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A new route for the synthesis of indolizidine (−)-209D: excellent diastereoselectivity in the intramolecular hydroamination of alkynes

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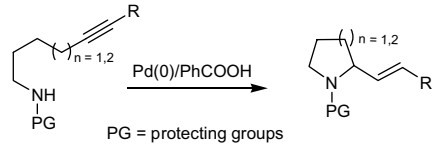
This paper is dedicated to Professor Iwao Oijma on the occasion of his 60th Birthday

Abstract—A highly efficient synthesis of indolizidine (−)-209D **I** has been accomplished. The key reaction in the synthesis is the palladium(0)/benzoic acid catalyzed intramolecular hydroamination of the ε-amino alkyne **6**. The excellent diastereoselectivity in the intramolecular hydroamination is discussed on the basis of the proposed transition state.

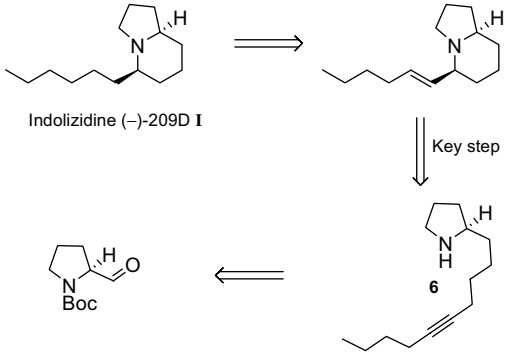
Indolizidine alkaloids, isolated from the skin secretions of certain neotropical frogs, represent a class of pharmacologically important compounds.[1] Even a structurally simple member of this class of natural products such as indolizidine 209D **I** acts as noncompetitive blocker of neuromuscular transmission.[2] Therefore, indolizidine 209D has attracted great attention from synthetic chemists in order to establish a general route for the preparation of more complex derivatives, which has resulted in several successful approaches to the optically pure form.[3]

The development of novel methods for the formation of C–N bonds and their applications to the synthesis of nitrogen-containing natural products are of keen interest to synthetic organic chemists. To date several methods for the formation of C–N bonds are known which, in general, involve substitution[4] or addition reactions.[5] The allylic substitution reactions of allylic substrates (acetates, carbonates, halides, phosphates, NR_2) by amines in the presence of a Pd(0) catalyst, commonly known as allylic amination,[4a] is one of the reliable approaches for the formation of C–N bonds. Nevertheless, the search for addition reactions is desirable because, in principle, they can be performed with 100% atom efficiency,[6] without any waste formation. With this in mind, we recently reported a Pd(0)/benzoic acid catalyzed hydroamination of alkynes, wherein the product is



(1)

formed via a formal addition of amines to alkynes (Eq. 1).[7] An asymmetric intramolecular hydroamination protocol for the synthesis of various enantiopure nitrogen heterocycles has been developed as well using (*R*,*R*)-RENORPHOS as a chiral ligand.[8] However, diastereoselectivity issues have not been addressed until now. We report herein the development of a novel approach to the synthesis of indolizidine (−)-209D **I** based on an intramolecular hydroamination strategy involving a high degree of diastereocontrol. As shown in the retrosynthetic analysis (Scheme 1), the key step in our approach is the intramolecular hydroamination of the ε-amino alkyne **6**.



Scheme 1. Retrosynthetic analysis for indolizidine (−)-209D.

Keywords: Palladium catalyst; Benzoic acid; Hydroamination; Alkaloid; Indolizidine 209D.
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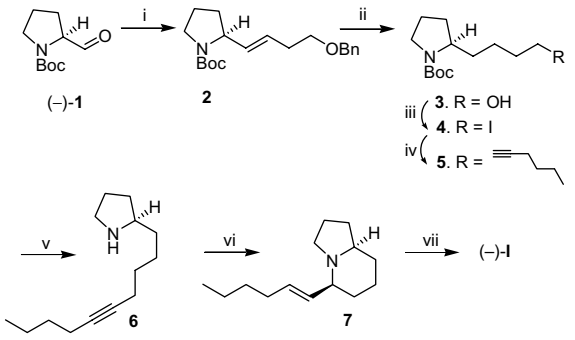
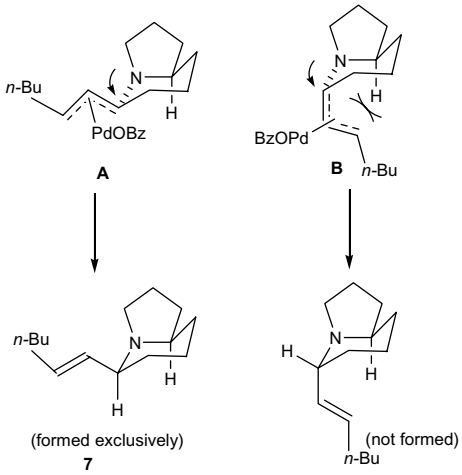


Scheme 2. Synthesis of indolizidine (−)-209D. Reagents and conditions: (i) $BnO(CH_2)_3PPh_3Br$, NaHMDS, THF, −78 °C, 1 h, 87%; (ii) H_2, 10% Pd/C, MeOH, 24 h, 70%; (iii) PPh_3, I_2, imidazole, THF, rt, 12 h, 75%; (iv) 1-hexyne, *n*-BuLi, −78 °C, 1 h then **4** in THF added dropwise, 8 h, 87%; (v) TFA–CH_2Cl_2 (3:2), 0 °C, 3 h, 80%; (vi) 5 mol % $Pd(PPh_3)_4$, 10 mol % benzoic acid, Et_3N (2 equiv), 1,4-dioxane, 100 °C, screw capped vial, 12 h, 74%; (vii) H_2, 10% Pd/C, MeOH, 24 h, 85%.



Scheme 3. Proposed transition states for the observed diastereoselectivity.

As depicted in Scheme 2 our synthesis started with the commercially available aldehyde **1**, which can be readily prepared on the basis of the literature protocol.[9] Wittig olefination of the aldehyde **1** with $BnO(CH_2)_3PPh_3Br$ using NaHMDS as base[10] gave the amino olefin **2** in 87% yield, which on subsequent hydrogenation on 10% Pd/C afforded the ε-amino alcohol **3**. The alcohol **3** was then converted to the desired iodide **4** using I_2, PPh_3, and imidazole in 75% yield. The next step was the introduction of the alkyne moiety. Thus, treatment of the iodo compound **4** with the lithium acetylide, prepared in situ by mixing an equimolar amount of 1-hexyne and *n*-BuLi, in THF–HMPA (8:2) gave the required *N*-protected alkyne **5**[11] in 87% yield. Removal of the *N*-Boc group of **5** using trifluoroacetic acid in dichloromethane at 0 °C proceeded smoothly to give the desired ε-amino alkyne **6**,[12] the precursor for the hydroamination reaction. We next examined the intramolecular hydroamination of **6** using our previously developed procedure.[7a,b] Thus, ε-amino alkyne **6** was treated with 5 mol % $Pd(PPh_3)_4$ and 10 mol % benzoic acid in 1,4-dioxane at 100 °C for 12 h. Gratifyingly, the ^1H NMR of the crude product showed the formation of only one diastereomer. Purification of the crude compound by silica gel column chromatography afforded the pure product **7**[13] in 40% yield. The yield could be increased by adding 2 equiv of triethylamine to the reaction system allowing us to isolate the product **7** in 74% yield. At this stage, it proved to be difficult to assign the relative stereochemistry of the newly generated tertiary carbon center. However, it was assigned to be *S* in the subsequent stage. Hydrogenation of **7** with 10% Pd/C in methanol proceeded smoothly giving the target molecule indolizidine (−)-209D **I** whose physical and spectral data as well as the optical rotation were consistent with those previously reported $[\alpha]_D^{25}$ −78.1 (*c* 0.98, CH_2Cl_2) [reported $[\alpha]_D^{20}$ −84.9 (*c* 0.98, CH_2Cl_2),[3h] $[\alpha]_D^{24}$ −77.7 (*c* 0.70, CH_2Cl_2).[3j]

A plausible explanation for the observed diastereoselectivity in the intramolecular hydroamination reaction is made on the basis of 1,3-diaxial interactions. As depicted in Scheme 3, two transition states **A** and **B** are conceivable. In the model **B**, the π-allyl palladium complex would be in an axial position, therefore it suffers from a severe 1,3-diaxial interaction. On the other hand such a 1,3-diaxial interaction is not present in the transition state **A**, as the π-allyl palladium complex is oriented in an equatorial position. This explains the exclusive formation of the desired diastereomer.

In conclusion, the diastereoselective synthesis of indolizidine (−)-209D has been achieved via the intramolecular hydroamination of ε-amino alkyne **6**. We believe that this newly developed intramolecular hydroamination protocol will find applicability for the synthesis of other complex naturally occurring alkaloids and current studies are directed in this way in our laboratory.

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12. Compound **6**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.45 (quin, $J = 8.5$ Hz, 1H), 3.31–3.24 (m, 2H), 2.20–2.05 (m, 6H), 2.01–1.90 (m, 1H), 1.88–1.77 (m, 1H), 1.72–1.60 (m, 2H), 1.55–1.35 (m, 8H), 0.90 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 80.7, 79.2, 60.2, 44.6, 31.6, 31.2, 30.3, 28.5, 25.8, 23.6, 21.9, 18.5, 18.4, 13.7. HRMS calcd for $C_{14}H_{25}N$ (M^+) 207.1987. Found: 207.1985.
13. Compound **7**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.48 (dt, $J = 15.6$, 6.4 Hz, 1H), 3.05 (dt, $J = 8.8$, 1.6 Hz, 1H), 2.36–2.30 (m, 1H), 1.98–1.03 (m, 19H), 0.81 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 133.2, 131.3, 67.1, 64.4, 52.7, 32.9, 31.9, 31.5, 30.8, 30.5, 24.5, 22.2, 20.2, 13.9. HRMS calcd for $C_{14}H_{25}N$ (M^+) 207.1987. Found: 207.1981.