Articles

Inhibition of Human Neutrophil Elastase. 3. An Orally Active Enol Acetate Prodrug†

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Several analogs of *N*-[4-(4-morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide (**1**), in which the chiral center of the P_1 residue has been eliminated, were synthesized and tested as inhibitors of human neutrophil elastase (HNE). Observations made during the course of this work led to the development of a single-step, stereoselective synthesis of *E*-enol acetate derivatives from HNE inhibitors containing a mixture of epimers at P_1. *In vitro* studies, in the presence of added esterase, and ^{19}F NMR studies, in biological media, indicated that the *E*-enol acetate derivatives should act as prodrugs *in vivo*. The ED_{50} value for (*E*)-*N*-[4-(4-morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[2-(acetyloxy)-3,3,4,4,4-pentafluoro-1-(1-methylethyl)-1-butenyl]-L-prolinamide (**20**), when administered orally in the hamster lung hemorrhage model, was 9 mg/kg.

Introduction

Human neutrophil elastase (HNE) (EC 3.4.21.37), a polyglycosylated, basic serine protease, is released from polymorphonuclear leukocytes by inflammatory stimuli. HNE is thought to contribute to the pathogenesis of emphysema,[1] cystic fibrosis,[2] adult respiratory distress syndrome (ARDS),[3] and rheumatoid arthritis.[4] Therefore, inhibition of HNE may attenuate the progression of these disease states, and synthetic inhibitors of HNE, both peptidic and nonpeptidic in nature, have been pursued by researchers in the area.[5]

In part 2 of this series,[6] we reported that tripeptidyl pentafluoroethyl ketones, exemplified by **1** (Figure 1), are orally active inhibitors of HNE, and the effect of variations in the N-protecting group (P_G) portion of the inhibitor (see Figure 2) has been described. We also noted, as have others,[7,8] the propensity for fluorinated ketone inhibitors to epimerize at the chiral center α to the ketone, which leads to a mixture of diastereomers. As a result, the development of an inhibitor as a diastereomeric mixture is a practice common to the area (for example, compounds **2**[9] and **3**;[7] see Figure 1), and indeed, the last step of our synthetic sequence for 1 is an epimerization step which leads to a ca. 1:1 equilibrium mixture of diastereomers.

In an effort to determine if this diastereomeric mixture could be circumvented, we investigated structural changes to the P_1 portion[10] of the fluorinated ketone which would lead to a single isomer as the inhibitory entity. Thus, the P_1 dehydrovaline (**4**), α,α-dimethylglycine (**5**), and glycine (**6**) analogs of **1** (see Figure 3) were synthesized and evaluated. Additionally, the high degree of enolic character observed for **6** prompted us to investigate the potential for a stereoselective synthesis of an enol acetate prodrug which culminated in the synthesis of a number of *E*-enol acetate derivatives of **1** and related trifluoromethyl ketones.

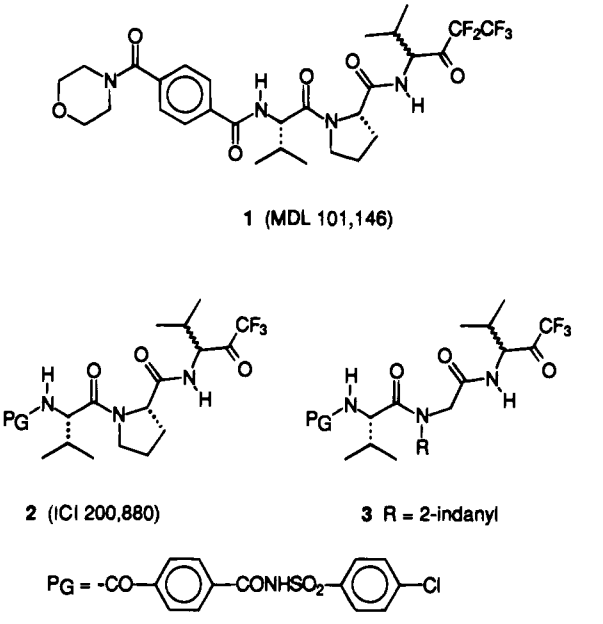

Figure 1.

Chemistry

N-*t*-Boc-L-valyl-L-proline was coupled to dehydrovaline methyl ester hydrochloride (**7**) using isobutyl chloroformate (IBCF) and *N*-methylmorpholine (NMM) to

† Abbreviations: HNE, human neutrophil elastase; ARDS, adult respiratory distress syndrome; P_G, N-protecting group; IBCF, isobutyl chloroformate; NMM, *N*-methylmorpholine; EDC, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; DMAP, 4-(dimethylamino)pyridine; NOE, nuclear Overhauser effect; USP, United States Pharmacopeia; HPLC, high-performance liquid chromatography; BAL, bronchoaveolar lavage; BOC, butyloxycarbonyl; A_G, activating group.

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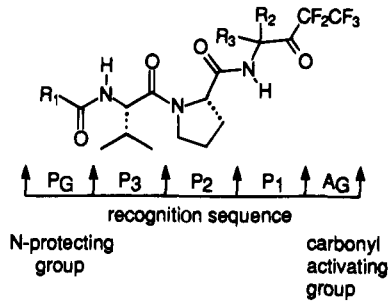
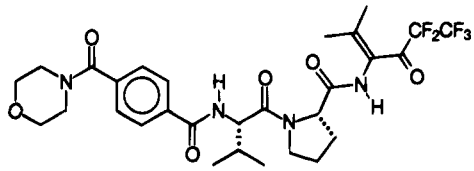


Figure 2. Generalized structure of tripeptidyl elastase inhibitors (P_G–P_3–P_2–P_1–A_G).



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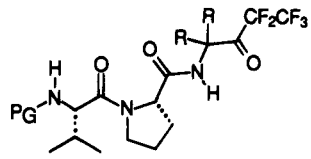
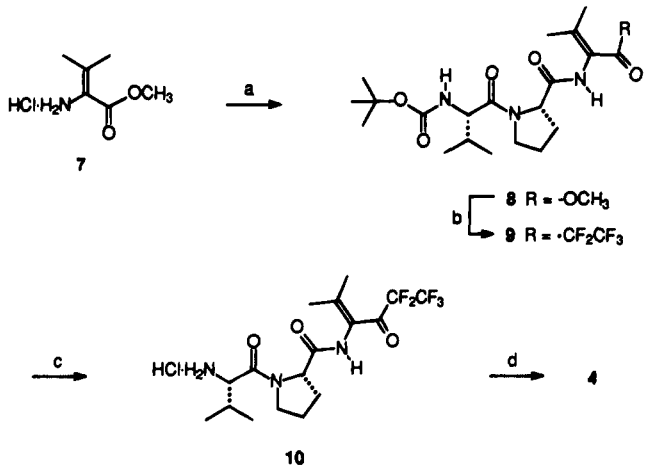


5 R = -CH_3, PG = -CO_2tBu

6 R = -H, PG = -CO-⟨⟩-CO-N⟨⟩O

Figure 3.

Scheme 1. Synthesis of **4**[a]



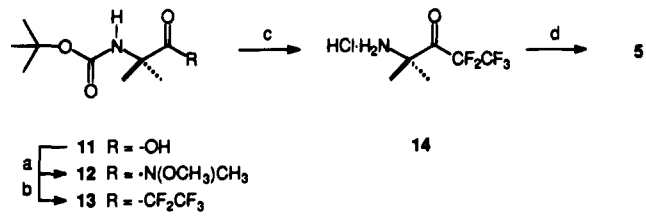
7 → 8 R = -OCH_3 (a); 8 → 9 R = -CF_2CF_3 (b); 9 → 10 (c); 10 → 4 (d)

[a] Reagents: (a) N-*t*-Boc-L-Val-L-Pro-OH, IBCF, NMM; (b) CF_3CF_2I, MeLi·LiBr; (c) HCl(g), EtOAc; (d) 4-(4-morpholinylcarbonyl)benzoyl chloride, NMM.

give **8** (Scheme 1). Treatment of **8** with (pentafluoroethyl)lithium, generated *in situ* from pentafluoroethyl iodide and methyllithium–lithium bromide complex,[11] gave ketone **9**. Deprotection, using hydrogen chloride in ethyl acetate, yielded amine hydrochloride **10** which was treated with 4-(4-morpholinylcarbonyl)benzoyl chloride in the presence of NMM to give **4**.

N-*t*-Boc-2-amino-2-methylpropanoic acid (**11**) was coupled with *N*,*O*-dimethylhydroxylamine hydrochloride using the mixed carbonic–carboxylic acid method to yield Weinreb amide[12] **12** (Scheme 2). Treatment of **12**

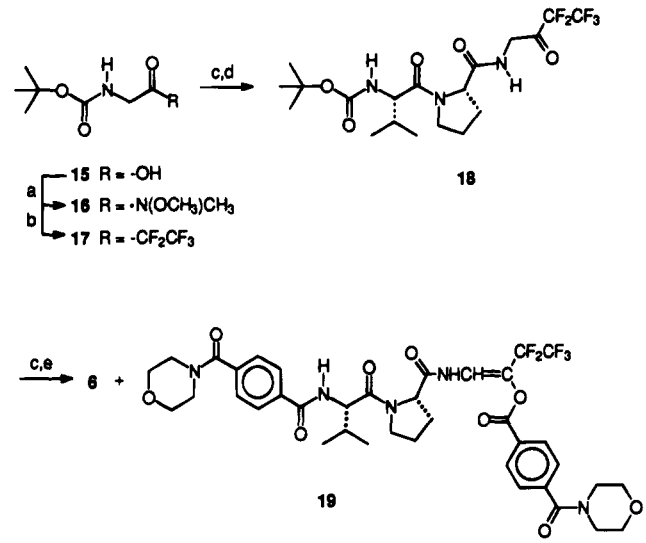
Scheme 2. Synthesis of **5**[a]



11 R = -OH; 12 R = -$N(OCH_3)CH_3$ (a); 13 R = -CF_2CF_3 (b); 11 → 14 (c); 14 → 5 (d)

[a] Reagents: (a) EDC, DMAP, NMM, HCl·$HN(OCH_3)CH_3$; (b) CF_3CF_2I, MeLi·LiBr; (c) HCl(g), EtOAc; (d) N-*t*-Boc-L-Val-L-Pro-OH, IBCF, NMM.

Scheme 3. Synthesis of **6**[a]



15 R = -OH; 16 R = -$N(OCH_3)CH_3$ (a); 17 R = -CF_2CF_3 (b); 15 → 18 (c,d); 18 → 6 + 19 (c,e)

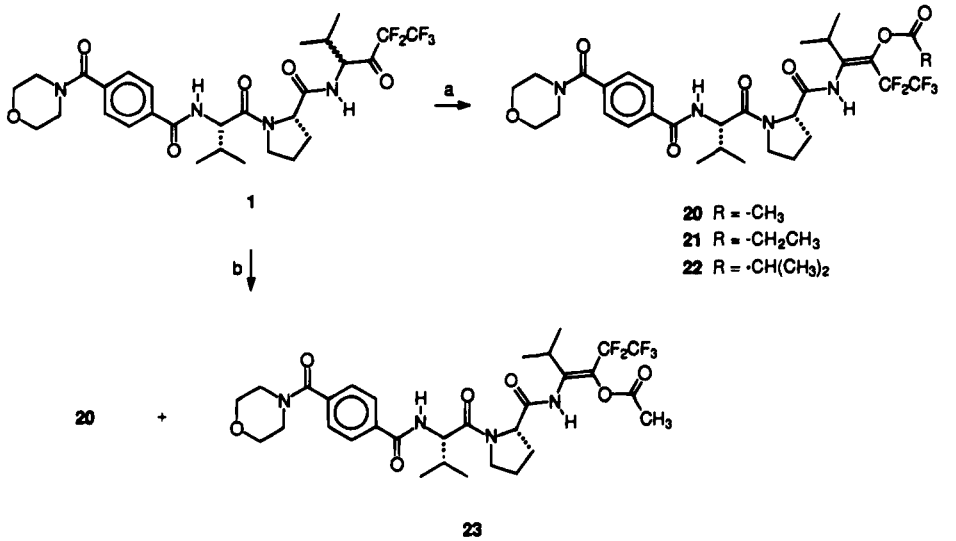
[a] Reagents: (a) EDC, NMM, HCl·$HN(OCH_3)CH_3$; (b) CF_3CF_2I, MeLi·LiBr; (c) HCl(g), EtOAc; (d) N-*t*-Boc-L-Val-L-Pro-OH, IBCF, NMM; (e) 4-(4-morpholinylcarbonyl)benzoyl chloride, NMM.

with (pentafluoroethyl)lithium generated ketone **13**, which was deprotected with hydrogen chloride in ethyl acetate to give amine hydrochloride **14**. Coupling of *N*-*t*-Boc-L-valyl-L-proline to **14** gave **5**.

N-*t*-Boc-glycine (**15**) was converted to the Weinreb amide **16** (Scheme 3) using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC), 4-(dimethylamino)pyridine (DMAP), and NMM in the presence of *N*,*O*-dimethylhydroxylamine hydrochloride. Treatment of **16** with (pentafluoroethyl)lithium gave ketone **17**. Deprotection and coupling of the resulting amine hydrochloride with *N*-*t*-Boc-L-valyl-L-proline yielded ketone **18**. Removal of the *N*-*t*-Boc protecting group from **18** followed by treatment of the resultant amine hydrochloride with 4-(4-morpholinylcarbonyl)benzoyl chloride and NMM provided **6**. Additionally, the enol benzoate **19**[13] was formed as a side product of the reaction.

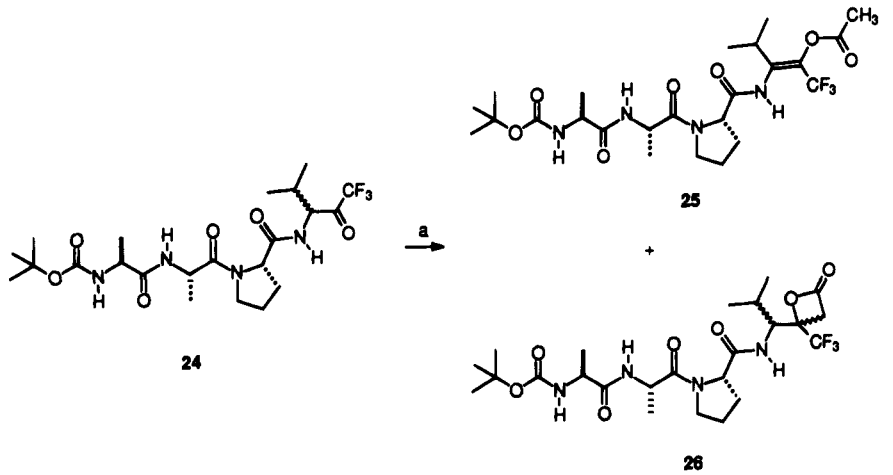
Prompted by the enolic character of **6** and the isolation of the enol benzoate side product **19**, we decided to investigate the possibility of stereoselectively generating a single enol ester from the diastereomeric mixture of pentafluoroethyl ketones (**1**). We now wish to report that, under suitable conditions (Table 1), **1** could be converted stereoselectively (*E*:*Z* = 93:1 for crude material by ^{19}F NMR) to the *E*-enol acetate **20** (Scheme 4) in high yield. Substitution of propionic anhydride and isobutyric anhydride for acetic anhydride gave **21** and **22**, respectively. However, substitution of pivaloyl anhydride failed to give the corresponding pivaloyl enol ester. Furthermore, by increasing the reaction temperature (Table 2), the ratio of the corresponding *Z*-enol

Scheme 4. Synthesis of Enol Acetate Derivatives of **1**[a]



[a] Reagents: (a) $(RCO)_2O$, Et_3N, DMAP, CH_2Cl_2, −20 °C; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, reflux.

Scheme 5. Synthesis of *E*-Enol Acetate **25**[a]



[a] Reagents: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, −20 °C.

Table 1. Optimization of Reaction Conditions for the Conversion of Pentafluoroethyl Ketone 1 to *E*-Enol Acetate **20**

1 → **20** (*E*-isomer) + **23** (*Z*-isomer)

			percent of crude product by ^{19}F NMR		
reagents[a]	temp (°C)	time (h)	**20**	**23**	recovered **1**[b]
A,B	rt	48	5	7	88
A,B,C	rt	2	57	23	2
A,B,C	−20 → rt	0.5, 0.5	63	15	22
A,B,C	−20	2	93	1	2

[a] Reagents: A, Ac_2O; B, Et_3N; C, DMAP. [b] 1:1 mixture of two diastereomers.

Table 2. Effect of Temperature on the Ratio of *E*- and *Z*-Enol Acetates Formed during the Conversion of **1**

1 → **20** (*E*-isomer) + **23** (*Z*-isomer)

		percent of crude product by ^{19}F NMR			
solvent	temp (°C)	**20**	**23**	recovered **1**	ratio of *E*:*Z*
CH_2Cl_2	−20	93	1	2	93:1
CH_2Cl_2	rt	57	23	2	2.5:1
CH_2Cl_2	40	29	39	2	1:1.3
$ClCH_2CH_2Cl$	83	17	31	19	1:1.8

acetate **23** to *E*-enol acetate **20** could be increased to a degree sufficient to allow isolation of **23**, after careful chromatography.

Extension of this methodology to trifluoromethyl ketones proved problematic. Treatment of **24** with acetic anhydride (Scheme 5), under the optimal conditions developed for the conversion of **1** to enol acetate **20**, gave a mixture of the desired *E*-enol acetate **25**, the corresponding *Z*-enol acetate (*E*:*Z* = 21:1 for crude material by ^{19}F NMR), and a chromatographically troublesome 2:1 mixture of two diastereomeric β-lactones (**26**).[14] Subsequent investigation (Table 3) showed that reaction of **24** at 0 °C with acetic anhydride in pyridine gave the desired *E*-enol acetate **25** in a stereoselective manner (*E*:*Z* = 31:1 for crude material by ^{19}F NMR) with less than 1% of β-lactones **26** present in the crude material.[15] Similarly, treatment of trifluoromethyl ketones **27**, **28**, and **2** with acetic anhydride under these conditions gave *E*-enol acetates **29**−**31**, respectively (Scheme 6).

Results and Discussion

Determination of *E*- and *Z*-Isomers. The olefin geometry assignments of the enol acetates were made

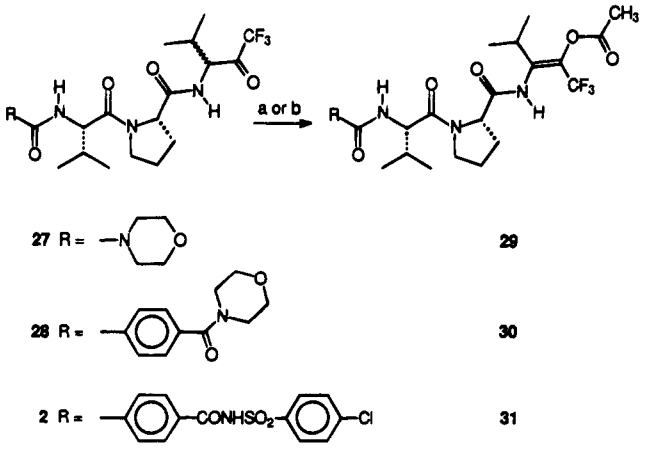
Table 3. Optimization of Reaction Conditions for the Conversion of Trifluoromethyl Ketone **24** to **25**

24 → **25** (*E*-isomer) + *Z*-isomer + **26**

exp	reagents[a]	solvent	temp (°C)	reaction time (h)	percent of crude product by ^{19}F NMR			
					25[b]	*Z*-isomer[b,c]	**26**[b]	recovered **24**[b]
1	A,B,C	CH_2Cl_2	−20	2	65	<3	20	6
2	A,B,C	CH_2Cl_2	−44	2	8	0	77	15
3	A,B,D	CH_2Cl_2	−20	1.25	57	<2	35	3
4	A,B	CH_2Cl_2	−20	2	61	<2	31	<2
5	A,B	CH_3CN	−20	2	75	<2	7	12
6	E,B	CH_3CN	−20	2	0	0	0	100
7	A,F	CH_3CN	−20 → rt	2, 4.5	9	<1	0	85
8	A	C_5H_5N	rt	5	83	6	<1	9
9	A	C_5H_5N	0	25	94	<3	<1	<1
10	A	C_5H_5N	40 → rt	1, 18	83	13	<1	<1

[a] Reagents: A, Ac_2O; B, DMAP; C, Et_3N; D, NMM; E, AcCl; F, C_5H_5N. [b] The ^{19}F NMR shift position (in $CDCl_3$, reported in ppm from $CFCl_3$) for each compound is as follows: compound **24**, −76.82 and −76.84; compound **25**, −66.0; *Z*-isomer, −61.3; compound **26**, −76.0 and −76.1 [c] The structure of the *Z*-isomer was assigned by analogy to **23** and ^1H, ^{19}F, and $^1H - [^{19}F]$ NOE experiments on the mixture obtained from experiment 10.

Scheme 6. Synthesis of *E*-Enol Acetates from Trifluoromethyl Ketones[a]



[a] Reagents: (a) Ac_2O, DMAP, CH_3CN, −20 °C; (b) Ac_2O, pyridine, 0 °C.

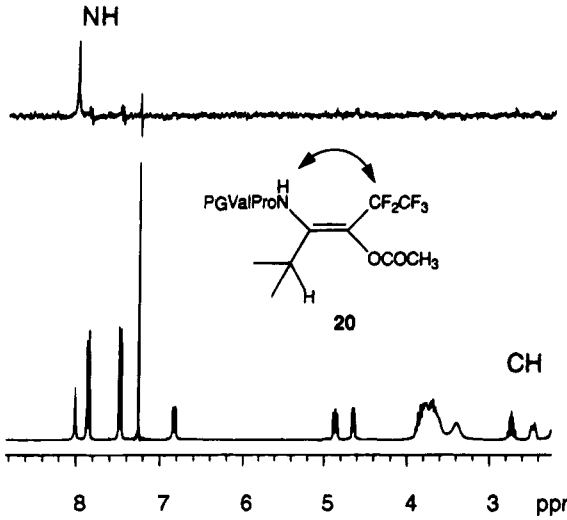


Figure 4. Top: $^1H - [^{19}F]$ NOE difference spectrum of **20**. Bottom: Off-resonance spectrum. Double arrow represents NOE observed.

using ^1H-observed, ^{19}F-irradiated ($^1H - [^{19}F]$) NOE difference spectroscopy. These heteronuclear steady-state NOE experiments result in signal enhancements of those protons in close spatial proximity (i.e., *cis*) to the irradiated fluorine atoms. Typical NOE difference

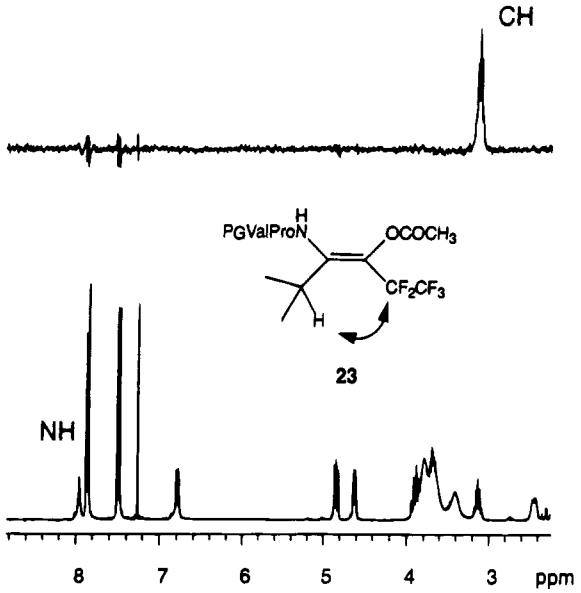


Figure 5. Top: $^1H-[^{19}F]$ NOE difference spectrum of **23**. Bottom: Off-resonance spectrum. Double arrow represents NOE observed.

spectra obtained for **20** and **23** are shown in Figures 4 and 5. In these experiments the CF_2 groups were irradiated with sufficient power for complete saturation. Unlike $^1H - [^1H]$ NOE difference experiments, with $^1H - [^{19}F]$ experiments there are no problems with incomplete saturation since saturation of nearby signals is typically not an issue. For **20**, a large (ca. 5%) NOE was observed to the amide proton, which is indicative of the *cis* relationship between the CF_2 and NH groups. No similar NOE was observed to the *trans* methine proton. Conversely, for **23**, no NOE was observed between the CF_2 and the NH groups but instead a 9% enhancement was observed to the *cis* methine signal upon irradiation of the CF_2 group. These results are consistent with the olefin geometries shown. Similar experiments for **29**–**31** also confirmed the *E*-olefin geometry assignments.

In Vitro. The *in vitro* testing results are summarized in Table 4. Compounds **4**–**6** are more than 2 orders of magnitude less potent as inhibitors of HNE than compound **1**. The poor affinity displayed by **4** is interesting in light of the previously reported[6] K_i values for the individual diastereomers of **1** (17 and 74 nM)

Table 4. *In Vitro* Inhibitory Activity

compd	K_i (nM)[a]	K_i (nM)[b] in the presence of pig liver esterase
1	25 ± 1[c]	
2	0.5[d]	
4	8000 ± 250	
5	>500000[b,e]	
6	150000 ± 260	
20	>2000[b]	25
21		25
22		25
23		ndh[f]
27	190 ± 34	
28	12 ± 1	
29	6300[b]	150
30		16
31	320[b]	3

[a] Value expressed as mean ± SDM for determinations at three inhibitor concentrations, unless otherwise noted. [b] Value for a single determination. [c] Value obtained from a double-reciprocal plot of $1/v$ vs $1/[S]$ at different inhibitor concentrations. [d] Reference 9. [e] K_i = 55 ± 2 nM for N-*t*-Boc-Val-Pro-Val-CF_2CF_3. [f] ndh = no detectable hydrolysis by pig liver esterase during the standard assay time period, determined by bioassay.

which showed only a modest stereochemical preference at P_1 for L versus D. This result may reflect steric constraints. In addition, a change in the electrophilicity of the ketone carbonyl, brought about by conjugation to the introduced double bond, may be reflected in the K_i value for **4**. The lack of affinity observed for **6** is in line with a recently reported[7] K_i value for the α,α-dimethylglycine analog of a trifluoromethyl ketone and may reflect a combination of the following factors: (a) the lack of a P_1 side chain to interact with a hydrophobic pocket at the S_1 subsite of HNE and (b) the distinctly enolic character of the P_1 ketone observed for **6**, which has not been observed for any other compound in this or any previous series[6,16,17] of compounds.

The *E*-enol acetate **20** also showed poor affinity for HNE. However, in the presence of added esterase (porcine liver esterase), compound **20** displayed a final K_i value of 25 nM, which was identical to the K_i value measured for **1**, indicating its prodrug character (Figure 6). Surprisingly, the corresponding *Z*-enol acetate **23** failed to generate **1** at a significant rate in the presence of added esterase. The *E*-enol acetate derivatives **21** and **22** were synthesized to determine if the rate of cleavage by esterase could be modified by adding steric bulk to the ester portion of the molecule. However, **21** and **22** showed no apparent difference in the rate of ester cleavage in the presence of porcine liver esterase when compared to **20**.

Table 5. *In Vivo* Inhibitory Activity of Selected Compounds in the Hamster[a]

compd	ED_{50} (mg/kg)	compd	ED_{50} (mg/kg)
1	15	**28**	>50
2	>50	**30**	>75
20	9	31	>50

[a] Various concentrations of compound were administered orally to hamsters 30 min before intratracheal instillation of HNE (25 μg). The ED_{50} was extrapolated from the dose–response curves and was statistically significant at the $p \leq 0.05$ level compared to animals that received vehicle (po) and HNE (it) for 1 and **20**. Six to fourteen hamsters were used for each concentration of compound.

To determine whether *E*-enol acetate derivatives of trifluoromethyl ketones would also function as prodrugs, compounds **29**–**31** were synthesized and tested *in vitro* against HNE. Again, in the presence of esterase, compounds **29**–**31** showed final K_i values identical to the corresponding trifluoromethyl ketone precursors (**27**, **28**, and **2**, respectively), indicating their prodrug status.

In Vivo. The *in vivo* activity of selected compounds, when administered orally (po), was determined in hamsters using the HNE-induced pulmonary hemorrhage model,[6] and the results are summarized in Table 5. *E*-Enol acetate **20** showed an ED_{50} of 9 mg/kg po compared to an ED_{50} of 15 mg/kg for **1** when tested in this model. Thus, **20** appears to be acting as a prodrug for **1** *in vivo*. As previously reported,[6] the trifluoromethyl ketone **2** showed no significant oral activity at the doses tested, and similar results were obtained for trifluoromethyl ketone **28**. The corresponding *E*-enol acetates (**31** and **30**, respectively) were tested to determine whether pharmacological parameters had been sufficiently altered by this structural change to allow oral activity. Unfortunately, **30** and **31** also failed to show oral activity at the doses tested (ED_{50} > 75 mg/kg and ED_{50} > 50 mg/kg, respectively).

Conversion of Enol Acetates in Biological Media. The conversion of enol acetates **20** and **23** to parent ketone **1** was examined by ^{19}F NMR spectroscopy in USP-simulated gastric fluid (pH = 1.2), USP-simulated intestinal fluid (pH = 7.5), and human blood plasma. The results are shown in Table 6. The product of these conversion studies was identified as **1** on the basis of

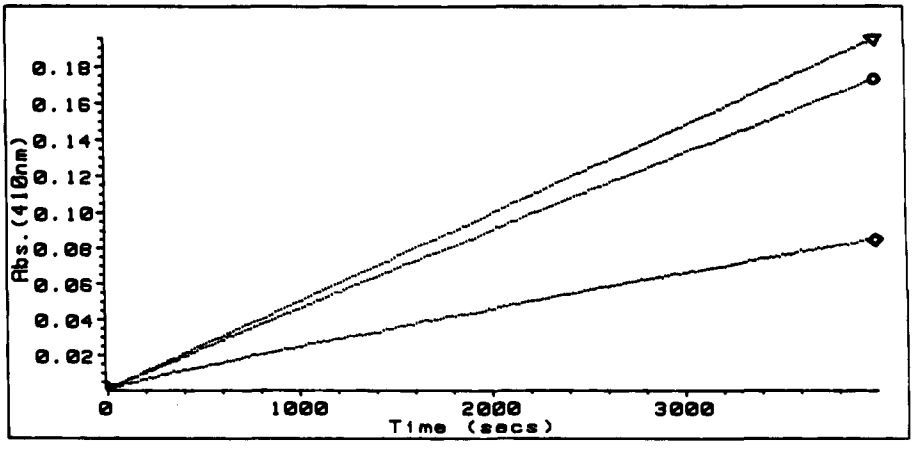


Figure 6. *In vitro* time course showing **20** in the presence of added pig liver esterase. Legend: ▽, HNE + HNE substrate (0.2 mM); ○, HNE + HNE substrate (0.2 mM) + esterase; ◇, HNE + HNE substrate (0.2 mM) + esterase + **20** (66 nM).

Table 6. Enol Acetate Conversion to the Corresponding Ketones in Biological Media

biological medium	compd	temp (°C)	half-life
USP-simulated gastric fluid	**20**	50	no[a]
	30	50	41 h
USP-simulated intestinal fluid	**20**	50	3.1 h
	20	37	7.3 h
	23	37	6.6 h
	30	37	2.9 h
	31	50	1.2 h
human blood plasma	**20**	37	25 min
	23	37	40 min
	30	37	15 min
	31	37	10 min

[a] no = conversion not observed.

the observation of signals consistent with a 1:1 mixture of diastereomers at the appropriate chemical shifts, the normal ratio of ketone to hydrated ketone, and spiking studies. Identical studies were conducted to monitor the conversion of *E*-enol acetate **30** to parent ketone **28** and of *E*-enol acetate **31** to ketone **2**.[18]

As can be seen in Table 6, in gastric fluid (pH = 1.2) no conversion to **1** was observed from **20**, even after 12 h at 50 °C. Compound **30** showed very slow (half-life of 41 h) conversion to **28** under these conditions.

The acid stability of the enol acetates arises from α-substitution by a fluorinated carbon. Protonation of the carbon–carbon double bond, leading to a carbonium ion adjacent to the fluorinated carbon, would be disfavored due to the electronegativity of the fluorines. From these studies, minimal conversion of enol acetate to ketone would be expected in the stomach.

In intestinal fluid (pH = 7.5), the half-lives for the conversion of *E*- and *Z*-isomers **20** and **23** to pentafluoroethyl ketone 1 were nearly identical (7.3 versus 6.6 h, respectively) at 37 °C. The conversions of *E*-enol acetates **30** and **31** to trifluoromethyl ketones **28** and **2**, respectively, were decidedly faster in this biological media. The rate enhancement observed for the alkaline hydrolysis of the enol acetate derivative upon replacement of the pentafluoroethyl by a trifluoromethyl substituent presumably results from the greater stabilization of the initially formed enolate by the more electronegative trifluoromethyl group. However, differences in steric bulk may also be playing a role. A rate enhancement was also observed for the conversion of **20** when the temperature was raised to 50 °C.

Much shorter half-lives were observed for the inhibitors in human blood plasma. For **20**, **23**, **30**, and **31**, the half-lives ranged from 10 to 40 min at 37 °C. Since the pH's of blood plasma and intestinal fluid are similar, the presence of esterases in plasma explains the rate enhancement observed in that medium. Additionally, the esterases present in human blood plasma apparently cleave a broader spectrum of esters than the pig liver esterase used in the *in vivo* experiments. This would account for the observed cleavage of **23** to **1** in human blood plasma and the lack of cleavage in the presence of pig liver esterase.

Lipophilicity and Oral Activity. A relationship between the lipophilicity of a compound and its retention time as determined by reversed-phase high-performance liquid chromatography (HPLC) has been proposed.[19] Since lipophilicity is a factor in cell membrane permeability, absorption through the gut wall should reflect the lipophilic nature of the compound being tested. Our earlier report[6] indicated an apparent correlation between relative retention time and oral activity for a series of pentafluoroethyl ketones. A window of relative retention time (0.8–1.0 with compound **1** having a value of 1.00 in the HPLC system) contained all of the orally active compounds in that study. A similar analysis of the compounds in this study was undertaken. Compound **20**, which has a relative time of 0.98, showed oral activity. By comparison, *E*-enol acetates **30** and **31**, with relative retention times of 0.66 and 0.39, respectively, were shown to be inactive upon po administration at the doses tested.

Summary

We have shown that a diastereomeric mixture of fluorinated ketone inhibitors can be stereoselectively converted to a single *E*-enol acetate derivative and that this derivative, in the presence of an esterase, is cleaved to the active inhibitors *in vitro*. Furthermore, compound **20** has been shown to be a potent inhibitor of HNE in the HNE-induced pulmonary hemorrhage model when administered orally in the hamster. This methodology thus allows for the conversion of a diastereomeric mixture to a single isomer drug entity, which then functions as an orally active prodrug of the inhibitor mixture. Future reports in this series will discuss the results of P_2, P_3, and A_G (Figure 2) modifications.

Experimental Section

General Methods and Materials. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. TLC analyses were performed with Merck DC-F254 or Analtech GHLF silica gel plates, with visualization by I_2, alkaline permanganate, or UV irradiation. Flash chromatography was performed with Merck silica gel 60 (0.040–0.063 mm). NMR spectra were recorded on Varian VXR-300, Unity 300, Unity 400, or Gemini-300 spectrometers in $CDCl_3$, unless otherwise stated. ^1H and ^{13}C NMR signals are reported in ppm from tetramethylsilane, ^{19}F NMR signals are reported in ppm from $CFCl_3$, and coupling constants are reported in hertz (Hz). IR spectra were recorded on a Perkin-Elmer Model 1800 or Mattson Galaxy 5020 FT-IR spectrophotometer. MS data were collected at 70 eV on a Finnigan MAT 4600, Mat TSQ-700, or VG Analytical Limited ZAB2-SE mass spectrophotometer, and computerized peak matching with perfluorokerosene as the reference was utilized for HRMS. Combustion analysis performed using a Perkin-Elmer Model 2400 elemental analyzer fell within ±0.4% of the calculated values. All reactions were run under an inert atmosphere. The organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4 prior to solvent removal on a rotary evaporator. Solvents and starting materials were purchased from Aldrich Chemical Co. with the following exceptions: N-*t*-Boc-L-Pro-OH was purchased from Bachem Bio-Science Inc. and Advanced ChemTech, hydrogen chloride gas was from AGA Burdox, *N*-*t*-Boc-glycine and *N*-*t*-Boc-2-amino-2-methylpropanoic acid were from Sigma Chemical Co., and Et_2O was from E.M. Science. The following compounds were prepared by literature methods: **2**,[6] **24**,[16] **27**,[6] **28**,[6] and **7**.[20].

NMR Determination of Enol Acetate Stereochemistry. The $^1H - [^{19}F]$ NOE difference spectra were obtained with a Varian Unity 300 spectrometer using a pulse sequence based on the standard steady-state NOE difference pulse sequence. Since our spectrometer is a single broad-banded system, it was necessary to run these experiments in the "reverse" mode, that is, the ^1H decoupler was used as the observe transmitter and the broad-band transmitter as the ^{19}F decoupler transmitter. Also, since this experiment requires a probe which is simultaneously tuned to both ^1H and ^{19}F, a Varian 4-nucleus $^1H/^{19}F/^{13}C/^{31}P$ Auto-NMR probe was used. The fluorine signals were irradiated during a 10 s preacquisition delay (not

optimized), and then a transient was acquired with the ^{19}F decoupler transmitter off using an acquisition time of 1 s. This process was repeated until 32 transients were accumulated. The process was repeated with the ^{19}F decoupler set far off resonance, and then the total procedure was repeated until 512–1024 transients were collected at each decoupler setting. The resulting FID's were subtracted, and the spectra obtained after Fourier transformation were displayed as the NOE difference spectra. Quantitation was estimated by dividing the integral of the enhanced signal by the integral of the same proton in the off-resonance spectrum.

***In Vitro* Evaluation.** K_i determinations were conducted with partially purified HNE using previously described procedures.[21] The K_i values reported for **20**, **29**, and **31**, in the absence of added esterase, represent lower limits due to the possibility of small amounts of parent ketone being present as a contaminant. For those experiments involving added esterase, the assays were performed in the presence of 12.5 units of porcine liver esterase (Sigma Chemical Co., cat. no. E-3128) and the following concentrations of compound to be tested: **20–23**, 66 nM; **29**, 1.67 μM; **30**, 133 nM; **31**, 100 nM. The time course of the reaction was followed, and a K_i value was determined from the final rate (obtained after complete hydrolysis of the enol acetate). To rule out interference of the esterase with the elastase assay, or a significant spontaneous (i.e., nonenzymatic) hydrolysis rate of enol acetate, the following experiments were performed, (A) elastase plus elastase substrate; (B) elastase plus elastase substrate plus porcine liver esterase; and (C) elastase plus elastase substrate plus **20**.

***In Vivo* Evaluation.** The ability of compounds to inhibit HNE-induced pulmonary hemorrhage was examined in hamsters as previously described.[6,22] Compound was administered orally (po) 30 min prior to intratracheal (it) instillation of 25 μg of HNE. The animals were sacrificed 1 h later, and the amount of hemorrhage in the bronchoalveolar lavage (BAL) fluid was determined. Bronchoalveolar lavage was performed by exposing and cannulating the trachea and gently instilling and withdrawing a single volume of saline (0.04 mL/g) three times. Hemorrhage was quantitated by determining the hemoglobin content in the BAL fluid using a spectrophotometric assay.[23] The data was evaluated using a one-way analysis of variance (ANOVA) followed by a Dunnett's multiple comparison test to determine if compound-treated groups were different from vehicle-treated groups ($p \leq 0.05$ was the criterion for statistical significance).

^{19}F NMR-Monitored Conversion Studies. The conversion of the enol acetates to the parent ketone was followed by ^{19}F NMR using a Varian Unity 400 spectrometer. Samples were prepared in freshly obtained human blood plasma or appropriately prepared USP-simulated gastric or intestinal fluid at a concentration of ca. 1 mg/mL. A sealed D_2O capillary tube was inserted into the 5 mm NMR tube for "lock". Spectra were obtained at 37 or 50 °C at various time points, and the integrated signals were used to calculate the amount of each component at each time point.

HPLC Relative Retention Time Determination. The HPLC system employed a Waters 600E HPLC equipped with a Waters WISP 712 autosampler and an Applied Biosystems 757 absorbance detector (240 nm). Data was acquired and analyzed by a computer-automated laboratory system (CALS) supplied by Beckman. The retention time comparison of 1 and related compounds was performed on a Zorbax Rx column (150 × 4.6 mm) with a mobile phase of acetonitrile/water (55/45) and a flow rate of 1 mL/min. Relative retention times for all inhibitors were as expressed relative to 1, whose retention time was designated as 1.00.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-[1-(methoxycarbonyl)-2-methyl-1-propenyl]-L-prolinamide (8).** To a solution of *N*-*t*-Boc-L-valyl-L-proline (3.1 g, 0.01 mol) and NMM (1.10 mL, 0.01 mol) in CH_2Cl_2 (100 mL) at −20 °C was added IBCF (1.26 mL, 0.01 mol) at −20 °C. After stirring for 20 min, an additional equivalent of NMM (1.10 mL, 0.01 mol) was added followed by the addition of **7**[20] (1.66 g, 0.01 mol) as a solid in one portion. The reaction was stirred at −20 °C for an additional 1 h and then allowed to warm to room temperature. The reaction mixture was then diluted with additional CH_2Cl_2 (50 mL) and washed with 1 N aqueous HCl (3 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and brine (1 × 50 mL). The resulting organic extract was dried and concentrated to afford 3.85 g (94.6%) of desired product **8** as a white foam: TLC R_f 0.45 (3:1 Et_2O:hexane); IR (KBr) 3412, 3308, 2974, 2876, 1714, 1701, 1641, 1508, 1437, 1390, 1367, 1309, 1286, 1236, 1170, 1091, 1043, 1016, 923, 879, 777, 750, 727, 657, 626, 584 cm^{-1}; ^1H NMR δ 8.19 (s, 1H, NH), 5.22 (d, 1H, J = 9.2 Hz, NH), 4.70 (dd, 1H, J = 7.8, 2.3 Hz, CH of Pro), 4.30 (app dd, 1H, J = 9.4, 6.5 Hz, α-CH of Val), 3.76–3.70 and 3.65–3.61 (pr m, 2H, CH_2N), 3.72 (s, 3H, OMe), 2.43 (m, 1H, β-CH of Val), 2.17–1.84 (m, 4H, CH_2CH_2), 2.09 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.44 (s, 9H, *t*-Bu), 0.99 (d, 3H, J = 6.8 Hz, CH_3), 0.94 (d, 3H, J = 6.7 Hz, CH_3); ^{13}C NMR δ 172.8, 169.3, 165.1, 155.7, 143.1, 121.3, 79.6, 77.4, 77.0, 76.5, 59.6, 56.8, 51.6, 47.7, 31.4, 28.3, 28.2, 26.7, 25.1, 22.0, 20.9, 19.4, 17.5; MS (CI/CH_4) *m/z* (rel intensity) 426 (MH^+, 22), 370 (52), 326 (100); HRMS $C_{21}H_{35}N_3O_6$ (M^+) calcd 426.2604, obsd 426.2603.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethylidene)-2-oxobutyl]-L-prolinamide (9).** To a −78 °C solution of **8** (3.8 g, 9.0 mmol) in Et_2O (100 mL) was added condensed pentafluoroethyl iodide (5.5 mL, 48.0 mmol). Methyllithium-lithium bromide complex (28.5 mL, 42.0 mmol) was added to the mixture at a rate which maintained an internal reaction temperature below −70 °C. The reaction mixture was stirred at −78 °C for 0.5 h, the cold bath removed, and stirring continued for 5 min. The mixture was poured into H_2O (100 mL), and the aqueous phase was acidified with 1 N HCl. The aqueous phase was extracted with additional Et_2O (100 mL), and the combined ethereal extracts were dried and concentrated to yield a crude yellow oil which was immediately flash chromatographed (3:1 Et_2O:hexane) to give **9** (2.6 g, 57%) as white foam: IR (KBr) 3433, 3302, 2976, 2937, 2879, 1714, 1687, 1635, 1510, 1444, 1392, 1369, 1321, 1284, 1221, 1199, 1174, 1045, 1016, 943, 881, 819, 800, 775, 746, 731, 680, 628, 586, 565 cm^{-1}; ^1H NMR δ 9.08 (s, 1 H, NH), 5.21 (d, 1 H, J = 9 Hz, NH), 4.73 (d, 1 H, J = ca. 8 Hz, CH of Pro), 4.30 (app dd, 1H, J = 9.1, 6.4 Hz, α-CH of Val), 3.77–3.74 and 3.64–3.58 (pr m, 2H, CH_2N), 2.49 (m, 1H, β-CH of Val), 2.11–1.83 (m, 4H, CH_2CH_2), 1.87 (d, 6H, J = 4.1 Hz, 2 × CH_3), 1.44 (s, 9H, *t*-Bu), 0.98 (d, 3H, J = 6.8 Hz, CH_3), 0.93 (d, 3H, J = 6.7 Hz, CH_3); ^{13}C NMR δ 173.7, 170.1, 155.7, 138.9, 125.6, 79.9, 77.4, 77.2, 77.1, 77.0, 76.6, 59.2, 56.8, 47.7, 31.2, 28.3, 25.9, 25.1, 20.7, 20.3, 19.4, 17.3; ^{19}F NMR δ −82.32 (s, CF_3), −122.13 and −123.63 (AB quartet, J = 285 Hz, CF_2); MS (CI/CH_4) *m/z* (rel intensity) 514 (MH^+, 23), 458 (100), 414 (33). Anal. ($C_{22}H_{32}F_5N_3O_5$) C, H, N.

General Procedure I. Representative Removal of an *N*-*t*-Boc Protecting Group. *N*-L-Valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethylidene)-2-oxobutyl]-L-prolinamide, Hydrochloride Salt (10). Into a stirred solution of **9** (0.50 g, 0.98 mmol) in EtOAc (20 mL) cooled in an ice–water bath was bubbled HCl gas for 4 min. The reaction mixture was then stoppered with a drying tube and allowed to warm to ambient temperature with stirring. After 1 h, the reaction mixture was concentrated, azeotroped with CCl_4, and placed under a high vacuum to give **10** (440 mg, 100%) as a white powder: mp 143–145 °C; IR (KBr) 3431, 3173, 2972, 2885, 2629, 1718, 1643, 1597, 1506, 1446, 1398, 1375, 1352, 1321, 1223, 1201, 1140, 1099, 1057, 993, 949, 939, 898, 887, 844, 815, 744, 729, 682, 592, 565 cm^{-1}; ^1H NMR δ 9.22 (s, 1H, NH), 8.33 (br s, 2H, NH_2), 4.89 (m, 1H, CH of Pro), 3.60 (m, 1H, α-CH of Val), 3.79–3.98 (pr m, 2H, CH_2N), 2.23–1.79 (m, 5H, β-CH of Val and CH_2CH_2), 1.92 (app d, 6H, J = 2.2 Hz, 2 × CH_3), 1.11 (d, 6H, J = 5.7 Hz, 2 × CH_3); ^{13}C NMR δ 171.1, 168.2, 142.8, 125.3, 77.4, 77.2, 77.0, 76.6, 60.0, 57.8, 48.3, 30.1, 28.5, 25.2, 21.6, 20.7, 18.6, 18.0; ^{19}F NMR δ −82.23 (s, CF_3), −120.95 and −123.30 (AB quartet, J = 291 Hz, CF_2); HRMS $C_{17}H_{24}F_5N_3O_3$ (M^+) calcd 414.1816, obsd 414.1833.

General Procedure II. Representative Coupling with 4-(4-Morpholinylcarbonyl)benzoic Acid. *N*-[4-(4-Morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethylidene)-2-oxobutyl]-L-prolinamide (4). To a stirred suspension of 4-(4-morpholinylcarbonyl)benzoic acid

(0.30 g, 1.25 mmol) and benzyltriethylammonium chloride (1 mg, 0.004 mmol) in 1,2-dichloroethane (25 mL) was added thionyl chloride (0.1 mL, 1.25 mmol), and the reaction mixture was heated at reflux. After 2.5 h the reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The residue was then azeotroped with CCl_4 and placed under vacuum to give the acid chloride as a light orange oil (quantitative) which was used without further purification. In a separate flask, a stirred solution of **10** (400 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) was cooled to −20 °C. NMM (0.45 mL, 4.0 mmol) was added and immediately followed by the dropwise addition of the acid chloride in CH_2Cl_2 (5 mL) at such a rate as to maintain the internal reaction temperature at −10 °C or less. After the addition was complete, the reaction mixture was allowed to warm to room temperature. After 1.5 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1 N aqueous HCl (2 × 30 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), and brine (1 × 25 mL). Drying and concentration afforded crude **4** (476 mg). The crude yellow oil was flash chromatographed (1:27 MeOH:CH_2Cl_2) to give **4** (281 mg, 50%) as a white foam: ^{1}H NMR δ 8.87 (s, 1H, NH), 7.87 (d, 2H, J = 8.4 Hz, aryl), 7.49 (d, 2H, J = 8.4 Hz, aryl), 6.86 (d, 1H, J = 8.9 Hz, NH), 4.85 (dd, 1H, J = 8.6, 6.6 Hz, α-CH of Val), 4.70 (dd, 1H, J = 7.9, 2.2 Hz, CH of Pro), 3.94−3.37 (m, 10H, 2 × NCH_2CH_2O and NCH_2 of Pro), 2.48 (m, 1H, β-CH of Val), 2.13 (m, 4H, CH_2CH_2), 1.90 (d, 6H, J = 6.6 Hz, 2 × CH_3), 1.06 (d, 3H, J = 6.8 Hz, CH_3), 1.01 (d, 3H, J = 6.7 Hz, CH_3); ^{13}C NMR δ 172.8, 169.9, 169.2, 166.4, 140.2, 138.6, 135.1, 127.39, 127.34, 127.3, 127.2, 125.4, 77.4, 77.1, 76.9, 76.5, 66.7, 59.3, 55.9, 47.9, 47.8, 42.5, 31.5, 26.2, 24.9, 20.8, 20.3, 19.4, 17.6; ^{19}F NMR δ −82.29 (s, CF_3), −121.93 and −123.34 (AB quartet, J = 285 Hz, CF_2); MS (CI/CH_4) m/z (rel intensity) 631 (MH^+, 100), 315 (92); HRMS $C_{29}H_{35}F_5N_4O_6$ (M^+) calcd 631.2555, obsd 631.2576.

[2-(Methoxymethylamino)-1,1-dimethyl-2-oxoethyl]carbamic Acid, 1,1-Dimethylethyl Ester (12). *N-t*-Boc-2-amino-2-methylpropanoic acid (**11**) (5.1 g, 25.2 mmol) was dissolved in CH_2Cl_2 (50 mL), and NMM was added (2.76 mL, 25.1 mmol). The mixture was cooled to −22 °C, and IBCF (3.25 mL, 25.1 mmol) was added. The mixture was stirred for 20 min followed by the addition of *N,O*-dimethylhydroxylamine hydrochloride (4.85 g, 49.7 mmol) and NMM (5.4 mL, 49.1 mmol). The mixture was stirred at −22 °C for 1 h, allowed to warm to room temperature, stirred for 1 h, poured into H_2O, and extracted with EtOAc. The combined organic extracts were washed with H_2O, dried, and concentrated. Purification by flash chromatography (1:4 EtOAc:hexane) gave 710 mg (11%) of **12** as a white solid: TLC R_f 0.23 (2:3 ethyl acetate:hexane); ^{1}H NMR δ 5.24 (m, 1H, NH), 3.69 (s, 3H, OCH_3), 3.21 (s, 3H, NCH_3), 1.55 (s, 6H, 2 × CH_3), 1.44 (s, 9H, 3 × CH_3); IR (KBr) 3323, 2982, 1726, 1635, 1523, 1365, 1271, 1253, 1163, 1076 cm^{-1}; MS (CI/CH_4) m/z (rel intensity) 247 (MH^+, 21), 219 (17), 191 (41), 147 (100); HRMS $C_{11}H_{23}N_2O_4$ (MH^+) calcd 247.1657, obsd 247.1656.

[3,3,4,4,4-Pentafluoro-1,1-dimethyl-2-oxobutyl]carbamic Acid, 1,1-Dimethylethyl Ester (13). Compound **12** (600 mg, 2.44 mmol) was dissolved in Et_2O (100 mL) and cooled to −78 °C. To the solution were added condensed pentafluoroethyl iodide (2.2 mL, 4.57 g, 18.7 mmol) and methyllithium−lithium bromide complex in Et_2O (12 mL, 1.5 M, 18.0 mmol). After 0.5 h, additional pentafluoroethyl iodide (2.2 mL) and methyllithium−lithium bromide complex (12 mL) were added. The reaction mixture was stirred at −78 °C for 1.5 h, poured into dilute aqueous $KHSO_4$, and extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and H_2O and dried. Concentration followed by flash chromatography (1:4 EtOAc:hexane) gave 590 mg (79%) of **13** as a white solid: TLC R_f 0.70 (2:3 ethyl acetate:hexane); ^{1}H NMR δ 4.98 (br s, 1H, NH), 1.53 (s, 6H, 2 × CH_3), 1.43 (s, 9H, 3 × CH_3); ^{19}F NMR δ −82.12 (s, CF_3), −118.04 (s, CF_2); IR (KBr) 3337, 2984, 1745, 1676, 1523, 1392, 1371, 1302, 1226, 1203, 1186, 1167, 1095 cm^{-1}; MS (CI/CH_4) m/z (rel intensity) 306 (MH^+, 3), 278 (19), 250 (100), 230 (10), 206 (32); HRMS $C_{11}H_{17}F_5NO_3$ (MH^+) calcd 306.1128, obsd 306.1132.

2-Amino-4,4,5,5,5-pentafluoro-2-methyl-3-pentanone, Hydrochloride Salt (14). Compound **13** (500 mg) was dissolved in EtOAc (100 mL) and treated as described in General Procedure I to yield 440 mg (99%) of **14** as a white solid: ^{1}H NMR δ 7.85 (m, 3H, NH_3^+), 3.33 (s, 3H, CH_3), 2.51 (s, 3H, CH_3); ^{19}F NMR δ −77.29 (s, CF_3), −119.21 (s, CF_2); IR (KBr) 2957, 2831, 1751, 1716, 1585, 1352, 1249, 1221 cm^{-1}; MS (CI/CH_4) m/z (rel intensity) 206 (MH^+, 100), 188 (9), 166 (5), 87 (3); HRMS $C_6H_9F_5NO$ (MH^+) calcd 206.0604, obsd 206.0612.

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-(3,3,4,4,4-pentafluoro-1,1-dimethyl-2-oxobutyl)-L-prolinamide (5).** *N-t*-Boc-L-Val-L-Pro-OH (785 mg, 2.5 mmol) was dissolved in CH_2Cl_2 (10 mL), and NMM (0.275 mL, 2.5 mmol) was added. The mixture was cooled to −22 °C, and IBCF (0.32 mL, 2.5 mmol) was added. The mixture was stirred for 20 min followed by the addition of **14** (400 mg, 1.66 mmol) and NMM (0.275 mL, 2.5 mmol). The mixture was stirred at −22 °C for 1 h, allowed to warm to room temperature, and stirred for 1 h. The reaction mixture was poured into 100 mL of H_2O and extracted with CH_2Cl_2. The combined extracts were dried and concentrated, and the crude product was purified by flash chromatography (3:1 EtOAc:hexane) to give 700 mg (84%) of **5** as a white solid: TLC R_f 0.67 (35:65 acetone:ethyl acetate); ^{1}H NMR δ 7.79 (br s, 1H, NH), 5.18 (d, J = 8.9 Hz, 1H, NH), 4.62 (dd, J = 8.0, 2.4 Hz, 1H, CH of Pro), 4.31 (dd, J = 9.6, 5.8 Hz, 1H, CH of Val), 3.70 (m, 1H, NCH_2), 3.57 (m, 1H, NCH_2), 2.42 (m, 1H, β-CH of Val), 2.15−1.70 (series of m, 4H, CH_2CH_2), 1.53 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.01 (d, J = 6.9 Hz, 3H, CH_3 of Val), 0.94 (d, J = 6.9 Hz, 3H, CH_3 of Val); ^{19}F NMR δ −82.03 (s, CF_3), −118.48 (s, CF_2); IR (KBr) 3437, 3289, 3018, 2980, 1746, 1706, 1679, 1623, 1501, 1436, 1234, 1173 cm^{-1}; MS (CI/CH_4) m/z (rel intensity) 502 MH^+, 18) 446 (100), 402 (70); HRMS $C_{21}H_{33}F_5N_3O_5$ (MH^+) calcd 502.2340, obsd 502.2322. Anal. ($C_{21}H_{32}F_5N_3O_5$) C, H, N.

[2-(Methoxymethylamino)-2-oxoethyl]carbamic Acid, 1,1-Dimethylethyl Ester (16). To a solution of N-*t*-Boc-Gly-OH (**15**) (25.0 g, 0.15 mol) in CH_2Cl_2 (500 mL) were added DMAP (17.3 g, 0.15 mol), *N,O*-dimethylhydroxylamine hydrochloride (13.9 g, 0.15 mol), NMM (14.3 g, 0.15 mol), and EDC (27.3 g, 0.15 mol). The mixture was stirred overnight at room temperature, washed with aqueous HCl (10%), saturated aqueous $NaHCO_3$, and brine, and dried. Concentration gave 24.9 g (78%) of **16** as a white solid: R_f 0.19 (2:3 ethyl acetate:hexane); ^{1}H NMR δ 5.29 (m, 1H, NH), 4.08 (br d, J = 4.9 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.21 (s, 3H, NCH_3), 1.46 (s, 9H, 3 × CH_3); IR (KBr) 3288, 2976, 1716, 1658, 1543, 1404, 1365, 1282, 1251, 1182, 1167 cm^{-1}; MS (CI/CH_4) m/z (rel intensity) 337 ((M + 119)$^+$, 4), 219 (MH^+, 15), 191 (17), 163 (100), 119 (80); HRMS $C_9H_{19}N_2O_4$ (MH^+) calcd 219.1344, obsd 219.1344.

(3,3,4,4,4-Pentafluoro-2-oxobutyl)carbamic Acid, 1,1-Dimethylethyl Ester (17). To a solution of **16** (5.0 g, 22.9 mmol) and pentafluoroethyl iodide (6.0 mL, 50.9 mmol) in Et_2O (500 mL) at −78 °C was added methyllithium−lithium bromide complex (32 mL, 1.5 M in Et_2O, 4.8 mmol). The mixture was stirred at −78 °C for 1 h, allowed to warm to −50 °C over 30 min, and poured into dilute aqueous $KHSO_4$. The product was extracted with Et_2O, washed with saturated aqueous $NaHCO_3$, and dried. Concentration followed by flash chromatography (2:3 EtOAc:hexane) gave 2.4 g (38%) of **17** as a white solid (5:4:1 mixture of ketone:hydrate:enol by ^{19}F NMR): R_f 0.71 (3:1 ethyl acetate:hexane); ^{1}H NMR δ 6.53 (br d, J = 7.9 Hz, 0.1H, NH of enol), 6.17 (d, J = 8.6 Hz, 0.1H, CH of enol), 5.26 (m, 0.4H, NH of hydrate), 5.13 (m, 0.5H, CH of ketone), 4.41 (d, J = 5.3 Hz, 0.5H, CH_2 of ketone), 4.29 (br s, 0.1H, OH of enol), 3.51 (d, J = 5.9 Hz, 0.4H, CH_2 of hydrate), 1.52 (s, 0.3H, $C(CH_3)_3$ of hydrate), 1.48 (s, 1.2H, $C(CH_3)_3$ of enol), 1.45 (s, 1.5H, $C(CH_3)_3$ of ketone); ^{19}F NMR δ −79.34 (s, CF_3 of hydrate), −82.06 (s, CF_3 of ketone), −83.58 (s, CF_3 of enol), −119.96 (s, CF_2 of enol), −123.76 (s, CF_2 of ketone), −125.31 (s, CF_2 of hydrate); IR (KBr) 3364, 3354, 2986, 2939, 1772, 1703, 1518, 1371, 1334, 1205, 1159, 1093 cm^{-1}; MS (CI/CH_4) m/z (rel intensity) 278 (MH^+, 22), 250 (20), 222 (100), 178 (10).

***N*-[(1,1-Dimethylethoxy)carbonyl]-L-valyl-*N*-(3,3,4,4,4-pentafluoro-2-oxobutyl)-L-prolinamide (18).** Compound **17** (3.1 g) was dissolved in EtOAc (100 mL), cooled to 0 °C, and treated with HCl (gas) until saturation. The mixture was

stirred at 0 °C for 0.5 h, concentrated to a volume of 10 mL, and poured into vigorously stirred hexane (150 mL). The amine hydrochloride (2.2 g, 92%) was collected by suction filtration and used without further purification. N-*t*-Boc-L-Val-L-Pro-OH (1.5 g, 4.7 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to −22 °C, and NMM (1.53 mL, 14.1 mmol) and IBCF (0.59 mL, 4.7 mmol) were added. The mixture was stirred for 30 min at −22 °C, and the amine hydrochloride (1.0 g, 4.7 mmol) from above was added. The mixture was stirred at −22 °C for 1 h, allowed to warm to room temperature, stirred for 0.5 h, and poured into dilute aqueous HCl. The mixture was extracted with EtOAc, and the combined extracts were washed with saturated aqueous $NaHCO_3$ and dried. The solvent was removed, and the crude product was dissolved in EtOAc/hexane (3:1) and filtered through a plug of silica gel to yield 1.7 g (83%) of **18** as a white solid (5:10:1 mixture of ketone:hydrate:enol by ^{19}F NMR): ^{19}F NMR δ −79.70 (s, CF_3 of hydrate), −82.61 (s, CF_3 of ketone), −84.21 (s, CF_3 of enol), −120.55 (s, CF_2 of enol), −124.23 (CF_2 of ketone), −127.50 (s, CF_2 of hydrate); IR (KBr) 3385, 2978, 1749, 1691, 1510, 1369, 1219, 1167 cm^{-1}; HRMS (MH^+) calcd 474.2027, obsd 474.2028.

***N*-[4-(4-Morpholinylcarbonyl)benzoyl]-L-valyl-*N*-(3,3,4,4,4-pentafluoro-2-oxobutyl)-L-prolinamide (6) and *N*-[4-(4-Morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-2-[[4-(4-morpholinylcarbonyl)benzoyl]oxy]-1-butenyl]-L-prolinamide (19).** The *N*-*t*-Boc protecting group of **18** (0.60 g, 1.27 mmol) was cleaved as described in General Procedure I to give 0.52 g (100%) of the corresponding amine hydrochloride as a white solid, which was used (see below) without further purification. A stirred solution of 4-(4-morpholinylcarbonyl)benzoyl chloride (1.40 mmol) and NMM (0.39 mL, 3.51 mmol) in CH_2Cl_2 (20 mL) was reacted with the above generated amine hydrochloride (0.48 g, 1.17 mmol) as described in General Procedure II. Purification by flash chromatography [gradient (25−45%) acetone in EtOAc] gave 305 mg (44%) of **6** as a white solid foam: TLC R_f 0.25 (2:3 acetone:EtOAc); initial ^{19}F NMR (DMSO-d_6, CF_3 signals only) δ −77.86 (s, CF_3 of hydrated ketone), −81.10 (s, CF_3 of ketone), −82.06 (t, J = 3 Hz, CF_3 of enol); ratio of ketone:hydrated ketone:enol ≈ 1:1.5:2. After standing for 6 days, the spectra for the DMSO-d_6 sample simplified due to the disappearance of ketone species (presumably due to the presence of a small amount of water in the solvent). The simplified spectra, showing a 4:1 ratio of enol to hydrated ketone, are detailed below.

6: ^1H NMR (DMSO-d_6) δ 9.84 (br d, 0.8H, J = 10.3 Hz, Gly NH of enol species), 9.28 (s, 0.8H, OH, enol species), 8.63 (br d, 0.8H, Val NH of enol species), 8.62 (br d, 0.2H, Val NH of hydrate species), 8.04 (t, 0.2H, J = 6.3 Hz, Gly NH of hydrate species), 7.98−7.93 (m, 2H, ½aryl), 7.51−7.45 (m, 2H, ½aryl), 7.11 and 7.06 (pr s, 0.4H, 2 × OH of hydrate species), 6.64 (d, 0.8H, J = 10.2 Hz, vinyl of enol species), 4.55−4.34 (m, 2H, 2 × CH), 4.03−3.88 (m, 1H, ½CH_2N), 3.77−3.20 (m), 2.22−2.06 (m, 2H), 2.06−1.76 (m, 3H), 1.02−0.94 (m, 6H, 2 × CH_3); ^{19}F NMR (DMSO-d_6) δ −77.86 (s, CF_3 of hydrate), −82.06 (t, J = 3 Hz, CF_3 of enol), −117.70 (q, J = 3 Hz, CF_2 of enol), −124.77 (s, CF_2 of hydrate); MS (CI/CH_4) m/z (rel intensity) 591 (MH^+, 31), 317 (14), 289 (15), 275 (100), 218 (10), 70 (8). Anal. ($C_{26}H_{31}F_5N_4O_6$) C, H, N.

Also isolated was 99 mg (10%) of **19** as a white foam: TLC R_f 0.23 (2:3 acetone:EtOAc); ^1H NMR (DMSO-d_6) δ 10.66 (br d, 1H, J = 10 Hz, NH), 8.62 (br d, 1H, J = 8 Hz, NH), 8.13−8.06 (m, 2H, aryl), 7.94−7.88 (m, 2H, aryl), 7.64−7.58 (m, 2H, aryl), 7.52−7.42 (m, 3H, aryl and vinyl), 4.50−4.36 (m, 2H, 2 × CH), 4.02−3.88 (m, 1H, ½CH_2N), 3.76−3.14 (m, 17H), 2.23−1.74 (m, 5H), 0.99 (d, 3H, J = 6.8 Hz, CH_3), 0.97 (d, 3H, J = 6.8 Hz, CH_3); ^{19}F NMR (DMSO-d_6) −82.64 (s, CF_3), −116.66 (s, CF_2); MS (CI/CH_4) m/z (rel intensity) 808 (MH^+, 12), 788 (4), 591 (4), 414 (22), 317 (35), 305 (100), 275 (24), 238 (27), 218 (81); HRMS $C_{38}H_{43}F_5N_5O_9$ (M^+) calcd 808.2981, obsd 808.2972.

General Procedure III. Synthesis of *E*-Enol Acetate Derivatives from Pentafluoroethyl Ketone 1. (*E*)-*N*-[4-(4-Morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[2-(acetyloxy)-3,3,4,4,4-pentafluoro-1-(1-methylethyl)-1-butenyl]-L-prolinamide (20). To a stirred solution of 1 (2.00 g, 3.16 mmol), Et_3N (0.66 mL, 4.74 mmol), and DMAP (0.77 g, 6.32 mmol) in CH_2Cl_2 (8 mL) cooled to −20 °C (dry ice−CCl_4 bath) was added acetic anhydride (0.89 mL, 9.48 mmol) dropwise over a 5 min period. After 1.5 h at −20 °C, the reaction mixture was diluted with CH_2Cl_2 (70 mL) and the organics were washed with 0.5 N aqueous HCl (2 × 50 mL) followed by 50 mL of a mixture of 0.5 N aqueous HCl−brine (1:9). Drying and concentration gave crude **20**. Recrystallization from EtOAc−hexane gave 2.25 g (85%, two crops) of **20** as a white crystalline solid: mp 127−137 °C dec; TLC R_f 0.34 (1:9 acetone:EtOAc); ^1H NMR δ 8.02 (br s, 1H, NHC=C), 7.88−7.84 (m, 2H, ½ aryl), 7.51−7.46 (m, 2H, ½aryl), 6.85 (br d, 1H, J = 8.9 Hz, NH), 4.87 (dd, 1H, J = 6.3, 8.8 Hz, CH), 4.65 (dd, 1H, J = 2.6, 8.0 Hz, CH), 3.92−3.54 (m, 8H), 3.39 (br s, 2H), 2.73 (septet, 1H, J = 6.9 Hz, CHC=C), 2.52−2.42 (m, 1H), 2.24 (s, 3H, $COCH_3$), 2.25−1.85 (m, 4H), 1.08 (d, 3H, J = 6.9 Hz, CH_3), 1.07 (d, 3H, J = 6.7 Hz, CH_3), 1.05 (d, 3H, J = 6.8 Hz, CH_3), 1.01 (d, 3H, J = 6.8 Hz, CH_3); ^{19}F NMR δ−83.55 (s, CF_3), −116.50 (br s, CF_2); MS (CI/CH_4) m/z (rel intensity) 675 (MH^+, 25), 359 (100), 317 (75), 262 (28), 230 (40), 210 (22), 70 (52). Anal. ($C_{31}H_{39}F_5N_4O_7$) C, H, N.

(*E*)-*N*-[4-(4-Morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-(1-oxopropoxy)-1-butenyl]-L-prolinamide (21). A solution of 1 (0.50 g, 0.79 mmol) in CH_2Cl_2 (2 mL) cooled to −20 °C was treated with Et_3N (0.16 mL, 1.19 mmol), DMAP (0.19 g, 1.58 mmol), and propionic anhydride (0.30 mL, 2.37 mmol) as described in General Procedure III. Purification by recrystallization from EtOAc gave 374 mg (69%) of **21** as a white solid: mp 138−144 °C dec; TLC R_f 0.35 (1:9 acetone:EtOAc); ^1H NMR δ 8.00 (br s, 1H, NHC=C), 7.88−7.84 (m, 2H, ½aryl), 7.52−7.46 (m, 2H, ½aryl), 6.85 (br d, 1H, J = 8.8 Hz, NH), 4.87 (dd, 1H, J = 6.3, 8.8 Hz, CH), 4.65 (dd, 1H, J = 2.6, 8.0 Hz, CH), 3.92−3.53 (m, 8H), 3.40 (br s, 2H), 2.71 (septet, 1H, J = 6.9 Hz, CHC=C), 2.52 (q, 2H, J = 7.5 Hz, $COCH_2$), 2.50−2.40 (m, 1H), 2.24−1.85 (m, 4H), 1.22 (t, 3H, J = 7.5 Hz, CH_3), 1.08 (d, 3H, J = 6.9 Hz, CH_3), 1.07 (d, 3H, J = 6.5 Hz, CH_3), 1.05 (d, 3H, J = 6.8 Hz, CH_3), 1.01 (d, 3H, J = 6.74 Hz, CH_3); ^{19}F NMR δ −83.57 (s, CF_3), −116.27 and −116.55 (AB quartet, J = 280 Hz, CF_2); MS (CI/CH_4) m/z (rel intensity) 689 (MH^+, 17), 414 (20), 373 (100), 317 (22), 77 (54), 75 (23), 70 (20). Anal. ($C_{32}H_{41}F_5N_4O_7$) C, H, N.

(*E*)-*N*-[4-(4-Morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-(2-methyl-1-oxopropoxy)-1-butenyl]-L-prolinamide (22). A solution of **1** (0.50 g, 0.79 mmol) in CH_2Cl_2 (2 mL) cooled to −20 °C was treated with Et_3N (0.16 mL, 1.19 mmol), DMAP (0.19 g, 1.58 mmol), and isobutyric anhydride (0.39 mL, 2.37 mmol) as described in General Procedure III. Purification by recrystallization from EtOAc gave 303 mg (54%) of **22** as a white solid: mp 135−142 °C dec; TLC R_f 0.34 (1:9 acetone:EtOAc); ^1H NMR δ 7.98 (br s, 1H, NHC=C), 7.89−7.84 (m, 2H, ½aryl), 7.51−7.46 (m, 2H, ½aryl), 6.87 (br d, 1H, J = 8.8 Hz, NH), 4.87 (dd, 1H, J = 6.3, 8.8 Hz, CH), 4.65 (dd, 1H, J = 2.6, 8.1 Hz, CH), 3.94−3.55 (m, 8H), 3.40 (br s, 2H), 2.74 (septet, 1H, J = 7.0 Hz, COCH), 2.68 (septet, 1H, J = 6.9 Hz, CHC=C), 2.50−2.40 (m, 1H), 2.25−1.86 (m, 4H), 1.26 (d, 6H, J = 7.0 Hz, 2 × CH_3), 1.09 (d, 3H, J = 6.9 Hz, CH_3), 1.07 (d, 3H, J = 6.8 Hz, CH_3), 1.05 (d, 3H, J = 6.9 Hz, CH_3), 1.01 (d, 3H, J = 6.7 Hz, CH_3); ^{19}F NMR δ −83.68 (s, CF_3), −116.16 and −116.66 (AB quartet, J = 282 Hz, CF_2); MS (CI/CH_4) m/z (rel intensity) 703 (MH^+, 20), 387 (56), 317 (78), 290 (28), 230 (35), 91 (100), 89 (80), 71 (90), 70 (80). Anal. ($C_{33}H_{43}F_5N_4O_7$) C, H, N.

(*Z*)-*N*-[4-(4-Morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[2-(acetyloxy)-3,3,4,4,4-pentafluoro-1-(1-methylethyl)-1-butenyl]-L-prolinamide (23). A stirred solution of 1 (0.50 g, 0.79 mmol), Et_3N (0.16 mL, 1.19 mmol), and DMAP (0.19 g, 1.58 mmol) in CH_2Cl_2 (2 mL) was heated to reflux and acetic anhydride (0.22 mL, 2.37 mmol) added dropwise. After 30 min, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (45 mL), and washed with 0.5 N aqueous HCl (2 × 35 mL) followed by 25 mL of a mixture of 0.5 N aqueous HCl−brine (1:9). Drying and concentration gave crude **23**. Purification by flash chromatography (EtOAc) followed by recrystallization from Et_2O gave 49 mg of **23** (containing ca. 5% **20** as a contaminant) as a white solid: TLC

R_f 0.17 (EtOAc); ^{1}H NMR δ 7.96 (br s, 1H, NHC=C), 7.89–7.83 (m, 2H, $^1/_2$aryl), 7.53–7.46 (m, 2H, $^1/_2$aryl), 6.78 (br d, 1H, J = 8.7 Hz, NH), 4.84 (dd, 1H, J = 6.6, 8.8 Hz, CH), 4.61 (dd, 1H, J = 2.6, 8.0 Hz, CH), 3.97–3.53 (m, 8H), 3.41 (br s, 2H), 3.13 (septet, 1H, J = 6.7 Hz, CHC=C), 2.50–2.39 (m, 1H), 2.20–2.03 and 2.01–1.87 (pr m, 4H), 2.13 (s, 3H, $COCH_3$), 1.11 (d, 6H, J = 6.7 Hz, 2 × CH_3), 1.06 (d, 3H, J = 6.7 Hz, CH_3), 1.02 (d, 3H, J = 6.7 Hz, CH_3); ^{19}F NMR δ −84.73 (t, J = 3 Hz, CF_3), −113.63 (br s, CF_2); MS (CI/CH_4) m/z (rel intensity) 675 (MH^+, 17), 635 (16), 385 (100), 121 (30).

General Procedure IV. Synthesis of *E*-Enol Acetate Derivatives from Trifluoromethyl Ketones. (*E*)-*N*-[(1,1-Dimethylethoxy)carbonyl]-L-alanyl-L-alanyl-*N*-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide (25). To a stirred solution of **24** (1.00 g, 1.97 mmol) in acetonitrile (5 mL) cooled to −20 °C (dry ice–CCl_4 bath) was added acetic anhydride (0.56 mL, 5.90 mmol) followed immediately by DMAP (480 mg, 3.93 mmol). After 2 h, the reaction mixture was diluted with CH_2Cl_2 (75 mL) and washed with 0.5 N aqueous HCl(2 × 50 mL) followed by 50 mL of a mixture of 0.5 N aqueous HCl–brine (1:9). Drying and concentration gave crude **25**. Purification by flash chromatography (85:15 EtOAc:hexane) gave 0.54 g (50%) of **25** as a white solid. A portion of **25** was recrystallized from Et_2O–pentane to provide an analytical sample: mp 111–114 °C dec; TLC R_f 0.35 (EtOAc); ^{1}H NMR δ 8.44 (br s, 1H, NHC=C), 7.88 (br d, 1H, J = 6.7 Hz, NH), 5.29 (br d, 1H, J = 7.4 Hz, NH), 4.94–4.82 (m, 1H, CH), 4.75 (dd, 1H, J = 2.8, 8.0 Hz, CH), 4.61–4.45 (m, 1H, CH), 3.79–3.68 and 3.68–3.57 (pr m, 2H, CH_2N), 2.70 (septet, 1H, J = 6.9 Hz, CHC=C), 2.36–1.96 (m, 4H), 2.23 (s, 3H, $COCH_3$), 1.44 (s, 9H, *t*-Bu), 1.33 (d, 3H, J = 6.8 Hz, CH_3), 1.24 (d, 3H, J = 6.8 Hz, CH_3), 1.00 (d, 3H, J = 6.8 Hz, CH_3), 0.96 (d, 3H, J = 6.90 Hz, CH_3); ^{13}C NMR δ 172.2, 171.9, 171.2, 167.9, 155.7, 139.9, 132.9 (q, J = 35.0 Hz), 119.9 (q, J = 274.5 Hz, CF_3), 80.4, 49.5, 47.5, 46.2, 30.2, 28.3, 28.25, 27.9, 24.9, 20.1, 20.02, 19.96, 19.1, 19.0, 18.5; ^{19}F NMR δ −66.04 (s, CF_3); IR ($CHCl_3$ film) 3428, 3293, 2980, 2936, 2878, 1788, 1670, 1630, 1460, 1370, 1333, 1244, 1219, 1179, 1141, 1117, 756 cm^{-1}; MS (CI/CH_4) m/z (rel intensity) 551 (MH^+, 38), 495 (100), 453 (18), 452 (17), 340 (17), 309 (52), 284 (13), 70 (19). Anal. ($C_{24}H_{37}F_3N_4O_7$) C, H, N.

(*E*)-*N*-(4-Morpholinylcarbonyl)-L-valyl-*N*-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide (29). A solution of **27** (0.65 g, 1.36 mmol) in acetonitrile (4 mL) cooled to −20 °C was treated with acetic anhydride (0.38 mL, 4.07 mmol) and DMAP (332 mg, 2.72 mmol) as described in General Procedure IV. Purification by repeated flash chromatography (1:9 acetone:EtOAc) gave 43 mg (6%) of **29** as a white solid: TLC R_f 0.33 (15:85 acetone:EtOAc); ^{1}H NMR δ 8.12 (br s, 1H, NHC=C), 5.12 (br d, 1H, J = 8.5 Hz, NH), 4.68 (dd, 1H, J = 1.6, 7.7 Hz, CH), 4.52 (dd, 1H, J = 6.5, 8.5 Hz, NH), 3.92–3.79 (m, 1H, $^1/_2CH_2N$), 3.75–3.59 (m, 5H, $^1/_2CH_2N$ and CH_2OCH_2), 3.49–3.31 (m, 4H, CH_2NCH_2), 2.71 (septet, 1H, J = 6.9 Hz, CHC=C), 2.55–2.43 (m, 1H), 2.25 (s, 3H, $COCH_3$), 2.16–1.81 (m, 4H), 1.05 (d, 3H, J = 6.8 Hz, CH_3), 1.04 (d, 3H, J = 7.0 Hz, CH_3), 1.01 (d, 3H, J = 6.8 Hz, CH_3), 0.96 (d, 3H, J = 6.6 Hz, CH_3); ^{19}F NMR δ −67.33 (s, CF_3); MS (CI/CH_4) m/z (rel intensity) 521 (MH^+, 59), 501 (10), 461 (17), 337 (10), 309 (68), 213 (100), 185 (22), 114 (10), 85 (10), 84 (15), 70 (12); HRMS $C_{23}H_{36}F_3N_4O_6$ (MH^+) calcd 521.2587, obsd 521.2603.

(*E*)-*N*-[4-(4-Morpholinylcarbonyl)benzoyl]-L-valyl-*N*-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-propenyl]-L-prolinamide (30). A solution of **28** (744 mg, 1.28 mmol) in acetonitrile (3.5 mL) cooled to −20 °C was treated with acetic anhydride (0.36 mL, 3.83 mmol) and DMAP (312 mg, 2.55 mmol) as described in General Procedure IV. Purification by flash chromatography (1:9 acetone:EtOAc) followed by recrystallization from EtOAc–hexane gave 300 mg (38%) of **30** as fine white needles: mp 121–129 °C dec; TLC R_f 0.34 (15:85 acetone:EtOAc); ^{1}H NMR δ 8.01 (br s, 1H, NHC=C), 7.89–7.84 (m, 2H, $^1/_2$aryl), 7.51–7.46 (m, 2H, $^1/_2$aryl), 6.83 (br d, 1H, J = 8.8 Hz, NH), 4.87 (dd, 1H, J = 6.3, 8.7 Hz, CH), 4.67 (dd, 1H, J = 2.4, 8.0 Hz, CH), 3.93–3.52 (m, 8H), 3.40 (br s, 2H), 2.72 (septet, 1H, J = 6.9 Hz, CHC=C), 2.55–2.45 (m, 1H), 2.25 (s, 3H, COCH), 2.23–2.02 (m, 3H), 1.99–1.85 (m, 1H), 1.07 (d, 3H, J = 6.9 Hz, CH_3), 1.06 (d, 3H, J = 6.9 Hz, CH_3), 1.05 (d, 3H, J = 6.9 Hz, CH_3), 1.01 (d, 3H, J = 6.7 Hz, CH_3); ^{19}F NMR δ −67.30 (s, CF_3); MS (CI/CH_4) m/z (rel intensity) 625 (MH^+, 90), 414 (17), 309 (100), 86 (35), 85 (38). Anal. ($C_{30}H_{39}F_3N_4O_7$) C, H, N.

(*E*)-*N*-[4-[[[(4-Chlorophenyl)sulfonyl]amino]carbonyl]-benzoyl]-L-valyl-*N*-[2-(acetyloxy)-3,3,3-trifluoro-1-(1-methylethyl)-1-propenyl]-L-prolinamide (31). To a stirred solution of **2** (687 mg, 1.00 mmol) in pyridine (3.5 mL) cooled to 0 °C (ice–water bath) was added acetic anhydride (0.94 mL, 10.00 mmol) dropwise. After 24 h at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with 0.5 N aqueous HCl (2 × 50 mL) followed by 50 mL of a mixture of 0.5 N aqueous HCl–brine (1:9). Drying and concentration gave crude **31**. Purification by flash chromatography [gradient (0–0.5%) of acetic acid in EtOAc] gave 463 mg (49%) of **31** as a white solid foam: TLC R_f 0.38 (0.5:99.5 acetic acid:EtOAc); ^{1}H NMR δ 10.08 (br s, 1H, $NHSO_2$), 8.06 (d, 2H, J = 8.0 Hz, aryl), 7.87 (br s, 1H, NHC=C), 7.77 (d, 2H, J = 7.8 Hz, aryl), 7.65 (d, 2H, J = 7.8 Hz, aryl), 7.51 (d, 2H, J = 8.0 Hz, aryl), 7.05 (br d, 1H, J = 7.3 Hz, NH), 4.92 (dd, 1H, J = 6.7, 7.8 Hz, CH), 4.65 (dd, 1H, J = 1.8, 7.3 Hz, CH), 3.96–3.83 (m, 1H, $^1/_2CH_2N$), 3.76–3.65 (m, 1H, $^1/_2CH_2N$), 2.71 (septet, 1H, J = 6.8 Hz, CHC=C), 2.46–2.34 (m, 1H), 2.25 (s, 3H, $COCH_3$), 2.25–1.89 (m), 1.07 (d, 3H, J = 6.7 Hz, CH_3), 1.03 (d, 3H, J = 6.8 Hz, CH_3), 1.01 (d, 3H, J = 6.8 Hz, CH_3), 0.99 (d, 3H, J = 6.9 Hz, CH_3); ^{19}F NMR δ −67.00 (s, CF_3); MS (CI/CH_4) m/z (rel intensity) 729 (MH^+, 100), 709 (10), 669 (13), 518 (25), 309 (100), 212 (10), 70 (28). Anal. ($C_{32}H_{36}ClF_3N_4O_8S\cdot 1H_2O$) C, H, N.

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