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A sort synthesis of polyhydroxylated pyrrolizidines via sequential 1,3-dipolar cycloaddition and reductive amination

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ABSTRACT

Polyhydroxylated pyrrolizidines bearing a methyl group at C-5 have been synthesized by 1,3-dipolar cycloaddition of five membered cyclic nitrones with methyl vinyl ketone followed by a N–O reductive cleavage and in situ intramolecular reductive amination. The stereochemistry of the obtained compounds is examined in relation to the reactions mechanism.

1. Introduction

Polyhydroxylated pyrrolizidines belong to an important class of alkaloids that display a wide range of biological activities mainly due to their action as specific glycosidase inhibitors.[1] Most of the naturally occurring polyhydroxylated pyrrolizidines possess a further hydroxymethyl group and representative alkaloids of this type, such as alexine, australine, casuarine and hyacinthacine (Fig. 1), have gained considerable interest as antiviral and anticancer agents.[2] Since the biological activity varies substantially with the number, the position and the stereochemistry of the hydroxy groups on the pyrrolizine skeleton, the synthesis of both naturally occurring compounds and their stereoisomers and analogues has received much attention.[3]

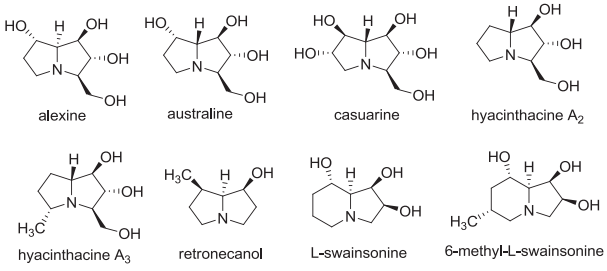
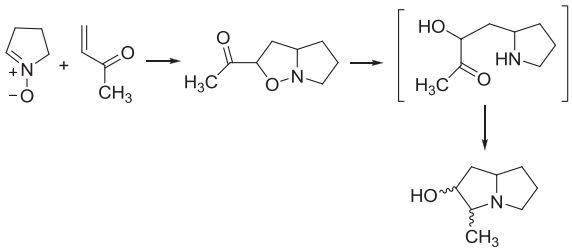


Fig. 1. Representative members of pyrrolizidine and indolizidine alkaloids.

A methyl group occurs also in many polyhydroxylated alkaloids as iminoaldilols, pyrrolizidines of hyacinthacine and necine families and indolizines.[1a,2b,4] In particular, the introduction of a methyl group at C-6 in L-swansonine increases its naringinase inhibition.[4]

In connection with our previous studies[5] on the synthesis of azasugars, we present in this paper a short and stereoselective synthesis of new polyhydroxylated pyrrolizidines bearing a methyl group at C-5. For this purpose we have planned a short reaction scheme comprised of 1,3-dipolar cycloaddition of five membered cyclic nitrones with methyl vinyl ketone followed by a N–O reductive cleavage and in situ intramolecular reductive amination to give pyrrolizidines (Scheme 1).



Scheme 1. General reaction scheme.

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The 1,3-dipolar cycloaddition of nitrones to alkenes and subsequent reductive cleavage is a well documented pathway for the formation of the pyrrolidine ring in many reaction schemes.[6] In most cases acrylates or allyl alcohol derivatives are chosen as alkenes and after the reductive cleavage of the N–O bond the cyclization to the pyrrolidine ring takes place through a nucleophilic attack by the amino group on the ester carbonyl or the activated hydroxymethyl group. Although the use of α,β-unsaturated ketones or aldehydes as dipolarophiles may offer a convenient alternative way for the formation of the pyrrolidine following an analogous methodology, to the best of our knowledge, has not received considerable attention with exception of a few cases.[7]

2. Results and discussion

For our study we chose the racemic protected *cis*-dihydroxy nitrone **1** and the enantiomerically pure nitrones **2**–**4** (Fig. 2). All these compounds were prepared from inexpensive starting materials applying previously described procedures with small modifications. In particular nitrone **1**[8a,b] and nitrone **4**[8e,f] were prepared from D-ribose, nitrone **2**[8c] from L-tartaric acid, and nitrone **3**[8d] from D-arabinose. The choice of these nitrones would permit to study the influence of the substituents geometry on both cycloaddition and reductive amination steps. Furthermore, the use of nitrones **3** and **4** bearing a 3,4-dihydroxy-5-hydroxymethyl substitution pattern will lead to hyacinthacine analogues.

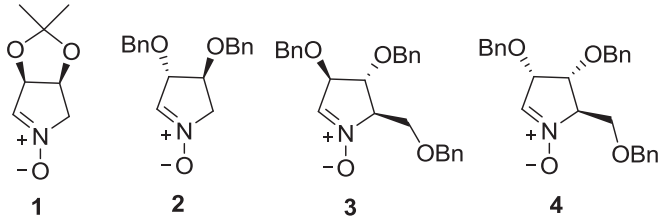
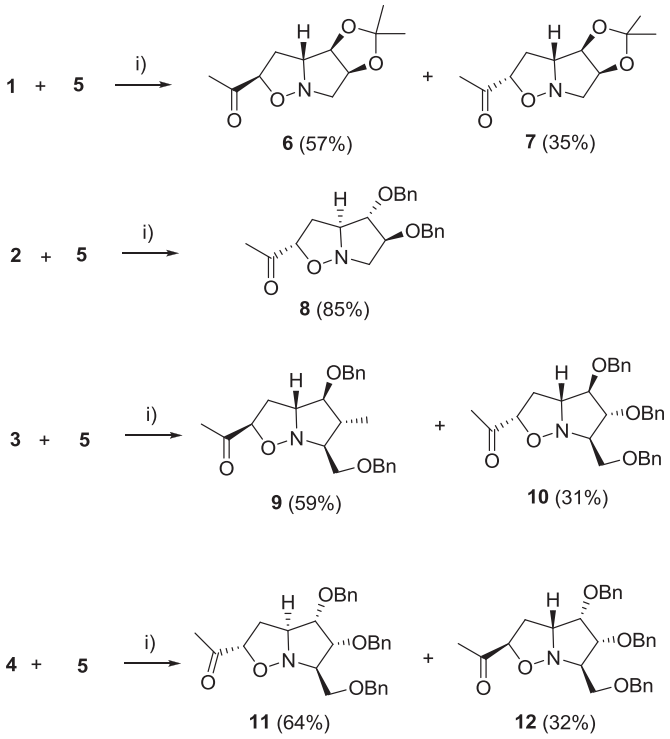


Fig. 2. Applied nitrones.

The cycloaddition reaction of the nitrones **1**–**4** with methyl vinyl ketone **5** took place under mild conditions (reflux in dichloromethane solution for 2 days) affording the expected cycloadducts in high yields. The reactions showed absolute regioselectivity and high stereoselectivity and among the eight possible isomers gave only isomers bearing the acetyl moiety at the 5-position of the isoxazolidine ring, two diastereoisomers in the case of nitrones **1**, **3** and **4** and one diastereoisomer in the case of nitrone **2** (Scheme 2). In particular, nitrone **1** gave the two cycloadducts **6** and **7** in a ratio 1.6:1 and 92% total yield. Cycloadducts **6** and **7** come from *exo*-anti and *endo*-anti transition states, respectively as a result of the tendency of the nitrone **1** to react from its less hindered face. The reaction of nitrone **2** was highly selective and afforded as sole product in 85% yield the isoxazolidine **8**, which comes from an *exo*-anti (relative the C-3 nitrone substituent) transition state. Nitrone **3** reacted also from its less hindered *Re*-face to give in a ratio 1.9:1 and 90% total yield cycloadducts **9** and **10** coming from *exo*-anti and *endo*-anti transition states, respectively. Nitrone **4** showed a lower face selectivity and gave in a ratio 2:1and 96% total yield cycloadducts **11** and **12** resulting from *exo*-anti and *exo*-syn transition states, respectively. The spectra data of the obtained cycloadducts are in accordance with the proposed structures.



Scheme 2. Reagents and conditions: i) CH_2Cl_2, reflux, 48 h.

The stereochemical assignment of the obtained cycloadducts was based mainly on NOE measurements performed either on the initial cycloadducts or on the sequential reductive amination products. In all cases the proton assignment was made by H,H, Cosy spectra. In Fig. 3 are given the observed crucial NOE enhancements, which strongly support the proposed stereochemistry for structures **7**–**11**. The stereochemistry of compound **6** the main product of the reaction with nitrone **1** was not possible to rely on NOE measurements due to the overlapping of the crucial for the structure determination protons. However, it was proved in its reduction products **13** and **14** as described below. Concerning the compound **12**, the minor product of the reaction with nitrone **4**, although NOE measurements are not so obvious due to the overlaps, offer considerable evidence. Thus the 3-H^1 is overlapped with methyl protons (δ 2.12–2.28), the 2-H with the methylene benzyl protons (δ 2.12–2.28), whereas 3a-H and 3-H^2 appear as separate peaks at δ 3.83 and 2.69, respectively. Saturation of 3a-H increases the intensity of the multiplet including 3-H^1 and not 3-H^2. Also saturation of 3-H^2 increases the intensity of the multiplet including 2-H and not 3a-H. These measurements show that 2-H is *cis* to the one of the two 3-H and 3a-H is *cis* to other one. So 2-H and 3a-H are in *trans*-disposition. This disposition is possible to the diastereoisomers that come from an *exo*-transition state. Since the structure from an *exo*-anti transition state was ascribed to the major cycloadduct **11**, the minor cycloadduct should have structure **12** from an *exo*-syn transition state.

The reductive cleavage of the N–O bond and the subsequent reductive amination of the obtained cycloadducts was carried out in one stage by hydrogenolysis over Pd/C catalyst at room temperature. Under these conditions the protective benzyl groups were not removed. For the cycloadducts **6**–**8** this procedure was not stereoselective and they gave both the expected isomers. Thus compound **6** gave the two pyrrolizidines **13** and **14** in a ratio 1.15:1 and 92% total yield, compound **7** the pyrrolizidines **15** and **16** in