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Radical Cyclization of β-Aminoacrylates: Stereoselective Synthesis of Indolizidines 167B and 209D

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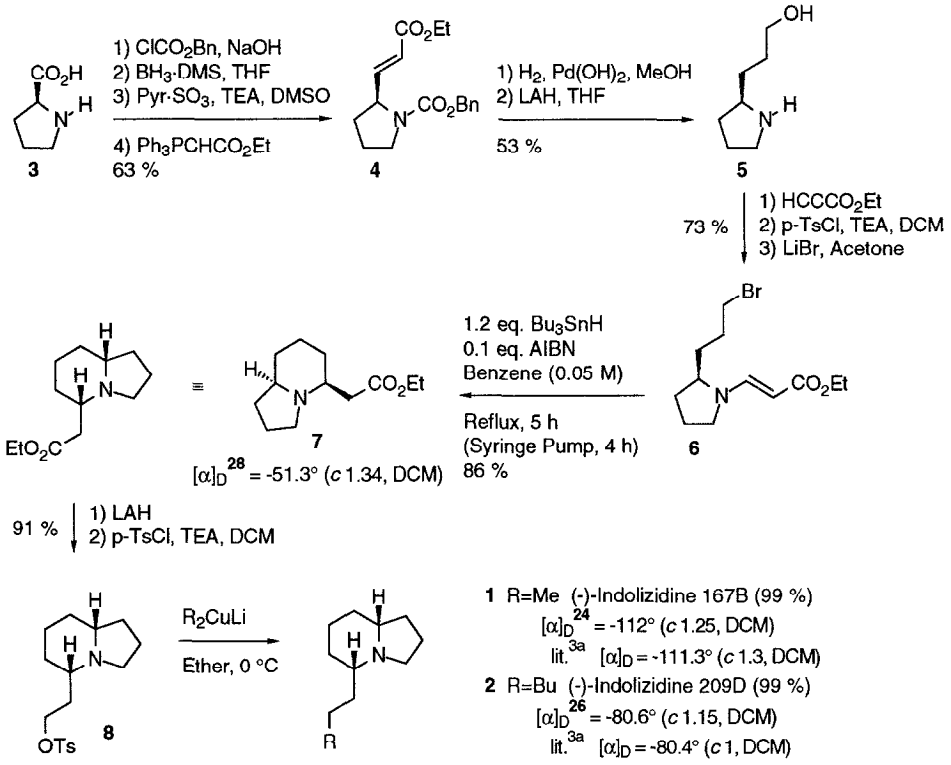
Abstract : Indolizidine alkaloids 167B and 209D were synthesized via radical cyclization of β-aminoacrylates.

The skin secretions of certain neotropical frogs have furnished a number of pharmacologically interesting indolizidine alkaloids.[1] Some of these compounds act as non-competitive blockers of neuromuscular transmission.[2] Indolizidines 167B(**1**) and 209D(**2**) are simplest members of this class of natural products and considerable amount of work was directed towards preparation of these rare alkaloids.[3]

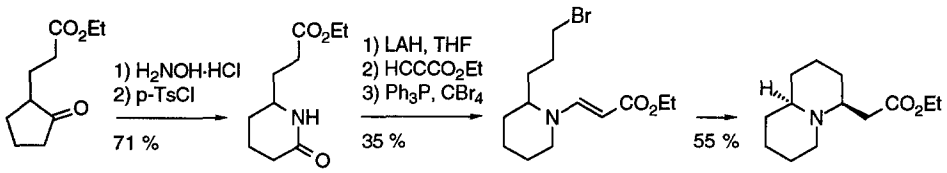


Scheme 1

Recently we reported that radical cyclization reactions of β-alkoxyacrylates[4,5] and β-aminoacrylates[6] might be used in the stereoselective synthesis of heterocyclic compounds. We now wish to report that **1** and **2** can be synthesized stereoselectively via radical cyclization of β-aminoacrylates.

(S)-Proline(**3**) was converted into the Cbz-protected (pyrrolidine)acrylate **4** via Cbz protection, borane reduction, oxidation,[7] and Wittig reaction. Subsequent hydrogenation and LAH reduction gave the bishomoprolinol **5**. The β-aminoacrylate **6** was synthesized upon reaction of **5** with ethyl propiolate and the routine bromide substitution. Under the standard high-dilution radical generating conditions using tributylstannane, the *6-exo* cyclization reaction of **6** occurred efficiently yielding the (indolizidine)acetate **7** as a single stereo isomer. The tosylate **8** was obtained when **7** was reduced with LAH and the product was reacted with tosyl chloride. Synthesis of **1** and **2** was accomplished[8] when **8** was allowed to react with lithium dimethylcuprate or dibutylcuprate (Scheme 1).

The above synthesis starts from readily available (S)-proline, and can easily be adopted for the large scale preparation of other indolizidine alkaloids.[9] The most striking feature of the synthesis is the complete stereo control in the *6-exo* radical cyclization. In this regards, formation of (quinolizidine)acetate was also found to be totally *cis* selective (Scheme 2).



Scheme 2

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8. They were identified by comparing with the known physical and spectroscopic data from the literature.
9. For example, piclavines can easily be synthesized: Raub, M. F.; Cardellina, J. H. II; Spande, T. F. *Tetrahedron Lett.* **1992**, *33*, 2257.

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