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A Chirospecific Synthesis of An Ant Venom Alkaloid (5*Z*,8*E*)-3-Heptyl-5-methylpyrrolizidine

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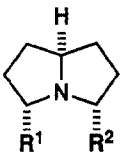
Summary: A straightforward and practical route for the chirospecific synthesis of both enantiomers of the ant venom alkaloid (5*Z*,8*E*)-3-heptyl-5-methylpyrrolizidine has been developed.

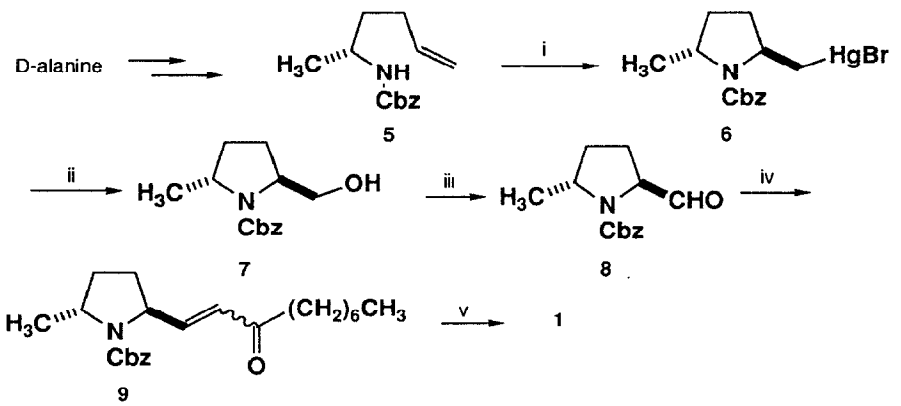
There have been found, in the venom of ants in the genera *Solenopsis* and *Monomorium*,[1] a variety of alkaloids of the piperidine, pyrrolidine, indolizidine, or pyrrolizidine system bearing alkyl appendages. However, the absolute configuration of most of these compounds remains unknown because of their short supply from natural sources. Accordingly, much attention has increasingly been focussed on their asymmetric synthesis.[2] During the course of our program directed towards the design and development of new strategies for the asymmetric synthesis of biologically active nitrogen-containing compounds,[3] we disclose a short and stereoselective synthesis of both enantiomers of (5*Z*,8*E*)-5-heptyl-3-methylpyrrolizidine (**1**), one of several (5*Z*,8*E*)-3,5-dialkylpyrrolizidines (**1**, **2**, **3**, and **4**) isolated from the cryptic thief ants *Solenopsis*[4] and *Monomorium*.[5]



1 $R^1 = CH_3$, $R^2 = (CH_2)_6CH_3$
2 $R^1 = CH_3$, $R^2 = (CH_2)_7CH{=}CH_2$
3 $R^1 = R^2 = (CH_2)_4CH{=}CH_2$
4 $R^1 = (CH_2)_8CH_3$, $R^2 = CH{=}CHCH_3$

Electrophile-mediated heterocycliztions have been powerfully employed for the stereoselective construction of oxygen- and nitrogen-heterocycles.[6] Recently, we reported the stereoselective synthesis of homochiral *trans*-2,5-dialkylpyrrolidines, constituents of ant venom, via intramolecular amidomercuration of α-alkylated 4-pentenylcarbamate.[7] Our synthesis of **1** began with the intramolecular amidomercuration of (*R*)-*N*-benzyloxycarbonyl-1-methyl-4-pentenylamine (**5**)[8] readily available from D-(-)-alanine. The unsaturated carbamate **5** underwent the cyclization mediated by mercuric acetate in THF followed by treatment with aq. NaBr to afford the organomercurial **6**, which was oxidatively demercurated[9] to provide only the *trans* diastereomer **7**, $[\alpha]_D^{24}$ -45.8 (*c* 3.895, $CHCl_3$), in 75% yield with no isolation of the *cis* isomer. The Parikh-Doering oxidation (DMSO/Pyridine-SO_3 complex)[10] of **7** gave the aldehyde **8**, and, without purification, subsequent Wittig-Horner reaction of **8** with dimethyl (2-oxononyl)phosphonate provided the α,β-unsaturated ketone **8** in 49% overall yield from **7**. Enantioselectivity for *E*-**9**, $[\alpha]_D^{24}$ -74.0 (*c* 0.94, $CHCl_3$) was determined by HPLC analysis with a Daicel AS column using a mixture of hexane/ethanol/diethylamine (95/5/0.1) as eluant, showing >99% ee. Exposure of **9** to an atmosphere of hydrogen in the presence of $Pd(OH)_2$ as a catalyst in MeOH caused simultaneous reduction of its double bond, debenzyloxycarbonylation, annulative imination, and reduction of the resulting imine to give stereoselectively the desired pyrrolizidine **1** (bp

80 °C/0.6 mmHg, $[\alpha]_D^{24}$ +11.7 (*c* 0.695, $CHCl_3$)) in 58% yield after purification by silica gel chromatography. Spectral data (^1H- and ^{13}C-NMR) for **1** were completely identical with the values reported.[4] However, the value of specific rotation was quite inconsistent with that {$[\alpha]_D$ -6.25 (*c* 0.16, $CHCl_3$)} reported by Takano.[2e] Therefore, *ent*-**1** was prepared from L-(-)-alanine according to the above procedure. Since the value of specific rotation for *ent*-**1** showed $[\alpha]_D^{24}$ -11.5 (*c* 0.51, $CHCl_3$), we believe the absolute configuration of **1** is of 3*S*-(3β,5β,8α)-3-heptyl-5-methylpyrrorizidine. Unfortunately, none of the ant-derived pyrrolizidine has been isolated in enough quantity to determine its optical rotation.[11]



Scheme 1 Reagents and conditions: i, $Hg(OAc)_2$/THF; $NaHCO_3$/NaBr; ii, O_2/$NaBH_4$/DMF; iii, Pyridine-sulfur trioxide complex/DMSO, iv, $(MeO)_2POCH_2CO(CH_2)_6CH_3$/NaH/THF; v, H_2/$Pd(OH)_2$/MeOH

L-alanine ⟹ *ent*-**1**

In summary, a chirospecific synthesis of both enantiomers of the ant venom alkaloid (5*Z*,8*E*)-3-heptyl-5-methylpyrrolizidine (**1** and *ent*-**1**) has been accomplished in quite short steps. Extensions of this methodology to the synthesis of a variety of (5*Z*,8*E*)- 3,5-dialkylpyrrolizidines such as **2**-**4** are the subjects of active investigations in our laboratory, the results of which will be presented in due course.

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