STEREOSELECTIVE SYNTHESIS OF 4-AMINOMETHYL-3-
HYDROXYPROLINOLS AND RING EXPANSION INTO ENANTIOPURE
POLYFUNCTIONALIZED PIPERIDINES

Abdallah Deyine, Jean-Marc Delcroix, and Nicole Langlois*

Institut de Chimie des Substances Naturelles
C.N.R.S., Avenue de la Terrasse, 91198 Gif-sur-Yvette, France
Fax:+33 1 69077247
E-mail: nicole.langlois@icsn.cnrs-gif.fr

Abstract—A stereoselective route was developed to synthesize enantiopure 3,4,5-
trisubstituted piperidines in few steps. The functionalities were introduced starting
from (S)-pyroglutaminol as chiral material. The method is based on the 1,3-
dipolar cycloaddition of \( \text{N-benzylnitrone} \) to a derived bicyclic \( \text{a,b-ethylenic} \)
lactam, followed by a ring enlargement of five to six membered nitrogen
heterocycles through aziridinium ions.

INTRODUCTION
The synthesis of chiral polysubstituted piperidines is still the focus of special interest.\(^1,2\) Indeed,
functionalized piperidines exhibit a great range of biological activities. Among them, polyhydroxylated
piperidines derivatives could be candidates for the inhibition of glycosidases,\(^3,4\) and related highly
functionalized piperidines could also be used to prepare novel PNAs (Peptide Nucleic Acids) with
promising properties.\(^5,6\) They can also constitute useful building blocks in the preparation of more
complex alkaloids or attractive synthetic targets.

RESULTS AND DISCUSSION
Taking advantage of easy functionalization of (S)-pyroglutaminol derivatives such as 2, we already
developed a strategy towards \( N\)-benzyl-4-benzylamino-3-hydroxypiperidine, involving a well known
expansion reaction of pyrrolidine rings.\(^7,8\) This enlargement of five to six membered nitrogen

\(^{\ddagger}\) Dedicated to Dr. Pierre Potier on the occasion of his 70th birthday
heterocycles requires the presence of a leaving-group or a leaving-group precursor in position to the heterocyclic nitrogen and proceeds through aziridinium ions.\textsuperscript{7-9} We extend here this methodology to the preparation of (3S,4S,5S)-5-aminomethyl-3,4-dihydroxypiperidine derivatives.

The aminomethyl and vicinal \textit{cis} hydroxyl groups could be simultaneously introduced by a highly regio- and stereo-selective 1,3-dipolar cycloaddition of \textit{N}-benzyl nitrone to the versatile bicyclic \textit{a,b}-ethylenic lactam (2) prepared from (S)-pyroglutaminol (1). This cycloaddition occurred by heating in toluene as we previously described,\textsuperscript{10} but the yield was now improved by using an excess of the nitrone (1.5 equiv.) and the major cycloadduct (3) was isolated in excellent yield (90\%). A deprotective reduction by LAH with the opening of both oxazolidine and isoxazolidine rings in a single step led to (2\textit{R},3\textit{S},4\textit{S})-1-benzyl-4-benzylaminomethyl-3-hydroxyprolinol (4) in 93\% yield (Scheme 1).

Scheme 1

The \textit{N}-benzyl 3,4-disubstituted prolinol (4) was treated under classical ring expansion conditions with trifluoroacetic anhydride and triethylamine and then with 2.5 N NaOH, affording 5 in 33\% yield, together with the starting pyrrolidine (4) (20\%, Scheme 2). The diol (5) was acetylated into 6 to make easier the identification of the shifted H-3 and H-4 signals in the $^1$H-NMR spectrum.

Scheme 2
One possible reason for the modest yield observed might be the incomplete trifluoroacylation of the secondary amino group in spite of the use of an excess of trifluoroacetic anhydride. Indeed, some elimination of the leaving group generated at C-3 could be postulated with the participation of the rather flexible aminomethyl group and a fragmentation reaction illustrated in the Scheme 3.

Scheme 3

To overcome this drawback, we tried to modify the chronology of the sequences with the enlargement of 5-membered ring of the compound (7). This derivative was obtained in high yield (90%) by reduction of the lactam carbonyl with selective opening of the oxazolidine ring by means of the complex BH₃-SMe₂. However, under the same conditions as above, the yield of piperidine (8) was not improved by this way (28%, Scheme 4).

Scheme 4

The classical protection of the secondary N-benzylamino group of the trisubstituted pyrrolidine (4) as t-butyl carbamate (9) was more efficient. It is worthy of note that this N-protecting group was stable under the ring expansion conditions which led more rapidly to the piperidine (10) with 42% yield (Scheme 2), along with starting pyrrolidine (35%). N-Boc protecting group was removed with diluted trifluoroacetic acid in dichloromethane affording 5.
CONCLUSION

In conclusion, from the bicyclic \( a,b \)-ethylenic lactam (2), a versatile derivative of (S)-pyroglutaminol, was developed a rapid and efficient access to interesting \((2R,3S,4S)\)-1-benzyl-4-aminomethyl-3-hydroxyprolinols. Ring expansion of these 5-membered nitrogen heterocycles was shown to be useful to prepare optically active highly functionalized piperidines in few steps, under experimental conditions which are compatible with a \( N \)-Boc protecting group.

EXPERIMENTAL

General. Optical rotations were measured on a JASCO P-1010 polarimeter and the concentrations were given in g/100 mL. IR spectra (film, CHCl\(_3\)) were recorded on Perkin Elmer Spectrum BX (FT). \(^1\)H NMR spectra were obtained (generally in CDCl\(_3\), CHCl\(_3\) \( \delta = 7.27 \) ppm) from Bruker AM 300 and the coupling constants are given in Hertz. \(^{13}\)C NMR spectra were recorded on AM 300 (75.0 MHz, CDCl\(_3\) centred at 77.14 ppm). MS and HRMS were measured on a Navigator (ESI), or a Micromass LC-TOF, or an Automass Thermo-Finnigan spectrometer. Chromatography was performed on silica gel (SDS 230-400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254 + 366). Usual workup means that the organic layer was dried over magnesium sulfate, filtered and evaporated under vacuum.

\((2R,3S,4S)\)-1-Benzyl-4-benzylaminomethyl-3-hydroxy-2-hydroxymethylpyrrolidine (4)

To a solution of cycloadduct (3) (777.7 mg, 2.31 mmol) in dry THF (6.0 mL), stirred at 0 °C under argon, was added a solution of LiAlH\(_4\) (600 mg, 15.81 mmol) in THF (28 mL). The mixture was heated at reflux for 17 h, cooled at 0 °C and the excess of reagent was carefully destroyed by addition of some drops of a saturated aqueous solution of Na\(_2\)SO\(_4\). The residue obtained after usual workup was purified by chromatography (eluent: CH\(_2\)Cl\(_2\)-MeOH-NH\(_4\)OH 9:1:0.1) to give \((2R,3S,4S)\)-1-benzyl-4-benzylaminomethyl-3-hydroxy-2-hydroxymethylpyrrolidine (4) (705.6 mg, 93%) as a colorless oil. \([\alpha]_D^{23} = -97^{\circ} (c 0.91, \text{CHCl}_3)\). IR: 3350, 3070, 3063, 3034, 2924, 2831, 1497, 1457 cm\(^{-1}\). MS (ESI, MeOH) \( m/z \): 349 [(MNa\(^+\) , 45 %), 327 [(MH\(^+\) , 100%]. \(^1\)H NMR: 7.29 (m, 10H, H-Ar), 4.33 (dd, 1H, \( J = 6.2, J' = 3.8, H-3 \)), 3.96 and 3.41 (2 d, 2H, \( J = 12.9, \text{NCH}_2\text{Ph} \)), 3.74 (2 d, 2H, \( J = 13, \text{NCH}_2\text{Ph} \)), 3.66 (2H, OCH\(_2\)), 3.20 (exch. OH, NH), 2.95 (dd, 1H, \( J = 8, J' = 6.4, \text{NCH} \)) and 2.31 (m, 1H, NCH), 2.82 (2H, NCH\(_2\)), 2.69 (m, 1H, H-2), 2.20 (m, 1H, H-4). \(^{13}\)C NMR (dihydrochloride, D\(_2\)O, dioxane \( \delta = 67.19 \) ppm): aromatic qC not visible, 131.53, 131.33, 131.02, 130.63, 130.49, 130.05, 129.96 (CH, Ar), 76.01, 71.64 (C-2 and C-3), 60.36 (CH\(_2\)), 58.34 (CH\(_2\)), 55.41 (CH\(_2\)), 52.31 (CH\(_2\)), 44.09 (CH\(_2\)), 38.99 (C-4). HRMS (ESI, MeOH) called for C\(_{20}\)H\(_{27}\)N\(_2\)O\(_2\) (MH\(^+\) ): 327.2073, found: 327.2072. Dihydrochloride: Anal. Caled for C\(_{20}\)H\(_{28}\)O\(_2\)N\(_2\)Cl\(_2\), CH\(_3\)OH: C, 58.46; H, 7.48; N, 6.49. Found: C, 58.12; H, 7.31; N, 6.41.
(3S,4S,5S)-1-Benzyl-5-benzylaminomethyl-3,4-dihydroxypiperidine (5)

Trifluoroacetic anhydride (1.0 mL, 7.08 mmol) was added to a stirred solution of pyrrolidine (4) (315.1 mg, 0.97 mmol) in dry THF (17.5 mL) at – 78 °C. The mixture was stirred at this temperature for 3 h, before the addition of triethylamine (2.0 mL, 14.35 mmol). After being stirred at – 78 °C for 0.25 h, the mixture was heated at 65 °C for 4 days, cooled at rt, and 2.5 M NaOH solution (4.5 mL) was then added. This mixture was stirred at rt for 2 h before extraction with CH₂Cl₂. The crude product obtained after usual workup was purified by flash chromatography (eluent : CH₂Cl₂-MeOH-NH₄OH 9:1 :0.1) to give the piperidine (5) as a colorless oil (102.8 mg, 33%) and starting pyrrolidine (4) (63.3 mg, 20 %). 5 : [α]D 24 = 1.0 ° (c 1.3, CHCl₃). IR: 3621, 3020, 1453 cm⁻¹. MS (ESI, MeOH) m/z: 327 [(MH)+, 100%]. 1H NMR (C₆D₆, d = 0: TMS): 7.14, 7.10 (2 m, H-Ar), 3.89 (m, 1H, H-3), 3.79 (m, 1H), 3.34–3.15 (m, 4H, 2 NCH₂), 2.93 (m, 1H, Ha-2), 2.74 (m, 1H), 2.25 [dd (J = 12.1, J' = 3.7) + m, 2H, Hb-7, Hb-2], 2.15 (m, 1H, Ha-6), 1.95 (m, 1H, Hb-6), 1.88 (m, 1H, H-5). 13C NMR (C₆D₆, d = 0: TMS): 139.71, 139.19 (qC, Ar), 129.06, 128.73, 128.57, 128.35, 128.03, 127.71, 127.47, 127.36 (CH, Ar), 75.43, 69.68 (OCH), 62.73 (NCH₂Ph), 57.2 (br, NCH₂), 54.14 (NCH₂), 51.13 (NCH₂), 36.89 (C-5). HRMS (ESI, MeOH) calcd for C₂₀H₂₇N₂O₂ (MH+): 327.2073, found: 327.2027. Dihydrochloride: Anal. Calcd for C₂₀H₂₈N₂O₂Cl₂, H₂O: C, 57.55; H, 7.25; N, 6.71. Found: C, 57.35; H, 7.31; N, 6.56.

(3S,4S,5R)-1-Benzyl-3,4-diacetoxy-5-(N-acetyl-N-benzylamino)methylpiperidine (6)

Pyridine (1.8 mL) and acetic anhydride (1.2 mL) were added at rt to piperidine (5) (78.9 mg, 0.24 mmol) and the mixture was stirred at rt for 22 h. After addition of methanol (17 mL), the solution was stirred for 0.25 h before the addition of aqueous Na₂CO₃ solution (10 % w/v, 12 mL). After extraction with CH₂Cl₂, and usual workup, the solvents were evaporated under reduced pressure. The crude product was purified by prepative TLC (eluent : Et₂O) to give the triacetylated compound (6) as a white crystals (83.1 mg, 76 %). Mp: 111-112 °C. [α]D 23 = – 44.4 ° (c 1.0, CHCl₃). IR : 3029, 3008, 2814, 1737, 1635, 1453 cm⁻¹. MS (ESI, MeOH) m/z: 475 [(MNa)+, 95%], 453 [(MH)+, 100%]. 1H NMR (conformers) : 7.25, 7.13, 7.05 (m, d, d, 10 H, J = 8, H-Ar), 4.87 (m, 3H, H-3, H-4, NCH₄Ph), 4.29 (2 d, 2H, J = 14.7, NCH₂), 4.14 (d, 1H, J = 14.7, NCH₂Ph), 3.66 and 3.25 (2 m, 2H, NCH₂), 3.56 (dd, 1H, J = 12.9, J' = 4.5, NCH), 3.42 (dd, 1H, J = 12.9, J' = 10.9, NCH), 2.90, 2.71 (NCH₄Ph), 2.53 (m, 1H), 2.30 (m, 1H, NCH₂Ph), 2.15, 2.05, 2.00, 1.97, 1.95, 1.90 (6 s, 9H, 3 COCH₃). 13C NMR (conformers): 171.46, 171.30 (CO), 170.26, 170.10, 170.04 (CO), 137.72, 137.27, 136.80, 136.71 (qC, Ar), 129.25, 129.18, 129.00, 128.67, 128.56, 128.39, 128.05, 127.71, 127.60, 127.43, 127.40, 126.01 (CH, Ar), 73.13, 70.92 (OCH), 68.17, 67.74 (OCH), 62.35, 62.19 (CH₂), 54.41, 52.90 (CH₂), 52.31 (CH₂), 47.58 (CH₂), 44.58, 44.17 (CH₂), 36.32, 36.05 (C-5), 21.79, 21.47, 21.12, 21.09, 20.97, 20.88 (COCH₃). HRMS (ESI, MeOH) calcd for C₂₀H₃₃N₂O₅ (MH+):
453.2389, found: 453.2353. Anal. Calcd for C_{26}H_{32}N_{2}O_{5}: C, 69.00; H, 7.13; N, 6.19. Found: C, 68.94; H, 7.32; N, 6.12.

**6R,6aS,3aR)-(2,5-Dibenzyloxypyrrolo[3,4-d]isoxazol-6-yl)methanol (7)**

To a solution of lactam (3) (544.5 mg, 1.62 mmol) in anhydrous THF (38.0 mL) was added at rt a solution of BH$_3$.DMS in THF (2 M, 5.0 mmol, 2.50 mL). The mixture was heated at reflux for 2 h. After cooling at rt, the solution was acidified by addition of 2.0 M aqueous HCl and evaporated to dryness. Aqueous 6N HCl (25 mL) was added, the mixture was heated at 70 °C for 0.25 h and 30 % aqueous NaOH was then added at 0 °C until pH > 10. The solution was extracted with CH$_2$Cl$_2$. The product obtained after usual workup was purified by flash chromatography (eluent : CH$_2$Cl$_2$-MeOH 9:1) and hydroxymethylpyrrolidine (7) was obtained as colorless oil (473.8 mg, 90 %). $\delta^{23-}$ = 23.8 ° (c 1.27, CHCl$_3$). IR: 3681, 3618, 3016, 1515, 1475, 1420 cm$^{-1}$. MS (ESI, MeOH) $m/z$: 347 [(MNa)$^+$, 81 %], 325 [(MH)$^+$ (100 %)]. $^{1}$H NMR (CDCl$_3$ + D$_2$O + Na$_2$CO$_3$): 7.35 (m, 10 H), 4.67 (dd, 1H, $J$ = 4.7, $J'$ = 8.2), 4.09 (d, 1H, $J$ = 13, NC$^a$HaPh ), 3.99 (d, 1H, $J$ = 13, NC$^a$Ha'Ph), 3.90 (br d, 1H, NCHbPh), 3.84 (dd, 1H, $J$ = 12, $J'$ = 1.9), 3.72 (d, 1H, $J$ = 13, NCHb'Ph), 3.19 (dd, 1H, $J$ = $J'$ = 8), 2.95 and 2.88 (2 m, 2H), 2.73 (m, 1H), 2.50 (m, 1H), 2.37 (dd, 1H, $J$ = $J'$ = 8). $^{13}$C NMR (CDCl$_3$ + D$_2$O + Na$_2$CO$_3$): 138.54 (qC, Ar), 137.35 (qC, Ar), 128.81, 128.73, 128.51, 128.42, 127.37, 127.34 (CH, Ar), 84.20 (C-6a), 69.91(C-6), 61.96, 61.69 (CH$_2$), 59.92 (CH$_2$), 59.40 (CH$_2$), 58.86 (CH$_2$), 57.41 (CH$_2$), 44.57 (C-3a). HRMS (ESI, MeOH): calcd for C$_{20}$H$_{25}$N$_2$O$_2$ (MH$^+$): 325.1916, found: 325.1909. Dihydrochloride: Anal. Calcd for C$_{20}$H$_{26}$N$_2$O$_2$Cl$_2$: C, 60.45; H, 6.60; N, 7.05. Found: C, 60.61; H, 6.81; N, 7.01.

**7S,7aS,3aR)-2,5-Dibenzyloctahydroisoxazolo[4,5-c]pyridin-7-ol (8)**

Trifluoroacetic anhydride (325 [L, 2.30 mmol) was added to a stirred solution of pyrrolidine (7) (202.2 mg, 0.62 mmol) in dry THF (8.5 mL) at – 78 °C. The mixture was stirred at this temperature for 3 h before the addition of triethylamine (670 [L, 4.80 mmol). After being stirred at – 78 °C for 0.25 h, and heated at 65 °C for 4 days, the mixture was cooled at rt, and 2.5 M NaOH solution (2.3 mL) was then added. This mixture was stirred at rt for 3 h before extraction with CH$_2$Cl$_2$. The product obtained after usual workup was purified by preparative TLC (eluent : heptane-EtOAc 3:7) giving the piperidine (8) as a colorless oil (56.2 mg, 28%). $\delta^{23-}$ = 51 ° (c 0.74, CHCl$_3$). IR: 3627, 3028, 1518 cm$^{-1}$. MS (ESI, MeOH) $m/z$: 347 [(MNa)$^+$, 20 %], 325 [(MH)$^+$, 100 %]. $^{1}$H NMR: 7.32, 7.30 (2 m, 10 H), 4.17, 4.10 (2 m, 2H), 3.97, 3.88 (2 m, 2H), 3.53 (middle of 2 d, 2H, $J$ = 13, NCH$_2$Ph), 2.95, 2.84 (2 m, 3H), 2.67, 2.60 (2 m, 3H), 2.32 (dd, 1H, $J$ and $J'$ ~ 9). $^{13}$C NMR: 138.05, 137.04 (qC, Ar), 129.32, 129.05, 128.85, 128.73, 128.51, 128.44, 127.56, 127.42 (CH, Ar), 65.84, 64.37 (CH$_2$), 62.42 (CH$_2$), 58.23 (CH$_2$), 55.22 (CH$_2$), 53.77 (CH$_2$), 40.21(CH). HRMS (ESI, MeOH) calcd for
C$_{20}$H$_{25}$N$_2$O$_2$ (MH)$^+$: 325.1916, found: 325.1921. Anal. Calcd for C$_{20}$H$_{24}$N$_2$O$_2$, 0.5 CH$_3$OH: C, 72.32; H, 7.70; N, 8.23. Found: C, 72.25; H, 7.44; N, 8.16.

(2R,3S,4R)-1-Benzyl-4-(N-benzyl-N-tert-butyloxycarbonylamino)methyl-3-hydroxy-2-hydroxymethylpyrrolidine (9)

A solution of Boc$_2$O (215.9 mg, 0.99 mmol) in dichloromethane (1.0 mL) and triethylamine (15 μL, 0.1 mmol) were added to a solution of aminopyrrolidine (4) (293.2 mg, 0.9 mmol) in dichloromethane (1.0 mL). The mixture was stirred for 4 h at 0 °C. After evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography (eluent: CH$_2$Cl$_2$-MeOH 95:5) and gave the N-Boc aminopyrrolidine (9) as a white foam (264.2 mg, 69%). [α]$_D$ = 1.5 ° (c 0.99, CHCl$_3$). IR : 3363, 3020, 1663 cm$^{-1}$. MS (ESI, MeOH) m/z: 427 [(MH)$^+$, 100 %], 371 (62 %). $^1$H NMR: 7.29, 7.15 (2 m, 10H, H-Ar), 5.06 (br s, 1H), 4.73, 3.96 (2 d, 2H, $J$ = 15.7, NCH$_2$Ph), 4.02 (m, 1H, H-3), 3.91, 3.56 (2 d, 2H, $J$ = 12.5, NCH$_2$Ph), 3.52 (m, 2H, H$_2$-6), 3.82, 2.63 (2 m, 2H, NCH$_2$), 2.88 (m, 1H, H-2), 2.71, 2.37 (2 m, 2H, NCH$_2$), 2.12 (m, 1H, H-4), 1.45 (s, 9H, t-Bu). $^{13}$C NMR: 157.25 (NCO$_2$), 139.26, 137.69 (qC, Ar), 128.92, 128.71, 128.52, 127.63, 127.36, 127.27 (CH, Ar), 81.29 (qC, Ar), 74.60 (C-3), 73.64 (C-2), 61.80 (C-6), 59.60 (NCH$_2$Ph), 54.70 (NCH$_2$), 50.93 (N$_2$C$_2$H$_2$Ph), 43.78 (C-4), 42.63 (NCH$_2$), 28.44 (CH$_3$, t-Bu). HRMS (ESI, MeOH) calcd for C$_{25}$H$_{35}$N$_2$O$_4$ (MH)$^+$: 427.2597, found: 427.2581. Hydrochloride : Anal. Calcd for C$_{25}$H$_{35}$N$_2$O$_4$Cl, CH$_3$OH : C, 63.08 ; H, 7.94. Found : C, 63.37 ; H, 7.64.

(3S,4S,5R)-1-Benzyl-5-(N-benzyl-N-tert-butyloxycarbonylamino)methyl-3,4-dihydroxypiperidine (10)

To a solution of pyrrolidine (9) (103.4 mg, 0.24 mmol) in dry THF (3.8 mL) was added at – 78 °C trifluoroacetic anhydride (270 μL, 1.91 mmol). The mixture was stirred at this temperature for 3 h before the addition of triethylamine (535 μL, 3.84 mmol). After being stirred at – 78 °C for 0.75 h, the mixture was heated at reflux for 17 h, cooled at rt, and 2.5 M NaOH solution (1.5 mL) was then added. This mixture was stirred at rt for 2 h before extraction with CH$_2$Cl$_2$. After usual workup, the crude product was purified by preparative TLC (eluent : CH$_2$Cl$_2$-MeOH 9:1) and gave the piperidine (10) as a colorless oil (43.7 mg, 42 %) and starting pyrrolidine (9) (36.4 mg, 35 %). [α]$_D$ = 29.5 ° (c 0.56, CHCl$_3$). IR: 3379, 2937, 1425 cm$^{-1}$. MS m/z: 427 [(MH)$^+$, 33 %], 371 (100 %), 327 (97.5 %). $^1$H NMR : 7.29, 7.17 (2 m, 10H, H-Ar), 4.72 (d, 1H, $J$ = 16, NCH$_2$Ph), 4.01 (d, 1H, $J$ = 16, NCH$_2$Ph), 3.87 (m, 1H, OCH), 3.69 (m, 1H), 3.63 (m, 3H, NCH, CH$_2$), 2.86 (m, 1H, NCH$_2$), 2.70 (d, 1H, $J$ = 11.8, NCH$_2$), 2.57 (d, 1H, $J$ = 14, NCH), 2.43 (m, 1H, NCH), 2.21 (m, 2H, H-5, NCH), 1.44 (s, 9H, t-Bu). $^{13}$C NMR : 157.60 (NCO$_2$), 137.59, 134.5 (qC, Ar), 129.65, 128.72, 128.67, 128.04, 127.53, 127.29 (CH, Ar), 81.33
(qC, t-Bu), 68.02 (OCH), 65.8, 62.49 (NCH₂), 53.75 (NCH₂), 50.75 (NCH₂), 44.96 (NCH₂), 34.48 (C-5), 28.40 (CH₃, t-Bu). HRMS (ESI, MeOH) calcd for C₂₅H₃₅N₂O₄ (MH⁺): 427.2597, found: 427.2597.

(3S,4S,5S)-1-Benzyl-5-benzylaminomethyl-3,4-dihydroxypiperidine (5) from 10
Trifluoroacetic acid was added to a solution of piperidine (10) (17.3 mg, 0.04 mmol) in CH₂Cl₂ (1.5 mL) at rt and the mixture was stirred for 20 h. The solution were evaporated under reduced pressure and the crude product was purified by preparative TLC (eluent : CH₂Cl₂-MeOH-NH₄OH 9:1:0.1) and gave the piperidine (5) as a colorless oil (6.2 mg, 63 %).

ACKNOWLEDGMENTS
We are grateful to Professor J.-Y. Lallemand, Director of I. C. S. N., for a grant (A. D).

REFERENCES