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A General Route for the Synthesis of Enantiopure Indolizidine Alkaloids from α-Amino Acids. Total Synthesis of (+)-Monomorine

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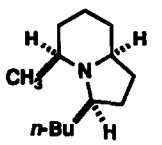
Abstract: The ant trail pheromone (+)-Monomorine was synthesized in 9 steps from *N*-*t*-BOC-*L*-alanine ethyl ester. The key step of the synthesis is the conformationally restricted Claisen rearrangement of lactone **9** to pipecolic ester **11**.

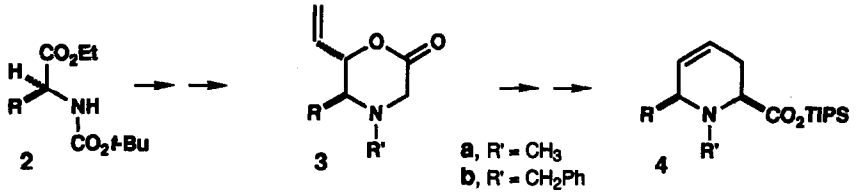
The indolizidine alkaloids display a wide range of biological activity[1] and have been the subject of a considerable number of synthetic studies.[2] The development of general methods for the synthesis of enantiopure indolizidines remains a challenge for the synthetic chemist.[2] We have recently developed an enantioselective synthesis of highly functionalized pipecolic esters[3] that might find application as part of a general synthetic route to enantiopure indolizidine alkaloids from readily available α-amino acids.[3] We report here the implementation of this strategy with the total synthesis of the Pharaoh ant trail pheromone (+)-monomorine.[4,5,6]



(+)-Monomorine, **1**

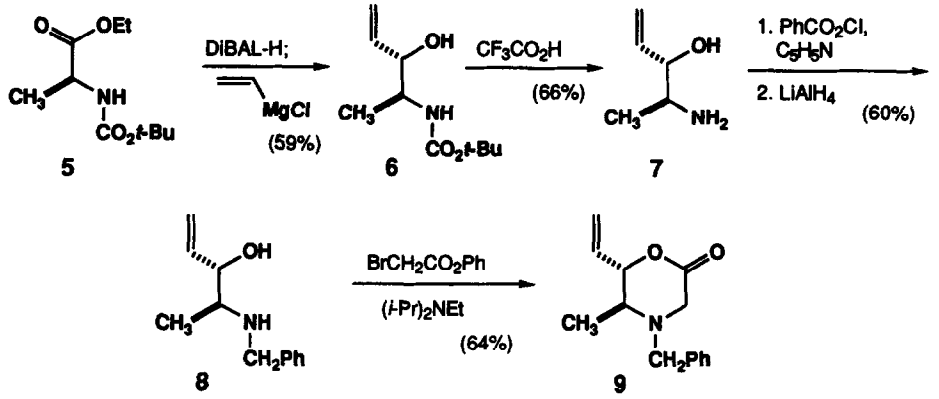
We have shown that esters of amino acids **2** could be converted to *N*-methyl pipecolic esters **4a** in good yields (Scheme 1).[3a] The key step of the synthetic sequence was a conformationally restricted Claisen rearrangement of ketene acetals derived from lactones **3a**.[7] The extension of this methodology to the synthesis of indolizidines required the preparation of pipecolic esters with a protecting group on nitrogen that could easily be removed. Since the proposed route required a hydrogenation, *N*-benzyl pipecolic esters **4b** were logical intermediates in the proposed indolizidine synthesis. The benzyl protecting group might allow the deprotection to be accomplished as one of several reductions in the penultimate step of the synthesis.

Scheme 1. Synthesis of Pipecolic Esters from Amino Esters.



We have previously described[3a] the synthesis of allyl alcohol **6** from readily available BOC-alanine ethyl ester **5** via Yamamoto's one pot reduction-alkylation procedure[8] in 59% yield (8:1 mixture of diastereomers). The mixture of diastereomers was carried forward without separation. Removal of the BOC protecting group was accomplished with triflouroacetic acid (10 equiv, CH_2Cl_2, 0 °C, 90 min) to afford amino alcohol **7**.[9] Amine **7** was then protected by acylation with benzoyl chloride (2.2 equiv, pyridine, 5h, 25 °C), followed by reduction of the amidoester with $LiAlH_4$ (5 equiv, THF, reflux, 1 h) to afford *N*-benzyl amine **8** in 60% overall yield from **7**. Formation of lactone **9** was accomplished in 64 % yield by treatment of **8** with α-bromophenylacetate (1.1 equiv) in the presence of Hunig's base (4.0 equiv, CH_3CN, 25 °C, 14 h).

Scheme 2. Synthesis of *N*-Benzyl Lactone 9.

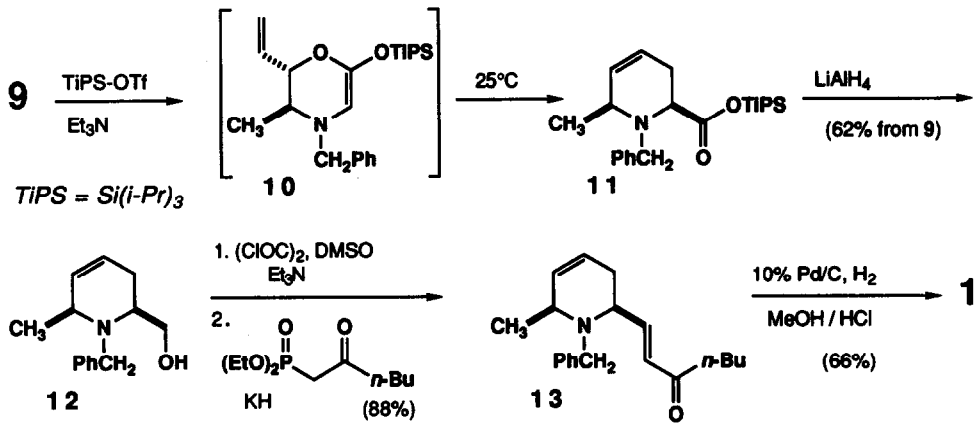


Lactone **9** was a mixture of diastereomers originating from the 8:1 mixture for **6**. At this point, the diastereomers could be separated by HPLC; however, we found this procedure to be unnecessary as described below. Addition of triethyl amine (1.5 equiv) and triisopropylsilyl triflouromethanesulfonate (TiPS-OTf, 1.1 equiv, C_6H_6) to the mixture of lactone diastereomers resulted in the immediate formation of silyl ketene acetals **10** by ^1H NMR analysis (Scheme 3). Claisen rearrangement of the major ketene acetal diastereomer, with the vinyl and methyl groups in a *trans*-orientation, proceeded at room temperature in 6 h; whereas the minor *cis*-diastereomer

failed to undergo rearrangement under these conditions. TiPS ester **11** was obtained as a single diastereomer. Reduction of crude silyl ester **11** ($LiAlH_4$, 5 equiv, ether, 25 °C, 2h) afforded alcohol **12** in 62% overall yield from **9**. One pot Swern oxidation[10]/Horner-Wittig olefination[11] (1.4 equiv phosphonate; KH, 1.2 equiv, THF, 25 °C, 3h) afforded enone **13** in 88% yield from **12** (95:5 *E/Z* mixture).

The completion of the synthesis required hydrogenation of the two alkenes, deprotection of the amine, iminium ion formation, and stereoselective reduction. *All of these transformations were accomplished in a single step!* Subjecting **13** to H_2 (1 atm) in the presence of 10% Pd/C (20:1 MeOH/1N HCl, 5 days) afforded (+)-monomorine $[\alpha]_D^{25}$ +35.4° ($CHCl_3$, c = 0.0089) in 66% yield.[12]

Scheme 3. Synthesis of (+)-Monormine 1.



The synthesis of (+)-monomorine was accomplished in 9 steps (5.4% overall yield) from amino ester **5**. The synthesis demonstrates the utility of our Claisen rearrangement strategy for the synthesis of enantiopure indolizidine alkaloids from readily available α-amino acids. Work is currently ongoing to apply this methodology to the synthesis of more complex indolizidine natural products.

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