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Synthesis of Novel Ring-Substituted Histidines and Histamines[1]

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Abstract *: Synthesis of novel 2-cycloalkyl-L-histidines and 2-cycloalkylhistamines via radical alkylation with cycloalkylcarboxylic acids and silver nitrate in the presence of 10% H_2SO_4 by ammonium persulfate is described. The method is also extended to the synthesis of 1,2-dialkyl-L-histidines and 1,2-dialkylhistamines.* © 1997 Elsevier Science Ltd.

Simple and complex 2-alkylhistamines have been of interest for more than twenty years as potential histamine agonists and/or antagonists.[2-3] The involvement of histamine in the allergic response has stimulated interest in the synthesis of numerous antihistamines as well as the synthesis of different histamine derivatives designed to study various histamine receptors. For example, 2-(aryloxyalkyl) and 2-(aminoalkyl)histamines have been known to mediate the affinity of the H_1 histamine receptors in the body.[4] More recently, several of these alkylbioimidazoles have been explored as antitubercular agents.[5-6] However, access to this important class of bioimidazoles has been made difficult by obstacles such as low overall yield, restrictions in size or complexity of synthesis-compatible substituents, and the frequent use of liquid ammonia at high temperature and pressure[7], which mitigate their value as general pathways to these compounds.

Similar obstacles present themselves in the synthesis of 2-alkylhistidines, and only the methyl[8] and benzyl[9] derivatives have been described previously. Both were obtained as racemates through multistep synthesis. The lack of availability of 2-substituted-L-histidines has severely restricted investigation of their biochemical and medicinal properties. For example, nothing is known concerning the effects of 2-substituted histidines on decarboxylation by histidine decarboxylase and, thus, on the possible use of these compounds as prodrugs for 2-substituted histamines. Our own interest in the synthesis of ring-substituted histidines and histamines was stimulated in part by the fact that 2-fluoro-L-histidine and 2-iodo-L-histidine have been found to possess antimalarial activity against the resistant strains of *P. falciparum*.[10-11]

As part of our continuing efforts to develop new and efficient routes to ring-substituted histidines and histamines, we have developed procedures for the regiospecific synthesis of $N(1)^{\tau}$-alkyl-L-histidines and $N(1)^{\tau}$-alkylhistamines[12] and, more recently a simple, novel and efficient synthesis of 2-alkyl-L-histidines and 2-

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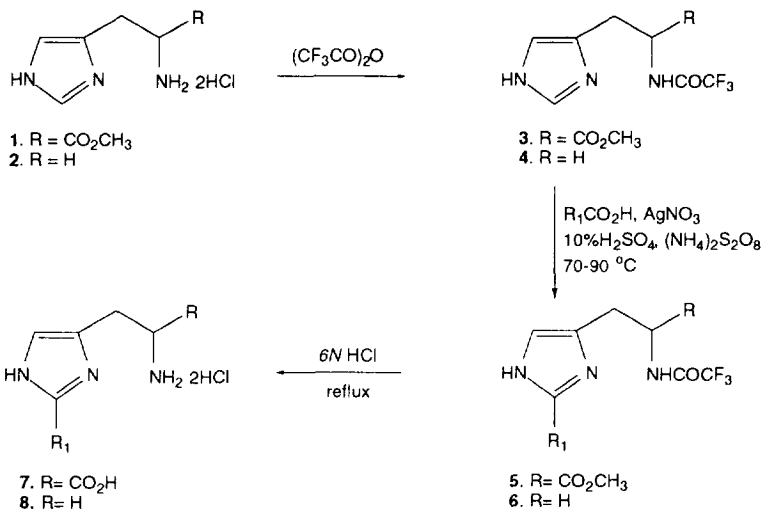
alkylhistamines.[13] The latter consists of direct regiospecific alkylation at C-2 of suitably protected histidines and histamines[13] *via* radical oxidative decarboxylation of alkylcarboxylic acids by ammonium persulfate in the presence of $AgNO_3$ in 10% H_2SO_4 based on modifications of the procedures used by Minisci *et al.*[14-17] for the alkylation of azaaromatics. We now report the extension of these methodologies to include 2-cycloalkyl-L-histidines and 2-cycloalkylhistamines (**7** and **8**) and 1,2-dialkyl-L-histidines and 1,2-dialkylhistamines (**17** and **18**). This report represents the first general route to the 2-cycloalkyl and 1,2-dialkyl bioimidazoles.



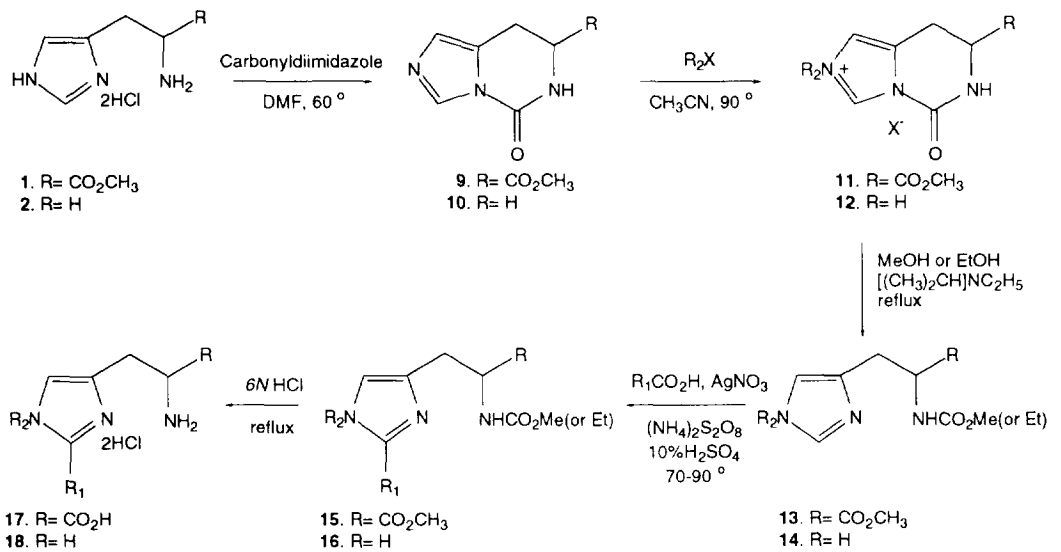
Scheme 1

Table I: Radical Cycloalkylation at C-2

R_1	% Yield 5	6
a) Cyclopropyl	3	6
b) Cyclobutyl	38	15
c) Cyclopentyl	43	22
d) Cyclohexyl[13]	39	39
e) Cycloheptyl	31	29
f) Adamantyl	12	10

N-α-Trifluoroacetyl-L-histidine methyl ester (**3**) and *N*-α-trifluoroacetylhistamine (**4**) on radical alkylation with cycloalkylcarboxylic acids using silver nitrate and ammonium persulfate in 10% H_2SO_4 gave compounds **5** and **6**. Other difficultly accessible and biologically important substituents such as cyclopropyl, cyclobutyl and adamantyl are easily introduced at the C-2 position of the imidazole ring in this manner without rearrangement (***Scheme I***). Yields range from 3-43% (***Table I***), though not surprisingly lower yields of the cyclopropyl adducts were observed. Presumably, this is a consequence of competitive degradation of the cyclopropyl radical *verses* oxidative decomposition of the imidazole ring. On the other hand, the reduced yield of the adamantyl products may be attributed to the lower solubility of adamantanecarboxylic acid in the

aqueous reaction medium rather than steric factors. In this case, unlike the other cycloalkylcarboxylic acids, a substantial quantity of the adamantanecarboxylic acid was found floating in the reaction vessel at the conclusion of the reaction. Alkylation is highly selective as reported previously,[13] with no alkylation observed at the C-4(5) position of imidazole ring. Compounds **5** and **6** on treatment with *6N* HCl at reflux provided the dihydrochlorides of the 2-cycloalkyl-L-histidines (**7**) and 2-cycloalkylhistamines (**8**). The free amino acids were obtained by Dowex ion-exchange chromatography of **7** (***Scheme 1***).



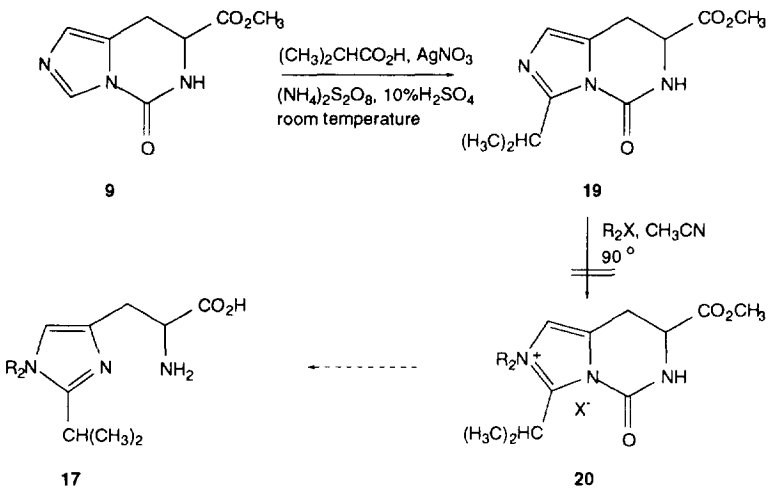
Scheme 2

Table II: C-2 Alkylation of 1-Alkyl-L-histidine and histamine

R_1	R_2	% Yield 15	16
a) c-C_3H_5	CH_3	22	11
b) c-C_6H_{11}	CH_3	38	38
c) $CH(CH_3)_2$	CH_3	40	41
d) $C(CH_3)_3$	CH_3	42	39
e) c-C_3H_5	$CH_2C_6H_5$	14	-
f) c-C_6H_{11}	$CH_2C_6H_5$	37	-
g) $CH(CH_3)_2$	$CH_2C_6H_5$	42	-
h) $C(CH_3)_3$	$CH_2C_6H_5$	40	-

5,6,7,8-Tetrahydro-5-oxoimidazo[1,5-c]pyrimidines (**9**,**10**), obtained by reaction of **1** and **2** with carbonyldiimidazole in DMF at 60 °C for 5h, provided quaternary salts **11** and **12**[12,18] on treatment with an alkyl halide in acetonitrile at 90 °C. Compounds **11** and **12** on reaction with methanol or ethanol in the presence of a tertiary amine at reflux temperature for 4 days gave 1-alkyl-*N*-α-carboalkoxy-L-histidine methyl esters (**13**) and 1-alkyl-*N*-α-carboalkoxyhistamines (**14**).[19-20] Radical alkylation of the *N*-α-carboalkoxy-L-histidine methyl esters (**13**) and *N*-α-carboalkoxyhistamines (**14**) with alkylcarboxylic acids in the presence of

ammonium persulfate and silver nitrate in 10% H_2SO_4 readily provided 1,2-dialkyl compounds **15** and **16** (***Scheme 2***). Yields range from 11-42% (***Table II***). 1,2-Dialkyl-L-histidines (**17**) and 1,2-dialkylhistamines (**18**) were obtained by refluxing solutions of **15** and **16** with *6N* HCl for 4-8 h, followed by Dowex ion-exchange chromatography for the amino acids.



Scheme 3

An alternative, shorter and more efficient pathway to the 1,2-dialkyl-L-histidines (**17**) and 1,2-dialkylhistamines (**18**) was attempted but proved to be unsuccessful. (+)(7S)-5,6,7,8-Tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo-[1,5-c]pyrimidine (**9**)[12,18] was alkylated with isobutyric acid in the presence of silver nitrate and ammonium persulfate in 10% H_2SO_4 to give (S)-3-isopropyl-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo-[1,5-c]pyrimidine **19** [R_1= $CH(CH_3)_2$] in 18% yield. Interestingly this yield is half the yield from alkylation of the protected histidines[13] or their *N*-1 derivatives (***Table II***), presumably because of the reduced electrophilicity of the ring or degradation of the ring system in competition with the alkylation process. However, all attempts to alkylate **19** with alkyl halides at *N*-1 failed (***Scheme 3***) and therefore this pathway was not pursued further.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) spectrometer. Mass spectra were provided by the Instrumentation Section of the Laboratory of Analytical Chemistry, NIDDK. Elemental analysis were performed by Atlantic Microlab, Norcross, GA or by Galbraith Laboratories, Knoxville, TN. Melting points were recorded on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 341 MC Polarimeter. Chromatographic purification was performed with silica gel 60 (230-400 mesh). All TLC (silica gel) development was performed by use of 5% CH_3OH in $CHCl_3$. All reagents were obtained from commercial sources and were of analytical grade.

Synthesis of 2-cycloalkyl-N-α-trifluoroacetyl-L-histidine methyl esters (5) and 2-cycloalkyl-N-α-trifluoroacetylhistamines (6). These compounds were synthesized by the method described previously.[13] A freshly prepared aqueous solution of ammonium persulfate (3 mmol) was added dropwise to a mixture of *N*-α-trifluoroacetyl-L-histidine methyl ester (**3**, 1 mmol) or *N*-α-trifluoroacetylhistamine (**4**, 1 mmol), silver nitrate

(0.6 mmol) and cycloalkylcarboxylic acid (3 mmol) in 10% H_2SO_4 during 15 minutes at 70-90 °C. The heating source was then removed and reaction proceeded with evolution of carbon dioxide. After 15 minutes, the reaction was terminated by pouring it onto ice. The resulting mixture was made alkaline with 30% ammonium hydroxide solution and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with NaCl solution (2 x 15 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* to afford an oil, which on chromatography over silica [ethyl acetate:hexanes (50:50)] gave **5** or **6** in 3-43% yield (***Table I***).

2-Cyclopropyl-N-α-trifluoroacetyl-L-histidine methyl ester(5a). Yield: 3%; oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 4H, 2 x CH_2, J=6.6 Hz), 1.78 (m, 1H, CH), 3.02 (m, 2H, CH_2), 3.65 (s, 3H, CH_3), 4.72 (m, 1H, CH), 6.62 (s, 1H, 4-H); analysis for $C_{12}H_{14}N_3O_3F_3$ (305.3), calcd, C, 47.22; H, 4.62, N, 13.77; found, C, 47.23; H, 4.74; N, 13.80; MS(CI-NH_3) m/z 306 (M+1); exact mass, calcd, 305.0987; found, 305.0979.

2-Cyclobutyl-N-α-trifluoroacetyl-L-histidine methyl ester (5b). Yield: 38%; oil; ^{1}H NMR ($CDCl_3$) δ 2.1 (m, 6H, 3 x CH_2), 3.1 (m, 1H, CH), 3.47 (m, 1H, CH), 3.68 (s, 3H, CH_3), 4.75 (m, 1H, CH), 6.67 (s, 1H, 4-H), 8.68 (bs, 1H, NH), 9.62 (bs, 1H, NH); analysis for $C_{13}H_{16}N_3O_3F_3$ (319.3), calcd, C, 48.9; H, 5.05; N, 13.16; found, C, 48.99; H, 5.05; N, 13.30; MS(CI-NH_3) m/z 320 (M+1); exact mass, calcd, 319.1143; found, 319.1147.

2-Cyclopentyl-N-α-trifluoroacetyl-L-histidine methyl ester (5c). Yield: 43%; oil; ^{1}H NMR ($CDCl_3$) δ 1.77 (m, 8H, 4 x CH_2), 3.1 (m, 3H, CH_2 and CH), 3.67 (s, 3H, CH_3), 4.76 (m, 1H, CH), 6.68 (s, 1H, 4-H); analysis for $C_{14}H_{18}N_3O_3F_3$ (333.3), calcd, C, 50.45; H, 5.44; N, 12.61; found, C, 50.35; H, 5.67; N, 12.55; MS(CI-NH_3) 334 (M+1); exact mass, calcd, 333.1300; found, 333.1309.

2-Cycloheptyl-N-α-trifluoroacetyl-L-histidine methyl ester (5e). Yield: 31%; oil; ^{1}H NMR ($CDCl_3$) δ 1.69 (m, 12H, 6 x CH_2), 2.85 (m, 1H. CH), 3.01 (m, 1H, CH), 3.15 (m, 1H, CH), 3.66 (s, 3H, CH_3), 4.76 (m, 1H, CH), 6.66 (s, 1H, 4-H), 8.56 (bs, 1H, NH), 9.58 (bs, 1H, NH); analysis for $C_{16}H_{22}N_3O_3F_3$ (361.2), calcd, C, 53.18; H, 6.14; N, 11.63; found, C, 53.39; H, 5.98; N, 11.85; MS(CI-NH_3) m/z 362 (M+1); exact mass, calcd, 361.1613; found, 361.1606.

2-Adamantyl-N-α-trifluoroacetyl-L-histidine methyl ester (5f). Yield: 12%; oil; ^{1}H NMR ($CDCl_3$) δ 1.66 (m, 15H, 7 x CH_2 and CH), 3.13 (m, 2H, CH_2), 3.66 (s, 3H, CH_3), 4.75 (m, 1H, CH), 6.67 (s, 1H, 4-H); analysis for $C_{19}H_{24}N_3O_3F_3$ (399.3), C, 57.14; H, 6.06; N, 10.52; found, C, 57.34; H, 6.23; N, 10.54; MS(CI-NH_3) m/z 400 (M+1); exact mass, calcd, 399.1769; found, 399.1775.

2-Cyclopropyl-N-α-trifluoroacetylhistamine (6a). Yield: 6%; mp 122-123 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (m, 4H, 2 x CH_2), 1.88 (m, 1H, CH), 2.32 (t, 2H, CH_2, J= 7.3 Hz), 2.63 (t, 2H, CH_2, J= 7.3 Hz), 6.68 (s, 1H, 4-H), 6.87 (bs, 1H, NH), 7.36 (bs, 1H, NH); analysis for $C_{10}H_{12}N_3OF_3$ (247.2), calcd, C, 48.58; H, 4.89; N, 17.0; found, C, 48.55; H, 4.89; N, 17.12; MS(CI-NH_3) m/z 248 (M+1).

2-Cyclobutyl-N-α-trifluoroacetylhistamine (6b). Yield: 15%; mp 138-139 °C; ^{1}H NMR ($CDCl_3$) δ 2.00 (m, 2H, CH_2), 2.35 (m, 4H, 2 x CH_2), 2.78 (t, 2H, CH_2, J=5.9 Hz), 3.51 (m, 1H, CH), 3.60 (q, 2H, CH_2, J=6 Hz), 6.70 (s, 1H, 4-H); analysis for $C_{11}H_{14}N_3OF_3$ (261.2), calcd, C, 50.57; H, 5.4; N, 16.08; found, C, 50.77; H, 5.52; N, 15.88; MS(CI-NH_3) m/z 262 (M+1).

2-Cyclopentyl-N-α-trifluoroacetylhistamine (6c). Yield: 22%; mp 131-132 °C; ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 6H, 3 x CH_2), 2.05 (m, 2H, CH_2), 2.77 (t, 2H, CH_2, J= 6.0 Hz), 3.08 (m, 1H, CH), 3.59 (m, 2H, CH_2), 6.70 (s, 1H, 4-H), 9.05 (bs, 1H, NH); analysis for $C_{12}H_{16}N_3OF_3$ (275.3), calcd, C, 52.36; H, 5.86; N, 15.26; found, C, 52.68; H, 5.88; N, 14.94; MS(CI-NH_3) 276 (M+1).

2-Cycloheptyl-N-α-trifluoroacetylhistamine (6e). Yield: 29%; mp 92-94 °C; ^{1}H NMR ($CDCl_3$) δ 1.8 (m, 12H, 6 x CH_2), 2.79 (t, 2H, CH_2, J=6.0 Hz), 2.88 (m, 1H, CH), 3.59 (q, 2H, CH_2, J= 5.9 Hz), 6.68 (s, 1H, 4-H), 8.9 (bs, 1H, NH); analysis for $C_{14}H_{20}N_3OF_3$ (303.3), calcd, C, 55.44; H, 6.65; N, 13.85; found, C, 55.43; H, 6.67; N, 13.66; MS(CI-NH_3) m/z 304 (M+1).

2-Adamantyl-N-α-trifluoroacetylhistamine (6f). Yield: 10%; mp 76-78 °C; ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 15H, 7 x CH_2 and CH), 2.78 (t, 2H, CH_2, J= 5.9 Hz), 3.58 (q, 2H, CH_2, J= 5.3 Hz), 6.69 (s, 1H, 4-H); analysis for $C_{17}H_{22}N_3OF_3$ (341.4), Calcd, C, 59.81; H, 6.5; N, 12.31; found, C, 59.91; H, 6.88; N, 12.22; MS(CI-NH_3) m/z 342 (M+1); exact mass, calcd, 341.1714; found, 341.1700.

Synthesis of 2-cycloalkyl-L-histidines (7) and 2-cycloalkylhistamines (8). A solution of 2-cycloalkyl-N-α-trifluoroacetyl-L-histidine methyl ester (**5**, 1 mmol) or 2-cycloalkyl-N-α-trifluoroacetylhistamine (**6**, 1 mmol) in *6N* HCl (15 mL) was refluxed for 4-8 h. The solvent was evaporated *in vacuo* to afford the dihydrochloride salt of the 2-cycloalkyl-L-histidine or 2-cycloalkylhistamine. The free amino acids **7** were obtained by passing a solution of the dihydrochloride through an ion-exchange column (Dowex, 50 x 2-200, H^+ form), and eluting the column with 15% NH_4OH solution.

2-Cyclopropyl-L-histidine (7a). Yield: 95%; mp 243-245 °C (dec); ^{1}H NMR (D_2O) δ 0.79 (m, 4H, 2 x CH_2), 1.86 (m, 1H, CH), 2.95 (m, 2H, CH_2), 3.76 (m, 1H, CH), 6.73 (s, 1H, 4-H); analysis for $C_9H_{13}N_3O_2$+0.51 H_2O (204.4), calcd, C 52.88; H, 6.91; N, 20.55; found, C, 53.21; H, 6.55; N, 20.22; $[\alpha]_D^{20}$ -33° (c=1, H_2O).

2-Cyclobutyl-L-histidine (7b). Yield: 92%; mp 253-255 °C (dec); ^{1}H NMR (D_2O) δ 1.97 (m, 6H, 3 x CH_2), 2.91 (m, 1H, CH), 3.05 (m, 1H, CH), 3.50 (m, 1H, CH), 3.78 (m, 1H, CH), 6.81 (s, 1H, 4-H); analysis for $C_{10}H_{15}N_3O_2$+0.5 H_2O (218.3), calcd, C, 55.03; H, 7.38; N, 19.25; found, C, 55.04; H, 7.13; N, 19.17; $[\alpha]_D^{20}$ -48.3° (c=1.2, H_2O).

2-Cyclopentyl-L-histidine (7c). Yield: 90%; mp 240-243 °C (dec); ^{1}H NMR (D_2O) δ 1.58 (m, 8H, 4 x CH_2), 1.97 (m, 1H, CH), 2.92 (m, 1H, CH), 3.07 (m, 1H, CH), 3.77 (m, 1H, CH), 6.81 (s, 1H, 4-H); analysis for $C_{11}H_{17}N_3O_2$+0.45 H_2O (231.4), calcd, C, 57.1; H, 7.79; N, 18.16; found, C, 56.94; H, 7.53; N, 17.87; $[\alpha]_D^{20}$ -53° (c=1.0, H_2O).

2-Cycloheptyl-L-histidine (7e). Yield: 96%; mp 215-218 °C (dec); ^{1}H NMR (D_2O) δ 1.52 (m, 10H, 5 x CH_2), 1.84 (m, 2H, CH_2), 2.95 (m, 3H, CH_2 and CH), 3.75 (m, 1H, CH), 6.77 (s, 1H, 4-H); analysis for $C_{13}H_{21}N_3O_2$+H_2O (269.3), calcd, C, 57.97; H, 8.60; N, 15.6; found, C, 58.04; H, 8.58; N, 15.47; $[\alpha]_D^{20}$ -27.7° (c=1.4, H_2O).

2-Adamantyl-L-histidine (7f). Yield: 88%; mp 278-280 °C (dec); ^{1}H NMR (D_2O) δ 1.85 (m, 14H, 7 x CH_2), 2.91 (m, 1H, CH), 3.05 (m, 1H, CH), 3.75 (m, 1H, CH), 6.80 (s, 1H, 4-H); analysis for $C_{16}H_{23}N_3O_2$+1.9H_2O (323.6), calcd, C, 59.38; H, 8.34; N, 12.98; found, C, 59.34; H, 8.32; N, 12.82; $[\alpha]_D^{20}$ -38.54° (c=1.4, CH_3OH).

2-Cyclopropylhistamine dihydrochloride (8a). Yield: 94%; mp 198-201 °C (dec); ^{1}H NMR (CD_3OD) δ 1.20 (m, 4H, 2 x CH_2), 2.22 (m, 1H, CH), 2.79 (t, 2H, CH_2, J= 6.4 Hz), 3.06 (t, 2H, CH_2, J= 7.3 Hz), 7.14 (s, 1H, 4-H); analysis for $C_8H_{13}N_3$.2HCl (224.1), calcd, C, 42.87; H, 6.57; N, 18.75; Cl, 31.64; found, C, 42.99; H, 6.75; N, 18.77; Cl, 31.55; MS(CI-NH_3) m/z 152 (M+1).

2-Cyclobutylhistamine dihydrochloride (8b). Yield: 100%; mp 220-222 °C (dec); ^{1}H NMR (D_2O) δ 2.24 (m, 6H, 3 x CH_2), 2.98 (t, 2H, CH_2, J= 7.4 Hz), 3.20 (t, 2H, CH_2, J= 7.1 Hz), 3.72 (m, 1H, CH), 7.09 (s, 1H, 4-H); analysis for $C_9H_{15}N_3$.2HCl (238.2), calcd, C, 45.39; H, 7.19; N, 17.64; Cl, 29.77; found, C, 45.44; H, 7.10; N, 17.51; Cl, 29.75; MS(CI-NH_3) m/z 166 (M+1).

2-Cyclopentylhistamine dihydrochloride (8c). Yield: 88%; mp 212-215 °C (dec); ^{1}H NMR (D_2O) δ 1.65 (m, 6H, 3 x CH_2), 2.10 (m, 3H, CH_2 and CH), 2.98 (t, 2H, CH_2, J= 6.8 Hz), 3.20 (t, 2H, CH_2, J= 6.6 Hz), 7.09 (s, 1H, 4-H); analysis for $C_{10}H_{17}N_3$.2HCl (252.1), calcd, C, 47.63; H, 7.59; N, 16.66; Cl, 28.12; found, C, 47.62; H, 7.38; N, 16.33; Cl, 28.11; MS(CI-NH_3) m/z 180 (M+1).

2-Cycloheptylhistamine dihydrochloride (8e). Yield: 91%; mp: 210-214 °C (dec); ^{1}H NMR (D_2O) δ 1.58 (m, 10H, 5 x CH_2), 1.93 (m, 2H, CH_2), 2.96 (t, 2H, CH_2, J= 7.3 Hz), 3.08 (m, 1H, CH), 3.19 (t, 2H, CH_2, J= 7.4 Hz), 7.07 (s, 1H, 4-H); analysis for $C_{12}H_{21}N_3$.2HCl+0.7 H_2O (292.9), calcd, C, 49.21; H, 8.39; N, 14.34; found, C, 49.33; H, 8.35; N, 14.37; MS(CI-NH_3) m/z 208 (M+1).

2-Adamantylhistamine dihydrochloride (8f).[lit.21] Yield: 87%; mp 224-227 °C (dec); ^{1}H NMR (D_2O) δ 1.71 (m, 14H, 7 x CH_2), 2.65 (m, 1H, CH); 2.89 (t, 2H, CH_2, J= 6.9 Hz), 3.11 (t, 2H, CH_2, J= 6.9 Hz), 7.04 (s, 1H, 4-H); analysis for $C_{15}H_{23}N_3.2HCl$ (316.3), calcd, C, 56.97; H, 7.33; N, 13.29; Cl, 22.42; found, C, 57.11; H, 7.43; N, 13.25; Cl, 22.43; MS(CI-NH_3) m/z 246 (M+1).

Synthesis of N-α-Carboethoxy-1-methylhistamine (14). This compound was synthesized by methods reported earlier.[12,19-20]

Yield: 85%; mp 97-98 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3, J= 7.0 Hz), 2.73 (t, 2H, CH_2, J= 6.5 Hz), 3.46 (q, 2H, CH_2, J= 6.1 Hz), 3.66 (s, 3H, N-CH_3), 4.10 (q, 2H, CH_2, J= 7.0 Hz), 6.66 (s, 1H, 4-H), 7.34 (s, 1H, 2-H); analysis for $C_9H_{15}N_3O_2$ (197.2), calcd, C, 54.81, H, 7.67, N, 21.3; found, C, 54.82, H, 7.62, N, 21.21; MS(CI-NH_3) m/z 198 (M+1).

Synthesis of N-α-carboalkoxy-1,2-dialkyl-L-histidine methyl esters (15) and N-α-carboalkoxy-1,2-dialkylhistamines (16). These compounds were synthesized by the method used for the synthesis of **5** or **6**.

N-α-Carbomethoxy-1-methyl-2-cyclopropyl-L-histidine methyl ester (15a). Yield: 22%; oil; ^{1}H NMR ($CDCl_3$) δ 0.93 (m, 4H, 2 x CH_2), 1.70 (m, 1H, CH), 2.95 (m, 2H, CH_2), 3.58 (s, 3H, N-CH_3), 3.67 (s, 3H, CO_2CH_3), 3.69 (s, 3H, CO_2CH_3), 4.51 (m, 1H, CH), 6.34 (bd, 1H, NH), 6.50 (s, 1H, 4-H); analysis for $C_{13}H_{19}N_3O_4$ (281.3), calcd, C, 55.51; H, 6.81; N, 14.94; found, C, 55.73; H, 6.98; N, 15.02; MS(CI-NH_3) m/z 282 (M+1); exact mass, calcd 281.1375, found 281.1369.

N-α-Carbomethoxy-1-methyl-2-cyclohexyl-L-histidine methyl ester (15b). Yield: 38%; oil; ^{1}H NMR ($CDCl_3$) δ 1.53 (m, 10H, 5 x CH_2), 2.54 (m, 1H, CH), 2.96 (m, 2H, CH_2), 3.48 (s, 3H, N-CH_3), 3.65 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 4.50 (m, 1H, CH), 6.47 (s, 1H, 4-H); analysis for $C_{16}H_{25}N_3O_4$ (323.4), calcd, C, 59.43; H, 7.79; N, 12.99; found, C, 59.68; H, 7.85; N, 13.17; MS(CI-NH_3) m/z 324 (M+1); exact mass, calcd 323.1845; found 323.1838.

N-α-Carbomethoxy-1-methyl-2-isopropyl-L-histidine methyl ester (15c). Yield: 40%; oil; ^{1}H NMR ($CDCl_3$) δ 1.27 (m, 6H, 2 x CH_3), 2.96 (m, 3H, CH_2 and CH), 3.49 (s, 3H, N-CH_3), 3.65 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 4.51 (m, 1H, CH), 6.49 (s, 1H, 4-H); analysis for $C_{13}H_{21}N_3O_4$ (283.3), calcd, C, 55.11; H, 7.47; N, 14.83; found, C, 55.33; N, 7.48; N, 14.65; MS(CI-NH_3) m/z 284 (M+1); exact mass, calcd 283.1532, found 283.1540.

N-α-Carbomethoxy-1-methyl-2-tert-butyl-L-histidine methyl ester (15d). Yield: 42%; oil; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H, 3 x CH_3), 2.93 (m, 2H, CH_2), 3.64 (s, 3H, N-CH_3), 3.65 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 4.50 (m, 1H, CH), 6.46 (s, 1H, 4-H), 6.65 (m, 1H, NH); analysis for $C_{14}H_{23}N_3O_4$ (297.4), calcd, C, 56.55; H, 7.8; N, 14.13; found, C, 56.47; H, 7.67; N, 14.29; MS(CI-NH_3) m/z 298 (M+1); exact mass, calcd 297.1688, found 297.1687.

N-α-Carbomethoxy-1-benzyl-2-cyclopropyl-L-histidine methyl ester (15e). Yield: 14%; oil; ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 4H, CH_2), 1.65 (m, 1H, CH), 2.97 (m, 2H, CH_2), 3.64 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3), 4.54 (m, 1H, CH), 4.97 (s, 2H, CH_2), 6.4 (m, 1H, NH), 6.54 (s, 1H, 4-H), 7.05 (m, 2H, Ar-H), 7.34 (m, 3H, Ar-H); analysis for $C_{19}H_{23}N_3O_4$ (357.4), calcd, C, 63.85; H, 6.49; N, 11.76; found, C, 64.11; H, 6.24; N, 11.77; MS(CI-NH_3) m/z 358 (M+1); exact mass, calcd, 357.1688, found 357.1675.

N-α-Carbomethoxy-1-benzyl-2-cyclohexyl-L-histidine methyl ester (15f). Yield: 37%; oil; ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 4H, 2 x CH_2), 1.70 (m, 6H, 3 x CH_2), 2.50 (m, 1H, CH), 2.98 (m, 2H, CH_2), 3.61 (s, 3H, CO_2CH_3), 3.65 (s, 3H, CO_2CH_3), 4.54 (m, 1H, CH), 4.98 (s, 2H, CH_2), 6.47 (s, 1H, 4-H), 6.97 (m, 2H, Ar-H), 7.29 (m, 3H, Ar-H); analysis for $C_{22}H_{29}N_3O_4$ (399.5), calcd, C, 66.14; H, 7.32; N, 10.52; found, C, 65.92; H, 7.32; N, 10.2; MS(CI-NH_3) 400 (M+1).

N-α-Carbomethoxy-1-benzyl-2-isopropyl-L-histidine methyl ester (15g). Yield: 42%; oil; ^{1}H NMR ($CDCl_3$) δ 1.21 (m, 6H, 2 x CH_3), 2.86 (m, 1H, CH), 2.99 (m, 2H, CH_2), 3.62 (s, 3H, CO_2CH_3), 3.65 (s, 3H, CO_2CH_3),

4.54 (m, 1H, CH), 4.99 (s, 2H, CH_2), 6.49 (s, 1H, 4-H), 6.97 (m, 2H, Ar-H), 7.28 (m, 3H, Ar-H); analysis for $C_{19}H_{25}N_3O_4$ (359.4), calcd, C, 63.49; H, 7.01; N, 11.69; found, C, 63.77; H, 7.12; N, 11.70; MS(CI-NH_3) m/z 360 (M+1); exact mass, calcd 359.1845, found 359.1833.

N-α-Carbomethoxy-1-benzyl-2-tert-butyl-L-histidine methyl ester (15h). Yield: 40%; oil; ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H, 3 x CH_3), 2.95 (m, 2H, CH_2), 3.62 (s, 3H, CO_2CH_3), 3.66 (s, 3H, CO_2CH_3), 4.52 (m, 1H, CH), 5.19 (s, 2H, CH_2), 6.42 (s, 1H, 4-H), 6.71 (bs, 1H, NH), 6.95 (m, 2H, Ar-H), 7.28 (m, 3H, Ar-H); analysis for $C_{20}H_{27}N_3O_4$ (373.5), calcd, C, 64.32; H, 7.29; N, 11.25; found, C, 64.12; H, 7.30; N, 11.32; MS(CI-NH_3) 374 (M+1); exact mass, calcd 373.2001, found 373.1993.

N-α-Carboethoxy-1-methyl-2-cyclopropylhistamine (16a). Yield: 11%; mp 66-67 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (m, 4H, 2 x CH_2), 1.23 (t, 3H, CH_3, J= 6.9 Hz), 1.73 (m, 1H, CH), 2.65 (t, 2H, CH_2, J= 6.4 Hz), 3.40 (m, 2H, CH_2), 3.61 (s, 3H, N-CH_3), 4.09 (m, 2H, CH_2), 6.54 (s, 1H, 4-H); analysis for $C_{12}H_{19}N_3O_2$ (237.3), calcd, C, 60.72; H, 8.07; N, 17.71; found, C, 60.66; H, 7.99; N, 17.58; MS(CI-NH_3) m/z 238(M+1).

N-α-Carboethoxy-1-methyl-2-cyclohexylhistamine (16b). Yield: 38%; mp 70-72 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3, J= 7.1 Hz), 1.33 (m, 4H, 2 x CH_2), 1.83 (m, 6H, 3 x CH_2), 2.58 (m, 1H, CH), 2.69 (t, 2H, CH_2, J= 6.5 Hz), 3.42 (q, 2H, CH_2, J= 6.2 Hz), 3.52 (s, 3H, N-CH_3), 4.10 (q, 2H, CH_2, J= 7.0 Hz), 5.36 (bs, 1H, NH), 6.51 (1H. 4-H); analysis for $C_{15}H_{25}N_3O_2$ (279.4), calcd, C, 64.49; H, 9.02; N, 15.04; found, C, 64.68; H, 9.05; N, 14.88; MS(CI-NH_3) m/z 280 (M+1).

N-α-Carboethoxy-1-methyl-2-isopropylhistamine (16c). Yield: 41%; mp 68-70 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3, J= 7.1 Hz), 1.30 (d, 6H, 2 x CH_3, J= 6.8 Hz), 2.73 (t, 2H, CH_2, J= 6.5 Hz), 2.96 (m, 1H, CH), 3.42 (q, 2H, CH_2, J= 6.1 Hz), 3.53 (s, 3H, N-CH_3), 4.10 (q, 2H, CH_2, J= 7.0 Hz), 5.41 (bs, 1H, NH), 6.52 (s, 1H, 4-H); analysis for $C_{12}H_{21}N_3O_2$ (239.3), calcd, C, 60.23; H, 8.84; N, 17.56; found, C, 59.93; H, 8.69; N, 17.33; MS(CI-NH_3) m/z 240 (M+1).

N-α-Carbomethoxy-1-methyl-2-tert-butylhistamine (16d). Yield: 39%; mp 60-62 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H, 3 x CH_3), 2.67 (t, 2H, CH_2, J= 6.3 Hz), 3.41 (m, 2H, CH_2), 3.66 (s, 3H, N-CH_3), 3.68 (s, 3H, CO_2CH_3), 6.50 (s, 1H, 4-H); analysis for $C_{12}H_{21}N_3O_2$ (239.3), calcd, C, 60.23; H, 8.84; N, 17.56; found, C, 59.95; H, 8.86; N, 17.32; MS(CI-NH_3) m/z 240 (M+1).

Synthesis of 1,2-dialkyl-L-histidines (17) and 1,2-dialkylhistamines (18). These compounds were synthesized by the procedure used for the synthesis of 7 or **8**.

1-Methyl-2-cyclopropyl-L-histidine (17a). Yield: 90%; mp 198-205 °C (dec); ^{1}H NMR (CD_3OD) δ 0.85 (m, 4H, 2 x CH_2), 1.81 (m, 1H, CH), 2.80 (m, 1H, CH), 2.99 (m, 1H, CH), 3.57 (s, 3H, N-CH_3), 3.65 (m, 1H, CH), 6.72 (s, 1H, 4-H); analysis for $C_{10}H_{15}N_3O_2$+1.6 H_2O (283.1), calcd, C, 50.45; H, 7.70; N, 17.65; found, C, 50.65; H, 7.39; N, 17.33; $[\alpha]_D^{20}$ -27.7° (c=1.3, CH_3OH).

1-Methyl-2-cyclohexyl-L-histidine (17b). Yield: 93%; mp 196-199 °C (dec); ^{1}H NMR (D_2O) δ 1.25 (m, 4H, 2 x CH_2), 1.73 (m, 6H, 3 x CH_2), 2.71 (m, 1H, CH), 2.90 (m, 2H, CH_2), 3.50 (s, 3H, N-CH_3), 3.77 (m ,1H, CH), 6.77 (s, 1H, 4-H); analysis for $C_{13}H_{21}N_3O_2$+2.5 H_2O (296.4), calcd, C, 52.68; H, 8.84; N, 14.14; found, C, 52.91; H, 8.66; N, 13.75; $[\alpha]_D^{20}$ -13.7° (c= 0.54, H_2O).

1-Methyl-2-isopropyl-L-histidine (17c). Yield: 68%, mp 194-197 °C (dec); ^{1}H NMR (D_2O) δ 1.14 (m, 6H, 2 x CH_3), 2.92 (m, 3H, CH_2 and CH), 3.49 (s, 3H, N-CH_3), 3.77 (m, 1H, CH), 6.76 (s, 1H, 4-H); analysis for $C_{10}H_{17}N_3O_2$+1.8 H_2O (243.7), calcd, C, 49.28; H, 8.52; N, 17.24; found, C, 49.12; H, 8.19; N, 16.93; $[\alpha]_D^{20}$ -27.66° (c= 0.6, H_2O).

1-Methyl-2-tert-butyl-L-histidine (17d). Yield: 89%; mp 210-212 °C (dec), ^{1}H NMR (D_2O) δ 1.28 (s, 9H, 3 x CH_3), 2.90 (m, 2H, CH_2), 3.66 (s, 3H, N-CH_3), 3.76 (m, 1H, CH), 6.78 (s, 1H, 4-H); analysis for $C_{11}H_{19}N_3O_2$+1.2 H_2O (246.9), calcd, C, 53.51; H, 8.73; N, 17.01; found, C, 53.73; H, 8.54; N, 16.96; $[\alpha]_D^{20}$ -20.2° (c= 0.52, H_2O).

1-Benzyl-2-cyclopropyl-L-histidine (17e). Yield: 94%; mp 174-180 °C (dec); ^{1}H NMR (CD_3OD) δ 0.78 (m, 4H, 2 x CH_2), 1.75 (m, 1H, CH), 2.82 (m, 1H, CH), 3.02 (m, 1H, CH), 3.66 (m, 1H, CH), 5.14 (s, 2H, CH_2), 6.80 (s, 1H, 4-H), 7.11 (m, 2H, Ar-H), 7.25 (m, 3H, Ar-H); analysis for $C_{16}H_{19}N_3O_2$+1.7 H_2O (315.9), calcd, C, 60.82; H, 7.16; N, 13.29; found, C, 60.8; H, 7.11; N, 13.41; $[\alpha]_D^{20}$ -15.5° (c=1.55, H_2O).

1-Benzyl-2-cyclohexyl-L-histidine (17f). Yield: 82%; mp 202-206 °C (dec); ^{1}H NMR (D_2O) δ 1.36 (m, 10H, 5 x CH_2), 2.65 (m, 1H, CH), 2.96 (m, 2H, CH_2), 3.82 (m, 1H, CH), 5.10 (s, 2H, CH_2), 6.86 (s, 1H, 4-H), 7.09 (m, 2H, Ar-H), 7.28 (m, 3H, Ar-H); analysis for $C_{19}H_{25}N_3O_2$+H_2O (345.4), calcd, C, 66.06; H, 7.87; N, 12.16; found, C, 65.76; H, 7.88; N, 12.12; $[\alpha]_D^{20}$ - 10.7° (c=0.9, CH_3OH).

1-Benzyl-2-isopropyl-L-histidine (17g). Yield: 90%; mp 186-189 °C (dec); ^{1}H NMR (D_2O) δ 1.06 (m, 6H, 2 x CH_3), 2.96 (m, 3H, CH_2 and CH), 3.82 (m, 1H, CH), 5.10 (s, 2H, CH_2), 6.86 (s, 1H, 4-H), 7.08 (m, 2H, Ar-H), 7.29 (m, 3H, Ar-H); analysis for $C_{16}H_{21}N_3O_2$+1.1 H_2O (307.2), calcd, C, 62.56; H, 7.61; N, 13.68; found, C, 62.24; H, 7.79; N, 13.51; $[\alpha]_D^{20}$ - 9.3° (c=2.2, CH_3OH).

1-Benzyl-2-tert-butyl-L-histidine (17h). Yield: 90%; mp 191-194 °C (dec); ^{1}H NMR (CD_3OD) δ 1.25 (s, 9H, 3 x CH_3), 2.82 (m, 1H, CH), 3.03 (m, 1H, CH), 3.68 (m, 1H, CH), 5.22 (s, 2H, CH_2), 6.65 (s, 1H, 4-H), 6.96 (m, 2H, Ar-H), 7.22 (m, 3H, Ar-H); analysis for $C_{17}H_{23}N_3O_2$+1.5 H_2O (328.4), calcd, C, 62.17; H, 7.98; N, 12.79; found, C, 61.86; H, 7.96; N, 12.41; $[\alpha]_D^{20}$ - 9.2° (c=1.3, CH_3OH).

1-Methyl-2-cyclopropylhistamine dihydrochloride (18a). Yield: 90%; mp 188-192 °C (dec); ^{1}H NMR (D_2O) δ 0.92 (m, 2H, CH_2), 1.14 (m, 2H, CH_2), 2.01 (m, 1H, CH), 2.89 (t, 2H, CH_2, J= 7.4 Hz), 3.14 (t, 2H, CH_2, J= 7.7 Hz), 3.69 (s, 3H, N-CH_3), 7.05 (s, 1H, 4-H); analysis for $C_9H_{15}N_3$.2HCl+0.5H_2O (247.2), calcd, C, 43.73; H, 7.34; N, 17.00; Cl, 28.68; found, C, 43.84; H, 7.17; N, 17.30; Cl, 28.60; MS(CI-NH_3) m/z 166 (M+1).

1-Methyl-2-cyclohexylhistamine dihydrochloride (18b). Yield: 98%; mp 170-175 °C (dec); ^{1}H NMR (D_2O) 1.50 (m, 10H, 5 x CH_2), 2.39 (t, 2H, CH_2, J= 7.4 Hz), 3.16 (t, 2H, CH_2, J= 7.6 Hz), 3.64 (s, 3H, N-CH_3), 7.05 (s, 1H, 4-H); analysis for $C_{12}H_{21}N_3$.2HCl+2.5 H_2O (325.3), calcd, C, 44.31; H, 8.67; N, 12.91; found, C, 44.02; H, 8.45; N, 13.17; MS(CI-NH_3) m/z 208 (M+1).

1-Methyl-2-isopropylhistamine dihydrochloride (18c). Yield: 98%; mp 190-194 °C (dec); ^{1}H NMR (D_2O) δ 1.23 (d, 6H, 2 x CH_3, J= 7.0 Hz), 2.94 (t, 2H, CH_2, J= 7.4 Hz), 3.20 (t, 2H, CH_2, J= 7.3 Hz), 3.27 (m, 1H, CH), 3.65 (s, 3H, N-CH_3), 7.07 (s, 1H, 4-H); analysis for $C_9H_{17}N_3$.2HCl+0.5 H_2O (249.2), calcd, C, 43.38; H, 8.09; N, 16.86; found, C, 43.68; H, 8.04; N, 16.79; MS(CI-NH_3) m/z 168 (M+1).

1-Methyl-2-tert-butylhistamine dihydrochloride (18d). Yield: 76%; mp 248-255 °C (dec); ^{1}H NMR (D_2O) δ 1.38 (s, 9H, 3 x CH_3), 2.93 (t, 2H, CH_2, J= 7.5 Hz), 3.17 (t, 2H, CH_2, J= 7.4 Hz), 3.80 (s, 3H, N-CH_3), 7.07 (s, 1H, 4-H); analysis for $C_{10}H_{19}N_3$.2HCl+0.5H_2O (263.2), calcd, C, 45.63; H, 8.42; N, 15.96; found, C, 45.89; H, 8.40; N, 16.02; MS(CI-NH_3) m/z 182 (M+1).

Synthesis of (+)-3-isopropyl-(7S)-5,6,7,8-tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo-[1,5-c]pyrimidine [19, R_1= CH(CH$_3$)$_2$]. To a mixture of (+)(7S)-5,6,7,8-Tetrahydro-7-(methoxycarbonyl)-5-oxoimidazo-[1,5-c]pyrimidine (**9**, 1 mmol), silver nitrate (0.6 mmol) and isobutyric acid (3 mmol) in 10% H_2SO_4 (10 mL) was added a freshly prepared aqueous solution of ammonium persulfate (3 mmol) dropwise during 20 minutes at room temperature. The reaction was allowed to stir for an additional 3 h. The reaction mixture was poured onto ice and made alkaline with 30% NH_4OH solution. The resulting mixture was extracted with ethyl acetate (3 x 25 mL), washed with brine (2 x 10 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* to afford crude **19**, which was purified by chromatography over silica [ethyl acetate:hexanes (7:3)].

Yield 18%; mp 102-103 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 6H, 2 x CH_3), 3.0 (m, 1H, CH), 3.30 (m, 1H, CH), 3.74 (m, 1H, CH), 3.79 (s, 3H, CH_3), 4.28 (m, 1H, CH), 5.96 (bs, 1H, NH), 6.70 (s, 1H, 1-H); analysis for $C_{11}H_{15}N_3O_3$ (237.3), calcd, C, 55.69; H, 6.37; N, 17.71; found, C, 55.75; H, 6.34; N,17.63; MS(CI-NH_3) m/z 238(M+1); $[\alpha]_D^{20}$ +33.2° (c=1.0, CH_3OH).

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