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A Scalable, Enantioselective Synthesis of the α_2-Adrenergic Agonist, Lofexidine

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Abstract:

A scalable and high-yielding synthetic route toward pure enantiomers of the α_2-adrenergic agonist, lofexidine hydrochloride, is presented. Salient features include a rapid one-pot amide alkylation-imidazoline formation sequence on the carboxamide function of α-(2,6-dichlorophenoxy)propionamide, while preserving the sensitive configuration about the α-carbon of the resulting product. A means to accelerate the sluggish *O*-alkylation of the carboxamide function of α-(2,6-dichlorophenoxy)propionamide by $Me_3O^+BF_4^-$ is also described, which may be of general applicability.

Introduction

A clinically useful manifestation of the agonist effect of the imidazoline, *rac*-lofexidine (**1**) (Figure 1), at α_2-adrenergic receptors is its ability to ameliorate physiological symptoms of opiate withdrawal.[1] Utilized for this purpose in Europe (as Britlofex, Britannia Pharmaceuticals), lofexidine is currently being developed as an opioid withdrawal therapy in the United States by US WorldMeds, Inc., and the results of a phase-III clinical trial were recently reported.[2]

The differential pharmacological properties of the two enantiomers of **1** have previously been documented. The work of Biedermann and co-workers demonstrates that (−)-**1** is 10-fold more potent in competing for specific [^{3}H]-clonidine binding to rat-brain homogenate than its antipode, (+)-**1**,[3] indicating that (−)-**1** is a superior ligand than (+)-**1** at the α_2-adrenergic receptors. This difference is mirrored in the vastly superior ability of (−)-**1** to lower mean arterial blood pressure in rats when compared to (+)-**1**.[3] Much intensified and broadened investigations are necessary, however, to begin drawing parallels between the above said effects and the actual amelioration of the symptoms of opiate addiction. *rac*-Lofexidine treatment is accompanied by side effects, such as hypotension, bradycardia, dry mouth, diarrhea, and sedation. In the light of differential affinities of the two enantiomers at α_2-adrenergic receptors, it is worthwhile to evaluate the difference in side effects caused individually by the two enantiomers. Second, the selectivity of the two enantiomeric forms toward the subclasses of α_2-adrenergic receptors (α_{2A} and α_{2B}) need not necessarily be the same, contributing to the possibility of different side-effect profiles for the two enantiomers.[4] This situation led us to attempt the development of a reliable and economic preparation of enantiomerically pure (−)-**1** and (+)-**1**.

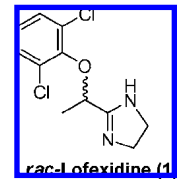

Figure 1. **Lofexidine (1).**

The enantioselective preparation of (−)-**1** and (+)-**1** carries ample literature precedent, and a successful optical resolution of *rac*-lofexidine has also been reported.[3,5] Since *rac*-lofexidine was readily available to us, we explored Biedermann's dibenzoyl tartarate-based optical resolution of *rac*-lofexidine as a potential methodology. In its original form, this method carried an overall yield of 10−15%, after two successive recrystallizations of the (−)-dibenzoyl tartarate salt from acetone and ethanol, yielding (−)-**1**, and the antipodal isomer when (+)-dibenzoyl tartarate was employed. This process typically requires a total of 5 days when operated on a normal bench scale at 8 h/d, and involves 4 filtration operations and requires about 2 L of acetone and 300 mL of ethanol per gram of enantiopure lofexidine obtained. Reduction in the quantity of acetone caused rapid crystallization, compromising the optical purity of the crystallized salt. After evaluating a number of alternative solvents, we concluded that the initial crystallization cycles from acetone were not essential, and that an enantiopure product could also be obtained after three crystallizations from absolute EtOH, with the consumption of only 900 mL of EtOH per gram of enantiopure lofexidine obtained. The overall yield, however, hovered around 10−15% and could not be further improved. Although trials with different resolving agents would have been the next logical step, the structural simplicity of lofexidine led us to direct our efforts at a scalable, enantioselective synthesis.

The two related syntheses of enantiopure lofexidine reported by Biederman et al. utilized a chirally pure ester of lactic acid as a starting point (Scheme 1). Since the authors did not have economical access to D-(+)-ethyl lactate, both approaches utilize L-(−)-ethyl lactate (**2**) as a starting point. The α-OH of ethyl lactate is replaced with a 2,6-dichlorophenoxy group either in

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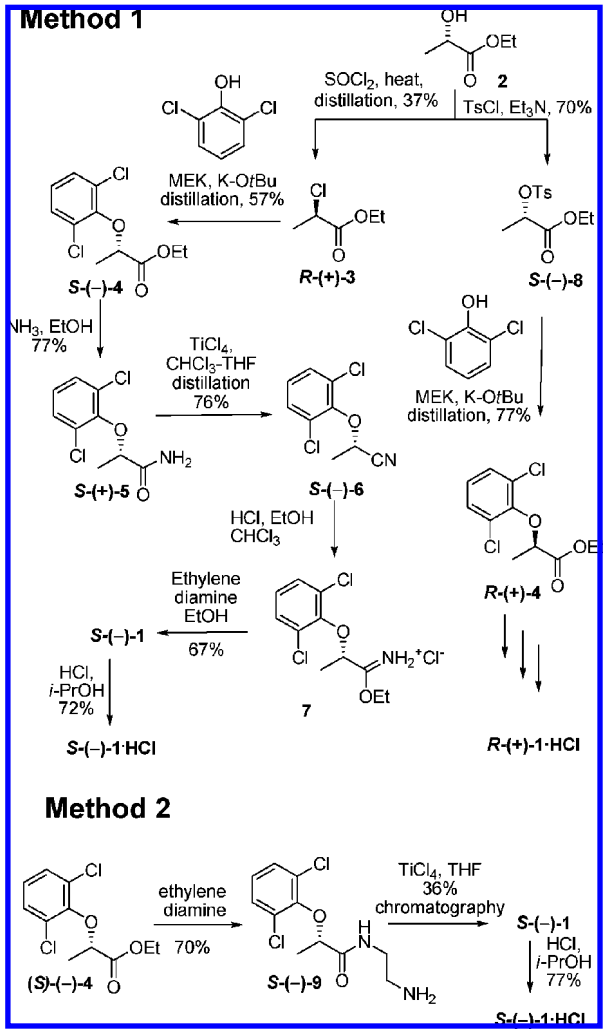
Scheme 1. **Biedermann et al.'s approaches to lofexidine enantiomers**



a double-inversion *via* the intermediate chloro analogue *R*-(+)-**3**, or a tosylation-S_N2 sequence *via* the tosyl derivative *S*-(−)-**8**, which yield respectively *S*-(−)-**4** or *R*-(+)-**4**. In Method 1, the ethyl ester function of both enantiomers is subjected to amidation, leading to *S*-(+)-**5** and *R*-(−)-**5**, respectively. The amide function is then subjected to a three-step sequence involving dehydration to nitrile, acid-mediated conversion of the nitrile to the imino ether, and reaction of the imino ether to yield the lofexidine enantiomers that are then converted to their HCl salts. An overall yield of 5% is obtained after eight synthetic transformations that employ two high-vacuum distillation processes. Method 2 also begins from the ethyl ester intermediate *S*-(−)-**4**, but involves direct amidation of the ethyl ester with excess ethylene diamine, followed by $TiCl_4$-mediated cyclization of the resulting amide *S*-(−)-**9**. An overall yield of 4% for *S*-(−)-**1**·HCl was reported over five transformations, which involved one column chromatography operation.

Discussion

We decided to attempt the adaptation and optimization of each of these methods to a large-scale operation. The large-scale preparation of the enantiomers of a suitable ester of 2-(2,6-dichlorophenoxy)lactate was initially sought, as this intermediate would be common to both methods, as well as to a variety of other possible synthetic approaches. Since both enantiomers of methyl lactate are currently available at a reasonable cost ($0.10/g for (−)-methyl lactate and $5.00/g for (+)-methyl lactate, retail cost, TCI America), we chose to utilize this ester as a starting material. We attempted a Mitsunobu inversion of (−)-methyl lactate with Ph_3P/DIAD instead of the previously reported two-step tosylation−phenoxide displacement sequence.[6,7] This transformation proceeded to completion within 4 h in THF as the solvent. Ph_3P═O and *N,N*-diisopropoxycarbonyl hydrazine could be removed as a 1:1 crystalline complex by stirring the evaporated reaction mixture in Et_2O−hexanes followed by filtration. We then evaluated solvent mixtures that would precipitate the Ph_3P═O/diisopropoxycarbonyl hydrazine complex during the reaction to avoid one of the two evaporation steps. A 1:1 mixture of Et_2O and hexanes satisfied this requirement, and the product *R*-(+)-**10**, after filtration and evaporation, was found to be contaminated with about 5 mol % each of Ph_3P═O and diisopropoxycarbonyl hydrazine, according to ^{1}H NMR spectral analysis. Although the addition of DIAD to the reaction is exothermic, the rise in temperature was found to harm neither the yield nor the chemical or optical purity of product. Last, no change in the yield was observed when reagent-grade (nondry) diethyl ether and hexanes were used for this scale.

Methyl ester *R*-(+)-**10** obtained in ∼90 mol % purity was then treated with 20 equiv of ethylene diamine, as reported for Method 2. In our hands, this reaction surprisingly led not only to the formation of the expected amide but also to its uncatalyzed cyclization to lofexidine. Encouraged by this result, we allowed the reaction to proceed to completion (∼5 days) and isolated lofexidine in 77% yield, after workup and crystallization. Unfortunately, this product was found to be optically inactive. The formation of lofexidine could be suppressed by conducting the reaction at 0 °C, which led to about 50% consumption of *R*-(+)-**10** within 8 h, and less than 5% conversion to *rac*-lofexidine. The amide (expected to be *R*-(+)-**9**), a viscous oil, could then be isolated in 30% yield. This amide product was found not to be *R*-(+)-**9**, but the racemate, and this is in conflict with the patent literature procedure,[5] which reports the (undescribed) isolation of *S*-(−)-**9** in 70% yield and 100% optical purity. The utilization of pure *R*-(+)-**10** (purified by silica gel chromatography) in this reaction caused no change in the product composition. No further attempts were made at optimizing this procedure.

We consequently repeated the chemical transformations in Method 1 on a gram scale and found the optical purities of the products and intermediates therein to be reproducible. With an aim to reduce the number of transformations in this method, we turned our attention to the electrophilic alkylation of amides by trialkyloxonium salts as a means to directly yield an imino ether intermediate such as **11**, with the plan to directly carry it

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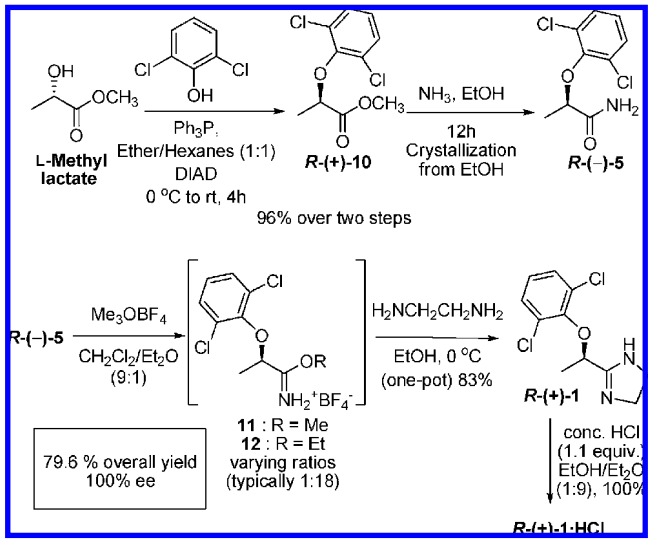
over to the cyclization step (Scheme 2). Treatment of *R*-(+)-**10** with ammonia in EtOH caused the immediate appearance of a small amount of a yellow solid, followed later by the deposition of a voluminous, colorless, crystalline mass. After filtration, the filter cake was mixed with ethanol and the mixture heated to reflux, whereupon the colorless crystalline material dissolved, and the hot mixture was then filtered to remove the insoluble yellow material. Crystallization of the filtrate from EtOH afforded the product *R*-(−)-**5**. The yellow material was identified as azobiscarboxamide, which apparently forms by ammoniolysis of small quantities of DIAD left over from the previous reaction. On larger scales (i.e., on 123 g of crude *R*-(+)-**10**), the reaction was run in an amount of EtOH previously judged to be optimal for crystallization, and the product was isolated by refluxing the completed reaction to dissolve the product. After removal of azobiscarboxamide by filtration and cooling of the filtrate, crystallization occurred to afford *R*-(−)-**5** in 96% yield. This product was found to have an optical rotation of −21.4° (*c* 1.0, acetone) (lit.[3] $[\alpha]^{20}_D$ = −19.9° (*c* 1.0, acetone).

Scheme 2. **Final optimized synthesis of *R*-(+)-1**



Armed with a generous supply of *R*-(−)-**5**, we next treated this compound with an equivalent of trimethyloxonium tetrafluoroborate in CH_2Cl_2, since this is the only trialkyloxonium reagent that is easily available and convenient to employ. Complete conversion to the soluble imino ether tetrafluoroborate **11** took place over 50 h at room temperature. The free base of **11** was stable to aqueous bicarbonate workup, enabling the monitoring of the course of this reaction by GC−MS analysis. Heating this reaction at reflux reduced the reaction time, but only to 36 h. Change of solvent to $CHCl_3$ and addition of excess Me_3OBF_4 did not lead to any change in the reaction rate. Presuming that the sluggish nature of this reaction was due to the very low solubility of the otherwise very reactive Me_3OBF_4 in CH_2Cl_2, we evaluated a number of solvents as additives to CH_2Cl_2. While the addition of toluene and ethyl acetate led to a decrease in the reaction rate, addition of THF (10 vol %) caused rapid disappearance of Me_3OBF_4, leading to a clear solution. However, this was accompanied by darkening of the reaction mixture and the appearance of several products that could not be characterized. THF is indeed known to react reversibly with Me_3OBF_4, forming a rather unstable cyclic oxonium ion that undergoes polymerization.[8] Since an identical reaction with diethyl ether would not be expected to form any unstable oxoniums, we ran the reaction in 9:1 CH_2Cl_2/Et_2O. Gratifyingly, the reaction went to completion within 6 h. GC−MS analysis indicated that the product was a mixture of **11** and the ethylimino ether, **12**, in a ratio of 1:18, in turn indicating that the rate of the reaction was greatly facilitated due to the equilibration between mixed trialkyloxoniums, likely of the formula $(Et)_x(Me)_yOBF_4$ ($x + y = 3$). The above concept of utilizing oxonium-exchange *in situ* to generate soluble oxoniums in equilibrium with insoluble Me_3OBF_4 may prove useful in many cases where alkylations are sluggish due to the insolubility of Me_3OBF_4, particularly in light of Et_3OBF_4 being more hygroscopic, unstable, and therefore difficult to handle.

A solution of **11** and **12** prepared in the above manner on a 2-g scale was then treated at 0 °C with 1.2 equiv of ethylene diamine. A white gum appeared immediately, with no visible change in the reaction after 30 min. GC−MS analysis indicated only a 10% conversion of **11/12** to lofexidine. However, addition of 10 vol % of absolute EtOH to this mixture at 0 °C led to an exothermic reaction, and GC−MS analysis reflected about 87% conversion to lofexidine. After bicarbonate workup and crystallization from hexanes, the product lofexidine could be isolated in 70% yield. This material was found to possess an optical rotation of +79.8° (*c* 1.0, EtOH) (lit.[3] $[\alpha]^{20}_D$ = +73.7° (*c* 1.0, EtOH). We then ran this transformation on a 10-g scale under identical conditions; however, the product was found to possess an optical rotation of +16.0 ° (*c* 1.0, EtOH). Repeat runs of this reaction on a 2-g scale also led to products of wildly varying optical rotations of +4.8° to +80.0°. Upon careful scrutiny of the reaction conditions, it appeared that the degree of racemization is dependent on the time for which the reaction was stirred at ambient temperature after the addition of EtOH. When epimerization occurred, however, it occurred extensively to give a product with an enantiomeric excess lower than 25%. A report on the racemization of imidazolines by primary and secondary amines in alcoholic media led us to suspect that the slight excess of ethylene diamine in the ethanolic solvent was responsible for the varying degrees of racemization of the product.[9] Consequently, we utilized 0.95 equiv of ethylene diamine under conditions identical to the above, to isolate a product with a very consistent optical rotation of +79.4° to +80.1° across four runs, albeit in only 30% yield. We also determined that if the entire operation is carried out at −30 °C with 1.2 equiv of ethylene diamine, about 90% conversion takes place over 10 h, and the product is optically pure.

After a number of attempted modifications in the mode of addition of the reagents, temperatures, etc., it was found that the yield of product obtained with 0.95 equiv of ethylene diamine could be improved to 80% if ethylene diamine is added dropwise as a 20 vol % solution in EtOH (half the volume of

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the reaction mixture) to the solution of **11** and **12** in the $CH_2Cl_2-Et_2O$ solvent at 0 °C. The entire reaction mixture remains a hazy solution under these conditions, with no significant accumulation of gummy matter, and the reaction is generally complete within 30 min. Across several runs on scales ranging from 1−10 g, the product, isolated in ∼85% yield had a consistent optical rotation of +80.0 ° ± 1.0°.

It was noted that the crystallization from hexanes affords a product that is extremely difficult to transfer due to its propensity to become airborne due to the accumulation of static charge, a fact that became apparent to us only upon carrying out this operation on multigram scale. However, if the solution in hexanes is slowly stirred during crystallization, the shorter needles obtained are dense and easily transferable, without significant static charge accumulation. A run on 96 g of *R*-(−)-**5** utilizing these above optimized conditions yielded (+)-**1** in 83% yield with the product possessing a specific rotation of +79.8°.

The HCl-salt formation of **1** has previously been reported utilizing a solution of anhydrous HCl in *i*-PrOH. It was particularly desirable to use aq HCl for this operation for obvious reasons of ease of handling and cost. The main difficulty with using aq HCl being the precipitation of (+)-**1**·HCl as a wet gummy mass from a solution of (+)-**1** in diethyl ether, cosolvents were added to diethyl ether that would efficiently dehydrate the (+)-**1**·HCl precipitate, but at the same time not dissolve the salt. After numerous trials with $EtOH-Et_2O$ mixtures, a 9:1 Et_2O−EtOH solvent mixture was found to be optimal for this operation; thus, addition of conc. aq HCl to a stirred solution of (+)-**1** in the above solvent mixture caused complete precipitation of a solid that was filtered and washed with diethyl ether. Drying afforded chemically pure (+)-**1**·HCl in 98% yield from (+)-**1** and afforded a specific rotation of +39.0° (lit.[3] +37.9°). This transformation was scaled to 25 g, which yielded (+)-**1**·HCl in quantitative yields. Smaller quantities of (−)-**1**·HCl were also prepared similarly, from (+)-methyl lactate in consistent yields and chiral purities over several batches.

There are several shortcomings to this process that would need to be addressed before it becomes adaptable for multikilogram manufacture of lofexidine enantiomers. Safer replacements would need to be identified for ether (flammability, low flash point), hexanes (neurotoxic), and methylene chloride (hepatotoxic). A reviewer has also raised the possibility of contamination of the final product with trace amounts of hydrazine derivatives arising from the utilization of DIAD in the first step, creating the necessity of an analytical method for monitoring such contaminants.

To summarize, the synthetic route developed proceeds in 75−80% overall yields and does not require purification by chromatography or high-vacuum distillation at any stage. The products obtained are consistent in their chiroptical purity. The process yields multigram quantities of lofexidine enantiomers that now support extensive pharmacological, metabolic, and formulation studies. Several other α_2-adrenergic agonist imidazolines, *m*-nitrobiphenylene in particular, are under pharmacological investigations by others.[10] This synthetic approach, particularly the conditions established for the rapid room-temperature amide alkylation as well as for imidazoline formation without epimerization of the α-carbon, may prove useful for the synthesis of such imidazolines.

Experimental Section

***R*-(−)-2-(2,6-Dichlorophenoxy)propionamide (*R*-(−)-5).** To a solution of (−)-methyl lactate (50.00 g, 480.52 mmol), Ph_3P (126.00 g, 481 mmol), 2,6-dichlorophenol (78.32 g, 480.52 mmol) in Et_2O−hexanes (1:1, 1000 mL) at 0 °C was added dropwise over 30 min DIAD (98.00 g, 482 mmol). The resulting yellow solution was warmed to room temperature over a period of 4 h, during which time a fine crystalline precipitate appeared. The mixture was diluted with 500 mL of heptanes, stirred for 30 min, and filtered. The filter cake was washed with heptanes (2 × 200 mL), and the filtrates were evaporated to an amber oil containing *R*-(+)-**10**, which was directly subjected to the next transformation without any further purification.

The amber oil obtained above (134 g crude) was dissolved in 1 L of absolute EtOH and cooled to 0 °C. Ammonia gas was passed through this solution until the solution was judged to be saturated (seen as greatly increased bubbling of gas). The mixture was allowed to warm to room temperature over 12 h, following which it was refluxed for 30 min. This mixture was filtered hot, and the filtrate was cooled for 2 h at 4 °C, which led to the formation of a voluminous mass of white needles, which was removed by filtration and dried to yield *R*-(−)-**5** (108 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.25 (m, 2H, Ar). 7.03 (t, J = 8.4 Hz, 1H, Ar), 6.93 (br, s, NH), 6.08 (br, s, NH), 4.93 (q, 1H, J = 6.9 Hz), 1.50 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 148.9, 129.7, 129.4, 125.7, 79.3, 18.1; mp = 192−193 °C (EtOH); $[\alpha]^{23}_D = -21.4°$ (c 1.0, acetone) (lit.[3] $[\alpha]^{20}_D = -19.9°$ (c 1.0, acetone) and lit.[5] for *S*-(+)-**5** = + 20.1° (c 1.0, acetone)).

***R*-(+)-2-[1-(2,6-Dichlorophenoxy)-ethyl]-1,3-diazacyclopent-2-ene (*R*-(+)-1).** A mixture of *R*-(−)-**5** (96 g, 410.62 mmol), trimethyloxonium tetrafluoroborate (63.74 g, 422.4 mmol), and $CH_2Cl_2-Et_2O$ (9:1, 400 mL) was stirred for 6 h, during which the coarse suspension changed to a clear, colorless solution. After cooling to 0 °C, ethylene diamine (21.1 g, 0.95 equiv) as a solution in EtOH (100 mL) was added dropwise over 30 min. The resulting solution was warmed to room temperature and evaporated to dryness. The pasty white residue was partitioned between 5% aqueous K_2CO_3 (200 mL) and CH_2Cl_2 (300 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The white solid was extracted with four 100-mL portions of boiling hexanes, and the combined hexane extracts were evaporated to half their volume. Cooling with concomitant slow stirring to room temperature afforded pure *R*-(+)-**1** as white needles that were removed by filtration and dried in air (88.19 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.44 (m, 2H, Ar), 7.14 (t, J = 7.8 Hz, 1H, Ar), 6.45 (s, 1H, NH), 4.79 (q, J = 6.6 Hz, 1H), 3.43−3.37 (s, broad, 4H), 1.47 (d, J = 6.6 Hz, 3H). ^{13}C NMR

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(75 MHz, $CDCl_3$) δ ppm 168.2, 149.0, 131.2, 129.4, 128.2, 73.1, 43.1, 19.3; mp = 129−130 °C (hexanes); $[\alpha]^{23}_D = +79.8°$ (*c* 1.0, EtOH) (lit.[3] $[\alpha]^{20}_D = +73.7°$ (*c* 1.0, EtOH) and lit.[3] $[\alpha]^{20}_D$ for *S*-(−)-**1** = −80.7° (*c* 1.0, EtOH)). Anal. Calcd ($C_{11}H_{12}Cl_2N_2O$): C, 50.98; H, 4.67; N, 10.81. Actual: C, 50.80; H, 4.90; N, 10.66.

***R*-(+)-2-[1-(2,6-Dichlorophenoxy)-ethyl]-1,3-diazacyclopent-2-ene hydrochloride (*R*-(+)-1·HCl).** To a solution of *R*-(+)-**1** (25.00 g, 97.5 mmol) in 9:1 Et_2O/EtOH (100 mL) was added in a dropwise fashion conc. aq HCl (8.75 mL, 1.1 equiv). Upon stirring for 10 min the suspension was diluted with Et_2O (100 mL) and filtered, and the filter-cake was washed with Et_2O (3 × 50 mL) and air-dried, affording *R*-(+)-**1**·HCl (28.5 g, 100%). ^{1}H NMR (300 MHz, d_6-DMSO) δ 10.86 (s, 2H, NH), 7.52 (d, J = 8.1 Hz, 2H, Ar), 7.23 (t, J = 8.1 Hz, 1H, Ar), 5.20 (q, J = 6.6 Hz, 1H) 3.87 (s, br, 4H), 1.66 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 169.5, 149.2, 130.3, 129.1, 127.5, 73.9, 45.2, 19.5; mp = 226−227 °C; $[\alpha]^{23}_D = +37.7°$ (*c* 1.0, EtOH) (lit. $[\alpha]^{20}_D$ +37.9° (*c* 1.0, EtOH) and lit.[5] $[\alpha]^{20}_D$ for *S*-(−)-**1**·HCl = −33.4° (*c* 1.0, EtOH)). Anal. Calcd ($C_{11}H_{13}Cl_3N_2O$): C, 44.70; H, 4.43; N, 9.48. Actual: C, 44.65; H, 4.80; N, 9.27.

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