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Enantioselective Synthesis of (5R,9R)-5-Propyl-octahydroindolizine [(-)-Gephyrotoxin 167B]

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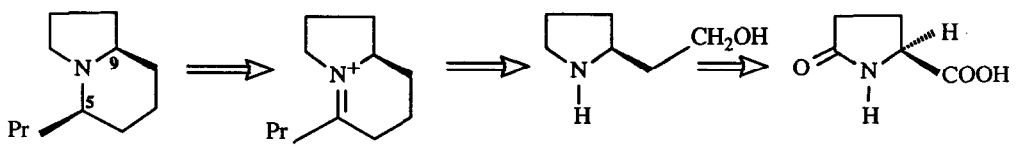
Summary: A versatile and practical synthesis of the dendrobatid alkaloid 167B is described using a chiral amino acid as starting material.

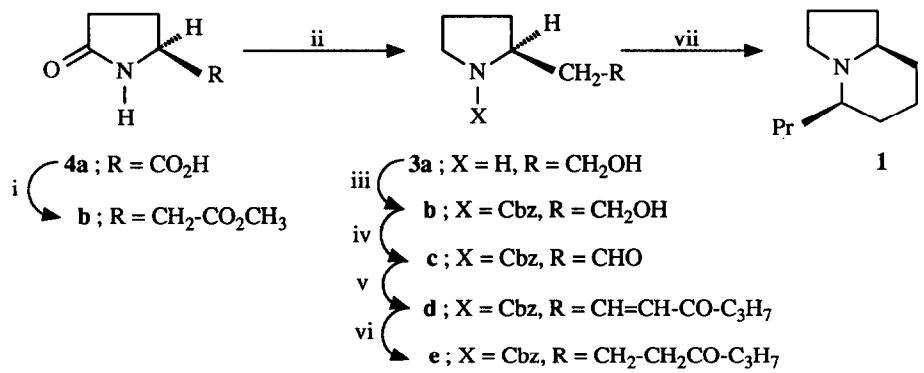
Indolizidine alkaloids bearing alkyl appendages have been isolated from the skin secretions of neotropical frogs (family Dendrobatidae)[1]. The simplest bicyclic indolizidinic alkaloids of this family possess a single substituent at the C5 of the indolizidine skeleton and represent a class of noncompetitive blockers of neuromuscular transmission[2]. When the substituent is a n-propyl, the indolizidine **1** occurs in trace amounts in the skin of a dendrobatid frog, caught on Isla de Colón, Panamá[2]. It has been synthesized twice in its racemic form[3] and as its (-) enantiomer[4]. In this paper we describe the highly enantioselective synthesis of (-)-gephyrotoxin 167B **1**. The key step of this synthesis depends, as the disconnective analysis shows, on the diastereoselective reduction of the intermediate **2**, enantiospecifically prepared from (S)-pyroglutamic acid **4a**.



1 **2** **3a** **4a**

The pivotal compound **3a** was prepared by reduction of the cyclic amido ester **4b** with $LiAlH_4$ in 71% yield $[\alpha]^{22}_D$=-8.3 (c=1.94 ,EtOH), and compound **4b** was readily available from (S)-pyroglutamic acid **4a** in five steps in a straightforward manner[5]: esterification followed by reduction, tosylation, cyanation, then acidic methanolysis.

The amino alcohol **3a** was converted into the carbamate **3b**, which in turn was transformed into the aldehyde **3c** with sulfur trioxide-pyridine complex[6]. Subsequent Wittig reaction of **3c** with 1-triphenylphosphoranylidene-pentan-2-one provided the ethylenic amino ketone **3d** which was catalytically reduced to lead to the amino ketone **3e** $[\alpha]^{21}_D$= -47.2 (c=2, EtOH), (95%), which is the direct precursor of compound **1**. Finally, hydrogenation of **3e**, and of the iminium intermediate **2** over Pd/C in methanol gave a single crude diastereoisomer (identified by correlation with ^{13}C NMR literature[4a,c]), which led after purification by flash chromatography on alumina (ether-pentane: 1-1) to the optically pure (-)-(5R,9R)-5-propyl-octahydroindolizine **1** in 70% yield[7] (Scheme 1).



Scheme 1

Reaction conditions: i Ref. 5; ii $LiAlH_4$, THF; iii $ClCO_2CH_2Ph$, K_2CO_3, acetone; iv Pyridine-SO_3, DMSO; v Ph_3P=CH-CO-C_3H_7, THF, Δ; vi H_2/PtO_2, MeOH; vii H_2, Pd/C, MeOH.

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

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References

1. (a) 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. (b) Daly, J.W.; Myers, C.W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023. (c) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M.W.; Daly, S.W. *Tetrahedron* **1987**, *43*, 643.
2. Aronstam, R.S.; Daly, S.W.; Spande, T.F.; Narayanan, T.K.; Albuquerque, E.X. *Neurochem. Res.* **1986**, *11*, 1227.
3. (a) Lions, F.; Willison, A.M. *J. Proc. R. Soc.*, N. S. W. **1940**, *73*, 240, *Chem. Abstr.* **1940**, *34*, 5841. (b) Holmes, A.B.; Smith, A.L.; Williams, S.F.; Hughes, L.R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, *56*, 1393.
4. (a) Polniaszek, R.P.; Belmont, S.E. *J. Org. Chem.* **1990**, *55*, 4688. (b) Zeller, E.; Sajus, H.; Grierson, D.S. *Synlett* **1990**, p.44 . (c) Jefford, C.W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513.
5. (a) Smith, A.L.; Williams, S.F.; Holmes, A.B.; Hughes, L.R.; Lidert, Z.; Swithenbank, C. *J. Am. Chem. Soc.* **1988**, *110*, 8696. (b) Silverman, R.B.; Levy, M.A. *J. Org. Chem.* **1980**, *45*, 815. (c) Nagao, Y.; Dai, W.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990**, *55*, 1148.
6. Parikh, J.R.; Von Doering, W.E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
7. Satisfactory analytical and spectral data were obtained for (-)-5-propyl-octahydroindolizine **1**. $[\alpha]^{20}_D$= -115 (c=1.17, CH_2Cl_2); IR (neat) ν(cm^{-1})= 2940, 2920, 2860, 2760, 2700, 1445, 1440, 1370; ^{1}H-NMR (500 MHz, $CDCl_3$) δ(ppm)= 0.88 (t, 3H, J=7 Hz), 1.10-1.33 (m, 5H), 1.35-1.50 (m, 2H), 1.58-1.68 (m, 2H), 1.69-1.92 (m, 7H), 1.94-2.05 (m, 1H), 3.26 (dt, 1H, J_1=8Hz, J_2=1.4Hz); ^{13}C-NMR (500 MHz, $CDCl_3$) δ(ppm)= 14.56, 19.16, 20.43, 24.70, 30.54, 30.78, 30.93, 36.86, 51.52, 63.79, 65.15.