HETEROCYCLES, Vol. 64, 2004, pp. 207 - 214
Received, 31st May, 2004, Accepted, 28th July, 2004, Published online, 30th July, 2004

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 *N*-benzylnitrone to a derived bicyclic □,□-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.

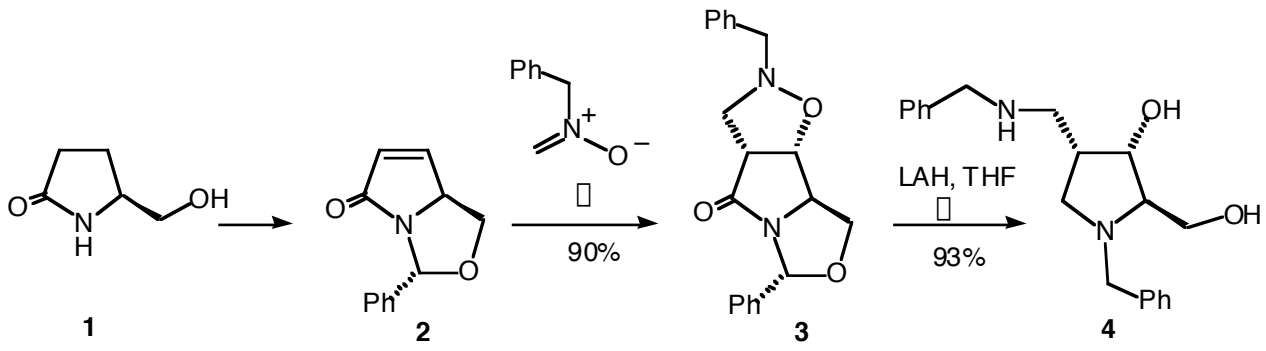
RESULTS AND DISCUSSION

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.[7,8a] This enlargement of five to six membered nitrogen

[#] Dedicated to Dr. Pierre Potier on the occasion of his 70th birthday

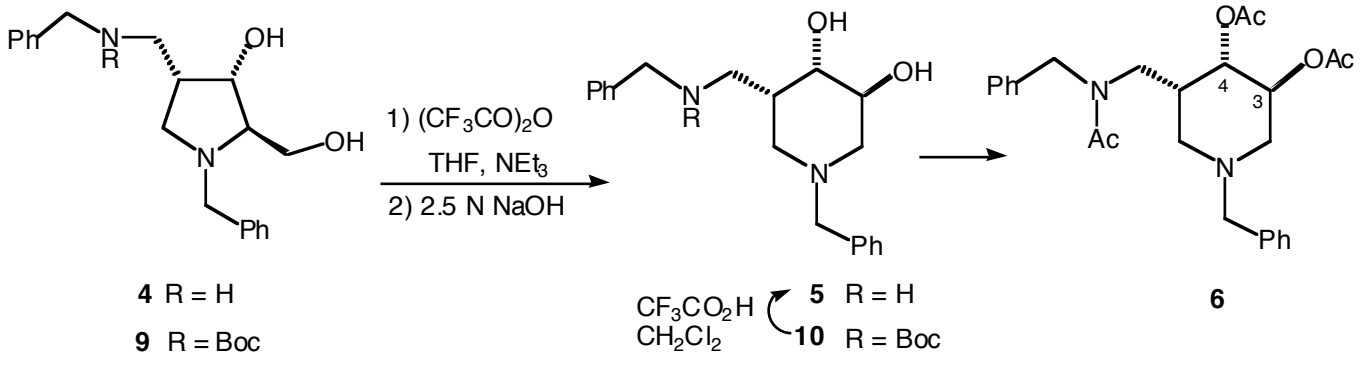
heterocycles requires the presence of a leaving-group or a leaving-group precursor in position to the heterocyclic nitrogen and proceeds through aziridinium ions.[7-9] We extend here this methodology to the preparation of (3*S*,4*S*,5*S*)-5-aminomethyl-3,4-dihydroxypiperidine derivatives.

The aminomethyl and vicinal *cis* hydroxyl groups could be simultaneously introduced by a highly regio- and stereo-selective 1,3-dipolar cycloaddition of *N*-benzylnitrone to the versatile bicyclic ,-ethylenic lactam (**2**) prepared from (*S*)-pyroglutaminol (**1**). This cycloaddition occurred by heating in toluene as we previously described,[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*R*,3*S*,4*S*)-1-benzyl-4-benzylaminomethyl-3-hydroxyprolinol (**4**) in 93% yield (Scheme 1).



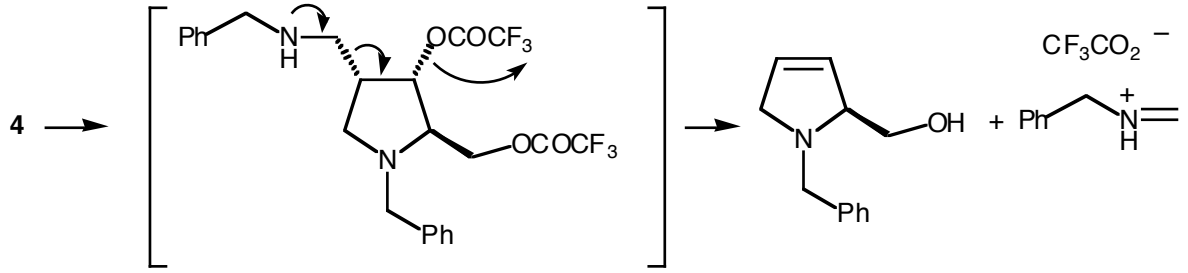
Scheme 1

The *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.



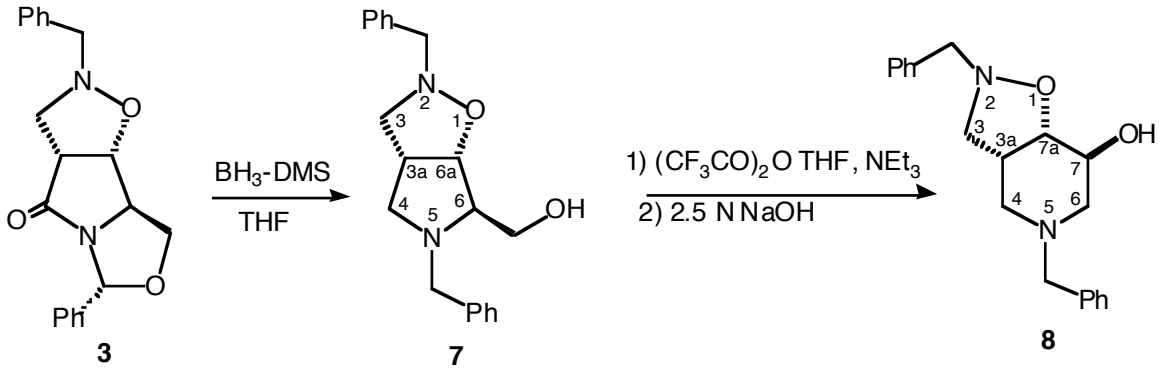
Scheme 2

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 BH_3-SMe_2.[11] 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 □,□□ethylenic lactam (**2**), a versatile derivative of (*S*)- pyroglutaminol, was developed a rapid and efficient access to interesting (2*R*,3*S*,4*S*)-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 $CDCl_3$, $CHCl_3$ □ = 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

(2*R*,3*S*,4*S*)-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_2SO_4. The residue obtained after usual workup was purified by chromatography (eluent : CH_2Cl_2-MeOH-NH_4OH 9:1:0.1) to give (2*R*,3*S*,4*S*)-1-benzyl-4-benzylaminomethyl-3-hydroxy-2-hydroxymethylpyrrolidine (**4**) (705.6 mg, 93%) as a colorless oil. $[\alpha]_D^{23}$ = – 97 ° (*c* 0.91, $CHCl_3$). 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, NC*H*$_2$Ph), 3.74 (2 d, 2H, *J* = 13, NC*H*$_2$Ph), 3.66 (2H, OCH_2), 3.20 (exch. OH, NH), 2.95 (dd, 1H, *J* = 8, *J'* = 6.4, 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_2O, dioxane □ = 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) calcd for $C_{20}H_{27}N_2O_2$ (MH^+): 327.2073, found: 327.2072. Dihydrochloride: Anal. Calcd for $C_{20}H_{28}O_2N_2Cl_2$, CH_3OH: C, 58.46; H, 7.48; N, 6.49. Found: C, 58.12; H, 7.31; N, 6.41.

(3*S*,4*S*,5*S*)-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 CH_2Cl_2. The crude product obtained after usual workup was purified by flash chromatography (eluent : CH_2Cl_2-MeOH-NH_4OH 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** $[\alpha]_D^{24}$ = 1.0 ° (c 1.3, $CHCl_3$). IR: 3621, 3020, 1453 cm^{-1}. MS (ESI, MeOH) *m/z*: 327 [$(MH)^+$, 100%]. ^1H NMR (C_6D_6, δ = 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 NCH_2), 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). ^{13}C NMR (C_6D_6, δ = 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 (N*C*H_2Ph), 57.2 (br, NCH_2), 54.14 (NCH_2), 51.13 (NCH_2), 36.89 (C-5). HRMS (ESI, MeOH) calcd for $C_{20}H_{27}N_2O_2$ (MH^+): 327.2073, found: 327.2027. Dihydrochloride: Anal. Calcd for $C_{20}H_{28}N_2O_2Cl_2$, H_2O: C, 57.55; H, 7.25; N, 6.71. Found: C, 57.35; H, 7.31; N, 6.56.

(3*S*,4*S*,5*R*)-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 Na_2CO_3 solution (10 % w/v, 12 mL). After extraction with CH_2Cl_2, and usual workup, the solvents were evaporated under reduced pressure. The crude product was purified by prepative TLC (eluent : Et_2O) to give the triacetylated compound (**6**) as a white crystals (83.1 mg, 76 %). Mp: 111-112 °C. $[\alpha]_D^{23}$ = – 44.4 ° (c 1.0, $CHCl_3$). 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, NC*Ha*Ph), 4.29 (2 d, 2H, *J* = 14.7, NCH_2), 4.14 (d, 1H, *J* = 14.7, NC*Hb*Ph), 3.66 and 3.25 (2 m, 2H, NCH_2), 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 (NC*Ha'*Ph), 2.53 (m, 1H), 2.30 (m, 1H, NC*Hb'*Ph), 2.15, 2.05, 2.00, 1.97, 1.95, 1.90 (6 s, 9H, 3 $COCH_3$). ^{13}C 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 (CH_2), 54.41, 52.90 (CH_2), 52.31 (CH_2), 47.58 (CH_2), 44.58, 44.17 (CH_2), 36.32, 36.05 (C-5), 21.79, 21.47, 21.12, 21.09, 20.97, 20.88 (CO*C*H_3). HRMS (ESI, MeOH) calcd for $C_{26}H_{33}N_2O_5$ (MH^+):

453.2389, found: 453.2353. Anal. Calcd for $C_{26}H_{32}N_2O_5$: C, 69.00; H, 7.13; N, 6.19. Found: C, 68.94; H, 7.32; N, 6.12.

(6*R*,6a*S*,3a*R*)-(2,5-Dibenzylhexahydropyrrolo[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_2Cl_2. The product obtained after usual workup was purified by flash chromatography (eluent : CH_2Cl_2-MeOH 9:1) and hydroxymethylpyrrolidine (**7**) was obtained as colorless oil (473.8 mg, 90 %). $[\alpha]_D^{23} = -23.8$ ° (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 %)], 190 (40 %). ^1H NMR ($CDCl_3 + D_2O + Na_2CO_3$): 7.35 (m, 10 H), 4.67 (dd, 1H, *J* = 4.7, *J'*= 8.2), 4.09 (d, 1H, *J* = 13, NC*Ha*Ph), 3.99 (d, 1H, *J* = 13, NC*Ha'*Ph), 3.90 (br d, 1H, NC*Hb*Ph), 3.84 (dd, 1H, *J*= 12, *J'* = 1.9), 3.72 (d, 1H, *J* = 12), 3.32 (d, 1H, *J* = 13, NC*Hb'*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 ($CDCl_3 + D_2O + Na_2CO_3$): 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 $C_{20}H_{25}N_2O_2$ (MH^+): 325.1916, found: 325.1909. Dihydrochloride: Anal. Calcd for $C_{20}H_{26}N_2O_2Cl_2$: C, 60.45; H, 6.60; N, 7.05. Found: C, 60.61; H, 6.81; N, 7.01.

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

Trifluoroacetic anhydride (325 μL, 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 μL, 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_2Cl_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%) and starting pyrrolidine (**7**) (47.3 mg, 23 %). **8** : $[\alpha]_D^{23} = 51$ ° (*c* 0.74, $CHCl_3$). IR: 3627, 3028, 1518 cm^{-1}. MS (ESI, MeOH) *m/z*: 347 [$(MNa)^+$, 20 %], 325 [$(MH)^+$, 100 %]. ^1H 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_2Ph), 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

$C_{20}H_{25}N_2O_2$ $(MH)^+$: 325.1916, found: 325.1921. Anal. Calcd for $C_{20}H_{24}N_2O_2$, 0.5 CH_3OH: C, 72.32; H, 7.70; N, 8.23. Found: C, 72.25; H, 7.44; N, 8.16.

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

A solution of Boc_2O (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_2Cl_2-MeOH 95:5) and gave the N-Boc aminopyrrolidine (**9**) as a white foam (264.2 mg, 69 %). $[\alpha]_D^{23}$ = 1.5 ° (*c* 0.99, $CHCl_3$). IR : 3363, 3020, 1663 cm^{-1}. MS (ESI, MeOH) *m/z*: 427 [$(MH)^+$, 100 %)], 371 (62 %). ^1H 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, NC*H*$_2$Ph), 4.02 (m, 1H, H-3), 3.91, 3.56 (2 d, 2H, *J* = 12.5, NC*H*$_2$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, *t*-Bu), 74.60 (C-3), 73.64 (C-2) , 61.80 (C-6), 59.60 (N*C*H_2Ph), 54.70 (NCH_2), 50.93 N*C*H_2Ph), 43.78 (C-4), 42.63 (NCH_2), 28.44 (CH_3, *t*-Bu). HRMS (ESI, MeOH) calcd for $C_{25}H_{35}N_2O_4$ $(MH)^+$: 427.2597, found: 427.2581. Hydrochloride : Anal. Calcd for $C_{25}H_{35}N_2O_4Cl$, CH_3OH : C, 63.08 ; H, 7.94. Found : C, 63.37 ; H, 7.64.

(3*S*,4*S*,5*R*)-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_2Cl_2. After usual workup, the crude product was purified by preparative TLC (eluent : CH_2Cl_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 %). **10**: $[\alpha]_D^{23}$ = 29.5 ° (*c* 0.56, $CHCl_3$). IR: 3379, 2937, 1661, 1425 cm^{-1}. MS *m/z*: 427 [$(MH)^+$, 33 %]$^+$, 371 (100 %), 327 (97.5 %). ^1H NMR : 7.29, 7.17 (2 m, 10H, H-Ar), 4.72 (d, 1H, *J* = 16, NC*Ha*Ph), 4.01 (d, 1H, *J* = 16, NC*Hb*Ph), 3.87 (m, 1H, OCH), 3.69 (m, 1H), 3.63 (m, 3H, NCH, CH_2), 2.86 (m, 1H, NCHa), 2.70 (d, 1H, *J* = 11.8, NCHb), 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 (NCH_2), 53.75 (NCH_2), 50.75 (NCH_2), 44.96 (NCH_2), 34.48 (C-5), 28.40 (CH_3, *t*-Bu). HRMS (ESI, MeOH) calcd for $C_{25}H_{35}N_2O_4$ (MH^+): 427.2597, found: 427.2597.

(3*S*,4*S*,5*S*)-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 CH_2Cl_2 (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 : CH_2Cl_2-MeOH-NH_4OH 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

1. S. Laschat and T. Dickner, *Synthesis*, 2000, 1781.
2. P. M. Weintraub, J. S. Sabol, J. M. Kane, and D. R. Borcherding, *Tetrahedron*, 2003, **59**, 2953.
3. U. Kazmaier and R. Grandel, *Eur. J. Org. Chem.,*1998, 1833 and references therein.
4. M. Achmatowicz and L. S. Hegedus, *J. Org. Chem.,* 2004, **69**, 2229 and references therein.
5. P. S. Lonkar and V. A. Kumar, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2147.
6. P. S. Lonkar, V. A. Kumar, and K. N. Ganesh, *Nucleosides, Nucleotides and Nucleic acids*, 2001, **20**, 1197.
7. a) R. C. Fuson and C. L. Zirkle, *J. Am. Chem. Soc*., 1948, **70**, 2760. b) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr*., 1958, 736.
8. a) N. Langlois and O. Calvez, *Synth. Comm.,* 1998, **28**, 4471. b) N. Langlois and O. Calvez, *Tetrahedron Lett.*, 1998, **39**, 9447.
9. a) J. Wilken, M. Kossenjans, W. Saak, D. Haase, S. Pohl, and J. Martens, *Liebig Ann. Chem.*, 1997, 573. b) J. Cossy, C. Dumas, and D. Gomez Pardo, *Eur. J. Org. Chem.,* 1999, 1693 and references therein.
10. N. Langlois, N. Van Bac, N. Dahuron, J. M. Delcroix, A. Deyine, D. Griffart-Brunet, A. Chiaroni, and C. Riche, *Tetrahedron*, 1995, **51**, 3571.
11. N. Langlois and F. Rakotondradany, *Tetrahedron,* 2000, **56**, 2437.