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ENANTIOSELECTIVE SYNTHESIS OF (-)-GEPHYROTOXINE 223AB [(3R,5R,9R)-3-BUTYL-5-PROPYLOCTAHYDROINDOLIZINE]

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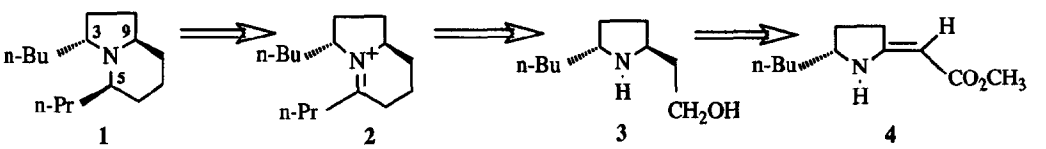
Summary: A highly enantioselective synthesis of the dendrobatid indolizidine alkaloid 223AB is described using a chiral amino acid as starting material.

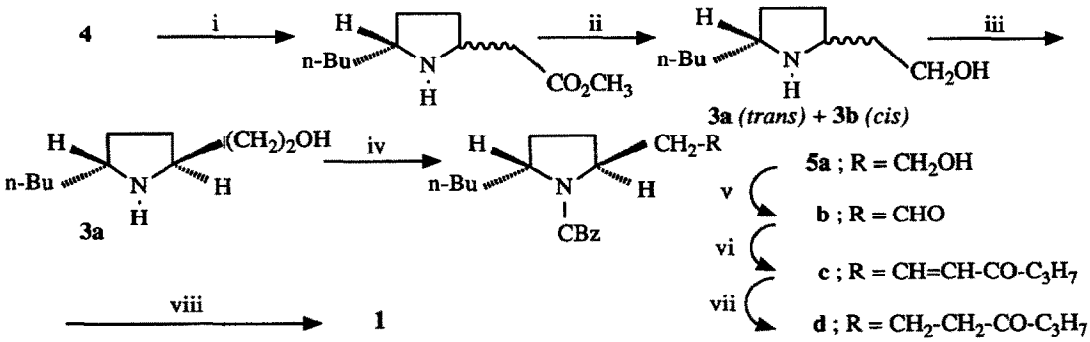
Numerous indolizidine alkaloids bearing alkyl appendages have been isolated from the skin secretions of neotropical frogs in the genus *Dendrobatidae* and present significant neuromuscular activity[1]. The first indolizidine isolated was the gephyrotoxin GTX 223AB **1** and its correct relative stereochemistry was established in 1981[2]. Then the absolute configuration was proved to be 3R,5R,9R in 1985[3a]. Several stereospecific syntheses of this compound were since reported but only three of them were enantioselective[3].

In this paper we report a highly enantioselective strategy for the synthesis of (-)-indolizidine 223AB **1** with control of both relative and absolute configuration. We had previously shown that the key step of the synthesis of 5-propyloctahydroindolizine depended on the diastereoselective reduction of the iminium intermediate[4]. As the disconnective analysis shows, this synthesis depends on this reaction step for the C-5 absolute configuration but also on the diastereoselective preparation of the amino alcohol intermediate **3** for the C-9 absolute configuration from the β-enamino ester **4**.



The compound **4** was prepared in seven steps from (S)-pyroglutamic acid in 26% overall yield[5], and then transformed in two steps into a diastereomeric mixture 1/1 of *trans* and *cis* cyclic amino alcohols **3a** and **3b** using firstly $NaBH_4$ in MeOH then $LiAlH_4$ in ether as reducing agents. The pure *trans* amino alcohol **3a** ($[\alpha]^{22}_D$ -20.2 c=0.56, $HCCl_3$) was isolated during the selective acylation of *cis* cyclic amino alcool **3b**[6]. The compound **3a** was then transformed into the carbamate **5a**; after oxidation of **5a** with the Corey-Suggs oxidizing reagent[7] leading to the amino aldehyde **5b**, subsequent Wittig reaction of **5b** with

1-triphenylphosphoranylidene-pentan-2-one provided **5c** as a mixture of geometric isomers. This mixture was of no consequence, as both of the *Z* and *E* alkenes were catalytically reduced to lead to the single diastereoisomer **5d**, direct precursor of compound **1**, in 42% overall yield from **3** ($[\alpha]^{20}_D$ -52.5; c=0.63, CH_2Cl_2). Hydrogenation of **5d**, and of the iminium intermediate **2** over Pd/C in methanol provided a single crude diastereoisomer, which stereochemistry was unambiguously determined by ^1H and ^{13}C NMR spectroscopy. Finally, purification by flash chromatography on alumina (ether-pentane: 2/8) gave the optically pure (-)-(3R,5R,9R)-3-butyl-5-propyloctahydroindolizine **1** in 85% yield[8].



Reaction conditions: i) $NaBH_4$ 3eq., $Et_2O.BF_3$ 2 eq., CH_2Cl_2; ii) $LiAlH_4$, ether reflux; iii) diastereomeric separation[6]; iv) CBzCl, K_2CO_3, acetone; v) PCC, CH_2Cl_2; vi) Ph_3P=CH-CO-C_3H_7, THF reflux; vii) H_2/PtO_2, MeOH; viii) H_2/Pd-C, MeOH.

This present synthesis is an easy and highly enantioselective route to dialkyl indolizidines.

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References

1. For a detailed account of the isolation and structure of the Dendrobated alkaloids including indolizidine 223AB, see: Daly, J.W.; Spande, T.F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S.W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1, pp 1-274.
2. Spande, T.F.; Daly, J.W.; Hart, D.J.; Tsai, Y.M.; Macdonald, T.L. *Experientia* **1981**, *37*, 1242.
3. (a) Royer, J.; Husson, H.P. *Tetrahedron Lett.* **1985**, *26*, 1515. (b) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178. (c) Taber, D.F.; Deker, P.B.; Silverberg, L.J. *J. Org. Chem.* **1992**, *57*, 5990.
4. Fleurant, A.; Célérier, J.P.; Lhommet, G. *Tetrahedron Asymmetry* **1992**, *3*, 695.
5. Saliou, C.; Fleurant, A.; Célérier, J.P.; Lhommet, G. *Tetrahedron Lett.* **1991**, *28*, 3365.
6. Fleurant, A.; Grandjean, C.; Provot, O.; Rosset, S.; Célérier, J.P.; Lhommet, G. *Heterocycles*, in press.
7. Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* **1975**, 2647.
8. Satisfactory analytical and spectral data were obtained for (-)-3-butyl-5-propyl-octahydroindolizine **1**. $[\alpha]^{20}_D$= -103 (c=1.12, Hexane); IR (neat) ν(cm^{-1})= 2960, 2940, 2860, 2800, 1460, 1440; ^1H-NMR (200 MHz, $CDCl_3$) δ(ppm)= 0.84 (t, 3H, J=7 Hz); 0.88 (t, 3H, J=7 Hz), 1.00-1.95 (m, 20H); 2.30-2.50 (m, 2H); 3.25-3.40 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ(ppm)= 14.2, 14.5, 19.1, 23.0, 24.5, 25.3, 26.2, 29.0, 29.8, 30.3, 31.9, 35.5, 57.0, 58.7, 59.5.