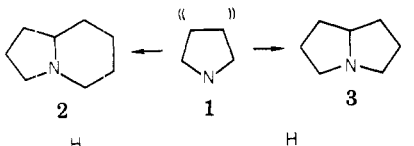
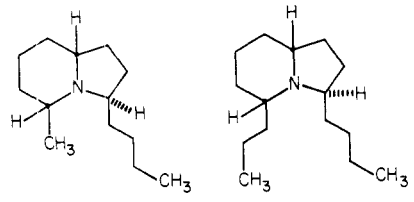
Indolizidine Alkaloid Synthesis. Preparation of the Pharaoh Ant Trail Pheromone and Gephyrotoxin 223 Stereoisomers

Summary: A stereoselective entry into the 3,5-dialkylindolizidine alkaloid skeleton proceeding via N1–C2 vicinal annulation of a 1,4-dibromoalkane onto a pyrroline system is described.

Sir: Alkaloids containing the indolizidine (**2**) and pyrrolizidine (**3**) skeletons have a wide and varied distribution within nature.[1] The members of these alkaloidal classes demonstrate a broad range of pharmacological activity and have generated substantial synthetic interest.[2] A synthetic approach to these bicyclic alkaloids, which would possess considerable flexibility by evolving from a common intermediate structure, is the 1,2-vicinal annulation of an appropriate three-carbon (pyrrolizidine) or four-carbon (indolizidine) unit onto the suitably substituted five-membered 1-azaheterocyclic ring **1** (**1** → **2** and **1** → **3**). Seebach was first to demonstrate the synthetic viability of this approach for pyrrolidine ring annulation.[3] We report the realization of this synthetic strategy in the pyrroline ring system as illustrated by the stereoselective syntheses of the two 3,5-dialkylindolizidine alkaloids **4** and **5**. The synthesized indolizidine alkaloids are stereoisomers of the nonstereochemically defined structures proposed for the pharaoh ant trial pheromone (**4**)[4a] and gephyrotoxin 223 (**5**),[5] an alkaloid isolated from the skin of the neotropical poison-dart frog (genus *Dendrobates*).

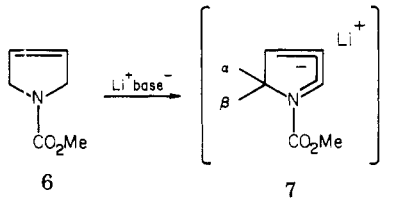


2 **1** **3**



4 **5**

We have focused on 1-(methoxycarbonyl)-3-pyrroline (**6**), previously examined by Pandit,[6,7] as the central five-membered azaheterocyclic unit in our indolizidine–pyrrolizidine alkaloid approach due to the facility of N-decarbomethoxylation[8] and to the synthetic desirability of incorporating the intact 3-pyrroline system into target molecules. In addition, it was felt that the well-defined and rigid conformation of the derived pyrroline allylic carbanion **7** of 2-substituted pyrroline systems might impart substantial control in the stereochemical outcome of the alkylation process adjacent to nitrogen (trans vs. cis 2,5-disubstituted pyrroline structures).



6 **7**

We have observed (Scheme I) that alkylation of the in situ generated carbanion **7** occurs with high regioselectivity at the α position (>97%) and that sequential bis alkylation (of **6**) generates *trans*-2,5-dialkylpyrroline structures **10** with high regio- and stereoselectivity (≥95%).[9] The observation of a single stereoisomer in the bis-alkylation process was determined by analytical and spectral analysis of the crude bis-alkylation products **9**.[10] The *trans*-2,5-dialkyl relationship in a representative pyrroline **9** (R = R′ = butyl) was established by the method of Hill and Chan[11] through conversion of pyrroline **9** into the *N*-benzyl-2,5-pyrrolidine and by NMR observation of the diastereotopic benzylic protons indicative of the trans isomer. *trans*-2,5-Dialkylpyrrolidines **11** have been identified as poison-gland products of a variety of ant species.[12] Olefin reduction and N-decarbomethoxylation (vide infra) of the requisite *trans*-2,5-dialkylpyrroline **9** provides a direct entry into these substances (~40% from **6**; >95% trans). In this fashion, *trans*-2-butyl-5-pentylpyrrolidine (**11**) (R = butyl, R′ = pentyl), a characteristic poison of the South African ant *S. punctaticeps*, was prepared (38% from **6**). In a related approach to these ant venoms involving α,α'-alkylation of pyrrolidine nitrosamide, Fraser observed a 1:1 mixture of *cis*- to *trans*-2,5-dialkylpyrrolidine isomers after denitrosation.[13a]

Our synthesis of the pharaoh ant trail pheromone stereoisomer **4** (Scheme II) proceeded by alkylation of pyrroline urethane **6** with *n*-butyl bromide[6] [*n*-BuBr (2.0 equiv), LDA (1.0 equiv), THF, −40 °C; 65%]. Subsequent alkylation of 2-butylpyrroline **12** with 1,4-dibromopentane[14] occurred exclusively at the primary carbon site of the dibromide and afforded the *trans*-2,5-dialkylpyrroline **13**[17a] as a 1:1 mixture of 4′-bromopentane isomers

(1) (a) Pelletier, S. W. "Alkaloids"; Van Nostrand-Reinhold: New York, 1970. (b) Warren, F. L. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1970; Vol. XII, p 246.

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(7) For examples of other nitrogen dipole stabilized α-carbanions see: (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. (b) Seebach, D.; Enders, O. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 15; **1976**, *15*, 313.

(8) (a) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315. (b) Corey, E. J.; Weigel, L. O.; Floyd, D.; Bode, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 2916.

(9) For alkylation processes of related 1-heterofunctionally substituted propenyl carbanions and factors controlling the regioselectivity (α vs. γ) see: (a) Tischler, A. N.; Tischler, M. H. *Tetrahedron Lett.* **1978**, 3407. (b) Martin, S. F.; Dupriest, M. T. *Ibid.* **1977**, 3925. (c) Still, W. C.; Macdonald, T. L. *J. Org. Chem.* **1976**, *41*, 3620. (d) Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 701.

(10) For example, **9** (R = R′ = butyl; obtained in 52% yield) was homogeneous under all TLC and GLC conditions examined. The ^{13}C NMR spectrum exhibited 12 resonances as a consequence of hindered urethane rotation and fortuitous doubling of the CH_2CH_3 butyl resonances [^{13}C NMR ($CDCl_3$) 154.4, 129.0, 128.8, 65.0, 64.3, 51.4, 32.8, 36.3, 26.1, 25.8, 22.5, 13.7 ppm].

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(13) (a) Fraser, R. R.; Passannarti *Synthesis* **1976**, 540. (b) Fraser, R. R.; Grindley, T. B.; Passannarti *Can. J. Chem.* **1975**, *53*, 2473.

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(15) The author is grateful for an authentic sample of this pharaoh ant trail pheromone isomer generously provided by Dr. P. E. Sonnet[4b,c] of the USDA and for his helpful comments and interest in this project.

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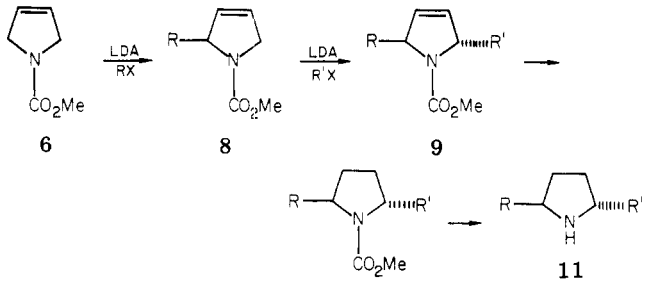
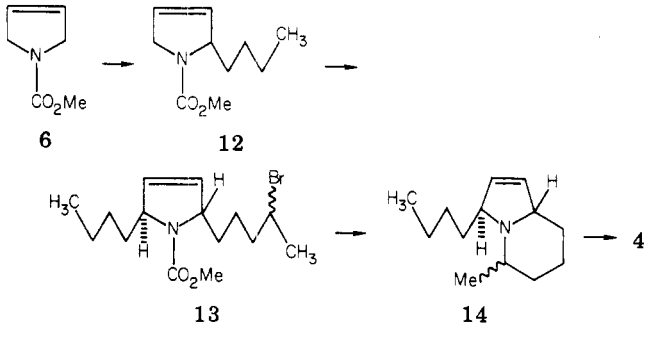
Scheme I



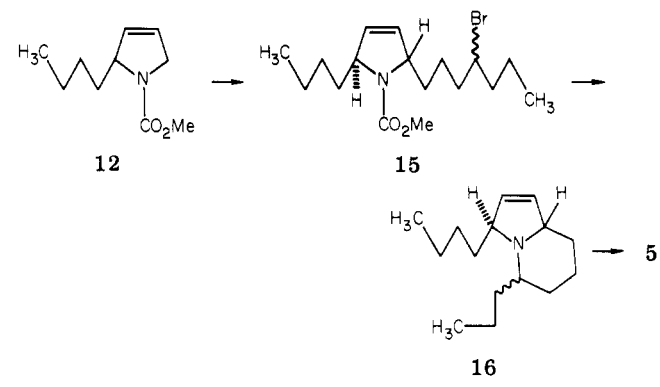
Scheme II



[1,4-dibromopentane (2.0 equiv), LDA (1.0 equiv), THF, −40 °C; 71%]. N-Decarbomethoxylation of pyrroline **13** [trimethylsilyl iodide (1.5 equiv), $CHCl_3$, 70 °C, 30 min][8a] followed by indolizidine formation via bromo–amine cyclization [MeOH, Na_2CO_3 (1.0 equiv), reflux, 3.0 h (cf. ref 3)] gave the dehydroindolizidine **14**[17b] as a 1:1 mixture of C-5 methyl stereoisomers (76%). In a mechanistically interesting and synthetically useful conversion, the stereoisomeric dehydro alkaloids **14** were catalytically hydrogenated (PtO_2, AcOH) to yield a single, isolable indolizidine alkaloid **4** (43%), which was compared to an authentic, stereochemically pure material.[15,4b,c]

Two possible rationales have been examined to explain the anomalous isolation of a single indolizidine stereoisomer **4** from the reduction of the epimeric dehydro alkaloids **14**. The possibility that C-5 isomerization occurred during catalytic hydrogenation appears to be discounted by the observation of less than 15% of the tri-deuterated product **4** after reduction with D_2. In addition, a selective adsorption process of the more sterically encumbered, alternate C-5 methyl isomer either by the hydrogenation catalyst or by a kinetically slow deprotonation of the ammonium salt could not be established, since additional indolizidine material could not be recovered from these media. The observed reduction phenomena (1 stereoisomer; ≤50% overall yield) does appear to be general, occurring with related 3,5-dialkyl-$\Delta^{3,4}$-dehydroindolizidine alkaloids and with different acidic reaction media and sources of hydrogenation catalyst.

Scheme III



Synthesis of indolizidine **5** was undertaken in an analogous fashion (Scheme III). 2-Butyl-3-pyrroline **12** was alkylated exclusively at the primary carbon site with 1,4-dibromoheptane[14] affording a 1:1 mixture of 4′-bromoheptyl stereoisomers of the *trans*-2,5-dialkyl-3-pyrroline **15**[17c] [1,4-dibromoheptane (2.0 equiv), LDA (1.0 equiv), THF, −40 °C; 78%]. N-Decarbomethoxylation of **15** and cyclization in the manner described above gave a 1:1 C-5 *n*-propyl epimeric mixture of dehydroindolizidine alkaloids **16**[17d] (81%). Catalytic hydrogenation afforded a single stereoisomer **5**[17e] of the gross structure proposed for gephyrotoxin 223 (38%).[5] The synthetic material **5** and natural gephyrotoxin were shown by GC/MS analysis to be chromatographically different, although identical in mass spectral fragmentation pattern.[16] The mass spectral data suggest that the two materials have a stereoisomeric relationship.

This approach to the indolizidine alkaloid skeleton is direct in its synthetic manipulation and general in its application. This scheme to substituted five-membered 1-azaheterocyclic rings complements the existing pyrrolidine nitrosamide α,α'-alkylation route[13a] but appears to be synthetically superior in obtaining and maintaining the stereochemical integrity of the sites adjacent to nitrogen in the five-membered ring and in incorporating additional functionality in the five-membered heterocyclic ring. We are currently examining the implementation of this approach in the synthesis of more complex indolizidine alkaloid structures and extension to the synthesis of pyrrolizidine alkaloids.

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Registry No. **4**, 53447-41-9; **5**, 72120-43-5; **6**, 63603-33-8; **9** (R = Bu, R′ = pentyl), 72049-60-6; **10** (R = Bu, R′ = pentyl), 72049-61-7; **11** (R = Bu, R′ = pentyl), 71732-78-0; **12**, 63603-35-0; **13**, isomer 1, 72049-62-8; **13**, isomer 2, 72049-62-8; **14**, isomer 1, 72049-63-9; **14**, isomer 2, 72074-81-8; **15**, isomer 1, 72049-64-0; **15**, isomer 2, 72074-82-9; **16**, isomer 1, 72049-65-1; **16**, isomer 2, 72074-83-0.

Timothy L. Macdonald
Department of Chemistry
Vanderbilt University
Nashville, Tennessee 37235

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(16) This comparison with authentic gephyrotoxin 223 was undertaken by Dr. J. A. Daly[5] at NIH. We thank Dr. Daly for his assistance in chemical comparison and interest in the synthetic gephyrotoxin 223 material.

(17) (a) IR 1710 (s), 1635 (w), 1460 (s), 1395 (s) cm^{-1}; ^1H NMR ($CDCl_3$), 5.73 (s, 2 H), 4.52 (m, 2 H), 4.10 (sextet, J = 7.0 Hz, 1 H), 3.65 (s, 3 H), 1.70 (br m, 8 H), 1.30 (br m, 7 H), 0.88 (t, J = 6.0 Hz, 3 H). (b) IR 1660 (w), 745 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.90 (m, 2 H), 3.60–3.95 (br m, 2 H), 2.80 (m, 1 H), 1.00–1.90 (br m, 12 H), 1.16 and 1.12 (pair of doublets, J = 7.0 Hz, 3 H), 0.92 (t, J = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 133.4, 132.7, 130.9, 67.3, 64.6, 63.9, 60.7, 50.5, 48.5, 34.9, 33.9, 29.65, 29.1, 28.6, 28.3, 27.6, 26.3, 24.6, 22.9, 20.5, 18.1, 13.9 ppm; MS (70 eV) m/e 193 (0.5%), 178 (32%), 136 (100%). (c) IR 1720 (s), 1640 (w), 1460 (s), 780 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.72 (s, 2 H), 4.50 (m, 2 H), 4.00 (pentet, J = 6.0 Hz, 1 H), 3.68 (s, 3 H), 1.70 (m, 8 H), 1.20 (m, 8 H), 0.88 (t, J = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 154.5, 129.6, 129.4, 128.8, 65.3, 65.0, 65.5, 64.3, 58.1, 47.7, 41.7, 41.3, 41.1, 39.0, 32.9, 32.7, 31.5, 30.9, 27.4, 26.3, 26.0, 22.6, 22.0, 20.7, 13.9, 13.3 ppm. (d) IR 1660 (s), 750 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.82 (m, 2 H), 4.00–3.75 (br m, 2 H), 2.95–2.80 (m, 1 H), 2.12–1.10 (br m, 16 H), 1.00 (m, 6 H); MS (70 eV) m/e 221 (6%), 178 (62%), 164 (100%). (e) IR 1190 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (m, 3 H), 2.78 (m, 6 H), 2.36 (br m, 14 H), 0.96 (m, 6 H); ^{13}C NMR ($CDCl_3$) 58.5, 57.7, 55.9, 34.7, 30.9, 29.6, 28.7, 28.3, 25.4, 24.3, 23.6, 21.9, 17.9, 13.4, 13.0 ppm; MS (70 eV) m/e 223 (4.2%), 180 (97.9%), 166 (100%).