Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 1187–1198

Enantioselective syntheses of two 5, 9*E* diastereomers of 223V, an alkaloid from the poison frog *Dendrobates pumilio*

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

[a]*Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan*
[b]*Department of Liberal Arts and Sciences, Faculty of Engineering, Toyama Prefectural University, Kurokawa 5180, Kosugi-Machi, Toyama 939-0398, Japan*
[c]*Laboratory of Bioorganic Chemistry, National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, DHHS, Bethesda, MD 20892, USA*

Received 21 October 2004; accepted 16 November 2004

Available online 8 December 2004

Abstract—Enantioselective syntheses of two 5, 9*E* diastereomers (**1** and **2**) of **223V** (**3**) are described. Neither corresponded on GC–MS and GC-FTIR analyses to alkaloid **223I**, previously tentatively proposed to be a 5,8-disubstituted indolizidine of the unusual 5, 9*E* relative stereochemistry. Synthetic (−)-(5, 9*Z*)-5-*n*-propyl-8-*n*-butylindolizidine (**3**) corresponds on GC–MS and GC-FTIR analyses to the natural indolizidine **223V** found in a *pumilio* from 'Split Hill', Panama.

1. Introduction

5,8-Disubstituted indolizidines represent a major class of alkaloids found in skins of poison frogs.[1] Over 60 such alkaloids have been proposed. Some structures are tentative, being based only on their GC–MS, dominated by a base peak due to α-cleavage of the 5-substituent, followed by a *retro*-Diels–Alder loss to yield a characteristic fragment at *m/z* 96.[2] Several of the 5,8-disubstituted indolizidines have been isolated from frog skin in sufficient quantities to allow structure confirmation by NMR spectral analysis. These include (−)-**203A**,[13] (−)-**205A**,[14] (−)-**207A**,[15] **233D**,[13] (−)-**235B′** and (+)-**235B″** (formerly **235B**).[14,15] Structures are shown in Figure 1. The structures of (−)-**207A**, (−)-**235B′**, and (+)-**235B″** have been confirmed by enantioselective synthesis.[3,16,17] The relative stereochemistry of **205A** is depicted on the basis of comparison with synthetic racemic material.[18] The structure and absolute stereochemistry of natural **209I**[15] was confirmed (unpublished results) by comparison to synthetic racemic material,[19] and the synthetic (−)-unnatural enantiomer.[20] Several laboratories have reported syntheses of (−)-**209B**.[18,21,22] Virtually all alkaloids of this class possess a 5, 9*Z* structure as shown by a characteristic sharp and intense Bohlmann

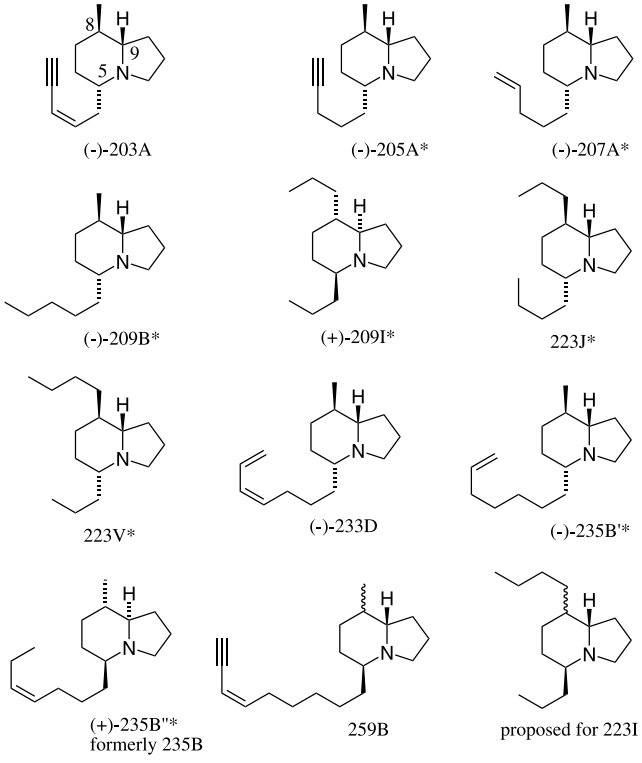


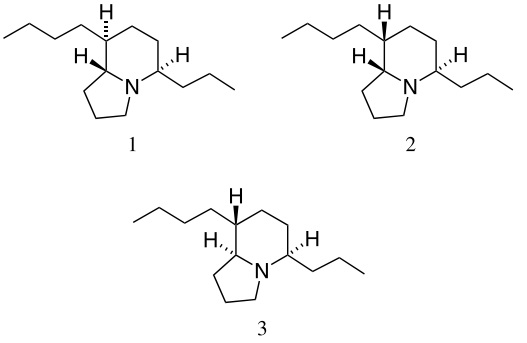
Figure 1. Alkaloids of the 5,8-disubstituted indolizidine class: structures of **203A**, **205A**, **207A**, **233D**, **235B′** and **235B″** were established by NMR spectral analysis, while structures indicated by an asterisk have been synthesized (see text). Absolute configurations have been established for the indicated alkaloids.

Keywords: Enantioselective syntheses; Diastereomers; Alkaloid.
* Corresponding authors. Tel.: +81 764 34 2281; fax: +81 76 434 4656; e-mail: toyooka@ms.toyama-ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.11.060

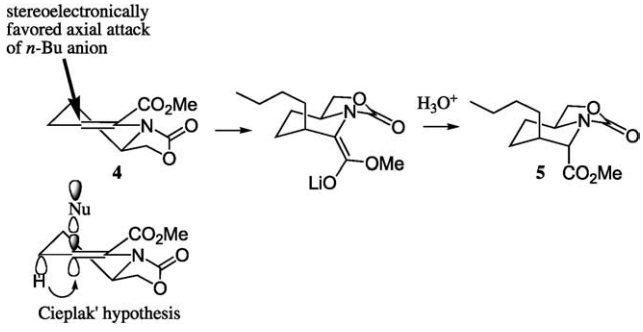
band near 2790 cm^{-1} in their GC-FTIR spectra.[2] Only two alkaloids have been tentatively proposed to be (5, 9*E*)-5,8-disubstituted indolizidines, based on GC–MS and a weak absorbance in the Bohlmann band region on GC-IR.[1] One of these is alkaloid **259B** from one population of *Dendrobates pumilio* with an EI-MS showing the α-cleavage expected of a 5-C_9H_{13}-8-CH_3-indolizidine, followed by *retro*-Diels–Alder cleavage of the fragment at *m/z* 138 to yield a significant diagnostic ion at *m/z* 96. The second was alkaloid **223I** from another population of the poison frog *D. pumilio*, tentatively proposed to have a (5, 9) *E*-5-propyl-8-butylindolizidine structure even though the diagnostic peak in EI-MS at *m/z* 96 was much weaker than expected.

In this paper, we would like to report the enantioselective syntheses of two 8-epimers of (5, 9*E*) 5-propyl-8-butyl-indolizidine (**1**, **2**) and comparison to alkaloid **223I**. In addition, a previously synthesized (−)-(5, 9*Z*) 5-propyl-8-butylindolizidine[3] (**3**) has now been shown to be identical in GC–MS and GC-FTIR to alkaloid **223V** from yet another population of the same poison frog, *D. pumilio* from 'Spilit Hill', Panama.



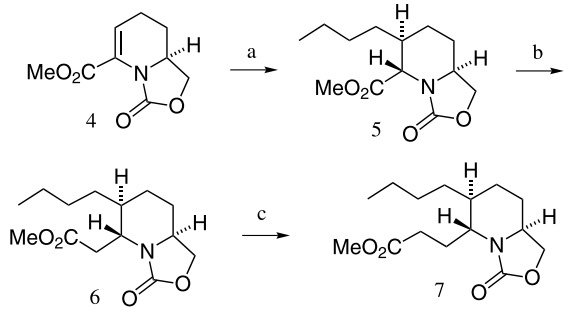
2. Results and discussion

The stereoselective synthesis of **3** has been described.[3] The synthesis of **1** began with the enaminoester **4**,[4] which was treated with lithium dibutylcuprate to afford the adduct **5** as a single isomer.[5] The stereoselectivity of this addition reaction can be explained by the stereoelectronic effect[6] and Cieplak's hypothesis[7] as shown below (Scheme 1).

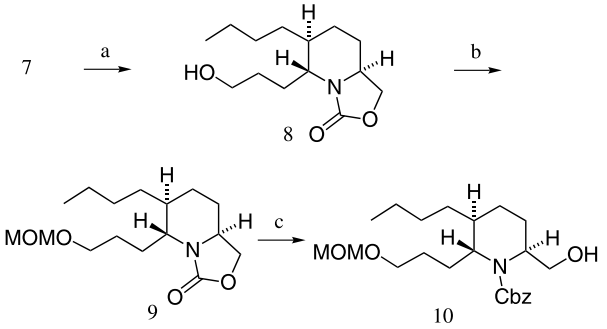


Scheme 1.

The carbon chain at the α-position of **5** was elongated by two Arndt–Eistert reactions to provide the two-carbon homologated ester **7**, which was converted to the methoxymethyl ether **9** by reduction of the ester moiety of **7** with Super-Hydride, followed by protection of the resulting alcohol **8** as shown in Schemes 2 and 3.

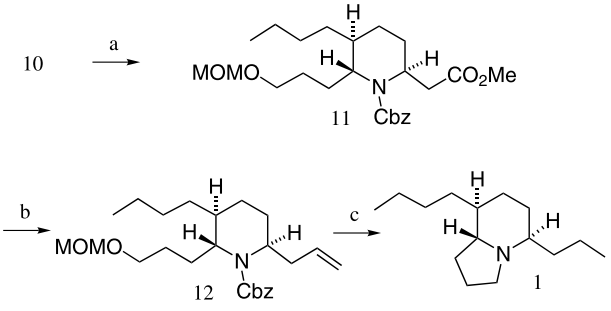


Scheme 2. (a) *n*-Bu_2CuLi, −78 to −10 °C (96%); (b) (1) LiOH, MeOH–H_2O, reflux; (2) $ClCO_2Et$, Et_3N, THF, 0 °C; (3) CH_2N_2; (4) $PhCO_2Ag$, Et_3N, MeOH, rt (80% in 4 steps); (c) same as (b) (86% in 4 steps).



Scheme 3. (a) Super-Hydride, THF, 0 °C (88%); (b) MOMCl, Hünig base, CH_2Cl_2, rt (87%); (c) (1) 2 M KOH/*i*-PrOH, 120 °C, sealed tube; (2) CbzCl, K_2CO_3, H_2O–CH_2Cl_2, rt (82% in 2 steps).

Hydrolysis of the oxazolizinone ring in **9** with KOH in a sealed tube, and protection of the resulting amino alcohol with CbzCl provided the alcohol **10**. Two-step oxidation of the alcohol **10** followed by Arndt–Eistert reaction afforded the methyl ester **11** (Scheme 4), which was reduced with DIBAL. Wittig olefination of the resulting aldehyde intermediate provided the olefin **12**. Hydrogenation of the double bond and hydrogenolysis of the Cbz-protecting group of **12**, and then removal of the methoxymethyl group with acid followed by indolizidine formation from the



Scheme 4. (a) (1) Swern ox.; (2) $NaClO_2$, H_2O–*t*-BuOH, 0 °C–rt; (3) $ClCO_2Et$, Et_3N, THF, 0 °C; (4) CH_2N_2; (5) $PhCO_2Ag$, Et_3N, MeOH, rt (54% in 5 steps); (b) (1) DIBAL, CH_2Cl_2, −78 °C (2) Witting reagent (57% in 2 steps); (c) (1) 10% Pd–C, H_2, EtOAc, 1 atm; (2) conc. HCl, MeOH, reflux; (3) CBr_4, Ph_3P, CH_2Cl_2, rt then Et_3N (67% in 3 steps).