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Enantioselective Synthesis of (-)-Indolizidine 239AB [(3R,5S,8aR)-3-Butyl-5-(3-hydroxypropyl)-octahydroindolizine]

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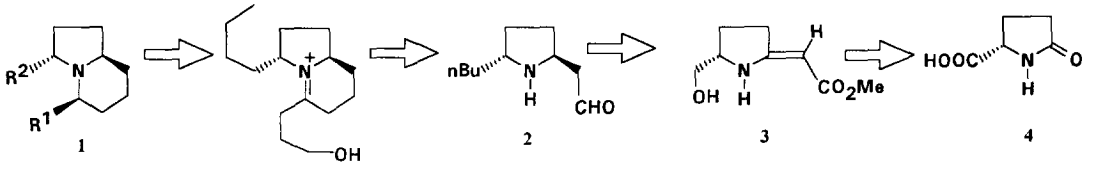
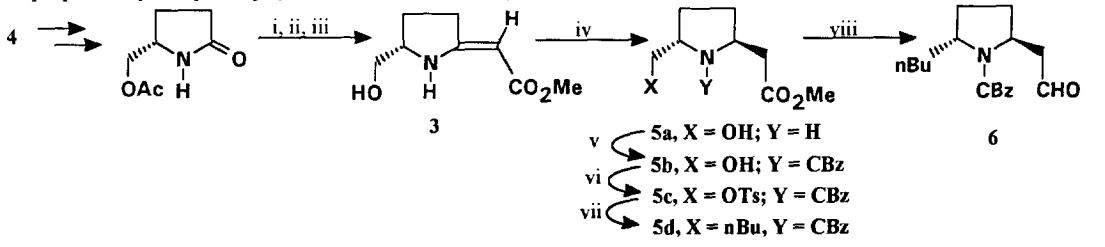
Abstract : A highly enantioselective synthesis of the indolizidine alkaloid **239AB** is described via the diastereoselective reduction of a chiral cyclic β-enamino ester prepared from (S)-pyroglutamic acid.

Poison-frogs of the Dendrobatidae family have been a source of numerous alkaloids which present a significant neuromuscular activity.[1] Among the bicyclic skeleta, 3,5-disubstituted indolizidines **1** occur in a limited number of alkaloids of this class. Substituents are generally 3- and 5-alkyl chains[2] but the 5-hydroxypropyl group was characterized in indolizidine **239AB**[2,3] **1** (R^1=$(CH_2)_3$-OH; R^2=nBu). No racemic and only one asymmetric synthesis of this compound has been reported in the literature by Kibayashi *et al.* using a chiral diepoxide as asymmetric synthon.[4] As a part of an investigation into the reactivity of chiral cyclic β-enamino esters, we have been engaged in the synthesis of *cis*[5] or *trans*[6] 3,5-disubstituted indolizidines bearing alkyl substituents.

In this paper we describe a general and highly enantioselective synthesis of the indolizidine **239AB** from a common chiral synthon. The key step of this synthesis depends, as shown in the disconnective analysis, on the diastereoselective reduction of the β-enamino ester **3** enantioselectivity prepared in few steps from (S)-pyroglutamic acid **4** and which permits a *trans* disubstituted pyrrolidine to be obtained.



We had previously shown that *cis* disubstituted pyrrolidines could be prepared by catalytic hydrogenation of cyclic β-enamino esters[5] but no useful diastereoselection was observed when using chemical reducing agents to prepare *trans* compounds.[6] We have recently described new reduction conditions using sodium polyacetoxyborohydride which lead to *trans* disubstituted pyrrolidines with good diastereomeric excesses.[7] This synthetic pathway involves interaction between a hydroxy function and the reducing agent. So we decided to prepare a hydroxymethyl-β-enamino ester and to perform a diastereoselective reduction of this compound.

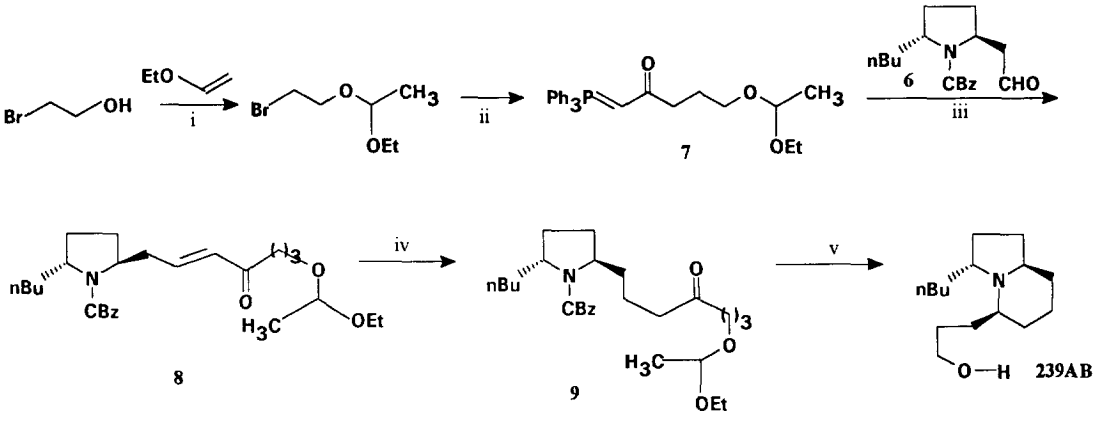


Reaction conditions : i) 1°) $(CH_3)_2SO_4$, 2°) K_2CO_3; ii) Meldrum's acid, $Ni(acac)_2$, $CHCl_3$, Δ; iii) MeONa/ MeOH, Δ; iv) $NaBH_4$, AcOH, CH_3CN, 0°C; v) diastereoselective carbamation; vi) TsCl, $(Et)_3N$; vii) Pr_2CuLi, Et_2O, -80°C; viii) DIBAH, toluene, -78°C.

β-Enamino ester **3** was enantioselectivity prepared in six steps from (S)-pyroglutamic acid **4** in 42% overall yield. Reduction of **3** with $NaBH_4$/AcOH in acetonitrile lead to a mixture of *trans* and *cis* β-amino esters **5a** with a good d.e. (80%).[7] After separation by kinetically controlled carbamation of the *trans* derivative[8] and

activation of the alcohol function, the tosylate **5c** was transformed into 5-alkylated β-amino ester **5d**. The DIBAH reduction of **5d** finally led directly to the *N*-protected aldehyde **6** in 70% yield[9].

Introduction of the hydroxypropyl substituent was achieved by Wittig condensation of **6** with a stabilized ylid **7** prepared in two steps from protected 2-bromoethanol[10], and condensation with lithiotriphenylphosphinioacetonide[11] with a 85% overall yield. Aminoenone **8** was obtained in 76% yield and then catalytically reduced to form the amino ketone **9.**



Reaction conditions : i) PPTs, 20°C; ii) BuLi, THF, Ph_3P=CH-CO-CH_3; iii) toluene, 80°C; iv) H_2, PtO_2, MeOH; v) 1°) H_2, Pd/C, MeOH, 2°) HCl 0.5M/CH_2Cl_2 2.5/1, 20°C.

Hydrogenation of aminoketone **9** using H_2/Pd-C led in one step and with a very high diastereoselectivity (d.e.=95%) to the enantiopure indolizidine **239AB** after final acidic hydrolysis to remove the protecting group.

In conclusion we report herein a highly enantioselective synthesis of natural indolizidine **239AB** in 15 steps and in a 5.6% overall yield. The strategy is sufficiently versatile to merit investigation of its generality in the synthesis of all natural hydroxyalkyl indolizidines.

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12. Satisfactory analytical and spectral data were obtained for (-) (3R,5S, 8aR)-3-butyl-5-(3-hydroxypropyl) octahydroindolizine **1**. $[\alpha]^{21}_D$ -96 (c=0.14, MeOH). *Anal.* Calcd. for $C_{15}H_{29}NO$: C, 75.26; H, 12.21; N, 5.85. Found: C, 75.02; H, 12.33; N, 5.97.IR (neat) ν (cm^{-1})= 3360; 2940; 2860; 2820; 1450. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm)= 0.86 (t, 3H, *J*=7Hz); 0.95-1.98 (m, 20H); 2.30-2.45 (m, 1H); 2.50-2.60 (m, 1H); 3.20-3.30 (m, 1H); 3.35-3.50 (m, 1H); 3.55-3.65 (m, 1H); 4.80-5.20 (br.s, 1H). ^{13}C NMR (64.25 MHz, $CDCl_3$) δ (ppm)=14.2, 23.0, 24.4, 25.0, 26.1, 28.0, 29.0, 29.2, 29.8, 30.8, 31.5, 55.2, 58.7, 59.3, 63.3.

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