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Enantioselective Syntheses of *Monomorium minutum* Ant Venom Alkaloids : (5R)-2-(5-Hexenyl)-5-nonyl-3,4-dihydro-2H-pyrrole and (2R,5R)-2-(5-Hexenyl)-5-nonylpyrrolidine from (S)-pyroglutamic acid.

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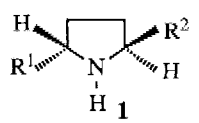
Key Words : (S)-pyroglutamic acid; cyclic imine formations; cyclic imine reductions.

Abstract : We describe enantioselective syntheses of 2,5-disubstituted pyrroline and pyrrolidine with unsaturated radical, starting from (S)-pyroglutamic acid.

2,5-Disubstituted pyrrolines and pyrrolidines characterize a large family of naturally occuring alkaloids, many of which display significant biological activity[1,2]. Termites in the genus *Reticulitermes* represent the largest source of food of ants in the genus *Monomorium*. When killing their prey, ants use a paralysing venom. The analysis of the chemical composition of the venom of european *Monomorium minutum* species and the determination of the quantity of each separate constituent were achieved using coupled GC-MS[3]. Three *trans* pyrrolidines (**1 a,b,c**), and two pyrrolines (**2 a,b**) were detected. Their absolute configurations have not been yet established, owing to the scarcity of the natural material.



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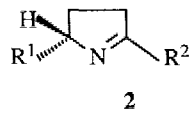


2

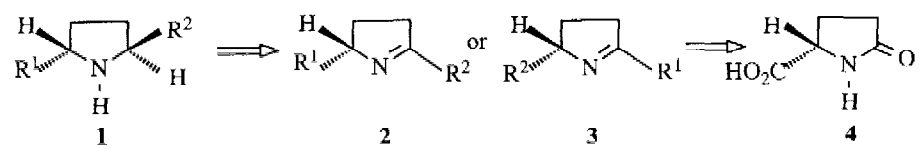
a ; R^1= $(CH_2)_7$-CH=CH_2, R^2= $(CH_2)_4$-CH=CH_2

b ; R^1= n-C_9H_{19}, R^2= $(CH_2)_4$-CH=CH_2

c ; R^1= n-C_9H_{19}, R^2= n-C_6H_{13}

Alkaloid	% in venom
1a	30
1b	59
1c	2
2a	5
2b	4

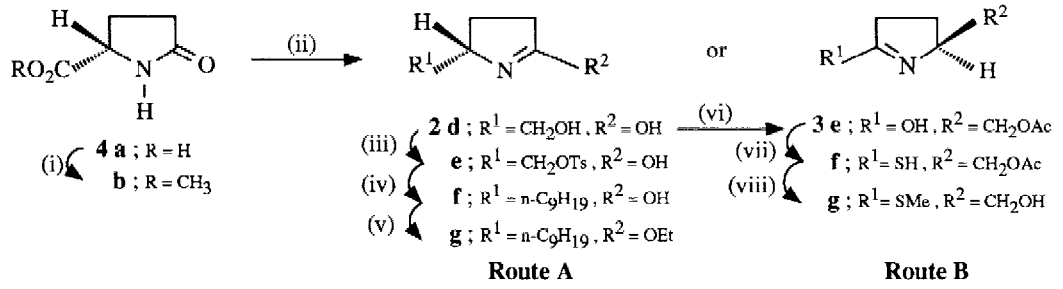
We have now developped general routes to optically active *trans*-2,5-dialkylated pyrrolidines and pyrrolines, especially with unsaturated substituents[4,5]. Our retrosynthetic approach includes the reduction of natural **2**, or unnatural **3** pyrrolines, starting from a readily available amino acid : (S)-pyroglutamic acid.



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

In this paper we describe the enantioselective preparations of the enantiomer (2R,5R)-2-(5-hexenyl)-5-nonyl-pyrrolidine **1b** which is the most important component of the venom and its biological precursor the (5R)-pyrroline **2b**. The two strategies reported introduce the nonyl substituent either

from the tosylate **2e**, or from the thiolactim ether **3g** (Scheme 1), to prepare respectively the natural (2R)-2-(5-hexenyl)-5-nonyl-3,4-dihydro-2H-pyrrole **2b** (**Route A** - Scheme 2), and the 5-hydroxymethyl cyclic imine **3h** (**Route B** - Scheme 3).

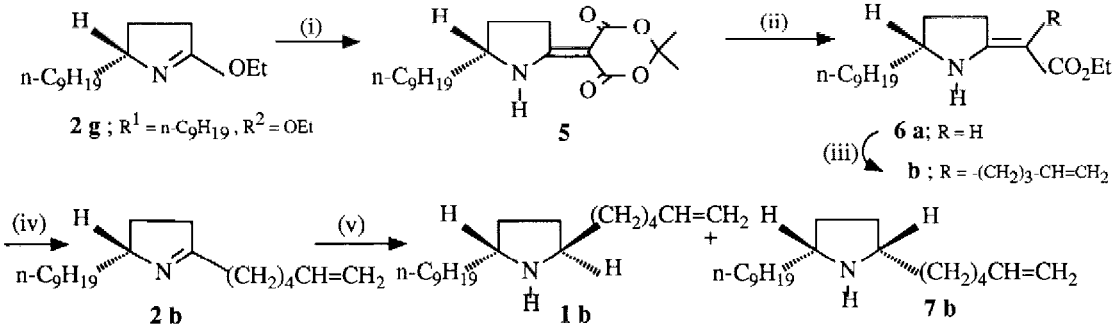


Reagents : (i) MeOH, $SOCl_2$; (ii) $NaBH_4$, EtOH; (iii) TsCl, $N(Et)_3$; (iv) $[n\text{-}C_8H_{17}]_2CuLi$; (v) Et_3OBF_4, CH_2Cl_2; (vi) Ac_2O, pyridine; (vii) Lawesson's reagent; (viii) CH_3I, then MeONa-MeOH.

Scheme 1

Route A : Syntheses of natural pyrroline **2b** and pyrrolidine **1b**.

(S)-Pyroglutamic acid is esterified, reduced, then the resulting alcohol **2d** is converted into the tosylate **2e**[6]. Lithium dioctyl cuprate reacts with compound **2e** to give (R)-5-nonylpyrrolidinone **2f** in 80% yield $[\alpha]^{22}_D$ +9 (c=0.91, EtOH). Lactim ether **2g** is prepared by reaction of lactam **2f** with Meerwein's salt (Et_3OBF_4) (Scheme 1), then condensed with isopropylidene malonate in chloroform with a catalytic amount of $Ni(acac)_2$ to give compound **5** in 84% yield $[\alpha]^{22}_D$ +17 (c=0.87, $CHCl_3$). A monodecarboxylating transesterification of β-enamino diester **5**, in EtOH at 230°C for 30 minutes leads to the (5R)-Z-ethyl (5-nonyl-2-tetrahydropyrrolidinylidene) acetate **6a** in 74% yield $[\alpha]^{22}_D$ -20 (c=2.12, $CHCl_3$). Afterwards the sodium salt of **6a** is generated by action of sodium hydride in toluene, then alkylated with 1-bromo-4-pentene leading to the C-alkylated β-enamino ester **6b** which is already decarboxylated using boric acid at 200°C to give the natural imine **2b**[7] in 30% yield (2 steps), $[\alpha]^{19}_D$ +36 (c=1.55, $CHCl_3$) (Scheme 2).



Reagents : (i) Meldrum's acid, $Ni(acac)_2$, $CHCl_3$; (ii) EtOH, 230°C; (iii) NaH, $Br\text{-}(CH_2)_3CH{=}CH_2$, toluene; (iv) H_3BO_3, 200°C; (v) $NaBH_4$, AcOH.

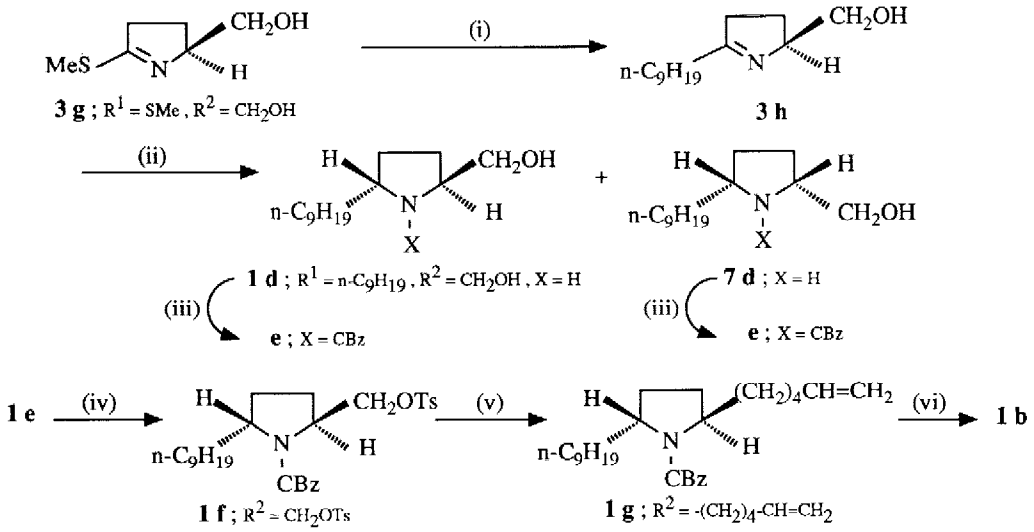
Scheme 2

Chemical reduction of imine **2b** with sodium borohydride in acetic acid leads to a mixture of *trans* and *cis*-pyrrolidines **1b** and **7b** (ratio 65/35 established by ^{13}C-NMR[8]) which is difficult to separate.

In continuation of our work on the synthesis of optically *trans*-2,5-dialkylated pyrrolidines we have developped a second strategy where we expected to provide better selectivity towards the reduction of imines and easier separation of pyrrolidines diastereoisomers.

Route B : Second synthesis of pyrrolidine **1b**.

The alcohol **2d**, resulting from the reduction of pyroglutamic acid is acetylated (Ac_2O-pyridine) to give the acetate **3e**, then followed by Lawesson's treatment, the cristalline thiolactam **3f** is obtained in 80% yield. Reaction of **3f** with methyl iodide in methylene chloride at room temperature followed by a sodium methoxide in methanol reaction gives the thioimidate **3g**[9] (Scheme 1). Then nonylmagnesium bromide reacts with thiolactim ether **3g** to lead to (S)-imino alcohol **3h** in 75% yield $[\alpha]^{20}_D$ +68 (c=1.35, $CHCl_3$). Reduction of imine **3h** using $NaBH(OAc)_3$ in toluene leads to a mixture of *trans* and *cis*-hydroxymethylpyrrolidines **1d** and **7d** (ratio 70/30 determined by G.C.) in 95% yield, followed by reaction with benzyl chloroformate at room temperature gives a mixture of carbamates **1e** and **7e**, a flash chromatography permits to isolate the pure *trans*-carbamate **1e** in 45% yield $[\alpha]^{20}_D$ -41 (c=1.08, $CHCl_3$). The benzyl methylene protons of compound **1e** appear as a well-resolved AB quartet consistent with a *trans* disposition of the two alkyl groups in which the methylene protons are nonequivalent. The *trans* carbamate **1e** is converted into the tosylate **1f** in 70% yield $[\alpha]^{20}_D$ -30 (c=1.04, $CHCl_3$), and reacts with lithium dipentenyl cuprate to afford the pyrrolidine carbamate **1g** in 91% yield $[\alpha]^{20}_D$ -50 (c=0.97, $CHCl_3$). Finally, treatment of **1g** with Me_3SiI gives the natural *trans* pyrrolidine **1b** in 66% yield $[\alpha]^{20}_D$ -3 (c=0.8, MeOH) (Scheme 3).



Reagents : (i) n-$C_9H_{19}MgBr$, ether-CH_2Cl_2; (ii) $NaBH(OAc)_3$, toluene; (iii) CBzCl, $NaHCO_3$, H_2O; (iv) TsCl, pyridine; (v) $[CH_2=CH-(CH_2)_3]_2CuLi$; (vi) Me_3SiI, $CHCl_3$.

Scheme 3

The diastereoisomeric excess observed for the pyrrolidine formation may be attributed to the participation of the hydroxy group which directs delivery of hydride ion from the *si*-face of the imino group by forming a boronate complex[10] to give the *trans*-2,5-dialkylpyrrolidine **1d**.

In conclusion, we describe the first enantioselective synthesis of 2,5-disubstitued pyrroline with a terminal double bond and the second preparation of optically active *trans*-2,5 disubstituted pyrrolidine with an unsaturated substituent which will permit, in the future, to establish the absolute configurations of the natural products.

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