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## ENANTIOSELECTIVE SYNTHESIS OF POISON-FROG ALKALOID 237D AND DETERMINATION OF ABSOLUTE STEREOCHEMISTRY

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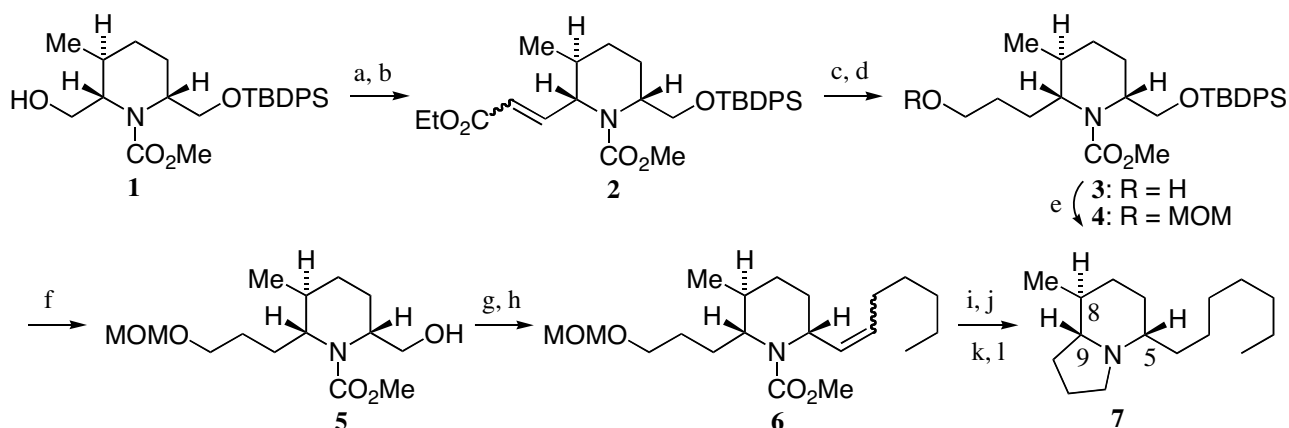
**Abstract** - An enantioselective synthesis of the 5-heptyl-8-methylindolizidine ((-)-**7**) has been achieved. Alkaloid ((-)-**7**, (MW 237)) was used to determine the relative and absolute stereochemistry of the natural indolizidine 237D from frog skin as 5*S*, 8*S*, 9*R* using GC-IR and GC-MS. Chiral gas-chromatographic comparisons with catalytically reduced (+)-235B'' and (-)-235B' indicated (-)-**7** had the same absolute stereochemistry as the dihydro-product resulting from (-)-235B' and is naturally occurring in certain extracts of Panamanian poison frogs (*Dendrobates*).

The 5,8-disubstituted indolizidines are one of the major subclasses of poison frog alkaloids, and over sixty such alkaloids have been detected to date.<sup>1</sup> Recently, a 5,8-disubstituted indolizidine was detected in a mixed collection of small arthropods and one group of these arthropods is presumed to be the source of the 5,8-disubstituted indolizidines found in the skin of poison frogs.<sup>2</sup> Alkaloid 237D, detected in extracts of *Dendrobates pumilio* and *D. speciosus*,<sup>3</sup> had the above indolizidine core, and the relative stereochemistry was expected to be 5,9-*Z* due to the intense Bohlmann bands observed in their GC-FTIR spectra.<sup>1</sup> However, the relative stereochemistry at the 8-position was not known, nor was the absolute stereochemistry.

We now report the synthesis of indolizidine ((-)-**7**) and its use to establish both the relative and absolute stereochemistry of natural 237D using GC-IR, GC-MS and GC with a chiral column.

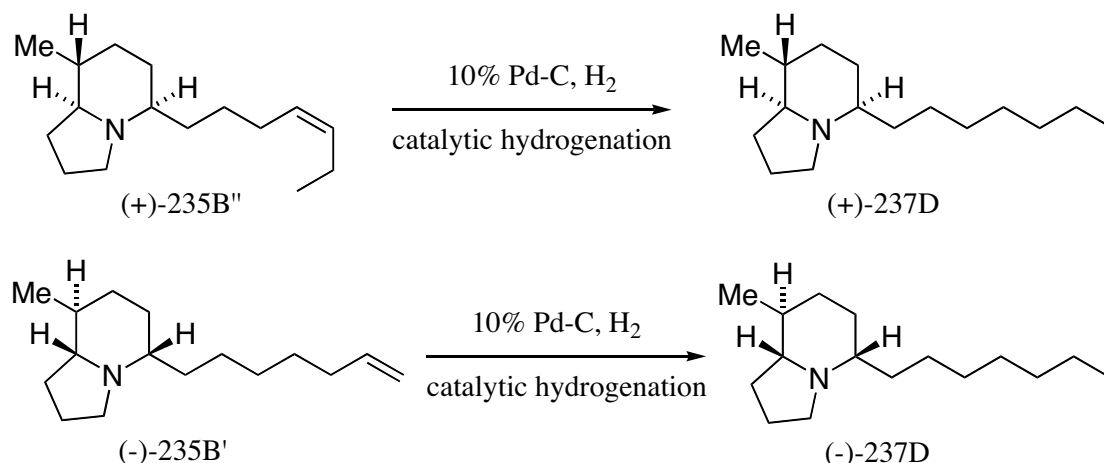
The synthesis (see Scheme 1) began with the known 2,3,6-trisubstituted piperidine (**1**),<sup>4</sup> prepared stereoselectively by our original Michael-type conjugate addition reaction to the enaminoester as the key step,<sup>5</sup> which was then converted to the  $\alpha,\beta$ -unsaturated ester (**2**). Hydrogenation of **2** followed by reduction of the ester moiety with Super-Hydride gave the alcohol (**3**). Treatment of **3** with MOMCl in the presence

of the Hünig base provided the MOM ether (**4**), which was treated with TBAF to provide the alcohol (**5**). Swern oxidation of **5** and Wittig olefination of the resulting aldehyde gave rise to the olefin (**6**) as a mixture of *E*- and *Z*-isomers. Hydrogenation of the double bond in **6** followed by indolizidine formation using a 3-step sequence furnished the indolizidine ((-)-**7**).<sup>6</sup> Synthetic (-)-**7** was co-chromatographed on a non-chiral GC-column with natural 237D found in an extract of *Dendrobates speciosus*,<sup>3b</sup> and had exactly the same mass and infrared spectrum as the natural product.



**Scheme 1: Reagents and conditions:** a: Swern ox.; b:  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Et}$ , NaH, THF, 0 °C-rt (95%); c: 10% Pd-C,  $\text{H}_2$ , EtOAc, 4 atm; d: Super-Hydride, THF, 0 °C (93%); e: MOMCl, Hünig base,  $\text{CH}_2\text{Cl}_2$ , 0 °C-rt (85%); f: TBAF, THF, 0 °C-rt (95%); g: Swern ox.; h:  $\text{Me}(\text{CH}_2)_5\text{P}^+\text{Ph}_3\text{Br}$ , *n*-BuLi, THF, 0 °C-rt (66%); i: 10% Pd-C,  $\text{H}_2$ , EtOAc, 1 atm; j: *n*-PrSLi, HMPA,<sup>7</sup> THF, 0 °C-rt; k: conc. HCl, MeOH, reflux; l:  $\text{CBr}_4$ ,  $\text{Ph}_3\text{P}$ , then  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C-rt (42%)

Lacking racemic 237D, to demonstrate enantiomer separation on a chiral column, we prepared (+)-237D by catalytic reduction of (+)-235B'' ( $[\alpha]_D +11.3^\circ$ ), which previously had been isolated from *D. pumilio*<sup>3a</sup> and (-)-237D by reduction of (-)-235B' ( $[\alpha]_D -61^\circ$ ) present in an extract of *D. speciosus*<sup>3b</sup> (see below). Gas chromatography using flame-ionization detection and a chiral column, permethylated  $\beta$ -cyclodextrin (SGE, 30 m x 0.25 mm; 130°-200°C at 0.5°C/ min), resulted in a baseline separation of (+)- and (-)-237D prepared in this way. The retention times were 31.9 and 32.4 min. respectively. The alkaloid 237D present in *D. pumilio* or *D. speciosus* was co-chromatographed with (-)-**7** on the chiral column using the above conditions.



The synthetic (-)-**7** and reduced 235B' co-chromatographed on GC-MS with a non-chiral column (Zebron-5 (Phenomenex) 100°-280°C at 5°C/ min) and had identical GC-EIMS and GC-FTIR spectra proving that they had the same relative stereochemistry. We conclude that the absolute stereochemistry of 237D occurring naturally in *D. pumilio* or *D. speciosus* is the same as that of (-)-**7** and has the 5*S*, 8*S*, 9*R* absolute stereochemistry as indicated in Scheme 1.

## ACKNOWLEDGMENT

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- 6 The spectral data for synthetic (-)-**7** are as follows.  
IR (neat) 2967, 2934, 2879, 2787, 2706, 1461, 1378, 1163, 1133 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz) δ 0.88 (3H, d, *J* = 6.8 Hz), 0.89 (3H, t, *J* = 6.8 Hz), 0.97 (1H, q-like, *J* = 11.5 Hz), 1.27-1.38 (13H, br), 1.51-2.18 (10H, br m), 3.31 (1H, br); <sup>13</sup>C NMR (75 MHz) δ 14.16 (q), 18.93 (q), 20.36 (t), 22.72 (t), 25.89 (t), 29.03 (t), 29.32 (t), 30.05 (t), 31.15 (t), 31.88 (t), 33.67 (t), 34.53 (t), 36.44 (d), 51.78 (t), 63.60 (d),

71.37 (d); MS: 237 ( $M^+$ ), 138 (100); HRMS Calcd for  $C_{16}H_{31}N$  237.2455, Found 237.2458;  $[\alpha]_D^{26}$   $-98.9^\circ$  ( $c$  1.59,  $CHCl_3$ ).

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