Pyridine-Derived Oxazolidines as Chiral 3-Alkyl-4,5-dihydropyridinium and 3-Alkyl-3,4,5,6-tetrahydropyridinium Salt Equivalents

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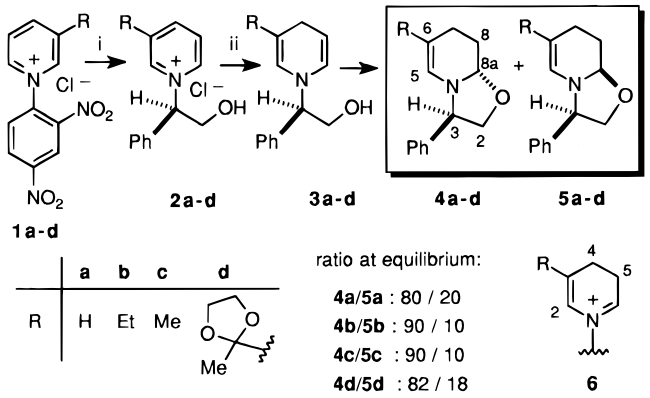
Reaction of Zincke salts **1** (Scheme 1) with (*R*)-(−)-phenylglycinol offers a practical entry to chiral 3-substituted pyridinium salts **2**.[1] Recently, we disclosed conditions[2] for the sodium dithionite reduction of these pyridinium salts to afford the corresponding 1,4-dihydropyridines **3a**−**c** in good yields. We now report details concerning the synthesis of dihydropyridines **3a**−**d** and their cyclization to give a mixture of isomeric oxazolidines **4a**−**d** and **5a**−**d**. These new chiral derivatives, which may be considered as masked 3-alkyl-4,5-dihydropyridinium salt equivalents **6**, are potentially useful intermediates for the asymmetric synthesis of polysubstituted piperidines.[3] In addition, we describe their stepwise reduction leading to an enantioselective access to 3-alkylpiperidines (Scheme 2) as illustrated by a synthesis, according to Scheme 3, of 3-(3-hydroxyphenyl)-1-*n*-propylpiperidine [(−)-PPP], a selective dopaminergic autoreceptor agonist.[4]

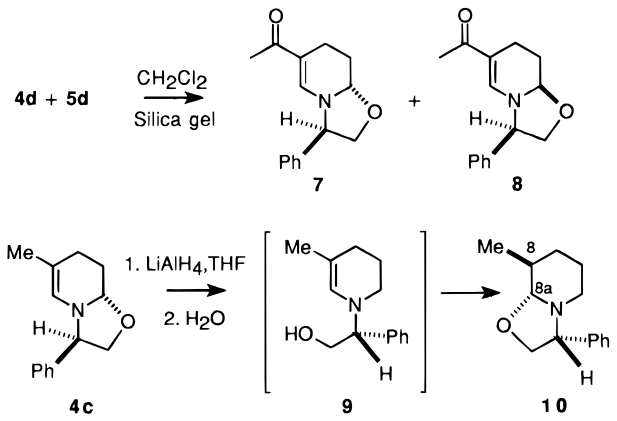
Treatment[2] under vigorous stirring of a two-phase system consisting of diethyl ether and an aqueous solution of salt **2a**, containing 2.5 M sodium dithionite and 2.5 M potassium carbonate, at reflux over 1 h gave 1,4-dihydropyridine **3a** in 73% yield. The crude dihydropyridine was sufficiently stable for characterization by spectroscopic methods but decomposed rapidly at ambient temperature, giving only polymers. Rapid bulb-to-bulb distillation of the crude dihydropyridine afforded a mixture of derivatives **4a**−**5a** in an 80:20 ratio (*vide infra* for a discussion of stereochemical assigments) and in about 50% combined yield, contaminated with polymers. Oxazolidines **4a**−**5a** were very unstable, presumably due to the presence of a reactive enamine function in their structure. 3-Substituted dihydropyridines **3b** and **3c**, which were found to be much more stable than dihydropyridine **3a**, slowly cyclized with complete regioselectivity to give inseparable mixtures of oxazolidines **4b**−**5b** and **4c**−**5c**, respectively. During the ^{1}H NMR studies in $CDCl_3$, it became apparent that the initial cyclization gave mainly derivatives **5b** or **5c** with minor **4b** or **4c** (in nearly 75:25 ratio), which, within 1 or 2 days reached an equilibrium where this ratio was inverted, giving **4b** or **4c** as the major component of the reaction mixture. This rather slow process was accompanied by significant decomposition. In practice, we found it more convenient to filter a diluted solution of the crude 1,4-dhps **3b**,**c** in pentane−dichloromethane (1:3) over alumina. Under these conditions, the equilibrated mixture of **4b**−**5b** or **4c**−**5c** (90:10 ratio in each case) was obtained directly in 60−70% yields. Surprisingly, the use of CH_2Cl_2 as eluant for filtration over alumina proved to be critical inasmuch as the use of diethyl ether or EtOAc resulted in extensive decomposition and yields less than 20%. Finally, reduction of salt **2d** gave in 90% yield dihydropyridine **3d**, which was found to be more stable than the analogs **3b**,**c**. This increased stability was very likely due to a moderate electron-withdrawing character of the dioxolane group at position 3 of the ring. Again, it was evident while recording the ^{1}H NMR spectrum in $CDCl_3$ that the cyclization occurred slowly to give mainly **5d** at first. Filtration over alumina resulted in partial hydrolysis of the dioxolane group, but filtration over Florisil with CH_2Cl_2 gave in 78% yield, as expected, an inseparable mixture of equilibrated oxazolidines **4d**−**5d** in an 82:18 ratio. The hydrolysis of the dioxolane group turned out to be very easy and was quantitatively performed by stirring a CH_2Cl_2 solution of **4d**−**5d** over silica gel. The new derivatives **7** and **8** were thus obtained in a 79:21 ratio (Scheme 2). The vinyloguous amide function exerts a strong stabilizing effect on these molecules. In particular, the isomerization of the oxazolidine ring was completely suppressed, thereby allowing chromato-

Scheme 1[a]



[a] Reagents and conditions: (i) (*R*)-(−)-phenylglycinol (1 equiv), *n*-butanol, reflux; (ii) $Na_2S_2O_4$, K_2CO_3, H_2O, refluxing Et_2O.

Scheme 2



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(1) (a) Génisson, Y.; Marazano, C.; Mehmandoust, M.; Gnecco, D.; Das, B. C. *Synlett* **1992**, 431. (b) Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052. (c) Génisson, Y.; Mehmandoust, M.; Marazano, C.; Das, B. C. *Heterocycles* **1994**, *39*, 811.

(2) Wong, Y.-S.; Marazano, C.; Gnecco, D.; Das, B. C. *Tetrahedron Lett.* **1994**, 35, 707.

(3) Gnecco, D.; Marazano C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1991**, 625.

(4) Wilkström, H.; Sanchez, D; Lindberg, P.; Hacksell, U.; Arvidsonn, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. *J. Med. Chem.* **1984**, *27*, 1030−1036.

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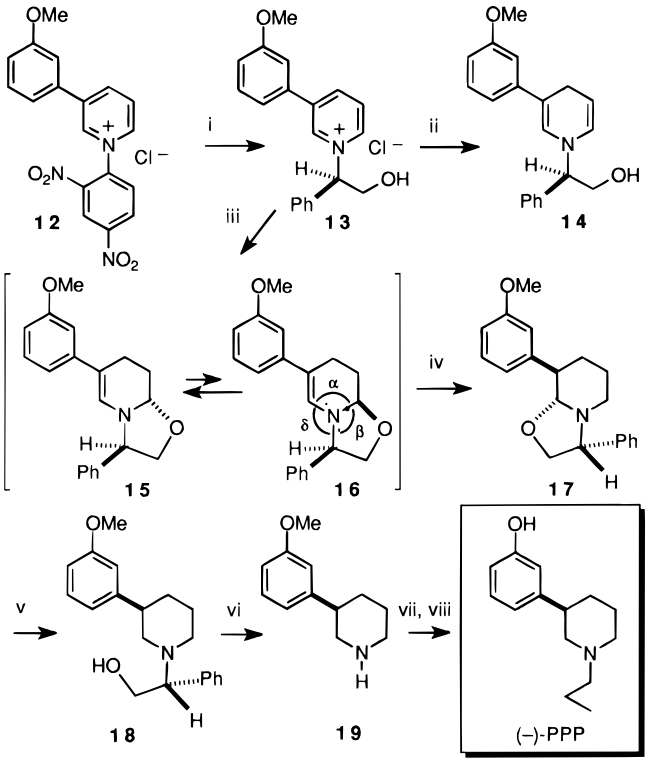
Scheme 3[a]



[a] Reagents and conditions: (i) (*R*)-(−)-phenylglycinol (1 equiv), *n*-butanol, reflux, 91%; (ii) $Na_2S_2O_4$, K_2CO_3, H_2O, refluxing ether, 85%; (iii) $Na_2S_2O_2$, K_2CO_2, H_2O, refluxing toluene, 81%; (iv) $LiAlH_4$, THF, then H_2O, 74%; (v) $LiAlH_4$, THF, 91% (86% de); (vi) H_2, Pd/C, HBF_4, 89% (44% from **12**, 86% ee): (vii) EtCOCl, then $LiAlH_4$, 80%; (viii) HBr 48%, reflux, 73% (26% from **12**, 86% ee).

graphic separation of isomers **7** and **8**, which were found to be stable at ambient temperature.

In our preliminary paper[3] we demonstrated the synthetic utility of these procedures by a short enantioselective access to indolizidine (+)-209B. This synthesis was performed by two successive Grignard alkylations of the intermediate **4c**.

The procedure employed for the reduction of these oxazolidines is also of interest. Thus, while the reduction of **4c** with $NaBH_4$ in methanol led to the fully reduced hexahydropyridines (1:1 epimeric mixture at C-3), the aprotic $LiAlH_4$ reduction in THF gave, after hydrolysis and *via* unstable intermediate **9**, the new oxazolidine intermediate **10** (8*S*, 8a*R*), accompanied by the diastereomer epimeric at C-8 (8*R*) and C-8a (8a*S*, tentative assignment) in an 85:15 ratio. As we will report separately, these readily accessible oxazolidine derivatives (as an example, **10** was obtained in three steps and a 45% overall yield from **1c**) are chiral synthetic equivalents of both 3-substituted 3,4,5,6-tetrahydropyridinium salts and 3-alkyl-1,4,5,6-tetrahydropyridines (**9**), which are of current interest in alkaloid synthesis.[5]

The enantioselective synthesis of (−)-PPP according to Scheme 3 confirmed our previous results, providing further insight into the chemistry of these new oxazolidine intermediates.

Zincke reaction of salt **12**, readily obtained from the corresponding pyridine,[6] gave salt **13**, in excellent yield. The sodium dithionite reduction of **13**, according to the procedure used for the preparation of intermediates **3a**−**d**, gave the 1,4-dihydropyridine **14**, which slowly cyclized in $CDCl_3$ affording, as expected, a mixture of oxazolidines **15** and **16**, the latter isomer predominating at first, but finally reaching an equilibrium in which the oxazolidine ratio was inverted to 70:30 in favor of isomer **15**. The presence of the methoxyphenyl substituent exerts in this case a stabilizing effect on the corresponding dihydropyridine intermediates. Accordingly, the dithionite reduction of salt **13** using refluxing toluene instead of ether, *i.e.*, under conditions that were previously[2] found to give overreduced products when applied to salts **2a**−**c,** now afforded oxazolidines **15** and **16** directly in good yield and in a 20:80 ratio. In addition, when this crude mixture of oxazolidines was dissolved in CH_2Cl_2−EtOAc, crystals of oxazolidine **16** separated out, allowing structural determination by X-ray analysis as depicted in Figure 1. It is very likely that the crystallization process displaces the equilibrium in favor of this less stable diastereomer.[7] An essential feature of the X-ray structure is the quasiplanarity of the nitrogen atom ($\alpha + \beta + \delta = 357.5°$), a consequence of which is the *sofa* arrangement of the nitrogen six-membered ring. The coplanarity of the methoxyphenyl ring with the enamine function suggests an electron delocalization, which can possibly explain the relative stability of this intermediate.

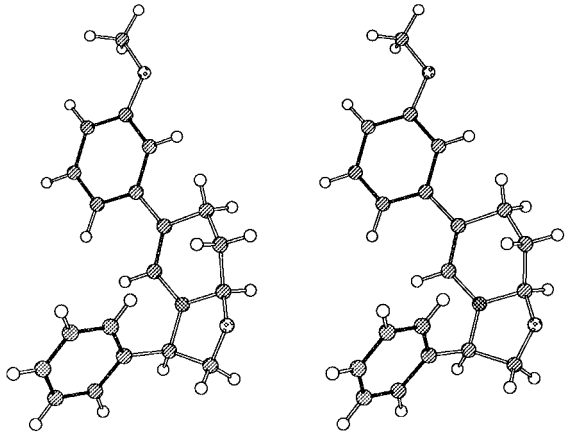


Figure 1. X-ray structure of (−)-**16**.

The ^1H NMR spectra of freshly dissolved crystalline **16** in $CDCl_3$ initially displayed this oxazolidine as a single compound, which slowly isomerized to **15** as the major component at equilibrium. This process can be easily followed by checking, in particular, the chemical shift of proton 8a in **16** at 4.84 ppm, which was deshielded to 5.06 ppm in **15**. These results secured stereochemical assigments of oxazolidines **4a**−**d**, **5a**−**d**, **7**, and **8**, which displayed the same essential features in their NMR spectra.[8]

$LiAlH_4$ reduction of the crude mixture of oxazolidines **15** and **16** obtained from the dithionite reduction using toluene as cosolvent gave, after hydrolysis, the new derivative **17**, accompanied by another isomer in a 93:7 ratio. Further $LiAlH_4$ reduction gave the 3-substituted piperidine derivative **18**, whose diastereoisomeric purity

(5) See, for exemple: (a) Heathcock, C. H.; Norman, M. H.; Dickman, D. A. *J. Org. Chem.* **1990**, *55*, 798. (b) Norman, M. H.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 3370.

(6) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, L. G. *J. Med. Chem.* **1981**, *24*, 1475.

(7) For a similar resolution process in oxazolidine series see: Just, G.; Potvin, P.; Uggowitzer, P.; Bird, P. *J. Org. Chem.* **1983**, *48*, 2923 and references cited therein.

(8) In our initial paper,[3] the structures of oxazolidines **4c** and **5c** were unfortunately misassigned and must thus be corrected accordingly.

at C-3 was firmly established by GC−MS measurements as 86%. Finally, hydrogenolysis afforded base **19**, whose hydrochloride salt was obtained in a pure crystalline form in 44% overall yield from **13**. A two-step propylation sequence (Scheme 3) led to (−)-PPP, thus securing the stereochemical assignments of intermediates **17**−**19**. Also secured by this sequence is the stereochemistry of the useful intermediates such as **10**.

The present synthesis of (−)-PPP (seven steps, 26% overall yield) does not compare favorably with a recently reported[9] procedure (four steps, 37% overall yield) using dibenzoyltartaric acid as a resolving agent for the readily obtained racemic PPP. But, in addition to revealing the essential features of our new oxazolidine intermediates and their absolute stereochemistry, we feel that our synthetic procedure offers a versatile access to a number of derivatives that are of current interest.[10]

Further use of 3-alkyl-4,5-dihydropyridinium salt equivalents such as **4a**−**d** and **5a**−**d** and 3-alkyl-3,4,5,6-tetrahydropyridinium salt equivalents such as **10** for the enantioselective syntheses of polysubstituted piperidines is currently under investigation.

Experimental Section

1-(2,4-Dinitrophenyl)-3-ethylpyridinium Chloride (1b). A solution of 3-ethylpyridine (23 mL, 202.2 mmol) and 1-chloro-2,4-dinitrobenzene (40 g, 197.5 mmol) was refluxed in acetone (70 mL) overnight. The precipitate of salt **1b** was collected by filtration as a white solid (48.38 g, 79%): mp 203−205 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.27 (1H, d, J = 2 Hz), 9.25 (1H, s), 9.14 (1H, d, J = 6 Hz), 8.90 (1H, dd, J = 2, 8 Hz), 8.82 (1H, d, J = 7 Hz), 8.31 (1H, d, J = 8 Hz), 8.29 (1H, dd, J = 6, 7 Hz), 3.04 (2H, q, J = 7 Hz), 1.44 (3H, t, J = 7 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 151.0, 149.6, 147.1 (2C), 146.1, 144.6, 140.2, 132.8, 131.2, 129.0, 123.1, 28.9, 14.7; MS (FAB$^+$, glycerol) m/z 274 (M$^+$, 100), 108 (14).

1-(2,4-Dinitrophenyl)-3-methylpyridinium Chloride (1c). A solution of 3-picoline (20 mL, 205.5 mmol) and 1-chloro-2,4-dinitrobenzene (40 g, 197.5 mmol) was refluxed in acetone (70 mL) overnight. The resulting precipitate was filtered and recrystallized from EtOH to give salt **1c** as a white solid (48.2 g, 83%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.28 (1H, d, J = 2 Hz), 9.24 (1H, s), 9.18 (1H, d, J = 6 Hz), 8.92 (1H, dd, J = 2, 8 Hz), 8.78 (1H, d, J = 7 Hz), 8.34 (1H, d, J = 8 Hz), 8.28 (1H, dd, J = 6, 7 Hz), 2.83 (3H, s); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 151.0, 150.6, 146.6, 144.4, 141.5 (2C), 140.1, 132.9, 131.3, 128.8, 123.2, 18.7; MS (FAB$^+$, glycerol) m/z 260 (M$^+$, 100), 98 (8).

1-(2,4-Dinitrophenyl)-3-(2-methyl-1,3-dioxolan-2-yl)pyridinium Chloride (1d). 3-(2-Methyl-1,3-dioxolan-2-yl) pyridine (21.1 g, 127.9 mmol) and 1-chloro-2,4-dinitrobenzene (26 g, 128.4 mmol) were refluxed in acetone (300 mL) during 48 h. The precipitate was filtered to give salt **1d** as a white powder (38.9 g, 83%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.41 (1H, s), 9.27 (2H, m), 8.97 (1H, m), 8.90 (1H, dd, J = 2, 8 Hz), 8.38 (1H, dd, J = 6, 8 Hz), 8.30 (1H, d, J = 8 Hz), 4.15 (2H, m), 3.90 (2H, m), 1.74 (3H, s); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 150.7, 146.9, 146.4, 144.5, 144.2, 139.7, 132.5, 130.9, 129.3, 122.8, 107.2, 66.3, 27.3; MS (FAB$^+$, glycerol) m/z 332 (M$^+$, 100), 166 (51).

(−)-3-Ethyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]pyridinium Chloride (2b). (*R*)-(−)-Phenylglycinol (5 g, 36.5 mmol) was added to a solution of Zincke salt **1b** (10.3 g, 33.3 mmol) in *n*-butanol (100 mL) at 20 °C . The resulting deep red solution was refluxed during 20 h. Removal of solvent under reduced pressure left a residue that was treated with H_2O (70 mL). The precipitate (2,4-dinitroaniline hydrochloride) was eliminated by filtration, and the operation was repeated twice. The combined aqueous phase was basified with concentrated ammonia (5 mL) and washed twice with EtOAc (200 mL) in order to remove the remaining 2,4-dinitroaniline and the excess of (*R*)-(−)-phenylglycinol. Evaporation of water gave salt **2b** (7.53 g, 86% from **1b**) as a pale orange gum: $[\alpha]_D$ −20° (*c* 2.2, EtOH); ^{1}H NMR (200 MHz, CD_3OD) δ 9.12(1H, s), 9.01 (1H, d, J = 6.2 Hz), 8.53 (1H, d, J = 8 Hz), 8.07 (1H, dd, J = 6, 7.5 Hz), 7.60−7.65 (2H, m), 7.43−7.52 (3H, m), 6.17 (1H, dd, J = 4.2, 9.1 Hz), 4.62 (1H, dd, J = 9.1, 12.5 Hz), 4.36 (1H, dd, J = 4.2, 12.5 Hz), 2.94 (2H, q, J = 7.6 Hz), 1.33 (3H, t, J = 7.6 Hz); ^{13}C NMR (50.2 MHz, CD_3OD) δ 146.8, 144.5, 142.6, 135.3, 130.6 (2C), 130.1, 129.3 (2C), 129.0, 77.3, 63.2, 26.8, 14.8; MS (FAB$^+$, glycerol) m/z 228 (M$^+$, 100), 121 (17), 108 (95).

(−)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-methylpyridinium Chloride (2c). Treatment of salt **1c** (58 g, 196.3 mmol) with (*R*)-(−)-phenylglycinol (28 g, 204 mmol) under the conditions used for the preparation of salt **2b** gave salt **2c** (39.7 g, 81% from **1c**): $[\alpha]_D$ −27° (*c* 3.8, EtOH); ^{1}H NMR (200 MHz, CD_3OD) δ 9.05 (1H, s), 8.95 (1H, d, J = 6 Hz), 8.44 (1H, d, J = 7.5 Hz), 8.02 (1H, dd, J = 6, 7.5 Hz), 7.40−7.61 (5H, m), 6.07 (1H, dd, J = 4, 8.5 Hz), 4.57 (1H, dd, J = 8.5, 13 Hz), 4.34 (1H, dd, J = 4, 13 Hz), 2.58 (3H, s); ^{13}C NMR (50.2 MHz, CD_3OD) δ 147.8, 144.7, 142.3, 141.0, 135.2, 131.0, 130.5 (2C), 129.3 (2C), 128.7, 77.0, 63.1, 18.7; MS (FAB$^+$, glycerol) m/z 214 (M$^+$, 100), 121 (18), 103 (12), 94 (64).

(−)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-(2-methyl-1,3-dioxolan-2-yl)pyridinium Chloride (2d). Treatment of salt **1d** (6 g, 16.3 mmol) with (*R*)-(−)-phenylglycinol (2.7 g, 19.7 mmol) under the conditions used for the preparation of salt **2b** gave salt **2d** (4.61 g, 88% from **1d**). Colorless hygroscopic crystals were obtained from dry MeOH−acetone: mp 208−210 °C; $[\alpha]_D$ −7° (*c* 2.2, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.10 (1H, s), 9.00 (1H, dd, J = 2, 6 Hz), 8.68 (1H, dt, J = 2, 8 Hz), 8.12 (1H, dd, J = 6, 8 Hz), 7.47−7.58 (5H, m), 6.13 (1H, dd, J = 4, 8 Hz), 4.53 (1H, dd, J = 8, 12 Hz), 4.35 (1H, dd, J = 4, 12 Hz), 4.11 (2H, m), 3.82 (2H, m), 1.69 (3H, s); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 146.3, 144.8 (2C), 143.1, 135.1, 131.2, 130.7 (2C), 129.5 (3C), 107.6, 77.4, 66.3 (2C), 63.4, 27.2; MS (FAB$^+$, glycerol) m/z 286 (M$^+$, 100), 166 (80), 121 (25), 103 (18). Anal. Calcd for $C_{17}H_{20}NO_3Cl$: C, 63.40; H, 6.26; N, 4.35; O, 14.91; Cl, 11.07. Found: C, 63.46; H, 6.19; N, 4.17; O, 14.79; Cl, 10.97.

Oxazolidines 4a−5a. Pyridinium salt **2a** (8.85 g, 37.6 mmol) was treated with sodium dithionite according to our reported protocol[2] to give very unstable 1,4-dihydropyridine **3a**. Bulb-to-bulb distillation gave unseparable oxazolidines **4a** and **5a** in an 80:20 ratio as a pale yellow oil (3.78 g, 50%): $[\alpha]_D$ −180° (*c* 1.2, $CHCl_3$); MS (EI) m/z 201 (M$^{\bullet+}$, 70), 170 (62), 104 (100); HRMS (EI) calcd for $C_{13}H_{15}NO$ m/z 201.1154, obsd m/z 201.1152. **(3*R*,8a*S*)-(−)-3-Phenyl-3,7,8,8a-tetrahydro-2*H*-oxazolo[3,2-*a*]pyridine (4a)** (major isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13−7.40 (5H, m), 5.88 (1H, d, J = 7.6 Hz), 5.02 (1H dd, J = 3.4, 9.3 Hz), 4.62 (1H, m), 4.26 (1H, d, J = 6.8 Hz), 4.22 (1H, dd, J = 6.8, 6.8 Hz), 3.66 (1H, dd, J = 6.8, 6.8 Hz), 2.04−2.13 (1H, m), 1.74 (1H, m), 1.50 (1H, m); ^{13}C-NMR (75.47 MHz, $CDCl_3$) δ 139.1, 130.6 (C-5), 128.6 (2C), 127.8 (2C), 127.2, 100.2 (C-6), 88.9 (C-8a), 73.5 (C-2), 64.7 (C-3), 27.0 (C-8), 19.6 (C-7). Minor isomer **5a**: ^{1}H NMR (200 MHz, $CDCl_3$) characteristic signals at δ 5.77 (1H, d, J = 7.7 Hz) and 4.77 (1H-8a, dd, J = 9.5, 3.3 Hz).

Oxazolidines 4b-5b. To a two-phase system of Et_2O (300 mL) and an aqueous solution (20 mL) of K_2CO_3 (12 g) and sodium dithionite (15 g) was added salt **2b** (3.55 g, 13.5 mmol) dissolved in water (15 mL). The mixture was refluxed for 1 h with vigorous stirring. The ether phase was decanted, washed with an aqueous solution of sodium bicarbonate, and dried over anhydrous Na_2SO_4. Removal of solvent gave crude **(2*R*)-(−)-2-(3-ethyl-4*H*-pyridin-1-yl)-2-phenylethanol (3b)** as a pale yellow oil (2.32 g, 75%): $[\alpha]_D$ −49° (*c* 0.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.21−7.40 (5H, m), 5.90 (1H, dm, J = 8 Hz), 5.67 (1H, m), 4.46 (1H, ddd, J = 8, 8, 3.2,Hz), 4.23 (1H, dd, J = 7.5, 6.6 Hz), 3.98 (1H, d, J = 6.6 Hz), 3.97 (1H, d, J = 7.5 Hz), 2.89 (2H, m), 1.83 (2H, q, J = 7.4 Hz), 0.97 (3H, t, J = 7.4 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 138.9, 129.6, 128.7 (2C), 127.6 (2C), 127.1, 123.5, 113.0, 97.9, 66.7, 63.1, 28.1, 26.8, 11.7; MS (EI) m/z 229 (M$^{\bullet+}$, 100), 214 (95), 198 (78), 104 (60). The crude dihydropyridine **2b** was then dissolved in a solution of pentane−CH_2Cl_2 (1:3, 200 mL), and the resulting mixture was filtered over alumina (140 g); further elution (600 mL) with the same solvent system gave a mixture of oxazolidines **4b** and **5b** in a 90:10 ratio (2.07 g, 67% from salt **2b**): $[\alpha]_D$ −301° (*c* 2.65, $CHCl_3$);

(9) Law, H.; Leclerc, G. A.; Neumeyer, J. L. *Tetrahedron: Asymmetry* **1991**, *2*, 989.

(10) See, for example: Cannon, J. G.; Kirschbaum, K. S.; Amoo, V. E. D.; Jonhson, A. K.; Long, J. P. *J. Med Chem.* **1993**, *36*, 2416−2419.

MS (EI) *m*/*z* (relative intensity) 229 ($M^{\bullet+}$, 100), 214 (98), 198 (48), 104 (65); HRMS (EI) calcd for $C_{15}H_{19}NO$ *m*/*z* 229.1466, obsd *m*/*z* 229.1467. **(3*R*,8a*S*)-(−)-6-Ethyl-3-phenyl-3,7,8,8a-tetrahydro-2*H*-oxazolo[3,2-*a*]pyridine (4b)** (major isomer): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22−7.43 (5H, m), 5.62 (1H, s), 4.97 (1H, dd, J = 9.4, 3.3 Hz), 4.23 (1H, dd, J = 7.4, 6.4 Hz), 4.14 (1H, d, J = 7.4, 6.4 Hz), 3.67 (1H, dd, J = 7.4, 7.4 Hz), 1.94−2.10 (3H, m), 1.89 (2H, m), 1.61 (1H, m), 0.94 (3H, t, J = 7.5 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 139.2, 128.6 (2C), 127.7, 127.2 (2C), 125.0, 116.3, 88.9, 73.4, 62.4, 27.8, 26.8, 22.8, 13.1. Minor isomer **5b**: ^{1}H NMR (200 MHz, $CDCl_3$) characteristic signals at δ 5.50 (1H, s) and 4.65 (1H, dd, J = 9.4, 3.3 Hz).

Oxazolidines 4c−5c. Pyridinium salt **1c** (3.62 g, 14.5 mmol) was treated with sodium dithionite, as for the preparation of dihydropyridine **3b**, to give crude dihydropyridine **3c**. Filtration over alumina under the conditions used to obtain oxazolidines **4b−5b** gave a mixture of oxazolidines **4c−5c** in a 90:10 ratio (1.96 g): $[\alpha]_D$ −227° (*c* 1.4, $CHCl_3$); MS (EI) *m*/*z* 215 ($M^{\bullet+}$, 100), 200 (6), 184 (80), 104 (70); HRMS (EI) calcd for $C_{14}H_{17}NO$ *m*/*z* 215.1310, obsd *m*/*z* 215.1293. **(3*R*,8a*S*)-(−)-6-Methyl-3-phenyl-3,7,8,8a-tetrahydro-2*H*-oxazolo[3,2-*a*]pyridine (4c)** (major isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.48 (5H, m), 5.62 (1H, s), 4.97 (1H, dd, J = 3.2, 8.9 Hz), 4.25 (1H, dd, J = 7, 7.9 Hz), 4.16 (1H, dd, J = 7, 7.9 Hz), 3.68 (1H, dd, J = 7.9, 7.9 Hz), 2.04 (1H, m), 2.02 (2H, m), 1.62 (1H, m), 1.58 (3H, s); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 140.0, 128.6 (2C), 127.8, 127.3 (2C), 125.7, 110.7, 88.6, 73.5, 65.2, 26.8, 24.9, 20.3. Minor isomer **5c**: ^{1}H NMR (300 MHz, $CDCl_3$) characteristic signals at δ 5.50 (1H, s) and 4.65 (1H, dd, J = 9.4, 3.3 Hz).

Oxazolidines 4d−5d. Pyridinium salt **2d** (2 g, 6.23 mmol) was treated with sodium dithionite, as for the preparation of dihydropyridine **3b**, to give crude dihydropyridine **3d** (1.6 g, 90%) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.19−7.42 (5H, m), 6.10 (1H, s), 5.89 (1H, m), 4.55 (1H, dt, J = 8, 3 Hz), 4.27 (1H, m); 4.01 (2H, m), 3.69−3.95 (4H, m), 2.94 (2H, m), 1.43 (3H, s); MS (EI) *m*/*z* 287 ($M^{\bullet+}$, 79), 286 (63), 272 (57), 256 (66), 166 (100), 122 (66), 102 (40), 87 (49). Filtration over Florisil (8 g) with CH_2Cl_2 gave a mixture of oxazolidines **4d−5d** as a colorless oil (1.4 g, 4.88 mmol, 78%) in an 82:18 ratio. Major isomer **4d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20−7.45 (5H, m), 5.92 (1H, s), 4.80 (1H, dd, J = 4, 10 Hz), 4.46 (1H, dd, J = 3, 6 Hz), 4.23 (1H, dd, J = 6, 8 Hz), 3.46−4.11 (5H, m), 2.10−2.34 (2H, m), 1.62−1.80 (2H, m), 1.39 (3H, s). Minor isomer **5d**: ^{1}H NMR (200 MHz, $CDCl_3$) characteristic signals at δ 6.10 (1H, s), 4.95 (1H, dd, J = 9.4, 3.3 Hz) and 1.44 (3H, s).

Oxazolidines 7 and 8. To the above mixture of oxazolidines **4d−5d** (1.36 g, 4.7 mmol) in CH_2Cl_2 (50 mL) was added silica gel (10 g), and the resulting mixture was stirred for 3 h. Filtration and removal of solvent under reduced pressure left a mixture of deprotected oxazolidines **7** and **8** (1.13 g, 4.6 mmol) that were separated by chromatography over alumina with heptane−EtOAc (80:20 to 60:40) as eluent. Major isomer **7** (0.67 g, 58%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30−7.50 (5H, m) 7.22 (1H, s), 5.54 (1H, dd, J = 4, 10 Hz), 4.64 (1H, dd, J = 6, 8 Hz), 4.49 (1H, dd, J = 6, 8 Hz), 3.76 (1H, dd, J = 8, 8 Hz), 2.85 (1H, ddd, J = 2, 2, 16 Hz), 2.36 (1H, m), 2.18 (1H, m), 2.07 (3H, s), 1.42 (1H, m); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 193.3, 141.8, 137.4, 129.0 (2C), 128.4, 126.7 (2C), 111.7, 88.6, 73.9, 63.5, 26.1, 23.9, 18.0; MS (EI) *m*/*z* 243 ($M^{\bullet+}$, 100), 228 (40), 212 (20); HRMS (EI) calcd for $C_{15}H_{17}NO_2$ *m*/*z* 243.1259, obsd *m*/*z* 243.1282. Minor isomer **8** (0.24 g, 21% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23−7.53 (5H, m), 7.07 (1H, s), 4.87 (1H, dd, J = 4, 10 Hz), 4.70 (1H, dd, J = 2, 6 Hz), 4.32 (1H, dd, J = 6, 9 Hz), 4.48 (1H, dd, J = 2, 9 Hz), 2.84 (1H, ddd, J = 2, 5, 16 Hz), 2.44 (1H, m), 2.16 (1H, m), 1.99 (3H, s), 1.64 (1H, m); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 193.1, 141.4, 140.7, 129.0 (2C), 128.4, 127.1 (2C), 110.3, 87.8, 73.7, 61.9, 25.8, 23.8, 18.3; MS (EI) *m*/*z* 243 ($M^{\bullet+}$, 100), 228 (40), 212 (20); HRMS (EI) calcd for $C_{15}H_{17}NO_2$ *m*/*z* 243.1259, obsd *m*/*z* 243.1286.

(3*R*,8*S*,8a*R*)-(−)-8-Methyl-3-phenylhexahydrooxazolo[3,2-*a*]pyridine (10). A mixture of oxazolidines **4c−5c** (1.32 g, 6.14 mmol) was reduced with $LiAlH_4$ (0.28 g, 7.4 mmol) in refluxing THF for 1 h. The resulting mixture was carefully added dropwise to a two-phase system of CH_2Cl_2 (80 mL) and a saturated aqueous solution of NH_4Cl (80 mL) with vigorous stirring. The organic phase was decanted and washed with water. Removal of solvent left an oil that was filtered over alumina (70 g) with CH_2Cl_2−pentane (3:1) as eluent to give oxazolidine **10** accompanied with the isomer epimeric at C-8 (8*R*) and C-8a (8a*S*, tentative assignment) in an 85:15 ratio. Crude mixture (0.98 g, 74%): $[\alpha]_D$ −109° (*c* 1.5, $CHCl_3$). Major isomer **11a**: ^{1}H NMR (200 MHz, $CDCl_3$) 7.24−7.43 (5H, m), 4.14 (1H, dd, J = 7.5, 7.5 Hz), 3.62 (1H, dd, J = 7.5, 7.5 Hz), 3.49 (1H, dd, J = 7.5, 7.5 Hz), 3.32 (1H, d, J = 8 Hz), 2.82 (1H, m, J = 10.6 Hz), 1.99 (1H, m), 1.77 (1H, m), 1.70 (1H, m), 1.50−1.60 (2H, m), 1.03 (1H, m), 1.01 (3H, d, J = 6.4 Hz); ^{13}C NMR (50.2 MHz, CD_3OD) δ 139.4, 128.6 (2C), 127.9 (2C), 127.8, 100.3, 73.2, 67.5, 48.0, 36.2, 31.9, 25.3, 17.2; MS (EI) *m*/*z* 217 ($M^{\bullet+}$, 80), 216 (77), 117 (48), 104 (100); HRMS (EI) calcd for $C_{14}H_{19}NO$ *m*/*z* 217.1466, obsd *m*/*z* 217.1472.

1-(2,4-Dinitrophenyl)-3-(3-methoxyphenyl)pyridinium Chloride (12). 1-Chloro-2,4-dinitrobenzene (5.89 g, 29 mmol) was added to 3-(3-methoxyphenyl)pyridine[6] (4.9 g, 26.4 mmol). The resulting homogeneous solution was stirred for 19 h at 60 °C. The yellow precipitate formed was separated by filtration, washed with acetone, and recrystallized from MeOH−acetone to give salt **12** (9.68 g, 94%): mp 175 °C; ^{1}H NMR (200 MHz, CD_3OD) δ 9.50 (1H, s), 9.31 (1H, d, J = 2.8 Hz), 9.25 (1H, dd, J = 1.5, 6 Hz), 9.22 (1H, dd, J = 1.5, 8 Hz), 8.95 (1H, dd, J = 2.8, 8.5 Hz), 8.42 (1H, dd, J = 6, 8 Hz), 8.38 (1H, d, J = 8.5 Hz), 7.54 (1H, dd, J = 8, 8 Hz), 7.44 (2H, m), 7.17 (1H, ddd, J = 1.2, 1.2, 8Hz), 3.89 (3H, s); ^{13}C NMR (50.2 MHz, CD_3OD) δ 162.2, 151.2, 147.4, 145.2 (2C), 144.8, 142.7, 140.1, 135.3, 132.9, 132.1, 131.2, 129.5, 123.1, 121.0, 117.6, 114.2, 56.2; MS (FAB$^+$, glycerol) *m*/*z* 352 (M^+, 100), 186 (87). Anal. Calcd for $C_{18}H_{14}N_3O_5Cl$: C, 55.56; H, 3.63; Cl, 9.17; O, 20.57; N, 10.80. Found: C, 55.49; H, 3.83; Cl, 9.10; O, 20.61; N, 11.05.

(−)-3-(3-Methoxyphenyl)-*N*-[(1*R*)-1-phenyl-2-hydroxyethyl]pyridinium Chloride (13). Zincke salt **12** (23.6 g, 60.9 mmol) was dissolved in *n*-butanol (200 mL). Addition of (*R*)-(−)-phenylglycinol (1.1 equiv, 9.2 g, 67 mmol) gave a deep red solution that was then refluxed for 14 h. Evaporation of the solvent gave the crude product, which was dissolved in H_2O (250 mL). After filtration, the aqueous phase was made alkaline by addition of concentrated ammonia (5 mL) and then washed four times with EtOAc (100 mL). Removal of water under reduced pressure gave pure salt **13** (18.9 g, 91%). Colorless crystals were obtained from MeOH−acetone: mp 183 °C; $[\alpha]_D$ −18° (*c* 2, EtOH); ^{1}H NMR (200 MHz, CD_3OD) δ 9.40 (1H, s), 8.98 (1H, d, J = 6.3 Hz), 8.87 (1H, d, J = 8 Hz), 8.15 (1H, dd, J = 6.3, 8 Hz), 7.62 (1H, m) 7.50(2H, m) 7.36 (2H, m) 7.12 (2H, dd, J = 2, 8.4 Hz), 6.21(1H, dd, J = 4, 8.7 Hz), 4.60 (1H, dd, J = 8.7, 12.4 Hz), 4.42 (1H, dd, J = 4, 12.4 Hz), 3.90 (3H, s); ^{13}C NMR (50.2 MHz, CD_3OD) δ 161.8, 144.8, 143.7, 142.7, 142.0, 135.6, 135.1, 131.8, 131.1, 130.5 (2C), 130.0, 129.5 (2C), 128.4, 120.8, 117.1, 113.9, 77.2, 63.3, 56.2; MS (FAB$^+$, glycerol) *m*/*z* 306 (M^+, 100), 186 (55). Anal. Calcd for $C_{20}H_{20}NO_2Cl$: C, 70.22; H, 5.89; Cl, 10.43; O, 9.36; N, 4.09. Found: C, 70.03; H, 5.85; Cl, 10.46; O, 9.50; N, 3.97.

(2*R*)-(−)-2-[3-(3-Methoxyphenyl)-4*H*-pyridin-1yl]-2-phenylethanol (14). To a two-phase system made of diethyl ether (50 mL) and an aqueous solution (10 mL) of K_2CO_3 (6 g) and sodium dithionite (8 g) was added dropwise pyridinium salt **13** (0.43 g, 1.23 mmol) in H_2O (2 mL). The resulting mixture was refluxed for 1 h with vigorous stirring. The organic phase was decanted and then washed with a saturated solution of NH_4Cl. Removal of solvent afforded the crude dihydropyridine **14** (0.32 g, 85%) as a pale yellow oil: $[\alpha]_D$ −14° (*c* 0.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (5H, m), 7.18 (1H, dd, J = 8, 8 Hz), 6.87 (1H, d, J = 8 Hz), 6.77 (1H, m), 6.68(1H, dd, J = 2, 8 Hz), 6.57 (1H, s), 5.94 (1H, d, J = 8 Hz), 4.69 (1H, dt, J = 4, 8 Hz), 4.38 (1H, dd, J = 7, 7 Hz), 4.05 (1H, dd, J = 7, 7 Hz), 3.77 (1H, s, 3H), 3.31 (2H, m); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 159.8, 141.5, 138.3, 129.1, 128.8, 128.4, 127.9, 127.6, 127.1, 115.8, 110.3, 109.4, 107.6, 100.3, 67.1, 63.3, 55.2, 25.5; MS (EI) *m*/*z* 307 ($M^{\bullet+}$, 100), 276 (62), 186 (73), 185 (67), 91 (78).

Oxazolidines 15 and 16. To a two-phase system consisting of toluene (100 mL) and an aqueous solution (100 mL) of $Na_2S_2O_4$ (20 g) and K_2CO_3 (15 g) was added dropwise pyridinium salt **13** (1.9 g, 5.5 mmol) in H_2O (10 mL). The resulting mixture was heated at 100 °C for 3 h with vigorous stirring. The organic phase was then decanted and washed with a saturated solution of NH_4Cl. Removal of the solvent left a mixture (1.4 g, 81%) of oxazolidines **15** and **16** in a 1:4 ratio. Pure crystalline oxazoli-

dine **16**, suitable for X-ray analysis,[11] was obtained from CH_2Cl_2−EtOAc. **(3*R*,8a*R*)-(−)-6-(3-Methoxyphenyl)-3-phenyl-3,7,8,8a-tetrahydro-2*H*-oxazolo[3,2a]pyridine (16)**: mp 120 °C; $[\alpha]_D$ −433° (*c* 1, $CHCl_3$);^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (5H, m), 7.10 (1H, dd, J = 8, 8 Hz), 6.77 (1H, d, J = 8 Hz), 6.67 (1H, m), 6.53 (1H, dd, J = 2.2, 8 Hz), 6.41 (1H, s), 4.84 (1H, dd, J = 3.6, 10 Hz), 4.53 (1H, dd, J = 3.6, 7 Hz), 4.23 (1H, dd, J = 7, 8 Hz), 3.94 (1H, dd, J = 3.6, 8 Hz), 3.75 (3H, s), 2.37−2.70 (3H, m), 1.90 (1H, m); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 159.9, 142.4, 141.3, 129.1, 128.8 (2C), 127.9, 127.6 (2C), 126.8, 115.6, 109.2, 107.4, 88.0, 73.8, 62.7, 55.1, 27.5, 22.4; MS (EI) *m*/*z* 307 ($M^{\bullet+}$, 100), 276 (43), 173 (65), 185 (67), 91 (39). Filtration over alumina (45 g) of the above mixture with CH_2Cl_2−pentane (1:1) as eluant gave oxazolidines **15** and **16** in a 70 to 30 ratio. Crude mixture: $[\alpha]_D$ −57° (*c* =1.1, $CHCl_3$). **(3*R*,8a*S*)-(−)-6-(3-Methoxyphenyl)-3-phenyl-3,7,8,8a-tetrahydro-2*H*-oxazolo[3,2-a]pyridine (15)**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (5H, m), 7.17 (1H, dd, J = 8, 8 Hz), 6.85 (1H, d, J = 8 Hz), 6.78 (1H, m), 6.60 (1H, m), 6.48 (1H, s), 5.60 (1H, dd, J = 4, 9.5 Hz), 4.36 (1H, dd, J = 6, 7 Hz), 4.27 (1H, dd, J = 7, 7 Hz), 3.68 (1H, dd, J = 6, 7 Hz), 3.68 (3H, s), 2.19−2.68 (3H, m), 1.65 (1H, m); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 159.9, 142.0, 138.7, 127.6 (2C), 128.6 (2C), 126.9 (2C), 115.7, 110.3, 109.3, 109.2, 88.4, 73.5, 62.5, 54.8, 27.1, 22.6; MS (EI) *m*/*z* 307 ($M^{\bullet+}$, 100), 276 (43), 173 (65), 185 (67), 91 (39).

(3*R*,8*R*,8a*R*)-(−)-8-(3-Methoxyphenyl)-3-phenyl-5,6,7,8,-8a-hexahydro-2*H*-oxazolo[3,2-a]pyridine (17). To the crude mixture of oxazolidines **15** and **16** (2.56 g, 8.34 mmol), obtained by the above dithionite reduction procedure using toluene, in THF (60 mL) was added $LiAlH_4$ (0.4 g, 10.5 mmol). This solution was refluxed for 1 h and then carefully added dropwise to a two-phase system of CH_2Cl_2 (100 mL) and a saturated aqueous solution of NH_4Cl (100 mL) with vigorous stirring. The organic phase was decanted and washed with water. Removal of solvent left an oil that was filtered over alumina (25 g) with CH_2Cl_2−pentane (3:2) as eluant to give oxazolidine **17** in equilibrium with the isomer epimeric at C-8 and C-8a in a 95:5 ratio (1.9 g, 74%): $[\alpha]_D$ −15° (*c* 2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.17−7.43 (6H, m), 6.92 (1H, d, J = 7.8 Hz), 6.88 (1H, m), 6.76 (1H, dd, J = 2.5, 8.2 Hz), 4.19 (1H, dd, J = 6.5, 6.5 Hz), 3.87 (1H, d, J = 8.8 Hz), 3.75 (3H, s), 3.62 (1H, m, J = 6.5, 8 Hz), 3.56 (1H, m, J = 6.5, 8 Hz), 2.88 (1H, m), 2.84 (1H, m), 2.12 (1H, ddd, J = 5.5, 9, 9 Hz), 1.98 (1H, d, J = 11.8 Hz), 1.58−1.76 (2H, m), 1.56 (1H, dddd, J = 1, 4.6, 11, 11.8 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 159.8, 143.7, 139.1, 129.5 (2C), 127.8 (2C), 120.1, 113.7, 111.9, 98.0, 73.3, 67.2, 55.1, 48.8, 47.6, 31.5, 25.4; HRMS (EI) calcd for $C_{20}H_{23}NO_2$ *m*/*z* 309.1728, obsd *m*/*z* 309.1726.

(2*R*,3*S*)-(−)-2-[3-(3-Methoxyphenyl)piperidin-1-yl]-2-phenylethanol (18). Oxazolidine **17** (1.47 g, 4.76 mmol) was reduced with $LiAlH_4$ (217 mg, 5.7 mmol) in refluxing THF (60 mL) for 1 h. The resulting solution was poured into water saturated with NH_4Cl. Extraction with CH_2Cl_2 and usual workup of the organic phase gave piperidine **18** as an oil (1.35 g, 91%): $[\alpha]_D$ −77° (*c* 1.9, $CHCl_3$) (86% de); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28−7.38 (3H, m), 7.12−7.25 (3H, m), 6.70−6.80 (3H), 4.04 (1H, dd, J = 10, 10 Hz), 3.78 (3H, s), 3.73 (1H, dd, J = 5, 10 Hz), 3.62 (1H, dd, J = 5, 10 Hz), 2.90−3.30 (2H, m), 2.86 (1H, dddd, J = 3.6, 3.6, 10.9, 10.9 Hz), 2.33(1H, dd, J = 10.9, 10.9 Hz), 1.87 (1H, m), 1.68−1.80 (2H, m), 1.62 (1H, m), 1.32 (1H, dddd, J = 3.6, 11, 12, 12 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 159.7, 146.1, 135.6, 129.4, 128.9 (2C), 128.2 (2C), 127.9, 119.7, 113.4, 111.5, 70.4, 60.5, 60.2, 55.2, 46.4, 44.0, 31.5, 26.1; HRMS (CI) calcd for $C_{20}H_{26}NO_2$ *m*/*z* 312.1963, obsd *m*/*z* 312.1964.

(11) The author has deposited atomic coordinates for **16** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(3*S*))-(−)-3-(3-Methoxyphenyl)piperidine (19). Piperidine **18** (1.93 g, 6.2 mmol) was dissolved in a mixture of EtOH (10 mL), EtOAc (10 mL), water (5 mL), and 50% aqueous HBF_4 (4 mL). The resulting homogeneous solution was hydrogenated in a Parr apparatus at 4.5 psi in the presence of a catalytic amount of 10% palladium on charcoal during 4 days. After filtration over Celite and removal of solvent under reduced pressure, the residue was dissolved in water (20 mL). This aqueous phase was washed with Et_2O (4 × 20 mL) and basified with Na_2CO_3. The free base was finally extracted with CH_2Cl_2 (4 × 20 mL). Usual workup gave base **19** as a pale yellow oil (1.05 g, 89%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.17 (1H, dd, J = 8, 8 Hz), 6.77 (1H, d, J = 8 Hz), 6.75 (1H, m), 6.72 (1H, dd, J = 1.5, 8 Hz), 3.74 (3H, s); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 26.6, 31.6, 43.8, 46.1, 53.5, 54.6, 110.9, 112.7, 119.0, 128.9, 146.1, 159.3. Colorless crystals of **19·HCl** were obtained from MeOH−acetone: mp 172 °C; $[\alpha]_D$ −8° (*c* 1.1, CH_3OH). Anal. Calcd for $C_{12}H_{18}NOCl$: C, 63.22; H, 7.96; N, 6.14; O, 7.02; Cl, 15.64. Found: C, 63.13; H, 7.66; N, 5.92; O, 7.32; Cl, 15.68.

(3*S*)-(−)-3-(3-Hydroxyphenyl)-1-propylpiperidine [(−)-PPP]. Base **19** (304 mg, 1.59 mmol) was dissoved in toluene (10 mL). To the resulting solution was added at 0 °C, with stirring, freshly distilled propionyl chloride (177 mg, 1.9 mmol) in toluene (1 mL) followed by triethylamine (0.5 mL), and the mixture was stirred at ambient temperature for 0.5 h. The solvent was removed under reduced pressure, and the crude product was reduced with excess $LiAlH_4$ (182 mg, 4.7 mmol) in refluxing THF for 3 h. The reaction mixture was carefully hydrolyzed with a concentrated aqueous solution of NH_4Cl. Extraction with CH_2Cl_2 gave crude **(3*S*)-(−)-3-(3-methoxyphenyl)-1-propylpiperidine** (302 mg, 80%): $[\alpha]_D$ − 6° (*c* 2.3, $CHCl_3$) (86% ee); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.22 (1H, dd, J = 8.4, 8.4 Hz), 6.82 (1H, d, J = 8.4 Hz), 6.78 (1H, m), 6.72 (1H, dd, J = 8.4, 1.5 Hz), 3.79 (3H, s), 3.02 (1H, m), 2.96 (1H, m), 2.81 (1H, dddd, J = 11, 11, 3.5, 3.5 Hz), 2.32 (2H, m), 1.96 (2H, m, J = 11 Hz), 1.90 (1H, m), 1.67−1.80 (2H, m), 1.52 (2H, m, J = 7.5 Hz), 1.45 (1H, dddd, J = 12, 12, 11, 5 Hz), 0.88 (3H, t, J = 7.5 Hz); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 159.6, 146.2, 129.2, 119.6, 113.3, 111.2, 61.3, 61.2, 55.0, 53.9, 43.0, 31.7, 25.8, 20.1, 12.0; HRMS (EI) calcd for $C_{15}H_{23}NO$ *m*/*z* 233.1780, obsd *m*/*z* 233.1785. Cleavage of the methoxy ether was performed on this last piperidine (360 mg, 1.36 mmol) by heating in a 48% HBr aqueous solution at 120 °C for 3 h. Treatment of the crude reaction mixture with an aqueous saturated solution of Na_2CO_3 (20 mL) and extraction with toluene (3 × 30 mL) gave, after usual workup of the organic phase, (−)-PPP (260 mg, 1.02 mmol, 73%, 85% ee): $[\alpha]_D$ −6° (*c* 1.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.17 (1H, dd, J = 7.7, 7.7 Hz), 6.67−6.78 (3H, m), 3.23 (1H, m), 3.08 (1H, m), 2.93 (1H, dddd, J = 11.8, 11.8, 3, 3 Hz), 2.37 (2H, m), 1.90−2.70 (3H, m), 1.70−1.86 (2H, m), 1.57 (1H, m), 0.86 (3H, t, J = 7.3 Hz); ^{13}C NMR (50.2 MHz, $CDCl_3$) δ 157.0, 145.7, 129.8, 117.8, 114.8, 114.3, 61.5, 61.3, 54.0, 42.0, 30.4, 25.3, 19.4, 12.1; HRMS (EI) calcd for $C_{14}H_{21}NO$ *m*/*z* 219.1623, obsd *m*/*z* 219.1630.

Supporting Information Available: Full X-ray data for intermediate (−)-**16**, copies of ^{1}H NMR spectra of **1c**,**d**, **3a**,**c**,**d**, **4a**−**c**, **7**, **8**, **10**, **12**−**19**, and 3-(3-methoxyphenyl)-1-propylpiperidine, PPP, and copies of ^{13}C NMR spectra of **1b**,**c**, **2c**,**d**, **3a**, **4c**, **7**, **8**, **10**, **12**−**14**, **16**−**19**, and 3-(3′-methoxyphenyl)-1-propylpiperidine, PPP (47 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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