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ASYMMETRIC SYNTHESIS XII[1] : STEREOCONTROLLED ELECTROPHILIC-NUCLEOPHILIC α,α'-SUBSTITUTION OF THE PYRROLIDINE RING.

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Abstract - The synthesis of 2-cyano-5-oxazolopyrrolidine 3, a chiral pyrrolidine synthon, is described. Conditions were established that permitted sequential chemoselective reactions at the C-2 aminonitrile (electrophilic substitution) and at the C-5 aminoether (nucleophilic substitution) centres of 3. A stereospecific decyanation of the alkylated aminonitrile allowed the formation of the first asymmetric centre at C-2 of the pyrrolidine ring. The first enantioselective synthesis of (+)-(S)-trans-2-heptyl-5-ethyl-pyrrolidine 9, a component of the venom of the ant Solenopsis punctaticeps served as an example of the method. Both enantiomers of cis-2-heptyl-5-ethyl pyrrolidine 13 were obtained from the minor diastereomers 7 and 8 which were formed on reaction of oxazolidines 5a and 5b with Grignard reagents. The stereochemical outcome of the substitution reactions is discussed. In addition, full data on the synthesis of ant venon alkaloid (+)-(S)-trans-2-heptyl-5-butyl-pyrrolidine and its cis stereomer are given.

Introduction

One of the most significant recent developments with regard to the total synthesis of optically active natural products has been the exploitation of synthons derived from the chiral pool[2].

In continuation of our program aimed at the asymmetric synthesis of alkaloids[3] we were interested in the preparation of pyrrolidine alkaloids[4].

In general, two main routes have been used to prepare this class of compounds in the racemic form : (a) synthesis from a preformed pyrrolidine ring[5], and (b) synthesis from appropriately functionalized acyclic precursors[6]. Most of the previous synthetic attempts in the first category have involved functionalization of the α-carbon atom via a carbanion or an iminium ion.

Following our studies in the piperidine alkaloid series, our strategy was based upon a pyrrolidine synthon 3 which combines masked (umpolung) and potential iminium reactivities in the same molecule (Scheme 1). However, Robinson-Schöpf condensation of succinaldehyde with phenylglycinol in the presence of KCN, according to our previous experiments[7a], was unsuitable for the production of the desired synthon[7b].

In a preliminary communication[1] we reported a satisfactory synthesis of the pyrrolidine synthon 3 and its application in the preparation of (+)-(S)-trans-2-heptyl-5-butyl-pyrrolidine[8] 16 and its stereomer 21. Full experimental and spectral data on theses derivatives are given in this paper.

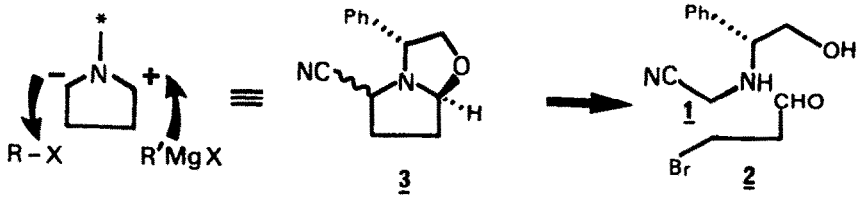
In view of the continued interest in dialkyl pyrrolidines as constituents of fire ant venom of the genera Solenopsis and Monomorium[9], we have extended the usefulness of our methodology to the first synthesis of (+)-(S)-trans-2-heptyl-5-ethyl-pyrrolidine 9, a component of the venom of Solenopsis punctaticeps[10,11].

By means of modern NMR techniques and X-ray crystallographic analyses we gained some insight into the stereochemical outcome of the key reaction steps in our work, i.e. the substitution reactions adjacent to the heterocyclic nitrogen atom.

Results and discussion

The condensation of (-)-(R)-phenylglycinol (219 mmol) with sodium bisulfite (219 mmol) and formaldehyde (219 mmol) in water (30mL) followed by the addition of KCN (219 mmol) afforded aminonitrile 1 (Scheme 1) in high yield (> 90%). Stirring of 1 in refluxing CH_2Cl_2 (1 mmol/mL) with freshly prepared 3-bromopropionaldehyde 2 (1.2 equiv.) for 1 h led to an intermediate oxazolidine which could not be isolated free of solvent due to its tremendous tendency to polymerize but which could be characterized by its 400 MHz ^1H NMR spectrum[12]. Finally the oxazolidine was cyclised *in situ* to 3 *via* the aminonitrile anion. Nearly equal amounts of diastereomeric compounds 3 were obtained (40 %) from (-)-phenylglycinol after purification by flash chromatography on silica gel. Our strategy consisted of metalation of the aminonitrile function followed by reaction with an electrophile, and finally reductive removal of the cyano group, which proved to be a valuable technique for achieving masked iminium reactivity.

Scheme 1



Treatment of 3 (diastereomeric mixture) with LDA, TMEDA at -70°C and reaction of the resultant anion with ethyl bromide gave 4a (Scheme 2) in 74% yield as a 1:1 diastereomeric mixture. In the same way alkylation with heptyl bromide led to 4b (72% ; 1:1 mixture). Each of the two diastereomers 3 (separated by flash chromatography), when subjected to alkylation afforded the same mixture 4a or 4b, providing evidence for the stereorandom character of the reaction.

The next problem to be tackled was the reductive decyanation of compounds 4 to 5. Indeed it was necessary to find reaction conditions which were selective for the removal of the cyano group without opening the oxazolidine ring. $Zn(BH_4)_2$ reduction[7a] provided 5 in an unattractive 10% yield together with unidentified polar material. A satisfactory alternative involved reduction with lithium metal in liquid NH_3. Clean formation of decyanated compounds 5 could be achieved through treatment with a modest excess of lithium (2-3 equiv.) in liquid NH_3/THF/-EtOH (100:10:1) at -40°C for 5 min. This key step produced, after flash column chromatography, derivatives 5 in ∿ 60% yield accompanied by 20% of recovered starting material (i.e. 75% conversion).

A remarkable stereospecificity was observed in this reaction, for the ^{13}C NMR spectra of 5a and 5b exhibited signals from only one single diastereomer.

The natural dialkyl pyrrolidines have a trans relative configuration and many syntheses suffer from lack of stereoselectivity (e.g. 60:40 in the case of alkylation of formamidines[5f]). It was expected in our case that the possibility existed for the control of the stereochemistry at C-5 via a nucleophilic substitution. Indeed such a reaction implies a mechanism in which there is prior formation of an iminium ion by opening of the oxazolidine ring, and addition of the nucleophile selectively occurs at the less hindered face of the molecule.

According to the postulated mechanism a heptyl side chain was introduced at C-5 of 5a on reaction with $C_7H_{15}MgBr$ giving a 72:28 mixture of trans:cis epimers (> 95 %). The trans compound 6 and its cis isomer 7 were easily separable by flash chromatography in quantitative yield (silica gel, EtOAc-hexane 1:4, 1% NH_4OH).

The trans to cis ratio did not vary when different solvents and reaction temperatures were used (Et_2O THF, $PhCH_3$ from -78°C to reflux).

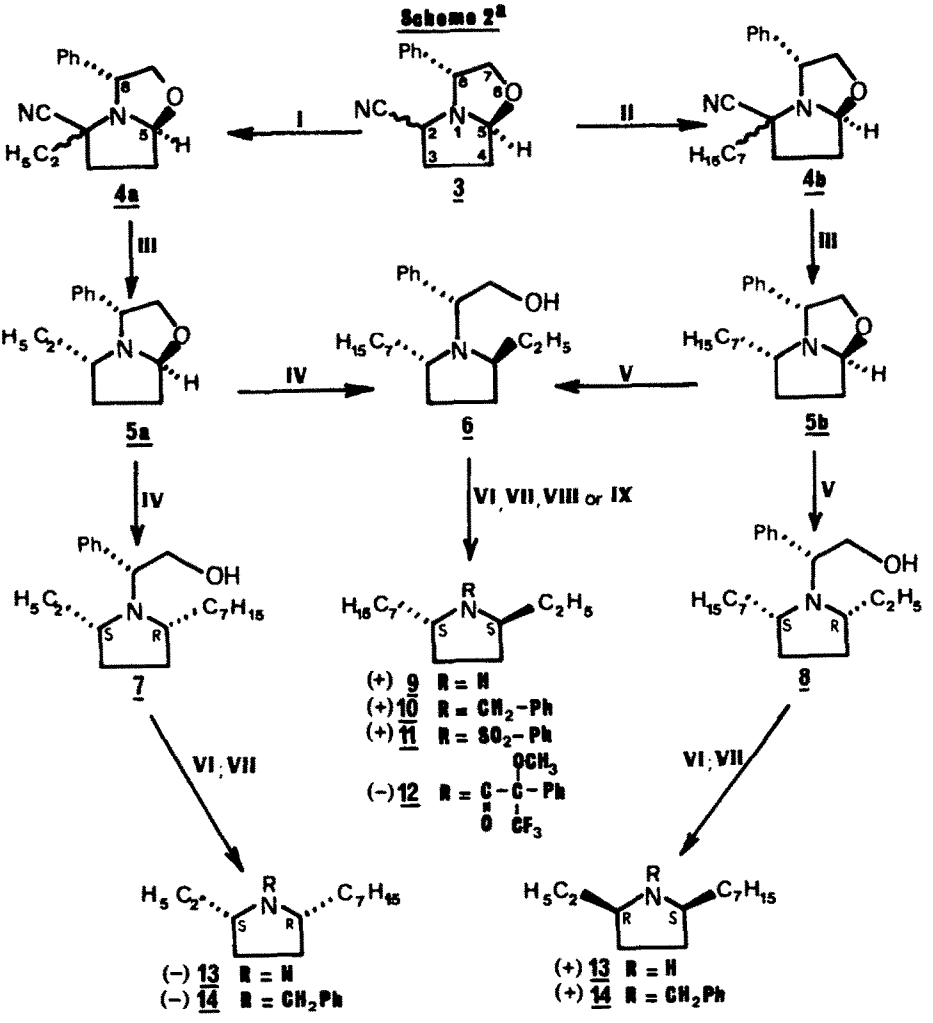
Conversely nucleophilic addition of EtMgBr at C-5 of 5b produced compound 6 accompanied by the cis isomer 8 which, as expected, appeared to be diastereomeric with the previously prepared cis derivative 7.

Under hydrogenolytic conditions the chiral auxiliary attached to the nitrogen of 6, 7 and 8 was cleaved to afford the corresponding secondary amines (+)-9, (+)-13 and (-)-13 quantitatively.

The trans 2,5 relative stereochemistry of 6 and 9 was verified by the method of Hill and Chan[13] on the basis of the appearance in the NMR spectrum of the benzylic protons of derivative 10 centered at δ 3.72ppm (AB quartet, J = 10 Hz). This observation was in agreement with our recent results for the 2-heptyl-5-butyl pyrrolidine series and led us to conclude that 7 and 8 belong to the cis series. The enantiomeric purity of 9 was assessed by examination of the ^1H, ^{13}C and ^{19}F NMR spectra of the Mosher's amide[14] derivative 12 and showed that hydrogenolytic cleavage of the chiral appendage of pure stereomer 6 gave 9 without appreciable racemization. Due to the low optical rotation values in this series and non-reproducible measurements on secondary amines, the benzenesulfonyl derivative 11 was prepared as the standard.

Structures of 2,5-dialkylpyrrolidines isolated from ants in minute amounts have been determined by gas chromatography-mass spectrometry techniques and have been confirmed by synthesis of the racemic material. For these reasons the optical rotation and absolute stereochemistry of the natural isomers have not been reported in most cases. It was thus necessary to assign the absolute configuration of our synthetic materials. X-ray crystallographic analysis of 4a showed a trans H-5, H-8 relationship[15] but compounds 5a and 5b did not provide crystals which were suitable for X-ray studies. Instead, the absolute stereochemistry of 5a and 5b was ascertained by the extensive use of modern multipulse NMR techniques. A 2D shift correlation COSY experiment[16] provided the assignments of the ^1H resonances. All ambiguities were removed by performing complementary experiments, such as heteronuclear ^{13}C-H correlation[17] or "long range" double quantum filtered COSY[18] which emphasizes very small couplings.

Scheme 2[a]



[a] Reagents : (I, II) LDA 1.15 equiv., TMEDA 1.8 equiv., THF, -78°C, 30 min. ; RX 2-3 equiv., -78°C, 2h. (III) Li 3 equiv., NH_3 liq , THF, EtOH, -40°C, 5 min. (IV, V) RMgBr, ether, r.t., 30 min (VI) 10% Pd/C, H_2, AcOH, 45 psi, 12h. (VII) EtMgBr 1.15 equiv., Et_2O, r.t. 40 min, PhCOCl, r.t., 1h. ; LAH, Et_2O, Δ, 4h. (VIII) Ref. 8. (IX) (-) MTPACl, 1.6 equiv., CH_2Cl_2, DMAP cat., r.t. 12h.

We made use of the "Phase Sensitive 2D NOESY"[19] experiment in our fine study of the stereochemistry of product 5a (Figure 1). This technique demonstrates in one plot a general view of all spatial proximities. It also obviates those artefacts often encountered in the 1D "NOE difference" method[20] which are due to small bursts of the decoupler in the spectrum. On the 2D surface, small effects having correct sign, symmetric structure and regular peak shape may be interpreted confidently. This technique allowed us to make assignments of the vicinal proton resonances (such as 7 and 7') which would be rather speculative if based on a consideration of shielding effects or J-coupling values.

The most important items concerning the stereochemistry of 5a are illustrated in Figure 2 which shows two distinct 2D experiments, with only one half of each drawn, these halves being joined by their diagonal $\Omega_1 = \Omega_2$. Each individual surface is symmetric around this diagonal, and this picture thus

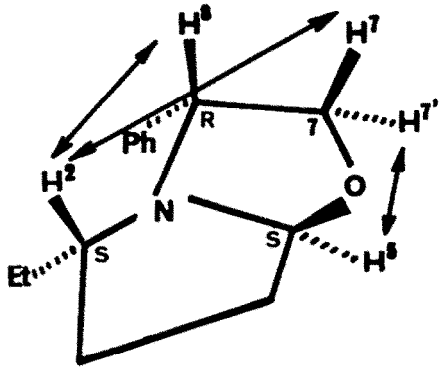


Fig. 1 : NOE effects in 5a

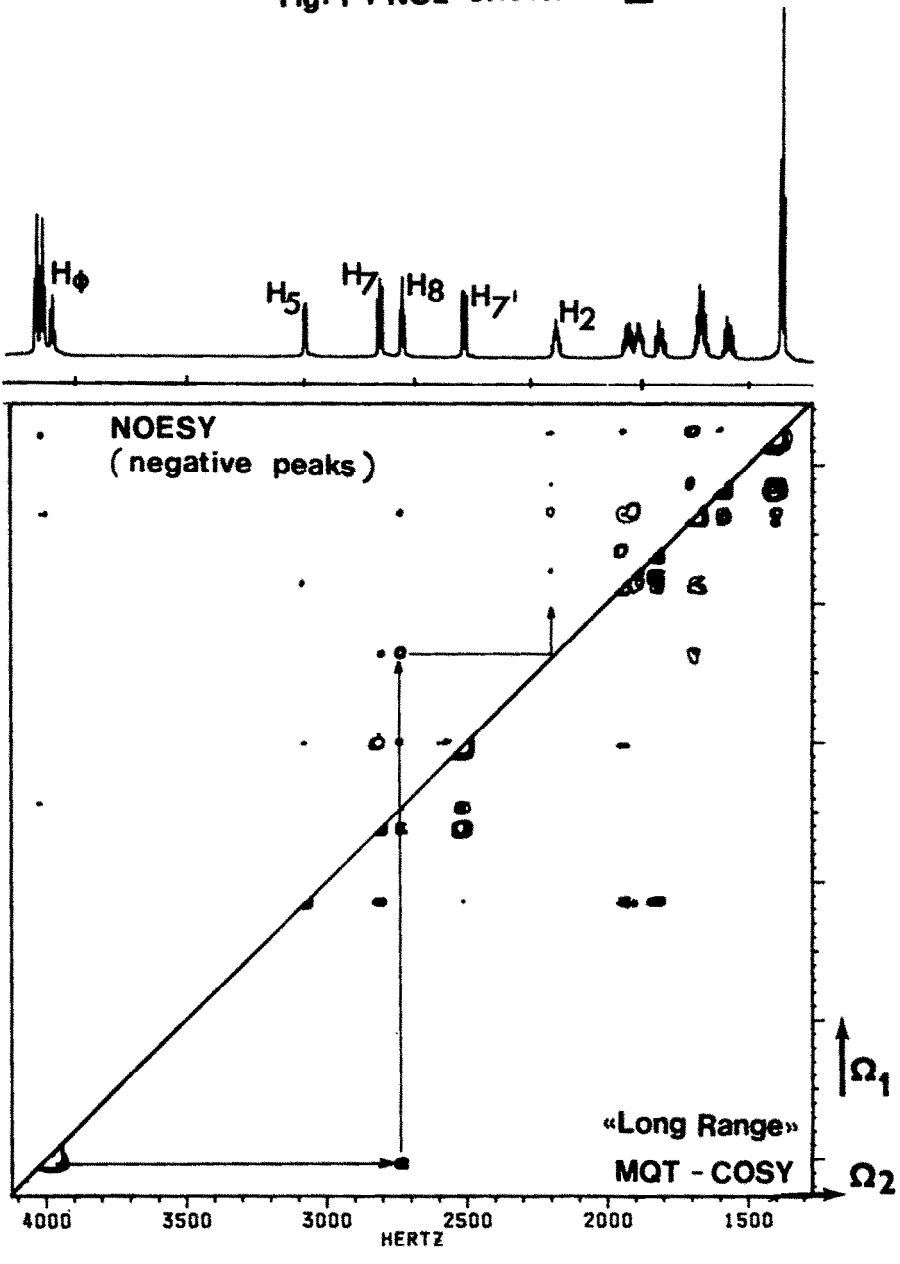
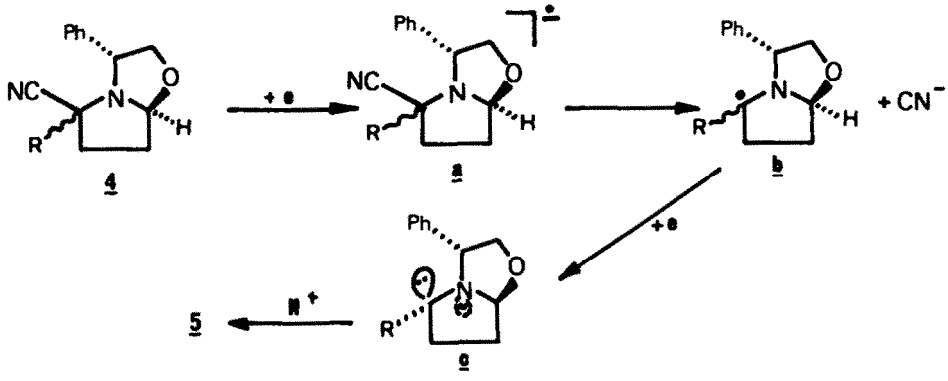


Figure 2 : 2D NMR experiments for compound 5a

contains all the relevant information. The lower right half of the map is a long-range double quantum filtered COSY which reveals, among other correlations, a cross-peak connecting the phenyl "ortho" protons and the H-8 of the heterocycle. This confirms the ^{13}C-^{1}H correlation-based assignment for the H-8, H-7 and H-7' resonances. The upper left half of the map shows the phase sensitive NOESY experiment. All peaks are negative with respect to the diagonal as is expected with a small molecule ("extreme narrowing conditions"). The off-diagonal peak at the intersection of the previously determined H-8 chemical shift column and of the H-2 row reveals that H-2 and H-8 mutually relax through their dipolar interaction ; H-8 and H-2 are thus close to each other in space. Moreover, H-2 and H-5 also manifest a dipolar interaction with one specific proton of the H-7, H-7' pair. This gives the endo/exo assignment of H-7 and H-7', H-7 being "near" H-2 and H-7' "near" H-5 and confirms the exo position of H-5. A rapid confirmation of this assignment is possible by use of 1D NOE difference technique. In particular the spatial relationship of H-8 and H-6 is clearly demonstrated. The results of this experiment are given in Figure 4. Presaturation of the H-2 resonance of either 5a or 5b resulted in enhancement of the signals for H-8 protons only.

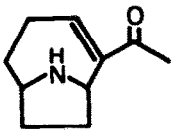
Scheme 3



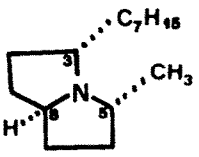
In conclusion it is possible to assign the 2S, 5S, 8R absolute configuration for compound 5a (Figure 1) and consequently that of the series of cis and trans-dialkyl-2,5-pyrrolidines synthesized during this work (Scheme 2).

The remarkable stereoselection observed in the key transformation of 4 to 5 requires some explanation. It can be assumed that the crucial C-H bond formation occurs via the protonation of an intermediate carbanion c (Scheme 3) formed by a stepwise two-electron reduction[21] (4 → a → b → c). Carbanion c is presumed to be tetrahedral and to exist in the thermodynamically preferred orientation where the alkyl substituent lies in the convex face of the molecule and the two electron pairs (the nitrogen lone pair and the carbanion) adopt a 1,2-anti relationship. This would appear to be the preferred structure from both steric and electronic considerations thus providing an unequivocal rationalization to the observed stereospecificity. This result is apparently in contrast with the alkylation of the anion of 3 which led to a mixture of stereomers 4. This contradiction can be rationalized if one considers that the intermediate deprotonated α-aminonitrile adopts a planar delocalized structure which reacts with alkylating agents from both faces.

Figure 3



23 Anatoxin-a



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Conclusion

Starting from synthon 3 this four step procedure constitutes the basis of a short, general method for the enantioselective synthesis of the natural trans-2,5-dialkyl pyrrolidines. Our initial work was confined to simple compounds in order to study the stereochemical outcome of the electrophilic or nucleophilic α-substitution of the pyrrolidine ring. Further studies are in progress to explore the application of this synthetic methodology to the preparation of more complex systems such as anatoxin-a[22] 23 and a number of pyrrolizidine alkaloids such as 3-heptyl-5-methyl-pyrrolizidine 24[23] (Figure 3).

TABLE - Specific rotations of 2,5-dialkylpyrrolidines and their derivatives

Trans	Cis	N	C-2	C-5	% trans/cis	$[\alpha]_D^{20}$ ($CHCl_3$)
(+) 6		Ph-CH-CH_2OH	C_7H_{15}	C_2H_5		+ 6° C = 1.6
(+) 9		H	C_7H_{15}	C_2H_5		+ 4° C = 2.0
(+) 10		Ph-CH_2	C_7H_{15}	C_2H_5		+ 82° C = 0.74
(+) 11		Ph-SO_2	C_7H_{15}	C_2H_5		+ 62° C = 0.87
12			C_7H_{15}	C_2H_5		- 39° C = 0.75
	7	Ph-CH-CH_2OH	C_2H_5	C_7H_{15}	74/26	- 64° C = 1.1
	8	Ph-CH-CH_2OH	C_7H_{15}	C_2H_5	72/28	- 3° C = 0.4
	(-) 13	H	C_2H_5	C_7H_{15}		- 5.5° C = 0.14
	(+) 13	H	C_7H_{15}	C_2H_5		+ 7° C = 0.56
	(-) 14	Ph-CH_2	C_2H_5	C_7H_{15}		- 22.5° C = 0.4
	(+) 14	Ph-CH_2	C_7H_{15}	C_2H_5		+ 23° C = 0.46
(+) 15		Ph-CH-CH_2OH	C_7H_{15}	C_4H_9		+ 40° C = 1.0 (MeOH)
(+) 16		H	C_7H_{15}	C_4H_9		+ 10° C = 1.1
(+) 17		Ph-CH_2	C_7H_{15}	C_4H_9		+ 81° C = 0.37
(+) 18		Ph-SO_2	C_7H_{15}	C_4H_9		+ 58° C = 1.1 (CH_2Cl_2)
19			C_7H_{15}	C_4H_9		- 28° C = 2.6
	20	Ph-CH-CH_2OH	C_7H_{15}	C_4H_9	72/28	- 21° C = 0.62
	21	H	C_7H_{15}	C_4H_9		0° C = 1.3 (MeOH)
	22	Ph-CH_2	C_7H_{15}	C_4H_9		0° C = 1.4

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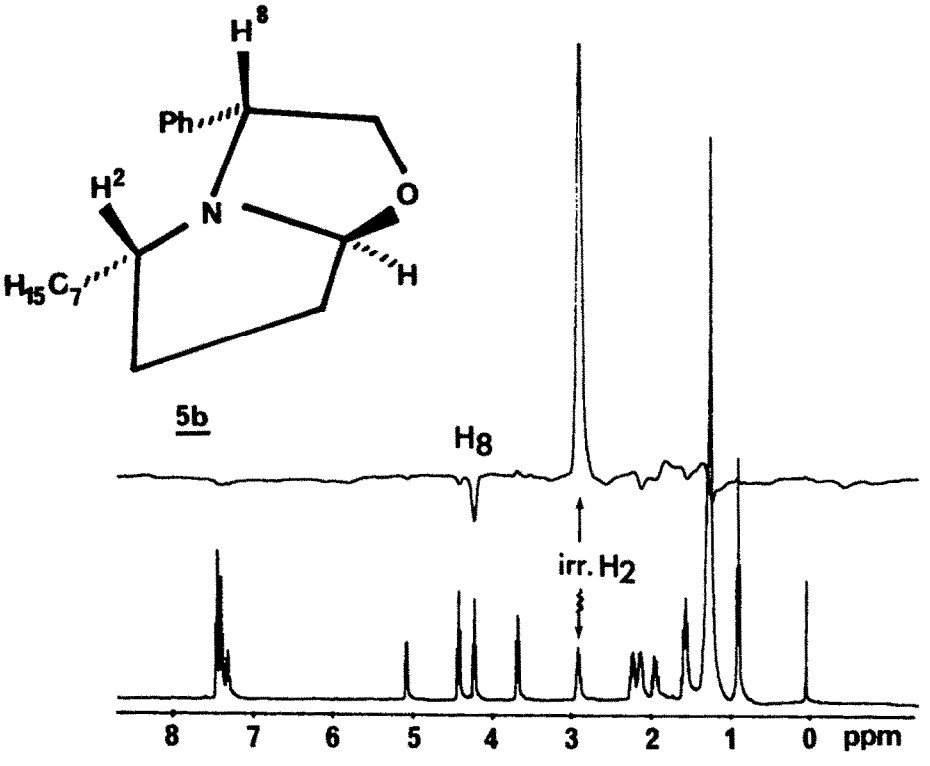

Figure 4 : 1D NOE difference NMR for compound 5b

Experimental section

THF was distilled either from LAH or sodium benzophenone ; CH_2Cl_2 was distilled from P_2O_5 ; all amine reagents were refluxed with and distilled from CaH_2. Heptyl and ethyl bromides were obtained from commercial suppliers and were distilled before use. The flash chromatography technique as described by Still[24] was employed. Thin layer chromatography was performed on commercial silica gel glass plates that were developped by immersion in 5% phosphomolybdic acid in ethanol 95%. IR spectra were recorded neat on a Perkin Elmer model 297 instrument. Optical rotations were determined in $CHCl_3$, MeOH or CH_2Cl_2 (as indicated) using a Perkin Elmer 243 polarimeter. Mass spectral data, recorded on AEI MS-50 (E.I. spectra) AEI MS-9 (C.I. spectra) or KRATOS MS-80 (High resolution mass spectra) instruments are reported in the form : m/z (intensity relative to base peak = 100). ^1H NMR were recorded on a IEF[25] or Bruker 400 MHz spectrometers in $CDCl_3$. Chemical shifts are expressed in ppm downfield from TMS (the ^1H NMR data are presented in the order : δ value of signal, peak multiplicity (s, singlet ; d, doublet ; t, triplet ; q, quartet ; m, multiplet), coupling constant in Hz and integrated number of protons. ^{19}F NMR were recorded on a Bruker instrument (56 MHz) with TFA used as external standard. ^{13}C spectra were obtained at 50.2 MHz on a Bruker WP 200 and the chemical shifts are reported relative to $CDCl_3$ (77,14 ppm). For all compounds investigated ^{13}C resonances were assigned by the SEFT technique[26].

Determinations of Nuclear Overhauser effects by the NOEDIF method were performed with the aid of Aspect 2000 microprograms which allowed direct accumulations of difference FID's. Samples were prepared as 10% (w/w) solutions in $CDCl_3$, degassed by several freeze-pump-thaw cycles and sealed in NMR tubes. The NOESY spectrum of fig. 3 was recorded with the usual 90°-t_1-90°-tm-90° pulse sequence, with tm randomly varied around 1s and by choosing a phase cycle which yields a pure absorption spectrum. The data matrix was 512 x 1024pts, zero filled to 1024 x 1024 before FT.

The MQT-COSY spectrum of the same fig. is a modification of the usual 90°-t_1-90°-90° sequence. The double quantum filter was preferred to normal COSY, since it yields in-phase diagonal and correlation peaks, which appear sharper. We also inserted a 500ms delay before and after the last pulse cluster ; during this echo-like part of the sequence, the system may evolve under very small J-couplings ($\sim$ 0.1 Hz). The matrix size was 512 x 1024pts zero filled to 1024 x 1024 before FT. The surface is shown in magnitude but phase sensitive pattern could also have been obtained with usual TPPI method[19].

N-cyanomethylphenylglycinol (1). A mixture of sodium bisulfite (22.7g, 219mmol), water (30 mL) and an aqueous solution of 37% of formaldehyde (17.8mL, 219mmol) was stirred for 45 min at 70°C. (-)-R-phenylglycinol (30.0g, 219mmol) in methanol (30mL) was added, and the reaction mixture heated at 60°C for 45 min, cooled to room temperature and treated with potassium cyanide (14.2g, 219 mmol) in water (30mL). Stirring continued for 3 h. Several extractions with methylene chloride followed by usual work up afforded > 91% of 1 as a white crystalline product after filtration on silica gel (6:4 EtOAc-Hexane as eluent) : m.p. 36-37°C (ether-hexane) ; IR (nujol) 3500-3200, 2920, 2860, 2230, 1450, 1200, 1050 ; ; ^{1}H NMR : δ 2.55 (s. brd. 2H) 3.33 (d, J = 17.8, 1H), 3.67 (d, J = 17.8, 1H), 3.62 (t, J = 10, 1H), 3.82 (dd, J = 10, 4, 1H), 4.06 (dd, J = 10, 3, 1H), 7.43 (m, 5H) ; ^{13}C NMR : δ 34.6, 63.3, 66.7, 117.4, 127.4, 127.7, 178.1, 128.6, 137.8 ; MS, E.I.: 145 (100), 106 (100), 104 (33), 77 (50) ; C.I. : 177 (MH^+ 100) 150 (38) ; $[\alpha]_D^{20}$ - 220° (c : 3.0, $CHCl_3$). Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16 ; H, 6.86 ; N, 15.97 ; O, 9.08. Found : C, 68.20 ; H, 6.80 ; N, 15.82 ; O, 9.15.

2-cyano-5-oxazolopyrrolidine (3). To a 2.75M solution of freshly prepared 3-bromopropionaldehyde [27] (102mmol, 37mL) in methylene chloride was added slowly 15.0g (85.2mmol) of 1 in 30mL of methylene chloride and ca 5g of 5A° molecular sieves. The resulting yellow colored mixture was stirred for 1 h at reflux and cooled to r.t. After filtration through celite, solvent was evaporated to ca 30mL and repeatedly diluted with dry THF (2 x 50mL) and concentrated to 30mL. The solution was transferred with a canula to a 0.3M THF solution of LDA (153mmol) and the reaction mixture stirred at -78°C for 2h. Careful quenching with a saturated solution of NH_4Cl aq. followed and the reaction temperature allowed to raise to 0°C. Methylene chloride was added and the organic layer was washed with brine dried and condensed. SiO$_2$ column flash chromatography of the crude (1:4 EtOAc-Hexane as eluent) afforded 40% of 3 as a 1:1 mixture of diastereoisomers easily separable for characterization (although unnecessary).

3 (faster eluting isomer) pale yellow oil : IR (film) : 3050, 2970, 2940, 2930, 2220, 1600, 1450, 1375, 1175, 1125, 1070, 1025, 885cm^{-1} ; ^{1}H NMR : δ 2.22 (m, 2H), 2.38 (m, 2H), 3.71 (dd, J = 8.0, 7.0, 1H), 4.15 (dd, J = 6.0 3.0, 1H), 4.64 (t, J = 7.0, 1H), 4.71 (t, J = 8.0, 1H), 5.14 (dd, J = 6.0, 3.0, 1H), 7.35-7.52 (m, 5H) ; ^{13}C NMR : δ 29.4, 31.2, 53.2, 64.6, 75.3, 98.0, 119.6, 126.3, 128.6, 127.4, 141.3 ; MS, EI : 214 M^+ (4), 184 (33), 131 (35), 104 (100) ; C.I. : 215 (MH^+ 99), 188 (100) ; H.R.M.S. calcd for $C_{13}H_{14}N_2O$, m/z 214.1106, found 214.1124. $[\alpha]_D^{20}$ -142° (c : 1.9, $CHCl_3$).

3 (slower eluting isomer) : Pale yellow oil : IR (film) : 3050, 2975, 2940, 2860, 2220, 1600, 1450, 1370, 1165, 1125, 1070, 1035, 1025, 1015, 890cm^{-1} ; ^{1}H NMR : δ 2.16 (m, 2H), 2.33 (m, 2H), 3.55 (dd, J = 8.5, 7.0, 1H), 3.79 (d, J = 7.0, 5.4, 1H), 4.18 (t, J = 7.0, 1H), 4.37 (dd, J = 8.5, 7.0, 1H), 5.00 (dd, J = 4.6, 2.4, 1H), 7.23-7.42 (m, 5H) ; ^{13}C NMR : δ 27.3, 29.9, 55.9, 69.1, 73.1, 97.6, 120.0, 126.1, 127.3, 128.5, 140.3. MS, E.I : 214 M^+ (4) 184 (33), 131 (35), 104 (100) ; C.I. : 215 (MH^+ 70) 188 (100) ; H.R.M.S. calcd for $C_{13}H_{14}N_2O$, m/z 214.1106 ; found 214.1124. $[\alpha]_D^{20}$ - 64.5° (c : 2.7, $CHCl_3$).

Alkylation of 3 : To a solution of 11.5mmol of lithium diisopropylamide in 100mL THF containing 18mmol of TMEDA at -78°C was added 3 (10mmol, mixture of diastereoisomers) in 50mL of THF over 5 min. The reaction mixture was stirred at -78°C for 30 min. Ethyl bromide (25mmol) was then added and stirring continued for 2h. The reaction was quenched at this temperature with a saturated solution of aqueous NH_4Cl (2mL/mmol). After usual work-up a 74% yield of 1:1 diastereomeric ratio was obtained. The alkylation was repeated with heptylbromide to yield 4b (72%, 1:1 diastereomeric ratio).

4a (faster eluting isomer) : oil : IR (film) 3070, 2975, 2950, 2875, 2225, 1610, 1455, 1385, 1145, 1120, 1060, 1020, 910cm^{-1} ; ^{1}H NMR : δ 0.97 (t, J = 7.4, 3H), 1.59, 1.74, 2.03, 2.19, 2.36, 2.49 (m, 12H), 3.62 (dd, J = 8.5, 7.4, 1H), 4.54 (t, J = 7.4, 1H), 4.69 (t, J = 8.5, 1H), 5.09 (dd, J = 6.0, 3.8, 1H), 7.26-7.36 (m, 5H) ; ^{13}C NMR : δ 8.8, 28.9, 32.6, 36.9, 63.9, 67.0, 75.4, 98.3, 126.1, 127.1, 128.5, 142.0 ; MS, E.I : 242 M^+ (2) 213 (57), 131 (69), 104 (100), 93 (28), 77 (11) ; C.I. : 243 (MH^+ 67), 216 (100) ; H.R.M.S. calcd for $C_5H_{18}N_2O$ m/z 242.1419 ; found 242.1405. $[\alpha]_D^{20}$ -164° (c : 0.69, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35 ; H, 7.49 ; N, 11.56 ; O, 6.60 ; found : C, 74.22 ; H, 7.59 ; N, 11.41 ; O, 6.65.

4a (slower eluting isomer) : White cristalline m.p. 55°C (acetone-hexane) : IR (nujol) : 3030, 2980, 2940, 2880, 2225, 1600, 1445, 1375, 1235, 1205, 1155, 1080, 1058, 940cm^{-1} ; ^{1}H NMR : δ 1.10 (t, J = 7.4, 3H), 1.70, 1.93, 2.14, 2.29 (m, 6H), 3.50 (t, J = 8.0, 1H), 4.29 (t, J = 7.5, 1H), 4.55 (t, J = 7.5, 1H), 5.08 (d, J = 3.8, 1H), 7.24-7.42 (m, 5H) ; ^{13}C NMR : δ 10.5, 27.4, 29.2, 35.2, 61.3, 66.8, 74.3, 98.2, 126.3, 127.4, 128.8, 141.8 ; MS, E.I : 242 M^+ (2) 213 (34), 131 (57), 104 (100), 93 (44), 77 (19) ; C.I. : 243 (MH^+, 20), 216 (100) ; H.R.M.S. calcd for $C_{15}H_{18}N_2O$ m/z 242.1419 ; found 242.1430. $[\alpha]_D^{20}$ - 45° (c : 0.50, $CHCl_3$). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35 ; H, 7.49 ; N, 11.56 ; O, 6.60. Found : C, 74.33 ; H, 7.22 ; N, 11.51 ; O, 6.55.

4b (faster eluting isomer) : oil : IR (film) : 3040, 2940, 2900, 2840, 2200, 1590, 1460, 1370, 1140, 1070, 1020, 920cm^{-1} ; ^{1}H NMR : δ 0.85 (t, J = 7.4, 3H), 1.19, 1.53, 1.69, 2.03, 2.20, 2.37, 2.49 (m, 16H), 3.62 (dd, J = 8.4, 7.0, 1H), 4.53 (t, J = 7.4, 1H), 4.68 (t, J = 8.4, 1H), 5.08 (dd, J = 6.0, 3.4, 1H), 7.26-7.34 (m, 5H) ; ^{13}C NMR : δ 13.9, 22.5, 24.5, 28.9, 29.1, 29.4, 31.5, 37.5, 39.7, 64.1, 66.5, 75.4, 98.3, 121.2, 126.3, 127.2, 128.6, 142.2 ; MS E.I. : 311 (15), 283 (10), 213 (4), 184 (23), 131 (92), 103 (100), 93 (75), 91 (45) ; C.I.: 313 (MH$^+$, 97) 286 (100) ; H.R.M.S. for $C_{20}H_{28}N_2O$ m/z 312.2202, found 312.2180 ; Anal. calcd for $C_{20}H_{28}N_2O$: C, 76.88 ; H, 9.03 ; N, 8.97 ; O, 5.12 ; found : C, 76.80 ; H, 9.03 ; N, 8.77 ; O, 5.43. $[\alpha]_D^{20}$ - 121° (c : 0.69, $CHCl_3$).

4b (slower eluting isomer) : oil : IR (film) : 3040, 2970, 2945, 2870, 2240, 1605, 1460, 1380, 1240, 1150, 1030, 975cm^{-1} ; ^{1}H NMR : δ 0.86 (t, J = 7.4, 3H), 1.25, 1.60, 1.84, 1.98, 2.05, 2.30 (m, 16H), 3.50 (t, J = 8.2, 1H), 4.29 (t, J = 7.6, 1H), 4.57 (t, J = 7.0, 1H), 5.05 (d, J = 4.2, 1H), 7.16-7.41 (m, 5H) ; ^{13}C NMR : δ 22.6, 26.3, 29.0, 29.3, 29.4, 29.7, 31.7, 34.4, 35.7, 61.3, 66.0, 74.3, 98.1, 122.4, 126.3, 127.4, 128.7, 141.6 ; MS E.I. : 312 M$^+$ (17) 283 (13), 282 (18), 213 (69), 184 (11), 131 (35), 121 (10), 104 (100), 93 (35), 91 (18) ; C.I. : 313 (MH$^+$ 35) 286 (100) ; H.R.M.S. calcd for $C_{20}H_{28}N_2O$, m/z 312.2202, found 312.2180. $[\alpha]_D^{20}$ - 64° (c : 0.88, $CHCl_3$).

Decyanation of 4a and 4b : To a solution of 4a (1.21g, 5mmol, diastereomeric mixture) in 150mL of liq. NH_3, 10mL of THF and 3mL of absolute ethanol was added 105mg (15mmol) of lithium metal. The solution was stirred for 5 min at -40°C. Solid ammonium chloride was then carefully added and ammonia allowed to evaporate, while hexane was added periodically. Finally water was added and the aqueous layer was extracted with hexane and then dichloromethane. The organic layer was dried, concentrated and flash chromatographed on silica gel (1:8 EtOAc-Hex) to give 5a in 60% yield together with 20% of unreacted starting material.

5a colorless oil : IR (film) : 3030, 2970, 2940, 2870, 1605, 1460, 1375, 1270, 1150, 1100, 1080, 1030, 885cm^{-1} ; ^{1}H NMR : δ 0.84 (t, J = 7.4, 3H), 1.31, 1.64, 1.91, 2.15 (m, 6H), 2.82 (m, 1H), 3.62 (dd, J = 8.5, 6.0, 1H), 4.17 (dd, J = 7.0, 6.0, 1H), 4.36 (dd, J = 8.5, 7.0, 1H), 5.01 (dd, J = 5.6, 2.6, 1H), 7.19-7.37 (m, 5H) ; ^{13}C NMR : δ 10.3, 28.6, 29.9, 68.1, 72.9, 98.8, 126.6, 128.1, 143.1 ; MS E.I. : 217 M$^+$ (52) 188 (100), 148 (26), 104 (95), 91 (23), 69 (96) ; C.I. : 218 (MH$^+$ 100) 98 (46) ; $[\alpha]_D^{20}$ - 55° (c : 0.88, $CHCl_3$).

Aminonitrile 4b was treated and purified as above to give :

5b colorless oil : IR (film) : 3040, 2940, 2900, 2840, 1590, 1450, 1365, 1140, 1100, 1054, 1030, 905cm^{-1} ; ^{1}H NMR δ 0.86 (t, J = 7.4, 3H), 1.22, 1.53, 1.91, 2.09, 2.18 (m, 16H), 2.87 (m, 1H), 3.63 (dd, J = 8.0, 6.4, 1H), 4.17 (t, J = 6.4, 1H), 4.36 (t, J = 8.0, 1H), 5.01 (dd, J = 6.0, 2.4, 1H), 7.23-7.38 (m, 5H) ; ^{13}C NMR : δ 14.2, 22.7, 26.5, 29.4, 29.9, 30.2, 31.86, 31.87, 36.2, 66.9, 68.2, 73.0, 99.0, 126.7, 126.9, 128.5, 143.4 : MS E.I. 287 M$^+$ (22), 258 (16), 188 (100), 148 (18), 104 (67), 77 (51) ; C.I. : 288 ; (MH$^+$ 100) 168 (75) ; $[\alpha]_D^{20}$ - 28.5° (c : 0.96, $CHCl_3$) ; Anal. calcd for $C_{19}H_{29}NO$: C, 79.39 ; H, 10.17 ; N, 4.87 ; O, 5.57. Found : C, 79.05 ; H, 10.37 ; N, 4.78 ; O, 5.74.

1-(2-phenylethanol)-2,5-dialkyl pyrrolidines (6), (7) and (8) To a solution of the decyanated product 5a (344mg, 1,6mmol) in 12mL of ether at room temperature was added dropwise a 2M solution of EtMgBr in Et_2O (3mmol, 1.5mL). The reaction mixture was stirred at room temperature for 30 min. Aqueous NH_4Cl solution was then added. The aqueous layer was extracted twice with ether and CH_2Cl_2, dried and concentrated to afford the crude product which was purified through a silica gel column chromatography using Hex-EtOAc 4:1, + 1% NH_4OH as eluant. The yield was quantitative and the diastereomeric ratio of the two products was calculated to be 72:28 favouring the trans (more polar) isomer 6 over the cis one 7 (less polar).

$C_7H_{15}MgBr$ addition to 5b afforded the same trans product 6 and the antipode of the formerly obtained cis 8 in comparable yields and diastereomeric excess.

6 oil : IR (film) : 3400, 3030, 2950, 2930, 2850, 1460, 1460, 1380, 1360, 1140, 1050, 1030cm^{-1} ; ^{1}H NMR : δ 0.81 (t, J = 7.4, 3H), 0.88 (t, J = 7.0, 3H), 1.25, 1.54, 1.71 (m, 18H), 3.05 (m, 1H), 3.11 (m, 1H), 3.67 (dd, J = 9.6, 6.0, 1H), 3.79 (dd, J = 9.6, 5.0, 1H), 3.73 (dd, J = 9.0, 6.0, 1H), 7.25-7.34 (m, 5H) ; ^{13}C NMR : δ 11.2, 14.1, 22.7, 27.1, 28.8, 29.3, 29.4, 29.9, 31.9, 60.7, 62.1, 63.6, 127.4, 128.0, 128.9, 129.2, 140.6 ; MS E.I. : 288 (9), 286 (100), 218 (11), 168 (8), 91 (12) ; C.I. : 318 (MH$^+$, 100), 300 (36), 198 (56) ; $[\alpha]_D^{20}$ + 6° (c : 1.6, $CHCl_3$). Anal. calcd for $C_{21}H_{35}NO$: C, 79.44 ; H, 11.11 ; N, 4.41 ; O, 5.04 ; found : C, 79.20 ; H, 11.01 ; N, 4.12 ; O, 5.15.

7 oil : IR (film) 3400, 2940, 2900, 2840, 1450, 1400, 1370, 1050, 1030 ; ^{1}H NMR : δ 0.82 (t, J = 7.4, 3H), 0.90 (t, J = 6.8, 3H), 1.31, 1.55, 1.70, 1.80 (m,

18H), 2.84 (m, 1H), 3.02 (m, 1H), 3.67 (dd, J = 9.8, 4.6, 1H), 3.88 (t, J = 9.8, 1H), 3.96 (dd, J = 9.8, 4.6, 1H), 7.19-7.31 (m, 5H) ; ^{13}C NMR : δ 11.1, 14.2, 22.8, 26.8, 29.1, 29.4, 29.9, 30.1, 30.8, 32.0, 36.4, 59.2, 61.8, 63.8, 64.7, 127.8, 128.3, 129.1, 137.3. MS E.I. : 284 (100), 218 (13), 98 (59), 91 (34) ; C.I. : 318 (MH^+, 100), 300 (39), 286 (21) ; $[\alpha]_D^{20}$ - 64° (c : 1.1, $CHCl_3$).

8 oil ; IR (film) : 3440, 3055, 2930, 2860, 2850, 1450, 1375, 1200, 1100, 1060, 1025cm^{-1} ; ^{1}H NMR : δ 0.88 (t, J = 7.4, 3H), 0.93 (t, J = 7.0, 3H), 1.30, 1.50, 1.71, 1.83 (m, 18H), 2.90 (m, 1H), 2.97 (m, 1H), 3.66 (dd, J = 9.6, 4.0, 1H), 3.89 (dd, J = 11.2, 9.6, 1H), 3.96 (dd, J = 11.2, 4.0, 1H), 7.20-7.35 (m, 5H) ; ^{13}C NMR : δ 10.8, 14.1, 22.8, 27.1, 28.8, 29.3, 29.5, 29.7, 29.9, 32.0, 58.7, 62.3, 65.8, 128.0, 128.5, 129.2 ; MS E.I. : 288 (13), 28 (100), 218 (18), 168 (10), 98 (13) ; C.I. : 318 (MH^+ 100), 300 (80), 286 (33), 198 (52) ; $[\alpha]_D^{20}$ - 3° (c, 0.69, $CHCl_3$).

(+)-(S)-trans-2-heptyl-5-ethyl-pyrrolidine (9). To a suspension of 140mg of 10% Pd/C in 10mL AcOH, was added 6 (0.9mmol, 285mg). The reaction mixture was shaken under 45 psi hydrogen pressure overnight. After filtration and evaporation to dryness in vacuo the residue was dissolved in ether and aqueous HCl was added. The aqueous layer was washed with ether, basified with 6N NaOH and extracted with dichloromethane. Solvent removal on rotary evaporator afforded pure 9 in quantitative yield : IR (film) : 3300, 2950, 2900, 2840, 1450, 1400, 1365, 1350, 1300, 1120cm^{-1} ; ^{1}H NMR : δ 0.88 (t, J = 6.0, 3H), 0.91 (t, J = 7.4, 3H), 1.19-1.56, 1.94 (m, 18H), 2.67 (m, 1H), 3.10 (m, 2H) ; ^{13}C NMR : δ 11.3, 13.9, 22.5, 27.2, 29.2, 29.57, 29.64, 31.7, 31.8, 32.3, 36.9, 58.0, 59.5 ; MS E.I. : 197 $M^{+\cdot}$ (2) 168 (55), 98 (100), 70 (14); C.I. : 198 (MH^+) ; H.R.M.S. for $C_{13}H_{27}N$ m/z 197.2143, found 197.2131 ; $[\alpha]_D^{20}$ + 4° (c : 2.0, $CHCl_3$).

(+) and (-)-cis isomers 13. Cis(2S), (5R) (-) 13 and (2R), (5S) (+) 13 pyrrolidines were obtained as described for the corresponding trans isomer (+) 9. oil : IR (film) : 3300, 2950, 2900, 2840, 1600, 1455, 1400, 1370, 1300, 1135, 1100, 1050cm^{-1} ; ^{1}H NMR : δ 0.88(t, J = 5.4, 3H), 0.95 (t, J = 7.4, 3H), 1.20-1.68, 1.85-2.05 (m, 18H), 3.02 (m, 1H), 3.37 (m, 2H) ; ^{13}C NMR : δ 11.6, 14.1, 22.7, 27.5, 28.8, 29.3, 29.8, 30.5, 31.0, 31.9, 36.0, 59.7, 61.1 ; MS E.I. : 197 $M^{+\cdot}$ (5) 196 (8), 170 (55), 168 (58), 156 (42), 98 (100) ; $[\alpha]_D^{20}$ - 5.5° (c, 0.14, $CHCl_3$) for (-) 13 and $[\alpha]_D^{20}$ + 7° (c, 0.56, $CHCl_3$) for (+) 13.

(+)-(S)-trans-2-heptyl-5-ethyl-1-benzylpyrrolidine (10). To a solution of 9 (30mg, 0.15mmol) in Et_2O (4mL) was added a 2M solution of EtMgBr in Et_2O (0,085mL, 0.17mmol) and the mixture was stirred for 40 min under argon r.t. C_6H_5COCl (0.02mL, 0.17mmol) was then added and stirring continued for an additional hour. The reaction mixture was taken with EtOAc (6mL and H_2O (3mL) and the organic layer extracted with EtOAc (3 x 7mL). The crude product thus obtained was directly treated with an excess of LAH in Et_2O (25mL). After a 4 h. reflux water was added and the organic layer washed with brine,dried, concentrated and flash chromatographed on silica gel (1:12 EtOAc-Hexane) to afford 10 in 80% yield. The corresponding cis pyrrolidines (+) 14 and (-) 14 were prepared as described above in comparative yields.

10 oil : IR (film) : 2960, 2930, 2850, 2800, 1490, 1455, 1380, 1210, 1140, 1025cm^{-1} ; ^{1}H NMR : δ 0.78 (t, J = 7.4, 3H), 0.86 (t, J = 6.8, 3H), 1.09-1.30, 1.45-1.65, 1.86 (m, 18H), 2.80 (m, 2H), 3.64 (d, J = 10, 1H), 3.80 (d, J = 10, 1H), 7.17-7.36 (m, 5H) ; ^{13}C NMR : δ 10.6, 14.2, 22.8, 2.35, 26.6, 27.9, 28.4, 29.4, 30.0, 30.6, 32.0, 51.6, 60.7, 62.0, 126.6, 128.2, 128.6 ; MS E.I. : 287 $M^{+\cdot}$ (3), 258 (62), 188 (100) ; C.I. : 288 (MH^+ 100), 258 (19), 188 (32) ; H.R.M.S. for $C_{20}H_{33}N$ m/z 287.2613, found 287.2627 ; $[\alpha]_D^{20}$ + 82° (c : 0.74, $CHCl_3$).

14 oil : IR (film), 2960, 2930, 2860, 2800, 1450, 1340, 1205, 1125cm^{-1} ; ^{1}H NMR : δ 0.80 (t, J = 7.4, 3H), 0.86 (t, J = 6.8, 3H), 1.21, 1.38, 1.57, 1.77 (m, 18H), 2.49 (m, 2H), 3.74 (s, 2H), 7.25 (m, 5H) ; ^{13}C NMR : δ 10.6, 14.2, 22.8, 26.5, 28.0, 28.7, 29.2, 29.4, 30.0, 32.0, 35.5, 56.6, 65.3, 66.6, 126.7, 128.0, 129.2 ; MS E.I. : 287 $M^{+\cdot}$ (1) 258 (69), 224 (52), 188 (100), 91 (75) ; C.I. : 288 (MH^+ 100), 198 (18) ; H.R.M.S. for $C_{20}H_{33}N$ m/z 287.2613, found 287.2605 ; $[\alpha]_D^{20}$ - 22.5° (c : 0.40, $CHCl_3$) for (-) 14 and $[\alpha]_D^{20}$ + 23° (c : 0.46, $CHCl_3$) for (+) 14.

(+)-(S)-trans-2-heptyl-5-ethyl-1-phenylsulfonylpyrrolidine (11). Compound 11 was prepared according to reference (8) : oil : IR (film) : 2950, 2920, 2850, 1440, 1335, 1155, 1095, 720cm^{-1} ; ^{1}H NMR : δ 0.81 (t, J = 7.4, 3H), 0.89 (t, J = 6.0, 3H), 1.03-1.35, 1.68, 1.94 (m, 18H), 3.83 (m, 2H), 7.54-8.16 (m, 5H) ; ^{13}C NMR : δ 10.7, 14.2, 22.7, 26.5, 26.9, 27.6, 28.1, 29.3, 29.5, 31.9, 34.0, 61.2, 62.4, 126.9, 128.9, 132.0, 127.1, 129.8, 135.3, 143.2 ; MS E.I. : 337 $M^{+\cdot}$ (2) 308 (57), 238 (100), 141 (18), 77 (28) ; C.I. : 338 (MH^+, 100), 238 (9), 198 (22), 196 (25). H.R.M.S. for $C_{17}H_{26}NO_2S$ m/z 308.1678, found 308.1676 ; for $C_{12}H_{16}NO_2S$, m/z 238.0898, found 238.0901 ; $[\alpha]_D^{20}$ + 62° (c, 0.87, $CHCl_3$).

Mosher's amide 12. To a solution of 9 (96mg, 0.49mmol) in THF and triethylamine (few drops) was added (-) MTPA acid chloride (197mg, 0,78mmol), methylene chloride (3mL) and a catalytic amount of DMAP. After an overnight stirring at room temperature under inert atmosphere, a 5% solution of saturated NaHCO (2mL) and brine were added. Drying and evaporating left a residue which was rapidly filtrated on a short silica column (1:4 EtOAc-Hexane as eluent) to afford 12 (oil) in quantitative yield.

IR (film) : 3080, 3040, 2960, 2930, 2860, 1640, 1455, 1390, 1180, 1160, 1120, 1100 ; ^{1}H NMR : δ 0.89 (t, 3H), 0.91 (t, 3H), 1.01-1.55 (m, 16H), 1.83 (m, 1H), 2.26 (m, 1H), 2.88 (m, 1H), 3.63 (3H), 3.97 (m, 1H), 7.4 (5H). ^{13}C NMR : δ 13.4, 22.1, 26.4, 27.1, 29.0, 29.1, 30.3, 31.3, 31.4, 33.7, 55.8, 58.6, 60.0, 61.3, 85.1, 127.5, 128, 128.6, 129.7, 135.4, 165.6. ^{19}F NMR : 9.48 (s). MS E.I. 413 $M^{+\cdot}$ (0.6), 313 (23), 224 (84), 223 (100), 188 (98) ; CI 414 MH^+. $[\alpha]_D$ - 39° (c : 0.75, $CHCl_3$).

1-(2-phenylethanol)-2,5-dialkylpyrrolidine (15) and (20). As described for the preparation of 6, 7 and 8, 5b was reacted with C_4H_9MgBr. Y : 96% : trans (15)/cis (20) = 72:28.

15 oil : IR (film) : 3400, 3070-2840, 1600, 1465, 1375, 1200, 1140, 1080, 1030cm^{-1} ; ^{1}H NMR : δ 0.86 (t, J = 7.0, 3H), 0.88 (t, J = 7.0, 3H), 1.15-1.31, 1.51, 1.68 (m, 22H), 3.11 (m, 1H), 3.34 (m, 1H), 3.67 (dd, J = 10.0, 6.0, 1H), 3.80 (dd, J = 10.0, 8.0, 1H), 4.04 (dd, J = 8.0, 6.0, 1H), 7.23-7.35 (m, 5H) ; ^{13}C NMR : δ 13.6, 22.5, 22.7, 26.8, 29.0, 29.4, 29.6, 31.7, 33.2, 33.5, 60.2, 61.9, 63.3, 127.1, 127.9, 129.0, 140.5 ; MS E.I. : 345(0.5), 314(100), 288(13), 246(21), 168(19), 126(18), 91(12) ; C.I. : 346 (MH^+ 100), 328(99), 314(50) ; $[\alpha]_D^{20}$ + 40° (c : 1.0, MeOH).

20 oil : IR (film) : 3400, 3075-2850, 1600, 1465, 1375, 1200, 1130, 1080, 1030cm^{-1} ; ^{1}H NMR : δ 0.88 (t, J = 7.0, 3H), 0.93 (t, J = 7.0, 3H), 1.17-1.39, 1.71, 1.80 (m, 22H), 2.89 (m, 1H), 3.00 (m, 1H), 3.66 (dd, J = 10.0, 4.0, 1H), 3.89 (t, J = 10.0, 1H), 3.95 (dd, J = 10.0, 4.0, 1H), 7.20-7.31 (m, 5H) ; ^{13}C NMR : δ 14.1, 22.7, 23.1, 27.0, 28.9, 29.4, 29.6, 29.8, 29.9, 31.9, 36.3, 38.4, 57.6, 61.8, 63.6, 64.8, 127.6, 128.2, 128.9, 137.6 ; MS E.I. : 345(1), 314(100), 288(14), 246(22), 168(18), 126(25) ; C.I. : 346 (MH^+ 100), 328(12) ; H.R.M.S. for $C_{23}H_{39}NO$ m/z 345.3032, found 345.3007 ; $[\alpha]_D^{20}$ - 21° (c : 0.62, $CHCl_3$).

(+)-(S)-trans-2-heptyl-5-butylpyrrolidine (16) : Following the same procedure described for 9 ; Y = 96% ; oil : IR (film) : 3300, 2940, 2900, 2860, 1440, 1365, 1200, 1020cm^{-1} ; ^{1}H NMR : δ 0.87 (t, J = 7.0, 3H), 0.89 (t, J = 6.0, 3H), 1.19-1.50 (m, 18H), 1.93 (m, 4H), 3.17 (m, 2H) ; ^{13}C NMR : δ 13.9, 22.6, 27.1, 29.2, 29.6, 35.5, 35.8, 58.4 ; MS E.I. : 225(7), 224(9), 168(100), 126(100) ; H.R.M.S. calcd for $C_{15}H_{31}N$, m/z 225.2456 ; found 225.2435 ; $[\alpha]_D^{20}$ + 16° (c : 1.1, $CHCl_3$), $[\alpha]_D^{20}$ +7.5° (c : 2.5, CH_3OH), lit.[8] : $[\alpha]_D^{20}$ + 60° (c : 1.5, CH_3OH).

cis-2-heptyl-5-butylpyrrolidine (21) : Following the procedure described for 9 ; Y : 95% ; oil : IR (film) : 2950-2850, 1580, 1475, 1240, 1090cm^{-1} ; ^{1}H NMR : δ 0.87, 089 (m, 6H), 1.23-1.91 (m, 22H), 3.09 (m, 2H), 4.40 (m, 1H) ; ^{13}C NMR : δ 13.9, 22.5, 22.7, 27.3, 29.1, 29.4, 29.6, 30.8, 31.7, 35.5, 59.5 ; MS E.I. : 225(4), 224(9), 168(100), 126(98) ; C.I. : 226 (MH^+) ; H.R.M.S. for $C_{15}H_{31}N$, m/z 225.2456 ; found 225.2461 ; $[\alpha]_D^{20}$ 0° (c : 1.3, CH_3OH), lit.[8] : $[\alpha]_D^{20}$ 0° (c : 0.5, CH_3OH).

(+)-(S)-trans-2-heptyl-5-butyl-1-benzyl pyrrolidine (17) : Following the procedure outlined for the preparation of 10 ; Y : 70% ; oil : IR (film) : 2950-2800, 1600, 1460, 1380, 1205, 1130, 1070, 1020cm^{-1} ; ^{1}H NMR : δ 0.81 (t, J = 7.0, 3H), 0.84 (t, J = 8.0, 3H), 1.02-1.53, 1.82 (m, 22H), 2.85 (m, 2H) 3.54 (d, J = 14.0, 1H), 3.74 (d, J = 14.0, 1H), 7.50 (m, 5H) ; ^{13}C NMR : δ 14.2, 22.8, 23.1, 26.6, 28.5, 28.8, 29.1, 29.4, 29.8, 30.0, 30.2, 30.4, 30.7, 32.0, 51.6, 60.7, 126.5, 128.2, 128.6, 140.8 ; MS E.I. : 315(12), 258(100), 216(98), 91(81) ; C.I. : 316 (MH^+) ; $[\alpha]_D^{20}$ + 81° (c : 0.37, $CHCl_3$).

Cis-2-heptyl-5-butyl-1-benzyl pyrrolidine (22) : Following the procedure described above for 10 ; Y : 80% ; oil (film) : 3030-2800, 1600, 1460, 1380, 1200, 1120, 1070, 1025cm^{-1} ; ^{1}H NMR : δ 0.85 (t, J = 7.0, 3H), 0.88 (t, J = 7.0, 3H), 1.12-1.44, 1.58, 1.79 (m, 22H), 2.52 (m, 2H), 3.76 (s, 2H), 7.29 (m, 5H) ; ^{13}C NMR : δ 14.2, 22.8, 23.1, 26.5, 28.8, 29.5, 30.1, 32.0, 35.4, 35.7, 57.1, 65.3, 126.7, 128.0, 129.2, 140.6 ; MS E.I. : 315(8), 258(100), 216(99), 91(99) ; C.I. : 316 (MH^+) ; $[\alpha]_D^{20}$ 0° (c : 1.4, $CHCl_3$).

(+)-(S)-trans-2-heptyl-5-butyl-1-phenyl sulfonyl pyrrolidine (18) : Compound 18 was obtained according to reference (8) : Y : 93% ; oil. IR (film) : 2920-2840, 1445, 1430, 1315, 1290, 1185, 1140, 1080cm^{-1} ; ^{1}H NMR : δ 0.84 (t, J = 7.0, 3H), 0.87 (t, J = 7.0, 3H), 1.10-1.28, 1.67, 1.88-1.95 (m, 22H), 3.83 (m, 2H), 7.47, 7.83 (m, 5H) ; ^{13}C NMR : δ 14.10, 14.13, 22.7, 26.5, 28.1, 28.7, 29.3, 29.5, 31.9, 33.8, 34.0, 61.1, 126.9, 128.8, 131.9, 143.2 ; MS E.I. : 365(1), 308(100), 266(98), 141(17), 77(31) ; $[\alpha]_D^{20}$ + 58° (c : 1.1, CH_2Cl_2), lit.[8] : $[\alpha]_D^{20}$ + 60° (c : 1.8, CH_2Cl_2).

Mosher's amide 19 : Compound 19 was prepared according to the procedure described for 12 (Y : 100%) ; oil ; IR (film) : 2950-2850, 1640, 1450, 1385, 1255, 1180, 1120, 1100, 1075cm^{-1} ; ^{1}H NMR : δ 0.87 (t, J = 6.0, 3H), 0.92 (t, J = 7.0, 3H), 1.19-1.33, 1.40, 1.56, 1.86, 2.26 (m, 22H), 2.93 (m, 1H), 3.63 (s, 3H), 4.01 (m, 1H), 7.35-7.49 (m, 10H) ; ^{13}C NMR : δ 14.1, 14.2, 22.7, 25.5, 27.0, 27.4, 27.8, 29.2, 29.3, 29.5, 30.6, 31.0, 31.9, 34.0, 34.3, 53.4, 56.0, 58.9, 60.1, 127.1, 128.1, 129.1, 135.0, 165.2 ; ^{19}F NMR : δ 8.92 (s). MS E.I. : 441(1), 385(11), 343(14), 252(100), 189(45), 105(8), 97(9) ; $[\alpha]_D^{20}$ - 28° (c : 2.5, $CHCl_3$).

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