Optically Active Mexiletine Analogues as Stereoselective Blockers of Voltage-Gated Na^+ Channels

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Optically active mexiletine analogues were synthesized and evaluated in vitro as use-dependent blockers of skeletal muscle sodium channels. The mexiletine analogues were obtained by replacing either the methyl group on the stereogenic center of mexiletine [1-(2,6-dimethylphenoxy)propan-2-amine] with a phenyl group or modifying the phenoxy moiety (by removal of one or both of the methyl groups, or introducing a chlorine atom), or both. The voltage clamp recordings showed that, regardless of the substitution pattern of the aryloxy moiety, all the compounds bearing a phenyl group on the stereogenic center (**3a**−**f**) were more active than mexiletine both in tonic and phasic block. This observation was in contrast with what was observed for mexiletine, where the removal of both methyls from the aryloxy moiety caused a dramatic reduction of potency. The most potent congener, (*R*)-2-(2-methylphenoxy)-1-phenylethanamine [(*R*)-**3b**], was 27-fold more potent than (*R*)-mexiletine in producing a tonic block, i.e., the reduction of peak sodium current in resting conditions after application of the compound. (*R*)-**3b** maintained a use-dependent behavior, being 23-fold more potent in condition of high frequency of stimulation (phasic block). Despite what was observed with mexiletine, the stereoselectivity held in phasic block conditions. Stereoselectivity indexes were generally low, ranging from 1 to 4, but except for that of the 2,6-xylyloxy congener **3c**, they were higher for the congeners bearing a phenyl ring on the stereogenic center than for mexiletine and its strictly related analogue 1-methyl-2-phenoxyethanamine (**1**). This finding was in agreement with Pfeiffer's rule. The introduction of a chlorine atom in the 4-position of the aryloxy moiety caused a reduction of potency and a reversal of stereoselectivity as well. On the basis of the model to date accepted for the sodium channel local anesthetic-like molecule receptor, some possible explanations of our observations will be proposed.

Introduction

Mexiletine [1-(2,6-dimethylphenoxy)propan-2-amine] (Figure 1) is a well-known orally effective antiarrhythmic drug of the IB class,[1−4] which is also effective in the treatment of the muscular hyperexcitability of myotonic syndromes.[5] The clinical term myotonia is used to identify a series of dominant and recessive forms of genetic skeletal muscle diseases characterized by abnormal membrane excitability and delayed muscle relaxation after voluntary contraction. Sodium channel myotonias, paramyotonia congenita, and hyperkaliemic periodic paralysis are due to mutations of the gene coding for the skeletal muscle type of voltage-gated sodium channels.[6,7] The effect of mexiletine can be correlated with the block of voltage-dependent Na^+ channels present in both cardiac and skeletal muscle fibers,[7,8] and its activity increases with the level of depolarization and the frequency of stimulation. As well-known, the use-dependent blockers of Na^+ channels stabilize the channels in the inactivated state.[9] This mechanism allows a higher potency on tissues characterized by excessive excitability (e.g., myotonic muscles with nonphysiological phenotypes of sodium or chlorine channels). As reported, cardiac and skeletal muscles show different types of sodium channels.[10] In therapy,

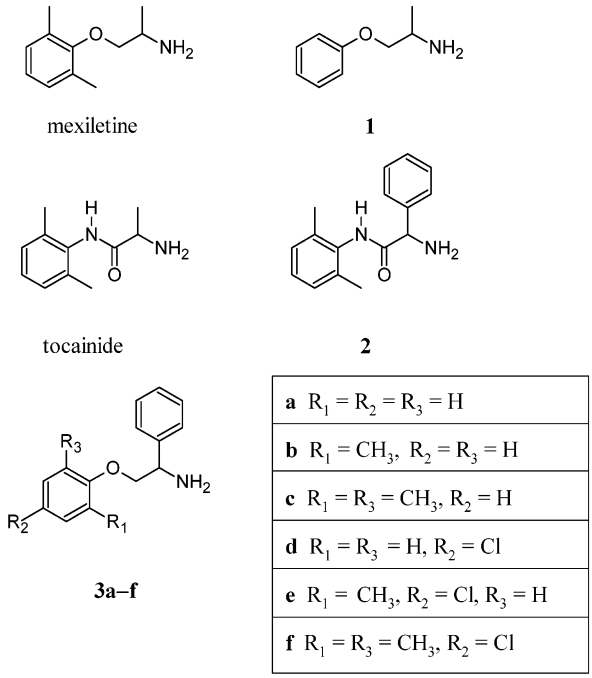

Figure 1. Structure of mexiletine and its analogues **1** and **3a**−**f**, tocainide, and its phenyl analogue **2**.

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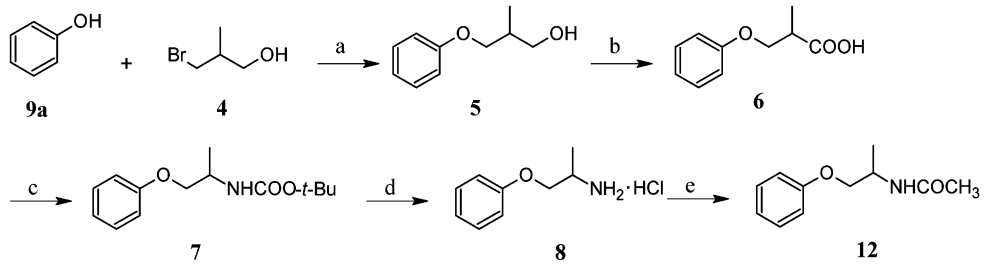
Scheme 1[a]



[a] Reagents and conditions: (a) NaOH/DMF; (b) $RuO_2/NaIO_4$; (c) DPPA/*t*-BuOH; (d) HCl(g); (e) Ac_2O, Et_3N/THF.

mexiletine is used as a racemate even though in vivo[11] and in vitro[12] studies showed the presence of stereoselective active sites on the cardiac sodium channel which preferentially bind the (−)-(*R*)-enantiomer. (−)-(*R*)-Mexiletine is more active than (+)-(*S*)-mexiletine also on native skeletal muscular fibers.[2,13b] Nevertheless, the use of mexiletine in the therapy of myotonic syndromes is restricted by its side effects on the cardiac functions, on the central nervous system (CNS), and on the hematopoietic system.[12] In the past decade our efforts were focused on the development of new antimyotonic drugs such as mexiletine- and tocainide-like compounds.[1−3,13] Recently, we have reported that in a series of mexiletine analogues, variously substituted on the stereogenic center, the potency of the pore-blocking activity was positively related to lipophilicity.[1] That is, the replacement of the methyl group on the stereogenic center of mexiletine with an isopropyl, phenyl, or benzyl group led to a 3−10-fold increase in potency. This finding was in agreement with previous results from both our [2,3] and other research groups.[4] In particular, these results parallel those observed in the tocainide series, where formally replacing the methyl group on the stereogenic center with a phenyl to obtain **2** led to a marked increase in the antiarrhytmic potency.[14] However, lipophilicity alone cannot explain all aspects of the blocking activity of the analogues bearing a phenyl group on the stereogenic center. 2-(2,6-Dimethylphenoxy)-1-phenylethanamine (**3c**) was 5−10-fold more potent than mexiletine. However, in all protocols used, its blocking activity was devoid of stereoselectivity, whereas with mexiletine, the stereospecific index (SSI) in the tonic block experiments was low, but differed significantly from unity. With mexiletine, the (*R*)-enantiomer was the eutomer. Furthermore, the mexiletine analogue from which the two *o*-methyl groups on the xylyloxy moiety were formally removed (1-methyl-2-phenoxyethanamine, **1**) showed in all protocols a dramatic reduction of potency with respect to the parent compound. The same was not true for **3a** and **3b**; the latter was even more potent than **3c** despite a reasonably predictable lowering of lipophilicity (the calculated logP values[15] for **3a**, **3b**, and **3c** are 2.6 ± 0.2, 3.1 ± 0.2, and 3.6 ± 0.2, respectively). **3a** and **3b** SSIs were also significantly different from unity (3−4 and 2−3, respectively), the (*R*)-enantiomers being more potent and, opposite to what was observed with mexiletine, the stereoselectivity was maintained when fibers were stimulated by trains of depolarizing pulses (at a frequency of 10 Hz), i.e., in conditions of use-dependent or phasic block. Indeed the 3-21G*//3-21G* models of the phenyl analogue structures show that **3a**−**f** are relatively less planar than the RX Mex structure (data not shown).[13] This easily anticipated observation suggests that **3a**−**f** may bind differently from Mex in the sodium channel. The sum of these findings suggested some sterical constraint emerging in phasic block conditions only for the more potent compounds according to Pfeiffer's rule[16] and prompted us to the stereospecific synthesis of the analogues **3d**−**f**, to evaluate the relative importance of lipophilicity and steric requirements for potent and use-dependent block of skeletal muscle sodium channels. The synthesis and full characterization of new as well as previously incompletely described compounds will be given.

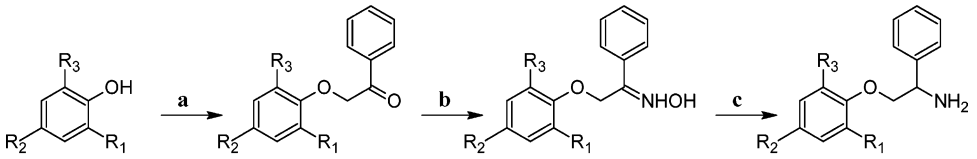
Chemistry

Mexiletine analogues (**1** and **3a**−**f**) were prepared following different synthetic approaches (Scheme 1−3). (*R*)- and (*S*)-1-Methyl-2-phenoxyethylamine (**1**) were obtained, allowing the enantiomerically pure 3-bromo-2-methylpropan-1-ol (**4**) to react with phenol to give 2-methyl-3-phenoxypropan-1-ol (**5**) that in turn was oxidized by $RuO_2/NaIO_4$. The resulting 2-methyl-3-phenoxypropanoic acid (**6**) was converted into the corresponding carbamate **7**, that by treatment with HCl(g) afforded the product **8** (i.e., **1**·HCl) (Scheme 1) in high yield and enantiomeric excess (>98%).

2-(2,6-Dimethylphenoxy)-1-phenylethanamine (**3c**) was prepared in racemic form as depicted in Scheme 2.

The synthesis of 2-(2,6-dimethylphenoxy)-1-phenylethanone (**10c**) was carried out in DMSO/NaOH by reacting 2-bromoacetophenone and 2,6-dimethylphenol (**9c**). **10c** was transformed into the corresponding oxime **11c**, that was then reduced to racemic **3c** by H_2 (20 atm) in the presence of a catalytic amount of 5% Pd/C. The halogenated compound (±)-**3e** was prepared following the same route except for the last step, where the reduction was carried out with $LiAlH_4$ in anhydrous Et_2O under reflux in order to avoid reductive dehalogenation. Optically active **3a**−**f** were prepared with enantiomeric excess ranging between 80% and 99%, following the route reported in Scheme 3. In this procedure each **3a**−**f** enantiomer was obtained starting from (*R*)- or (*S*)-styrene oxide (**13**). Thus, **14a**−**f** were obtained by reacting the suitable optically active styrene oxide and phenol (**12**). The ring-opening reaction is virtually regiospecific in a dipolar aprotic medium, and the isomeric purity of the alcohols so obtained can be easily checked by EIMS.[17] The chiral alcohols **14** were transformed into **15a**−**f** by a stereospecific substitution reaction of the hydroxy group with phthalimide performed in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) following a typical

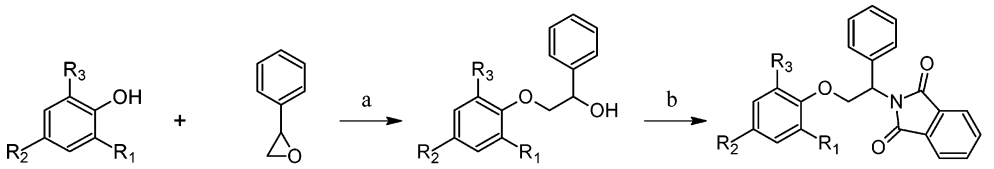
Scheme 2[a]



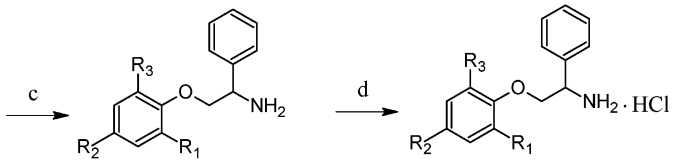
9 **10** **11** **(±)-3**

[a] Reagents and conditions: (a) 2-Bromoacetophenone, NaOH/DMSO; (b) EtOH/Py, $NH_2OH \cdot HCl$; (c) 5% Pd/C, H_2 (20 atm), EtOH or $LiAlH_4$.

Scheme 3[a]



9a–f **(*R*)-13 [or (*S*)-13]** **(*S*)-14a–f [or (*R*)-14a–f]** **(*R*)-15a–f [or (*S*)-15a–f]**



(*R*)-3a–f [or (*S*)-3a–f] **(*R*)-3a–f [or (*S*)-3a–f]·HCl**

a	$R_1 = R_2 = R_3 = H$
b	$R_1 = CH_3$, $R_2 = R_3 = H$
c	$R_1 = R_3 = CH_3$, $R_2 = H$
d	$R_1 = R_3 = H$, $R_2 = Cl$
e	$R_1 = CH_3$, $R_2 = Cl$, $R_3 = H$
f	$R_1 = R_3 = CH_3$, $R_2 = Cl$

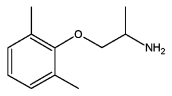
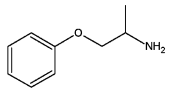
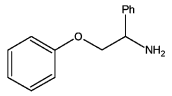
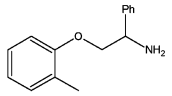
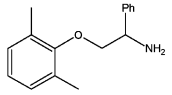
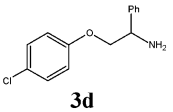
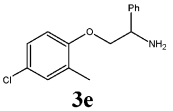
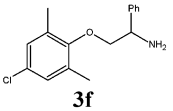
[a] Reagents and conditions: (a) $NaOH/CH_3CN$, reflux; (b) phthalimide, PPh_3/DIAD, THF; (c) 55% aq N_2H_4, AcOH/EtOH; (d) HCl(g).

Mitsunobu procedure.[18,34] This reaction occurs with inversion of configuration at the stereogenic center, and little or no racemization was observed. Finally, by hydrazinolysis of the phthalimido aryl alkyl ethers **15a**−**f**, the phenyl mexiletine analogues **3a**−**f** were obtained, which in turn were purified as hydrochloride salts **3a**−**f**·HCl. This synthetic strategy allowed the preparation of both enantiomers of each new compound in good yields, in high enantiomeric excesses [determined by HPLC analyses using a Daicel Chiralcel OD column (tris-3,5-dimethylphenylcarbamate, derivatized cellulose film) or OD-R column], and with known absolute configuration.

Biological Studies

All above-mentioned compounds were evaluated for activity as sodium channel blockers on single muscle fibers. Concentrations for half-maximal tonic and use-dependent block of sodium currents (IC_{50}) are reported in Table 1. Single enantiomers were tested with the aim of evaluating the presence of stereoselectivity in blocking I_{Na}. The results obtained on both enantiomers of **1** demonstrate that when the propyl chain of mexiletine is not changed, the two *o*-methyl groups play an important role. In fact, (*R*)- and (*S*)-**1** were less active than (*R*)- and (*S*)-mexiletine, respectively. On the contrary, the new compounds with a phenyl replacing the methyl on the stereogenic center of mexiletine were all more active than mexiletine. In particular, (*R*)-**3b** was 27-fold more potent than (*R*)-mexiletine in producing a tonic block, i.e., the reduction of peak sodium current in resting conditions after application of the compound, and it was 23-fold more potent in condition of high frequency of stimulation (phasic block, that may be considered as an indication of the antimyotonic activity). Furthermore, **3b** presented the same pattern of stereoselectivity as that of mexiletine, (*S*)-**3b** being approximately 3-fold less potent than (*R*)-**3b**. Other structural modifications of the phenoxy group of **3b** led to compounds that in all cases were more potent than mexiletine, presenting IC_{50} values ranging from 8 μM to 50 μM and from 3 μM to 23 μM for tonic and phasic block, respectively. The (*R*)-enantiomers of **1**, **3a**, and **3b** behaved as eutomers. The formal introduction of a chlorine atom in the 4-position of the aryloxy moiety of **3a**, **3b**, and **3c** to give **3d**, **3e**, and **3f**, respectively, caused a reversal of stereoselectivity in both tonic and phasic block, (*S*)-**3d**, (*S*)-**3e**, and (*S*)-**3f** being more potent than the respective enantiomers. Furthermore, this finding was accompanied by another intriguing observation. The IC_{50} values displayed by **3a**−**c** in phasic block conditions point to a beneficial role of one *o*-methyl group on the aryloxy moiety (**3b** > **3c** > **3a**). When introducing a chlorine atom in the 4-position of this ring, a partial loss of potency was accompanied by a reversal of the hierarchy of potency as a function of the ortho substitution pattern, the congener with no

Table 1. Concentrations for Half-Maximal Block of Sodium Currents of Skeletal Muscle Fibers by Mexiletine and Its Analogues

 mexiletine	(R)	54 ± 12	23 ± 4	2	1
	(S)	114 ± 21	27 ± 6	4	1
	(R,S)	83 ± 14	29 ± 4	3	
 **1**	(R)	497 ± 9	208 ± 16	2	0.1
	(S)	600 ± 6	236 ± 4	2	0.1
 **3a**	(R)	8.0 ± 0.8	4.0 ± 0.5	2	6
	(S)	30 ± 1	16.0 ± 0.4	2	2
 **3b**	(R)	2.0 ± 0.4	1.0 ± 0.1	2	23
	(S)	7.0 ± 0.4	3.0 ± 0.2	2	9
 **3c**	(R)	11.0 ± 0.3	3.0 ± 0.3	4	8
	(S)	9.0 ± 0.8	3.0 ± 0.4	3	9
 **3d**	(R)	29 ± 1	10 ± 1	3	2
	(S)	23 ± 7	3.0 ± 0.6	8	9
 **3e**	(R)	50 ± 5	23 ± 4	2	1
	(S)	23 ± 1	18 ± 1	1	2
	(R,S)	29 ± 3	15 ± 2	2	2
 **3f**	(R)	48 ± 6	18 ± 7	3	1
	(S)	21 ± 1	8 ± 2	3	3

[a] The half-maximal concentration (IC_{50}) of each compound for producing a tonic block (block of sodium channel at resting conditions evaluated during infrequent depolarizing pulses) and the phasic block (cumulative sodium current reduction by the drug at 10 Hz stimulation frequency) have been obtained by concentration−response curves (see the Experimental Section). [b] Putative antimyotonic activity: potency in phasic block in relation to mexiletine (see the Experimental Section), mexiletine = 1.

o-methyl group (**3d**) being the most effective in the chloro-substituted series (**3d** > **3f** > **3e**).

Discussion

Mexiletine is one of the few drugs currently available for the treatment of patients suffering from myotonia.[4,5] However, the use of mexiletine as an antimyotonic drug is tainted with pharmacological promiscuity: the recommended doses for myotonic patients are in the same range as that used to treat arrhythmia, with the possibility of adverse effects on both the cardiac and the nervous system functions.[5b] Considering that sodium channels of cardiac and skeletal muscle tissues are genetically distinct and consequently have different pharmacological and kinetic properties,[20,13b] the possibility to develop new use-dependent sodium channel blockers more selective on skeletal than on heart muscle may be envisaged. The structural requirements for molecules able to exert a potent and use-dependent block on the sodium channels have not yet been completely defined. Different evidence points to the lipophilicity as the property that modulates the blocking potency[1−4] and the basicity as the property able to affect the use-dependent blocking activity of compounds acting as blockers of such channels. However, both basicity and lipophilicity cannot explain all aspects of local anesthetic action: as reported above, further stereoelectronic aspects should be considered. The interaction of basic local anesthetics with the binding site is assumed to involve the protonated species. Recently, an interaction of the cationic moiety of mexiletine with an anionic residue of the receptor site has been proposed,[21] but site-specific mutagenesis studies disagree with this hypothesis, indicating two aromatic residues (Phe and Tyr) on the D4-S6 transmembrane segment in brain type IIA, brain type III, and skeletal muscle Na^+ channels as the main binding sites of pore-blocking drugs.[22] Probably, D1 and D3 also contribute to the receptor,[23] a major role being played by lipophilic residues. The results herein presented are in agreement with these assumptions. The insertion of a phenyl group on the asymmetric center causes a significant increase in the potency of tonic block: all phenyl analogues of mexiletine are more potent than (*R*)-mexiletine. This increase is independent of the substituents present on the aryloxy ring and, although less evident, is conserved in phasic block experiments. These observations might be rationalized, assuming the hydrophobic interaction

of the phenyl ring with one of the aromatic amino acids scarcely involved in mexiletine binding. The stereoselectivity of block, though modest, does imply that at least three binding sites are involved. The low stereospecificity indexes observed may be explained, noting that all the interaction sites putatively involved in the binding are lipophilic. Due to molecular flexibility, the distomer of each compound may easily access a conformation that fits the relevant interaction sites. Molecular flexibility, however, should play a minor role; otherwise the peculiar behavior of **3c**, in principle less flexible than **3b**, would remain unexplained: **3c** is the only potent mexiletine analogue that presents no stereoselectivity at all, and this means that **3c** may easily fit the receptor regardless of its stereochemistry. This observation implicitly suggests that phenyl and amine groups are viewed as interchangeable by the receptor, and this is in agreement with previous observations claiming a possible π-cation interaction between the protonated amino group of local anesthetics[24] and amitriptyline,[25] and the aromatic ring of Phe. Despite what is observed with mexiletine and some of its analogues, the stereoselectivity displayed in the Na^+ channel blocking activity of **3a**,**b**,**d**−**f** does not dissipate when passing from tonic to phasic block. Thus, the same receptor stereoelectronic requirements should be hypothesized regardless of the Na^+ channel state (resting or inactivated), and the gain in potency observed at higher frequency of stimulation might be attributed more plausibly to a closer interaction of the ligands with the host than to a dramatic change in the receptor conformation causing a disclosure of further interaction sites. The reversal of the stereoselectivity pattern and hierarchy of potency observed when introducing a chlorine atom in the 4-position imposes the assumption of two different fitting modes for these mexiletine analogues depending on steric and/or electronic features at the xylyloxy ring. Several interaction models assume that local anaesthetic-like molecules enter the pore, orienting the charged amino group upward.[1,23−25] Thus, the amino group should be placed uppermost, and the rest of the molecule should be oriented downward. Assuming as improbable an upside down reorientation of the molecule, which would not be possible due to the negative gradient and the dimension of the pore, it should be assumed that **3d**−**f** bind the receptor at a level differing from that affected by **3a**−**c**. The causes of this differential mode of binding (steric, electronic, or both) are currently under investigation.

Conclusions

From a heuristic point of view, this study has provided some new evidence in favor of the model presently accepted for the local anesthetic-like molecule receptor located in the sodium channel pore. However, our results suggest that strictly related compounds may bind the receptor in different ways, and much effort is needed prior to formulation of a comprehensive receptor model. From a practical point of view, a facile stereospecific synthesis of phenyl analogues of mexiletine has been proposed. This route gave us the access to **3a**−**f** which present themselves as valuable pharmacological tools, all being more potent than mexiletine. In particular, **3b** showed a marked increase in both potency and use-dependence of action: compared to mexiletine, it was 25 and 20 times more potent than mexiletine in tonic and phasic block experiments, respectively. The 4-chlorinated analogues (**3d**−**f**) were generally less potent. However, (*S*)-**3d** was 8 times more potent than mexiletine in exerting a phasic block and was the most use-dependent blocking agent in the series [IC_{50} (tonic block)/IC_{50} (phasic block) = 8]. Thus (*R*)-**3b** and (*S*)-**3d** might be usefully employed to explore the local anesthetic-like molecule receptor in the cardiac and nervous sodium channels as well, in view of a possible pharmacological dissociation disclosing the access to safer drugs selectively targeted to each of them.

Experimental Section

Pharmacology. 1. Preparation and Solutions. For sodium current recordings, semitendinosus muscle fibers were perfused with the following "external" solution (mM): NaCl 77, choline-Cl 38, $CaCl_2$ 1.8, Na_2HPO_4 2.15, NaH_2PO_4 0.85; and dialyzed with the following "internal" solution (mM): CsF 105, MOPS 5, $MgSO_4$ 2, EGTA 5, Na_2ATP 0.55 (pH = 7.2 with NaOH concentrated solution). Stock solutions of mexiletine and its analogues were prepared in physiological and/or "external" solutions. All the stock solutions were prepared daily, and the final concentrations to be tested in vitro were obtained by further diluting the stock solution as needed. DMSO at the highest concentration used (0.2%) was without effect on any of the parameters recorded.

2. Voltage Clamp Recordings of Sodium Current and Pulse Protocols. The voltage clamp recordings of sodium current were performed on single muscle fibers obtained with microsurgery from the ventral brunch of semitendinosus muscle of *Rana esculenta* by means of the three vaseline gap voltage clamp technique as detailed elsewhere.[13b] After an equilibration time of 10 min, Na^+ currents recordings were performed at 10 °C. The holding potential (hp) was −100 mV. The inward sodium traces were recorded using a voltage clamp amplifier based on that described by Hille and Campbell[26] connected via a 12-bit AD/DA interface (digidata 1200, Axon Instruments, Forster City, CA) to an 80486 DX2/66 PC and stored on the hard disk. The stimulation protocols and data acquisition were driven by Clampex program (pClamp 6 software package, Axon Instruments). The currents flowing in response to depolarizing command voltages were low pass filtered at 10 kHz (Frequency Devices, Inc., Haverhill, MA) visualized on an oscilloscope and sampled at 20 kHz. When necessary, leak and capacity currents were subtracted by the P/4 method. The acquired traces were later analyzed with the Clampfit program (pClamp 6 software package, Axon Instruments). Maximal sodium currents were elicited with test pulses from the hp to −20 mV for 10 ms. Tonic block exerted by the test compounds was evaluated as percent reduction of the peak sodium current elicited by single test pulses. The evaluation of use-dependent block by the drugs was made by using a 10 Hz train of test pulses for a period of 30 s and by normalizing the residual current at the end of this stimulation protocol with respect to that in the absence of drug.

Statistical Analysis. The data were expressed as mean ± SEM. The statistical significances of the differences between groups of means was calculated by unpaired Student's *t* test. Molar concentration of the drugs producing a 50% block of I_{Na} (IC_{50}) were determined by using a nonlinear least-squares fit of the concentration−response curve as previously detailed.[13b] When normalized values of the various experimental parameters were used, estimates of SEM and the calculated number of normalized fibers were obtained as described previously.[13b,23]

Chemistry. General. Yields refer to purified products and were not optimized. The structures of the compounds were confirmed by routine spectrometric analyses. Only spectra for compounds to our knowledge never previously described are given. Compounds used as starting materials were purchased from either Aldrich Chemical Co., Inc. or Lancaster Synthesis, Inc. in the highest commercially available quality. (−)-(*R*)- and

(+)-(*S*)-Mexiletine were prepared as previously described.[19] Solvents were RP grade, unless otherwise indicated. Melting points were determined on a Gallenkamp melting point apparatus in open glass capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT spectrophotometer, and band positions are given in reciprocal centimeters (cm^{-1}). ^1H NMR and ^{13}C NMR spectra (300 MHz) were recorded on an FT Bruker Aspect 3000 or a Varian Mercury 300 spectrometer using $CDCl_3$ as solvent, unless otherwise indicated. Chemical shifts are reported in parts per million (ppm) relative to solvent resonance: $CDCl_3$, δ 7.26 (^1H NMR) and δ 77.0 (^{13}C NMR); $(CD_3)_2SO$, δ 2.50 (^1H NMR) and δ 39.5 (^{13}C NMR). *J* values are given in hertz. EIMS spectra were recorded on a Hewlett-Packard 6890−5973 MSD gas chromatograph/mass spectrometer at low resolution; where amine salts are concerned, MS analyses were performed on the corresponding free base forms obtained by extraction. Elemental analyses were performed on a Eurovector Euro EA 3000 analyzer; where indicated, C, H, and N were within ±0.4 of theoretical values. Optical rotations were measured on a Perkin-Elmer Mod 341 spectropolarimeter; concentrations are expressed in g/100 mL, and the cell length was 1 dm; thus $[\alpha]^{20}_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. HPLC ee evaluation was performed on a Waters chromatograph model 600 equipped with a U6K model injector and a 481 model variable wavelength detector. The enantiomeric purity of **3a**−**f**·HCl was determined by direct HPLC on Daicel OD or OD-R columns as specified below (flow rate 0.5 mL/min, λ 254 nm). The enantiomeric purity of **8** enantiomers was evaluated by analysis of the corresponding *N*-acetyl derivatives (**12**) using a Daicel OD-R column eluted at a flow rate of 0.5 mL/min with 40:60 CH_3CN/H_2O (λ 254 nm). Chromatographic separations were performed on silica gel columns by flash chromatography (Kieselgel 60, 0.040−0.063 mm, Merck) using the technique described by Still et al.[27] TLC analyses were performed on precoated silica gel on aluminum sheets (Kieselgel 60 F_{254}, Merck).

(+)-(*R*)-2-Methyl-3-phenoxy-1-propanol [(+)-(*R*)-5]. NaH (60%) (0.783 g, 19.6 mmol) was added in small portions to a stirred solution of phenol (3.68 g, 39.2 mmol) in 110 mL of anhydrous DMF kept under a nitrogen atmosphere. After H_2 evolution ceased, (−)-(*R*)-3-bromo-2-methyl-1-propanol [(−)-(*R*)-**4,** 3.0 g, 19.6 mmol] was added. The reaction mixture was stirred for 3 h, and then DMF was removed under reduced pressure. The residue was solubilized in ethyl acetate and washed with 0.5 N NaOH and water till neutral pH. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. Purification of the crude oil residue by column chromatography (petroleum ether/EtOAc 8:2) afforded 2 g of yellowish product (61%): $[\alpha]^{20}_D$ = +6.7 (*c* 2, $CHCl_3$); IR (neat): 3356 (OH), 2877, 1244 (C−O−C) cm^{-1}; ^1H NMR δ 7.32−7.25 (m, 2H, Ar HC-3,5), 7.00−6.84 (m, 3H, Ar HC-2,4,6), 4.00−3.90 (m, 2H, OCH_2), 3.71 (d, *J* = 5.8 Hz, 2H, CH_2OH), 2.28−2.14 (m, 1H, CH), 1.95 (br s, 1H, exch D_2O, OH), 1.04 (d, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR δ 158.8 (1C), 129.5 (2C), 120.9 (1C), 114.5 (2C), 71.2 (1C), 66.2 (1C), 35.7 (1C), 13.6 (1C); MS (70 eV) *m*/*z* (%) 166 (M^+, 32), 94 (100).

(−)-(*S*)-2-Methyl-3-phenoxy-1-propanol [(−)-(*S*)-5]. It was prepared in 60% yield by the method above-described for (+)-(*R*)-**5**, starting from (+)-(*S*)-3-bromo-2-methyl-1-propanol: $[\alpha]^{20}_D$ = −5.5 (*c* 2, $CHCl_3$).

(+)-(*S*)-2-Methyl-3-phenoxypropanoic Acid [(+)-(*S*)-6]. A mixture of EtOAc (15 mL) and 10% $NaIO_4$ aqueous solution (30 mL) was kept under mechanical stirring by means of Teflon blades supporting catalytic amounts of $RuO_2 \cdot H_2O$.[13a,28] A solution of (+)-(*R*)-**5** (0.50 g, 3 mmol) in EtOAc (15 mL) was added dropwise, and the mixture was stirred for 18 h. Then, the two phases were separated, and the aqueous phase was washed twice with ethyl acetate. The combined organic extracts were treated with saturated $NaHCO_3$ aqueous solution. The aqueous phase was acidified with 2 N HCl and extracted with ethyl acetate. The so obtained organic solution was dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. The brown oil obtained (0.38 g, 70% yield) was used without any further purification in the successive step: $[\alpha]^{20}_D$ = +3.6 (*c* 2.5, $CHCl_3$); IR (neat): 3550−2005 (CO_2H), 1708 (C=O), 1244 (C−O−C) cm^{-1}. ^1H NMR δ 10.35 (br s, 1H exch D_2O, COOH), 7.31−7.26 (m, 2H, Ar HC-3,5), 6.98−6.90 (m, 3H, Ar HC-2,4,6), 4.20 (dd, *J* = 9.1, 7.0 Hz, 1H, C*H*H), 4.05−4.00 (dd, *J* = 9.1, 6.0 Hz, 1H, CH*H*), 3.05−2.91 (m, 1H, CH), 1.34 (d, *J* = 7.1 Hz, 3H, CH_3); MS (70 eV) *m*/*z* (%) 180 (M^+, 26), 94 (100).

(−)-(*R*)-2-Methyl-3-phenoxypropanoic Acid [(−)-(*R*)-6]. It was prepared in 80% yield via the method above-described for (+)-(*S*)-2-methyl-3-phenoxypropanoic acid but starting from (−)-(*S*)-**5**: $[\alpha]^{20}_D$ = −2.5 (*c* 2.5, $CHCl_3$).

(−)-(*S*)-*tert*-Butyl 1-Methyl-2-phenoxyethylcarbamate [(−)-(*S*)-7]. A solution of (+)-(*S*)-**6** (0.84 g, 4.67 mmol), diphenylphosphoryl azide (DPPA, 2.57 g, 9.34 mmol), and Et_3N (1.04 g, 10.27 mmol) in 50 mL of *t*-BuOH was stirred under reflux for 7 h.[29] After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed with 2 N HCl, and the aqueous phase was washed with ethyl acetate. The two organic phases were washed, separately, with 2 N NaOH and then mixed and dried over anhydrous Na_2SO_4. By evaporating the solvent under reduced pressure, 1.7 g of crude product were obtained. After chromatography (petroleum ether/ethyl acetate 9:1) and crystallization (EtOAc−hexane), 0.4 g (34%) of a white solid was obtained: mp 81−82 °C; $[\alpha]^{20}_D$ = −45 (*c* 2, $CHCl_3$); ^{13}C NMR δ 185.7 (1C), 155.3 (1C), 129.5 (2C), 121.0 (1C), 114.5 (2C), 70.8 (1C), 62.7 (1C), 45.7 (1C), 28.5 (3C), 18.2 (1C); MS (70 eV) *m*/*z* (%) 251 (M^+, 26), 57 (100). Other spectroscopic data were in agreement with those reported in the literature.[30]

(+)-(*R*)-1-*tert*-Butyl 1-Methyl-2-phenoxyethylcarbamate [(+)-(*R*)-7]. It was prepared in 30% yield via the method above-described for (−)-(*S*)-**7** starting from (−)-(*R*)-**6**: mp 81−82 °C (EtOAc−hexane); $[\alpha]^{20}_D$ = +48 (*c* 2, $CHCl_3$).

(+)-(*S*)-1-Methyl-2-phenoxyethylamine Hydrochloride [(+)-(*S*)-1·HCl]. A solution of (−)-(*S*)-**7** (0.57 g, 2.27 mmol) in anhydrous Et_2O (15 mL) was saturated with gaseous HCl and stirred at room temperature for 15 min. Removal of the solvent under reduced pressure gave a solid which was recrystallized from EtOH−Et_2O (0.38 g, 90%): mp 195−196 °C; $[\alpha]^{20}_D$ = +7.7 (*c* 2, CH_3OH); ^{13}C NMR [$(CD_3)_2SO$] δ 157.8 (1C), 129.5 (2C), 121.1 (1C), 114.7 (2C), 68.5 (1C), 46.0 (1C), 15.0 (1C); MS (70 eV) *m*/*z* (%) 151 (M^+, 3), 44 (100). Other spectroscopic data were in agreement with those reported in the literature[30] for the (*R*)-enantiomer. Anal. ($C_9H_{14}ClNO$) C, H, N.

(−)-(*R*)-1-Methyl-2-phenoxyethylamine Hydrochloride [(−)-(*R*)-1·HCl]. It was prepared in 90% yield via the method above-described for (+)-(*S*)-**1·HCl** starting from (+)-(*R*)-**7**: mp 195−196 °C (EtOH−Et_2O), lit.[30] 186−189 °C; $[\alpha]^{20}_D$ = −4.4 (*c* 2.3, CH_3OH). Anal. ($C_9H_{14}ClNO \cdot 0.20\ H_2O$) C, H, N.

(−)-(*S*)-*N*-(1-Methyl-2-phenoxyethyl)acetamide [(−)-(*S*)-12]. To a solution of 0.272 g of (+)-(*S*)-**1·HCl** in 2 mL of H_2O, 2 N NaOH was added until basic, and the emulsion was extracted three times with ethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4, and then the solvent was removed under reduced pressure to give 0.195 g (89%) of (*S*)-**1**. (*S*)-**1** (0.195 g, 1.29 mmol) and 0.36 mL (0.261 g, 2.58 mmol) of Et_3N were solubilized in 9 mL of anhydrous THF. To the stirred solution, kept in an ice bath, was slowly added 0.24 mL (0.263 g, 2.58 mmol) of acetic anhydride. The reaction mixture was stirred at room temperature for 5 h, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, and the organic phase was washed with 2 N HCl and then with $NaHCO_3$ saturated aqueous solution and H_2O until neutral pH. The recovered organic phase was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to give 0.281 g of a crude yellow oil. After purification by chromatography (petroleum ether/EtOAc 8:2), 0.240 g (86%) of the desired product was obtained: $[\alpha]^{20}_D$ = −59 (*c* 2.2, $CHCl_3$), 70% ee (t_R 12.7 min); IR (neat): 3283 (NH), 2876 (C−O−C), 1651 (C=O) cm^{-1}. ^1H NMR δ 7.33−7.20 (m, 2H, Ar HC-3,5), 7.02−6.87 (m, 3H, Ar HC-2,4,6), 5.95 (br d, *J* = 4.0 Hz, 1H, exch D_2O, NH), 4.45−4.29 (m, 1H, CH), 3.96 (dd, *J* = 9.0, 4.5 Hz, 1H, C*H*H),

3.90 (dd, $J = 9.0, 4.5$ Hz, 1H, CH*H*), 1.97 (s, 3H, $COCH_3$), 1.29 (d, $J = 6.9$ Hz, 3H, $CHCH_3$); ^{13}C NMR δ 169.5 (1C), 158.6 (1C), 129.5 (2C), 121.0 (1C), 114.4 (2C), 70.4 (1C), 44.6 (1C), 23.3 (1C), 17.5 (1C); MS (70 eV) *m/z* (%) 193 (M^+, 1), 100 (100).

(+)-(*R*)-*N*-(1-Methyl-2-phenoxyethyl)acetamide [(+)-(*R*)-12]. (+)-(*R*)-**12** was prepared in 98% yield via the method above-described for (−)-(*S*)-**12** starting from (−)-(*R*)-**1·HCl**: $[\alpha]^{20}_D = +79$ (*c* 2, $CHCl_3$), 98% ee (t_R 11.4 min).

General Procedure for the Synthesis of 2-Aryloxy-1-phenylethanones (10c,e). The preparation of 2-(2,6-dimethylphenoxy)-1-phenylethanone (**10c**) is typical. To a magnetically stirred mixture of NaOH (7.20 g, 180 mmol) and 100 mL of DMSO was added a solution of 2,6-dimethylphenol (**9c**, 20.0 g, 164 mmol) in DMSO (20 mL). Then a solution of 2-bromoacetophenone (35.9 g, 180 mmol) in DMSO (20 mL) was added dropwise. The resulting reaction mixture was stirred for 4 h at room temperature and then poured onto ice. The aqueous layer was extracted with Et_2O (6 × 50 mL), and the so obtained organic phase was washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a crude oil (27.2 g). Crystallization from EtOAc−petroleum ether provided **10c** as a pale yellow solid (24.8 g, 63%): mp 60−61 °C, lit.[31] 53 °C; IR (KBr): 1665 (C=O) cm^{-1}; ^1H NMR δ 7.98−7.95 (m, 2H, Ar HC-2,6), 7.59−7.45 (m, 3H, Ar HC-3,4,5), 7.12−7.02 (m, 3H, ArO HC-3,4,5), 5.06 (s, 2H, CH_2), 2.24 (s, 3H, CH_3);[32] MS (70 eV) *m/z* (%) 240 (M^+, 25), 105 (100).

2-(4-Chloro-2-methylphenoxy)-1-phenylethanone (10e). Obtained in 86% yield via the above-described procedure as a crude yellow solid which was checked for purity by GC MS and judged suitable for the next step: mp 60−61 °C (EtOH); IR (KBr): 1690 (C=O) cm^{-1}; ^1H NMR δ 8.00−7.97 (m, 2H, Ar HC-2,6), 7.65−7.59 (m, 1H, Ar HC-4), 7.52−7.47 (m, 2H, Ar HC-3,5), 7.13 (d, $J = 2.5$ Hz, 1H, ArO HC-3), 7.06 (dd, $J = 8.6, 2.5$ Hz, 1H, ArO HC-5), 6.64 (d, $J = 8.7$, 1H, ArO HC-6), 5.25 (s, 2H, CH_2), 2.26 (s, 3H, CH_3); ^{13}C NMR δ 194.5 (1C), 154.9 (1C), 134.6 (1C), 134.0 (1C), 130.8 (1C), 129.2 (1C), 128.9 (2C), 128.2 (2C), 126.4 (2C), 126.1 (1C), 71.2 (1C), 16.2 (1C); MS (70 eV) *m/z* (%) 260 (M^+, 22), 105 (100).

General Procedure for the Synthesis of (*E,Z*)-2-Aryloxy-1-phenylethanone Oxime (11c,e). The preparation of (*E,Z*)-2-(2,6-dimethylphenoxy)-1-phenylethanone oxime [(*E,Z*)-**11c**] is typical. A mixture of **10c** (24.0 g, 100 mmol), NH_2OH·HCl (22.1 g, 320 mmol), and pyridine (15 mL) in 30 mL of EtOH was refluxed for 3 h. Then, the solvent was evaporated, and the residue, dissolved in CH_2Cl_2 was washed with 2 N HCl. The organic layer, dried over anhydrous Na_2SO_4, was then evaporated under reduced pressure to give a crude solid which was purified by recrystallization from EtOH−H_2O (3:1) affording **11c** as yellow needles (10.7 g, 42%): mp 131−132 °C. For the sake of simplicity only spectral data for the most abundant geometrical isomer (>90%) will be given: IR (KBr): 3297 (OH), 2860, 1264 (C−O−C), 1591 (C=N) cm^{-1}; ^1H NMR δ 9.17 (br s, 1H, exch D_2O, OH), 7.80−7.77 (m, 2H, Ar HC-2,6), 7.72−7.71 (m, 3H, Ar HC-3,4,5), 7.03−7.00 (m, 2H, ArO HC-3,5), 6.97−6.92 (m, 1H, ArO HC-4), 5.08 (s, 2H, CH_2), 2.22 (s, 6H, CH_3); ^{13}C NMR δ 156.3 (1C), 156.0 (1C), 134.1 (1C), 130.9 (1C), 129.5 (2C), 128.8 (2C), 128.4 (2C), 127.2 (2C), 124.1 (1C), 63.9 (1C), 16.4 (1C); MS (70 eV) *m/z* (%) 255 (M^+, 36), 122 (100).

(*E,Z*)-2-(4-Chloro-2-methylphenoxy)-1-phenylethanone Oxime [(*E,Z*)-11e]. 94% yield, mp 113−115 °C (EtOH); IR ($CHCl_3$): 3577, 3299 (OH), 1598 (C=N) cm^{-1}; ^1H NMR δ 9.04 (br s, 1H, OH), 7.87−7.56 (m, 2H, Ar HC-2,6), 7.47−7.31 (m, 3H, Ar HC-3,4,5), 7.09 (dd, $J = 8.5, 2.7$ Hz, 1H, ArO HC-5), 7.04 (d, $J = 2.7$ Hz, 1H, ArO HC-3), 6.85 (d, $J = 8.5$ Hz, 1H, ArO HC-6), 5.29 (s, 2H, CH_2), 2.00 (s, 3H, CH_3); ^{13}C NMR δ 156.2 (1C), 154.7 (1C), 133.2 (1C), 130.5 (1C), 129.6 (2C), 128.9 (1C), 128.3 (2C), 127.2 (2C), 126.4 (1C), 125.7 (1C), 60.1 (1C), 16.0 (1C); MS (70 eV) *m/z* (%) 275 (M^+, 47), 103 (100).

(±)-2-(2,6-Dimethylphenoxy)-1-phenylethanamine [(±)-3c]. A solution of **2c** (7.01 g, 27.5 mmol) in 200 mL of EtOH was treated with H_2 at 20 atm for 24 h in the presence of 5% Pd/C (600 mg) as a catalyst. The solution was filtered on a kaolin pellet, and the filtrate was concentrated under reduced pressure. The residue was taken up with Et_2O, and the organic layer was extracted with 2 N HCl. The aqueous phase was treated with 2 N NaOH until basic and then extracted with Et_2O (3 × 50 mL). The combined organic phases, washed with water and dried over anhydrous Na_2SO_4, were evaporated under reduced pressure to give a crude oil in quantitative yield (6.6 g). (±)-**3c** was converted into the corresponding hydrochloride [(±)-**3c·HCl**] by treating with a few drops of 2 N HCl and removing water azeotropically. The crude solid obtained was purified by recrystallization from EtOH−Et_2O affording 5.3 g (69%) of the hydrochloride salt as white crystals: mp 242 °C; MS (70 eV) *m/z* (%) 241 (M^+, 1), 106 (100). Spectroscopic data were identical to those reported below for the individual enantiomers. Anal. ($C_{16}H_{20}ClNO$) C, H, N.

(±)-2-(4-Chloro-2-methylphenoxy)-1-phenylethanamine [(±)-3e]. A solution of **2e** (3.86 g, 14.0 mmol) in 50 mL of Et_2O was added dropwise to a suspension of $LiAlH_4$ (1.04 g, 28.0 mmol) in Et_2O (100 mL). The reaction mixture was refluxed for 3 h and then quenched by adding H_2O. The organic phase was filtered on Celite pellet and extracted with 1 N HCl (3 × 50 mL). The aqueous layer, treated with 1 N NaOH until basic, was extracted with Et_2O (3 × 50 mL). The combined organic phases, washed with water and dried over anhydrous Na_2SO_4, were evaporated under reduced pressure to give (±)-**3e** (1.6 g, 44%) as a colorless oil. (±)-**3e** was converted into the corresponding hydrochloride [(±)-**3e**·HCl] by treating with a few drops of 2 N HCl and removing water azeotropically. The crude solid obtained was recrystallized from EtOH−Et_2O affording 0.75 g (18%) of the hydrochloride salt as white crystals: mp 237 °C; MS (70 eV) *m/z* (%) 261 (M^+, 1), 106 (100). Spectroscopic data were identical to those reported below for the individual enantiomers. Anal. ($C_{15}H_{17}Cl_2NO$) C, H, N.

General Procedure for the Synthesis of 2-Aryloxy-1-phenylethanols (14a−f).[17,33] The preparation of (−)-(*R*)-2-(2,6-dimethylphenoxy)-1-phenylethanol will be described [(−)-(*R*)-**14c**]. To a suspension of NaOH (1.06 g, 26.7 mmol) in MeCN (50 mL) heated to 90 °C was added 3.05 g (25 mmol) of 2,6-dimethylphenol (**9c**) under stirring; then a solution of (+)-(*R*)-styrene oxide [(+)-(*R*)-**13**] (1.00 g, 8.33 mmol) in MeCN (50 mL) was added over a period of 1.5 h. The final reaction mixture was heated for 6.5 h and then stirred at room temperature for 12 h. The removal, under vacuum, of the reaction solvent gave a crude oil taken up with ethyl acetate and washed with H_2O. The organic phase was dried (Na_2SO_4) and concentrated under vacuum affording a crude brown oil. After purification on column chromatography (petroleum ether/EtOAc 9:1), a yellowish oil was obtained which was crystallized from EtOAc−petroleum ether to give (−)-(*R*)-**14c** (0.91 g, 45%) as a white solid: mp 79−81 °C; $[\alpha]^{20}_D = -20$ (*c* 2, $CHCl_3$); IR ($CHCl_3$): 3588 (OH), 2860, 1264 (C−O−C) cm^{-1}; ^1H NMR δ 7.47−7.29 (m, 5H, Ar), 7.03−7.01 (m, 2H, ArO HC-3,5), 6.96−6.91 (m, 1H, ArO HC-4), 5.16 (dd, $J = 6.9, 5.0$ Hz, 1H, CH), 3.90 (dd, $J = 9.6, 5.0$ Hz, 1H, C*H*H), 3.85 (dd, $J = 9.6, 6.9$ Hz, 1H, CH*H*), 2.99 (br s, 1H, exch D_2O, OH), 2.28 (s, 6H, CH_3); ^{13}C NMR δ 155.1 (1C), 139.8 (1C), 130.7 (2C), 128.9 (2C), 128.4 (2C), 128.0 (1C), 126.2 (2C), 124.1 (1C), 76.9 (1C), 73.4 (1C), 16.3 (2C); MS (70 eV) *m/z* (%) 242 (M^+, 9), 122 (100).

(+)-(*S*)-2-(2,6-Dimethylphenoxy)-1-phenylethanol [(+)-(*S*)-14c]. 40% yield, mp 77−79 °C (EtOAc−petroleum ether); $[\alpha]^{20}_D = +19$ (*c* 2, $CHCl_3$).

(−)-(*R*)-2-Phenoxy-1-phenylethanol [(−)-(*R*)-14a]. 72% yield, mp 58−60 °C (EtOAc−petroleum ether); $[\alpha]^{20}_D = -27$ (*c* 2, $CHCl_3$); ^{13}C NMR δ 158.3 (1C), 139.5 (1C), 129.3 (2C), 128.5 (2C), 128.2 (1C), 126.3 (2C), 121.3 (1C), 114.6 (2C), 72.6 (1C), 72.4 (1C). All other spectral data were in agreement with those reported in the literature for the (+)-(*S*)-enantiomer[34] and the racemic mixture.[35]

(+)-(*S*)-2-Phenoxy-1-phenylethanol [(+)-(*S*)-14a]. 88% yield, mp 58−60 °C (EtOAc−petroleum ether); $[\alpha]^{20}_D = +19$ (*c* 2, $CHCl_3$), lit.[34] +28.2 (*c* 1, MeOH).

(−)-(*R*)-2-(2-Methylphenoxy)-1-phenylethanol [(−)-(*R*)-14b]. 34% yield, oil; $[\alpha]^{20}_D = -38$ (*c* 2, $CHCl_3$); IR ($CHCl_3$): 3589 (OH), 2871, 1289 (C−O−C) cm^{-1}; ^1H NMR δ 7.49−7.45

(m, 2H, Ar HC-2,6), 7.43−7.30 (m, 3H, Ar HC-3,4,5), 7.15 (d overlapping apparent t at 7.14, J = 8.1 Hz, 1H, ArO HC-3), 7.14 (apparent t overlapping d at 7.15, J = 7.8 Hz, 1H, ArO HC-5), 6.89 (apparent t, J = 7.8 Hz, 1H, ArO HC-4), 6.80 (d, J = 8.1 Hz, 1H, ArO HC-2), 5.15 (dd, J = 8.38, 3.50 Hz, 1H, CH), 4.13 (dd, J = 9.48, 3.50 Hz, 1H, C*H*HO); 4.03 (dd, J = 9.48, 8.38 Hz, 1H, CH*H*O), 2.8 (br s, 1H, exch D_2O, OH), 2.17 (s, 3H, CH_3); ^{13}C NMR δ 156.4 (1C), 139.8 (1C), 130.8 (1C), 128.5 (2C), 128.1 (1C), 126.8 (1C), 126.7 (1C), 126.2 (2C), 120.9 (1C), 113.3 (1C), 73.3 (1C), 72.6 (1C), 16.2 (1C); MS (70 eV) *m*/*z* (%) 228 (M^+, 35), 108 (100).

(+)-(*S*)-2-(2-Methylphenoxy)-1-phenylethanol [(+)-(*S*)-14b]. 43% yield, oil; $[\alpha]^{20}_D$ = +22 (*c* 2, $CHCl_3$).

(−)-(*R*)-2-(4-Chlorophenoxy)-1-phenylethanol [(−)-(*R*)-14d]. 46% yield, oil; $[\alpha]^{20}_D$ = −27 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 3541 (OH), 2855, 1170 (C−O−C) cm^{-1}; ^1H NMR δ 7.38−7.27 (m, 5H, Ar), 7.22−7.11 (m, 2H, ArO HC-3,5), 6.82−6.74 (m, 2H, ArO HC-2,6), 5.21 (dd, J = 8.1, 3.6 Hz, 1H, CH), 3.92 (dd, J = 12.5, 8.1 Hz, 1H, C*H*H), 3.81 (dd, J = 12.5, 3.6 Hz, 1H, CH*H*), 2.21 (br d, 1H, exch D_2O, OH); ^{13}C NMR δ 156.4 (1C), 137.3 (1C), 129.3 (2C), 128.9 (2C), 128.4 (1C), 126.3 (2C), 126.2 (1C), 117.3 (2C), 81.6 (1C), 67.5 (1C); MS (70 eV) *m*/*z* (%) 248 (M^+, 3), 128 (100).

(+)-(*S*)-2-(4-Chlorophenoxy)-1-phenylethanol [(+)-(*S*)-14d]. 37% yield, oil; $[\alpha]^{20}_D$ = +36 (*c* 2, $CHCl_3$).

(−)-(*R*)-2-(4-Chloro-2-methylphenoxy)-1-phenylethanol [(−)-(*R*)-14e]. 42% yield, oil; $[\alpha]^{20}_D$ = −26 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 3591 (OH), 2861, 1133 (C−O−C) cm^{-1}; ^1H NMR δ 7.48−7.31 (m, 5H, Ar), 7.12 (s, 1H, ArO HC-3), 7.08 (d, J = 8.4 Hz, 1H, ArO HC-5), 6.70 (d, J = 8.4 Hz, 1H, ArO HC-6), 5.14 (dd, J = 9.2, 2.8 Hz, 1H, CH), 4.07 (dd, J = 9.2, 9.1 Hz, 1H, C*H*H), 4.01 (dd, J = 9.2, 2.8 Hz, 1H, CH*H*), 2.74 (br s, 1H, exch D_2O, OH), 2.22 (s, 3H, CH_3); ^{13}C NMR δ 155.0 (1C), 139.6 (1C), 130.4 (2C), 128.4 (2C), 128.0 (1C), 126.3 (1C), 126.1 (2C), 125.6 (1C), 112.7 (1C), 73.5 (1C), 72.5 (1C), 16.0 (1C); MS (70 eV) *m*/*z* (%) 262 (M^+, 25), 142 (100).

(+)-(*S*)-2-(4-Chloro-2-methylphenoxy)-1-phenylethanol [(+)-(*S*)-14e]. 39% yield, oil; $[\alpha]^{20}_D$ = +24 (*c* 1.6, $CHCl_3$).

(−)-(*R*)-2-(4-Chloro-2,6-dimethylphenoxy)-1-phenylethanol [(−)-(*R*)-14f]. 39% yield, oil; $[\alpha]^{20}_D$ = −13 (*c* 1.8, $CHCl_3$); IR ($CHCl_3$): 3599 (OH), 2866, 1183 (C−O−C) cm^{-1}; ^1H NMR δ 7.45−7.28 (m, 5H, Ar), 6.98 (s, 2H, ArO), 5.12 (dd, J = 6.4, 5.3 Hz, 1H, CH), 3.89 (dd, J = 9.6, 6.4 Hz, 1H, C*H*H), 3.81 (dd, J = 9.6, 5.3 Hz, 1H, CH*H*), 2.93 (br s, 1H, exch D_2O, OH), 2.17 (s, 6H, CH_3); ^{13}C NMR δ 153.7 (1C), 140.2 (1C), 139.6 (1C), 132.4 (1C), 128.7 (1C), 128.5 (2C), 128.3 (2C), 128.1 (1C), 126.1 (2C), 76.5 (1C), 73.3 (1C), 16.2 (2C); MS (70 eV) *m*/*z* (%) 276 (M^+, 1), 156 (100).

(+)-(*S*)-2-(4-Chloro-2,6-dimethylphenoxy)-1-phenylethanol [(+)-(*S*)-14f]. 36% yield, oil; $[\alpha]^{20}_D$ = +16 (*c* 2, $CHCl_3$).

General Procedure for the Synthesis of 2-(2-Aryloxy-1-phenylethyl)-1*H*-isoindole-1,3(2*H*)-diones (15a−f).[18] The preparation of (+)-(*S*)-2-[2-(2,6-dimethylphenoxy)-1-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(+)-(*S*)-**15c**] will be described. To a mixture of (−)-(R)-**14c** (0.87 g, 3.6 mmol), phthalimide (0.79 g, 5.4 mmol) and triphenylphosphine (1.41 g, 5.4 mmol) in 50 mL of anhydrous THF was added dropwise 1.08 g (5.37 mmol) of diisopropylazodicarboxylate (DIAD) in 50 mL of anhydrous THF. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated, and the crystals of the side products were precipitated by addition of Et_2O. After their removal by filtration, column chromatography (petroleum ether/ethyl acetate 9:1) of the crude oil afforded **15c** (1.07 g, 80%) as a yellowish oil; $[\alpha]^{20}_D$ = +35 (*c* 2.2, $CHCl_3$); IR ($CHCl_3$): 1776, 1721 (C=O) cm^{-1}; ^1H NMR δ 7.87−7.82 [m, 2H, Ar$(CO)_2$N HC-4,7], 7.73−7.69 [m, 2H, Ar$(CO)_2$N HC-5,6], 7.58−7.55 (m, 2H, Ph HC-2,6), 7.38−7.30 (m, 3H, Ph HC-3,4,5), 6.98−6.94 (m, 2H, ArO HC-3,5), 6.91−6.86 (m, 1H, ArO HC-4), 5.85 (dd, J = 10.0, 5.7 Hz, 1H, CH), 5.06 (apparent t, J = 9.8 Hz, 1H, C*H*H), 4.28 (dd, J = 9.5, 5.6 Hz, 1H, CH*H*), 2.21 (s, 6H, CH_3); ^{13}C NMR δ 168.4 (2C), 155.3 (1C), 136.8 (1C), 134.0 (2C), 132.0 (1C), 130.8 (1C), 128.9 (2C), 128.8 (2C), 128.3 (2C), 128.2 (2C), 124.0 (2C), 123.3 (2C), 70.0 (1C), 55.2 (1C), 16.3 (2C); MS (70 eV) *m*/*z* (%) 371 (M^+, 2), 250 (100).

(−)-(*R*)-2-[(2,6-Dimethylphenoxy)-1-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(−)-(*R*)-15c]. 81% yield, oil; $[\alpha]^{20}_D$ = −43 (*c* 2, $CHCl_3$).

(−)-(*S*)-2-(2-Phenoxy-1-phenylethyl)-1*H*-isoindole-1,3-(2*H*)-dione [(−)-(*S*)-15a]. 45% yield, oil; $[\alpha]^{20}_D$ = −42 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 1776, 1713 (C=O) cm^{-1}; ^1H NMR δ 7.86−7.80 [m, 2H, Ar$(CO)_2$N HC-4,7], 7.73−7.67 [m, 2H, Ar$(CO)_2$N HC-5,6], 7.60−7.57 (m, 2H, Ph HC-2,6), 7.41−7.31 (m, 3H, Ph HC-3,4,5), 7.27−7.21 (m, 2H, ArO HC-3,5), 6.96−6.88 (m, 3H, ArO HC-2,4,6), 5.79 (dd, J = 9.9, 5.4 Hz, 1H, CH), 5.19 (apparent t, J = 9.0 Hz, 1H, C*H*H), 4.54 (dd, J = 9.6, 5.4 Hz, 1H, CH*H*); ^{13}C NMR δ 168.3 (2C), 158.2 (1C), 136.5 (1C), 134.0 (2C), 131.7 (2C), 129.4 (2C), 128.8 (2C), 128.2 (2C), 123.3 (2C), 121.2 (2C), 114.9 (2C), 66.5 (1C), 54.4 (1C); MS (70 eV) *m*/*z* (%) 343 (M^+, 3), 236 (100).

(+)-(*R*)-2-(2-Phenoxy-1-phenylethyl)-1*H*-isoindole-1,3-(2*H*)-dione [(+)-(*R*)-15a]. 31% yield, oil; $[\alpha]^{20}_D$ = +42 (*c* 2, $CHCl_3$).

(−)-(*S*)-2-[2-(2-Methylphenoxy)-1-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(−)-(*S*)-15b]. 75% yield, oil; $[\alpha]^{20}_D$ = −44 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 1778, 1730 (C=O) cm^{-1}; ^1H NMR δ 7.85−7.81 [m, 2H, Ar$(CO)_2$N HC-4,7], 7.74−7.69 [m, 2H, Ar$(CO)_2$N HC-5,6], 7.61−7.59 (m, 2H, Ph HC-2,6), 7.41−7.35 (m, 3H, Ph HC-3,4,5), 7.14 (apparent t, J = 8.1 Hz, 1H, ArO HC-5), 7.06 (d, J = 6.0 Hz, 1H, ArO HC-3), 6.87 (d overlapping apparent t at 6.85, J = 8.1 Hz, 1H, ArO HC-6), 6.85 (apparent t overlapping d at 6.87, J = 7.8 Hz, 1H, ArO HC-4), 5.86 (dd, J = 9.0, 6.0 Hz, 1H, CH), 5.11 (t, J = 9.4 Hz, 1H, C*H*H), 4.58 (dd, J = 9.0, 6.0 Hz, 1H, CH*H*), 1.98 (s, 3H, CH_3); ^{13}C NMR δ 168.4 (2C), 156.3 (1C), 136.6 (1C), 134.1 (2C), 131.9 (1C), 130.7 (2C), 128.8 (2C), 128.4 (1C), 128.2 (2C), 126.8 (2C), 123.4 (2C), 120.9 (1C), 111.4 (1C), 66.4 (1C), 54.4 (1C), 15.9 (1C); MS (70 eV) *m*/*z* (%) 357 (M^+, 6), 250 (100).

(+)-(*R*)-2-[2-(2-Methylphenoxy)-1-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(+)-(*R*)-15b]. 76% yield, oil; $[\alpha]^{20}_D$ = +26 (*c* 2, $CHCl_3$).

(−)-(*S*)-2-[2-(4-Chlorophenoxy)-1-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(−)-(*S*)-15d]. 46% yield, oil; $[\alpha]^{20}_D$ = −46 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 1775, 1724 (C=O) cm^{-1}; ^1H NMR δ 7.87−7.81 [m, 2H, Ar$(CO)_2$N HC-4,7], 7.74−7.68 [m, 2H, Ar$(CO)_2$N HC-5,6], 7.48−7.45 (m, 2H, Ph HC-2,6), 7.39−7.27 (m, 3H, Ph HC-3,4,5), 7.09−7.03 (m, 2H, ArO HC-3,5), 6.76−6.70 (m, 2H, ArO HC-2,6), 5.51 (dd, J = 9.1, 4.3 Hz, 1H, CH), 4.27 (dd, J = 14.0, 9.2 Hz, 1H, C*H*H), 3.91 (dd, J = 14.0, 4.3 Hz, 1H, CH*H*); ^{13}C NMR δ 167.5 (2C), 155.8 (1C), 137.4 (1C), 133.6 (2C), 131.4 (1C), 128.7 (2C), 128.4 (2C), 128.1 (2C), 125.8 (2C), 125.6 (1C), 122.9 (2C), 116.8 (2C), 76.1 (1C), 43.7 (1C); MS (70 eV) *m*/*z* (%) 250 (M^+ − 127, 100).

(+)-(*R*)-2-[2-(4-Chlorophenoxy)-1-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(+)-(*R*)-15d]. 81% yield, oil; $[\alpha]^{20}_D$ = +30 (*c* 2, $CHCl_3$).

(−)-(*S*)-2-[2-(4-Chloro-2-methylphenoxy)-1-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(−)-(*S*)-15e]. 79% yield, oil; $[\alpha]^{20}_D$ = −59 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 1776, 1714 (C=O) cm^{-1}; ^1H NMR δ 7.85−7.81 [m, 2H, Ar$(CO)_2$N HC-4,7], 7.74−7.70 [m, 2H, Ar$(CO)_2$N HC-5,6], 7.59−7.55 (m, 2H, Ph HC-2,6), 7.40−7.30 (m, 3H, Ph HC-3,4,5), 7.08 (dd, J = 8.5, 2.2 Hz, 1H, ArO HC-5), 7.02 (d, J = 1.9 Hz, 1H, ArO HC-3), 6.78 (d, J = 8.6 Hz, 1H, ArO HC-6), 5.81 (dd, J = 9.9, 5.6 Hz, 1H, CH), 5.07 (apparent t, J = 9.7 Hz, 1H, C*H*H), 4.53 (dd, J = 9.5, 5.6 Hz, 1H, CH*H*), 1.94 (s, 3H, CH_3); ^{13}C NMR δ 168.3 (2C), 155.0 (1C), 136.4 (1C), 134.1 (2C), 131.8 (1C), 130.5 (2C), 128.8 (2C), 128.5 (2C), 128.2 (2C), 126.4 (2C), 123.4 (2C), 112.6 (1C), 66.8 (1C), 54.4 (1C), 15.8 (1C); MS (70 eV) *m*/*z* (%) 391 (M^+, 4), 250 (100).

(+)-(*R*)-2-[2-(4-Chloro-2-methylphenoxy)-1-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(+)-(*R*)-15e]. 75% yield, oil; $[\alpha]^{20}_D$ = +40 (*c* 2, $CHCl_3$).

(+)-(*S*)-2-[2-(4-Chloro-2,6-dimethylphenoxy)-1-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(+)-(*S*)-15f]. 39% yield, oil; $[\alpha]^{20}_D$ = +12 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 1775, 1711 (C=O) cm^{-1}; ^1H NMR δ 7.88−7.82 [m, 2H, Ar$(CO)_2$N HC-4,7], 7.74−

7.70 [m, 2H, Ar(CO)$_2$N HC-5,6], 7.56−7.53 (m, 2H, Ph HC-2,6), 7.38−7.30 (m, 3H, Ph HC-3,4,5), 6.94 (s, 2H, ArO HC-3,5), 5.81 (dd, J = 9.9, 5.5 Hz, 1H, CH), 5.03 (apparent t, J = 9.8 Hz, 1H, C*H*H), 4.23 (dd, J = 9.5, 5.5 Hz, 1H, CH*H*), 2.17 (s, 6H, CH_3); ^{13}C NMR δ 168.4 (2C), 154.0 (1C), 136.8 (1C), 134.1 (2C), 132.6 (2C), 139.9 (2C), 128.8 (2C), 128.5 (4C), 128.2 (2C), 123.4 (2C), 70.2 (1C), 55.1 (1C), 16.2 (2C); MS (70 eV) *m*/*z* (%) 405 (M^+, 1), 250 (100).

(−)-(*R*)-2-[2-(4-Chloro-2,6-dimethylphenoxy)-1-phenylethyl]-1*H*-isoindole-1,3(2*H*)-dione [(−)-(*R*)-15f]. 80% yield, oil; $[\alpha]^{20}_D$ = −16 (*c* 2, $CHCl_3$).

General Procedure for the Synthesis of 2-Aryloxy-1-phenylethanamines (3a−f) and the Respective Hydrochlorides (3a−f·HCl).[36] The preparation of (+)-(*S*)-2-(2,6-dimethylphenoxy)-1-phenylethanamine [(+)-(*S*)-**3c**] and of the corresponding hydrochloride [(+)-(*S*)-**3c·HCl**] will be described. To a stirred solution of (+)-(*S*)-**15c** (1 g, 2.69 mmol) in 10 mL of absolute EtOH was added glacial AcOH (0.46 mL, 8.1 mmol) and soon after 55% aq N_2H_4 (0.40 g, 8.1 mmol). The reaction mixture was refluxed for 2 h. The precipitated solid was filtered off and the solvent evaporated under reduced pressure. The residue, dissolved in EtOAc, was extracted with 2 N HCl and the aqueous layer was treated with 2 N NaOH until basic. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the organic layer, dried over anhydrous Na_2SO_4, was evaporated under reduced pressure to give 0.58 g (90%) of the expected amine (**3c**) as a colorless oil: $[\alpha]^{20}_D$ = +11 (*c* 2, MeOH); IR ($CHCl_3$): 3380 (NH_2), 2863, 1264 (C−O−C) cm^{-1}; ^{1}H NMR δ 7.46−7.43 (m, 2H, Ph HC-2,6), 7.38−7.27 (m, 3H, Ph HC-3,4,5), 7.00−6.98 (m, 2H, ArO HC-3,5), 6.93−6.88 (m, 1H, ArO HC-4), 4.45 (dd, J = 8.8, 3.3 Hz, 1H, CH), 3.85 (dd, J = 8.0, 3.3 Hz, 1H, C*H*H), 3.81 (dd, J = 8.8, 8.0 Hz, 1H, CH*H*), 2.17 (s, 6H, CH_3), 1.98 (s, 2H, exch D_2O, NH_2); ^{13}C NMR δ 155.0 (1C), 141.8 (1C), 130.4 (1C), 128.5 (2C), 128.1 (2C), 127.2 (2C), 126.5 (2C), 123.5 (1C), 77.2 (1C), 55.9 (1C), 15.9 (2C); MS (70 eV) *m*/*z* (%) 241 (M^+, 2), 106 (100). (+)-(*S*)-**3c**·HCl was obtained dissolving the free base in anhydrous Et_2O and treating with gaseous HCl for a few seconds. 38% yield, mp 275−277 °C (EtOH−Et_2O), lit.[37] 270.3−270.9 °C (EtOH−Et_2O); $[\alpha]^{20}_D$ = +3.0 (*c* 2, MeOH; ee 99%, t_R 27.1 min, Daicel OD-R, 50:50 CH_3CN/0.1 M $NaClO_4$), lit.[37] +3.5 (*c* 0.48, MeOH, ee not given). Anal. ($C_{16}H_{20}ClNO·0.25H_2O$) C, H, N.

(−)-(*R*)-2-(2,6-Dimethylphenoxy)-1-phenylethanamine [(−)-(*R*)-3c]. 90% yield, oil; $[\alpha]^{20}_D$ = −14 (*c* 2, MeOH).

(−)-(*R*)-2-(2,6-Dimethylphenoxy)-1-phenylethanamine Hydrochloride [(−)-(*R*)-3c·HCl]. 55% yield, mp 264−266 °C (EtOH−Et_2O), lit.[37] 273.0−273.5 °C (EtOH); $[\alpha]^{20}_D$ = −3.6 (*c* 2, MeOH; ee 95%, t_R 30.4 min, Daicel OD-R, 50:50 CH_3CN/0.1 M $NaClO_4$), lit.[37] −4.2 (*c* 0.55, MeOH, ee not given). Anal. ($C_{16}H_{20}ClNO$) C, H, N.

(+)-(*S*)-2-Phenoxy-1-phenylethanamine [(+)-(*S*)-3a]. 65% yield, oil; $[\alpha]^{20}_D$ = +35 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 3381 (NH_2), 2869, 1290 (C−O−C) cm^{-1}; ^{1}H NMR δ 7.48−7.25 (m, 7H, Ph + ArO HC-3,5), 6.98−6.89 (m, 3H, ArO HC-2,4,6), 4.43 (dd, J = 8.8, 3.7 Hz, 1H, CH), 4.10 (dd, J = 9.2, 3.7 Hz, 1H, C*H*H), 3.94 (apparent t, J = 9.1 Hz, 1H, CH*H*), 1.88 (s, 2H, exch D_2O, NH_2); ^{13}C NMR δ 158.6 (1C), 141.9 (1C), 129.5 (2C), 128.6 (2C), 127.7 (1C), 126.9 (2C), 121.0 (1C), 114.7 (2C), 74.0 (1C), 55.3 (1C); MS (70 eV) *m*/*z* (%) 213 (M^+, 1), 106 (100).

(+)-(*S*)-2-Phenoxy-1-phenylethanamine Hydrochloride [(+)-(*S*)-3a·HCl]. 51% yield, mp 206−208 °C (EtOH−Et_2O); $[\alpha]^{20}_D$ = +30 (*c* 2, MeOH; ee 99%, t_R 29.2 min, Daicel OD-R, 50:50 CH_3CN/0.1 M $NaClO_4$). Anal. ($C_{14}H_{16}ClNO$) C, H, N.

(−)-(*R*)-2-Phenoxy-1-phenylethanamine [(−)-(*R*)-3a]. 90% yield, oil; $[\alpha]^{20}_D$ = −35 (*c* 2, $CHCl_3$).

(−)-(*R*)-2-Phenoxy-1-phenylethanamine Hydrochloride [(−)-(*R*)-3a·HCl]. 56% yield, mp 206−208 °C (EtOH−Et_2O); $[\alpha]^{20}_D$ = −27 (*c* 2, MeOH; ee 98%, t_R 24.5 min, Daicel OD-R, 50:50 CH_3CN/0.1 M $NaClO_4$). Anal. ($C_{14}H_{16}ClNO·0.20H_2O$) C, H, N.

(+)-(*S*)-2-(2-Methylphenoxy)-1-phenylethanamine [(+)-(*S*)-3b]. 76% yield, oil; $[\alpha]^{20}_D$ = +32 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 3381 (NH_2), 2869, 1290 (C−O−C) cm^{-1}; ^{1}H NMR δ 7.49−7.46 (m, 2H, Ph HC-2,6), 7.40−7.30 (m, 3H, Ph HC-3,4,5), 7.13 (d overlapping apparent t at 7.12, J = 7.2 Hz, 1H, ArO HC-3), 7.12 (apparent t overlapping d at 7.13, J = 8.0 Hz, 1H, ArO HC-5), 6.86 (apparent t, J = 7.0 Hz, 1H, ArO HC-4), 6.78 (d, J = 8.1 Hz, 1H, ArO HC-6), 4.55 (dd, J = 8.4, 3.8 Hz, 1H, CH), 4.10 (dd, J = 9.1, 4.0 Hz, 1H, C*H*H), 3.95 (apparent t, J = 8.8 Hz, 1H, CH*H*), 2.17 (s, 3H, CH_3), 1.84 (s, 2H exch D_2O, NH_2); ^{13}C NMR δ 156.6 (1C), 141.9 (1C), 130.5 (1C), 128.4 (2C), 127.5 (1C), 126.8 (2C), 126.6 (1C), 126.5 (1C), 120.4 (1C), 110.9 (1C), 73.8 (1C), 55.2 (1C), 16.1 (1C); MS (70 eV) *m*/*z* (%) 227 (M^+, 8), 106 (100).

(+)-(*S*)-2-(2-Methylphenoxy)-1-phenylethanamine Hydrochloride [(+)-(*S*)-3b·HCl]. 51% yield, mp 244−246 °C (EtOH−Et_2O); $[\alpha]^{20}_D$ = +11.6 (*c* 2, EtOH; ee 99%, t_R 39.7 min, Daicel OD-R, 50:50 CH_3CN/0.1 M $NaClO_4$). Anal. ($C_{15}H_{18}ClNO$) C, H, N.

(−)-(*R*)-2-(2-Methylphenoxy)-1-phenylethanamine [(−)-(*R*)-3b]. 76% yield, oil; $[\alpha]^{20}_D$ = −30 (*c* 2, $CHCl_3$).

(−)-(*R*)-2-(2-Methylphenoxy)-1-phenylethanamine Hydrochloride [(−)-(*R*)-3b·HCl]. 40% yield, mp 242−243 °C (EtOH−Et_2O); $[\alpha]^{20}_D$ = −13 (*c* 2, EtOH; ee 99%, t_R 35.2 min, Daicel OD-R, 50:50 CH_3CN/0.1 M $NaClO_4$). Anal. ($C_{15}H_{18}ClNO·0.20H_2O$) C, H, N.

(+)-(*S*)-2-(4-Chlorophenoxy)-1-phenylethanamine [(+)-(*S*)-3d]. 95% yield, oil; $[\alpha]^{20}_D$ = +17.8 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 3382 (NH_2), 2870, 1287 (C−O−C) cm^{-1}; ^{1}H NMR δ 7.46−7.41 (m, 2H, Ph HC-2,6), 7.40−7.23 (m, 3H, Ph HC-3,4,5), 7.22−7.19 (m, 2H, ArO HC-3,5), 6.85−6.80 (m, 2H, ArO HC-2,6), 4.41 (dd, J = 8.7, 3.6 Hz, 1H, CH), 4.04 (dd, J = 8.9, 3.7 Hz, 1H, C*H*H), 3.89 (apparent t, J = 8.9 Hz, 1H, CH*H*), 1.80 (s, 2H, exch D_2O, NH_2); ^{13}C NMR δ 157.4 (1C), 141.7 (1C), 129.4 (2C), 128.6 (2C), 127.8 (2C), 126.9 (2C), 115.9 (2C), 74.4 (1C), 55.2 (1C); MS (70 eV) *m*/*z* (%) 247 (M^+, 1), 106 (100).

(+)-(*S*)-2-(4-Chlorophenoxy)-1-phenylethanamine Hydrochloride [(+)-(*S*)-3d·HCl]. 80% yield, mp 223−225 °C (EtOH−Et_2O); $[\alpha]^{20}_D$ = +27 (*c* 2, EtOH; ee 99%, t_R 13.8 min, Daicel OD, 95:5 hexane/*i*-PrOH). Anal. ($C_{14}H_{15}Cl_2NO$) C, H, N.

(−)-(*R*)-2-(4-Chlorophenoxy)-1-phenylethanamine [(−)-(*R*)-3d]. 90% yield, oil; $[\alpha]^{20}_D$ = −16.5 (*c* 2, $CHCl_3$).

(−)-(*R*)-2-(4-Chlorophenoxy)-1-phenylethanamine Hydrochloride [(−)-(*R*)-3d·HCl]. 80% yield, mp 234−235 °C (EtOH−Et_2O); $[\alpha]^{20}_D$ = −24 (*c* 2, MeOH; ee 98%, t_R 20.2 min, Daicel OD, 95:5 hexane/*i*-PrOH). Anal. ($C_{14}H_{15}Cl_2NO$) C, H, N.

(+)-(*S*)-2-(4-Chloro-2-methylphenoxy)-1-phenylethanamine [(+)-(*S*)-3e]. 76% yield, oil; $[\alpha]^{20}_D$ = +30 (*c* 2, $CHCl_3$); IR ($CHCl_3$): 3382 (NH_2), 2867, 1296 (C−O−C) cm^{-1}; ^{1}H NMR δ 7.47−7.44 (m, 2H, Ph HC-2,6), 7.40−7.28 (m, 3H, Ph HC-3,4,5), 7.11 (d, J = 2.3 Hz, 1H, ArO HC-3), 7.07 (dd, J = 8.6, 2.6 Hz, 1H, ArO HC-5), 6.68 (d, J = 8.5 Hz, 1H, ArO HC-6), 4.44 (dd, J = 8.4, 4.0 Hz, 1H, CH), 4.05 (dd, J = 9.0, 4.0 Hz, 1H, C*H*H), 3.92 (apparent t, J = 8.7 Hz, 1H, CH*H*), 2.17 (s, 3H, CH_3), 1.88 (s, 2H, exch D_2O, NH_2); ^{13}C NMR δ 155.4 (1C), 141.8 (1C), 130.5 (1C), 128.6 (2C), 127.8 (2C), 126.9 (2C), 126.4 (1C), 125.3 (1C), 112.2 (1C), 74.3 (1C), 55.3 (1C), 16.2 (1C); MS (70 eV) *m*/*z* (%) 261 (M^+, 2), 106 (100).

(+)-(*S*)-2-(4-Chloro-2-methylphenoxy)-1-phenylethanamine Hydrochloride [(+)-(*S*)-3e·HCl]. 52% yield, mp 240−242 °C (EtOH−Et_2O); $[\alpha]^{20}_D$ = +21 (*c* 1.9, MeOH; ee 97%, t_R 12.9 min, Daicel OD, 95:5 hexane/*i*-PrOH). Anal. ($C_{15}H_{17}Cl_2NO$) C, H, N.

(−)-(*R*)-2-(4-Chloro-2-methylphenoxy)-1-phenylethanamine [(−)-(*R*)-3e]. 66% yield, oil; $[\alpha]^{20}_D$ = −31 (*c* 2, $CHCl_3$).

(−)-(*R*)-2-(4-Chloro-2-methylphenoxy)-1-phenylethanamine Hydrochloride [(−)-(*R*)-3e·HCl]. 48% yield, mp 240−242 °C (EtOH−Et_2O); $[\alpha]^{20}_D$ = −21 (*c* 2, MeOH; ee 97%, t_R 15.8 min, Daicel OD, 95:5 hexane/*i*-PrOH). Anal. ($C_{15}H_{17}Cl_2NO·0.25H_2O$) C, H, N.

(+)-(*S*)-2-(4-Chloro-2,6-dimethylphenoxy)-1-phenylethanamine [(+)-(*S*)-3f]. 63% yield, oil; $[\alpha]^{20}_D$ = +8.7 (*c* 0.95, $CHCl_3$); IR ($CHCl_3$): 3379 (NH_2), 2858, 1290 (C−O−C) cm^{-1}; ^{1}H NMR δ 7.44−7.41 (m, 2H, Ph HC-2,6), 7.38−7.28 (m, 3H, Ph HC-3,4,5), 6.96 (s, 2H, ArO HC-3,5), 4.41 (dd, J = 7.8, 4.0

Hz, 1H, CH), 3.81 (dd, J = 9.8, 4.0 Hz, 1H, C*H*H), 3.77 (dd, J = 9.8, 7.8 Hz, 1H, CH*H*), 2.17 (s, 6H, CH_3), 1.96 (s, 2H, exch D_2O, NH_2); ^{13}C NMR δ 154.0 (1C), 141.5 (1C), 132.2 (2C), 128.1 (3C), 127.3 (2C), 126.4 (2C), 104.4 (1C), 76.2 (1C), 55.8 (1C), 15.8 (2C); MS (70 eV) m/z (%) 275 (M^+, <1), 106 (100).

(−)-(*S*)-2-(4-Chloro-2,6-dimethylphenoxy)-1-phenylethanamine Hydrochloride [(−)-(*S*)-3f·HCl]. 23% yield, mp 248−250 °C (EtOH−Et_2O); $[\alpha]^{20}_D = -4.0$ (c 1, EtOH; ee 80%, t_R 8.9 min, Daicel OD, 95:5 hexane/*i*-PrOH). Anal. ($C_{16}H_{19}Cl_2NO \cdot 0.25\ H_2O$) C, H, N.

(−)-(*R*)-2-(4-Chloro-2,6-dimethylphenoxy)-1-phenylethanamine [(−)-(*R*)-3f]. 98% yield, oil; $[\alpha]^{20}_D = -9.0$ (c 1.7, $CHCl_3$).

(+)-(*R*)-2-(4-Chloro-2,6-dimethylphenoxy)-1-phenylethanamine Hydrochloride [(+)-(*R*)-3f·HCl]. 40% yield, mp 248−250 °C (EtOH−Et_2O); $[\alpha]^{20}_D = +4.3$ (c 1, EtOH; ee 98%, t_R 11.8 min, Daicel OD, 95:5 hexane/*i*-PrOH). Anal. ($C_{16}H_{19}Cl_2NO$) C, H, N.

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