A Novel Stereoselective Route to (S)-(+)-α-(Fluoromethyl)histidine: α-Halomethylation of (2R,4S)-3-Benzoyl-2-(1,1-dimethylethyl)-1-methyl-4-[(N-tritylimidazol-4'-yl)methyl]-1,3-imidazolidin-5-one. Synthesis and ^{1}H NMR Spectroscopy

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A method is described for the α-enantioretentive methylation of L-histidine (S) to give (S)-(+)-α-(fluoromethyl)histidine (8). The synthesis involves the conversion of N_{im}-trityl-L-histidine methyl ester (1) to both the "*trans*"-(2S,4S)- and "*cis*"-(2R,4S)-2-(1,1-dimethylethyl)-1-methyl-1,3-imidazolidin-5-one analogs 4 and 5. The cis isomer was regioselectively alkylated with chlorofluoromethane to give a single diastereomer 6 with retention of the original absolute configuration of the histidine α-position (S). Deprotection and hydrolysis of the 1,3-imidazolidin-5-one intermediate 6 yielded the desired (S)-(+)-α-(fluoromethyl)histidine (8). Additionally, this reaction sequence was repeated using bromochloromethane as the alkylating agent to yield (S)-(+)-α-(chloromethyl)histidine (8a). Yields of this product, however, were very low due to an intramolecular alkylation reaction to give 3-benzoyl-2-(1,1-dimethylethyl)-1-methylspiro[imidazolidine-4,6'(7'H)-[5H]pyrrolo[1,2-c]imidazol]-5-one (9). The structure and stereochemistry of the trans and cis 1,3-imidazolidin-5-one intermediates, as well as other members of the series, were confirmed using ^{1}H NMR spectroscopy, including two-dimensional NOE correlation spectroscopy (2D NOESY). The existence of slow chemical exchange in solution was detected for several members of the series based on the appearance of both positive and negative cross-peaks in the 2D NOESY spectra.

Introduction

(R,S)-α-(Fluoromethyl)histidine is an irreversible inhibitor of histidine decarboxylase, with the (S)-(+)-stereoisomer 8 responsible for biological activity as an antihistamine agent in the treatment of mastocytosis.[1] An established synthesis of 8 from L-histidine via a Schiff's base followed by alkylation[2] is nonideal because it leads to a 1:1 mixture of enantiomers and requires a difficult chiral separation step.[3] For large-scale preparations, the use of expensive chlorofluoromethane for alkylation can only be considered economical if a useful chiral synthesis is found. We report here a procedure for the enantioselective synthesis of (S)-(+)-α-(fluoromethyl)histidine which could be extended to the synthesis of other α-fluoromethylated amino acid analogs without the use of toxic fluorinating agents.[4]

Results and Discussion

Chemistry. As a basis for the enantioselective synthesis of 8 we chose the asymmetric 2-(1,1-dimethylethyl)-1-methyl-1,3-imidazolidin-5-one procedure for α-alkylation that has been used previously with other α-amino acids by Naef and Seebach.[5] The synthetic procedure is outlined in Scheme I. The N_{im}-trityl-protected L-histidine methyl ester 1 prepared according to the method of Stelakatos et al.[6] was converted to the methylamide 2, followed by condensation with pivaldehyde to yield the Schiff's base 3. The Schiff's base was cyclized with benzoic anhydride to give, after chromatographic separation, (2S,4S)- and (2R,4S)-1,3-imidazolidin-5-one 4 (26%) and 5 (61%) (referred to for convenience as the "trans" and the "cis" isomers, respectively). The *cis*-(2R,4S)-(−) isomer 5 was treated with LDA, followed by α-alkylation using chlorofluoromethane to yield a single diasteroisomer 6 in 94% yield. (In larger batches, the unwanted trans isomer 4 could be hydrolyzed to L-histidine for recycling.)

The synthesis of 6 from 5 involves abstraction of the hydrogen at position 4 by LDA to form the enolate anion, followed by attack of the haloalkyl electrophile. The regioselectivity of this reaction is due to steric hindrance of approach of the haloalkyl electrophile to the ring by the bulky *tert*-butyl moiety, resulting in attack only from the *Re*-face of the molecule (i.e., away from the *tert*-butyl group). The regioselectivity of alkylation leads to retention of the original L-histidine stereochemistry in the final product 8, which is obtained by deprotection of the imidazole ring followed by hydrolysis of the 1,3-imidazolidin-5-one ring using HCl. The optical purity of 8 was confirmed using measurements of optical rotation of the hydrochloride salt ($[\alpha]^{20}_D$ +16°); this result is consistent with the optical rotation reported by Kollonisch et al.[3] for (S)-(+)-α-(fluoromethyl)histidine.

The α-alkylation sequence was repeated using bromochloromethane with very low yield (19%) of the target (S)-(+)-α-(chloromethyl)histidine (8a). The low yield results from competing intramolecular alkylation of the imidazole ring by the α-chloromethyl moiety which occurs during hydrolysis of 7a. The side product 9 can be

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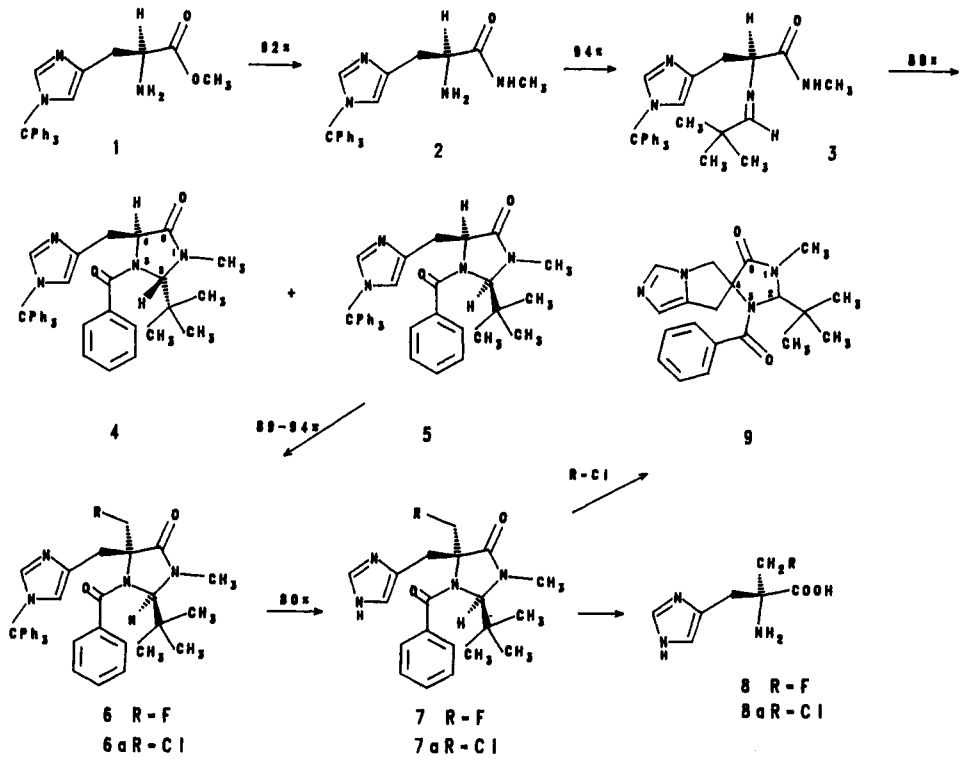
Scheme I



synthesized from **7a** under mild conditions. The structure of **9** was determined using both ^1H and ^{13}C NMR spectroscopic techniques. The appearance of this side-product in the α-chloromethyl series and not in the α-fluoromethyl series reflects the preference of chloro- versus fluoroalkanes to undergo alkylation reactions.

NMR Spectroscopy. The structure analysis of the nonalkylated and alkylated 1,3-imidazolidin-5-one products was performed using 1D and 2D ^1H NMR spectroscopy. In 2D NOE correlation spectroscopy[7] (NOESY) spectra, cross-peaks with frequency coordinates F_1, F_2 indicate that hydrogens which resonate at F_1 and F_2 are close in space (internuclear distance <4 or 5 Å).[8]

^1H NMR assignments were made using decoupling experiments and 2D correlation spectroscopy[9] (COSY). In the case of the fluoromethyl series, the nonequivalent-CH_2F hydrogens could be assigned (Table I) on the basis of the large (≈40 Hz) ^1H–^{19}F geminal spin–spin coupling constant. In the case of the chloromethyl series, this heteronuclear coupling is absent; consequently, the $-CH_2$-Cl and histidine β hydrogens are not readily assigned in the 1D ^1H NMR spectra. We have, however, successfully assigned the histidine β hydrogens of **6a** and **7a** on the basis of long-range coupling of these hydrogens to the hydrogen at position 4 of the imidazole ring. Although the small coupling between the histidine β CH_2 and imidazole H-4 hydrogens cannot be detected in the 1D spectra, this coupling can be observed using COSY optimized for small coupling constants (<1 Hz).[10]

The ^1H NMR chemical shift assignments for compounds **4** through **9** (Table I) were confirmed and the stereochemistry of compounds **4** through **7** was assigned using 2D NOESY experiments. The trityl and benzoyl hydrogens resonate between 7.9 and 7.0 ppm. Figure 1 shows F_2 cross-sections taken from ^1H pure-phase 2D NOESY spectra of **4** and **5**; the large positive resonance at ≈1 ppm in each cross-section (the two upper traces) corresponds to the diagonal peak of the *tert*-butyl hydrogens in the 2D spectra. The smaller negative cross-peaks indicate NOE's between the *tert*-butyl hydrogens and other hydrogens which are nearby in space. In Figure 1A, the NOE to H-4 indicates that this hydrogen is near the *tert*-butyl methyls; therefore, **4** must be the trans isomer. Similarly, Figure 1B shows the 2D NOESY cross-section for **5**. The negative peak at 3.18 ppm indicates that the histidyl β methylene hydrogens are near the *tert*-butyl methyls; therefore, **5** is the cis isomer. Other NOE's observed in these two molecules and other members of the series are summarized in Table II.

Analysis of the NOESY spectra of **6**, **6a**, **7**, and **7a** were additionally complicated by the presence of *Z* and *E* isomers due to restricted rotation about the exocyclic amide bond. This produces two sets of resonances in the ^1H NMR spectra (for example, see 1D spectrum in Figure 2). At higher temperatures (>340 K), rotation about the amide bond is rapid enough to cause coalescence of the two sets of peaks into a single set (data not shown). However, at room temperature, rotation occurs at an intermediate rate, producing additional cross-peaks due to rotational isomerism (chemical exchange)[7] in the NOESY spectra. Fortunately, for small molecules, exchange and NOE cross-peaks are of opposite sign[7], allowing the two types to be easily recognized.

The CH_2F region of the NOESY spectrum of **6** is shown in Figure 2B together with its corresponding 1D spectrum. The nonequivalent CH_2 peaks of the major rotamer are labeled A and X and those of the minor A′ and X′. The large splitting (40 Hz) is due to ^1H–^{19}F coupling. The

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Table I. ^{1}H NMR Chemical Shifts[a]

	compd							
	4	5	6	6a	7	7a	8	9[b]
^{1}H imidazolidinone ring								
1-CH_3	2.93	3.02	3.06	3.06	3.13	3.10[c]		3.14
						3.06		
2	5.28	5.55	5.72[d]	5.59[d]	5.82[c]	5.48[c]		5.89[d]
			5.27	5.32	5.42			5.40
2-$(CH_3)_3$	1.02	1.12	0.98	0.99	1.03	1.03		1.13
			0.81	0.80	0.81	0.79		0.85
4	4.49	4.07						
histidine β-CH_2								
A	3.14	3.18	3.04	3.17	3.87	3.91	2.93[e,f]	3.55
			3.24	3.36	3.26	3.30		
B	2.23	3.18	2.98	3.10	3.38	3.52	2.82	3.50
			3.53	3.65	3.17	3.38		
histidine α-CH_2X[g]								
A			4.56	3.93	5.06		4.66	4.28
			4.80	4.11	3.69			4.40
B			3.81	3.07	4.44		4.47	3.83
			5.37	4.80	4.29			3.83
imidazole ring								
2′	7.38	7.30	ovlp[h]	ovlp	ovlp	ovlp	ovlp	6.57
								6.78
5′	6.16	6.36	6.58	6.59	6.97	7.15	6.87	6.52
			6.68	6.70	6.66	6.83		7.40

[a] ppm relative to internal TMS; in $CDCl_3$, except where noted. [b] The imidazole ring atoms are numbered to be consistent with other compounds in the table. CAS numbering is given in the Experimental Section. [c] 50:50 rotamer population ratio (see text); identification of resonances for each rotamer was not possible. [d] 80:20 rotamer population ratio (see text); more abundant isomer listed first. [e] In DMSO-d_6. [f] Insoluble in $CDCl_3$. [g] X = F, Cl, or N4-imidazole ring. [h] Chemical shift obscured by overlap.

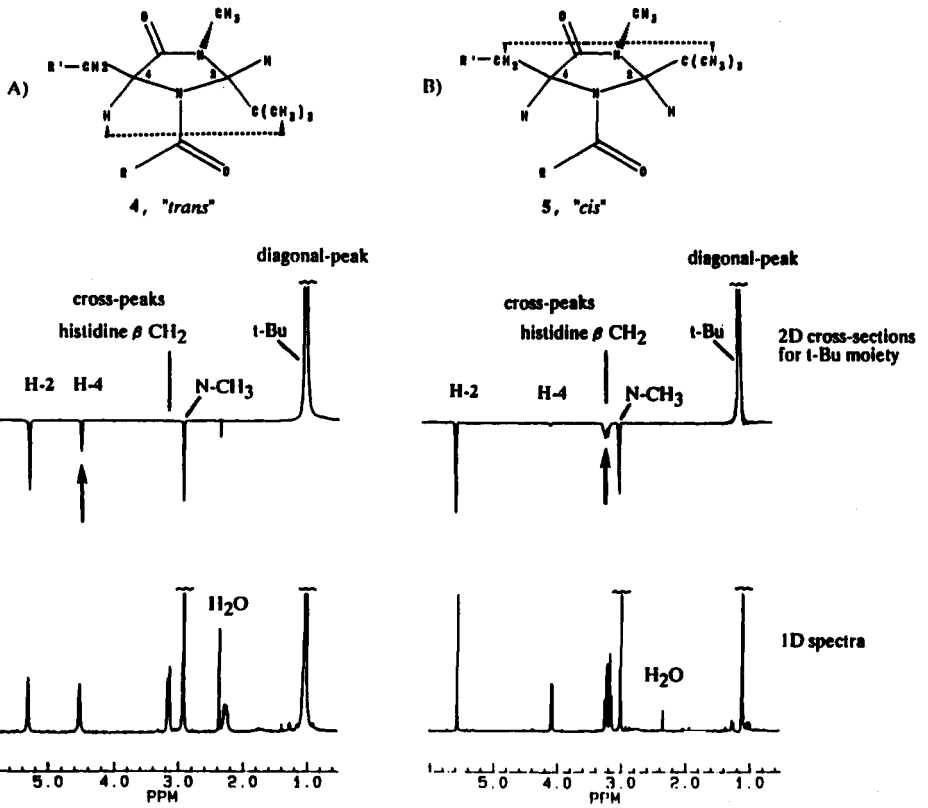

Figure 1. Cross sections from 2D NOESY NMR spectra of (A) (4) (trans) and (B) (5) (cis) showing NOE's from t-Bu methyl hydrogens to spatially proximal hydrogens.

NOE cross-peaks are negative (filled contours), and the chemical exchange cross-peaks are positive (open contours). In the NOESY spectrum, the negative cross-peak labeled 2 represents an NOE between hydrogens A and X of the major rotamer. The positive cross-peak labeled 4 represents chemical exchange transfer of magnetization which occurs when hydrogen X becomes hydrogen X′ due to rotation about the amide bond. The negative cross-peak labeled 3 results from a two-step process involving both an NOE and chemical exchange. Using this approach, it was possible to identify the NOE cross peaks in the NOESY spectra of **6**, **6a**, **7**, **7a** and thereby determine their stereochemistry.

The structure of the side product **9** was confirmed using the above-mentioned ^{1}H NMR techniques (decoupling and 2D NOESY) as well as ^{13}C NMR techniques (broad-band

Table II. Pairs of Hydrogens Connected by NOE's ((+) NOESY Cross-Peak Observed, (-) NOESY Cross-Peak Not Observed)

hydrogens	compd 4	5	6	6a	7	7a
H-2 and *tert*-butyl CH_3	+	+	+	+	+	+
N-CH_3	+	+	+	+	+	+
H-4	-	-				
imidazole H-5	+	-	-	-	-	-
tert-butyl CH_3 and N-CH_3	+	+	+	+	+	+
H-4	+	-		-		
CH_2X[a]			-		-	
His-β CH_2	-	+	+	+	+	
H-4 and His-β CH_2	+	+				
imidazole H-5	-	+				
CH_2X and His-β CH_2			+	+	+	
imidazole H-5			+	+	-	
His-β CH_2 and imidazole H-5	+	+	+	+	+	

[a] X = F or Cl.

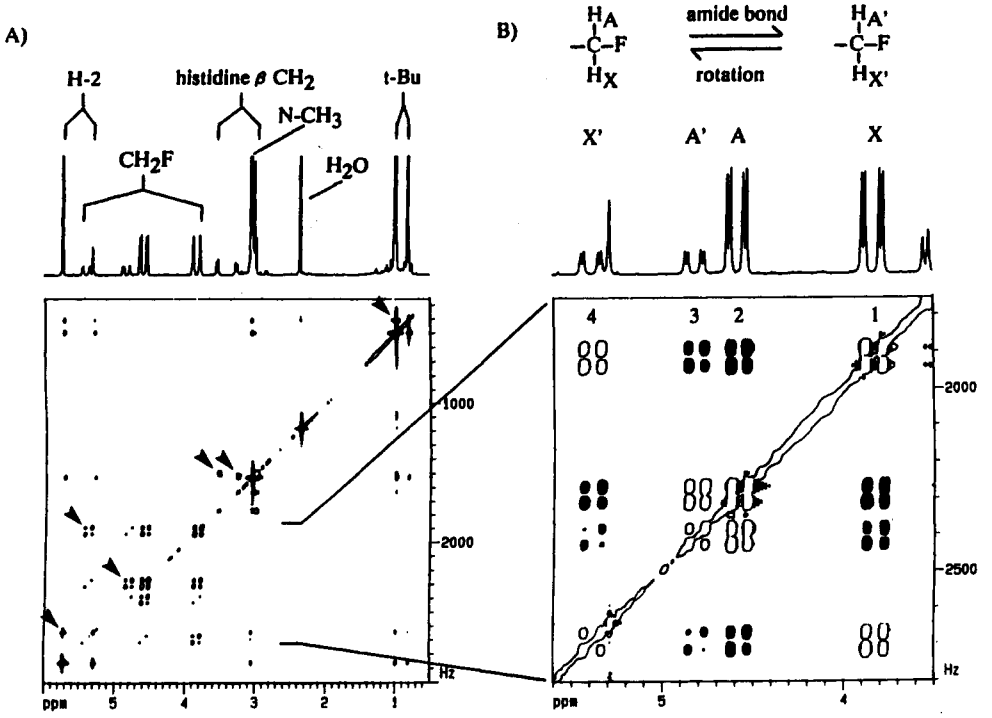

Figure 2. Aliphatic region of (A) 2D NOESY NMR spectrum of (6). Arrowheads indicate exchange cross-peaks. (B) Expansion of CH_2F region of spectrum.

^1H decoupled and INEPT[11] spectra, and 2D ^1H-detected ^{13}C–^1H correlation spectroscopy (2D CH COSY).[12] The ^1H NMR spectrum of **9** in both DMSO-d_6 and $CDCl_3$ is broad and contains two sets of peaks due to slow rotation of the amide moiety (confirmed as for the above compounds). The 2D ^1H-detected CH COSY spectrum of **9** in $CDCl_3$ exhibits the correct number of methyl, methylene, and methine CH correlation resonances if the existence of slow chemical exchange is taken into account. Additionally, the mass spectrum indicates the loss of HCl with respect to **7a**. The ^1H chemical shift assignments for **9** are given in Table I; the ^{13}C chemical shift assignments are given in the Experimental Section.

In summary, we have described a novel and efficient asymmetric synthesis of (*S*)-(+)-α-(fluoromethyl)histidine starting from L-histidine. Also, we have shown an example of the application of pure-phase 2D NOESY in the investigation of spin systems in which both NOE and chemical exchange occur.

Experimental Section

All reactions of air- and water-sensitive organometallic reagents were carried out under nitrogen using standard techniques. THF was distilled from a purple solution of disodium benzophenone dianion prior to use. HMPA was distilled from sodium at reduced pressure and stored over 4-Å molecular sieves. Melting points are uncorrected. Polarimetry measurements were performed using a quartz sample cell (1 × 10 mm, 0.1 mL).

N_{im}-Trityl-L-histidine *N'*-Methylamide (2). To a cold stirred suspension of 100 g (0.2 mol) of N_{im}-trityl-L-histidine methyl ester dihydrochloride[6] in 500 mL of ethanol was added 62 g (2 mol) of monomethylamine, previously condensed into 200 mL of ethanol at 10 °C. The mixture was stirred for 3 d at rt. The solvent was partially evaporated in vacuum, and the mixture was diluted with 4 L of H_2O. The precipitate was filtered, washed with H_2O, and dried at 50 °C. The crude product was dissolved in hot methanol, and CH_2Cl_2 and filtered through a

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pad of silica gel. The filtrate was concentrated to dryness. Addition of ether gave 75.5 g (92%) of **2**, mp 162–164 °C, as a white crystalline solid. Anal. Calcd for $C_{26}H_{26}N_4O$: C, 76.07; H, 6.38; N, 13.65. Found: C, 75.92; H, 6.56; N 13.35.

***N*-(2,2′-Dimethylpropylidene)-N_{im}-trityl-L-histidine *N*′-Methylamide (3).** To a solution of 75 g (0.18 mol) of N_{im}-trityl-L-histidine *N*-methylamide (**2**) in 300 mL of CH_2Cl_2 was added 25 g (0.18 mol) of K_2CO_3, 15 g (0.18 mol) of $NaHCO_3$, 45 g of 4-Å molecular sieves (2–3-μm powder), and 21.5 g (0.25 mol) of pivaldehyde. The mixture was stirred for 4 d, and the insoluble material was filtered off. The filtrate was concentrated in vacuum to dryness. Addition of ether to the residue gave 82 g (94%) of **3**, mp 151–152 °C. Anal. Calcd for $C_{31}H_{34}N_4O$: C, 77.79; H, 7.16; N, 11.71. Found: C, 77.65; H, 7.26; N, 11.50.

(2*S*,4*S*)-3-Benzoyl-2-(1,1-dimethylethyl)-1-methyl-4-[(N_{im}-tritylimidazol-4′-yl)methyl]-1,3-imidazolidin-5-one (4) and (2*R*,4*S*)-3-Benzoyl-2-(1,1-dimethylethyl)-1-methyl-4-[(N_{im}-tritylimidazol-4′-yl)methyl]-1,3-imidazolidin-5-one (5). A mixture of 28 g (0.058 mol) of **3** and 25 g (0.11 mol) of benzoic anhydride was heated at 150 °C for 1 h. After cooling, the mixture was dissolved in CH_2Cl_2 and stirred with 2 N Na_2CO_3 for 1 h. The organic phase was washed with H_2O, dried over $MgSO_4$ and concentrated to dryness to give 30 g of diastereomers **4** and **5** which were separated by column chromatography on silica gel. Elution with toluene–ethyl acetate (1:1) gave 9.0 g (26%) of trans isomer **4**, mp 194–196 °C: $[\alpha]^{25}_D$ +104.6° (*c* = 1, in CH_2Cl_2). Anal. Calcd for $C_{38}H_{38}N_4O_2$: C, 78.32; H, 6.57; N, 9.62. Found: C, 78.58; H, 6.86; N, 9.69. After all the trans isomer was eluted, the polarity of the solvent was increased to ethyl acetate/methanol (9:1) to give the cis isomer **5** (21.0 g, 61%), mp 189–191 °C: $[\alpha]^{25}_D$ −1.2° (*c* = 1, in CH_2Cl_2), $[\alpha]^{25}_{365}$ −24.4° (*c* = 1, CH_2Cl_2). Anal. Calcd for $C_{38}H_{38}N_4O_2$: C, 78.32; H, 6.57; N, 9.62. Found: C, 78.18; H, 6.72; N, 9.45.

(2*R*,4*S*)-3-Benzoyl-2-(1,1-dimethylethyl)-4-(fluoromethyl)-4-[(N_{im}-tritylimidazol-4′-yl)methyl]-1-methyl-1,3-imidazolidin-5-one (6). To a suspension of 10 g (0.017 mol) of cis isomer **5**, 60 mL of THF, 12.2 g (0.068 mol) of HMPA, and 5 g of 4-Å molecular sieves (2–3-μm powder) was added 22.7 mL (0.034 mol) of a 1.5 M LDA solution at −70 °C. The cooling bath was removed, and the temperature of the reaction mixture was allowed to rise to −10 °C. At this temperature 3.9 g (0.034 mol) of TMEDA was added followed by the rapid addition of 4.6 g (0.068 mol) of condensed chlorofluoromethane (purchased from Alliance Chem., Edmonton, Canada). At the end of the addition, the reaction mixture was warmed to rt and stirred for 90 min. The reaction mixture was poured into saturated NaCl solution, extracted with ethyl acetate, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was dried in vacuum at 50 °C to give 9.9 g (94%) of a resin: $[\alpha]^{25}_D$ +57.6° (*c* = 1, CH_2Cl_2). Anal. Calcd for $C_{39}H_{39}FN_4O_2$: C, 76.20; H, 6.39; F, 3.09; N, 9.11. Found: C, 76.63; H, 6.32; F, 2.84; N, 8.67.

(2*R*,4*S*)-3-Benzoyl-2-(1,1-dimethylethyl)-4-(chloromethyl)-4-[(N_{im}-tritylimidazol-4′-yl)methyl]-1-methyl-1,3-imidazolidin-5-one (6a). To a stirred suspension of 11.6 g (0.02 mol) of **5**, 12.2 g (0.068 mol) of HMPA, and 5 g of 4-Å molecular sieves (2–3-μm powder) in 60 mL of THF was added 22.7 mL (0.034 mol) of a 1.5 M LDA solution at −70 °C. The mixture was stirred for 10 min, and then 3.9 g (0.034 mol) of TMEDA was added. The dry ice bath was removed, the reaction mixture was warmed to −30 °C, and 4.4 g (0.034 mol) of bromochloromethane was added. The temperature was allowed to rise to rt and stirred for 1 h. The mixture was poured into H_2O/NaCl/ethyl acetate and filtered to remove the molecular sieves. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to an oil which was purified by flash chromatography on silica gel (eluent EtOAc/toluene (3:7) to provide **6a** (11.2 g, 89%). Recrystallization from toluene gave white crystals containing 0.5 mol of toluene: mp 109–110 °C; $[\alpha]^{25}_D$ +53.8° (*c* = 1, CH_2Cl_2); MS (CI) *m/z* MH^+ 631, 595 (M − HCl), 353, 243 $[Ph_3C]^+$. Anal. Calcd for $C_{39}H_{39}ClN_4O_4 \cdot {}^1/_2$ toluene: C, 75.37; H, 6.40; N, 8.27; Cl, 5.23. Found: C, 75.13; H, 6.74; N, 8.44; Cl, 5.37.

(2*R*,4*S*)-3-Benzoyl-2-(1,1-dimethylethyl)-4-(fluoromethyl)-4-(4′-imidazolylmethyl)-1-methyl-1,3-imidazolidin-5-one (7). A two-phase mixture of 9.22 g (0.015 mol) of **6** in 20 mL of toluene and 25 mL of 6 N HCl solution was heated in an oil bath at 110 °C for 15 h. The reaction mixture was cooled, and the aqueous phase was separated, washed with toluene, and neutralized with NH_4OH. The product was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated in vacuum to dryness. Recrystallization from ethanol and ether gave 4.5 g (81%) of **7**, mp 227–228 °C: $[\alpha]^{25}_D$ +1.43° (*c* = 1, MeOH). Anal. Calcd for $C_{20}H_{25}FN_4O_2$: C, 64.49; H, 6.77; F, 5.11; N, 15.04. Found: C, 64.01; H, 6.91; F, 5.34; N, 14.32.

(2*R*,4*S*)-3-Benzoyl-2-(1,1-dimethylethyl)-4-(chloromethyl)-4-(4′-imidazolylmethyl)-1-methyl-1,3-imidazolidin-5-one (7a). A mixture of 6.3 g (0.01 mol) of **6a**, 50 mL of toluene, and 50 mL of 6 N HCl solution was heated at 100 °C for 4 h. The aqueous layer was separated and neutralized with NH_4OH and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated to yield 3.9 g (90%) of **7a** as a colorless solid, mp 103–107 °C: $[\alpha]^{25}_D$ +32.7° (*c* = 1, MeOH); MS MH^+ 389. Anal. Calcd for $C_{20}H_{25}ClN_4O_2$: C, 61.77; H, 6.48; Cl, 9.11; N, 14.41. Found: C, 62.05; H, 6.41; Cl, 8.80; N, 14.01.

(*S*)-(+)-α-(Fluoromethyl)histidine (8). A suspension of 4 g (0.011 mol) of **7** and 20 mL of 36% HCl was heated in a sealed glass tube at 150–160 °C for 15 h. After cooling, the mixture was diluted with H_2O and washed with ether. The aqueous phase was concentrated under reduced pressure to dryness. The residue was dissolved in 10 mL of H_2O and applied to a column containing 25 g of Dowex 50×8-400 ion-exchange resin. The resin was washed with H_2O until neutral followed by 1 N HCl. The HCl fraction was concentrated under reduced pressure to dryness. Recrystallization of the crude HCl salt from methanol/ether gave 1.92 g (69%) of **8** dihydrochloride, mp 200–203 °C $[\alpha]^{25}_D$ +16° (*c* = 1, $CF_3COOH \cdot H_2O$ (1:1) of white crystals. Anal. Calcd for $C_7H_{10}FN_3FN_3O_2 \cdot 2HCl$: C, 32.32; H, 4.65; F, 7.30; N, 16.15; Cl, 27.26. Found: C, 33.07; H, 4.81; F, 7.29; N, 16.15; Cl, 27.22.

The free amino acid (*S*)-(+)-α-(fluoromethyl)histidine was obtained by dissolving 1.9 g of the dihydrochloride in 10 mL of H_2O. The solution was applied to a column containing 25 g of Dowex 50×8-400. The resin was washed with H_2O followed by 1 N NH_4OH. The NH_4OH fraction was concentrated in vacuum and dried under high vacuum for 24 h to yield 0.85 g (60%) of a white powder: $[\alpha]^{20}_D$ +17° (*c* = 1, $CF_3COOH \cdot H_2O$ (1:1). Anal. Calcd for $C_7H_{10}FN_3O_2 \cdot {}^1/_4H_2O$: C, 43.86; H, 5.52; F, 9.91; N, 21.92. Found: C, 43.72; H, 6.03; F, 9.32; N, 21.75.

(*S*)-(+)-α-(Chloromethyl)histidine (8a). A suspension of **7a** (2.5 g, 6.44 mmol) in 15 mL of 36% HCl was heated in a sealed glass tube at 180 °C for 15 h. After cooling, the mixture was washed with ether. The aqueous layer was concentrated to dryness and purified using 20 g of Dowex 50×8-400 ion-exchange resin. The product was eluted with 2 N HCl to give 300 mg (19%) of a white powder: $[\alpha]^{25}_D$ +13.3° (*c* = 1, $CF_3COOH \cdot H_2O$ (1:1).

3-Benzoyl-2-(1,1-dimethylethyl)-1-methylspiro[imidazolidine-4,6′(7′*H*)-[5*H*]pyrrolo[1,2-*c*]imidazol]-5-one (9). Compound **7a** (389 mg, 1 mmol) was stirred and refluxed with Na_2CO_3 (318 mg, 3 mmol) in *i*-Pr (10 mL) for 15 h. The solvent was evaporated and stirred with H_2O. The product was extracted with ethyl acetate, washed with brine, dried ($MgSO_4$) and concentrated. Recrystallization from ethyl acetate and ether gave 250 mg (71%) of **9**, mp > 300 °C: $[\alpha]^{25}_D$ +13.8 (*c* = 0.3, CH_2Cl_2); MS (CI) MH^+ 353; ^{13}C NMR ($COCl_3$) δ 172.7; 171.6 (*C*ON × 2); 135.3 (*C*7a′); 133.9 (benzoyl *C*1″); 131.8 (benzoyl *C*4″); 129.7 (*C*3′); 128.2, 126.7 (benzoyl *C*3″, 5″, and *C*2″,6″); 119.4 (*C*1′); 80.2 (*C*2); 74.5 (*C*4); 54.7 (*C*5′); 38.4 (*tert*-butyl-*C*–); 32.0 (N*C*H$_3$); 26.8 (*tert*-butyl *C*H$_3$). Anal. Calcd for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.12; H, 6.73; N, 15.35.

NMR Spectroscopy. ^1H NMR spectra were obtained at 500.13 and 270.13 MHz. ^{13}C NMR spectra were obtained at 67.9 MHz. INEPT spectra were acquired using the pulse sequence of Morris and Freeman[11] with refocusing and broad-band WALTZ[12] ^1H decoupling.