Tetrahedron 67 (2011) 7412–7417

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Organocatalytic enantioselective synthesis of quinolizidine alkaloids (+)-myrtine, (−)-lupinine, and (+)-*epi*epiquinamide

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ARTICLE INFO

Article history:
Received 9 May 2011
Received in revised form 4 July 2011
Accepted 6 July 2011
Available online 14 July 2011

Keywords:
Organocatalysis
Quinolizidine alkaloids
Intramolecular aza-Michael reaction
Myrtine
Lupinine
Epiquinamide

ABSTRACT

The organocatalytic synthesis of quinolizidine alkaloids (+)-myrtine, (−)-lupinine, and (+)-*epi*-epiquinamide is described. It involved, as the key step, an enantioselective intramolecular aza-Michael reaction (IMAMR) catalyzed by Jørgensen catalyst **I**, affording the common precursor with high enantioselectivity. This compound was subsequently transformed into the three alkaloids in a highly diastereoselective manner.

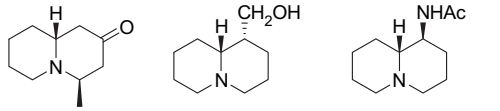
1. Introduction

The azabicyclic skeleton of quinolizidine is a relevant structural subunit present in numerous alkaloids. The wide range of biological activities found in this family of natural products make them ideal targets for total synthesis.[1]

In the past decade organocatalysis has become a thriving area of widely applicable asymmetric reactions,[2] thereby accelerating the development of new methods to assemble useful molecules with high enantiomeric purity. On the other hand, the aza-Michael reaction constitutes one of the best methods for the formation of C–N bonds and has emerged as a very powerful tool for the synthesis of nitrogen-containing heterocycles in its intramolecular version.

Despite the synthetic utility of this transformation, the catalytic enantioselective aza-Michael reaction remained undeveloped until very recently.[3] Furthermore, most of the examples reported in this field are intermolecular reactions, while the intramolecular version has remained almost unexplored.[4] In this context, we have recently developed a catalytic enantioselective intramolecular aza-Michael reaction (IMAMR). Thus, when carbamates bearing a remote α,β-unsaturated aldehyde moiety were treated with chiral diarylprolinol ethers, the IMAMR took place with high levels of enantioselection, giving rise to the corresponding enantiomerically enriched nitrogen heterocycles.[4c,e]

The synthetic utility of our approach is now illustrated with the total synthesis of three quinolizidine alkaloids, namely (+)-myrtine **1**, (−)-lupinine **2**, and (+)-*epi*epiquinamide **3** (Fig. 1).



1 [(+)-myrtine] **2** [(−)-lupinine] **3** [(+)-*epi*epiquinamide]

Fig. 1. Quinolizidine alkaloids.

2. Results and discussion

A common carbamate precursor, *N*-Boc 2-[(*R*)-piperidin-2-yl] acetaldehyde (**5**), was assembled by means of an organocatalytic IMAMR. Accordingly, conjugated aldehyde **4** was treated with Jørgensen diarylprolinol **I** in $CHCl_3$ at −50 °C in the presence of benzoic acid as an additive, thus affording the piperidine aldehyde **5** in 63% yield and 94% ee (Scheme 1).[4e] The synthesis of compound

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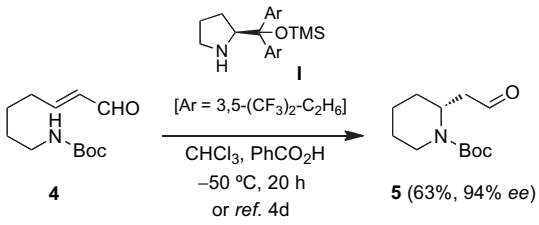
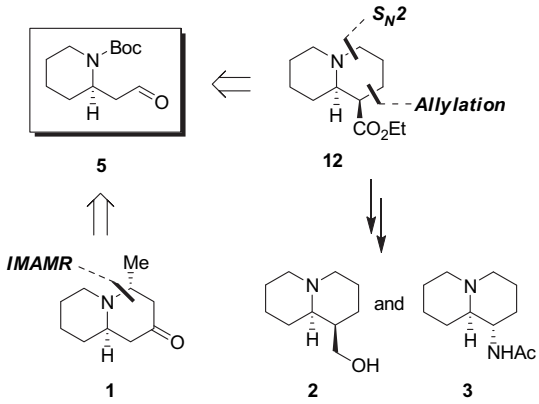
doi:10.1016/j.tet.2011.07.017

5 was also described by Carter et al. starting from **4** in a MeOH–DCE mixture at −25 °C by using the same catalyst.[4d] This aldehyde was used as the starting substrate for the synthesis of alkaloids **1**–**3**. The retrosynthetic analysis is depicted in Scheme 1.



Scheme 1. Synthesis of the common precursor **5**.

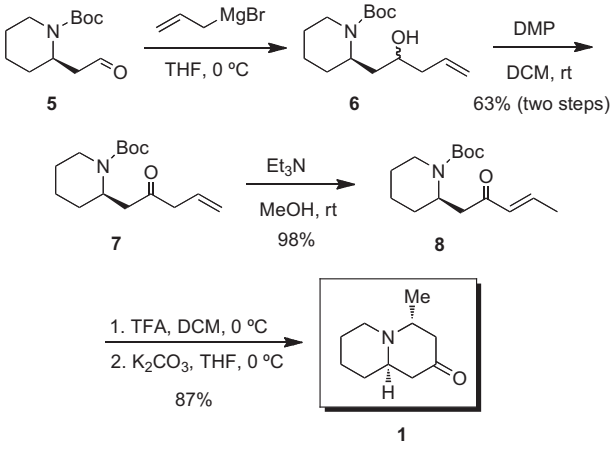
In our approach, the key step in the synthesis of **1** involved a highly diastereoselective IMAMR on the appropriate precursor that was in turn prepared from piperidine **5**. On the other hand, the key intermediate for the synthesis of **2** and **3** was the bicyclic β-amino ester **12**. In these cases, the second chiral center was installed by means of a highly diastereoselective allylation reaction followed by further cyclization onto the nitrogen atom through an S_N2-type displacement (Scheme 2).



Scheme 2. Retrosynthetic analysis.

(+)-Myrtine **1** (see Fig. 1) is a naturally occurring quinolizidine alkaloid isolated from *Vaccinium myrtillus*. Although it was discovered more than three decades ago -its structure and absolute configuration were determined in 1978-,[5] only six asymmetric synthesis of this alkaloid have been described to date. Two of them relied on the use of enantiomerically pure starting materials derived from the chiral pool.[6] Two more syntheses employed either sulfoxides or 8-phenylmenthol as chiral auxiliaries.[7] The last one was based on a copper-catalyzed enantioselective conjugated addition reaction.[8] Finally, an organocatalytic enantioselective synthesis of (+)-myrtine appeared in the literature early this year.[9]

In our strategy, aldehyde **5** reacted with allylmagnesium bromide to afford a diastereomeric mixture of alcohols **6**, which were readily oxidized with Dess–Martin periodinane (DMP). The resulting ketone **7** was then treated with Et_3N in MeOH, thus promoting a highly efficient double bond isomerization that gave access to the α,β-unsaturated ketone **8**.[10] Removal of the Boc *N*-protecting group provided the substrate for the IMAMR. Complete selectivity was achieved in this cyclization step when K_2CO_3 was employed as a base in THF at 0 °C. In this manner, the desired alkaloid **1** was obtained in 87% yield (Scheme 3).[11]



Scheme 3. Synthesis of (+)-myrtine **1**.

As a result, we have performed the second organocatalytic synthesis of (+)-myrtine in six steps and 34% overall yield starting from the *N*-Boc protected aldehyde **4**.

(−)-Lupinine **2** (see Fig. 1) is one of the parent members of the quinolizidine group of alkaloids isolated from the yellow lupin seeds (*Lupinus luteus*) and it was first reported over a hundred years ago.[12] Several asymmetric syntheses of this alkaloid have been devised, most of them based on chiral pool-derived starting materials.[13] Only one synthesis reported by Ma and Ni in 2004 took advantage of the Sharpless asymmetric epoxidation in order to generate the corresponding chiral centers of the molecule.[14]

On the other hand, (−)-epiquinamide **3′** (Fig. 2) was isolated in 2003 from the poison frog *Epipedobates tricolor* and it was claimed to act as an agonist of the nicotinic receptors.[15] This alkaloid has attracted considerable attention from the synthetic community, and several asymmetric syntheses have been recently reported. Again, most of them made use of starting materials coming from the chiral pool.[16] Optically active precursors obtained by enzymatic resolution have also been employed in the preparation of **3**.[17] Very recently, two more asymmetric syntheses of (−)-epiquinamide involving an asymmetric hydroxylation reaction as the key step have been reported in the literature.[18] However, only one report deals with the preparation of the epiquinamide C1-epimer **3** (Fig. 2).[17]

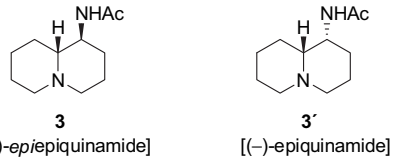


Fig. 2. Epiquinamide epimers.

In accordance with the retrosynthetic analysis shown in Scheme 2, we have performed the first organocatalytic synthesis of (−)-lupinine **2** and (+)-*epi*epiquinamide **3** from a common precursor **12**. Thus, aldehyde **5** was transformed into the corresponding methyl ester **9** through oxidation followed by treatment with $TMSCHN_2$. The installation of the second stereocenter of the molecule was achieved by treatment of the lithium enolate of **9** with allyl iodide at −100 °C, thus affording compound **10** in 94% yield and excellent diastereoselectivity (96:4 dr).[19] Next, the double bond was transformed into the corresponding alcohol **11** by means of the sequence hydroboration–oxidation. After mesylation of the hydroxyl functionality and removal of the Boc protecting group, a smooth cyclization through an S_N2-type process took place upon