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

Naoki Toyooka,*[,1] Masashi Kawasaki,[2] Hideo Nemoto,*[,1] John W. Daly,[3] Thomas F. Spande,[3] and H. Martin Garraffo[3]

1: Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan; 2: Department of Liberal Arts and Sciences, Faculty of Engineering, Toyama Prefectural University, Kurokawa 5180, Kosugi-Machi, Toyama 939-0398, Japan; 3: Laboratory of Bioorganic Chemistry, National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, DHHS, Bethesda, Maryland 20892, USA

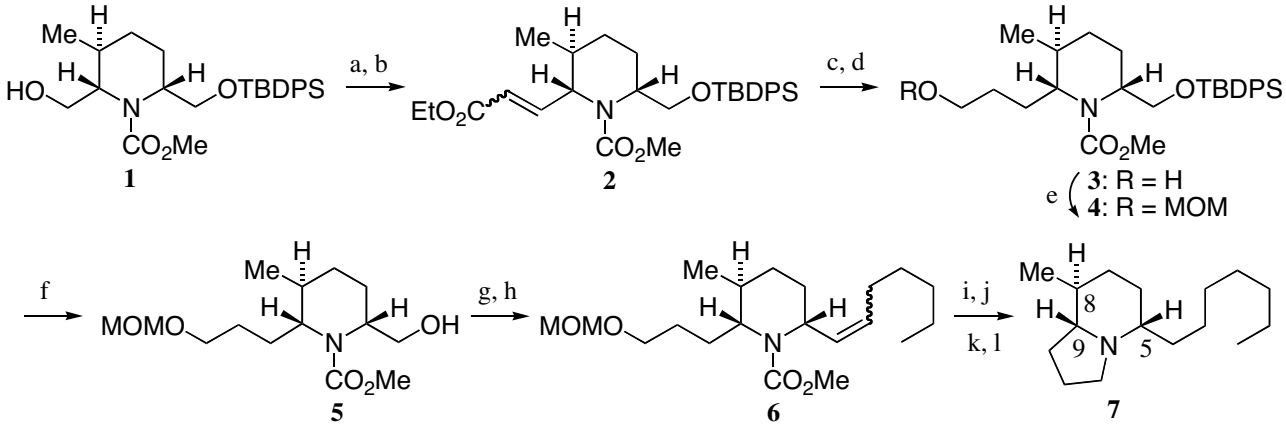
Abstract - An enantioselective synthesis of the 5-heptyl-8-methylindolizidine ((−)-**7**) has been achieved. Alkaloid ((−)-**7**, (MW 237)) was used to determine the relative and absolute stereochemistry of the natural indolizidine 237D from frog skin as 5*S*, 8*S*, 9*R* using GC-IR and GC-MS. Chiral 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.[1] 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.[2] Alkaloid 237D, detected in extracts of *Dendrobates pumilio* and *D. speciosus*,[3] 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.[1] 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.

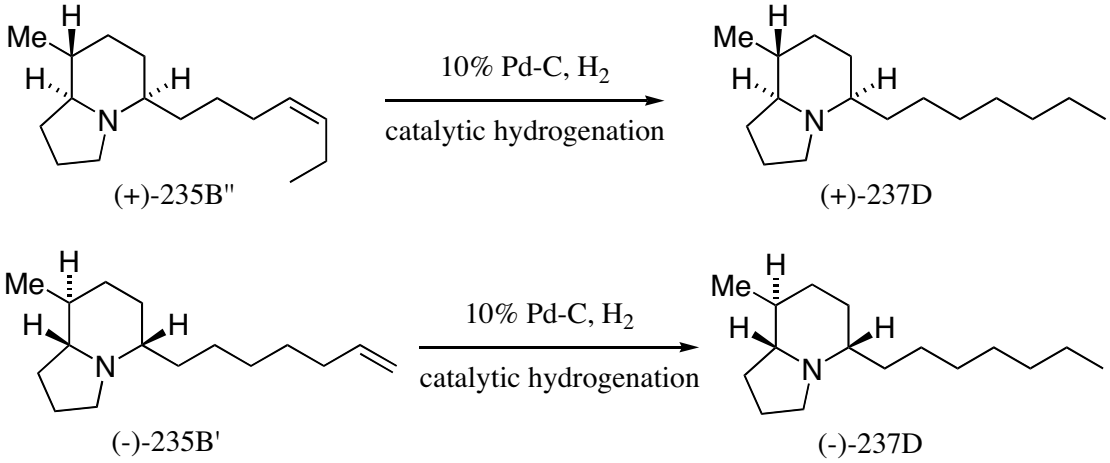
The synthesis (see Scheme 1) began with the known 2,3,6-trisubstituted piperidine (**1**),[4] prepared stereoselectively by our original Michael-type conjugate addition reaction to the enaminoester as the key step,[5] which was then converted to the α,β-unsaturated ester (**2**). Hydrogenation of **2** 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**).[6] Synthetic (–)-**7** was co-chromatographed on a non-chiral GC-column with natural 237D found in an extract of *Dendrobates speciosus*,[3b] and had exactly the same mass and infrared spectrum as the natural product.



Scheme 1: Reagents and conditions: a: Swern ox.; b: $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C-rt (95%); c: 10% Pd-C, H_2, EtOAc, 4 atm; d: Super-Hydride, THF, 0 °C (93%); e: MOMCl, Hünig base, CH_2Cl_2, 0 °C-rt (85%); f: TBAF, THF, 0 °C-rt (95%); g: Swern ox.; h: $Me(CH_2)_5P^+Ph_3Br^-$, *n*-BuLi, THF, 0 °C-rt (66%); i: 10% Pd-C, H_2, EtOAc, 1 atm; j: *n*-PrSLi, HMPA,[7] THF, 0 °C-rt; k: conc. HCl, MeOH, reflux; l: CBr_4, Ph_3P, then Et_3N, CH_2Cl_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°), which previously had been isolated from *D. pumilio*[3a] and (–)-237D by reduction of (–)-235B' ($[\alpha]_D$ –61°) present in an extract of *D. speciosus*[3b] (see below). Gas chromatography using flame-ionization detection and a chiral column, permethylated β-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^{-1}; ^{1}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); ^{13}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° (*c* 1.59, $CHCl_3$).

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