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

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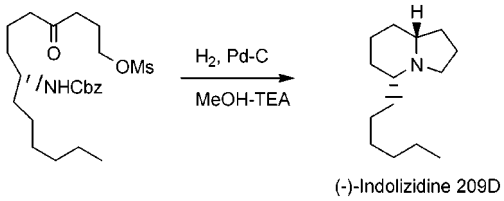
## ABSTRACT




**(–)-Indolizidine 209D has been synthesized using consecutive amination reactions of compound 11. The precursor was prepared concisely using *B*-alkyl Suzuki cross coupling of chiral homoallyl amine and vinyl iodide compounds.**

The indolizidine alkaloids have been isolated from the skin secretions of neotropical frogs,[1] and some have been shown to function as noncompetitive blockers for muscle-type and ganglionic nicotinic receptor channels.[2] Of these, indolizidines 167B and 209D, the structurally simpler bicyclic gephyrotoxin alkaloids possessing a single substituent at C5 of the indolizidine skeleton,[3] have been isolated in minute quantities from unidentified dendrobatid frogs in a single population and have been attractive synthetic targets.[4]

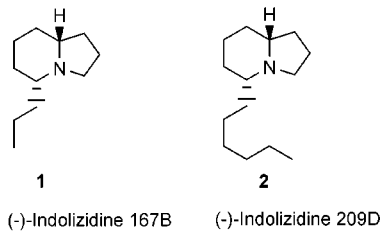
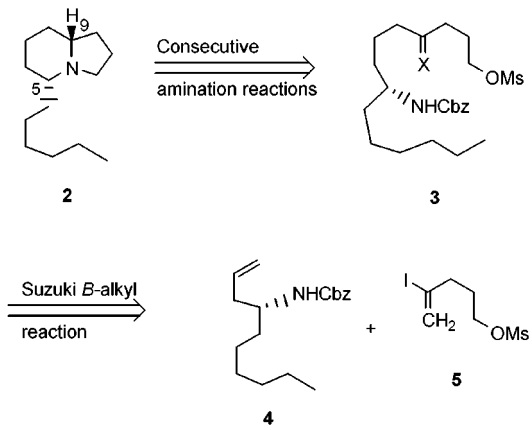



**Figure 1.**

To suggest a new route, we envisioned that cyclization to the indolizidine skeleton would be feasible upon deprotection of nitrogen under reductive conditions, inducing condensation followed by amination (Scheme 1). The stereochemistry of the chiral center would determine the delivery of hydrogen atom at the developing tetrahedral center at C9 from the least

**Scheme 1**




(1) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453.

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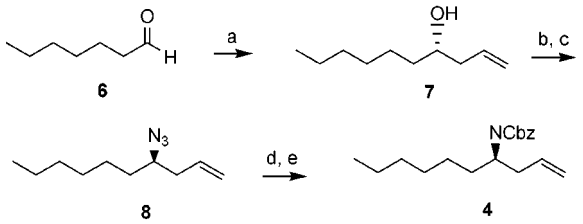
hindered site with respect to hexyl group.[4b,5] For the consecutive amination reactions, we considered the intermediate **3** to be an ideal precursor in which *N*-Cbz, carbonyl, and mesyl groups are arranged in proper position.

We thought the requisite intermediates for the route could be prepared via *B*-alkyl Suzuki coupling of a homoallyl amine moiety and the vinyl iodide compound containing a mesyl leaving group. Recently, Suzuki−Miyamura coupling has been applied appropriately for the synthesis of potent natural molecules by taking advantage of its mild reaction condition, substrate versatility, control of olefin geometry, and even tolerance for water.[6] We expected the mesyl group would be compatible in the coupling and serve as a good leaving group in the final step.

Synthesis of intermediate **4** was initiated by preparing the known chiral homoallylic alcohol **7** from heptanal. Among many well developed methods of catalytic asymmetric allylation of aldehydes,[7] we chose a relatively practical route using allyltributyltin, (*R*)-BINOL-Ti(IV) (10 mol %) complex, and $B(OMe)_3$ (50 mol %) to prepare **7**, which was synthesized in 70% yield.[8] After treatment of the alcohol **7** with MsCl (90% yield), inversion of the chiral center was carried out by reaction of the mesylate intermediate with $NaN_3$ in 97% yield. The azide **8** was reduced by LAH in THF to an amine, which was readily protected by $ClCO_2Bn$ in THF with $K_2CO_3$ to provide the desired compound **4** in 94% yield for two steps (Scheme 2).

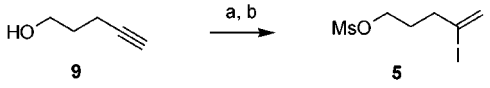
**Scheme 2**[a]




[a] (a) $AllSnBu_3$, (*R*)-BINOL-Ti(IV), $B(OMe)_3$, $CH_2CH_2$, 0 °C, 70%; (b) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 90%; (c) $NaN_3$, HMPA, 40 °C, 97%; (d) LAH, THF, rt; (e) $ClCO_2Bn$, THF, $K_2CO_3$, 94% for 2 steps.

The coupling partner, internal alkenyl iodide **5**, was made selectively by treatment of 4-pentyne-1-ol with HI, generated in situ,[9] affording an internal iodoalkenyl alcohol as a major compound in a 6:1 mixture of inseparable regioisomers, and reaction of the resulting alcohol with MsCl in $CH_2Cl_2$ gave the compound **5** in 36% yield for two steps (Scheme 3).

**Scheme 3**[a]




[a] (a) TMSCl, NaI, $CH_3CN/H_2O$, rt; (b) MsCl, $CH_2Cl_2$, $Et_3N$, 36% for 2 steps.

The Suzuki coupling of **4** and **5** furnished the methylene compound **10** in 64% yield, and conversion of **10** to the carbonyl precursor **11** was performed by ozonolysis in $CH_2Cl_2$/MeOH in 80% yield. To obtain the optimal yield in the ozonolysis process, immediate aqueous workup, after addition of DMS to the resulting peroxide intermediates at −78 °C, was necessary (Scheme 4).[10]


(2) Aronstam. R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res*. **1986**, *11*, 1227.

(3) Their structures have been tentatively assigned on the basis of the mass spectrum [Daley, J. W. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205].

(4) For asymmetric syntheses of indolizidine 167B, see: (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem*. **1990**, *55*, 4688. (b) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem*. Soc. **1991**, *113*, 3513. (c) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 3119. (d) Takahata, H.; Bandoh, H.; Momose, T. *Heterocycles* **1995**, *41*, 1797. (e) Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett*. **1996**, *37*, 1445. (f) Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151. (g) Angle, S. R.; Henry, R. M. *J. Org. Chem*. **1997**, *62*, 8549. (h) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C.; Canet, I. *Tetrahedron Lett*. **1999**, *40*, 1661. (i) Chênevert, R.; Ziarani, G. M.; Dasser, M. *Heterocycles* **1999**, *51*, 593. For asymmetric syntheses of indolizidine 209D, see:. (j) Åhman, J.; Somfai, P. *Tetrahedron Lett*. **1995**, 36, 303. (k) Åhman, J.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747. (l) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem*. **1995**, *60*, 398. (m) Jefford, C. W.; Sienkiewicz, K.; Thornton, S. R. *Helv. Chim. Acta* **1995**, *78*, 1511. (n) Takahata, H.; Kubota, M.; Ihara, K.; Okamoto, N.; Momose, T.; Azer, N.; Eldefrawi, A. T.; Eldefrawi, M. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3289. (o) Chênevert, R.; Ziarani, G. M.; Morin, M. P.; Dasser, M. *Tetrahedron: Asymmetry* **1999**, *10*, 3117. (p) Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett*. **2000**, *2*, 465. (q) Back, T. G.; Nakajima, K. *J. Org. Chem*. **2000**, *65*, 4543.

(5) Robins, D. J.; Sakdaret, S. *J. Chem. Soc., Perkins Trans. 1* **1981**, 909.

(6) (a) Miyamura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem*. **1999**, *576*, 147. For recent application to natural product syntheses, see: (c) Ohba, M.; Kawase, N.; Fujii, T. *J. Am. Chem*. Soc. **1996**, *118*, 8250. (d) Su, D.-S.; Sorensen, E. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2801. (e) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem*. **1996**, *61*, 4876. (f) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E.; Danishefsky, S. J. *J. Am. Chem*. Soc. **1997**, *119*, 10073. (g) Su, D.-S.; Balog, A.; Meng, D.; Bertinato, P.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2093. (h) Fürstner, A.; Seidel, G. *J. Org. Chem*. **1997**, *62*, 2332. (i) Trost, B. M.; Lee, C. B. *J. Am. Chem*. Soc. **1998**, *120*, 6818. (j) Balog, A.; Harris, C.; Savin, K.; Zhang, G.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 2675. (k) Fürstner, A.; Konetzki, I. *J. Org. Chem*. **1998**, *63*, 3072. (l) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron lett*. **1998**, *39*, 9027. (m) Meng, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **1999**, *38*, 1485. (n) Meng, D.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **1999**, *38*, 3197. (o) Trauner, D.; Schwartz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed*. **1999**, *38*, 3542. (p) Trauner, D.; Danishefsky, S. J. *Tetrahedron lett*. **1999**, *40*, 6511. (q) Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem*. Soc. **1999**, *121*, 7050. (r) Zhu, B.; Panek, J. S. *Org. Lett*. **2000**, *2*, 2695. (s) Lee, C. B.; Chou, T.-C.; Zhang, X.-G.; Wang, Z.-G.; Kuduk, S. K.; Chappell, M.; Stachel, S. J.; Danishefsky, S. J. *J. Org. Chem*. **2000**, *65*, 6525. (t) Sasaki, M.; Noguchi, K.; Fuwa, H.; Tachibana, K. *Tetrahedron Lett*. **2000**, *41*, 1425−1428. (u) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett*. **2000**, *41*, 8371−8375. (v) Nakamura, T.; Shiozaki, M. *Tetrahedron Lett*. **2001**, *42*, 2701−2704. (w) Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed*. **2001**, *40*, 1090−1093.

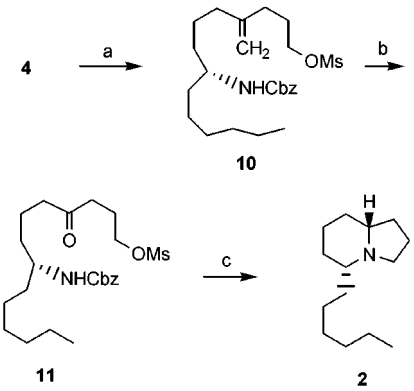
(7) (a) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 27. (b) Kii, S.; Maruoka, K. *Tetrahedron Lett.* **2001**, *42*, 1935 and references therein.

(8) Yu, C.-M.; Choi, H.-S.; Yoon, S.-K.; Jung, W.-H. *Synlett* **1997**, 889. The enantiomeric purity was determined to be >92% via $^1H$ NMR using $Eu(hfc)_3$ in $CDCl_3$.

(9) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675.

(10) Otherwise, an increasing amount of byproducts was formed, presumably by reaction with MeOH under these conditions. However, after separation, the product was relatively stable in MeOH solution even at room temperature.

**Scheme 4**[a]




[a] (a) (i) 9-BBN-H, THF, 23 °C, (ii) **5**, Pd(dppf)$Cl_2$, $AsPh_3$, $Cs_2CO_3$, DMF, $H_2O$, 64%; (b) (i) $O_3$, $CH_2Cl_2$/MeOH, −78 °C, (ii) DMS, −78 °C, 80%; (c) $H_2$, 10% Pd−C, MeOH, $Et_3N$, 77%.

Gratifyingly, under 1 atm of $H_2$ the precursor **11** was smoothly converted to (−)-indolizidine 209D **2**[11] in 12 h at room temperature and in 77% yield. The spectral data ($^1$H and $^{13}$C NMR and MS) were identical to those reported:[4a] $[\alpha]^{24}_D$ −77.7 (*c* 0.70, $CH_2Cl_2$) [lit.[4n] $[\alpha]^{20}_D$ −89.64 (*c* 1.880, $CH_2Cl_2$)].

In conclusion, we described the asymmetric synthesis of (−)-indolizidine 209D by employing a new consecutive amination−reductive amination pathway. A *B*-alkyl Suzuki reaction was efficiently applied to furnish the precursors. Further application of this strategy for related compounds and investigation of the mechanism for the reductive process is under study.

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**Supporting Information Available:** Experimental procedures and spectral data of new compounds and copies of $^1$H NMR spectrum of **5** and $^1$H NMR and $^{13}$C NMR spectra of **4**, **8**, **10**, **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The formation of diastereomer **2** was not observed by NMR.