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Enantioselective syntheses of poison-frog alkaloids: 219F and 221I and an epimer of 193E

Naoki Toyooka,[a,*] Zhou Dejun,[a] Hideo Nemoto,[a,*] H. Martin Garraffo,[b]
Thomas F. Spande[b] and John W. Daly[b]

[a]*Faculty of Pharmaceutical Sciences, University of Toyama, Sugitani 2630, Toyama 930-0194, Japan*
[b]*Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health,
DHHS, Bethesda, MD 20892, USA*

Abstract—Enantioselective syntheses of indolizidines (−)-**219F** and (−)-**221I** have been achieved and the relative stereochemistries of natural **219F** and **221I** were determined by the present synthesis. A levorotatory indolizidine, corresponding to one proposed structure for **193E**, was also synthesized, but was found to differ from **193E**. It seems likely that natural **193E** is the 8-epimer of the synthesized indolizidine.
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In the preceding paper, we have reported the first total syntheses of the poison-frog alkaloids **203A**, **231C**, and **233D**. The absolute stereochemistry of **203A** and **233D**, and the relative stereochemistry of **231C** were determined by these total syntheses.[1] Among 5,8-disubstituted indolizidines reported from frog skin, none of the fifteen 8-ethyl substituted indolizidines have been synthesized at the present time and in the stereochemistry of the C-8 ethyl group has not been assigned.[2] In the present letter, we report the first total synthesis and determination of the relative stereochemistry of two 8-ethyl indolizidine poison-frog alkaloids, **219F**[2] and **221I**[2] starting from a common chiral lactam intermediate **5**. An epimer of another 8-ethyl indolizidine **193E**[2] also was synthesized.

A Michael-type conjugate addition reaction of **1** with lithium divinylcuprate generated in situ afforded the trisubstituted piperidine **2** as a single isomer.[3] Reduction of the ester moiety with Super-Hydride provided alcohol **3**, which was transformed into the α,β-unsaturated ester **4** using Swern oxidation of **3** followed by a Horner–Emmons reaction of the resulting aldehyde. Hydrogenation of **4** followed by treatment of the resulting amino ester with trimethyl aluminum under Weinreb's reaction

conditions[4] gave rise to the key lactam **5**. Removal of the silyl group in **5** with TBAF yielded alcohol **6**. A two-step oxidation of **6** followed by Arndt–Eistert reaction of the resulting carboxylic acid provided the homologated ester **7**. Reduction of **7** with LiAlH₄, Swern oxidation of the resulting alcohol and Wittig olefination afforded (−)-**8**. Coinjections of synthetic material **8** with natural **193E**, detected in a Madagascan mantellid frog, *Mantella viridis* (unpublished results), indicated that the synthetic material had a slightly longer GC retention time than the natural alkaloid. Consequently, it is likely that the natural alkaloid **193E** is the 8-epimer of the synthetic material **8**. The GC–mass spectra of synthetic and natural materials were virtually identical and their GC–FTIR spectra were very similar in the Bohlmann band region (indicating 5,9-*Z* configurations), although differing slightly in their fingerprint regions.

Ester **7** was also converted to (−)-**221I** with a procedure analogous to that used in the synthesis of (−)-**8**, as shown in Scheme 1. The relative stereochemistry of natural **221I** was determined by comparison of synthetic material with natural product detected in a Madagascan mantellid frog, *Mantella viridis* (unpublished results), on GC–MS and GC–FTIR analysis. Alcohol **6**, by another sequence, was transformed into olefin **9** using Swern oxidation followed by a Wittig olefination. Hydrogenation of the double bond in **9** and removal of the silyl group provided alcohol **10**. Finally construction of the

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* Corresponding authors. Tel.: +81 76 434 7532; fax: +81 76 434
4656; e-mail: toyooka@ms.toyama-mpu.ac.jp
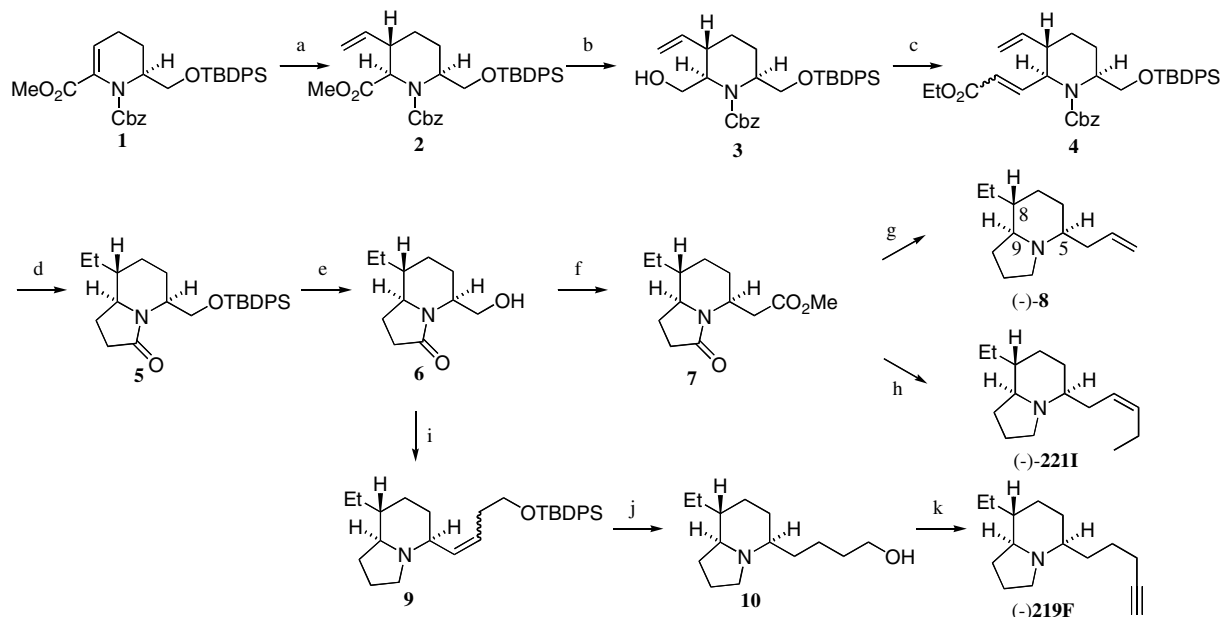
Scheme 1. Reagents and conditions: (a) (vinyl)$_2$CuLi, Et$_2$O, −78 °C to −10 °C (99%); (b) Super-Hydride, THF, 0 °C (92%); (c): (1) Swern oxidation; (2) (EtO)$_2$P(O)CH$_2$CO$_2$Et, NaH, THF, 0 °C to rt (97%); (d): (1) 20% Pd(OH)$_2$/C, H$_2$, MeOH, 4 atm; (2) Me$_3$Al, CH$_2$Cl$_2$, reflux (68%); (e): TBAF, THF, rt (91%); (f): (1) Swern oxidation; (2) NaClO$_2$, NaH$_2$PO$_4$, t-BuOH/H$_2$O, 0 °C to 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 (81%); (g): (1) LiAlH$_4$, THF, reflux; (2) Swern oxidation; (3) MeP$^+$Ph$_3$I$^−$, n-BuLi, THF, 0 °C to rt (63%); (h): (1) LiAlH$_4$, THF, reflux; (2) Swern oxidation; (3) n-PrP$^+$Ph$_3$I$^−$, NaHMDS, THF, −78 °C to rt (62%); (i): (1) LiAlH$_4$, THF, reflux; (2) Swern oxidation; (3) TBDPSO(CH$_2$)$_3$P$^+$PhBr$^−$, n-BuLi, THF, 0 °C to rt (72%); (j): (1) 10% Pd/C, H$_2$, EtOAc, 1 atm; (2) TBAF, THF, rt (81%); (k): (1) Swern oxidation; (2) (MeO)$_2$P(O)CHN$_2$, t-BuOK, THF, −78 °C to rt (64%).

terminal triple bond was performed by reaction of the corresponding aldehyde, derived from **10**, with the Seyferth–Gilbert reaction[5] to give rise to (−)-**219F**. The GC–MS and GC-FTIR spectra of the synthetic alkaloid were identical in every respect with those of natural alkaloid detected in the Madagascan mantellid frog, *Mantella betsileo*, and the relative stereochemistry of natural **219F** was thus determined by this total synthesis. For alkaloids **221I** and **219F**, the relative configuration of the 8-ethyl group is the same as in the levorotatory 8-methylindolizidines, (−)-**203A**, (−)-**205A**, (−)-**207A**, (−)-**233D**, and (−)-**235B′**.[6]

In summary, we achieved the first asymmetric syntheses of the following 8-ethyl substituted indolizidines: (−)-**219F**, (−)-**221I**, and an epimer of **193E**. The relative stereochemistry of natural **219F** and **221I** was determined unambiguously by the present synthesis. The relative stereochemistry of natural **193E** will likely correspond to the 8-ethyl epimer of our synthetic material **8**.

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References and notes

1. Toyooka, N.; Dejun, Z.; Nemoto, H.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron Lett.* **2006**, *47*, preceding paper doi:10.1016/j.tetlet.2005.11.047.
2. Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: New York, 1999; Vol. 13, pp 1–161; Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556–1575. These reviews cite the structures of **193E**, **219F** and **221I** as otherwise unpublished work.
3. Toyooka, N.; Nemoto, H. *Recent Res. Devel. Organic Chem.* **2002**, *6*, 611–624.
4. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171–4174.
5. Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379–1385.
6. Toyooka, N.; Nemoto, H.; Kawasaki, M.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron* **2005**, *61*, 1187–1198; . *Tetrahedron* **2005**, *61*, 5139.