# Alkylation of phenylglycinol-derived bicyclic lactams. Enantioselective synthesis of 3-alkylpiperidines

**Mercedes Amat,* Carmen Escolano, Núria Llor, Oscar Lozano, Arantxa Gómez-Esqué, Rosa Griera, and Joan Bosch***

*Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Av. Joan XXIII s/n, Barcelona 08028, Spain*
*E-mail: amat@ub.edu ; joanbosch@ub.edu*

**This work is dedicated to Professors José Elguero and Pedro Molina**

**(received 08 Nov 04; accepted 10 Feb 05; published on the web 02 Mar 05)**

**Abstract**

The stereochemical outcome of the alkylation of simple phenylglycinol-derived bicyclic lactams has been studied. The method provides a simple and concise route to 3-alkylpiperidines in both enantiomeric series. The synthesis of (+)-R-decarbomethoxytetrahydrosecodine, an indole alkaloid embodying a 3-ethylpiperidine moiety, is reported.

**Keywords:** Chiral bicyclic lactams, phenylglycinol, alkylation, enantioselective synthesis

## Introduction

Chiral non-racemic bicyclic -lactams formed by cyclo-condensation of simple -oxoesters and (*R*)- or (*S*)-phenylglycinol have emerged as powerful materials for easy access to a variety of enantiopure substituted piperidines by stereoselective introduction of the substituents on the ring, taking advantage of the functionalization and conformational rigidity of the bicyclic lactam system.[1] In this context, we have published a preliminary report [2] that alkylation of the enolate derived from the lactam carbonyl takes place with high facial stereoselectivity to give, ultimately, enantiopure 3-alkylpiperidines.

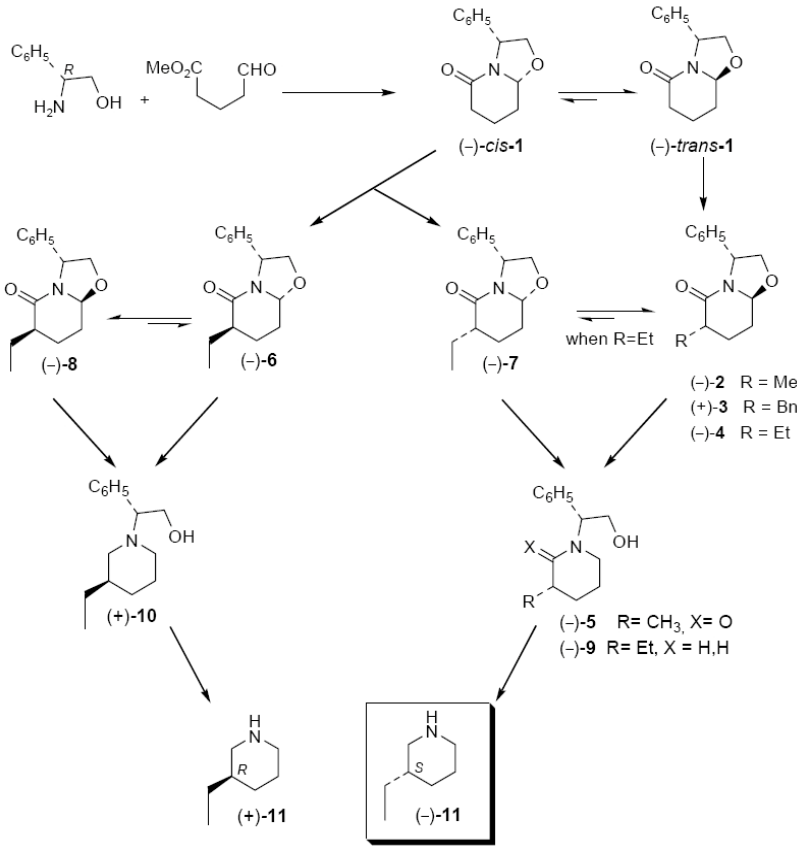
Although alkylation at the position α- to the carbonyl group of bicyclic γ- and δ- lactams derived from phenylglycinol or other chiral aminoalcohols has received considerable attention, both from the synthetic and theoretical standpoint,[3] the origin of the facial stereoselectivity remains controversial and the observed stereoselectivities are difficult to rationalize. We report here a short and convenient route for the synthesis of enantiopure 3-alkylpiperidines based on the alkylation of simple phenylglycinol-derived bicyclic lactams, *cis*-**1** and *trans*-**1**, and illustrate the potential and usefulness of this approach with the enantioselective synthesis of (+)-*R*decarbomethoxytetrahydrosecodine, an indole containing a 3-ethylpiperidine moiety, and its enantiomer.

## Results and Discussion

The pure lactam (–)-*cis*-**1** is easily accessible by cyclo-condensation of (*R*)-phenylglycinol with methyl 5-oxopentanoate under neutral conditions, followed by column chromatography of the resulting 85:15 diastereomeric mixture of lactams, while the lactam (–)-*trans*-**1** is obtained by equilibration of the above mixture under acidic conditions followed by chromatographic purification.[1a,4]

The enolate of the lactam (–)-*trans*-**1** was initially generated by treatment with LDA. Subsequent alkylation with methyl iodide or benzyl bromide gave the corresponding *exo* 3-substituted 2-piperidones (–)-**2** and (+)-**3** with good stereoselectivity (only one diastereomer was observed by NMR) but only moderate chemical yield (44% and 26%, respectively).[5] This low yield can be attributed to the fact that LDA removes the benzylic methine proton of (–)-*trans*-**1**, with irreversible opening of the oxazolidine ring to give an *N*-styryl lactam.[6] In fact, singlets at δ 5.3 and 5.7, attributable to the vinyl protons, were observed in the $^1$H-NMR spectrum of the crude reaction mixtures. The above yields were improved to 77% and 50%, respectively, when LiHMDS [lithium bis(trimethylsilyl)amide] was used as the base. Under these conditions, alkylation of (–)-*trans*-**1** with ethyl iodide gave (–)-**4** in 83% yield, also with excellent *exo* facial stereoselectivity. Only one diastereoisomer was observed by NMR in the crude reaction mixture (Scheme 1).




**Scheme 1**

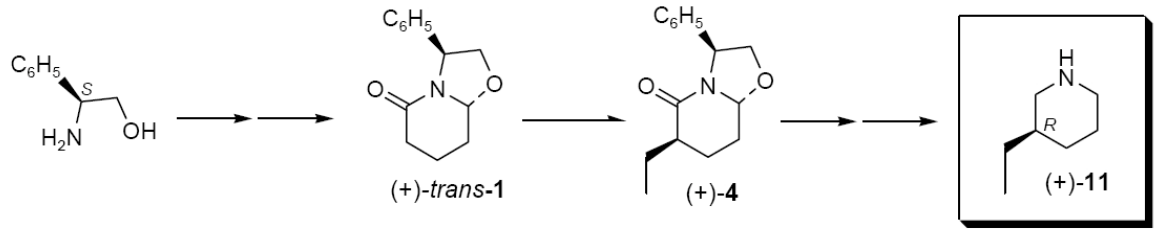
The configuration of the new stereogenic center in the alkylated lactams was determined by X-ray diffraction analysis of the ethyl lactam (–)-**4**, and by reducing the bicyclic lactam (–)-**2** to the known[7] (α*R*,3*S*)- hydroxylactam (–)-**5**, whose configuration had previously been determined by X-ray analysis.

In contrast with the above satisfactory results, alkylation (LiHMDS) of the lactam (–)-*cis*-**1** with ethyl iodide took place with moderate stereoselectivity to give a 1:2 diastereomeric mixture of *exo*- and *endo*- lactams (–)-**6** and (–)-**7** in 77% overall yield. The configuration of the stereocenter (C-6) generated in the above alkylation was determined by equilibration experiments. Thus, treatment of the major *endo* epimer (–)-**7** with TFA in $CH_2Cl_2$ led to the previously prepared lactam (–)-**4** [(–)-**4**/(–)-**7** in a 13:1 ratio], whereas the minor *exo* epimer (–)-**6** was converted to a 2:1 mixture of a new lactam (–)-**8** and (–)-**6**.

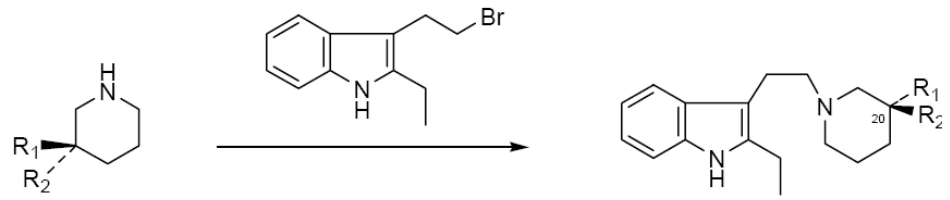
Treatment of lactam (–)-**4** with $LiAlH_4$ brought about both the reduction of the lactam carbonyl group and reductive cleavage of the oxazolidine ring to give the piperidine (–)-**9**. A similar reduction of (–)-**7** led to the same piperidine (–)-**9**, thus confirming that (–)-**4** and (–)-**7** are epimers at the methine 8a- carbon. Finally, removal of the chiral auxiliary by hydrogenolysis in the presence of Pd/C gave (*S*)-3-ethylpiperidine (–)-**11** in 76% yield. By following a similar sequence, the minor epimeric lactams (–)-**6** and (–)-**8** were converted to piperidine (+)-**10** and then to (*R*)-3-ethylpiperidine (+)-**11**.

A more convenient access to 3-alkylpiperidines in the *R*- enantiomeric series simply involves starting from (*S*)-phenylglycinol, which is also commercially available. Thus, the bicyclic lactam (+)-*trans*-**1** was alkylated stereoselectively to (+)-**4** and then converted in excellent yield to (*R*)-3-ethylpiperidine (+)-**11** via the piperidine (+)-**9** (Scheme 2; see Experimental Section). The above approach provides a simple and concise route to 3-alkylpiperidines in both enantiomeric series. It is worth mentioning that, with only one recent exception,[8] both (*R*)- and (*S*)-3-ethylpiperidine have been obtained previously by resolution of the racemate.[9]

To illustrate the potential of chiral lactams **1**, the enantiopure piperidines (+)-**11** and (–)-**11** were alkylated with 3-(2-bromoethyl)-2-ethylindole[2b] to give, respectively the alkaloid (+)-decarbomethoxytetrahydrosecodine and its enantiomer.[10]




**Scheme 2**




(+)-**11** $R_1$= Et, $R_2$=H (+)-Decarbomethoxytetrahydrosecodine
(–)-**11** $R_1$= H, $R_2$= Et (–)-Decarbomethoxytetrahydrosecodine

**Scheme 3**

## Experimental Section

**General Procedures.** All reactions were performed under an argon or nitrogen atmosphere with dry, freshly distilled solvents using standard procedures. Drying of organic extracts during the work-up of reactions was performed over anhydrous $Na_2SO_4$ or $MgSO_4$. Evaporation of solvents was accomplished with a rotary evaporator. Thin-layer chromatography used $SiO_2$ (silica gel 60 F254), and the spots were located by UV and either a 1% $KMnO_4$ solution or iodine. Chromatography refers to flash column chromatography and was carried out on $SiO_2$ (silica gel 60, SDS, 230–400 mesh). Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated, NMR spectra were recorded in $CDCl_3$. The chemical shifts are reported as δ values, in parts per million (ppm) relative to $Me_4Si$ (0 ppm) or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, integrated intensity, coupling constant (*J*) in Hertz (Hz) and assignment (when possible). Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; ap, apparent. Assignments and stereochemical determinations are given only when they are derived from definitive two-dimensional NMR experiments (HMQC–COSY). Only noteworthy IR absorptions ($cm^{-1}$) are listed. Mass spectra (MS) data are reported as *m*/*z* (%). High-resolution mass spectra (HMRS) were performed in the Unidade de Espectrometria de Masas, Santiago de Compostela. Microanalyses were performed by the Centre d'Investigació i Desenvolupament (CSIC), Barcelona.

**General procedure for the alkylation of lactams**

*cis*-**1** and *trans*-**1.** A solution of **1** (1 mmol) in THF was added to a cooled (–78 °C) solution of LiHMDS (1 *M* in THF, 1.5 mmol) in THF. After stirring the solution at –78 °C for 1 h, the alkylating reagent (2.7 mmol) was added and stirring was continued for an additional 2 h. The reaction was quenched by addition of saturated aqueous NaCl, and the resulting mixture was extracted with EtOAc and $CH_2Cl_2$. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed.

**(3*R*,6*S*,8a*S*)-6-Methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine [(–)-2].** The lactam, (–)-*trans*-**1** (600 mg, 2.76 mmol) in THF (6 mL), LiHMDS (4.14 mL, 4.14 mmol) in THF (24 mL), and methyl iodide (0.44 mL, 7.05 mmol) afforded **(–)-2** (491 mg, 77%) after flash chromatography (2:3

EtOAc–hexane): IR (NaCl) 1648 $cm^{-1}$; $^1$H- NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 1.25 (d, *J* = 7.2 Hz, 3H, $CH_3$), 1.44–1.62 (m, 2H, H-7, H-8), 2.03 (m, 1H, H-7), 2.31–2.41 (m, 2H, H-6, H-8), 3.73 (dd, *J* = 9.0, 8.1 Hz, 1H, H-2), 4.48 (dd, *J* = 9.0, 8.4 Hz, 1H, H-2), 5.01 (dd, *J* = 8.7, 4.5 Hz, 1H, H-8a), 5.24 (app t, *J* = 8.1 Hz, 1H, H-3), 7.21– 7.32 (m, 5H, H-Ar); $^{13}$C- NMR ($CDCl_3$, 75.4 MHz) δ 18.2 ($CH_3$), 26.0 (C-7), 28.2 (C-8), 37.0 (C-6), 58.0 (C-3), 72.7 (C-2), 88.7 (C-8a), 125.7 (2C, Ar), 127.3 (C, Ar), 128.6 (2C, Ar), 139.5 (C, *ipso*), 172.0 (NCO); $[\alpha]^{22}_D$ – 104.7 (*c* 1.0 MeOH). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found C, 72.31; H, 7.46; N, 5.97%.

**(3*R*,6*R*,8a*S*)-6-Benzyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine [(+)-3].** The lactam, (–)-*trans*-**1** (1 g, 4.61 mmol) in THF (15 mL), LiHMDS (6.92 mL, 6.92 mmol) in THF (35 mL), and benzyl bromide (1.41 mL, 2.35 mmol) afforded (+)-**3** (711 mg, 50%) after flash chromatography (1:9 EtOAc–hexane): IR (NaCl) 1653 $cm^{-1}$; $^1$H-NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 1.45–1.53 (m, 2H, H-7, H-8), 1.81 (m, 1H, H-7), 2.28 (m, 1H, H-8), 2.62 (m, 1H, H-6), 2.94 (dd, *J* = 13.5, 8.0 Hz, 1H, $CH_2Ph$), 3.16 (dd, *J* = 13.5, 4.0 Hz, 1H, $CH_2Ph$), 3.66 (dd, *J* = 9.0, 8.0 Hz, 1H, H-2), 4.47 (dd, 9.0, 8.0 Hz, 1H, H-2), 4.84 (dd, *J* = 8.5, 5.0 Hz, 1H, H-8a), 5.26 (app t, *J* = 7.8 Hz, 1H, H-3), 7.10–7.36 (m, 10H, H-Ar); $^{13}$C- NMR ($CDCl_3$, 75.4 MHz) δ 22.1 (C-7), 28.0 (C-8), 38.0 ($CH_2Ph$), 43.4 (C-6), 58.3 (C-3), 72.8 (C-2), 88.7 (C-8a), 125.9 (2C Ar), 126.1 (C Ar), 127.4 (C Ar), 128.1 (2C Ar), 128.6 (2C Ar), 129.1 (2C Ar), 138.7 (C *ipso* Bn), 139.3 (C *ipso* Ph), 170.5 (NCO); $[\alpha]^{22}_D$ + 26.5 (*c* 1.0 MeOH); MS-EI *m/z* 307 ($M^+$, 95), 104 (100), 216 (72); HRMS calcd for $C_{20}H_{21}NO_2$ 307.1572, found 307.1569.

**(3*R*,6*S*,8a*S*)-6-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo-[3,2-*a*]-pyridine [(–)-4].** The lactam, (–)-*trans*-**1** (200 mg, 0.92 mmol) in THF (2 mL), LiHMDS (1.38 mL, 1.38 mmol) in THF (8 mL), and ethyl iodide (0.19 mL, 2.36 mmol) afforded **(–)-4** (187 mg, 83%) after flash chromatography (1:1 EtOAc–hexane): IR (NaCl) 1640 $cm^{-1}$; $^1$H- NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 0.93 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.50–1.60 (m, 2H, H-7, H-8), 1.66 (m, 1H, CH$_3$C*H*$_2$), 1.90 (m, 1H, CH$_3$C*H*$_2$), 2.04 (m, 1H, H-7), 2.32 (m, 1H, H-6), 2.40 (m, 1H, H-8), 3.73 (dd, *J* = 9.0, 8.0 Hz, 1H, H-2), 4.51 (dd, *J* = 9.0, 8.0 Hz, 1H, H-2), 5.02 (dd, *J* = 8.6, 4.8 Hz, 1H, H-8a), 5.28 (t, *J* = 8.0 Hz, 1H, H-3), 7.20–7.38 (m, 5H, ArH); $^{13}$C- NMR ($CDCl_3$, 75.4 MHz) δ 10.7 (*C*H$_3$CH$_2$), 22.2 (C-7), 25.4 (CH$_3$*C*H$_2$), 28.1 (C-8), 42.8 (C-6), 58.2 (C-3), 72.7 (C-2), 88.8 (C-8a), 125.7 (C Ar), 127.4 (C Ar), 128.7 (C Ar), 139.7 (C *ipso*), 171.7 (NCO); mp 90–92 °C ($Et_2O$–hexane); $[\alpha]^{22}_D$ – 103.0 (*c* 1.0 EtOH); MS-EI *m*/*z* 245 ($M^+$, 25), 55 (88), 104 (100). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.29; H, 7.87; N, 5.70%.

**(3*S*,6*R*,8a*R*)-6-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine [(+)-4].** Following the general procedure, the lactam (+)-*trans*-**1** gave (+)-**4**: mp 91–92°C; $[\alpha]^{22}_D$ +102.9 (*c* 1.0 EtOH). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.76; H, 7.81; N, 5.52%.

**(3*R*,6*R*,8a*R*)- and (3*R*,6*S*,8a*R*)-6-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo-[3,2-*a*]pyridine [(–)-6 and (–)-7].** The lactam, (–)-*cis*-**1** (400 mg, 1.84 mmol) in THF (4 mL), LiHMDS (2.76 mL, 2.76 mmol) in THF (18 mL), and ethyl iodide (0.37 mL, 4.59 mmol) afforded **(–)-7** (234 mg, 52%) and **(–)-6 (**112 mg, 25%**)** after flash chromatography (1:1 EtOAc–

hexane). **(–)-7**: $^1$H-NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 0.90 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.44 (m, 1H, CH$_3$C*H*$_2$), 1.74 (m, 1H, CH$_3$C*H*$_2$), 1.80–1.96 (m, 3H, 2H-7, H-8), 2.16 (m, 1H, H-6), 2.27 (m, 1H, H-8), 3.99 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.15 (dd, *J* = 9.0, 6.8 Hz, 1H, H-2), 4.86 (dd, *J* = 8.7, 3.8 Hz, 1H, H-8a), 4.90 (dd, *J* = 6.8, 1.2 Hz, 1H, H-3), 7.19–7.35 (m, 5H, ArH); $^{13}$C- NMR ($CDCl_3$, 75.4 MHz) δ 11.9 (*C*H$_3$CH$_2$), 21.8 (C-7), 24.7 (CH$_3$*C*H$_2$), 25.5 (C-8), 41.2 (C-6), 58.4 (C-3), 73.9 (C-2), 88.2 (C-8a), 126.1 (C Ar), 127.2 (C Ar), 128.3 (C Ar), 141.6 (C- *ipso*), 170.3 (NCO); $[\alpha]^{22}_D$ – 52.0 (*c* 0.5 EtOH). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found C, 73.31; H, 8.03; N, 5.51%. **(–)-6**: $^1$H- NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 0.91 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$), 1.50 (m, 2H, CH$_3$C*H*$_2$, H-7), 1.80 (m, 1H, H-8a), 1.90 (m, 1H, CH$_3$C*H*$_2$), 2.06–2.23 (m, 2H, H-6, H-7), 2.42 (ddd, *J* = 12.3, 6.9, 3.3 Hz, 1H, H-8), 4.02 (dd, *J* = 9.0, 1.2 Hz, 1H, H-2), 4.16 (dd, *J* = 9.0, 6.8 Hz, 1H, H-2), 4.83 (dd, *J* = 9.9, 3.3 Hz, 1H, H-8a), 4.87 (br. d, *J* = 6.8 Hz, 1H, H-3), 7.20–7.35 (m, 5H, ArH); $^{13}$CNMR ($CDCl_3$, 75.4 MHz) δ 11.0 (*C*H$_3$CH$_2$), 23.3 (C-7), 24.2 (CH$_3$*C*H$_2$), 28.2 (C-8), 42.4 (C-6), 59.0 (C-3), 73.8 (C-2), 88.6 (C-8a), 126.2 (C Ar), 127.2 (C Ar), 128.3 (C Ar), 141.6 (C- *ipso*), 169.4 (NCO); mp 104–106 °C ($Et_2O$–hexane); $[\alpha]^{22}_D$ – 100.0 (*c* 0.93 EtOH). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found C, 73.33; H, 7.85; N, 5.60%.

**(3*S*,6*S*,8a*S*)- and (3*S*,6*R*,8a*S*)-6-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo-[3,2-*a*]pyridine [(+)-6 and (+)-7].** Following the general procedure, lactam (+)-*cis*-**1** gave (+)-**6** and (+)-**7.** (+)-**6**: mp 104–105 °C ($Et_2O$–hexane); $[\alpha]^{22}_D$ + 103.2 (*c* 1.0 EtOH). (+)-**7**: $[\alpha]^{22}_D$ + 53.7 (*c* 0.5 EtOH).

**Equilibration of (–)-6 and (–)-7.** TFA (1 mL) was added to a solution of **(–)-6** (315 mg, 1.29 mmol) in $CH_2Cl_2$ (25 mL) and the mixture was stirred at RT for 40 h. Then $CH_2Cl_2$ was added, and the mixture was washed with saturated aqueous $NaHCO_3$ and water. The organic phase was dried and concentrated to afford **(–)-6** and **(–)-8** (1:2 mixture; determined by $^1$H-NMR). Column chromatography (1:1 EtOAc–hexane) afforded **(–)-8**: $^1$H- NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 1.00 (t, *J* = 7.4 Hz, 3H, $CH_3$), 1.49 (m, 1H, $CH_2$), 1.60–2.05 (m, 4H, CH$_3$C*H*$_2$, H-7, H-8$_{ax}$), 2.23 (m, 2H, H-6, H- 8$_{eq}$), 3.77 (dd, *J* = 8.9, 7.7 Hz, 1H, H-2), 4.47 (dd, *J* = 8.8, 8.1 Hz, 1H, H-2), 5.01 (dd, *J* = 7.7, 4.7 Hz, 1H, H-8a), 5.26 (t, *J* = 7.9 Hz, 1H, H-3), 7.20–7.38 (m, 5H, ArH); $^{13}$C- NMR ($CDCl_3$, 50 MHz) δ 12.2 ($CH_3$), 20.7 (C-7), 24.0 (CH$_3$*C*H$_2$), 25.4 (C-8), 41.4 (C-6), 58.1 (C-3), 72.2 (C-2), 88.2 (C-8a), 126.0 (C Ar), 127.3 (C Ar), 128.6 (C Ar), 139.6 (C *ipso*), 171.7 (NCO); mp 63–64 °C; $[\alpha]^{22}_D$ – 156.4 (*c* 0.5 EtOH). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found C, 73.42; H, 7.89; N, 5.73%. From lactam (+)-**6**, (+)-**8** was obtained: mp 64–65 °C; $[\alpha]^{22}_D$ + 154.0 (*c* 0.5 $CHCl_3$). From **(–)-7** as described above, a mixture of **(–)-7** and **(–)-4** (1:13 ratio; determined by $_1$H- NMR) was obtained.

**(3*S*)-*N*-[(1*R*)-2-Hydroxyethyl-1-phenyl]-3-methyl-2-piperidone (–)-5.** Triethylsilane (0.04 mL, 0.2 mmol) and $TiCl_4$ (0.02 mL, 0.3 mmol) were added to a cooled solution (–78 °C) of (–)-**2** (30 mg, 0.2 mmol) in $CH_2Cl_2$. The mixture was allowed to warm to RT, stirred for 8 h, and poured into saturated aqueous $NH_4Cl$. The aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were dried and concentrated to give a residue, which was

chromatographed (EtOAc) to afford (–)-**5** (21 mg, 70%): IR (NaCl) 3406, 1618 $cm^{-1}$; $^1$H- NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 1.28 (d, *J* = 7.2 Hz, 3H, C*H*$_3$CH), 1.45 (m, 1H, H-4), 1.73 (m, 2H, H-5), 1.96 (m, 1H, H-4), 2.52 (m, 1H, H-3), 2.89 (ddd, *J* = 12.1, 7.4, 5.8 Hz, 1H, H-6), 3.18 (ddd, *J* = 12.1, 6.2, 6.2 Hz, 1H, H-6), 3.40 (br. s, 1H, OH), 4.13 (m, 2H, C*H*$_2$OH), 5.78 (dd, *J* = 8.8, 5.5, 1H, NCHAr), 7.25–7.33 (m, 5H, ArH); $^{13}$C- NMR ($CDCl_3$, 75.4 MHz) δ 18.2 ($CH_3$), 21.3 (C-5), 28.7 (C-4), 36.7 (C-3), 43.7 (C-6), 58.5 (NCHAr), 61.7 ($CH_2OH$), 127.6 (C Ar), 127.7 (C Ar), 128.5 (C Ar), 137.0 (C- *ipso*), 175.4 (NCO); MS-EI *m*/*z* 234 ($M^+$+1, 100), 216 (26), 114 (50); $[\alpha]^{22}_D$ – 70.0 (*c* 0.7 $CHCl_3$).

**General procedure for $LiAlH_4$ reduction**

$LiAlH_4$ (500 mg, 13.2 mmol) was added in portions to a solution of lactams **4**, **6**, **7**, or **8** (1 g, 4.08 mmol) in THF (50 mL). The mixture was stirred at RT for 1 h. Then 15% aqueous NaOH was carefully added, the resulting suspension was filtered, and the residue was washed with $Et_2O$. The combined organic extracts were concentrated to give (902 mg, 95%) of the respective piperidines, **9** (from **4** or **7**) or **10** (from **6** or **8**).

**(3*S*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine [(–)-9].** $^1$H- NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 0.71 (qd, *J* = 11.6, 3.0 Hz, 1H, H-4), 0.88 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.19 (m, 2H, $CH_3$C*H*$_2$), 1.43–1.53 (m, 2H, H-3, H-5), 1.57–1.75 (m, 3H, H-4, H-5, H-6), 1.95 (t, *J* = 10.5 Hz, 1H, H-2), 2.79 (m, 2H, H-2, H-6), 3.40 (br. s, 1H, OH), 3.60 (dd, 1H, *J* = 10.2, 5.1 Hz, H-2'), 3.70 (dd, *J* = 10.2, 5.1 Hz, 1H, H-1'), 3.98 (t, *J* =10.2 Hz, 1H, H-2'), 7.12–7.40 (m, 5H, ArH); $^{13}$C- NMR ($CDCl_3$, 50 MHz) δ 11.3 ($CH_3$), 25.1 (C-5), 26.9 ($CH_3$*C*$H_2$), 30.2 (C-4), 38.0 (C-3), 47.2 (C-6), 58.6 (C-2), 60.0 (C-2'), 70.3 (C-1'), 128.1 (C- *p*), 128.2 (C- *o*), 129.1 (C- *m*), 134.7 (C- *ipso*); $[\alpha]^{22}_D$ – 27.2 (*c* 0.5 EtOH). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found C, 77.13; H, 7.97; N, 6.00%. (+)-**9**: $[\alpha]^{22}_D$ + 28.1 (*c* 0.5 EtOH).

**(3*R*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine [(+)-10].** $^1$H- NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 0.63 (m, 1H, H-4), 0.77 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.07 (m, 2H, $CH_3$C*H*$_2$), 1.29 (m, 2H, H-2, H-3), 1.43–1.68 (m, 3H, H-4, H-5), 2.17 (td, *J* = 11.2, 3.4 Hz, 1H, H- 6ax), 2.64–2.75 (m, 2H, H- 2eq, H- 6eq), 3.27 (br. s, 1H, OH), 3.52 (dd, 1H, *J* = 10.2, 5.2 Hz, H-2'), 3.60 (dd, *J* = 10.0, 5.2 Hz, 1H, H-1'), 3.92 (t, *J* =10.0 Hz, 1H, H-2'), 7.10 (br. d, *J* = 7.0 Hz, 2H, ArH); $^{13}$C- NMR ($CDCl_3$, 50 MHz) δ 11.5 ($CH_3$), 25.9 (C-5), 27.1 ($CH_3$*C*$H_2$), 30.5 (C-4), 38.3 (C-3), 52.5 (C-2), 53.1 (C-6), 59.8 ($CH_2O$), 70.0 (C-1'), 127.7 (C- *p*), 128.0 (C- *o*), 128.9 (C- *m*), 135.4 (C- *ipso*); $[\alpha]^{22}_D$ + 15.1 (*c* 0.8 $CH_2Cl_2$). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.20; H, 9.94; N, 6.00. Found C, 77.20; H, 10.04; N, 6.00%. (–)-**10**: $[\alpha]^{22}_D$ – 15.9 (*c* 0.9 $CH_2Cl_2$).

**General procedure for debenzylation reaction**

(*S*)- and (*R*)-3-ethylpiperidine [(–)-**11** and (+)- **11**]. A solution of the ethylpiperidine (–)-**9** or (–)-**10** (950 mg, 4.08 mmol) in methanol–HCl (10 mL) was concentrated to give a residue, which was dissolved in methanol (50 mL). The resulting solution containing 5% Pd/C (100 mg) was hydrogenated at RT until starting material disappeared in the TLC. The catalyst was removed by filtration, and the solvent was evaporated. The resulting solid was digested in $Et_2O$ to give (462 mg, 76%) pure (–)-**11** hydrochloride: $^1$HNMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 1.06

(t, *J* = 7.7 Hz, 3H, $CH_3$), 1.30 (m, 1H, H- 4ax), 1.45 (m, 2H, $CH_3CH_2$), 1.65–1.96 (m, 2H, H-3ax, H- 5ax), 1.98–2.10 (m, 2H, H- 4eq, H- 5eq), 2.71 (t, *J* = 12.0 Hz, 1H, H- 2ax), 2.99 (td, *J* = 12.8, 2.7 Hz, 1H, H- 6ax), 3.38–3.48 (m, 2H, H- 2eq, H- 6eq), 3.60 (dd, *J* = 10.0, 5.2 Hz, 1H, H-1'), 3.92 (t, *J* =10.0 Hz, 1H, H- 2'), 7.10 (br. d, *J* =7.0 Hz, 2H, ArH); $^{13}$C- NMR ($CDCl_3$, 75 MHz) δ 11.2 ($CH_3$), 28.3 (C-5), 27.5 ($CH_3CH_2$), 29.4 (C-4), 36.5 (C-3), 45.4 (C-6), 49.9 (C-2); mp 161–162 °C; $[\alpha]^{22}_D$ –3.5 (*c* 1.0 EtOH). (–)- **11**: $^1$H- NMR ($CDCl_3$, 300 MHz, COSY, HETCOR) δ 0.88 (t, *J* = 7.4 Hz, 3H, $CH_3$), 0.97 (dddd, *J* = 12.6, 12.6, 11.0, 4.0 Hz, 1H, H- 4ax), 1.17 (m, 2H, $CH_3CH_2$), 1.29 (m, 1H, H-3), 1.42 (qt, *J* = 12.6, 4.0 Hz, 1H, H- 5ax), 1.64 (dm, *J* = 12.6 Hz, 1H, H- 5eq), 1.83 (dm, *J* = 12.6 Hz, 1H, H- 4eq), 1.88 (br. s, 1H, NH), 2.20 (dd, *J* = 11.9, 10,2, 1H, H- 2ax), 2.51 (td, *J* = 12.2, 2.8 Hz, 1H, H- 6ax), 2.99 (dm, *J* = 12.2 Hz, 1H, H-6eq), 3.03 (dm, *J* = 12.2 Hz, 1H, H- 2eq); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 11.2 ($CH_3$), 26.7 (C-5), 27.2 ($CH_3CH_2$), 31.2 (C-4), 38.9 (C-3), 47.0 (C-6), 52.8 (C-2); $[\alpha]^{22}_D$ – 2.6 (*c* 0.68 EtOH). As above, from (+)-**9** or (+)-**10**, (+)-**11** hydrochloride was obtained: $[\alpha]^{22}_D$ + 3.2 (*c* 1.0 EtOH). (+)-**11**: $[\alpha]^{22}_D$ + 2.0 (*c* 0.68 EtOH).

**(+)-(*R*)-Decarbomethoxytetrahydrosecodine.** A mixture of (+)-**11** (140 mg, 0.94 mmol), 3-(2-bromoethyl)-2-ethylindole (230 mg, 0.91 mmol) and $NaHCO_3$ (250 mg, 2.98 mmol) in acetonitrile (3 mL) was heated at 80 °C for 30 h. The mixture was cooled at RT and $Et_2O$ (100 mL) and water (10 mL) were added. The phases were separated, and the organic phase was dried and concentrated. Column chromatography ($Et_2O$) of the residue gave the alkaloid (166 mg, 64%): $^1$H-NMR ($CDCl_3$, 500 MHz, COSY, HETCOR) δ 0.85 (qd, *J* = 12.0, 5.0 Hz, 1H, H- 15ax), 0.90 (t, *J* = 7.5 Hz, 3H, H-18), 1.24 (m, 2H, H-19), 1.27 (t, *J* = 7.5 Hz, 3H, H-17), 1.54 (m, 1H, H- 20ax), 1.62–1.74 (m, 3H, H- 21ax, H-14), 1.80 (dm, *J* = 12.0 Hz, 1H, H- 15eq), 1.96 (td, *J* = 11.0, 2.5 Hz, 1H, H- 3ax), 2.56 (m, 2H, H-5), 2.75 (q, *J* = 7.5 Hz, 2H, H-16), 2.92 (dd, *J* = 9.5, 8.0 Hz, 2H, H-6), 3.02–3.10 (m, 3H, H- 3eq, H- 21eq), 7.05 (td, J = 7.0, 1.0 Hz, 1H, H-10), 7.09 (td, *J* = 7.0, 1.0 Hz, 1H, H-11), 7.26 (dm, *J* = 7.0 Hz, 1H, H-12), 7.51 (dm, *J* = 7.0 Hz, 1H, H-9), 7.79 (br. s, 1H, NH); $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 11.4 (C-18), 14.5 (C-17), 19.3 (C-6), 21.7 (C-16), 25.5 (C-14), 27.5 (C-19), 30.8 (C-15), 37.9 (C-10), 54.4 (C-3), 60.2 (C-21), 60.4 (C-5), 108.8 (C-7), 110.3 (C-12), 118.0 (C-9), 118.9 (C-10), 128.5 (C-8), 135.1 (C-2), 137.0 (C-13); $[\alpha]^{22}_D$ + 10.5 (*c* 1.0 EtOH).

**(–)-(*S*)-Decarbomethoxytetrahydrosecodine** was obtained as above, from (–)-**12:** $[\alpha]^{22}_D$ – 10.8 (*c* 1.0 EtOH).

## Acknowledgments

This work was supported by the DGICYT, Spain (BQU2003-0505). Thanks are also due to the DURSI. Generalitat de Catalunya, for Grant 2001SGR-0084, the Ministry of Education, Culture and Sport for a fellowship to O. L., and the SCT of the University of Barcelona for recording the NMR and mass spectra. We thank DSM Deretil (Almería, Spain) for a generous gift of (*R*)-phenylglycine.

## References


1. (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem*. **2000**, *65*, 3074. (b) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. For reviews, see: (c) Meyers, A. I.; Brengel, G. P. *Chem. Commun*. **1997**, 1. (d) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843.
2. (a) Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 977. (b) Amat, M.; Pshenichnyi, G.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 3091.
3. (a) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G. *J. Am. Chem. Soc*. **1998**, 120, 7429. (b) Ando, K.; Green, N. S.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc*. **1999**, *121*, 5334. (c) Bailey, J. H.; Byfield, A. T. J.; Davis, P. J.; Foster, A. C.; Leech, M.; Moloney, M. G.; Müller, M.; Prout, C. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1977. (d) Hughes, R. C.; Dvorak, C. A.; Meyers, A. I. *J. Org. Chem*. **2001**, *66*, 5545. (e) Ikuta, Y.; Tomoda, S. *Tetrahedron Lett*. **2003**, *44*, 5931. (f) Ikuta, Y.; Tomoda, S. *Org. Lett*. **2004**, *6*, 189. (g) Brewster, A. G.; Broady, S.; Davies, C. E.; Heightman, T. D.; Hermitage, S. A.; Hughes, M.; Moloney, M. G.; Wood, G. *Org. Biomol. Chem*. **2004**, *2*, 1031.
4. Amat, M.; Llor, N.; Escolano, C.; Huguet, M.; Pérez, M.; Molins, E.; Bosch, J. *Tetrahedron: Asymmetry* **2003**, *14*, 293.
5. Previous attempts to alkylate this lactam using LDA as the base had resulted in failure: Micouin, L.; Varea, T.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett*. **1994**, *35*, 2529.
6. Westrum, L. J.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 973.
7. Micouin, L.; Varea, R.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett*. **1994**, *35*, 2529.
8. For an alternative synthetic route to enantiopure 3-alkylpiperidines, including (*R*)-3-ethylpiperidine, see: Pedrosa, R.; Andrés, C.; Duque-Soladana J. P.; Rosón, C. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2809.
9. (a) Günther, A. *Chem. Ber*. **1898**, *31*. (b) Ripperger, H.; Schreiber, K.; Sych, F. J. *J. Prakt. Chem*. **1970**, *312*, 471. (c) Sakai, S.; Aimi, N.; Kato, K.; Ido, H.; Masuda, K.; Watanabe, Y.; Haginiwa, J. *Yakugaku Zasshi* **1975**, *95*, 1152. (d) Morlacchi, F.; Losacco, V.; Tortorella, V. *J. Heterocyclic Chem.* **1979**, *16*, 297.
10. Isolation: (a) Croks, P. A.; Robinson, B.; Smith, G. F. *J. Chem. Soc., Chem. Commun*. **1968**, 1210. (b) Robert, G. M. T.; Ahond, A.; Poupat, C.; Potier, P.; Jollès, C.; Jousselin, A.; Jacquemin, H. *J. Nat. Prod*. **1983**, *46*, 694. (c) Atta-ur-Rahman; Zaman, K.; Perveen. S.; Habib-ur-Rehman; Muzaffar, A.; Choudhary, M. I.; Pervin, A. *Phytochemistry* **1991**, *30*, 1285. (d) Mroue, M. A.; Ghuman, M. A.; Alam, M. *Phytochemistry* **1993**, *33*, 217. (e) Mroue, M. A.; Euler, K. L.; Ghuman, M. A.; Alam, M. *J. Nat. Prod*. **1996**, *59*, 890. Synthesis: (f) Palmisano, G.; Santagostino, M.; Riva, S.; Sisti, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1229. (g) Sakagami, H.; Samizu, K.; Kamikubo, T.; Ogasawa, K. *Synlett* **1996**, 163.