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Dynamic Kinetic Resolution of Racemic γ-Aryl-δ-oxoesters. Enantioselective Synthesis of 3-Arylpiperidines

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Cyclodehydration of *racemic* γ-aryl-δ-oxoesters with (*R*)- or (*S*)-phenylglycinol stereoselectively affords bicyclic δ-lactams, in a process that involves a dynamic kinetic resolution. Subsequent reduction of these lactams leads to enantiopure 3-arylpiperidines. Starting from racemic aldehyde esters, this short sequence has been applied to the synthesis of (*R*)-3-phenylpiperidine and the antipsychotic drug (−)-3-PPP (an (*S*)-3-arylpiperidine), whereas starting from racemic ketone esters enantiopure *cis*-2-alkyl-3-arylpiperidines are prepared.

The preparation of a single enantiomer from a racemate may be achieved via a conventional resolution or by exploiting the differences in reactivity (kinetic resolution). Although enzyme-catalyzed kinetic resolution of racemates has become a classical approach for the synthesis of enantiopure compounds,[1] it suffers, like conventional resolution processes, from the drawback that the maximum yield of one enantiomer is always limited to 50%. This situation dramatically changes when the racemic substrate or the two diastereomers resulting from the initial reaction with a chiral reagent have a chirally labile stereogenic center capable of undergoing in situ racemization[2] or epimerization during the reaction to form a chirally stable enantiopure product in up to 100% chemical yield (dynamic kinetic resolution).[3] Although these processes represent a viable and useful tool for preparing enantiopure chiral compounds, they have been scarcely used in synthetic sequences due to the particular requirements imposed by the substrate. When the reaction involves the generation of an additional stereogenic center, under appropriate conditions this methodology can convert a racemic compound into one of four possible enantiopure stereoisomers.

Despite the impressive advances in the enantioselective synthesis of piperidine derivatives over the last 10 years,[4] the preparation of enantiopure 3-arylpiperidines, an important group of compounds that has been thoroughly investigated in view of their interesting dopaminergic activity,[5,6] has received very little attention.[7] In fact, the enantiomers of 3-phenylpiperidine[8] and most enantiopure 3-arylpiperidines reported so far have been obtained by routes involving the conventional resolution of a racemate.[9]

In the context of the enantioselective synthesis of piperidine derivatives, chiral nonracemic bicyclic δ-lactams formed by cyclodehydration of simple δ-oxoesters and (*R*)- or (*S*)-phenylglycinol have proven to be versatile

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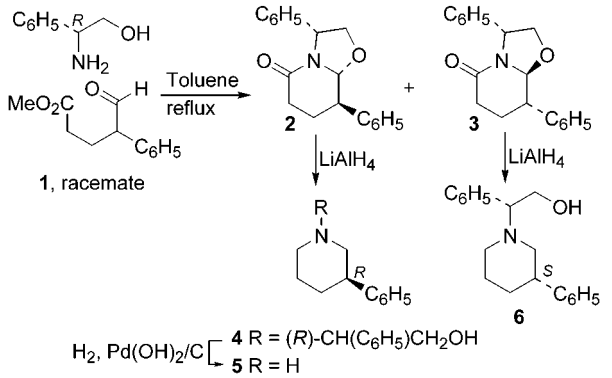
synthons that provide easy access to a variety of enantiopure mono- and disubstituted piperidines by successive introduction of the substituents taking advantage of the functionalization and conformational rigidity of the bicyclic lactam system.[10] In particular, alkylation of the enolate derived from the lactam carbonyl takes place with high stereoselectivity to ultimately give enantiopure 3-alkylpiperidines.[10d,11] However, this alkylation method cannot be extended to the synthesis of 3-arylpiperidines.

In this paper we present an efficient and straightforward procedure for the enantioselective synthesis of 3-arylpiperidines, involving as the key step a dynamic kinetic resolution during cyclodehydration of *racemic* γ-aryl-δ-oxoesters with (*R*)- or (*S*)-phenylglycinol. To illustrate the versatility and potential of this methodology we applied it to the synthesis of the antipsychotic drug (−)-3-PPP (preclamol),[9b,12] as well as several 2-alkyl substituted analogues (*cis*-2-alkyl-3-arylpiperidines).

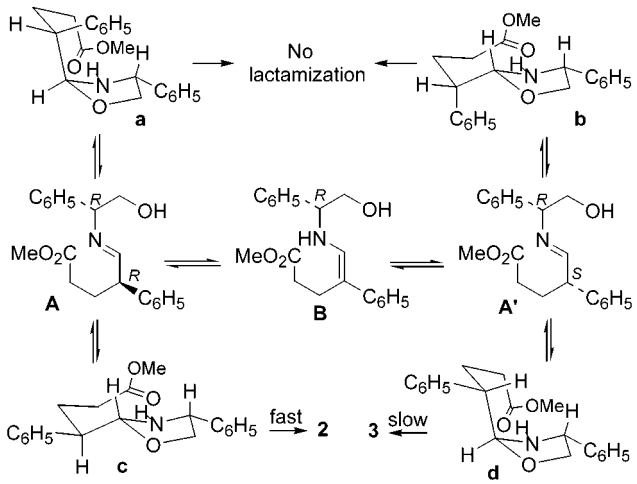
Results and Discussion

The required racemic aldehyde ester **1** was prepared by reaction of the piperidine enamine of phenylacetaldehyde with methyl acrylate. Cyclodehydration of **1** with (*R*)-phenylglycinol was carried out by heating at reflux in toluene solution to give a major trans 3-C_6H_5/8-C_6H_5 lactam **2** (49% yield), accompanied by minor amounts (9% yield) of a second diastereomer **3** in which the two phenyl groups are cis[13] (Scheme 1). The trans H-8/H-8a relationship in both isomers was evident from the coupling constant (∼9 Hz) of these protons in the ^{1}H NMR spectra. The above result clearly indicated that a dynamic kinetic resolution had occurred during the cyclodehydration reaction. The diastereomeric imines **A** and **A′** initially formed after the interaction of (*R*)-phenylglycinol with racemic oxoester **1** are in equilibrium via enamine **B** (Scheme 2). Consequently, a mixture of four equilibrating oxazolidines (**a**−**d**) at the two chirally

SCHEME 1. Synthesis of Enantiopure 3-Phenylpiperidines



SCHEME 2. Dynamic Kinetic Resolution



labile stereogenic centers is formed. Subsequent lactamization takes place via a transition state in which the phenyl substituent of the incipient chairlike six-membered lactam is equatorial, thus leading to isomers **2** (major) and **3** (minor). The preferential formation of **2** is a consequence of lactamization occurring faster from the diastereomeric oxazolidine (**c**) that allows a less hindered approach of the ester group to the nitrogen atom.

Lactam **2** was easily converted to (*R*)-3-phenylpiperidine (**5**) by $LiAlH_4$ reduction followed by debenzylation by hydrogenolysis of the resulting *N*-substituted piperidine **4**. A similar reduction from the minor lactam **3** led to piperidine **6**, which was a diastereomer of **4** according to the NMR data, thus confirming the *S* configuration at the piperidine 3-position in the minor lactam **3**. The ^{13}C NMR data of piperidines **4** and **6** (as well as the related 3-arylpiperidines **10** and **14**, see below) are in agreement with the above stereochemical assignment. Thus, in the preferred conformation, which involves a hydrogen bond between the nitrogen atom and the hydroxy group, the phenyl substituent of the phenylglycinol moiety lies near one of the piperidine α carbons, thus shielding the corresponding signal in the ^{13}C NMR spectra (Figure 1).

The above three-step sequence constitutes the first enantioselective synthesis of (*R*)-3-phenylpiperidine. Taking into account that (*S*)-phenylglycinol is also commercially available, this procedure provides access to 3-arylpiperidines in both enantiomeric series. This was

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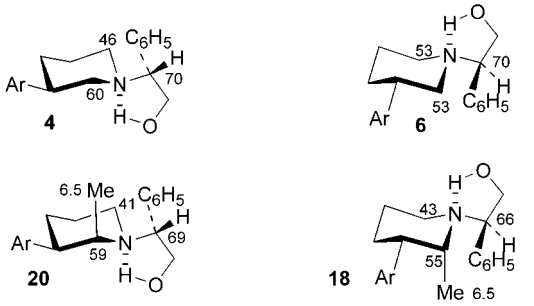
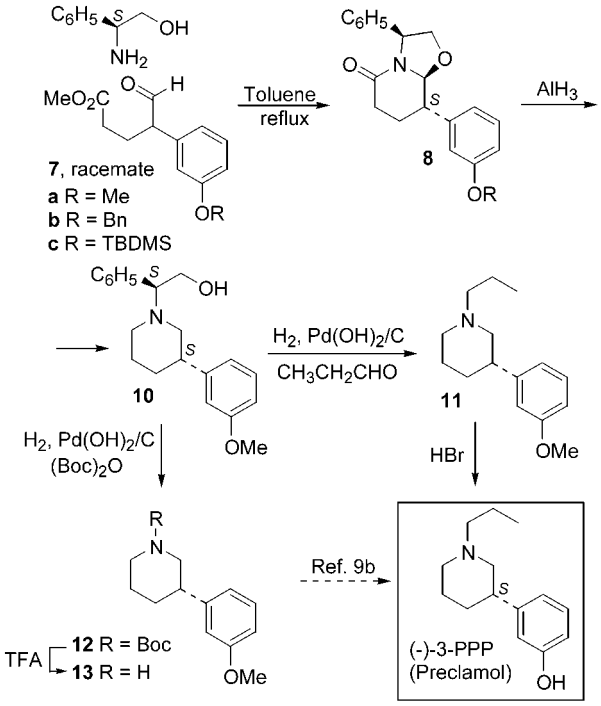


FIGURE 1. Diagnostic ^{13}C NMR chemical shifts (δ) of 3-arylpiperidines **4**, **6**, **20**, and **18**.

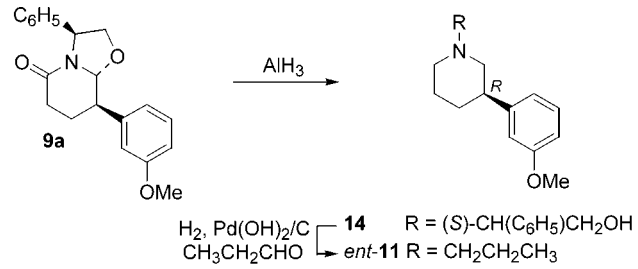
SCHEME 3. Enantioselective Synthesis of (−)-3-PPP



exemplified by the synthesis of (−)-3-PPP (preclamol), an (*S*)-3-arylpiperidine that acts as a selective dopaminergic autoreceptor agonist and has been extensively studied both as a pharmacological tool to investigate dopaminergic mechanisms and from the therapeutic point of view.[5,12] Accordingly, the synthesis of (−)-3-PPP required starting from (*S*)-phenylglycinol and racemic δ-oxoester **7a**, which bears a *m*-methoxyphenyl substituent (Scheme 3). This ester was conveniently prepared by reaction of methyl acrylate with the pyrrolidine enamine of (*m*-methoxyphenyl)acetaldehyde. The use of a benzyl or *tert*-butyldimethylsilyl protecting group instead of methyl was not satisfactory due to the difficulties encountered in the purification of the corresponding δ-oxoesters **7b** and **7c**.[14]

As expected, heating a toluene solution of (*S*)-phenylglycinol and racemic oxoester **7a** stereoselectively led to lactam **8a** in 59% yield (Scheme 3). Minor amounts (10%) of the isomeric lactam **9a** were also isolated. The H-8/H-8a coupling constant (∼9 Hz) in the ^1H NMR spectra of these lactams again was indicative of the trans relationship of these protons. Moreover, the configuration at the piperidine 3-position in **8a** was confirmed by X-ray crystallographic analysis of piperidine **10**,[15] which was obtained in 67% yield by reduction of **8a** with alane. Piperidine **10** was converted to the target drug (−)-3-PPP (preclamol) by catalytic hydrogenation in the presence of propionaldehyde followed by demethylation of the resulting *N*-alkylated piperidine **11**. Alternatively, hydrogenolysis of **10** in the presence of di-*tert*-butyl dicarbonate, followed by removal of the *N*-Boc protecting group of **12**, gave the *N*-unsubstituted piperidine **13**, which had previously been converted[9b] to (−)-3-PPP.[16] In a similar manner, for the sake of comparison,[16c] the minor lactam **9a** was converted to *ent*-**11** via the α*S*,3*R*-piperidine **14** (Scheme 4).

SCHEME 4



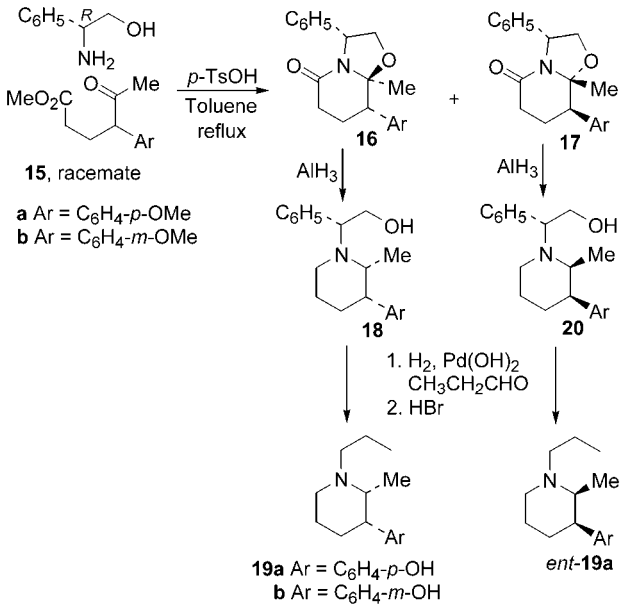
We then planned to extend the above methodology to the synthesis of preclamol analogues bearing an alkyl

(14) Cyclodehydration of crude mixtures containing esters **7b** and **7c** with (*S*)-phenylglycinol also occurred stereoselectively to give bicyclic lactames **8b** and **8c**, respectively, as the major products (85:15 approximate **8**/**9** ratios).

(15) The X-ray experiments were done on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo Kα radiation. The structure was solved by direct methods (SHELXS-97) after applying Lorentz, polarization, and absorption (semiempirical PSI scan method) corrections. Full-matrix least-squares refinement (SHELXL-97) with anisotropic thermal parameters for non-H atoms and riding thermal parameters for H-atoms (positioned at calculated positions) converged to *R* factors of 0.051 (for **10**) and 0.049 (for **16b**) (calculated for the reflections with $I > 2\sigma(I)$). **10**: crystal data, $C_{20}H_{26}ClNO_2$, monoclinic, space group $P2_1$, $a = 6.610(4)$ Å, $b = 24.892(8)$ Å, $c = 11.648(3)$ Å, $V = 1885(1)$ Å^3, $Z = 4$, μ(Mo Kα) = 0.214 mm^{-1}, $D_c = 1.226$ g/cm^3. Approximate dimensions: 0.10 × 0.18 × 0.35 mm^3. Data collection was up to a resolution of $2\theta = 52.4°$ producing 4088 reflections. The asymmetric unit contains two independent molecules. Largest peak and hole at the final difference Fourier synthesis were 0.233 and −0.375 e Å^{-3}. **16b**: crystal data, $C_{21}H_{23}NO_3$, monoclinic, space group *C*2, $a = 19.789(3)$ Å, $b = 7.393(9)$ Å, $c = 37.051(11)$ Å, $V = 5397(7)$ Å^3, $Z = 12$, μ(Mo Kα) = 0.083 mm^{-1}, $D_c = 1.246$ g/cm^3. Approximate dimensions: 0.5 × 0.3 × 0.06 mm^3. Data collection was up to a resolution of $2\theta = 60.8°$ producing 2160 reflections. The asymmetric unit contains three independent molecules. Largest peak and hole at the final difference Fourier synthesis were 0.317 and −0.234 e Å^{-3}.

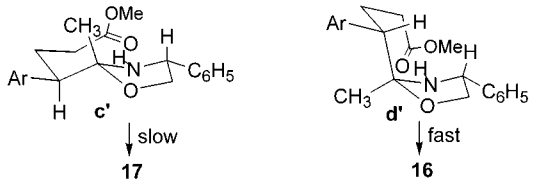
(16) (a) For syntheses of (−)-3-PPP via resolution of a racemate, see refs 7a and 9a−d. (b) For a previous enantioselective synthesis of (−)-3-PPP, see ref 7a. (c) An enantioselective synthesis of (−)-3-PPP has also been reported in ref 7b. This synthesis proceeds via the intermediates *ent*-**10**, *ent*-**13**, and *ent*-**11**, with an *R* configuration at the piperidine 3-position. In fact, the sign and absolute value of specific rotation of *ent*-**13**·HCl in this synthesis are in agreement with the data reported in the literature for the *R* enantiomer,[9b,d] whereas the [α] values of *ent*-**10** and *ent*-**11** reveal that these compounds are enantiomers of intermediates **10** and **11**, respectively, in our synthesis. Furthermore, the ^1H and ^{13}C NMR data reported for *ent*-**10** are identical with those of **10** (α*R*,3*S*; absolute configuration confirmed by X-ray crystallography)[15] but different from those of the diastereomer **14** (α*S*,3*R*). The *R* configuration of intermediates *ent*-**10**, *ent*-**13**, and *ent*-**11** is correctly depicted in the scheme of reference 7b, although these compounds are named as 3*S* in the Experimental Section. The above intermediates should unambiguously lead to the *R* enantiomer of 3-PPP, which is known[7a,9a−c] to be (X-ray) dextrorotatory. However, surprisingly, the article talks about the formation of levorotatory 3-PPP (depicted with the *R* configuration in the scheme but named as *S* in the Experimental Section).

SCHEME 5. Enantioselective Synthesis of *cis*-2-Alkyl-3-arylpiperidines



substituent at the piperidine 2-position, starting from appropriate racemic α-aryl ketones instead of aldehydes.[13] The required aryl ketoesters **15a** and **15b**, with a methoxy group at either the para or meta position of the phenyl ring, were prepared from the corresponding 1-phenyl-2-propanones, by reaction of the respective enolates with methyl acrylate. Cyclodehydration reaction of racemic esters **15a** and **15b** with (*R*)-phenylglycinol was most conveniently effected in the presence of catalytic amounts of *p*-TsOH to provide in each series a 4:1 mixture of bicyclic lactams **16** and **17** in yields higher than 70%, thus clearly indicating that a dynamic kinetic resolution had again occurred (Scheme 5). The absolute configuration of the major lactams was unambiguously proven by X-ray diffraction techniques from a crystal of **16b**,[15] whereas the cis relationship of the 8-aryl and 8a-alkyl substituents in the minor isomers **17** was evident after **17a** was converted to *ent*-**19a** (see below). Interestingly, the stereochemical outcome of these reactions involving keto esters differs from that observed in the above cyclodehydrations from aldehyde esters, as lactams with a cis 3-C_6H_5/8-aryl relationship are now formed as the major stereoisomers.[17] This result can be accounted for by considering that, when starting from ketones, lactamization of the diastereomeric oxazolidines in equilibrium occurs faster from **d′**, as this oxazolidine allows a less hindered approach (anti with respect both the C_6H_5 and CH_3 ring substituents) of the ester group to the nitrogen, via a chairlike transition state bearing an equatorial aryl substituent[18] (Scheme 6).

SCHEME 6



Lactams **16a** and **16b** proved to be convenient precursors of enantiopure *cis*-2-methyl-3-arylpiperidines. Thus, treatment of **16a** or **16b** with alane brought about both the reduction of the carbonyl lactam and the stereoselective opening of the oxazolidine ring, with retention of configuration,[17b] to give the respective *cis*-piperidines **18a** and **18b** in excellent yields. Only trace amounts of the corresponding epimers at C-2 were detected by NMR from the crude reaction mixtures. The cis relationship between the substituents at the piperidine 2 and 3 positions in **18** (and **20**, see below) was evident from the chemical shifts of the methyl and piperidine α carbons in the ^{13}C NMR spectra (Figure 1). Removal of the chiral auxiliary by hydrogenolysis with simultaneous introduction of the propyl substituent by reductive amination with propionaldehyde, followed by demethylation, led to the target preclamol analogues **19a** and **19b**. The above route constitutes an enantioselective entry to *cis*-2-alkyl-3-arylpiperidines. In a similar manner, the minor lactams **17a** and **17b** were converted into the corresponding piperidines **20**, and **20a** was elaborated into the *cis*-piperidine *ent*-**19a**.

In conclusion, cyclodehydration of racemic γ-aryl-δ-oxoesters with *R*- or *S*-phenylglycinol efficiently leads to enantiopure bicyclic δ-lactams, in a process that involves a dynamic kinetic resolution of the stereocenter α to the aldehyde or the ketone carbonyl group. Further elaboration of these substituted lactams provides the first general entry to enantiopure 3-aryl- and *cis*-2-alkyl-3-arylpiperidines.

Experimental Section

General Procedures. Melting points were determined in a capillary tube and are uncorrected. Unless otherwise indicated, NMR spectra were recorded at 200 or 300 MHz (^1H) and 50.3 or 75 MHz (^{13}C) and are reported downfield from TMS. Only noteworthy IR absorptions are listed. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located with aqueous potassium permanganate solution or with iodoplatinate reagent. All nonaqueous reactions were performed under an inert atmosphere. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried following standard procedures. Drying of the organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HRMS were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona.

Methyl 5-Oxo-4-phenylpentanoate (1). Phenylacetaldehyde (7.0 g, 58 mmol) was added over a 1-h period with a syringe pump to a cooled (0 °C) mixture of piperidine (14.3 mL, 145 mmol) and Na_2CO_3 (2.1 g, 20 mmol), and the mixture was stirred for 2 h at 0 °C. The solid was filtered through a Celite pad and the excess of piperidine was removed by distillation to give 1-styrylpiperidine (8,5 g, 78%). A solution of methyl acrylate (5.2 mL, 58 mmol) in anhydrous acetonitrile (15 mL) was slowly added to a stirred solution of the above

(17) Similar differences in stereoselectivity between unsubstituted aldehyde[10c] and keto acid derivatives[17a−c] have been observed in related cyclodehydrations: (a) Bahajaj, A. A.; Bailey, P. D.; Moore, M. H.; Morgan, K. M.; Vernon, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2511−2512. (b) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084−7085. (c) Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Lett.* **1999**, *40*, 739−742.

(18) For mechanistic considerations about the stereoselectivity in related cyclodehydrations from unsubstituted keto acids, see: Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413−1419.

enamine in anhydrous acetonitrile (32 mL) at 0 °C. The mixture was stirred at room temperature for 8 h, and then heated at reflux for 36 h. Glacial acetic acid (2.7 mL) and water (20 mL) were added, and the resulting solution was heated at reflux for 8 h. The mixture was allowed to cool to room temperature, the aqueous phase was saturated with NaCl, and the solution was extracted with Et_2O. The combined organic layers were successively washed with 5% aqueous HCl, 5% aqueous $NaHCO_3$, and brine, then dried, filtered, and concentrated to give a crude mixture. Distillation under reduced pressure (95−105 °C, 0.01 mmHg) afforded pure **1** (4.2 g, 45%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03 (m, 1H), 2.30 (m, 2H), 2.40 (m, 1H), 3.63 (m, 1H), 3.64 (s, 3H), 7.25−7.50 (m, 5H), 9.68 (d, J = 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 24.8 (CH_2), 31.2 (CH_2), 51.7 (CH_3), 58.0 (CH), 127.9 (CH), 128.9 (2 CH), 129.3 (2 CH), 135.1 (C), 178.8 (C), 199.9 (CH).

(3*R*,8*R*,8a*R*)-3,8-Diphenyl-5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (2). (*R*)-Phenylglycinol (2.7 g, 19.7 mmol) was added to a solution of oxoester **1** (4.0 g, 19.4 mmol) in anhydrous toluene (60 mL), and the mixture was heated at reflux for 24 h with azeotropic elimination of water produced by a Dean−Stark apparatus. The resulting suspension was filtered through a Celite pad, the solution was concentrated under reduced pressure, and the residue was taken up with AcOEt. The organic solution was washed with 5% aqueous Na_2CO_3, dried, and concentrated to give an oil. Flash chromatography (SiO_2 previously washed with 8:2 Et_3N−AcOEt; gradient from 7:3 AcOEt−hexane to AcOEt) afforded lactam **2** (2.8 g, 49%) and its 3*R*,8*S*,8*aS* diastereomer **3** (0.5 g, 9%). **2** (lower R_f): IR (film) 1658 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (m, 2H), 2.50 (ddd, J = 18.0, 10.5, 7.1 Hz, 1H), 2.58 (ddd, J = 18.0, 6.3, 3.3 Hz, 1H), 3.08 (ddd, J = 11.0, 9.2, 5.5 Hz, 1H), 4.00 (dd, J = 9.1, 1.2 Hz, 1H), 4.10 (dd, J = 9.1, 6.7 Hz, 1H), 4.93 (d, J = 9.2 Hz, 1H), 4.97 (dd, J = 6.7, 1.2 Hz, 1H), 7.20−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 26.0 (CH_2), 31.7 (CH_2), 45.7 (CH), 59.1 (CH), 73.7 (CH_2), 92.2 (CH), 126.4 (2 CH), 127.5 (CH), 127.6 (2 CH), 128.5 (2 CH), 128.7 (2 CH), 139.2 (C), 141.3 (C), 166.8 (C); $[\alpha]^{22}_D$ +80.5 (*c* 1.0, MeOH); mp 82−84 °C (Et_2O−hexane). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.69; H, 6.59; N, 4.86. **3** (higher R_f): IR (film) 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08 (dddd, J = 13.5, 6.8, 3.4, 1.5 Hz, 1H), 2.19 (dddd, J = 13.5, 12.6, 11.4, 6.0 Hz, 1H), 2.55 (ddd, J = 18.3, 11.4, 6.8 Hz, 1H), 2.71 (ddd, J = 18.3, 6.0, 1.5 Hz, 1H), 2.83 (ddd, J = 12.6, 8.7, 3.4 Hz, 1H), 3.70 (dd, J = 9.0, 8.0 Hz, 1H), 4.47 (dd, J = 9.0, 8.0 Hz, 1H), 5.03 (d, J = 8.7 Hz, 1H), 5.32 (t, J = 8.0 Hz, 1H), 7.20−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 24.8 (CH_2), 31.8 (CH_2), 46.1 (CH), 58.4 (CH), 72.4 (CH_2), 92.7 (CH), 126.1 (2 CH), 127.4 (2 CH), 127.5 (CH), 127.6 (2 CH), 128.7 (CH), 128.8 (2 CH), 139.4 (C), 139.5 (C), 168.4 (C); $[\alpha]^{22}_D$ −9.64 (*c* 0.25, MeOH); mp 160−162 °C (Et_2O−hexane). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.54; H, 6.61; N, 4.87.

(3*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-phenylpiperidine (4). To a solution of lactam **2** (350 mg, 1.19 mmol) in anhydrous THF (15 mL) was slowly added $LiAlH_4$ (145 mg, 3.8 mmol), and the resulting suspension was stirred at room temperature for 1 h. The reaction was quenched with 10% aqueous NaOH, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic solution was dried, filtered, and concentrated to give a yellow oil. Purification by flash chromatography (Et_2O) afforded pure piperidine **4** (242 mg, 72%) as a white solid: IR (film) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (qd, J = 12.6, 4.0 Hz, 1 H), 1.55−1.80 (m, 3H), 1.87 (dm, J = 12.6 Hz, 1 H), 2.33 (t, J = 11.0 Hz, 1 H), 2.80−3.02 (m, 3 H), 3.18 (br s, 1 H), 3.62 (dd, J = 10.2, 5.3 Hz, 1 H), 3.71 (dd, J = 10.2, 5.3 Hz, 1 H), 4.00 (t, J = 10.2 Hz, 1 H), 7.10−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 26.0 (CH_2), 31.4 (CH_2), 43.9 (CH), 46.2 (CH_2), 60.1 (CH_2), 60.5 (CH_2), 70.3 (CH), 126.4 (CH), 127.2 (2 CH), 127.8 (CH), 128.1 (2 CH), 128.4 (2 CH), 128.9 (2 CH), 135.4 (C), 144.3 (C); $[\alpha]^{22}_D$ −70.7 (*c* 0.6, MeOH); mp 60−62 °C (Et_2O−hexane). Anal. Calcd for $C_{19}H_{23}NO\cdot{}^1/_3H_2O$: C, 79.42; H, 8.30; N, 4.87. Found: C, 79.22; H, 8.21; N, 4.83.

(*R*)-3-Phenylpiperidine (5). A solution of compound **4** (200 mg, 0.71 mmol) in AcOEt (25 mL) containing 20% $Pd(OH)_2$/C (80 mg) was hydrogenated at 25 °C for 15 h. Then, more $Pd(OH)_2$/C (20 mg) was added and the resulting suspension was stirred under hydrogen for 10 additional hours. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated, and the resulting oil was purified by flash chromatography (98:2 AcOEt−DEA) to give pure 3-phenylpiperidine **5** (86 mg, 75%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (m, 2H), 1.85 (m, 1H), 1.90 (br, 1H), 2.00 (m, 1H), 2.67 (m, 3H), 3.10 (dm, J = 12.0 Hz, 1H), 3.18 (dm, J = 11.5 Hz, 1H), 7.15−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 27.1 (CH_2), 32.1 (CH_2), 44.3 (CH), 46.6 (CH_2), 54.1 (CH_2), 126.2 (CH), 127.1 (2 CH), 128.3 (2 CH), 144.9 (C). **5**·hydrochloride: IR (film) 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.66 (qd, J = 12.5, 4.0 Hz, 1H), 1.95−2.21 (m, 3H), 2.86 (masked, 1H), 2.91 (t, J = 12.5 Hz, 1H), 3.24 (tm, J = 12.5 Hz, 1H), 3.54 (m, 2H), 7.20−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 22.7 (CH_2), 30.3 (CH_2), 39.6 (CH), 43.9 (CH_2), 49.3 (CH_2), 126.9 (2 CH), 127.5 (CH), 128.9 (2 CH), 140.7 (C); $[\alpha]^{22}_D$ −10.3 (*c* 0.5, MeOH); mp 179−181 °C {lit.[8a] (for the (*S*)-enantiomer) $[\alpha]_D$ +12.2 (MeOH); mp 182 °C}. Anal. Calcd for $C_{11}H_{16}ClN$: C, 66.83; H, 8.16; N, 7.08. Found: C, 66.89; H, 7.96; N, 6.77.

(3*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-phenylpiperidine (6). Operating as described for **4**, starting from lactam **3** (74 mg, 0.25 mmol) piperidine **6** (50 mg, 70%) was obtained as a transparent oil after flash chromatography (Et_2O): IR (film) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (m, 1H), 1.76 (t, J = 11.2 Hz, 1H), 1.70−1.80 (m, 2H), 1.84 (dm, J = 12.8 Hz, 1H), 2.33 (m, 1H), 2.71 (tt, J = 11.2, 3.6 Hz, 1H), 2.92 (m, 2H), 3.05 (br s, 1H), 3.60 (dd, J = 10.2, 5.1 Hz, 1H), 3.75 (dd, J = 10.2, 5.1 Hz, 1H), 3.96 (t, J = 10.2 Hz, 1H), 7.10−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 26.3 (CH_2), 31.8 (CH_2), 43.5 (CH), 53.0 (CH_2), 53.3 (CH_2), 60.0 (CH_2), 70.2 (CH), 126.3 (CH), 127.2 (2 CH), 127.8 (CH), 128.1 (2 CH), 128.3 (2 CH), 128.9 (2 CH), 135.3 (C), 144.5 (C); $[\alpha]^{22}_D$ +11.2 (*c* 0.6, MeOH); HRMS calcd for $C_{19}H_{23}NO$ 281.1775, found 281.1779.

Methyl 4-(3-Methoxyphenyl)-5-oxopentanoate (7a). A mixture of (3-methoxyphenyl)acetaldehyde[19] (1.8 g, 12 mmol), anhydrous Na_2CO_3 (445 mg, 4.2 mmol), and pyrrolidine (2.5 mL, 30 mmol), containing 4 Å molecular sieves, was stirred at 0 °C for 2 h. The solids were filtered through a Celite pad, and the excess of pyrrolidine was removed by distillation to give a crude enamine (2.17 g, 89%). A mixture of this enamine and methyl acrylate (1.9 mL, 21.4 mmol) in anhydrous EtOH (3.8 mL) containing 4 Å molecular sieves was heated in a sealed tube at 80 °C for 14 h. Then, acetic acid (0.6 mL) and water (5.0 mL) were added, and the resulting mixture was heated at 80 °C for 3 h and filtered. The solution was concentrated to give a residue, which was dissolved in Et_2O. The ethereal solution was washed with 2 N aqueous HCl and brine, dried, and concentrated to give an orange oil. Distillation of this oil (120−125 °C, 0.5 mmHg) afforded aldehyde ester **7a** (934 mg, 37%) as a transparent oil: IR (film) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02 (m, 1H), 2.30 (m, 2H), 2.38 (m, 1H), 3.59 (m, 1H), 3.65 (s, 3H), 3.80 (s, 3H), 6.71 (m, 1H), 6.77 (dm, J = 8.0 Hz, 1H), 6.84 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 7.27 (t, J = 8.3 Hz, 1H), 9.67 (d, J = 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 24.6 (CH_2), 31.1 (CH_2), 51.6 (CH_3), 55.1 (CH_3), 57.9 (CH), 113.1 (CH), 114.6 (CH), 121.1 (CH), 130.2 (CH), 136.7 (C), 160.1 (C), 173.3 (C), 199.7 (CH); HRMS calcd for $C_{13}H_{16}O_4$ 236.1048, found 236.1048.

(19) This aldehyde was prepared in 60% overall yield by epoxidation of *m*-methoxybenzaldehyde[19a] followed by treatment of the resulting epoxide with $LiClO_4\cdot Et_2O$:[19b] (a) Alvarez, M.; Granados, R.; Lavilla, R.; Salas, M. *J. Heterocycl. Chem*. **1985**, *22*, 745−750. (b) Sudha, R.; Narasimhan, K. M.; Saraswathy, V. G.; Sankararaman, S. *J. Org. Chem*. **1996**, *61*, 1877−1879.

(3*S*,8*S*,8a*S*)-8-(3-Methoxyphenyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (8a). Operating as described for **2**, starting from pure **7a** (317 mg, 1.34 mmol) and (*S*)-phenylglycinol (184 mg, 1.34 mmol) in toluene (6.7 mL), lactam **8a** (238 mg, 59%) and its 3*S*,8*R*,8a*R* diastereomer **9a** (44 mg, 10%) were obtained after flash chromatography (SiO_2 previously washed with 8:2 Et_3N−AcOEt; gradient from 7:3 AcOEt−hexane to AcOEt). **8a** (lower R_f): IR (film) 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.03−2.16 (m, 2H), 2.40−2.56 (m, 2H), 3.04 (ddd, J = 11.5, 9.1, 4.7 Hz, 1H), 3.82 (s, 3H), 3.98 (dd, J = 9.1, 1.3 Hz, 1H), 4.02 (dd, J = 9.1, 6.7 Hz, 1H), 4.88 (d, J = 9.1 Hz, 1H), 4.93 (dd, J = 6.7, 1.3 Hz, 1H), 6.84 (ddd, J = 8.2, 2.4, 0.8 Hz, 1H), 6.90 (m, 1H), 6.95 (dm, J = 7.7 Hz, 1H), 7.24−7.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 26.0 (CH_2), 31.6 (CH_2), 45.6 (CH), 55.1 (CH_3), 59.0 (CH), 73.7 (CH_2), 92.0 (CH), 112.4 (CH), 113.6 (CH), 119.7 (CH), 126.3 (2 CH), 127.5 (CH), 128.5 (2 CH), 129.7 (CH), 140.7 (C), 141.2 (C), 159.7 (C), 166.9 (C); $[\alpha]^{22}_D$ −91.9 (*c* 0.82, MeOH). Anal. Calcd for $C_{20}H_{21}NO_3 \cdot H_2O$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.74; H, 6.79; N, 4.10. **9a** (higher R_f): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.04−2.24 (m, 2H), 2.53 (ddd, J = 18.4, 11.3, 7.1 Hz, 1H), 2.70 (ddd, J = 18.4, 6.0, 2.0 Hz, 1H), 2.79 (ddd, J = 12.4, 8.7, 3.6 Hz, 1H), 3.70 (dd, J = 9.1, 7.8 Hz, 1H), 3.82 (s, 3H), 4.47 (dd, J = 9.1, 7.8 Hz, 1H), 5.02 (d, J = 8.6 Hz, 1H), 5.30 (t, J = 7.8 Hz, 1H), 6.83−6.88 (m, 2H), 6.90 (d, J = 7.6 Hz, 1H), 7.21−7.36 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 24.9 (CH_2), 31.8 (CH_2), 46.2 (CH), 55.2 (CH_3), 58.5 (CH), 72.5 (CH_2), 92.6 (CH), 112.5 (CH), 113.6 (CH), 119.7 (CH), 126.2 (2 CH), 127.6 (CH), 128.8 (2 CH), 129.8 (CH), 139.4 (C), 141.2 (C), 159.8 (C), 168.4 (C); $[\alpha]^{22}_D$ +15.8 (*c* 0.12, MeOH); HRMS calcd for $C_{20}H_{21}NO_3$ 323.1518, found 323.1521.

(3*S*)-1-[(1*S*)-2-Hydroxy-1-phenylethyl]-3-(3-methoxyphenyl)piperidine (10). $LiAlH_4$ (752 mg, 20 mmol) was slowly added to a cooled (0 °C) suspension of $AlCl_3$ (880 mg, 6.6 mmol) in anhydrous THF (66 mL), and the mixture was stirred at room temperature for 30 min. The temperature was lowered to −78 °C, lactam **8a** (1.0 g, 3.3 mmol) was added, and the resulting suspension was stirred at −78 °C for 90 min and at room temperature for 2 h. The mixture was cooled to 0 °C, and the reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were dried and concentrated to give a foam. Flash chromatography (1:1 AcOEt−hexane) afforded pure piperidine **10** (751 mg, 78%): IR (film) 3429 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (qd, J = 12.1, 3.9 Hz, 1H), 1.70−1.84 (m, 3H), 1.89 (dm, J = 12.5 Hz, 1H), 2.35 (t, J = 11.0 Hz, 1H), 2.95−3.06 (m, 3H), 3.67 (dd, J = 10.4, 4.2 Hz, 1H), 3.78 (masked, 1H), 3.79 (s, 3H), 4.07 (t, J = 10.4 Hz, 1H), 6.74 (m, 1H), 6.77 (m, 1H), 6.79 (m, 1H), 7.16−7.24 (m, 3H), 7.33−7.35 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 25.9 (CH_2), 31.3 (CH_2), 43.9 (CH), 45.9 (CH_2), 55.1 (CH_3), 59.9 (CH_2), 60.5 (CH_2), 70.2 (CH), 111.4 (CH), 113.2 (CH), 119.6 (CH), 127.8 (CH), 128.1 (2 CH), 128.9 (2 CH), 129.3 (CH), 135.1 (C), 145.9 (C), 159.6 (C); $[\alpha]^{22}_D$ +83.5 (*c* 1.9, $CHCl_3$). **10**·Hydrochloride: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (qd, J = 12.7, 3.1 Hz, 1H), 1.96−2.08 (m, 2H), 2.42−2.64 (m, 3H), 3.71 (m, 2H), 3.79 (s, 3H), 4.11 (dm, J = 12.8 Hz, 1H), 4.38−4.55 (m, 2H), 5.21 (m, 1H), 6.70−6.80 (m, 3H), 7.26 (m, 1H), 7.39 (m, 2H), 7.46 (m, 3H), 11.4 (br s, 1H); $[\alpha]^{22}_D$ +86.6 (*c* 1.16, $CHCl_3$); mp 155−157 °C (CH_2Cl_2-Et_2O). Anal. Calcd for $C_{20}H_{26}ClNO_2$: C, 69.05; H, 7.53; N, 4.03. Found: C, 68.69; H, 7.58; N, 3.99.

(*S*)-3-(3-Methoxyphenyl)-1-propylpiperidine (11). To a solution of piperidine **10** (297 mg, 0.95 mmol) in AcOEt (10 mL) containing 20% $Pd(OH)_2/C$ (119 mg) was added propionaldehyde (0.27 mL, 3.8 mmol), and the mixture was hydrogenated at 25 °C for 20 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give a yellow oil (314 mg). Flash chromatography (from 4:1 to 7:3 hexane−DEA) afforded pure compound **11** (133 mg, 60%): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 7.3 Hz, 3H), 1.43 (qd, J = 12.3, 4.5 Hz, 1H), 1.50−1.60 (m, 2H), 1.68−1.81 (m, 2H), 1.88−1.97 (m, 2H), 1.95 (t, J = 11.4 Hz, 1H), 2.31 (m, 2H), 2.81 (tt, J = 11.4, 3.6 Hz, 1H), 2.99 (dm, J = 11.2 Hz, 1H), 3.03 (dm, J = 11.4 Hz, 1H), 3.79 (s, 3H), 6.72−6.86 (m, 3H), 7.21 (t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 12.0 (CH_3), 20.0 (CH_2), 25.7 (CH_2), 31.6 (CH_2), 42.9 (CH), 53.9 (CH_2), 55.1 (CH_3), 61.1 (CH_2), 61.2 (CH_2), 111.2 (CH), 113.2 (CH), 119.6 (CH), 129.2 (CH), 146.5 (C), 159.5 (C); $[\alpha]^{22}_D$ +7.2 (*c* 2.3, $CHCl_3$). **11**·hydrochloride: IR (film) 3410 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, J = 7.3 Hz, 3H), 1.67 (qm, J = 11.8 Hz, 1H), 1.97 (m, 3H), 2.13 (dm, J = 11.0 Hz, 1H), 2.45−2.78 (m, 3H), 2.93 (m, 2H), 3.59 (m, 3H), 3.79 (s, 3H), 6.78−6.83 (m, 3H), 7.25 (t, J = 10.0 Hz, 1H), 12.38 (br s); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 11.2 (CH_3), 17.0 (CH_2), 22.6 (CH_2), 29.5 (CH_2), 39.5 (CH), 52.7 (CH_2), 55.3 (CH_3), 57.8 (CH_2), 59.4 (CH_2), 112.8 (CH), 112.9 (CH), 119.0 (CH), 129.9 (CH), 141.9 (C), 159.9 (C); $[\alpha]^{22}_D$ −6.9 (*c* 1.76, MeOH) {lit.[7a] $[\alpha]^{20}_D$ −6.5 (*c* 2.6, MeOH); lit.[9b] $[\alpha]^{22}_D$ −6.7 (*c* 2.1, MeOH); lit.[9d] (for the hydrobromide) $[\alpha]^{25}_D$ −6.7 (*c* 3.0, MeOH)}; mp 198−200 °C (CH_2Cl_2−Et_2O). Anal. Calcd for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.49; H, 8.83; N, 5.24.

(*S*)-3-(3-Hydroxyphenyl)-1-propylpiperidine [(−)-3-PPP]. A solution of piperidine **11** (77 mg, 0.33 mmol) in 48% HBr was heated at reflux for 90 min. After cooling, the resulting solution was basified by dropwise addition of saturated aqueous Na_2CO_3. The mixture was extracted with Et_2O, and the resulting ethereal solution was dried, filtered, and concentrated to give (−)-3-PPP (58 mg, 72%): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 7.3 Hz, 3H), 1.42−1.65 (m, 3H), 1.80 (m, 2H), 1.98 (t, J = 11.4 Hz, 1H), 1.94−2.05 (m, 2H), 2.37 (m, 2H), 2.93 (tt, J = 11.4, 3.5 Hz, 1H), 3.07 (dm, J = 11.2 Hz, 1H), 3.23 (dm, J = 11.4, 1H), 6.65−6.83 (m, 3H), 7.18 (t, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 12.0 (CH_3), 19.2 (CH_2), 25.2 (CH_2), 29.8 (CH_2), 41.7 (CH), 54.0 (CH_2), 61.2 (CH_2), 61.4 (CH_2), 114.2 (CH), 114.6 (CH), 117.4 (CH), 129.8 (CH), 145.4 (C), 156.8 (C); $[\alpha]^{22}_D$ −8.9 (*c* 1.2, MeOH). The hydrochloride was obtained by treatment of the crude reaction mixture with an ethereal solution of HCl: IR (film) 3470 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, J = 7.3 Hz, 3H), 1.68 (qd, J = 12.3, 3.0 Hz, 1H), 1.87 (m, 1H), 2.02 (m, 1H), 2.25 (qm, J = 13.0 Hz, 1H), 2.75 (t, J = 12.0 Hz, 1H), 2.71−2.83 (m, 1H), 2.96 (m, 2H), 3.35 (tt, J = 12.0, 3.2 Hz, 1H), 3.51 (dm, J = 12.0 Hz, 1H), 3.60 (dm, J = 11.2, 1H), 6.65−6.79 (m, 3H), 7.14 (dd, J = 8.7, 7.6 Hz, 1H), 10.83 (br s); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 10.9 (CH_3), 17.0 (CH_2), 22.7 (CH_2), 28.9 (CH_2), 39.6 (CH), 52.4 (CH_2), 57.9 (CH_2), 59.1 (CH_2), 114.1 (CH), 114.7 (CH), 117.5 (CH), 129.8 (CH), 141.4 (C), 157.3 (C); $[\alpha]^{22}_D$ −6.8 (*c* 0.68, MeOH) {lit.[7a] $[\alpha]^{20}_D$ −6.8 (*c* 2.1, MeOH); lit.[9a,c] $[\alpha]^{20}_D$ −7.4 (*c* 2.2, MeOH); lit.[9b] $[\alpha]^{22}_D$ −7.1 (*c* 2.2, MeOH)}.

(*S*)-1-(*tert*-Butoxycarbonyl)-3-(3-methoxyphenyl)piperidine (12). A solution of piperidine **10** (190 mg, 0.61 mmol) and di-*tert*-butyl dicarbonate (278 mg, 1.3 mmol) in anhydrous AcOEt (21 mL) containing 20% $Pd(OH)_2/C$ (47 mg) was hydrogenated at room temperature for 15 h. The catalyst was removed by filtration and washed with hot MeOH. The combined organic solutions were concentrated to give a yellow oil, which was chromatographed (gradient from hexane to 1:1 hexane−AcOEt) affording pure *N*-Boc piperidine **12** (127 mg, 71%) as a transparent oil: IR (film) 1694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 1.59 (m, 2H), 1.75 (m, 1H), 2.02 (m, 1H), 2.60−2.76 (m, 2H), 2.74 (t, J = 11.5 Hz, 1H), 3.80 (s, 3H), 4.17 (m, 2H), 6.78 (m, 3H), 7.23 (dd, J = 7.1, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 25.4 (CH_2), 28.4 (3 CH_3), 31.7 (CH_2), 42.5 (CH), 44.1 (CH_2), 50.5 (CH_2), 55.1 (CH_3), 79.4 (C), 111.6 (CH), 113.0 (CH), 119.4 (CH), 129.4 (CH), 145.2 (C), 154.7 (C), 159.6 (C); $[\alpha]^{22}_D$ −50.7 (*c* 0.8, $CHCl_3$).

(*S*)-3-(3-Methoxyphenyl)piperidine (13). To a solution of carbamate **12** (107 mg, 0.36 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was added TFA (2.0 mL, 26 mmol), and the mixture was stirred at room temperature for 15 min. The solution was basified by slow addition of saturated aqueous Na_2CO_3, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried and the solvent was removed under reduced pressure. The resulting yellow oil was purified by flash

chromatography (98:2 AcOEt−DEA) to give compound **13** (42 mg, 60%): IR (film) 3390 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61 (m, 2H), 1.78 (m, 1H), 2.01 (m, 1H), 2.19 (br s, 1H), 2.59−2.74 (m, 3H), 3.10 (dm, J = 12.3 Hz, 1H), 3.17 (dm, J = 7.5 Hz, 1H), 3.79 (s, 3H), 6.74−6.83 (m, 3H), 7.23 (td, J = 7.6, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 26.8 (CH_2), 31.9 (CH_2), 44.2 (CH), 46.5 (CH_2), 53.7 (CH_2), 55.1 (CH_3), 111.2 (CH), 113.1 (CH), 119.5 (CH), 129.3 (CH), 146.4 (C), 159.6 (C); $[\alpha]^{22}_D$ +6.2 (*c* 0.75, MeOH). **13**·hydrochloride: mp 170−172 °C (CH_2Cl_2−Et_2O); $[\alpha]^{22}_D$ +9.3 (*c* 2.1, MeOH) {lit.[9b] $[\alpha]^{22}_D$ +10.1 (*c* 2.1, MeOH); lit.[9d] $[\alpha]^{25}_D$ +10.3 (*c* 1.48, MeOH)}. Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 62.97; H, 7.88; N, 6.06.

(3*R*)-1-[(1*S*)-2-Hydroxy-1-phenylethyl]-3-(3-methoxyphenyl)piperidine (14). Operating as described for the reduction of **8a** to give **10**, starting from minor lactam **9a** (120 mg, 0.38 mmol) pure piperidine **14** (71 mg, 60%) was obtained after flash chromatography (1:1 AcOEt−hexane): IR (film) 3500 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (m, 1H), 1.75−1.89 (m, 4H), 2.40 (td, J = 11.3, 3.6 Hz, 1H), 2.85 (m, 1H), 3.05 (m, 2H), 3.67 (m, 2H), 3.78 (s, 3H), 3.98 (t, J = 10.4 Hz, 1H), 6.69−7.81 (m, 3H), 7.10−7.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 26.2 (CH_2), 31.6 (CH_2), 43.5 (CH), 53.0 (CH_2), 53.1 (CH_2), 55.1 (CH_3), 59.9 (CH_2), 70.2 (CH), 111.4 (CH), 113.3 (CH), 119.6 (CH), 127.6 (CH), 127.9 (CH), 128.4 (2 CH), 129.0 (2 CH), 135.0 (C), 146.0 (C), 159.5 (C); $[\alpha]^{22}_D$ −25.7 (*c* 0.29, $CHCl_3$).

(3*R*)-3-(3-Methoxyphenyl)-1-propylpiperidine (*ent*-11). Following the procedure described for the preparation of **11**, starting from piperidine **14** (59 mg, 0.19 mmol) pure compound *ent*-**11** (20 mg, 45%) was obtained after flash chromatography: $[\alpha]^{22}_D$ −5.5 (*c* 1.15, $CHCl_3$). *ent*-**11**·hydrochloride: $[\alpha]^{22}_D$ +6.25 (*c* 1.28, MeOH) {lit.[9b] $[\alpha]^{22}_D$ +6.4 (*c* 2.1, MeOH)}.

(3*R*,8*S*,8a*S*)-8-(4-Methoxyphenyl)-8a-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (16a). To a mixture of methyl 4-(4-methoxyphenyl)-5-oxohexanoate[20] (**15a**; 1.0 g, 4.0 mmol) and (*R*)-phenylglycinol (660 mg, 4.8 mmol) in anhydrous toluene (8 mL) was added a catalytic amount of *p*-TsOH. The mixture was heated at reflux for 14 h, cooled, and concentrated under reduced pressure. The residue was dissolved in AcOEt, washed with 5% aqueous $NaHCO_3$, and dried. Removal of the solvent followed by flash chromatography (95:5 Et_2O−DEA) afforded pure lactam **16a** (822 mg, 61%) and its 3*R*,8*R*,8a*R* diastereomer **17a** (200 mg, 15%). **16a** (higher R_f): IR (film) 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (s, 3H), 2.11 (dddd, J = 14.0, 8.1, 3.3, 1.5 Hz, 1H), 2.34 (dddd, J = 14.0, 14.0, 10.2, 7.0 Hz, 1H), 2.61 (ddd, J = 18.0, 10.2, 8.1 Hz, 1H), 2.80 (ddm, J = 18.0, 7.0 Hz, 1H), 3.05 (dd, J = 14.0, 3.3 Hz, 1H), 3.80 (s, 3H), 3.88 (dd, J = 9.0, 8.1 Hz, 1H), 4.56 (t, J = 9.0 Hz, 1H), 5.42 (t, J = 8.1 Hz, 1H), 6.90 (dm, J = 8.7 Hz, 2H), 7.20−7.35 (m, 7H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 18.9 (CH_3), 22.4 (CH_2), 31.2 (CH_2), 48.9 (CH), 54.9 (CH_3), 58.9 (CH), 69.4 (CH_2), 95.6 (C), 113.4 (2 CH), 125.2 (2 CH), 126.9 (CH), 128.4 (2 CH), 129.4 (2 CH), 130.6 (C), 139.5 (C), 158.6 (C), 168.8 (C); $[\alpha]^{22}_D$ −60.4 (*c* 1.25, MeOH); mp 115−117 °C (THF−Et_2O). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 75.00; H, 6.87; N, 4.10. **17a** (lower R_f): IR (film) 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 3H), 2.11 (dddd, J = 13.5, 8.5, 4.8, 2.5 Hz, 1H), 2.31 (m, 1H), 2.50 (ddd, J = 18.3, 8.5, 8.5 Hz, 1H), 2.56 (ddd, J = 18.3, 8.5, 2.5 Hz, 1H), 3.33 (dd, J = 13.5, 4.8 Hz, 1H), 3.81 (s, 3H), 3.99 (dd, J = 9.3, 2.0 Hz, 1H), 4.40 (dd, J = 9.3, 7.5 Hz, 1H), 5.00 (dd, J = 7.5, 2.0 Hz, 1H), 6.93 (dm, J = 8.7 Hz, 2H), 7.23−7.39 (m, 7H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 18.4 (CH_3), 22.9 (CH_2), 30.8 (CH_2), 48.6 (CH), 55.1 (CH_3), 59.3 (CH), 71.2 (CH_2), 95.1 (C), 113.6 (2 CH), 126.3 (2 CH), 127.4 (CH), 128.5 (2 CH), 129.7 (2 CH), 130.4 (C), 141.6 (C), 158.9 (C), 166.8 (C); $[\alpha]^{22}_D$ +113.6 (*c* 1.0, MeOH); mp 95−97 °C (hexanes−Et_2O). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.72; H, 6.83; N, 4.25.

(3*R*,8*S*,8a*S*)-8-(3-Methoxyphenyl)-8a-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (16b). Operating as described for **16a**, from methyl 4-(3-methoxyphenyl)-5-oxohexanoate[20] (**15b**; 672 mg, 1.9 mmol), lactams **16b** (534 mg, 59%) and **17b** (130 mg, 14%) were obtained after flash chromatography (3:1 AcOEt−hexane). **16b** (higher R_f): IR (KBr) 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (s, 3H), 2.11 (dddd, J = 13.5, 7.8, 3.3, 1.5 Hz, 1H), 2.34 (dddd, J = 13.5, 13.5, 10.5, 7.8 Hz, 1H), 2.59 (ddd, J = 18.6, 10.5, 7.8 Hz, 1H), 2.82 (ddm, J = 18.6, 7.8 Hz, 1H), 3.06 (dd, J = 13.5, 3.3 Hz, 1H), 3.80 (s, 3H), 3.87 (dd, J = 9.0, 8.0 Hz, 1H), 4.55 (t, J = 9.0 Hz, 1H), 5.42 (t, J = 8.0 Hz, 1H), 6.83 (ddd, J = 8.4, 3.0, 0.9 Hz, 1H), 6.90−6.95 (m, 2H), 7.19−7.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 19.2 (CH_3), 22.4 (CH_2), 31.3 (CH_2), 49.8 (CH), 55.0 (CH_3), 58.9 (CH), 69.5 (CH_2), 95.6 (C), 111.9 (CH), 115.1 (CH), 120.9 (CH), 125.3 (2 CH), 127.0 (CH), 128.4 (2 CH), 128.9 (CH), 139.6 (C), 140.2 (C), 159.1 (C), 168.8 (C); $[\alpha]^{22}_D$ −60.6 (*c* 2.0, MeOH); mp 98−100 °C (THF−Et_2O). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.93; H, 6.89; N, 4.13. **17b** (lower R_f): IR (film) 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (s, 3H), 2.13 (m, 1H), 2.32 (m, 1H), 2.48 (m, 1H), 2.57 (ddd, J = 18.0, 8.7, 2.0 Hz, 1H), 3.34 (dd, J = 13.2, 3.9 Hz, 1H), 2.82 (s, 3H), 3.99 (dd, J = 9.0, 2.0 Hz, 1H), 4.40 (dd, J = 9.0, 7.5 Hz, 1H), 4.99 (dd, J = 7.5, 2.0 Hz, 1H), 6.86 (ddd, J = 8.4, 2.4, 0.6 Hz, 1H), 6.99−7.03 (m, 2H), 7.24−7.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 18.6 (CH_3), 22.8 (CH_2), 30.8 (CH_2), 49.4 (CH), 55.1 (CH_3), 59.2 (CH), 71.2 (CH_2), 94.9 (C), 111.9 (CH), 115.3 (CH), 121.1 (CH), 126.2 (2 CH), 127.3 (CH), 128.4 (2 CH), 128.9 (CH), 139.9 (C), 141.4 (C), 159.2 (C), 166.5 (C); $[\alpha]^{22}_D$ +122.8 (*c* 1.0, MeOH). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.58; H, 6.88; N, 4.09.

(2*R*,3*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-(4-methoxyphenyl)-2-methylpiperidine (18a). Operating as described for the reduction of lactam **8a**, starting from lactam **16a** (763 mg, 2.26 mmol) pure piperidine **18a** (610 mg, 83%) was obtained after flash chromatography (4:1 AcOEt−hexane). A fraction (79 mg, 11%) of **18a** containing trace amounts of the C-2 epimer was also obtained. **18a**: IR (film) 3402 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.60 (d, J = 6.6 Hz, 3H), 1.68 (m, 2H), 1.83 (m, 2H), 2.70 (td, J = 11.4, 3.3 Hz, 1H), 2.77 (dm, J = 11.4 Hz, 1H), 2.95−3.08 (m, 2H), 3.69−3.80 (m, 2H), 3.73 (s, 3H), 3.91 (dd, J = 10.5, 5.0 Hz, 1H), 6.78 (dm, J = 8.7 Hz, 2H), 7.02 (dm, J = 8.7 Hz, 2H), 7.24−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 6.5 (CH_3), 23.8 (CH_2), 25.5 (CH_2), 42.6 (CH_2), 45.4 (CH), 55.1 (CH_3), 55.2 (CH), 63.1 (CH_2), 66.4 (CH), 113.4 (2 CH), 127.5 (CH), 128.3 (2 CH), 128.4 (2 CH), 128.7 (2 CH), 136.0 (C), 140.0 (C), 157.7 (C); $[\alpha]^{22}_D$ −60.9 (*c* 1.12, MeOH). **18a**·hydrochloride: ^1H NMR ($CDCl_3$, 200 MHz, broad signals) δ (most significant signals) 0.87 (d, J = 6.4 Hz, 3H), 3.00 (tm, J = 13.0 Hz, 1H), 3.75 (s, 3H), 3.95 (dd, J = 12.4, 3.2 Hz, 1H), 4.55 (dd, J = 12.4, 7.2 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 7.0 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$−CD_3OD, 75.4 MHz, broad signals) δ 6.0 (CH_3), 21.3 (CH_2), 22.5 (CH_2), 42.5 (CH_2), 46.3 (CH), 55.2 (CH_3), 59.0 (CH), 63.5 (CH_2), 71.0 (CH), 113.8 (2 CH), 128.5 (CH), 128.7 (2 CH), 129.0 (2 CH), 129.2 (2 CH), 132.9 (C), 144.1 (C), 158.3 (C); $[\alpha]^{22}_D$ −75.4 (*c* 0.65, MeOH); mp 238−240 °C (acetone−MeOH). Anal. Calcd for $C_{21}H_{28}ClNO_2$: C, 69.69; H, 7.80; N, 3.87. Found: C, 69.30; H, 7.84; N, 3.88.

(2*R*,3*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-(3-methoxyphenyl)-2-methylpiperidine (18b). Operating as described for the reduction of lactam **8a**, starting from lactam **16b** (348 mg, 1.03 mmol) piperidine **18b** (275 mg, 82%) impurified by trace amounts of the C-2 epimer was obtained after flash chromatography (9:1 Et_2O−hexane). Pure piperidine **18b** was obtained by crystallization of the hydrochloride (acetone−MeOH). **18b**: IR (film) 3410 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.62 (d, J = 6.6 Hz, 3H), 1.71 (m, 2H), 1.86 (m, 2H), 2.61 (br s, 1H), 2.71 (td, J = 11.4, 3.9 Hz, 1H), 2.82 (dm, J = 11.4 Hz,

(20) Keto esters **15a** and **15b** were prepared in 65% yield by reaction of the corresponding 1-(methoxyphenyl)-2-propanones with methyl acrylate in the presence of NaH.

1H), 3.03 (dt, J = 11.0, 4.0 Hz, 1H), 3.08 (m, 1H), 3.74 (s, 3H), 3.71−3.80 (m, 2H), 3.91 (dd, J = 10.5, 5.0 Hz, 1H), 6.65−6.70 (m, 2H), 7.14 (t, J = 7.8 Hz, 1H), 7.24−7.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 6.5 (CH_3), 23.5 (CH_2), 25.4 (CH_2), 42.6 (CH_2), 46.1 (CH), 54.9 (CH), 55.1 (CH_3), 63.2 (CH_2), 66.5 (CH), 110.6 (CH), 113.9 (CH), 120.2 (CH), 127.5 (CH), 128.2 (2 CH), 128.3 (2 CH), 128.8 (CH), 139.8 (C), 145.5 (C), 159.2 (C); $[\alpha]^{22}_D$ −55.1 (*c* 0.8, MeOH). **18b**·hydrochloride: ^{1}H-RMN ($CDCl_3$, 300 MHz, broad signals) δ 0.85 (d, J = 6.9 Hz, 3H), 1.82−2.00 (m, 4H), 2.80 (m, 1H), 3.06 (m, 1H), 3.53 (m, 1H), 3.72 (s, 3H), 3.95 (dm, J = 12.3 Hz, 1H), 4.06 (s, 1H), 4.16 (dm, J = 13.0 Hz, 1H), 4.36 (dm, J = 13.0 Hz, 1H), 4.57 (m, 1H), 4.78 (br s, 1H), 6.59 (s, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.72 (dd, J = 8.0, 2.1 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.42 (m, 3H), 7.77 (d, J = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 5.4 (CH_3), 20.7 (CH_2), 22.3 (CH_2), 42.6 (CH_2), 47.0 (CH), 55.2 (CH_3), 59.1 (CH), 63.2 (CH_2), 71.7 (CH), 112.2 (CH), 113.7 (CH), 119.9 (CH), 129.3 (2 CH), 129.4 (CH), 129.6 (2 CH), 132.5 (C), 142.0 (C), 160.1 (C); $[\alpha]^{22}_D$ −18.5 (*c* 0.5, MeOH); mp 168−170 °C. Anal. Calcd for $C_{21}H_{28}ClNO_2$: C, 69.69; H, 7.80; N, 3.87. Found: C, 69.29; H, 7.79; N, 3.77.

(2*R*,3*S*)-3-(4-Hydroxyphenyl)-2-methyl-1-propylpiperidine (19a). Operating as described in the preparation of **11**, piperidine **18a** (200 mg, 0.62 mmol) was converted to the corresponding *N*-propylpiperidine, which was obtained in 79% yield (120 mg) after flash chromatography (95:5 Et_2O−DEA): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.69 (d, J = 6.6 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H), 1.60 (m, 2H), 1.70−1.90 (m, 4H), 2.40−2.54 (m, 3H), 2.67 (dt, J = 11.7, 4.2 Hz, 1H), 3.11−3.24 (m, 2H), 3.83 (s, 3H), 6.89 (dm, J = 8.4 Hz, 2H), 7.19 (dm, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 3.8 (CH_3), 12.0 (CH_3), 20.7 (CH_2), 23.2 (CH_2), 25.5 (CH_2), 45.0 (CH), 45.7 (CH_2), 55.2 (CH_3), 57.1 (CH_2), 58.0 (CH), 113.5 (2 CH), 128.6 (2 CH), 136.3 (C), 157.7 (C); $[\alpha]^{22}_D$ +5.3 (*c* 0.89, MeOH); HRMS calcd for $C_{16}H_{25}NO$ 247.1936, found 247.1941. Operating as described in the preparation of (−)-3-PPP, the above *N*-propylpiperidine (90 mg, 0.36 mmol) was converted into piperidine **19a** in 94% yield (80 mg): IR (film) 3220 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.72 (d, J = 6.9 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H), 1.64 (m, 3H), 1.79 (m, 3H), 2.48 (m, 3H), 2.75 (dm, J = 11.1 Hz, 1H), 3.17 (m, 1H), 3.38 (m, 1H), 6.83 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.75 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 3.3 (CH_3), 11.9 (CH_3), 19.4 (CH_2), 22.1 (CH_2), 24.7 (CH_2), 43.8 (CH), 45.9 (CH_2), 56.9 (CH_2), 57.5 (CH), 115.6 (2 CH), 128.5 (2 CH), 133.8 (C), 155.4 (C); $[\alpha]^{22}_D$ +3.7 (*c* 1.0, MeOH). **19a**·hydrochloride: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.0 (d, J = 7.0 Hz, 3H), 1.01 (t, J = 7.0 Hz, 3H), 1.81−2.05 (m, 6H), 2.20 (m, 1H), 2.85−3.00 (m, 3H), 3.32 (dm, J = 10.5 Hz, 1H), 3.67 (m, 1H), 3.90 (br s, 1H), 6.82 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 5.0 (CH_3), 10.9 (CH_3), 17.4 (CH_2), 20.7 (CH_2), 22.5 (CH_2), 41.7 (CH), 46.1 (CH_2), 55.8 (CH_2), 59.3 (CH), 115.3 (2 CH), 128.3 (2 CH), 130.2 (C), 155.8 (C); mp 270−272 °C (EtOH−hexane). Anal. Calcd for $C_{15}H_{24}$-ClNO: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.83; H, 9.08; N, 5.04.

(2*R*,3*S*)-3-(3-Hydroxyphenyl)-2-methyl-1-propylpiperidine (19b). Operating as described in the preparation of **11**, piperidine **18b** (144 mg, 0.44 mmol) was converted to the corresponding *N*-propylpiperidine, which was obtained in 74% yield (81 mg) after flash chromatography (4:1 Et_2O−hexane): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.65 (d, J = 6.6 Hz, 3H), 0.91 (t, J = 7.8 Hz, 3H), 1.53 (m, 2H), 1.65−1.91 (m, 4H), 2.39 (t, J = 7.8 Hz, 2H), 2.46 (td, J = 11.7, 3.6 Hz, 1H), 2.60 (dt, J = 11.7, 2.7 Hz, 1H), 3.11 (dt, J = 12.0, 3.6 Hz, 1H), 3.19 (m, 1H), 3.79 (s, 3H), 6.74 (ddd, J = 7.8, 2.4, 0.6 Hz, 1H), 6.79−6.83 (m, 2H), 7.23 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 3.9 (CH_3), 12.1 (CH_3), 20.9 (CH_2), 23.1 (CH_2), 25.6 (CH_2), 45.7 (CH_2), 45.9 (CH), 55.1 (CH_3), 57.2 (CH_2), 57.9 (CH), 110.7 (CH), 113.9 (CH), 120.2 (CH), 128.9 (CH), 146.1 (C), 159.3 (C); $[\alpha]^{22}_D$ +4.2 (*c* 1.2, MeOH); HRMS calcd for $C_{16}H_{25}NO$ 247.1936, found 247.1930. Operating as described in the preparation of (−)-3-PPP, the above *N*-propylpiperidine (58 mg, 0.23 mmol) was converted into piperidine **19b** in 91% yield (50 mg): IR (film) 3255 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (d, J = 6.9 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H), 1.58 (m, 2H), 1.76−1.84 (m, 4H), 2.48 (m, 3H), 2.77 (dm, J = 11.7 Hz, 1H), 3.28 (m, 1H), 3.60 (m, 1H), 6.65 (d, J = 7.8 Hz, 1H), 6.74 (dd, J = 7.8, 2.1 Hz, 1H), 6.84 (s, 1H), 7.18 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 2.9 (CH_3), 12.1 (CH_3), 18.9 (CH_2), 21.5 (CH_2), 24.9 (CH_2), 41.4 (CH), 46.7 (CH_2), 56.4 (CH), 56.7 (CH_2), 114.3 (CH), 114.5 (CH), 117.0 (CH), 129.7 (CH), 144.2 (C), 157.1 (C); $[\alpha]^{22}_D$ +4.8 (*c* 0.28, MeOH). **19b**·hydrochloride: ^{1}H NMR ($CDCl_3$, 300 MHz) δ (most significant signals) 0.97 (br, 3H), 6.62 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 7.00 (br, 1H), 7.14 (t, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$−CD_3OD, 75.4 MHz) δ 5.0 (CH_3), 11.2 (CH_3), 17.4 (CH_2), 20.5 (CH_2), 22.8 (CH_2), 42.7 (CH), 46.5 (CH_2), 56.4 (CH_2), 59.6 (CH), 114.7 (CH), 114.9 (CH), 117.6 (CH), 129.6 (CH), 140.7 (C), 157.2 (C); mp 170−172 °C (EtOH−Et_2O). Anal. Calcd for $C_{15}H_{24}ClNO\cdot{}^1/_3H_2O$: C, 65.33; H, 9.01; N, 5.08. Found: C, 65.02; H, 9.33; N, 5.10.

(2*S*,3*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-(4-methoxyphenyl)-2-methylpiperidine (20a). Operating as described in the preparation of **18**, starting from **17a** (224 mg, 0.66 mmol) piperidine **20a** (188 mg, 87%) impurified with trace amounts of its C-2 epimer was obtained after flash chromatography (Et_2O). Pure piperidine **20a** was obtained by crystallization of the hydrochloride (acetone−MeOH). **20a**: IR (film) 3410 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.64 (d, J = 7.0 Hz, 3H), 1.59−1.92 (m, 4H), 2.48 (td, J = 11.4, 2.8 Hz, 1H), 2.66 (dm, J = 11.4 Hz, 1H), 3.13 (dt, J = 12.4, 3.6 Hz, 1H), 3.34 (m, 1H), 3.69 (dd, J = 8.7, 3.3 Hz, 1H), 3.72−3.84 (m, 2H), 3.78 (s, 3H), 6.85 (dm, J = 8.7 Hz, 2H), 7.09 (dm, J = 8.7 Hz, 2H), 7.27−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 6.4 (CH_3), 22.7 (CH_2), 26.0 (CH_2), 40.8 (CH_2), 45.5 (CH), 55.2 (CH_3), 58.8 (CH), 62.1 (CH_2), 68.7 (CH), 113.5 (2 CH), 127.7 (CH), 128.4 (2 CH), 128.5 (2 CH), 128.7 (2 CH), 135.7 (C), 139.8 (C), 157.8 (C); $[\alpha]^{22}_D$ −29.1 (*c* 1.3, MeOH). **20a**·hydrochloride: IR (film) 3412 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz; two epimers at the nitrogen atom were observed) δ (most significant signals for the major epimer)1.21 (d, J = 7.0 Hz, 3H), 2.78 (tm, J = 12.5 Hz, 1H), 2.90 (dm, J = 12.5 Hz, 1H), 3.82 (s, 3H), 6.90 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 9.0 Hz, 2H); δ (most significant signals for the minor epimer)1.14 (d, J = 7.0 Hz, 3H), 3.75 (s, 3H), 6.70 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz; two epimers at the nitrogen atom were also observed) δ (major epimer) 5.3 (CH_3), 20.3 (CH_2), 22.7 (CH_2), 41.7 (CH), 45.4 (CH_2), 54.9 (CH_3), 60.6 (CH), 61.4 (CH_2), 69.4 (CH), 113.7 (2 CH), 127.6 (CH), 128.3 (2 CH), 129.3 (2 CH), 129.6 (2 CH), 131.6 (C), 132.7 (C), 158.3 (C); δ (minor epimer) 10.0 (CH_3), 18.2 (CH_2), 20.2 (CH_2), 36.0 (CH), 43.5 (CH_2), 54.8 (CH_3), 58.5 (CH), 63.0 (CH_2), 66.5 (CH), 113.8 (2 CH), 127.8 (CH), 128.6 (2 CH), 129.6 (2 CH), 129.8 (2 CH), 130.1 (C), 132.7 (C), 158.3 (C); mp 247−250 °C (acetone−MeOH). Anal. Calcd for $C_{21}H_{28}ClNO_2$: C, 69.69; H, 7.80; N, 3.87. Found: C, 69.39; H, 7.85; N, 3.93.

(2*S*,3*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-3-(3-methoxyphenyl)-2-methylpiperidine (20b). Operating as described in the preparation of **18**, starting from **17b** (93 mg, 0.27 mmol) piperidine **20b** (57 mg, 64%) impurified with trace amounts of its C-2 epimer was obtained after flash chromatography (7:3 Et_2O−hexane). Pure piperidine **20b** was obtained by crystallization of the hydrochloride (acetone−MeOH). **20b**: IR (KBr) 3232 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.65 (d, J = 6.6 Hz, 3H), 1.59−1.91 (m, 4H), 2.50 (td, J = 12.0, 2.7 Hz, 1H), 2.70 (dm, J = 12.0 Hz, 1H), 3.15 (dt, J = 13.0, 3.6 Hz, 1H), 3.39 (m, 1H), 3.67 (dd, J = 10.0, 5.4 Hz, 1H), 3.72−3.70 (m, 2H), 3.79 (s, 3H), 6.70−6.75 (m, 3H), 7.18−7.35 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 6.7 (CH_3), 22.7 (CH_2), 26.2 (CH_2), 40.7 (CH_2), 46.5 (CH), 55.1 (CH_3), 58.7 (CH), 62.2 (CH_2), 68.7 (CH), 110.9 (CH), 113.6 (CH), 120.0 (CH), 127.6 (CH), 128.3 (2 CH), 128.7 (2 CH), 129.0 (CH), 140.1 (C), 145.4 (C), 159.4 (C); $[\alpha]^{22}_D$ −18.1 (*c* 1.4, MeOH); mp 216−218 °C (THF−hexane). Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.67; H, 8.42; N, 4.60. **20b**·hydrochloride: ^{1}H NMR ($CDCl_3$,

300 MHz; two epimers at the nitrogen atom were observed) δ (most significant signals for the major epimer) 1.16 (d, J = 6.9 Hz, 3H), 3.80 (s, 3H); δ (most significant signals for the minor epimer) 1.25 (d, J = 7.2 Hz, 3H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz; two epimers at the nitrogen atom were also observed) δ (major epimer) 6.08 (CH_3), 20.4 (CH_2), 22.9 (CH_2), 42.3 (CH), 45.5 (CH_2), 55.3 (CH_3), 61.9 (CH), 62.1 (CH_2), 70.7 (CH), 112.2 (CH), 113.8 (CH), 120.1 (CH), 129.5 (2 CH), 129.8 (2 CH), 130.0 (CH), 131.9 (C), 141.7 (C), 159.8 (C); δ (minor epimer) 10.0 (CH_3), 18.2 (CH_2), 20.2 (CH_2), 37.1 (CH), 44.2 (CH_2), 55.3 (CH_3), 58.5 (CH), 63.7 (CH_2), 67.4 (CH), 112.6 (CH), 113.8 (CH), 119.1 (CH), 129.6 (2 CH), 129.8 (2 CH), 130.0 (CH), 132.0 (CH), 141.5 (C), 159.8 (C).

(2*S*,3*R*)-3-(4-Hydroxyphenyl)-2-methyl-1-propylpiperidine (*ent*-19a). Following the procedure described above from **18**, starting from **20a** (86 mg, 0.26 mmol) (2*S*,3*R*)-3-(4-methoxyxyphenyl)-2-methyl-1-propylpiperidine (52 mg, 80%) was obtained after flash chromatography: $[\alpha]^{22}_D$ −5.7 (*c* 0.75, MeOH). This compound (45 mg, 0.2 mmol) was *O*-demethylated as described for the preparation of **19a** to give pure *ent*-**19a** (27 mg, 66%) after flash chromatography: $[\alpha]^{22}_D$ −4.1 (*c* 1.31, MeOH).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **2**−**6**, **8a**, **9a**, **10**-**14**, **(−)-3-PPP**, **16a**−**20a**, **16b**−**19b**, and (2*R*,3*S*)-3-[4-(and 3-)methoxyphenyl]-2-methyl-1-propylpiperidine, and ORTEP diagrams and X-ray crystallographic data of compounds **10** and **16b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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