A Simple Stereoselective Synthesis of Enantiopure 2-Substituted Pyrrolidines and Piperidines from Chiral (*R*)-Phenylglycinol-Derived Bicyclic 1,3-Oxazolidines

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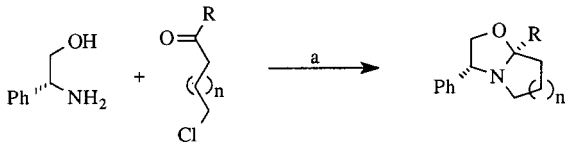
Chiral, nonracemic 2-substituted pyrrolidines and piperidines were prepared in high *ee* and moderate to good chemical yields in three steps from (*R*)-phenylglycinol and γ- or δ-chloroketones. The key step of the synthesis was the stereoselective reductive ring-opening of chiral bicyclic 1,3-oxazolidines prepared by condensation of (*R*)-phenylglycinol and the corresponding ketones.

Introduction

The pyrrolidine and piperidine ring systems are present in many natural products and biologically important substances.[1] As a part of an ongoing project directed to this type of heterocycle,[2] we describe now a short route to enantiopure 2-substituted pyrrolidines and piperidines from the chiral perhydropyrrolo[2,1-*b*][1,3]oxazoles **3a−f** and perhydropyrido [2,1-*b*][1,3]oxazoles **3g−i** (bicyclic oxazolidines) derived from (*R*)-phenylglycinol. Both enantiomers of phenylglycinol have been used as chiral auxiliaries in mono- and bicyclic oxazolidine-mediated diastereoselective synthesis.[3] Recently, the preparation of alkaloids,[4] amino acids,[5] piperidines,[6] and isoindoline derivatives[7] by using oxazolidines derived from phenylglycinol has been reported. In the same way, bicyclic oxazolidines prepared from phenylglycinols and dialdehydes have been demonstrated to be excellent starting materials in the synthesis of enantiopure morpholines,[8] pyrrolidines,[9] piperidines[10] or aminophosphonates;[11] chiral bicyclic lactams have also been successfully used in the preparation of both pyrrolidines[12] and piperidines.[13]

The chiral bicyclic oxazolidines **3a−i** were prepared (Scheme 1) by condensation of (*R*)-(−)-phenylglycinol and the corresponding γ- or δ-chloroketones **2a−i** at room temp. in chloroform or toluene and triethylamine as solvents. It should be noted that it was necessary to work at high concentration (ca. 10 M) to ensure that the condensation finished in 24−120 h.[14] Chloroketone **2a** was commercially available and **2b**,[15] **2c**,[16] **2d**,[17] **2e**,[15] **2f**,[18] **2g**,[19] **2h**[20] and **2i**[21] were easily prepared from 4-chlorobutanoyl chloride or 5-chloropentanoyl chloride by reaction with organometallic reagents.[22]

The condensation was diastereoselective, leading to a mixture of epimers at the angular carbon of the bicyclic system in good diastereomeric excesses (84−92%). The only exception was the δ-chloroketone **2g**, which gave **3g** as an 80:20 mixture of diastereoisomers at C-8a. NOESY experiments allowed us to assign a *cis* relationship between the phenyl group and the substituent at the angular carbon for all the bicyclic structures **3a−i**, showing that the condensation of γ- and δ-chloroketones followed the same stereochemical outcome as that described for keto acids.[12]



1 n = 1 **2a** R = CH_3; **2b** R = CH_2CH_3; **2c** R = $CH_2CH_2CH_3$; **2d** R = $CH(CH_3)_2$; **2e** R = $CH_2CH_2CH_2CH_3$; **2f** R = $CH_2CH_2C_6H_5$; n = 2 **2g** R = CH_3; **2h** R = CH_2CH_3; **2i** R = $CH_2CH_2CH_3$ → **3a-i**

Scheme 1. (a) Et_3N, $CHCl_3$, room temp., 24−96 h

The mixtures of diastereoisomers were used in the next stage because they could not be separated. The ring opening of bicyclic oxazolidines **3a−i** was first tested by hydrogenation. This method would allow the preparation of 2-substituted pyrrolidines and piperidines in one step. Unfortunately, hydrogenation of **3a** with palladium on carbon yielded 2-methylpyrrolidine in good yield but with very low enantiomeric excess (7%). The preparation of pyrrolidine and piperidine derivatives was envisaged in two steps by reductive ring opening of the oxazolidine ring followed by hydrogenolytic elimination of the phenylethanol appendage (Scheme 2).

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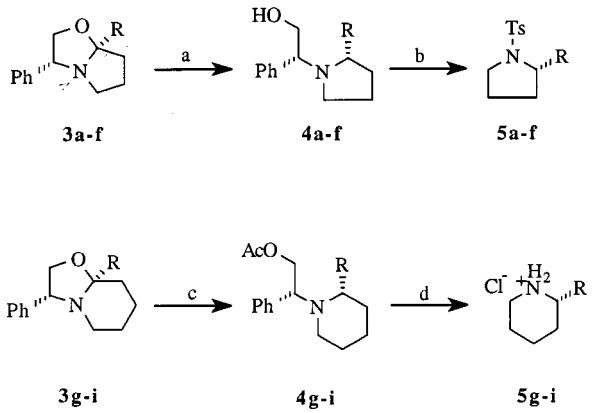


Scheme 2. (a) $LiBHEt_3$, THF, 0 °C, 10 h; (b) i: H_2, Pd(C) 10%, EtOH; ii: TsCl, iPr_2NEt; (c) i: $LiAlH_4$, THF, 0 °C, 12 h; ii: Ac_2O, DMPA, room temp. 1.5 h; (d) H_2, $Pd(OH)_2$, HCl, Et_2O

Treatment of **3a−i** with one equivalent of lithium aluminium hydride in THF at room temperature gave the desired ring-opened compounds but with considerable epimerization. On the contrary, the reaction of **3a−f** with 1.5 equivalents of lithium triethylborohydride in THF at 0 °C led to **4a−f** in good chemical yields and with complete diastereoselectivity (Table 1) as demonstrated by ^1H NMR spectroscopy of the reaction mixture. At this stage the diastereomeric amino alcohols were separated by flash chromatography giving **4a−f** as enantiopure compounds. The perhydropyperido[2,1-*b*][1,3]oxazoles **3g−i** also reacted with lithium triethylborohydride in THF at 0 °C leading, after the corresponding hydrogenolysis, to the amino alcohols. The diasteromeric mixture of these amino alcohols could not be separated, so they were transformed into acetates **4g−i** by reaction with Ac_2O and DMAP in dichloromethane and readily purified to single diastereoisomers by flash chromatography.

The transformation of **4a−f** into (*R*)-2-methylpyrrolidine,[23] (*R*)-2-ethylpyrrolidine,[24] (*R*)-2-propylpyrrolidine,[25] (*S*)-2-isopropylpyrrolidine,[26] (*R*)-2-butylpirrolidine,[27] and (*R*)-2-phenethylpyrrolidine,[28] isolated as tosylates, was carried out by removal of the *N*-benzyl moiety by hydrogenolysis over palladium on carbon and treatment with tosyl chloride. The enantiomeric purity of the corresponding pyrrolidines was measured by ^{19}F NMR spectroscopy of the MTPA derivatives and the configuration of the final products was determined by comparison of the sign of the optical rotation previously described.

In the same way, (+)-pipecoline hydrochloride (**5g**),[13b] (*R*)-2-ethylpiperidine hydrochloride (**5h**)[13b] and (−)-coniine (**5i**)[29] were obtained from **4g−i** by hydrogenolysis over $Pd(OH)_2$ on carbon followed by treatment with hydrogen chloride in anhydrous diethyl ether.

These results indicated that reductive ring opening of the *N*,*O*-acetal moiety in bicyclic oxazolidines **3a−i** took place with total retention of the configuration at the angular carbon and that the stereochemical outcome in the opening of our compounds is similar to those described for related bicyclic oxazolidines[11] or lactams.[12]

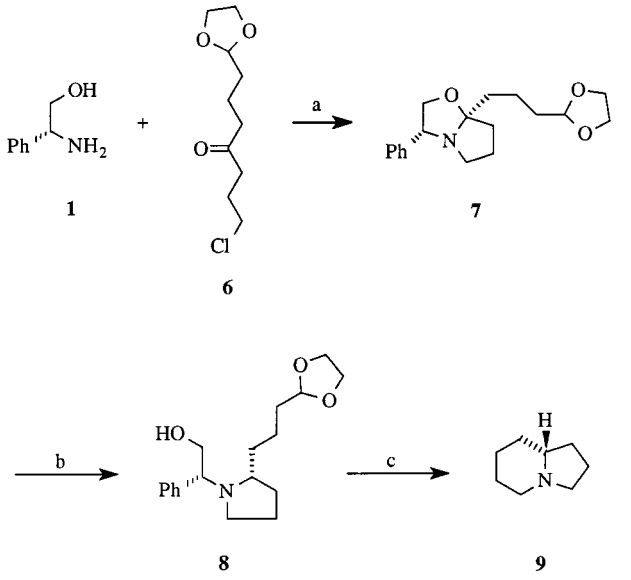
In order to broaden the scope of both the pyrrolidine and piperidine routes, we tested the preparation of (−)-δ-coniceine **9** and (−)-anabasine **13**. The proposed way to **9** was complementary to that described by Meyers,[13b] since in our case the six-membered ring was closed on the acetal-containing 2-substituted pyrrolidine **8**. To this end, the ethylene acetal of 8-chloro-5-oxooctanal **6**, prepared from 4-chlorobutanoyl chloride and the copper derivative of 2-(3-chloropropyl)-1,3-dioxolane, was condensed with (*R*)-phenylglycinol to give the angular substituted bicyclic oxazolidine **7** in 78% yield and 90% *de*. Reductive ring opening of **7** by treatment with lithium triethylborohydride in THF yielded a mixture of diastereomeric 2-substituted pyrrolidines in 74% yield with total retention of configuration. After purification by flash chromatography, the major diastereoisomer **8** was transformed into enantiopure (−)-δ-coniceine[30] by hydrolysis and hydrogenation over 10% Pd/C in methanol containing a 2 M solution of HCl (Scheme 3).

Finally, enantiopure (−)-anabasine **13** was prepared, in three steps, from the pyridine derivative **10** as outlined in Scheme 4. Ketone **10** was obtained by SO_3·Py oxidation of the alcohol prepared by reaction of 3-pyridylcarboxaldehyde and 4-chlorobutylmagnesium bromide in 63% total yield. Condensation of **10** with (*R*)-phenylglycinol in the presence of triethylamine by refluxing in toluene for 36 h. led to perhydro[2,1-*b*][1,3]oxazole **11** as an 80:20 mixture of

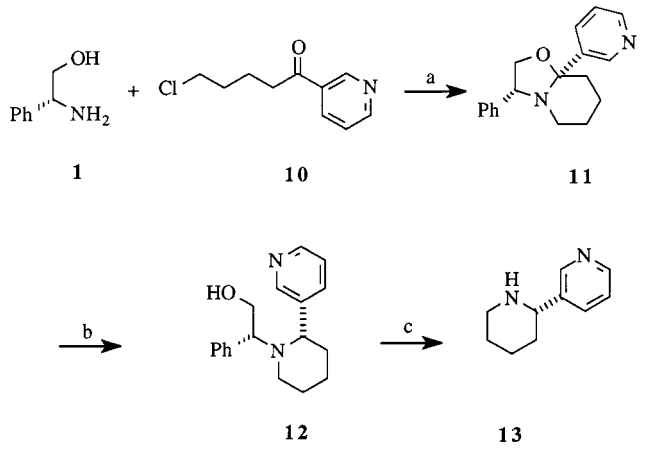
Table 1. Synthesis of chiral bicyclic oxazolidines **3a−i**, reductive ring opening to **4a−i** and their transformation into enantiopure pyrrolidines **5a−f** or piperidines **5g−i**

Starting		Oxazolidines			Amino alcohols			Pyrrolidine or Piperidine	
Entry	Compounds	Yield (%)[a]		*de*[b]	Yield (%)[a]		*de*[b]	Yield (%)[a]	
1	**2a**	**3a**	92	84	**4a**	67	84	**5a**	80
2	**2b**	**3b**	72	88	**4b**	84	90	**5b**	87
3	**2c**	**3c**	89	87	**4c**	77	88	**5c**	86
4	**2d**	**3d**	60	88	**4d**	80	88	**5d**	80
5	**2e**	**3e**	84	88	**4e**	89	90	**5e**	91
6	**2f**	**3f**	60	87	**4f**	78	86	**5f**	84
7	**2g**	**3g**	81	60	**4g**	90	62	**5g**	68
8	**2h**	**3h**	83	92	**4h**	89	91	**5h**	75
9	**2i**	**3i**	82	92	**4i**	85	92	**5i**	73

[a] Yields refer to compounds obtained in each transformation after isolation and purification. − [b] Determined by integration in ^1H NMR spectra of the reaction mixtures.



Scheme 3. (a) Et_3N, $CHCl_3$; (b) $LiAlH_4$, Et_2O, 0 °C; (c) H_2, Pd(C) 10%, EtOH, HCl 2 M



Scheme 4. (a) Et_3N, Toluene; (b) $LiAlH_4$, Et_2O, 0 °C; (c) Swern Ox., DNP

diastereomers at C-8a in 66% yield. The major *cis* stereoisomer was obtained by recrystallization of the mixture in pentane.

Reductive ring opening of **11** with lithium aluminium hydride in THF at 0 °C yielded the enantiopure phenylglycinol derivative **12** in 62% yield with total retention of configuration. Attempts to remove the benzyl moiety by hydrogenolysis with palladium on carbon were not synthetically efficient because a complex mixture of overreduction products were formed. Therefore, debenzylation was carried out in a two-step sequence[31] by Swern oxidation of **12** to the corresponding α-aminoaldehyde followed by treatment with 2,4-dinitrophenylhydrazine. After purification by flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, 180:15:1) enantiopure (−)-anabasine **13**[32] was obtained in 40% yield.

In summary, a simple method has been designed for the preparation of chiral, nonracemic 2-substituted pyrrolidines and piperidines in high enantiomeric purity and moderate to good chemical yields from γ- or δ-chloroketones.

Experimental Section

General: Optical rotations were measured on a digital polarimeter in a 1-dm cell and concentrations are given in g/100 mL. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, in $CDCl_3$ as solvent; chemical shifts are given in ppm relative to TMS as internal standard. − Only the most significant IR signals are given. − Mass Spectra were measured by chemical ionization (CI). Chromatographic separations were performed by flash chromatography using Merck silica gel (240−400 mesh), and TLC analysis was done on Merck 0.25 mm silica gel plates (60F − 254). Melting points were determined in open capillary tubes and are uncorrected.

All the reactions were carried out in oven-dried glassware under an argon atmosphere. Solvents were distilled prior to use: toluene and THF from benzophenone ketyl, $CHCl_3$ from CaH_2, and methanol from magnesium turnings.

General Procedure for the Synthesis of Bicyclic Oxazolidine 3a−g: A mixture of the corresponding ketone **2a−g** (10.0 mmol), phenylglycinol (1.50 g, 11.0 mmol), and triethylamine (10.0 mmol), in 1 mL of chloroform, was stirred until the reaction was finished (24−96 h). The reaction mixture was diluted by addition of Et_2O (50 mL), the solids were separated by filtration and the filtrate was concentrated in vacuo to give a residue which was purified by flash chromatography or by distillation under reduced pressure. Compounds **3a−g** were obtained as an inseparable mixture of epimers at the angular carbon (see Table 1). The spectroscopic data are given for the major diastereoisomer.

(3*R*,7a*S*)-7a-Methyl-3-phenylperhydropyrrolo[2,1-*b*][1,3]oxazole (3a): Colorless liquid, b.p. 152−154 °C/0.9 Torr, yield 92%, R_f = 0.7 (hexane/EtOAc, 1:1, v/v), $[\alpha]_D^{23}$ = −94.6 (*c* = 2.7, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 1.7−2.1 (m, 4 H, 6-H and 7-H), 2.73−2.8 (m, 1 H, 5-H), 3.03−3.11 (m, 1 H, 5-H′), 3.71 (t, *J* = 8.8 Hz, 1 H, 2-H), 3.96 (dd, *J* = 8.8 and 6.9 Hz, 1 H, 3-H), 4.27 (dd, *J* = 8.6 and 6.8 Hz, 1 H, 2-H′), 7.20−7.40 (m, 5 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 24.8 (C-6), 26.3 (CH_3), 38.9 (C-7), 55.9 (C-5), 71.2 (C-3), 72.5 (C-2), 105.5 (C-7a), 126.8 (2C), 127.1, 128.3 (2C), 141.8. − CI-MS: *m*/*z* (%) = 204 (100) [M^+ + 1], 188 (4), 137 (3), 122 (3).

(3*R*,7a*S*)-7a-Ethyl-3-phenylperhydropyrrolo[2,1-*b*][1,3]oxazole (3b): Colorless liquid, b.p. 107−109 °C/1.5 Torr, yield 72%, R_f = 0.63 (hexane/EtOAc, 5:1, v/v), $[\alpha]_D^{23}$ = −96.3 (*c* = 1.2, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 0.99 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.56−2.0 (m, 6 H), 2.74−2.82 (m, 1 H, 5-H), 2.95−3.03 (m, 1 H, 5-H′), 3.62 (t, *J* = 8.9 Hz, 1 H, 2-H), 3.98 (dd, *J* = 9.3 and 7.0 Hz, 1 H, 3-H), 4.25 (dd, *J* = 8.6 and 6.0 Hz, 1 H, 2-H′), 7.19−7.41 (m, 5 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 9.2 (CH_3), 24.3 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 55.7 (C-5), 71.0 (C-3), 72.5 (C-2), 108.2 (C-7a), 126.8 (2C), 127.0, 128.3 (2C), 142.0. − CI-MS: *m*/*z* (%) = 218 (100) [M^+ + 1], 206 (15), 188 (11), 140 (5), 121 (5), 105 (3).

(3*R*,7a*S*)-3-Phenyl-7a-propylperhydropyrrolo[2,1-*b*][1,3]oxazole (3c): Colorless liquid, yield 89%, R_f = 0.6 (hexane/EtOAc, 1:1, v/v), $[\alpha]_D^{23}$ = −84.1 (*c* = 1.4, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 0.95 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.4−2.0 (m, 8 H), 2.74−2.81 (m, 1 H, 5-H), 2.94−3.02 (m, 1 H, 5-H′), 3.63 (dd, *J* = 9.2 and 8.6 Hz, 1 H, 2-H), 3.98 (dd, *J* = 9.2 and 7.0 Hz, 1 H, 3-H), 4.25 (dd, *J* = 8.6

and 7.0 Hz, 1 H, 2-H′), 7.03−7.68 (m, 5 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 14.6 (CH_3), 18.2 (CH_2), 24.2 (CH_2), 36.5 (CH_2), 41.5 (CH_2), 55.5 (C-5), 70.9 (C-3), 72.4 (C-2), 107.8 (C-7a), 126.9 (2C), 127.1, 128.3 (2C), 141.9. − CI-MS: *m*/*z* (%) = 232 (100) [M^+ + 1], 216 (3), 202 (2), 188 (55), 140 (5), 154 (10).

(3*R*,7a*R*)-7a-Isopropyl-3-phenylperhydropyrrolo[2,1-*b*][1,3]oxazole (3d): Colorless liquid, yield 60%, b.p. 141−143 °C/1.5 Torr, R_f = 0.66 (hexane/EtOAc, 5:1, v/v), $[\alpha]_D^{23}$ = −103.9 (*c* = 2.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.98 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.04 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.61−2.04 (m, 5 H), 2.76−2.94 (m, 2 H, 5-H), 3.58 (dd, 1 H, *J* = 9.4 and 8.5 Hz, 2-H), 4.01 (dd, *J* = 9.4 and 7.1 Hz, 1 H, 3-H), 4.23 (dd, 1 H, *J* = 8.5 and 7.1 Hz, 2-H′), 7.00−7.67 (m, 5 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 17.6 (CH_3), 18.0 (CH_3), 23.9 (CH_2), 31.7 (CH_2), 34.7 (CH), 55.8 (C-5), 71.0 (C-3), 72.3 (C-2), 111.0 (C-7a), 126.9, 127.1 (2C), 128.3 (2C), 142.2. − CI-MS: *m*/*z* (%) = 232 (100) [M^+ + 1], 188 (24).

(3*R*,7a*S*)-7a-Butyl-3-phenylperhydropyrrolo[2,1-*b*][1,3]oxazole (3e): Colorless liquid, yield 84%, b.p. 105−110 °C/0.6 Torr, R_f = 0.63 (hexane/EtOAc, 5:1, v/v), $[\alpha]_D^{23}$ = −84.4 (*c* = 2.1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.3−2.0 (m, 10 H), 2.74−2.82 (m, 1 H, 5-H), 2.93−3.03 (m, 1 H, 5-H′), 3.64 (dd, *J* = 9.1 and 8.6 Hz, 1 H, 2-H), 3.97 (dd, *J* = 9.2 and 7.0 Hz, 1 H, 3-H), 4.25 (dd, *J* = 8.6 and 7.0 Hz, 1 H, 2-H′), 7.21−7.42 (m, 5 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 23.1 (CH_2), 24.2 (CH_2), 27.1 (CH_2), 36.4 (CH_2), 38.8 (CH_2), 55.5 (C-5), 70.9 (C-3), 72.3 (C-2), 107.9 (C-7a), 126.8 (2C), 127.0, 128.3 (2C), 141.8. − CI-MS: *m*/*z* (%) = 246 (100) [M^+ + 1], 244 (65), 188 (93).

(3*R*,7a*R*)-3-Phenyl-7a-(phenylethyl)perhydropyrrolo[2,1-*b*][1,3]-oxazole (3f): Colorless solid, yield 60%, m.p. 62−65 °C (from pentane), R_f = 0.64 (hexane/EtOAc, 3:1, v/v). − $[\alpha]_D^{23}$ = −58.2 (*c* = 2.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.67−2.19 (m, 6 H), 2.76−2.85 (m, 3 H), 2.99−3.08 (m, 1 H, 5-H), 3.67 (t, *J* = 9.2 Hz, 1 H, 2-H), 4.02 (dd, *J* = 9.2 and 7.0 Hz, 1 H, 3-H), 4.3 (dd, 1 H, *J* = 8.6 and 7.0 Hz, 1 H, 2-H), 7.19−7.40 (m, 10 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 24.3 (CH_2), 31.4 (CH_2), 36.6 (CH_2), 40.9 (CH_2), 55.5 (C-5), 70.9 (C-3), 72.5 (C-2), 107.5 (C-7a) 125.6 (2C), 126.8 (2C), 127.1 (2C), 128.2 (2C),128.3 (2C), 141.6, 142.5. − CI-MS: *m*/*z* (%) = 294 (100) [M^+ + 1], 188 (15).

(3*R*,7a*S*)-7a-(2,5-Dioxalylpropyl)-3-phenylperhydropyrrolo[2,1-*b*]-[1,3]oxazole (7): Colorless liquid, yield 66%, R_f = 0.37 (hexane/EtOAc, 1:1, v/v). − $[\alpha]_D^{23}$ = −61.4 (*c* = 2.2, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.52−2.13 (m, 10 H), 2.74−2.81 (m, 1 H, 5-H), 2.93−3.03 (m, 1 H, 5-H′), 3.63 (t, *J* = 8.9 Hz, 1 H, 2-H), 3.79−4.01 (m, 5 H), 4.25 (dd, *J* = 7.0 and 8.6 Hz, 1 H, 2-H′), 4.87 (t, *J* = 4.6 Hz, 1 H), 7.21−7.42 (m, 5 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 19.5 (CH_2), 24.2 (CH_2), 34.1 (CH_2), 36.4 (CH_2), 38.9 (CH_2), 55.5 (C-5), 64.8 (CH_2), 70.9 (C-3), 72.4 (C-2), 104.5 (C-7a), 107.7 (CH), 126.8 (2C), 127.1, 128.3 (2C), 141.8. − CI-MS: *m*/*z* (%) = 304 (100) [M^+ + 1], 188 (9).

Synthesis of Bicyclic Oxazolidines 3g−i: A solution of ketone **2g−i** (11.1 mmol), (*R*)-phenylglycinol (1.68 g, 12.3 mmol) and triethylamine (1.67 mL, 12.0 mmol) in toluene (5 mL) was refluxed overnight. The solution was cooled to room temp. and the solids were separated by filtration. The solvent was removed under vacuum and the residue was purified by distillation, or by flash chromatography (silica gel, EtOAc/hexane, 1:20, v/v).

(3*R*,8a*S*)-8a-Methyl-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole (3g): Colorless oil, yield 81%, b.p. 175 °C/2 Torr, R_f = 0.19 (CH_2Cl_2). − $[\alpha]_D^{23}$ = −153.5 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.13−1.2 (m, 1 H), 1.48 (s, 3 H), 1.4−1.8 (m, 5 H), 2.76−2.9 (m, 2 H, 5-H), 3.68 (dd, *J* = 7.8 and 7.6 Hz, 1 H, 2-H), 4.21 (t, *J* = 7.5 Hz, 1 H, 2-H′), 4.36 (t, *J* = 7.8 Hz, 1 H, 3-H), 7.23−7.41 (m, 5 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 18.7 (CH_2), 22.6 (CH_2), 24.1 (CH_3), 31.4 (CH_2), 43.2 (C-5), 62.5 (C-3), 72.1 (C-2), 93.5 (C-8a), 127.5, 127.7 (2C), 128.4 (2C), 140.6. − CI-MS: *m*/*z* (%) = 218 (100) [M^+ + 1], 216 (40), 202 (31).

(3*R*,8a*S*)-8a-Ethyl-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole (3h): Colorless oil, b.p 175 °C/2 Torr, yield 83%, R_f = 0.42 (CH_2Cl_2). − $[\alpha]_D^{23}$ = −102.5 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ($CHCl_3$): δ = 1.0 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.11−1.16 (m, 1 H), 1.38−1.77 (m, 6 H), 1.91−2.03 (m, 1 H), 2.67−2.8 (m, 2 H, 5-H), 3.61 (dd, *J* = 7.5 and 8.5 Hz, 1 H, 2-H), 4.2 (t, *J* = 7.3 Hz, 1 H, 2-H′), 4.4 (dd, *J* = 7.4 and 8.5 Hz, 1 H, 3-H), 7.23−7.42 (m, 5 H, Ar H).− ^{13}C NMR ($CDCl_3$): δ = 7.4 (CH_3), 18.7 (CH_2), 22.6 (CH_2), 27.8 (CH_2), 30.9 (CH_2), 42.6 (CH_2, C-5), 62.3 (C-3), 73.1 (C-2), 94.8 (C-8a), 127.6, 127.8 (2C), 128.4 (2C), 140.6. − CI-MS: *m*/*z* (%) = 232 (100) [M^+ + 1], 202 (73).

(3*R*,8a*S*)-3-Phenyl-8a-propylperhydropyrido[2,1-*b*][1,3]oxazole (3i): Colorless oil, yield 81%, R_f = 0.6 (CH_2Cl_2). − $[\alpha]_D^{23}$ = −124.7 °C (*c* = 1.1, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.11 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.13−1.27 (m, 1 H), 1.56−1.99 (m, 8 H), 2.0−2.07 (m, 1 H), 2.85−2.9 (m, 2 H), 3.73 (dd, *J* = 7.5 and 8.5 Hz, 1 H, 2-H), 4.32 (t, *J* = 7.3 Hz, 1 H, 2-H′), 4.51 (dd, *J* = 7.4 and 8.4 Hz, 1 H, 3-H), 7.53−7.35 (m, 5 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 14.6 (CH_3), 16.4 (CH_2), 18.7 (CH_2), 22.6 (CH_2), 31.1 (CH_2), 37.6 (CH_2), 42.6 (C-5), 62.2 (C-3), 73.0 (C-2), 94.8 (C-8a), 127.6, 127.8 (2C), 128.4 (2C), 140.6. − CI-MS: *m*/*z* (%) = 246 (100) [M^+ + 1], 230 (7), 202 (57).

(3*R*,8a*R*)-3-Phenyl-8a-(3′-pyridyl)-perhydropyrido[2,1-*b*][1,3]-oxazole (11): A mixture of ketone **10** (2.24 g, 11.3 mmol), (*R*)-phenylglycinol (1.87 g, 13.6 mmol) and Et_3N (2.78 mL, 20.0 mmol) in toluene (25 mL) was refluxed for 36 h. The solution was filtered and the solvent was removed under vacuum yielding **11** as a mixture of diastereomers (66%). The major product was purified by recrystallization (40%). Orange solid, m.p. 103−105 °C, R_f = 0.35 (hexane/EtOAc, 1:1, v/v). − $[\alpha]_D^{23}$ = −53.6 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 1.28−1.35 (m, 2 H), 1.72−1.83 (m, 2 H), 2.0−2.1 (m, 1 H), 2.22−2.28 (m, 1 H), 2.76−2.9 (m, 2 H), 3.6 (dd, *J* = 8.1 and 8.9 Hz, 1 H, 2-H), 4.25 (t, *J* = 7.5 Hz, 1 H, 2-H′), 4.44 (dd, *J* = 7.2 and 8.9 Hz, 1 H, 3-H), 7.26 −7.38 (m, 4 H), 7.43−7.46 (m, 2 H), 8.04−8.08 (m, 1 H, Ar H), 8.57 (dd, *J* = 1.6 and 4.8 Hz, 1 H, Ar H), 9.03 (1 H, d, *J* = 1.6 Hz, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 19.0 (CH_2), 19.7 (CH_2), 30.7 (CH_2), 43.7 (CH_2), 64.6 (C-3), 72.0 (C-2), 94.3 (C-8a), 123.0, 127.6 (2C), 127.7, 128.5 (2C), 134.8, 138.7, 139.6, 149.0, 149.1. − CI-MS: *m*/*z* (%) = 281 (100) [M^+ + 1], 202 (30).

Reductive Ring Opening of 3a−f and 7 With Lithium Triethylborohydride: To a solution of the corresponding oxazolidine (1.0 mmol) in anhydrous THF (10 mL) cooled to 0 °C, was added 1 M solution of Super-Hydride® (1.5 mL) in the same solvent, and the mixture was stirred overnight at this temperature. The reaction was quenched by addition of water (1 mL), and the solvent was eliminated under vacuum. The residue was diluted with Et_2O (10 mL) and 2 N solution of HCl (5 mL), the aqueous layer was decanted and then it was brought to pH = 10 by addition of a concentrated solution of KOH. The resulting aqueous phase was extracted with dichloromethane (3 × 20 mL), and the organic layer was separated and dried over anhydrous $MgSO_4$. After filtration, the solvent was eliminated under vacuum, and the residue was purified by flash chromatography to give **4a−i** in enantiopure form.

(2*R*)-2-[(2′*R*)-2′-Methyl-*N*-pyrrolidinyl]-2-phenyl-1-ethanol (4a): Colorless oil, yield 67%, R_f = 0.4 (hexane/EtOAc, 1:1, v/v). −

$[\alpha]_D^{23} = -93.25$ (c = 2.5, $CHCl_3$). − IR (film) $\tilde{\nu}$ = 3400, 1585, 1350 cm^{-1}. − ^1H NMR: δ = 1.19 (d, J = 6.1 Hz, 3 H), 1.24−1.83 (m, 4 H), 2.16 (q, J = 8.6 Hz, 1 H), 2.54−2.65 (m, 1 H), 2.86−2.92 (m, 1 H), 3.64 (dd, J = 4.3 and 9.2 Hz, 1 H), 3.95 (dd, J = 9.3 and 10.4 Hz, 1 H), 4.02 (dd, J = 4.2 and 10.5 Hz, 1 H), 7.12−7.37 (m, 5 H). − ^{13}C NMR: δ = 19.2 (CH_3), 21.5 (CH_2), 32.0 (CH_2), 45.1 (CH_2N), 54.2 (CHN), 60.8 (CH_2O), 61.8 (PhCHN), 127.7, 128.0 (2C), 129.2 (2C), 135.0 − CI-MS: m/z (%) = 206 (100) [M^+ + 1], 188 (20), 174 (28), 128 (5).

(2*R*)-2-[(2′*R*)-2′-Ethyl-*N*-pyrrolidinyl]-2-phenyl-1-ethanol (4b): Colorless oil, yield 84%, R_f = 0.38 (hexane/EtOAc, 1:1, v/v). − $[\alpha]_D^{23}$ = −92.5 (c = 1.2, $CHCl_3$). −IR (film): $\tilde{\nu}$ = 3380, 1440, 1390, 1340 cm^{-1}. − ^1H NMR($CDCl_3$): δ = 0.93 (t, J = 7.4 Hz, 3 H), 1.29−1.94 (m, 6 H), 2.21 (q, J = 8.7 Hz, 1 H), 2.47−2.58 (m, 1 H), 2.91−3.01 (m,1 H), 3.63 (dd, J = 4.5 and 9.5 Hz, 1 H), 3.96 (t, J = 10 Hz, 1 H), 4.04 (dd, J = 4.5 and 10.7 Hz, 1 H), 7.14−7.61 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 10.2 (CH_3), 21.9 (CH_2), 26.1 (CH_2), 29 (CH_2), 45.8 (CH_2N), 60.6 (CHN), 61.3 (CH_2O), 62.6 (PhCHN), 127.8, 128.1 (2C), 129.3 (2C), 135.1. − CI-MS: m/z (%) = 220 (100) [M^+ + 1], 202 (17), 188 (16).

(2*R*)-2-Phenyl-2-[(2′*R*)-2′-propyl-*N*-pyrrolidinyl]-1-ethanol (4c): Colorless oil, yield 77%, R_f = 0.31 (hexane/EtOAc, 1:1, v/v). − $[\alpha]_D^{23}$ = −131.8 (c = 1.1, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3420, 1350 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.97 (t, J = 7.1 Hz, 3 H), 1.25−1.83 (m, 8 H), 2.11−2.2 (m, 1 H), 2.51−2.6 (m, 1 H), 2.85−2.91 (m,1 H), 3.63 (dd, J = 4.7 and 9.Hz, 1 H), 3.96 (t, J = 10.2 Hz, 1 H), 4.05 (dd, J = 4.7 and 10.7 Hz, 1 H), 7.13−7.17 (m,2 H), 7.26−7.37 (m, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 14.5 (CH_3), 19.3 (CH_2), 22.0 (CH_2), 29.6 (CH_2), 36.3 (CH_2), 45.2 (CH_2N), 58.6 (CHN), 60.8 (CH_2O), 61.9 (PhCHN), 127.6 (2C), 128.0, 129.2 (2C), 135.1. − CI-MS: m/z (%) = 234 (100) [M^+ + 1], 216 (21), 202 (28).

(2*R*)-2-[(2′*S*)-2′-Isoproyl-*N*-pyrrolidinyl]-2-phenyl-1-ethanol (4d): Colorless oil, yield 80%, R_f = 0.37 (hexane/EtOAc, 3:1, v/v). − $[\alpha]_D^{23}$ = −77.8 (c = 2.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3440, 1345 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.90 (d, J = 3.8 Hz, 3 H), 0.91 (d, J = 4.0 Hz, 3 H), 1.34−1.60 (m, 4 H), 2.04−2.26 (m, 2 H), 2.56−2.62 (m, 1 H), 2.90−2.95 (m, 1 H), 3.58−3.68 (m, 1 H), 3.96−4.05 (m, 2 H), 7.13−7.38 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 14.9 (CH_3), 20.3 (CH_3), 22.7 (CH_2), 23.6 (CH_2), 27.8 (CH), 45.5 (CH_2N), 61.1 (CH_2O), 62.1 (CHN), 63.3 (CHN), 127.7 (2C), 128.1, 129.4 (2C), 135.0. − CI-MS: m/z (%) = 234 (100) [M^+ + 1], 216 (9), 202 (28).

(2*R*)-2-[(2′*R*)-2′-Butyl-*N*-pyrrolidinyl]-2-phenyl-1-ethanol (4e): Colorless oil, yield 89%, R_f = 0.26 (EtOAc). − $[\alpha]_D^{23}$ = −119.5 (c = 2.4, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3420, 1655, 1490 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.94 (t, J = 7.0 Hz, 3 H), 1.23−1.86 (m, 10 H), 2.15 (q, J = 8.7 Hz, 1 H), 2.51−2.57 (m, 1 H), 2.86−2.92 (m,1 H), 3.63 (dd, J = 4.7 and 9.7 Hz, 1 H), 3.96 (t, J = 10.2 Hz, 1 H), 4.06 (dd, J = 4.7 and 10.8 Hz, 1 H), 7.13−7.16 (m,2 H), 7.27−7.38 (m, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 14.1 (CH_3), 22 (CH_2), 23 (CH_2), 28.3 (CH_2), 29.7 (CH_2), 33.7 (CH_2), 45.3 (CH_2N), 59 (CH), 60.8 (CH_2O), 62 (CH), 127.7, 128.0 (2C), 129.2 (2C), 135.1. − CI-MS: m/z (%) = 248 (100) [M^+ + 1], 246 (64), 230 (71), 216 (73).

(2*R*)-2-Phenyl-2-[(2′*R*)-2′-phenylethyl-*N*-pyrrolidinyl]-1-ethanol (4f): Colorless oil, yield 78%, R_f = 0.33 (EtOAc). − $[\alpha]_D^{23}$ = −178.5 (c = 2.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3180, 1600, 1580 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.52−1.83 (m, 4 H), 2.09 −2.19 (m, 2 H), 2.49−2.59 (m, 3 H), 2.73−2.82 (m, 1 H), 2.87−2.92 (m,1 H), 3.56−3.66 (m, 1 H), 3.91−4.0 (m, 2 H), 6.90−7.0 (m,2 H), 7.22−7.34 (m, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 22.2 (CH_2), 29.7 (CH_2), 32.5 (CH_2), 36.0 (CH_2), 45.4 (CH_2N), 57.9 (CHN), 61 (CH_2O), 62.2 (CHN), 125.8, 127.6, 128.0 (2C), 128.4 (3C), 128.5 (2C), 129.3, 134.9, 142.2. − CI-MS: m/z (%) = 296 (100) [M^+ + 1], 278 (14), 230 (71).

(2*R*)-2-[(2′*R*)-2′-(2,5-Dioxalylpropyl)-*N*-pyrrolidinyl]-2-phenyl-1-ethanol (8): Colorless oil, yield 60%, R_f = 0.25 (EtOAc/MeOH, 20:1, v/v). − $[\alpha]_D^{23}$ = −120.1 (c = 1.5, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3150 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.24−1.91 (m, 10 H), 2.17 (q, J = 8.0 Hz, 1 H), 2.53−2.62 (m, 1 H), 2.86−2.92 (m,1 H), 3.63 (dd, J = 4.6 and 9.5 Hz, 1 H), 3.81−4.8 (m, 6 H), 4.88 (t, J = 4.7 Hz, 1 H), 7.14−7.17 (m,2 H), 7.27−7.37 (m, 3 H). − ^{13}C NMR ($CDCl_3$): δ = 20.5 (CH_2), 21.9 (CH_2), 29.6 (CH_2), 34.0 (CH_2), 45.3 (CH_2N), 58.7 (CHN), 60.9 (CH_2O), 62.0 (CHN), 64.7 (CH_2O), 104.4 (CHO_2), 127.6, 128.0 (2C), 129.2 (2C), 135.1. − CI-MS: m/z (%) = 306 (100) [M^+ + 1], 304 (12), 274 (39), 190 (12).

Synthesis of Compounds 4g−i: A solution of **3g−i** (0.2 g, 0.92 mmol) in anhydrous ether (4 mL) was added dropwise to a suspension of $LiAlH_4$ (35.0 mg, 0.92 mmol) in Et_2O (4 mL) at 0 °C. The mixture was stirred for 12 h at that temperature and then quenched by addition of 15% NaOH aqueous solution. The mixture was filtered off, and the solids were washed with Et_2O. The solvent was eliminated under vacuum, and the residue was redissolved in CH_2Cl_2 (5 mL) and treated with Ac_2O (0.15 mL, 1.52 mmol) and DMAP (28.0 mg, 0.23 mmol). The solution was stirred for 1.5 h and quenched with water (5 mL). After separation, the organic layer was washed with a saturated $NaHCO_3$ solution (2 × 5 mL) and brine (5 mL), and then dried over anhydrous $MgSO_4$. The solvent was distilled and the residue was purified by flash chromatography.

(2*R*)-2-[(2′*R*)-2′-Methyl-*N*-piperidinyl]-2-phenyl-1-ethyl Acetate (4g): Colorless oil, yield 90%, R_f = 0.26 (EtOAc/hexane, 1:8, v/v). − $[\alpha]_D^{23}$ = −67.4 (c = 1.7, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1735 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.1−1.18 (m, 1 H), 1.17 (d, J = 6.2 Hz, 3 H), 1.25−1.58 (m, 5 H), 1.92−1.97 (m, 1 H), 1.97 (s, 3 H), 2.33−2.37 (m, 1 H), 2.77−2.8 (m, 1 H), 4.26−4.37 (m, 2 H), 4.53 (dd, J = 6.4 and 10.3 Hz, 1 H), 7.2−7.32 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 18.7 (CH_3), 20.9 (CH_3), 23.4 (CH_2), 26.4 (CH_2), 35.2 (CH_2), 46.6 (CH_2N), 52.7 (CHN), 60.3 (CHN), 64.8 (CH_2N), 127.2, 127.9 (2C), 128.6 (2C), 136.7, 170.9 (CO). − CI-MS: m/z (%) = 262 (2) [M^+ + 1], 248 (5), 220 (100).

(2*R*)-2-[(2′*R*)-2′-Ethyl-*N*-piperidinyl]-2-phenyl-1-ethyl Acetate (4h): Colorless oil, yield 89%, R_f = 0.47 (EtOAc/hexane, 1:8, v/v). − $[\alpha]_D^{23}$ = −65.2 (c = 2.3, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1730 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.86 (t, J = 7.4 Hz, 3 H), 1.14−1.19 (m,1 H), 1.34−1.77 (m, 7 H), 1.98 (s, 3 H), 1.98−2.03 (m, 1 H), 2.25−2.3 (m, 1 H), 2.76−2.81 (m, 1 H), 4.24−4.35 (m, 2 H), 4.54 (dd, J = 6.1 Hz, 1 H), 7.21−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 9.2 (CH_3), 20.9 (CH_3), 22.8 (CH_2), 25.8 (CH_2), 29.5 (CH_2), 46.2 (CH_2N), 57.4 (CH), 60.1 (CH), 65.1 (CH_2O), 127.1, 127.9 (2C), 128.6 (2C), 137.4, 170.8 (CO). − CI-MS: m/z (%) = 276 (5) [M^+ + 1], 234 (100).

(2*R*)-2-Phenyl-2-[(2′*R*)-2′-propyl-*N*-piperidinyl]-1-ethyl Acetate (4i): Colorless oil, yield 85%, R_f = 0.54 (EtOAc/hexane, 1:5, v/v). − $[\alpha]_D^{23}$ = −44.2 (c = 2.4, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1730 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.9 (t, J = 7.3 Hz, t), 1.12−1.63 (m, 10 H), 1.97 (s, 3 H), 2.04−2.11 (m, 1 H), 2.31−2.41 (m, 1 H), 2.71−2.79 (m, 1 H), 4.21−4.34 (m, 2 H), 4.5 (dd, J = 6.5 and 10.8 Hz, 1 H), 7.23−7.35 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 14.6 (CH_3), 18.4 (CH_2), 20.9 (CH_3, CH_3CO), 22.4 (CH_2), 25.6 (CH_2), 29.8 (CH_2), 32.0 (CH_2), 45.9 (CH_2N), 56.1 (CH), 60.6 (CH), 65.4 (CH_2O), 127.1, 127.9 (2C), 128.6 (2C), 137.9, 170.8 (CO). − CI-MS: m/z (%) = 289 (1) [M^+ + 1], 276 (11), 248 (100).

(2*R*)-2-Phenyl-2-[(2′*R*)-2′-(3′′-pyridyl)-1-piperidinyl]-1-ethanol (12): A solution of **11** (0.2 g, 0.92 mmol) in anhydrous ether (15 mL) was added dropwise to a suspension of $LiAlH_4$ (52.0 mg, 1.38 mmol) in ether (10 mL) at 0 °C, and the suspension was stirred for 12 h at this temperature. After work up, the solvent was removed under vacuum. The compound was purified by flash chromatography (silica gel, EtOAc). Colorless oil, yield 62%, R_f = 0.39 (EtOAc). − $[\alpha]_D^{23}$ = −123.1 (*c* = 1.3, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3420, 1590 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.17−1.28 (m, 2 H), 1.51−1.74 (m, 5 H), 1.91−2.0 (m, 1 H), 3.12−3.16 (m, 1 H), 3.32 (dd, *J* = 2.6 and 11.0 Hz, 1 H), 3.42 (dd, *J* = 5.4 and 10.5 Hz, 1 H), 3.87 (dd, *J* = 5.4 and 11.0 Hz, 1 H), 4.05 (t, *J* = 11.0 Hz, 1 H), 6.97−7.0 (m, 1 H, Ar H), 7.29−7.39 (m, 4 H, Ar H), 7.78−7.82 (m, 1 H, Ar H), 8.55−8.6 (m, 2 H, Ar H). − ^{13}C NMR ($CDCl_3$): δ = 24.6 (CH_2), 26.1 (CH_2), 37.8 (CH_2), 45.6 (CH_2), 59.5 (CH_2O), 62.4 (CH), 62.6 (CH), 124.1, 127.9, 128.0 (2C), 129.2 (2C), 133.9, 135.3, 139.6, 148.7, 149.6. − CI-MS: *m*/*z* (%) = 283 (100) [M^+ + 1], 265 (17), 251 (17).

Hydrogenolytic Cleavage of the Chiral Appendage. Preparation of Pyrrolidines 5a−f and Piperidines 5g−i: A mixture of the corresponding amino alcohols **4a−f** or acetates **4g−i** (1.0 mmol) in EtOAc (30 mL) and 40.0 mg of 10% palladium on carbon was stirred at room temp. for 48−72 h under hydrogen at 9 atm. After the reaction was over, the catalyst was filtered and to the solution were added *i*Pr_2NEt (0.87 mL, 5.0 mmol) and TsCl (0.47 g, 2.5 mmol) and the mixture was stirred overnight. The crude reaction mixture was washed with 0.5 N solution of HCl and water, and then dried over anhydrous $MgSO_4$. The solvent was eliminated under reduced pressure and tosylates **5a−f** were purified by flash chromatography (silica gel, hexane/ethyl acetate, 20:1, v/v) and recrystallization.

Hydrochlorides **5g−i** were isolated after treatment of the solution resulting from hydrogenolysis with a saturated solution of HCl in Et_2O, elimination of the solvents and recrystallization.

(*R*)-2-Methylpyrrolidinium Tosylate (5a): White solid, yield 80%, m.p. 69−71 °C (from pentane), R_f = 0.29 (EtOAc/hexane, 1:8, v/v). − $[\alpha]_D^{23}$ = −57.3 (*c* = 1.0, $CHCl_3$). − IR (nujol) $\tilde{\nu}$ = 1590, 1160 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.31 (d, *J* = 6.4 Hz, 3 H), 1.43−1.87 (m, 4 H), 2.43 (s, 3 H), 3.1−3.18 (m,1 H), 3.40−3.47 (m, 1 H), 3.66- 3.75 (m, 1 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.72 (d, *J* = 8.1 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 21.4 (CH_3), 22.8 (CH_3), 23.8 (CH_2), 33.4 (CH_2), 49.0 (CH_2N), 56.0 (CHN), 127.4 (2C), 129.5 (2C), 134.8, 143.1. − CI-MS: *m*/*z* (%) = 240 (100) [M^+ + 1], 224 (42). − $C_{12}H_{17}NO_2S$ (239.09): calcd. C 60.22, H 7.17, N 5.85; found C 60.45, H 6.99, N 5.81.

(*R*)-2-Ethylpyrrolidinium Tosylate (5b): White solid, yield 87%, m.p. 59−61 °C (from pentane), R_f = 0.29 (EtOAc/hexane, 1:8, v/v). − $[\alpha]_D^{23}$ = −81.9 (*c* = 1.1, $CHCl_3$). − IR (nujol) $\tilde{\nu}$ = 1600 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3 H), 1.51- 1.61 (m, 4 H), 1.7−1.93 (m, 2 H), 2.43 (s, 3 H), 3.15−3.23 (m, 1 H), 3.34−3.43 (m, 1 H), 3.50−3.58 (m, 1 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 7.71−7.74 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 10.3 (CH_3), 21.1 (CH_3), 24.0 (CH_2), 29.1 (CH_2), 30.1 (CH_2), 48.9 (CH_2N), 61.7 (CHN), 127.4 (2C), 129.5 (2C), 134.8, 143.1. − CI-MS: *m*/*z* (%) = 254 (100) [M^+ + 1], 224 (19), 162 (34), 105 (2). − $C_{13}H_{19}NO_2S$ (253.11): calcd. C 61.63, H 7.56, N 5.53; found C 61.75, H 7.42, N 5.59.

(*R*)-2-Propylpyrrolidine Tosylate (5c): White solid, yield 86%, m.p. 54−56 °C (from pentane), R_f = 0.32 (EtOAc/hexane, 1:8, v/v), $[\alpha]_D^{23}$ = −99.3 (*c* = 1.0, $CHCl_3$). − IR (nujol) $\tilde{\nu}$ = 1590 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.94 (t, *J* = 7.2 Hz, 3 H), 1.28−1.58 (m, 6 H), 1.72−1.87 (m, 2 H), 2.42 (s, 3 H), 3.14−3.22 (m, 1 H), 3.33−3.41 (m, 1 H), 3.56−3.64 (m, 1 H), 7.20−7.32 (m, 2 H), 7.69−7.73 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 19.3 (CH_2), 21.4 (CH_3), 24.0 (CH_2), 30.6 (CH_2), 38.6 (CH_2), 48.8 (CH_2N), 60.3 (CH), 127.4 (2C), 129.5 (2C), 134.9, 143.1. − CI-MS: *m*/*z* (%) = 268 (100) [M^+ + 1], 224 (34). − $C_{14}H_{21}NO_2S$ (267.13): calcd. C 62.89, H 7.92, N 5.24; found C 62.93, H 7.77, N 5.29.

(*S*)-2-Isopropylpyrrolidine tosylate (5d): White solid, yield 80%, m.p. 86−88 °C (from pentane), R_f = 0.36 (EtOAc/hexane, 1:8, v/v). − $[\alpha]_D^{23}$ = −91.3 (*c* = 1.0, $CHCl_3$). − IR (nujol) $\tilde{\nu}$ = 1600 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.89 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 1.30−1.69 (m, 4 H), 2.12−2.18 (m, 1 H), 2.42 (s, 3 H), 3.27−3.31 (m, 2 H), 3.47−3.53 (m, 1 H), 7.29−7.32 (m, 2 H), 7.69−7.72 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 16.3 (CH_3), 19.5 (CH_3), 21.2 (CH_3), 24.3 (CH_2), 25.9 (CH_2), 31.8 (CH), 49.2 (CH_2N), 65.3 (CHN), 127.2 (2C), 129.3 (2C), 134.8, 142.9. − CI-MS: *m*/*z* (%) = 268 (100) [M^+ + 1], 266 (12), 224 (8). − $C_{14}H_{21}NO_2S$ (267.13): calcd. C 62.89, H 7.92, N 5.24; found C 62.98, H 7.79, N 5.29.

(*R*)-2-Butylpyrrolidine Tosylate (5e): White solid, yield 91%, m.p. 66−68 °C (from pentane), R_f = 0.39 (EtOAc/hexane, 1:8, v/v). − $[\alpha]_D^{23}$ = −108.0 (*c* = 1.1, $CHCl_3$). − IR (nujol) $\tilde{\nu}$ = 1590 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.91 (t, *J* = 7.0 Hz, 3 H), 1.22−1.89 (m, 10 H), 2.43 (s, 3 H), 3.14−3.22 (m, 1 H), 3.34−3.41 (m, 1 H), 3.55-3.63 (m, 1 H), 7.30(d, *J* = 8.1 Hz, 2 H), 7.71 (d, *J* = 8.1 Hz, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 14.0 (CH_3), 21.4 (CH_3), 22.6 (CH_2), 24.0 (CH_2), 28.2 (CH_2), 30.6 (CH_2), 36.1 (CH_2), 48.8 (CH_2N), 60.5 (CHN), 127.4 (2C), 129.5 (2C), 134.8, 143.1. − CI-MS: *m*/*z* (%) = 282 (100) [M^+ + 1], 224 (94), 184 (7), 155 (13). − $C_{15}H_{23}NO_2S$ (281.14): calcd. C 64.02, H 8.24, N 4.98; found C 63.93, H 7.99, N 4.97.

(*R*)-2-Phenethylpyrrolidine Tosylate (5f): White solid, yield 84%, m.p. 83−85 °C (from pentane), R_f = 0.19 (EtOAc/hexane, 1:8, v/v). − $[\alpha]_D^{23}$ = −143.3 (*c* =1.0, $CHCl_3$). − IR (nujol) $\tilde{\nu}$ = 1590 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.40−1.84 (m, 5 H), 2.16−2.28 (m, 1 H), 2.40 (s, 3 H), 2.58−2.78 (m, 2 H), 3.15−3.24 (m, 1 H), 3.37−3.44 (m, 1 H), 3.53−3.61 (m, 1 H), 7.17−7.32 (m, 7 H), 7.59−7.60 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 21.4 (CH_3), 24 (CH_2), 30.7 (CH_2), 32.3 (CH_2), 37.6 (CH_2), 49 (CH_2N), 59.7 (CH), 125.7, 127.4 (2C), 128.3 (2C), 128.4 (2C), 129.5 (2C), 134.5, 141.5, 143.1. − CI-MS: *m*/*z* (%) = 330 (100) [M^+ + 1], 224 (10), 174 (10), 105 (2). − $C_{19}H_{23}NO_2S$ (329.14): calcd. C 69.27, H 7.04, N 4.25; found C 69.19, H 6.95, N 4.18.

(+)-Pipecoline Hydrochloride (5g): White solid, yield 76%, m.p. 194−196 °C, $[\alpha]_D^{23}$ = +3.97 (*c* = 2, EtOH), {ref.[13b] *ent* − **5g** $[\alpha]_D^{23}$ = −3.91 (*c* = 0.46, EtOH)}. − IR (nujol) $\tilde{\nu}$ = 3380, 3185, 1380 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.48−1.51 (m, 1 H), 1.5 (d, *J* = 6.4 Hz, 3 H), 1.68−1.99 (m, 5 H), 2.83−2.87 (m, 1 H), 3.11 (br. s, 1 H), 3.41−3.45 (m, 1 H), 9.18 (br. s, 1 H), 9.56 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 19.2 (CH_3), 21.7 (CH_2), 22.3 (CH_2), 30.3 (CH_2), 44.3 (CH_2N), 53 (CH).

(*R*)-2-Ethylpiperidine Hydrochloride (5h): Colorless solid, yield 70%, m.p. 210−212 °C. − $[\alpha]_D^{23}$ = −1.42 (*c* = 1.8, MeOH). − IR (nujol) $\tilde{\nu}$ = 3380, 3185, 1380 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.03 (m, 3 H), 1.6−2.1 (m, 8 H), 2.8−3.0 (m, 2 H), 3.47−3.49 (m, 1 H), 9.06 (br. s, 1 H), 9.31 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 9.8 (CH_3), 22.1 (CH_2), 22.3 (CH_2), 26.4 (CH_2), 27.6 (CH_2), 44.7 (CH_2N), 58.6 (CH).

(−)-Coniine Hydrochloride (5i): Colorless solid, yield 75%. m.p. 212−213 °C. − $[\alpha]_D^{23}$ = −7.3 (*c* = 0.33, EtOH), {ref.[29] $[\alpha]_D^{23}$ =

−7.6 (c = 1.0, EtOH)}. − IR (nujol) $\tilde{\nu}$ = 1585, 3200, 3380 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.95 (t, J = 7.2 Hz, 3 H), 1.46−2.01 (m, 10 H), 2.82−2.95 (m, 2 H), 3.44−3.48 (m, 1 H), 9.2 (br. s, 1 H), 9.47 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 13.7 (CH_3), 18.5 (CH_2), 22.1 (CH_2), 22.4 (CH_2), 28.0 (CH_2), 35.3 (CH_2), 44.7 (CH_2N), 57.1 (CH).

8-Chloro-5-oxooctanal Ethylene Acetal (6): A solution of the Grignard derivative prepared from magnesium turnings (202.0 mg, 8.3 mmol) and 2-(3-chloropropyl)-1,3-dioxolane (1.28 g, 8.5 mmol) in THF (10 mL). was cooled to −50 °C and $CuBr{\cdot}SMe_2$ (0.85 g, 4.1 mmol) was added. The mixture was stirred for 40 min and warmed to −25 °C. A solution of 4-chlorobutanoyl chloride (0.78 mL, 6.96 mmol) in THF (20 mL) was slowly added and the mixture was stirred at −25 °C for 2.5 h. The reaction was quenched with saturated NH_4Cl solution and heated to room temp. The mixture was extracted with Et_2O (3 × 50 mL), and the organic layer was dried over anhydrous $MgSO_4$. The solvents were eliminated under vacuo, and the residue was distilled to afford **6** (1.2 g, 78%) as a colorless liquid, b.p. 130−132 °C/0.8 Torr, R_f = 0.25 (ethyl acetate/hexane, 1:8, v/v). − IR (film): $\tilde{\nu}$ = 1700, 1400 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.64−1.74 (m, 4 H), 2.03 (q, J = 6.7 Hz, 2 H), 2.50 (t, J = 7.1 Hz, 2 H), 2.61 (t, J = 7.1 Hz, 2 H), 3.57 (t, J = 6.3 Hz, 2 H), 3.81−3.98 (m, 4 H), 4.84 (t, J = 4.3 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 17.9 (CH_2), 26.1 (CH_2), 32.7 (CH_2), 39 (CH_2), 42.2 (CH_2), 44.3 (CH_2Cl), 64.6 (CH_2O), 104 (CH), 209.1 (CO).

(−)-δ-Coniceine (9): To a solution of **8** (0.8 g, 2.6 mmol) in methanol (100 mL) containing 5 mL of HCl 2 M was added Pd/C (10%, 200.0 mg), and the mixture was stirred at 45 °C under 1 atm. of hydrogen for 3 days. The pressure was then increased to 10 atm. After 2 days the reaction mixture was filtered through a Celite pad, and the filtrate was concentrated. The residue was washed with Et_2O (3 × 50 mL) and neutralized with $NaHCO_3$ and KOH. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and $CHCl_3$ (2 × 50 mL), dried over $MgSO_4$ and evaporated. The residue was distilled to afford **9** (203 mg, 62%) as a colorless liquid, b.p. 50−51 °C/35 Torr. − $[\alpha]_D^{23}$ = −10.1 (c = 1.8, EtOH) {ref.[30] $[\alpha]_D^{23}$ = −10.2 (c = 1.76, EtOH)}, R_f = 0.4 (Ethyl acetate/MeOH, 1:1, v/v). − IR (film): $\tilde{\nu}$ = 2920, 1320 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.12−1.87 (m, 11 H), 1.95 (dt, J = 3.4 and 11.4 Hz, 1 H), 2.05 (q, J = 8.9 Hz, 1 H), 3.0−3.12 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 20.5 (CH_2), 24.5 (CH_2), 25.4 (CH_2), 30.4 (CH_2), 31.0 (CH_2), 53.0 (CH_2N), 54.2 (CH_2N), 64.3 (CH). − CI-MS: m/z (%) = 126 (100) [M^+ + 1], 124 (90).

(*S*)-Anabasine (13): A mixture of DMSO (1.18 mL, 16.6 mmol), oxalyl chloride (0.7 mL, 8.0 mmol) and **12** (1.8 g, 6.4 mmol) in CH_2Cl_2 (16 mL) cooled to −78 °C was stirred for 20 min and then Et_3N (2.33 mL, 16.7 mmol) was added and the reaction mixture was allowed to reach room temp. The solution was quenched with water (20 mL), decanted, and the organic layer was washed with a solution of $NaHCO_3$ and brine. The solvents were removed under vacuum and the crude aldehyde was redissolved in a 1:1 mixture of acetic acid and 2-propanol (40 mL) and DNP (3.62 g, 18.3 mmol) was added, and the solution was refluxed for 24 h. After concentration, the mixture was treated with 15% NaOH solution (150 mL) and extracted with Et_2O (5 × 50 mL). The organic layer was dried over anhydrous $MgSO_4$, the solvent was eliminated under reduced pressure and the residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_4OH, 180:15:1) to give (*S*)-anabasine (407 mg, 40%). Analysis by HPLC as *N*-4-nitrobenzoylanabasine (Chiracel OD, isopropanol/hexane, 95:5, flow rate 0.7 mL/min, UV detector) and coinjection with a racemate showed that the product was a single enantiomer. Brown oil, yield 40%, R_f = 0.42 (CH_2Cl_2/MeOH/NH_4OH, 90:10:1). − $[\alpha]_D^{23}$ = −75.5 (c = 0.1, $CHCl_3$). *N*-4-Nitrobenzoylanabasine: $[\alpha]_D^{23}$ = −133.6 (c = 0.76, MeOH) {ref.[32] $[\alpha]_D^{23}$ = −130.8 (c = 1.2, MeOH)}, − IR (film): $\tilde{\nu}$ = 3259 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.45−1.9 (m, 6 H), 2.74−2.83 (m, 1 H), 3.16−3.21 (m, 1 H), 3.60−3.64 (m, 1 H), 7.21−7.25 (m, 1 H), 7.69−7.72 (m, 1 H), 8.47 (dd, J = 1.7 and 4.8 Hz, 1 H), 8.57 (d, J = 2.0 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 25.0 (CH_2), 25.5 (CH_2), 34.7 (CH_2), 47.6 (CH_2N), 59.6 (CH), 123.4, 134.0, 140.5, 148.4, 148.5. − CI-MS: m/z (%) = 163 (100) [M^+ + 1], 161 (22).

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