# 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

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#### 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 $\alpha$ - to the carbonyl group of bicyclic $\gamma$ - and $\delta$ - 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- $\mathbf{1}$ is obtained by equilibration of the above mixture under acidic conditions followed by chromatographic purification. ${ }^{1 \mathrm{a}, 4}$

The enolate of the lactam (-)-trans- $\mathbf{1}$ was initially generated by treatment with LDA. Subsequent alkylation with methyl iodide or benzyl bromide gave the corresponding exo 3substituted 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 $\delta$ 5.3 and 5.7, attributable to the vinyl protons, were observed in the ${ }^{1} \mathrm{H}-\mathrm{NMR}$ 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 ${ }^{7}(\alpha R, 3 S)$ - 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ 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 $\mathrm{LiAlH}_{4}$ 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 8 a - carbon. Finally, removal of the chiral auxiliary by hydrogenolysis in the presence of $\mathrm{Pd} / \mathrm{C}$ gave (S)-3-ethylpiperidine (-)-11 in $76 \%$ yield. By following a similar sequence, the minor epimeric lactams $(-)-6$ and $(-)-\mathbf{8}$ were converted to piperidine $(+)-10$ and then to $(R)$-3-ethylpiperidine $(+)-\mathbf{1 1}$.

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- $\mathbf{1}$ was alkylated stereoselectively to $(+)-4$ and then converted in excellent yield to $(R)-$ 3-ethylpiperidine $(+)-\mathbf{1 1}$ 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)-3ethylpiperidine 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 ${ }^{2 b}$ to give, respectively the alkaloid (+)decarbomethoxytetrahydrosecodine and its enantiomer. ${ }^{10}$


Scheme 2



$(+)-11 \quad \mathrm{R}_{1}=\mathrm{Et}, \mathrm{R}_{2}=\mathrm{H} \quad(+)$-Decarbomethoxytetrahydrosecodine
$(-)-11 \quad \mathrm{R}_{1}=\mathrm{H}, \mathrm{R}_{2}=\mathrm{Et} \quad(-)$-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 $\mathrm{Na}_{2} \mathrm{SO}_{4}$ or $\mathrm{MgSO}_{4}$. Evaporation of solvents was accomplished with a rotary evaporator. Thin-layer chromatography used $\mathrm{SiO}_{2}$ (silica gel 60 F254), and the spots were located by UV and either a $1 \% \mathrm{KMnO}_{4}$ solution or iodine. Chromatography refers to flash column chromatography and was carried out on $\mathrm{SiO}_{2}$ (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 $\mathrm{CDCl}_{3}$. The chemical shifts are reported as $\delta$ values, in parts per million ( ppm ) relative to $\mathrm{Me}_{4} \mathrm{Si}(0 \mathrm{ppm})$ or relative to residual chloroform ( $7.26 \mathrm{ppm}, 77.0 \mathrm{ppm}$ ) 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 $\left(\mathrm{cm}^{-1}\right)$ are listed. Mass spectra (MS) data are reported as $\mathrm{m} / \mathrm{z}(\%)$. 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 $\mathbf{1}(1 \mathrm{mmol})$ in THF was added to a cooled $\left(-78^{\circ} \mathrm{C}\right)$ solution of LiHMDS ( 1 M in THF, 1.5 mmol ) in THF. After stirring the solution at $-78^{\circ} \mathrm{C}$ 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed.
(3R,6S,8aS)-6-Methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine [(-)-2]. The lactam, (-)-trans-1 ( $600 \mathrm{mg}, 2.76 \mathrm{mmol}$ ) in THF ( 6 mL ), LiHMDS ( $4.14 \mathrm{~mL}, 4.14 \mathrm{mmol}$ ) in THF ( 24 mL ), and methyl iodide ( $0.44 \mathrm{~mL}, 7.05 \mathrm{mmol}$ ) afforded ( - )-2 ( $491 \mathrm{mg}, 77 \%$ ) after flash chromatography ( $2: 3$

EtOAc-hexane): IR ( NaCl$) 1648 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}, \mathrm{COSY}, \mathrm{HETCOR}\right) \delta 1.25$ (d, $J=7.2 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}$ ), 1.44-1.62 (m, 2H, H-7, H-8), $2.03(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-7), 2.31-2.41(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-$ $6, \mathrm{H}-8), 3.73$ (dd, $J=9.0,8.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2), 4.48(\mathrm{dd}, J=9.0,8.4 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2), 5.01(\mathrm{dd}, J=$ $8.7,4.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-8 \mathrm{a}), 5.24$ (app t, $J=8.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-3$ ), $7.21-7.32(\mathrm{~m}, 5 \mathrm{H}, \mathrm{H}-\mathrm{Ar}) ;{ }^{13} \mathrm{C}-\mathrm{NMR}$ $\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta 18.2\left(\mathrm{CH}_{3}\right), 26.0(\mathrm{C}-7), 28.2(\mathrm{C}-8), 37.0(\mathrm{C}-6), 58.0(\mathrm{C}-3), 72.7(\mathrm{C}-2), 88.7$ (C-8a), 125.7 (2C, Ar), 127.3 (C, Ar), 128.6 (2C, Ar), 139.5 (C, ipso), $172.0(\mathrm{NCO}) ;[\alpha]^{22} \mathrm{D}-$ 104.7 (c 1.0 MeOH ). Anal. Calcd for $\mathrm{C}_{14} \mathrm{H}_{17} \mathrm{NO}_{2}: \mathrm{C}, 72.70 ; \mathrm{H}, 7.41 ; \mathrm{N}, 6.06$. 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-5H-oxazolo[3,2-a]pyridine
[(+)-3]. The lactam, (-)-trans- $\mathbf{1}(1 \mathrm{~g}, 4.61 \mathrm{mmol})$ in THF $(15 \mathrm{~mL})$, LiHMDS ( $6.92 \mathrm{~mL}, 6.92$ mmol ) in THF ( 35 mL ), and benzyl bromide ( $1.41 \mathrm{~mL}, 2.35 \mathrm{mmol}$ ) afforded ( + ) $-3(711 \mathrm{mg}$, $50 \%$ ) after flash chromatography (1:9 EtOAc-hexane): IR ( NaCl ) $1653 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}\right.$, $300 \mathrm{MHz}, \mathrm{COSY}, \mathrm{HETCOR}) \delta 1.45-1.53(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-7, \mathrm{H}-8), 1.81(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-7), 2.28(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-$ 8), $2.62(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-6), 2.94$ (dd, $J=13.5,8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{CH}_{2} \mathrm{Ph}$ ), 3.16 (dd, $J=13.5,4.0 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{CH}_{2} \mathrm{Ph}$ ), $3.66(\mathrm{dd}, J=9.0,8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2), 4.47(\mathrm{dd}, 9.0,8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2), 4.84(\mathrm{dd}, J=8.5$, $5.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-8 \mathrm{a}$ ), 5.26 (app t, $J=7.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-3$ ), $7.10-7.36(\mathrm{~m}, 10 \mathrm{H}, \mathrm{H}-\mathrm{Ar}) ;{ }^{13} \mathrm{C}-\mathrm{NMR}$ $\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta 22.1(\mathrm{C}-7), 28.0(\mathrm{C}-8), 38.0\left(\mathrm{CH}_{2} \mathrm{Ph}\right), 43.4(\mathrm{C}-6), 58.3(\mathrm{C}-3), 72.8(\mathrm{C}-2)$, 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 $307\left(\mathrm{M}^{+}, 95\right), 104$ (100), 216 (72); HRMS calcd for $\mathrm{C}_{20} \mathrm{H}_{21} \mathrm{NO}_{2}$ 307.1572, found 307.1569.
(3R,6S,8aS)-6-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo-[3,2-a]-pyridine [(-)-4]. The lactam, ( - )-trans- $\mathbf{1}$ ( $200 \mathrm{mg}, 0.92 \mathrm{mmol}$ ) in THF ( 2 mL ), LiHMDS ( $1.38 \mathrm{~mL}, 1.38$ mmol ) in THF ( 8 mL ), and ethyl iodide ( $0.19 \mathrm{~mL}, 2.36 \mathrm{mmol}$ ) afforded ( - ) $\mathbf{- 4}(187 \mathrm{mg}, 83 \%)$ after flash chromatography ( $1: 1 \mathrm{EtOAc}-$ hexane $)$ : IR $(\mathrm{NaCl}) 1640 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 300\right.$ $\mathrm{MHz}, \mathrm{COSY}, \mathrm{HETCOR}) \delta 0.93\left(\mathrm{t}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}\right), 1.50-1.60(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-7, \mathrm{H}-8), 1.66$ $\left(\mathrm{m}, 1 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}\right), 1.90\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}\right), 2.04(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-7), 2.32(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-6), 2.40(\mathrm{~m}, 1 \mathrm{H}$, $\mathrm{H}-8), 3.73(\mathrm{dd}, J=9.0,8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2), 4.51(\mathrm{dd}, J=9.0,8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2), 5.02(\mathrm{dd}, J=8.6$, $4.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-8 \mathrm{a}), 5.28(\mathrm{t}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-3), 7.20-7.38(\mathrm{~m}, 5 \mathrm{H}, \mathrm{ArH}) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}\right.$, $75.4 \mathrm{MHz}) \delta 10.7\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 22.2(\mathrm{C}-7), 25.4\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 28.1(\mathrm{C}-8), 42.8(\mathrm{C}-6), 58.2(\mathrm{C}-3), 72.7$ (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 $90-92{ }^{\circ} \mathrm{C}\left(\mathrm{Et}_{2} \mathrm{O}-\right.$ hexane $) ;[\alpha]^{22}$ D - 103.0 (c 1.0 EtOH$) ;$ MS-EI m/z $245\left(\mathrm{M}^{+}, 25\right), 55$ (88), 104 (100). Anal. Calcd for $\mathrm{C}_{15} \mathrm{H}_{19} \mathrm{NO}_{2}$ : C, 73.44; H, 7.81; N, 5.71. Found: C, 73.29; H, 7.87; N, 5.70\%.
(3S,6R,8aR)-6-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine [(+)4]. Following the general procedure, the lactam (+)-trans-1 gave (+)-4: mp $91-92^{\circ} \mathrm{C}$; $[\alpha]^{22} \mathrm{D}$ +102.9 ( с 1.0 EtOH ). Anal. Calcd for $\mathrm{C}_{15} \mathrm{H}_{19} \mathrm{NO}_{2}$ : C, 73.44; H, 7.81; N, 5.71. Found: C, 73.76; H, 7.81; N, 5.52\%.
(3R,6R,8aR)- and (3R,6S,8aR)-6-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo-[3,2-a]pyridine [(-)-6 and (-)-7]. The lactam, (-)-cis-1 (400 mg, 1.84 mmol ) in THF ( 4 mL ), LiHMDS ( $2.76 \mathrm{~mL}, 2.76 \mathrm{mmol}$ ) in THF ( 18 mL ), and ethyl iodide ( $0.37 \mathrm{~mL}, 4.59 \mathrm{mmol}$ ) afforded (-)-7 (234 mg, 52\%) and (-)-6 (112 mg, 25\%) after flash chromatography (1:1 EtOAc-
hexane). (-)-7: ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}, \mathrm{COSY}, \mathrm{HETCOR}\right) \delta 0.90(\mathrm{t}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H}$, $\mathrm{CH}_{3} \mathrm{CH}_{2}$ ), $1.44\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}\right), 1.74\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}\right), 1.80-1.96(\mathrm{~m}, 3 \mathrm{H}, 2 \mathrm{H}-7, \mathrm{H}-8), 2.16$ (m, 1H, H-6), 2.27 (m, 1H, H-8), 3.99 (dd, $J=9.0,1.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2$ ), 4.15 (dd, $J=9.0,6.8 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{H}-2), 4.86(\mathrm{dd}, J=8.7,3.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-8 \mathrm{a}), 4.90(\mathrm{dd}, J=6.8,1.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-3), 7.19-7.35$ $(\mathrm{m}, 5 \mathrm{H}, \mathrm{ArH}) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta 11.9\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 21.8(\mathrm{C}-7), 24.7\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 25.5$ (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); $[\alpha]^{22}{ }_{\mathrm{D}}-52.0(c 0.5 \mathrm{EtOH})$. Anal. Calcd for $\mathrm{C}_{15} \mathrm{H}_{19} \mathrm{NO}_{2}$ : C, 73.44; H, 7.81; N, 5.71. Found C, 73.31; H, 8.03; N, 5.51\%. (-)-6: ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}, \mathrm{COSY}\right.$, HETCOR) $\delta 0.91\left(\mathrm{t}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}\right), 1.50\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}, \mathrm{H}-7\right), 1.80(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-8 \mathrm{a})$, $1.90\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}\right), 2.06-2.23(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-6, \mathrm{H}-7), 2.42$ (ddd, $\left.J=12.3,6.9,3.3 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-8\right)$, 4.02 (dd, $J=9.0,1.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2), 4.16(\mathrm{dd}, J=9.0,6.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2), 4.83(\mathrm{dd}, J=9.9,3.3$ $\mathrm{Hz}, 1 \mathrm{H}, \mathrm{H}-8 \mathrm{a}$ ), 4.87 (br. d, $J=6.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-3$ ), $7.20-7.35(\mathrm{~m}, 5 \mathrm{H}, \mathrm{ArH}) ;{ }^{13} \mathrm{CNMR}\left(\mathrm{CDCl}_{3}\right.$, $75.4 \mathrm{MHz}) \delta 11.0\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 23.3(\mathrm{C}-7), 24.2\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 28.2(\mathrm{C}-8), 42.4(\mathrm{C}-6), 59.0(\mathrm{C}-3), 73.8$ (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 $104-106{ }^{\circ} \mathrm{C}\left(\mathrm{Et}_{2} \mathrm{O}\right.$-hexane $) ;[\alpha]^{22} \mathrm{D}-100.0(c 0.93 \mathrm{EtOH})$. Anal. Calcd for $\mathrm{C}_{15} \mathrm{H}_{19} \mathrm{NO}_{2}$ : C, 73.44; H, 7.81; N, 5.71. Found C, 73.33; H, 7.85; N, 5.60\%.
(3S,6S,8aS)- and (3S,6R,8aS)-6-Ethyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo-[3,2-a]pyridine [(+)-6 and (+)-7]. Following the general procedure, lactam (+)-cis-1 gave (+)-6 and (+)-7. (+)-6: mp 104-105 ${ }^{\circ} \mathrm{C}\left(\mathrm{Et}_{2} \mathrm{O}\right.$-hexane); $[\alpha]^{22} \mathrm{D}+103.2$ (c 1.0 EtOH). $(+)-7:[\alpha]^{22} \mathrm{D}+$ 53.7 ( с 0.5 EtOH$)$.

Equilibration of (-)-6 and (-)-7. TFA ( 1 mL ) was added to a solution of (-)-6 (315 mg, $1.29 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(25 \mathrm{~mL})$ and the mixture was stirred at RT for 40 h . Then $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added, and the mixture was washed with saturated aqueous $\mathrm{NaHCO}_{3}$ and water. The organic phase was dried and concentrated to afford (-)-6 and (-)-8 (1:2 mixture; determined by ${ }^{1} \mathrm{H}-$ NMR). Column chromatography (1:1 EtOAc-hexane) afforded (-)-8: ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}\right.$, $300 \mathrm{MHz}, \mathrm{COSY}, \mathrm{HETCOR}) \delta 1.00\left(\mathrm{t}, J=7.4 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.49\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{CH}_{2}\right), 1.60-2.05(\mathrm{~m}$, $4 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}, \mathrm{H}-7, \mathrm{H}-8 \mathrm{ax}$ ), 2.23 ( $\mathrm{m}, 2 \mathrm{H}, \mathrm{H}-6, \mathrm{H}-8_{\mathrm{eq}}$ ), 3.77 (dd, $J=8.9,7.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2$ ), 4.47 (dd, $J=8.8,8.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2), 5.01(\mathrm{dd}, J=7.7,4.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-8 \mathrm{a}), 5.26(\mathrm{t}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-$ 3), $7.20-7.38(\mathrm{~m}, 5 \mathrm{H}, \mathrm{ArH}) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 50 \mathrm{MHz}\right) \delta 12.2\left(\mathrm{CH}_{3}\right), 20.7(\mathrm{C}-7), 24.0$ $\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 25.4(\mathrm{C}-8), 41.4(\mathrm{C}-6), 58.1(\mathrm{C}-3), 72.2(\mathrm{C}-2), 88.2(\mathrm{C}-8 \mathrm{a}), 126.0(\mathrm{C} \mathrm{Ar}), 127.3(\mathrm{C}$ $\mathrm{Ar})$, 128.6 (C Ar), 139.6 (C ipso), 171.7 (NCO); mp $63-64{ }^{\circ} \mathrm{C}$; $[\alpha]^{22} \mathrm{~d}-156.4$ (c 0.5 EtOH$)$. Anal. Calcd for $\mathrm{C}_{15} \mathrm{H}_{19} \mathrm{NO}_{2}$ : 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: $\mathrm{mp} 64-65^{\circ} \mathrm{C} ;[\alpha]^{22} \mathrm{D}+154.0\left(c 0.5 \mathrm{CHCl}_{3}\right)$. From (-)-7 as described above, a mixture of (-)-7 and (-)-4 (1:13 ratio; determined by $1 \mathrm{H}-\mathrm{NMR}$ ) was obtained.
(3S)-N-[(1R)-2-Hydroxyethyl-1-phenyl]-3-methyl-2-piperidone (-)-5. Triethylsilane $(0.04 \mathrm{~mL}, 0.2 \mathrm{mmol})$ and $\mathrm{TiCl}_{4}(0.02 \mathrm{~mL}, 0.3 \mathrm{mmol})$ were added to a cooled solution $\left(-78{ }^{\circ} \mathrm{C}\right)$ of $(-)-2(30 \mathrm{mg}, 0.2 \mathrm{mmol})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. The mixture was allowed to warm to RT, stirred for 8 h , and poured into saturated aqueous $\mathrm{NH}_{4} \mathrm{Cl}$. The aqueous phase was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$. 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, $1618 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}-\mathrm{NMR}$ $\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}, \mathrm{COSY}, \mathrm{HETCOR}\right) \delta 1.28\left(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}\right), 1.45(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4)$, 1.73 (m, 2H, H-5), 1.96 (m, 1H, H-4), 2.52 (m, 1H, H-3), 2.89 (ddd, $J=12.1,7.4,5.8 \mathrm{~Hz}, 1 \mathrm{H}$, $\mathrm{H}-6$ ), 3.18 (ddd, $J=12.1,6.2,6.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-6$ ), 3.40 (br. s, $1 \mathrm{H}, \mathrm{OH}$ ), 4.13 (m, 2H, CH2OH), 5.78 (dd, $J=8.8,5.5,1 \mathrm{H}, \mathrm{NCHAr}), 7.25-7.33(\mathrm{~m}, 5 \mathrm{H}, \mathrm{ArH}) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta$ $18.2\left(\mathrm{CH}_{3}\right), 21.3(\mathrm{C}-5), 28.7(\mathrm{C}-4), 36.7(\mathrm{C}-3), 43.7(\mathrm{C}-6), 58.5(\mathrm{NCHAr}), 61.7\left(\mathrm{CH}_{2} \mathrm{OH}\right), 127.6$ (C Ar), 127.7 (C Ar), 128.5 (C Ar), 137.0 (C-ipso), 175.4 (NCO); MS-EI m/z $234\left(\mathrm{M}^{+}+1,100\right)$, 216 (26), 114 (50); $[\alpha]^{22}{ }_{\mathrm{D}}-70.0\left(c 0.7 \mathrm{CHCl}_{3}\right)$.

## General procedure for $\mathrm{LiAlH}_{4}$ reduction

$\mathrm{LiAlH}_{4}(500 \mathrm{mg}, 13.2 \mathrm{mmol})$ was added in portions to a solution of lactams 4, 6, 7, or $\mathbf{8}(1 \mathrm{~g}$, 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 $\mathrm{Et}_{2} \mathrm{O}$. The combined organic extracts were concentrated to give ( $902 \mathrm{mg}, 95 \%$ ) of the respective piperidines, 9 (from 4 or 7 ) or $\mathbf{1 0}$ (from 6 or 8).
(3S)-3-Ethyl-1-[(1R)-2-hydroxy-1-phenylethyl]piperidine [(-)-9]. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 300\right.$ $\mathrm{MHz}, \mathrm{COSY}, \mathrm{HETCOR}) \delta 0.71(\mathrm{qd}, J=11.6,3.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-4), 0.88\left(\mathrm{t}, J=7.3 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right)$, 1.19 (m, 2H, CH $\mathrm{CH}_{2}$ ), 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, $J=10.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2), 2.79(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-2, \mathrm{H}-6), 3.40$ (br. s, $1 \mathrm{H}, \mathrm{OH}$ ), 3.60 (dd, $1 \mathrm{H}, J=10.2,5.1$ Hz, H-2'), 3.70 (dd, $\left.J=10.2,5.1 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-1^{\prime}\right), 3.98$ (t, $\left.J=10.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2^{\prime}\right), 7.12-7.40$ (m, $5 \mathrm{H}, \mathrm{ArH}) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 50 \mathrm{MHz}\right) \delta 11.3\left(\mathrm{CH}_{3}\right), 25.1(\mathrm{C}-5), 26.9\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 30.2(\mathrm{C}-4)$, 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 (Cm), 134.7 (C-ipso); $[\alpha]^{22}{ }_{\mathrm{D}}-27.2$ (c 0.5 EtOH ). Anal. Calcd for $\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{NO}: \mathrm{C}, 77.20 ; \mathrm{H}, 9.94 ; \mathrm{N}$, 6.00. Found C, 77.13; H, 7.97; N, 6.00\%. (+)-9: $[\alpha]^{22}{ }_{\mathrm{D}}+28.1$ (c 0.5 EtOH$)$.
(3R)-3-Ethyl-1-[(1R)-2-hydroxy-1-phenylethyl]piperidine [(+)-10]. ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 300\right.$ $\mathrm{MHz}, \mathrm{COSY}, \mathrm{HETCOR}) \delta 0.63(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4), 0.77\left(\mathrm{t}, J=7.3 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 1.07(\mathrm{~m}, 2 \mathrm{H}$, $\mathrm{CH}_{3} \mathrm{CH}_{2}$ ), 1.29 ( $\mathrm{m}, 2 \mathrm{H}, \mathrm{H}-2, \mathrm{H}-3$ ), $1.43-1.68(\mathrm{~m}, 3 \mathrm{H}, \mathrm{H}-4, \mathrm{H}-5), 2.17$ (td, $J=11.2,3.4 \mathrm{~Hz}, 1 \mathrm{H}$, H-6ax), 2.64-2.75 (m, 2H, H- 2eq, H- 6eq), 3.27 (br. s, 1H, OH), 3.52 (dd, $1 \mathrm{H}, J=10.2,5.2 \mathrm{~Hz}$, H-2'), 3.60 (dd, $J=10.0,5.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-1$ '), 3.92 (t, $J=10.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2^{\prime}$ ), 7.10 (br. d, $J=7.0$ $\mathrm{Hz}, 2 \mathrm{H}, \mathrm{ArH}) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 50 \mathrm{MHz}\right) \delta 11.5\left(\mathrm{CH}_{3}\right), 25.9(\mathrm{C}-5), 27.1\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 30.5(\mathrm{C}-$ 4), $38.3(\mathrm{C}-3), 52.5(\mathrm{C}-2), 53.1(\mathrm{C}-6), 59.8\left(\mathrm{CH}_{2} \mathrm{O}\right), 70.0(\mathrm{C}-1$ '), $127.7(\mathrm{C}-p), 128.0(\mathrm{C}-o)$, 128.9 (C-m), 135.4 (C-ipso); $[\alpha]^{22}{ }_{\mathrm{D}}+15.1\left(c 0.8 \mathrm{CH}_{2} \mathrm{Cl}_{2}\right)$. Anal. Calcd for $\mathrm{C}_{15} \mathrm{H}_{23} \mathrm{NO}: \mathrm{C}, 77.20$; H, 9.94; N, 6.00. Found C, 77.20 ; H, 10.04; N, 6.00\%. (-)-10: $[\alpha]^{22}{ }_{\mathrm{D}}-15.9\left(c 0.9 \mathrm{CH}_{2} \mathrm{Cl}_{2}\right)$.

## General procedure for debenzylation reaction

$(S)-$ and $(R)$-3-ethylpiperidine $[(-)-11$ and $(+)-11]$. A solution of the ethylpiperidine ( - )-9 or $(-)-$ $10(950 \mathrm{mg}, 4.08 \mathrm{mmol})$ in methanol- $\mathrm{HCl}(10 \mathrm{~mL})$ was concentrated to give a residue, which was dissolved in methanol ( 50 mL ). The resulting solution containing $5 \% \mathrm{Pd} / \mathrm{C}(100 \mathrm{mg})$ 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 $\mathrm{Et}_{2} \mathrm{O}$ to give ( $462 \mathrm{mg}, 76 \%$ ) pure (-)-11 hydrochloride: ${ }^{1} \mathrm{HNMR}\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}, \mathrm{COSY}, \mathrm{HETCOR}\right) \delta 1.06$
( $\mathrm{t}, J=7.7 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}$ ), $1.30(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-4 \mathrm{ax}), 1.45\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}\right), 1.65-1.96(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-$ $3 \mathrm{ax}, \mathrm{H}-5 \mathrm{ax}), 1.98-2.10(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-4 \mathrm{eq}, \mathrm{H}-5 \mathrm{eq}), 2.71$ (t, $J=12.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2 \mathrm{ax}$ ), 2.99 (td, $J=$ $12.8,2.7 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-6 \mathrm{ax}$ ), 3.38-3.48 (m, 2H, H-2eq, H-6eq), 3.60 (dd, J = 10.0, $5.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-$ $1^{\prime}$ ), 3.92 (t, $J=10.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2^{\prime}$ ), 7.10 (br. d, $J=7.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{ArH}$ ); ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}\right.$, $75 \mathrm{MHz}) \delta 11.2\left(\mathrm{CH}_{3}\right), 28.3(\mathrm{C}-5), 27.5\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 29.4(\mathrm{C}-4), 36.5(\mathrm{C}-3), 45.4(\mathrm{C}-6), 49.9(\mathrm{C}-$ 2); mp $161-162{ }^{\circ} \mathrm{C} ;[\alpha]^{22}{ }_{\mathrm{D}}-3.5$ (c 1.0 EtOH$) .(-)-11:{ }^{1} \mathrm{H}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}, \mathrm{COSY}\right.$, HETCOR) $\delta 0.88\left(\mathrm{t}, J=7.4 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{CH}_{3}\right), 0.97$ (dddd, $J=12.6,12.6,11.0,4.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-4 \mathrm{ax}$ ), $1.17\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{CH}_{3} \mathrm{CH}_{2}\right), 1.29(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}-3), 1.42(\mathrm{qt}, J=12.6,4.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-5 \mathrm{ax}), 1.64(\mathrm{dm}, J=$ $12.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-5 \mathrm{eq}), 1.83(\mathrm{dm}, J=12.6 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-4 \mathrm{eq}), 1.88$ (br. s, $1 \mathrm{H}, \mathrm{NH}$ ), 2.20 (dd, $J=$ $11.9,10,2,1 \mathrm{H}, \mathrm{H}-2 \mathrm{ax}), 2.51(\mathrm{td}, J=12.2,2.8 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-6 \mathrm{ax}), 2.99$ (dm, $J=12.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-$ $6 \mathrm{eq}), 3.03(\mathrm{dm}, J=12.2 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-2 \mathrm{eq}) ;{ }^{13} \mathrm{C}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 75 \mathrm{MHz}\right) \delta 11.2\left(\mathrm{CH}_{3}\right), 26.7(\mathrm{C}-5)$, $27.2\left(\mathrm{CH}_{3} \mathrm{CH}_{2}\right), 31.2(\mathrm{C}-4), 38.9(\mathrm{C}-3), 47.0(\mathrm{C}-6), 52.8(\mathrm{C}-2)$; $[\alpha]^{22}{ }_{\mathrm{D}}-2.6(c 0.68 \mathrm{EtOH}) . \mathrm{As}$ above, from $(+)-\mathbf{9}$ or $(+)-\mathbf{1 0},(+)-\mathbf{1 1}$ hydrochloride was obtained: $[\alpha]^{22}{ }_{\mathrm{D}}+3.2(c 1.0 \mathrm{EtOH}) .(+)-$ 11: $[\alpha]^{22}{ }_{\mathrm{D}}+2.0(c 0.68 \mathrm{EtOH})$.
$\left.\mathbf{(}^{+}\right)-(\boldsymbol{R})$-Decarbomethoxytetrahydrosecodine. A mixture of (+)-11 ( $140 \mathrm{mg}, 0.94 \mathrm{mmol}$ ), 3-(2-bromoethyl)-2-ethylindole ( $230 \mathrm{mg}, 0.91 \mathrm{mmol}$ ) and $\mathrm{NaHCO}_{3}(250 \mathrm{mg}, 2.98 \mathrm{mmol})$ in acetonitrile ( 3 mL ) was heated at $80{ }^{\circ} \mathrm{C}$ for 30 h . The mixture was cooled at RT and $\mathrm{Et}_{2} \mathrm{O}$ $(100 \mathrm{~mL})$ and water $(10 \mathrm{~mL})$ were added. The phases were separated, and the organic phase was dried and concentrated. Column chromatography $\left(\mathrm{Et}_{2} \mathrm{O}\right)$ of the residue gave the alkaloid ( $166 \mathrm{mg}, 64 \%$ ): ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 500 \mathrm{MHz}, \mathrm{COSY}, \mathrm{HETCOR}\right) \delta 0.85(\mathrm{qd}, J=12.0,5.0 \mathrm{~Hz}, 1 \mathrm{H}$, H- 15 ax ), $0.90(\mathrm{t}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{H}-18), 1.24(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-19), 1.27(\mathrm{t}, J=7.5 \mathrm{~Hz}, 3 \mathrm{H}, \mathrm{H}-17), 1.54$ (m, 1H, H-20ax), 1.62-1.74 (m, 3H, H-21ax, H-14), 1.80 (dm, $J=12.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-15 \mathrm{eq}), 1.96$ ( td, $J=11.0,2.5 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-3 \mathrm{ax}), 2.56(\mathrm{~m}, 2 \mathrm{H}, \mathrm{H}-5), 2.75(\mathrm{q}, J=7.5 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{H}-16), 2.92$ (dd, $J$ $=9.5,8.0 \mathrm{~Hz}, 2 \mathrm{H}, \mathrm{H}-6), 3.02-3.10(\mathrm{~m}, 3 \mathrm{H}, \mathrm{H}-3 \mathrm{eq}, \mathrm{H}-21 \mathrm{eq}), 7.05(\mathrm{td}, \mathrm{J}=7.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-$ 10), $7.09(\mathrm{td}, J=7.0,1.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-11), 7.26(\mathrm{dm}, J=7.0 \mathrm{~Hz}, 1 \mathrm{H}, \mathrm{H}-12), 7.51(\mathrm{dm}, J=7.0 \mathrm{~Hz}$, $1 \mathrm{H}, \mathrm{H}-9), 7.79$ (br. s, $1 \mathrm{H}, \mathrm{NH}$ ); ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(\mathrm{CDCl}_{3}, 75 \mathrm{MHz}\right) \delta 11.4$ (C-18), 14.5 (C-17), 19.3 (C6), 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 (C13); $[\alpha]^{22}{ }_{\mathrm{D}}+10.5$ (c 1.0 EtOH$)$.
(-)-(S)-Decarbomethoxytetrahydrosecodine was obtained as above, from (-)-12: $[\alpha]^{22}{ }_{\mathrm{D}}-10.8$ (c 1.0 EtOH ).

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