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Enantioselective Synthesis of (-)-Indolizidine 167B

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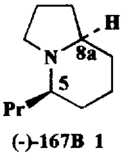
Abstract :

The enantioselective total synthesis of (-)-indolizidine 167B is described. The key step is the intramolecular cyclization of the chiral *N*-acyliminium ion **6**. Indolizidine 167B was obtained in 7 steps and 17% yield from ethyl (*R*)-3-aminohexanoate, with an enantiomeric excess of 93%. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords : Allylsilane ; Acyliminium ion ; Alkaloid ; Indolizidine

Indolizidine alkaloids have been isolated from the skin secretions of neotropical frogs of the family Dendrobatidae [1,2]. The lack of availability of the natural material and the important biological activities of the compounds make these alkaloids ideal targets for total synthesis. The simplest member of these alkaloids is indolizidine 167B **1**. It has been synthesized in its racemic form [3-8], as its (5*S*,8a*S*)-(+)-enantiomer [9] and as its (5*S*,8a*R*)- and (5*R*,8a*R*)-(-) enantiomers [10-17].

We have found that intramolecular cyclization of acyliminium ions substituted by an allylsilyl side chain as an internal π-nucleophile constituted an excellent route to nitrogen bicyclic ring systems [18] and we have used this strategy to prepare racemic [19,20] and chiral [21] quinolizidine alkaloids. This method represents an efficient and stereoselective strategy for the preparation of 5-substituted indolizidines and we report in this paper its application to the synthesis of (-)-indolizidine 167B **1**.



(-)-167B 1

The source of chirality was the aminoester (*R*)-**3** which was prepared according to Davies' methodology [22] (Scheme 1). Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-

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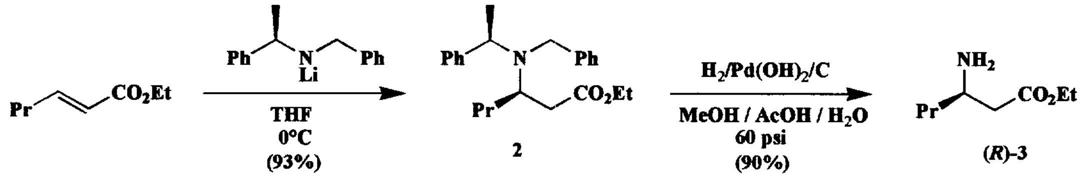
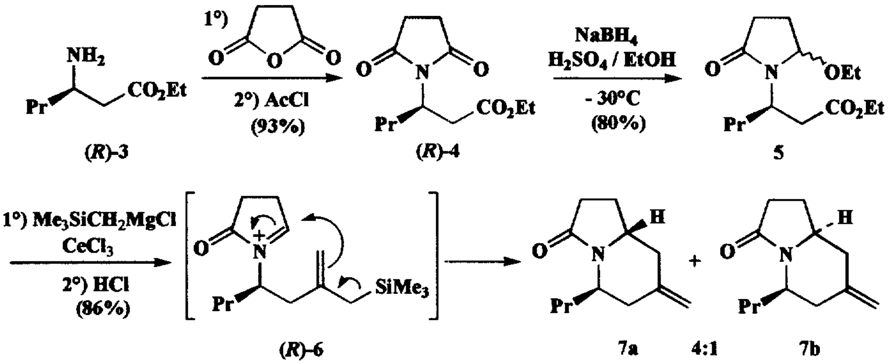
methylbenzylamide to ethyl hex-2-enoate afforded the tertiary amine **2** in 93% yield with an excellent diastereoselectivity (>92%). Debenzylation of **2** with Pearlman's catalyst and hydrogen gave the aminoester **3** in 90% yield. Enantiomeric excess of **3** was determined by deuterium NMR of its *N*-trideuteroacetyl derivative in a chiral solvent [dichloromethane solution of γ-benzyl L-glutamate (PBLG)] as described previously by Courtieu and coll. [23] and was found to be 93%. Absolute configuration of **3** was assigned as *R* by analogy with related Davies' experiments [24] and was confirmed on the final product **1** by comparison of its specific rotation and spectroscopic and NMR data with literature values.



Scheme 1

Synthesis of the indolizidine skeleton was carried out as shown in Scheme 2. Reaction of **3** with succinic anhydride and then with acetyl chloride in refluxing toluene gave imide **4** in 93% yield. Imide **4** was reduced into ethoxylactam **5** in 80% yield. **5** was isolated as a mixture of two diastereomers. In the next step, ethoxylactam **5** was treated with the cerium reagent derived from trimethylsilylmethylmagnesium chloride and CeCl3. The mixture was then hydrolyzed with 1N HCl, to give methyleneindolizidinones **7a** and **7b** in a 4:1 ratio and 86% yield. These isomers could not be separated. This reaction involved formation of allylsilyl substituted acyliminium ion (*R*)-**6** which cyclized spontaneously.

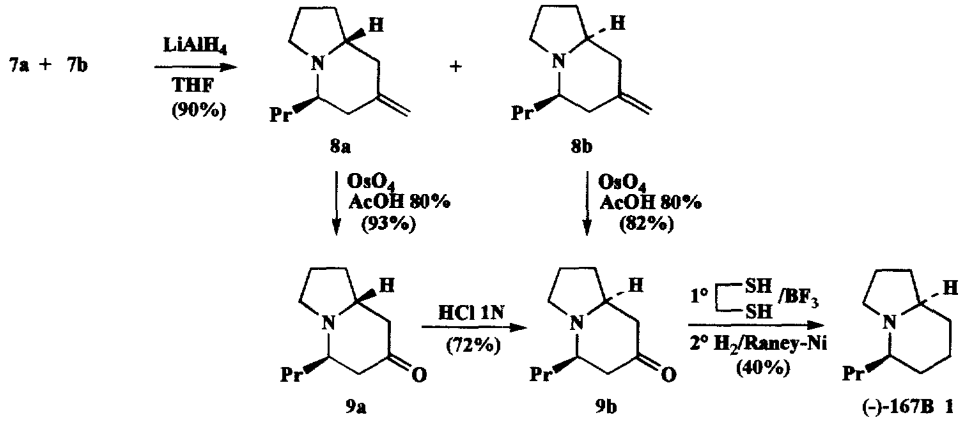


Scheme 2

The stereochemical course of the cyclization can be explained from Hart's models [25] in which the most favoured transition state minimizes $A^{(1,3)}$ strain. The transition state leading to **7a**, in which the propyl chain occupies an axial position, would be preferred to the transition state leading to **7b** where the propyl group develops a severe $A^{(1,3)}$ strain with the carbonyl of the lactam function.

Indolizidine 167B **1** was prepared according to Scheme 3. Reduction of the mixture of lactams **7a** and **7b** with lithium aluminium hydride gave methyleneindolizidines **8a** and **8b**.

These isomers were easily separated by flash column chromatography. They were isolated in respectively 72 and 18% yields. Osmium tetroxide catalyzed periodate oxydation of the olefinic bond of **8a** and **8b** led respectively to indolizidin-3-ones **9a** ($[\alpha]_D$ -48.6 (c 3.38, chloroform)) and **9b** ($[\alpha]_D$ -21.3 (c 1.97, chloroform) ; lit [17] $[\alpha]_D$ -20.4 (c 3.38, chloroform)) in 93 and 82% yields. Structure of **9b** was confirmed by comparing its NMR data with literature values [17]. Obtention of **9b** from **7b** unambigously confirmed the stereochemistry of **7b**.



Scheme 3

Upon treating an aqueous solution of **9a** with HCl 1N (reflux for six days) the thermodynamically more stable indolizidinone **9b** was obtained in 72% yield, probably through a retro-Mannich fragmentation-cyclization process. The last two steps were the conversion of **9b** into its dithiolane and subsequent desulfurization using Raney nickel, as previously described [17]. Enantiomerically pure (5*R*,8a*R*)-indolizidine 167B **1** was obtained in 70% yield. This compound was identified by comparison of its ^1H and ^{13}C NMR spectra with the literature data [10]. The specific rotation ($[\alpha]_D$ -106.6 (c 1.33, dichloromethane)) was in agreement with the literature value [10] ($[\alpha]_D$ -111.3 (c 1.3, dichloromethane)).

In conclusion, the synthesis of (-)-indolizidine 167B has been achieved in 7 steps and 17% overall yield from ethyl (3*R*)-3-aminohexanoate, with an enantiomeric excess of 93%. This synthesis demonstrates the utility of our cyclization strategy for the synthesis of enantiopure indolizidine alkaloids from readily available β-aminoesters. Work is currently ongoing to apply this methodology to the synthesis of more complex indolizidine natural products.

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