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Asymmetric Synthesis. XXXIX.[1] Synthesis of 3-substituted Piperidin-2-ones from Chiral Non-Racemic Lactams.

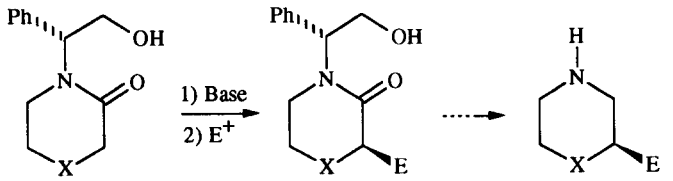
Laurent Micouin, Martine Bonin, Marie-Pierre Cherrier, Alain Mazurier°, Alain Tomas°, Jean-Charles Quirion*, Henri-Philippe Husson

Laboratoire de Chimie Thérapeutique Associé au CNRS, ° Laboratoire de Physique,
Faculté des Sciences Pharmaceutiques et Biologiques,
Université R. Descartes, 4, Av. de l'Observatoire, 75270 Paris Cedex 06, France.

Abstract : A series of 3-substituted piperidines in enantiomerically pure form has been synthesized from lactam **1** via the bromo derivative **2i**. *t*-Butyl acetate and 5-methylpyridine derivatives **2g** and **2h** were obtained optically pure by direct alkylation of **1** with corresponding halides. Azido, amino or benzyloxy products were obtained by diastereoselective substitution of **2i**.

INTRODUCTION

In our previous papers [2] we reported the diastereoselective alkylation of lactams derived from R-(-)-phenylglycinol (scheme 1). This methodology allowed the preparation of differently substituted piperidines and piperazines. However the reported examples only dealt with non functionalized electrophiles (MeI, $PhCH_2Br$, $CH_2 = CHCH_2$ Br). In order to extend the scope of our strategy we decided to investigate the reactivity of lactam **1** [2a] towards heterosubstituted reagents. Our goal was to prepare derivatives **2** bearing amino, alcohol or carboxylic acid functions at C-3 (R = NHR', N_3, OH, CO_2R',COHNR',...) to provide a general access to biologically interesting products.[3]



X : CH_2, NBoc

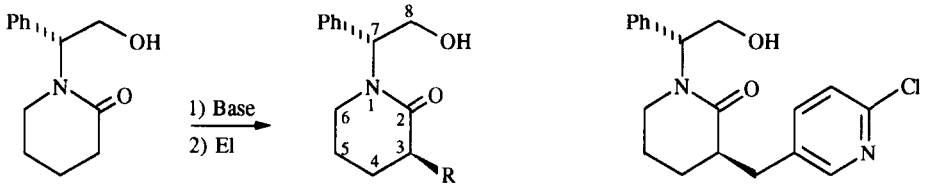
Scheme 1

RESULTS AND DISCUSSION

Lactam **1** was first prepared by our previously described method[2d], but recently we observed that it was possible to obtain this compound in 45% yield by condensation of (*R*)-phenylglycinol with methyl 5-bromovalerate in EtOH in the presence of DBU (see experimental). A first series of experiments was conducted

with electrophiles generally used for the introduction of a potential amino function (table 1). When the enolate of **1** was reacted with di-*tert*-butyl azodicarboxylate (DBAD)[4] (entry 1), no substitution product was observed. Reaction with trisyl azide (TrsN3)[5] as the electrophile led to azide derivative **2b** though in poor yield (10%) as a 1/1 mixture of two C-3 epimers (entry 2). Reaction of the enolate of **1** with Davis's oxaziridine[6] led to a complex mixture of products in which it has been impossible to detect the expected hydroxyl derivative.

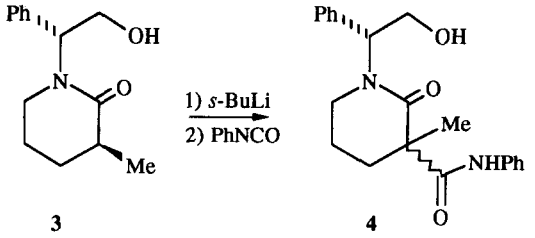
We then turned our attention to the introduction of a potential carboxylic acid function. Reaction of the enolate of **1** with CO_2 (g) furnished acid **2c** in quantitative yield but as a 1/1 mixture of two inseparable diastereomeric compounds (entry 3). Reaction with methyl chloroformate led to a complex mixture of C-3 substituted and non substituted carbonates; replacement of *s*-BuLi by NaHMDS as the base did neither improve the yield of substituted product nor favour the formation of one isomer (entries 4 and 5). The substituted products were also isolated after reaction with tosylcyanide and phenyl isocyanate in 69 % and 52 % yield respectively, however without any diastereoselectivity (entries 6 and 7). In order to determine the origin of the lack of diastereoselection, methyl derivative **3**[2a] was alkylated with phenyl isocyanate (scheme 2). A 1/1 mixture of epimers was also isolated indicating that the absence of diastereoselection was not due to a C-3 epimerization of compounds **2** after alkylation.



1 **2 a-i** **2h**

Entry	Base	El	R	Product	Yield (%)	de (%)
1	s-BuLi	DBAD	(NCb_zNHCb_z)	**2a**	0	-
2	s-BuLi	TrsN3	N_3	**2b**	10	0
3	s-BuLi	CO_2	CO_2H	**2c**	100	0
4	s-BuLi	$ClCO_2Me$	CO_2Me	**2d** (+ carbonate)	50	0
5	NaHMDS	$ClCO_2Me$	-	only carbonate	-	-
6	s-BuLi	TsCN	CN	**2e**	69	0
7	s-BuLi	PhNCO	C(O)NHPh	**2f**	52	0
8	s-BuLi	$BrCH_2CO_2t$-Bu	CH_2CO_2t-Bu	**2g**	44	≥ 95
9	s-BuLi	5-chloromethyl-2-chloropyridine	(2-chloro-5 pyridinyl)-methyl	**2h**	69	≥ 95
10	s-BuLi (-76°C)	Br_2	Br	**2i**	83	60
11	s-BuLi (-100°C)	Br_2	Br	**2i**	69	90

Table 1 : alkylation of lactam **1** with functionalized electrophiles.

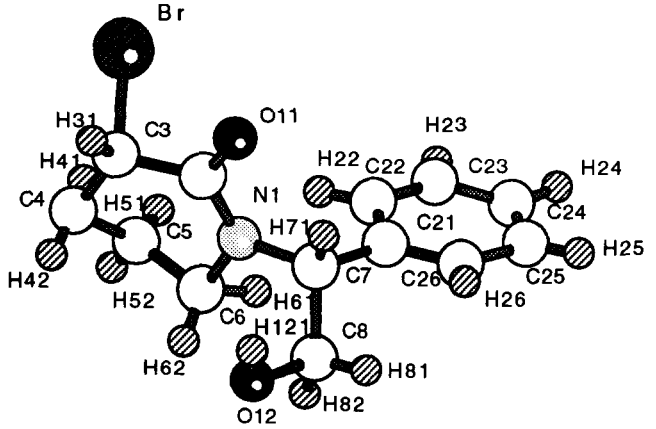


3 4

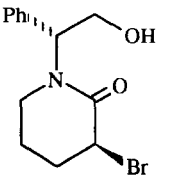
Scheme 2

When the functionalization of the electrophile was not located at the reacting center, an excellent diastereoselectivity was observed. Thus, alkylation of lactam **1** with *tert*-butyl bromoacetate in standard conditions (entry 8) led to compound **2g** in moderate yield (44 %) but as a single diastereomer detectable in NMR. By analogy with previous results [2] a (*R*) configuration was attributed to the newly created center. When 5-chloromethyl-2-chloropyridine[7] was used as the electrophile, methylchloropyridine derivative **2h** was also obtained in good yield (69%) and without any trace of C-3 epimeric compound (entry 9).

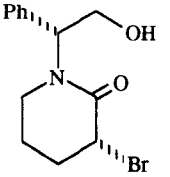
As the direct functionalization of C-3 position proved to be problematic, we decided to investigate a two-step process involving bromination then nucleophilic substitution. For this purpose the enolate of **1** was reacted with bromine (entries 10 and 11). When the reaction was performed at -100°C, compounds **2i** and **5** were isolated in 69 % yield in a 95/5 ratio; at - 70°C a 80/20 ratio was observed. The use of NBS did not improve the diastereoselectivity. The two isomers can be easily separated. An X-ray analysis of the major isomer **2i** furnished the C-3 configuration [8] (Figure). The configuration of this asymmetric center was the same as the 3-alkylated piperidin-2-ones previously synthesized by the same method. It is noteworthy that major isomer **5** slowly epimerized to a 80/20 thermodynamic mixture analogous to the reacting mixture obtained at -78°C while the minor isomer furnished the same mixture by treatment with K_2CO_3 in DMF at rt for 2h.



Figure



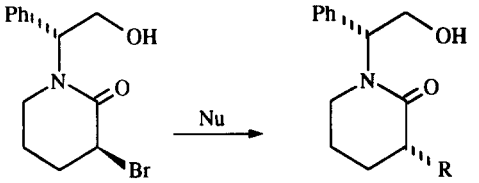
2i



5

Having in hand a method providing optically pure bromo derivative **2i** on a multigram scale we decided to study the reactivity of this compound towards different nucleophiles (Table 2).

Bromo derivative **2i** reacted with NaN_3 in CH_3CN in the presence of crown ether (18-C-6) to give **6a** in 63 % yield and 81 % de. The major isomer can be obtained optically pure after chromatography on silicagel. Although it has been impossible to obtain **6a** as a crystalline product suitable for X-ray analysis, we assumed that the reaction occurred with complete inversion of configuration. Cyano derivative **6b** was obtained in 71 % yield as an inseparable mixture of two isomers. It is likely that in this case a rapid epimerisation of C-3 due to H-3 acidity could explain this result.

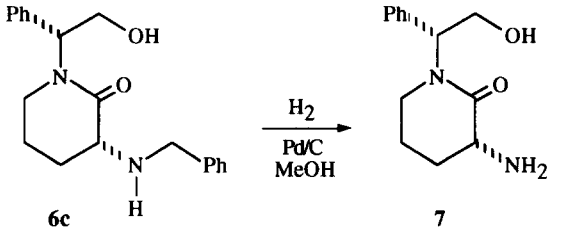


2i **6a-d**

Entry	Nucleophilic	Product	R	Yield (%)	de (%)
1	NaN_3, 18-C-6	**6a**	N_3	63	81
2	$Bu_4N^+CN^-$	**6b**	CN	71	0
3	$PhCH_2NH_2$	**6c**	$NHCH_2Ph$	95	80
4	$PhCH_2OH$	**6d**	OCH_2Ph	46	≥ 95

Table 2 : Substitution of bromo derivative **2i** with nucleophiles.

Benzylamine reacted with **2i** in CH_3CN at rt (entry 3) furnishing derivative **6c** in 95 % yield and with good diastereoselectivity (de : 80%). Hydrogenolysis of **6c** (H_2, Pd/C) quantitatively furnished 3-amino-piperidin-2-one **7** (scheme 3). Unfortunately, all our attempts to obtain **6c** and **7** as single isomers failed. These products were always contaminated by 10-15% of C-3 isomer. However pure amino compound **7** could be obtained independently by reduction of azide **6a**.[11]

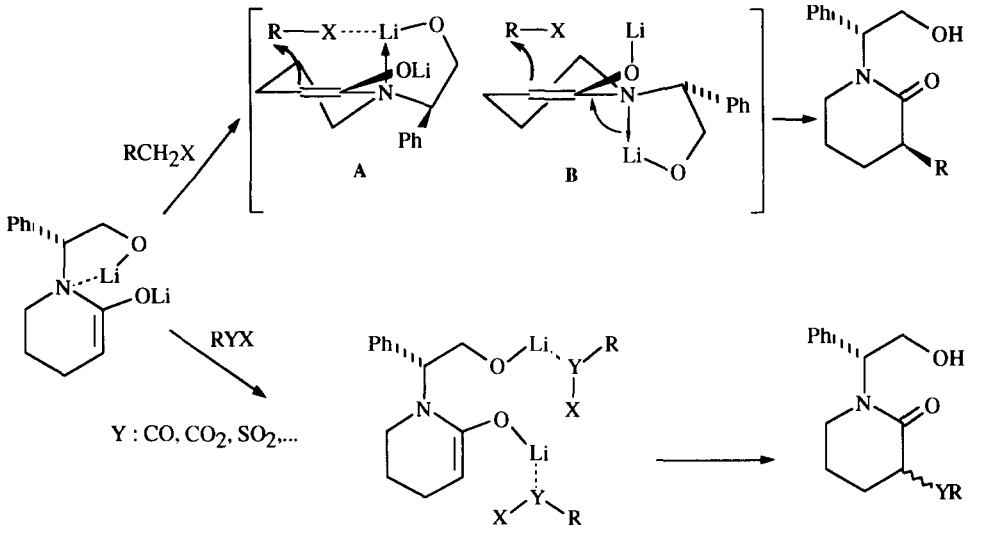


6c **7**

Scheme 3

In order to provide C-3 O-substituted derivatives, bromo derivative **2i** was reacted with benzyl alcohol. The reaction was complete after 2 h at rt in DMF, after formation of the alcoholate (NaH). A single isomer **6d** was obtained in 46 % yield.

The model proposed to explain the diastereoselectivity observed with lactam **1** involves an intramolecular chelation (scheme 4)[2a] in which the reacting intermediates (A or B) are rigidified thereby allowing a facial differentiation during the attack.



Scheme 4

During this work, we observed no diastereoselection with some electrophiles which possess an electron rich function (Lewis base) in the vicinity of the reacting center of the electrophile. Presumably this leads to an intermolecular chelation process with the lithium atom of the alcoholate which would modify the geometry of the intermediate, and therefore the diastereoselectivity. If this function is separated from the reacting center by at least one non substituted carbon (e.g. $BrCH_2CO_2tBu$) diastereoselectivity was then recovered.

EXPERIMENTAL SECTION

^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively on a Bruker AC 300 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 automatic polarimeter. Product purification was performed by flash chromatography on Silica Gel (Merck 60). All reactions involving air sensitive materials were carried out under a N_2 atmosphere. Compound **2d** which has been obtained as an inseparable mixture of diastereoisomers and carbonates is not described.

(*αR*)-N-(2-Hydroxy-1-phenylethyl)piperidine-2-one 1 :

A solution of (*R*)-(-)-phenylglycinol (1.37 g, 10^{-2} mol), methyl 5-bromovalerate (1.95g, 10^{-2} mol) and DBU (3.04g, 2 10^{-2} mol) in EtOH (20 mL) was stirred at reflux for 48 h. After evaporation of the solvent under reduced pressure, the residue was diluted with CH_2Cl_2 (50 mL) then washed with a saturated aqueous solution of NH_4Cl. The organic layer was dried over $MgSO_4$ then evaporated furnishing an oil which was purified by flash-chromatography (CH_2Cl_2/MeOH : 95/5). Lactam **1** was obtained as an oil (985 mg, 45%) which slowly crystallized. For physical and spectroscopic data see ref. 2d.

General procedure for preparation of compounds 2c-h :

To a solution of lactam **1** in THF (50 mL / 1g of **1**) under nitrogen, was added s-BuLi (2.5 eq) at -78°C. The mixture was stirred for 20 min, and electrophile (2.5 eq) in minimum of THF was added dropwise. After stirring at -78°C for 3 h, the mixture was treated with saturated aqueous solution of NH_4Cl, extracted twice

with AcOEt, dried over $MgSO_4$ and concentrated. The crude product was then purified by flash chomatography.

(αR, 3*R*) and (αR, 3*S*)-[*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one-3-yl]carboxylic acid 2c :

Reaction of enolate of **1** with CO_2 (gas) furnished an inseparable mixture of epimeric acids in a 1/1 ratio. ^1H NMR (δ ppm): 1.45-2.10 (m, 8H), 2.23 (m, 2xH-3), 2.92-3.50 (m, 4xH-6), 4.10-4.20 (m, 4H, 4xH-8), 5.82 (t, J = 6.3 Hz, H-7), 5.93 (t, J = 6.3 Hz, H-7), 7.10-7.40 (m, 10H). ^{13}C NMR (δ ppm) : 21.2, 21.5, 23.2, 23.4 (C-4 and C-5), 43.1, 43.7 (C-6), 46.1, 46.4 (C-3), 58.5, 59.0 (C-7), 60.5 (2xC-8), 127.6, 127.8, 128.3, 129.0, 135.6, 135.9, 170.5 and 171.6 (C-2), 182.3 ($\underline{C}O_2H$). IR (cm^{-1}) : 3390, 1720 ; 1620. MS (CI) : 264 (MH^+).

(αR, 3*R*) and (αR, 3*S*)-3-cyano-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one 2e :

Cyano derivative **2e** was obtained as a 1/1 mixture of two epimeric compounds. ^{13}C NMR (δ ppm) : 19.7, 20.9, 23.9, 25.7 (C-4 and C-5), 35.3, 35.7 (C-3), 42.6, 42.8 (C-6), 58.5, 58.9 (C-8), 60.6, 60.7 (C-7), 118.2 (CN), 127.8, 128.2, 128.7, 128.9, 136.0, 171.6 (C-2).

(αR, 3*R*) and (αR, 3*S*)-*N*-(2-hydroxy-1-phenylethyl)-3-benzamidopiperidin-2-one 2f :

Benzamide **2f** was obtained as a 1/1 mixture of two epimeric compounds in 52% yield. ^1H NMR (δ ppm) : 1.6-2.3 (m, 8H), 2.90-3.25 (m, 4H, 4xH-6), 3.50 (m, 2xH-3), 4.10-4.20 (m, 4xH-8), 5.80-5.90 (m, 2xH-7), 7.05-7.55 (m), 9.6-9.7 (br.s, NH). ^{13}C NMR (δ ppm) : 21.0, 21.3, 23.1, 23.2 (C-4, C-5), 43.5, 43.7 (C-6), 48.8, 48.9 (C-3), 58.4, 58.9 (C-7), 60.8, 61.2 (C-8), 119.9, 120.0, 124.1, 124.2, 127.5, 127.8, 128.0, 128.2, 128.7, 128.9, 136.3, 138.1, 166.8 and 167.0 ($\underline{C}ONHPh$), 170.1 (C-2). IR (cm^{-1}) : 3320, 1682, 1614. MS (EI) : 338, 320, 308, 77.

(αR, 3*R*)-3-*tert*-Butyloxycarbonylmethyl-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one 2g :

2g was obtained in 44% yield as a colourless oil. $[\alpha]_D$ = -72 (c : 1.07 ; EtOH). ^1H NMR (δ ppm): 1.45 (s, 9H, 3 Me), 1.61-1.70 (m, 1H, H-4), 1.70-1.86 (m, 2H, 2 H-5), 1.88-1.97 (m, 1H, H-4), 2.68-2.80 (m, 3H, 2 H-9, H-3), 3.12 (m, 1H, H-6), 3.22 (m, 1H, H-6), 4.1 (dd, J = 11.6, 4.8 Hz, 1H, H-8), 4.28 (dd, J = 11.6, 9.6 Hz, 1H, H-8), 5.31 (dd, J = 9.6, 4.8, 1H, H-7), 7.23-7.38 (m, 5H ar.). ^{13}C NMR (δ ppm) : 22.6 (C-4), 26.3 (C-5), 28.2 (3 Me), 37.6 (C-9), 39.2 (C-3), 46.4 (C-6), 62.5 (C-7, C-8), 80.9 (C-11), 127.8, 127.9, 128.7 (C ar.), 137.3 (C ar. quat.), 172.0 (C-10), 173.4 (C-2). IR (cm^{-1}) : 3409 ; 1720 ; 1621. MS (CI) : 334 (MH^+). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found : C, 68.78, H, 7.96, N, 4.31.

(αR,3*R*)-3-(2-Chloropyridin-5-yl-methyl)-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one 2h :

2h was obtained in 69% yield as a colourless oil. $[\alpha]_D$ = -22 (c : 1.09, EtOH). ^1H NMR (δ ppm): 1.43 (m, 1H, H-4), 1.6-1.8 (m, 3H), 2.68-2.82 (m, 2H, H-3 and H-6), 2.91 (dd, J=13.8, 8.4, 1H, H-6), 3.21 (m, 2H, 2 H-9), 3.80 (br. s, 1H, OH), 4.03-4.18 (m, 2H, 2 H-8), 5.86 (dd, J = 8.8, 5.8 Hz, 1H, H-7), 7.18 (m, 2H ar), 7.21 (d, J = 8.1 Hz, H-3'), 7.27-7.35 (m, 3H ar), 7.53 (dd, J = 8.1, 2.5 Hz, 1H, H-4'), 8.21 (d, J = 2.5 Hz, 1H, H-6'). ^{13}C NMR (δ ppm): 21.5, 25.2 (C-4 and C-5), 34.2 (C-9), 43.0 (C-3), 43.4 (C-6), 58.4 (C-7), 61.2 (C-8), 124.0 (C-2'), 128.7 (C ar), 134.1 (C quat. ar), 136.8 (C-5'), 139.9 (C-4'), 149.4 (C-2'), 150.4 (C-6'), 172.7 (C-2). IR (cm^{-1}) : 3394, 3018, 1619, 1215. MS (CI) : 346, 344. Anal. Calcd for $C_{19}H_{21}N_2O_2Cl$ + 1/2 AcOEt : C, 64.86, H : 6.48, N : 7.20. Found : C, 65.41, H, 6.66, N, 7.42.

(αR, 3*S*)-3-Bromo-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one 2i and (αR, 3*R*)-3-Bromo-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one 5 :

To a solution of lactam **1** (1.2 g, 5.4 mmol) in THF (100 ml) under nitrogen was added s.BuLi (2.5 eq.) at -78°C. After being stirred for 20 min, the mixture temperature was lowered to -100°C and bromine (288 µl, 5.4 mmol) was added dropwise. After being stirred at -100°C for 5 min, the mixture was treated with saturated NH_4Cl, extracted twice with AcOEt, dried over $MgSO_4$ and concentrated. The crude product was then roughly purified by flash chomatography (AcOEt) to give the bromo derivative as a 95/5 diastereomeric mixture. Optically pure **2i** (1.02g, 65%) and **5** (64 mg, 4%) were then obtained after a second flash

chromatography (AcOEt). The same reaction performed at -76°C led to **2i** and **5** in 66% and 17% yield respectively.

2i $[\alpha]_D$= -112 (c : 0.8 ; MeOH). mp = 129°C (ethyl acetate). ^{1}H NMR (δ ppm): 1.71 (m, 1H, H-5) ; 2.11-2.38 (m, 3 H, 2 H-4, H-5) ; 2.61 (s, 1H, OH) ; 3.12 (m, 1H, H-6 eq.) ; 3.32 (td, J = 6.4, 4.7 Hz, 1H, H-6 ax.) ; 4,12 (m, 1H, H-8) ; 4.22 (dd, J = 5.1, 5.0 Hz, 1H, H-8) ; 4.68 (td, J = 3.3, 1.3 Hz, 1H, H-3) ; 5.85 (dd, J = 5.1, 4.3 Hz, 1H, H-7) ; 7.20 - 7.40 (m, 5H, ar.). ^{13}C NMR (δ ppm): 18.6 ; 30.9 (C 4, C 5) ; 42.2 (C 6) ; 46.0 (C 3) ; 57.3 (C 7) ; 60.2 (C 8) ; 127.2 ; 127.6 ; 128.6 (C ar.) ; 136.5 (C ar. quat.) ; 168.0 (C 2). IR (cm^{-1}) : 3382 ; 1631. MS (EI) : 300 ; 298 ($MH^{+\cdot}$) ; 268 ; 266 ; 200 ; 188 ; 186 ; 180 ; 178 ; 159 ; 130 ; 121 ; 104 ; 86 ; 84 ; 70. HRMS calcd. for 298.0442 (M+ H^+) : found : 298.0450.

5 $[\alpha]_D$= -104 (c : 1.1, MeOH). Amorphous. ^{1}H NMR (δ ppm) 1.60 (m, 1H), 2.20 (m, 3H), 3.05 (m, 1H, H-6 eq), 3.30 (m, 2H, H-6ax and OH), 4.12 (m, 2H, 2 H-8), 4.63 (td, J = 4.4, 1.2 Hz, H-3), 5.53 (dd, J = 8.1, 5.8 Hz, H-8), 7.20-7.40 (m, 5H ar). ^{13}C NMR (δ ppm) : 19.5, 31.1 (C-4 and C-5), 44.3 (C-6), 45.9 (C-3), 60.3 (C-8), 61.8 (C-7), 128.0, 128.9 (CH ar), 136.4 (Cq ar), 168.1 (C-2). IR (cm^{-1}) : 3395, 1635. MS (EI) : 300, 298 (MH^+).

(α*R*, 3*R*)-3-Azido-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one 6a :

To a solution of bromo lactam **2i** (70 mg ; 0.24 mmol) in anhydrous acetonitrile (5 ml) was added sodium azide (17 mg, 0.26 mmol) and a catalytic amount of crown 18-C-6 (4 mg). The mixture was stirred at rt for 2 h, filtered and dried over $MgSO_4$. The solvent was evaporated and the crude product was roughly purified by flash chromatography (AcOEt) to give **6a** (38 mg, 63% yield) as a 90/10 diastereomeric mixture. Optically pure **6a** was then obtained after a second flash chromatography (AcOEt) as a colourless oil (27 mg, 44% yield). $[\alpha]_D$ = + 30 (c : 0.75 ; $CHCl_3$). ^{1}H NMR (δ ppm): 1.61-2.09 (m, 4H, 2 H-5, 2 H-4), 2.95 (m, 1H, H-6), 3.19 (m, 1H, H-6), 4.12 (m, 3H, 2 H-8, H3), 5.73 (dd, J = 8.5, 6.0 Hz, 1 H, H-7), 7.12-7.36 (m, 5 H ar.). ^{13}C NMR (δ ppm) : 20.4, 27.4 (C-4 , C-5), 43.4 (C-6), 59.1 (C-7), 59.9 (C-3), 61.4 (C-8), 127.9, 128.2, 128.9 (C ar.), 136.4 (Cq ar.), 169.3 (C-2). IR (cm^{-1}) : 3426 ; 2103 (N_3) ; 1635 ; 1443. MS (EI) : 261 ($MH^{+\cdot}$), 242, 229, 200, 121, 103, 91, 77. HRMS calcd. for 261.1352 (M+ H^+) : found : 261.1364.

(α*R*, 3*S*)-3-Benzylamino-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one 6c :

To a solution of bromo lactam **2i** (104 mg ; 0.35 mmol) in anhydrous acetonitrile (3 ml) was added benzylamine (76 µl, 0.27 mmol). The mixture was stirred at rt for 12 h, treated with aqueous potassium carbonate extracted twice with CH_2Cl_2 and dried over $MgSO_4$. Solvant was evaporated and the crude product was purified by flash chromatography (CH_2Cl_2 / MeOH 98:2) to give **6c** (70 mg, 62% yield) as a 90/10 diastereomeric mixture. Major diastereoisomer : ^{1}H NMR (δ ppm) (CD_3OD): 1.62-2.32 (m, 4H, 2 H-4, 2 H-5), 3.13 (m, 1H, H-3), 3.82 (d, J = 13.5 Hz, 1H, H-9), 3.95 (d, J = 13.5 Hz, 1H, H-9), 4.11-4.23 (m, 2H, 2 H-8), 5.91 (m, 1H, H-7), 7.31-7.52 (m, 10H ar.). ^{13}C NMR (δ ppm) (CD_3OD) : 21.9, 27.1 (C-4, C-5), 43.7 (C-6), 51.7 (C-9), 58.5 (C-3), 59.2 (C-7), 61.1 (C-8), 128.4, 128.6, 128.8, 128.9, 129.6 (CH ar.), 138.6, 140.4 (Cq ar.), 173.1 (C-2). MS (CI) : 325 (MH^+).

(α*R*, 3*S*)-3-Benzyloxy-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one 6d :

To a suspension of NaH (29 mg ; 1.2 mmol) in DMF (3 mL) was added benzyl alcohol (130 mg ; 1.2 mmol) at rt. After stirring for 20 min, a solution of bromo lactam **2i** (180 mg ; 0.6 mmol) in DMF (3 mL) was added slowly. Stirring was maintained at rt for 1 h, then a saturated solution of NH_4Cl (10 mL) was added. The mixture was extracted with Et_2O. Organic layer was dried over $MgSO_4$ then evaporated. Crude product was purified by flash-chromatography (AcOEt / cyclohexane : 90/10) furnishing **6d** (90 mg ; 46% yield) as a colourless oil. $[\alpha]_D$ = -28 (c : 1.0, MeOH). ^{1}H NMR (δ ppm) : 1.55-2.85 (m, 4H, 2 H-5 and 2 H-4), 3.21 (m, 1H, H-6eq), 3.45 (m, 1H, H-6ax), 3.82 (t, J = 5.9 Hz, 1H, H-3), 4.05 (m, 2H, 2 H-8), 4.71 and 4.85 (2 d, J = 11.9 Hz, 2H, OCH_2Ph), 5.68 (dd, J = 8.0, 5.9 Hz, 1H, H-7), 7.15-7.40 (m, 5H ar). ^{13}C NMR (δ ppm) 19.7, 27.6 (C-4 and C-5), 43.0 (C-6), 58.7 (C-3), 61.5 ($O\underline{C}H_2Ph$), 72.8 (C-8), 75.1 (C-7), 126.9, 128.6 (CH ar), 136.9, 138.3 (C quat. ar), 171.3 (C-2). IR (cm^{-1}) : 3402, 1635, 1453. MS (EI) : 325 (1), 294 (15), 266 (15), 219 (100), 188 (100), 91 (100). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82, H, 7.12, N, 4.30. Found : C, 73.59, H, 7.31, N, 4.34.

(αR, 3S)-3-Amino-*N*-(2-hydroxy-1-phenylethyl)piperidin-2-one 7:

A solution of benzylamine **6c** (90/10 diastereomeric mixture) (572 mg, 1.76 mmol) in MeOH (5 mL) was stirred for 48h under H_2 in the presence of $Pd(OH)_2$ (10 mg). After the catalyst was removed by filtration over celite and the solvent was evaporated, primary amine **7** (413 mg, 100% yield) was obtained as a 90/10 diastereomeric mixture. Major isomer : ^1H NMR (CD_3OD) (δ ppm) : 1.9-2.4 (m, 4H, 2 H-4 and 2 H-5), 3.25 (dtd, J = 12.5, 4.5 1.0 Hz, 1H, H-6eq), 3.51 (ddd, J = 12.5, 10.0, 4.6 Hz, 1H, H-6ax), 4.10 (dd, J = 11.5, 6.2 Hz, 1H, H-3), 4.20 (m, 2H, 2 H-8), 5.85 (dd, J = 7.7, 7.3 Hz, 1H, H-7), 7.3-7.5 (m, 5H ar). ^{13}C NMR (CD_3OD) (δ ppm) : 20.8, 25.3 (C-4 and C-5), 41.8 (C-6), 51.2 (C-3), 57.8 (C-7), 59.8 (C-8), 127.6, 128.0, 128.8 (CH ar), 136.4 (C quat ar), 168.0 (C-2). IR (cm^{-1}) : 3376, 1649. MS (CI) : 235.

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REFERENCES AND NOTES

1. For part XXXVIII see V. Schanen, M.-P. Cherrier, J.-C. Quirion, H.-P. Husson, *Synthesis*, in press.
2. a) L. Micouin, T. Varea, C. Riche, A. Chiaroni, J.-C. Quirion, H.-P. Husson, *Tetrahedron Lett.* **1994**, *35*, 2529-2532.
   b) V. Schanen, C. Riche, A. Chiaroni, J.-C. Quirion, H.-P. Husson, *Tetrahedron Lett.* **1994**, *35*, 2533-2536.
   c) T. Varea, M. Dufour, L. Micouin, C. Riche, A. Chiaroni, J.-C. Quirion, H.-P. Husson, *Tetrahedron Lett.* **1995**, *36*, 1035-1039.
   d) L. Micouin, J.-C. Quirion, H.-P. Husson, *Synthetic Commun.* in press.
3. For recent examples of such products see a) M.C. Desai, S.L. Lefkowitz, P.F. Thadeio, K.P. Longo, R.M. Snider, *J.Med.Chem.* **1992**, *35*, 4911-4913. b) T. Harrison, B.J. Williams, C.J. Swain, R.G. Ball, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545-2550.
4. a) D.A. Evans, T.C. Britton, R.L. Dorow, J.F. Dellaria, *J.Am.Chem.Soc.* **1986**, *108*, 6395.
   b) L.A. Trimble, J.C. Vederas, *J.Am.Chem.Soc.* **1986**, *108*, 6397.
5. D.A. Evans, T.C. Britton, J.A. Ellman, R.L. Dorow, *J.Am.Chem.Soc.* **1990**, *112*, 4011.
6. F.A. Davis, B.-C. Chen, *Chem. Rev.* **1992**, *92*, 913-934.
7. We thank Roussel-Uclaf Company (Dr. J.-P. Demoute and Dr. J.-L. Brayer) for a generous gift of 5-chloromethyl-2-chloropyridine.
8. Crystal data : $C_{13}H_{16}NBr0_2$. M_W = 298.19. A suitable crystal was investigated on a Siemens P_3 diffractometer (λ(MoKα) = 0.71069 Å, graphite monochromator). Orthorhombic, space group $P2_12_12_1$, Z=4, a=8.995(4), b=9.8445(5), c=14.267(8), d_c = 1.57g.cm^{-3}, F(000) = 310, μ = 0,31 mm^{-1}. 2118 reflections up to 2θ = 60° of wich 1360 with I> 3 σ(I) were kept in refinement calculations. The structure was solved by direct methods using SHELX86[9] and refined by least squares with SHELX76[10], minimising the quantity $\Sigma w(Fo-Fc)^2$; all non-hydrogens atoms were located in difference Fourier maps and refined at observed positions with isotropic temperature factors. Final $R=\Sigma(Fo-Fc)/\Sigma Fo$ = 0,046, $W_r=(\Sigma w(Fo-Fc)^2/\Sigma wFo^2)^{1/2}$=0,046 with $w=1/\sigma^2(Fo)$.
9. Sheldrick, G.M. (1986).*SHELX86*. Program for the solution of crystal structure. Univ. of Göttingen, Germany.
10. Sheldrick, G.M. (1976).*SHELX76*. Program for of crystal structure determination. Univ. of Cambridge, U.K..
11. R. Rodríguez, M. A. Estiarte, A. Diez, M. Rubiralta, A. Colell, C. García-Ruiz J. C. Fernández-Checa, following paper in this issue. The two samples were found to be identical (^1H and ^{13}C NMR). The differences observed in ^1H NMR were due to a difference of solvents (CD_3OD and $CDCl_3$).

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