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Asymmetric Synthesis And Absolute Stereochemistry Of 4,4-Bis-(trifluoromethyl)imidazoline Based ACAT Inhibitors

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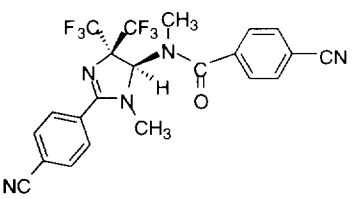
Key Words: Imidazoline, Asymmetric synthesis, ACAT inhibitor, Stereoselectivity, Steroidal mimic

Abstract: An asymmetric synthesis of **1**, a potent orally active ACAT inhibitor, is reported. The absolute configuration of **1** has been determined by exciton CD spectra and X-ray crystal structure analysis.

As part of an ongoing program on the design and syntheses of novel antihypercholesterolemic agents for the treatment of hypercholesterolaemia and atherosclerosis, we reported[3-6] a series of 4,4-bis(trifluoromethyl)imidazolines as a new class of potent ACAT inhibitors[7-10] and/or cholesterol biosynthesis inhibitors. Compound **1** was found to be a very potent ACAT inhibitor with remarkable oral activity in lowering the serum cholesterol level in several animal models. After extensive molecular modeling, X-ray crystal structure analyses, and biological activity studies, we concluded that **1** and its analogs are cholesterol and/or steroidal mimics. Since cholesterol is a chiral molecule and *ent*-cholesterol possesses different biological activity from natural cholesterol,[11] our imidazoline ACAT inhibitors also showed high stereoselectivity. As we expected, the "right' *R*-enantiomer **1** was about 25 times more potent than the "wrong" *S*-enantiomer **24** in the ACAT in vitro assay. So far, all the enantiomerically pure **1** used in biological studies was obtained by chiral HPLC separation. We report here the first asymmetric synthesis of **1** and the details of its absolute configuration determination.



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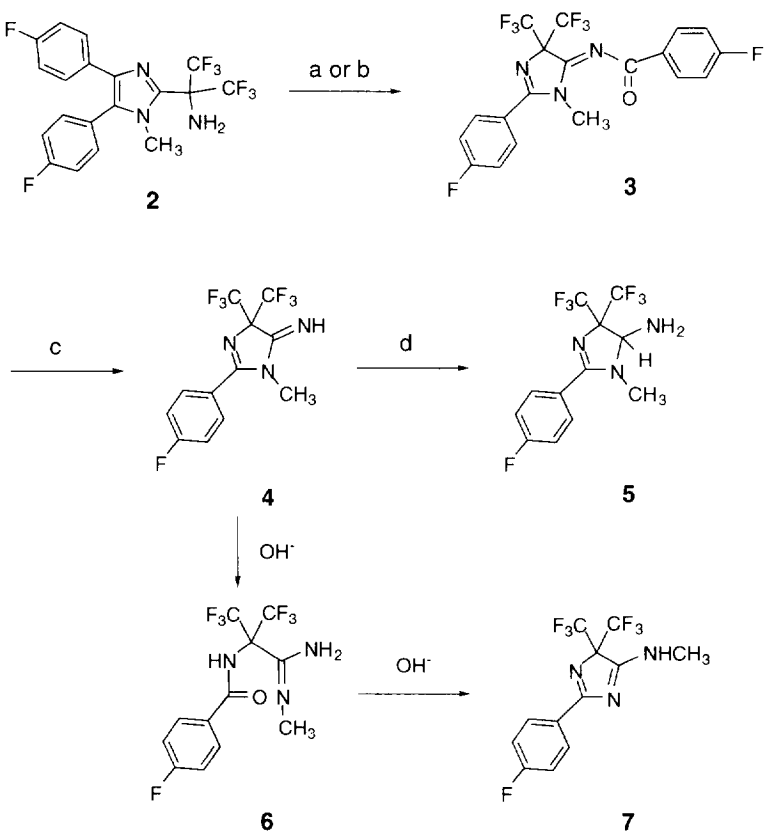
RESULTS AND DISCUSSIONS

Starting material **3** (Scheme 1) was readily prepared by a *m*CPBA or a singlet oxygen oxidation of imidazole **2**.[4] Treatment of **3** with conc. H_2SO_4 followed by a basic work-up gave the amidine **4** in 62% yield. Compound **4** was found to be unstable during the basic work-up and underwent a facile Dimroth rearrangement to give the *exo-N*-methyl imidazole **7**, presumably through a ring-opening and ring closing process.[12,13] However, the amidine **4** was obtained in good yield with careful control of the temperature (<5 °C) and pH (< 8) during the work-up. Reduction of **4** with zinc dust in acetic acid afforded the racemic aminal **5** in 73% yield.[14] The resulting aminal **5**, unlike its *N*-methyl derivative **27**, was surprisingly stable as a white crystalline solid which offers an advantage for further transformations.

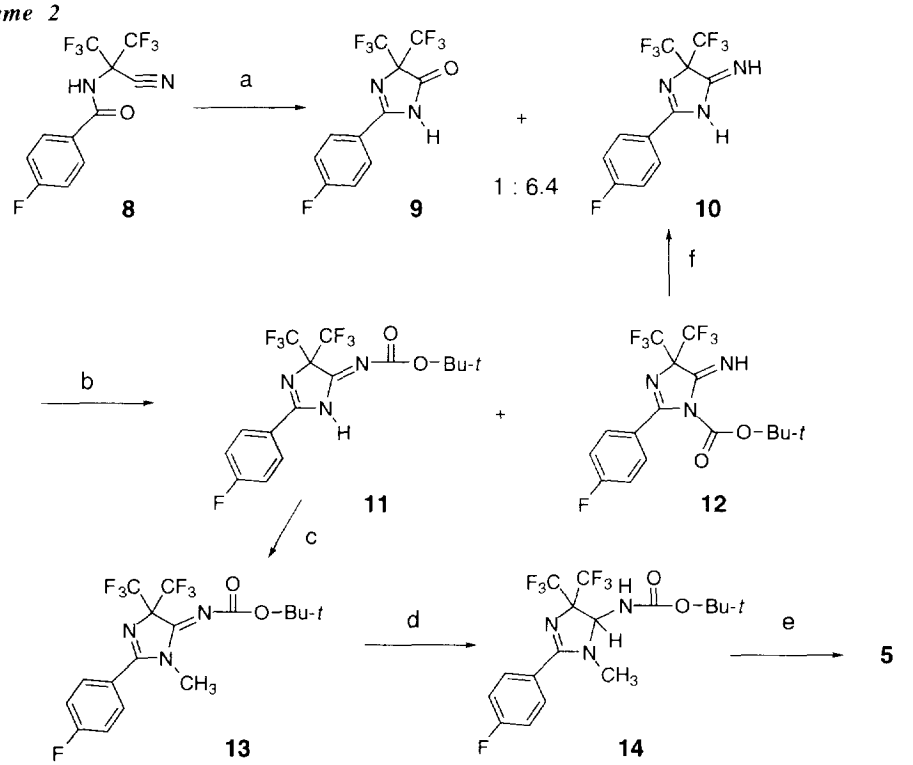
Scheme 1



(a) *m*CPBA, CH_2Cl_2; (b) (i) Oxygen, methylene blue, methanol, sunlight; (ii); HCl; (c) conc. H_2SO_4, 62%; (d) Zn/HOAc, 73%.

Alternatively, aminal **5** could be synthesized from **8** as shown in Scheme 2. Compound **8** was prepared from very economical starting materials: hexafluoroacetone and *p*-fluorobenzamide.[15,16] Compound **8** was converted to **10** with the treatment of NH_4OAc in one step with the formation of small amount of **9** as a minor byproduct. Acylation of **10** with a variety of acyl chlorides gave only the undesired *N*-1 acylated product, which was very labile and readily hydrolyzed to starting material **10** upon aqueous work-up. Treatment of **10** with di-*tert*-butyl dicarbonate afforded a 1:1 mixture of **11** and **12**. This mixture was then treated with $TMSCHN_2$ and compound **13** was obtained after chromatography together with the starting material **10** which was recovered from hydrolysis of **12** during the work-up. It is interesting to note that diacylated product was never observed. The C=N double bond of **13** was reduced with zinc dust in acetic acid smoothly and the BOC group was deprotected with a TFA/CH_2Cl_2 solution to provide **5**, which was identical to the sample obtained form **4**.

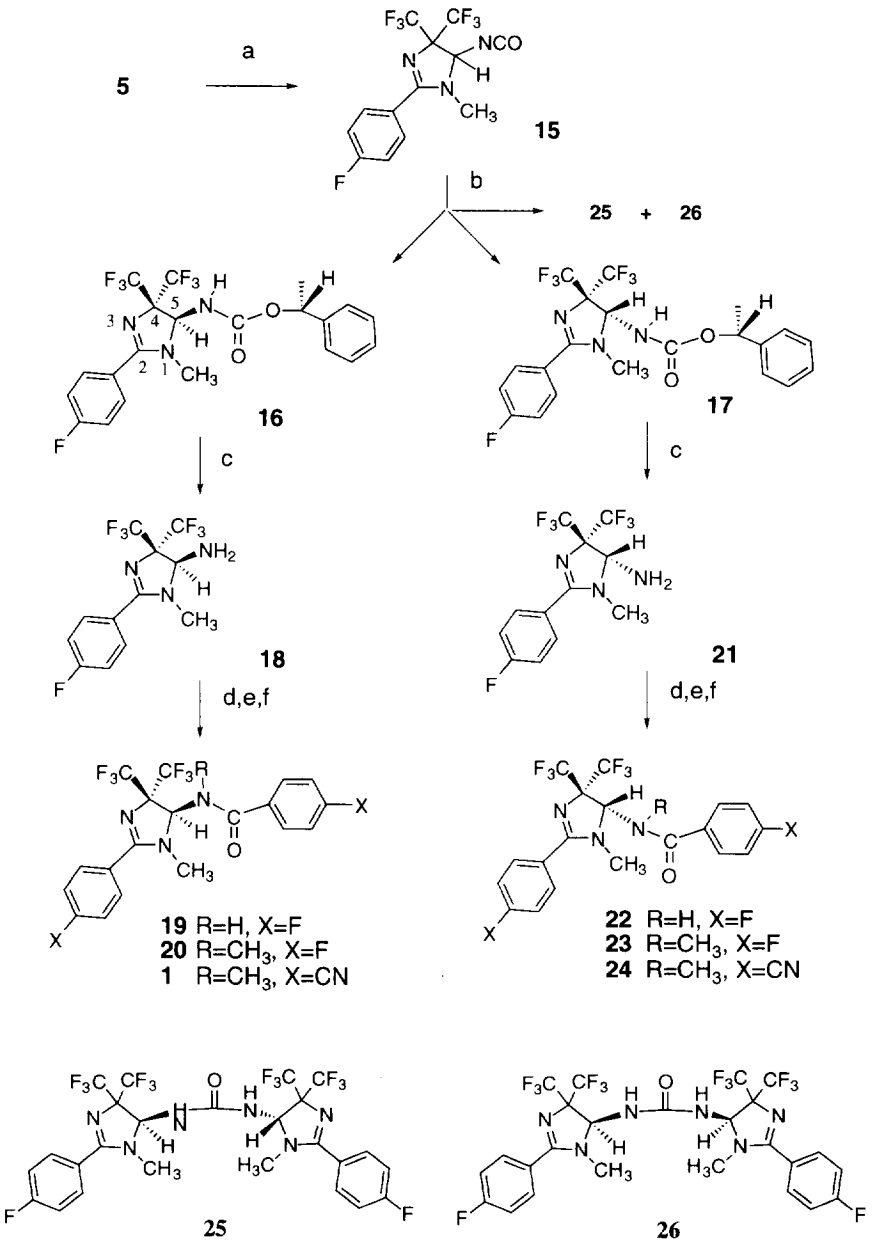
Scheme 2



(a) NH_4OAc (neat), 120-140 °C, 59%; (b) $(BOC)_2O$, THF, Et_3N, DMAP; (c) $TMSCHN_2$, CH_3OH/Et_2O, 51% from **10**; (d) Zn/HOAc, 77%; (e) TFA/CH_2Cl_2 (v/v 50/50), 92%; (f) H_2O.

Aminal **5** (Scheme 3) was converted to isocyanate **15** upon treatment with diphosgene in dioxane. Treatment of the resulting isocyanate **15** with *R*-(+)-*sec*-phenethyl alcohol in pyridine gave the carbamates **16** and **17,** which were separated by flash column chromatography. The absolute stereochemistry at 5-position in **16** was determined to be *S* by a single crystal structure analysis (Figure 1) based on the known *R* configuration of the side chain from *R*-(+)-*sec*-phenethyl alcohol. The desired pure *S* enantiomer of aminal **18** was obtained in 91% yield by

Scheme 3



(a) (i) HCl in dioxane; (ii) diphosgene, dioxane, reflux 16 h; (b) pyridine, *R*-(+)-*sec*-phenethyl alcohol, 54%; (c) H_2, Pd/C(10%); (d) 4-F-PhCOCl, pyridine; (e) CH_3I/NaH, DMF; (f) LiCN in DMF, K_2CO_3, KI, DMSO.

hydrogenolysis of **16** with Pd/C as a catalyst. Acylation of **18** with *p*-fluorobenzoyl chloride provided amide **19** in good yield. Methylation of **19** with CH_3I in the presence of NaH in DMF provided **20** in excellent yield. Interestingly, the absolute stereochemistry at 5-position in **20** has a *R* configuration while **19** has a *S* configuration according to the Cahn-Ingold-Prelog rule. The nucleophilic displacement of *para*-fluorine group with cyano group using a LiCN/DMF solution in the presence of KI and K_2CO_3 afforded the desired product **1** in good yield and high enantiomeric purity (>99% ee). The less active enantiomer **24** was also synthesized by similar transformations as shown in Scheme 3.

Treatment of aminal **27** (Scheme 4) with *S*-(-)-camphanic chloride afforded two diastereoisomers **28** and **29**, which were readily separated by chromatography. The absolute configuration of compound **29** was established by a single crystal X-ray analysis unambiguously (Figure 2). Subsequently, **26** was transferred to **29** which further confirmed the stereochemistry of these new imidazolines. Both **28** and **29** can be hydrolyzed back to **27** by using "dry hydroxide" condition[17] in good yield, but the product **27** was completely racemized.

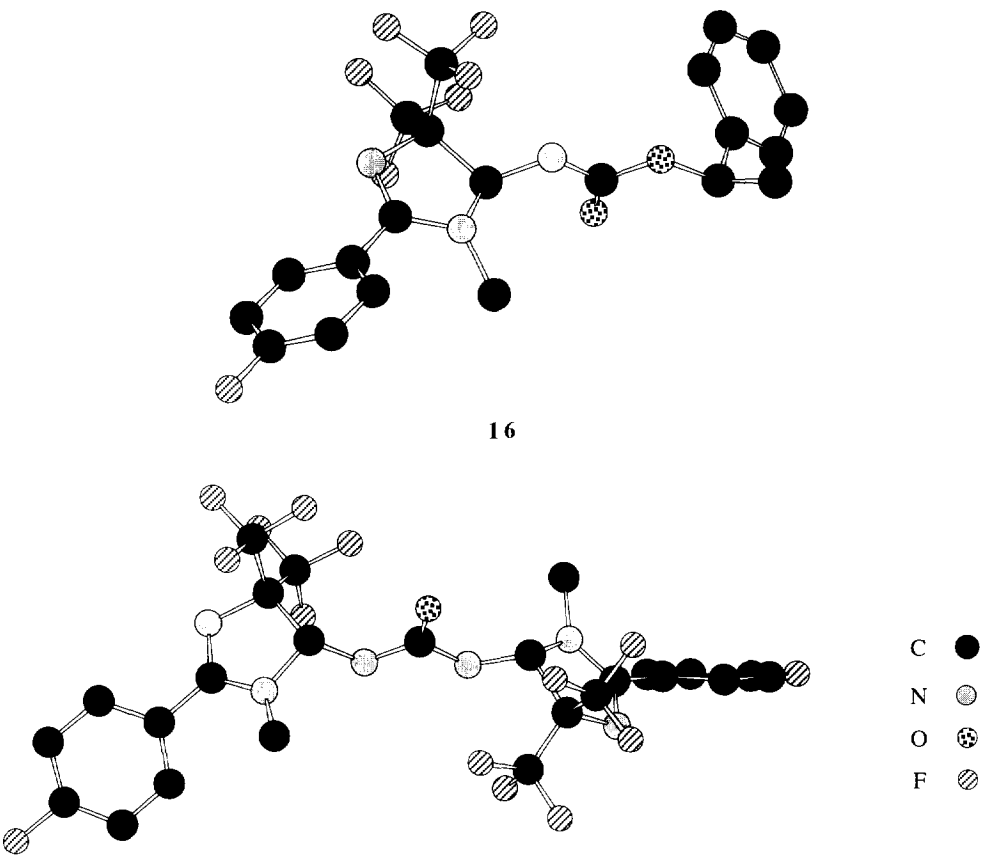
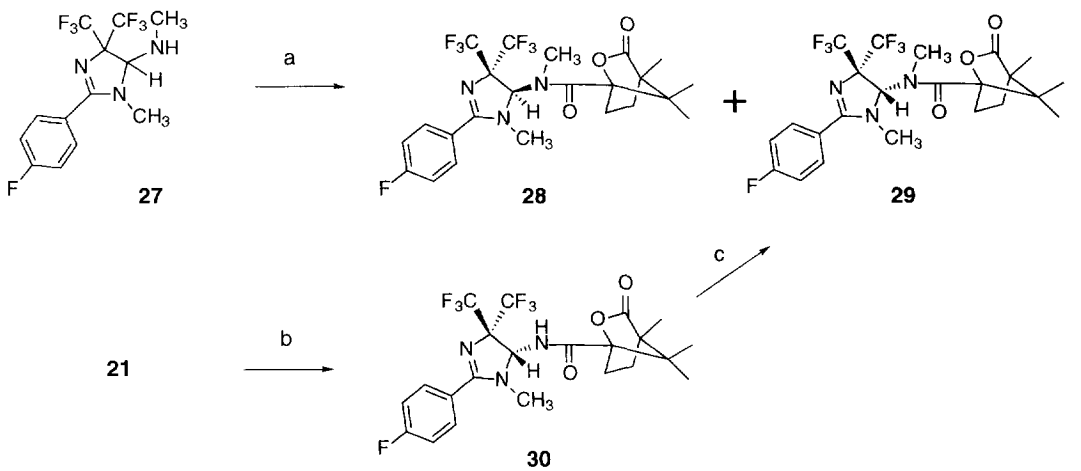


Figure 1. X-ray crystal structures of **16** and **25** regenerated by Chem 3D based on their PDB files.

In fact, the absolute configuration of both **1** and **24** were established earlier using on exciton CD spectra .[18,19] This method is generally useful for determination of the absolute configuration of these new synthesized imidazolines as shown in Figure 3.

In summary, we have developed an efficient asymmetric synthesis method for the preparation of both enantiomeric forms of imidazoline **1**. This method is general for preparation of enantiomerically pure analogs of this series.

Scheme 4



(a) (1*S*)-(-)-camphanic chloride, pyridine, CH_2Cl_2, 59%; (b) (1*S*)-(-)-camphanic chloride, pyridine, CH_2Cl_2, 61%; (c) CH_3I/NaH, DMF, 79%.

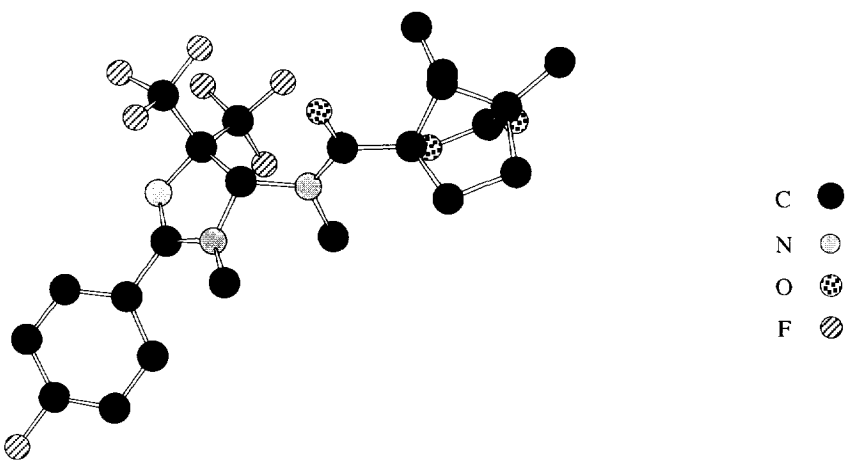


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Figure 2. X-ray crystal structure of **29** regenerated by Chem 3D based on its PDB file.

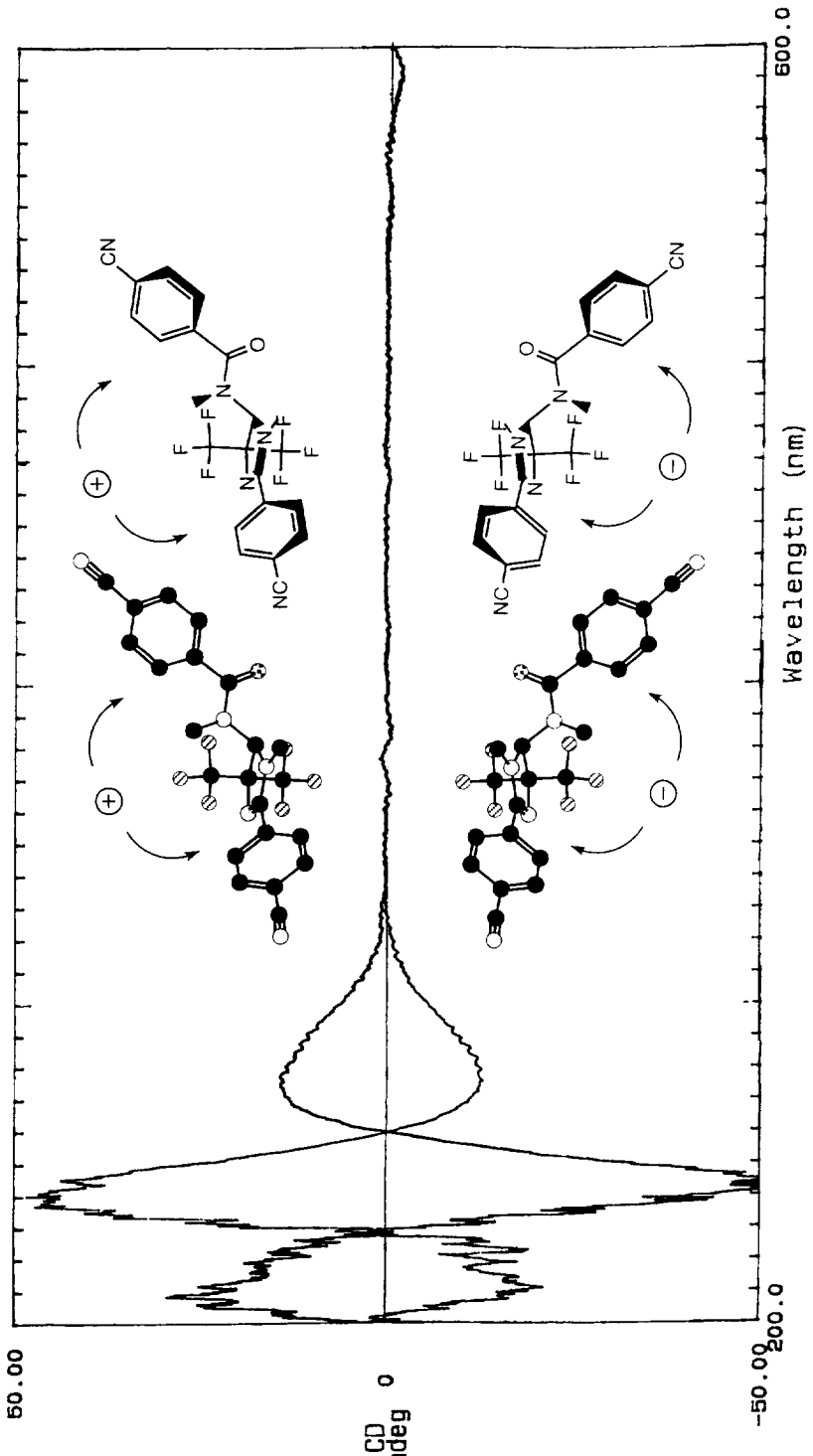

Figure 3. CD Spectra of **1** and **24** (in methanol)

EXPERIMENTAL SECTION

General Experimental. Melting points were measured with a Thomas-Hoover Unimelt apparatus and were uncorrected. IR spectra were obtained on a Perkin-Elmer 1710 series FTIR and were run as KBr pellets. ^{1}H, ^{19}F, and ^{13}C NMR spectra were obtained by using a Varian Unity 300 spectrometer and were referenced to TMS for proton and Freon 11 for ^{19}F. High-resolution mass spectra were determined on a Finnegan MAT 8230 spectrometer. Combustion analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Solvents and reagents were used as purchased from Aldrich Chemical Co. unless otherwise stated. Column chromatography was performed with E. Merck silica gel 60 (230-400 mesh).

2-(4-Fluorophenyl)-3,5-dihydro-3-methyl-5,5-bis(trifluoromethyl)-4*H*-imidazol-4-imine (4). To a solution of conc. H_2SO_4 (100 mL) was added **3** (2.67 g, 5.9 mmol) portionwise and the reaction mixture was stirred at rt for 15 min. The reaction mixture was poured on ice, neutralized to pH 7-8 with 6 N NaOH at < 5 °C, and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the title compound **4** (1.21 g, 62%) as a white crystalline solid: mp 94-96 °C; IR (KBr) 3133, 1766, 1632, 1602, 1270 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (s, 3H, NC$\underline{H}_3$), 7.23 (t, J = 8.5 Hz, 2H), 7.73 (dd, J = 5., 8.5 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -74.11 (s, 6F, 2 x C$\underline{F}_3$), -106.44 (m, 1F); MS (CI, *m/z*) 328.0 $(M+H)^+$; HRMS for $C_{12}H_8F_7N_3$ calcd 327.0606, found 327.0603.

2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (5). To a solution of **4** (1.2 g, 3.7 mmol) in glacial acetic acid (15 mL) was added zinc dust (4.0 g) portionwise and the reaction mixture was stirred at rt for overnight. After quenching with water (100 mL), excess zinc was removed by filtration. The filtrate was neutralized to pH 7-8 with 6 N NaOH and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to give the title compound **10** (0.89 g, 73%) as a white crystalline solid: mp 128-129 °C; IR (KBr) 1611, 1276, 1217, 1198 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97 (s, 3H, NC$\underline{H}_3$), 4.91 (s, 1H), 7.18 (m, 2H), 7.62 (m, 2H); ^{19}F NMR (300 MHz, $CDCl_3$, $CFCl_3$) δ -69.33 (m, C$\underline{F}_3$), -76.62 (m, C$\underline{F}_3$), -108.73 (m, 1F); MS (CI, *m/z*) 330.0 $(M+H)^+$; HRMS for $C_{12}H_{10}F_7N_3$ calcd 329.0763, found 329.0766.

2-(4-Fluorophenyl)-3,5-dihydro-5,5-bis(trifluoromethyl)-4*H*-imidazol-4-imine or 2-(4-fluorophenyl)-4,4-bis(trifluoromethyl)-4*H*-imidazol-5-amine (10). Compound **8** (3.5 g, 11.2 mmol) was mixed with ammonium acetate (50 g, 0.65 mol) and the mixture was heated at 120-140 °C for 20 min. After cooling to rt, the reaction mixture was poured into water (300 mL) and extracted with diethyl ether (4 x 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, saturated aqueous ammonium chloride, and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 140 g), eluting with hexane/ethyl acetate (50:1 to 3:1), to give the unreacted starting material (0.71 g, 20%), compound **7** (0.28 g, 8%, identical with authentic sample[16]), and compound **10** (1.8 g, 51%): mp 163-165 °C; IR (KBr) 3124,

1670, 1271, 1199, 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (br s, 1H, NH), 7.16 (br s, 1H, NH), 7.71 (t, J = 8.8 Hz, 2H), 8.23 (dd, J = 5.5, 8.8 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -72.44 (s, 6F, 2 x CF_3), -106.11 (m, 1F); MS (ESI, *m/z*) 314.2 $(M+H)^+$; HRMS for $C_{11}H_7F_7N_2$ calcd 314.0528, found 314.0518.

1,1-Dimethylethyl [2-(4-fluorophenyl)-3,5-dihydro-3-methyl-5,5-bis(trifluoromethyl)-4*H*-imidazol-4-ylidene]carbamate (13). To a solution of **10** (302 mg, 0.96 mmol) in anhydrous THF (5 mL) was added triethylamine (0.18 mL), dimethylaminopyridine (35 mg) and di-*tert*-butyl dicarbonate (285 mg, 1.3 mmol) and the reaction mixture was stirred at rt for 6 h. After removing the solvent under reduced pressure, the residue was purified by flash column chromatography to give a mixture of **11** and **12** as a solid (353 mg). This solid (200 mg) was then dissolved in ether (5 mL) and methanol (5 mL). To this solution, (trimethylsilyl)diazomethane (2.0 M solution in hexanes) was added until the yellow color lasted more than 20 min. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to give the starting material **10** (68 mg) and the title compound **13** (117 mg, 51%): mp 104-105 °C; IR (KBr) 1721, 1620, 1224, 1150 986 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 9H, 3 x CH_3), 3.22 (s, 3H, NCH_3), 7.24 (t, J = 8.8 Hz, 2H), 7.20 (dd, J = 5.1, 8.8 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -71.985 (s, 6F, 2 x CF_3), -105.719 (m, 1F); MS (ESI, *m/z*) 428.2 $(M+H)^+$; HRMS for $C_{17}H_{17}F_7N_3O_2$ (M+H) calcd 428.1209; found 428.1205.

1,1-Dimethylethyl [2-(4-fluorophenyl)-3,5-dihydro-3-methyl-5,5-bis(trifluoromethyl)-4*H*-imidazol-4-yl]carbamate (14). To a solution of **4** (254 mg, 0.59 mmol) in glacial acetic acid (4 mL) was added zinc dust (650 mg) portionwise and the reaction mixture was stirred at rt for 6 h. After quenching with water (50 mL), excess zinc was removed by filtration. The filtrate was neutralized to pH 8-9 with 6 N NaOH and extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the residue, which was crystallized from ethyl acetate and hexanes to give the title compound **13** (196 mg, 77%) as a white crystalline solid: mp 126-128 °C; IR (KBr) 1713, 1612, 1226, 1158, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H, 3 x CH_3), 2.92 (s, 3H, NCH_3), 5.17 (d, J = 11.2 Hz, 1H), 5.90 (d, J = 11.2 Hz, 1H), 7.15 (t, J = 8.8 Hz, 2H), 7.60 (dd, J = 5.1, 8.8 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -70.165 (q, J = 9.5 Hz, CF_3), -76.734 (q, J = 9.5 Hz, CF_3), -108.069 (m, 1F); MS (ESI, *m/z*) 430.3 $(M+H)^+$; HRMS for $C_{17}H_{19}F_7N_3O_2$ $(M+H)^+$ calcd 430.1366; found 430.1361.

2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (5). Compound **14** (98 mg, 0.23 mmol) was dissolved in 4 mL of TFA/CH_2Cl_2 (50/50 v/v) and the reaction mixture was stirred at rt for 2 h. The solvent was evaporated under the reduced pressure and the residue was partitioned between ether (20 mL) and saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was then extracted with ether (2 x 10 mL). The combined organic layer was washed with water and concentrated under reduced pressure to give the title product as a white crystalline solid (63 mg, 84%), which was identical (TLC, MS, ^1H NMR, and ^{19}F NMR) with the authentic sample obtained above.

[*S*-(*R,*S**)]-1-Phenylethyl [2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]carbamate (16), [*R*-(*R**,*R**)]-1-phenylethyl [2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]carbamate (17), [*R*-(*R**,*R**)]/[*S*-(*S**,*S**)]-*N*,*N*'-bis[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]urea (25) and [*R*-(*R**,*S**)]/[*S*-(*S**,*R**)]-*N*,*N*'-bis[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]urea (26).** To a hot solution of compound **5** (322 mg, 0.98 mmol) in anhydrous dioxane (25 mL) was added a 4 N hydrogen chloride solution in dioxane (0.5 mL) and diphosgene (0.15 mmol). The reaction mixture was refluxed for overnight (16 h) and the solvent was evaporated under reduced pressure. The residue was dissolved in anhydrous pyridine. To this solution, *R*-(+)-*sec*-phenethyl alcohol (0.12 mL, 1.2 mmol) was added. After the mixture was stirred at rt for 2 h, pyridine was removed under reduced pressure to give a residue, which was purified by flash column chromatography (hexanes/ethyl acetate 3:1 to 1:1) to provide four products: Compound **17** (Rf 0.62, hexanes/EtOAc 3:1): 102 mg, 22% yield. Compound **16** (Rf 0.55): 92 mg, 20% yield. Compound **25** (Rf 0.15): 20.4 mg, 6% yield. Compound **26** (Rf 0.08): 19.2 mg, 6% yield. For compound **17**: mp 119-121 °C; $[\alpha]_D^{22}$ -34.2 (c = 1.17, $CHCl_3$) IR (KBr) 3332, 1723, 1612, 1514, 1224 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, *J* = 6.5 Hz, 3H), 2.81 (s, 3H, NC<u>H</u>3), 5.35 (d, *J* = 11.0 Hz, 1H), 5.87 (q, *J* = 6.5 Hz, 1H), 5.91 (d, *J* = 11.0 Hz, 1H), 7.14 (t, *J* = 8.7 Hz, 2H), 7.30-7.39 (m, 5H), 7.57 (dd, *J* = 8.7, 5.3 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -70.06 (q, *J* = 10.3 Hz, C<u>F</u>3), -76.71 (q, *J* = 10.3 Hz, C<u>F</u>3), -107.86 (m, 1F); MS (ESI, *m/z*) 478.3 $(M+H)^+$; HRMS for $C_{21}H_{19}F_7N_3O_2$ calcd 478.1366, found 478.1359. For compound **16**: mp 102-104 °C; $[\alpha]_D^{22}$ +24.5 (c = 1.48, $CHCl_3$); IR (KBr) 3331, 1726, 1612, 1515, 1224 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, *J* = 6.5 Hz, 3H), 2.96 (s, 3H, NC<u>H</u>3), 5.40 (d, *J* = 11.0 Hz, 1H), 5.87 (q, *J* = 6.5 Hz, 1H), 5.91 (d, *J* = 11.0 Hz, 1H), 7.16 (t, *J* = 8.7 Hz, 2H), 7.28-7.45 (m, 5H), 7.60 (dd, *J* = 8.7, 5.3 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -69.98 (q, *J* = 9.5 Hz, C<u>F</u>3), -76.73 (q, *J* = 9.5 Hz, C<u>F</u>3), -107.84 (m, 1F); MS (ESI, *m/z*) 478.3 $(M+H)^+$; HRMS for $C_{21}H_{19}F_7N_3O_2$ calcd 478.1366, found 478.1366. For compound **25** : mp 220-222 °C; IR (KBr) 1727, 1710, 1603, 1223, 1198 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.94 (s, 6H, 2 x NC<u>H</u>3), 5.34 (d, *J* = 10.6 Hz, 2H), 6.20 (d, *J* = 10.6 Hz, 2H), 7.17 (t, *J* = 8.6 Hz, 4H), 7.62 (dd, *J* = 5.2, 8.6 Hz, 4H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -69.85 (q, *J* = 9.5 Hz, 2 x C<u>F</u>3); -76.69 (q, *J* = 9.5 Hz, 2 x C<u>F</u>3), -107.56 (m, 2F); MS (CI, *m/z*) 685.2 $(M+H)^+$; HRMS for $C_{25}H_{19}F_{14}N_6O$ (M+H) calcd 685.1397, found 685.1380. For compound **26** : mp 232-234 °C; IR (KBr) 1710, 1692, 1611, 1274, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (s, 6H, 2 x NCH<u>3</u>), 5.54 (d, *J* = 10.6 Hz, 2H), 6.14 (d, *J* = 10.6 Hz, 2H), 7.16 (t, *J* = 8.4 Hz, 4H), 7.59 (dd, *J* = 5.2, 8.4 Hz, 4H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -69.97 (q, *J* = 9.5 Hz, 2 x C<u>F</u>3); -76.71 (q, *J* = 9.5 Hz, 2 x C<u>F</u>3), -107.50 (m, 2F); MS (CI, *m/z*) 685.2 $(M+H)^+$; HRMS for $C_{25}H_{19}F_{14}N_6O$ $(M+H)^+$ calcd 685.1397, found 685.1384.

(*S*)-2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (18). Compound **16** (48.3 mg, 0.1 mmol) in ethyl acetate (5 mL) was hydrogenated for 6 h at atmospheric pressure with 10% Pd/C (wet with 50% water, 18 mg) as catalyst. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound (**18**) as a white crystalline solid (31.1 mg, 93%): mp 123-124 °C; $[\alpha]_D^{22}$ -32.53 (c = 0.33., $CHCl_3$); IR (KBr) 1611, 1276, 1217, 1198 cm^{-1}; MS (ESI, *m/z*) 330.11 $(M+H)^+$; HRMS for $C_{12}H_{11}F_7N_3O$ calcd 330.0841, found 330.0853; ^1H NMR and ^{19}F NMR were identical to those of **5**.

(*S*)-4-Fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]benzamide (19). To a solution of **18** (51 mg, 0.16 mmol) in pyridine (1 mL) was added *N,N*-dimethylaminopyridine (DMAP, 2 mg) and *p*-fluorobenzoyl chloride (36 mg, 0.23 mmol). The reaction mixture was stirred for 2 h at rt. The crude reaction mixture was quenched with methanol (1 mL) and concentrated under reduced pressure. The residue was dissolved in diethyl ether (25 mL) and washed successively with saturated aqueous sodium carbonate, saturated aqueous ammonium chloride and brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography eluting with hexane-ethyl acetate (3:1) to give the title compound (**19**) as a white solid (62 mg, 89%): mp 184-186 °C; $[\alpha]_D^{22}$ +42.8 (c = 0.18, $CHCl_3$); IR (KBr) 1656, 1604, 1227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.97 (s, 3H, NCH_3), 6.44 (d, *J* = 10.4 Hz, 1H), 6.60 (d, *J* = 10.4 Hz, 1H), 7.18 (m, 4H), 7.64 (dd, *J* = 8.7, 5.1 Hz, 2H), 7.84 (dd, *J* = 8.7, 5.1 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -69.63 (q, *J* = 9.47 Hz, CF_3), -76.59 (q, *J* = 9.47 Hz, CF_3),-106.23 (m, 1F), -107.564 (m, 1F); MS (ESI, *m/z*) 452.2 $(M+H)^+$; HRMS for $C_{19}H_{14}F_8N_3O$ calcd 452.1009, found 452.0992.

(*R*)-4-Fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (20). To a suspension of sodium hydride (60% suspension in oil, 8 mg) in anhydrous DMF was added a solution of compound **19** (47 mg, 0.1 mmol) in DMF (0.5 mL) and the mixture was allowed to stir at rt for 1 h. Methyl iodide (29 mg, 0.2 mmol) was added and the reaction mixture was allowed to stir at rt for overnight. The reaction mixture was then poured into water (20 mL) and extracted with ether (3 x 40 mL). The organic layer was washed successively with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by flash column chromatography eluting with hexane-ethyl acetate (3:1) to give the title compound (42 mg, 87%) as an amorphous solid: $[\alpha]_D^{22}$ +11.60 (c = 0.73, $CHCl_3$); IR (KBr) 1656, 1605, 1227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.92 (s, 3H, NCH_3), 3.01 (s, 3H, NCH_3), 6.80 (br s, 1H, CH), 7.16 (t, 2H, *J* = 8.4 Hz), 7.19 (t, 2H, *J* = 8.4 Hz), 7.46 (dd, 2H, *J* = 5.3, 8.4 Hz), 7.66 (dd, 2H, *J* = 5.3, 8.4 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -69.23 (s, 3F, CF_3), -77.24 (s, 3F, CF_3), -106.96 (m, 1F), -109.43 (m, 1F); MS (ESI, *m/z*) $(M+H)^+$; 466.13; HRMS for $C_{20}H_{16}F_8N_3O$ calcd 466.1166, found 466.1168.

(*R*)-4-Cyano-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (1). To a solution of **20** (37 mg, 0.08 mmol) in dimethyl sulfoxide (5 mL) was added potassium iodide (16 mg, 0.1mmol), potassium carbonate (140 mg, 1 mmol), and LiCN 0.5 M solution in DMF (0.5 mL). The reaction mixture was heated at 135°-140 °C for 72 h under nitrogen. The solution was cooled to rt, poured into water (50 mL) and extracted with ether (3 x 50 mL) and ethyl acetate (2 x 25 ml). The combined organic layers were washed with saturated aqueous ammonium chloride and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated under vacuum to give the crude product, which was purified by flash column chromatography to provide the title compound (26 mg, 68%) as an amorphous solid: mp 112-114 °C; $[\alpha]_D^{22}$ -8.3 (c = 0.46, $CHCl_3$); IR (KBr) 2232, 1659, 1263, 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.88 (s, 3H, NCH_3), 3.02 (s, 3H, NCH_3), 6.80 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.80 (m, 6H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -69.13 (m, 3F, CF_3), -77.99 (m, 3F, CF_3); MS (ESI, *m/z*) 480.3 $(M+H)^+$; HRMS for $C_{22}H_{16}F_6N_5O$ calcd 480.1259, found 480.1252.

(*R*)-2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-amine (21). This compound was prepared in 91% yield from **17** (46 mg, 0.14 mmol) following the same procedure as that described above for **18** as an amorphous solid: mp 121-124 °C; $[\alpha]_D^{22}$ +31.76 (c = 0.37, $CHCl_3$); IR (KBr) 1611, 1276, 1217, 1198 cm^{-1}; MS (ESI, *m/z*) 330.18 $(M+H)^+$; HRMS for $C_{12}H_{11}F_7N_3O$ calcd 330.0841, found 330.0846; ^1H NMR and ^{19}F NMR were identical to those of **18**.

(*R*)-4-Fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]benzamide (22). This compound was prepared in 84% yield from **21** (24 mg, 0.07 mmol) following the same procedure as that described above for **19** as an amorphous solid: mp 185-186 °C; $[\alpha]_D^{22}$ -41.5 (c = 0.23, $CHCl_3$); IR (KBr) 1658, 1604, 1226 cm^{-1}; MS (ESI, *m/z*) 452.3 $(M+H)^+$; HRMS for $C_{19}H_{14}F_8N_3O$ calcd 452.1009, found 452.0981; ^1H NMR and ^{19}F NMR were identical to those of **19.**

(*S*)-4-Fluoro-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (23). This compound was prepared in 94% yield from **22** (28 mg, 0.06 mmol) following the same procedure as that described above for **20** as an amorphous solid: $[\alpha]_D^{25}$ -10.68 (c = 0.42, $CHCl_3$); IR (KBr) 1658, 1605, 1226 cm^{-1}; MS (ESI, *m/z*) $(M+H)^+$; 466.13; HRMS for $C_{20}H_{16}F_8N_3O$ calcd 466.1166, found 466.1183; ^1H NMR and ^{19}F NMR were identical to those of **20.**

(*S*)-4-Cyano-*N*-[2-(4-cyanophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylbenzamide (24). This compound was prepared in 54% yield from **23** (25 mg, 0.05 mmol) following the same procedure as that described above for **1** as an amorphous solid: mp 112-114 °C; $[\alpha]_D^{22}$ +7.2 (c = 0.49, $CHCl_3$); IR (KBr) 2232, 1659, 1264, 1204 cm^{-1}; MS (ESI, *m/z*) 480.3 $(M+H)^+$; HRMS for $C_{22}H_{16}F_6N_5O$ (M+H) calcd 480.1259, found 480.1253; ^1H NMR and ^{19}F NMR were identical to those of **1**.

[1*S*-[1α(*R),4β]]-*N*-[2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl-1*H*-imidazol-5-yl]-*N*,4,7,7-tetramethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamide (28) and [1*S*-[1α(*S**),4β]]-*N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*,4,7,7-tetramethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamide (29).** To a solution of **27** (0.34 g, 1.0 mmol) in dichloromethane (10 mL) and pyridine (0.24 g, 3.0 mmol) was added (1*S*) - (-) - camphanic chloride (0.65 g, 3.0 mmol). The reaction mixture was stirred at rt for overnight . The crude reaction mixture was quenched with water (100 mL) and extracted with ether (3 x 100 mL). The organic layers were washed successively with saturated aqueous sodium carbonate, saturated aqueous ammonium chloride and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with hexane and hexane-ethyl acetate (10:1) to give two compounds: compound **28** (100 mg, 19 %) and compound **29** (80 mg, 15 %). For compound **28:** mp 126-127 °C; $[\alpha]_D^{22}$ -18.47 (c = 0.88, $CHCl_3$); IR (KBr) 1788, 1659, 1611, 1228, 1031, 978 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H, C<u>H</u>3), 1.13 (s, 3H, C<u>H</u>3), 1.23 (s, 3H, C<u>H</u>3), 1.75 (m, *J* = 13.0, 9.1, 4.2 Hz, 1H); 1.96 (m, *J* =

13.0, 10.8, 4.6 Hz, 1H); 2.16 (m, *J* = 13.8, 9.1, 4.6 Hz, 1H); 2.34 (ddd, *J* = 13.8, 10.8, 4.2 Hz, 1H); 2.96 (s, 3H, NCH3), 3.11 (s, 3H, NCH3), 6.51 (s, 1H), 7.20 (t, *J* = 8.7 Hz, 2H), 7.65 (dd, *J* = 8.7, 5.3 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -69.24 (q, *J* = 10.3 Hz, CF3), -77.05 (q, *J* = 10.3 Hz, CF3), -106.96 (m, 1F); MS (ESI, *m/z*) 524.4 $(M+H)^+$; HRMS for $C_{23}H_{25}F_7N_3O_3$ (M+H) calcd 524.1784, found 524.1784. For compound **29:** mp 87-88 °C; $[\alpha]_D^{22}$ +17.34 (c = 0.88., $CHCl_3$); IR (KBr) 1791, 1664, 1610, 1263, 1226, 1203, 1089, 1030, 979 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H, CH3), 1.13 (s, 3H, CH3), 1.16 (s, 3H, CH3), 1.70 (m, *J* = 13.3, 9.1, 4.2 Hz, 1H); 1.96 (m, *J* = 13.3, 10.6, 4.6 Hz, 1H); 2.08 (m, *J* = 13.3, 9.1, 4.6 Hz, 1H); 2.55 (ddd, *J* = 13.3, 10.6, 4.2 Hz, 1H); 2.95 (s, 3H, NCH3), 3.15 (s, 3H, NCH3), 6.59 (s, 1H), 7.20 (t, *J* = 8.7 Hz, 2H), 7.66 (dd, *J* = 8.7, 5.1 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -69.24 (q, *J* = 10.3 Hz, CF3), -77.05 (q, *J* = 10.3 Hz, CF3), -106.98 (m, 1F); MS (ESI, *m/z*) 524.4 $(M+H)^+$; HRMS for $C_{23}H_{25}F_7N_3O_3$ (M+H) calcd 524.1784, found 524.1776.

[1*S*-[1α(*R),4β]]-*N*-[2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamide (30).** Following the same procedure as that described above for **19**, this compound was prepared from **21** (27.3 mg, 0.1 mmol), 1*S*-(-)-camphanic chloride (25 mg, 0.12 mmol), DMAP (2 mg, 0.016 mmol) in pyridine (1 mL) as a white solid (25.8 mg, 61%): mp 158-160 °C; $[\alpha]_D^{25}$ -24.03 (c = 1.37, $CHCl_3$); IR (KBr) 3340, 2971, 1788, 1690, 1612, 1515, 1268, 12227, 1202 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 3H, CH3), 1.14 (s, 3H, CH3), 1.15 (s, 3H, CH3), 1.73 (m, 1H); 1.91-2.10 (m, 2H); 2.59 (m, 1H); 2.89 (s, 3H, NCH3), 6.19 (d, *J* = 10.5 Hz, 1H), 7.05 (d, *J* = 10.5 Hz, 1H), 7.18 (t, *J* = 8.3 Hz, 2H), 7.64 (dd, *J* = 8.7, 5.3 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ - 69.78 (q, *J* = 10.3 Hz, CF3), -78.56 (q, *J* = 10.3 Hz, CF3), -107.59 (m, 1F); MS (ESI, *m/z*) 510.18 $(M+H)^+$; HRMS for $C_{22}H_{23}F_7N_3O_3$ (M+H) calcd 510.1628, found 510.1625.

[1*S*-[1α(*S),4β]]-*N*-[2-(4-Fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*,4,7,7-tetramethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxamide (29).** This compound was prepared in 67% yield from **30** (5 mg, 0.01 mmol) following the same procedure as that described above for **20**, which was identical (optical rotation. TLC, MS, ^{1}H NMR, and ^{19}F NMR) with the authentic sample obtained above.

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