PREPARATION OF NEW CHIRAL PIPERIDINE EPOXIDES[1]

Anna Diez, Lluís Vilaseca, Isabel López, and Mario Rubiralta*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona. Spain

Christian Marazano, David S. Grierson, and Henri-Philippe Husson

Institut de Chimie des Substances Naturelles du C.N.R.S., F-91190, Gif-sur-Yvette, France

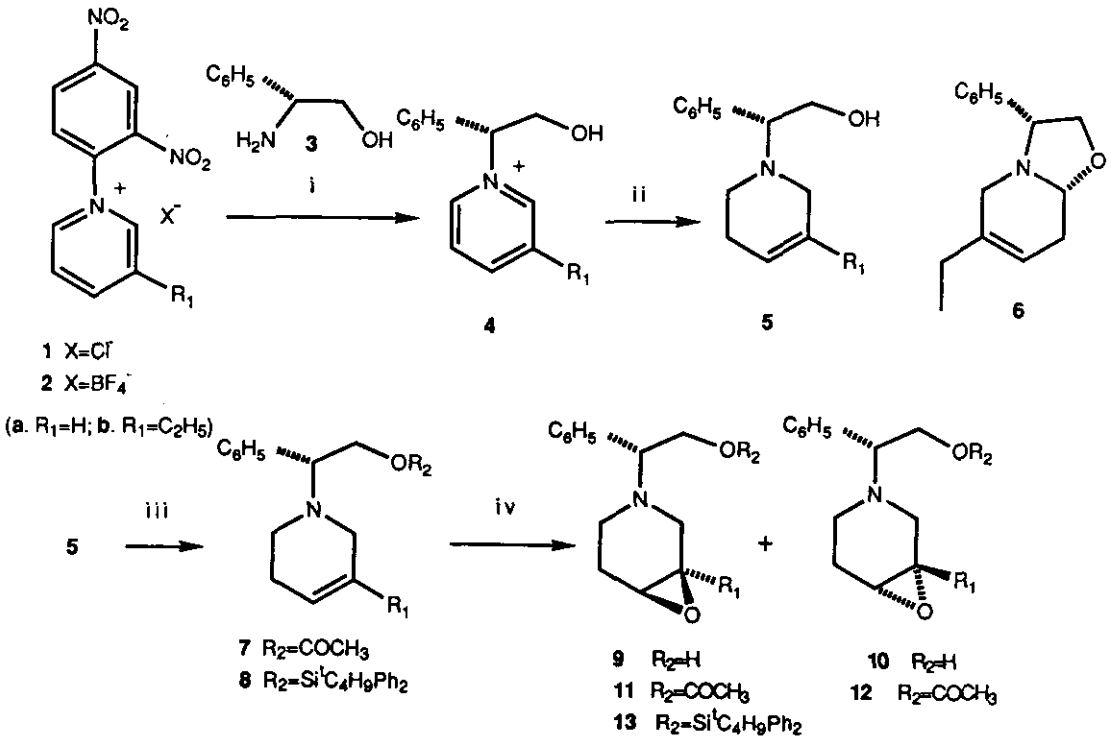
Abstract-- The new chiral piperidine epoxides (**11b**), (**12b**), and (**13b**) were prepared by MCPBA oxidation of 1,2,3,6-tetrahydropyridine (**5b**). Compound (**5b**) was obtained by $NaBH_4$ reduction of pyridinium salt (**4b**) derived from the Zincke-König reaction of **2b** and (*R*)-(-)-phenylglycinol.

In an earlier paper[2] we reported a new synthetic approach to *Strychnos* alkaloids, which involved, in the key step, the condensation of 2-indolylacyl anion equivalent with an appropriate epoxypiperidine. In this way the synthesis of *Na*-methyl-20-hydroxydasycarpidone was achieved from 1-methyl-2-(1,3-dithian-2-yl)indole and 1-methyl-3-ethyl-3,4-epoxypiperidine. Concerning the two components of this reaction, until now, our attention has been focused upon the preparation and study of the reactivity of protected 2-(1,3-dithian-2-yl)indoles.[3] In the present paper we describe our work on a new approach to the asymmetric synthesis of *N*-substituted 1,2,5,6-tetrahydropyridines and their transformation into the corresponding monochiral 3,4-epoxypiperidines, valuable intermediates for the construction of monochiral polycyclic alkaloid systems.

The required 1,2,5,6-tetrahydropyridine (**5a,b**) were prepared in two steps involving: i) the reaction of (R)-(-)-phenylglycinol (**3**) with Zincke´s salts (**1a,b**)[4,5] (*n*-butanol, reflux, 15 h, 79%) followed by ii) borohydride reduction of the resulting pyridinium salt (**4**). The latter transformation was carried out in a two phase system (ether-5*M* NaOH) as described for the corresponding synthesis of chiral oxazolidin-Δ^4-piperideines,[6,7] in which case the intermediate iminium ion was trapped through reaction with the side chain hydroxyl group (**6**).

The structure of piperideine (**5a**) was confirmed from nmr data (^1H and ^{13}C nmr, and 2D heterocorrelation experiments). The more relevant data were the two sets of signals at δ 2.36 and 2.76, corresponding to C-6 pseudoequatorial and pseudoaxial protons. These resonances correlate with the ^{13}C-signal at δ 46.2. Similarly, the resonances at δ 3.76 and 4.06 for the methylene protons of the hydroxyethyl chain correlate with the ^{13}C-signal at δ 61.0.

All attempts to epoxidize (**5a**) by reaction with MCPBA or NBS followed by base treatment led to a complex mixture from which a dimeric compound (m/z 438) was detected. The formation of this partially characterized compound may result from the intermolecular reaction of the hydroxyl and oxirane functions between two epoxidized molecules.[8] Therefore, the acetylated derivative (**7a**) was prepared by treatment of **5a** with acetic anhydride in the presence of triethylamine. This transformation was accompanied by a downfield shift of the nonequivalent methylene protons on the oxygen bearing center in the ^1H nmr spectrum. Unfortunately, the epoxides (**11a**) and (**12a**) formed from the reaction of **7a** with MCPBA were too unstable to permit complete purification and

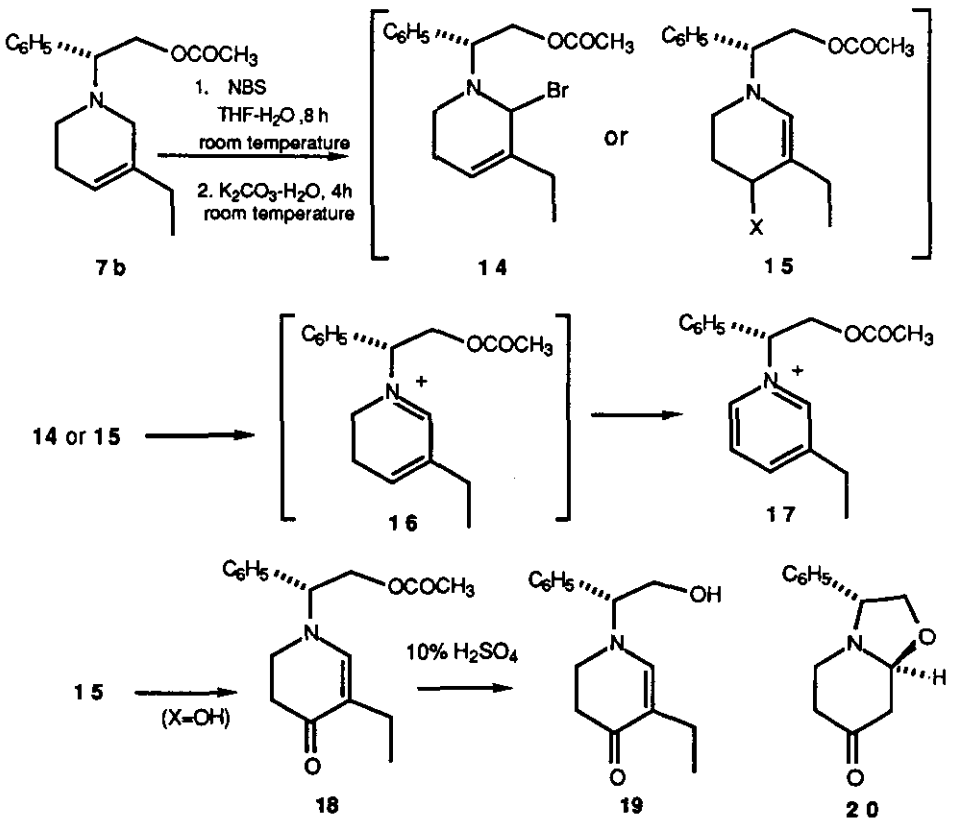


Reagents and conditions: (i) n-Propanol , Δ, overnight or *n*-butanol, Δ, 4 h. (ii) $NaBH_4$, CH_3OH, 0°C, 15 min. (iii) Ac_2O, $(C_2H_5)_3N$, CH_2Cl_2, Δ, or Imidazole, CH_2Cl_2, $^tC_4H_9Ph_2SiCl$, Δ. (iv) a. CH_2Cl_2, CF_3COOH. b. MCPBA , Δ, 24 h.

Scheme 1

characterization. This result prompted us to study the epoxidation of the *O*-acetyl derivative(**7b**)of the C-3 ethyl substituted tetrahydropyridine (**5b**).

Compound (**7b**) formed by treatment of **5b** with acetic anhydride displayed in its ^{1}H nmr spectrum, characteristic signals at δ 1.95 and 5.45 due to the acetyl methyl group and the olefinic proton, respectively, as well as signals at δ 4.39 and 4.52, for the nonequivalent exocyclic methylene protons. It is also worth noting that the borohydride reduction of **4b** to **5b** was accompanied by formation of oxazolidin-Δ^4-piperidine (**6b**) as a by-product. The signals for the two aliphatic methine carbons at δ 68.7 and 92.3, corresponding to C-9 and C-6, respectively, were characteristic of the oxazolidine ring formation.



7b 14 15 16 17 18 19 20

Scheme 2

Epoxidation of tetrahydropyridine (**7b**) required blocking the amine function as its trifluoroacetic acid salt prior to addition of MCPBA. Under these conditions a 2:1 mixture of epoxides (**11b**) and (**12b**) was obtained in good yield. Formation of the oxirane system was confirmed from the nmr data. By conducting 2D heterocorrelated experiments the unequivocal assignment of the ^{1}H and ^{13}C nmr signals was possible. In accordance with the structure of the major isomer the methine carbon signals at δ 66.9 and 71.9 and the quaternary carbon resonance at δ 69.9 were attributed to NCH, C-4 and C-3, respectively. The major epoxidation was rationalized to occur syn respect the nitrogen electron lone pair (β-side) by considering the steric hindrance exerted by the N-(2-silyloxy-1-phenyl)ethyl chain upon the opposite side of the piperidine ring. Such consideration would mean that a bulkier protective group upon the hydroxy function might allow the control of the epoxidation stereochemistry.

Epoxidation of **7b** using NBS followed by base treatment was also examined. However, neither the intermediate bromohydrin nor the expected epoxide products were isolated from these experiments. Instead, a 1: 2.5 mixture of enaminone (**18**) and pyridinium salt (**17**) was obtained as a result of an oxidation process, which may involve the allylic bromide (**14**) and **15** (X=Br or OH) as intermediates (Scheme 2).[9] NBS oxidation of the hydroxy function in **15** could produce enaminone (**18**) whereas nitrogen lone pair assisted elimination of the Br in **14** or **15** (X=Br) would give **16** which can undergo facile oxidation to **17**.[10] The structure of **18** was deduced from the presence of absorptions at δ 150.8 (C-2), δ 112.0 (C-3), 170.8 (ester CO) and 191.3 (enone CO) in the ^{13}C spectrum and the observed signal at δ 7.08 (C-2H) in the proton spectrum. These values are in agreement with those described for other 5,6-dihydropyridones.[11] The acetate group in **18** was cleaved under acidic conditions (10% H_2SO_4) in the hope that ring closure to give the corresponding oxazolopiperidine compound (**20**) would also occur. However, cyclization was not observed and piperideine (**19**) was obtained in 87% yield after purification.

In order to increase the stereoselectivity of the oxidation reaction the preparation of tetrahydropyridine (**8b**) (80% yield) was undertaken by reaction of alcohol (**5b**) with the appropriate silyl chloride in the presence of imidazole. Reaction of tetrahydropyridine (**8b**) with MCPBA generated epoxide (**13b**) diastereoselectively. Compound (**13b**) was obtained in 47 % yield after column chromatography. Its ^{1}H nmr spectrum showed a characteristic signal at δ 3.55 for the methine C-4 proton and two doublets of doublets at δ 3.75 and 3.95 corresponding to the non-equivalent methylene protons of the exocyclic chain. In the ^{13}C nmr spectrum, the presence of two methine carbons at δ 70.6 and 71.1 is also important, since, together with the absence of the olefinic methine carbon, they clearly indicate the epoxidation of the double bond.

In conclusion we have developed a short and efficient route to the monochiral piperidine epoxides (**11b**), (**12b**), and (**13b**).

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H- And ^{13}C-nmr spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Varian Gemini-200 spectrometer using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS. Ir spectra were registered with a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. Tlc was carried out on SiO_2 (silica gel 60, Merck 0.0063-0.200 mm), and the spots were located with uv light or iodoplatinate reagent. Flash column chromatography was carried out on SiO_2 (silica gel 60, 0.040-0.063 mm, Macherey Nagel). Drying of organic extracts during the workup of reactions was performed over anhydrous sodium sulfate. Microanalyses were performed on a Carlo-Erba 1106 analyzer by Departament de Química Orgànica Biològica, Barcelona.

(*R*)-1-(1-Phenyl-2-hydroxyethyl)-1,2,3,6-tetrahydropyridine (5a). A solution of 1-chloro-2,4-dinitrobenzene (21.2 g, 0.105 mol) and pyridine (12.71 ml, 0.157 mol) in anhydrous acetone (175 ml) was refluxed overnight. The resulting mixture was filtered and the precipitate was washed with anhydrous acetone to give 2,4-dinitrophenylpyridinium chloride as a white solid (**1a**, 25 g, 85%); m p : 194-196 °C (CH_3OH, lit.,[12] 190-191 °C); ir (KBr) 1470, 1535, 1605, 1630; ^{1}H nmr (CD_3OD) 8.44 (d, *J*= 8.3 Hz, 1H, Ph-3H), 8.51 (br t, *J*=7 Hz, 2H, Pyr-3H), 9.02 (dd, *J*=8.3 and 2.4 Hz, 1H, Ph-5H), 9.10 (m, 1H, Pyr-4H), 9.36 (d, *J*=2.4 Hz, 1H, Ph-3H), 9.46 (dd, *J*=7 and 1.5 Hz, 2H, Pyr-2H); ^{13}C nmr (CD_3OD) 123.1 (Ph-C3), 129.5 (Pyr-C3), 131.1 (Ph-C1), 132.6 (Ph-C5), 140.1 (Pyr-C4), 147.3 (Pyr-C2), 150.1 and 151.2 (Ph-C2 and Ph-C4). Anal. Calcd for $C_{11}H_8N_3O_4Cl$: C, 46.93; H, 2.86; N, 14.91. Found: C, 46.91; H, 3.06; N, 14.70.

Method A: A solution of **1a** (11.14 g, 39.7 mmol) and (*R*)-(-)-phenylglycinol (**3**) (4.53 g, 33.1 mmol) in *n*-propanol (150 ml) was refluxed overnight. After evaporation and flash chromatography (8:2 CH_2Cl_2-CH_3OH), 2-hydroxy-1-phenylethyl)pyridinium chloride (**4a**, 6.2 g, 67%) was obtained as a colorless oil: $[\alpha]_D$ -44° (CH_3OH, c=0.7); ir ($CHCl_3$) 3100-3500 (OH); ^{1}H nmr (CD_3OD) 4.48 (dd, *J*=12 and 4 Hz, 1H, NCH), 4.72 (dd, *J*=12 and 9 Hz, 1H, HOC*H*), 6.39 (dd, *J*= 9 and 4 Hz, 1H, HOC*H*), 7.65-7.70 (br s, 5H, ArH), 8.39 (t, *J*= 7 Hz, 1H, Pyr-3H), 8.87 (t, *J*=7 Hz, 1H, Pyr-4H), 9.48 (d, *J*=7 Hz, 1H, Pyr-2H); ^{13}C nmr (CD_3OD) 63.1 ($HOCH_2$), 77.2 (NCH), 129.1 and 129.3 (Pyr-C3 and Ph-*ortho*), 131.0 (Ph-*meta*), 134.8 (Ph-*para*), 145.2 (Pyr-C2), 147.3 (Pyr-C2). Anal. Calcd for $C_{13}H_{14}NOCl$: C, 66.24; H, 5.98; N, 5.94. Found: C, 66.66; H, 5.63; N, 5.63.

Method B: A solution of **1a** (2 g, 7.13 mmol) and (*R*)-phenylglycinol (**3**) (1.07 g, 7.84 mmol) in *n*-butanol (75 ml), was refluxed for 4 h, *n*-butanol was evaporated and the resulting residue was dissolved in H_2O and CH_2Cl_2. The layers were separated and the aqueous phase was washed twice with CH_2Cl_2 and then evaporated to give **4a** (1.32 g, 79%) as a brown oil.

To a solution of **4a** (1.83 g, 7.77 mmol) in methanol (250 ml) cooled to 0°C sodium borohydride (2.99 g, 7.77 mmol) was slowly added. After stirring at 0°C for 15 min the reaction mixture was poured on ice-water and extracted with CH_2Cl_2. The organic layer was dried and evaporated to give tetrahydropyridine (**5a**, 1.38 g, 88%) as an oil after flash chromatography (8:2 CH_2Cl_2-CH_3OH); ir ($CHCl_3$) 3100-3500 (OH); ^{1}H nmr 2.13 (br s, 2H, 3-H), 2.36 (ddd, J=12, 6 and 5 Hz, 1H, 2-Ha) , 2.76 (ddd, J=12, 6, and 5 Hz, 1H, 2-He), 3.05 (br s, 2H, 6-H), 3.76 (m, 1H, HOC*H*), 4.06 (dd, J=13 and 12 Hz, 1H, HOC*H*), 5.66 (br s, 2H, =CH), 7.05-7.40 (m, 5H, PhH); ^{13}C nmr 26.6 (C-3), 46.2 (C-2), 49.0 (C-6), 61.0 ($OHCH_2$), 69.9 (NCH), 125.0 (C-5), 125.4 (C-4), 127.8 (C-*ipso*), 128.2 (C-*meta*), 128.6 (C-*para*, 128.8 (C-*ortho*). Anal. Calcd for $C_{13}H_{17}NO$. 1/2H_2O: C, 73.21; H, 8.50; N, 6.56. Found: C, 73.66; H, 8.46; N, 6.49.

(*R*)-3-Ethyl-1-(1-phenyl-2-hydroxyethyl)-1,2,5,6-tetrahydropyridine (5b). Operating as above from 3-ethylpyridine (17.1 ml, 150 mmol) and 1-chloro-2,4-dinitrobenzene (20 g, 100 mmol) in anhydrous acetone (300 ml), pyridinium salt (**1b**, 22 g, 73%) was obtained; crystal form, mp 180-183°C (CH_3OH); ir (KBr) 1610, 1530, 1350; ^{1}H nmr 1.51 (t, J=7 Hz, 3H, CCH_3), 3.13 (q, J=7 Hz, 2H, CH_2), 8.41 (dd, J=8 and 6 Hz, 1H, Pyr-5H), 8.43 (d, J=9 Hz, 1H, 6-H), 8.94 (br d, J= 8 Hz, 1H, Pyr-4H), 9.02 (dd, J=9 and 2.3 Hz, 1H, 5-H), 9.27 (br d, J=6 Hz, 1H, Pyr-6H), 9.36 (d, J=2.3 Hz, 1H, 3-H), 9.37 (s, 1H, Pyr-2H); ^{13}C nmr (CD_3OD) 14.7 (CH_3), 27.0 (CH_2), 123.1 (C-3), 129.0 (C-6), 131.1 (C-5), 132.7 (Pyr-C5), 140.2 (C-2), 144.6 (Pyr-C6), 146.1 (Pyr-C4), 147.1 (C-1), 149.6 (Pyr-C2), 151.1 (Pyr-C4); ms (m/z, %) 274 (M^+, 1), 259 (1), 202 (34), 126 (9), 107 (76), 92 (84), 75 (100). Anal. Calcd for $C_{13}H_{12}N_3O_4Cl$: C, 50.41; H, 3.88; N, 13.57, Cl, 11.46. Found: C, 50.64; H, 4.01; N, 13.43; Cl, 11.42.

Method A: To a solution of **1b** (8.19 g, 26.46 mmol) in dry methanol (100 ml), $AgBF_4$ (5.15 g, 12.9 mmol) was added and the precipitate formed was eliminated by filtration (Celite). The organic layer was evaporated to give **2b** (8.1 g, 88%): mp 130-131°C (CH_3OH-acetone); ^{1}H nmr 1.48 (t, J=7 Hz, 3H, CH_3), 3.09 (q, J=7 Hz, 2H, CH_2), 8.32 (d, J=9 Hz, 1H, 6-H), 8.34 (dd, J=9 and 6.5 Hz, 1H, Pyr-5H), 8.89 (br d, J=9 Hz, 1H, Pyr-4H), 8.92 (br d, J=9 Hz, 1H, 5-H), 9.08 (br d, J=6.5 Hz, 1H, Pyr-6H), 9.16 (br s, 1H, Pyr-2H), 9.29 (d, J=2.6 Hz, 1H, 3-H). Anal. Calcd for $C_{13}H_{13}N_3BF_4O_4$: C, 43.23; H, 3.60; N, 11.60. Found: C, 43.12; H, 3.52; N, 11.66. Operating as above from pyridinium salt **2b** (480 mg, 1.215 mmol), (*R*)- (-)-phenylglycinol (138 mg, 1.01 mmol) in dry methanol (5 ml), **4b** tetrafluoroborate (0.31 g, 61%) was obtained as a brown solid: m p : 130-131°C (CH_3OH-acetone); $[\alpha]_D$= -42° (c=1,

CH_3OH); ir ($CHCl_3$) 3100-3300 (OH); ^1H nmr (CD_3OD) 1.39 (t, J=7 Hz, 3H, CH_3), 2.99 (q, J=7 Hz, 2H, CH_2CH_3), 4.43 (dd, J=13 and 4 Hz, 1H, CHOH), 4.64 (dd, J=13 and 9 Hz, 1H, CHOH), 6.09 (dd, J=9 and 4 Hz, 1H, N^+CH), 7.52-7.68 (m, 5H, C_6H_5), 8.10 (t, J=8 Hz, 1H, C-5), 8.57 (d, J=8 Hz, 1H, C-4), 8.95 (d, J=8 Hz, 1H, C-6), 9.04 (s, 1H, C-2); ^{13}C nmr (CD_3OD) 14.6 (CH_3), 26.6 (CH_3CH_2), 63.3 (CH_2OH), 77.5 (N^+CH), 129.2 (Ar-*para*), 129.5 (Ar-*ortho*), 130.8 (Ar-*meta*), 131.3 (C-5), 135.4 (C-3), 142.7 (C-6), 144.6 (C-2), 147.1 (Ar-*ipso*), 147.2 (C-4); ms (*m/z*, %) 225 (M^+, 0.7), 120 (19), 107 (55), 92 (100), 91 (92), 65 (34), 49 (35). Anal. Calcd for $C_{15}H_{18}NOBF_4.1/2H_2O$: C, 55.64; H, 5.86; N, 4.32. Found: C, 55.56; H, 5.81; N, 4.65.

Method B: Operating as in the case of **4a** (Method B), from **1b** (2.25 g, 7.29 mmol), (*R*)-(-)phenylglycinol (1 g, 7.29 mmol) and *n*-butanol (50 ml), **4b** chloride was obtained (1.6 g, 87%).

Operating as for compound **5a**, from **4b** (1.64 g, 5.2 mmol) in CH_3OH (70 ml) and $NaBH_4$ (1.97 g, 5.2 mmol) a mixture of tetrahydropyridine (**5b**) and (**6b**) was obtained which was separated by flash chromatography (9:1 CH_2Cl_2-CH_3OH) **5b**: (oil, lower Rf, 1.03 g, 79%): $[\alpha]_D$=-35° (c=0.62, CH_3OH); ir ($CHCl_3$) 3400-3100 (OH); ^1H nmr 0.97 (t, J=7 Hz, 3H, CH_3), 1.90 (q, J=7 Hz, 2H, CH_2CH_3), 2.00-2.30 (m, 2H, 5-H), 2.30-2.50 (m, 1H, 2-Hα), 2.60-3.00 (m, 1H, 2-Hβ), 3.72 (d, J=2 Hz, 1H, NCHPh), 3.98 (d, J=11 Hz, 1H, CHOH), 4.06 (dd, J=11 and 2 Hz, 1H, CHOH), 5.38 (s, 1H, =CH), 7.00-7.50 (m, 5H, C_6H_5); ^{13}C nmr 11.1 (CH_3CH_2), 25.2 (CH_2CH_3), 26.8 (C-5), 45.0 (C-6), 51.2 (C-2), 60.0 (CH_2OH), 68.9 (CHPh), 116.8 (C-4), 127.3 (Ar-*para*), 127.6 and 128.4 (Ar-*ortho* and Ar-*para*), 136.0 (Ar-*ipso*), 137.5 (C-3); ci ms (*m/z*, %) 232 (M^++1, 100), 155 (17), 127 (27), 110 (38).

5-Ethyl-7-phenyloxazolidin-Δ^4-piperideine (**6b**, oil, higher Rf, 119 mg, 10%) ; ^1H nmr 0.92 (t, J=7 Hz, 3H, CH_2CH_3), 1.95 (q, J=7 Hz, 2H, CH_2CH_3), 2.65 (br d, J=12 Hz, 1H, =C-CHN), 3.15 (d, J=12 Hz, 1H, =C-CHN), 3.58 (t, J=8 Hz, 1H, OCHN), 3.75 (t, J=8 Hz, 1H, NCHPh), 3.98 (dd, J=8 and 4 Hz, 1H, OCH), 4.20 (m, 1H, OCH), 5.40 (br, 1H, =CH), 7.00-7.50 (m, 5H, ArH); ^{13}C nmr 12.5 (CH_2CH_3), 27.7 (CH_2CH_3), 31.9 (C-3), 52.5 (C-6), 68.3 (C-7), 74.1 (C-8), 92.3 (C-2), 116.1 (C-4), 128.4, 128.8, and 129.2 (phenyl), 134.0 (Ar-*ipso*), 138.8 (C-5); ms (*m/z*, %) 228 (M^++1, 33), 212 (21), 148 (48), 125 (74). Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.10. Found: C, 78.64; H, 8.24; N, 6.06.

2-Phenyl-2-(1,2,3,6-tetrahydro-1-pyridyl)ethyl Acetate (7a). To a solution of **5a** (250 mg, 1.23 mmol) and triethylamine (0.34 ml, 2.46 mmol) in anhydrous CH_2Cl_2 (15 ml) acetic anhydride (0.23 ml, 2.46 mmol) was slowly added. The reaction mixture was refluxed overnight, cooled, poured into ice-water and extracted with CH_2Cl_2. The organic layer was dried and evaporated to give **7a** (290 mg, 96%) as an oil after flash chromatography (9:1 CH_2Cl_2-CH_3OH): $[\alpha]_D$ +4° (CH_3OH, c=1); ir ($CHCl_3$) 1730 (CO); ^1H nmr 1.89 (s, 3H, $COCH_3$), 2.07 (br s, 2H, 5-

H), 2.37 (ddd, J=9, 4 and 3 Hz, 1H, 2-H), 2.59 (m, 1H, 2-H), 2.92 and 3.05 (2 d, J_{AB}=15 Hz, 2H, 6-H), 3.59 (t, J=7 Hz, 1H, NCH), 4.31 (m, 1H, OCH), 4.39 (m, 1H, OCH), 5.57 and 5.62 (2 d, J=10 Hz, 2H, =CH), 7.25 (s, 5H, ArH); ^{13}C nmr 20.6 ($COCH_3$), 26.0 (C-5), 47.1 (C-6), 50.3 (C-2), 65.2 (OCH_2), 67.8 (NCH), 125.2 (=C), 127.4 128.1 and 128.4 (Ar-*ortho* and Ar-*para*), 138.8 (Ar-*ipso*), 171.0 (C=O); ms (*m/z*, %) 245 (M^+, 1), 172 (100), 118 (20), 91 (28), 43 (10). Anal. Calcd for $C_{15}H_{19}NO_2.1/2H_2O$: C, 70.86; H, 7.48; N, 5.51. Found: C, 71.10; H, 7.49; N, 5.79.

2-Phenyl-2-(3-ethyl-1,2,5,6-tetrahydro-1-pyridyl)ethyl Acetate (7b). Operating as above, from **5b** (0.89 g, 3.88 mmol) in anhydrous CH_2Cl_2 (70 ml), triethylamine (1.08 ml, 7.7 mmol) and acetic anhydride (0.73 ml, 7.7 mmol) , acetate (**7b**, 1.06 g, 84%) was obtained as an oil which was purified by column chromatography (Al_2O_3) using 95:5 CH_2Cl_2-CH_3OH as the eluent ; ir (NaCl) 1710 (CO); ^{1}H nmr 0.98 (t, J=7 Hz, 3H, CH_2CH_3), 1.95 (s, 3H, $COCH_3$), 2.95 (q, J=7 Hz, 2H, CH_2CH_3), 3.67 (t, J=6 Hz, 1H, PhCHN), 4.39 (dd, J=13 and 6 Hz, 1H, CHO), 4.52 (dd, J=13 and 6 Hz, 1H, CHO), 5.45 (s, 1H, =CH), 2.38 (m, 1H, 2-Hα), 2.63 (m, 1H, 2-Hβ), 1.80-2.20 (m, 4H, 5-H and 6-H), 7.20-7.50 (m, 5H, ArH); ^{13}C nmr 11.7 (CH_2CH_3), 20.7 ($COCH_3$), 25.6 (CH_2CH_3), 27.5 (C-5), 47.3 (C-6), 53.4 (C-2), 65.3 (OCH_2), 67.7 (ArCHN), 117.6 (C-4), 127.6 (Ar-*para*), 128.3 and 128.5 (Ar-*ortho* and *meta*), 137.7 (C-3), 138.9 (Ar-*ipso*), 171.0 (C=O); ms (*m/z*, %) 273 (M^+, 0.4), 201 (100), 163 (2), 118 (23), 91 (31), 43 (43). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.72; H, 8.49; N, 5.12. Found: C, 74.70; H, 8.48; N, 5.27.

3-Ethyl-1-[1-phenyl-2-(*tert*-butyldiphenylsilyloxy)ethyl]-1,2,5,6-tetrahydropyridine (8b). To a solution of **5b** (0.08 g, 0.34 mmol) and imidazole (0.046 g, 0.68 mmol) in anhydrous CH_2Cl_2 (1 ml) *tert*-butyldiphenylsilyl chloride (106 µl, 0.41 mmol) in anhydrous CH_2Cl_2 (1 ml) was slowly added. The reaction mixture was refluxed overnight under argon atmosphere, cooled and then pentane (20 ml) was added. The resulting organic mixture was filtered (Celite) and evaporated to give **8b** (0.11 g, 71%) as an oil after flash chromatography (1:1 heptane-ether): $[\alpha]_D$ -0.1° (CH_3OH, c=1); ^{1}H nmr 0.95 (s, 9H, $SiCCH_3$), 0.98 (t, J=7 Hz, 3H, CH_2CH_3), 1.85 (q, J=7 Hz, 2H, CH_2CH_3), 2.00 (m, 2H, 5-H), 2.35 and 2.50 (2 m, 1H each , 6-H), 2.85 and 3.10 (2 d, J_{AB}= 12 Hz, 1H each, $=CCH_2N$), 3.48 (t, J=4 Hz, 1H, PhCHN), 3.85 (dd, J=8 and 4 Hz, 1H, OCH), 4.05 (m, 1H, OCH), 5.40 (br s, 1H, =CH), 7.10-7.60 (m, 15H, ArH); ^{13}C nmr 12.1 (CH_2CH_3), 19.1 ($SiCCH3$), 25.9 (CH_2CH_3), 26.7 ($SiCCH3$), 27.9 (C-5), 48.2 (C-6), 54.4 (C-2), 66.6 (CH_2O), 71.8 (PhCHN), 117.8 (C-4), 127.2, 127.7, 128.1, 128.8, 129.6, 133.6, 134.9, 135.7, 137.9, 140.7; ms (*m/z*, %) 470 (M^++1, 20), 469 (M^+, 48), 257 (5), 209 (1), 112 (3), 57 (100). Anal. Calcd for $C_{30}H_{39}NOSi$: C, 78.71; H, 8.58; N, 3.01. Found: C, 78.66; H, 8.32; N, 3.44.

(αR,3R,4S)- and (αR,3S,4R)-2-(3-Ethyl-3,4-epoxy-1-piperidyl)-2-phenylethyl Acetates (11b) and (12b). To a solution of tetrahydropyridine **7b** (0.25 g, 0.94 mmol) in CH_2Cl_2 (70 ml) stirred under nitrogen atmosphere at 0°C, CF_3COOH (0.07 ml, 0.94 mmol) was added. After 10 min stirring, MCPBA (0.25 g, 1.4 mmol) was added. The resulting reaction mixture was refluxed for 24 h, cooled, basified with saturated aqueous potassium carbonate and extracted with CH_2Cl_2. The organic extracts were dried and evaporated, and the residue was purified by flash chromatography (1:1 hexane-ether) to give epoxides **11b** (colorless oil, 166 mg, 61%) and **12b** (colorless oil, 93 mg, 34%).

11b: $[\alpha]_D$ -13.5° (CH_3OH, c=0.148); ir (NaCl) 1730 (CO); ^1H nmr 0.86 (br t, *J*=7 Hz, 3H, CH_2CH_3), 1.35-1.55 (m, 3H, CH_2CH_3 and 5-H), 1.85-1.95 (m, 1H, CH_2CH_3), 1.97 (s, 3H, $COCH_3$), 2.35-2.40 (m, 2H, 2-H and 6-H) , 2.45-2.55 (m, 2H, 2-H and 6-H), 3.56 (br s, 1H, 4-H), 3.74 (m, 1H, PhCHN), 4.31 (dd, *J*=10 and 6 Hz, 1H, $COOCH_2$), 4.53 (dd, *J*=10 and 7 Hz, 1H, $COOCH_2$), 7.10-7.40 (m, 5H, Ar-H); ^{13}C nmr 6.1 (CH_2CH_3), 20.6 ($COCH_3$), 26.1 (C-5), 29.6 ($CH2CH3$), 46.3 (C-6), 56.4 (C-2), 63.5 ($COOCH_2$), 66.9 (PhCHN), 69.9 (C-3), 71.9 (C-4), 127.9, 128.2, 128.4 , 136.9 (Ar-*ipso*), 171.4 (CO); ms (m/z, %) 234 (100), 176 (3), 144 (5), 118 (8), 91 (42), 43 (85). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01, N, 4.84. Found: C, 70.36; H, 8.27; N, 4.63.

12b: $[\alpha]_D$ -9.8° (CH_3OH, c=0.1); ir (NaCl) 1730 (CO); ^1H nmr 0.85 (t, *J*=7 Hz, 3H, CH_2CH_3), 1.25 (m, 1H, CH_3CH_2), 1.45 (m, 1H, CH_3CH_2), 1.70 (m, 2H, 5-H), 2.00 (s, 3H, $COCH_3$), 2.35 (br t, *J*=10 Hz, 1H, 6-Ha), 2.60-2.90 (m, 3H, 2-H and 6-He), 3.55 (br s, 1H, 4-H), 4.20 (m, 1H, PhCHN), 4.45 (m, 1H, CH_2O), 4.65 (m, 1H, CH_2O), 7.00-7.30 (m, 5H, ArH); ^{13}C nmr 6.06 (CH_2CH_3), 20.8 ($COCH_3$), 26.7 and 27.1 (C-5 and CH_2CH_3), 45.9 (C-6), 54.9 (C-2), 63.8 (OCH2), 67.1 (PhCHN), 69.8 (C-3), 75.7 (C-4), 128.3, 128.6 and 128.9 (C_6H_5), 136.7 (Ar-*ipso*), 171.1 (CO); ms (m/z, %) 234 (100), 202 (3), 144 (4), 91 (35), 43 (64).

(αR,3R,4S)-3,4-Epoxy-3-ethyl-1-[2-(*tert*-butyldiphenylsilyl)oxy]-1-phenyl]ethylpiperidine (13b). Operating as above, from tetrahydropyridine **8b** (1 g, 2 mmol) in anhydrous CH_2Cl_2 (80 ml), CF_3COOH (1 ml, 12 mmol) and MCPBA (0.69 g, 4 mmol), epoxypiperidine **13b** (colorless oil, 441 mg, 47%) was obtained after flash chromatography (1:1 hexane-ether): $[\alpha]_D$ -6.96 (C_2H_5OH, c=4.53); ^1H nmr 0.75 (t, *J*=7 Hz, 3H, CH_2CH_3), 0.85 (s, 3H, $SiCCH_3$), 1.15-1.50 (m, 4H, CH_2CH_3 and 5-H), 2.00 (br t, *J*= 10 Hz, 1H, 6-Ha), 2.25-2.50 (m, 2H, 2-H), 2.70 (br d, *J*=10 Hz, 1H, 6-He), 3.45-3.60 (m, 1H, PhCHN), 3.55 (br s, 1H, 4-H), 3.75 (dd, *J*=11.3 and 5 Hz, 1H, CHOSi), 3.95 (dd, *J*=11.3 and 6.5 Hz, 1H, CHOSi), 7.00-7.60 (m, 15 H, ArH); ^{13}C nmr 6.2 (CH_2CH_3), 18.8 ($SiCCH_3$), 26.5 ($SiCCH_3$), 26.8 (C-5), 29.3 (CH_2CH_3), 46.2 (C-6), 56.2 (C-2), 64.7 (OCH2), 70.6 and 71.1 (C-4 and

PhCHN), 71.5 (C-3), 127.7, 128.4 128.6, 129.1, 129.8, 130.8, 135.7, 138.0, 138.1, 138.5. Anal. Calcd for $C_{31}H_{39}NO_2Si.2H_2O$: C, 71.40; H, 7.86; N, 2.68. Found: C, 71.65; H, 8.10; N, 2.38.

(R)-1-(2-Acetyloxy-1-phenyl)ethyl-5,6-dihydro-1*H*-pyridin-4-one (18). To a solution of tetrahydropyridine **7b** (0.25 g, 0.91 mmol) in wet THF (50 ml), NBS (0.32 g, 1.83 mmol) was added portionwise. The reaction mixture was stirred for 8 h at room temperature, and 10% KOH was added. The dispersion was then stirred for 4h, poured on water and extrcated twice with ether and twice with CH_2Cl_2. The combined organic layers were dried, filtered and evaporated to yield a mixture of enaminone (**18**) and the pyridinium salt (**17**), which was separated by flash chromatography (93:7 , CH_2Cl_2-CH_3OH). Enaminone **18**: (pale oil, higher Rf , 60 mg, 23%); $[\alpha]_D$ -29.0° (CH_3OH, c=1); ir (NaCl) 1590, 1620, 1695, and 1725 ; ^1H nmr 1.02 (t, *J*=7 Hz, 3H, CH_2CH_3), 2.15 (s, 3H, $COCH_3$), 2.19 (q, *J*=7 Hz, 2H, CH_2CH_3), 2.40 (t, *J*=8 Hz, 2H, CH_2CO), 3.10-3.40 (m, 2H, NCH_2), 4.50-4.75 (m, 3H, $NCHPhCH_2$), 7.08 (s, 1H, =CH), 7.27-7.42 (m, 5H, ArH); ^{13}C nmr 14.4 (CH_2CH_3), 20.3 (CH_2CH_3), 20.6 ($COCH_3$), 35.8 ($COCH_2$), 44.5 (NCH_2), 62.4 (CH_2OCO), 65.6 (NCHPh), 112.5 (=C), 127.1, 128.8 and 129.2 (C_6H_5), 136.0 (Ar-ipso), 150.8 (=CH), 170.8 (COO), 191.3 (CO); ms (*m/z*, %) 287 (M^+, 17), 272 (18), 214 (100), 186 (17), 91 (23), 43 (73). Anal. Calcd for $C_{17}H_{21}NO_3.1/2H_2O$: C, 68.84; H, 7.42; N, 4.72. Found: C, 68.51; H, 7.37; N, 4.76. **1-(2-Acetoxy-1-phenyl)ethyl-3-ethylpyridinium salt (17):** (oil, lower Rf, 0.15 g, 56%); ^1H nmr 1.35 (t, *J*=7 Hz, 3H, $CH_2C\underline{H}_3$), 2.00 (s, 3H, $COCH_3$), 2.99 (q, *J*=7 Hz, 2H, $C\underline{H}_2CH_3$), 4.92 (dd, *J*= 3.6 and 12.5 Hz, 1H, CHOCO), 5.25 (dd, *J*=9 and 12.5 Hz, 1H, CHOCO), 7.19 (dd, *J*=3.6 and 9 Hz, 1H, $PhCHN^+$), 7.43 (m, 3H, ArH), 7.78-7.89 (m, 2H, ArH), 8.09 (dd, *J*=6 and 7 Hz, 1H, Pyr-5H), 8.32 (d, *J*=7 Hz, 1H, Pyr-4H), 9.43 (d, *J*=6 Hz, 1H, Pyr-6H), 9.71 (br s, 1H, Pyr-2H); ^{13}C nmr 14.2 (CH_2CH_3), 20.5 ($COCH_3$), 25.8 (CH_2CH_3), 63.5 (CH_2OCO), 71.7 (NCHPh), 128.2 (Ar-*para*), 128.7 and 129.8 (Ar-*ortho* and Ar-*meta*), 130.6 (Pyr-C5), 132.6 (Pyr-C3), 141.8 (Pyr-C6), 142.7 (Pyr-C4), 145.5 (Pyr-C2), 170.3 (CO).

(S)-1-(2-Hydroxy-1-phenyl)ethyl-5,6-dihydro-1H-pyridin-4-one (19). A solution of enaminone (**18**) (47 mg, 0.163 mmol) and 10% aqueous H_2SO_4 (40 ml) was refluxed overnight, cooled and extracted with ether. The organic layer was dried and evaporated to give **19** (oil, 35 mg, 87%) after flash chromatography (93:7 CH_2Cl_2-CH_3OH): ir ($CHCl_3$) 1590, 1625; ^1H nmr 1.01 (t, *J*=7 Hz, 3H, CH_2CH_3), 2.15 (q, *J*=7 Hz, 2H, CH_2CH_3), 2.40 (m, 2H, CH_2CO), 3.05-3.30 (m, 2H, NCH_2), 4.09-4.20 (m, 2H, CH_2OH), 4.48 (br t, *J*=5 Hz, 1H, PhCHN), 7.20-7.40 (m, 5H, ArH); ^{13}C nmr 14.2 (CH_2CH_3), 20.3 (CH_2CH_3), 35.6 (CH_2CO), 44.7 (NCH_2), 61.7 (CH_2OH), 69.2 (PhCHN), 111.5 (=C), 127.2 128.0 and 129.1 (C_6H_5),136.9 (Ar-*ipso*), 152.1 (=CH), 191.4 (CO); ms (*m/z*, %) 245 (M^+, 17),

214 (100), 186 (31), 103 (35), 91 (57), 77 (33). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.48; H, 7.75; N, 5.71. Found: C, 73.54; H, 7.98; N, 5.58.

ACKNOWLEDGEMENTS

This work was supported by the DGICYT (Spain) through Grant PB-88/0316 and by the "Acción Integrada Hispano-Francesa" N° HF-111 (1990) and HF-167 (1991).

REFERENCES AND NOTES

1. A. Diez, H. Pé-Quiang, D. S. Grierson, H.-P. Husson, and M. Rubiralta, *Heterocycles*, **1990**, *31*, 485.
2. M. Rubiralta, A. Torrens, I. Reig, D. S. Grierson, and H.-P. Husson, *Heterocycles*, **1989**, *29*, 2121.
3. M. Rubiralta, A. Diez, I. Reig, J. Castells, J.-L. Bettiol, D. S. Grierson, and H.-P. Husson, *Heterocycles*, **1990**, *31*, 173, and references cited therein.
4. A. N. Kost, S. P. Gromov, and R. S. Sagitullin, *Tetrahedron*, **1981**, *37*, 3423.
5. M. Mehmandoust, C. Marazano, R. Singh, B. Gillet, M. Césario, J.-L. Fourrey, and B. C. Das, *Tetrahedron Lett.*, **1988**, *29* , 4423.
6. M. Mehmandoust, C. Marazano, and B. C. Das, *J. Chem. Soc., Chem. Commun.*, **1989**, 1185.
7. D. Gnecco, C. Marazano, and B. C. Das, *J. Chem. Soc., Chem. Commun.*, **1991**, 625
8. J. M. McIntosh and R. K. Leavitt, *J. Org. Chem.*, **1984**, *49*, 3407.
9. N. Ikota and B. Ganem, *J. Am.Chem.Soc.*, **1978**, *100*, 351.
10. (a) A. P. Kozikowski and P. Park, *J. Org. Chem.*, **1984**, *49*, 1676. (b) D. L. Comins and R. M. A. Foley, *Tetrahedron Lett.*, **1988**, *29*, 6711. (c) G. J. Hanson and M. A. Rusell, *Tetrahedron Lett.*, **1989**, *30*, 5751.
11. J. F. Jr. Kerwin and S. Danishefsky, *Tetrahedron Lett.* ,**1982**, *23* , 3739.
12. A. F. Vompe and N. F. Turitsyna, *Zhur. Obshchei Khim.*, **1957**, *27*, 3282 (*Chem. Abstr.*, **1958**, *52*, 9112).

Received, 5th July, 1991