Highly Diastereoselective Synthesis and NMR Characterization of Natural Indolizidine Alkaloids

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A diastereoselective, general and versatile access to disubstituted indolizidines is described. The nmr conformational analysis permits us to establish preferred conformations.

Numerous natural bicyclic azaheterocycles such as 5-alkyl, or 3,5-dialkylindolizidines have been identified as venomous constituents of ant species or neotropical frogs. The disconnective analyses starting from pyrrolidine or piperidine derivatives show that the last asymmetric carbon is formed after reduction of the iminium salts **I** or **II**.
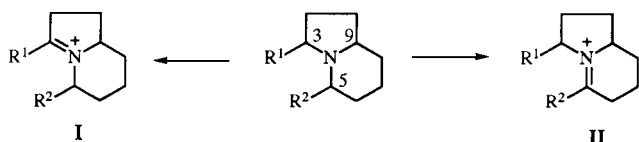
We are developing a general enantioselective synthesis of such alkaloids from (*S*)-pyroglutamic acid as a common source of chiral pyrrolidines which induce in fact the iminium **II** formation. The accesses to such intermediates have been obtained from ketones **8** which have been prepared by oxydation of 2-pyrrolidine-ethanol **7a** and subsequent Wittig reaction with stabilized yields [1-4] (Scheme 1).

Scheme 1
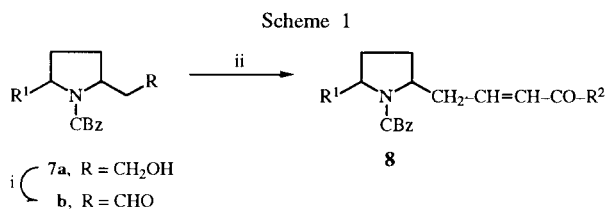
Reaction conditions: i) PCC, CH$_2$Cl$_2$; ii) Ph$_3$P=CH-CO-R^2, THF reflux.

Herein we report the six-membered ring formation for the synthesis of natural indolizidines: (-)-(5*R*,9*R*)-gephyrotoxine 167B (**4a**, R^1 = H, R^2 = *n*-Pr), (+)-(3*R*,5*S*,9*S*)-monomorine I (**1a**, R^1 = *n*-Bu, R^2 = Me), and (-)-(3*R*,5*R*,9*R*)-gephyrotoxine 223AB (**4b**; R^1 = *n*-Bu, R^2 = *n*-Pr).

Due to the iminium instability, this intermediate should be immediately quenched after formation by reduction; the suitable reagent is hydrogen according to the CBz amino protective group. The indolizidine syntheses starting from α-unsaturated ketones **8** need the

four steps of the following sequence: (i) C=C reduction, (ii) nitrogen deprotection, (iii) iminium formation, (iv) C=N$^+$ reduction.

A clear study of diastereoselective iminium reduction requires two non competitive first step reactions and requires the previous C=C reduction to obtain ketones **9** (Scheme 2).

Scheme 2
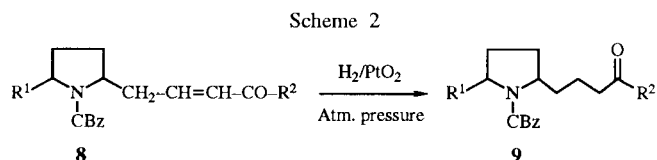
The iminium reduction of compounds **6a**, **6b**, and **5** is highly diastereoselective leading exclusively to gephyrotoxine 167B **4a**, 223AB **4b**, and monomorine I **1a** contrary to the literature [5].

Scheme 3
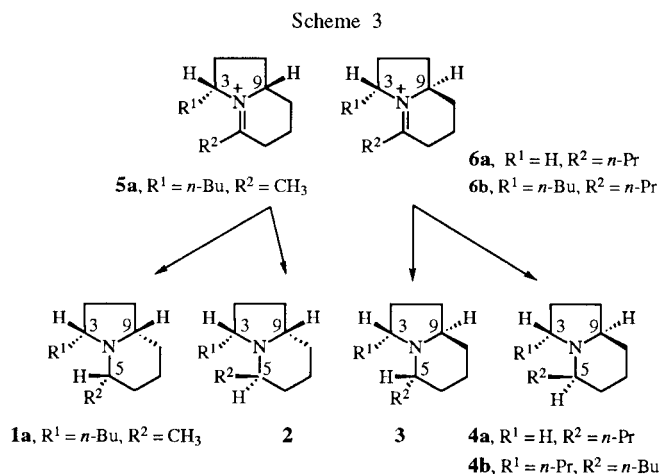
In fact we did not observe the C-5 epimer formation. These results are based on nmr analysis.

The complete analysis of the ^{1}H and ^{13}C nmr data respectively obtained at 500.13 and 125.76 MHz was performed for compounds **4a** and **1a**. While the ^{1}H and ^{13}C spectra of gephyrotoxine **4a** show narrow signals as expected for small molecules, the monomorine **1a** spectra

show significantly broadened signals. The complete assignments of the spectra of **4a** were obtained by use of $\delta^1H\delta^1H$ and $\delta^1H\delta^{13}C$ two dimensional correlations. For compound **1a**, the short transverse relaxation times of the protons did not allow the observation of all the correlations in the COSY type 2D experiment and the HOHAHA 2D experiment was also used. In the δ^1H-$\delta^{13}C$ 2D contour plot some correlations were missing. Thus for several protons only approximate positions, within ± 0.05 ppm, have been evaluated from the integration of the various regions. The data are collected in Table 1.

Scheme 4

Gephyrotoxines **4a** and **4b**

Table 1

^1H and ^{13}C NMR data for compounds **4a** and **1a** δ(ppm) with respect to tetramethylsilane

Site	5R,9R-gephyrotoxine		3R,5S,9S-monomorine	
	4a		**1a**	
	^1H	^{13}C	^1H	^{13}C
1	1.80	30.64	1.62	30.4*
	1.42		1.43	
2	1.73	20.52	1.8	29.8
	1.64 anti		1.4	
3	3.25 syn	51.62	2.45	63.1
	1.97 anti			
5	1.88	63.83	2.2	60.4
6	1.70 eq	30.94	1.49	35.9
	1.13 ax		~1.3	
7	1.74 eq	24.80	1.68	25.0
	1.23 ax		1.25	
8	1.76 eq	31.07	1.7	30.9*
	1.18 ax		~1.3	
9	1.82	65.17	2.05	67.4
5–α	1.61	37.00	1.13	23.0
	1.28			
5–β	1.38	19.18		
	1.28			
5–γ	0.89	14.58		
3–α			1.64	39.7
			~1.3	
3–β			~1.15	29.4
3–γ			1.27	23.3
3–δ			0.88	14.2

*The assignments of these two signals are reversed with respect to those previously published [6].

For all the compounds under study four different forms must be considered due to nitrogen inversion or ring inversion as shown in Schemes 4 and 5. Scheme 4 corresponds to gephyrotoxins **4a** and **4b**.

The spectroscopic data for gephyrotoxine 167B **4a** (R_1 = H_3) are in fair agreement with the occurence of a highly
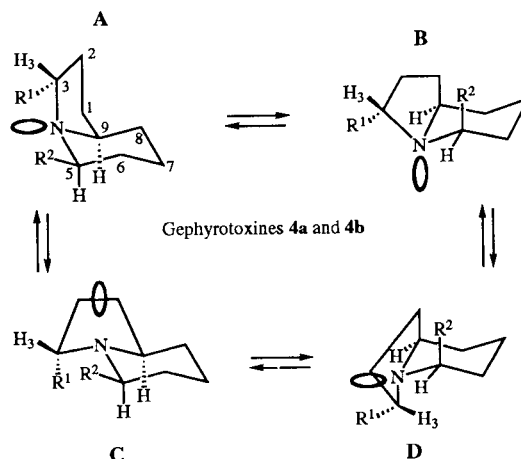
preferred form **C** drawn in Scheme 4. H-3, the pro S proton at C-3, is strongly deshielded by the effect of the proximate nitrogen lone pair of electrons. For the pro R proton H-3' and both tertiary H-5 and H-9 protons situated in similar antiparallel positions with respect to the nitrogen lone pair, the chemical shifts are smaller and the signals are observed within a very narrow range. The multiplet patterns observed for the H-3 protons are in accordance with a preferred envelop conformation of the five membered ring (N, C-9, C-1, and C-2 nearly coplanar and C-3 in endo position) which results in a dihedral angle circa 80° between the bonds C-3, H-3 and C-2, H-2 anti. Thus H-3 gives a triplet of doublet: $^3J_{H-3,H-2syn} = {}^2J_{H-3,H-3'}$ 8.8 Hz and $^3J_{H-3,H-2anti} = 2.2$ Hz and the proton H-3' gives a quadruplet with equal coupling constants (J = 8.8 Hz) for the two vicinal and for the geminal interactions. The multiplicity of the signal of the shielded axial H-6 proton, quadruplet of doublet with three coupling interactions equal to 12.9 Hz and only one small coupling of 3.7 Hz, agree well with the equatorial position of the chain at C-5. Finally the chemical shift calculated for the carbon C-7 by use of characteristic increments [7] (27.4 ppm) does not significantly differ from the measured value.

The second gephyrotoxine 223 AB **4b** bears a new alkyl substituant at C-3. With the *trans* disposition of the two alkyl substituants the two forms **B** and **D** appear highly unfavorable due to strong 1,3 steric interactions while the two forms **A** and **C** resulting from nitrogen inversion must be considered. In both forms the proton H-3 undergoes significantly the deshielding effect of the nitrogen electrons pair. In form **A** the protons H-5 and H-9 undergo the same deshielding effect while in form **C** they are too remote from the nitrogen lone pair. The narrow signals observed in ^{13}C and ^1H spectra show that rapid exchange occurs between both forms. As a result the proton H-3 exhibits the characteristic deshielding previously observed in gephyrotoxine **4a** while the protons H-5 and H-9 resonate at intermediate positions being more

shifted than in gephyrotoxine **4a** but less deshielded than the proton H-3 in both compounds. The data [8] are in accordance with previous publications [5].

As previously outlined, monomorine **1a** gave unexpected broad signals in both ^{13}C and ^{1}H spectra. The ^{13}C spectrum recorded at 50.3 MHz instead of 125.6 MHz at ambiant temperature shows narrow signals. Contrarily the broadening was significantly enhanced for both nuclei by lowering the temperature to 223 K. From these observations it might be inferred that an equilibrium occurs between different forms at a rate which does not result in rapid averaging.

Scheme 5

Monomorine **1a**
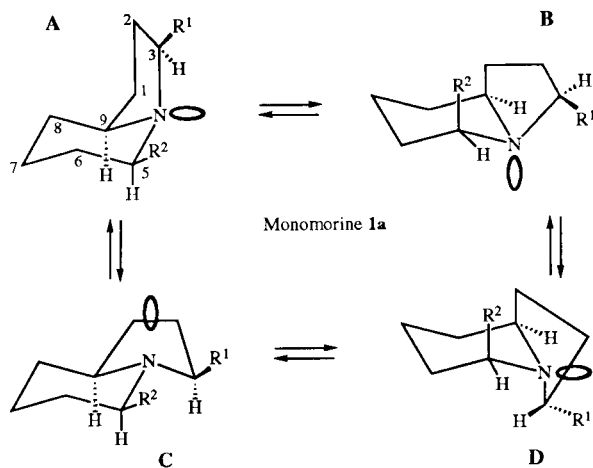
Among the four geometric patterns of the Scheme 5 one, **D**, seems to be very unfavorable due to the *trans* diaxial disposition of the bonds C-9, C-1 and N, C-3 and one, **C**, with three bonds C-9, C-1 C-5, CH$_3$ and N, C-3 in the equatorial position would have been thought to be highly favored. Nevertheless, the shieldings of the three protons H-3, H-5, H-9 are in between the shieldings observed in compound **4a** for the proton which undergoes the effect of the electrons lone pair of the nitrogen atom and the shieldings of the more remote tertiary protons. Thus forms **A** and **B** might also significantly contribute to the equilibrium. However it might be observed that the signal of C-7 is only slightly broadened. This carbon undergoes nearly the same through space interactions in **A** and **C** and is thus expected to have in both cases the same chemical shift while in **B** it loses two 1-3 H,H diaxial interactions and is thus expected to be significantly shielded. Then the lack of intense broadening for the signal of C-7 indicates a small contribution of form **B**. For all the other carbons of the six membered ring which give strongly broadened signals, changes in chemical shifts are expected between forms **A** and **C**. The exchange phenomenom is thus essentially related to the inversion of the nitrogen atom. In the five membered ring, C-1 is more

affected than C-2. As regards the alkyl substituants, the signals of the first carbons namely the methyl carbon at C-5 and the α carbon of the butyl chain are also significantly enlarged.

These results are in contradiction with those of Sonnet *et al.* [6] who envisaged only one form. Nevertheless the exchange phenomenom is certainly rapid on the nmr time scale when the spectra are recorded at 20 MHz and thus more difficult to demonstrate.

In conclusion annelation of cyclic amino ketones by intramolecular reductive amination is a good and highly diastereoselective route to disubstituted indolizidines. Conformational analysis by nmr shows that preferred conformations depend on the degree of substitution of these compounds but are always in accordance with the nitrogen inversion. Monosubstituted indolizidines present only one preferred conformation but a second alkyl chain induces an equilibrium between two forms due to interactions with hydrogens in C-5 and C-9 positions.

EXPERIMENTAL

The nmr spectra were recorded either at 200 MHz (Bruker AC 200), at 250 MHz (Bruker WM 250) or at 500 MHz (Bruker AM 500). The ^{1}H chemical shifts are reported in ppm from an internal standard tetramethylsilane. The ^{13}C chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.1 ppm). For the two-dimensional δ ^{1}H, δ ^{13}C correlation experiments, the standard Bruker programs were used. The dihedral angles for the preferred conformation of gephyrotoxine **3a** were obtained by use of Alchemy III minimiser program. The ir spectra were recorded on a Philips PU 9700 spectrometer. Analytical tlc were performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (230-400 mesh) and Merck aluminium oxide 90 neutral were used for column chromatography.

General Method for Preparation of Cyclic Amino Ketones **9**.

A solution of 2.8 mmoles of ethylenic ketone **8** in 30 ml of methanol was hydrogenated at atmospheric pressure over platinium oxide (0.1 g). After filtration, the solution was evaporated under reduced pressure and the crude product was chromatographed over silica gel.

(*S*)-1-Benzyloxycarbonyl-2-(4-oxoheptyl)pyrrolidine (**9**) (R^1 = H, R^2 = *n*-C$_3$H$_7$).

This compound was obtained in a yield of 95%, eluent: diethyl oxide/pentane 2:8; ir (neat): ν 1720, 1700, 1620, 1490 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.90 (t, 3H, J = 7 Hz), 1.20-2.05 (m, 10H), 2.35 (t, 4H, J = 7 Hz), 3.30-3.55 (m, 2H), 3.75-3.90 (m, 1H), 5.15 (s, 2H), 7.30-7.40 (m, 5H); ^{13}C nmr (deuteriochloroform): δ 13.5, 17.0, 20.0, 23.2, 29.9, 33.4, 42.2, 44.4, 46.2, 57.1, 66.2, 127.6, 128.2, 136.8, 154.6, 210.6; [α]$^{22}_D$ = -38.4° (c = 1.98, ethanol).

Anal. Calcd. for C$_{19}$H$_{27}$NO$_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.62; H, 8.64; N, 4.44.

(2*R*,5*S*)-1-Benzyloxycarbonyl-2-(4-oxopentyl)-5-butylpyrrolidine (**9**) (R^1 = *n*-C$_4$H$_9$, R^2 = CH$_3$).

This compound was obtained in a yield of 80%, eluent: diethyl oxide/pentane 1:1; ir (neat): ν 1775, 1680, 1590, 1490 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.88 (t, 3H, J = 7 Hz), 1.05-2.60 (m, 15 Hz), 2.15 (s, 3H), 3.40-4.40 (m, 3H), 5.00-5.30 (m, 2H), 7.20-7.60 (m, 5H); ^{13}C nmr (deuteriochloroform): δ 14.1, 20.5, 22.6, 28.5, 29.5, 29.8, 35.2, 35.5, 43.4, 58.3, 58.8, 66.5, 127.8, 128.4, 137.1, 155.4, 208.8; [α]$^{20}_D$ = +0.8° (c = 1.52, chloroform).

Anal. Calcd. for C$_{21}$H$_{31}$NO$_3$: C, 73.00; H, 9.05; N, 4.05. Found: C, 72.74; H, 9.14; N, 4.29.

(2R,5R)-1-Benzyloxycarbonyl-2-(4-oxoheptyl)-5-butylpyrrolidine (9) (R^1 = n-C$_4$H$_9$, R^2 = n-C$_3$H$_7$).

This compound was obtained in a yield of 90%, eluent diethyl oxide/pentane 2:8; ir (neat): ν cm^{-1}1700, 1680, 1580, 1490; ^{1}H nmr (deuteriochloroform): δ 0.80-1.00 (m, 6H), 1.10-1.40 (m, 6H), 1.40-1.75 (m, 6H), 1.75-2.05 (m, 4H), 2.15-2.55 (m, 4H), 3.60-3.85 (m, 2H), 4.95-5.20 (dd, 2H, J = 14 Hz and J = 8 Hz), 7.35 (br s, 5H); ^{13}C nmr (deuteriochloroform): two conformers are observed, δ 13.7 and 14.0, 17.2, 20.5, 22.5 and 22.6, 26.6, 27.6, 28.7, 32.1 and 32.2, 33.5, 42.3 and 42.4, 44.7, 57.3, 57.7, 58.2, 66.3, 127.8 and 128.4, 137.0, 154.1 and 154.3, 210.7 and 211.1; [α]$^{20}_D$ = -52.5° (c = 0.63, dichloromethane).

Anal. Calcd. for C$_{23}$H$_{35}$NO$_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.68; H, 9.35; N, 3.62.

General Method for Preparation of Substituted Indolizidines 1 and 4.

A solution of **2** mmoles of ethylenic ketone **9** in 20 ml of anhydrous methanol was hydrogenated during 4 hours at atmospheric pressure over palladium on activated carbon (10% Pd) (0.1 g). After filtration, the solution was evaporated without reduced pressure and the crude product was chromatographed over aluminium oxide.

(5R,9R)-5-Propylindolizidine 4a (gephyrotoxine 167B).

This compound was obtained in a yield of 70%, eluent diethyl oxide/pentane 1:9; ir (neat): ν 2940, 2920, 2850, 2760, 2580, 1440 cm^{-1}; ^{1}H-^{13}C nmr: *cf* Table 1; [α]$^{20}_D$ = -115.0° (c = 1.16, dichloromethane).

Anal. Calcd. for C$_{11}$H$_{21}$N: C, 78.97; H, 12.65; N, 8.37.

Found: C, 78.83; H, 12.45; N, 8.34.

(3R,5S,9S)-3-Butyl-5-methylindolizidine 1a (monomorine I).

This compound was obtained in a yield of 50%, eluent diethyl oxide/hexane 1:9; ir (neat): ν 2800, 2720, 2585, 1455 cm^{-1}; ^{1}H-^{13}C nmr: *cf* Table 1; [α]$^{20}_D$ = +35.8° (c = 1.08, hexane).

Anal. Calcd. for C$_{13}$H$_{25}$N: C, 79.93; H, 12.90; N, 7.17. Found: C, 79.92; H, 12.65; N, 7.37.

(3R,SR,9R)-3-Butyl-5-propylindolizidine 4b (gephyrotoxine 223AB).

This compound was obtained in a yield of 85%, eluent diethyl oxide/pentane 2:8; ir (neat): ν 2960, 2940, 2860, 2800, 1460 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.84 (t, 3H, J = 7 Hz), 0.88 (t, 3H, J = 7 Hz), 1.00-1.95 (m, 20H), 2.30-2.40 (m, 2H), 3.20-3.35 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 14.2, 14.5, 19.1, 23.0, 24.5, 25.3, 26.2, 29.0, 29.8, 30.5, 31.9, 33.5, 57.0, 58.7, 59.5; [α]$^{20}_D$ = -102.9° (c = 1.12, hexane).

Anal. Calcd. for C$_{15}$H$_{29}$N: C, 80.64; H, 13.09; N, 6.27. Found: C, 80.37; H, 13.15; N, 6.36.

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[8]   The characteristic ^{1}H nmr data for gephyrotoxine **4b** are: 3-H 3.28 ppm, 5-H and 9-H 2.37 ppm.