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The enantioselective synthesis of poison-frog alkaloids (−)-203A, (−)-209B, (−)-231C, (−)-233D, and (−)-235B″

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Abstract—The enantioselective synthesis of indolizidines (−)-**203A**, (−)-**209B**, (−)-**231C**, (−)-**233D**, and (−)-**235B″** has been achieved and the absolute stereochemistry of both indolizidines **203A** and **233D** was established as 5*S*,8*R*,9*S*. The relative stereochemistry of natural **231C** was established by the present asymmetric synthesis.
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The 5,8-disubstituted indolizidines are one of a large indolizidine subclass of alkaloids found in amphibian skin.[1] Recently, such indolizidines have been detected in mixed arthropod collections.[2] Poison-frog alkaloids including these indolizidines continue to be of interest as synthetic targets[3] due to their intriguing biological activities. Indeed, we found recently that the synthetic indolizidine (−)-**235B′**, an alkaloid originally isolated from poison-frog skin, acts as a selective and non-competitive blocker of α4β2 nicotinic acetylcholine receptors.[4] The potency of (−)-**235B′** for this receptor was comparable with one of the best studied antagonists, dihydro-β-erythroidine. As part of a program directed at studying the synthesis of biologically active alkaloids,[5] we would like to report here the chiral synthesis of (−)-**203A**, an alkaloid originally isolated from *Dendrobates auratus*,[6] and the determination of its absolute stereochemistry. The total synthesis of **209B**,[7] **231C**,[8] **233D**,[8] and **235B″**[9] has also been achieved starting from a common chiral lactam **9**.

The synthesis began with the enantiomerically pure piperidone **1**,[10] which was converted to the Cbz-urethane **2** in good yield. Treatment of **2** with LiHMDS followed by 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent)[11] provided the enol triflate

3, which was subjected to a palladium catalyzed carbonylation to give rise to the enaminoester **4**. The methyl substituent at the 3-position was introduced by our original Michael-type conjugate addition reaction[12] of **4** to afford **5** in a highly stereoselective manner. The carbon-chain extension at the 2-position of **5** was performed by reduction of **5** with lithium triethylborohydride (Super-Hydride), Swern oxidation of the resulting alcohol **6** followed by a Horner–Emmons reaction to give the α,β-unsaturated ester **7**. Hydrogenation of **7** over Pearlman's catalyst and a trimethylaluminum-catalyzed cyclization[13] of the resulting aminoester yielded the lactam **8**. Cleavage of the silylether with TBAF provided the corresponding alcohol **9**, which was subjected to two-step oxidation and the Arndt–Eistert sequence to afford the homologated ester **10**. Reduction of both lactam and ester moieties with LiAlH₄ and oxidation of the resulting alcohol with the Dess–Martin periodinane[14] gave rise to the aldehyde, which was transformed into the *Z*-iodoolefin **11** under Stork's reaction conditions.[15] The Sonogashira coupling[16] reaction of **11** using the trimethylsilylacetylene provided the eneyne derivative **12**, whose trimethylsilyl group was removed with K₂CO₃ in MeOH to furnish the (−)-indolizidine **203A** ($[\alpha]_D^{26}$ −94.5 (*c* 2.0, CHCl₃), lit.[6] $[\alpha]_D$ −23.3 (*c* 0.30, CHCl₃)). The spectral data of synthetic (−)-**203A** were identical with those of the natural product. This absolute configuration is the same as that reported previously for levorotatory **205A** and **207A**. It should be noted that in all cases of 5,8-disubstituted indolizidines,

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the rotations of the natural alkaloids were significantly less than those of synthetic materials. The presence of some naturally occurring racemic material is one possible explanation (Scheme 1).

Reduction of **9** with lithium aluminum hydride gave an indolizidine, whose side chain at the 5-position was elongated in two steps by Swern oxidation followed by Wittig olefination to provide the indolizidine **13**. Hydrogenation of the double bond of **13** and treatment of the resulting silyl ether with TBAF gave the alcohol **14**. Swern oxidation of **14** and Wittig reaction of the resulting aldehyde with iodomethyltriphenylphosphonium iodide[15] gave rise to the Z-iodoolefin **15**. A cross-coupling reaction of **15** with vinylmagnesium bromide in the presence of a phosphine–nickel catalyst[17] provided the alkaloid (−)-**233D** previously isolated from a Panamanian poison frog, *Dendrobates pumilio*.[8] The spectroscopic data of synthetic material were identical with those of natural **233D**. Comparison of the optical rotation of synthetic (−)-**233D** ($[\alpha]_D^{26}$ −93.6 (c 1.32, CHCl$_3$), HCl salt: $[\alpha]_D^{26}$ −48.9 (c 1.50, MeOH)) with that of the natural alkaloid (lit.[8] HCl salt: $[\alpha]_D$ −3.4 (c 0.16, MeOH)) suggests that the absolute stereochemistry of natural **233D**, like those of other levorotatory 5,8-disubstituted indolizidines, is 5R,8R,9S. The presence in the natural material of a portion of the alkaloid as a racemate appears possible, if not likely.

The Sonogashira coupling[16] of **15** with trimethylsilylacetylene followed by deprotection of the TMS group with K$_2$CO$_3$ in MeOH furnished (−)-**231C**, whose relative stereochemistry was determined to be 5,8-E, and

5,9-Z by GC–MS and GC–FTIR comparison of synthetic material with natural **231C** in extracts from a Panamanian dendrobatid frog, *D. pumilio*.[8] The rotation of the natural alkaloid is unknown.

In another synthesis, the lactam **9** was converted to olefin **16** in three steps shown in Scheme 2. Hydrogenation of **16** over 10% Pd–C afforded (−)-**209B** ($[\alpha]_D^{26}$ −91.7 (c 1.06, MeOH), lit.[18] $[\alpha]_D^{28}$ −91.3 (c 0.58, MeOH)). The spectral data were identical with those previously reported.[18] The rotation of the natural material is unknown.

Comins et al.[19] reported the synthesis of **235B″** from the alcohol **14**. Thus, Wittig olefination of the aldehyde, derived from Swern oxidation of **14**, under high dilution and 'salt free' conditions gave rise to (−)-**235B″** ($[\alpha]_D^{26}$ −80.9 (c 1.71, MeOH), lit.[18] $[\alpha]_D^{28}$ −85.4 (c 0.79, MeOH), lit.[19] $[\alpha]_D^{24}$ −88.0 (c 1.0, MeOH)). The spectral data of synthetic **235B″** were identical with reported values. Remarkably natural **235B″** appears to be the (+)-enantiomer with an $[\alpha]_D$ +11.3 (c 1.0, MeOH).[9] The presence of some racemic alkaloid in that sample appears possible.

In summary, we have achieved the first asymmetric synthesis of indolizidine (−)-**203A** and, by the present asymmetric synthesis, we unambiguously determined its absolute stereochemistry to be 5S,8R,9S. The asymmetric syntheses of poison frog-indolizidines (−)-**209B**, (−)-**231C**, (−)-**233D**, and (−)-**235B″** are also presented. The absolute stereochemistry of natural **233D** appears to be likely 5R,8R,9S based on the present asymmetric
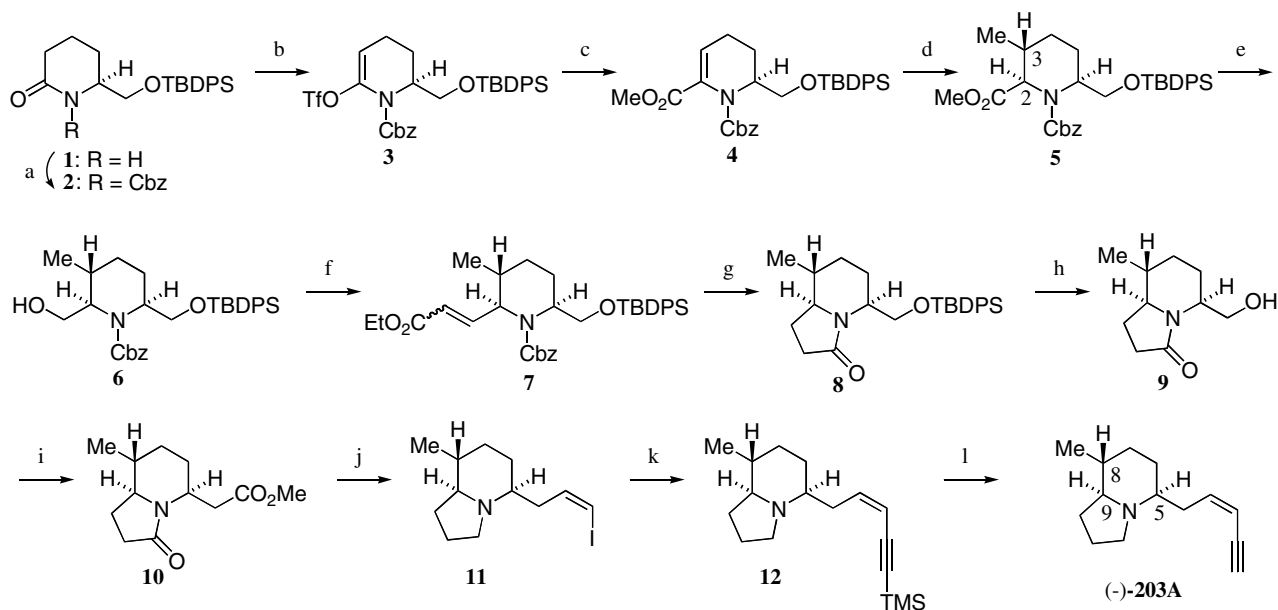
Scheme 1. Reagents and conditions: (a) *n*-BuLi, CbzCl, THF, −78 to 0 °C (86%); (b) LiHMDS, 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent), THF, −78 to −40 °C (91%); (c) Pd(Ph$_3$P)$_4$, CO, MeOH, Et$_3$N, DMF, 75 °C (78%); (d) Me$_2$CuLi, Et$_2$O −78 to −10 °C (99%); (e) Super-Hydride, THF, 0 °C (92%); (f) Swern oxidation then NaH, (EtO)$_2$P(O)CH$_2$CO$_2$Et, THF, 0 °C–rt (97%); (g) 20% Pd(OH)$_2$/C, MeOH, 4 atm then Me$_3$Al, CH$_2$Cl$_2$, reflux (71%); (h) TBAF, THF, rt (99%); (i) (1) Swern oxidation; (2) NaClO$_2$, NaH$_2$PO$_4$, *t*-BuOH/H$_2$O, 0 °C–rt; (3) ClCO$_2$Et, Et$_3$N, THF, 0 °C; (4) CH$_2$N$_2$, Et$_2$O, rt; (5) PhCO$_2$Ag, Et$_3$N, MeOH, rt (69%); (j) (1) LiAlH$_4$, THF, reflux; (2) 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benzoiodoxol-3-(1H)-one (Dess–Martin reagent), CH$_2$Cl$_2$, rt; (3) ICH$_2$P$^+$Ph$_3$I$^-$, NaHMDS, HMPA, THF, −78 °C to rt (60%); (k) CuI, trimethylsilylacetylene, Pd(Ph$_3$P)$_4$, *i*-Pr$_2$NH, THF, rt (93%); (l) K$_2$CO$_3$, MeOH, rt (91%).
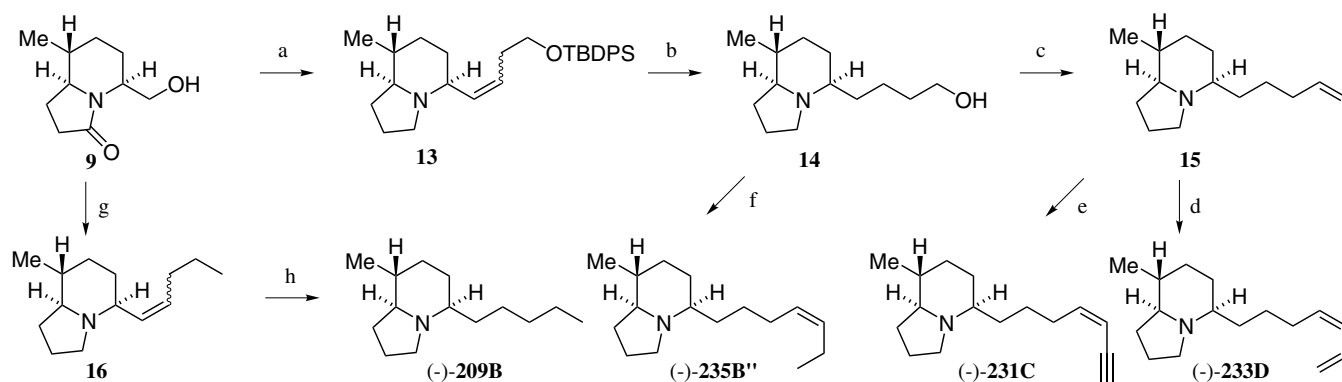
Scheme 2. Reagents and conditions: (a) (1) Lithium aluminum hydride, THF, reflux; (2) Swern oxidation; (3) TBDPSO(CH$_2$)$_3$P$^+$Ph$_3$Br$^-$, *n*-BuLi, THF, 0 °C–rt (83%); (b) (1) 10% Pd/C, H$_2$, EtOAc, 1 atm; (2) TBAF, THF, rt (79%); (c) (1) Swern oxidation; (2) ICH$_2$P$^+$Ph$_3$I$^-$, NaHMDS, HMPA, THF, −78 °C to rt (61%); (d) NiCl(dppp), vinylmagnesium bromide, Et$_2$O, rt (86%); (e) (1) CuI, TMS–acetylene, Pd(Ph$_3$P)$_4$, *i*-Pr$_2$NH, THF, rt (90%); (2) K$_2$CO$_3$, MeOH, rt, (89%); (f) (1) Swern oxidation; (2) *n*-PrP$^+$Ph$_3$Br$^-$, NaHMDS, THF, −78 °C to rt (66%); (g) (1) Lithium aluminum hydride, THF, reflux; (2) Swern oxidation; (3) *n*-BuP$^+$Ph$_3$Br$^-$, *n*-BuLi, THF, 0 °C–rt (78%); (h) 10% Pd/C, H$_2$, EtOAc, 1 atm (95%).

synthesis and analogies to other levorotatory indolizidines, namely **203A**, **205A**, **207A**, and **235B′**. In addition, the relative stereochemistry of natural **231C** was also determined. These 5,8-disubstituted indolizidines will likely provide useful compounds for selective and non-competitive inhibition of nicotinic acetylcholine receptors, widely distributed in the mammalian brain. Such studies of these synthetic indolizidines are now in progress, and the results will be published in due course.

Acknowledgments

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