[12] provided the expected δ-keto benzoate **3** readily separable from other products by flash chromatography (63% isolated yield for the two-step process). The heptenulose **3** was then heated at 40°C in dry methanol containing allylamine, $NaBH_3CN$ and acetic acid. After 6 days, the olefin metathesis precursors **5a** and **5b** were obtained in 78% overall yield (ratio 3/1); it was established by 2D COSY and T-ROESY NMR experiments that the major epimer had the D-*manno* configuration. This efficient process allowed the formation of the pyrrolidine ring in a single operation, the new stereogenic center (C-(3) in the final product) being created with a reasonable degree of diastereoselectivity. Mass spectral analysis performed at an early stage of the reaction confirmed that intermolecular reductive amination is indeed the first step of the process (amino-heptenitols **4** were detected along with the final pyrrolidine products **5a** and **5b**). The second step involves the spontaneous intramolecular nucleophilic displacement of the allylic benzoate ester by the secondary amino group, which occurred with complete inversion of configuration.[8]

Since the early 1990s, ring-closing metathesis (RCM) has established itself as a powerful method for the elaboration of medium-sized rings, including carbohydrates[13] and alkaloids.[14] In our case, the pivotal issues were the ring strain of the [3.3.0] bicyclic product **6**[15] and the amino function of the pyrrolidine ring that could potentially chelate the metal center of the metathesis catalyst and thus form unproductive complexes.[14] The planned synthetic scheme, designed to be expeditious, allowed no interconversion of the (tertiary) amine to less coordinating functions frequently employed in the synthesis of nitrogen-containing systems (e.g. amide or carbamate). We therefore, performed the RCM reaction using the epimeric mixture of the corresponding hydrochloride salts[16] (**5a·HCl**, **5b·HCl)** in the presence 16 mol% of Grubb's catalyst in toluene at 60°C (Scheme 3). Using these conditions, the tetrahydropyrrolizine **6** was obtained as the main product in 30% yield (75% based on recovered starting material).

Finally, the one-step removal of the benzyl protecting groups and reduction of the double bond in **6** was




**Scheme 3.** *Reagents and conditions*: (e) Bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (Grubb's catalyst), toluene, 60°C, 72 h; 30%; (f) $H_2$, Pd/C, MeOH/THF/HCl 6N (4/1/0.25), rt, 20 h; 82%.

conducted with 10% palladium on carbon to complete the synthesis of (+)-hyacinthacine $A_2$, $[\alpha]_D$ +12.5 (*c* 0.4, $H_2O$), in 82% yield.[17] The configurations of the stereogenic centers in this product were confirmed by the definite nOe effects between C(1)H and C(3)H and between C(2)H and C(7a)H in the corresponding triacetate. Thus, (+)-hyacinthacine $A_2$ was determined to be (1*R*,2*R*,3*R*,7a*R*)-1,2-dihydroxy-3-hydroxymethylpyrrolizidine.

In conclusion, we have achieved the first synthesis of (+)-hyacinthacine $A_2$ in only six steps and 11% overall yield from commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose. It is noteworthy that very recently, Yoda et al. reported the synthesis of 7-deoxyalexine (i.e. 7a-*epi*hyacinthacine $A_2$) from the same starting material in 26 steps (with an impressive overall yield of 25%).[18] Our synthetic strategy is currently being optimized and extended to other pyrrolizidines such as casuarine and australine.

## Acknowledgements

This work was supported by a grant from CNRS. We are grateful to Drs. B. Perly (CEA) and S. Chierici (Grenoble University) for 2D NMR experiments. We thank Professor Asano (Hokuriku University, Japan) for optical activity measurements and J. Yuan (State University of New York, Binghamton) for preliminary experiments.

## References

1. Stütz, A. E. *Iminosugars as Glycosidase Inhibitors*: *Nojirimycin and Beyond*; Wiley–VCH: Weinheim, 1999.
2. For a review on carbohydrate mimetics-based glycosyltransferase inhibitors, see: Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, in press.
3. (a) Winchester, B.; Fleet, G. W. J. *J. Carbohydr. Chem.* **2000**, *19*, 471–483; (b) Häusler, H.; Kawakami, P.; Mlaker, E.; Severn, W. B.; Wrodnigg, T. M.; Stütz, A. E. *J. Carbohydr. Chem.* **2000**, *19*, 435–449.
4. (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.
5. 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.
6. Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Girdhar, A.; Ramsden, N. G.; Peach, J. M.; Hegarty, M. P.; Scofield, A. M. *Phytochemistry* **1990**, *29*, 111–114.
7. (a) Fellows, L.; Nash, R. PCT *Int. Appl. WO* GB Appl. 89/7,951; *Chem. Abstr.* **1991**, *114*, 143777s; (b) Taylor, D. L.; Nash, R.; Fellows, L. E.; Kang, M. S.; Tyms, A. S. *Antiviral Chem. Chemother.* **1992**, *3*, 273–277.
8. One example of such a cyclization has been reported: Liotta, L. J.; Ganem, B. *Synlett* **1990**, 503–504.
9. For total syntheses of (+)-australine, see: (a) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129–9142; (b) Romero, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 8264–8268; (c) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785–5793; (d) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046–3056; (e) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359–7360; (e) Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513–5516.
10. For total synthesis of (+)-casuarine, see: Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875–2886.
11. (a) Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1988**, *53*, 4181–4185; (b) Alternatively, **1** could be obtained in high yield from tri-*O*-benzyl-D-glucal by dihydroxylation ($OsO_4$, NMO) followed by Wittig reaction ($Ph_3P^+CH_3Br^-$, *n*BuLi); see: Charette, A. B.; Marcoux, J.-P.; Côté, B. *Tetrahedron Lett.* **1991**, *32*, 7215–7218; Vidal, T.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 5677–5680.
12. Martin, O. R.; Liu, L.; Yang, F. *Tetrahedron Lett.* **1996**, *37*, 1991–1994.
13. For a recent review, see: Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519–529.
14. For a review, see: Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75–89.
15. Overkleeft, H. S.; Bruggeman, P.; Pandit, U. K. *Tetrahedron Lett.* **1998**, *39*, 3869–3872.
16. (a) Fu, G. C.; Nguyen, S. N.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857; (b) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 3013–3015.
17. Spectral properties of synthetic (+)-hyacinthacine $A_2$ are in good agreement with the reported data for the natural product.[5] Selected data: $^{13}C$ NMR ($D_2O$-TSP) for synthetic hyacinthacine $A_2$: $\delta$ 27.4; 32.6; 57.7; 65.8; 68.8; 72.0; 80.1; 83.0. {lit.[5] $^{13}C$ NMR ($D_2O$-TSP): $\delta$ 27.3, 32.5, 57.7, 65.3, 69.2, 72.1, 79.8, 82.9}. $[\alpha]_D$ +12.5 (*c* 0.4, $H_2O$), a small sample purified by Professor Asano under the same conditions as the natural product gave $[\alpha]_D$ +23 (*c* 0.04, $H_2O$), {lit.[5] $[\alpha]_D$ +20.1 (*c* 0.44, $H_2O$)}.
18. Yoda, H.; Asai, F.; Takabe, K. *Synlett* **2000**, 1001–1003.