Asymmetric Synthesis of (−)-Indolizidine 209D via B-Alkyl Suzuki Coupling and Amination Reactions

Guncheol Kim, Jae Hak Shim, and Jin Hee Kim

Department of Chemistry, College of Natural Science, Chungnam National University, Daejeon 305-764, Korea

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The indolizidine alkaloids have been isolated from the skin secretions of neotropical frogs, and some have been shown to function as non-competitive blockers for muscle-type and ganglionic nicotinic receptor channels. The simplest bicyclic gephyrotoxin alkaloid Indolizidine 209D possessing a single substituent at C5 of the indolizidine skeleton, has been isolated in the limited amount of these compounds available from natural sources, and the pharmacological interest has made it an attractive synthetic subject.

Recently, we reported the synthesis of (−)-indolizidine 209D via B-alkyl Suzuki coupling and amination reaction, and the utilization of furan for 1,3-dicarbonyl moiety for (+)-monomorine synthesis. As an extension, we wanted to suggest a new way for the concise synthesis of (−)-indolizidine 209D. For the purpose, we considered that intermediate 1 would be the proper precursor, as the mild hydrogenation condition was expected to induce the consecutive reductive amination reaction as well as hydrogenation of double bond to afford the final product. In this course, stereochemistry of the chiral center in 3 would determine the delivery of hydrogen atom at the developing tetrahedral center at C9 from the least hindered site with respect to hexyl group.

The intermediate 3 was readily prepared by the reported route and the 2-iodofuran 4 was obtained by slight modification of the known procedure. The Suzuki coupling of 3 and 4 provided the required intermediate 2 in 81% yield. Oxidative opening of the furan ring in 2 was accomplished with NBS in THF-acetone at -20 °C to yield 71% of 1. Finally, the precursor 1 was smoothly converted to (−)-indolizidine 209D under 1 atm of H2 in 10h at rt and in 63% yield. The spectral data (1H and MS) were identical to those reported.

In conclusion, we described the asymmetric synthesis of (−)-indolizidine 209D employing a new consecutive reductive amination pathway using keto-aldehyde moiety. 2-Iodofuran was employed for the B-alkyl Suzuki reaction and

**Scheme 1**

**Scheme 2.** Synthesis of (−)-indolizidine 209D. (a) i. 9-BBN-H, THF, 23 °C; ii. 4, Pd(PPh3)4, AsPh3, Cs2CO3, DMF, H2O, 81%; (b) NBS, Pyridine, THF-Acetone, -20 °C, 71%; (c) H2, 10% Pd-C, MeOH, 63%.
afterward transformed to the proper precursors.

**Experimental Section**

**General for the selected experiments.** $^1$H NMR spectra were recorded on a Bruker AC 200 spectrometer using tetramethysilane as an internal standard. Chemical shifts are measured in part per million (d) and coupling constants, $J$, are reported in Hz. All reactions were carried out under nitrogen atmosphere and anhydrous solvents were used.

2-Idofuran 4. $n$-BuLi (5.8 mL, 14.6 mmol of 2.5 M in hexane) was added slowly to a solution of furan (1.1 mL, 14.6 mmol) in dry ether (10 mL) at -78 °C. The solution was warmed to 0 °C, and to this solution was added water (310 mg, 17.35 mmol) which contained Pd(PPh$_3$)$_4$ (200 mg, 0.173 mmol), Ph$_3$As (53 mg, 0.173 mmol) and water (30 mL), saturated NaHCO$_3$ solution, water, brine, and dried over MgSO$_4$. After filtration, the organic layer was concentrated to afford 10 mg of (−)-209D (65%): [α$_D$]$_{28}$ -77.0 (c 0.80, CH$_2$Cl$_2$).HRMS C$_{22}$H$_{31}$NO$_4$, 373.2247 (cald. 373.2253).

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**References**

3. Their structures have been tentatively assigned on the basis of the mass spectrum [Daley, J. W. Fortschr. Chem. Org. Naturst. 1982, 61, 205].