

A New Synthesis of Ant Venom Alkaloid : (3S,5R,8S)-3-Heptyl-5-methylpyrrolizidine

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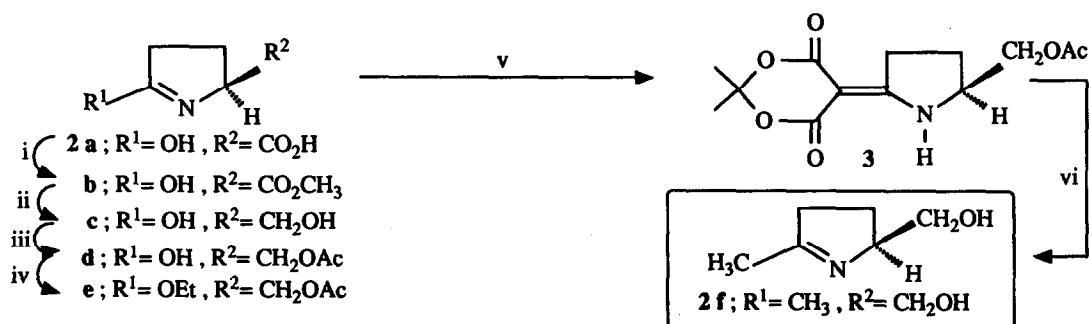
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Abstract : A highly enantioselective synthesis of (3S,5R,8S)- 3-heptyl-5-methylpyrrolizidine is described by using (S)-pyroglutamic acid as starting material.

Four syntheses of 3S,5R,8S xenovenine **1**, isolated from *Solenopsis xenovenenum* have already been published¹. We had previously shown^{1c} that the iminium reduction reaction allowed the introduction of the asymmetric carbon C-3 with a high diastereomeric excess (98%), but on the contrary no selectivity was observed during the reduction of the imine **2** ($R^1 = (\text{CH}_2)_3\text{-OH}$; $R^2 = \text{CH}_3$) to allow the carbon C-8 formation. In this paper we report a selective synthesis of *trans*-pyrrolidine **4a** (diastereomeric ratio : 83:17)² by reduction of imino alcohol **2f** using $\text{NaBH}(\text{OAc})_3$ ³ in 80% yield, the participation of the hydroxy group of **2f** directs delivery of hydride ion from the *si* face of the imino group by forming a boronate intermediate.

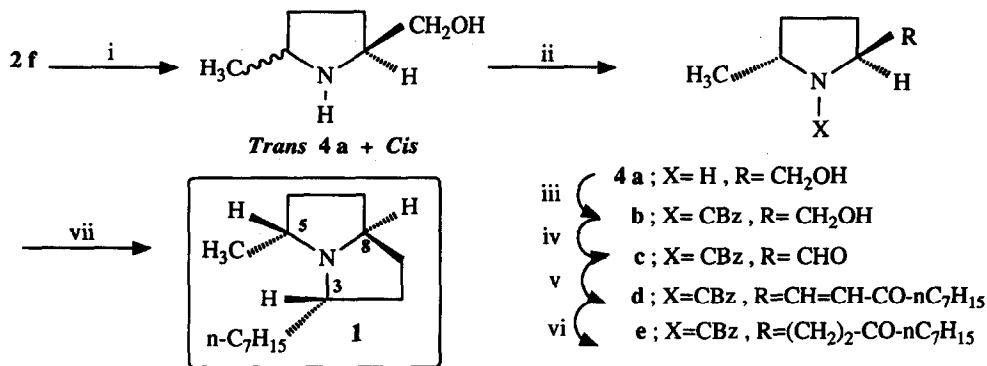
(S)-Pyroglutamic acid was esterified, reduced, and the resulting alcohol **2c** was then acetylated (Ac_2O -pyridine) to give the acetate **2d** in 65% overall yield (Scheme 1).



Reagents : i) MeOH , SOCl_2 ; ii) NaBH_4 , EtOH ; iii) Ac_2O , Pyr ; iv) Et_3OBF_4 , CH_2Cl_2 ; v) Meldrum's acid, $\text{Ni}(\text{acac})_2\text{CHCl}_3$ reflux; vi) HCl (5N), 60°C .

Scheme 1

Lactim ether **2e**, prepared by reaction of Meerwein salt with lactam **2d**, was condensed with Meldrum's acid to give compound **3** (63%)³ which, by hydrolysis and decarboxylation with 5N hydrochloric acid, led to the imino alcohol **2f** in 83% yield ($[\alpha]_{D}^{20} = +113$, $c = 1.00$, EtOH)(Scheme 1).



Reagents : i) $\text{NaHB}(\text{OAc})_3$, toluene; ii) diastereomeric separation⁴; iii) CBzCl (2 eq.), $\text{NaHCO}_3/\text{H}_2\text{O}$, 80°C , 48h; iv) $(\text{COCl})_2$, DMSO, $\text{N}(\text{Et})_3$, -78°C , 1h; v) $\text{Ph}_3\text{P}=\text{CH}-\text{CO}-\text{C}_7\text{H}_{15}$ **5**, toluene, 80°C , 48h; vi) H_2/PtO_2 , MeOH; vii) $\text{H}_2/\text{Pd}-\text{BaSO}_4$, MeOH^{1c}.

After reduction, the pure *trans*-amino alcohol **4a** ($[\alpha]_{D}^{25} = +2$, $c = 1.91$, EtOH) was isolated during the selective acylation of *cis* pyrrolidine (61%)⁴. Compound **4a** was N-protected as the carbamate **4b** (87%), and then oxidized by the Swern method⁶ leading to the amino aldehyde **4c**. Subsequent Wittig reaction⁵ of crude **4c** with stabilized ylid **5** provided the unsaturated ketone **4d** in 56% overall yield from **4c** (Scheme 2). Selective reduction of the double bond of **4d** over PtO_2 afforded the ketone **4e** in 85% yield ($[\alpha]_{D}^{22} = -49$, $c = 1.20$, CHCl_3), which, by reductive annelation gave the desired pyrrolizidine **1**^{1c}.

In summary, (S)-pyroglutamic acid is a good starting synthon for the synthesis of dialkylated azabicyclic alkaloids.

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