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

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> 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. 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 ¹H-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 known⁷ (αR ,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 LiAlH₄ 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 = 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 Na₂SO₄ or MgSO₄. Evaporation of solvents was accomplished with a rotary evaporator. Thin-layer chromatography used SiO₂ (silica gel 60 F254), and the spots were located by UV and either a 1% KMnO₄ solution or iodine. Chromatography refers to flash column chromatography and was carried out on SiO₂ (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 CDCl₃. The chemical shifts are reported as δ values, in parts per million (ppm) relative to Me₄Si (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 CH₂Cl₂. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed.

(*3R*,6*S*,8*aS*)-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; ¹H- NMR (CDCl₃, 300 MHz, COSY, HETCOR) δ 1.25 (d, J = 7.2 Hz, 3H, CH₃), 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); ¹³C- NMR (CDCl₃, 75.4 MHz) δ 18.2 (CH₃), 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 C₁₄H₁₇NO₂: C, 72.70; H, 7.41; N, 6.06. Found C, 72.31; H, 7.46; N, 5.97%.

(3R,6R,8aS)-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; ¹H-NMR (CDCl₃, 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, CH₂Ph), 3.16 (dd, J = 13.5, 4.0 Hz, 1H, CH₂Ph), 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); ¹³C- NMR (CDCl₃, 75.4 MHz) δ 22.1 (C-7), 28.0 (C-8), 38.0 (CH₂Ph), 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); [α]²² D+26.5 (*c* 1.0 MeOH); MS-EI *m/z* 307 (M⁺, 95), 104 (100), 216 (72); HRMS calcd for C₂₀H₂₁NO₂ 307.1572, found 307.1569.

(*3R*,6*S*,8*aS*)-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; ¹H- NMR (CDCl₃, 300 MHz, COSY, HETCOR) δ 0.93 (t, *J* = 7.5 Hz, 3H, CH₃CH₂), 1.50–1.60 (m, 2H, H-7, H-8), 1.66 (m, 1H, CH₃CH₂), 1.90 (m, 1H, CH₃CH₂), 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); ¹³C- NMR (CDCl₃, 75.4 MHz) δ 10.7 (CH₃CH₂), 22.2 (C-7), 25.4 (CH₃CH₂), 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 (Et₂O–hexane); [α]²² D – 103.0 (*c* 1.0 EtOH); MS-EI *m/z* 245 (M⁺, 25), 55 (88), 104 (100). Anal. Calcd for C₁₅H₁₉NO₂: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.29; H, 7.87; N, 5.70%.

(3*S*,6*R*,8*aR*)-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 C₁₅H₁₉NO₂: 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 EtOAchexane). (-)-7: ¹H-NMR (CDCl₃, 300 MHz, COSY, HETCOR) δ 0.90 (t, J = 7.5 Hz, 3H, CH₃CH₂), 1.44 (m, 1H, CH₃CH₂), 1.74 (m, 1H, CH₃CH₂), 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); ¹³C- NMR (CDCl₃, 75.4 MHz) δ 11.9 (CH₃CH₂), 21.8 (C-7), 24.7 (CH₃CH₂), 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 C₁₅H₁₉NO₂: C, 73.44; H, 7.81; N, 5.71. Found C, 73.31; H, 8.03; N, 5.51%. (-)-6: ¹H- NMR (CDCl₃, 300 MHz, COSY, HETCOR) $\delta 0.91$ (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.50 (m, 2H, CH_3CH_2 , H-7), 1.80 (m, 1H, H-8a), 1.90 (m, 1H, CH_3CH_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); ¹³CNMR (CDCl₃, 75.4 MHz) δ 11.0 (CH₃CH₂), 23.3 (C-7), 24.2 (CH₃CH₂), 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 (Et₂O–hexane); $[\alpha]^{22}$ D–100.0 (*c* 0.93 EtOH). Anal. Calcd for C₁₅H₁₉NO₂: C, 73.44; H, 7.81; N, 5.71. Found C, 73.33; H, 7.85; N, 5.60%.

(35,65,8aS)- and (35,6R,8aS)-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 (Et₂O–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 CH₂Cl₂ (25 mL) and the mixture was stirred at RT for 40 h. Then CH₂Cl₂ was added, and the mixture was washed with saturated aqueous NaHCO₃ and water. The organic phase was dried and concentrated to afford (–)-6 and (–)-8 (1:2 mixture; determined by ¹H-NMR). Column chromatography (1:1 EtOAc–hexane) afforded (–)-8: ¹H- NMR (CDCl₃, 300 MHz, COSY, HETCOR) δ 1.00 (t, J = 7.4 Hz, 3H, CH₃), 1.49 (m, 1H, CH₂), 1.60–2.05 (m, 4H, CH₃CH₂, 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); ¹³C- NMR (CDCl₃, 50 MHz) δ 12.2 (CH₃), 20.7 (C-7), 24.0 (CH₃CH₂), 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; [α]²² D – 156.4 (*c* 0.5 EtOH). Anal. Calcd for C₁₅H₁₉NO₂: 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; [α]²² D + 154.0 (*c* 0.5 CHCl₃). From (–)-7 as described above, a mixture of (–)-7 and (–)-4 (1:13 ratio; determined by 1H- NMR) was obtained.

(3S)-N-[(1R)-2-Hydroxyethyl-1-phenyl]-3-methyl-2-piperidone (-)-5. Triethylsilane (0.04 mL, 0.2 mmol) and TiCl₄ (0.02 mL, 0.3 mmol) were added to a cooled solution (-78 °C) of (-)-2 (30 mg, 0.2 mmol) in CH₂Cl₂. The mixture was allowed to warm to RT, stirred for 8 h, and poured into saturated aqueous NH₄Cl. The aqueous phase was extracted with CH₂Cl₂. 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; ¹H- NMR (CDCl₃, 300 MHz, COSY, HETCOR) δ 1.28 (d, J = 7.2 Hz, 3H, CH₃CH), 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, CH₂OH), 5.78 (dd, J = 8.8, 5.5, 1H, NCHAr), 7.25–7.33 (m, 5H, ArH); ¹³C- NMR (CDCl₃, 75.4 MHz) δ 18.2 (CH₃), 21.3 (C-5), 28.7 (C-4), 36.7 (C-3), 43.7 (C-6), 58.5 (NCHAr), 61.7 (CH₂OH), 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); [α]²² D – 70.0 (*c* 0.7 CHCl₃).

General procedure for LiAlH4 reduction

LiAlH₄ (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]. ¹H- NMR (CDCl₃, 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, CH₃), 1.19 (m, 2H, CH₃CH₂), 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); ¹³C- NMR (CDCl₃, 50 MHz) δ 11.3 (CH₃), 25.1 (C-5), 26.9 (CH₃CH₂), 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*); [α]²² D – 27.2 (*c* 0.5 EtOH). Anal. Calcd for C₁₅H₂₃NO: C, 77.20; H, 9.94; N, 6.00. Found C, 77.13; H, 7.97; N, 6.00%. (+)-9: [α]²² D + 28.1 (*c* 0.5 EtOH).

(*3R*)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]piperidine [(+)-10]. ¹H- NMR (CDCl₃, 300 MHz, COSY, HETCOR) δ 0.63 (m, 1H, H-4), 0.77 (t, J = 7.3 Hz, 3H, CH₃), 1.07 (m, 2H, CH₃CH₂), 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); ¹³C- NMR (CDCl₃, 50 MHz) δ 11.5 (CH₃), 25.9 (C-5), 27.1 (CH₃CH₂), 30.5 (C-4), 38.3 (C-3), 52.5 (C-2), 53.1 (C-6), 59.8 (CH₂O), 70.0 (C-1'), 127.7 (C- *p*), 128.0 (C- *o*), 128.9 (C- *m*), 135.4 (C- *ipso*); [α]²² P + 15.1 (*c* 0.8 CH₂Cl₂). Anal. Calcd for C₁₅H₂₃NO: C, 77.20; H, 9.94; N, 6.00. Found C, 77.20; H, 10.04; N, 6.00%. (-)-**10**: [α]²² P - 15.9 (*c* 0.9 CH₂Cl₂).

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 Et₂O to give (462 mg, 76%) pure (–)-**11** hydrochloride: ¹HNMR (CDCl₃, 300 MHz, COSY, HETCOR) δ 1.06

(t, J = 7.7 Hz, 3H, CH₃), 1.30 (m, 1H, H- 4ax), 1.45 (m, 2H, CH₃CH₂), 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); ¹³C- NMR (CDCl₃, 75 MHz) δ 11.2 (CH₃), 28.3 (C-5), 27.5 (CH₃CH₂), 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**: ¹H- NMR (CDCl₃, 300 MHz, COSY, HETCOR) δ 0.88 (t, J = 7.4 Hz, 3H, CH₃), 0.97 (dddd, J = 12.6, 12.6, 11.0, 4.0 Hz, 1H, H- 4ax), 1.17 (m, 2H, CH₃CH₂), 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); ¹³C-NMR (CDCl₃, 75 MHz) δ 11.2 (CH₃), 26.7 (C-5), 27.2 (CH₃CH₂), 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 NaHCO₃ (250 mg, 2.98 mmol) in acetonitrile (3 mL) was heated at 80 °C for 30 h. The mixture was cooled at RT and Et2O (100 mL) and water (10 mL) were added. The phases were separated, and the organic phase was dried and concentrated. Column chromatography (Et₂O) of the residue gave the alkaloid (166 mg, 64%): ¹H-NMR (CDCl₃, 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); ¹³C-NMR (CDCl₃, 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); [α]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).

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