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Synthesis of D-arabinose-derived polyhydroxylated pyrrolidine, indolizidine and pyrrolizidine alkaloids. Total synthesis of hyacinthacine A_2

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ABSTRACT

Several new polyhydroxylated alkaloids including pyrrolidines with a long side chain and 3-(hydroxymethyl) indolizidines were prepared from a common nitrone easily obtained from D-arabinose. In addition, a total synthesis of hyacinthacine A_2 has been achieved in five steps and 67.7% overall yield starting from the same D-*arabino*-derived nitrone. All synthesized compounds have a common structural feature consisting of a pyrrolidine ring with D-*arabino* configuration.

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1. Introduction

Polyhydroxylated nitrogen saturated heterocycles, such as pyrrolidines, indolizidines, and pyrrolizidines constitute one of the most extensively examined family of compounds that have been shown to be potent inhibitors of a great variety of glycosidases.[1] This biological activity confers those compounds a well-recognized chemotherapeutic potential as antibacterial,[2] antidiabetic,[3] antitumoral,[4] and antiviral[5] agents and, as a consequence, they have been broadly studied subjects of synthetic chemistry for many years.[6] Among the pleyade of natural and unnatural polyhydroxylated alkaloids of biological interest, those found in *Hyacinthaceae* plants have received considerable attention from both biological[7] and synthetic[8] points of view. Most derivatives isolated from the leaves of bluebells (*Hyacinthoides non-scripta*) possess a common structural motif consisting of a pyrrolidine having D-*arabino* substitution pattern, that is, three contiguous centers bearing two hydroxyl groups and a hydroxymethyl group, all having R configuration. The simplest member of this family is DAB-1 **1**. Other structural variations reside in the side chain at C-1 of the pyrrolidine ring leading to DMDP **2** and homo-DMDP **3** among others like **4**–**6** (Fig. 1).[9] The same structural motif has also been found in radicamines A **7** and B **8**, both isolated from *Lobelia chinensis*.[10] The side chain at C-1 can also be linked to the nitrogen atom forming a bicyclic structure as in the

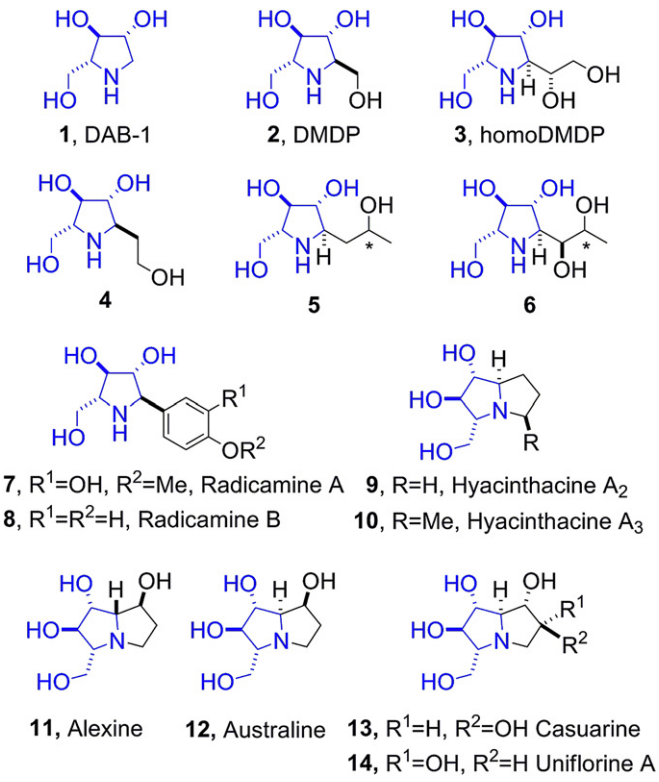

Figure 1. Alkaloids with D-*arabino* configuration.

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case of hyacinthacines A2 **9** and A3 **10**[11] as well as in the well-known pyrrolizidines alexine **11**,[12] australine **12**[13], casuarine **13**,[14] and uniflorine A **14**.[15]

Among the various approaches reported in the literature, nucleophilic additions to cyclic nitrones have demonstrated to be an expeditious and efficient method for preparing a variety of polyhydroxylated pyrrolidines and derivatives.[16] The main advantage of this approach resides in the fact that a variety of cyclic nitrones can be prepared from sugars having a different configuration in such a way that most of stereocenters are incorporated in the starting materials. Previous work in our laboratories[17] illustrated this concept and a variety of natural compounds including codonopsinine,[18] lentiginosine,[19] DAB-1,[20] DMDP,[21] and radicamine B[22] have been synthesized.

We describe herein the synthesis of the naturally occurring *hyacinthacine* A_2 **9** and the non-natural polyhydroxylated alkaloids **15**–**18**, compounds, which have the D-*arabino* configuration at the pyrrolidine ring (Fig. 2). We envisaged preparing compounds **15**–**18** using nitrone **19** as a suitable starting material. Nitrone **19** can be readily prepared from D-arabinose as described by one of us[22] in four steps and 21% overall yield,[23] and it has already been used in our laboratories for preparing DAB-1,[19] radicamine B,[20] and hyacinthacine A_2,[21] in the last case through a dipolar cycloaddition approach.

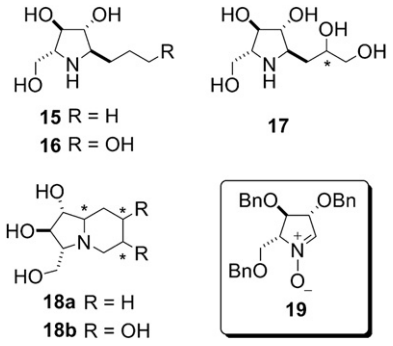


Figure 2. Target compounds from nitrone **19**.

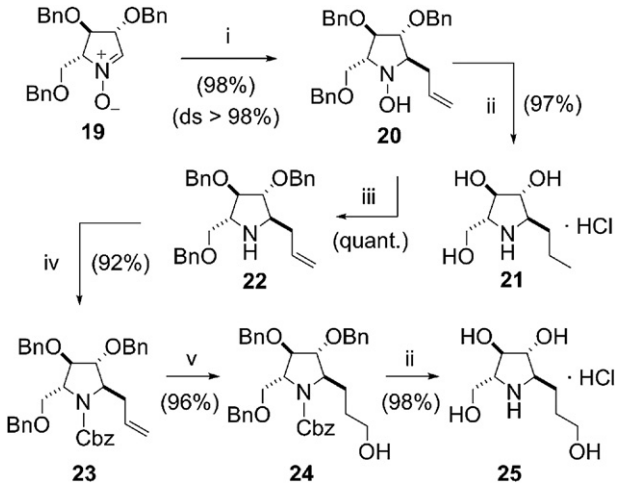
2. Results and discussion

2.1. Synthesis of pyrrolidines with a long side chain

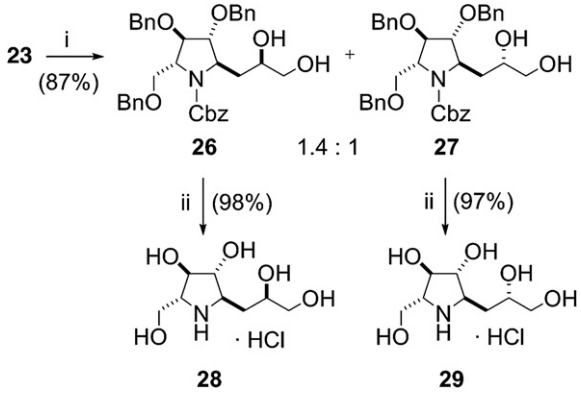
Allylation of nitrone **19** took place with complete selectivity and excellent chemical yield furnishing hydroxylamine **20** as the only product of the reaction (Scheme 1).[24] The configurational assignment of **20** was unambiguously determined by 2D NMR techniques (NOESY, COSY). Concomitant deoxygenation, reduction of the double bond, and removal of the benzyl groups were achieved by catalytic hydrogenation (Pearlman's catalyst, 3 bar) in acidic methanol. Purification of the resulting material afforded **21** (90% from **19**), which was characterized as the hydrochloride salt.

Selective deoxygenation of hydroxylamine **20** was achieved by using Zn in aqueous acetic acid as reducing system. The resulting pyrrolidine **22** was then protected at the nitrogen atom as the *N*-Cbz derivative **23**. The olefin **23** was then submitted to a typical hydroboration with 9-BBN[25] to afford primary alcohol **24** in 96% yield after purification (Scheme 1). Compound **24** was subjected to hydrogenolysis under 3 bar of hydrogen in acidic methanol to give **25** in 80.6% overall yield (six steps from **19**).

Compound **23** was treated with catalytic osmium tetroxide and *N*-methylmorpholine oxide (NMO) to give a 1.4:1 mixture of hydroxylated derivatives **26** and **27** in 87% combined yield. In seeking a higher selectivity for the hydroxylation reaction we checked different conditions including the use of AD-MIX α and β complexes.[26] In all cases the reaction proceeded with no selectivity, lower chemical yield and with the formation of a large number of by-products. The benzyl and benzyloxycarbonyl protecting groups in **26** and **27** could be removed in the same reaction vessel by treatment of those compounds with hydrogen at 3 bar under catalytic conditions (10% Pearlman's catalyst) in acidic methanol. Purification of **28** and **29** by C-18 reverse-phase chromatography and further liophylization afforded those target compounds in 98% and 97% yield, respectively (Scheme 2).

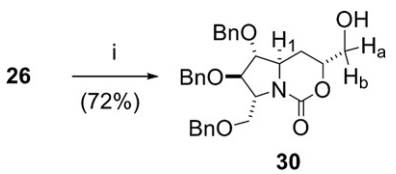


Scheme 1. Synthesis of pyrrolidines with a long side chain. (i) allylmagnesium bromide, THF, 0 °C. (ii) H_2, 3 bar, $Pd(OH)_2$–C, MeOH–HCl,. (iii) Zn, AcOH. (iv) Cbz_2O, dioxane. (v) 9-BBN, then H_2O_2.



Scheme 2. Synthesis of pyrrolidines with a long side chain. (i) OsO_4, NMO, acetone–H_2O. (ii) H_2, 3 bar, $Pd(OH)_2$–C, MeOH–HCl.

The relative stereochemistry of the newly created stereogenic center in **26** and **27** was determined by transforming the major isomer **26** into the bicyclic **30** through a NaH-mediated intramolecular cyclization (Scheme 3). 2D NMR NOESY experiments (C_6D_6, 500 MHz) indicated an NOE between H-1 and H-a and H-b of the hydroxymethyl group, thereby confirming that in **26** the hydroxyl group at the side chain possessed the indicated configuration.



Scheme 3. Determination of configuration for **26**. (i) NaH, THF, rt.

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