Synthesis of Enantiopure *trans*-3,4-Disubstituted Piperidines. An Enantiodivergent Synthesis of (+)- and (−)-Paroxetine

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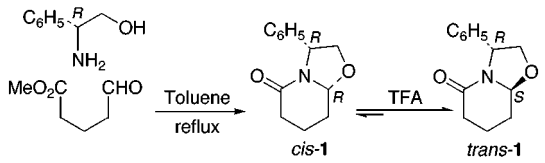
Reaction of (*R*)-phenylglycinol with methyl 5-oxopentanoate gave either bicyclic lactam *cis*-**1** (the kinetic product) or its isomer *trans*-**1** (under equilibrating conditions) as the major products, which were converted to the corresponding (*cis* or *trans*) unsaturated lactams **4** and **5**. On treatment with lithium alkyl (or aryl) cyanocuprates, these chiral building blocks undergo conjugate addition to give enantiopure *trans*-3,4-substituted 2-piperidone derivatives in high yield and stereoselectivity. The synthetic potential of this transformation is illustrated by the synthesis of (+)-femoxetine and the two enantiomers of the known antidepressant paroxetine.

The piperidine nucleus can be frequently recognized in the structure of numerous naturally occurring alkaloids and synthetic compounds with interesting biological and pharmacological properties. As a consequence, the development of general methods for the enantioselective synthesis of piperidine derivatives has been the subject of considerable synthetic efforts.[1] In previous reports from this laboratory we have described our studies in the enantioselective preparation of diversely substituted piperidines from a common synthetic intermediate, the bicyclic lactam *trans*-**1**, which have resulted in the synthesis of 2-alkyl [(*R*)-coniine],[2] *cis*-2,6-dialkyl [(2*R*,6*S*)-dihydropinidine],[3] *trans*-2,6-dialkyl [lupetidine, solenopsin A],[4] and 3-alkyl [(*R*)-decarbomethoxytetrahydrosecodine][5] substituted piperidine alkaloids. In this paper we describe the enantioselective preparation of *trans*-3,4-disubstituted piperidines by conjugate addition of cyanocuprates to α,β-unsaturated lactams derived from both the bicyclic lactam *trans*-**1** and its C-8a epimer *cis*-**1**, and the application of this methodology to the enantioselective synthesis of the antidepressive drugs (+)-femoxetine and the two enantiomers of paroxetine.[6]

Scheme 1



Chiral, nonracemic bicyclic lactams have been extensively employed by Meyers for the synthesis of enantiopure carbocycles and carboxylic acids containing quaternary stereocenters[7] and, more recently, nitrogen-containing heterocycles.[8] Although cyclodehydration of γ- or δ-keto acids and amino alcohols constitutes an excellent procedure for the synthesis of angular-substituted bicyclic lactams,[7a,9] the use of aldehyde acids under the same conditions is less satisfactory, and alternative methods for the preparation of angular hydrogen lactams have been described.[9] Nevertheless, in our hands, heating a toluene solution of (*R*)-phenylglycinol and methyl 5-oxopentanoate at reflux temperature for 36 h under neutral conditions, with azeotropic removal of water, afforded a 85:15 mixture of bicyclic lactams *cis*-**1** and *trans*-**1**, respectively, in 86% overall yield (Scheme 1). These lactams were efficiently separated by column chromatography. On the other hand, when a solution of lactam *cis*-**1** and TFA in dichloromethane was stirred for 64 h at 25 °C, a 14:86 mixture of *cis*-**1** and *trans*-**1** was recovered quantitatively. Thus, pure lactam *cis*-**1** can be directly obtained by cyclodehydration whereas lactam *trans*-**1** is accessible by cyclodehydration followed by

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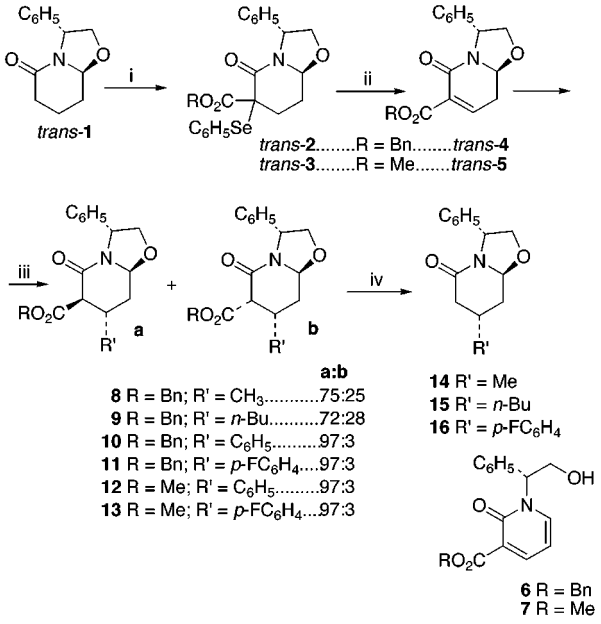
Scheme 2[a]



[a] Reagents and conditions: (i) LHMDS, $ClCO_2R$, PhSeBr, THF, −78 °C, 77% (*trans*-**2**), 96% (*trans*-**3**); (ii) O_3, CH_2Cl_2, −78 °C, then O_2, 25 °C; (iii) R′Cu(CN)Li, THF, −78 °C, 65% (**8**), 63% (**9**), 72% (**10**), 70% (**11**), 86% (**12**), 80% (**13**); (iv) HCO_2NH_4, Pd−C, MeOH, 25 °C, then toluene, reflux, 73% (**14**), 74% (**15**), 98% (**16**).

equilibration under acidic conditions of the initially formed reaction mixture.[10]

Since simple α,β-unsaturated lactams are known to be poor Michael acceptors,[11] we decided to use the unsaturated lactams *trans*-**4** and *trans*-**5**, in which the presence of an additional electron-withdrawing substituent on the α position would enhance the reactivity of the conjugated system,[12] thus allowing the efficient addition of organocuprates. These lactams were prepared in excellent overall yield by sequential treatment of *trans*-**1** with LHMDS (2.2 equiv), benzyl or methyl chloroformate (1.0 equiv), respectively, and phenylselanyl bromide (1.4 equiv), followed by ozonolysis of the resulting selenides *trans*-**2** and *trans*-**3** under neutral conditions (Scheme 2). Interestingly, when oxidation of these intermediate selenides was effected with *m*-CPBA, the corresponding 6,7-epoxides were formed instead.[13] Lactams *trans*-**4** and *trans*-**5** proved to be sensitive to both mild acid and basic conditions, affording the corresponding pyridones **6** and **7**, respectively. For this reason, they were prepared immediately before the next reaction and used without further purification. In this manner, when *trans*-**4** was treated with alkylcyanocuprates (lithium methyl- or *n*-butylcyanocuprate), the corresponding conjugate addition products **8** and **9** were obtained in 65% and 63% yield, respectively, as approximately 3:1 mixtures of 6,7-*trans* (series **a**) and 6,7-*cis* (series **b**) C-6 epimers. In some runs, small amounts (<5%) of pyridone **6** were isolated. Similarly, addition of arylcyanocuprates (lithium phenyl- or *p*-fluorophenylcyanocuprate) to the unsaturated lactam *trans*-**4** afforded the corresponding conjugate addition products **10** and **11**, although in higher yield (70−75%) and stereoselectivity (ratio **a**:**b** 97:3, determined by 300-MHz ^{1}H NMR). Even slightly better chemical yields (>80%) were obtained when the reaction with arylcyanocuprates was carried out from the α-methoxycarbonyl unsaturated lactam *trans*-**5**. To confirm that compounds **8a**−**13a** and **8b**−**13b**, obtained in the above conjugate addition reactions, were isomers at the epimerizable C-6 carbon, the mixtures of α-benzyloxycarbonyl compounds **8ab**, **9ab**, and **11ab** were subjected to hydrogenolysis with subsequent decarboxylation of the resulting β-keto acid. Compounds **14**, **15**, and **16** were obtained as single isomers detectable by NMR, making evident the high stereoselectivity in the diastereofacial addition of the cuprates on the *Si* face of the electrophilic carbon of the double bond. On the other hand, the absolute stereochemical outcome of the cuprate additions was unambiguously proven by X-ray diffraction techniques from a crystal of **12a**.[14] Thus, compounds **8a**−**13a** are 6*R*,7*S* whereas the isomers **8b**−**13b** are 6*S*,7*S*.

Next we decided to study the addition of organocuprates to the C-8a epimeric α,β-unsaturated lactams *cis*-**4** and *cis*-**5**, which were prepared from the bicyclic lactam *cis*-**1**, via the seleno derivatives *cis*-**2** and *cis*-**3**, following the same procedure described above for the corresponding *trans* isomers (Scheme 3). Addition of lithium methylcyanocuprate to *cis*-**4** afforded a 3:1 mixture of isomers **17a** (*trans*) and **17b** (*cis*) in 64% overall yield, which, by hydrogenolysis followed by decarboxylation in refluxing toluene, were converted to the methyl derivative **21** as a single stereoisomer. This result again makes evident the high stereoselectivity in the cuprate addition to the α,β-unsaturated dicarbonyl moiety of *cis*-**4**. Similarly, compounds **18**−**20** were obtained as 97:3 mixtures of isomers by addition of arylcyanocuprates to the unsaturated lactams *cis*-**4** or *cis*-**5**.

To compare the stereochemical outcome of the conjugate addition to the *trans* and *cis* isomers of unsaturated lactams **4** and **5**, compounds **12a** and **18a** were treated with alane ($LiAlH_4/AlCl_3$), which caused the cleavage of the C−O bond of the oxazolidine ring and the simulta-

(10) Bicyclic lactams *trans*-**1** and *cis*-**1** have also been prepared by alternative multistep sequences: (a) Royer, J.; Husson, H.-P. *Heterocycles* **1993**, *36*, 1493. (b) Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Synth. Commun.* **1996**, *26*, 1605.

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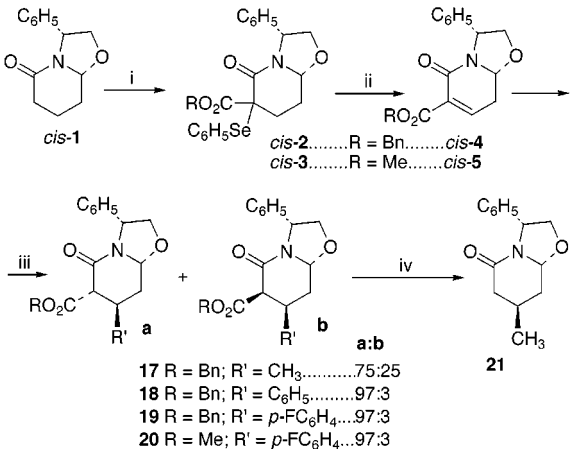
(12) The presence of an alkoxycarbonyl group facilitates the conjugate addition of organocuprates to unsaturated five-[12a,b] and six-membered[12c] lactams: (a) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814. (b) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36. (c) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300. See also: Amat, M.; Llor, N.; Bosch, J.; Solans, X. *Tetrahedron* **1997**, *53*, 719.

(13) Amat, M.; Llor, N.; Hidalgo, J.; Bosch, J.; Molins, E.; Miravitlles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 2501.

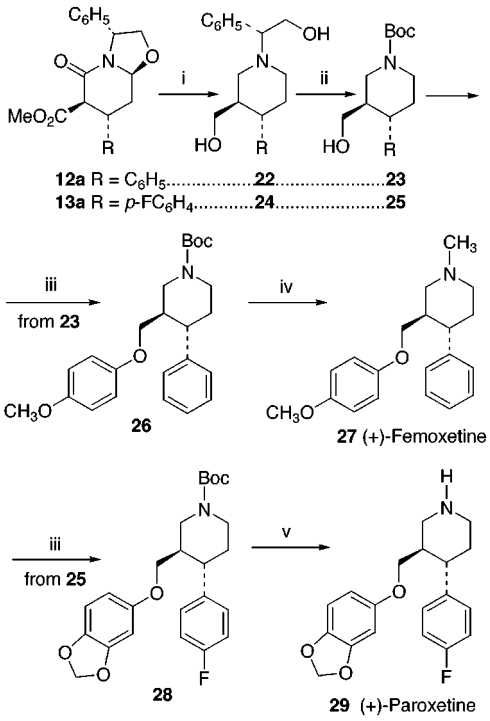
(14) The experiment was done on a diffractometer using graphite monochromated Mo Kα radiation. The structure was solved by direct methods (SHELXS-86) after applying Lorentz, polarization, and absorption (empirical PSI scan method) corrections. Full-matrix least squares refinement (SHELXL-93) using anisotropic thermal parameters for non-H atoms and a global isotropic thermal parameters for H-atoms (positioned at calculated positions) converged to a *R* factor of 0.075 (for **12a**) and 0.057 (for **22**) (calculated for the reflections with $I > 2\sigma(I)$). Complete data have been deposited at the Cambridge Crystallographic Data Centre. **12a**: Crystal data: $C_{21}H_{21}NO_4$, monoclinic, space group $P2_12_12_1$, a = 5.947(2) Å, b = 7.876(2) Å, c = 38.968-(7) Å, V = 1825.2 Å^3, μ (Mo Kα) = 0.089 mm^{-1}, D_c = 1.279 g/cm^3. Approximate dimensions: 0.29 × 0.16 × 0.15 mm. Data collection was up to a resolution of 2θ = 50° producing 1902 reflections. Maximum and minimum heights at the final difference Fourier synthesis were 0.301 and −0.324 eÅ^{-3}. **22**: Crystal data: $C_{20}H_{25}NO_2$, monoclinic, space group C2, a = 21.889(3) Å, b = 5.876(1) Å, c = 13.842(2) Å, V = 1780.2-(5) Å^3, μ (Mo Kα) = 0.074 mm^{-1}, D_c = 1.162 g/cm^3. Approximate dimensions: 0.35 × 0.10 × 0.10 mm. Data collection was up to a resolution of 2θ = 50° producing 1569 reflections. Maximum and minimum heights at the final difference Fourier synthesis were 0.249 and −0.168 eÅ^{-3}.

Scheme 3[a]



[a] Reagents and conditions: (i) LHMDS, $ClCO_2R$, PhSeBr, THF, −78 °C, 77% (*cis*-**2**), 81% (*cis*-**3**); (ii) O_3, CH_2Cl_2, −78 °C; then O_2, 25 °C; (iii) R′Cu(CN)Li, THF, −78 °C, 64% (**17**), 75% (**18**), 64% (**19**), 67% (**20**); (iv) HCO_2NH_4, Pd−C, MeOH, 25 °C, then toluene, reflux, 85%.

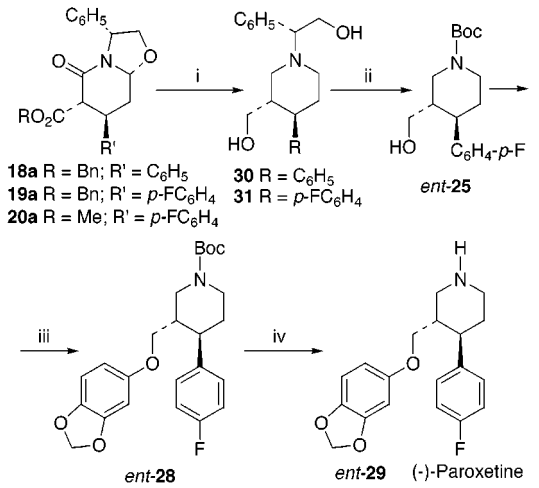
Scheme 4[a]



[a] Reagents and conditions: (i) $AlCl_3$, $LiAlH_4$, THF, −78 °C to 25 °C, 86% (**22**), 74% (**24**); (ii) H_2, (*t*-BuOCO)$_2$O, 20% Pd(OH)$_2$−C, AcOEt, 25 °C, 88% (**23**), 73% (**25**); (iii) MsCl, pyr, 10 °C, then NaH, Ar−OH, THF, reflux, 50% (**26**), 56% (**28**); (iv) $LiAlH_4$, Et_2O, 0 °C, 74%; (v) TFA, CH_2Cl_2, rt, 77%.

neous reduction of the ester and amide carbonyl groups to give the alcohols **22** (Scheme 4) and **30** (Scheme 5), respectively, as the only stereoisomers detectable by NMR. The *trans* relative stereochemistry of the hydroxymethyl and phenyl substituents of piperidines **22** and **30** was inferred by NMR, and for compound **22** it was confirmed by X-ray crystallography.[14] In these piperidines the formation of a hydrogen bond between the nitrogen atom and the hydroxy group of the (*R*)-1-phenyl-2-hydroxyethyl substituent situates the phenyl group near one of the α carbons of the piperidine ring, thus

Scheme 5[a]



[a] Reagents and conditions: (i) $AlCl_3$, $LiAlH_4$, THF, −78 °C to 25 °C, 50% (**30**), 75% (**31**); (ii) H_2, (*t*-BuOCO)$_2$O, 20% Pd(OH)$_2$−C, AcOEt, 25 °C, 57%; (iii) MsCl, pyr, 10 °C, then NaH, Ar−OH, THF, reflux, 66%; (iv) TFA, CH_2Cl_2, rt, 72%.

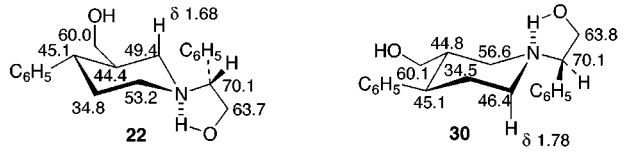


Figure 1.

shielding the corresponding signal in the ^{13}C NMR spectra by about 7 ppm (see Figure 1). Moreover, due to the anisotropic affect of the phenyl group, the axial H-2 proton in **22** and H-6 proton in **30** are shielded by about 0.6 ppm in the ^1H NMR spectra as compared with the axial proton on the alternative position α to the nitrogen.

The diastereomeric nature of the *trans*-3,4-substituted piperidines **22** and **30** confirms that the conjugate addition of cyanocuprates to the above *trans* and *cis* α,β-unsaturated lactams takes place stereoselectively on different faces (*Si* and *Re*, respectively) of the double bond. These results deserve attention because lactams **4** and **5** are derived from the same chiral inductor, (*R*)-phenylglycinol; removal of the chiral substituent on the piperidine nitrogen from the above diastereomeric *trans*-3,4-substituted piperidines would provide the two enantiomers in an enantiodivergent process.

To understand the origin of the stereoselectivity in the conjugate addition of cyanocuprates to the carbon−carbon double bond in the *cis* and *trans* isomers of lactams **4** and **5**, we examined the reactivity pattern of the *cis* and *trans* isomers of the model unsaturated bicyclic lactam **A** from GMIPp[15,16] calculations (see Computational Methods). To this end, we determined the GMIPp interaction energy profile for the approach of a negatively charged classical point particle along the line perpendicular to the six-membered ring passing through carbon atoms 6 and 7. The GMIPp values and their components are given in Table 1.

Inspection of the total interaction energies clearly shows the different susceptibility of the two faces of the

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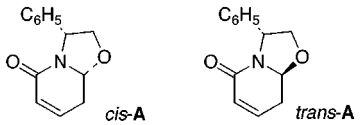
(16) Luque, F. J.; Orozco, M. *J. Comput. Chem.* **1998**, *19*, 866.

Table 1. Electrostatic (E_{ele}), Polarization (E_{pol}), van der Waals (E_{vW}), and Total Interaction Energy (E_{total}) Determined from GMIPp Calculations for the Attack of a Negatively Charged Classical Point Charge to the *Si* and *Re* Faces of the Carbon−Carbon Double Bond in *cis*-A and *trans*-A[a]



	face *Re*				face *Si*			
	E_{ele}	E_{pol}	E_{vW}	E_{total}	E_{ele}	E_{pol}	E_{vW}	E_{total}
				Attack on C-7				
cis-**A**	−4.9	−12.2	+2.5	−14.5	+1.0	−11.6	+2.3	−8.3
trans-**A**[b]	−0.7	−10.7	+3.0	−8.5	−4.9	−12.4	+1.7	−15.6
trans-**A**[c]	−1.8	−10.7	+2.6	−9.9	−3.3	−12.3	+2.2	−13.3
				Attack on C-6				
cis-**A**	−0.7	−11.3	+1.3	−10.7	+8.0	−11.5	+1.1	−2.4
trans-**A**[b]	+6.2	−10.7	+1.4	−3.1	−0.7	−12.3	+1.0	−12.0
trans-**A**[c]	+4.4	−10.7	+1.3	−4.9	+1.8	−11.5	+1.1	−8.7

[a] All values are in kcal/mol. [b] Conformation with C-2 *down*. [c] Conformation with C-2 *up*.

double bond to the attack of a nucleophilic reagent. Thus, in *cis*-**A** the attack on the *Re* face is energetically more favorable than on the *Si* face. Conversely, a nucleophilic attack on the *Si* face is preferred in *trans*-**A**. Comparison of the GMIPp energetic contributions for the attack on each face shows that the origin of such a preference lies mainly in the electrostatic term, which favors the approach of the nucleophile by the *Re* face in *cis*-**A**, whereas the reverse trend is found for *trans*-**A**. As it could be expected, the results in Table 1 also show that for a given isomer the attack on C-7 is energetically preferred to the attack on C-6.

The synthetic potential of this transformation is illustrated by the synthesis of (+)-femoxetine and the two enantiomers of the known antidepressant paroxetine. Femoxetine (**27**) and paroxetine (**29**)[17] are closely related serotonin (5-hydroxytryptamine) reuptake inhibitors, which have been used clinically for the treatment of depression.[18] For the eutomer of paroxetine, the configurations at the C-3 and C-4 stereocenters are 3*S*,4*R*, whereas for femoxetine they are 3*R*,4*S*.[19] The method for obtaining the requisite configuration of these compounds in enantiopure form employs the chemical or enzymatic resolution of a racemic intermediate, although very recently an enantioselective synthesis of femoxetine and paroxetine involving the stereoselective conjugate addition to a 1,2,5,6-tetrahydro-3-pyridyl ester derived from a chiral alcohol has been reported.[20]

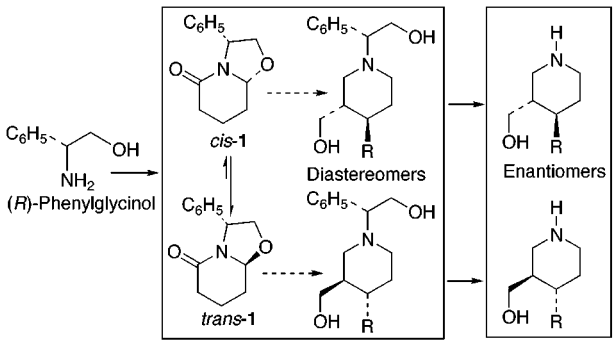
The synthesis of (+)-femoxetine (**27**) from piperidine **22** simply required the exchange of the chiral inductor on the piperidine nitrogen by a methyl group and the etherification of the hydroxymethyl substituent with an appropriate aryl group. This was accomplished by hydrogenolysis of the benzylic *N*-substituent in the presence of di-*tert*-butyl dicarbonate, followed by conversion of the resulting alcohol **23** into the corresponding mesylate, subsequent nucleophilic substitution with the sodium salt of *p*-methoxyphenol, and finally $LiAlH_4$ reduction of the protecting N-*tert*-butoxycarbonyl group in the resulting aryl ether **26** (Scheme 4).

On the other hand, alane reduction of the *p*-fluorophenyl derivative **13a** afforded the *trans* piperidine **24**, which was converted into alcohol **25** by hydrogenolysis in the presence of di-*tert*-butyl dicarbonate. Mesylation of this alcohol, followed by reaction with the sodium salt of sesamol gave **28**, which, on treatment with TFA, afforded the secondary amine **29**. The spectroscopic data of **29** were coincident with those found for a sample of paroxetine obtained from commercial Seroxat except for the sign of the specific rotation.

Finally, the synthesis of the eutomer of paroxetine was accomplished from esters **19a** and **20a**. As in the above series, alane reduction brought about the cleavage of the oxazolidine ring and the reduction of the ester and lactam carbonyl groups to give the enantiopure *trans* piperidine **31**, which was converted to (−)-paroxetine (*ent*-**29**) following a synthetic sequence parallel to that previously performed in the opposite enantiomeric series (Scheme 5).

In summary, we have developed an enantiodivergent synthesis of *trans*-3,4-substituted piperidines. Starting from a single enantiomer of phenylglycinol it is possible to gain access to the two enantiomeric series of these piperidine derivatives. It is simply a matter of using either the kinetic bicyclic lactam *cis*-**1** formed in the cyclodehydration of (*R*)-phenylglycinol with methyl 5-oxopentanoate or the most stable isomer *trans*-**1** (Scheme 6). Conjugate addition of appropriate organocopper re-

Scheme 6



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(18) (a) Femoxetine: *Drugs Fut.* **1977**, *2*, 309. (b) Paroxetine: *Drugs Fut.* **1986**, *11*, 112. (c) For a review, see: Dechant, K. L.; Clissold, S. P. *Drugs* **1991**, *41*, 225.

(19) Jones, P. G.; Kennard, O.; Horn, A. S. *Acta Crystallogr.* **1979**, B*35*, 1732.

(20) Murthy, K. S. K.; Rey, A. W. WO Patent 9907680, 1999; *Chem. Abstr.* **1999**, *130*, 182361.

agents to α,β-unsaturated lactams derived from either *cis*-**1** or *trans*-**1** provides enantiopure diastereomeric *trans*-3,4-substituted piperidines, which are ultimately converted to the corresponding separate enantiomers.

The above results significantly expand the potential of bicyclic lactams *cis*-**1** and *trans*-**1**, derived from (*R*)-phenylglycinol, as chiral building blocks for the synthesis of diversely substituted enantiopure piperidine derivatives.

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 (^{1}H) 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}, Merck), and the spots were located with aqueous potassium permanganate solution or with iodoplatinate reagent. Column chromatography was carried out on SiO_2 (silica gel 60, SDS, 70−200 μm). Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 35−70 μm). All reagents were purchased from Aldrich or Fluka and were used without further purification. Solvents for chromatography were distilled at atmospheric pressure prior to use and dried using standard procedures. Drying of the organic extracts during the workup of reactions was performed over Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Microanalyses and HRMS were performed by Centre d'Investigació i Desenvolupament (CSIC), Barcelona.

(3*R*,8a*R*)- and (3*R*,8a*S*)-5-Oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*cis*-1 and *trans*-1). Methyl 5-hydroxypentanoate (23.7 g, 0.18 mol), prepared in 90% yield by methanolysis of δ-valerolactone, was slowly added to a suspension of PCC (59.2 g, 0.27 mol) and Celite (59.2 g) in anhydrous CH_2Cl_2 (370 mL), and the resulting mixture was stirred at 25 °C for 1.5 h. The solution was decanted, and the solids were washed with Et_2O (3 × 100 mL). The combined organic solutions were filtered through an alumina column to afford methyl 5-oxopentanoate (19.1 g, 82%). A stirred solution of (−)-(*R*)-phenylglycinol (18.3 g, 133 mmol) and methyl 5-oxopentanoate (20.8 g, 160 mmol) in toluene (380 mL), containing molecular sieves (4 Å, 15 g), was heated at reflux for 36 h, with azeotropic elimination of water produced. The resulting solution was concentrated, and the residue was taken up with Et_2O. The organic solution was washed with saturated aqueous NH_4Cl (3 × 50 mL), dried, and concentrated to give an orange oil (30 g). Column chromatography (97:3 AcOEt−EtOH) afforded a mixture of *cis*-**1** (21.2 g, 73%) and its C-8a epimer *trans*-**1** (3.8 g, 13%). *cis*-**1**: IR (KBr) 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.77 (m, 2 H), 2.05 (m, 1 H), 2.26 (ddd, *J* = 18.5, 11.0, 7.0 Hz, 1 H), 2.33−2.40 (m, 2 H), 4.00 (dd, *J* = 9.0, 1.5 Hz, 1 H), 4.15 (dd, *J* = 9.0, 7.0 Hz, 1 H), 4.85 (dd, *J* = 9.5, 3.4 Hz, 1 H), 4.92 (dd, *J* = 7.0, 1.5 Hz, 1 H), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.6 (CH_2), 28.0 (CH_2), 30.8 (CH_2), 58.7 (CH), 73.7 (CH_2), 88.9 (CH), 126.4 (CH), 127.6 (CH), 128.6 (CH), 141.6 (C), 167.6 (C); mp 65−67 °C; $[\alpha]^{22}_D$ −66.3 (*c* 1.0, EtOH); $[\alpha]^{22}_D$ −45.8 (*c* 2.2, CH_2Cl_2), {lit.:[10a] $[\alpha]^{22}_D$ −51.0 (*c* 2.2, CH_2Cl_2)}. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.78; H, 6.93; N, 6.48. *trans*-**1**: IR (film) 1646 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.53 (dddd, *J* = 13.5, 12.5, 9.0, 3.5 Hz, 1 H), 1.75 (m, 1 H), 1.98 (m, 1 H), 2.34 (ddd, *J* = 18.0, 11.5, 6.5 Hz, 1 H), 2.36 (m, 1 H), 2.51 (ddm, *J* = 18.0, 6.0 Hz, 1 H), 3.76 (dd, *J* = 9.0, 8.0 Hz, 1 H), 4.50 (dd, *J* = 9.0, 8.0 Hz, 1 H), 5.02 (dd, *J* = 9.0, 5.0 Hz, 1 H), 5.28 (t, *J* = 8.0 Hz, 1 H), 7.20−7.45 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.7 (CH_2), 28.1 (CH_2), 31.0 (CH_2), 57.8 (CH), 72.2 (CH_2), 88.5 (CH), 126.0 (CH), 127.5 (CH), 128.7 (CH), 139.6 (C), 169.0 (C); mp 88−90 °C (C_6H_6−hexane); $[\alpha]^{22}_D$ −122.0 (*c* 1.0, EtOH); $[\alpha]^{22}_D$ −90.8 (*c* 0.6, CH_2Cl_2), {lit.:[10a] $[\alpha]^{22}_D$ −88.0 (*c* 0.6, CH_2Cl_2)}. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.92; H, 6.96; N, 6.56.

Epimerization of *cis*-1. A solution of pure lactam *cis*-**1** (25 g, 0.11 mol) in anhydrous CH_2Cl_2 (80 mL) was added to a solution of TFA (80 mL, 1.04 mol) in anhydrous CH_2Cl_2 (1.8 L) cooled with an ice−water bath. After 10 min the bath was removed, and the solution was stirred at 25 °C for 64 h. The resulting acidic solution was neutralized with a 2 M aqueous $NaHCO_3$ (530 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic solutions were dried and concentrated, and the residue was chromatographed (97:3 AcOEt−EtOH) to give pure *trans*-**1** (21.5 g, 86%) and *cis*-**1** (3.5 g, 14%).

(3*R*,8a*S*)-6-(Benzyloxycarbonyl)-5-oxo-3-phenyl-6-(phenylselanyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*trans*-2). Lithium bis(trimethylsilyl)amide (10.1 mL of a 1 M solution in THF) was slowly added at −78 °C to a solution of lactam *trans*-**1** (1.0 g, 4.6 mmol) in anhydrous THF (65 mL), and the resulting mixture was stirred for 45 min. Then, benzyl chloroformate (0.65 mL, 4.6 mmol) and, after 20 min of continuous stirring at −78 °C, PhSeBr (1.52 g, 6.4 mmol) were sequentially added to the solution. The resulting mixture was stirred for 50 min and poured into 5% aqueous NH_4Cl. The aqueous layer was extracted with AcOEt (4 × 10 mL), and the combined organic extracts were dried and concentrated. Flash chromatography (2:3 AcOEt−hexane) of the resulting oil afforded compound *trans*-**2** (1.8 g, 77% overall yield) as a mixture of C-6 epimers. *trans*-**2** (higher R_f epimer): IR (film) 1734, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.85−2.20 (m, 4 H), 3.72 (t, *J* = 8.5 Hz, 1 H), 4.47 (t, *J* = 8.5 Hz, 1 H), 4.90 (br s, 1 H), 5.13 (d, *J* = 12.3 Hz, 1 H), 5.28 (d, *J* = 12.3 Hz, 1 H), 5.34 (t, *J* = 8.5 Hz, 1 H), 7.00−7.60 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 24.8 (CH_2), 27.4 (CH_2), 55.0 (C), 58.6 (CH), 67.7 (CH_2), 72.1 (CH_2), 87.5 (CH), 135.2 (C), 138.4 (CH), 138.8 (C), 165.1 (C), 170.2 (C). *trans*-**2** (lower R_f epimer): ^{1}H NMR ($CDCl_3$) δ 1.50−2.50 (m, 4 H), 3.80 (dd, *J* = 9.0, 7.4 Hz, 1 H), 4.42 (dd, *J* = 9.0, 7.8 Hz, 1 H), 4.73 (dd, *J* = 9.1, 4.5 Hz, 1 H), 5.24 (s, 2 H), 5.30 (t, *J* = 7.4 Hz, 1 H), 7.10−7.70 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 26.9 (CH_2), 29.7 (CH_2), 54.0 (C), 58.9 (CH), 68.0 (CH_2), 72.4 (CH_2), 88.1 (CH), 135.3 (C), 138.2 (CH), 138.4 (CH), 138.8 (C), 165.1 (C), 170.2 (C).

(3*R*,8a*S*)-6-(Methoxycarbonyl)-5-oxo-3-phenyl-6-(phenylselanyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (*trans*-3). Operating as in the above preparation of *trans*-**2**, from lactam *trans*-**1** (1.0 g, 4.6 mmol), methyl chloroformate (0.35 mL, 4.6 mmol), and PhSeBr (1.52 g, 6.4 mmol) was obtained selenide *trans*-**3** as a mixture of C-6 epimers (1.9 g, 96% overall yield) after column chromatography (2:3 AcOEt−hexane). Both epimers could be purified by crystallization (THF−hexane). *trans*-**3** (higher R_f epimer): ^{1}H NMR ($CDCl_3$) δ 1.95−2.20 (m, 4 H), 3.77 (t, *J* = 8.0 Hz, 1 H), 3.78 (s, 3 H), 4.48 (t, *J* = 8.0 Hz, 1 H), 4.97 (t, *J* = 6.0 Hz, 1 H), 5.34 (t, *J* = 8.0 Hz, 1 H), 7.18−7.45 (m, 8 H), 7.70 (dm, *J* = 6.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.9 (CH_2), 27.3 (CH_2), 53.2 (CH_3), 54,8 (C), 58.6 (CH), 72,2 (CH_2), 87.6 (CH), 125.7 (CH), 126.8 (C), 127.6 (CH), 128.7 (CH), 128.9 (CH), 129.7 (CH), 138,2 (CH), 138.8 (C), 165.1 (C), 170.9 (C). *trans*-**3** (lower R_f epimer): ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 1 H), 2.00−2.23 (m, 2 H), 2.41 (m, 1 H), 3.80 (masked, 1 H), 3.80 (s, 3 H), 4.44 (t, *J* = 7.9 Hz, 1 H), 4.72 (dd, *J* = 9.3, 4.4 Hz, 1 H), 5.3 (t, *J* = 7.7 Hz, 1 H), 7.10−7.40 (m, 8H), 7.50 (dm, *J* = 7.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 26.8 (CH_2), 29.6 (CH_2), 53.4 (CH_3), 53.9 (C), 58.8 (CH), 72.4 (CH_2), 88.0 (CH), 126.1 (C), 126.8 (CH), 127.7 (CH), 128.6 (CH), 128.8 (CH), 129.4 (CH), 138.1 (CH), 138.6 (C), 165.1 (C), 170.7 (C).

[3*R*,6*R*(and 6*S*),7*S*,8a*S*]-6-(Benzyloxycarbonyl)-7-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (8a and 8b). A stream of ozone gas was bubbled through a cooled (−78 °C) solution of the selenide *trans*-**2** (500 mg, 0.99 mmol) in anhydrous CH_2Cl_2 (40 mL) until it turned pale blue. The solution was purged with O_2, and the temperature was slowly raised to 25 °C. After 30 min of stirring, the mixture was poured into brine (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and concentrated under reduced pressure (external temperature 25 °C) to give **(3*R*,8a*S*)-6-(benzyloxycarbonyl)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo-**

[3,2-*a*]pyridine (*trans*-4) as an oil, which was used in the next reaction without further purification: IR (film) 1735, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.56 (ddd, J = 18.0, 10.2, 2.4 Hz, 1 H), 2.92 (ddd, J = 18.0, 6.8, 5.5 Hz, 1 H), 3.93 (dd, J = 9.0, 6.5 Hz, 1H), 4.47 (dd, J = 9.0, 7.0 Hz, 1 H), 5.26 (s, 2 H), 5.31 (t, J = 6.5 Hz, 1 H), 5.43 (dd, J = 10.2, 5.5 Hz, 1 H), 7.30 (m, 1 H), 7.35 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 29.8 (CH_2), 58.0 (CH), 66.3 (CH_2), 72.8 (CH_2), 85.9 (CH), 135.3 (C), 138.5 (C), 142.6 (CH), 157.0 (C), 162.6 (C). A solution of the above crude unsaturated lactam *trans*-**4** in anhydrous THF (2 mL) was added dropwise at −78 °C to a solution of $CH_3Cu(CN)Li$ (2.5 equiv) [prepared from 1.6 M CH_3Li in Et_2O (1.55 mL) and CuCN (245 mg, 2.74 mmol)] in anhydrous THF (22 mL), and the resulting solution was stirred for 90 min. The mixture was allowed to reach 25 °C and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with AcOEt (3 × 10 mL), and the combined organic extracts were dried and concentrated. The residue was chromatographed (2:3 AcOEt−hexane) to give (234 mg, 65% from *trans*-**2**) a 3:1 mixture of C-6 epimers **8a** and **8b**, respectively. **8a**: IR (film) 1739, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, J = 6.8 Hz, 1 H), 1.98 (ddd, J = 14.0, 8.3, 5.0 Hz, 1 H), 2.22 (ddd, J = 14.0, 5.0, 5.0 Hz, 1 H), 2.52 (m, 1 H), 3.21 (d, J = 7.2 Hz, 1 H), 3.80 (dd, J = 8.5, 8.0 Hz, 1 H), 4.50 (dd, J = 8.5, 8.0 Hz, 1 H), 5.02 (t, J = 5.0 Hz, 1 H), 5.23 (s, 2 H), 5.40 (t, J = 8.0 Hz, 1 H), 7.15−7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 19.6 (CH_3), 27.8 (CH), 32.3 (CH_2), 55.7 (CH), 58.5 (CH), 67.0 (CH_2), 71.8 (CH_2), 85.9 (CH), 135.5 (C), 139.4 (C), 165.8 (C), 169.6 (C). **8b**: ^1H NMR ($CDCl_3$, selected resonances) δ 1.12 (d, J = 6.6 Hz, 3 H), 3.56 (d, J = 5.0 Hz, 1 H), 3.69 (dd, J = 8.5, 8.0 Hz, 1 H), 4.51 (dd, J = 8.5, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.3 (CH_3), 27.7 (CH), 32.0 (CH_2), 54.2 (CH), 57.9 (CH), 67.0 (CH_2), 72.0 (CH_2), 86.3 (CH), 134.5 (C), 139.4 (C), 164.5 (C), 168.3 (C). Anal. Caldc for $C_{22}H_{23}NO_4 \cdot 1/4H_2O$ (mixture of epimers): C, 71.43; H, 6.40; N, 3.78. Found: C, 71.79; H, 6.42; N, 3.79. In some runs, small amounts (<5%) of pyridone **6** were isolated: IR (film) 3430, 1727, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.20 (dd, J = 12.2, 6.5 Hz, 1 H), 4.30 (dd, J = 12.2, 5.2 Hz, 1 H), 5.27 (s, 2 H), 6.10 (t, J = 7.0 Hz, 1 H), 6.47 (dd, J = 6.5, 5.2 Hz, 1 H), 7.20−7.45 (m, 10 H), 7.55 (dd, J = 7.0, 2.2 Hz, 1 H), 8.06 (dd, J = 7.0, 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 59.5 (CH), 62.2 (CH_2), 66.4 (CH_2), 104.6 (CH), 119.2 (C), 135.7 (C), 136.7 (C), 141.3 (CH), 144.3 (CH), 160.0 (C), 164.3 (C); mp 115−116 °C (Et_2O−acetone); $[\alpha]^{22}_D$ −274.8 (*c* 1.0, EtOH). Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.24; H, 5.46; N, 3.95.

[3*R*,6*R*(and 6*S*),7*S*,8a*S*]-6-(Benzyloxycarbonyl)-7-butyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (9a and 9b). Operating as in the above preparation of **8**, from selenide *trans*-**2** (500 mg, 0.99 mmol) and *n*-BuCu(CN)Li (2.5 equiv) [prepared from 1.6 M *n*-BuLi in hexane (1.55 mL) and CuCN (245 mg, 2.74 mmol)] was obtained a 72:28 mixture of C-6 epimers **9a** and **9b**, respectively, (253 mg, 63% from *trans*-**2**) after purification by column chromatography (2:3 AcOEt−hexane). **9a**: IR (film) 1739, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3 H), 1.20−1.50 (m, 6 H), 2.08 (m, 1 H), 2.17 (ddd, J = 14.0, 6.5, 4.4 Hz, 1 H), 2.34 (m, 1 H), 3.30 (d, J = 5.7 Hz, 1 H), 3.78 (dd, J = 9.0, 8.0 Hz, 1 H), 4.50 (t, J = 8.6 Hz, 1 H), 5.03 (dd, J = 6.5, 5.2 Hz, 1 H), 5.17 (d, J = 12.6 Hz, 2 H), 5.23 (d, J = 12.6 Hz, 2 H), 5.36 (t, J = 8.0 Hz, 1 H), 7.15−7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 22.4 (CH_2), 28.9 (CH_2), 29.8 (CH_2), 33.1 (CH), 33.5 (CH_2), 54.0 (CH), 58.5 (CH), 67.0 (CH_2), 72.0 (CH_2), 86.1 (CH), 135.5 (C), 139.4 (C), 165.5 (C), 170.0 (C); MS *m/e* (relative intensity): 407 (M^+, 3), 316 (61), 298 (12), 120 (23), 111 (18), 104 (64), 77 (16), 65 (15), 55 (32). **9b**: ^1H NMR ($CDCl_3$, selected resonances) δ 3.62 (d, J = 4.1 Hz, 1 H), 3.67 (dd, J = 9.0, 8.0 Hz, 1 H), 4.48 (t, J = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 22.4 (CH_2), 29.6 (CH_2), 31.7 (CH_2), 32.7 (CH), 52.9 (CH), 57.9 (CH), 67.1 (CH_2), 71.8 (CH_2), 86.4 (CH), 135.6 (C), 139.5 (C), 165.2 (C), 168.5 (C). Anal. Calcd for $C_{25}H_{29}NO_4$ (mixture of epimers): C, 73.68; H, 7.17; N, 3.44. Found: C, 73.44; H, 7.13; N, 3.40.

(3*R*,6*R*,7*S*,8a*S*)-6-(Benzyloxycarbonyl)-5-oxo-3,7-diphenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (10a). Operating as in the preparation of **8**, from selenide *trans*-**2** (500 mg, 0.99 mmol) and PhCu(CN)Li (2.5 equiv) [prepared from 1.6 M PhLi in cyclohexanes−Et_2O (1.55 mL) and CuCN (245 mg, 2.74 mmol)] was obtained a 97:3 mixture of C-6 epimers **10a** and **10b**, respectively, (304 mg, 72% from *trans*-**2**) after column chromatography (2:3 AcOEt−hexane). Crystallization from acetone−Et_2O−hexane afforded pure **10a**: IR (film) 1740, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (ddd, J = 14.3, 8.7, 4.7 Hz, 1 H), 2.47 (dt, J = 14.3, 4.7 Hz, 1 H), 3.67 (td, J = 8.7, 4.7 Hz, 1 H), 3.80 (dd, J = 8.3, 7.6 Hz, 1 H), 3.85 (d, J = 8.7 Hz, 1 H), 4.53 (t, J = 8.3 Hz, 1 H), 4.90 (t, J = 4.7 Hz, 1 H), 5.09 (d, J = 12.4 Hz, 1 H), 5.12 (d, J = 12.4 Hz, 1 H), 5.47 (dd, J = 8.3, 7.6 Hz, 1 H), 7.10−7.40 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 33.3 (CH_2), 38.1 (CH), 54.0 (CH), 58.6 (CH), 67.0 (CH_2), 71.7 (CH_2), 85.9 (CH), 135.3 (C), 139.3 (C), 140.4 (C), 166.0 (C), 169.0 (C); mp 121−123 °C; $[\alpha]^{22}_D$ −30.2 (*c* 0.5, CH_2Cl_2). Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.86; H, 5.81; N, 3.29.

(3*R*,6*R*,7*S*,8a*S*)-6-(Benzyloxycarbonyl)-7-(*p*-fluorophenyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (11a). Operating as in the preparation of **8**, from selenide *trans*-**2** (800 mg, 1.58 mmol) and lithium (*p*-fluorophenyl)cyanocuprate (1.6 equiv) [prepared from 0.13 M (*p*-fluorophenyl)lithium[21] in THF (20 mL) and CuCN (252 mg, 2.8 mmol)] was obtained a 97:3 mixture of C-6 epimers **11a** and **11b**, respectively, (490 mg, 70% from *trans*-**2**) after purification by column chromatography (2:3 AcOEt−hexane). Crystallization from acetone−Et_2O−hexane afforded pure **11a**: IR (film) 1743, 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (ddd, J = 14.5, 9.5, 5.0 Hz, 1 H), 2.44 (dt, J = 14.5, 4.3 Hz, 1 H), 3.62 (td, J = 9.5, 4.3 Hz, 1 H), 3.75 (d, J = 9.5 Hz, 1 H), 3.81 (dd, J = 8.8, 7.5 Hz, 1 H), 4.51 (t, J = 8.8 Hz, 1 H), 4.91 (t, J = 4.8 Hz, 1 H), 5.06 (d, J = 12.0 Hz, 1 H), 5.10 (d, J = 12.0 Hz, 1 H), 5.47 (t, J = 7.8 Hz, 1 H), 6.97 (t, J = 8.5 Hz, 1 H), 7.05−7.40 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 33.4 (CH_2), 37.3 (CH), 54.6 (CH), 58.6 (CH), 67.0 (CH_2), 71.5 (CH_2), 85.7 (CH), 115.6 (d, J = 21.0 Hz, CH), 126.1 (CH), 135.2 (C), 136.0 (d, J = 3.6 Hz, C), 139.3 (C), 161.2 (d, J = 244.8 Hz, C), 166.1 (C), 168.6 (C); mp 132 °C; $[\alpha]^{22}_D$ −52.2 (*c* 0.5, CH_2Cl_2). Anal. Calcd for $C_{27}H_{24}FNO_4$: C, 72.80; H, 5.43; N, 3.14. Found: C, 72.63; H, 5.42; N, 3.10.

(3*R*,6*R*,7*S*,8a*S*)-6-(Methoxycarbonyl)-5-oxo-3,7-diphenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (12a). Operating as in the preparation of the unsaturated lactam *trans*-**4**, the selenide *trans*-**3** (500 mg, 1.16 mmol) was converted to **(3*R*,8a*S*)-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine (*trans*-5)**, which was used without further purification: IR (film) 1736, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.58 (ddd, J = 17.8, 10.0, 2.4 Hz, 1 H), 2.94 (ddd J = 17.8, 6.7, 5.3 Hz, 1 H), 3.80 (s, 3 H), 3.94 (dd, J = 8.9, 6.3 Hz, 1 H), 4.48 (dd, J = 8.9, 7.0 Hz, 1 H), 5.29 (dd, J = 7.0, 6.3 Hz, 1 H), 5.45 (dd, J = 10.0, 5.3 Hz, 1 H), 7.6 (m, 1 H), 7.10−7.50 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 30.1 (CH_2), 52.2 (CH_3), 58.3 (CH), 73.1 (CH_2), 86.3 (CH), 126.1 (CH), 127.6 (CH), 128.6 (CH), 129.4 (C), 138.7 (C), 142.6 (CH), 157.2 (C), 164.2 (C). A solution of the above crude lactam *trans*-**5** in anhydrous THF (2 mL) was allowed to react with PhCu(CN)Li (2.5 equiv) [prepared from 1.7 M PhLi in THF (1.7 mL, 2.9 mmol) and CuCN (293 mg, 3.2 mmol)] as in the above preparation of **10**. The resulting crude oil (598 mg) was chromatographed (4:1 to 2:1 AcOEt−hexane) to afford (352 mg, 86% from *trans*-**3**) a 97:3 mixture of C-6 epimers **12a** and **12b**, respectively. Crystallization from THF−hexane rendered pure **12a**: IR (film) 1745, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (ddd, J = 14.0, 8.3, 5.0 Hz, 1 H), 2.45 (dt, J = 14.0, 5.0 Hz, 1 H), 3.65 (s, 3 H), 3.66 (td, J = 8.3, 5.0 Hz, 1 H), 3.78 (dd, J = 9.0, 7.7 Hz, 1 H), 3.79 (d, J = 8.3 Hz, 1 H), 4.51 (dd, J = 9.0, 7.7 Hz, 1 H), 4.87 (t, J = 5.0 Hz, 1 H), 5.41 (t, J = 7.7 Hz, 1 H), 7.20−7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 33.2 (CH_2), 37.9 (CH), 52.3 (CH_3), 53.6 (CH), 58.6 (CH), 71.6 (CH_2), 85.8 (CH), 126.1 (CH), 126.7 (CH), 127.2 (CH), 127.6 (CH), 128.6 (CH), 128.7 (CH), 139.3 (C), 140.5 (C), 165.8 (C), 169.50 (C); mp 112−114 °C; $[\alpha]^{22}_D$ −45.2 (*c* 1.0, MeOH). Anal. Calcd for $C_{21}H_{21}NO_4$: C,

(21) Brandsma, L.; Verkruijsse, H. *Preparative Polar Organometallic Chemistry 1*; Springer-Verlag: Heidelberg, 1987; p 189.

71.77; H, 6.02; N, 3.98. Found: C, 71.64; H, 6.01; N, 3.94. In some runs small amounts (<5%) of pyridone **7** were isolated: IR (film) 1729, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (s, 3 H), 4.25 (dd, J = 12.0, 6.7 Hz, 1 H), 4.33 (dd, J = 12.0, 5.0 Hz, 1 H), 6.23 (t, J = 6.9 Hz, 1 H), 6.49 (dd, J = 6.7, 5.0 Hz, 1 H), 7.35 (m, 5 H), 7.60 (dd, J = 6.9, 2.1 Hz, 1 H), 8.13 (dd, J = 6.9, 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 51.9 (CH_3), 59.7 (CH), 61.9 (CH_2), 104.7 (CH), 119.1 (C), 127.8 (CH), 128.0 (CH), 128.7 (CH), 136.8 (C), 141.4 (CH), 144.5 (CH), 159.9 (C), 165.3 (C). $[\alpha]^{22}_D$ −280.9 (*c* 1.1, MeOH). Anal. Calcd for $C_{15}H_{15}NO_4 \cdot 1/4H_2O$: C, 64.86; H, 5.62; N, 5.04. Found: C, 65.09; H, 5.95; N, 5.23.

(3*R*,6*R*,7*S*,8a*S*)-7-(*p*-Fluorophenyl)-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (13a). Operating as in the above preparation of **12**, from selenide *trans*-**3** (644 mg, 1.5 mmol) and lithium (*p*-fluorophenyl)cyanocuprate (2.5 equiv) [prepared from 0.16 M (*p*-fluorophenyl)lithium[21] in THF (24 mL) and CuCN (374 mg, 4.18 mmol)] was obtained a 97:3 mixture of C-6 epimers **13a** and **13b**, respectively, (429 mg, 80% from *trans*-**3**) after purification by column chromatography (2:3 AcOEt−hexane). Crystallization from THF−hexane afforded pure **13a**: IR (film) 1746, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.24 (ddd, J = 14.5, 9.0, 5.0 Hz, 1 H), 2.34 (dt, J = 14.5, 4.5 Hz, 1 H), 3.54 (td, J = 9.0, 4.5 Hz, 1 H), 3.55 (s, 3 H), 3.62 (d, J = 9.0 Hz, 1 H), 3.71 (dd, J = 8.5, 7.0 Hz, 1 H), 4.41 (t, J = 8.5 Hz, 1 H), 4.80 (t, J = 4.5 Hz, 1 H), 5.34 (t, J = 8.0 Hz, 1 H), 6.94 (t, J = 8.5 Hz, 1 H), 7.11 (dd, J = 8.5, 5.0 Hz, 1 H), 7.16−7.22 (m, 3 H), 7.26 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 33.1 (CH_2), 37.2 (CH), 52.2 (CH_3), 54.1 (CH), 58.5 (CH), 71.5 (CH_2), 85.6 (CH), 115.5 (d, J = 21.0 Hz, CH), 126.0 (CH), 127.6 (CH), 128.3 (d, J = 8.2 Hz, CH), 128.6 (CH), 136.2 (d, J = 2.7 Hz, C), 139.2 (C), 161.5 (d, J = 244.8 Hz, C), 165.8 (C), 169.2 (C); mp 127 °C; $[\alpha]^{22}_D$ −37.1 (*c* 0.5, CH_2Cl_2). Anal. Calcd for $C_{21}H_{20}FNO_4$: C, 68.28; H, 5.46; N, 3.79. Found: C, 68.26; H, 5.46; N, 3.77.

(3*R*,7*S*,8a*S*)-7-Methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (14). Ammonium formate (110 mg, 1.75 mmol) and 10% Pd−C (47 mg) were added to a solution of **8** (80 mg, 0.22 mmol) in anhydrous MeOH (3 mL). The resulting suspension was stirred at 25 °C for 20 h, filtered, and concentrated to give an oil, which was dissolved in toluene (17 mL). The solution was heated to reflux for 2 h, cooled, and poured into brine. The aqueous layer was extracted with AcOEt (2 × 15 mL), and the combined organic layers were dried and concentrated. The residue was chromatographed (1:1 AcOEt−hexane) to afford pure lactam **14** (37 mg, 73%) as a white solid: IR (film) 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, J = 6.8 Hz, 3 H), 1.92 (ddd, J = 13.6, 6.0, 4.0 Hz, 1 H), 2.05 (m, 1 H), 2.15−2.35 (m, 2 H), 2.52 (dd, J = 16.7, 4.0 Hz, 1 H), 3.74 (dd, J = 8.8, 7.6 Hz, 1 H), 4.50 (t, J = 8.6 Hz, 1 H), 5.04 (t, J = 5.8 Hz, 1 H), 5.37 (t, J = 7.8 Hz, 1 H), 7.20−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.0 (CH_3), 24.3 (CH), 34.0 (CH_2), 39.4 (CH_2), 57.9 (CH), 71.9 (CH_2), 86.4 (CH), 125.8 (CH), 127.5 (CH), 128.8 (CH), 139.9 (C), 169.4 (C); $[\alpha]^{22}_D$ −168.2 (*c* 0.5, MeOH). Anal. Calcd for $C_{14}H_{17}NO_2 \cdot 1/4H_2O$: C, 71.32; H, 7.48; N, 5.94. Found: C, 71.32; H, 7.38; N, 5.82.

(3*R*,7*S*,8a*S*)-7-Butyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (15). Operating as above, from lactam **9** (350 mg, 0.86 mmol), ammonium formate (432 mg, 6.88 mmol), and 10% Pd−C (183 mg) was obtained compound **15** (176 mg, 74%) as an oil: IR (film) 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3 H), 1.25−1.55 (m, 6 H), 1.91 (m, 1 H), 2.10−2.15 (m, 2 H), 2.24 (dd, J = 17.0, 7.0 Hz, 1 H), 2.52 (dd, J = 17.0, 5.0 Hz, 1 H), 3.73 (dd, J = 8.8, 7.6 Hz, 1 H), 4.48 (t, J = 8.5 Hz, 1 H), 5.00 (t, J = 5.0 Hz, 1 H), 5.36 (t, J = 8.0 Hz, 1 H), 7.20−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 22.4 (CH_2), 29.0 (CH), 29.1 (CH_2), 32.1 (CH_2), 33.7 (CH_2), 37.7 (CH_2), 57.8 (CH), 71.7 (CH_2), 86.2 (CH), 125.6 (CH), 127.3 (CH), 128.6 (CH), 139.7 (C), 169.4 (C); $[\alpha]^{22}_D$ −114,9 (*c* 1.6, MeOH). Anal. Calcd for $C_{17}H_{23}NO_2 \cdot 1/4H_2O$: C, 73.50; H, 8.46; N, 5.05. Found: C, 73.53; H, 8.56; N, 5.03.

(3*R*,7*S*,8a*S*)-7-(*p*-Fluorophenyl)-5-oxo-3-phenyl-2,3,6,7,8,-8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (16). Operating as in the preparation of **14**, from lactam **11** (120 mg, 0.26 mmol), ammonium formate (131 mg, 2.08 mmol), and 5% Pd−C (110 mg) was obtained compound **16** (84 mg, 98%) as white solid: IR (film) 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.09 (ddd, J = 13.5, 6.0, 4.0 Hz, 1 H), 2.34 (ddd, J = 13.5, 7.0, 4.5 Hz, 1 H), 2.66 (d, J = 5.0 Hz, 2 H), 3.35 (m, 1 H), 3.61 (dd, J = 8.5, 7.0 Hz, 1 H), 4.40 (t, J = 9.0 Hz, 1 H), 4.68 (t, J = 5.5 Hz, 1 H), 5.30 (t, J = 8.0 Hz, 1 H), 6.97 (m, 1 H), 7.10−7.22 (m, 7 H), 7.27 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 33.7 (CH), 34.6 (CH_2), 37.3 (CH_2), 58.2 (CH), 72.0 (CH_2), 86.1 (CH), 115.5 (d, J = 21.0 Hz, CH), 125.8 (CH), 127.6 (CH), 128.2 (d, J = 8.1 Hz, CH), 128.8 (CH), 137.5 (d, J = 3.0 Hz, C), 139.6 (C), 161.6 (d, J = 244.8 Hz, C), 168.8 (C); $[\alpha]^{22}_D$ +15.1 (*c* 0.5, CH_2Cl_2). Anal. Calcd for $C_{19}H_{18}FNO_2$: C, 73.29; H, 5.83; N, 4.50. Found: C, 73.01; H, 5.86; N, 4.43.

(3*R*,8a*R*)-6-(Benzylox-ycarbonyl)-5-oxo-3-phenyl-6-(phenylselanyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]-pyridine (*cis*-2). Operating as in the preparation of *trans*-**2**, from lactam *cis*-**1** (1.0 g, 4.6 mmol), benzyl chloroformate (0.65 mL, 4.6 mmol), and PhSeBr (1.5 g, 6.4 mmol) was obtained compound *cis*-**2** as a mixture of C-6 epimers (1.8 g, 77%) after column chromatography (1:1 AcOEt−hexane). *cis*-**2** (higher R_f epimer): ^1H NMR ($CDCl_3$) δ 1.82 (m, 1 H), 2.12 (m, 2 H), 2.37 (m, 1 H), 3.95 (dd, J = 9.0, 1.7 Hz, 1 H), 4.03 (dd, J = 9.0, 6.9 Hz, 1 H), 4.38 (dd, J = 10.0, 3.2 Hz, 1 H), 4.84 (dd, J = 6.9, 1.7 Hz, 1 H), 5.06 (s, 2 H), 7.10−7.40 (m, 13 H), 7.60 (d, J = 6.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.1 (CH_2), 31.0 (CH_2), 54.0 (C), 59.3 (CH), 67.8 (CH_2), 74.0 (CH_2), 88.6 (CH), 135.1 (C), 138.2 (CH), 140.4 (C), 163.3 (C), 170.1 (C). *cis*-**2** (lower R_f epimer): ^1H NMR ($CDCl_3$) 2.00−2.30 (m, 4 H), 4.00−4.10 (m, 2 H), 4.71 (dd, J = 8.5, 4.5 Hz, 1 H), 4.92 (dd, J = 6.0, 2.0 Hz, 1 H), 5.14 (d, J = 12.2 Hz, 1 H), 5.23 (d, J = 12.2 Hz, 1 H), 7.17−7.40 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 25.7 (CH_2), 28.0 (CH_2), 55.2 (C), 59.0 (CH), 67.6 (CH_2), 74.0 (CH_2), 87.4 (CH), 135.3 (C), 138.2 (CH), 140.6 (C), 163.0 (C), 169.7 (C).

(3*R*,8a*R*)-6-(Methoxycarbonyl)-5-oxo-3-phenyl-6-(phenylselanyl)-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]-pyridine (*cis*-3). Operating as in the preparation of *trans*-**2**, from lactam *cis*-**1** (755 mg, 3.5 mmol), methyl chloroformate (0.27 mL, 3.5 mmol), and PhSeCl (932 mg, 4.9 mmol) was obtained compound *cis*-**3** as a mixture of C-6 epimers (1.21 g, 81%) after column chromatography (1:1 AcOEt−hexane); IR (film) 1727, 1663 cm^{-1}. *cis*-**3** (higher R_f epimer): ^1H NMR ($CDCl_3$) δ 1.80 (dddd, J = 12.5, 12.5, 10.2, 3.5 Hz, 1 H), 2.08 (td, J = 14.2, 3.5 Hz, 1 H), 2.18 (dq, J = 12.5, 3.5 Hz, 1 H), 2.34 (td, J = 14.2, 3.5 Hz, 1 H), 3.60 (s, 3 H), 4.00 (dd, J = 9.5, 1.8 Hz, 1 H), 4.10 (dd, J = 9.5, 7.0 Hz, 1 H), 4.54 (dd, J = 10.2, 3.5 Hz, 1 H), 4.87 (dd, J = 7.0, 1.8 Hz, 1 H), 7.20−7.45 (m, 8 H), 7.66 (d, J = 6.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 27.0 (CH_2), 30.8 (CH_2), 52.8 (CH_3), 52.9 (C), 59.0 (CH), 73.9 (CH_2), 88.6 (CH), 126.6 (CH), 126.7 (CH), 127.4 (CH), 128.1 (CH), 128.7 (CH), 138.1 (CH), 140.4 (C), 163.3 (C), 170.8 (C). *cis*-**3** (lower R_f epimer): ^1H NMR ($CDCl_3$) δ 2.05−2.35 (m, 4 H), 3.73 (s, 3 H), 4.08 (dd, J = 9.0, 1.4 Hz, 1 H), 4.19 (dd, J = 9.0, 6.7 Hz, 1 H), 4.90 (dd, J = 8.8, 4.2 Hz, 1 H), 4.94 (dd, J = 6.7, 1.4 Hz, 1 H), 7.20−7.42 (m, 8 H), 7.47 (d, J = 6.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.6 (CH_2), 28.1 (CH_2), 53.1 (CH_3), 55.2 (C), 59.0 (CH), 74.0 (CH_2), 87.7 (CH), 126.8 (CH), 127.6 (CH), 128.4 (CH), 128.7 (CH), 129.5 (CH), 138.1 (CH), 140.5 (C), 163.0 (C), 170.5 (C).

[3*R*,6*S*(and 6*R*),7*R*,8a*R*]-6-(Benzyloxycarbonyl)-7-methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (17a and 17b). Operating as in the preparation of the unsaturated lactam *trans*-**4**, the selenide *cis*-**2** (530 mg, 1.05 mmol) was converted to **(3*R*,8a*R*)-6-(benzyloxycarbonyl)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-a]pyridine** (*cis*-**4**), which was used without further purification: IR (film) 1733, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (ddd, J = 17.5, 11.5, 2.2 Hz, 1 H), 2.96 (ddd, J = 17.5, 6.8, 4.5 Hz, 1 H), 4.18 (dd, J = 9.0, 1.8 Hz, 1 H), 4.23 (dd, J = 9.0, 6.3 Hz, 1 H), 5.05 (dd, J = 6.3, 1.8 Hz, 1 H), 5.14 (dd, J = 11.5, 4.5 Hz, 1 H), 5.20 (d, J = 12.4 Hz, 1 H), 5.22 (d, J = 12.4 Hz, 1 H), 7.25−7.63 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 30.0 (CH_2), 58.0 (CH), 66.9 (CH_2), 74.5 (CH_2), 86.1 (CH), 126.6 (CH), 128.1 (CH), 128.4 (CH), 127.6 (C), 130.3 (C), 135.4 (C), 140.3 (C), 143.3 (CH), 157.7 (C), 163.4 (C). A solution of crude lactam *cis*-**4** was allowed to react with $CH_3Cu(CN)Li$ (2.5 equiv) [prepared from

1.7 M CH_3Li in Et_2O (1.54 mL) and CuCN (258 mg, 2.88 mmol)] as in the above preparation of **8** to give (245 mg, 64% from *cis*-**2**) a 3:1 mixture of C-6 epimers **17a** and **17b**, respectively, after purification by column chromatography (3:7 AcOEt−hexane). **17a**: IR (film) 1739, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 7.2 Hz, 3 H), 2.10 (m, 1 H), 2.32 (ddd, J = 13.1, 9.3, 6.6 Hz, 1 H), 2.59 (m, 1 H), 3.13 (d, J = 5.4 Hz, 1 H), 4.04 (dd, J = 9.0, 1.2 Hz, 1 H), 4.19 (dd, J = 9.0, 6.8 Hz, 1 H), 4.94 (dd, J = 6.8, 1.2 Hz, 1 H), 4.99 (dd, J = 9.4, 4.7 Hz, 1 H), 5.08 (d, J = 12.4 Hz, 1 H), 5.13 (d, J = 12.4 Hz, 1 H), 7,22−7,35 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 20.5 (CH_3), 28.5 (CH), 32.5 (CH_2), 54.9 (CH), 58.7 (CH), 66.9 (CH_2), 74.1 (CH_2), 85.8 (CH_2), 126.3 (CH), 127.5 (CH), 128.3 (CH), 128.4 (CH), 135.4 (C), 140.5 (C), 163.2 (C), 169.5 (C). **17b**: ^1H NMR ($CDCl_3$, selected resonances) δ 1.08 (d, J = 6.7 Hz, 3 H), 3.40 (d, J = 5.0 Hz, 1 H), 4.03 (dd, J = 9.0, 1.2 Hz, 1 H), 4.17 (dd, J = 9.0, 7.0 Hz, 1 H), 4,88 (dd, J = 7.0, 1.2 Hz, 1 H), 5.15 (masked, 1 H), 5.15 (s, 2 H), 7.22−7.35 (m, 10 H); ^{13}C NMR ($CDCl_3$, selected resonances) δ 17.6 (CH_3), 28.4 (CH), 33.1 (CH_2), 54.4 (CH), 58.3 (CH), 66.8 (CH_2), 73.8 (CH_2), 86.1 (CH), 135.3 (C), 141.1 (C), 163.4 (C), 168.6 (C).

(3*R*,6*S*,7*R*,8a*R*)-6-(Benzyloxycarbonyl)-5-oxo-3,7-diphenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (18a). Operating as above, from the selenide *cis*-**2** (377 mg, 0.74 mmol) and PhCu(CN)Li (2.5 equiv) [prepared from 1.7 M C_6H_5Li in cyclohexane (1.1 mL) and CuCN (186 mg, 2.1 mmol)] was obtained a 97:3 mixture of C-6 epimers **18a** and **18b**, respectively, (240 mg, 75% from *cis*-**2**) after purification by column chromatography (3:7 AcOEt−hexane). Crystallization from Et_2O−hexane afforded pure **18a**: IR (film) 1737, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2,42 (m, 1 H), 2.57 (ddd, J = 13.2, 6.7, 2.9 Hz, 1 H), 3.73 (m, 2 H), 4.03 (dd, J = 9.0, 1.5 Hz, 1 H), 4.13 (dd, J = 9.0, 6.8 Hz, 1 H), 4.81 (dd, J = 9.2, 4.5 Hz, 1 H), 4.97 (dd, J = 6.8, 1.5 Hz, 1 H), 5.03 (d, J = 12.4 Hz, 1 H), 5.07 (d, J = 12.4 Hz, 1 H), 7.13−7.40 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 33.7 (CH_2), 39.0 (CH), 53.1 (CH), 58.9 (CH), 67.1 (CH_2), 74.1 (CH_2), 86.0 (CH), 126.4 (CH), 126.9 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 129.0 (CH), 127.2 (CH), 127.7 (CH), 128.1 (CH), 135.2 (C), 140.4 (C), 141.8 (C), 163.1 (C), 169.3 (C); mp 93−96 °C; $[\alpha]^{22}_D$ −93.5 (*c* 1.0, MeOH). Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.90; H, 5.90; N, 3.29.

(3*R*,6*S*,7*R*,8a*R*)-6-(Benzyloxycarbonyl)-7-(*p*-fluorophenyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (19a). Operating as above, from the selenide *cis*-**2** (664 mg, 1.3 mmol) and *p*-$FC_6H_4Cu(CN)Li$ (2.6 equiv) [prepared from 0.13 M (*p*-fluorophenyl)lithium[21] in THF (25 mL) and CuCN (319 mg, 3.6 mmol)] was obtained a 97:3 mixture of C-6 epimers **19a** and **19b**, respectively, (383 mg, 64% from *cis*-**2**) after purification by column chromatography (1:4 to 1:1 AcOEt−hexane). **19a**: IR (film) 1741, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (dt, J = 13.5, 5.0 Hz, 1 H), 2.56 (ddd, J = 13.5, 9.0, 7.0 Hz, 1 H), 3.68 (m, 2 H), 4.06 (dd, J = 9.0, 1.5 Hz, 1 H), 4.16 (dd, J = 9.0, 6.8 Hz, 1 H), 4.85 (dd, J = 9.5, 5.0 Hz, 1 H), 4.98 (dd, J = 6.8, 1.5 Hz, 1 H), 7.11 (t, J = 8.5 Hz, 2 H), 7.14 (m, 4 H), 7.20−7.40 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 34.1 (CH_2), 38.3 (CH), 53.7 (CH), 58.7 (CH), 67.0 (CH_2), 74.2 (CH_2), 85.9 (CH), 115.6 (d, J = 21.5 Hz, CH), 126.3 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.3 (d, J = 8.1 Hz, CH), 128.5 (CH), 128.6 (CH), 135.2 (C), 137.5 (d, J = 3.0 Hz, C), 140.3 (C), 161.5 (d, J = 244.7 Hz, C), 163.0 (C), 168.8 (C); mp 76−78 °C (Et_2O); $[\alpha]^{22}_D$ −72.4 (*c* 1.0, MeOH), $[\alpha]^{22}_D$ −66.0 (*c* 0.2, CH_2Cl_2). Anal. Calcd for $C_{27}H_{24}FNO_4$: C, 72.79; H, 5.43; N, 3.14. Found: C, 72.71; H, 5.46; N, 3.12.

(3*R*,6*S*,7*R*,8a*R*)-7-(*p*-Fluorophenyl)-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (20a). Operating as in the preparation of the unsaturated lactam *trans*-**4**, the selenide *cis*-**3** (675 mg, 1.57 mmol) was converted to **(3*R*,8a*R*)-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine** (*cis*-**5**), which was used without further purification: ^1H NMR ($CDCl_3$) δ 2.71(ddd, J = 17.5, 11.6, 2.2 Hz, 1 H), 3.00 (ddd, J = 17.5, 6.8, 4.5 Hz, 1 H), 3.79 (s, 3 H), 4.20 (dd, J = 9.0, 1.9 Hz, 1 H), 4.26 (dd, J = 9.0, 6.3 Hz, 1 H), 5.03 (dd, J = 6.3, 1.9 Hz, 1 H), 5.15 (dd, J = 11.6, 4.5 Hz, 1 H), 7.20−7.40 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 30.5 (CH_2), 52.2 (CH_3), 58.0 (CH), 74.4 (CH_2), 86.1 (CH), 126.7 (CH), 127.6 (CH), 128.4 (CH), 130.0 (C), 140.2 (C), 143.4 (CH), 157.3 (C), 164.2 (C). A solution of crude lactam *cis*-**5** in anhydrous THF (5 mL) was allowed to react with *p*-$FC_6H_4Cu(CN)Li$ (2.5 equiv) [prepared from 0.13 M (*p*-fluorophenyl)lithium[21] in THF (30 mL) and CuCN (372 mg, 4.2 mmol)] as in the above preparation of **19**. The resulting crude oil (705 mg) was chromatographed (1:4 to 1:1 AcOEt−hexane) to give a 97:3 mixture of C-6 epimers **20a** and **20b** (388 mg, 67%), respectively. **20a**: IR (film) 1744, 1681 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (dt, J = 13.2, 4.7 Hz, 1 H), 2.55 (ddd, J = 13.2, 9.3, 7.0 Hz, 1 H), 3.59 (s, 3 H), 3.63 (d, J = 6.0 Hz, 1 H), 3.72 (m, 1 H), 4.04 (dd, J = 9.0, 1.3 Hz, 1 H), 4.14 (dd, J = 9.0, 6.8 Hz, 1 H), 4.81 (dd, J = 9.3, 4.7 Hz, 1 H), 4.96 (dd, J = 6.8, 1.3 Hz, 1 H), 7.03 (t, J = 8.5 Hz, 2 H), 7.18 (dd, J = 8.5, 5.0 Hz, 2 H), 7.20−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 33.8 (CH_2), 38.4 (CH), 52.4 (CH_3), 53.3 (CH), 58.9 (CH), 74.2 (CH_2), 85.9 (CH), 115.7 (d, J = 21.2 Hz, CH), 126.5 (CH), 127.7 (CH), 128.3 (d, J = 8.2 Hz, CH), 128.5 (CH), 137.6 (d, J = 2.6 Hz, C), 140.4 (C), 161.7 (d, J = 244.7 Hz, C), 163.0 (C), 169.6 (C); mp 116−118 °C (Et_2O); $[\alpha]^{22}_D$ −99.2 (*c* 1.0, MeOH), $[\alpha]^{22}_D$ −120.8 (*c* 0.2, CH_2Cl_2). Anal. Calcd for $C_{21}H_{20}FNO_4$: C, 68.28; H, 5.46; N, 3.79. Found: C, 68.19; H, 5.49; N, 3.77.

(3*R*,7*R*,8a*R*)-7-Methyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine (21). Operating as in the preparation of **14**, from lactam **17** (200 mg, 0.55 mmol), ammonium formate (275 mg, 4.38 mmol), and 10% Pd−C (116 mg) was obtained compound **21** (107 mg, 85%) as a solid: IR (film) 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (d, J = 7.1 Hz, 1 H), 2.02 (ddd, J = 13.0, 8.8, 6.3 Hz, 1 H), 2.07 (dd, J = 16.5, 5.1 Hz, 1 H), 2.13 (td, J = 13.0, 5.0 Hz, 1 H), 2.34 (dd, J = 6.3, 12.1 Hz, 1 H), 2.43 (dd, J = 16.5, 5.7 Hz, 1 H), 4.03 (dd, J = 9.0, 1.3 Hz, 1 H), 4.18 (dd, J = 9.0, 6.8 Hz, 1 H), 4.93 (d, J = 6.8 Hz, 1 H), 5.00 (dd, J = 8.8, 5.0 Hz, 1 H), 7.13−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3), 24.5 (CH), 34.3 (CH_2), 39.0 (CH_2), 58.2 (CH), 73.8 (CH_2), 85.9 (CH), 126.1 (CH), 128.3 (CH), 127.2 (C), 141.2 (C), 167.4 (C); mp 61−64 °C (*i*-Pr_2O−hexane); $[\alpha]^{22}_D$ −46.3 (*c* 1.0, MeOH). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.78; H, 7.44; N, 6.06.

(3*R*,4*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-4-phenyl-3-piperidinemethanol (22). To a suspension of $AlCl_3$ (163 mg, 1.2 mmol) in anhydrous THF (9.5 mL) at 0 °C was slowly added $LiAlH_4$ (142 mg, 3.7 mmol). After the mixture was stirred at 25 °C for 30 min and cooled to −78 °C, lactam **12a** (200 mg, 0.56 mmol) was slowly added. The stirring was continued for 90 min at −78 °C and for 2 h at 25 °C. Then, 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 × 10 mL), and the combined organic extracts were dried and concentrated to give a foam. Column chromatography (98:2 AcOEt−DEA) afforded pure **22** (152 mg, 86%): IR (film) 3383 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (t, J = 11.0 Hz, 1 H), 1.78−2.40 (m, 3 H), 2.17 (td, J = 11.5, 4.5 Hz, 1 H), 2.41 (td, J = 11.5, 2.8 Hz, 1 H), 3.01 (dm, J = 11.5 Hz, 1 H), 3.14 (dd, J = 11.0, 7.1 Hz, 1 H), 3.20 (dm, J = 11.0 Hz, 1 H), 3.35 (dd, J = 11.0, 3.3 Hz, 1 H), 3.67 (dd, J = 10.2, 4.8 Hz, 1 H), 3.80 (dd, J = 10.2, 4.8 Hz, 1 H), 4.08 (t, J = 10.2 Hz, 1 H), 7.10−7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 34.8 (CH_2), 44.4 (CH), 45.1 (CH), 49.4 (CH_2), 53.2 (CH_2), 60.0 (CH_2), 63.7 (CH_2), 70.1 (CH), 126.4 (CH), 127.3 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 135.1 (C), 144,08 (C); mp 124−126 °C (AcOEt−hexane); $[\alpha]^{22}_D$ +28.6 (*c* 0.5, MeOH). Anal. Calcd for $C_{20}H_{25}NO_2 \cdot 1/4H_2O$: C, 76.04; H, 8.14; N, 4.43. Found: C, 75.86; H, 7.86; N, 4.49.

(3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-phenyl-3-piperidinemethanol (23). A solution of piperidine **22** (191 mg, 0.61 mmol) and di-*tert*-butyl dicarbonate (267 mg, 1.22 mmol) in AcOEt (20 mL) containing 20% $Pd(OH)_2$−C (48 mg) was hydrogenated at 25 °C for 15 h. The catalyst was removed by filtration, and the solvent was evaporated. The resulting oil was chromatographed (3:7 AcOEt−hexane with 4% DEA) to give a mixture (214 mg) of compound **23** and phenylethanol. Crystallization (THF−hexane) afforded pure carbamate **23** (150 mg, 88%): IR (film) 3400, 1692, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H), 1.60−1.74 (m, 3 H), 2.51 (td, J = 11.3,

4.1 Hz, 1 H), 2.69 (dd, J = 13.2, 11.5 Hz, 1 H), 2.78 (tm, J = 12.7 Hz, 1 H), 3.25 (dd, J = 11.0, 6.5 Hz, 1 H), 3.42 (dd, J = 11.0, 3.3 Hz, 1 H), 4.20 (dm, J = 12.7 Hz, 1 H), 4.36 (dm, J = 13.2 Hz, 1 H), 7.15−7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 28.5 (CH_3), 33.9 (CH_2), 43.7 (CH), 44.5 (CH_2), 44.9 (CH), 46.9 (CH_2), 63.1 (CH_2), 79.6 (C), 126.6 (CH), 127.4 (CH), 128.6 (CH), 143.8 (C), 154.9 (C); mp 132−133 °C; $[\alpha]^{22}_D$ +6.4 (*c* 0.4, MeOH). Anal. Calcd for $C_{17}H_{25}NO_3 \cdot 1/4H_2O$: C, 69.01; H, 8.69; N, 4.73. Found: C, 69.10; H, 8.51; N, 4.64.

(3*R*,4*S*)-4-(*p*-Fluorophenyl)-1-[(1*R*)-2-hydroxy-1-phenylethyl]-3-piperidinemethanol (24). Operating as in the preparation of **22**, from lactam **13a** (595 mg, 1.61 mmol), $AlCl_3$ (462 mg, 3.47 mmol), and $LiAlH_4$ (396 mg, 10.45 mmol) was obtained compound **24** (370 mg, 74%) after column chromatography (97:3 AcOEt−DEA): IR (film) 3416 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.65 (t, J = 11.0 Hz, 1 H), 1.70−1.95 (m, 3 H), 2.14 (td, J = 11.3, 4.6 Hz, 1 H), 2.37 (td, J = 11.5, 3. 3 Hz, 1 H), 2.39 (br s, 2 H), 2.95 (dm, J = 11.5 Hz, 1 H), 3.09 (dd, J = 11.0, 7.3 Hz, 1 H), 3.18 (dm, J = 11.0 Hz, 1 H), 3.30 (dd, J = 11.0, 3.2 Hz, 1 H), 3.63 (dd, J = 10.4, 5.0 Hz, 1 H), 3.77 (dd, J = 10.4, 5.0 Hz, 1 H), 4.04 (t, J = 10.4 Hz, 1 H), 6.92 (t, J = 8.8 Hz, 2 H), 7.06 (dd, J = 8.8, 5.6 Hz, 2 H), 7.19 (m, 2 H), 7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 35.0 (CH_2), 44.2 (CH), 44.6 (CH), 49.3 (CH_2), 53.2 (CH_2), 60.0 (CH_2), 63.6 (CH_2), 70.1 (CH), 115.2 (d, J = 21.0 Hz, CH), 127.9 (CH), 128.2 (CH), 128.6 (d, J = 7.5 Hz, CH), 128.9 (CH), 135.1 (C), 139.7 (d, J = 3.0 Hz, C), 161.0 (d, J = 243.2 Hz, C); mp 138−139 °C (Et_2O); $[\alpha]^{22}_D$ +31.4 (*c* 0.5, MeOH). Anal. Calcd for $C_{20}H_{24}FNO_2$: C, 72.92; H, 7.34; N, 4.25. Found: C, 73.06; H, 7.49; N, 4.26.

(3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(*p*-fluorophenyl)-3-piperidinemethanol (25). Operating as in the preparation of **23**, from compound **24** (495 mg, 1.60 mmol), di-*tert*-butyl dicarbonate (625 mg, 2.87 mmol), and 20% $Pd(OH)_2$−C (150 mg) was obtained carbamate **25** (363 mg, 73%) after column chromatography (1:1 CH_2Cl_2-Et_2O): IR (film) 3515, 1666 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 1 H), 1.48 (s, 9H), 1.55−1.90 (m, 3 H), 2.53 (td, J = 11.5, 4.1 Hz, 1 H), 2.70 (dd, J = 13.3, 11.2 Hz, 1 H), 2.77 (td, J = 12.4, 2.8 Hz, 1 H), 3.25 (dt, J = 11.0, 6.1 Hz, 1 H), 3.43 (ddd, J = 11.0, 4.6, 3.4 Hz, 1 H), 4.18 (dm, J = 13.0 Hz, 1 H), 4.35 (ddd, J = 13.2, 4.1, 1.7 Hz, 1 H), 6.98 (m, 2 H), 7.13 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.5 (CH_3), 34.4 (CH_2), 43.9 (CH), 44.2 (CH), 44.4 (CH_2), 47.0 (CH_2), 63.0 (CH_2), 79.6 (C), 115.4 (d, J = 20.5 Hz, CH), 128.7 (d, J = 7.6 Hz, CH), 139.6 (d, J = 3.3 Hz, C), 154.8 (C), 161.3 (d, J = 243.1 Hz, C); $[\alpha]^{22}_D$ +5.8 (*c* 1.75, MeOH). Anal. Calcd for $C_{17}H_{24}FNO_3$: C, 65.99; H, 7.82; N, 4.53. Found: C, 65.78; H, 7.89; N, 4.37.

(3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-(*p*-methoxyphenoxymethyl)-4-phenylpiperidine (26). Methanesulfonyl chloride (141 mL, 1.82 mmol) was slowly added to a solution of alcohol **23** (391 mg, 1.40 mmol) in pyridine (2 mL) at 10 °C, and the mixture was stirred at this temperature for 1 h. The resulting suspension was poured into 10% aqueous $NaHCO_3$ and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried and concentrated to give a crude mesylate (670 mg) as an oil: IR (film) 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H), 1.62−1.90 (m, 2 H), 2.10 (m, 1 H), 2.56 (td, J = 11.7, 4.1 Hz, 1 H), 2.66−2.88 (m, 2 H), 2.86 (s, 3 H), 3.83 (dd, J = 9.9, 6.6 Hz, 1 H), 3.97 (dd, J = 9.9, 3.0 Hz, 1 H), 4.23 (m, 1 H), 4.40 (m, 1 H), 7.15−7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 28.4 (CH_3), 33.8 (CH_2), 36.9 (CH_3), 40.8 (CH), 44.5 (CH_2), 44.7 (CH), 46.9 (CH_2), 69.7 (CH_2), 79.9 (C), 127.2 (CH), 127.4 (CH), 128.9 (CH), 142.3 (C), 154.6 (C). To a suspension of NaH (122 mg, 2.8 mmol, 55−65% dispersion in mineral oil) in anhydrous THF (3.5 mL) at 0 °C was added *p*-methoxyphenol (347 mg, 2.8 mmol), and the mixture was stirred for 45 min. Then, a solution of the above crude mesylate in anhydrous THF (2 mL) was slowly added, and the resulting mixture was heated at reflux for 3 h, cooled, and poured into 2 N aqueous NaOH. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried and concentrated to give an oil. Column chromatography (CH_2Cl_2) afforded compound **26** (261 mg, 50%): IR (film) 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H), 1.65−1.90 (m, 2 H), 2.09 (m, 1 H), 2.65 (td, J = 11.4, 4.5 Hz, 1 H), 2.80 (t, J = 11.4 Hz, 1 H), 2.83 (masked, 1 H), 3.48 (dd, J = 9.6, 6.9 Hz, 1 H), 3.63 (dd, J = 9.6, 3.0 Hz, 1 H), 3.71 (s, 3 H), 4.25 (dm, J = 12.3 Hz, 1 H), 4.47 (dm, J = 11.4 Hz, 1 H), 6.34 (d, J = 9.0 Hz, 2 H), 6.72 (d, J = 9.0 Hz, 2 H), 7.11−7.29 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 28.4 (CH_3), 33.8 (CH_2), 41.6 (CH), 44.3 (CH_2), 44.8 (CH), 47.4 (CH_2), 55.6 (CH_3), 68.6 (CH_2), 79.5 (C), 114.5 (CH), 115.4 (CH), 126.6 (CH), 127.3 (CH), 128.6 (CH), 143.5 (C), 152.9 (C), 153.7 (C), 154.7 (C); $[\alpha]^{22}_D$ +22.9 (*c* 0.26, MeOH). Anal. Calcd for $C_{24}H_{31}O_4N \cdot H_2O$: C, 69.59; H, 7.99; N, 3.38. Found: C, 69.59; H, 7.52; N, 3.28.

(3*R*,4*S*)-3-(*p*-Methoxyphenoxymethyl)-1-methyl-4-phenylpiperidine (Femoxetine, 27). A solution of carbamate **26** (188 mg, 0.45 mmol) in anhydrous Et_2O (1.7 mL) was added to a suspension of $LiAlH_4$ (78 mg, 2.05 mmol) in anhydrous Et_2O (1.0 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of 2 N aqueous NaOH, and the aqueous layer was extracted with Et_2O. The combined ethereal extracts were dried and concentrated, and the resulting residue was chromatographed (98:2 Et_2O−DEA) to give femoxetine (**27**, 135 mg, 74%) as an oil: IR (film) 1509, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.84 (dm, J = 12.7 Hz, 1 H), 1.92 (m, 1 H), 2.04 (m, 2 H), 2.32 (m, 1 H), 2.38 (s, 3 H), 2.44 (td, J = 11.3, 4.4 Hz, 1 H), 2.99 (dm, J = 10.3 Hz, 1 H), 3.25 (dm, J = 11.2 Hz, 1 H), 3.48 (dd, J = 9.4, 7.1 Hz, 1 H), 3.61 (dd, J = 9.4, 2.9 Hz, 1 H), 3.72 (s, 3 H), 6.66 (d, J = 9.0 Hz, 2 H), 6.74 (d, J = 9.0 Hz, 2 H), 7.10−7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ 34.1 (CH_2), 41.7 (CH), 44.1 (CH), 46.3 (CH_3), 55.5 (CH_3), 56.1 (CH_2), 59.5 (C-2), 69.2 (CH_2), 114.3 (CH), 115.2 (CH), 126.4 (CH), 127.4 (CH), 128.5 (CH), 143.8 (C), 152.9 (C), 153.5 (C); $[\alpha]^{22}_D$ +75.7 (*c* 0.6, MeOH). Femoxetine hydrochloride: mp 179−180 °C (acetone-Et_2O); $[\alpha]^{22}_D$ +78.7 (*c* 0.2, MeOH). Anal. Calcd for $C_{20}H_{26}NO_2Cl$: C, 69.05; H, 7.53; N, 4.03. Found: C, 69.12; H, 7.58; N, 4.03.

(3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(*p*-fluorophenyl)-3-[3,4-(methylenedioxy)phenoxymethyl]piperidine (28). Operating as in the preparation of **26**, from alcohol **25** (260 mg, 0.84 mmol) and methanesulfonyl chloride (73 mL, 0.94 mmol) was obtained a crude mesylate (238 mg): ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9 H), 1.67 (qd, J = 12.8, 4.3 Hz, 1 H), 1.80 (dm, J = 12.8 Hz, 1 H), 2.05 (m, 1 H), 2.56 (td, J = 11.7, 3.8 Hz, 1 H), 2.76 (m, 2 H), 2.89 (s, 3 H), 3.81 (dd, J = 10.0, 6.6 Hz, 1 H), 3.97 (dd, J = 10.0, 3.0 Hz, 1 H), 4.23 (m, 1 H), 4.38 (m, 1 H), 7.02 (t, J = 8.6 Hz, 2 H), 7.15 (dd, J = 8.6, 5.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.2 (CH_3), 33.8 (CH_2), 36.8 (CH_3), 40.8 (CH), 43.6 (CH), 43.9 (CH_2), 46.1 (CH_2), 68.3 (CH_2), 79.6 (C), 115.4 (CH), 128.4 (CH), 137.9 (C), 157.0 (C), 163.1 (C). To a solution of sodium methoxide, prepared from sodium (80 mg) and MeOH (0.6 mL), was added 3,4-(methylenedioxy)phenol (464 mg, 3.4 mmol), and the mixture was stirred at room temperature for 20 min. Then, a solution of the above crude mesylate in MeOH (1 mL) was added, and the resulting mixture was heated at reflux for 90 min, cooled, and concentrated. The residue was taken up with Et_2O, washed with 0.5 N aqueous NaOH, dried, and concentrated. The residue was chromatographed (97:3 CH_2Cl_2−Et_2O), affording pure compound **28** (200 mg, 56%) as an oil: IR (film) 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H), 1.60−1.90 (m, 2 H), 2.02 (m, 1 H), 2.67 (td, J = 11.6, 4.0 Hz, 1 H), 2.80 (m, 2 H), 3.44 (dd, J = 9.3, 6.6 Hz, 1 H), 3.58 (dd, J = 9.6, 2.8 Hz, 1 H), 4.24 (dm, J = 13.3 Hz, 1 H), 4.44 (dm, J = 13.5 Hz, 1 H), 5.88 (s, 2 H), 6.13 (dd, J = 8.5, 2.5 Hz, 1 H), 6.36 (d, J = 2.5 Hz, 1 H), 6.63 (d, J = 8.5 Hz, 1 H), 6.98 (t, J = 8.6 Hz, 2 H), 7.13 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.4 (CH_3), 33.8 (CH_2), 41.8 (CH), 44.0 (CH), 44.2 (CH_2), 47.1 (CH_2), 68.7 (CH_2), 79.6 (C), 97.9 (CH), 101.0 (CH_2), 105.4 (CH), 107.8 (CH), 115.4 (d, J = 21.1 Hz, CH), 128.7 (d, J = 7.7 Hz, CH), 139.0 (C), 141.8 (C), 148.0 (C), 154.2 (C), 154.8 (C), 161.5 (d, J = 243.0 Hz, C); $[\alpha]^{22}_D$ +24.8 (*c* 1.0, MeOH). Anal. Calcd for $C_{24}H_{28}FNO_5$: C, 67.11; H, 6.57; N, 3.26. Found: C, 66.96; H, 6.58; N, 3.22.

(3*R*,4*S*)-4-(*p*-Fluorophenyl)-3-[(3,4-(methylenedioxy)-phenoxymethyl]piperidine [(+)-Paroxetine, 29]. TFA (2.4 mL, 31 mmol) was slowly added to a solution of carbamate **28** (180 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (2.5 mL), and the resulting solution was stirred at room temperature for 15 min. The mixture was poured into saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL).

The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (95:5 AcOEt−DEA) to afford pure **29** (110 mg, 77%) as a colorless oil: IR (film) 2919 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66−1.90 (m, 2 H), 2.10 (m, 1 H), 2.60 (td, J = 12.0, 5.0 Hz, 1 H), 2.71 (t, J = 12.0 Hz, 1 H), 2.76 (td, J = 12.0, 3.0 Hz, 1 H), 3.21 (dm, J = 12.0 Hz, 1 H), 3.44 (dd, J = 9.5, 7.0 Hz, 1 H), 3.44 (masked, 1 H), 3.56 (dd, J = 9.5, 3.0 Hz, 1 H), 5.88 (s, 2 H), 6.12 (dd, J = 8.5, 2.5 Hz, 1 H), 6.34 (d, J = 2.5 Hz, 1 H), 6.62 (d, J = 8.5 Hz, 1 H), 6.98 (t, J = 8.8 Hz, 2 H), 7.13 (dd, J = 8.8, 5.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 32.9 (CH_2), 41.3 (CH), 43.2 (CH), 45.8 (CH_2), 48.6 (CH_2), 68.5 (CH_2), 97.8 (CH), 101.1 (CH_2), 105.4 (CH), 107.8 (CH), 115.6 (d, J = 20.7 Hz, CH), 128.7 (d, J = 7.3 Hz, CH), 138.6 (d, J = 3.0 Hz, C), 141.7 (C), 148.1 (C), 154.0 (C), 161.0 (d, J = 243.3 Hz, C); $[\alpha]^{22}_D$ +81.7 (c 1.3, MeOH). Sample from Seroxat: $[\alpha]^{22}_D$ −89.4 (c 0.75, MeOH).

(3*S*,4*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-4-phenyl-3-piperidinemethanol (30). Operating as in the preparation of **22**, from lactam **18a** (265 mg, 0.62 mmol), $AlCl_3$ (165 mg, 1.2 mmol), and $LiAlH_4$ (165 mg, 4.3 mmol) was obtained compound **30** (96 mg, 50%) after column chromatography (98:2 AcOEt−DEA): IR (film) 3393 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (m, 3 H), 2.05−2.16 (m, 2 H), 2.25 (t, J = 10.5 Hz, 1 H), 2.96 (dm, J = 7.0 Hz, 1 H), 3.18 (dd, J = 11.0, 7.0 Hz, 1 H), 3.24 (ddd, J = 10.5, 3.2, 2.0 Hz, 1 H), 3.37 (dd, J = 11.0, 3.0 Hz, 1 H), 3.66 (dd, J = 10.2, 5.2 Hz, 1 H), 3.80 (dd, J = 10.2, 5.2 Hz, 1 H), 4.03 (t, J = 10.2 Hz, 1 H), 7.13−7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 34.5 (CH_2), 44.8 (CH), 45.1 (CH), 46.4 (CH_2), 56.6 (CH_2), 60.1 (CH_2), 63.8 (CH_2), 70.1 (CH), 126.4 (CH), 127.9 (CH), 127.3 (CH), 128.1 (CH), 128.6 (CH), 129.0 (CH), 135.0 (C), 144.0 (C); $[\alpha]^{22}_D$ −36,2 (c 1.0, MeOH); **30** hydrochloride: mp 227−230 °C (acetone−EtOH−hexane). Anal. Calcd for $C_{20}H_{26}NO_2Cl\cdot H_2O$: C, 65.65; H, 7.71; N, 3.82. Found: C, 65.61; H, 7.48; N, 3.82.

(3*S*,4*R*)-4-*p*-Fluorophenyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-3-piperidinemethanol (31). From lactam **19a**: Operating as in the preparation of **22**, from lactam **19a** (145 mg, 0.32 mmol), $AlCl_3$ (93 mg, 0.7 mmol), and $LiAlH_4$ (81 mg, 2.15 mmol; stirring at 25 °C for 4 h) was obtained compound **31** (80 mg, 75%) after column chromatography (92:8 AcOEt−DEA). IR (film) 3381 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65−1.86 (m, 3 H), 2.05 (m, 1 H), 2.17 (td, J = 10.7, 4.2 Hz, 1 H), 2.26 (t, J = 11.0 Hz, 1 H), 2.96 (dm, J = 10.7 Hz, 1 H), 3.19 (dd, J = 10.8, 7.2 Hz, 1 H), 3.23 (ddd, J = 11.0, 3.6, 1.8 Hz, 1 H), 3.38 (dd, J = 10.8, 3.0 Hz, 1 H), 3.66 (dd, J = 10.0, 5.0 Hz, 1 H), 3.80 (dd, J = 10.0, 5.0 Hz, 1 H), 4.03 (t, J = 10.0 Hz, 1 H); 6.97 (t, J = 8.7 Hz, 2 H), 7.11 (m, 2 H), 7.23 (m, 2 H), 7.34 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 34.6 (CH_2), 44.2 (CH), 44.9 (CH), 46.4 (CH_2), 56.5 (CH_2), 60.2 (CH_2), 63.5 (CH_2), 70.1 (CH), 115.3 (d, J = 20.8 Hz, CH), 127.9 (CH), 128.2 (CH), 128.6 (d, J = 7.7 Hz, CH), 128.9 (CH), 135.3 (C), 139.7 (d, J = 3.0 Hz, C), 161.5 (d, J = 242.8 Hz, C); $[\alpha]^{22}_D$ −40.1 (c 0.5, MeOH); **31** hydrochloride: 191−193 °C (THF−hexane). Anal. Calcd for $C_{20}H_{25}ClFNO_2\cdot 1/4H_2O$: C, 64.85; H, 6.94; N, 3.78. Found: C, 64.89; H, 7.01; N, 3.86.

From lactam **20a**: Operating as in the preparation of **22**, from lactam **20a** (78 mg, 0.21 mmol), $AlCl_3$ (61 mg, 0.45 mmol), and $LiAlH_4$ (1.4 mL of a 1 M THF solution, 1.4 mmol; stirring at 25 °C for 5 h) was obtained compound **31** (80 mg, 75%) after column chromatography (92:8 AcOEt−DEA).

(3*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*p*-fluorophenyl)-3-piperidinemethanol (*ent*-25). Operating as in the preparation of **23**, from diol **31** (473 mg, 1.33 mmol), di-*tert*-butyl dicarbonate (521 mg, 2.39 mmol), and 20% $Pd(OH)_2$−C (133 mg) was obtained carbamate *ent*-**25** (232 mg, 57%) after column chromatography (9:1 CH_2Cl_2−Et_2O): $[\alpha]^{22}_D$ −6.8 (c 1.75, MeOH). Anal. Calcd for $C_{17}H_{24}FNO\cdot 1/2H_2O$: C, 64.13; H, 7.91; N, 4.39. Found: C, 64.46; H, 8.13; N, 4.26).

(3*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*p*-fluorophenyl)-3-[3,4-(methylenedioxy)phenoxymethyl]piperidine (*ent*-28). Operating as in the opposite enantiomeric series, alcohol *ent*-**25** (83 mg, 0.26 mmol) was converted to a crude mesylate (100 mg). Operating as in the preparation of **26**, from this crude mesylate, NaH (35 mg, 0.8 mmol, 55−65% dispersion in mineral oil), and 3,4-(methylenedioxy)phenol (111 mg, 0.8 mmol) was obtained compound *ent*-**28** (76 mg, 66%) after column chromatography (gradient of eluents hexanes−Et_2O): $[\alpha]^{22}_D$ −25.1 (c 1.0, MeOH). Anal. Calcd for $C_{24}H_{28}FNO_5$: C, 67.12; H, 6.57; N, 3.26. Found: C, 67.06; H, 6.74; N, 3.20.

(3*S*,4*R*)-4-(*p*-fluorophenyl)-3-[(3,4-(methylenedioxy)-phenoxymethyl]piperidine [(−)-Paroxetine, *ent*-29]. Operating as in the opposite enantiomeric series, from carbamate *ent*-**28** (119 mg, 0.27 mmol) and TFA (1.55 mL, 20.3 mmol) was obtained pure *ent*-**29** [(−)-paroxetine] (65 mg, 72%) after column chromatography (95:5 AcOEt−DEA): $[\alpha]^{22}_D$ −80.8 (c 1.25, MeOH), sample from Seroxat: $[\alpha]^{22}_D$ −89.4 (c 0.75, MeOH). An HPLC analysis showed that the sample was not contaminated by defluoroparoxetine (a common impurity in paroxetine samples). Anal. Calcd for $C_{19}H_{18}FNO_3\cdot 1/4H_2O$ C, 68.35; H, 6.18; N, 4.19. Found: C, 68.38; H, 6.25; N, 4.21.

Computational Methods. The generalized molecular interaction potential with polarization (GMIPp)[15,16] has been used to investigate the reactivity pattern of the model unsaturated bicyclic lactams *cis*-**A** and *trans*-**A**. The GMIPp computes the interaction energy between the molecule, which is treated at the quantum mechanical (QM) level, and a classical probe entity. Such an interaction energy is determined from the addition of three terms (see eq 1): (i) an electrostatic contribution that is computed from the electrostatic potential computed at the QM level; (ii) a classical dispersion-repulsion term; and (iii) a polarization contribution derived from perturbational theory. In eq 1 R_A and R_B stand for the positions of the nuclei (Z_A) in the QM molecule and of the atoms in the classical particle, c denotes the coefficient of atomic orbitals in the molecular orbital−linear combination of atomic orbitals (MO-LCAO) approximation, $P_{\mu\nu}$ is the first-order density matrix, ϕ is the set of atomic orbitals, ϵ_{AB} and R^*_{AB} are the van der Waals parameters, and ξ denotes the energy of molecular orbitals. Let us note that the perturbational estimates of the polarization contribution are very similar to the self-consistent field values.[16] The QM molecule was described by using the wave function and geometry determined at the restricted Hartree−Fock level with a 6-31G(d) basis set,[22] and the van der Waals parameters were taken from an in-house quantum mechanical−molecular mechanical parametrization.[23] The classical particle was defined by a point charge of −1 units of electrons and van der Waals parameters of a carbon atom. The parameters ϵ_{AB} and R^*_{AB} were computed from the atomic parameters using the relationships $\epsilon_{AB} = (\epsilon_A\epsilon_B)^{0.5}$ and $R^*_{AB} = R^*_A + R^*_B$.

$$\mathrm{GMIPp} = \sum_A \frac{Z_A}{|R_B - R_A|} - \sum_i^{occ} \sum_\mu \sum_\nu P_{\mu\nu} \left\langle \phi_\mu \left| \frac{1}{|R_B - r|} \right| \phi_\nu \right\rangle + \sum_A \epsilon_{AB} \left[\left(\frac{R^*_{AB}}{|R_B - R_A|} \right)^{12} - 2 \left(\frac{R^*_{AB}}{|R_B - R_A|} \right)^{6} \right] + \sum_i^{occ} \sum_j^{vir} \frac{1}{\xi_i - \xi_j} \left\{ \sum_\mu \sum_\nu c_{\mu i} c_{\nu j} \left\langle \phi_\mu \left| \frac{1}{R_B - r} \right| \phi_\nu \right\rangle \right\}^2 \quad (1)$$

GMIPp calculations were performed on the most stable conformations of the *cis* and *trans* isomers of **A**. To this end, a preliminary exploration was performed at the molecular mechanical level using the CVFF91[24] force field implemented in the Insight-II[25] program, and the geometry of the selected conformers was subsequently optimized at the RHF/6-31G(d) level. One and two stationary points were found for *cis*-**A** and *trans*-**A**, respectively, and their minimum energy nature was

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(25) Insight-II (version 97.0), Molecular Simulations, San Diego, 1997.

verified from harmonic frequency calculations. The two conformers found for *trans*-**A** differ in the position of carbon 2 (*down* or *up*) in the five-membered ring. The difference in stability between the three optimized structures was determined to be less than 0.5 kcal/mol at this level of theory.

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Supporting Information Available: Copies of ^{1}H- and ^{13}C NMR spectra of compounds *cis*-**2**, *trans*-**2**, *cis*-**3**, *trans*-**3**, *cis*-**4**, *trans*-**4**, *cis*-**5**, *trans*-**5**, **17a**,**b**, and **29**, ORTEP diagrams and X-ray crystallographic data of compounds **12a** and **22**, and complete computational results for *cis*-**A** and *trans*-**A**. This material is available free of charge via the Internet at http://pubs.acs.org.

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