and the mixture was heated at reflux for 6 h. During the initial heating a precipitate formed which slowly redissolved. The cooled reaction was diluted with water (250 mL) and twice extracted with CH_2Cl_2 and filtered. The aqueous filtrate was evaporated in vacuo, giving the crude amino acid hydrochloride. This was recrystallized from acetone/ether. Yields were 60–85%: mp 266–267 °C dec; IR (KBr) 3650–2300 (br), 1731 (s), 1497 (s) cm^{-1}. Anal. Calcd for $C_{10}H_{10}FNO_3$·HCl: C, 48.50; H, 4.48; N, 5.66. Found: C, 48.37; H, 4.51; N, 5.54. Similar hydrolysis of 4-acetamido-2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-carboxylic acid (*N*-acetyl-**5**) gave **5** in 88% yield.

(4*R*,*S*)-Amino-2,3-dihydro-6-fluoro-2(*R*)-methyl-4*H*-1-benzopyran-4-carboxylic Acid (*rac*-18). *rac*-**14** (3 g, 0.01 mol) was refluxed in a mixture of formic acid (10 mL) and concentrated HCl (10 mL). The reaction was evaporated to dryness and the residue dissolved in water and extracted twice with ether. The aqueous layer was adjusted to pH 5 with 1 N NaOH and evaporated to a solid. Recrystallization from acetone gave *rac*-**18**, 1 g, 46% yield: mp 229–233 °C; IR (KBr) 1624 (s), 1564 (s), 1489 (s), 1444 (m) cm^{-1}; NMR (D_2O, 250 MHz) δ 7.25–6.9 (m, 3), 4.35 (m, 0.5), 2.7–2.28 (m, 2), 1.5 (d, 1.5), 1.48 (d, 1.5).

2,3-Dihydro-6-fluoro-4*H*-ureido-1-benzopyran-4-carboxylic Acid (16).[19] Crude **5**·HCl (0.12 mol) was dissolved in water (100 mL) and 6 N NaOH added to give pH 6. Sodium cyanate (16.4 g, 0.25 mol) was added in one portion and the reaction stirred overnight at room temperature. The reaction was filtered to remove a haze and the solution was then acidified to pH 3 with 6 N HCl to precipitate **16** as a white solid, which was dried in vacuo; 24.32 g, 76% yield from **10b**: mp 189–191 °C dec; IR (KBr) 3466 (s), 3382 (s), 1721 (s), 1645 (s), 1562 (s), 1537 (s), 1496 (s) cm^{-1}.

Methyl (4*R*,*S*)-amino-2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-carboxylate (*rac*-15) was prepared from **5** (15 g, 0.17 mol) according to Brenner[18] with thionyl chloride (9 mL) in methanol (75 mL) and crystallized from ether as the hydrochloride, 18 g, 97% yield, mp 200–202 °C dec. This was dissolved in water (60 mL) and extracted into ethyl acetate after adjusting the aqueous solution to pH 10. The organics were dried over $MgSO_4$, evaporated in vacuo, and crystallized from hexanes, 11.7 g, 73% yield: mp 64–65.5 °C; NMR ($CDCl_3$, 60 MHz) δ 7.0 (m, 3), 4.4 (m, 2), 3.8 (s, 3), 2.8–2.3 (m, 1), 2.1–1.7 (m and s (NH_2), 3). Anal. Calcd for $C_{11}H_{12}FNO_3$: C, 58.66; H, 5.37; N, 6.22. Found: C, 58.48; H, 5.24; N, 6.08.

In a similar manner was obtained methyl (4*R*,*S*)-amino-2,3-dihydro-6-fluoro-2(*R*)-methyl-4*H*-1-benzopyran-4-carboxylate (*rac*-**18**) as an oil in 51% yield from **14**: IR ($CHCl_3$) 2947 (w), 1732 (s), 1484 (s), 1425 (s) cm^{-1}; NMR ($CDCl_3$, 60 MHz) δ 7.5–8.3 (m, 3), 4.6 (m, 1), 3.8 (s, 3), 2.65–1.65 (m, 4), 1.5 and 1.4 (dd, 3); mass spectrum, *m/e* 239 (M^+), 180 ($M^+ - CO_2CH_3$). A sample was analyzed as its *d*-di(*p*-toluoyl)tartaric acid salt from ethyl acetate. Anal. Calcd for $C_{32}H_{32}FNO_{11}$: C, 61.44; H, 5.12; N, 2.24. Found: C, 61.15; H, 5.21; N, 2.04.

Methyl (4*S*)-Amino-2,3-dihydro-6-fluoro-4*H*-1-benzopyran-4-carboxylate ((*S*)-15). *rac*-**15** (11.5 g, 0.051 mol) was dissolved in 0.125 N sodium chloride solution (100 mL) by the addition of 6 N HCl to pH 5. α-Chymotrypsin (0.75 g) was added to the mixture. After stirring at 20 °C for several hours, hydrolysis commenced and the pH was maintained at pH 5 by a pHstat (0.5 N NaOH). When 0.5 molar equiv had been taken up hydrolysis ceased (48 to 60 h). The reaction was acidified to pH 2 and stirred for 3 h with activated carbon (1 g) and then filtered and extracted with ethyl acetate. The aqueous layer was adjusted to pH 10 with 6 N NaOH and extracted with ethyl acetate (3 × 100 mL). The resolved ester was recovered from the organic solution as a colorless oil, 4.17 g, 36% yield: $[\alpha]_D$ +51.2° (*c* 0.64, $CHCl_3$); spectral data identical with racemic. Similar treatment of *rac*-**18** gave (4*S*)-**18** in 38% yield as a colorless oil: $[\alpha]_D$ +132.2° (*c* 0.69, $CHCl_3$); NMR ($CDCl_3$, 60 MHz) δ 7.4–6.8 (m, 3), 4.8–4.2 (m, 1), 3.8 (s, 3), 2.5/2.3 (dd, 1), 2.1 (s, 2), 1.8 (d, 1), 1.35 (d, 3).

Sorbinil (1). (*S*)-**15** (4.17 g, 0.019 mol) and sodium cyanate (2.55 g, 0.0392 mol) were stirred in glacial acetic acid (40 mL) at room temperature for 24 h. The solution was heated to 90 °C for 3 h, cooled, and concentrated to a low volume. Addition of water precipitated **1**, which was crystallized from 2-propanol, 2.58 g, 61% yield: mp 240–241 °C; $[\alpha]_D$ +54.1° (*c* 0.9, MeOH) [lit.[2] $[\alpha]_D$ +54.0° (MeOH)].

In the same manner, (2*R*,4*S*)-**18** (1.84 g, 0.0077 mol) and sodium cyanate (1.0 g, 0.015 mol) gave **2** in 79% yield: mp 231–234 °C (from acetone/hexanes); $[\alpha]_D$ +212.2° (*c* 0.55, MeOH) [lit.[25] $[\alpha]_D$ +226.3° (MeOH)]; NMR (Me_2SO-d_6, 250 MHz) δ 8.4 (s, 1), 7.1 (dt, 1), 6.9 (m, 2), 4.8 (m, 1), 3.4 (br s, 1), 2.3 (d, 1), 1.85 (t, 1), 1.35 (d, 3); mass spectrum, *m/e* 250 (M^+), 207 (M^+ – HNCO).

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Phenacyl-Directed Alkylation of Imidazoles: A New Regiospecific Synthesis of 3-Substituted L-Histidines

Cleo J. Chivikas and John C. Hodges*

Warner-Lambert/Parke Davis Pharmaceutical Research, Ann Arbor, Michigan 48105

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A new strategy for regiospecific imidazole alkylation of suitably protected histidines is described wherein a phenacyl group serves as a protecting group of the distal imidazole nitrogen atom. Alkylation of *N*-BOC-1-phenacyl-L-histidine methyl ester at N(3), followed by reductive removal of the phenacyl group from N(1) of the resulting imidazolium intermediate with zinc and acetic acid offers an efficient and flexible route to 3-substituted L-histidines.

Introduction

The frequent location of a histidine residue at catalytic sites of enzymes as well as the essential presence of histidine in certain peptide hormones has led us to investigate modified versions of the natural amino acid which when incorporated in peptides or modified peptides might afford enzyme inhibitors or hormone antagonists. Our initial studies led to the synthesis of 3-substituted histidines by alkylation of *N*,1-bis(BOC)histidine methyl ester (**1**) with alkyl and aryl sulfonates (Scheme I).[1] Although this route provides a wide variety of 3-substituted histidines, it has limitations. Secondary alkyl groups and certain benzyl groups with multiple electron-donating functions cannot be installed at N(3) by this method. We reasoned that part of the difficulty in these cases is that the BOC-protected imidazole, being a very poor nucleophile, requires highly

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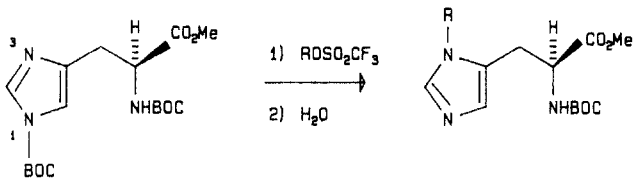
Scheme I. Alkylations of *N*,1-Bis-BOC-L-histidine Methyl Ester



1 2

Table I. Phenacyl-Directed Histidine Alkylations

entry	R′-X	N-Boc-Methyl ester (% yield)	parent histidine (% yield)
a	$PhCH_2Br$	**5** (82)	**11** (89)
b	$PhCH(CH_3)Br$	**6** (33)	**12** (79)
c	$(Ph)_2CHBr$	**7** (50)	**13** (85)
d	$3,4\text{-}(MeO)_2PhCH_2Cl$	**8** (52)	**14** (90)
e	$n\text{-}C_4H_9I$	**9** (69)	**15** (79)
f	$n\text{-}C_4H_9Br$	**9** (56)	**15** (79)
g	$n\text{-}C_4H_9Cl$	**9** (0)	
h	c-HexBr	**10** (0)	
i	c-HexI	**10** (0)	

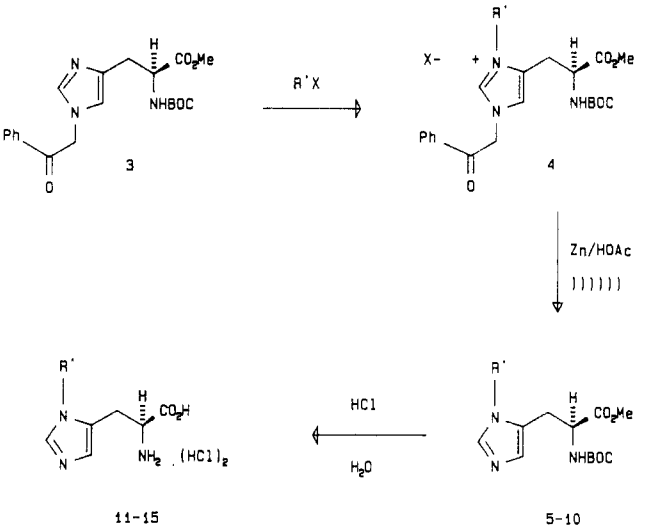
activated alkylating agents. In the cases described above the reason for the failure of the alkylation step is probably that the respective triflates or mesylates are not stable under the conditions required for alkylation.

In order to circumvent this difficulty we searched for an imidazole-protecting group which would be less electron withdrawing than a BOC group and could be regiospecifically attached at N(1). A limited number of protection–alkylation–deprotection strategies for the modification of imidazoles that utilize nonacyl protecting groups have been reported in the literature. Included are acid labile blocking groups such as methoxymethyl (MOM),[2] (pivaloyloxy)methyl (POM),[3,4] and triphenylmethyl.[5,6] In addition, we have found the phenacyl group[7] to be particularly useful. Thus, when *N*-BOC-1-phenacyl-L-histidine methyl ester (**3**) is treated with benzyl or alkyl halides, alkylation occurs at N(3) to afford an imidazolium salt (**4**, Scheme II). A solution of this salt in methanol–acetic acid is then sonicated in the presence of zinc powder to effect the reductive cleavage of the phenacyl group, giving a variety of 3-substituted histidines in good overall yield (Table I).

Results and Discussion

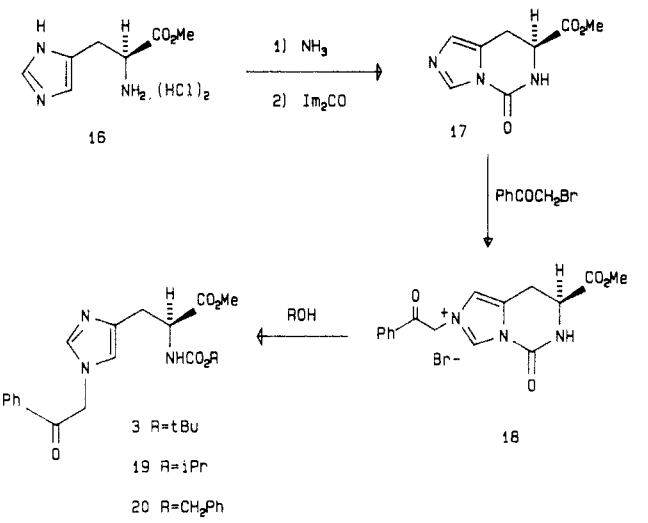
The regiospecific introduction of 1-phenacyl and *N*-BOC protecting groups on histidine methyl ester is accomplished according to Scheme III. Commercially available L-histidine methyl ester dihydrochloride (**16**) is first converted to the free base by treatment with anhydrous ammonia in chloroform and is then treated with *N,N*-carbonyldiimidazole in dichloromethane to afford the cyclic urea **17** as a crystalline solid. Subsequent treatment of **17** with phenacyl bromide in refluxing acetonitrile affords **18** as a solid that precipitates directly from the reaction mixture in analytically pure form. This salt is minimally

Scheme II. Alkylations of *N*-BOC-1-phenacyl-L-histidine Methyl Ester



3 4 11-15 5-10

Scheme III. Synthesis of *N*-BOC-1-phenacyl-L-histidine Methyl Ester



16 17 18

3 R=tBu
19 R=iPr
20 R=CH_2Ph

hygroscopic and can be stored in a tighly sealed bottle at room temperature for months with no evidence of decomposition. Prolonged heating of a solution of **18** in dry *tert*-butyl alcohol in the presence of 1 equiv of diisopropylethylamine cleaves the urea, affording *N*-BOC-1-phenacyl-L-histidine methyl ester (**3**). Substitution of dry 2-propanol for *tert*-butyl alcohol affords the corresponding 2-propyl carbamate **19** in less than an hour. Similarly, the corresponding carbobenzyloxy (Cbz) adduct **20** is available by treatment with excess benzyl alcohol and 1 equiv of diisopropylethylamine in refluxing tetrahydrofuran.

Compound 3 reacts smoothly with many commercially available benzyl and alkyl halides when refluxed in acetonitrile solution for a period of 12–48 h (Table I). In all cases studied the resulting imidazolium salt intermediates were not crystalline compounds; however, they could be conveniently isolated in crude form by dropwise addition of the acetonitrile solution into vigorously stirred diethyl ether and filtration of the resultant precipitate. Attempts to further purify these intermediates generally resulted in substantial losses of the desired material. The crude imidazolium salts were used directly in the reductive cleavage without rigorous characterization. Treatment with acetic acid–methanol (1:1) and a large excess of zinc dust gives the desired 3-substituted histidine derivatives **5–9** after chromatography to remove acetophenone and other un-

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identified minor byproducts. Ultrasonication of this reaction gives markedly superior results compared to heating the reaction mixture and reduction is not observed at room temperature. Polished zinc dust recovered from these sonicated reactions enhances the rate of subsequent reductions relative to the commercially available zinc dust.

The 3-substituted *N*-BOC-L-histidine methyl esters **5–9** were typically isolated as gums which were dried to constant weight at 0.5 mmHg and 25 °C. These materials were homogeneous by TLC and contained no visible impurities by NMR. For analytical purposes they were converted to the respective amino acid dihydrochlorides by treatment with refluxing 6 N hydrochloric acid (Table I).

With the exceptions of compounds **5** and **11**, the 3-substituted histidines reported in Table I are new chemical entities and reflect attempts to achieve alkylations that are not possible using the previously mentioned bis(BOC)histidine and sulfonate methodology.[1] We found that it is possible to alkylate with secondary alkyl halides so long as they are benzylic. Attempts to alkylate with less reactive secondary halides such as cyclohexyl bromide and cyclohexyl iodide, however, were unsuccessful. With primary alkyl halides the expected order of reactivity was observed (Cl < Br < I). Primary alkyl iodides are the reagent of choice over alkyl bromides, whereas alkyl chlorides were found to be unreactive. Both benzyl chlorides and bromides were found to be sufficiently reactive in the alkylation step. Success was also achieved with electron-rich benzyl halides such as 3,4-dimethoxybenzyl chloride, a transformation which is not possible by the bis(BOC)histidine and sulfonate methodology. The optical purity of the final products has not been rigorously established; however, the observed rotations for compounds **11** and **20** are consistent with the literature values (see Experimental Section), and thus this method presumably affords optical purity comparable to the state of the art.

In summary, alkylation of *N*-BOC-1-phenacyl-L-histidine methyl ester followed by reductive removal of the phenacyl protecting group and acidic hydrolysis is a flexible and efficient route to 3-substituted L-histidines and is the method of choice for introduction of secondary benzylic alkyl groups and electron-rich benzyl substituents. Additionally, where the cost of reagents is of concern this route uses commercially available and inexpensive alkylating agents and thereby may be of advantage compared to in situ generation of triflates and mesylates as described in previous methodology.

Experimental Section

General. All reagents were of commercial quality from freshly opened containers. L-histidine methyl ester dihydrochloride, carbonyldiimidazole, alkyl halides, and phenacyl bromide were purchased from Aldrich Chemical Co. Reagent quality solvents were used without further purification. Analytical TLC plates and silica gel (230–400 mesh) were purchased from EM Reagents. Melting points were taken by using a MelTemp apparatus and are uncorrected. All temperatures are reported in degrees Celsius, and pressures are reported in mmHg. Room temperature is 25 ± 3 °C. Elemental analyses were obtained by using Perkin-Elmer 240 elemental analyzer and observed rotations at the Na D line were obtained at 25 °C by using a Perkin-Elmer 141 polarimeter. Proton NMR (^{1}H NMR) spectra were obtained using either a Varian XL 200-MHz spectrometer (for final products) or a Varian EM-390 90-MHz spectrometer (for intermediates) and are reported in ppm downfield from Me_4Si. IR spectra were obtained with samples prepared as KBr pellets by using a Nicolet IR80 spectrometer and are reported in cm^{-1}. Mass spectra were obtained by using a VG model 7070E/HF spectrometer with either DEI or FAB ionization and are reported in atomic mass units. A branson Model B-12 ultrasonic cleaner was used in ultrasonicated reactions.

(*S*)-Methyl 5,6,7,8-Tetrahydro-5-oxoimidazo[1,5-*c*]pyrimidine-7-carboxylate (17). A suspension of L-histidine methyl ester dihydrochloride (12.1 g, 50 mmol) in chloroform (150 mL) was treated at 0 °C with a vigorous stream of anhydrous ammonia for 15 min. The resulting suspension was stirred an additional 15 min and filtered, and the filtrate was evaporated to give L-histidine methyl ester as an oil. This oil was dissolved in dichloromethane (100 mL) and added dropwise to a refluxing solution of carbonyl diimidazole (8.12 g, 50 mmol) in dichloromethane (150 mL). Refluxing was continued 15 min after completion of addition then the reaction mixture was cooled to room temperature and concentrated at reduced pressure until it began to crystallize. Ethyl ether was added dropwise until a thick slurry formed then an additional 200 mL was added, and the solid was collected by filtration. Recrystallization from acetonitrile gave **17** (6.2 g, 64%) as off-white crystals, mp 159–164 °C. This material is suitable for use in the next step without further purification. An analytical sample was prepared by repeating the recrystallization: mp 167–168 °C (lit.[8] mp 166–168 °C); ^{1}H NMR ($CDCl_3$ + Me_2SO-d_6) 8.07 (s, 1 H, H-3), 7.84 (br, 1 H, NH), 6.80 (s, 1 H, H-1), 4.30 (d of t, 1 H, CH), 3.72 (s, 3 H, OMe), 3.23 (d, 2 H, CH_2); IR 1758 (CO_2Me), 1720 (NCON). Anal. Calcd for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.24; H, 4.37; N, 21.69. $[\alpha]^{25}_D$ +59.3° (c 1.10, MeOH) [lit.[9] $[\alpha]^{25}_D$ +59° (*c* 1.10, MeOH)].

(*S*)-5,6,7,8-Tetrahydro-7-(methoxycarbonyl)-5-oxo-2-(2-oxo-2-phenylethyl)imidazo[1,5-*c*]pyrimidinium Bromide (18). A mixture of **17** (7.8 g, 40 mmol), phenacyl bromide (8.0 g, 40.2 mmol), and acetonitrile (200 mL) was heated at reflux 6 h. The resulting suspension was cooled to room temperature and filtered to afford **18** (14.9 g, 95%) as analytically pure material: mp 223–224 °C (decomposes with gas evolution); ^{1}H NMR (Me_2SO-d_6) 9.77 (s, 1 H, H-3), 9.63 (d, 1 H, NH), 8.07 (d, 2 H, Ar), 7.80 (t, 1 H, Ar), 7.68 (s, 1 H, H-1), 7.63 (t, 2 H, Ar), 6.10 (s, 2 H, $COCH_2$), 4.75 (q, 1 H, CH), 3.70 (s, 3 H, OMe), 3.45 (d, 2 H, CH_2); IR 1776 (NCON + CO_2Me), 1741 (CO). Anal. Calcd for $C_{16}H_{16}BrN_3O_4$: C, 48.75; H, 4.09; N, 10.66; Br, 20.27. Found: C, 48.95; H, 4.12; N, 10.88; Br, 20.13. Solubility in suitable solvents was too low to obtain a rotation.

***N*-(*tert*-Butoxycarbonyl)-1-(2-oxo-2-phenylethyl)-L-histidine, Methyl Ester (3).** A suspension **18** (10.0 g, 25.4 mmol) in *tert*-butyl alcohol (250 mL) was treated with diisopropylethylamine (4.5 mL, 25.8 mmol) under nitrogen atmosphere and heated at reflux for 5 days or until solution occurred. The solvent was evaporated at reduced pressure, and the residue was partitioned between dichloromethane (500 mL) and water (200 mL). The organic layer was washed with a potassium phosphate buffer (pH 7, 0.25 M, 200 mL), dried over magnesium sulfate, and concentrated at reduced pressure to give a yellow gum. Flash chromatography on silica gel (chloroform to chloroform–methanol 98:2) gave **3** (8.4 g, 85%) as a light yellow foam after drying 24 h, at 1.0 mm, room temperature: ^{1}H NMR ($CDCl_3$) 7.85 (d, 2 H, Ar), 7.50 (m, 3 H, Ar), 7.31 (s, 1 H, 2-imidazole), 6.64 (s, 1 H, 5-imidazole), 5.80 (br, 1 H, NH), 5.22 (s, 2 H, $COCH_2$), 4.47 (m, 1 H, CH), 3.61 (s, 3 H, OMe), 3.00 (d, 2 H, CH_2), 1.40 (s, 9 H, *t*-Bu); IR 2990 (NH), 1705 (CO); MS (DEI), 387 (M).

***N*-(2-Propyloxycarbonyl)-1-(2-oxo-2-phenylethyl)-L-histidine, Methyl Ester (19).** A solution of **18** (1.0 g, 2.5 mmol) in anhydrous 2-propanol (25 mL) was treated with diisopropylethylamine (0.45 mL, 2.58 mmol) and heated at reflux 1 h until solution occurred. Workup and chromatography was performed as for **3** above to give **19** as a gum (870 mg, 92%): ^{1}H NMR ($CDCl_3$) 7.88 (d, 2 H, Ar), 7.52 (d, 2 H, + t, 1 H, Ar), 7.30 (s, 1 H, 2-imidazole), 6.64 (s, 1 H, 5-imidazole), 6.17 (d, 1 H, NH), 5.25 (s, 2 H, $COCH_2$), 4.79 (p, 1 H, OCH), 4.49 (m, 1 H, NCH), 3.60 (s, 3 H, OMe), 2.97 (d, 2 H, CH_2), 1.17 (d, 6 H, Me_2); IR 2990 (NH), 1705 (CO); MS (DEI), 373 (M).

***N*-(Benzyloxycarbonyl)-1-(2-oxo-2-phenylethyl)-L-histidine, Methyl Ester (20).** A suspension of **18** (2.0 g, 5.1 mmol) in dry THF (50 mL) was treated with diisopropylethylamine (0.88 mL, 5.1 mmol) and anhydrous benzyl alcohol (6.3 mL, 60.9 mmol). The mixture was heated at reflux for 16 h and filtered, and workup was performed as for **3** above to give **20** as a slightly

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colored gum after chromatography (2.1 g, 96%). Crystallization was induced by dissolving the gum in toluene and evaporating to a gum once again. This gum was allowed to stand 2 weeks at room temperature, and the resulting crystalline mass was triturated with ether to afford an analytical sample: mp 71–74 °C (lit.[2] mp 67–70 °C); ^{1}H NMR ($CDCl_3$) 7.96 (d, 2 H, Ar), 7.68 (t, 1 H, Ar), 7.54 (t, 2 H, Ar), 7.35 (m, 6 H, Ar + 2-imidazole), 6.70 (s, 1 H, 5-imidazole), 6.31 (d, 1 H, NH), 5.31 (s, 2 H, $COCH_2$), 5.12 (s, 2 H, OCH_2), 4.64 (m, 1 H, CH), 3.72 (s, 3 H, OMe), 3.12 (m, 2 H, CH_2), 1.70 (2 H, H_2O); IR 3300 (H_2O), 3034 (NH), 1706 (CO); MS (DEI), 421 (M). Anal. Calcd for $C_{23}H_{23}N_3O_5 \cdot H_2O$: C, 62.86; H, 5.50; N, 9.56. Found: C, 62.79; H, 5.59; N, 9.48. $[\alpha]^{25}_D$ +21.2° (c 1.10, $CHCl_3$) [lit.[2] $[\alpha]^{25}_D$ +20.8 (c 1.00, $CHCl_3$)].

Preparation of 3-Substituted L-Histidines: Representative Procedures and Physical Data. ***N*-(*tert*-Butoxycarbonyl)-3-[(3,4-dimethoxyphenyl)methy]-L-histidine, Methyl Ester (8).** A solution of **3** (2.0 g, 5.2 mmol) in acetonitrile (60 mL) was treated with 3,4-dimethoxybenzyl chloride (1.4 g, 7.7 mmol) and heated at reflux for 24 h. The reaction mixture was concentrated to approximately 20 mL at reduced pressure and added dropwise to vigorously stirred anhydrous ethyl ether (250 mL). The resulting precipitate (2.7 g) was collected under a stream of nitrogen, dissolved in methanol (35 mL) and treated with glacial acetic acid (35 mL) and zinc powder (7.3 g). These materials were sonicated at ambient bath temperature with vigorous mechanical stirring under nitrogen atmosphere for 7 h. The reaction mixture was filtered to remove excess zinc powder. The filtrate was diluted with dichloromethane (300 mL) and neutralized by dropwise addition of 10% aqueous sodium carbonate (300 mL). The dichloromethane layer was dried over magnesium sulfate and evaporated to give a light orange gum which was purified by flash chromatography on silica gel (chloroform to 1% methanol in chloroform) to yield **8** as a slightly colored gum (1.1 g, 52%): ^{1}H NMR ($CDCl_3$) 7.37 (s, 1 H, 2-imidazole), 6.76 (m, 2 H, 5-imidazole + Ar), 6.58 (m, 2 H, Ar), 5.13 (m, 1 H, NH), 4.91 (s, 2 H, CH_2Ar), 4.40 (m, 1 H, CH), 3.76 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.63 (s, 3 H, CO_2CH_3), 2.92 (d, 2 H, CH_2), 1.37 (s, 9 H, *t*-Bu).

***N*-(*tert*-Butoxycarbonyl)-3-(phenylmethyl)-L-histidine, Methyl Ester (5)**: ^{1}H NMR ($CDCl_3$) 7.41 (s, 1 H, 2-imidazole), 7.30 (m, 3 H, Ar), 7.04 (m, 2 H, Ar), 6.83 (s, 1 H, 5-imidazole), 5.07 (m, 3 H, CH_2Ph + NH), 4.57 (m, 1 H, CH), 3.70 (s, 3 H, CO_2CH_3), 2.95 (m, 2 H, CH_2), 1.40 (s, 9 H, *t*-Bu).

***(RS)*-*N*-(*tert*-Butoxycarbonyl)-3-(1-phenylethyl)-L-histidine, Methyl Ester (6)**: ^{1}H NMR ($CDCl_3$) 7.65 (d, 1 H, 2-imidazole), 7.28 (m, 3 H, Ar), 7.02 (t, 2 H, Ar), 6.82 (d, 1 H, 5-imidazole), 5.34 (m, 2 H, CHPh + NH), 4.50 (m, 1 H, CH), 3.64 (s, 3 H, CO_2CH_3), 2.90 (d, 2 H, CH_2), 1.85 (d, 3 H, CH_3), 1.41 (s, 9 H, *t*-Bu).

***N*-(*tert*-Butoxycarbonyl)-3-(diphenylmethyl)-L-histidine, Methyl Ester (7)**: ^{1}H NMR ($CDCl_3$) 7.30 (m, 7 H, 2-imidazole + Ar), 7.04 (m, 4 H, Ar), 6.78 (s, 1 H, 5-imidazole), 6.40 (s, 1 H, $CHPh_2$), 5.23 (m, 1 H, NH), 4.50 (m, 1 H, CH), 3.67 (s, 3 H, CO_2CH_3), 2.90 (d, 2 H, CH_2), 1.37 (s, 9 H, *t*-Bu).

***N*-(*tert*-Butoxycarbonyl)-3-butyl-L-histidine, Methyl Ester (9)**: ^{1}H NMR ($CDCl_3$) 7.33 (s, 1 H, 2-imidazole), 6.67 (s, 1 H, 5-imidazole), 5.12 (d, 1 H, NH), 4.43 (m, 1 H, CH), 3.73 (t, 2 H, NCH_2), 3.68 (s, 2 H, CO_2CH_3), 3.00 (d, 2 H, CH_2), 1.60 (m, 2 H, CH_2), 1.40 (s, 9 H, *t*-Bu), 1.24 (m, 2 H, CH_2), 0.91 (t, 3 H, CH_3).

3-[(3,4-Dimethoxyphenyl)methyl]-L-histidine, Dihydrochloride (14). Compound **8** (1.05 g, 2.50 mmol) was heated in refluxing 6 N HCl (100 mL) for 1.5 h. The resulting solution was evaporated at reduced pressure to give a gum which was dissolved in absolute ethanol (100 mL), concentrated to approximately 10 mL at reduced pressure and added dropwise to vigorously stirred ethyl acetate (300 mL). The precipitate was collected by filtration under a stream of nitrogen and dried (60°, 25 mm, overnight) to afford **14** (0.69 g, 90%) as a hygroscopic solid: mp 83–110 °C (glass); ^{1}H NMR (D_2O) 8.73 (s, 1 H, 2-imidazole), 7.54 (s, 1 H, 5-imidazole), 7.08 (m, 3 H, Ar), 5.42 (s, 2 H, CH_2Ar), 3.88 (s, 3 H, OMe), 3.86 (s + m, 4 H, OMe + CH), 3.36 (m, 2 H, CH_2); IR 3400 (OH), 2890 (NH), 1780 (CO); MS (FAB), 306 (M + 1). Anal. Calcd for $C_{15}H_{19}N_3O_4 \cdot 2HCl \cdot 0.5H_2O$: C, 46.52; H, 5.72; N, 10.85. Found: C, 46.79; H, 5.51; N, 10.67. $[\alpha]^{25}_D$ +0.55, (c 2.20, H_2O).

3-(Phenylmethyl)-L-histidine, Dihydrochloride (11): mp 201–210 °C (dec) (lit.[1] 199–210 °C (dec)); ^{1}H NMR (D_2O) 8.79 (s, 1 H, 2-imidazole), 7.47 (m, 4 H, 5-imidazole + Ar), 7.35 (m, 2 H, Ar), 5.50 (s, 2 H, CH_2Ph), 3.86 (t, 1 H, CH), 3.30 (m, 2 H, CH_2); IR 3400 (OH), 2880 (NH), 1745 (CO); MS (DEI), 246 (M + 1). Anal. Calcd for $C_{13}H_{15}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 47.71; H, 5.54; N, 12.84. Found: C, 47.52; H, 5.67; N, 12.66. $[\alpha]^{26}_D$ +7.2 (c 2.04, H_2O) [lit.[1] $[\alpha]^{25}_D$ +6.5 (c 2.0, H_2O)].

3-(1-Phenylethyl)-L-histidine, Dihydrochloride (12): mp 89–110 °C (glass); ^{1}H NMR (D_2O) 9.12 (d, 1 H, 2-imidazole), 7.61 (m, 4 H, 5-imidazole + Ar), 7.41 (m, 2 H, Ar), 5.82 (m, 1 H, CHPh), 4.0-3.1 (complex, 3 H, CH + CH_2), 2.02 (d, 3 H, CH_3); IR 3400 (OH), 2890 (NH), 1745 (CO); MS (FAB) 260 (M + 1). Anal. Calcd for $C_{14}H_{17}N_3O_2 \cdot 2HCl \cdot 1.5H_2O$: C, 46.81; H, 5.75; N, 11.84. Found: C, 46.54; H, 5.60; N, 11.95. $[\alpha]^{25}_D$ +4.41 (c 2.04, H_2O).

3-(Diphenylmethyl)-L-histidine, Dihydrochloride (13): mp 85–100 °C (glass); ^{1}H NMR (D_2O) 8.29 (d, 1 H, 2-imidazole), 7.64 (s, 1 H, 2-imidazole), 7.53 (m, 6 H, Ar), 7.28 (m, 4 H, Ar), 7.04 (s, 1 H, $CHPh_2$), 3.82 (d of d, 1 H, CH), 3.27 (d of q, 2 H, CH_2); IR 3400 (OH), 2900 (NH), 1747 (CO); MS (DEI), 322 (M + 1). Anal. Calcd for $C_{19}H_{19}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 56.58; H, 5.00; N, 10.42. Found: C, 56.56; H, 5.37; N 10.75. $[\alpha]^{25}_D$ +1.43 (c 2.03, H_2O).

3-Butyl-L-histidine, Dihydrochloride (15): mp 174–188 °C; ^{1}H NMR (D_2O) 8.78 (s, 1 H, 2-imidazole), 7.47 (s, 1 H, 5-imidazole), 4.28 (t, 1 H, CH), 4.20 (t, 2 H, NCH_2), 3.43 (d of q, 2 H, CH_2), 1.86 (m, 2 H, CH_2), 1.39 (m, 2 H, CH_2), 0.95 (t, 3 H, CH_3); IR 3400 (OH), 2900 (NH), 1747 (CO); MS (DEI), 212 (M + 1). Anal. Calcd for $C_{10}H_{17}N_3O_2 \cdot 2HCl \cdot 1.75H_2O$: C, 38.04; H, 7.18; N, 13.31. Found: C, 38.36; H, 6.85; N, 13.40. $[\alpha]^{25}_D$ +10.2 (c 2.18, H_2O).

Registry No. **3**, 109013-55-0; **4** (R′ = CH_2-3,4-$(MeO)_2C_6H_4$, X = Cl), 109013-69-6; **5**, 109013-56-1; (*R*)-**6**, 109013-57-2; (*S*)-**6**, 109013-68-5; **7**, 109013-58-3; **8**, 109013-59-4; **9**, 109013-60-7; **11**, 109013-61-8; **12**, 109013-62-9; **13**, 109034-01-7; **14**, 109013-63-0; **15**, 109013-64-1; **16**, 7389-87-9; **17**, 109013-65-2; **18**, 109013-66-3; **19**, 109013-67-4; **20**, 68262-62-4; H-His-OMe, 1499-46-3; $PhCOCH_2Br$, 70-11-1; $PhCH_2Br$, 100-39-0; (*RS*)-PhCHMeBr, 38661-81-3; Ph_2CHBr, 776-74-9; BuI, 542-69-8; BuBr, 109-65-9; *t*-BuOH, 75-65-0; *i*-PrOH, 67-63-0; $PhCH_2OH$, 100-51-6; 3,4-dimethoxybenzyl chloride, 7306-46-9.