stretching modes [3207 cm^{-1}, asymmetric stretch (ν_7); 3169 cm^{-1}, symmetric stretch (ν_1)], C=C stretching (1663 cm^{-1}), and of a C–H bending mode [563 cm^{-1} (ν_4 or ν_6)]. The most intense band at 912 cm^{-1} ostensibly shifts very little on deuterium substitution and is unlikely to be due to a C–H deformation mode but is perhaps an S-wagging mode, ν_8.

We also feel moved to comment on criteria of proof of structure for new matrix-isolated species. In many instances only infrared spectral evidence is available because of the difficulty of applying multiple spectroscopic probes and obtaining definitive chemical evidence for the species in situ. Proof of structure must at least be based on isotopic labeling experiments which establish the symmetry and molecular formula of the species.

That isothiazole and 1 are independent precursors to a common species X which is photoisomerized to **3** and **4** means that X must have the formula C_2H_2S. The fact that [4- and 5-^{13}C]-1,2,3-thiadiazoles are independent precursors to a single species ^{13}C–X, which is converted to ethynyl mercaptan and thioketene, both with randomized label, establishes the symmetry of X as C_{2v}. The effect of deuterium and methyl groups on the "double bond stretch" of X (–50 cm^{-1} per D, +125 cm^{-1} per methyl) is positive evidence for the cyclopropenoid nature of X. Such evidence raises the argument above a claim; it is proof of structure.

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Direct Synthesis of α-Halogenomethyl-α-amino Acids from the Parent α-Amino Acids

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A general approach to the preparation of α-halogenomethyl-α-amino acids **2**, **15**, and **16** which are potential enzyme-activated irreversible inhibitors of the parent α-amino acid decarboxylases is described. The key step in the synthesis is the regioselective alkylation of a Schiff base ester **6**, readily available from the parent α-amino acid, with poly(halomethanes) such as bromochloromethane, chlorofluoromethane, and chlorodifluoromethane to give the corresponding α-halogenomethylated adducts **8**, **9**, and **10**, respectively. Subsequent removal of the protecting groups from these adducts upon acidic treatment yields the corresponding α-halogenomethyl-α-amino acids **2**, **15**, and **16**. The mechanism of the key alkylation reaction appears to depend on the degree and the nature of the substitution of the halomethanes; it is suggested that bromochloromethane and chlorofluoromethane react via an S_N2 type mechanism, whereas chlorodifluoromethane reacts by a chain process involving the intermediacy of difluorocarbene.

We recently reported that α-halogenomethyl analogues of ornithine and 3,4-dihydroxyphenylalanine (DOPA) are potent and specific irreversible inhibitors[1,2] of pyridoxal phosphate-dependent ornithine decarboxylase (E.C. 4.1.1.17) and aromatic L-α-amino acid decarboxylase (E.C. 4.1.1.26), respectively. Kinetic studies indicated that these inactivators most probably belong to a novel class of inhibitors recognized by Bloch[3] 10 years ago which demand activation by the "target" enzyme. They are now referred to as k_{cat} inhibitors,[4] suicide enzyme inactivators,[5] or enzyme-activated irreversible inhibitors.[6] The mechanism of inhibition which we proposed[1,2] (depicted in Figure 1) has recently been demonstrated by Kollonitsch and coworkers for the inactivation of aromatic L-α-amino acid decarboxylase by (*S*)-α-monofluoromethyl-3,4-dihydroxyphenylalanine.[7] The high selectivity of these inhibitors results from the fact that they can act only on those enzymes which accept them as substrates. As all pyridoxal phosphate-dependent decarboxylases operate by a similar mechanism, it could be anticipated as already commented on by Kollonitsch and co-workers[7] that the specificity of α-halogenomethyl-α-amino acids as potential decarboxylase inhibitors will be determined essentially by the chain residue R. We detail now the synthesis of α-halogenomethyl analogues **2b,c,e–i**, **15b–g,i,k,l** and **16b,e** of the α-amino acids **5b,c,e–i,k,l** whose decarboxylases are known to have essential metabolic functions in mammals, bacteria, and/or plants.

These highly functionalized α-amino acid analogues constitute a class of compounds which thus far has seen very few representatives. The difficulty associated with the preparation of these molecules lies in the presence of halogen atom(s) on a carbon atom vicinal to a quaternary center bearing an amine and a carboxylic acid functionality. The classical Bucherer–Lieb or Strecker synthesis of α-amino acids does not appear as an attractive approach to this problem. These routes imply that the preparation of the key starting halogenomethyl ketones has to be tailored to each specific side chain of the α-amino acids and also to each specific halogenomethyl group. Furthermore, the formation of the intermediate hydantoins or α-aminonitriles has been reported to be troublesome with halogenomethyl ketones[8] in many instances. Moreover, the hydrolysis of these intermediates to the

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(2) (a) M. G. Palfreyman, C. Danzin, P. Bey, M. J. Jung, G. Ribereau-Gayon, M. Aubry, and A. Sjoerdsma, *J. Neurochem.*, **31**, 927 (1978); (b) P. Bey, "Enzyme-Activated Irreversible Inhibitors", N. Seiler, M. J. Jung, and J. Koch-Weser, Eds., Elsevier, Amsterdam, 1978, p 27.
(3) K. Bloch, *Acc. Chem. Res.*, **2**, 193 (1969).
(4) R. R. Rando, *Sciences*, **185**, 320 (1974).
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(6) Reference 2b, pp 123, 221.
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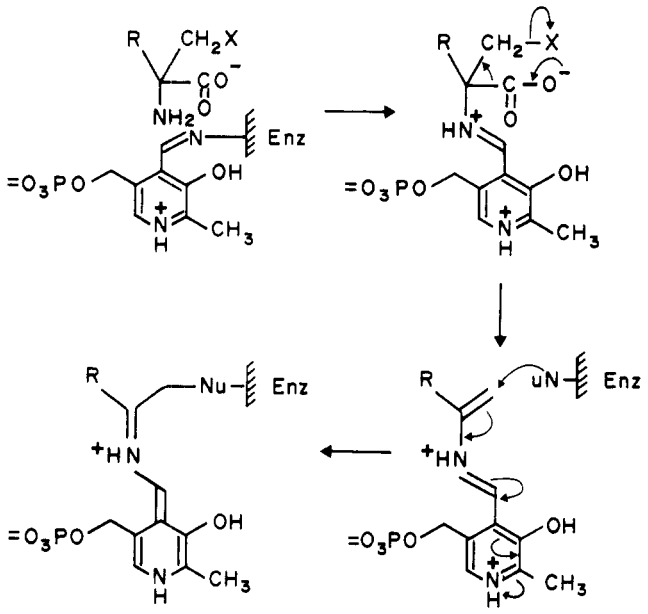


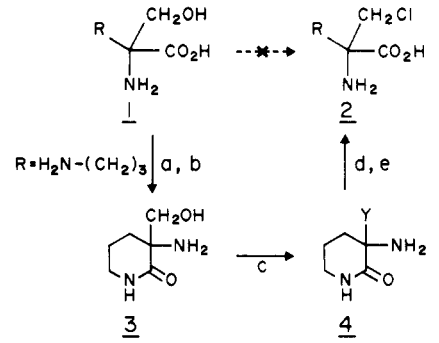
Figure 1. Proposed mechanism for inactivation of pyridoxal phosphate dependent α-amino acid decarboxylases by α-(halogenomethyl)-α-amino acids. Loss of CO_2 and elimination of the halogen atom X from the Schiff base intermediate formed between the inhibitor and pyridoxal phosphate leaves a highly reactive Michael acceptor which can be alkylated by a nucleophilic residue (Nu) in or near the active site to irreversibly bind the enzyme.

corresponding α-amino acids requires drastic conditions which, according to Tahara and co-workers,[9] do not seem to be compatible with an α-chloromethyl group. So, at the onset of this work, only the reverse mode of synthesis that entails the direct introduction of a functionalized methyl group onto an appropriate synthon derived from naturally occurring and hence easily available α-amino acids was given consideration.

Results

The ease with which α-hydroxymethyl-α-amino acids **1** can be prepared from the parent amino acids **5**[10] encouraged us to explore the possibility of utilizing these α-amino acid derivatives as starting material for the synthesis of α-monohalogenomethyl-α-amino acids. α-Hydroxymethylornithine,[11] α-hydroxymethylphenylalanine,[10] and α-methylserine,[10] when subjected to reaction sequences which transform β-hydroxy-α-amino acids into β-chloro-α-amino acids,[12,13] failed to give practical yields of the corresponding α-chloromethyl-α-amino acids **2**. α-Chloromethylornithine (**2b**), however, was eventually obtained in 15% yield by the route depicted in Scheme I. Inasmuch as the failure of the first attempts seemed associated with the insolubility of the reactants and/or the deleterious participation of the α functionalities in the replacement of the hydroxy group by chlorine, the partial success of this sequence could be attributed to the use of the lactam **3** derived from α-hydroxymethylornithine in the key chlorination reaction. In line with this general approach based on the utilization of α-hydroxymethyl-

Scheme I. Synthesis of α-(Chloromethyl)ornithine from α-(Hydroxymethyl)ornithine (Y = CH_2Cl).[a]



[a] (a) MeOH/HCl; (b) NaOMe; (c) $SOCl_2$/DMF; (d) HCl 6 M; (e) NEt_3.

α-amino acids **1**, Kollonitsch and co-workers[14] described a selective replacement of the hydroxy group by fluorine in hydroxy-α-amino acids with sulfur tetrafluoride in liquid hydrogen fluoride. This "fluorodehydroxylation" reaction which necessitates the use of toxic and not easy to handle reagents proceeds in good yield with β-hydroxy-α-amino acids. However, α-methylserine, the simplest α-hydroxymethyl-α-amino acid, was reported to be converted to 2-fluoromethylalanine in only 23% yield.[15]

In view of the difficulties encountered with this synthetic approach, attention was turned to a direct introduction of the desired halogenomethyl group onto the α-carbon atom of an appropriate α-amino acid derivative. Prior experience from this laboratory using the alanine series as a model[16,17] has demonstrated the utility of the Schiff base ester synthon **6a** for the preparation of α-functionalized methyl-α-amino acids. The intermediate objective became therefore the synthesis of Schiff base alkyl ester derivatives **6b–i** of the selected α-amino acids. At this stage, it was anticipated that the halogenomethyl analogues of arginine and *S*-adenosylmethionine (SAM) could be prepared from the corresponding ornithine and methionine analogues.

Standard procedures, i.e., esterification of the parent α-amino acids **5a–f,h,j** with methanol saturated with dry hydrochloric acid followed by treatment of the intermediate ester hydrochlorides with benzaldehyde in the presence of triethylamine, afforded the expected Schiff base methyl ester derivatives **6a–f,h,j** (Scheme II). In the course of this two-step transformation, the terminal carboxylic acid and amine functions of glutamic acid **5h** and ornithine **5b** and lysine **5c** were converted to the methyl ester **6h** and benzylidene derivatives **6b** and **6c**, respectively. Under these conditions, cyclization of the ornithine and lysine methyl esters to the corresponding 2-piperidone and 2-hexahydroazepinone derivatives was not observed.[18] The benzaldimine methyl ester derivatives of DOPA and of histidine could not be obtained from the parent α-amino acids **5g** and **5i** under these standard conditions. In the presence of carbonyl compounds, these α-amino acid esters form Schiff bases which cyclize to give tetrahydropyridine derivatives.[19,20] In the histidine case,

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(14) J. Kollonitsch, S. Maburg, and L. M. Perkins, *J. Org. Chem.*, **40**, 3808 (1975).
(15) J. Kollonitsch and co-workers, ref 7, described the preparation of the α-(monofluoromethyl) analogues of DOPA, histidine, ornithine, tyrosine, and glutamic acid via this sequence. Yields were not reported.
(16) P. Bey and J. P. Vevert, *Tetrahedron Lett.*, 1455 (1977).
(17) P. Bey and J. P. Vevert, *Tetrahedron Lett.*, 1215 (1978).
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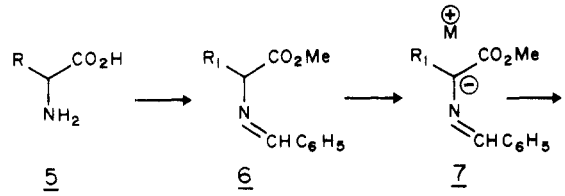
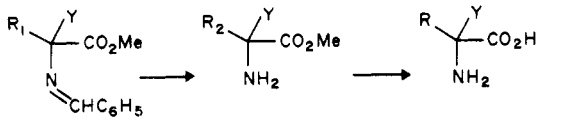
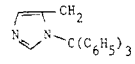
Scheme II



5 6 7

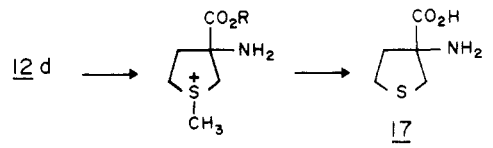


8 Y = CH_2Cl 12 Y = CH_2Cl 2 Y = CH_2Cl
9 Y = CHF_2 13 Y = CHF_2 15 Y = CHF_2
10 Y = CH_2F 14 Y = CH_2F 16 Y = CH_2F
11 Y = $CBrF_2$

	R	R_1	R_2
a	CH_3	CH_3	CH_3
b	$H_2N(CH_2)_3$	$C_6H_5CH{=}N(CH_2)_3$	$H_2N(CH_2)_3$
c	$H_2N(CH_2)_4$	$C_6H_5CH{=}N(CH_2)_4$	$H_2N(CH_2)_4$
d	$CH_3S(CH_2)_2$	$CH_3S(CH_2)_2$	$CH_3S(CH_2)_2$
e	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_6H_5CH_2$
f	$4\text{-}HOC_6H_4CH_2$	$4\text{-}HOC_6H_4CH_2$	$4\text{-}HOC_6H_4CH_2$
g	$3,4\text{-}(HO)_2C_6H_3CH_2$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2$
h	$HO_2C(CH_2)_2$	$CH_3O_2C(CH_2)_2$	$CH_3O_2C(CH_2)_2$
i			
j	$C_6H_5CH_2S(CH_2)_2$	$C_6H_5CH_2S(CH_2)_2$	
k	$H_2NC(=NH)NH(CH_2)_3$		
l	 Adenosyl		

the cyclization could be prevented by protecting the imidazole ring with a trityl group. Thus, the stable benzylidene derivative **6i** was obtained in almost quantitative yield upon treatment of the N^{Im}-tritylhistidine methyl ester[21] with 1 equiv of benzaldehyde in methylene chloride. In the case of DOPA, a suitable benzaldimine derivative *6g* was prepared indirectly via a controlled monoalkylation of the anion generated from the Schiff base methyl ester of glycine **6** (R = H) with 3,4-dimethoxybenzyl bromide according to the method described by Stork and co-workers.[22] The crude alkylated product **6g** was contaminated with 5–10% of the dialkylated adduct but could be used without further purification in the subsequent alkylation reaction. Pure **6g** could eventually be obtained by fractional crystallization of the α-amino acid methyl ester hydrochloride formed upon hydrolysis under mild conditions of the crude alkylation mixture, followed by regeneration of the Schiff base from the pure α-amino acid methyl ester hydrochloride as described above.

Scheme III



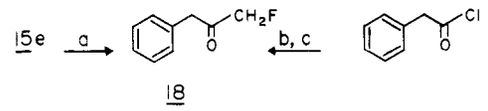
12 d 17

Anion formation from the Schiff base ester intermediates **6** could be achieved under a variety of conditions. The anions **7** were rapidly generated in tetrahydrofuran (THF) with 1 equiv of lithium diisopropylamide at −70 °C or with 1 equiv of potassium hydride at room temperature. Anion formation was slower with sodium hydride (1 equiv) (6 to 24 h at room temperature) but could be considerably accelerated by addition of 15–20% hexamethylphosphoramide (HMPA) to the medium. The lithium, potassium, or sodium derivatives **7** with the exception of **7h** were stable for many hours at room temperature in THF or HMPA as evidenced by the clean formation of the corresponding α-methylated adduct upon quenching the anion solution with an excess of methyl iodide.[16] Alkylation of the anion **7** with chlorobromomethane and chlorodifluoromethane under reaction conditions similar to those reported earlier for the synthon derived from alanine[17] produced the chloromethyl and difluoromethyl adducts **8** and **9**, respectively. Owing to their instability to distillation and to chromatography (partial hydrolysis of the Schiff base occurred), the alkylated products **8** and **9** were usually not purified. Convincing evidence for the high regioselectivity of the alkylation on the carbon atom α to the ester function of **7** was readily available from the ^1H NMR spectra of the crude reaction mixtures. Thus, the spectra of the chloromethyl adducts **8** display an AB or A_2 pattern centered around δ 3.9–4.0 for the hydrogen atoms of the CH_2Cl group and a singlet (δ 8.1) attributable to the hydrogen atom of the imine group. Similarly, the spectra of the difluoromethyl adducts **9** display a singlet for the hydrogen atom of the imine and a triplet at δ 6.0–6.2 with a coupling constant of 52–55 Hz characteristic for a CHF_2 group linked to a quaternary carbon atom. The presence of an AB part of an ABX pattern in the ^{19}F NMR spectra confirms this interpretation. As judged from the NMR spectra, the chloromethyl and difluoromethyl adducts **8** and **9** were produced in fair to excellent yields (60 to 90%) with the exception of **9i** (yield <50%) and **9h** for which only a weak signal corresponding to a CHF_2 group could be detected. It is noteworthy that the unprotected phenol function of **6f** did not interfere with the regioselectivity of the alkylation reaction.

Selective removal of the benzylidene groups from the amine functions of **8** and **9** under mild acidic conditions (HCl M, room temperature, 1 h) and subsequent cleavage of the other protecting groups (HCl 6 M, room temperature for the *N*-trityl group of **8i** and **9i**; HCl 6 M, 100 °C, 24 h for the methyl esters; HBr 47%, 100 °C, 12 h for the methyl ethers of **12g** and **13g**) readily gave the corresponding α-chloromethyl- and α-difluoromethyl-α-amino acids **2** and **15** with the exception of **2d**. Upon deprotection of the amino group, **8d** yielded the expected α-chloromethylmethionine methyl ester hydrochloride (**12d**), but hydrochloric acid hydrolysis of **12d** afforded 3-amino-3-(tetrahydrothienyl)carboxylic acid[23] (**17**) as the sole product. The formation of **17** can be rationalized by an intramolecular nucleophilic displacement of the chlorine atom by the sulfide to give a cyclic sulfonium intermediate which is then demethylated upon nucleophilic attack by

(20) N. Zenker, *J. Med. Chem.*, 9, 826 (1966).
(21) G. C. Stelakatos, D. M. Theodoropoulos, and L. Zervas, *J. Am. Chem. Soc.*, 81, 2884 (1959).
(22) G. Stork, A. Y. M. Leong, and A. M. Touzin, *J. Org. Chem.*, 41, 3491 (1976).
(23) A. W. Coveter, J. B. Lombardini, J. R. Sufrin, and P. Talalay, *Mol. Pharmacol.*, 10, 319 (1974).

Scheme IV[a]

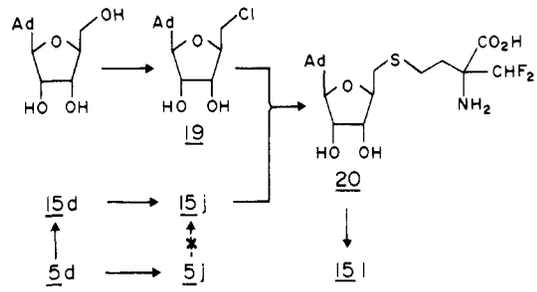


[a] (a) Pyridoxal 0.1 equiv, phosphate buffer pH 6.3, 80 °C. (b) CH_2N_2/Et_2O. (c) HF/pyridine.

the chloride anion (Scheme III). Direct hydrolysis of the Schiff base esters **8** and **9** to the corresponding α-amino acid derivatives **2** and **15** proceeded usually in yields lower than those obtained in the stepwise procedure. An oxidative decarboxylation of the α-halogenomethyl-α-amino acids catalyzed by the benzaldehyde liberated consequently to the hydrolysis of the Schiff base could explain this result. This assumption was corroborated by the conversion of α-(difluoromethyl)phenylalanine (**15e**) to the fluoromethyl ketone **18** in 85% yield upon heating at 80 °C for 12 h in a phosphate buffer containing a catalytic amount of pyridoxal. The structure of the fluoro ketone **18** was established by comparison with an authentic sample obtained from phenylacetyl chloride by following the synthetic sequence described by Olah and Welch[24] (Scheme IV). The α-chloromethyl- and α-difluoromethyl analogues of ornithine **2b** and **15b**, lysine **2c** and **15c**, and histidine **2i** and **15i** were crystallized as the monohydrochloride salts, whereas the corresponding analogues of phenylalanine **2e** and **15e**, tyrosine **2f** and **15f**, DOPA **2g** and **15g**, methionine **15d**, and glutamic acid **2h** were obtained in their zwitterionic form. They were isolated by neutralization with triethylamine[25] or propylene oxide of the crude hydrohalide salts obtained after acid treatment of the corresponding esters **12** and **13**. Interestingly, the individual enantiomers of **15b** were obtained directly from the difluoromethyl ester dihydrochloride **13b**. Neutralization of **13b** with 2 equiv of sodium methylate gave quantitatively the lactam **4** (Y = CHF_2). Resolution with (+)- and (−)-binaphthylphosphoric acid[26] followed by acid hydrolysis (HCl 6 M) afforded the pure (+) and (−) isomers of **15b**.

The synthesis of α-(difluoromethyl)arginine (**15k**) and α-(difluoromethyl)-*S*-adenosylmethionine (**15l**) was patterned after the methods developed by Odo[27] and Borchardt and co-workers[28] for the preparation of arginine and *S*-adenosylhomocysteine from ornithine and methionine, respectively. Thus, **15b** upon treatment with ethylthiouronium at pH 10.5 afforded after ion exchange column purification **15k** in 50% yield. The preparation of α-(chloromethyl)arginine (**2k**) via this sequence was precluded by the instability of α-chloromethyl analogues of α-amino acids in basic aqueous solution.[29] The synthesis of **15l** is outlined in Scheme V. Condensation of 5′-deoxy-5′-chloroadenosine[30] (**19**) with the sulfur anion of α-(difluoromethyl)homocysteine generated from *S*-benzyl-α-(difluoromethyl)homocysteine (**15j**) by reductive cleavage with sodium in liquid ammonia[31] gave *S*-

Scheme V. Synthesis of α-(difluoromethyl)-*S*-adenosylmethionine (Ad = adenin-9-yl)



adenosyl-α-(difluoromethyl)homocysteine (**20**) which was converted to **15l** upon treatment with an excess of methyl iodide in a mixture of formic and acetic acids.[32] The chloroadenosine derivative **19** obtained directly from adenosine[30] had to be prepared freshly prior to use for the condensation to proceed in good yield. Attempts to synthesize *S*-benzyl-α-(difluoromethyl)homocysteine (**15k**) from the Schiff base methyl ester **6j** of *S*-benzylhomocysteine (**5j**) proved fruitless. Though lithiation of **6j** with lithium diisopropylamide at −78 °C proceeded smoothly, subsequent addition of difluorochloromethane at 40 °C led to an inseparable product mixture. Eventually **15j** was obtained from **15d** via exchange of *S*-methyl for *S*-benzyl upon treatment with 1 equiv of benzyl chloride in concentrated hydrochloric acid.[33]

The structures of **2** and **15** are in agreement with the analytical and spectroscopic data. Thus, the pK_a values of the α-amino group are, as expected, decreased by 0.9–1.1 units for the α-chloromethyl analogues **2** and by 1.9–2.2 units for the α-difluoromethyl analogues **15** as compared with the corresponding values of the parent α-amino acids **5**.[34] The ^{19}F NMR spectra of all α-difluoromethyl analogues **15** display a signal which consists of a doublet of a quartet assignable to an AB part of a deceptively simple ABX spectrum.[35] Moreover, the structure of some of these novel α-halogenated methyl-α-amino acids was confirmed by an independent synthesis. Thus, α-(difluoromethyl)phenylalanine (**15e**) and α-(difluoromethyl)ornithine (**15b**) proved indistinguishable from samples prepared by an alternate route relying on a Curtius rearrangement of appropriately substituted α-(difluoromethyl)malonic acid hemiesters.[36] Similarly, samples of α-(chloromethyl)-ornithine (**2b**) prepared from α-(hydroxymethyl)ornithine according to the method described in Scheme I and from the general approach outlined in Scheme II were identical in all respects. The possibility that aziridine hydrochlorides **22** resulting from an internal nucleophilic displacement of chlorine by the α-amino group were isolated rather than the α-(chloromethyl)-α-amino acids **2** (**22** and **2** would have similar elemental analyses) could be ruled out on the following grounds: (a) The NMR spectra of **2** display for the two diastereotopic hydrogen atoms of the newly introduced methylene group an AB pattern centered around δ 3.9–4.1 with a geminal coupling constant of 12–14 Hz.[37] For an aziridine hydrochloride structure, one would

(24) G. A. Olah and J. Welch, *Synthesis*, 896 (1974).
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(29) α-(Chloromethyl)-α-amino acids are hydrolyzed in buffered water solution with liberation of a proton. The rate of hydrolysis is a function of the pH. At pH 7.4 the half-lives of **2** range between 30 and 120 min depending on the side chain residues.
(30) D. E. Gibbs and J. G. Verkade, *Synth. Commun.*, **6**, 563 (1976).
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(34) The pK_a values were determined from the titration curve of the amino acid analogues using a combined glass electrode.
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(36) P. Bey and D. Schirlin, *Tetrahedron Lett.*, 5225 (1978).
(37) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, New York, 1972, p 164.

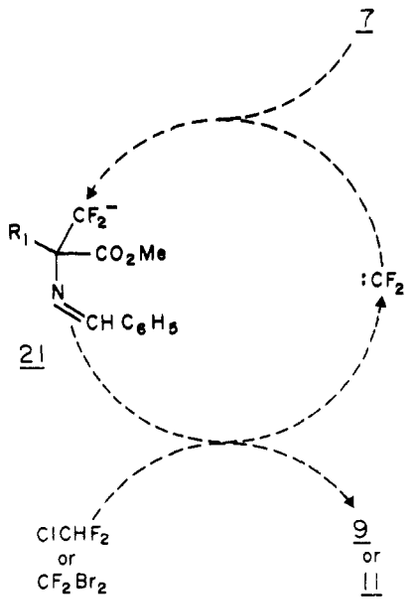
expect a chemical shift of about 2.7 ppm[38] with a coupling constant of 2 Hz.[39] Additional evidence derives from the fact that we observe no change in the geminal coupling constant and only a slight difference in the chemical shift of the methylene group when the free amino acid is compared with its hydrochloride salt. (b) It is unlikely that the hydrochloride salt of the weakly basic aziridines[40] would not be neutralized upon treatment with triethylamine or propylene oxide to yield a free aziridine derivative. Together with the determination of the ionic chloride content (one chloride ion per mol was found for the hydrochloride salts, no chloride ion for the free amino acids (see Experimental Section)) the CHN elemental analyses unequivocally suggest our reaction products to be α-(chloromethyl)amino acids.

Discussion

Although the clean product formation in the key alkylation step of the anions 7 with chlorobromomethane and chlorodifluoromethane could superficially appear straightforward, closer examination of the reaction conditions reveals that the conversions of 6 to the chloromethyl adducts 8 and to the difluoromethyl adducts 9 follow quite different courses. The chloromethyl derivatives 8 were obtained upon treatment of the lithium or sodium derivative 7 with 1.0–1.1 equiv of chlorobromomethane. The alkylation proceeded slowly at room temperature in THF and usually required 12 to 24 h. Addition of 15% HMPA to the reaction medium shortened the reaction time to 1–2 h. As far as difluoromethyl derivatives 9 are concerned, optimal conditions for their preparation consisted of a rapid saturation with gaseous chlorodifluoromethane of a warmed THF solution (40–50 °C) of the anion 7. The reaction was complete within a short period of time and was very much dependent for its initiation on the temperature of the anion solution. The presence of HMPA in the medium and/or a slow rate of addition of chlorodifluoromethane resulted in an important recovery of the starting Schiff base ester 6. Interestingly, new addition of base or/and chlorodifluoromethane to the reaction mixture failed to restore the reaction process.

These data are strongly suggestive of the existence of two different mechanisms. The alkylation with chlorobromomethane could be accounted for by an S_N2 mechanism, whereas that with chlorodifluoromethane would be best accommodated by a chain process. This interpretation is supported by the known reactivity of poly(halomethanes) toward nucleophiles. Depending on their degree and nature of substitution, they react either by an S_N2 mechanism,[41] by a homolytic process,[42] or via an α elimination[43] which usually generates intermediarily a carbenoid species. Hine and co-workers reported that the reaction of methylene halides with nucleophiles proceeds essentially by the S_N2 mechanism and that chlorine is displaced less readily than bromine in the nucleophilic

Scheme VI



reaction. In line with that proposal, we found the sodium derivative **7a** to be alkylated very sluggishly with dichloromethane in THF at room temperature and the lithium derivative **7a** to be completely inert unless HMPA (15%) was added to the reaction medium.[17]

Interestingly, fluorochloromethane could also be expected to react by a similar mechanism[44] and thus provide an entry to the α-(monofluoromethyl)-α-amino acid series **16**. In preliminary experiments, the monofluoromethyl derivatives **10a,b,e** were obtained in good yield by adding a solution of 3 equiv of fluorochloromethane[45] in THF to the sodium derivatives **7a,b,e** generated from **6a,b,e** with 1 equiv of sodium hydride in HMPA. Treatment of the monofluoromethyl adducts **10a,b,e** in a manner similar to that described for the corresponding difluoromethyl analogues **9** led ultimately to the α-(monofluoromethyl)-α-amino acids **16a,b,e**.

The reactivity of haloforms toward nucleophiles has been extensively studied and these reactions are considered today as the most thoroughly investigated examples of α elimination.[43] In particular, numerous reports indicate the formation of difluoromethylene by action of a base upon chlorodifluoromethane.[46] On the basis of the propensity displayed by chlorodifluoromethane for generating difluoromethylene, the formation of the difluoromethyl adducts **9** from the Schiff base esters **6** could reasonably be rationalized by the mechanism depicted in Scheme VI. The reaction would be initiated by formation of difluoromethylene possibly by action of the anion **7** or of an excess of base used to generate **7** upon chlorodifluoromethane. Electrophilic addition of difluoromethylene to the anion **7** would give intermediarily the fluorinated carbanion **21** which in turn could abstract a proton from chlorodifluoromethane to afford the difluoromethyl adduct **9**. Difluoromethylene would be regenerated as a result of this last reaction, thus allowing a chain process. In support of this mechanism, dibromodifluoromethane (1.1 equiv), a particularly well suited tetrahalomethane for the generation of difluoromethylene,[47] was found to react almost instantaneously with the sodium or potassium derivative

(38) A downfield shift of about 1 ppm (see ref 37, p 180) was admitted for a methylene group of a protonated aziridine compared to the unprotonated form; the latter displays a signal around 1.7 ppm (see ref 39).
(39) E. Kyburz, H. Els, St. Majnoni, G. Englert, C. von Planta, A. Fürst, and Pl. A. Plattner, *Helv. Chem. Acta*, **49**, 359 (1966) and literature cited therein.
(40) R. C. Weast, Ed., "Handbook of Chemistry and Physics", 55th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1974–1975, p D 126.
(41) J. Hine, C. H. Thomas, and S. Ehrenson, *J. Am. Chem. Soc.*, **77**, 3886 (1955), and references cited.
(42) For recent examples of such a mechanism, see: (a) R. T. Arnold and S. T. Kulenovic, *J. Org. Chem.*, **43**, 3687 (1978); (b) C. Y. Meyers and H. M. Kolb, *ibid.*, **43**, 1985 (1978), and references cited.
(43) For a review, see W. Kirmse, "Organic Chemistry. A Series of Monograph, Carbene Chemistry", Vol. 1, Academic Press, New York, 1964, p 145.
(44) J. E. Boggs and H. P. Mosher, *J. Am. Chem. Soc.*, **82**, 3517 (1960).
(45) O. Paleta, *Collect. Czech. Chem. Commun.*, **36**, 2062 (1971).
(46) (a) J. Hine and P. B. Langford, *J. Am. Chem. Soc.*, **79**, 5497 (1957); (b) T. Y. Shen, S. Lucas, and L. H. Sarett, *Tetrahedron Lett.*, 43 (1961).
(47) V. Frantzen and L. Fikentscher, *Chem. Ber.*, **95**, 1958 (1962).

7a at −78 °C in THF to afford the difluorobromomethyl adduct **11a** contaminated with 15–25% of the difluoromethyl adduct **9a**. Inasmuch as **11a** was shown not to be transformed to **9a** under the conditions of the reaction, the presence of **9a** among the reaction products is strongly in favor of the intermediacy of the difluorinated anion **21** (R = CH_3) and consequently of difluorocarbene in the reaction process. The highly unstable carbanion **21** then would have the alternative to react with dibromodifluoromethane to give the bromodifluoromethyl adduct **11a** and a new molecule of difluoromethylene or to abstract a proton (possibly from the solvent) to afford **9a**.

Conclusion

In summary, α-halogenomethyl-α-amino acids can be prepared in good yield by the sequence depicted in Scheme II. This synthetic approach, which relies on a regioselective alkylation of the anions **7** with poly(halomethanes), presents the following advantages: (a) only a single construction step on a synthon conveniently derived from the commercially available parent α-amino acids is required; (b) fluorinated α-amino acids can be obtained without resorting to the use of toxic or explosive fluorinating reagents; (c) scale-up preparation can easily be achieved, thus making these molecules available in sufficient quantity for studying their potential pharmacological and therapeutic importance.[6]

Experimental Section

Melting points were determined with a Büchi SMP-20 or a Kofler hot bank melting point apparatus and are uncorrected as are boiling points. ^1H magnetic resonance spectra (60 MHz) were recorded on a Varian Associates T-60 spectrometer and are reported in parts per million from internal tetramethylsilane or 2,2-dimethyl-2-silapentane-5-sulfonate on the δ scale. ^{19}F magnetic resonance spectra (84.6 MHz) were recorded on a Perkin-Elmer R-32 spectrometer and are reported in parts per million from CCl_3F on the φ scale. Trifluoroacetic acid or $CFCl_3$ was used as an internal standard and trifluoroacetic acid was given the value φ = 77.0. Data are presented as follows: solvent, chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants, and interpretation. Infrared spectra were taken on a Perkin-Elmer IR-577 or IR-277 spectrophotometer. Ultraviolet spectra were recorded on a Cary 118 instrument. Microanalyses were conducted on a Perkin-Elmer 240 CHN analyzer. Ionic chloride was determined using a Beckman chloride electrode and a $Hg|Hg_2SO_4$ reference electrode through end-point titration with silver nitrate.

Solvents and reagents were dried prior to use when deemed necessary. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride and diisopropylamine from solid KOH; hexamethylphosphoric triamide (HMPA) was distilled from sodium at low pressure.

Reactions were routinely followed by ^1H NMR analysis of aliquots or by thin layer chromatography (TLC) analysis. Analytical TLC were performed using Merck precoated silica gel 60F-254 plates that were 0.25-mm thick. Four eluant systems were used: system A, EtOH–12 M NH_4OH (4:1); system B, EtOH–H_2O (7:3); system C, BuOH–AcOH–H_2O (3:1:1); system D, phenol–H_2O (3:1). Unless otherwise specified, reaction workups consisted of drying the solvent over anhydrous $MgSO_4$ and removing the solvent by evaporation at reduced pressure. Bulb-to-bulb distillations were accomplished in a Büchi GKR-50 Kugelrohrapparat at the oven temperature and pressure indicated. Reactions described as run under nitrogen employed a mercury bubbler arranged so that the system could alternatively be evacuated and filled with inert gas and left under a positive pressure. Lithium diisopropylamide (LDA) was always prepared in the following manner: a solution of diisopropylamine (1 M) in THF (1 equiv) was cooled to −70 °C followed by addition of a hexane solution of *n*-BuLi (2 M, 1 equiv) via syringe. The cooling bath was removed and the temperature of the reaction mixture was allowed to rise to −20 °C where it was maintained for a few minutes. The resulting solution of lithium diisopropylamide was then cooled to the temperature desired for subsequent operations.

Preparation of the Schiff Base Esters 6. Methyl 2,5-Bis(benzylideneamino)pentanoate (6b). To a suspension of 65 g (0.3 mol) of ornithine methyl ester dihydrochloride and 63.6 g (0.6 mol) of freshly distilled benzaldehyde in 200 mL of methylene chloride cooled to 0 °C and magnetically stirred was added slowly a solution of 60.6 g (0.6 mol) of triethylamine in 70 mL of methylene chloride. The reaction mixture was allowed to stand overnight at room temperature with stirring. After removal of the solvent, the residue was taken up in anhydrous ether, and the insoluble material was filtered off. The filtrate was washed many times with water, then with brine, dried over $MgSO_4$, and concentrated to give 80.8 g of **6b**. Recrystallization from pentane afforded the analytical sample: mp 42 °C; ^1H NMR ($CDCl_3$) δ 1.35–2.35 (m, 4, $-CH_2CH_2-$), 3.5–3.8 (m, 2, $-CH_2N=$), 3.70 (s, 3, $-CO_2CH_3$), 4.02 (broad t, 1, J = 6 Hz, $>CHCO_2-$), 7.18–7.85 (complex m, 10, C_6H_5), 8.21 (s, 2, N=CH–); IR (Nujol) 1743, 1641 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.49; H, 6.89; N, 8.69. Found: C, 74.24; H, 6.88; N, 8.72.

Methyl 2,6-bis(benzylideneamino)hexanoate (6c) was prepared in a similar manner as was **6b**: oil (crude 91%); ^1H NMR ($CDCl_3$) δ 1.0–2.3 (m, 6 H, $-CH_2-$), 3.53 (broad t, 2, J = 7 Hz, $-CH_2N=$), 3.63 (s, 3, $-CO_2CH_3$), 3.93 (t, 1, J = 6 Hz, $>CHCO_2-$), 7.18–7.85 (m, 10, C_6H_5), 8.07 (broad s, 2, –CH=N–).

No analysis.

The following benzylidene α-amino ester derivatives were prepared in a similar manner except that only 1 equiv each of triethylamine and of benzaldehyde were used.

Methyl 2-(benzylideneamino)propionate (6a): (80% after distillation) bp 84 °C (0.04 mm); ^1H NMR ($CDCl_3$) δ 1.52 (d, 3, J = 7 Hz, CH_3-), 3.69 (s, 3, $-CO_2CH_3$), 4.12 (q, 1, J = 7 Hz, $>CHCO_2$), 7.18–7.85 (m, 5, C_6H_5), 8.22 (s, 1, –CH=N–); IR (neat); 1745, 1645 cm^{-1}; UV_{max} (EtOH) 247.5 nm (ε 16 400), 278 (sh), 286 (sh).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.08; H, 6.86; N, 7.32. Found: C, 68.43; H, 6.74; N, 7.18.

Methyl 2-(benzylideneamino)-3-phenylpropionate (6e): (70%) bp 185 °C (0.02 mm); mp (ether–pentane) 33.5 °C; ^1H NMR ($CDCl_3$) δ 2.90–3.42 (m, 2, $-CH_2-$), 3.60 (s, 3, CO_2CH_3), 4.1 (d of d, 1, J_1 = 5.5 Hz, J_2 = 8.5 Hz, $>CHCO_2-$), 7.01 (s, 5, $C_6H_5CH_2-$), 7.05–7.65 (m, 5, $C_6H_5C=N-$), 7.75 (s, 1, –CH=N–); IR (Nujol) 1738, 1640 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.36; H, 6.42; N, 5.24. Found: C, 76.53; H, 6.46; N, 5.12.

Methyl 2-(benzylideneamino)-3-(4-hydroxyphenyl)-propionate (6f): (70%) mp (CH_2Cl_2/pentane) 100 °C; ^1H NMR ($CDCl_3$) δ 2.85–3.30 (m, 2, $-CH_2-$), 3.68 (s, 3, CO_2CH_3), 4.15 (m, 1, $>CHCO_2-$), 5.65 (broad s, 1, OH), 6.6–7.0 (m, 4, C_6H_4-), 7.20–7.75 (m, 5, $C_6H_5C=N-$), 7.90 (s, 1, CH=N); IR (Nujol) 3460, 1708, 1645 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.05; H, 6.06; N, 4.94. Found: C, 71.99; H, 6.10; N, 4.77.

Dimethyl 2-(benzylideneamino)glutarate (6h): (85%) bp 135 °C (0.01 mm); ^1H NMR ($CDCl_3$) δ 2.2–2.5 (m, 4, $-CH_2-$), 3.61 (s, 3, CO_2CH_3), 3.72 (s, 3, CO_2CH_3), 4.04 (m, 1, $>CHCO_2-$), 7.23–7.90 (m, 5, C_6H_5-), 8.21 (s, 1, –CH=N–); IR (film) 1740, 1645 cm^{-1}; UV_{max} (EtOH) 248.5 nm (ε 17 600), 277 (sh), 287 (sh).

Anal. Calcd for $C_{14}N_{17}NO_4$: C, 63.85; H, 6.52; N, 5.32. Found: C, 63.85; H, 6.55; N, 5.27.

Methyl 2-(benzylideneamino)-4-(methylthio)butyrate (6d): (82%) bp 140 °C (0.04 mm); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3, $-SCH_3$), 2.1–2.8 (m, 4, $-CH_2-$), 3.67 (s, 3, CO_2CH_3), 4.15 (t, 1, J = 6 Hz, $>CHCO_2-$), 7.2–7.8 (m, 5, C_6H_5), 8.25 (s, 1, –CH=N–); IR (film) 1738, 1642 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.10; H, 6.83; N, 5.57. Found: C, 62.08; H, 6.82; N, 5.42.

Methyl 2-(benzylideneamino)-3-(*N*-trityl-5-imidazolyl)-propionate (6i): (90%) mp (ether/pentane) 144 °C; ^1H NMR ($CDCl_3$) δ 2.8–3.2 (m, 2, $-CH_2-$), 3.46 (s, 3, CO_2CH_3), 4.26 (d of d, 1, J_1 = 5.5 Hz, J_2 = 9 Hz, $>CHCO_2-$), 6.36 (broad s, 1, H imidazolyl), 6.7–7.7 (complex m, 20, C_6H_5), 7.9 (s, 1, –CH=N–), 9.73 (s, 1, H imidazolyl); IR (Nujol) 1740, 1640 cm^{-1}.

Anal. Calcd for $C_{33}H_{29}N_3O_2$: C, 79.32; H, 5.86; N, 8.41. Found: C, 79.62; H, 5.73; N, 8.44.

Methyl 2-(Benzylideneamino)-3-(3,4-dimethoxyphenyl)-propionate (6g). To a solution of lithium diisopropylamide (52 mmol) in THF cooled to −78 °C was added under nitrogen a solution of 8.85 g (50 mmol) of methyl *N*-benzylideneglycinate in 50 mL of THF. The reaction mixture was stirred for 1 h at −78 °C followed by the addition of a solution of 11.55 g (50 mmol) of 3,4-dimethoxybenzyl bromide in 60 mL of THF. The cooling bath was removed, and the mixture was allowed to warm to room temperature. The resulting solution was quenched with water and then extracted with ether. Removal of the solvent left 14.2 g of crude **6g** which was used in subsequent reactions without purification. An analytical sample was obtained by bulb-to-bulb distillation (extensive decomposition took place): bp 205 °C (0.05 mm); ^{1}H NMR ($CDCl_3$) δ 3.20 (m, 2, $-CH_2-$), 3.64 (s, 3, $-OCH_3$), 3.72 (s, 3, $-OCH_3$), 3.78 (s, 3, OCH_3), 4.11 (m, 1, $>CHCO_2-$), 6.69 (m, 3, C_6H_3), 7.18–7.75 (m, 5, $C_6H_5C{=}N-$), 7.83 (s, 1, $-CH{=}N-$).

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.69; H, 6.48; N, 4.28. Found: C, 69.62; H, 6.59; N, 4.15.

Methyl 2-Amino-3-(3,4-dimethoxyphenyl)propionate Hydrochloride. To a solution of 6.54 g (20 mmol) of crude **6g** in 150 mL of ether was added 100 mL of 1 M aqueous hydrochloric acid. The mixture was stirred for 3 h. The aqueous phase was washed with ether and concentrated in vacuo. The residue was crystallized from H_2O/THF to give 2.75 g (50%) of amino ester hydrochloride: mp 176 °C; ^{1}H NMR (D_2O) δ 3.18 (m, 2, $-CH_2-$), 3.78 (s, 9, OCH_3), 4.25 (broad t, 1, J = 6.5 Hz, $>CHCO_2-$), 6.88 (m, 3, C_6H_3); UV_{max} (EtOH) 279 nm (ε 3000); TLC (system A) 0.85.

Anal. Calcd for $C_{12}H_{17}NO_4$-HCl: C, 52.26; H, 6.59; N, 5.08. Found: C, 52.27; H, 6.61; N, 4.92.

The mother liquors were concentrated to afford a residue which was dissolved in CH_2Cl_2. Triethylamine was added until the solution became basic. Evaporation of the solvent gave a crystalline residue which was extracted with ether. The solid which precipitated upon concentration of the organic phase was filtered and recrystallized from AcOEt–pentane to give 0.3 g of methyl 2-amino-2-(3,4-dimethoxyphenyl)methyl-3-(3,4-dimethoxyphenyl)propionate: mp 133 °C; ^{1}H NMR ($CDCl_3$) 1.60 (s, 2, NH_2), 2.98 (AB, 4, J_{AB} = 13 Hz, ν_{AB} = 31.7 Hz, $-CH_2-$), 3.62, (s, 3, CO_2CH_3), 3.79 (s, 12, OCH_3), 6.70 (m, 6, C_6H_3); UV_{max} (EtOH) 280 nm (ε 6000); TLC (AcOEt) 0.22.

Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.63; H, 6.88; N, 3.35.

Alkylation of Schiff Base Esters 6 with Bromochloromethane. Methyl 2-(Benzylideneamino)-2-(chloromethyl)-3-(4-hydroxyphenyl)propionate (8f). To a solution of diisopropylamide (8 mmol) in THF cooled to −78 °C and magnetically stirred under nitrogen was added 25 mL of HMPA and a solution of 1.13 g (4 mmol) of **6f** in 30 mL of THF. The reaction mixture was stirred for 30 min at −78 °C followed by addition of a solution of 1.05 g (8 mmol) of chlorobromomethane in 5 mL of THF in a single portion. The cooling bath was removed, the mixture was allowed to warm to room temperature, and stirring was continued overnight. The resulting solution was quenched with water and extracted with ether. The organic phase was thoroughly washed with water. Concentration at reduced pressure gave 1.21 g of **8f** (oily residue) which was crystallized from ether–pentane: mp <50 °C; ^{1}H NMR ($CDCl_3$) δ 3.23 (s, 2, $-CH_2-$), 3.71 (s, 3, CO_2CH_3), 3.83 (s, 2, CH_2Cl), 5.0 (broad s, 1, OH), 6.80 (m, 4, C_6H_4), 7.16–7.8 (m, 5, $C_6H_5C{=}N-$), 8.1 (broad s, 1, $-CH{=}N$); IR (Nujol) 3400, 1730 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}NO_3Cl$: C, 65.15; H, 5.48; N, 4.22. Found: C, 65.05; H, 5.53; N, 3.95.

The following α-chloromethyl benzylideneamino ester derivatives were prepared in a similar manner except that only 1 equiv of LDA and 1.1 equiv of chlorobromomethane were used.

Methyl 2,5-Bis(benzylideneamino)-2-(chloromethyl)-pentanoate (8b). Better yields were obtained in the absence of HMPA in the reaction medium. **8b** was obtained as an oil which could not be purified. ^{1}H NMR of crude material ($CDCl_3$): δ 1.43–2.25 (m, 4, $-CH_2CH_2-$), 3.7 (s, 3, CO_2Me), 3.93 (s, 2, $-CH_2Cl$), 7.03 (complex m, 10, $C_6H_5C{=}N-$), 8.13 (broad s, 1, $-CH{=}N-$), 8.2 (s, 1, $-CH{=}N-$).

No analysis.

Methyl 2-(benzylideneamino)-2-(chloromethyl)-3-(*N*-trityl-5-imidazolyl)propionate (8i): oil (80%); ^{1}H NMR ($CDCl_3$) of crude material δ 3.30 (s, 2, $-CH_2-$), 3.68 (s, 3, CO_2CH_3), 4.05 (AB, 2, J_{AB} = 10 Hz, ν_{AB} = 10 Hz, CH_2Cl), 6.53 (s, 1, H imidazolyl), 6.8–7.8 (complex m, 21, C_6H_5), 8.23 (s, 1, $-N{=}CH-$).

No analysis.

Methyl 2-(benzylideneamino)-2-(chloromethyl)-3-phenylpropionate (8e): (75%) bulb-to-bulb distilled; bp 187 °C (0.03 mm); solidified on standing; mp 53 °C; ^{1}H NMR ($CDCl_3$) δ 3.31 (s, 2, $-CH_2-$), 3.71 (s, 3, CO_2CH_3), 3.81 (s, 2, CH_2Cl), 7.1 (s, 5, C_6H_5-), 7.16–7.73 (m, 5, $C_6H_5C{=}N-$), 8.13 (s, 1, $-CH{=}N-$); IR (Nujol) 1732, 1645 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}NO_2Cl$: C, 68.45; H, 5.76; N, 4.43. Found: C, 67.93; H, 5.66; N, 4.20.

Methyl 2-(benzylideneamino)-2-(chloromethyl)-4-(methylthio)butyrate (8d): oil (87%); decomposed during distillation; ^{1}H NMR of crude material ($CDCl_3$) δ 2.1 (s, 3, SCH_3), 2.15–2.73 (m, 4, $-CH_2CH_2-$), 3.73 (s, 3, CO_2Me), 3.90 (s, 2, CH_2Cl), 7.2–7.8 (m, 5, $C_6H_5C{=}N$), 8.25 (s, 1, $-CH{=}N-$).

No analysis.

Methyl 2,6-bis(benzylideneamino)-2-(chloromethyl)-hexanoate (8c): oil (77%); ^{1}H NMR of crude material ($CDCl_3$) δ 1.2–2.4 (complex m, 6, $-CH_2-$), 3.56 (broad t, 2, J = 7 Hz, $CH_2N{=}C-$), 3.73 (s, 3, CO_2CH_3), 3.91 (s, 2, CH_2Cl), 7.2–7.9 (m, 10, C_6H_5-), 8.16 (broad s, 1, $-CH{=}N-$), 8.26 (s, 1, $-CH{=}N-$).

No analysis.

Methyl 2-(benzylideneamino)-2-methyl-3-chloropropionate (8a): oil (85%) bulb-to-bulb distilled; bp 155 °C (0.05 mm); ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 3, CH_3), 3.66 (s, 3, CO_2CH_3), 3.86 (AB, 2, J_{AB} = 10 Hz, ν_{AB} = 10 Hz, CH_2Cl), 7.0–7.8 (m, 5, C_6H_5), 8.13 (s, 1, $-CH{=}N-$); IR (film) 1735, 1638 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}NO_2Cl$: C, 60.11; H, 5.89; N, 5.84. Found: C, 60.15; H, 6.18; N, 5.84.

Dimethyl 2-(benzylideneamino)-2-(chloromethyl)glutarate (8h): oil (64%) bulb-to-bulb distilled; bp 175 °C (0.03 mm); ^{1}H NMR ($CDCl_3$) δ 2.23–2.53 (m, 4, $-CH_2CH_2-$), 3.56 (s, 3, $-CO_2CH_3$), 3.72 (s, 3, CO_2CH_3), 3.83 (s, 2, CH_2Cl), 7.18–7.82 (m, 5, C_6H_5), 8.22 (s, 1, $-CH{=}N$); IR (film) 1735, 1643 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}NO_4Cl$: C, 57.78; H, 5.83; N, 4.49. Found: C, 57.93; H, 5.83; N, 4.49.

Methyl 2-(benzylideneamino)-2-(chloromethyl)-3-(3,4-dimethyoxyphenyl)propionate (8g): oil (83%); ^{1}H NMR of crude **8g** ($CDCl_3$) δ 3.26 (s, 2, CH_2), 3.63, 3.73 and 3.80 (three s, 9, OCH_3), 3.83 (s, 2, CH_2Cl), 6.76 (m, 3, H aromatic), 7.2–7.8 (m, 5, H aromatic), 8.1 (s, 1, $-CH{=}N-$).

No analysis.

Alkylation of Schiff Base Esters 6 with Chlorodifluoromethane. Methyl 2-(Difluoromethyl)-2,5-bis(benzylideneamino)pentanoate (9b). To a solution of lithium diisopropylamide (0.9 mol) in THF cooled to −78 °C and magnetically stirred under nitrogen was added a solution of 261 g (0.81 mol) of **6b** in 1.5 L of THF. At the end of the addition, the cooling bath was replaced by a warm-water bath. When the temperature of the reaction mixture reached 40 °C, the nitrogen inlet was disconnected and replaced by an expandable balloon. The reaction mixture was then saturated with chlorodifluoromethane by passing a rapid stream of chlorodifluoromethane through the solution (saturation was obtained when the balloon started to expand) maintained at a temperature of 40 to 50 °C. After the mixture was stirred for 1 h under freon atmosphere, the reaction mixture was quenched with brine and extracted with ether to give 294 g (97%) of crude **9b**: oil, unstable to distillation and to chromatography; ^{1}H NMR ($CDCl_3$) δ 1.50–2.43 (m, 4, $-CH_2-$), 3.59 (broad t, 2, $-CH_2N{=}$), 3.73 (s, 3, CO_2CH_3), 6.12 (t, 1, J = 54.5 Hz, $-CHF_2$), 7.14–7.81 (m, 10, C_6H_5-), 8.17 (s, 1, $-CH{=}N-$), 8.32 (s, 1, $-CH{=}N-$); ^{19}F NMR ($CDCl_3$) φ −129.4 [AB part of an ABX system (4 lines), J_{HF} = 54.5 Hz].

No analysis.

The following α-(difluoromethyl)-α-(benzylideneamino) ester derivatives were prepared in a similar manner.

Methyl 2-(benzylideneamino)-2-(difluoromethyl)-3-phenylpropionate (9e): oil (72%) bulb-to-bulb distilled; bp 165 °C (0.02 mm); ^{1}H NMR ($CDCl_3$) δ 3.0–3.6 (m, 2, $-CH_2-$), 3.70 (s, 3, CO_2CH_3), 6.05 (t, 1, J = 54 Hz, $-CHF_2$), 7.1 (s, 5, C_6H_5-), 7.2–7.88 (m, 5, $C_6H_5C{=}N-$), 8.08 (s, 1, $-CH{=}N-$); IR (film) 1745, 1645 cm^{-1}.

Anal. Calcd for $C_{18}H_{17}NO_2F_2$: C, 68.13; H, 5.40; N, 4.41. Found: C, 68.10; H, 5.61; N, 4.45.

Methyl 2-(difluoromethyl)-2-(benzylideneamino)-3-(4-hydroxyphenyl)propionate (9f) (2 equiv of LDA were used to generate the anion **7f**): oil (crude 78%); ^{1}H NMR ($CDCl_3$) δ 3.27 (m, 2, CH_2–), 3.66 (s, 3, CO_2CH_3), 5.70 (broad s, 1, OH), 6.04 (t, 1, J = 54 Hz, –CHF_2), 6.75 (m, 4, C_6H_4–), 7.15–7.75 (m, 5, C_6H_5–), 8.09 (s, 1, –CH=N–).

No analysis.

Methyl 2-(benzylideneamino)-2-(difluoromethyl)-3-(3,4-dimethoxyphenyl)propionate (9g): oil (86%); ^{1}H NMR ($CDCl_3$) δ 3.26 (m, 2, $-CH_2-$), 3.63 (s, 3, $-OCH_3$), 3.72 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 6.02 (t, 1, J = 54 Hz, $-CHF_2$), 6.62 (m, 3, C_6H_3–), 7.12–7.72 (m, 5, C_6H_5–), 8.0 (s, 1, –CH=N–); ^{19}F NMR ($CDCl_3$) φ –128.9 (ABX, 4 lines, J_{HF} = 54 Hz).

No analysis.

Methyl 2-(benzylideneamino)-2-methyl-3,3-difluoropropionate (9a): (83%) bulb-to-bulb distilled; bp 95 °C (0.04 mm); ^{1}H NMR ($CDCl_3$) δ 1.55 (broad s, 3, small coupling with F, CH_3), 3.73 (s, 3, CO_2CH_3), 6.22 (t, 1, J = 55 Hz, $-CHF_2$), 7.25–7.85 (m, 5, C_6H_5), 8.27 (s, 1, –CH=N–); ^{19}F NMR ($CDCl_3$) φ –130.8 [AB part of an ABX system (8 lines), J_{HF} = 55 Hz, J_{FF} = 278 Hz, ν_{FF} = 452 Hz]; IR (Nujol) 1740, 1642 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_2F_2$: C, 59.74; H, 5.43; N, 5.81. Found: C, 59.96; H, 5.54; N, 5.97.

Methyl 2-(benzylideneamino)-2-(difluoromethyl)-4-(methylthio)butyrate (9d): (crude 72%) bulb-to-bulb distilled; bp 139 °C (0.03 mm); ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3, $-SCH_3$), 2.2–2.9 (m, 4, $-CH_2-$), 3.76 (s, 3, CO_2CH_3), 6.13 (t, 1, J = 55 Hz, $-CHF_2$), 7.2–7.95 (m, 5, C_6H_5), 8.3 (s, 1, –CH=N–).

No analysis.

Methyl 2,5-bis(benzylideneamino)-2-(difluoromethyl)-hexanoate (9c): oil (crude 80%); ^{1}H NMR ($CDCl_3$) δ 1.0–2.35 (m, 6, $-CH_2-$), 3.58 (broad t, 2, J = 7 Hz, $-CH_2N=$), 3.71 (s, 3, CO_2CH_3), 6.13 (t, 1, J = 55 Hz, $-CHF_2$), 7.1–7.9 (m, 10, C_6H_5–), 8.16 (s, 1, –CH=N–), 8.33 (s, 1, –CH=N–).

No analysis.

Methyl 2-(benzylideneamino)-2-(difluoromethyl)-3-(*N*-trityl-5-imidazolyl)propionate (9i): yellow powder (crude 90%). The following peaks in the ^{1}H NMR spectrum were assigned to **9i**: ^{1}H NMR ($CDCl_3$) δ 3.30 (m, $-CH_2-$), 3.66 (s, CO_2CH_3), 6.2 (t, J = 54 Hz, $-CHF_2$), 6.50 (broad s, H imidazolyl), 6.6–7.9 (m, C_6H_5), 8.26 (s, –CH=N–); the integration of the aromatic H was far in excess of the expected value. **9i** was evaluated to represent 45% of the mixture.

Alkylation of Schiff Base Esters 6 with Chlorofluoromethane. Methyl 2-(Fluoromethyl)-2-(benzylideneamino)-3-phenylpropionate (10e). To 10 mmol of NaH, washed with pentane, was added under N_2 2.67 g (10 mmol) of **6e** in 20 mL of HMPA. After stirring the mixture for 4 h at room temperature, the nitrogen inlet was disconnected and replaced by an expandable balloon. Then, a solution of 2.8 g (40 mmol) of chlorofluoromethane in 20 mL of THF cooled to –50 °C was added. After stirring the solution for 20 h at room temperature, the solvent was concentrated under reduced pressure, and the residue was taken up with water and extracted with ether. Usual workup yielded 2.9 g of crude **10e**: oil, ^{1}H NMR ($CDCl_3$) δ 3.26 (m, 2, $-CH_2-$), 3.67 (s, 3, $-OCH_3$), 4.60 (d, 2, J_{HF} = 47 Hz, $-CH_2F$), 6.92–7.82 (m, 10, C_6H_5), 8.25 (s, 1, –CH=N).

No analysis.

The following α-(fluoromethyl)-α-(benzylideneamino) ester derivatives **10** were obtained in a similar manner.

Methyl 2-(fluoromethyl)-2,5-bis(benzylideneamino)-pentanoate (10b): oil (crude 87%); ^{1}H NMR ($CDCl_3$) δ 1.50–2.30 (m, 4, $-CH_2CH_2-$), 3.58 (m, 2, $-CH_2N=$), 3.68 (s, 3, $-CO_2CH_3$), 4.67 (d, 2, J_{HF} = 47 Hz, $-CH_2F$), 7.06–7.78 (m, 10, C_6H_5), 8.16 (s, 1, –CH=N–), 8.27 (s, 1, –CH=N–).

No analysis.

Methyl 2-(benzylideneamino)-2-methyl-3-fluoropropionate (10a): oil (crude 72%); ^{1}H NMR ($CDCl_3$) δ 1.58 (d, 3, J = 1.5 Hz, $-CH_3$), 3.75 (s, 3, CO_2CH_3), 4.27 and 5.02 (two AB system, 2, J_{HH} = 8.5 Hz, ν_{HH} = 10.5 Hz, J_{HF} = 47 Hz), 7.10–7.81 (m, 5, C_6H_5), 8.28 (s, 1, –CH=N–).

No analysis.

Alkylation of the Schiff Base Ester 6a with Dibromodifluoromethane. Methyl 2-(Benzylideneamino)-2-methyl-3,3-difluoro-3-bromopropionate (11a). A mixture of 3.37 g (75 mmol) of NaH (washed with pentane) and 14.32 g (75 mmol) of **6a** in 150 mL of THF was stirred at room temperature for 24 h. The **7a** anion solution was then cooled to –78 °C, and a solution of 17.3 g (83 mmol) of dibromodifluoromethane in 120 mL of THF was added over a period of 5 min. The temperature of the reaction mixture was allowed to rise slowly to 20 °C over a period of 2 h. Concentration of the solvent under reduced pressure left a residue which was extracted with ether. Usual workup afforded 17 g of an oil which according to the ^{1}H and ^{19}F NMR spectra consisted of a 5:1 mixture of **11a** and **9a**. A part (8.55 g) of this mixture, containing an estimated 4.5 mmol of **11a**, was dissolved in 300 mL of pentane and stirred for 12 h with 50 mL of aqueous HCl (0.1 M). The organic phase was separated, washed with water and brine, and dried over $MgSO_4$. Bulb-to-bulb distillation of the residue afforded benzaldehyde and analytically pure **11a**: bp 86 °C (0.02 mm); ^{1}H NMR ($CDCl_3$) δ 1.75 (broad s, 3, $-CH_3$), 3.78 (s, 3, CO_2CH_3), 7.18–7.90 (m, 5, C_6H_5), 8.24 (s, 1, –CH=N–); ^{19}F NMR ($CDCl_3$) (ref CCl_3F) φ –55.5 (unsymm. d, J = 4 Hz); IR (film) 1745, 1650 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}NO_2F_2Br$: C, 45.02; H, 3.78; N, 4.37. Found: C, 44.92; H, 3.73; N, 4.15.

Hydrolysis of 8, 9, and 10 to the Corresponding Amino Esters 12, 13, and 14. Methyl 2-(Difluoromethyl)-2,6-diaminohexanoate Dihydrochloride (13c). A mixture of 15.4 g (40 mmol) of **9c** in 20 mL of ether and 110 mL of 2 N aqueous hydrochloric acid was vigourously stirred at room temperature for 3 h. The aqueous phase was decanted, washed with ether, and concentrated in vacuo. The residue was crystallized from CH_3OH–ether to give 9.15 g (85%) of **13c**: mp 207 °C; ^{1}H NMR (D_2O) δ 1.0–2.4 (m, 6, $-CH_2-$), 3.0 (broad t, 2, J = 7 Hz, $-CH_2NH_2$), 3.88 (s, 3, CO_2CH_3), 6.43 (t, 1, J = 53 Hz, $-CHF_2$); ^{19}F NMR (D_2O) (ref CF_3COOH) φ –129.6 [AB part of an ABX system (8 lines), J_{HF} = 53 Hz, J_{FF} = 284 Hz, ν_{FF} = 481 Hz]; IR (Nujol) 1758 cm^{-1}; TLC (system A) 0.38.

Anal. Calcd for $C_8H_{16}N_2O_2F_2$·2HCl: C, 33.93; H, 6.41; N, 9.89. Found: C, 34.12; H, 6.47; N, 9.66.

By following a similar procedure, **12a–i**, **13a,b,d–g,i**, and **14a,e** were obtained from the corresponding **8a–i**, **9a,b,d–g,i**, and **10a,e**. These amino ester hydrochlorides were not purified with the exception of the following.

12f: mp 45 °C (amorphous); ^{1}H NMR (D_2O) δ 3.23 (AB, 2, J_{AB} = 13 Hz, ν_{AB} = 10 Hz, $-CH_2-$), 3.83 (s, 3, CO_2CH_3), 4.06 (AB, 2, J_{AB} = 11 Hz, ν_{AB} = 13 Hz, $-CH_2Cl$), 6.9 (m, 4, C_6H_4).

Anal. Calcd for $C_{11}H_{14}NO_3Cl$·HCl: C, 47.15; H, 5.40; N, 5.00. Found: C, 46.93; H, 5.63; N, 4.66.

12i: mp (MeOH–ether) 180 °C dec; ^{1}H NMR (D_2O) δ 3.56 (s, 2, $-CH_2-$), 3.93 (s, 3, CO_2CH_3), 4.1 (AB, 2, J_{AB} = 12 Hz, ν_{AB} = 8 Hz, CH_2Cl), 7.46 (s, 1, H imidazolyl), 8.66 (s, 1, H imidazolyl); IR (Nujol) 1750 cm^{-1}.

Anal. Calcd for $C_8H_{12}N_3O_2Cl$·2HCl: C, 33.06; H, 4.86; N, 14.46. Found: C, 33.02; H, 5.04; N, 14.97.

13e: mp (CH_3OH–ether) 103 °C (crystallized with 1 mol of CH_3OH); ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 3, CH_3OH), 3.39 (AB, 2, J_{AB} = 14 Hz, ν_{AB} = 18.5 Hz, $-CH_2-$), 3.88 (s, 3, CO_2CH_3), 6.55 (t, 1, J_{HF} = 53 Hz, $-CHF_2$), 7.05–7.60 (m, 5, C_6H_5); ^{19}F NMR (D_2O) (ref CF_3CO_2H) φ –130 [AB part of an ABX system (8 lines), J_{HF} = 53 Hz, J_{FF} = 284 Hz, ν_{FF} = 448 Hz]; IR (Nujol) 1758 cm^{-1}; TLC (system C) 0.81.

Anal. Calcd for $C_{11}H_{13}NO_2F_2$·HCl·CH_3OH: C, 48.21; H, 6.09; N, 4.70. Found: C, 48.21; H, 5.98; N, 4.54.

14a: oil; ^{1}H NMR (D_2O) δ 1.58 (d, 3, J = 1.5 Hz, CH_3), 3.82 (s, 3, CO_2CH_3), 4.73 (two q, ABX system, 2, J_{HH} = 10 Hz, ν_{HH} = 12.5 Hz, J_{HF} = 47 Hz, CH_2F); ^{19}F NMR (D_2O) (ref CF_3CO_2H) φ –226.85 (t, J_{HF} = 47 Hz).

No analysis.

14e. The crude amino ester hydrochloride was neutralized by 1 equiv of triethylamine in CH_2Cl_2 and the free base was purified by silica gel column chromatography (eluant C_6H_6–ether 9–1): oil; ^{1}H NMR ($CDCl_3$) δ 1.70 (broad s, 2, NH_2), 2.87 (AB, 2, J_{HH} = 12 Hz, ν_{HH} = 16.5 Hz, $-CH_2-$), 3.75 (s, 3, CO_2CH_3), 4.46 (two q, ABX system, J_{HH} = 8.5 Hz, ν_{HH} = 18.5 Hz, J_{HF} = 47 Hz, CHF_2), 7.10 (m, 5, C_6H_5).

No analysis.

Preparation of 2-Piperidone Derivatives 4. 3-Amino-3-(fluoromethyl)-2-piperidone (4, Y = CH_2F). To a solution of 2.5 g (10 mmol) of **14b** in 30 mL of methanol was added under nitrogen a solution of sodium methylate (prepared from 0.46 g

of sodium) in 20 mL of methanol. The reaction mixture was stirred for 1 h at room temperature and then concentrated in vacuo. The residue was taken up in CH_2Cl_2. The insoluble material was removed by filtration, and the filtrate was concentrated to give 1 g (68%) of **4** (Y = CH_2F): mp (CH_2Cl_2–pentane) 134 °C; ^1H NMR ($CDCl_3$) δ 1.5–2.4 (m, 6, $-CH_2-$ and NH_2), 3.2–3.6 (m, 2, CH_2N), 4.32 (two q, ABX system, 2, J_{HH} = 8 Hz, ν_{HH} = 22.5 Hz, J_{HF} = 47 Hz, CH_2F), 6.95 (s, 1, CONH); ^{19}F NMR ($CDCl_3$) ϕ −226.7 (t, J_{HF} = 47 Hz); IR (Nujol) 3400, 3290, 3205, and 1655 cm^{-1}; TLC (system A) 0.56.

Anal. Calcd for $C_6H_{11}N_2OF$: C, 49.30; H, 7.58; N, 19.16. Found: C, 49.35; H, 7.48; N, 19.35.

3-Amino-3-(difluoromethyl)-2-piperidone (**4**, Y = CHF_2) was prepared in a similar manner from **13b**: (73%) mp (chloroform–pentane) 149 °C; bp (bulb-to-bulb distillation) 135 °C (0.05 mm); ^1H NMR (D_2O) δ 1.58–2.30 (m, 4, $-CH_2CH_2-$), 3.09–3.51 (m, 2, CH_2N-), 5.96 (t, 1, J = 55 Hz, $-CHF_2$); ^{19}F NMR (D_2O) (ref CF_3COOH) ϕ −131.5 [AB part of an ABX system (8 lines), J_{FF} = 278 Hz, ν_{FF} = 814 Hz, $J_{HF_1} = J_{HF_2}$ = 55 Hz]; TLC (system A) 0.66.

Anal. Calcd for $C_6H_{10}N_2OF_2$: C, 43.90; H, 6.14; N, 17.05. Found: C, 44.16; H, 6.05; N, 17.15.

3-Amino-3-(hydroxymethyl)-2-piperidone (**4**, Y = CH_2OH) was prepared in a similar manner from α-(hydroxymethyl)-ornithine methyl ester dihydrochloride (81%): mp ($CHCl_3$) 145 °C; ^1H NMR (D_2O) δ 1.5–2.3 (m, 4, $-CH_2-$), 3.0–3.4 (m, 2, $-CH_2N$), 3.56 (AB, 2, J_{AB} = 10 Hz, ν_{AB} = 14 Hz, CH_2OH).

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.97; H, 8.47; N, 19.43. Found: C, 49.55; H, 8.17; N, 18.97.

3-(Chloromethyl)-3-amino-2-piperidone Hydrochloride (4, Y = CH_2Cl). To a solution of 3.6 mL (49 mmol) of thionyl chloride in 50 mL of anhydrous dimethylformamide was added 7 g (49 mmol) of **4** (Y = CH_2OH). The reaction mixture was stirred for 24 h at 80 °C whereupon another equiv of thionyl chloride (3.6 mL) was added and stirring continued at 80 °C for 2 h. The residue obtained after elimination of the solvent under reduced pressure gave upon trituration with chloroform 2.1 g (21%) of analytically pure 3-(chloromethyl)-3-amino-2-piperidone hydrochloride: mp 230 °C; ^1H NMR (D_2O) δ 1.80–2.60 (m, 4, $-CH_2-$), 3.33 (broad t, 2, J = 7 Hz, CH_2N), 4.03 (AB, 2, J_{AB} = 13 Hz, ν_{AB} = 8.5 Hz, CH_2Cl); IR (Nujol) 1680 cm^{-1}.

Anal. Calcd for $C_6H_{10}N_2OCl\cdot HCl$: C, 36.19; H, 6.08; N, 14.07. Found: C, 36.39; H, 6.04; N, 14.21.

(+)- and (−)-3-Amino-3-(difluoromethyl)-2-piperidone Hydrochloride (4, Y = CHF_2). To a solution of 1.27 g (3.6 mmol) of (−)-binaphthylphosphoric acid in 50 mL of boiling EtOH was added a solution of 0.55 g of (±)-**4** (Y = CHF_2) in 5 mL of EtOH. On cooling, crystals separated. The mixture was aged overnight at 4 °C. Filtration of the solid gave 0.69 g of the crystalline salt of the (−)-binaphthylphosphoric acid: mp 300 °C; $[\alpha]_D$ −409° (*c* 0.3, CH_3OH). Anal. Calcd for $C_{26}H_{23}N_2O_5F_2P$: C, 60.94; H, 4.52; N, 5.47. Found: C, 61.03; H, 4.61; N, 5.47. Concentration under reduced pressure of the filtrate left 1.1 g of a gummy material which was treated with 10 mL of 3 M aqueous HCl for 3 h at room temperature. The solid which separated was filtered, and the filtrate was concentrated in vacuo to give 0.32 g of a solid residue. Two recrystallizations from EtOH yielded 0.16 g of (+)-3-amino-3-(difluoromethyl)-2-piperidone hydrochloride: mp 238 °C; $[\alpha]_D$ +18.6° (*c* 1, CH_3OH); ^1H NMR (D_2O) δ 1.70–2.55 (m, 4, $-CH_2-$), 3.30 (broad t, 2, J = 7 Hz, CH_2N), 6.25 (t, 1, J = 54 Hz, CHF_2); TLC (system A) 0.63. Anal. Calcd for $C_6H_{10}F_2N_2O\cdot HCl$: C, 35.91; H, 5.52; N, 13.96. Found: C, 36.10; H, 5.59; N, 14.03. Treatment of 0.44 g of the crystalline salt of (−)-binaphthylphosphoric acid under similar conditions gave 0.07 g of the (−)-enantiomer: mp 240 °C; $[\alpha]_D$ −19° (*c* 1.02, CH_3OH). Anal. Found: C, 35.84; H, 5.45; N, 14.07.

Preparation of α-(Halogenomethyl)-α-amino Acids 2, 15, and 16. 2-(Difluoromethyl)-2-amino-3-(3,4-dihydroxyphenyl)propionic Acid Dihydrate (15g). A solution of 3.5 g of **13g** in 125 mL of 47% aqueous hydrobromic acid was heated at reflux temperature under nitrogen for 24 h. Concentration in vacuo left a residue which was dissolved in 15 mL of water. The pH of the solution was adjusted to 5.6 by addition of triethylamine. To the solution was added 70 mL of acetone. The crystals which separated on cooling were filtered, washed with chloroform, and then recrystallized from 25 mL of water to give 2.5 g of **15g**: mp 250 °C; ^1H NMR (D_2O) δ 3.21 (AB, 2, J_{AB} = 14 Hz, ν_{AB} = 21 Hz, $-CH_2-$), 6.44 (t, 1, J_{HF} = 53 Hz, CHF_2), 6.5–7.0 (m, 3, C_6H_3-); ^{19}F NMR (D_2O) (ref CF_3COOH) ϕ −129.3 [AB part of an ABX system (8 lines), $J_{F_1F_2}$ = 284 Hz, $J_{F_1H} = J_{F_2H}$ = 53 Hz, $\nu_{F_1F_2}$ = 447 Hz, CF_2H]; UV_{max} (H_2O) 279.5 nm (ϵ 2700), 220 (ϵ 6100); TLC (system C) 0.44.

Anal. Calcd for $C_{10}H_{11}NO_4F_2\cdot 2H_2O$: C, 42.41; H, 5.34; N, 4.94. Found: C, 42.57; H, 5.21; N, 4.71.

α-(Difluoromethyl)phenylalanine (15e). A solution of 3.2 g of **13e** in 100 mL of 6 M hydrochloric acid was heated at reflux for 12 h. The residue obtained after concentration in vacuo was dissolved in 20 mL of ethanol and treated with an excess of propylene oxide. The crystals which separated were collected, washed with ethanol and chloroform, and recrystallized from H_2O–EtOH to give 1.4 g of **15e** (62%): mp 240 °C (sublime); ^1H NMR (D_2O) δ 3.15 (AB, 2, J_{AB} = 14 Hz, ν_{AB} = 22 Hz, $-CH_2-$), 6.38 (t, 1, J_{HF} = 53 Hz, $-CHF_2$), 7.15–7.50 (m, 5, C_6H_5); ^{19}F NMR (D_2O) (ref CF_3COOH) ϕ −130.1 (AB part of an ABX system (8 lines), $J_{F_1F_2}$ = 278 Hz, $J_{F_1H} = J_{F_2H}$ = 53 Hz, $\nu_{F_1F_2}$ = 423 Hz, CF_2H); UV_{max} (H_2O) 251 nm (ϵ 140) 256.5 (ϵ 170), 261.5 (ϵ 130); TLC (system A) 0.69.

Anal. Calcd for $C_{10}H_{11}NO_2F_2$: C, 55.81; H, 5.15; N, 6.51. Found: C, 55.71; H, 5.03; N, 6.40.

The following α-(halogenomethyl)-α-amino acids were prepared in a similar manner from the corresponding α-(halogenomethyl) amino esters **12**, **13**, and **14** or 2-piperidone derivatives **4**.

α-(Difluoromethyl)tyrosine (15f): mp (EtOH–propylene oxide) >260 °C; ^1H NMR (D_2O + DCl) δ 3.45 (AB, 2, J_{AB} = 14 Hz, ν_{AB} = 20 Hz, $-CH_2-$), 6.60 (t, 1, J_{HF} = 53 Hz, $-CHF_2$), 6.9–7.4 (m, 4, C_6H_4-); ^{19}F NMR (D_2O + DCl) (ref CF_3COOH) ϕ −129.5 [AB part of an ABX system (8 lines), $J_{F_1F_2}$ = 282 Hz, $J_{F_1H} = J_{F_2H}$ = 53 Hz, $\nu_{F_1F_2}$ = 440 Hz]; UV_{max} (1 N HCl) 279 nm (ϵ 1180), 273.5 (ϵ 1350) 223.5 (ϵ 8150); TLC (system B) 0.73.

Anal. Calcd for $C_{10}H_{11}NO_3F_2$: C, 51.95; H, 4.79; N, 6.06. Found: C, 51.99; H, 4.94; N, 6.01.

2-(Difluoromethyl)-2-amino-3-(3,4-dimethoxyphenyl)-propionic acid was obtained by treating the parent methyl ester with 3.6 M HCl at 95 °C for 4 days (45%): mp (H_2O) 194 °C; ^1H NMR (D_2O) δ 3.06 (AB, 2, J_{AB} = 14 Hz, ν_{AB} = 23 Hz, $-CH_2-$), 3.67 (s, 6, OCH_3), 6.2 (t, 1, J_{HF} = 53 Hz, CHF_2), 6.80 (m, 3, C_6H_3-); ^{19}F NMR (D_2O) (ref CF_3COOH) ϕ −129.6 [AB part of an ABX system (8 lines), $J_{F_1F_2}$ = 282 Hz, $J_{HF_1} = J_{HF_2}$ = 53 Hz, $\nu_{F_1F_2}$ = 434 Hz]; UV_{max} (H_2O) 228.5 nm (ϵ 7930), 276.5 (sh); TLC (system C) 0.48.

Anal. Calcd for $C_{12}H_{15}NO_4F_2\cdot 0.55H_2O$: C, 50.54; H, 5.69; N, 4.91. Found: C, 50.34; H, 5.44; N, 5.01.

α-(Difluoromethyl)ornithine hydrochloride monohydrate (15b): (70% from **13b**) mp (H_2O–EtOH) 183 °C; ^1H NMR (D_2O) δ 1.50–2.2 (m, 4, $-CH_2-$), 2.95–3.2 (m, 2, $-CH_2NH_2$), 6.3 (t, 1, J_{HF} = 53 Hz, $-CHF_2$); ^{19}F NMR (H_2O) (ref CF_3COOH) ϕ −130 [AB part of an ABX system (8 lines), $J_{F_1F_2}$ = 282 Hz, $J_{F_1H} = J_{F_2H}$ = 53 Hz, $\nu_{F_1F_2}$ = 439 Hz]; TLC (system A) 0.22.

Anal. Calcd for $C_6H_{12}N_2O_2F_2\cdot H_2O\cdot HCl$: C, 30.45; H, 6.38; N, 11.84. Found: C, 30.46; H, 6.28; N, 11.62.

(+)-α-(Difluoromethyl)ornithine monohydrochloride [(+)-15b]: [40% from (−)-**4** (Y = CHF_2)] mp (H_2O–EtOH) 240 °C; $[\alpha]_D$ +7° (*c* 0.48, MeOH); ^1H NMR and ^{19}F NMR identical with **15b**.

Anal. Calcd for $C_6H_{12}N_2O_2F_2\cdot HCl$: C, 32.95; H, 5.99; N, 12.81. Found: C, 32.74; H, 5.97; N, 12.67.

(−)-α-(Difluoromethyl)ornithine monohydrochloride [(−)-15b]: [60% from (+)-**4** (Y = CHF_2)] mp (H_2O–EtOH) 244 °C; $[\alpha]_D$ −10° (*c* 0.7, MeOH); ^1H NMR and ^{19}F NMR identical with **15b**.

Anal. Found: C, 32.86; H, 5.94; N, 12.72.

α-(Difluoromethyl)alanine (15a): (91% from **13a**) mp (EtOH) 220 °C; ^1H NMR (D_2O) δ 1.57 (broad s, 3, CH_3), 6.10 (t, 1, J_{HF} = 53 Hz, CHF_2); ^{19}F NMR (D_2O) (ref CF_3COOH) ϕ −129.8 [AB part of an ABX system (8 lines), $J_{F_1F_2}$ = 278 Hz, $J_{HF_1} = J_{HF_2}$ = 53 Hz, $\nu_{F_1F_2}$ = 512 Hz]; TLC (system C) 0.41.

Anal. Calcd for $C_4H_7NO_2F_2$: C, 34.54; H, 5.07; N, 10.07. Found: C, 34.66; H, 4.99; N, 9.79.

α-(Difluoromethyl)lysine hydrochloride (15c): (65% from **13c**) mp (H_2O–EtOH) >260 °C dec; ^1H NMR (D_2O) δ 1.0–2.2 (m, 6, $-CH_2-$), 3.03 (t, 2, J = 7 Hz, CH_2NH_2), 6.3 (t, 1, J_{HF} = 53 Hz, CHF_2); ^{19}F NMR (D_2O) (ref CF_3COOH) ϕ −129.8 [AB part of an

ABX system (8 lines), $J_{F_1F_2}$ = 278 Hz, J_{HF} = 53 Hz, $\nu_{F_1F_2}$ = 456 Hz, $-CF_2H$]; TLC (system A) 0.20.

Anal. Calcd for $C_7H_{14}N_2O_2F_2$·HCl: C, 36.14; H, 6.50; N, 12.04. Found: C, 36.25; H, 6.53; N, 11.97.

α-(Difluoromethyl)methionine (15d): (75% from **13d**) mp (H_2O–acetone) 217 °C; ^1H NMR (D_2O) δ 2.12 (s, 3, SCH_3), 2.1–2.9 (m, 4, $-CH_2-$), 6.23 (t, 1, J_{HF} = 53 Hz, CHF_2); ^{19}F NMR (D_2O) (ref CF_3COOH) φ −129.6 [AB part of an ABX system (8 lines), $J_{F_1F_2}$ = 280 Hz, $J_{HF_1} = J_{HF_2}$ = 53 Hz, $\nu_{F_1F_2}$ = 430 Hz]; TLC (system A) 0.59.

Anal. Calcd for $C_6H_{11}NO_2F_2S$: C, 36.17; H, 5.56; N, 7.03. Found: C, 36.02; H, 5.48; N, 6.92.

α-(Difluoromethyl)histidine hydrochloride (15i): (10% from **13i**) mp (H_2O–EtOH) 250 °C; ^1H NMR (D_2O) δ 3.53 (AB, 2, J_{AB} = 15 Hz, ν_{AB} = 12 Hz, $-CH_2-$), 6.43 (t, 1, J_{HF} = 53 Hz, $-CHF_2$), 7.46 (s, 1, H imidazolyl), 8.83 (s, 1, H imidazolyl); ^{19}F NMR (D_2O) (ref CF_3COOH) φ −131 [AB part of an ABX system (8 lines), $J_{F_1F_2}$ = 282 Hz, $J_{HF_1} = J_{HF_2}$ = 53 Hz, $\nu_{F_1F_2}$ = 315 Hz]; TLC (system D) 0.36.

Anal. Calcd for $C_7H_9N_3O_2F_2$·HCl: C, 34.80; H, 4.17; N, 17.39. Found: C, 34.88; H, 4.43; N, 17.46.

α-(Fluoromethyl)phenylalanine (16e): (77% from **14e**) mp 212 °C; ^1H NMR (D_2O + DCl) δ 3.3 (AB, 2, J_{AB} = 15 Hz, ν_{AB} = 11.5 Hz, $-CH_2-$), 4.93 (two q, ABX system, 2, $J_{H_1H_2}$ = 10 Hz, $\nu_{H_1H_2}$ = 15.5 Hz, $J_{H_1F} = J_{H_2F}$ = 47 Hz, $-CH_2F$), 7.2–7.6 (m, 5, C_6H_5); ^{19}F NMR (H_2O + HCl) (ref CF_3COOH) φ −230 (t, J_{HF} = 47 Hz); UV_{max} (H_2O) 262.5 nm (ε 140), 256.5 (ε 185), 250.5 (ε 145); TLC (system C) 0.46.

Anal. Calcd for $C_{10}H_{12}NO_2F$: C, 60.90; H, 6.13; N, 7.10. Found: C, 60.74; H, 6.21; N, 7.12.

α-(Fluoromethyl)alanine (16a): (70% from **14a**) mp (H_2O–EtOH); ^1H NMR (D_2O) δ 1.45 (s, 3, CH_3), 4.62 (two q, ABX system, 2, $J_{H_1H_2}$ = 10 Hz, $\nu_{H_1H_2}$ = 11.5 Hz, $J_{H_1F} = J_{H_2F}$ = 47 Hz, CH_2F); ^{19}F NMR (D_2O) (ref CF_3COOH) φ −226.9 (t, J_{HF} = 47 Hz); TLC (system A) 0.65.

Anal. Calcd for $C_4H_8NO_2F$: C, 39.67; H, 6.66; N, 11.57. Found: C, 40.46; H, 6.80; N, 11.58.

α-(Fluoromethyl)ornithine hydrochloride (16b): (85% from **14b**) mp (H_2O–EtOH) >260 °C dec; ^1H NMR (D_2O) δ 1.6–2.2 (m, 4, $-CH_2-$), 2.9–3.2 (m, 2, CH_2N), 4.68 (two q, ABX system, 2, $J_{H_1H_2}$ = 10 Hz, $\nu_{H_1H_2}$ = 8.5 Hz, $J_{H_1F} = J_{H_2F}$ = 47 Hz, CH_2F); ^{19}F NMR (D_2O) (ref CF_3COOH) φ −230.5 (t, J_{HF} = 47 Hz); TLC (system A) 0.18.

Anal. Calcd for $C_6H_{13}N_2O_2F$·HCl: C, 35.92; H, 7.03; N, 13.96. Found: C, 35.83; H, 6.93; N, 13.83.

α-(Chloromethyl)alanine hydrochloride (2a): (80% from **12a**) mp (CH_3OH–acetone) 244 °C; ^1H NMR (D_2O) δ 1.57 (s, 3, $-CH_3$), 3.70 (AB, 2, J_{AB} = 13 Hz; ν_{AB} = 13 Hz, $-CH_2Cl$); IR (Nujol) 1730 cm^{-1}.

Anal. Calcd for $C_4H_8NO_2Cl$·HCl: C, 27.60; H, 5.22; N, 8.04; Cl^-, 20.37. Found: C, 27.86; H, 5.12; N, 7.95; Cl^-, 20.32.

α-(Chloromethyl)alanine (2a) was isolated by treating a solution of its hydrochloride in methanol with an excess of propylene oxide: mp 178 °C dec; ^1H NMR (D_2O) δ 1.55 (s, 3, $-CH_3$), 3.91 (AB, 2, J_{AB} = 13 Hz, ν_{AB} = 13 Hz, $-CH_2Cl$).

Anal. Calcd for $C_4H_8NO_2Cl$: C, 34.92; H, 5.87; N, 10.18; Cl^-, 0.00. Found: C, 34.41; H, 5.79; N, 9.85; $Cl^- \leq 0.2$.

α-(Chloromethyl)lysine hydrochloride (2c): (75% from **12c**) mp (H_2O–CH_3OH) 216 °C dec; ^1H NMR (D_2O) δ 1.0–2.2 (m, 6, $-CH_2-$), 3.01 (t, 2, J = 7 Hz, $-CH_2NH_2$), 3.91 (AB, 2, J_{AB} = 13.5 Hz, ν_{AB} = 7 Hz, $-CH_2Cl$); TLC (system A) 0.4.

Anal. Calcd for $C_7H_{15}N_2O_2Cl$·HCl: C, 36.36; H, 6.99; N, 12.12. Found: C, 36.26; H, 7.01; N, 12.07.

α-(Chloromethyl)-4-(hydroxyphenyl)alanine (2f): (65% from **12f**) mp (H_2O) 256 °C; ^1H NMR (D_2O + DCl) δ 3.23 (AB, 2, J_{AB} = 12 Hz, ν_{AB} = 6 Hz, $-CH_2-$), 4.05 (AB, 2, J_{AB} = 12 Hz, ν_{AB} = 15.5 Hz, CH_2Cl), 6.93 (m, 4, C_6H_4-); TLC (system D) 0.43.

Anal. Calcd for $C_{10}H_{12}NO_3Cl$: C, 52.29; H, 5.27; N, 6.10. Found: C, 52.02; H, 5.35; N, 5.91.

α-(Chloromethyl)phenylalanine (2e): (70% from **12e**) mp 250 °C; ^1H NMR (D_2O + DCl) δ 3.31 (AB, 2, J_{AB} = 13 Hz, ν_{AB} = 11 Hz, $-CH_2-$), 4.08 (AB, 2, J_{AB} = 12 Hz, ν_{AB} = 16 Hz, CH_2Cl), 7.28 (m, 5, C_6H_5).

Anal. Calcd for $C_{10}H_{12}NO_2Cl$: C, 56.20; H, 5.67; N, 6.56. Found: C, 56.14; H, 5.57; N, 6.46.

2-(Chloromethyl)-2-amino-3-(3,4-dihydroxyphenyl)propionic acid CH_3OH (2g) (82% from **12g**) was isolated by treating a solution of the hydrobromide in methanol with an excess of propylene oxide: mp 220 °C (crystallized with 1 mol of CH_3OH); ^1H NMR (D_2O) 3.05 (AB, 2, J_{AB} = 14 Hz, ν_{AB} = 11 Hz, $-CH_2-$), 3.33 (s, 3, CH_3OH), 3.93 (AB, 2, J_{AB} = 12 Hz, ν_{AB} = 14 Hz, $-CH_2Cl$) 6.7 (m, 3, C_6H_3-); TLC (system C) 0.31.

Anal. Calcd for $C_{10}H_{12}NO_4Cl$·CH_3OH: C, 47.56; H, 5.81; N, 5.04. Found: C, 47.75; H, 5.77; N, 5.02.

α-(Chloromethyl)histidine (2i) was isolated by treating a solution of its hydrochloride in water with 1 equiv of triethylamine: mp 230 °C; ^1H NMR (D_2O + DCl) δ 3.45 (s, 2, $-CH_2-$), 4.0 (AB, 2, J_{AB} = 12 Hz, ν_{AB} = 6.5 Hz, CH_2Cl), 7.66 (broad s, 1, H imidazolyl), 8.9 (broad s, 1, H imidazolyl); TLC (system C) 0.17.

Anal. Calcd for $C_7H_{10}N_3O_2Cl$: C, 41.28; H, 4.96; N, 20.64. Found: C, 41.17; H, 4.98; C, 20.84.

α-(Chloromethyl)glutamic acid (2h): (80% from **12h**) mp 175 °C; ^1H NMR (D_2O) δ 2.0–2.8 (m, 4, $-CH_2$), 3.96 (AB, 2, J_{AB} = 12 Hz, ν_{AB} = 7.5 Hz, CH_2Cl); TLC (system C) 0.22.

Anal. Calcd for $C_6H_{10}NO_4Cl$: C, 36.83; H, 5.16; N, 7.16. Found: C, 36.56; H, 5.54; N, 6.92.

α-(Chloromethyl)ornithine hydrochloride (2b): [80% from **4** (Y = CH_2Cl)] mp 140 °C; ^1H NMR (D_2O) δ 1.15–2.75 (m, 4, $-CH_2CH_2-$), 2.40–2.80 (m, 2, CH_2N), 3.48 (AB, 2, J_{AB} = 13 Hz, ν_{AB} = 8.2 Hz, $-CH_2Cl$).

Anal. Calcd for $C_6H_{13}N_2O_2Cl$·HCl: C, 33.18; H, 6.51; N, 12.90; Cl^-, 16.33. Found: C, 33.21; H, 6.71; N, 13.00; Cl^-, 15.58.

3-Amino-3-(tetrahydrothienyl)carboxylic acid (17): (70% from **12d**) mp <260 °C; ^1H NMR (D_2O) δ 2.37–2.84 (m, 2, CCH_2C), 2.84–3.46 (m, 2, SCH_2C), 3.31 (AB, 2, J_{AB} = 11.5 Hz, ν_{AB} = 19 Hz, $-SCH_2-$); TLC (system D) 0.42.

Anal. Calcd for $C_5H_9NO_2S$: C, 40.79; H, 6.17; N, 9.52. Found: C, 40.71; H, 6.00; N, 9.32.

2-(Difluoromethyl)-2-amino-5-guanidinopentanoic Acid (15k). To a solution of 5 g (21.1 mmol) of **15b** in 8.5 mL of 2 M sodium hydroxide was added 7.2 g (42.2 mmol) of (ethylthio)-uronium hydrobromide. The pH of the solution was adjusted to 10.5 with sodium hydroxide (2 M) where it was maintained for 4 days. The reaction mixture was then neutralized to pH 7 with 1 M hydrochloric acid and concentrated in vacuo. The residue was passed on an Amberlite IR 120 H^+ form resin column. Elution with 2 M ammonium hydroxide afforded 2.3 g of **15k** (50%): mp (H_2O–EtOH) 257 °C; ^1H NMR (D_2O) δ 1.2–2.0 (m, 4, $-CH_2CH_2-$), 2.96–3.38 (m, 2, $-CH_2N$), 5.98 (t, 1, J = 55 Hz, $-CHF_2$); ^{19}F NMR (D_2O) (ref CF_3COOH) φ −130.8 [AB part of an ABX system (8 lines), $J_{F_1F_2}$ = 272 Hz, $\nu_{F_1F_2}$ = 409 Hz, $J_{HF_1} = J_{HF_2}$ = 55 Hz]; TLC (system A) 0.29.

Anal. Calcd for $C_7H_{14}N_4O_2F_2$: C, 37.50; H, 6.29; N, 24.99. Found: C, 37.38; H, 6.30; N, 24.85.

***S*-Benzyl-α-(difluoromethyl)homocysteine (15j).** A mixture of 10.4 g (44 mmol) of **15d**, 44 mL of concentrated HCl, and 6.0 g (44 mmol) of benzyl chloride was heated under N_2 at 150–160 °C (oil bath temperature) for 24 h. The residue obtained upon concentration in vacuo was taken up in 100 mL of water. The aqueous solution was washed with ether (2 × 100 mL), and then its pH was adjusted to 4.5 by addition of 12 M NH_4OH. The pale red colored precipitate which formed was filtered, and the filtrate was acidified to pH 1.3 by addition of 2 N HCl, whereupon 2.2 g of **15j** precipitated. The reddish solid was redissolved in the minimum volume of 1 M HCl and a similar pH adjustment of this solution afforded another 2.5 g of **15j** (combined yield 39%) which was of sufficient purity to be used in the subsequent step of the synthesis of **15l**. The analytical sample was recrystallized from EtOH: mp 176 °C; ^1H NMR (CD_3OD) δ 1.1–2.1 (m, 4, $-CH_2-$), 3.02 (s, 3, $-SCH_2C_6H_5$), 5.60 (t, 1, J = 53 Hz, CHF_2), 6.5 (m, 5, C_6H_5); ^{19}F NMR (D_2O + DCl) (ref CF_3COOH) φ −128.6 [AB part of an ABX system (8 lines), J_{FF} = 278 Hz, J_{HF} = 53 Hz, ν_{FF} = 400 Hz]; UV_{max} (EtOH) 266 nm (ε 220), 260 (ε 340); TLC (system C) 0.61.

Anal. Calcd for $C_{12}H_{15}NO_2F_2S$: C, 52.35; H, 5.49; N, 5.09. Found: C, 52.38; H, 5.47; N, 4.99.

***S*-Adenosyl-α-(difluoromethyl)homocysteine Monohydrate (20).** To a solution of 2.75 g (10 mmol) of **15j** in 100 mL of liquid ammonia (freshly distilled from sodium) maintained at −78 °C was added under N_2 small pieces of sodium (about 0.45 g) until a blue color persisted for at least 30 min. Then, 2.86 g

(20 mmol) of **19** was added at once. The dry ice–acetone cooling bath was removed. After stirring the solution for 8 h under ammonia reflux, the ammonia was evaporated under a continuous stream of N_2. The residue was dissolved in 25 mL of water, and the pH of the solution was adjusted to 4–5 by addition of 0.5 M H_2SO_4. The unreacted **19** which precipitated was removed by filtration. The filtrate was concentrated in vacuo, and the residue was crystallized from H_2O–EtOH three times to give 0.42 g (10%) of **20**: mp 168 °C dec; ^1H NMR (D_2O) δ 2.2 (m, 2, $-CH_2-$), 2.6 (broad m, 2, $-SCH_2-$), 3.0 (m, 2, $-CH_2S-$), 4.4 (m, 3, OCH–), 5.93 (d, 1, J = 4 Hz, NCHO–), 6.27 (t, 1, J = 52 Hz, CHF_2), 8.20 and 8.03 (two s, 2 (NCH=N); UV_{max} (H_2O) 259 nm (ϵ 13700); TLC (system C) 0.21.

Anal. Calcd for $C_{15}H_{20}N_6O_5S\cdot H_2O$: C, 39.82; H, 4.90; N, 18.57. Found: C, 39.90; H, 4.80; N, 18.20.

***S*-Adenosyl-α-(difluoromethyl)methionine (15l).** A mixture of 2 mL of AcOH, 2 mL of HCO_2H, 100 mg (0.2 mmol) of **20**, and 1.5 g (10.6 mmol) of methyl iodide was stirred in the dark for 5 days and then quenched with 10 mL of ice–water. The reaction mixture was extracted with ether (3 × 10 mL). Lyophilization of the aqueous phase gave the unstable mixture of diasteroisomers **15l** contaminated with about 25% of starting material: electrophoresis, Schleicher and Schuell (Dassel, G.F.R.) silica gel G 1500 plate; 0.5 M pyridium acetate buffer pH 4.8; 600 V, 3 h; ninhydrin staining 2 spots, *Rf* 0.5 and 0.3 (corresponding to **20**); ^1H NMR (D_2O + DCl) δ 2.6, 3.6, and 4.1 (three m, $CH_2SCH_2CH_2$), 3.08 and 3.11 (two s, $^+SCH_3$), 4.4 (m, OCH–), 6.0 (d, J = 3 Hz, NCHO), 6.3 (t, J = 52 Hz, CHF_2), 8.3 and 8.5 (two s, N=CHN).

No analysis.

Decarboxylation of 15e. To a solution of 0.11 g of **15e** and 24 mg of pyridoxal hydrochloride in 3 mL of phosphate buffer (0.5 M, pH 6.5) was added 10 mL of benzene. The mixture was heated at 80–85 °C under N_2 for 18 h. The organic phase was separated, washed with brine, and dried over $MgSO_4$. Concentration in vacuo gave 63 mg of analytically pure 1-fluoro-3-phenylacetone (**18**) identified by comparison with an authentic sample prepared from 2-phenylacetyl chloride according to the method described by Olah and Welch.[24]

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Registry No. 2a, 16975-24-9; **2a**·HCl, 70470-89-2; **2b**·HCl, 69955-50-6; **2c**·HCl, 70470-90-5; **2e**, 70470-91-6; **2f**, 69955-07-3; **2g**, 70470-92-7; **2g**·HBr, 70470-93-8; **2h**, 70470-94-9; **2i**, 70470-95-0; **2i**·HBr, 70470-96-1; **4** (Y = CH_2F), 70470-97-2; **4** (Y = CH_2OH), 69955-53-9; **4** (Y = CH_2Cl)·HCl, 69955-54-0; (+)-**4** (Y = CHF_2)·HCl, 69955-41-5; (−)-**4** (Y = CHF_2)·HCl, 69961-02-0; (±)-**4** (Y = CHF_2), 70470-98-3; (−)-**4** (Y = CHF_2) (−)-binaphthylphosphoric acid salt, 70471-00-0; (+)-**4** (Y = CHF_2) (−)-binaphthylphosphoric acid salt, 70471-40-8; **6a**, 40216-71-5; **6b**, 69955-51-7; **6c**, 69955-44-8; **6d**, 40216-74-8; **6e**, 40216-77-1; **6f**, 69955-04-0; **6g**, 70471-01-1; **6h**, 70471-02-2; **6i**, 69356-05-4; **7a** (M = Na), 70471-03-3; **7f** (M = Li), 70471-37-3; **8a**, 67654-60-8; **8b**, 70471-04-4; **8c**, 69955-48-2; **8d**, 70471-05-5; **8e**, 70471-06-6; **8f**, 69955-05-1; **8g**, 70471-07-7; **8h**, 70471-08-8; **8i**, 70471-09-9; **9a**, 67654-61-9; **9b**, 70471-10-2; **9c**, 69955-45-9; **9d**, 70471-11-3; **9e**, 70471-12-4; **9f**, 70471-13-5; **9g**, 69955-02-8; **9i**, 70471-14-6; **10a**, 67654-67-5; **10b**, 70471-15-7; **10e**, 70471-16-8; **11a**, 67654-66-4; **12a**·HCl, 67654-62-0; **12c**·2HCl, 69955-49-3; **12d**·HCl, 70471-17-9; **12e**·HCl, 70471-18-0; **12f**·HCl, 70471-19-1; **12g**·HCl, 70471-20-4; **12h**·HCl, 70471-21-5; **12i**·2HCl, 70471-22-6; **13a**·HCl, 67654-63-1; **13b**·4HCl, 70471-23-7; **13c**·2HCl, 70471-24-8; **13d**·HCl, 70471-25-9; **13e**·HCl, 70471-26-0; **13g**·HCl, 69955-20-0; **13i**·4HCl, 70471-27-1; **14a**·HCl, 70471-28-2; **14b**·2HCl, 70471-29-3; **14e**, 70471-30-6; **14e**·HCl, 70471-31-7; **15a**, 67654-65-3; **15b**·HCl, 70050-56-5; (+)-**15b**·HCl, 70050-55-4; (−)-**15b**·HCl, 69955-42-6; **15c**·HCl, 69955-47-1; **15d**, 69955-35-7; **15e**, 70471-32-8; **15f**, 70471-33-9; **15g**, 69955-03-9; **15i**·HCl, 69937-69-5; **15j**, 69955-56-2; **15k**, 69955-43-7; **15l**, 70471-34-0; **16a**, 679-79-8; **16b**·HCl, 70494-47-2; **16e**, 70471-35-1; **17**, 32418-99-8; **18**, 1524-06-7; **19**, 892-48-8; **20**, 69955-37-9; ornithine methyl ester dihydrochloride, 40216-82-8; benzaldehyde, 100-52-7; chlorobromomethane, 74-97-5; chlorodifluoromethane, 75-45-6; chlorofluoromethane, 593-70-4; dibromodifluoromethane, 75-61-6; α-(hydroxymethyl)ornithine methyl ester dihydrochloride, 69955-52-8; 2-(difluoromethyl)-2-amino-3-(3,4-dimethoxyphenyl)propionic acid, 70471-36-2; methyl 2-amino-3-(3,4-dimethoxyphenyl)propionate hydrochloride, 70494-48-3; methyl *N*-benzylideneglycinate, 66646-88-6; methyl 2-amino-2-(3,4-dimethoxyphenyl)methyl-3-(3,4-dimethoxyphenyl)propionate, 70471-38-4; benzyl chloride, 100-44-7.

The Reaction of Some Carbohydrate α-Enones with Iron Carbonyls[1a,b]

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The reactions of the carbohydrate α-enones and ethyl 2,3-dideoxy-α-D-*erythro*-hexenopyranosid-4-ulose (**6a**) and its tritylated derivative (**6b**) with $Fe_2(CO)_9$ give tetracarbonyl complexes **7** (**a** and **b**) and **8** (**a** and **b**), respectively. There is no evidence for the formation of dienic tricarbonyl complexes such as **3**. The structures of the products were established by examination of their IR, Mössbauer, NMR, and mass spectra. From the IR spectra, it is evident that each enone gives two diastereomers representing the two possible orientations of complexation. Because of the instability of the complexes, it was not possible to make definite assignments of these diastereomers.

The chemical modification of sugars by employing reactions of α-enone derivatives has been a focus of attention in our laboratory for a number of years.[2] In the past, our emphasis has been mainly on the addition of nucleophilic[3] and photochemically generated[4] species, and some interesting syntheses have resulted from these studies.[5,6] Electrophilic substitution could conceivably open alternative pathways for modifying the pyranose ring, and

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