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Articles

A Large-Scale Synthesis of Enantiomerically Pure Cetirizine Dihydrochloride Using Preparative Chiral HPLC

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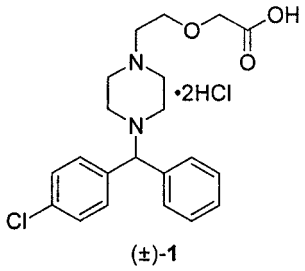
Abstract:

Enantiomerically pure cetirizine can be prepared by preparative HPLC separation of cetirizine amide. The amide has an α value of 2.76 (USP resolution of 8.54) using a Chiralpak AD column, and 0.5 wt % of the amide (based on packing material) can be injected per run.

Introduction

Racemic cetirizine dihydrochloride (**1**, sold under the trade name Zyrtec [see Figure 1] is a second generation H_1 receptor antagonist antihistamine (replacing the sedating hydroxazine), and evidence suggests that the levorotatory (*S*) enantiomer of cetirizine displays an improved pharmacological profile compared to the racemate. The reported syntheses of single-enantiomer cetirizine require either a low-yielding resolution of a cetirizine precursor[1] or the use of a stoichiometric heavy metal.[2] We sought an alternative approach that would allow access to either enantiomer of cetirizine in a rapid fashion.

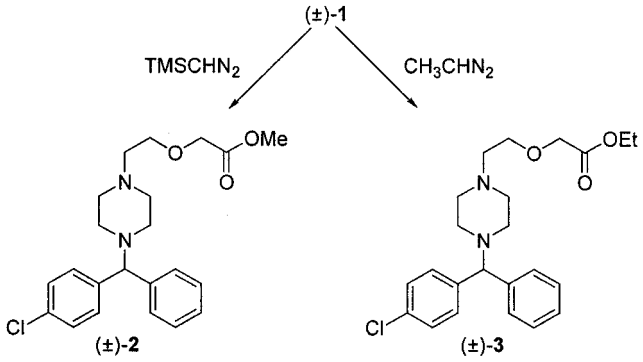
The low-yielding resolutions led us to concentrate on asymmetric synthesis and preparative chiral HPLC. Recently, we disclosed synthesis of both enantiomers of cetirizine by addition of phenylmagnesium bromide or phenyllithium to a chiral imine.[3] While this approach is appealing, a more economic and scalable route was desired. To develop a practical chiral separation, the separation must be (1) performed with an inexpensive and readily available compound,[4] (2) efficient (have a large α value and high loading capacity), and (3) cost-competitive with a resolution or asymmetric synthesis. Herein, we disclose an economic and operationally simple technology for the separation of the enantiomers of cetirizine utilizing chiral HPLC of the inexpensive and readily available amide **5**.



(±)-**1**

Figure 1. **Cetirizine dihydrochloride.**

Scheme 1



Results and Discussion

Initial efforts were focused on converting cetirizine to a derivative suitable for chiral HPLC chromatography. To gain rapid access to cetirizine esters, the first experiments involved reaction of cetirizine with trimethylsilyldiazomethane to provide methyl ester **2,** and with diazoethane to afford **3** (Scheme 1). When these esters were subjected to HPLC on a Chiral Technologies Chiralpak AD column, the enantiomers separated readily (Table 1).

To investigate the chromatographic efficiency (with the intent to perform preparative separations), other analogues were produced. The methyl ester could be reacted with $Ti(O\textit{i}\text{-}Pr)_4$ in 2-propanol to afford isopropyl ester **4**, or with ammonia in methanol at 15−30 psi to provide amide **5** (Scheme 2). While **4** showed less separation than the methyl ester, the separation of the amide was remarkable (using 60:40 ACN:IPA and the Chiralpak AD column, the first peak eluted at 4.80 min and the second at 8.84 min, Table 2). The separation led us to look for a more practical synthesis of the amide.

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(1) Opalka, C. J.; D'Ambra, T. E.; Faccone, J. J.; Bodson, G.; Cossement, E. *Synthesis* **1995**, 766.

(2) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 4837.

(3) Pflum, D. A.; Wald, S. A.; Senanayake, C. H. Synthesis of Enantiomerically Enriched Cetirizine. Presented at the 219th National Meeting of the American Chemical Society, San Francisco, CA, April, 2000; Paper ORGN 62. Manuscript in preparation.

(4) Cetirizine dihydrochloride is inexpensive ($100/kg) and widely available. The material used in this study was purchased from Bombay Drugs & Pharmas, Ltd.

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Table 1. **Chiral HPLC separation of cetirizine methyl and ethyl esters**[a]

analog	USP resolution	α value
2	3.25	1.53
3	2.79	1.44

[a] While separations are traditionally reported as α values ($\alpha = k_2'/k_1'$, $k_1' = (t_{r1} - t_0)/t_0$, $k_2' = (t_{r2} - t_0)/t_0$, t_{r1}= retention time of the first component, t_{r2} = retention time of the second component, t_0 = void time), a more meaningful measure of separation is USP resolution, which includes a factor for peak width ($R = 2(t_{r2} - t_{r1})/(w_1 + w_2)$, where w = peak width at the baseline of the peak tangents).

Table 2. **Chiral HPLC separation of cetirizine isopropyl ester and cetirizine amide**

analog	USP resolution	α value
4	2.29	1.37
5	8.54	2.76

Initial efforts directed toward Fischer esterification for the preparation of intermediate **2** proved unsatisfactory. The reaction proceeded very quickly, but 1−4% of cetirizine consistently remained and could not be removed easily.

Acid **1** could be reacted with thionyl chloride to provide the acid chloride dihydrochloride (**6**) as a slurry in toluene (Scheme 3). The excess thionyl chloride was distilled, fresh toluene was added, and ammonia gas was then bubbled through the slurry to provide cetirizine amide and ammonium chloride. The inorganic salt was then filtered to provide a toluene solution which was concentrated to provide a solution from which cetirizine amide crystallized. The crystallization could be completed by addition of heptane to provide racemic **5** in approximately 79% yield. Using this protocol, nearly 300 g of cetirizine amide could be made in a 5 L flask or 4.6 kg in a 50 gallon reactor.[5]

The availability of acid chloride **6** allowed rapid access to numerous cetirizine derivatives. After reaction of **1** with thionyl chloride (neat), the reaction mixture was diluted with toluene and filtered to afford cetirizine acid chloride dihydrochloride as a stable white solid. Reaction of **6** with alcohols or amines provided esters or amides that were subjected to the chiral HPLC (Scheme 4). In general, the more polar derivatives separated better under the chromatography conditions investigated. While the separations of several of the esters were better than that of **2**, none surpassed the separation of **5** (Table 3).

Injections of (±)-**5** on the Chiralpak AD column were reproducible and could be automated. Using a 10 × 250 mm column and 200 μL injections, 17.7 g of (+)-cetirizine amide (1.2% unknown impurities, 99.6% ee) and 18.8 g of (−)-cetirizine amide (0.7% unknown impurities and 98.8% ee) were collected with 95% recovery. These conditions were used on larger scale to produce 1.6 kg of (+)-**5** (0.26% total impurities, 99.8% ee) and 1.6 kg of (−)-**5** (0.08% total impurities, 99.7% ee) with 98% recovery.[5] Attention then turned to converting the amide to optically active **1**.

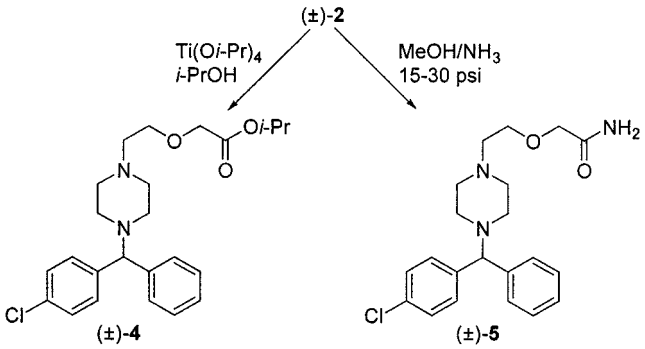
(5) The large-scale synthesis of racemic **5** and chiral HPLC separation were performed by Regis Technologies, 8210 Austin Ave, Morton Grove, IL 60053. The large-scale chiral HPLC was performed using an automated, computer-controlled isocratic/gradient preparative HPLC system and a Prochem LC150 column (40 × 15 cm) packed with Chiralpak AD packing material (2 kg).

Table 3. **Chiral HPLC separation of cetirizine analogues**

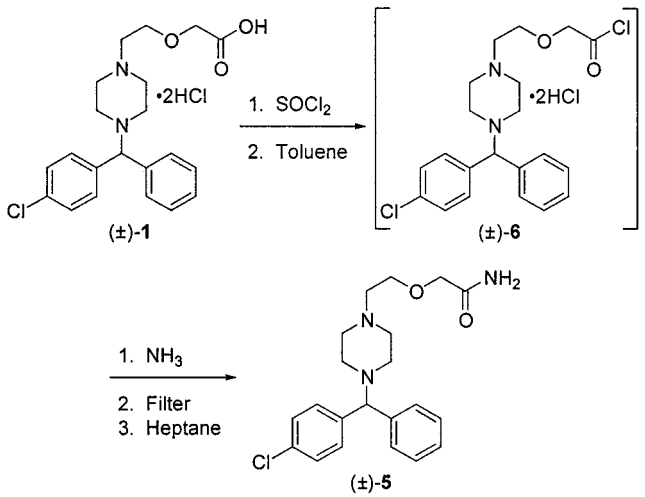
analog	USP resolution	α value
7	4.26	2.06
8	2.43	1.35
9	1.74	1.27
10	0.83	1.15
11[a]	not separated	not separated
12	5.22	1.65

[a] The separation was performed under conditions similar to those used with the other analogues and is unoptimized.

Scheme 2

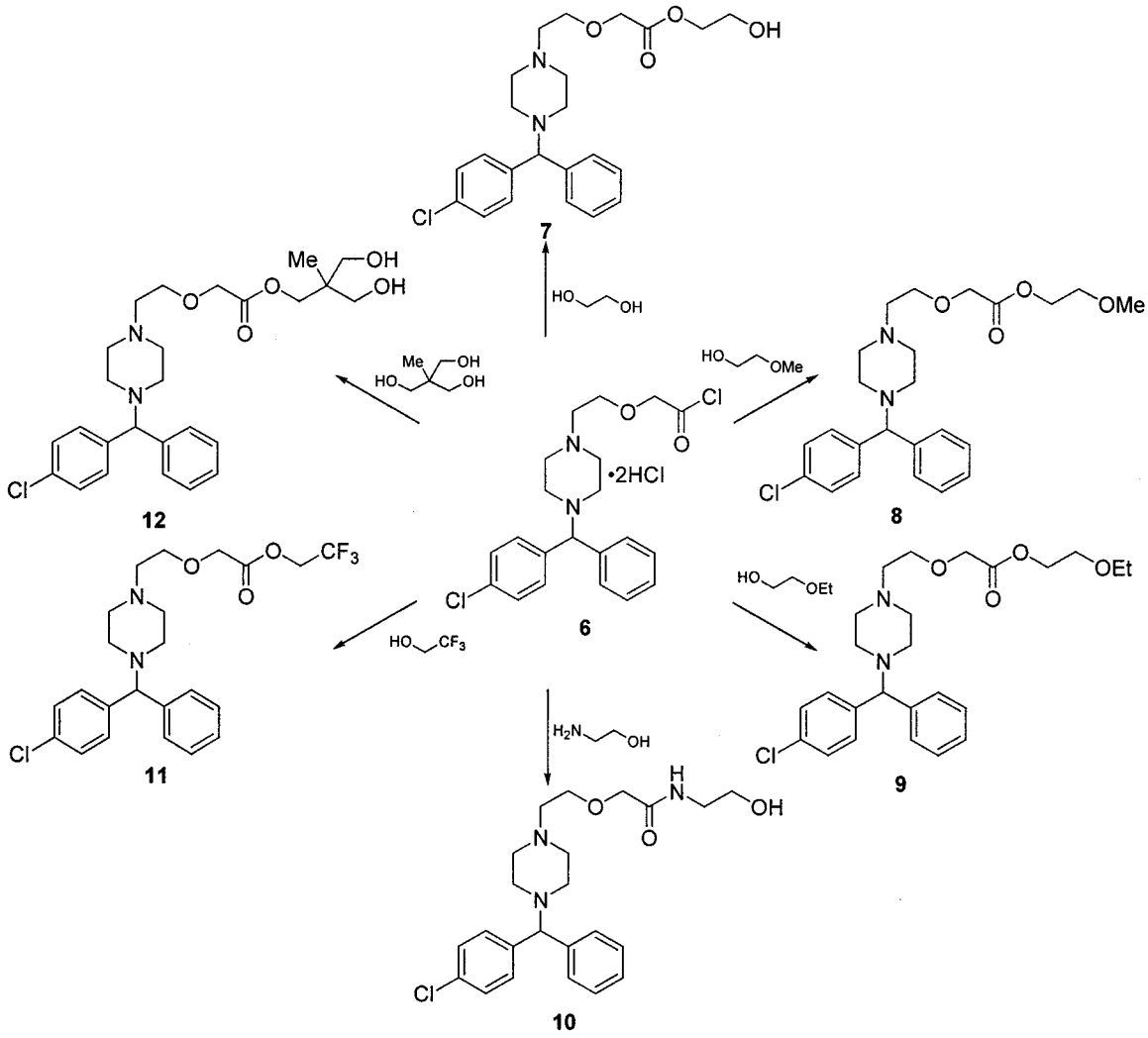


Scheme 3

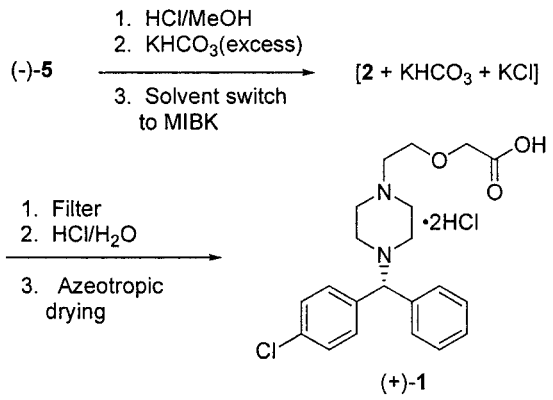


Due to the ease of trans-esterification and amidation (Scheme 2), we imagined that hydrolysis of the amide would be straightforward. Indeed, after treating the amide with 4 N HCl for 3 h at 60 °C, the reaction was complete. Isolation by azeotropic removal of water with methyl ethyl ketone (MEK) as cosolvent provided an excellent yield of cetirizine dihydrochloride that was exceedingly pure by HPLC. The chloride content, however, was consistently greater than 120%—the ammonia (not surprisingly) reacted with HCl to form ammonium chloride and precipitated with the product. Cetirizine dihydrochloride is exceedingly soluble in water (>1 g/mL). Cetirizine exists as a free base at pH between 7 and 9; however, the partitioning coefficient between water and any practical process solvent is less than 1 and would

Scheme 4



Scheme 5



therefore require prohibitive volumes to recover a good yield of the product. Additionally, cetirizine is a good emulsifier, with both a hydrophobic diphenyl methyl portion and a hydrophilic side chain, making any extraction very sensitive to pH, agitation, and temperature. These results led us to turn to a lengthier hydrolysis procedure.

Cetirizine amide was esterified rapidly by reaction with-refluxing acidic methanol (Scheme 5). The acid was quenched with solid potassium bicarbonate until the pH exceeded 7. A solvent switch to methyl isobutyl ketone (MIBK) resulted in a reaction mixture of cetirizine methyl ester in solution and solid inorganic salts. The salts were removed by filtration, and the cetirizine methyl ester solution was treated with aqueous hydrochloric acid to hydrolyze the ester and form the dihydrochloride salt. The organic phase was discarded, and the aqueous layer was dried by azeotropicdistillation with MEK as the cosolvent (solubility of **1** in MEK <2 mg/mL). Filtration of the resulting slurry provided enantiomerically enriched cetirizine in 85% yield. This procedure has been performed with 1.37 kg of (−)-cetirizine amide (99.7% ee) to provide 1.27 kg of (+)-(*R*)-cetirizine·2HCl with excellent chemical purity and with no loss in optical purity (80% yield, 99.8% ee, 0.3% total impurities, 101% expected chloride content).[6]

In conclusion, we have described an efficient synthesis of enantiomerically pure cetirizine via chiral HPLC separation of amide **5**. More than 1 kg of each enantiomer of cetirizine·2HCl (>99% pure, >99% ee) has been produced in this manner. Results from applying this method to simulated moving bed (SMB) technology will be reported in due course.

(6) The absolute stereochemistry has been assigned by single-crystal X-ray analysis. See ref 2 and Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153.

Experimental Section

(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-ethoxy)acetic Acid Methyl Ester Dihydrochloride (2·2HCl). Method 1: To a solution of cetirizine dihydrochloride (461 mg, 1.0 mmol, 1.0 equiv) in methanol (100 mL) at 0 °C was added trimethylsilyldiazomethane (2.0 M in hexanes, 2.5 mL, 5.0 equiv). After stirring for 10 min, the excess $TMSCHN_2$ was quenched with acetic acid (100 μL) and the solution concentrated to provide a thick oil. Chromatography (1:1 hexanes:ethyl acetate with 1% triethylamine) provided **2** (free base, 390 mg, 97.0%) as a colorless oil. Method 2: A solution of cetirizine·2HCl (**1**, 7.52 g, 16.3 mmol, 1.0 equiv) in methanol (100 mL) was heated to reflux for 2 h. Rotary evaporation afforded the dihydrochloride salt of **2** (7.68 g, 99% yield) as a white solid. The product was contaminated with 1% cetirizine dihdrochloride (HPLC analysis using Waters Symmetry C18 column (5 μm, 150 mm × 3.9 mm) and 0.05 M NaH_2PO_4−0.01 M hexanesulfonic acid, (pH 5.5)/methanol (40:60) as mobile phase. ^{1}H NMR (DMSO-d_6, 120 °C) δ 9.63 (br s, 2H), 7.79 (cm, 4H), 7.42−7.27 (cm, 5H), 5.45 (br s, 1H), 4.19 (s, 2H), 4.00 (m, 2H), 3.68 (s, 7H), 3.43 (app. t., J = 4.2 Hz, 2H), 3.20 (br s, 4H); ^{13}C NMR (DMSO-d_6, 120 °C) δ 170.8, 138.2, 137.6, 133.9, 131.0, 130.8, 129.8, 129.4, 129.1, 128.9, 73.1, 69.0, 68.6, 66.1, 55.4, 52.1, 49.6, 48.4, 48.0, 47.7; IR (thin film NaCl) 3424 (br, m) 2952 (m), 2364 (br, s) 1747 (s), 1438 (s), 1221 (s), 1134 (s), 1091 (m) cm^{-1}.

(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-ethoxy)acetic Acid Ethyl Ester (3). To a solution of cetirizine (**1**, 594 mg, 1.29 mmol, 1.0 equiv) in THF (5 mL) at 0 °C was added a solution of diazoethane until a yellow color persisted. Rotary evaporation provided crude **3**. Chromatography (1:1 hexanes:ethyl acetate, 1% NEt_3) afforded **3** (484 mg, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (cm, 9H), 4.28 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.01 (s, 2H), 3.90 (app. t., J = 4.7 Hz, 2H), 2.99 (br s, 6H), 2.55 (br s, 4H), 1.25 (app. t., J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.9, 141.2, 140.5, 132.7, 128.8, 128.7, 128.6, 127.4, 127.3, 74.6, 68.1, 68.0, 67.1, 60.8, 56.8, 53.1, 49.6, 14.0.

(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-ethoxy)acetic Acid Isopropyl Ester (4). To a solution of **2** (200 mg, 0.480 mmol) in 2-propanol (2 mL) was added titanium isopropoxide (142 μL, 0.480 mmol), and the mixture was heated to reflux for 3 h. The reaction was cooled to room temperature, and 0.2 mL of saturated $NaHCO_3$ solution was added. The crude reaction mixture was filtered and concentrated under reduced pressure to provide crude **4**. Column chromatography of this oil (1:1 hexanes:ethyl acetate, 1% NEt_3) furnished **4**. ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (cm, 9H), 5.03 (quint, J = 6.3 Hz, 1H), 4.28 (s, 1H), 4.02, (s, 2H), 3.91 (app. t., J = 4.7 Hz, 2H), 3.02 (br s, 6H), 2.67 (br s, 4H), 1.21 (d, 6H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 169.3, 141.1, 40.3, 132.6, 128.8, 128.7, 128.6, 127.4, 127.3, 76.6, 74.5, 68.6, 68.2, 66.8, 56.7, 53.0, 49.4, 21.6.

2-(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}ethoxy)acetamide (5). Cetirizine dihydrochloride (**1**, 7.0 kg, 15.1 mmol) was treated with thionyl chloride (9.0 kg, 75.6 mmol) and DMF (66 mL, 0.8 mmol) at room temperature for approximately 3 h. To this solution was added toluene (70 L), and the reaction mixture was distilled under vacuum to approximately 21 L. Additional toluene (70 L) was added, and ammonia gas (2.7kg) was bubbled through the reaction mixture at 0−30 °C over approximately 4 h. When the reaction was complete by HPLC, water (70 L) and ethyl acetate (53 L) were added. The reaction mixture was stirred, the phases were allowed to separate, and the aqueous layer was removed. The organic layer was washed with 10% sodium bicarbonate (82.5 kg, additional water (360 L) was added to break the emulsion) and brine (2 × 23kg). The organic layer was filtered, and the solids were washed with toluene (20 L). The filtrate was concentrated to 20 L (maintaining the temperature below 50 °C), cooled to 20 °C, and stirred for 2 h. Heptane (28 L) was added over 1 h, the reaction mixture stirred for 1 h, and the slurry filtered. The wet cake was washed with heptane:toluene (32 L:8 L) to provide **5** (4.6 kg, 78.5%) as an off-white solid. ^{1}H NMR ($CDCl_3$) δ 7.99 (br s, 1H), 7.4−7.2 (cm, 9H), 5.77 (br s, 1H), 4.23 (s, 1H), 3.96 (s, 2H), 3.67 (app. t., J = 5.0 Hz, 2H), 2.64 (br s, 6H), 2.45 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 173.7, 141.9, 141.1, 132.6, 129.1, 128.7, 128.6, 127.7, 127.2, 75.4, 70.2, 69.1, 57.8, 53.6, 51.8; IR (thin film NaCl) 3278 (br m), 3014 (br m), 2949 (m), 2086 (m), 1680 (s), 1485 (m), 1401 (m), 1334 (m), 1128 (m), 760 (m) cm^{-1}.

(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-ethoxy)acetyl Chloride Dihydrochloride (6). To **1** (350 g, 760 mmol) were added thionyl chloride (220 mL, 3.0 mol) and DMF (2.5 mL, 3.2 mmol). This slurry was stirred for 3 h, until homogeneous. Toluene (900 mL) was added, and the white precipitate was stirred for 60 min. The solution was filtered and washed with toluene (200 mL) to provide **6** (336 g, 92%) as a white solid which is stable in an airtight container for >6 months. ^{1}H NMR ($CDCl_3$) δ 12.73 (br s, 1H), 7.89 (cm, 4H), 7.45 (cm, 5H), 6.37 (br s, 1H), 5.25 (s, 1H), 4.53 (s, 2H), 4.41 (br s, 2H), 4.16 (br s, 2H), 3.97 (m, 2H), 3.82 (m, 2H), 3.62 (cm, 4H); ^{13}C NMR ($CDCl_3$) δ 172.1; 136.4, 132.9, 131.8, 130.4, 130.3, 130.1, 128.5, 75.9, 66.0, 49.0, 48.8.

(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-ethoxy)acetic Acid 2-Hydroxyethyl Ester (7). To acid chloride **6** (500 mg, 1.0 mmol) was added ethylene glycol (5 mL, 90 mmol). This slurry was stirred at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate (100 mL), and this solution was washed with saturated sodium bicarbonate solution (30 mL) and water (30 mL). The organic layer was concentrated to provide **7** (379 mg, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.4−7.2 (cm, 9H), 4.25 (m, 2H), 4.22 (s, 1H), 4.14 (s, 2H), 3.9−3.6 (cm, 5H), 2.65 (app. t., J = 5.2 Hz, 2H), 2.59 (br s, 4H), 2.45 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 170.5, 141.9, 141.1, 132.4, 129.0, 128.6, 128.5, 127.6, 127.0, 75.3, 68.8, 68.3, 66.4, 60.1, 57.6, 53.6, 51.3.

(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-ethoxy)acetic Acid 2-Methoxyethyl Ester (8). To acid chloride **6** (500 mg, 1.0 mmol) was added 2-methoxyethanol (5 mL, 63 mmol), and the reaction was stirred at ambient temperature for 16 h. The reaction mixture was concentrated

to approximately 1 mL. The thick oil was then diluted with ethyl acetate and extracted with saturated sodium bicarbonate (60 mL) and water (2 × 60 mL). Concentration of the organic layer afforded ester **8** (428 mg, 88%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.4−7.2 (cm, 9H), 4.24 (app. t., J = 4.6 Hz, 2H), 4.19 (s, 1H), 4.11 (s, 2H), 3.64 (app. t., J = 5.4 Hz, 2H), 3.53 (app. t., J = 4.7 Hz, 2H), 3.30 (s, 3H), 2.60 (app. t., J = 5.6 Hz, 2H), 2.52 (br s, 4H), 2.41 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 170.5; 141.9, 141.1, 132.3, 132.0, 128.5, 128.4, 127.6, 127.0, 75.3, 68.8, 68.3, 66.3, 63.4, 60.1, 57.5, 53.5, 51.3.

(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-ethoxy)acetic Acid 2-Ethoxyethyl Ester (9). To acid chloride **6** (500 mg, 1.0 mmol) was added 2-ethoxyethanol (5 mL, 52 mmol), and the reaction was stirred at ambient temperature for 16 h. The reaction mixture was concentrated to approximately 1 mL. The thick oil was then diluted with ethyl acetate and extracted with saturated sodium bicarbonate (60 mL) and water (2 × 60 mL). Concentration of the organic layer afforded ester **9** (413 mg, 86%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (cm, 9H), 4.27 (app. t., J = 4.8 Hz, 2H), 4.21 (s, 1H), 4.13 (s, 2H), 3.67 (app. t., J = 5.6 Hz, 2H), 3.61 (m, 2H), 3.49 (q, J = 7.0 Hz, 2H), 2.63 (app. t., J = 5.5 Hz, 2H), 2.55 (br s, 4H), 2.43 (br s, 4H), 1.18 (app. t., J = 7.1 Hz, 3H), ^{13}C NMR ($CDCl_3$) δ 170.5; 142.2, 141.4, 132.4, 129.2, 128.6, 128.6, 127.8, 127.1, 75.4, 68.9, 68.3, 68.1, 66.6, 63.9, 57.7, 53.7, 51.6, 15.1.

2-(2-{4-[(4-Chlorophenyl)phenylmethyl]piper-azin-1-yl}ethoxy)-N-(2-hydroxyethyl)acetamide (10). To acid chloride **6** (3 g, 6.3 mmol) was added ethanolamine (12 mL, 200 mmol), and the reaction was stirred at ambient temperature for 16 h at which time the reaction mixture was a homogeneous solution. The reaction was diluted with ethyl acetate (120 mL), and the two-phase mixture was washed with saturated sodium bicarbonate (100 mL). The organic layer was washed with water (3 × 100 mL) and brine (50 mL). The organic layer was then concentrated to afford amide **10** (2.7 g, 96.1%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.99 (br s, 1H), 7.36−7.18 (cm, 9H), 4.25 (s, 1H), 3.97 (s, 2H), 3.69 (app. t., J = 4.9 Hz, 2H), 3.61 (app. t., J = 4.9 Hz, 2H), 3.40 (q, J = 5.1 Hz, 2H), 2.57 (cm, 4H), 2.44 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 171.4, 141.9, 141.2, 129.3, 128.8, 128.8, 128.0, 127.4, 75.4, 70.7, 68.4, 62.0, 57.8, 53.6, 51.5, 42.1.

(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-ethoxy)acetic Acid 2,2,2-Trifluoroethyl Ester (11). To acid chloride **6** (500 mg, 1.0 mmol) was added 2,2,2-trifluoroethanol (5 mL, 68 mmol), and the reaction was stirred at ambient temperature for 1 h. The reaction mixture was concentrated to approximately 100 mg. The oil was dissolved in ethyl acetate, passed through a plug of potassium bicarbonate, and concentrated to yield **11** (451 mg, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.5−7.2 (cm, 9H), 4.53 (q, J = 8.6 Hz, 2H), 4.24 (s, 1H), 4.23 (s, 2H), 3.71 (app. t., J = 5.7 Hz, 2H), 2.67 (app. t., J = 5.4 Hz, 2H), 2.58 (br s, 4H), 2.47 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 168.9, 142.0, 141.2, 132.4, 129.1, 128.5, 128.4, 127.7, 127.0, 75.3, 75.2, 68.9, 67.7, 60.1 (q, J = 36.9 Hz), 57.6, 53.5, 51.4.

(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-ethoxy)acetic Acid 2-Hydroxy-1-hydroxymethyl-1-methylethyl Ester (12). To acid chloride **6** (1.05 g, 2.2 mmol) was added 1,1,1-tris(hydroxymethyl)ethane (6 g, 50 mmol) in tetrahydrofuran (30 mL) and the reaction was stirred at ambient temperature for 16 h. The reaction was diluted with ethyl acetate (200 mL) and washed with 1:4 saturated sodium bicarbonate:water (125 mL) and water (2 × 100 mL). The organic phase was concentrated to provide ester **12** (190 mg, 30%). ^{1}H NMR ($CDCl_3$) δ 7.4−7.1 (cm, 9H), 4.24 (s, 2H), 4.23 (s, 1H), 4.14 (s, 2H), 3.68 (app. t., J = 5.5 Hz), 3.58 (d, J = 11.3 Hz, 2H), 3.53 (d, J = 11.1 Hz, 2H), 3.24 (br s, 2H), 2.65 (app. t., J = 5.6, 2H), 2.51 (br s, 4H), 2.45 (br s, 4H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 171.0; 141.9, 141.1, 132.4, 129.1, 128.6, 128.5, 127.7, 127.1, 75.2, 68.7, 68.2, 66.9, 57.5, 53.6, 51.2, 40.4, 29.3, 16.8.

Separation of (+)- and (−)-5. (±)-**5** (4.4 kg) was dissolved in 60:40 acetonitrile:IPA (37 L). This solution (100 mL injections (12 g racemic amide)) was injected onto a column packed with ChiralPak AD packing material (2.0 kg, flow rate = 500 mL/min, detector set at 230 nm, run time = 23 min, first peak eluted at approximately 10 min, second peak eluted at approximately 16 min). After approximately 4 days of automated injections, 630 L of mobile phase containing enantiomer 1 ((+)-**5**) and 2000 L of mobile phase containing enantiomer 2 ((−)-**5**) had been collected. The solution of (+)-**5** was concentrated to approximately 2 L and diisopropyl ether (DIPE, 5 L) was added. The slurry was cooled to 5 °C, filtered, washed with DIPE (3 L), and dried to afford (+)-**5** (1.6 kg, 99.8% ee, 0.26% total impurities). The solution of (−)-**5** was similarly concentrated, crystallized with DIPE (19 L), cooled to 5 °C, filtered, washed with DIPE (3 L), and dried to afford (−)-**5** (1.6 kg, 99.7% ee, 0.08% total impurities). The uninjected (±)-**5** was concentrated and crystallized to afford 1.1 kg, thus giving an overall recovery of 98%.

(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}-ethoxy)acetic Acid ((*R*)-(+)-1). To a solution of (*R*)-(−)-**5** (1.4 kg, 3.0 mol) in methanol (10 L) was added HCl in methanol (22% HCl, 0.5 kg HCl, 13 mol), and the mixture was heated to reflux for 4 h. Solid potassium bicarbonate (1.3 kg, 13 mmol) was added and the solution was stirred for 7 h, and the methanol was exchanged for methyl isobutyl ketone (MIBK) by distillation. The slurry was clarified through a 1.0 μm polypropylene polish filter to afford a solution of (*R*)-**2**. To this solution was added HCl (37%, 1.1 kg, 8.2 mmol), and the reaction mixture was distilled to remove the methanol as it formed. The organic phase was removed, and to the aqueous phase was added methyl ethyl ketone (MEK, 70 L total). Azeotropic removal of water (to <1% w/w by Karl Fischer titration) provided a slurry of (*R*)-**1** in MEK which was filtered, washed with MEK (5.5 kg), and dried to furnish the title compound (1.2 kg, 74%) with >99% purity and >99% ee.

Chiral HPLC Analysis of 1. Cetirizine dihydrochloride is both acidic and basic, which makes it very difficult to separate using a chiral column. Therefore, to determine the enantiomeric purity of cetirizine, it is first derivatized to the

cetirizine methyl ester, which easily separates on a chiral column. Dissolve approximately 25 mg of **1** in 30.0 mL of methanol and add approximately 40 μL of thionyl chloride. Place the flask into a beaker of water and heat on a hot plate for 1 h at 50−55° C, swirling occasionally. After 1 h, remove the flask from the beaker and allow to cool to room temperature. The methyl ester is analyzed using a Chiralpak AD column (4.6 × 250 mm) with methanol:acetonitrile: diethylamine (95:5:0.1) at 1 mL/min, detecting at 230 nm. The first peak elutes at 5.4 min (from (+)-cetirizine·2HCl), and the second peak elutes at 6.4 min.

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