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Syntheses from chiral heterocyclic β-amino esters. A new versatile access to pyrrolizidine and quinolizidine alkaloids

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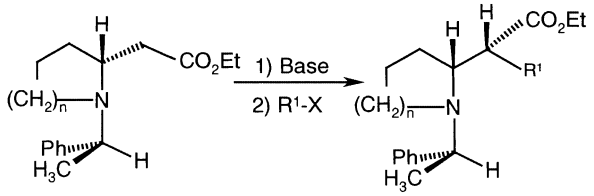
Abstract—Chiral heterocyclic β-amino esters can be easily transformed into bicyclic alkaloids after a diastereoselective alkylation followed by specific chemical transformations.

Pyrrolizidine and quinolizidine alkaloids have a wide and varied distribution in nature and they display a broad range of interesting biological activities. Accordingly, novel strategies for the enantioselective synthesis of these azabicyclic skeletons continue to receive considerable attention.[1,2]

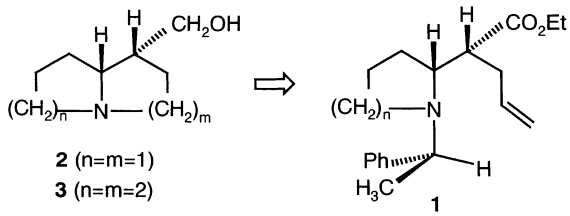
We recently developed a new general and highly diastereoselective method for the alkylation of chiral pyrrolidyl and piperidyl acetates using respectively LDA[3] or LiHMDS[4] as bases.



1, n = 1,2

It can be noted that (+) isoretronecanol **2** ($n=m=1$) and (–) lupinine **3** ($n=m=2$) present two asymmetric centers where the two hydrogens are in a *syn* position according to our previous results.[3,4]

A disconnective analysis of these hydroxymethyl-azabicyclic alkaloids shows that all these compounds can be obtained after the reduction of an intermediate ester itself prepared by annelation of an alkylated cyclic β-amino ester **1**.



2 (n=m=1)
3 (n=m=2)

1

A propenyl substituent was a very good choice due to the well-known reactivity of the allyl halides and to the potential cyclization sites of the two ethylenic carbons.

The formation of the pyrrolizidinic skeleton of the isoretronecanol from **1** ($n=1$) needed an oxidative cleavage of the double bond followed by a reductive annelation.

This was performed in two steps. Firstly by ozonolysis in acidic ethanol[5] due to the nucleophile of the tertiary amine. After reduction with DMS then acidic hydrolysis, the β-amino aldehyde **4** was obtained in good yield. Hydrogenolysis of **4** with 10% Pd/C in ethanol leaded directly to the pyrrolizidinic ester **5**[6] with a very good chemical yield and only one diastereomer was detected. It could be noted that **5** is also a natural product named Chysine B.[7] The picrate of **5** was then formed and the melting point of the salt (110°C) was in agreement with that of the *syn* diastereomer described earlier.[8]

Confirmation of the structure was performed by epimerizing **5** with sodium ethoxide. After neutralization then action of picric acid, the resulting salt presented a melting point (180°C) in agreement with the literature.[8]

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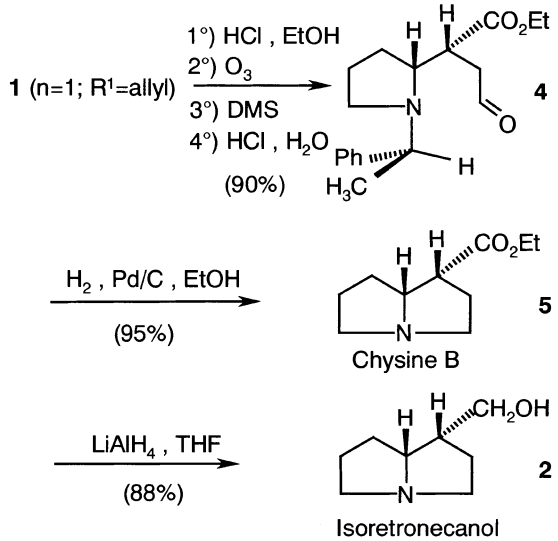
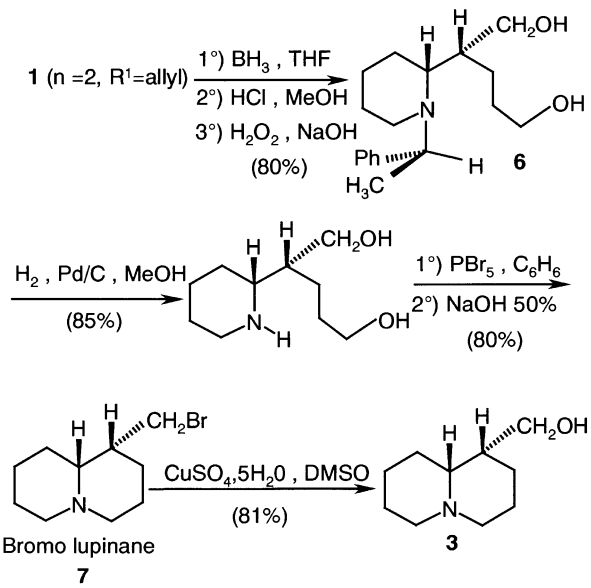


Further chemical reduction of the ester function led selectively to isoretronecanol **2**[9] with excellent yield. However, due to the possible epimerization α to the ester function, a reverse reduction of $LiAlH_4$ was performed (addition of **5** at −78°C to a suspension of $LiAlH_4$ in THF). One more time, $[\alpha]_D^{20}=74$ (*c* 0.45, EtOH) which agrees with the literature.[10]

For the synthesis of quinolizidinic skeleton, a regioselective hydroxylation of the double bond of **1** ($n=2$) was performed byhydroboration. However, the presence of a nucleophilic nitrogen in the molecule did not permit to apply classical conditions (BH_3/DMS) described by Knight et al.[4,11] No hydrogenolysis was possible with this β-amino ester but an excess of complex BH_3/THF led with good yield to the β-amino diol **6**. After debenzylation of **6**, a treatment with PBr_5 in refluxing benzene as described Schöpf et al.[12] led to the cyclized bromo lupinane **7**.[13] The very good optical purity of this compound was established by comparison with an analytical sample



of **7** prepared by direct bromination of natural lupinine.[14]

Direct substitution of the bromine by acetate was described with a very poor yield,[15] but recent conditions using aqueous copper sulfate in DMSO[16] were particularly performing with compound **7**. In fact, optically pure lupinine **3**[17] was finally isolated in 80% yield. Once more, optical purity was in complete agreement with literature data.[18]

In conclusion, chiral cyclic β-amino esters are very versatile synthons for the synthesis of pyrrolizidine and quinolizidine alkaloids. After diastereoselective introduction of an allyl substituent, appropriate chemical transformations can easily lead to bicyclic structures found in many natural products.

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