Pergamon

Tetrahedron, Vol. 52, No. 34, pp. 11153-11162, 1996

Published by Elsevier Science Ltd

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00578-9

Singlet Oxygen Oxidation Of Pyrroles: Synthesis And Chemical Transformations Of Novel 4,4-Bis(trifluoromethyl)imidazoline Analogs

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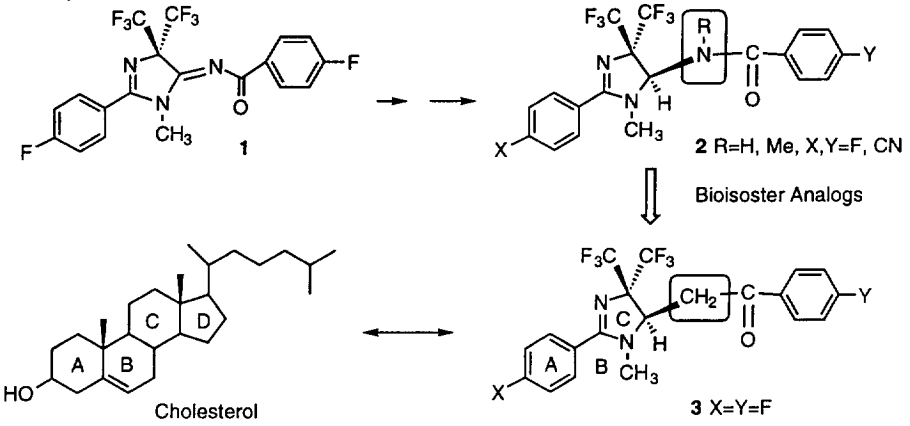
Key Words: Pyrrole, Imidazoline, Singlet oxygen, Oxidation, Dehydrocyclization

Abstract: A novel singlet oxygen ring cleavage of pyrrole **5a** and subsequent acid-catalyzed facile dehydrocyclization afforded a new series of 4,4-bis(trifluoromethyl)imidazolines with a *p*-fluorophenacyl side chain at the 5-position, which have shown potent acyl CoA: cholesterol acyltransferase (ACAT) and cholesterol biosynthesis inhibitory activities.

Singlet oxygen, which is normally generated from molecular oxygen (air) in the presence of a sensitizer and visible light, is capable of oxidizing a wide range of substrates.[3] It is one of the most economical and environmentally friendly chemical process in organic synthesis because the oxidants used are oxygen (air) and sunlight.[4] Photooxidations of pyrroles,[5-7] imidazoles[8] and other heterocycles[9] have been extensively studied, because these heterocyclic systems are involved in photobiosynthesis and other biological processes. However, very limited success[4,10] has been achieved in terms of applying these reactions to practical organic synthesis. One of the problems associated with these photooxidations is low chemoselectivity. Photooxidations of pyrroles and imidazoles often give a mixture of products derived from both [1,2]- and [1,4]- oxygen additions.

We have reported a very practical photooxidation process that oxidizes imidazoles and provides novel 4,4-bis(trifluoromethyl)imidazoline **1** in high selectivity and good yield,[10] which is the key intermediate for preparation of novel acyl CoA: cholesterol acyltransferase (ACAT) inhibitors **2**.[11] Based on extensive molecular modeling and preliminary biological studies, we propose that these new 4,4-bis(trifluoromethyl)imidazoline ring systems with proper substitutions are novel steroidal mimics. As part of our effort in searching for more potent cholesterol lowering agents, we wish to report here the design and synthesis of a new series of 4,4-bis(trifluoromethyl)imidazolines with a *p*-fluorophenacyl side chain at the 5 position, using a facile photooxidative cleavage of pyrrole **5a** with singlet oxygen as a key step. We have demonstrated that this photooxidation process is

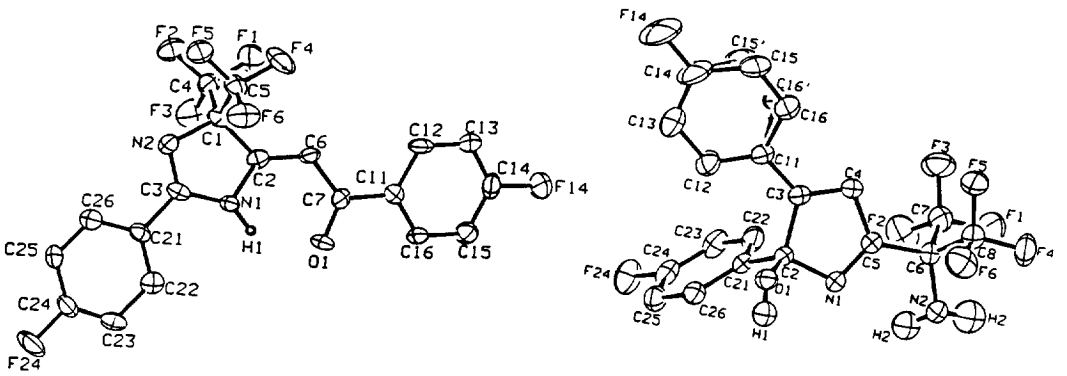
amenable to scale up. Finally, **3** and its analogs show good to excellent activities as ACAT inhibitors and cholesterol biosynthesis inhibitors.



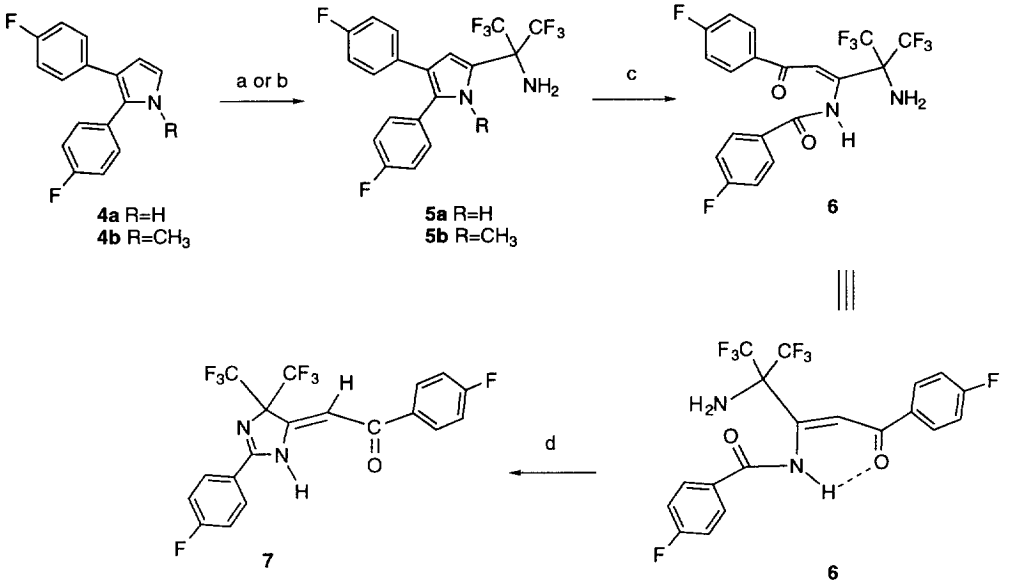
RESULTS AND DISCUSSIONS

Pyrrole **5a** was prepared according to the literature procedure[12] and subjected to oxidation. Oxidation of **5a** with singlet oxygen, generated by oxygen (air) in the presence of methylene blue as a photosensitizer and a 400 watt tungsten lamp as the light source, followed by an acid catalyzed cyclization produced 4,4-bis(trifluoromethyl)imidazoline **7** in 49% yield. Compound **7** was easily purified from the reaction mixture by filtering through a silica gel column, eluting with ethyl acetate/hexane (v/v, 1/8), because all of the byproducts were highly polar. The acid-catalyzed dehydrocyclization went selectively between the amino group and the amide carbonyl group because the more reactive ketone carbonyl is at the trans position to the amine. The strong hydrogen bonding between the amide NH and ketone carbonyl, observed in **6** and **7**, may also stabilize the geometry of the carbon-carbon double bond which leads to the exclusive formation of **7**. The structure of **7** was determined by spectroscopic analysis and confirmed by an X-ray crystal structure. (Figure 1).

Figure 1. X-ray crystal structures of **7** and **13**

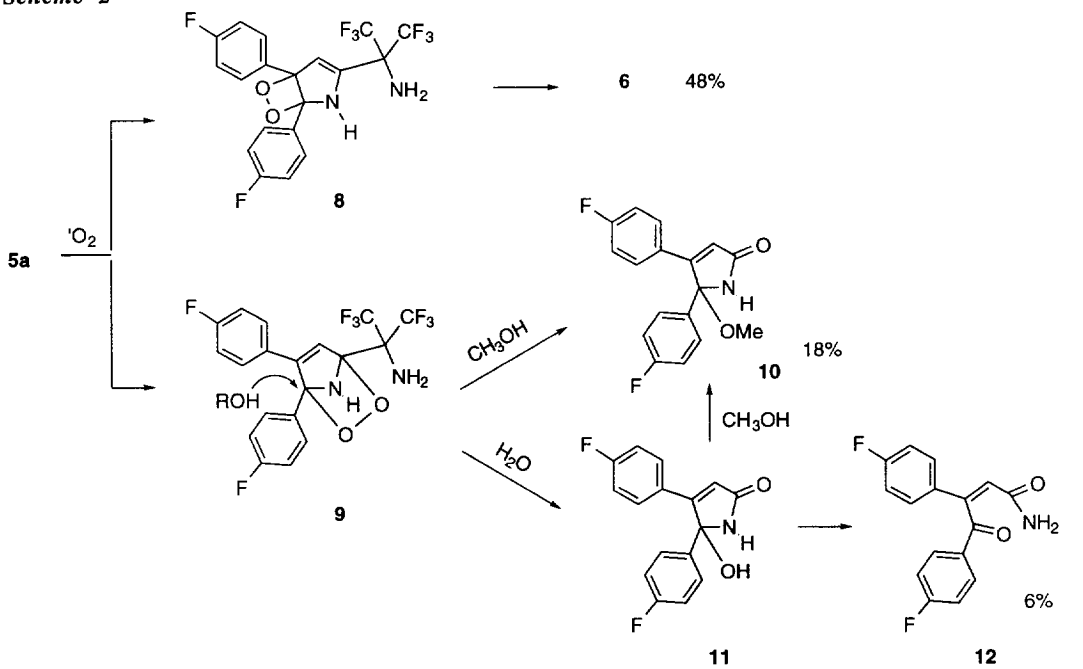


Scheme 1



(a) $(CF_3)_2C{=}NH$, $AlCl_3$, toluene, reflux(73%); (b) *n*-BuLi, $(CF_3)_2C{=}NTMS$; (c) Air, methylene blue, sun light, methanol or methanol/chloroform; (d) 1N HCl, 49% from **5a**.

Scheme 2

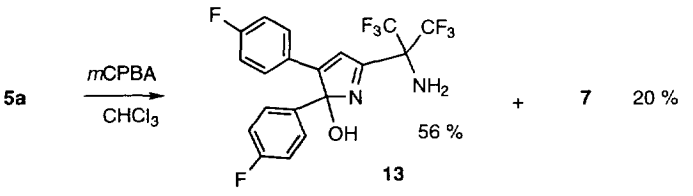


The ring-opened compound **6** has been isolated from the reaction mixture and identified after the singlet

oxygen ring-opening of **5a**, along with two major byproducts, **10** and **12**. The formation of these compounds can be explained by the mechanism of the singlet oxygen addition to pyrroles. Singlet oxygen can be added to the pyrrole ring, in a similar fashion as with the imidazole ring,[10] to form either the 1,2 addition dioxetane intermediate **8,** or the 1,4 addition endoperoxide **9**. Decomposition of the dioxetane **8** would give the ring-opened compound **6**. On the other hand, decomposition of the endoperoxide **9** would give the bis(trifluoromethyl)methylamine moiety cleaved compound **11**, which subsequently affords the ring-opened compound **12**.

Oxidation of **5a** with *m*CPBA provided only a 20% yield of the desired product **7** along with **13**, isolated as a major product (56%). The ring-opened compound **6** was not observed as facile cyclization occurred in the acidic reaction media. The result can be explained by the formation of a common epoxide intermediate **14** . The product distribution is then controlled by the regioselectivity of the epoxide ring opening. Path A leads to **13** which is stable and resistant to further oxidation. On the other hand, path B gives the intermediate **16,** which has an activated imine bond and can be oxidized further by *m*CPBA to undergo the ring opening as shown in Scheme 3. Apparently, path A is favored in this case, leading to **13** as the major product. Oxidation of pyrroles with peroxide has rarely been studied. Oxidation of 3-amino pyrroles, leading to the formation of 2-hydroxy-2*H*-pyrroles, has been reported.[13-15] To our knowledge, this is the first oxidative cleavage of a pyrrole of this kind by *m*CPBA. The *N*-methyl pyrrole

Scheme 3



analog **5b** was also prepared. Surprisingly, it resists both singlet oxygen and *m*CPBA oxidations. It is obvious that further studies are needed to fully understand this photooxidation process.

The carbon-carbon double bond of **7** was reduced by zinc dust [16,17] in acetic acid to give **18** in excellent yield. The strong hydrogen bonding between the NH and carbonyl groups in **7** and **18** forced the side chain to bend as shown by the X-ray crystal structure (Figure 1) and molecular modeling. Both compounds possessed very weak ACAT and/or cholesterol biosynthesis inhibitory activity. *N*-Substituted derivatives would not show this kind of hydrogen bonding. Treatment of **7** with NaH or K_2CO_3 and alkyl halide provide *N*-methyl and ethyl substituted derivatives **19** and **20** in good yield. Reduction of the carbon carbon double bond by zinc in acetic acid afford the desired analogs **3** and **21**. Both compounds showed good activity as ACAT inhibitors and cholesterol biosynthesis inhibitors (CBI) as shown in Scheme 5. A superimposition of MM-2 minimized structure **3** and cholesterol shows that the conformation of two structures have striking similarity (Figure 2). We believe that these novel imidazolines act as "super steroids" and displace the cholesterol and other sterols from active site of the enzymes or receptors.

Scheme 4

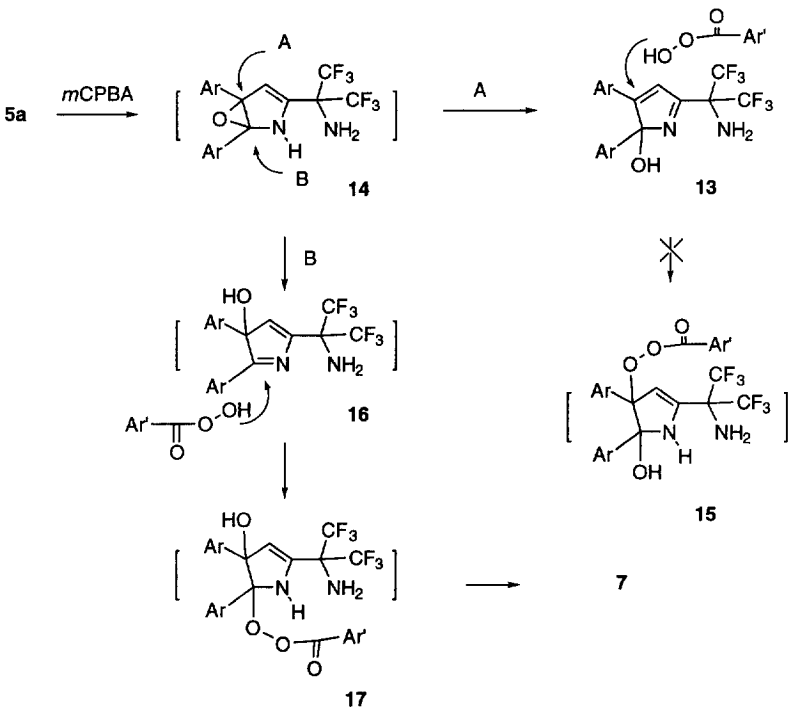
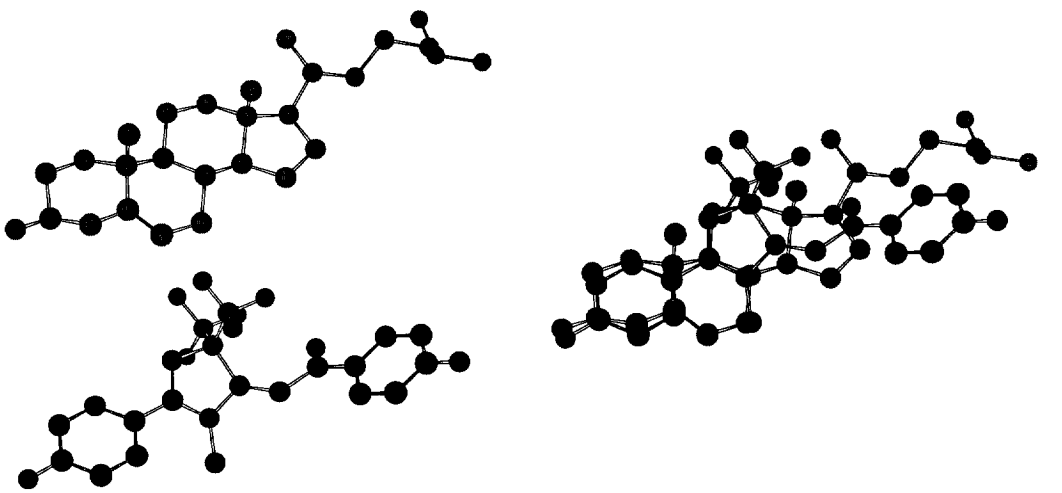


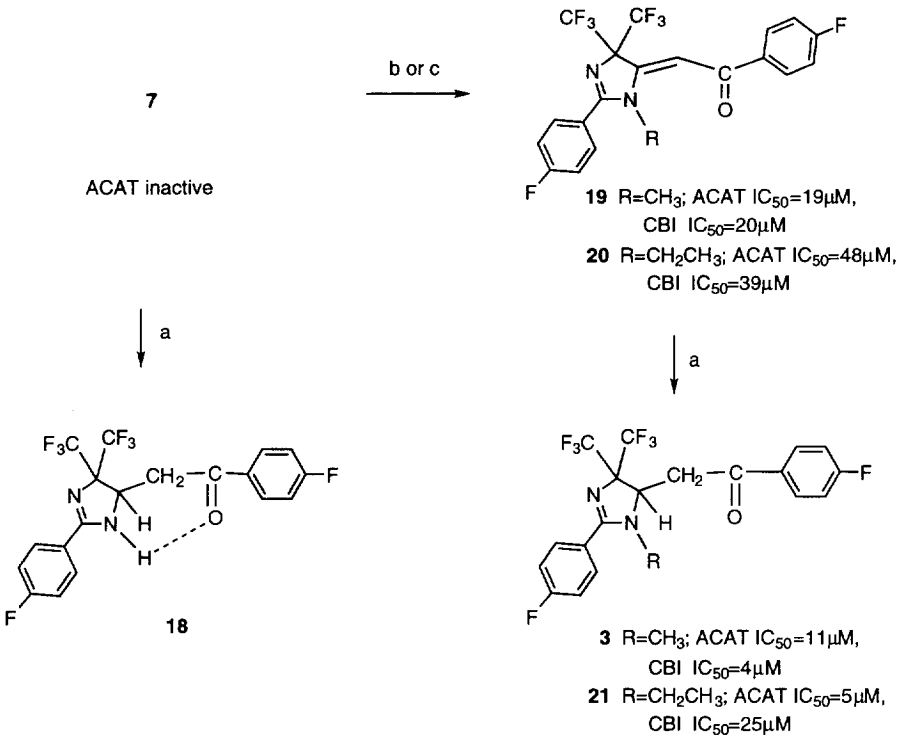
Figure 2. Superimposition of **3** (left bottom) and cholesterol (left top).



In summary, we have developed an efficient process that converts a 4,5-diaryl pyrrole (**5a**) to a 2-aryl-4,4-

bis(trifluoromethyl)imidazoline **7**. This method allowed us to synthesize a new series of analogs derived from **7**, which were not readily accessible by other synthetic methods.

Scheme 5



(a) Zn dust, acetic acid; (b) NaH, CH_3I, DMF, 91%; (c) K_2CO_3, CH_3CH_2I, DMF, 76%.

EXPERIMENTAL SECTION

General Experimental. Melting points were measured with a Thomas-Hoover Unimelt apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1710 series FTIR and were run as KBr pellets. Proton, ^{19}F, and ^{13}C NMR data were obtained using a Varian Unity 300 spectrometer and are 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).

Preparation of α,α-bis(trifluoromethyl)-4,5-bis(4-fluorophenyl)-1*H*-pyrrole-2-methanamine (5a). The title compound was prepared according to the lit. procedure[12] from 2,3-bis(4-fluoromethyl)-1*H*-pyrrole (**4a**) and hexafluoroisopropylidenimine with $AlCl_3$ in toluene in 73% yield: mp 88-89°C; IR (KBr) 3449,

1609, 1520, 1224, 1200 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 2.22(s, 2H), 6.59(s, 1H), 6.96(t, *J* = 8.4 Hz, 2H), 7.03(t, *J* = 8.3 Hz, 2H), 7.26(m, 4H), 8.69(s, 1H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -76.14(s, 6F), -114.25(m, 1F), -117.04(m, 1F); HRMS for $C_{19}H_{13}F_8N_2$ $(M+H)^+$ cald 421.0951, found 421.0946; Anal. Calcd for $C_{19}H_{12}F_8N_2$ C, 54.30; H, 2.88; N, 6.67; F, 36.16. Found: C, 54.27; H, 2.55; N, 6.57; F, 36.21.

Preparation of 2-[4,4-bis(trifluoromethyl)-2-(4-fluorophenyl)-4,5-dihydro-1*H*-imidazol-5-ylidine]-1-(4-fluorophenyl)-1-ethanone (7). To a solution of **5a** (4.0 g, 0.009 mole) in chloroform and methanol (1.5 l, 1:1) was added methylene blue (10 mg). Oxygen gas or air was bubbled through the solution while irradiating with a Tungsten lamp (400 watt) for 1 hour. 1M hydrochloric acid in ether (10 mL) was added to the reaction mixture and stirred for 1 hour at room temperature. The mixture was treated with saturated aqueous sodium carbonate solution (15 mL) and the organic layer was separated, concentrated, resuspended in ethyl acetate (200 mL), and washed with saturated aqueous ammonium chloride solution, saturated aqueous sodium chloride solution, dried over sodium sulfate (anhyd.) and evaporated under vacuum. The residue was purified by column chromatography, eluting with hexane-ethyl acetate (10:1) to give the title compound **7** (2.03 g, 49%): mp 134-135°C; IR (KBr) 3290, 3090, 2930, 1658, 1620, 1600, 1580, 1514, 1428, 1390, 1290, 1244, 1184, 1084, 1062, 986, 848, 800, 732 cm^{-1}; UV (MeOH) 265(3.40), 331(4.41); ^1H NMR(300 MHz, $CDCl_3$) δ 6.76(s, 1H), 7.23(m, 4H), 8.04(m, 4H), 11.82(s, 1H, NH); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -73.94(s, 6F), -104.32(m, 1F), -105.22(m, 1F); HRMS for $C_{19}H_{10}F_8N_2O$ cald 434.0665, found 434.0660; Anal. Calcd for $C_{19}H_{10}F_8N_2O$ C, 52.55; H, 2.32; N, 6.45; F, 35.00. Found: C, 52.81; H, 2.36; N, 6.26; F, 34.33.

Preparation of 7 and *N*-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-5,5-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-*N*-methylacetamide (13). To a solution of α,α-bis(tri-fluoromethyl)-4,5-bis(4-fluorophenyl)-1*H*-pyrrole-2-methanamine (5.0 g, 0.012 mole) in chloroform (100 mL) was added in portions m-chloroperbenzoic acid (*m*CPBA, 4.09 g, 0.024 mole). The reaction mixture was refluxed under nitrogen for one hour. Then, additional *m*CPBA (2.05 g, 0.012 mole) was added and the mixture was refluxed for 1 hour. The solution was cooled to room temperature and poured into saturated aqueous sodium bicarbonate (200 mL). The organic layer was washed successively with saturated aqueous sodium bicarbonate solution, 10% sodium sulfite solution, water, and saturated aqueous sodium chloride solution, dried over magnesium sulfate and evaporated under vacuum. The residue was purified by flash column chromatography eluting with hexane-ethyl acetate 20:1 then 10:1 to give **7** (1.02 g, 20%) as a yellow solid and **13** (2.09 g, 56%) as a solid. For compound **7**: mp 121-123°; MS m/e 435(M^++H). For compound **13**: mp 114-115°; mp 114-115°C; IR (KBr) 3346, 1603, 1506, 1236, 1160 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 2.60(s, 2H, NH_2), 3.40(s, 1H, NH), 6.80(s, 1H, C=CH), 6.95-7.04(m, 4H), 7.36(dd, *J* = 5.3, 8.4 Hz, 2H), 7.61(dd, *J* = 5.3, 8.4 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -73.94(q, *J* = 9.5 Hz, CF_3), -74.18(q, *J* = 9.5 Hz, CF_3), -109.12(m, 1F), -113.63(m, 1F); HRMS for $C_{19}H_{13}F_8N_2O$ cald 437.0900, found 437.0883; Anal. Calcd for $C_{19}H_{12}F_8N_2O$ C, 52.31; H, 2.77; N, 6.42; F, 34.84. Found: C, 52.08; H, 2.90; N, 6.27; F, 34.46.

Preparation of 6, 10, and 12. To a solution of α,α-bis(trifluoromethyl)-4,5-bis(4-fluorophenyl)-1*H*-pyrrole-2-methanamine (0.5 g, 1.19 mmole) in methanol (250 mL) was added methylene blue (14 mg). Oxygen gas or air was bubbled through the solution while irradiating with a Tungsten lamp (400 watt) for 40 min.. The

solvent was evaporated under vacuum and the residue was purified by column chromatography, eluting with hexane-ethyl acetate (10:1 to 1:1) to give three compounds: Compound **6** (261 mg, 48%), Compound **10** (64 mg, 18%), and Compound **12** (21 mg, 6%) all as viscous oils. For **6**: IR (KBr) 3342, 1732, 1708, 1626, 1602, 1506, 1236 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 2.68(s, 2H), 6.89(s, 1H), 6.95(t, *J* = 8.8 Hz, 2H), 7.05(t, *J* = 8.8 Hz, 2H), 7.32(dd, *J* = 8.8, 5.1 Hz, 1H), 7.71(dd, *J* = 8.8, 5.1 Hz, 1H); ^{13}C NMR(75.4MHz, $CDCl_3$) δ 64.65(m, C), 110.78(s, C), 115.67(d, *J* = 18.6 Hz, CH), 115.95(d, *J* = 18.6 Hz, CH), 120.50(s, C), 122.59(q, 281.8 Hz, 2x$\underline{C}F_3$), 127.11(d, *J* = 3.6 Hz, C), 128.45(d, *J* = 9.0 Hz, CH), 129.32(d, *J* = 2.8 Hz, C), 129.86(d, *J* = 8.3 Hz, CH), 161.18(d, *J* = 45.6 Hz, C), 165.06(s, C=O), 165.16(d, *J* = 48.3 Hz, C), 167.61(s, C=O); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -73.49(q, *J* = 9.5 Hz, 3F), -74.47(q, *J* = 9.5 Hz, 3F), -108.80(m, 1F), -111.25(m, 1F); HRMS for $C_{19}H_{13}F_8N_2O_2$ (M+H) cald 453.0849, found 453.0842. For **10** : IR (KBr) 3226, 1705, 1602, 1508, 1233 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 3.38(s, 3H, O$\underline{CH_3}$), 6.60(d, *J* = 1.1 Hz, 1H), 6.66(br.s, 1H), 7.07(t, *J* = 8.8 Hz, 4H), 7.57(m, 1H), 7.64(m, 1H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -109.06(m, 1F), -113.48(m, 1F); ^{13}C NMR(75.4MHz, $CDCl_3$) δ 50.50(s, CH_3), 94.01(s, C), 116.00(d, *J* = 22.1 Hz, CH), 116.38d, *J* = 22.4 Hz, CH), 121.7(d, *J* = 1.4 Hz, CH), 126.54(d, *J* = 2.8 Hz, C), 127.76(d, *J* = 8.3 Hz, CH), 129.98(d, *J* = 9.0 Hz, CH), 135.07(d, *J* = 2.8 Hz, CH), 157.83(s, C), 162.40(d, *J* = 84.2 Hz, CH), 165.91(d, *J* = 89.1 Hz, CH), 171.60(s, $\underline{C}$=O); HRMS for $C_{11}H_5F_7N_2O$ cald 301.0914, found 301.0918. For **12**: IR (KBr) 1745, 1603, 1509, 1235, 1162, 838 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 2.81(br.s, 2H, N$\underline{H_2}$), 6.36(s, 1H), 7.01(m, 4H), 7.51(dd, *J* = 8.7, 5.3 Hz, 2H), 7.78(dd, *J* = 8.7, 5.3 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -108.01(m, 1F), -112.74(m, 1F); ^{13}C NMR(75.4MHz, $CDCl_3$) δ 98.78(s, CH), 120.01(s, C), 125.46(d, *J* = 3.4 Hz, CH), 127.89(d, *J* = 8.5 Hz, CH), 130.76(d, *J* = 8.5 Hz, CH), 133.10(d, *J* = 3.2 Hz, CH), 162.93(d, *J* = 87.0 Hz, CH), 165.26(s, C=O), 165.26(d, *J* = 91.7 Hz, CH), 170.59(s, C=O).

Preparation of 1-(4-fluorophenyl-2-[2-(4-fluorophenyl)-4,5-dihydro-1H-4,4-bis(trifluoromethyl)-1*H*-imidazol-5-yl]-ethanone (18). To a solution of 2-[4, 4-bis(trifluoromethyl)-2-(4-fluorophenyl)-4,5-dihydro-1*H*-imidazol-5-ylidene]-1-(4-fluorophenyl)-1-ethanone (526 mg, 1.2 mmol) in 5 mL of glacial acetic acid was added zinc dust (0.8 g, 12.3 mmol). The reaction mixture was stirred at room temperature overnight and poured into water(125 mL) and neutralized with saturated aqueous sodium carbonate to pH 8. The mixture was then extracted with ether. The combined organic layers were washed successively with saturated aqueous ammonium chloride and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford **18** as a crystalline solid: (518 mg, 98%): mp 131-132 °C; IR (KBr) 3446, 1674, 1614, 1462, 1284, 1230, 1210, 1062, 846, 818, 740, 714, 578 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 3.50(dd, *J* = 10.9, 17.9 Hz, 1H), 3.67(d, *J* = 17.9 Hz, 1H), 4.77(d, *J* = 10.9 Hz, 1H), 6.11(s, 1H), 7.13(t, *J* = 8.8 Hz, 2H), 7.21(t, *J* = 8.8 Hz, 2H), 7.86(dd, *J* = 5.1, 8.8 Hz, 2H), 8.05(dd, *J* = 5.1, 8.8 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ -70.226(q, *J* = 10.3 Hz, 3F, C$\underline{F_3}$), -75.402(q, *J* = 10.3 Hz, 3F, C$\underline{F_3}$), -103.388(s, 1F), 107.074(s, 1F); LRMS (M+H)+542.2; Anal. Calcd for $C_{19}H_{12}F_8N_2O$ C, 52.31; H, 2.77; N, 6.42; F, 34.83. Found: C, 52.38; H, 2.73; N, 6.38; F, 34.90.

Preparation of 2-[4,4-bis(trifluoromethyl)-2-(4-fluorophenyl)-4,5-dihydro-1-methyl-1*H*-imidazol-5-ylidene]-1-(4-fluorophenyl)-1-ethanone (19). Sodium hydride (80 mg of 60% suspension in oil, 2.0 mmole) was washed with hexane and suspended in anhydrous dimethylformamide (5 mL). To this

suspension was added in portions **7** (0.43 g, 1.0 mmole), and the mixture was stirred at room temperature for 1 h. Iodomethane (0.28 g, 2.0 mmole) was added dropwise and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into water and extracted with ether. The combined organic layers were washed successively with water and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was recrystallized from dichloromethane-hexane to afford **19** (0.20 g, 91%) as white crystals: mp 128-129°; IR (KBr) 1664, 1629, 1604, 1234, 1128, 1098, 960 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 3.18(s, 3H, NCH_3), 6.64(s, 1H), 7.17(t, *J* = 8.7 Hz, 2H), 7.23(t, *J* = 8.7 Hz, 2H), 7.81(dd, *J* = 8.7, 5.7 Hz, 2H), 7.99(dd, *J* = 8.7, 5.7 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -74.55(s, 6F, $2xCF_3$), -105.34(m, 1F), -105.91(m, 1F); MS m/e 449(M^++H); HRMS for $C_{20}H_{13}F_8N_2O$ $(M+H)^+$ cald 449.0900, found 449.0897; Anal. Calcd for $C_{20}H_{12}F_8N_2O$ C, 53.58; H, 2.70; N, 6.25; F, 33.90. Found: C, 53,37; H, 2.65; N, 6.18; F, 33.75.

Preparation of 2-[4,4-bis(trifluoromethyl)-2-(4-fluorophenyl)-4,5-dihydro-1-ethyl-1*H*-imidazol-5-ylidene]-1-(4-fluorophenyl)-1-ethanone (20). Anhydrous potassium carbonate (7.5 g, 54 mmole) was suspended in anhydrous dimethylformamide (50 mL). To this suspension was added **7** (2.3 g, 5.3 mmole) and iodoethane (4.1 g, 26 mmol). The reaction mixture was allowed to stir at room temperature for 3 days and poured into water and extracted with ether. The combined organic layers were washed successively with water and saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by flash column chromatography to give the title compound **20** (1.86 g, 76%) as a crystalline solid: mp 108-109°C; IR (KBr) 1705, 1602, 1508, 1234 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 0.73(t, *J* = 6.9 Hz, CH_3), 4.02(q, *J* = 6.9 Hz, CH_2), 6.69(s, 1H), 7.19(t, *J* = 8.7 Hz, 2H), 7.23(t, *J* = 8.7 Hz, 2H), 7.71(dd, *J* = 8.7, 5.7 Hz, 2H), 7.99(dd, *J* = 8.7, 5.3 Hz, 4H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -73.38(s, 6F, $2xCF_3$), -105.27(m, 1F), -106.69(m, 1F); HRMS for $C_{21}H_{15}F_8N_2O$ $(M+H)^+$ cald 463.1057, found 463.1070. Anal. Calcd for $C_{21}H_{14}F_8N_2O$ C, 54.56; H, 3.05; N, 6.06; F, 32.87. Found: C, 54.50; H, 2.65; N, 6.03; F, 32.94.

Preparation of 1-(4-fluorophenyl-2-[2-(4-fluorophenyl)-4,5-dihydro-1-methyl-4,4-bis-(trifluoromethyl)-1*H*-imidazol-5-yl]-ethanone (3). To a refluxing solution of **19** (100 mg, 0.22 mmole) in acetic acid (15 mL) was added zinc dust (3.7 g, 56.6 mmole) over a period of 5 minutes. After 10 minutes, the mixture was filtered and washed with hot acetic acid. The filtrate was diluted with saturated aqueous sodium bicarbonate solution (120 mL) and extracted with ether (4x50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate (anhyd.) and evaporated under vacuum to give the title compound **3** (78 mg, 79%) as colorless needles: mp 145-146.6°C; IR (KBr) 3046, 2930, 1698, 1602, 1564, 1414, 1286, 1230, 1204 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 2.77(s, 3H, NCH_3), 3.56(m, 2H), 4.91((m, 2H), 7.13(t, *J* = 8.7 Hz, 2H), 7.21(t, *J* = 8.7 Hz, 2H), 7.59(t, *J* = 8.7 Hz, 2H), 8.06(t, *J* = 8.7 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -69.61(q, *J* = 10.3 Hz, 3F), -76.31(q, *J* = 10.3 Hz, 3F), -103.79(m, 1F), -108.35(m, 1F); HRMS for $C_{20}H_{14}F_8N_2O$ cald 464.1135, found 464.1142; Anal. Calcd for $C_{20}H_{14}F_8N_2O$ C, 53.34; H, 3.13; N, 6.22; F, 33.75. Found: C, 53,30; H, 3.01; N, 6.14; F, 33.58.

Preparation of 1-(4-fluorophenyl-2-[2-(4-fluorophenyl)-4,5-dihydro-1-ethyl-4,4-bis(trifluoro-methyl)-1*H*-imidazol-5-yl]-ethanone (21). Following the procedure for the preparation of **18**, the title

compound **21** was obtained from the reduction of 2-[4,4-bis(trifluoromethyl)-2-(4-fluorophenyl)-4,5-dihydro-1-ethyl-1*H*-imidazol-5-ylidene]-1-(4-fluorophenyl)-1-ethanone (2.03 g, 4.4mmol) in 20 mL of glacial acetic acid with zinc dust (3.0 g, 46 mmol) as white crystals (2.01 g, 99%): mp 93-95°C; IR (KBr) 1690, 1600, 1514, 1281, 1219 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 0.96(t, J = 7.0 Hz, $C\underline{H}_3$), 2.93(m, 1H), 3.33(m, 1H), 3.57(m, 2H), 5.12(br.s, 1H), 7.13(t, J = 8.4 Hz, 2H), 7.21(t, J = 8.4 Hz, 2H), 7.56(dd, J = 5.4, 8.4 Hz, 2H), 8.05(dd, J = 5.4, 8.4 Hz, 2H); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -109.79(m, 1F), -103.87(m, 1F), -76.17(q, J = 9.5 Hz, 3F), -69.39(q, J = 9.5 Hz, 3F); HRMS for $C_{21}H_{16}F_8N_2O$ cald 464.1135, found 464.1142; Anal. Calcd for $C_{21}H_{16}F_8N_2O$ C, 54.32; H, 3.47; N, 6.03; F, 32.73. Found: C, 53.79; H, 3.02; N, 5.95; F, 32.23.

ACKNOWLEDGMENT We want to thank Prof. E. Taylor of Princeton University, Prof. H. Rapoport of the University of California, Berkeley and Prof. D. F. Taber of University of Delaware for very helpful discussions and the DuPont Merck Physical Sciences group for obtaining most of the NMR, IR and MS data. Drs. J. T. Billheimer and P. J. Gillies obtained IC_{50} data for the ACAT in vitro assay and Drs. H. Chen and J. M. Trzaskos obtained IC_{50} data for the CBI assay.

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(*Received in USA* 24 *April* 1996; *revised* 10 *June* 1996; *accepted* 11 *June* 1996)