First Enantioselective Synthesis of a Hydroxyindolizidine Alkaloid from the Ant *Myrmicaria melanogaster*

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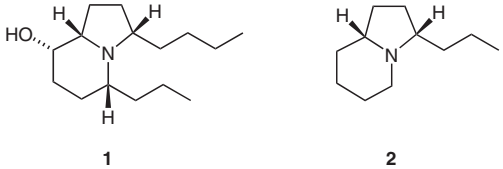
Abstract: The first enantioselective synthesis of the recently reported ant alkaloid **1** has been achieved starting from commercially available lactam **3** in seven steps and 25% overall yield. The proposed structure of the natural product was confirmed by comparison with synthetic **1** and its absolute configuration established as 3*S*,5*R*,8*S*,9*S*.

Key words: hydroxyindolizidine, venoms of ant, *Myrmicaria melanogaster*, chelation control, new ant alkaloid

The bicyclic indolizidine skeleton has been found in natural sources such as skin extracts of poison frogs,[1] venoms of ants,[2] and many of these natural products showed intriguing biological activities.[3] The stereoselective construction of the substituted indolizidine ring system remains a substantial challenge in organic chemistry.[4] Very recently, five new alkaloids, along with six known indolizidines and three known pyrrolidines, have been detected in the extracts of the ant *Myrmicaria melanogaster* from Brunei in the Indonesian archipelago.[5] Although the structures of two new indolizidine alkaloids (**1** and **2**, Figure 1) were proposed on the basis of a nonstereoselective synthesis and GC-FTIR analysis of each stereoisomer,[5] no stereoselective synthesis of **1** has yet been reported. As part of our ongoing program of devising syntheses of biologically active alkaloids,[6] we report here the first enantioselective synthesis of the above venom alkaloid **1** starting from the commercially available lactam **3** in seven steps and 25% overall yield.

The lactam **3** was converted to the Cbz-imide **4** in high yield, which was subjected to Martin's transformation[7] to produce the 2,5-*cis*-disubstituted pyrrolidine **6** via the ketone **5** in a highly diastereoselective manner. Treatment of **6** with DIBAL followed by addition of vinyl Grignard reagent to the resulting aldehyde provided the alcohol **7** as a mixture of diastereomers. The cross-metathesis reaction of **7** with 1-hexen-3-one in the presence of the Grubbs second-generation catalyst[8] in refluxing methylene chloride afforded the homologated product **8**. Exposure of **8** to hydrogenation in the presence of Pearlman's catalyst furnished the two indolizidines (–)-**1** and **9**. These indolizidines were easily separated by column chromatography to furnish (–)-**1**[9] as a major isomer and **9**[10] as a minor isomer in 62% and 19% isolated yields, respectively. The stereochemistry of the synthetic major isomer (–)-**1** was determined by the NOE experiments indicated in Scheme 1.



1 2

Figure 1

The stereochemical course of the addition of the vinyl anion to the aldehyde intermediate from **6** can be explained by the chelation control model as shown in Figure 2. The use of excess Grignard reagent (3 equiv) resulted in the formation not of the Felkin–Anh type of transition state but rather a chelated transition state, where the anticipated preference for β-attack of the vinyl anion would yield the major isomer. In the chelated transition state, steric hindrance of the α-hydrogen at the 3-position of pyrrolidine ring would also favor β-attack of the vinyl anion.

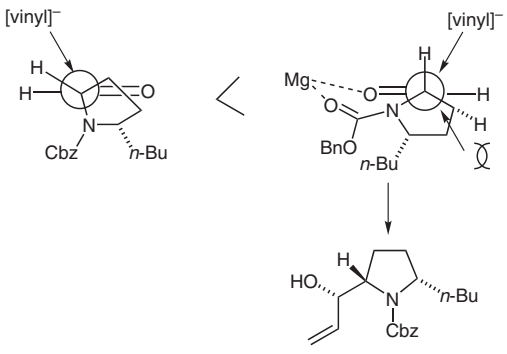


Figure 2 Stereochemical course of the addition of vinyl anion

We found that synthetic (–)-**1** had a retention time (t_R) and mass spectrum identical with the natural product from the *Myrmicaria melanogaster* ant as well as the first eluting isomer (±)-**1** of the mixture of four components [(±)-**1** and

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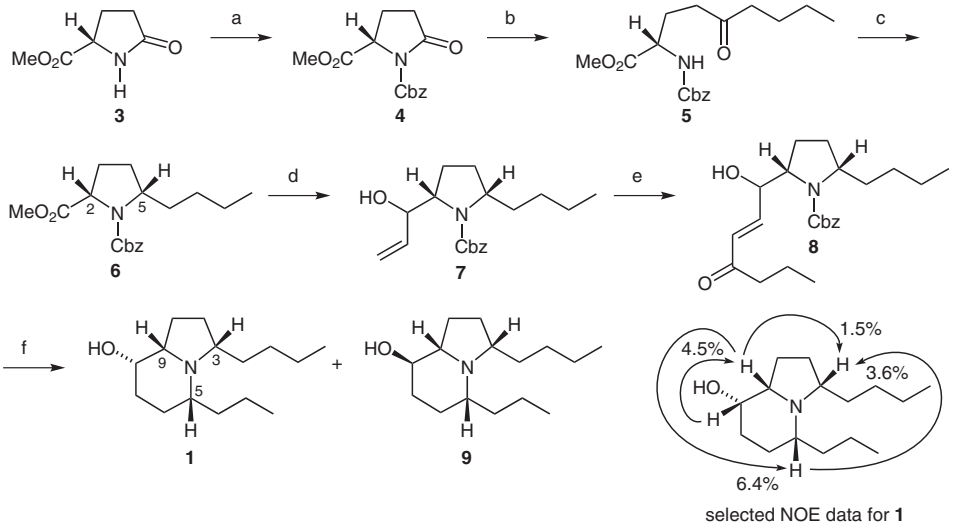

Scheme 1 *Reagents and conditions*: a) LiHMDS, CbzCl, THF, –78 to 0 °C (92%); b) *n*-BuMgBr, TMEDA, THF, –78 °C (65%); c) Ph_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to r.t. (98%); d) DIBAL, CH_2Cl_2, –78 °C then vinylMgBr (3 equiv), THF, –78 °C to r.t. (72%); e) 1-hexen-3-one, Grubbs second-generation catalyst (0.1 equiv), CH_2Cl_2, reflux (97%); f) 20% $Pd(OH)_2$, EtOH, 1 atm (**1**: 62%, **9**: 19%).

three (±)-diastereomers] synthesized earlier in a nonenantioselective manner by Jones et al.[5] The absolute configuration of the natural product was shown identical to that of (–)-**1** by the correspondence of its t_R after co-injection with (±)-**1** from Jones' synthetic mixture and the crude ant extract using a chiral permethylated β-cyclodextrin column.[11] Thus the natural product has the same absolute configuration as (–)-**1**, that is, 3*S*,5*R*,8*S*,9*S*. This is the same configuration at C-3, C-5, and C-9 as the recently synthesized natural (–)-monomorine from ants.[12]

In summary, we achieved the first enantioselective synthesis of the new ant alkaloid, 3-butyl-5-propyl-8-hydroxyindolizidine, starting from lactam **3** in seven steps, and the absolute configuration as well as the proposed relative structure of the natural ant alkaloid was confirmed by comparison with synthetic (–)-**1**. The relative configuration reported[5] for the hydroxyindolizidine as structure **10a** was arbitrarily depicted but fortuitously shows the correct absolute configuration as this work indicates.

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(9) **Spectral Data of 1**
IR (neat): 3482, 2956, 2872, 1513, 1457, 1378, 1234, 1130, 1054, 970, 826 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.90 (3 H, t, *J* = 7.2 Hz), 0.91 (3 H, t, *J* = 7.2 Hz), 1.17–1.49 (11 H, br m), 1.53–1.62 (4 H, m), 1.68–1.86 (3 H, m), 2.25 (1 H, t-like, *J* = 9.8 Hz), 2.40 (1 H, m), 2.75 (1 H, t-like, *J* = 8.5 Hz), 3.03 (1 H, d, *J* = 10.3 Hz), 3.74 (1 H, d, *J* = 9.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.27 (q), 14.50 (q), 19.16 (t), 22.98 (t), 25.92 (t), 26.67 (t), 28.75 (t), 28.98 (t), 32.18 (t), 37.83 (t), 39.43 (t), 60.43 (d), 64.07 (d), 65.45 (d), 70.06 (d). MS: *m/z* (%) = 239 [M^+], 196 (100). HRMS: *m/z* calcd for

$C_{15}H_{29}ON$: 239.2103; found: 239.2121. $[\alpha]_D^{26}$ –48.92 (*c* 0.62, $CHCl_3$).

(10) **Spectral Data of 9**
Mp 39–40 °C. IR (KBr): 3343, 2955, 2933, 2859, 2784, 1466, 1378, 1259, 1207, 1194, 1158, 1123, 1062, 1019 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3 H, t, *J* = 7.3 Hz), 0.91 (3 H, t, *J* = 7.3 Hz), 1.18–1.36 (8 H, m), 1.42 (1 H, m), 1.45–1.64 (4 H, m), 1.80–1.84 (2 H, m), 1.92–2.08 (3 H, m), 2.15 (1 H, br), 2.66 (1 H, t-like, *J* = 8.5 Hz), 3.43 (1 H, br). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.24 (q), 14.53 (q), 19.55 (t), 22.88 (t), 27.91 (t), 29.22 (t), 29.68 (t), 30.87 (t), 34.08 (t), 37.51 (t), 39.37 (t), 62.10 (d), 63.75 (d), 72.87 (d), 73.05 (d). MS: *m*/*z* (%) = 239 [M^+], 182 (100). HRMS: *m*/*z* calcd for $C_{15}H_{29}ON$: 239.2103; found: 239.2127; $[\alpha]_D^{26}$ –53.55 (*c* 1.05, $CHCl_3$).

(11) For proof of identity of (–)-**1** with the natural ant alkaloid (**10a**, see ref. 5), a Shimadzu QP-2010 GC/MS equipped with an RTX-5 column (30 m × 0.25 mm i.d.) was used employing a program of 60 °C to 250 °C at 10 °C/min. Here, both synthetic (–)-**1** and natural product **10a** coeluted and had identical mass spectra. Synthetic (–)-**1** also had a retention time and mass spectrum identical to the first eluting isomer, (±)-**1**, of the mixture of diastereomers synthesized in a nonstereoselective manner by Jones et al.[5] For the determination of the absolute configuration of **10a**, an HP 5890 GC with flame-ionization detection was used with He carrier gas and a head pressure of 20 psi. This was fitted with a chiral permethylated β-cyclodextrin column (SGE, 30 m × 0.22 mm i.d., 0.25 μm film thickness) operated with a program of 100 °C at a rate of 1 °C/min. Using these conditions, the *Myrmicaria melanogaster* ant hydroxyindolizidine **10a** and (–)-**1** each coeluted with the slightly more slowly eluting enantiomer (156.5 °C) of the (±)-**1** racemate present in Jones' synthetic mixture, whereas the (+)-**1** enantiomer, from Jones' synthetic mixture eluted at 156.0 °C.

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