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One-Pot Racemization Process of 1-Phenyl-1,2,3,4-tetrahydroisoquinoline: A Key Intermediate for the Antimuscarinic Agent Solifenacin

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Supporting Information

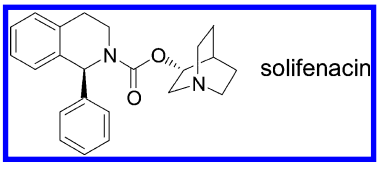
ABSTRACT: (*S*)-(+)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline, which is the key intermediate in preparing the urinary antispasmodic drug solifenacin, was racemized in quantitative yield by a simple one-pot procedure through N-chlorination with trichloroisocyanuric acid, conversion of the *N*-chloroamine into the imine hydrochloride, and reduction of the imine double bond. The racemized amine was successfully resolved by D-(−)-tartaric acid obtaining (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline in 81% yield and with 96.7% ee and, from the crystallization mother liquors, the *R* enriched form. This was racemized by the same one-pot process and resolved by D-(−)-tartaric acid with the same efficiency. Such an approach to the racemization of 1-phenyl-1,2,3,4-tetrahydroisoquinoline can be industrially useful to recycle the waste *R* enantiomer resulting from the classical resolution used to obtain the *S* enantiomer on a large scale.

INTRODUCTION

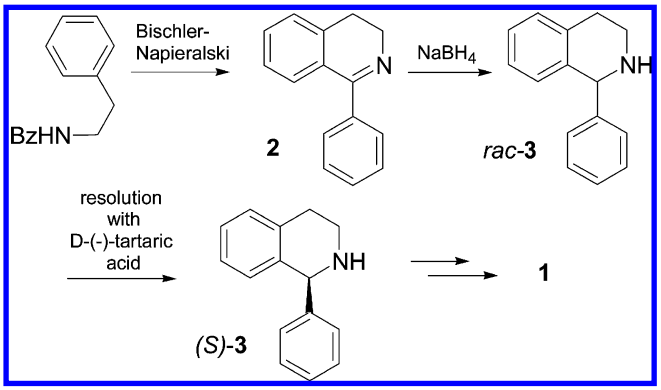
Phenyl-1,2,3,4-tetrahydroisoquinoline is the chiral key substructure of many bioactive compounds.[1] One of these is the (*R*)-3-quinuclidinyl ester of (*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinoline carboxylic acid, solifenacin (**1**), a potent and bladder-selective muscarinic M_3 receptor antagonist.[2] Its succinate salt, commercialized as Vesicare, is, along with other antimuscarinics such as tolterodine, fesoterodine, and darifenacin, one of the most used urinary antispasmodic drugs for the treatment of urinary frequency, urinary incontinence, or urgency associated with overactive bladder (OAB).

The increasing interest, by both academic and industrial research groups, in new synthetic strategies for the preparation of these anticholinergics is justified by the continued growth of the urinary incontinence market and by the approach of the expiry date of the patents, which will allow their manufacture as generics by several companies. In particular, **1** will come off patent in 2015.[3] On industrial scale, **1** is prepared by (a) Bischler−Napieralski cyclization of *N*-(2-phenylethyl)-benzamide; (b) reduction of the resulting imine, 1-phenyl-3,4-dihydroisoquinoline **2**, to racemic 1-phenyl-1,2,3,4-tetrahydroisoquinoline *rac*-**3**; (c) classical resolution of the diastereomeric tartrate salts of **3** to give (*S*)-**3**; and (d) transformation of (*S*)-**3** into the carboxylate of (*R*)-quinuclidin-3-ol **1** by slightly different procedures (Scheme 1).[4,5] As the availability of enantiomerically pure **3** is crucial for the whole process, innovative approaches to the enantiomers of this intermediate are actively pursued to avoid patent protections and, in their turn, be patented. Obviously, the asymmetric reduction of the prochiral imine **2**, the immediate synthetic precursor of **3**, can be regarded as a first-choice alternative option; examples of asymmetric reduction have been described,[6−8] but also asymmetric Pictet−Spengler condensations and enantioselective 1-arylations have been investigated.[9,10] It is widely accepted that asymmetric catalysis in industrial processes can provide superior performances in the synthesis of pharmaceutical intermediates relative to racemate resolutions, penalized by the waste of the undesired enantiomer. However, such a drawback can be overcome by associating a practical racemization method with an efficient resolution. A dynamic kinetic resolution occurred when the *in situ* racemization of 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline promoted by an iridium catalyst was combined with the enzyme catalyzed resolution of the amine.[11] In the case of **1**, the combination of

Chart 1. Structure of the muscarinic antagonist solifenacin (1)



Scheme 1. Synthetic route to solifenacin (1)



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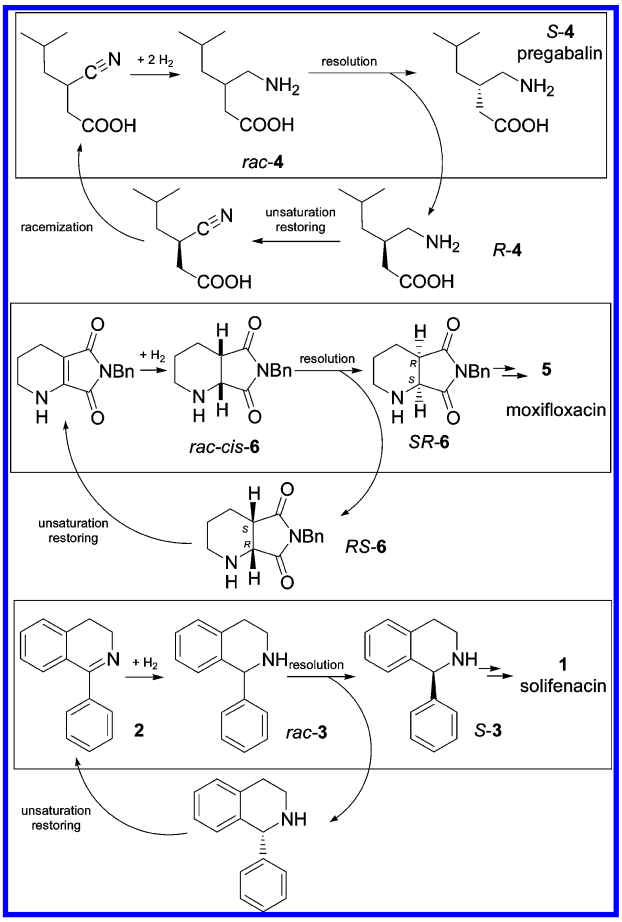
resolution with racemization would be not only competitive in the crowded scenario of patented and not patented processes but also applicable without restriction because the resolution of *rac*-**3** with tartrate is efficient and well documented since the 1920s.[5] That is why we focused on the racemization of **3**, and here we report a new simple and efficient one-pot procedure to accomplish it.

RESULTS AND DISCUSSION

Suggestions on how to racemize **3** came from our recent studies on pregabalin [(*S*)-**4**] and on moxifloxacin (**5**),[12,13] two drugs also near to becoming generics. Like solifenacin, pregabalin and moxifloxacin are industrially prepared or preparable by diastereomeric resolution, respectively, of 3-amino-5-methylhexanoic acid (*rac*-**4**) with (+)-mandelic acid and of the intermediate *N*-benzylimide of *cis*-piperidine-2,3-dicarboxylic acid (*rac-cis*-**6**) with (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid (Scheme 2).[14,15] Two other close and more

Scheme 2. Analogies between the syntheses of pregabalin, moxifloxacin, and solifenacin and the proposed racemization routes



interesting analogies relate *rac*-**3** to *rac*-**4** and *rac-cis*-**6**: (a) they are prepared by hydrogenation of unsaturated precursors; (b) the multiple bond of these unsaturated precursors directly involves the stereogenic carbons of the hydrogenation products (**3** and **6**) or is vicinal to the stereocenter and can promote its racemization under mild conditions before the conversion into the hydrogenated derivative (**4**). Therefore, in all three cases, the conversion back to the unsaturated precursor can be exploited to accomplish the racemization (Scheme 2). Indeed, restoration of the C(2)═C(3) double bond in one enantiomer of the *cis*-piperidine **6** and conversion of the aminomethyl group of one enantiomer of **4** into nitrile were successful, and the unsaturated products could be easily racemized by hydrogenation of C(2)═C(3) and, after treatment with a base, of CN, respectively.[12,13] Analogously, we required that the restoration of the C(1)═C(2) double bond in (*S*)- or (*R*)-**3** and the successive achiral saturation be easy, quantitative, and possibly accomplished without isolating intermediates. On these conditions, such a strategy would be advantageous in comparison to the claimed racemizations of (*R*)-**3** that are effected, in moderate yield, by treatment with KOH in DMSO at high temperature for several hours[16] or, in higher yields, by two separate steps, namely by transformation into an amide and successive heating of the isolated amide in concentrated mineral acid mixtures.[17] On the other hand, many examples for the conversion of 1,2,3,4-tetrahydroisoquinolines into 3,4-dihydroisoquinolines are reported in literature, but their applicability on a large scale is limited by the use of hazardous and/or costly reagents or severe conditions, by modest yields, or by the need to isolate intermediates.[18]

On the basis of the results of our recent studies on the N-chlorination and dehydrochlorination of various substrates,[12,13,19] we decided to follow the same approach to convert **3** into **2**. To the best of our knowledge, the only example of conversion of **3** into **2** by N-chlorination and dehydrochlorination was effected in high yield but under conditions (*t*-BuOCl, KO_2, 18-crown-6-ether, diethyl ether) quite inappropriate for industrial applications.[20] In contrast, trichloroisocyanuric acid (TCCA) and sodium dichloroisocyanurate (NaDCC) are inexpensive, stable, and safe and we had already successfully exploited their N-chlorinating properties on amides, amino acids, and amino imides according to simple protocols assuring quantitative yields in a short time and with very simple reaction workup.[12,13,19,21] In particular, TCCA seemed appropriate for our target, which was a one-pot procedure to convert chirally pure **3** into the racemate through the *N*-chloroamine **7** and the imine **2** intermediates and thus required, first of all, neat and quantitative N-chlorination of the substrate and quantitative separation of the dechlorinated chlorinating agent, that is isocyanuric acid. In fact, only upon these two conditions, the successive dehydrochlorination of **7** to imine **2** and reduction to racemic **3** would be directly feasible without extractions and purifications. This notwithstanding, before developing a one-pot process, we studied the single steps starting from (*S*)-**3**, the enantiomer available to us (Scheme 3). In particular, we carefully characterized the intermediates with particular focus on **7**, which is described as not isolable due to its instability and its tendency to rapidly convert to the imine **2**.[20]

Treatment of (*S*)-**3** with a slight excess of TCCA, that is little more than a 0.33 molar portion (0.37 mol TCCA/1 mol (*S*)-**3**), in DCM[22] at 5 °C for 90 min gave (*S*)-**7** as an oil, which was isolated in quantitative yield by simple filtration of the reaction mixture at −15 °C and concentration of the filtrate. At room temperature, the *N*-chloroamine rapidly solidifies and is indefinitely stable if stored at low temperatures (−15 °C), whereas it transforms into the imine hydrochloride **2**·HCl in the course of several days at room temperature or instantaneously at 60 °C. Such a conversion is observable in the DSC trace of (*S*)-**7**, where an exothermic event occurs at 60 °C and is followed by an endothermic transformation at 228

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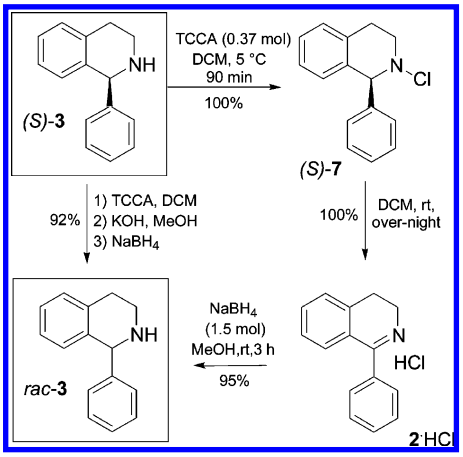
Scheme 3. Three-step and one-pot racemization of (*S*)-3



°C, that is the melting point of **2**·HCl. This coincidence and the fact that no mass loss is associated with the exothermic event, as shown by the TGA curve, indicate that **7** undergoes dehydrochlorination and salification by the formed hydrogen chloride. The transformation of the solid chloroamine into imine hydrochloride, which is slowly progressive at room temperature, is confirmed and monitored by the ^{1}H NMR spectra registered for samples drawn immediately after isolation and in the subsequent days. The same transformation takes place in solution: we observed that the DCM solution of (*S*)-**7**, filtered at −15 °C to remove isocyanuric acid and excess TCCA, stirred at room temperature overnight and then concentrated, furnished **2**·HCl as a sole product.

The subsequent step, that is the dehydrochlorination, was easily and quantitatively effected as suggested by the above-described behaviour of the chloroamine in solution, namely by dissolving (*S*)-**7** in dichloromethane, storing the solution at room temperature overnight, and concentrating it. The resulting white solid was confirmed to be **2**·HCl by comparison of the analytical data (mp and ^{1}H and ^{13}C NMR spectra) with literature. Alternatively, (*S*)-**7** was dissolved in methanol and treated with stoichiometric KOH, and after 1 h, **2** (free imine) was isolated by filtering off KCl and concentrating the filtrate.

To convert **2**·HCl into the racemic tetrahydroisoquinoline *rac*-**3**, a solution of the former in methanol was treated with sodium borohydride. After 3 h, methanol was evaporated and the residue was poured into water and dichloromethane: *rac*-**3** was recovered in 95% yield as a white solid by concentration of the organic phase. The reaction product had no optical rotation, and HPLC analysis on a chiral stationary phase confirmed that it was a racemate. No other peaks except those of the two enantiomers of **3** were observed in the chromatogram. ^{1}H and ^{13}C NMR spectra were identical with those in literature.

After ascertaining that the three reactions, N-chlorination, dehydrochlorination, and imine reduction, were quantitative, we developed a one-pot procedure to transform (*S*)-**3** into *rac*-**3** (Scheme 3). The N-chlorination was accomplished as described above, that is with 0.37 mol of TCCA per 1 mol of (*S*)-**3**. After the precipitated isocyanuric acid was removed, a methanol solution of KOH, equimolar to the starting substrate, was added. Again, the formed precipitate, KCl, was removed and the reaction solution was concentrated. The residue was taken up into methanol, and sodium borohydride, 1.5 mol per 1 mol of starting (*S*)-**3**, was added. Successive addition of water caused the precipitation of *rac*-**3**, which was isolated as a unitary product by filtration.

The overall yield of the one-pot procedure, scaled up to a multigram scale, was 92%. According to a recently reported method,[23] we then verified the resolvability of the racemate obtained from (*S*)-**3** by tartaric acid and, in sequence, the resolvability of the racemate obtained from the *R* enriched amine recovered from the mother liquors of the first resolution. In detail, the racemized amine was resolved with D-(−)-tartaric acid with 0.78 experimental resolution efficiency, calculated by multiplying the yield of the precipitated tartrate of (*S*)-**3** (81%) and the enantiomeric excess of liberated (*S*)-**3** (96.74%). The *R* enriched amine (63.28% ee), recovered from the crystallization mother liquors, was racemized in 89% yield by the same one-pot procedure previously used to racemize the *S* enantiomer and the subsequent resolution with D-(−)-tartaric acid accomplished with 0.77 efficiency (79% yield, 97.43% ee).

The two amounts of resolved (*S*)-**3**, having 96.74% and 97.43% ee respectively, were brought together to be recrystallized in order to increase the enantiomeric excess. The success and the optimization of such a practice is greatly improved by the knowledge of the enantiomeric system nature, that is existence, number, and location of eutectics both in the binary melting point diagram and in the ternary solubility diagram. According to procedures previously accomplished for other enantiomer systems,[24] we performed IR and DSC analyses and solubility measurements to determine the racemate type formed by **3**. The IR spectra of (*S*)-**3** and of *rac*-**3** were different, and the final melting temperature of (*S*)-**3**, 91 °C, was lower than that of *rac*-**3**, 103 °C. These data indicated that **3** forms a racemic compound. The nature of the racemic compound was confirmed by DSC analyses of *rac*-**3**, (*S*)-**3**, and a number of their mixtures, which allowed us to construct the binary phase diagram for mole fractions of (*S*)-**3** ranging from 0.5 to 1 (Figure 1). The DSC melting profiles of

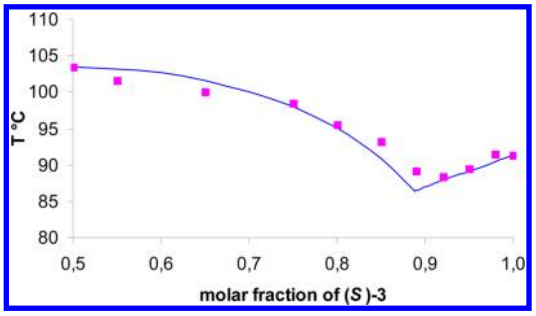


Figure 1. Binary melting-point phase diagram for 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**3**). The solid curve represents the values calculated on the basis of the Prigogine−Defay and the Schröder−van Laar equations.

differently proportioned *rac*-**3**/(*S*)-**3** mixtures were characterized by the presence of two peaks, the former, between 85 and 86 °C, representing the fusion of the eutectic E^{+}, and the latter, representing the fusion of the excess of the racemic compound or (*S*)-enantiomer over the eutectic composition at temperatures that increase with such an excess. As can be seen in Figure 1, the experimental values fit well with the theoretical ones (solid curves), calculated on the basis of the melting point of (*S*)-**3** and of its heat of fusion (125.9 J/g) by the Schröder−van Laar equation[25] and of the melting point of *rac*-**3** and of its heat of fusion (146.2 J/g) by the Prigogine−Defay equation.[26]

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The two curves intersect at the 0.889 molar fraction of (*S*)-**3**. Such a theoretical value of the E^+ composition is consistent with the experimental observation that, unique among the DSC curves recorded for the nine differently proportioned (*S*)-**3**/*rac*-**3** mixtures, a sample with a 0.89 mol fraction of (*S*)-**3** shows only one sharp melting peak at 89.1 °C. The solubility measurements were made for (*S*)-**3**, *rac*-**3**, the eutectic mixture E^+ (89/11 (*S*)-**3**/(*R*)-**3**), and two enantiomeric mixtures close to E^+ (80/20 and 95/5) in the 86/14 (v/v) methanol/water mixture at 23 °C.[21] The data, listed in Table 1 and plotted in a ternary diagram (Figure 2), show that E^+ has the highest solubility (92.5 mg/mL, 10.1% w/w). These findings imply that, since (*S*)-**3** liberated from the two precipitated diastereomeric tartrates has an *S* enantiomer content sensibly higher than 89%, namely ~98.5% (97% ee), its recrystallization under equilibrium conditions can maximize the enantiomeric excess with minimal yield decrease. Indeed, (*S*)-**3** crystallized in 80.6% yield and with 99.04% ee using a slight excess (28%) of the 86/14 (v/v) methanol/water mixture[22] over the volume necessary to solubilise E^+, calculated on the basis of the solubility of E^+ at 23 °C and of the E^+ content (14%) of starting 97% enantiomerically pure (*S*)-**3**. The 19.4% loss of amine was consistent with the fact that just the eutectic fraction (14%) was retained in the mother liquors. Chiral HPLC analysis confirmed that unprecipitated amine had a composition nearly identical to that of E^+, that is 89.55% of (*S*)-**3** and 10.45% of (*R*)-**3**.

Table 1. Compositions (weight percentages) of saturated solutions of *rac*-3, (*S*)-3, and *S* enriched 3 in aqueous methanol at 23 °C

solute	% (+)-(*S*)-**3**	% (−)-(*R*)-**3**	% 86/14 MeOH/H_2O
(*S*)-**3**	6.74	0	93.26
95/5 (*S*)**3**/(*R*)-**3**	7.53	0.40	92.07
89/11 (*S*)**3**/(*R*)-**3**	9.02	1.11	89.87
80/20 (*S*)**3**/(*R*)-**3**	5.39	1.35	93.26
rac-**3**	2.31	2.31	95.38

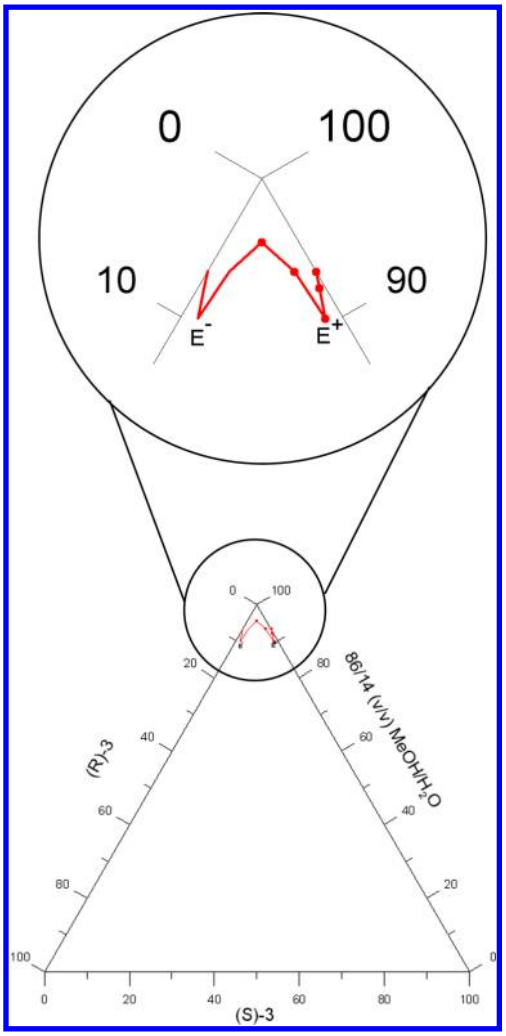

Figure 2. Solubility diagram for 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**3**) in 86/14 (v/v) methanol/water at 23 °C. The concentrations of the components are expressed as weight percentages and are listed in Table 1. The magnified upper part of the diagram shows the solubility curve and the location of the two eutectics [E^+: 9.02% (+)-(*S*)-**3**, 1.11% (−)-(*R*)-**3**, 89.87% solvent mixture; E^-: 9.02% (−)-(*R*)-**3**, 1.11% (+)-(*S*)-**3**, 89.87% solvent mixture].

CONCLUSIONS

In summary, we have developed an efficient one-pot procedure, which racemizes 1-phenyl-1,2,3,4-tetrahydroisoquinoline via N-chlorination, dehydrochlorination, and imine reduction by using mild reaction conditions and safe and cheap reagents. As the *S* enantiomer of 1-phenyl-1,2,3,4-tetrahydroisoquinoline, which is the key intermediate in the industrial synthesis of antispasmodic drug solifenacin, is prepared by classical resolution of the racemate, such a simple procedure might be profitably applied on a large scale to racemize and to recycle the undesired *R* enantiomer. To demonstrate that the racemic substrate maintains suitable quality for resolution through this one-pot process, two successful resolutions of previously racemized 1-phenyl-1,2,3,4-tetrahydroisoquinoline were accomplished in sequence with tartaric acid.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on a Varian Gemini 300 operating at 300 MHz and ^{13}C NMR at 75 MHz. Chemical shifts are reported in ppm relative to residual solvent ($CHCl_3$ or DMSO) as an internal standard. ESI-MS analyses were acquired using a Thermo Finnigan TSQ Quantum Mass Spectrometer. IR spectra were recorded with an FT-IR ALPHA-P Bruker spectrometer. The melting points were determined by DSC analysis and correspond to the peak maximum, while the final melting temperatures were utilized to construct the binary phase diagram of **3**. The DSC curves were recorded and integrated with the aid of a TA Instruments DSC 2010 apparatus. The enantiomer mixtures of **3** were prepared by mixing the solid racemate with the solid (*S*)-enantiomer. The TGA curves were recorded with the aid of a TA Instruments TGA Q50 apparatus. Optical rotations were determined in a 1 dm cell with a 1 mL capacity using a Perkin-Elmer 241 polarimeter. HPLC analyses of **3** were performed after conversion into the corresponding acetamide using a Kromasil AmyCoat column (250 mm × 4.6 mm i.d.).

Synthesis of (*S*)-*N*-Chloro-1-phenyl-1,2,3,4-tetrahydroisoquinoline [(*S*)-7]. TCCA (0.408 g, 1.75 mmol) was added to a solution of (*S*)-**3** (1 g, 4.78 mmol) in DCM (10 mL) at 3 °C. The mixture was stirred at 5 °C for 90 min and then cooled to −15 °C and filtered to remove precipitated isocyanuric acid. The filtrate was concentrated at room temperature under vacuum to give (*S*)-**7** in quantitative yield

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as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (dt, J_1 = 4.1 Hz, J_2 = 16.5 Hz, 1 H), 3.28−3.39 (m, 1 H), 3.51 (ddd, J_1 = 4.1 Hz, J_2 = 9.6 Hz, J_3 = 11.0 Hz, 1 H), 3.80 (ddd, J_1 = 4.1 Hz, J_2 = 5.5 Hz, J_3 = 9.6 Hz, 1 H), 5.14 (s, 1 H), 6.72 (d, J = 8.0 Hz,1 H), 7.1 (dt, J_1 = 2.5 Hz, J_2 = 6.3 Hz, 1 H), 7.18−7.22 (m, 2 H), 7.33−7.42 (m, 5 H). ^{13}C NMR(75 MHz, $CDCl_3$) δ 29.76, 58.21, 76.51, 126.39, 127.14, 128.27, 128.48, 128.57, 128.76, 128.94, 129.84, 133.01, 136.99, 142.49. MS (ESI) m/z calcd for $C_{15}H_{15}ClN$ (MH^+ + 2) 246.09 and (MH^+) 244.09, for $C_{15}H_{16}N$ ($MH^+ - Cl^+ + H^+$) 210.13, for $C_{15}H_{14}N$ (MH^+ − HCl) 208.11: found 246.10, 244.10 (base peak), 210.15, and 208.12.

Synthesis of 1-Phenyl-3,4-dihydroisoquinoline HCl [2·HCl]. A solution of (*S*)-**7** (1 g, 4.10 mmol) in DCM (8 mL) was stirred at room temperature overnight. After evaporating the solvent, **2**·HCl was obtained in quantitative yield as a white solid: Mp 228.8 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.21 (t, J = 7.7 Hz, 2H), 3.96 (t, J = 7.7 Hz, 2 H), 7.39 (d, J = 7.7 Hz, 1 H), 7.50 (pseudo t, 1H), 7.60 (d, J = 7.4 Hz, 1 H), 7.65−7.81 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 25.32, 41.75, 126.31, 128.57, 129.46, 129.55, 130.38, 131.52, 133.67, 134.35, 137.19, 140.23, 173.52. Alternatively, (*S*)-**7** was dissolved in methanol and treated with a stoichiometric 1 M methanol solution of KOH, and after 1 h, **2** (free imine) was isolated in quantitative yield by filtering off KCl and concentrating the filtrate.

Synthesis of *rac*-1-Phenyl-1,2,3,4-tetrahydroisoquinoline [*rac*-3]. Sodium borohydride (0.233 g, 6.15 mmol) was added to a solution of **2**·HCl (1 g, 4.10 mmol) in methanol (10 mL). After the reaction mixutre stirred at room temperature for 3 h, it was concentrated under vacuum, and DCM (20 mL) and water (10 mL) were added to the resulting residue. The layers were separated, and the organic phase was dried over Na_2SO_4, filtered, and evaporated to give *rac*-**3** (0.815 g, 95%) as a white solid: Mp = 98.9 °C;$[\alpha]_D^{20}$ ∼0 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 1H), 2.79−2.90 (m, 1H), 2.99−3.15 (m, 2 H), 3.24−3.32 (m, 1H), 5.12 (s, 1H), 6.76 (d, J = 7.6 Hz, 1H), 7.02−7.08 (m, 1H), 7.12−7.17 (m, 2H), 7.24−7.36 (m, 5H). ^{13}C (75 MHz, $CDCl_3$) δ 30.07, 42.56, 62.40, 125.91, 126.53, 127.66, 128.39, 129.69, 129.27, 129.32, 135.72, 138.57, 145.17. Chiral HPLC analysis of the corresponding acetamide (Amycoat, Kromasil, el. *N*-hexane/2-propanol 9/1, 0.8 mL/min, λ 220 nm) proved complete racemization, showing only two peaks of identical area, the first-eluted acetamide of (*R*)-**3** ($t_R \approx$ 13 min) and the second-eluted acetamide of (*S*)-**3** ($t_R \approx$ 16 min).

One-Pot Racemization of (*S*)-3 on Multigram Scale. TCCA (4.08 g, 17.5 mmol) was added to a solution of (*S*)-**3** (10 g, 47.8 mmol) in DCM (100 mL) at 3 °C. The mixture was stirred at 5 °C for 90 min and then cooled to −15 °C and filtered to remove isocyanuric acid. A methanol solution of KOH (1 M, 48 mL) was added to the filtrate, and the mixture was stirred at room temperature for 1 h. Precipitated KCl was removed by filtration, and the clear filtrate was concentrated to remove dichloromethane. The residue was diluted with methanol (50 mL), and $NaBH_4$ (2.7 g, 7.17 mmol) was slowly added. After the reaction mixture stirred at room temperature for 3 h, it was poured into cool water (200 mL) and stirred for 10 min.The resulting solid was collected, washed with water, and oven-dried at 60 °C for 30 min to give *rac*-**3** (9.16 g, 92%) as a white solid that was analytically identical to *rac*-**3** obtained by the three-step procedure.

Resolutions of Racemized 3. *rac*-**3** (9 g), obtained from the above one-pot racemization of (*S*)-**3**, was resolved with D-(−)-tartaric acid according to the procedure described in ref 22. The precipitated salt was decomposed to give (*S*)-**3** (3.61 g, 80% yield) with 96.74% ee, while (*R*)-**3** (5.30 g, 63.28% ee) was isolated from the mother liquors. The *R* enriched amine was one-pot racemized, obtaining *rac*-**3** (4.69 g, 89%), which was resolved with D-(−)-tartaric acid again. The resolution provided (*S*)-**3** (1.85 g, 79% yield) with 97.43% ee and (*R*)-**3** (2.78 g, 62.22% ee).

Recrystallization of (*S*)-3 Obtained by Resolution. The two amounts (3.61 and 1.85 g) of (*S*)-**3**, resulting from the resolutions, were brought together and recrystallized from 86/14 v/v MeOH/H_2O (11.1 mL). The precipitate was isolated by filtration at 23 °C, obtaining 4.40 g of (*S*)-**3** (80.6%) with 99.04% ee. The amine recovered from the mother liquors showed a 79.10% ee.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR, IR, and MS spectra; DSC and TGA traces; HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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