Notes

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

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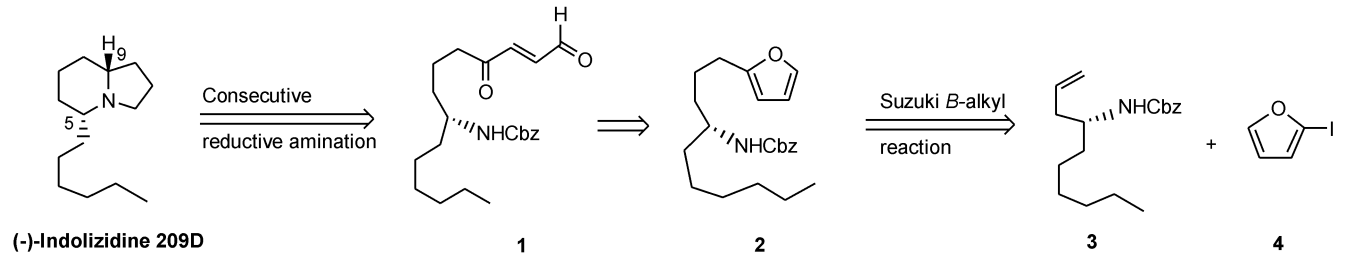
The indolizidine alkaloids have been isolated from the skin secretions of neotropical frogs,[1] and some have been shown to function as non-competitive blockers for muscle-type and ganglionic nicotinic receptor channels.[2] The simplest bicyclic gephyrotoxin alkaloid Indolizidine 209D possessing a single substituent at C5 of the indolizidine skeleton,[3] 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.[4]

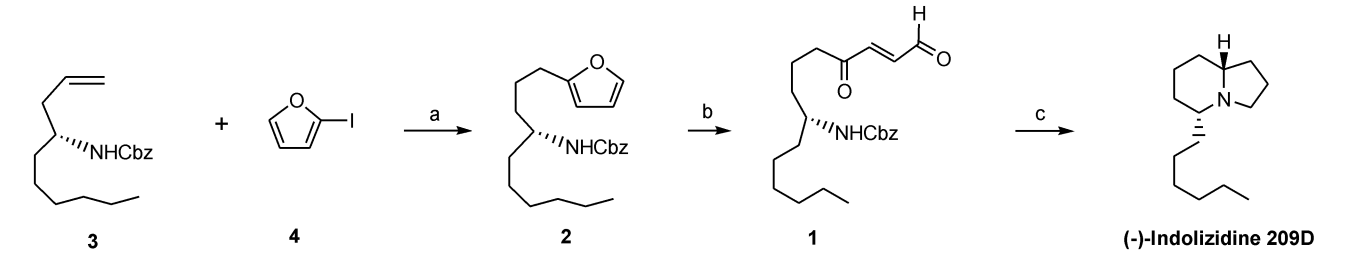
Recently, we reported the synthesis of (−)-indolizidine 209D *via B*-alkyl Suzuki coupling and amination reaction, and the utilization of furan for 1,3-dicarbonyl moiety for (+)-monomorine synthesis. As an extension, we wanted to suggest a new way for the concise synthesis of (−)-indolizidine 209D. For 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.[5]

The intermediate **3**[6] was readily prepared by the reported route and the 2-iodofuran **4** was obtained by slight modification of the known procedure.[4i,7] The Suzuki coupling[8] 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 **2** under 1 atm of H_2 in 10h at rt and in 63% yield. The spectral data (^{1}H and MS) were identical to those reported[4c].

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**, $Pd(PPh_3)_4$, $AsPh_3$, Cs_2CO_3, DMF, H_2O, 81%; (b) NBS, Pyridine, THF-Acetone, -20 °C, 71%; (c) H_2, 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 tetramethylsilane 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-Iodofuran 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. To this solution was added slowly iodine (3.7 g, 14.6 mmol) in 10 mL of dry ether *via* syringe. The resulting solution was warmed to 0 °C using ice bath and stirred for 2.5 hr. After quenching the reaction with 30 mL of water, the reaction mixture was extracted diethyl ether (70 mL × 2). The organic layer was washed with 30 mL of aqueous $Na_2S_2O_3$ solution, water, brine, and dried over $MgSO_4$. After filtration, the organic layer was concentrated to yield 2.27 g of relatively pure 2-iodofuran **4** (80% yield): ^{1}H NMR (80 MHz, $CDCl_3$) δ 6.29 (m, 1H), 6.50 (m, 1H), 7.50 (m, 1H).

4-Benzyloxycarbonylamino-1-(2-furyl)-decane 2. To a solution of *N*-Cbz-homoallylic amine (0.50 g, 1.735 mmol) in THF (15 mL) was added 9-BBN (637 mg, 2.606 mmol) in 1 mL of THF under Ar. The solution was stirred at rt for 2 hr, and to this solution was added water (310 mg, 17.35 mmol). The resulting solution was transferred by syringe to a solution of 2-iodoform (670 mg, 3.47 mmol) in DMF (25 mL) containing $Pd(PPh_3)_4$ (200 mg, 0.173 mmol), Ph_3As (53 mg, 0.173 mmol) and water (310 mg, 17.35 mmol) which had been stirred for 1 hr. The combined mixture was stirred at rt overnight. After dilution of the solution with 20 mL of EtOAc, the organic layer was washed with saturated NH_4Cl solution (30 mL), saturated $NaHCO_3$ solution, water (20 mL), and brine. The organic layer was dried over $MgSO_4$, filtered through celite, and concentrated. The crude product was separated by column chromatography (hex : EtOAc = 10 : 1) to yield 507 mg of compound **2** (81%): IR (thin film) 3324, 2934, 2853, 1685, 1541 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 6.2 Hz, 3H), 1.23-1.69 (m, 16H), 2.58-2.62 (m, 2H), 3.61 (m, 1H), 4.44 (d, J = 8.90 Hz, 1H), 5.07 (s, 2H), 5.94 (m, 1H), 6.24 (m, 1H), 7.26 (m, 1H), 7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 24.3, 25.7, 27.7, 29.2, 31.7, 34.8, 35.4, 51.1, 66.5, 104.9, 110.2, 128.0, 128.5, 136.7, 140.8, 155.9, 156.1; HRMS $C_{22}H_{31}NO_3$, 357.2304 (cald. 357.2304).

8-Benzyloxycarbonylamino-4-oxo-*trans*-penta-2-decenal 1. To a solution furan compound **2** (100 mg, 0.28 mg) in a solution of acetone-H_2O (10 : 1, 1 mL) was added NBS (75 mg, 0.42 mmol) at -15 °C. After the mixture was stirred at -15 °C for 40 mins, pyridine (0.10 mL) was added, and the resulting solution was stirred at rt for 2 hr. After dilution of the mixture with 10 mL of EtOAc, the organic layer was washed with 1 N HCl solution and dried over $MgSO_4$. Filtration was followed by concentration and silica-gel column chromatography (hex : EtOAc = 1 : 1) to afford a yellowish product (75 mg, 71%): IR (thin film) 3328, 2932, 2853, 1687, 1538 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 6.3 Hz, 3H), 1.23-1.71 (m, 16H), 2.61-2.75 (m, 2H), 3.62 (m, 1H), 4.50 (d, J = 8.90 Hz, 1H), 5.08 (s, 2H), 6.83 (d, J = 16.2 Hz, 1H), 6.74 (dd, J = 16.2 Hz, J = 6.7 Hz, 1H), 7.29 (m, 5H), 9.73 (d, J = 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 19.6, 22.5, 25.7, 29.1, 31.7, 34.6, 35.4, 40.9, 50.7, 66.5, 127.9, 128.1, 128.5, 136.6, 137.4, 144.7, 156.2, 193.4, 199.7; HRMS $C_{22}H_{31}NO_4$, 373.2247 (cald. 373.2253).

(−)-Indolizidine 209D. A solution of **1** in MeOH (2 mL) was stirred with 10% palladium on activated carbon under 1atm of H_2 at rt for 10 hr. After dilution with Et_2O (5 mL), the mixture was filtered through celite and concentrated to afford 10 mg of (−)-209D (65%): $[\alpha]_D^{24}$ -77.0 (*c* 0.80, CH_2Cl_2)[lit.[4e] $[\alpha]_D^{20}$ -89.64 (*c* 1.880, CH_2Cl_2)].

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