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Enantioselective Synthesis of Indolizidine (-) 237A [(3R,5S,8aR)-3-Butyl-5-(1-oxopropyl)-octahydroindolizine]

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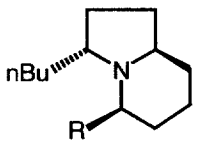
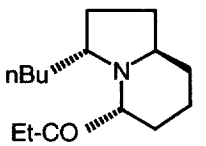
Abstract : A highly enantioselective synthesis of the indolizidine alkaloid (-) **237A** is described via the diastereoselective reduction of a heterocyclic enamine.

Among the bicyclic skeleton, 3,5-disubstituted indolizidines of type **1** are well represented occuring in numerous alkaloids contained in poisons of frogs[1] and ants[2]. Substituents are generally 3- and 5-alkyl chains but functionalized groups have also been found such as the 5-hydroxypropyl chain in indolizidine **239AB** of *Dendrobatidae* frogs[3].



1a , R = CO-Et [(-) Myrmicarine **237A**]
1b , R = n-Pr [(-) Indolizidine **223AB**]
1c , R = $(CH_2)_3$-OH [(-) Indolizidine **239 AB**]



2 [(+) Myrmicarine **237B**]

So far only one potentially epimerizable substituent has been found in the poison of an African ant, *Myrmicaria eumenoides* (Myrmicinae), which is a 1-oxopropyl group born at the 5-position of the bicyclic system. The analysis of a pentane extract of this poison was performed by Francke and coworkers in 1995[4].

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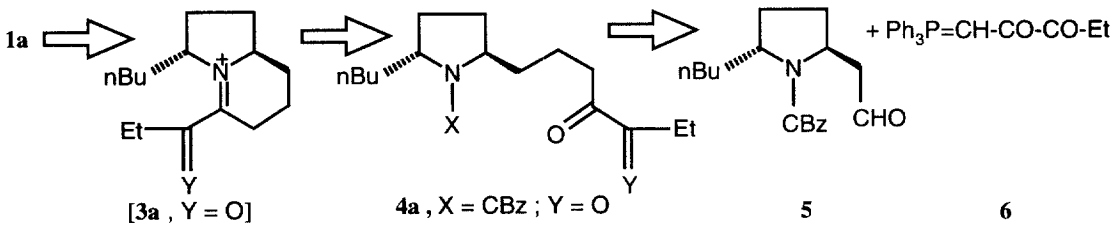
The authors have found that the two epimers at the 5-position were present in equal proportion in the indolizidine of the ant poison and they have proposed the only enantioselective synthesis of these two compounds **1a** and **2**[4]. As a part of our investigation of the reactivity of chiral cyclic β-enamino esters, we have been engaged in the diastereoselective synthesis of the major component of the venom : the (-) indolizidine **237A** (**1a**).

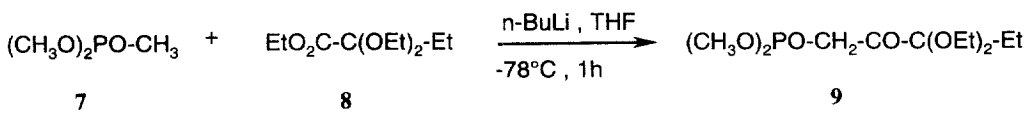
In this paper we describe a highly enantioselective synthesis of the indolizidine **237A** from a pivotal chiral synthon. The disconnective analysis presents two key steps :

* the diastereoselective reduction of the transient iminium **3**, which was postulated[5] to occur during the hydrogenation of the pyrrolidine **4a** in methanol;

* the condensation of the *trans* disubstituted pyrrolidine **5**, prepared in few steps from (S)-pyroglutamic acid with the phosphorane **6**.

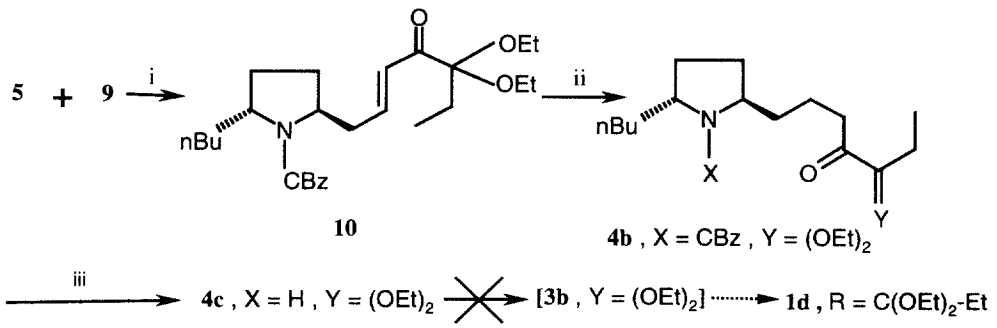


We have previously shown that *trans* disubstituted pyrrolidines **5** can be prepared from β-enamino esters by new reducing conditions using sodium polyacetoxyborohydride to give *trans* disubstituted pyrrolidines with good diastereomeric excess[6]. On the other hand, the retrosynthetic pathway involves the preliminary preparation of an ylid bearing the desired functionality. Phosphorane **6** was isolated in a 60% overall yield according to the method described by Chopard *et al*[7]. Unfortunately **6** reacted with amino aldehyde **5** only in 12% yield. This lack of reactivity was probabily due to the presence of asecond carbonyl function of **6**. We therefore tried then to mask this function by using a ketal protection. Direct condensation of phosphonate **7** and ketal ester **8** permitted to obtain keto phosphonate **9** in 75% yield[8].



A Wittig-Horner condensation between amino aldehyde **5** and phophonate **9** gave the cyclic enamino ketone **10** in 85% yield which was then catalytically reduced to keto pyrrolidine **4b** (X = CBz ; Y = $(OEt)_2$). Subsequent debenzylation over Pd/C occurred fairly giving the pyrrolidine **4c** (X = H , Y = $(OEt)_2$); this amino

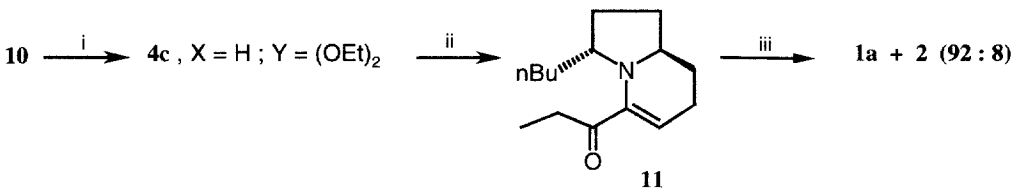
ketone could not be cyclized into iminium **3** according to our previous results[9]. In fact the steric hindrance of the ketal protective group did not permit the amino reductive annelation of **4c** (Scheme 1).



Reaction conditions : i) KHMDS, THF, 0 °C; ii) H_2 (1bar), PtO_2, MeOH, RT; iii) H_2 (1bar), Pd/C, MeOH, RT;

Scheme 1

We therefore directly reduced the enamino ketone **10** under debenzylating conditions, deprotected the ketal function by an acidic hydrolysis and then isolated bicyclic enamine **11** in 98 % overall yield.



Reaction conditions : i) H_2 (1bar), Pd/C, MeOH, RT; ii) TFA-H_2O (1:1) then K_2CO_3; iii) $NaBH_3CN$, HCl (1 eq.).

Scheme 2

Chemical reduction of bicyclic enamine **11** using sodium cyanoborohydride in acidic medium led in one step and with a good diastereoselectivity (d.e.=84%) to a mixture of indolizidines **237A** and **237B**.

After separation by chromatography on silica gel, enantiopure indolizidine **237A** was finally obtained in 84 % yield[10].

In conclusion we report here a highly enantioselective synthesis of natural indolizidine **237A** in 15 steps from (S)-pyroglutamic acid and in 8 % overall yield. For the first time, heterocyclic enamine was isolated as an intermediate for the formation of the indolizidine skeleton. The strategy is sufficiently versatile to merit investigation of its generality in the synthesis of all natural oxoalkyl indolizidines.

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10. Satisfactory analytical and spectral data were obtained for (3R,5S,8aR)-3-Butyl-5-(1-oxopropyl)-octahydroindolizine **1a**. $[\alpha]^{21}_{D}$ -128 (c=0.72, hexane). *Anal.* Calcd. for $C_{15}H_{27}NO_2$: C, 75.90; H, 11.46; N, 5.90. Found: C, 75.78; H, 11.35; N, 5.72.IR (neat) ν (cm^{-1})= 1710; 1450; 1380; 1160. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm)= 0.80 (t, 3H, *J*=7Hz); 1.00 (t, 3H, *J*=7Hz); 1.10-2.20 (m, 18H); 2.40-2.80 (m, 2H); 3.50-3.60 (m, 1H). ^{13}C NMR (64.25 MHz, $CDCl_3$) δ (ppm)=14.8, 23.4, 24.5, 27.8, 28.5, 29.0, 29.2, 30.3, 30.8, 32.1, 60.8, 61.2, 68.8, 210.0.