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Heterocycle Formation Through Aza-Annulation: A Stereochemically Controlled Route to (±)-Lupinine.

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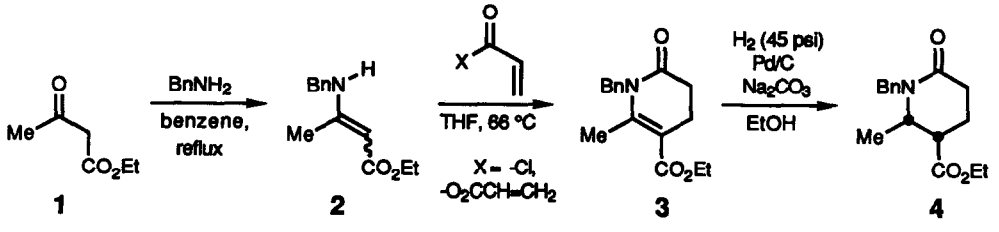
Abstract: The aza-annulation of an acyclic β-enaminoester with acryloyl chloride was found to be a very efficient method for nitrogen heterocycle formation. Stereospecific hydrogenation of the unsaturated dihydropyridone generated from aza-annulation gave a single disubstituted lactam product. The cis stereochemical relationship of the substituents was confirmed by transformation of the lactam to (±)-lupinine.

Recently, we reported the aza-annulation of acrylate derivatives with alkyl imines not in conjugation with adjacent functionality, as a method of tetrahydropyridone formation.[1] In these studies, reaction occurred as a result of the imine/enamine tautomerization, and produced a mixture of products when the imines were treated with α,β-unsaturated acid chlorides. Efficient annulation with these imine substrates required the use of alternate acrylate derivatives such as the corresponding acid anhydride or use of the acrylic acid derivative activated by addition of $ClCO_2Et$ or $(PhO)_2P(O)Cl$. Alternatively, by using substrates in which the alkyl imine is in conjugation with a carbonyl, the amine functionality exists predominantly as the enamine tautomer, and the annulation process was more facile. In particular, cyclic enamine species conjugated with esters have been annulated with α,β-unsaturated esters,[2] acid anhydrides,[2a,3] acids,[4] and acid chlorides.[2] In contrast, we have found only one report of heterocycle formation by aza-annulation of an acyclic β-enaminoester with an acrylic acid derivative.[5]

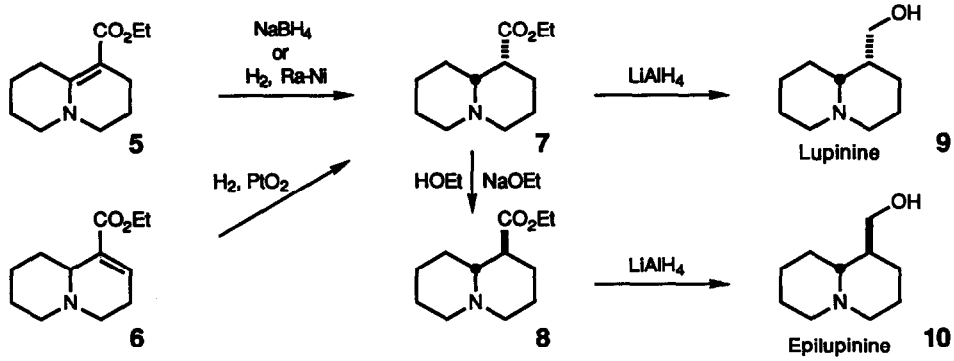


(1)

Further investigation of the aza-annulation methodology with acyclic β-enaminoesters has led to development of an efficient method for the regiospecific formation of heterocyclic amines. The condensation of 1 with $BnNH_2$, driven to completion by azeotropic removal of H_2O, produced β-enaminoester 2, which was used without further purification (eq. 1). Treatment with either acryloyl chloride or acrylic acid anhydride gave

3 as the only reaction product in 64% and 63% yields, respectively, for the two-step condensation/aza-annulation of 1 to 3. Compound 3, the product of carbon-carbon bond formation by conjugate addition followed by *N*-acylation, was formed to the exclusion of the 4-pyridone, the product of *C*-acylation of the enamine and conjugate addition of the amine. Hydrogenation of 3 gave 4 (84% yield) with >98:2 cis selectivity. In order to demonstrate the selective cis formation of 4, and the applicability of this methodology toward architecturally more complex molecules, we chose (±)-lupinine as a target of a stereocontrolled total synthesis.

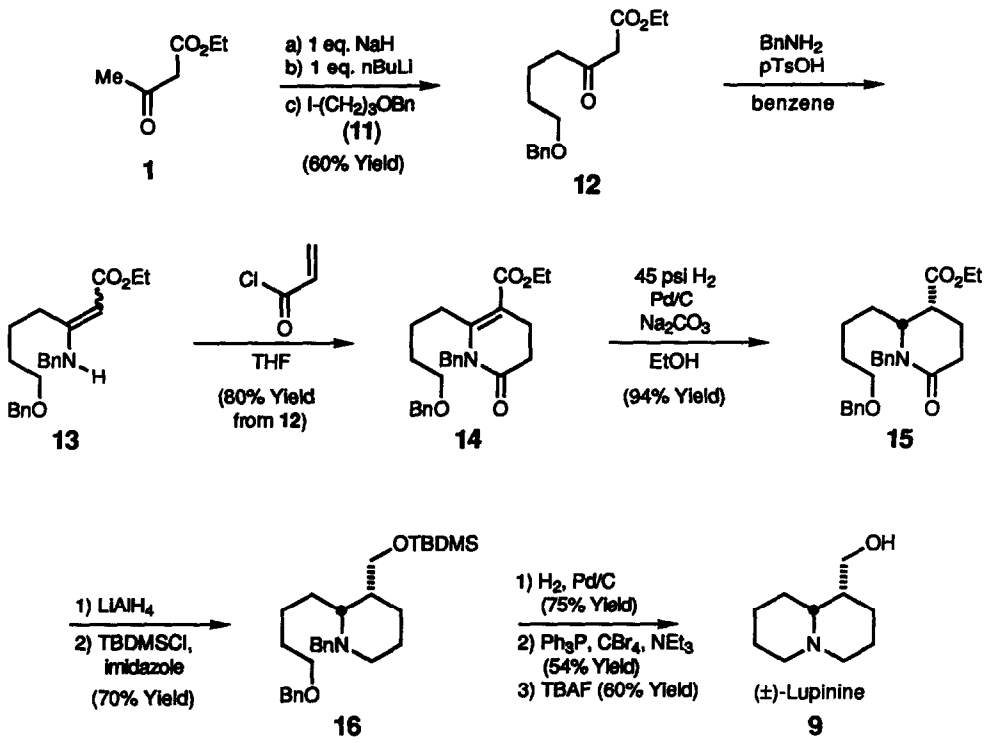
Scheme I. Established Methods for the Generation and Conversion of Lupinine Stereochemistry.



A number of routes to the selective synthesis of lupinine have been reported (Scheme I). With only two exceptions,[6] the relative stereochemistry of the two asymmetric centers has been established either through reduction of 5[7] or 6[8] to produce 7. Subsequent reduction of 7 with $LiAlH_4$ was then used to prepare lupinine (9). Alternatively, epimerization of 7 to the more thermodynamically stable isomer 8, followed by reduction to 10 provided a route to epilupinine (10).[6b,7b,7e,8a] In each total synthesis that has appeared, at least one of the two heterocycle rings was already present in the starting material.

The use of this aza-annulation methodology provided easy access to the naturally occurring quinolizidine ring skeleton. Alkylation of the mixed dianion[9] of 1 by reaction with 11 for 10 hours at room temperature in THF resulted in a 60% isolated yield of the β-ketoester 12 (Scheme II). Condensation of 12 with $BnNH_2$ in benzene, assisted by the azeotropic removal of H_2O, generated the β-enaminoester 13 as the sole product. After removal of the benzene, 13 was dissolved in THF and acryloyl chloride was added. The reaction mixture was heated at reflux for 15 hours to produce an 80% yield of 14 in the two-step process from 12. The presence of Na_2CO_3 during hydrogenation of 14 limited uptake of H_2 to 1 equivalent, and produced stereoselective reduction to 15 (cis:trans, >98:2) in 94% yield without removal of the benzyl protecting groups.[10] Subsequent reduction of both amide and ester functional groups gave the corresponding piperidine compound containing a tertiary alcohol, which was then protected as the TBDMS ether. Removal of the benzyl protecting groups allowed formation of the second six-membered ring in 54% unoptimized yield through the use of $PPh_3/CBr_4/NEt_3$.[11] Final removal of the TBDMS group gave (±)-lupinine.[12]

Scheme II. The Total Synthesis of (±)-Lupinine.



Several important steps were illustrated through this synthesis of (±)-lupinine in which both rings were constructed. The pivotal transformation was the high yield condensation and subsequent aza-annulation of the resulting β-enaminoester. Stereoselective hydrogenation then produced the first example in which both asymmetric centers of lupinine were established at the stage of a monocyclic intermediate. Formation of the second ring of this bicyclic target showed that PPh3/CBr4/NEt3 was an effective method of generating six-membered nitrogen heterocycles. We are currently pursuing the application of the aza-annulation methodology to the preparation of alkaloids with indolizidine and decahydroquinoline ring systems, and exploring the possibility of enantioselective synthesis of natural products by asymmetric hydrogenation of a chiral β-enaminoester intermediate.[13]

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§Undergraduate research participant in the Research Experiences for Undergraduates program at Michigan State University.

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