Pergamon

Tetrahedron Vol. 51, No. 17, pp. 5143-5156, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00182-4

Synthetic Applications of 2-Aryl-4-piperidones. X[1] Synthesis of 3-Aminopiperidines, Potential Substance P Antagonists

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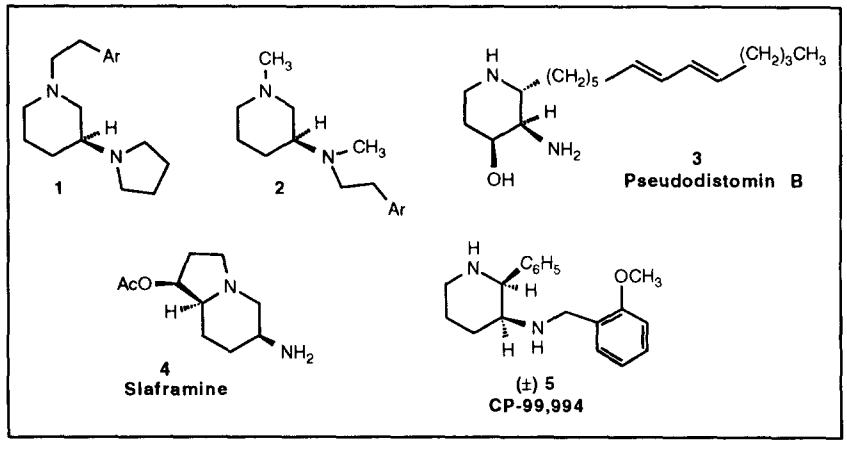
Abstract: A general method is described for the synthesis of 3-aminopiperidines from 4-piperidones based on a KOEt treatment of the tosylate of the corresponding oximes (Neber rearrangement). The procedure is applied to the synthesis of *N*-benzyl-3-amino-4,4-diethoxypiperidine (**13**), (*R*)-*N*-(2-hydroxy-1-phenyl)ethyl analogues **18**, and 2-phenyl derivatives **27-28**. The methoxybenzylation of the primary amino group of these aminopiperidines leads to a series of potential substance P antagonists.

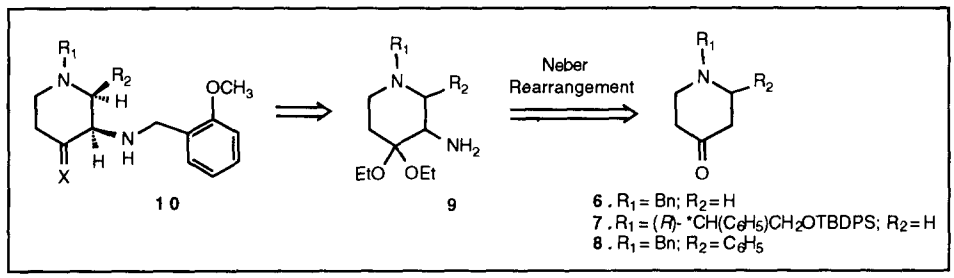
Numerous 3-aminopiperidine compounds have recently aroused great interest owing to their diverse and significant pharmacological effects. For instance, piperidines **1** and **2**, reported in 1992, have a strong affinity for σ receptors in the central nervous system.[2] Pseudodistomines (**3**)[3] are marine alkaloids with *in vitro* anti tumour activity, and slaframine (**4**) is responsible for cattle intoxication due to its conversion to a metabolite with muscarinic effects.[4] Of particular interest the last five years has been the racemic CP-99,994 (**5**), a non-peptidic antagonist of substance P.[5,6]



Scheme 1

So far three different approaches to the synthesis of the 2-aryl-3-aminopiperidine backbone have been reported: i) elaboration of the piperidine ring by condensation of γ-nitrobutyrate with benzaldehyde in the presence of ammonium acetate;[7] ii) formation of a 2-aryl-3-methoxycarbonylpiperidine from an appropriately substituted 5-chloropentylamine;[8] and iii) reduction of a 2-aryl-3-aminopyridine.[9] However, these routes do not allow either the chiral synthesis of these compounds, or easy structural modifications. We noted that a synthesis with these advantages might be based on the Neber rearrangement, which consists of the introduction of an amino group on the α position of a ketone. Although this reaction was originally described by Neber in 1936,[10] and despite its great potential applicability to the synthesis of pharmacologically interesting compounds, it has not been developed for use on piperidone nuclei.

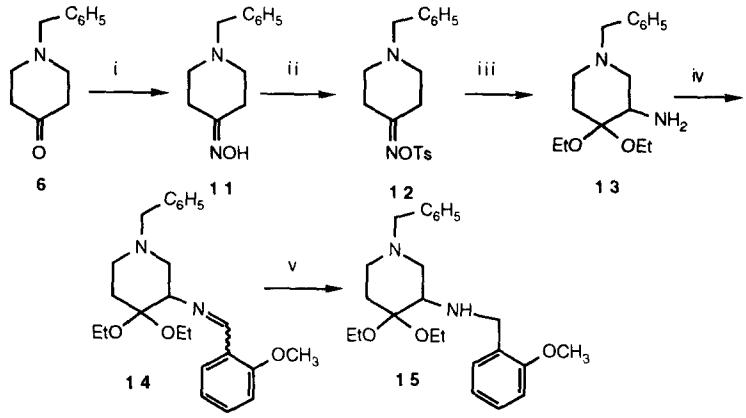
In this paper we describe the application of the Neber rearrangement to the preparation of 3-aminopiperidines **9** from *N*-benzyl-4-piperidone (**6**), its chiral analogue (*R*)-*N*-[2-(*tert*-butyldiphenylsilyloxy)-1-phenylethyl]-4-piperidone (**7**),[11] and *N*-benzyl-2-phenyl-4-piperidone (**8**). The eventual transformation of compounds **9** into CP-99,994 (**5**) analogues **10** has been carried out by means of imination and $NaBH_4$ reduction (Scheme 2).



Scheme 2

Commercial *N*-benzyl-4-piperidone (**6**) was first used in order to define the reaction conditions on a symmetrical nitrogenated model (Scheme 3). Oxime **11** was prepared from 4-piperidone **6** by a standard anhydrous method, and transformed into the corresponding tosylate by treatment with tosyl chloride in THF in the presence of anhydrous K_2CO_3. Formation of tosylate **12** was demonstrated by the presence of a singlet at δ 2.48 (Ar-CH_3) and two doublets at δ 7.8 and 7.3 (tosyl aromatic protons) in its ^1H NMR spectrum, and by the deshielding (Δδ 9.4 ppm) of the C-4 signal with respect to the parent oxime, in the ^{13}C NMR spectrum. Tosylate **12** was unstable under any purification conditions and decomposed on standing. Therefore, as soon as the total transformation of the oxime into the tosylate had been checked by NMR, **12** was immediately submitted to the Neber rearrangement conditions. Thus, treatment of **12** with 2 equivalents of KOEt in the presence of a desiccating agent (anhydrous sulphate) led to 3-amino-1-benzyl-4,4-diethoxypiperidine (**13**) in 63% yield. A methine signal at δ 50.1, only assignable to C-3, and a signal at δ 99.8 for the acetal carbon atom were characteristic of the 3-aminopiperidine system in the ^{13}C NMR spectrum. The ^1H NMR spectrum of **13** showed a triplet at δ 1.12 and a multiplet at δ 3.40-3.50 corresponding to the ethoxy protons of the acetal function, the latter overlapping with the AB system of the *N*-benzyl methylene group. The complete assignment of the δ 1.60-3.00 region of the ^1H NMR spectrum of **13** was carried out on the basis of 2D NMR experiments. Thus, in the COSY (H,C) experiment correlation of the C-5 methylene carbon (δ 27.4) with the proton signals at δ 1.72 (dm) and 1.79 (td), and of C-6 (δ 49.3) with the signals centered at δ 2.02 (td) and 2.60 (br d), allowed their identification as the equatorial and axial 5-H protons, and the axial and equatorial 6-H protons, respectively. The

assignment of the 3-H methine proton (a narrow doublet of doublets at δ 2.90) was accomplished by its correlation with C-3 (δ 50.1). In turn, 3-H was correlated with the doublet of doublets at δ 2.38 (J = 12 and 4 Hz) and with the broad doublet at δ 2.76 in the COSY (H,H) spectrum; therefore, these signals were assigned to 2-H_a and 2-H_e. The coupling constants of 3-H and 2-H protons indicate an axial disposition of the amino group. This preferred conformation can be explained as a result of the electronic repulsion between the primary amino group and the oxygens of the vicinal acetal function.



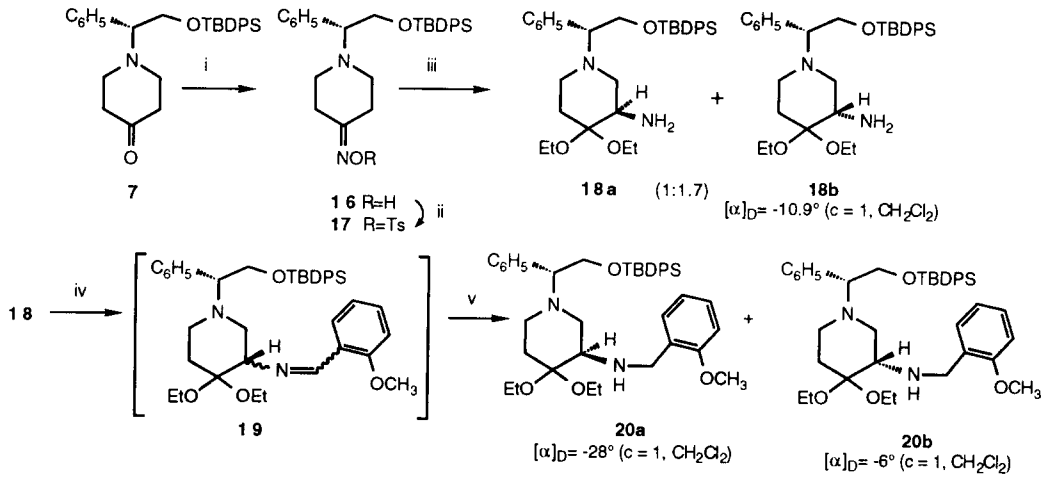
Reagents and conditions: i) $NH_2OH.HCl$ (2 equivalents), anhydrous K_2CO_3 (2 equivalents), dry EtOH, room temperature, 1 h (97%); ii) TsCl (1 equivalent), anhydrous K_2CO_3 (2 equivalents), THF, room temperature, 18 h; iii) KOEt (2 equivalents), EtOH, anhydrous $MgSO_4$, 0°C to room temperature, 1 h; 60°C, 1 h (63%); iv) 2-methoxybenzaldehyde (1 equivalent), C_6H_6, Dean-Stark, 48 h; (v) $NaBH_4$ (2 equivalents), CH_3OH, room temperature, 1 h (79%).

Scheme 3

Condensation of aminoacetal **13** with 2-methoxybenzaldehyde yielded imine **14**, whose formation was confirmed in the ^1H NMR spectrum by the singlets at δ 8.73 and 3.79 corresponding to the imine proton and the new methoxy group. Direct reduction of **14** using $NaBH_4$ in MeOH afforded amine **15** in 79% yield. The mass spectrum of **15** showed the molecular peak at *m/z* 398 and peaks at *m/z* 369 and 307, characteristic of the loss of the acetal moiety. The ^{13}C NMR spectrum of **15** showed four methylene signals at δ 28.9 (C-5), 46.8 (NCH_2), 50.1 (C-6) and 52.0 (C-2). All assignments were confirmed by the 2D NMR COSY (H,C) and (H,H) experiments. The facts that both protons on C-2 appear as broad doublets (J = 12 Hz), and that 3-H is a broad singlet (δ 2.62) indicate that the secondary amino group on C-3 still adopts an axial disposition, and that the electronic repulsion mentioned above is stronger than the steric one.

A similar reaction sequence was then applied on (*R*)-*N*-[2-(*tert*-butyldiphenylsilyloxy)-1-phenylethyl]-4-piperidone (**7**) (Scheme 4). Oxime **16** showed, in the ^1H NMR spectrum, three double doublets at δ 3.48, 3.85 and 4.04, which constitute the ABM system characteristic of the methine and methylene protons of the chiral chain, as well as two singlets at δ 0.96 and 1.05 for the *tert*-butyl protective group. However, the oximation was actually shown in the ^{13}C NMR spectrum by the shift of the C-4 signal (δ 157.9) and by the presence of four methylene signals at δ 24.7 (C-5; *Z* with respect to the hydroxyl), 31.4 (C-3; *E*), 50.1 (C-6) and 51.3 (C-2). As above, further tosylation of oxime **16** was verified as being complete by NMR. The presence of a singlet at δ 2.39 (Ar-CH_3) and a doublet at δ 7.90 (*ortho*

tosyl protons) in the ^1H NMR spectrum, together with a deshielding ($\Delta\delta$ ~10 ppm) of C-4 in the ^{13}C NMR spectrum were characteristic of the unstable tosylate **17**. Finally, the Neber rearrangement of **17** furnished a (1:1.7) mixture of diastereomeric 3-aminopiperidines **18a** and **18b** in 36% total yield. A sample of pure chiral amine **18a**[12] was obtained by flash chromatography. The structure of **18b** was confirmed by the presence of two triplets at δ 1.10 and 1.15 and a multiplet at δ 3.36-3.48 corresponding to the non-equivalent ethoxy substituents, as well as the presence of a broad singlet at δ 2.83 assigned as 3-H, in the ^1H NMR spectrum. The axial proton on the 2-position appeared as a doublet of doublets at δ 2.43. Its coupling constant with 3-H (2 Hz) indicated that the amino group on C-3 adopts an axial disposition, as in the previous series. The ^{13}C NMR spectrum showed the characteristic methine C-3 signal at δ 50.5, C-4 at δ 100.0, and the two *O*-methylene carbons of the acetal at δ 54.7 and 55.2.[13]



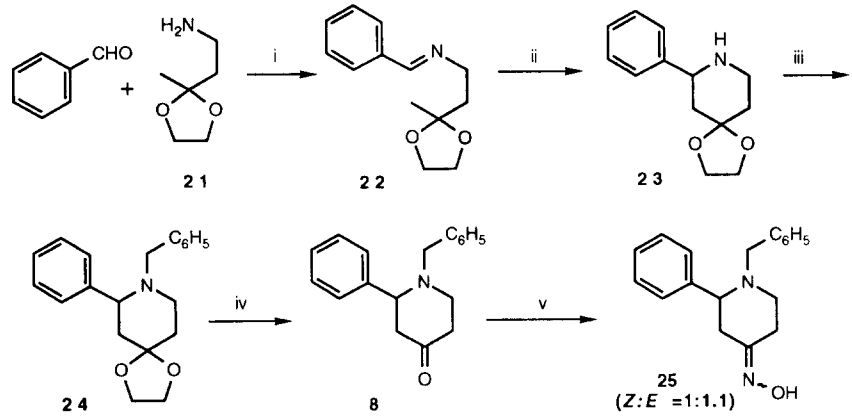
Reagents and conditions: i) $NH_2OH.HCl$ (2 equivalents), anhydrous K_2CO_3 (2 equivalents), dry EtOH, room temperature, 1 h (89%); ii) TsCl (1 equivalent), anhydrous K_2CO_3 (2 equivalents), THF, room temperature, 18 h; iii) KOEt (2 equivalents), EtOH, anhydrous $MgSO_4$, 0°C to room temperature, 1 h; 60°C, 1 h (36%); iv) 2-methoxybenzaldehyde (1 equivalent), C_6H_6, Dean-Stark, 48 h; (v) $NaBH_4$ (2 equivalents), CH_3OH, room temperature, 1 h (85%).

Scheme 4

The imination and reduction steps were carried out on the mixture of 3-aminopiperidines **18**, yielding the corresponding secondary amines **20a** and **20b**, which were separated by column chromatography. The most relevant ^1H NMR signals of **20a** were: i) a singlet at δ 3.70 (OMe) and a benzylic AB system (δ 3.47 and 3.78), showing that the *N*-alkylation had taken place; ii) the 3-H broad singlet at δ 2.54, a broad doublet at δ 2.69 for the equatorial 2-H, and a doublet at δ 2.22 corresponding to the axial 2-H, indicating that the C-3 susbtituent is axial. The benzyl methylene carbon resonated at δ 46.7, and the aromatic methoxy group at δ 54.9. As expected, isomer **20b** presented almost identical NMR data since the most stable chair conformation also has the amino substituent on C-3 in an axial orientation.[12,13]

Our third objective was to study the Neber rearrangement on 2-phenyl-4-piperidone **8**, which was synthesized according to our usual method for the preparation of 2-aryl-4-piperidones (Scheme 5). Thus, condensation of amine **21**[14] with benzaldehyde and further *p*-TsOH cyclization of the resulting imine **22** furnished piperidine **23** in 68% yield.[15] *N*-Benzylation and the hydrolysis of the acetal function led to the required piperidine **8**, which showed the

characteristic doublet of doublets at δ 3.58 corresponding to the axial 2-H in its ^{1}H NMR spectrum, and the carbonyl signal at δ 208.3 in its ^{13}C NMR spectrum. Treatment of **8** with hydroxylamine chlorohydrate in the presence of pyridine gave a (1:1.1) mixture of oximes **25**. The oximation was once again made evident by the ^{13}C NMR shift of C-4: δ 157.9 for ***E*-25** and δ 157.5 for ***Z*-25**. The stereochemical assignment of oximes **25** was inferred from the ^{13}C NMR data. Thus, the major isomer ***E*-25** presented C-3 and C-5 at δ 40.9 and 24.8, while the same carbons resonated at δ 33.8 and 31.4 in the minor product ***Z*-25** (Δδ = -6.2 for C-3 and +6.6 for C-5).



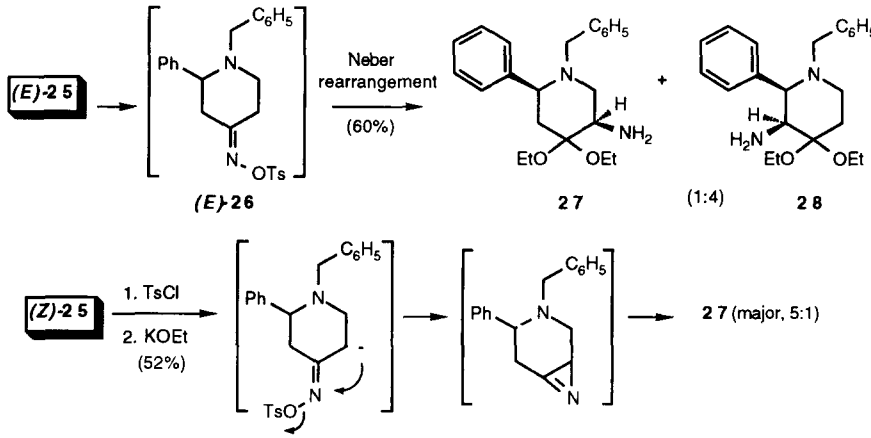
Reagents and conditions: (i) C_6H_6, Dean-Stark, 18 h (96%); ii) *p*-TsOH (2 equivalents), C_6H_6, Dean-Stark, 4 h (68%); iii) $C_6H_5CH_2Br$ (1.2 equivalents), anhydrous K_2CO_3, dry C_6H_6, room temperature, 6 h (80%); iv) 4N HCl-dioxane, Δ, 1.5 h (52%); v) $NH_2OH.HCl$,(2 equivalents), pyridine (2 equivalents), EtOH, 18 h, room temperature, and 1 h, Δ (59%).

Scheme 5

The Neber rearrangement was carried out first on the major oxime ***E*-25**, following the optimized methodology (Scheme 6). Thus, once the complete tosylation of ***E*-25** had been checked by NMR, tosyloxime **26** was immediately submitted to KOEt treatment in EtOH in the presence of anhydrous carbonate. Flash chromatography of the reaction mixture allowed the isolation of aminopiperidines **27** and **28** in a (1:4) proportion (60% total yield), which were identified from their spectral data. The major product, 3-amino-2-phenylpiperidine **28**, showed two methine signals at δ 68.3 and 56.0 (C-3), and two methylene piperidine carbons at δ 27.5 (C-5) and 49.1 (C-6) in the ^{13}C NMR spectrum. In its ^{1}H NMR spectrum, 2-H and 3-H protons appeared as narrow doublets (J = 2.6 Hz), showing the axial disposition of the amino group on C-3, which is *cis* with respect to the phenyl group. Compound **27** presented in its ^{1}H NMR spectrum the 2-H axial proton as a double doublet (δ 3.33), which implied the non-substitution on C-3, and the axial 6-H as a double doublet at δ 2.46, as the most characteristic data. The coupling constant values allowed the identification of **27** as the isomer in which the amino substituent is axial. The relative stereochemistry (2,5) was confirmed in the ^{13}C NMR spectra by the shielding γ-gauche effect observed on C-3 for compound **27** (Δδ = 3.2), compared with the 2,5-*trans* product **29**, whose formation was detected only in one occasion. As observed for amines **13** and **18**, aminopiperidines **27-29** showed non-equivalent acetal ethoxy chains due to the influence of the neighboring amine substituents.

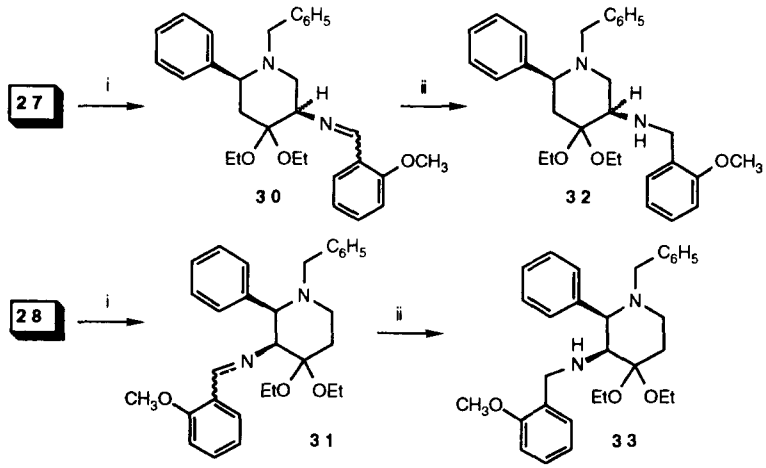
When ***Z*-25** was used as the substrate for the Neber rearrangement, compounds **27** and **28** were isolated from the reaction mixture in a (5:1) proportion and in 52% total yield. The regioselectivity thus observed in the Neber

rearrangement allows us to suppose that the intermediate azetine[10b,10f] is formed by an *anti* displacement of the tosyl group.



Scheme 6

Compounds **27** and **28** were transformed into their methoxybenzyl derivatives **32** and **33** *via* reduction of imines **30** and **31**. The secondary amino substituents maintained their axial disposition as shown in their ^1H NMR spectra by the signal shape of 5-H_e in **32**, and 3-H_e in **33** (broad singlets), and the coupling constants of the axial neighboring protons (6-H_a and 2-H_a, respectively).



Reagents and conditions: i) 2-Methoxybenzaldehyde (1 equivalent), C_6H_6, Dean-Stark, 48 h; (ii) $NaBH_4$ (2 equivalents), CH_3OH, room temperature, 1 h (85%).

Scheme 7

In this work we have defined the conditions which allow synthesis of 3-aminopiperidines from 4-piperidones using the Neber rearrangement, and we have demonstrated the general utility of the reaction for this purpose. We have thus achieved the synthesis of five analogues of CP-99,994 (**5**). Methoxybenzylaminopiperidines **15**, **32** and **33** are currently under pharmacological study.

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 instrument (200 MHz) and 2D NMR COSY experiments were performed on a Varian XL-500 instrument (500 MHz). Unless otherwise noted, NMR spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Flash column chromatography was carried out on SiO_2 (silica gel 60, 40-63 mm, Macherey-Nagel). TLC was performed on SiO_2 (silica gel 60 F254, Merck) and developed with the solvent described in each case for flash chromatography. The spots were located by UV light and Draggendorff or hexachloroplatinate reagent. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica i Biològica, CID, Barcelona.

***N*-Benzyl-4-piperidone Oxime (11)**. To a mixture of $NH_2OH.HCl$ (1.47 g, 21.15 mmol) and K_2CO_3 (2.9 g, 21.15 mmol) in dry EtOH (8 ml), commercial 1-benzyl-4-piperidone (2 g, 10.57 mmol) diluted in dry EtOH (2 ml) was added. The reaction mixture was refluxed for 1 h, and filtered after cooling. The residue was washed with dry EtOH, and the filtrate was evaporated to yield oxime **11** (2.1 g, 97 %) as a solid which was used without further purification: mp 125-126 °C; IR (NaCl) 3678-3624 (OH) cm^{-1}; ^1H NMR 2.40 (t, J = 7 Hz, 2H, 3-H_a and 5-H_a), 2.55 and 2.60 (2t, J = 7 Hz, 2H each, 3-H_e, 5-H_e, 2-H_a and 6-H_a), 2.65 (t, J = 7 Hz, 2H, 2-H_e and 6-H_e), 3.55 (s, 2H, $CH_2C_6H_5$), 7.30 (s, 5H, Ph-H), 8.89 (br s, 1H, OH) ; ^{13}C NMR 24.3 (C-3), 31.2 (C-5), 52.1 and 53.3 (C-2 and C-6), 62.5 (NCH_2Ph), 127.2, 128.2, 129.2, and 137.5 (Ph), 157.3 (C=N); MS m/z (%) 204 (M^+, 15), 187 (6), 127 (9), 113 (19), 91 (100). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.59; H, 7.84; N, 13.72. Found: C, 70.98; H, 7.76; N, 13.81.

3-Amino-1-benzyl-4,4-diethoxypiperidine (13). A mixture of oxime **11** (3.67 g, 18 mmol), tosyl chloride (3.43 g, 18 mmol) and K_2CO_3 (4.97 g, 36 mmol) in dry THF (100 ml) was stirred at room temperature under nitrogen atmosphere for 16 h. The carbonate was filtered off and the solvent evaporated yielding ***N*-benzyl-4-piperidone *O*-tosyloxime (12)** (6.98 g) which was immediately used without further purification: ^1H NMR 2.30-2.65 (m, 8H, piperidine), 2.48 (s, 3H, $PhCH_3$), 3.50 (s, 2H, $PhCH_2$), 7.25-7.40 (m, 7H, Ph-H), 7,30 (d, J = 7 Hz, 2H, Ph-m), 7.89 (d, J =7 Hz, 2H, Ph-*o*); ^{13}C NMR 21.4 (CH_3), 26.0 (C-3), 30.5 (C-5), 51.1 and 52.1 (C-2 and C-6), 61.4 (CH_2Ph), 127.2, 128.1 128.4, 128.8, 129.3, 132.3, and 144.6 (Ph), 166.1 (C=N). Potassium (1.4 g, 36 mmol) was slowly added in dry EtOH (20 ml) under N_2 atmosphere until complete dissolution of the metal. To the resulting KOEt solution cooled at 0°C, a solution of tosylate **12** (6.9 g, 18 mmol) in dry EtOH (40 ml) was slowly added in the presence of anhydrous Na_2SO_4 (10 g). The reaction mixture was stirred at room temperature for 1 h, heated at 60°C for 1 h, and once cooled, it was filtered and evaporated. The residue was flash chromatographed (Et_2O-MeOH, 95:5) yielding 3-aminopiperidine **13** (3.13 g, 63%): IR (NaCl) 3372 (NH_2) cm^{-1}; ^1H NMR (500 MHz) 1.12 (t, J = 7 Hz, 3H, CH_3), 1.72 (dm, J = 12 Hz, 1H, 5-H_e), 1.79 (td, J = 12 and 4 Hz, 1H, 5-H_a), 1.96 (br s, 2H, NH_2), 2.02 (td, J = 12 and 2 Hz, 1H, 6-H_a), 2.38 (dd, J = 12 and 4 Hz, 1H, 2-H_a), 2.60 (br d, J =12 Hz, 1H, 6-H_e), 2.76 (br d, J =12 Hz, 1H, 2-H_e), 2.90 (dd, J = 6 and 4 Hz, 1H, 3-H), 3.40-3.50 (m, 6H, CH_2Ph and OCH_2), 7.28 (m, 5H, Ph-H) ; ^{13}C NMR 14.9 (CH_3), 27.4 (C-5), 49.3 (C-6), 50.1 (C-3), 54.6 (CH_2Ph), 55.2 (C-2), 61.9 (OCH_2), 99.9 (C-4), 126.6, 127.9, 128.5, 138.3; MS m/z (%) 279 (M^++1, 2), 257 (1), 219 (2), 216 (3), 187 (8), 147 (5), 120 (19), 91 (100). Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.98; H, 9.34; N, 11.21.

1-Benzyl-3-[2-(methoxybenzyl)amino]-4,4-diethoxypiperidine (15). To a solution of piperidine **13** (859 mg, 3.09 mmol) in dry C_6H_6 (80 ml), 2-methoxybenzaldehyde (427.7 mg, 3.09 mmol) was added and the mixture was refluxed for 48 h. The organic phase was evaporated to yield **1-benzyl-4,4-diethoxy-3-[(2-methoxybenzylidene)amino]piperidine (14**, 1.3 g) which was directly reduced. IR (NaCl) 1680 (C=N); ^{1}H NMR 1.13 and 1.14 (2t, J = 7 Hz, 3H each, CH_3), 1.80 (br d, J = 12 Hz, 1H, 5-H_e), 2.30 (br t, J = 12 Hz, 1H, 6-H_a), 2.55 (br t, J = 12 Hz, 1H, 5-H_a), 2.65-2.70 (m, 3H, 3-H, 6-H_e and 2-H_a), 3.45-3.65 (m, 7H, 2-H_e, CH_2Ph and OCH_2), 3.79 (s, 3H, OCH_3), 6.85 (d, J = 7 Hz, 1H, Ph-*m*), 7.02 (t, J = 7 Hz, 1H, Ph-*m*'), 7.15-7.35 (m, 6H, Ph-H and Ph-*p*), 8.05 (d, J = 7 Hz, 1H, Ph-*o*'), 8.73 (s, 1H, =CH); ^{13}C NMR 15.5 (CH_3), 31.5 (C-5), 50.1 (C-2), 55.2 and 55.2 (C-6 and OCH_3), 55.7 (C-3), 57.2 (CH_2Ph), 62.0 (OCH_2),99.3 (C-4), 110.8, 120.6, 126.7, 127.0, 127.8, 128.0, 128.2, 128.9, 129.0, 131.5, 157.0 (CH=N); MS m/z (%) 396 (M^+, 1), 351 (4), 321 (2), 280 (2), 234 (51), 216 (17), 188 (11), 119 (20), 91 (100). To a suspension of $NaBH_4$ (233 mg, 6.2 mmol) in dry MeOH (3 ml) cooled at 0°C under N_2 atmosphere, a solution of imine **14** (1.3 g, 3.9 mmol) in dry MeOH (12 ml) was added dropwise. The reaction mixture was stirred at 0°C for 1 h and then was poured on ice-H_2O and extracted with Et_2O. The organic extract was evaporated to give amine **15** (974 mg, 79%) after flash chromatography (DEA-Et_2O, 0.5:99.5): IR (NaCl) 3340 (NH) cm $^{-1}$; ^{1}H NMR (500 MHz) 1.10 (t, J=7 Hz, 6H, CH_3), (br d, J=12 Hz, 1H, 5-H_e), 1.92 (td, J=12 and 5 Hz, 1H, 5-H_a), 2.10 (t, J=12 Hz, 1H, 6-H_a), 2.18 (m, 1H, 2-H_a), 2.62 (br s, 1H, 3-H), 2.67 (br d, J = 12 Hz, 1H, 6-H_e), 2.74 (br d, J=12 Hz, 1H, 2-H_e), 3.23-3.40 (m, 4H, OCH_2), 3.39 (d, J = 13 Hz, 1H, NCHPh), 3.56 (d, J = 13 Hz, 1H, NCHPh), 3.60 (d, J = 13 Hz, 1H, $NCHC_6H_5$), 3.75 (s, 3H, OCH_3), 3.82 (d, J = 13 Hz, 1H, $NCHC_6H_5$), 6.78 (d, J = 7 Hz, 1H, Ph-3H)), 6.83 (td, J = 7 and 1 Hz, 1H, Ph-5H), 7.08 (dd, J = 7 and 2 Hz, 1H , Ph-6H), 7.17 (td , J = 7 and 2 Hz, 1 H, Ph-4H), 7.20-7.26 (m, 1H, Ph-*p*) , 7.29 (2 t, J = 7 Hz, 2 H, Ph-*m*), 7.35 (br d, J = 7 Hz, 1H, Ph-*o*); ^{13}C NMR 15.1 and 15.3 (CH_3), 28.9 (C-5), 46.8 (NCH_2Ph), 50.1 (C-6), 52.0 (C-2), 54.5 and 54.7 (OCH_2), 54.9 (OCH_3), 55.9 (C-3), 62.4 (NCH_2Ph), 99.7 (C-4), 109.8 (Ph-C3), 120.1 (Ph-C5), 126.7 (Ph-*p*), 128.0 (Ph-*o*), 128.8 (Ph-*m*), 130.0 (C_6H_5-*ipso*), 157.6 (Ph-C2); MS m/z (%) 398 (M^+, 12), 369 (14), 307 (16), 278 (9), 216 (13), 132 (20), 121 (68), 91 (100). Anal. Calcd for $C_{24}H_{34}N_2O$.HCl: C, 66.27; H, 8.11; N, 6.44. Found: C, 66.09; H, 8.23; N, 6.34.

(α*R*)-*N*-[2-(*tert*-Butyldiphenylsilyloxy)-1-phenylethyl]-4-piperidone Oxime (16). Operating as for the preparation of oxime **11**, from piperidone **7**[12] (1 g, 2.18 mmol), NH_2OH.HCl (304 mg, 4.37 mmol) and K_2CO_3 (603 mg, 4.37 mmol) in dry EtOH, oxime **16** was obtained (920 mg, 89%): $[\alpha]_D$ = -9.1 (c=1, CH_2Cl_2); IR (NaCl) 3596 (OH) cm^{-1}; ^{1}H NMR 0.96 (s, 6H, $SiCCH_3$), 1.05 (s, 3H, $SiCCH_3$), 2.22 (t, J = 5 Hz, 2H, 2-H_e and 6-H_e), 2.45-2.60 (m, 6H, 3-H, 5-H, 2-H_a, and 6-H_a), 3.48 (dd, J = 7 and 5 Hz, 1H, α-H), 3.85 (dd, J = 12 and 5 Hz, 1H, β-H_A), 4.04 (dd, J = 12 and 7 Hz, 1H, β-H_B), 7.15-7.75 (m, 15H, Ph-H); ^{13}C NMR 19.1 (Si*C*CH_3), 24.7 (C-5), 26.7 (SiC*C*H_3), 31.4 (C-3), 50.1 (C-6), 51.3 (C-2), 65.8 ($SiOCH_2$), 70.8 (C-α), 127.1, 127. 5, 128.0, 128.4, 129.5, 129.6, 133.4, 134.8, 135.5, 135.6, and 140.0 (3xPh), 157.9 (C=N); MS m/z (%) 473 (M^+, 1), 455 (1), 415 (2), 203 (100), 146 (2), 135 (5), 91 (8). Anal. Calcd for $C_{29}H_{36}N_2O_2Si$: C, 73.69; H, 7.68; N, 5.93. Found: C, 73.33, H, 7.92; N, 5.97.

(α*R*,3*R)-3-Amino-*N*-[2-(*tert*-butyldiphenylsilyloxy)-1-phenylethyl]-4,4-diethoxypiperidine (18a-b)**. Operating as for the preparation of tosylate **12**, from piperidone oxime **16** (1.98 g, 4.2 mmol), tosyl chloride (799 mg, 4.2 mmol) and K_2CO_3 (1.12 g, 8.4 mmol) in dry THF (50 ml), tosyloxime **17** was obtained, which was used immediately without further purification: ^{1}H NMR 1.04 and 1.11 (2 s, 6H and 3H, $SiCCH_3$), 2.39 (s, 3H, $PhCH_3$), 3.55 (t, J = 5 Hz, 1H, α-H), 3.90 (dd, J = 12 and 5 Hz, 1H, β-H_A), 4.05 (dd, J = 12 and 5 Hz, 1H, β-H_B), 7.10-7.85 (m, 17H, Ph-H), 7.90 (d, J = 7 Hz, 2H, Ph-*o*); ^{13}C NMR 19.0 (Si*C*CH_3), 21.5 (CH_3), 25.5 (C-5), 26.7 (SiC*C*H_3), 31.3 (C-3), 49.6

(C-6), 50.6 (C-2), 65.7 ($SiOCH_2$), 70.2 (C-α), 126.9, 127.3, 127.5, 127.6, 128.1, 128.6, 129.2, 129.5, 129.7, 133.2, 134.8, 135.4, 139.7, and 144.7 (3xPh), 167.4 (C=N). Operating as for the preparation of 3-aminopiperidine **13**, from potassium (327 mg, 8.4 mmol), dry EtOH (20 ml) and tosylate **17**, a 1:1.7 mixture of diastereomeric 3-aminopiperidines **18a** and **18b** (828 mg, 36%) was obtained. Piperidine **18a** (major isomer, lower R_f): $[\alpha]_D$ = -10.9 (CH_2Cl_2, c =1); IR (NaCl) 3692 and 3600 (NH_2) cm^{-1}; ^1H NMR (500 MHz) 0.95 (s, 9H, $SiCCH_3$), 1.10 and 1.15 (2 t, J = 7 Hz, 3H each, OCH_2CH_3), 1.75 (m, 2H, 5-H), 2.25 (td, J = 12 and 5 Hz, 1H, 6-H_a), 2.43 (dd, J = 12 and 2 Hz, 1H, 2-H_a), 2.69 (br d, J = 12 Hz, 1-H, 2-H_e), 2.83 (br s, 1H, 3-H), 3.05 (br d, J = 12 Hz, 1H, 6-H_e), 3.36-3.48 (m, 5H, OCH_2 and α-H), 3.82 (dd, J = 12 and 7 Hz, 1H, β-H_A), 3.93 (dd, J = 12 and 7 Hz, 1H, β-H_B), 7.10-7.50 (m, 15 H, Ph-H); ^{13}C NMR 15.3 (OCH_2CH_3), 19.1 ($SiCCH_3$), 26.7 ($SiCCH_3$), 28.8 (C-5), 47.2 (C-6), 50.5 (C-3), 53.3 (C-2), 54.8 (OCH_2), 55.2 (OCH_2), 65.4 (Cβ), 70.2 (Cα), 100.0 (C-4), 126.9, 127.1, 127.6, 128.0, 128.3, 129.3, 133.4, 135.5, and 140.3 (3xPh); MS m/z (%) 546 (M^+, 0.1), 277 (39), 231 (100), 183 (11), 135 (33), 91 (11). Anal. Calcd for $C_{33}H_{46}N_2O_3Si$: C, 72.52; H, 8.42; N, 5.13.Found: C, 72.73; H, 8.29; N, 5.13. Piperidine **18b** (minor isomer, higher Rf, from the mixture): ^{13}C NMR 15.3 (CH_2CH_3), 19.1 ($SiCCH_3$), 26.7 ($SiCCH_3$), 28.7 (C-5), 48.0 (C-6), 50.5 (C-3), 53.1 (C-2), 54.8 (OCH_2), 55.2 (OCH_2), 65.5 (Cβ), 70.3 (Cα), 100.0 (C-4), 126.9, 127.1, 127.6, 128.0, 128.3, 129.3, 133.4, 135.5, and 140.3 (Ph).

(α*R*,3*R)-*N*-[2-(*tert*-Butyldiphenylsilyloxy)-1-phenylethyl]-3-[(2-methoxybenzyl)amino]-4,4-diethoxypiperidine (20a-b).** Operating as for the preparation of imine **14**, from 3-aminopiperidines **18a-b** (365 mg, 0.71 mmol), 2-methoxybenzaldehyde (96.7 mg, 0.71 mmol), and dry C_6H_6 (40 ml), a mixture of **(α*R*,3*R**)-*N*-[2-(*tert*-butyldiphenylsilyloxy)-1-phenyl]ethyl-4,4-diethoxy-3-(2-methoxybenzylidene)aminopiperidines (19**, 500 mg) were obtained, which were used without further purification: ^1H NMR 8.65 and 8.75 (2s, 1H each, N=CH); ^{13}C NMR 156.6 and 156.7 (C=N). Operating as for the preparation of compound **15**, from imines **19** (470 mg, 0.71 mmol), $NaBH_4$ (53.7 mg, 1.42 mmol), and dry MeOH (2 ml), a crude was obtained, which was flash chromatographed (CH_2Cl_2-MeOH, 97:3) to yield piperidines **20a-b** (402 mg, 85%) which were separated by preparative chromatography (CH_2Cl_2-MeOH, 99:1, 3 migrations). Compound **20a** (Higher Rf, 140 mg, 35%): $[\alpha]_D$ = -28° (c = 1, CH_2Cl_2); IR (NaCl) 3336 (NH) cm^{-1}; ^1H NMR (500 MHz) 0.94 (s, 9H, $SiCCH_3$), 1.10-1.14 (m, 6H, OCH_2CH_3), 1.77 (dd, J = 12 and 2 Hz, 1H, 5-H_e), 1.90 (td, J = 12 and 4 Hz, 1H, 5-H_a), 2.06 (br s, 1H, NH), 2.22 (d, J = 12 Hz, 1H, 2-H_a), 2.34 (td, J = 12 and 2 Hz, 1H, 6-H_a), 2.54 (br s, $W_{1/2}$ = 6 Hz, 1H, 3-H_e), 2.69 (br d, J = 12 Hz, 1H, 2-H_e), 2.93 (m, 1H, 6-H_e), 3.27 and 3.34 (2 m, 2H each, OCH_2), 3.38 (m, 1H, α-H), 3.47 (d, J = 13 Hz, 1H, $NHCH_A$), 3.70 (s, 3H, OCH_3), 3.78 (br d, J = 13 Hz, 1H, $NHCH_B$), 3.85 (dd, J = 11 and 6 Hz, 1H, β-H_A), 4.04 (dd, J = 11 and 6 Hz, 1H, β-H_B), 6.76 (d, J = 8 Hz, 2H, Ph-H), 6.81 (td, J = 8 and 1 Hz, 2H, Ph-H), 7.02 (dd, J = 8 and 1 Hz, 2H, Ph-H), 7.15-7.54 (m, 13H, Ph-H); ^{13}C NMR 15.2 and 15.4 (OCH_2CH_3), 19.1 ($SiCCH_3$), 26.7 ($SiCCH_3$), 29.5 (C-5), 46.7 ($NHCH_2$), 47.7(C-6), 51.0 (C-2), 54.5 and 54.9 (OCH_2), 54.9 (OCH_3), 56.0 (C-3), 66.1 (C-β), 71.2 (C-α), 99.7 (C-4), 109.9, 120.2, 126.9, 127.5, 127.6, 127.7, 127.9, 128.5, 129.5, 130.1, 133.5, 135.6, and 141.4 (Ph); MS m/z (%) 622 (M^+, 1), 576 (71), 485 (1), 411 (1), 351 (43), 305 (22), 248 (37), 197 (15), 121 (100), 91 (65). Compound **20b** (Lower Rf, 189 mg, 47%): $[\alpha]_D$ = +6° (c = 1, CH_2Cl_2); ^1H NMR (500 MHz) 0.93 (s, 9H, $SiCCH_3$), 1.09 and 1.10 (2 t, J = 7 Hz, 3H each, OCH_2CH_3), 1.63 (br d, J = 12 Hz, 1H, 5-H_e), 1.75 (td, J = 12 and 2 Hz, 5-H_a), 2.65 (t, J = 12 Hz, 1H, 6-H_a), 2.39 (d, J = 12 Hz, 1H, 2-H_a), 2.49 (d, J = 12 Hz, 1H, 6-H_e), 2.66 (br s, $W_{1/2}$ = 6 Hz, 1H, 3-H_e), 2.94 (d, J = 12 Hz, 1H, 2-H_e), 3.32-3.37 (m, 4H, OCH_2), 3.66 (s, 3H, OCH_3), 3.70 (t, J = 11 Hz, 1H, α-H), 3.71 (d, J = 10 Hz, 1H, $NHCH_A$), 3.81 (d, J = 10 Hz, 1H, $NHCH_B$), 3.89 (dd, J = 11 and 6 Hz, 1H, β-H_A), 4.00 (dd, J = 11 and 6 Hz, 1H, β-H_B), 6.67 (d, J = 7 Hz, Ph(OMe)-3H), 6.80 (br t, J = 7 Hz, Ph(OMe)-5H), 7.08 (t, J = 7 Hz, Ph(OMe)-4H), 7.15-7.58 (m, 16H, Ph-H); ^{13}C NMR

15.2 and 15.3 (OCH_2CH_3), 19.0 ($SiCCH_3$), 26.7 ($SiCCH_3$), 29.6 (C-5), 47.4 (CH_2Ph), 48.4 (C-6), 50.2 (C-2), 54.7 and 54.8 (OCH_2), 55.0 (OCH_3), 56.6 (C-3), 65.0 (C-β), 70.8 (C-α), 99.7 (C-4), 109.9, 120.2, 126.9, 127.5,127.7, 127.9, 128.2, 128.5, 129.5, 129.7, 130.2, 133.5, 135.5, 135.7, 139.6, and 141.3 (Ph). Anal Calcd for $C_{41}H_{54}N_2SiO_4$. 1/2 H_2O: C, 72.85; H, 8.20; N, 4.14. Found: C, 72.55; H, 8.21; N, 4.31.

4,4-Ethylenedioxy-2-phenylpiperidine (23). A solution of amine **21**[14] (3.2 g, 24.6 mmol) and benzaldehyde (2.35 g, 22.2 mmol) in dry C_6H_6 (100 ml), was stirred under N_2 atmosphere at 0°C for 30 min, at room temperature for 1 h, and at reflux for 4 h, using a Dean-Stark trap. After cooling, the solvent was evaporated to yield a mixture of ***N*-benzylidene-4,4-ethylenedioxybutylamines (22-*Z*:22-*E***, 1:8.5, 5.4 g, 96% yield) which was used without purification: IR ($CHCl_3$) 1650 (C=N) cm^{-1}; ^1H NMR 1.29 (minor isomer)* and 1.37 (2s, 3H each, CH_3), 1.95* and 2.06 (2t, J = 7 Hz, 2H each, CH_2), 2.90* and 3.70 (2t, J = 7 Hz, 2H each, NCH_2), 3.90 (s, OCH_2), 7.30-7.37 (m, Ph-H), 7.69 and 7.85* (2m, 2H each, Ph-*o*), 8.27 and 8.65* (2s, 1H each, CH=N). To a solution of *p*-TsOH (8.98 g, 49.2 mmol) in dry C_6H_6 (200 ml), previously anhydrated by refluxing in a Dean-Stark trap for 2 h, a solution of imines **22** (5.4 g, 23.6 mmol) in dry C_6H_6 (50 ml) was added. The mixture was refluxed for 4 h, poured on aqueous Na_2CO_3 and extracted with Et_2O. The organic extract was washed with a saturated solution of Na_2CO_3 and the organic phase was evaporated. The residue was flash chromatographed (CH_2Cl_2-CH_3OH, 98:2) to give piperidine **23** (3.5 g, 68%): IR (NaCl) 3316 (NH) cm^{-1}; ^1H NMR 1.55-1.90 (m, 4H, 3-H and 5-H), 3.85 (dd, J = 11 and 3 Hz, 1H, 2-H_a), 3.15 (dm, J = 11 Hz, 1H, 6-H_e), 3.00 (td, J = 12 and 6 Hz, 1H, 6-H_a), 3.99 (s, 4H, OCH_2), 7.20-7.50 (m, 5H, Ph-H); ^{13}C NMR 35.0 (C-5), 43.4 and 44.1 (C-6 and C-3), 59.0 (C-2), 63.9 and 64.1 (OCH_2), 107.5 (C-4), 126.4 (Ph-*o*), 127.0 (Ph-*p*), 128.2 (Ph-*m*), 143.7 (Ph-*ipso*); MS m/z (%) 219 (M^+, 5), 190 (15), 188 (10), 174 (100), 158 (22), 132 (27), 118 (33), 104 (45), 87 (50). Anal Calcd for $C_{13}H_{17}NO_2$: C, 61.10; H, 7.09; N, 5.48. Found: C, 60.96; H, 7.03; N, 5.43. **23.HCl**: mp 218-219°C (acetone); ^1H NMR (d_6-DMSO) 1.90 (t, J = 11 Hz, 1H), 4.00 (m, 4H, OCH_2), 4.35 (d, J = 11 Hz, 1H, 2-H), 7.40 and 7.65 (2m, 5H, Ph-H), 9.00-9.80 (br, 2H, NH_2).

***N*-Benzyl-4,4-ethylenedioxy-2-phenylpiperidine (24).** To a solution of piperidine **23** (3.5 g, 16 mmol) in dry C_6H_6 (100 ml) benzyl bromide (2.28 ml, 19 mmol) was added dropwise, in the presence of K_2CO_3 (5 g). The mixture was stirred under N_2 atmosphere at room temperature for 6 h. After filtration on Celite® the solvent was evaporated and the residue was flash chromatographed (C_6H_6-hexane, 4:6) to yield piperidine **24** (3.95 g, 80%): ^1H NMR 1.65 (dt, J = 12 and 4 Hz, 1H, 5-H_e), 1.80-2.00 (m, 3H, 3-H and 5-H_a), 2.22 (dt, J = 12 and 4 Hz, 1H, 6-H_a), 2.80 (d, J = 15 Hz, 1H, CH_APh), 2.95 (dm, J = 12 Hz, 1H, 6-H_e), 3.40 (dd, J = 12 and 5 Hz, 1H, 2-H_e), 3.75 (d, J = 15 Hz, 1H, CH_BPh), 3.90-4.00 (m, 4H, OCH_2), 7.10-7.50 (m, 10 H, Ph-H); ^{13}C RMN 34.6 (C-5), 44.6 (C-3), 49.7 (C-6), 58.5 (CH_2Ph), 63.8 and 64.0 (OCH_2), 66.1 (C-2), 106.9 (C-4), 126.4 (Ph-*o*), 1270 (Ph-*p*), 127.8 (Ph'-*o*), 128.0 (Ph -*p*), 128.3 (Ph-*m*), 128.4 (Ph'-*m*), 139.4 (Ph'-*ipso*), 143.9 (Ph-*ipso*); MS m/z (%) 309 (M^+, 35), 264 (11), 232 (100), 218 (30), 194 (18), 146 (67), 91 (76). **24. HCl**: mp 197-198°C (acetone). Anal. Calcd for $C_{20}H_{23}NO_2$.HCl: C, 62.51; H, 6.94; N, 4.05; Cl, 10.27. Found: C, 62.12; H, 7.22; N, 4.19; Cl, 10.39.

***N*-Benzyl-2-phenyl-4-piperidone (8)**. A solution of piperidine acetal **24** (3.96 g, 12.8 mmol), in dioxane-4N HCl (1:1, 80 ml) was refluxed for 1.5 h. The reaction mixture was poured on ice, basified with Na_2CO_3, and extracted with CH_2Cl_2. The dry organic extract was evaporated to give piperidone **8** (1.75 g, 52%) after flash chromatography (CH_2Cl_2-CH_3OH, 95:5): IR (NaCl) 1723 (CO) cm^{-1}; ^1H NMR 2.24-2.42 (m, 2H, 3-H_a and 5-H_a), 2.53-2.75 (m, 3H, 6-H_a, 3-H_e and 5-H_e), 2.94 (d, J = 14 Hz, 1H, CH_APh), 3.16-3.30 (ddd, J = 12, 6 and 5 Hz, 1H, 6-H_e), 3.58 (dd, J = 11 and 4

Hz, 1H, 2-H_a), 3.84 (d, J = 14 Hz, 1H, CH_BPh), 7.10-7.50 (m, 10H, Ph-H); ^{13}C NMR 41.3 (C-5), 50.2 and 51.0 (C-6 and C-3), 58.0 (CH_2Ph), 68.2 (C-2), 125.9, 127.2, 127.8, 128.2, 128.4, 128.9, 138.9, and 142.4 (Ph), 208.3 (C=O); MS m/z (%) 265 (M^+, 24), 264 (21), 222 (7), 194 (24), 188 (29), 177 (25), 91 (100). Anal. calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.21; N, 5.28. Found: C, 81.44; H, 7.22; N, 5.28.

***N*-Benzyl-2-phenyl-4-piperidone Oxime (25).** To a solution of $NH_2OH.HCl$ (779 mg, 11.2 mmol) and pyridine (0.91 ml, 11.2 mmol) in dry EtOH (10 ml), a solution of 4-piperidone **8** (1.5 g, 5.6 mmol) in dry EtOH (20 ml) was added. The reaction mixture was stirred overnight at room temperature and refluxed for 1 h. The EtOH was evaporated, the residue was dissolved with saturated aqueous $NaHCO_3$, and extracted with Et_2O. The organic extract was washed with H_2O and evaporated to give an oil which was flash chromatographed (hexane-Et_2O, 80:20) to isolate oximes **25**. Oxime ***(E)*-25** (higher Rf, 496 mg, 32%): IR (NaCl) 3248 (OH) cm^{-1}; ^1H NMR (500 MHz) 2.05-2.15 (m, 2H, 5-H_a and 6-H_a), 2.45-2.55 (m, 2H, 3-H), 2.84 (d, J = 14 Hz, 1H, CH_APh), 3.05-3.10 (m, 1H, 6-H_e), 3.20 (d, J = 12 Hz, 1H, 5-H_e), 3.35 (dd, J = 12 and 4 Hz, 1H, 2-H_a), 3.75 (d, J = 14 Hz, 1H, CH_BPh), 7.25 (m, 8H, Ph-H), 7.35 (t, J = 7 Hz, 1H, Ph-H), 7.45 (d, J = 7 Hz, 1H, Ph-H), 8.20 (br, 1H, OH); ^{13}C NMR 24.8 (C-5), 40.9 (C-3), 50.8 (C-6), 58.5 (CH_2Ph), 68.6 (C-2), 126.8, 127.4, 127.5, 128.2, 128.6, 128.7, 139.0, and 143.1 (Ph), 157.9 (C=N); MS m/z (%) 280 (M^+, 20), 263 (33), 203 (16), 194 (11), 187 (12), 144 (11), 118 (16), 106 (15), 91 (100). Oxime ***(Z)*-25** (lower Rf, 455 mg, 29%) IR (NaCl) 3248 (OH) cm^{-1}; ^1H NMR (500 MHz) 2.00-2.10 (m, 2H, 6-H_a and 3-H_a), 2.25 (dq, J = 14 and 3 H, 1H, 5-H_e), 2.35 (td, J = 12 and 5 Hz, 1H, 5-H_a), 2.79 (d, J = 14 Hz, 1H, CH_APh), 3.08 (ddd, J = 12, 6 and 2 Hz, 1H, 6-H_e), 3.25 (dd, J = 11 and 4 Hz, 1H, 2-H_a), 3.35 (ddd, J = 14, 4 and 2 Hz, 1H, 3-H_e), 3.71 (d, J = 14 Hz, 1H, CH_BPh), 7.20-7.40 (m, 10H, Ph-H), 8.10 (br, 1H, OH); ^{13}C NMR 31.4 (C-5), 33.8 (C-3), 52.0 (C-6), 58.5 (CH_2Ph), 67.2 (C-2), 126.8, 127.4, 127.5, 128.0, 128.5, 128.7, 139.0, 143.3, and 157.5 (C=N); MS m/z (%) 280 (M^+, 14), 263 (26), 203 (11), 187 (20), 144 (14), 118 (14), 91 (100). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: 77.09; H, 7.20; N, 9.71.

***cis*-5-Amino-*N*-benzyl-4,4-diethoxy-2-phenylpiperidine (27) and *cis*-3-Amino-*N*-benzyl-4,4-diethoxy-2-phenylpiperidine (28).** From ***(E)*-25:** Operating as for the preparation of tosyloxime **17**, from oxime ***(E)*-25** (455 mg, 1.6 mmol), tosyl chloride (310 mg, 1.6 mmol), K_2CO_3 (449 mg, 3.2 mmol) and dry THF (1.5 ml), ***N*-benzyl-2-phenyl-4-piperidone *O*-tosyloxime (*E*-26)** was obtained (750 mg), which was used without further purification: ^1H NMR 2.11 (br t, J = 12 Hz, 1H, 5-H_a), 2.43 (s, 3H, CH_3), 2.52 (br t, J = 12 Hz, 1H, 6-H_a), 2.80 (d, J = 14 Hz, 1H, CH_APh), 3.11 (br d, J - 12 Hz, 1H, 6-He), 3.35 (dd, J = 12 and 5 Hz, 1H, 2-H_a), 3.71 (d, J = 14 Hz, 1H, CH_BPh), 7.10-7.50 (m, 12 H, Ph-H), 7.85 (d, J = 7 Hz, 2H, tosyl Ph-*o*); ^{13}C NMR 21.4 (CH_3), 26.7 (C-3), 39.9 (C-5), 50.0 (C-6), 57.9 (CH_2Ph), 67.6 (C-2), 126.6-129.3 (Ph), 132.6 and 138.3 (Ph-*ipso*), 142.0 (tosyl Ph-*ipso*), 144.6 (tosyl Ph-*p*), 166.6 (C=N). Operating as for the preparation of 3-aminopiperidine **13**, from tosyloxime ***(E)*-26** (750 mg, 1.6 mmol), potassium (130 mg, 3.3 mmol), anhydrous Na_2SO_4 (1.5 g) and dry EtOH (5 ml), compounds **27** and **28** were isolated after flash chromatography (CH_2Cl_2-MeOH, 95:5), in a 1:4 proportion (60% total yield). ***cis*-5-Aminopiperidine 27** (75 mg, 12%): IR ($CHCl_3$) 3750 and 3650 (NH_2) cm^{-1}; ^1H NMR (500 MHz) 1.16 and 1.25 (2t, J = 7 Hz, 3H each, CH_3), 1.74-1.90 (m, 2H, 3-H), 2.46 (dd, J = 11.5 and 2.2 Hz, 1H, 6-H_a), 2.82 (d, J = 13 Hz, 1H, CH_APh), 2.89 (dd, J = 11.5 and 4 Hz, 1H, 6-H_e), 2.94 (br s, $W_{1/2}$=8 Hz, 1H, 5-H_e), 3.33 (dd, J = 11.5 and 5 Hz, 1H, 2-H_a), 3.42-3.60 (m, 4H, OCH_2), 3.75 (d, J = 13 Hz, 1H, CH_BPh), 7.05-7.45 (m, 10 H, Ph-H); ^{13}C NMR 15.3 and 15.5 (CH_3), 38.3 (C-3), 50.1 (C-5), 53.8 (C-6), 54.9 and 55.3 (OCH_2), 58.3 (CH_2Ph), 65.4 (C-2), 100.3 (C-4), 126.7-127.3, 128.1-128.6, 139.2, and 143.8 (Ph); MS m/z (%) 309 (M^+-OEt, 4), 279 (11), 217 (56), 196 (26), 171 (10), 118 (10), 91 (100). Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.57; H, 8.47; N, 7.90. Found: C, 74.96; H, 8.16; N, 7.81. ***cis*-3-**

Aminopiperidine 28 (300 mg, 48%): IR (NaCl) 3750 and 3650 (NH_2) cm^{-1}; ^1H NMR (500 MHz) 1.17 and 1.27 (2 t, J = 7 Hz, 3H each, CH_3), 1.60-170 (br s, 2H, NH_2), 1.77 (dm, J = 12 Hz, 1H, 5-H_e), 1.90 (td, J = 12 and 3.5 Hz, 1H, 5-H_a), 2.10 (td, J = 12 and 3.5 Hz, 1H, 6-H_a), 2.80 (d, J = 14 Hz, 1H, CH_APh), 2.80-2.85 (m, 1H, 6-H_e), 2.90 (d, J = 2.6 Hz, 1H, 3-H_e), 3.40-3.60 (m, 4H, OCH_2), 3.75 (d, J = 2.6 Hz, 1H, 2-H_a), 3.97 (d, J = 14 Hz, 1H, CH_BPh), 7.20-7.50 (m, 10H, Ph-H); ^{13}C NMR 15.2 and 15.4 (2 CH_3), 27.5 (C-5), 49.1 (C-6), 54.7 and 55.1 (OCH_2), 56.0 (C-3), 59.1 (CH_2Ph), 68.3 (C-2), 100.5 (C-4), 126.6-127.4, 128.1-128.6, 139.7, and 141.1 (Ph). Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.57; H, 8.47; N, 7.90. Found: C, 74.65; H, 8.23; N, 7.79. **From *(Z)*-25:** Operating as for the preparation of tosyloxime **17**, from oxime ***(Z)*-25** (496 mg, 1.76 mmol), tosyl chloride (338 mg, 1.77 mmol), K_2CO_3 (489 mg, 3.54 mmol) and dry THF (1.5 ml), ***N*-benzyl-2-phenyl-4-piperidone *O*-tosyloxime (*Z*-26)** was obtained (792 mg), which was used without further purification: ^1H NMR 2.11 (br t, J = 12 Hz, 1H, 5-H_a), 2.43 (s, 3H, CH_3), 2.52 (br t, J = 12 Hz, 1H, 6-H_a), 2.80 (d, J = 14 Hz, 1H, CH_APh), 3.11 (br d, J = 12 Hz, 1H, 6-He), 3.35 (dd, J = 12 and 5 Hz, 1H, 2-H_a), 3.71 (d, J = 14 Hz, 1H, CH_BPh), 7.10-7.50 (m, 12 H, Ph-H), 7.85 (d, J = 7 Hz, 2H, tosyl Ph-*o*); ^{13}C NMR 21.4 (CH_3), 26.7 (C-3), 31.0 (C-5), 51.1 (C-6), 57.9 (CH_2Ph), 67.6 (C-2), 126.6-129.3 (Ph), 132.6 and 138.3 (Ph-*ipso*), 142.0 (tosyl Ph-*ipso*), 144.6 (tosyl Ph-*p*), 166.2 (C=N). Operating as for the preparation of 3-aminopiperidine **13**, from potassium (144 mg, 3.7 mmol), dry EtOH (8 ml) and tosylate ***(Z)*-26** (830 mg, 1.8 mmol), aminopiperidines **27** and **28** were obtained, after flash chromatography, in a 5:1 proportion (52% total yield). **From a mixture:** When the reaction was carried out following the above procedure from a mixture of oximes ***(E)*-** and ***(Z)*-25** (1.3 g, 2.56 mmol), aminopiperidines **27** and **28** were accompanied with a third compound, identified as ***trans*-5-amino-*N*-benzyl-4,4-diethoxy-2-phenylpiperidine (29)**: ^1H NMR 1.15 and 1.25 (2 t, J = 7 Hz, 3H each, CH_3), 1.60-1.70 (br s, 2H, NH_2), 1.75 (dd, J = 12 and 11 Hz, 1H, 3-H_a), 2.05 (t, J = 12 Hz, 1H, 6-H_a), 2.10 (dd, J = 12 and 2 Hz, 1H, 3-H_e), 2.75 (d, J = 13 Hz, 1H, CH_APh), 2.80 (dd, J = 12 and 4 Hz, 1H, 6-H_e), 3.05 (dd, J = 12 and 4 Hz, 1H, 5-H_a), 3.32 (dd, J = 12 and 2 Hz, 2-H_a), 3.50-3.70 (m, 4H, OCH_2), 3.75 (d, J = 13 Hz, 1H, CH_BPh), 7.00-7.50 (m, 10H, Ph-H); ^{13}C NMR 15.6 and 15.8 (CH_3), 41.5 (C-3), 54.8 (C-5), 56.1 (C-6), 57.4 and 58.0 (OCH_2), 58.7 (CH_2Ph), 65.2 (C-2), 99.7 (C-4), 126.8, 127.2, 127.4, 128.0, 128.3, 128.5, 139.4, and 142.0 (Ph). Anal. Calcd for $C_{22}H_{30}N_2O_2$: C, 74.57; H, 8.47; N, 7.90. Found: C, 74.76; H, 8.29; N, 8.12.

***N*-Benzyl-4,4-diethoxy-5-[2-(methoxybenzyl)amino]-2-phenylpiperidine (32)**. Operating as for the preparation of imines **14**, from amine **27** (303 mg, 0.85 mmol), 2-methoxybenzaldehyde (116 mg, 0.85 mmol) in dry C_6H_6, imines **30** were obtained, which were directly reduced: ^1H NMR (*Z*-*E* mixture)1.05 and 1.30 (2t, J =7 Hz, CH_3), 3.35-3.60 (m, OCH_2), 3.80 and 3.90 (2s, 3H each, OCH_3), 6.70-7.55 (m, Ph-H), 8.00 and 8.70 (2 s, 1H each, CH=N); ^{13}C NMR 156.4 and 158.2 (C=N). Operating as for the preparation of compound **15**, from imines **30** (404 mg, 0.85 mmol), $NaBH_4$ (65 mg, 1.7 mmol) and dry MeOH (25 ml), amine **32** was obtained (253 mg, 63%); IR (NaCl) 3640 (NH) cm^{-1}; ^1H NMR 1.12 and 1.21 (2t, J = 7 Hz, 3H each, CH_3), 1.92 (br d, J = 12 Hz, 1H, 3-H_e), 2.11 (br t, J = 12 Hz, 1H, 3-H_a), 2.25 (dd, J = 12 and 2 Hz, 1H, 6-H_a), 2.70 (br s, 1H, 5-H_e), 2.80 (d, J = 14 Hz, 1H, CH_APh), 2.95 (dd, J = 12 and 4 Hz, 1H, 6-H_e), 3.20-3.50 (m, 5 H, 2-H_a and OCH_2), 3.50 (d, J = 14 Hz, 1H, CH_BPh), 3.75 (s, 3H, OCH_3), 6.80 (d, J = 7 Hz, 1H, Ph(OMe)-3), 6.85 (t, J = 7 Hz, 1H, Ph(OMe)-5), 7.00-7.55 (m, H, Ph-H); ^{13}C NMR 15.2 and 15.4 (CH_3), 38.9 (C-3), 46.7 (CH_2Ph), 51.3 (C-6), 54.7 (OCH_2), 55.1 (OCH_3), 55.6 (C-5), 58.4 (CH_2Ph), 65.4 (C-2), 110.4 (C-4), 120.3, 126.6-128.9, 140.0, and 158.0 (Ph); MS m/z (%) 475 (M^+, 2), 474 (3), 445 (5), 429 (4), 383 (11), 337 (15), 292 (10), 234 (17), 121(73), 91 (100). Anal. Calcd for $C_{30}H_{38}N_2O_3$: C, 75.95; H, 8.02; N, 5.91. Found: C, 76.02; H, 7.98; N, 5.86.

***N*-Benzyl-4,4-diethoxy-3-[2-(methoxybenzyl)amino]-2-phenylpiperidine (33).** Operating as for the preparation of imines **14**, from amine **28** (293 mg, 0.83 mmol), 2-methoxybenzaldehyde (113 mg, 0.83 mmol) in dry C_6H_6 (60 ml), imine **31** was obtained, which were directly reduced: ^{1}H NMR 1.00 and 1.25 (2t, J =7 Hz, CH_3), 3.40-3.70 (m, OCH_2), 3.62 (s, 3H, OCH_3), 6.75-7.55 (m, Ph-H), 7.79 (s, 1H, CH=N); ^{13}C NMR 158.5 (C=N). Operating as for the preparation of compound **15**, from imines **30** (404 mg, 0.85 mmol), $NaBH_4$ (65 mg, 1.7 mmol) and dry MeOH (25 ml), amine **32** was obtained (253 mg, 63%); IR (NaCl) 3640 (NH) cm^{-1}; ^{1}H NMR (500 MHz) 1.11 and 1.24 (2 t, J = 7 Hz, 3H, CH_3), 1.72 (ddd, J = 12, 4 and 3 Hz, 1H, 5-H_e), 1.96 (td, J = 12 and 3 Hz, 1H, 5-H_a), 2.07 (m, 1H, 6-H_a), 2.80 (apparent d, J = 13 Hz, 4H, CH_APh, CH_APh', 3-He, and 6-H_e), 3.17 (d, J = 13 Hz, 1H, CH_BPh'), 3.29- 3.34 (m, 2H, OCH_A), 3.4-3.5 (m, 2H, OCH_B), 3.71 (s, 3H, OCH_3), 3.77 (d, J = 5 Hz, 1H, 2-H_a), 4.03 (d, J = 13 Hz, 1H, CH_BPh), 6.72 (dd, J = 7.5 and 1 Hz, 1H, Ph(OMe)-3), 6.82 (td, J = 7.5 and 1.5 Hz, 1H, Ph(OMe)-5), 7.02 (dd, J = 7.5 and 1.5 Hz, 1H, Ph(OMe)-6), 7.13 (td, J = 7.5 and 1.5 Hz, 1H, Ph(OMe)-4), 7.19-7.38 (m, 10H, Ph-H); ^{13}C NMR 15.2 and 15.4 (CH_3), 28.1 (C-5), 49.0 (C-6, CH_2Ph), 54.7 and 55.0 (OCH_2), 54.9 (OCH_3), 59.4 (CH_2Ph), 63.2 (C-3), 68.4 (C-2), 100.7 (C-4), 109.9, 120.0, 126.5, 126.7, 127.5, 127.9, 128.4, 129.9, 139.4, 141.5, 157.3; MS m/z (%) 475 (M^+, 2), 474 (3), 445 (5), 429 (4), 383 (11), 337 (15), 292 (10), 234 (17), 121(73), 91 (100). Anal. Calcd for $C_{30}H_{38}N_2O_3$.HCl: C, 70.50; H, 7.69; N, 5.48. Found: C, 70.33; H, 7.48; N, 5.26.

ACKNOWLEDGEMENTS

Support for this research has been provided by the CIRIT (Generalitat de Catalunya) through grant QFN92-4303. We also thank the "Departament d'Ensenyament" (Generalitat de Catalunya) for the doctorate fellowship given to I.López, and the Université Blaise Pascal (Clermont-Ferrand) for a fellowship given to A. Voldoire.

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11. Compound **10** was prepared by reaction of *N,N*-dimehyl-4-oxopiperidinium iodide with (*R*)-(-)-phenylglycinol: Rubiralta, M.; Diez, A.; Vila, C.; Castells, J.; López, I. *Heterocycles*, **1992**, *34*, 643-650.
12. For convenience, we have represented isomers **a** as (αR, 3R) and isomers **b** as (αR, 3S), even though the absolute configuration at C-3 has not been proved.
13. All assignments were confirmed by 2D NMR experiments.
14. Rubiralta, M.; Diez, A.; Vila, C. *Tetrahedron*, **1990**, *46*, 4443-4456.
15. This moderate yield in the *p*-TsOH cyclization step compared to other series of 2-arylpiperidines is due to the absence of activating substituents on the phenyl ring.

(*Received in UK* 8 *February* 1995; *accepted* 24 *February* 1995)