# Development of New Hydroxamate Matrix Metalloproteinase Inhibitors Derived from Functionalized 4-Aminoprolines

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A series of hydroxamates was prepared from an aminoproline scaffold and tested for efficacy as matrix metalloproteinase (MMP) inhibitors. Detailed SAR for the series is reported for five enzymes within the MMP family, and a number of inhibitors, such as compound **47**, display broad-spectrum activity with sub-nanomolar potency for some enzymes. Modifications of the P1′ portion of the molecule played a key role in affecting both potency and selectivity within the MMP family. Longer-chain aliphatic substituents in this region of the molecule tended to increase potency for MMP-3 and decrease potency for MMP-1, as exemplified by compounds **48**−**50**, while aromatic substituents, as in compound **52**, generated broad-spectrum inhibition. The data is rationalized based upon X-ray crystal data which is also presented. While the in vitro peroral absorption seemed to be less predictable, it tended to decrease with longer and more hydrophilic substituents. Finally, a rat model of osteoarthritis was used to evaluate the efficacy of these compounds, and a direct link was established between their pharmacokinetics and their in vivo efficacy.

## Introduction

The matrix metalloproteinases (MMPs) are a family of enzymes that are intimately involved in tissue remodeling. They have thus received a great deal of detailed attention,[1] and inhibitors for these enzymes have been developed for the treatment of a startlingly wide array of disease processes where matrix remodeling plays a key role. These indications include osteoarthritis,[2−4] rheumatoid arthritis,[3,5,6] tumor metastasis,[7] multiple sclerosis,[8−11] congestive heart failure,[11−13] and a host of others.

A number of MMPIs have progressed into clinical trials for cancer, rheumatoid arthritis, and possibly osteoarthritis; selected examples are shown in Figure 1.[14] Marimastat is a broad-spectrum inhibitor and was the first MMPI to enter clinical trials for cancer treatment.[15] So far, progression through these trials has been hampered due to musculoskeletal syndrome (MSS) which manifests itself as musculoskeletal pain after a few weeks of treatment. One hypothesis suggests that inhibition of MMP-1 may play a role in the appearance of MSS. Consequently, recent efforts in the field have been directed toward designing MMP-1-sparing inhibitors. Out of this new generation, BA-129566 emerged as a highly selective inhibitor which reportedly showed no signs of MSS in phase 2 clinical trials.[2]

Our group has been developing both succinamide[16] and heterocyclic[17−20] inhibitors with a focus on understanding the structural modifications which might deliver the appropriate inhibitory profile which will slow the progression of osteoarthritis while minimizing or eliminating the occurrence of MSS. From this effort, a series of inhibitors based on an aminopyrrolidine scaffold was developed which displayed a wide range of enzyme profiles and is described below. Further investigation led to the identification of a number of selective, orally active inhibitors which protected cartilage against degradation in a rat model of osteoarthritis.

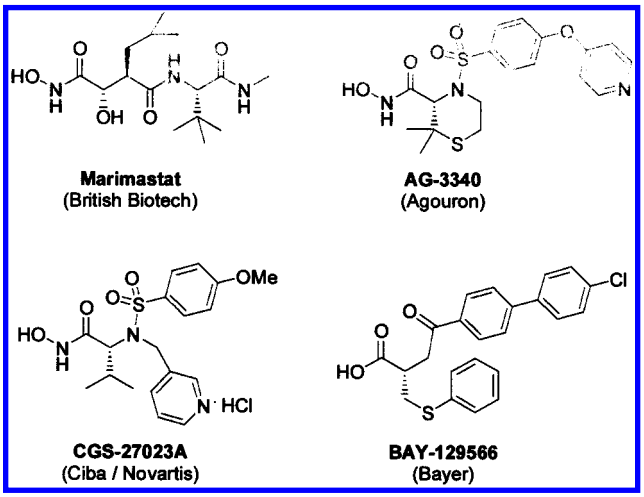


**Figure 1.** Clinical candidates that inhibit MMPs.

## Synthesis

All compounds were derived from *cis*-4-hydroxy-D-proline (**1**) as exemplified in Scheme 1. The presence of a hydroxyl group at C4 provided a functionalizable handle from which various moieties were obtained stereospecifically. Mesylates of type **2** were obtained via a conventional sequence of esterification, sulfonylation, and treatment with methanesulfonyl chloride. This key intermediate was isolated and stored for long periods

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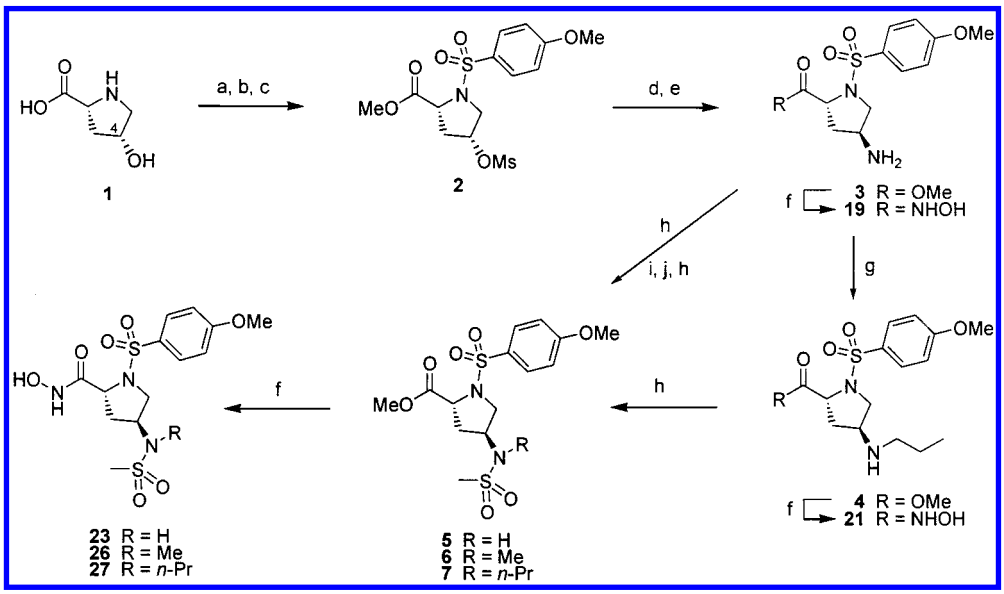
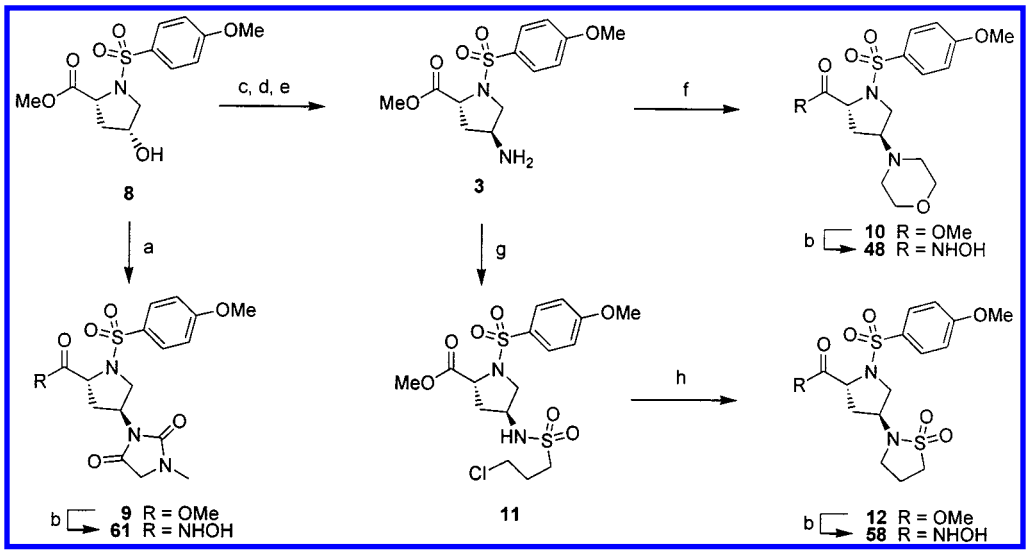
**Scheme 1**[a]




[a] Reagents: (a) MeOH, $SOCl_2$; (b) $ClSO_2C_6H_4OMe$; (c) MsCl, $NEt_3$, $CH_2Cl_2$; (d) $NaN_3$, DMF, 60 °C; (e) 10% Pd−C, $H_2$, EtOAc; (f) $NH_2OH$, MeOH; (g) $CH_3CH_2CHO$, $NaCNBH_3$, NaOAc; (h) $ClSO_2Me$, $NEt_3$, $CH_2Cl_2$; (i) $HCO_2H$, $(CH_3OCO)_2O$; (j) $BH_3$, THF.

**Scheme 2**[a]



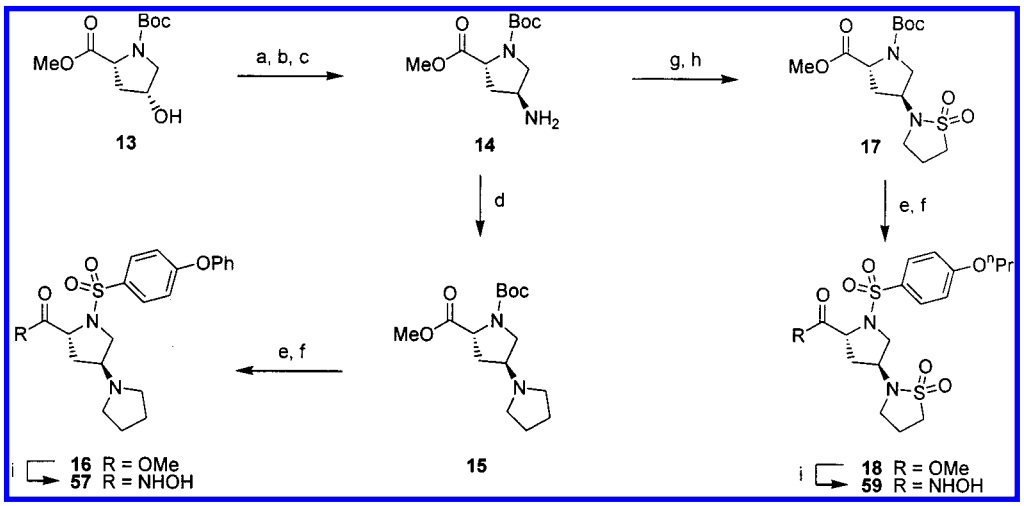

[a] Reagents: (a) 3-*N*-methylhydantoin, $PPh_3$, DEAD, $CH_2Cl_2$; (b) $NH_2OH$, KOH, MeOH; (c) MsCl, $NEt_3$, $CH_2Cl_2$; (d) $NaN_3$, DMF, 60 °C; (e) 10% Pd−C, $H_2$, EtOAc; (f) $(BrCH_2CH_2)_2O$, $Et_3N$, DMF, 65 °C; (g) $Cl(CH_2)_3SO_2Cl$, $NEt_3$, $CH_2Cl_2$; (h) DBU, DMF.

of time and was resistant to elimination even under mildly basic conditions. The mesylate can then be readily displaced upon treatment with sodium azide. Subsequent hydrogenation over 10% Pd−C gave the versatile primary amine **3** in high yield as a single diastereomer.

The free primary amine allowed for a diverse array of functionalization. Reductive amination with alkylaldehydes such as propanal gave monoalkylation products of type **4**. Mixtures of monoalkylation and both bisalkylation products were obtained with formaldehyde. Monomethylation was achieved by first forming a formamide with free amine **3** and then reduction with $BH_3$·THF. Acyl groups were coupled with either the primary amine **3** or the alkylamine **4** to give a wide range of functionality such as amides, sulfonamides, and ureas. Sulfonamides **5**−**7** are typical examples. The methyl esters in these derivatives were then converted to their respective hydroxamic acids (e.g. **19**, **21**, **23**, **26**, and **27**) upon treatment with hydroxylamine.

Heterocyclic structures were introduced at C4 of the pyrrolidine ring by direct substitution or via functionalization of primary amine **3** as seen in Scheme 2. Treatment of alcohol **8** with functionalized hydantoins under Mitsunobu conditions provided clean substitution at C4 to give heterocyclic compounds of type **9**. Direct displacement of mesylates such as **2** with secondary amines such as morpholine was also possible, but tertiary amines of type **10** could be explored much more efficiently via primary amines of type **3**. Cycloalkylation was carried out cleanly upon heating **3** with dibromoalkanes such as dibromoethyl ether in DMF which afforded compound **10**. Additionally, cyclic amides and sulfonamides were prepared upon acylation of **3** with haloalkylacyl chlorides and haloalkylsulfonyl chlorides of type **11**. Subsequent exposure to DBU in DMF then

**Scheme 3**[a]




[a] Reagents: (a) MsCl, $NEt_3$, $CH_2Cl_2$; (b) $NaN_3$, DMF, 60 °C; (c) 10% Pd−C, $H_2$, EtOAc; (d) $(BrCH_2CH_2)_2$, $Et_3N$, DMF, 65 °C; (e) TFA, $CH_2Cl_2$; (f) $PhOC_6H_4SO_2Cl$, $NEt_3$, $CH_2Cl_2$; (g) $Cl(CH_2)_3SO_2Cl$, $NEt_3$, $CH_2Cl_2$; (h) *t*-BuOK, THF; (i) $NH_2OH$, MeOH.

afforded clean cyclization to give structures of type **12**. The methyl esters of these hyterocyclic structures were then converted to their respective hydroxamic acids upon treatment with hydroxylamine.

An alternate synthetic method shown in Scheme 3 was developed to allow for rapid SAR development of the sulfonamide group. Protection of the ring amine as a *tert*-butylcarbamate allowed the C4 substituent to be functionalized as desired followed by subsequent generation of a wide range of different sulfonamides. The protected alcohol **13** was available in two steps from *cis*-hydroxy-D-proline via esterification and treatment with di-*tert*-butoxycarbonyl anhydride. The primary amine **14** could then be prepared via a sequence of mesylation, displacement with sodium azide, and hydrogenation over 10% Pd−C. Cycloalkylation of **14** could be accomplished with a variety of dibromoalkanes to give tertiary amines of type **15**. Similarly, cyclic sulfonamides of type **17** were prepared on protected scaffolds as described for sulfonamide **12**. Variously substituted sulfonamides were then prepared upon deprotection of the secondary amine followed by sulfonation with a variety of sulfonyl chlorides including the *n*-propoxybenzene derivative which was used for the preparation of compounds **18** and the phenoxybenzene derivative which was used for the preparation of compound **16**. Treatment with hydroxylamine then completed the final transformation of the methyl esters to the corresponding hydroxamic acids.

## Results and Discussion

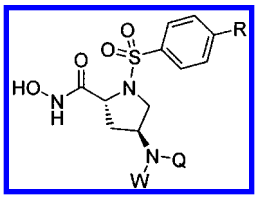
**SAR Analysis.** All compounds were assayed in vitro for the inhibition of truncated collagenase-1 (MMP-1),[21] gelatinase-A (MMP-2),[21] stromelysin (MMP-3),[22] matrilysin (MMP-7),[21] and collagenase-3 (MMP-13).[21] Several general SAR observations can be made which apply broadly to most of the aminoprolines described in this paper. The class in general inhibits MMP-2 and -13 very potently with many examples showing sub-nanomolar potency and only a select few showing >10 nM potency. MMP-7 on the other hand was poorly inhibited relative to the other enzymes with only a few examples of submicromolar potency. The aminoproline structure is therefore an excellent scaffold from which to design selective compounds which strongly inhibit MMP-2 and -13 while sparing MMP-7. On the other hand, the inhibition of MMP-1 and -3 varied much more broadly. While MMP-3 was generally inhibited more potently than MMP-1, selectivities between these enzymes were much more sensitive to functional group manipulation.

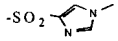
**Substituted Amine SAR.** The C4 amine functionality tolerated diverse monosubstitution with remarkably little effect on potency as seen in Table 1 with the comparison of free amine **19** against *n*-propylamine **21**, sulfonamides **23** and **29**, and lactic acid amide **37**. Only the urea substitution in **32** seemed to be poorly tolerated and resulted in 1 order of magnitude loss in potency for all enzymes tested. The potencies of the *N*-sulfonamides increased for MMP-1 and -3 upon *N*-alkylation as seen with **23** vs **26**−**28**. A similar potency boost was not observed with amide **33** or any of the lactic acid amides in Table 2.

All of the substituted amines in Tables 1 and 2 appear to be sensitive to modifications of the S1′ portion of the molecule (R). This sensitivity is typified by free amines **19** and **20**, sulfonamides **23** and **24**, and amides **34** and **35** where longer-chain substituents increase the potency for MMP-3 and decrease the potency for MMP-1. This observation is supported by X-ray data which place the alkoxyaryl group in the S1′ pocket of the MMP enzymes. This pocket is very deep for most enzymes, but it is blocked by an arginine and a tyrosine residue in MMP-1 and -7, respectively.[23] As a result, the selectivity for MMP-3 vs MMP-1 increased from 10-fold, which is typical for a methoxy substituent, to 50−100-fold, which is typical for an *n*-butoxy substituent.

**C4 Heterocycle SAR.** The heterocyclic compounds in Tables 3 and 4 displayed inhibition profiles which closely mimicked those of the substituted amines. The heterocycles which were bonded through a basic tertiary amine, such as **44**, **48**, and **53**, provided consistent profiles regardless of the ring size or extra heteroatoms within the ring. Also, like the substituted amines, these compounds were very sensitive to modifications of the P1′ substituent (R). Compounds **48**−**50** exemplify the increase in selectivity for MMP-3 over MMP-1 that is commonly observed as longer alkoxy chains are introduced. Sultams of type **58** showed a significant potency

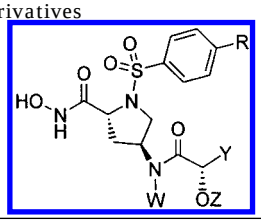
**Table 1.** Substituted Amine-Bearing MMP Inhibitors



| | | | | $IC_{50}$ (nM)[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| no. | Q | W | R | MMP-1 | MMP-2 | MMP-3 | MMP-7 | MMP-13 | abs %[b] |
| **19** | −H | −H | −OMe | 250 | 6 | 23 | 4300 | 5 | 9−39 |
| **20** | −H | −H | −O$^n$Bu | 380 | nd | 8 | nd | nd | 2 |
| **21** | −$(CH_2)_2CH_3$ | −H | −OMe | 150 | nd | 87 | 2200 | 5 | 1 |
| **22** | −$(CH_2)_2$Ph | −H | −OMe | 560 | 1 | 57 | 1400 | 1 | 1 |
| **23** | −$SO_2CH_3$ | −H | −OMe | 260 | 2 | 42 | 2700 | 2 | 44 |
| **24** | −$SO_2CH_3$ | −H | −O$^n$Bu | 1300 | 0.8 | 16 | 3900 | 0.7 | 23 |
| **25** | −$SO_2CH_3$ | −H | −O-4-Pyr | 450 | nd | 22 | >10000 | 0.8 | nd |
| **26** | −$SO_2CH_3$ | −Me | −OMe | 19 | nd | 6 | 520 | 0.5 | nd |
| **27** | −$SO_2CH_3$ | −$CH_2$-3-Pyr | −OMe | 74 | 2 | 6 | 2700 | 1 | 40−42 |
| **28** | −$SO_2CH_3$ | −$CH_2CH_2CH_3$ | −OMe | 33 | 0.8 | 10 | 920 | 0.8 | 11−13 |
| **29** | −$SO_2$-*p*-$C_6H_4$OMe | −H | −OMe | 350 | 3 | 36 | 3000 | 2 | 2 |
| **30** |  | −H | −O$^n$Bu | 700 | nd | 6 | nd | nd | 13−22 |
| **31** | −CO-*p*-Ph-Ph | −H | −OMe | >1000 | nd | 400 | nd | nd | nd |
| **32** | −CONHMe | −H | −OMe | 3100 | nd | 300 | nd | 27 | nd |
| **33** | −CO$^i$Pr | −$CH_2$-3-Pyr | −OMe | 270 | 2.2 | 10 | nd | 17 | nd |
| **34** | −$COCH_2OMe$ | −H | −O$^n$Pr | 500 | nd | 30 | >10000 | 3 | nd |
| **35** | −$COCH_2OMe$ | −H | −O$^n$Bu | 1200 | nd | 14 | 4900 | 0.7 | 2 |

[a] See Experimental Section for details of experimental assays. Standard deviations for enzyme assays were typically ±60% of the mean or less. [b] Data obtained from both single and multiple determinations; for experimental details see ref 19. nd, not determined.

**Table 2.** MMP Inhibitors with Lactic Acid Amide Derivatives



| | | | | | $IC_{50}$ (nM)[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| no. | W | Y | Z | R | MMP-1 | MMP-2 | MMP-3 | MMP-7 | MMP-13 | abs %[b] |
| **36** | −H | $-CH_3$ | $-CH_2Ph$ | −OMe | 140 | 0.3 | 7 | nd | nd | 19−23 |
| **37** | −H | $-CH_2Ph$ | $-CH_2Ph$ | −OMe | 240 | 0.2 | 10 | nd | 2 | nd |
| **38** | −$^n$Pr | $-CH_3$ | −H | −OMe | 87 | 0.7 | 2 | 8500 | 1 | 13−18 |
| **39** | −$^n$Pr | $-CH_2CH_2Ph$ | −H | −OMe | 260 | 0.6 | 12 | nd | 0.5 | 7−8 |
| **40** | −H | $-CH_3$ | −H | −O$^n$Pr | 140 | nd | 8 | 3500 | 1 | nd |
| **41** | −H | $-CH_3$ | −H | −O$^n$Bu | 1200 | nd | 10 | 4200 | 0.9 | 8−11 |
| **42** | −H | −$^i$Pr | −H | −O$^n$Bu | 270 | nd | 8 | 1700 | 0.8 | 3 |
| **43** | −H | $-CH_2{}^i$Pr | −H | −O$^n$Bu | 440 | nd | 10 | 2400 | 0.9 | 3 |

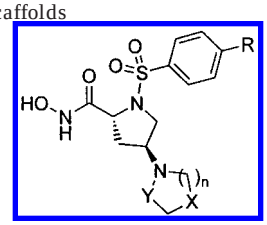
[a] See Experimental Section for details of experimental assays. Standard deviations for enzyme assays were typically ±60% of the mean or less. [b] Data obtained from both single and multiple determinations; for experimental details see ref 19. nd, not determined.

boost consistent with that observed with alkyl sulfonamides such as **26**. Compounds of this type displayed a 5-fold potency boost for both MMP-1 and -7. However, good selectivity for MMP-3 vs MMP-1 seemed to be unattainable as seen with compounds **58**−**60**.

The hydantoins shown in Table 4 presented potency profiles which were very similar to those seen with the heterocyclic amines in Table 3. Substitution of the hydantoin moiety played only a minor role in the overall potency of the compounds, as seen with **64**, **70**, and **72**. Substitution in the S1′ region of the molecule (R) reflected trends observed with other classes of molecules, and attempts to introduce hydrophilicity into this portion of the molecule resulted in a significant loss of potency (see **64** vs **66**). This lends support to the observation that the deep S1′ pocket is a lipophilic enviornment.[23]

**Structure of Inhibitor−Stromelysin Complex.**[24] A crystal structure of stromelysin was obtained with compound **24** bound in the active site, and the data is represented graphically in Figures 2 and 3. The structural data is in agreement with those reported previously for similar compounds.[18,19] The sulfonamide portion of the molecule clearly fits into the deep, hydrophobic S1′ pocket, and the hydroxamic acid is bound to the active site zinc atom in fashion. We also see key enzyme−substrate atomic distances that support the existence of hydrogen-binding interactions that are likely to be present in all of the inhibitors in this report. These include hydrogen bonds from the hydroxamic acid moiety to Ala 165 and Glu 202 and key hydrogen bonds from the sulfonamide oxygen to Ala 165 and Leu 164. A hydrogen bond also appears to exist between His 211 and the methane sulfonamide oxygen which is likely

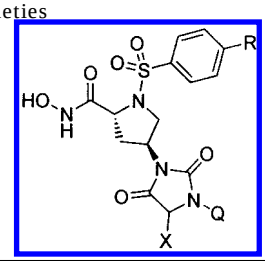
**Table 3.** MMP Inhibitors Containing Heterocyclic Scaffolds



| | | | | | $IC_{50}$ (nM)[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| no. | *n* | Y | X | R | MMP-1 | MMP-2 | MMP-3 | MMP-7 | MMP-13 | abs %[b] |
| **44** | 2 | $CH_2$ | $CH_2$ | −OMe | 280 | 6 | 48 | 7400 | 1 | 100 |
| **45** | 2 | $CH_2$ | $CH_2$ | −O$^n$Pr | 210 | nd | 9 | 620 | 0.4 | nd |
| **46** | 2 | $CH_2$ | $CH_2$ | −$^n$Pent | 2000 | nd | 12 | 9800 | 0.9 | nd |
| **47** | 2 | $CH_2$ | $CH_2$ | −OPh | 17 | nd | 8 | 610 | <0.4 | nd |
| **48** | 2 | $CH_2$ | O | −OMe | 220 | 6 | 14 | nd | nd | 24−39 |
| **49** | 2 | $CH_2$ | O | −O$^n$Pr | 490 | nd | 7 | 16500 | 1 | 12−15 |
| **50** | 2 | $CH_2$ | O | −O$^n$Bu | 920 | 4 | 5 | 5400 | 0.6 | 3−10 |
| **51** | 2 | $CH_2$ | O | −$^n$Pent | 2000 | nd | 12 | 7400 | 0.7 | nd |
| **52** | 2 | $CH_2$ | O | −OPh | 19 | nd | 7 | 710 | <0.4 | nd |
| **53** | 2 | $CH_2$ | $SO_2$ | −OMe | 300 | nd | 23 | 7100 | 1 | nd |
| **54** | 2 | $CH_2$ | $SO_2$ | −O$^n$Bu | >1000 | 7 | 12 | 3400 | 0.9 | 13−17 |
| **55** | 1 | $CH_2$ | $CH_2$ | −O$^n$Pr | 310 | <1 | 8 | 8700 | 1 | 33−48 |
| **56** | 1 | $CH_2$ | $CH_2$ | −O-4-$C_6H_4F$ | 20 | nd | 4 | 850 | <0.4 | 3 |
| **57** | 1 | $CH_2$ | $CH_2$ | −OPh | 19 | nd | 5 | 790 | <0.4 | 2−3 |
| **58** | 1 | $SO_2$ | $CH_2$ | −OMe | 42 | nd | 13 | 1400 | 0.4 | 16−25 |
| **59** | 1 | $SO_2$ | $CH_2$ | −O$^n$Pr | 100 | nd | 8 | 840 | <0.4 | 5−6 |
| **60** | 1 | $SO_2$ | $CH_2$ | −O$^n$Bu | 230 | nd | 13 | 680 | <0.4 | 2−4 |

[a] See Experimental Section for details of experimental assays. Standard deviations for enzyme assays were typically ±60% of the mean or less. [b] Data obtained from both single and multiple determinations; for experimental details see ref 19. nd, not determined.

**Table 4.** MMP Inhibitors Containing Hydantoin Moieties



| | | | | $IC_{50}$ (nM)[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| no. | Q | X | R | MMP-1 | MMP-2 | MMP-3 | MMP-7 | MMP-13 | abs %[b] |
| **61** | $-CH_3$ | −H | −OMe | 200 | nd | 8 | 1800 | 0.5 | 37−59 |
| **62** | $-CH_3$ | −H | −OEt | 580 | nd | 33 | 7500 | 4 | nd |
| **63** | $-CH_3$ | −H | −O$^n$Pr | 260 | nd | 9 | 2600 | 0.3 | nd |
| **64** | $-CH_3$ | −H | −O$^n$Bu | 920 | nd | 2 | 1600 | 0.3 | 3−4 |
| **65** | $-CH_3$ | −H | $-OCH_2CH(CH_2)_2$ | 300 | nd | 3 | 2300 | 2.8 | 3 |
| **66** | $-CH_3$ | −H | $-OCH_2CH_2OCH_3$ | 1800 | 1 | 26 | 9100 | 4.4 | 3 |
| **67** | $-CH_3$ | −H | −OPh | 21 | nd | 6 | 310 | <0.4 | nd |
| **68** | $-CH_3$ | −H | −O-4-Pyr | 600 | nd | 11 | 7400 | 0.7 | 9−13 |
| **69** | −H | $-SCH_3$ | −O$^n$Bu | 750 | 49 | 42 | 850 | <0.5 | 4−6 |
| **70** | −H | $-(CH_3)_2$ | −O$^n$Bu | 780 | 2 | 3 | 450 | <0.5 | 2 |
| **71** | $-CH_2CH{=}CH_2$ | −H | −O$^n$Pr | 350 | 0.8 | 11 | 2600 | 0.4 | nd |
| **72** | $-CH_2CH{=}CH_2$ | −H | −O$^n$Bu | 480 | nd | 7 | 1000 | 0.4 | 39−100 |
| **73** | $-CH_2CH{=}CH_2$ | −H | $-OCH_2CH_2OCH_3$ | 2900 | 2 | 46 | 11000 | 2 | nd |
| **74** | $-CH_2CH_2CH_3$ | −H | −O$^n$Bu | 570 | 0.4 | 10 | 1200 | 0.3 | nd |
| **75** | $-CH_2CH_2CH_3$ | −H | $-OCH_2CH_2OCH_3$ | 2500 | 2 | 30 | 11000 | 2 | nd |

[a] See Experimental Section for details of experimental assays. Standard deviations for enzyme assays were typically ±60% of the mean or less. [b] Data obtained from both single and multiple determinations; for experimental details see ref 19. nd, not determined.

specific for this particular compound and those that have similarly situated sulfonamide groups.

**In Vitro Absorption.** The relative peroral intestinal absorption potentials of select compounds shown in Tables 1−4 were predicted from in vitro rat ileum transport studies.[19,25] The results suggest that there was a general trend toward lower absorption when the substitutions on the molecules became larger, i.e. increase in molecular radius. Examples of this can be seen in series **19** and **20**, series **19**, **21**, and **22**, and series **23** and **24** from Table 1, series **38** and **39** and series **41** and **42** in Table 2, series **48**−**50** and series **58**−**60** in Table 3, and series **61**, **64**, and **65** in Table 4. However, compound **27**, a pyridyl derivative of compound **23**, showed a greater absorption potential than would be anticipated from its size alone. A recent report has shown that several pyridyl-substituted compounds have a greater transcellular permeability than the corresponding phenyl-substituted molecule by an undetermined mechanism.[26] The addition of hydrophilicity in the molecules also reduced its absorption potential as exemplified by comparing compounds **44** vs **48** and **55**

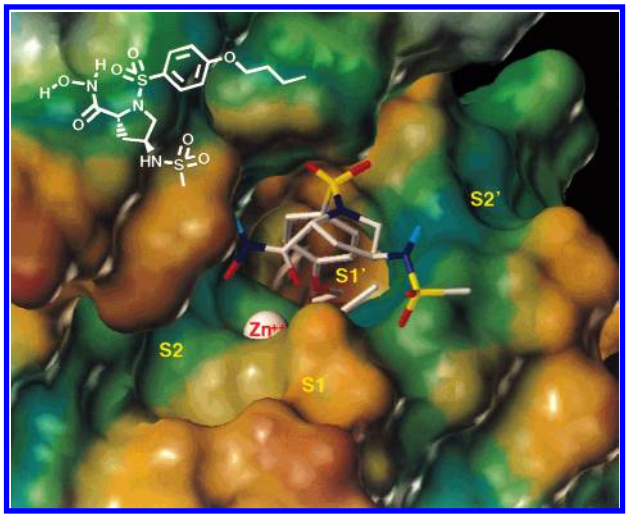



**Figure 2.** Surface structure of the stromelysin−**24** complex.

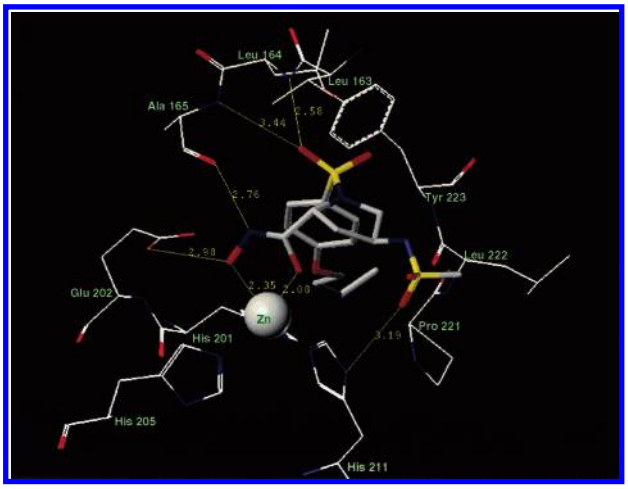



**Figure 3.** Binding interactions in the stromelysin−**24** complex.

vs **59**. Several compounds (**21**, **22**, **29**, **55**, and **56**) showed substantial partitioning into the intestinal tissue based on significant disappearance of drug in the donor (mucosal) chamber. In effect, it is possible that these compounds may be absorbed to a greater extent in vivo relative to that predicted from in vitro studies and will depend, in part, on the compounds solubility/protein binding in blood. Finally, there is evidence that other compounds from this general class are substrates for the various concentration-dependent efflux systems (including P-glycoprotein), encoded by the *MDR1* gene, present in the enterocytes of the intestinal tract (data not shown). Therefore, the extent of absorption will depend on the total dose administered and the affinity for the compound for the efflux transporter. Further characterization would be necessary to better understand potential solubility, tissue partitioning behavior, and/or efflux mechanisms on overall peroral absorption.

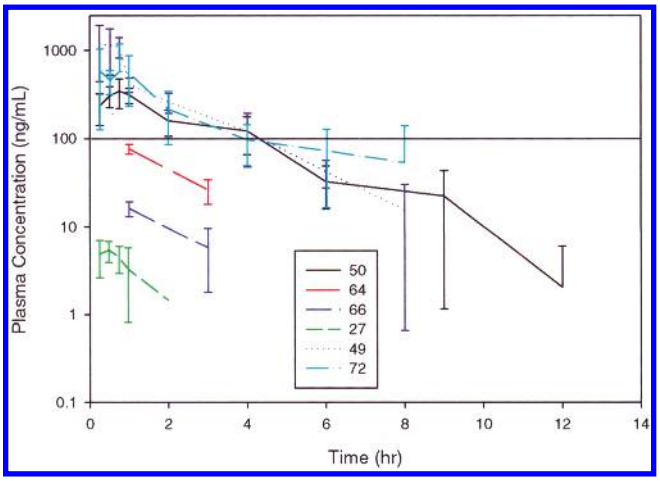
**PK and Efficacy Analysis.** The pharmacokinetics for many of the aminopyrrolidine-based hydroxamates were investigated using the N-in-One (cassette dosing) technique, and the data for many of these is shown in Table 5 and depicted in Chart 1. The studies were conducted in fasted rats ($n$ = 3/4) using 4−10 hydroxamates per experiment at dose of 35/N mg/kg of each hydroxamate. Each animal study included a control compound that had been previously characterized in a single-compound experiment which served to validate each data set and illuminate problems such as saturation of elimination. The data suggests that most of the compounds have somewhat short half-lives and low absolute bioavailability. We were able to develop an empirical relationship between plasma concentrations and in vivo efficacy data. When plasma concentrations were >100 ng/mL for >3 h as in compounds **49**, **50**, and **72**, seven of eight compounds demonstrated in vivo efficacy (data not shown). We were therefore able to use the technique as a means of screening potent compounds to narrow the list of candidates for efficacy screening in more resource intensive in vivo studies.

**Table 5.** Pharmacokinetic and in Vivo Efficacy Data

| no. | time over 100 ng/mL (h) | in vivo[a] damage reduction (%) | $p$ value |
|---|---|---|---|
| **27** | 0 | 5 | 0.43 |
| **49** | 4.5 | 21* | 0.03 |
| **50** | 3.5 | 26* | 0.01 |
| **64** | 0 | 5 | 0.32 |
| **66** | 0 | 0 | 0.50 |
| **72** | 4 | 17* | 0.05 |

[a] Compounds were administered orally twice daily at a dose of 35 mg/kg. The data are expressed as the mean percent inhibition of joint damage relative to a vehicle-treated control group. Each group consisted of 15 rats. *$p$ < 0.05. The broad-spectrum MMP inhibitor CGS-27023 was used as a positive control in this model and inhibited joint damage by 26 ± 6% (mean ± SD) from 13 separate experiments.

**Chart 1.** Plasma Concentration vs Time Profile after Cocktail Oral Administration of MMPIs




**In Vivo Efficacy.** The in vivo activity of selected compounds was determined in rats using the iodoacetate-induced arthritis model,[27−29] and the results are summarized in Table 5. Compounds were administered orally twice daily at a dose of 35 mg/kg for the first 7 days after intraarticular injection of iodoacetate. Animals were sacrificed 21 days after iodoacetate admin-

The pharmacokinetics of compound **50** was investigated in detail in rats as a single-compound study. It was dosed intravenously and orally in male Sprague−Dawley rats in a parallel group design. The data from the study is depicted in Chart 2 and interpreted in Table 6 and supports the N-in-One data. Compound **50** demonstrated an oral bioavailability of 6% with a half-life of 1.7 h. The volume of distribution was relatively low and the clearance was high. Despite this, the compound was sufficiently available at the articular cartilage to produce efficacy in vivo when dosed twice per day.

**Chart 2.** Mean Plasma Concentration vs Time Profile after Administration of Compound **50** to Rats

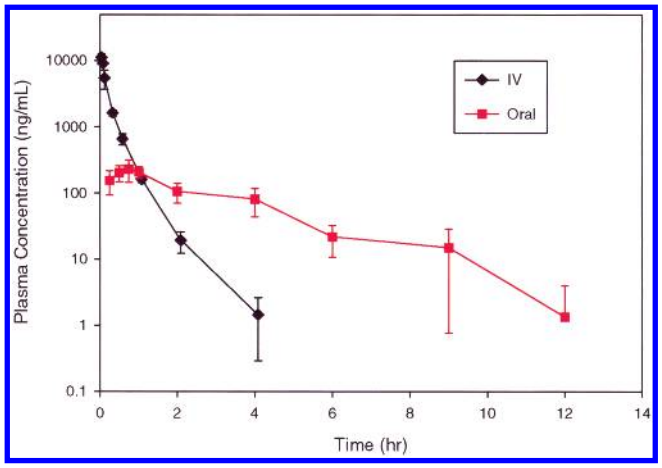



**Table 6.** Mean (%CV) PK Parameters for Compound **50** in Rats

| route | $t_{1/2}$ (h) | $CL_t$ (mL/min/kg) | $V_{dss}$ (mL/kg) | $F$ (%) |
|---|---|---|---|---|
| iv | 0.4 (22) | 30 (12) | 408 (23) | |
| po | 1.7 (41) | | | 6 |

istration, and joint damage was assessed. Compounds **49**, **50**, and **72** significantly ($p \leq 0.05$) inhibited joint damage, whereas **27**, **64**, and **66** were not effective. All of the compounds that significantly inhibited cartilage degradation maintained plasma concentrations above 100 ng/mL for greater than 3 h, whereas all of the compounds that were ineffective demonstrated much lower plasma concentrations of drug.

## Conclusion

A diverse variety of aminopyrrolidine-based hydroxamate inhibitors are described here and are synthetically available in optically pure form from *cis*-hydroxy-D-proline. They tend to be very potent for most members in the MMP family with the exception of MMP-1 and -7. This selectivity against the shallow S1′ pocket enzymes can be enhanced by incorporating long-chain aliphatic groups at the 4-position of the aromatic sulfonamide group. X-ray crystallography data for a stromelysin−**24** complex confirms that this aromatic sulfonamide structure indeed fits into the S1′ pocket which helps explain the selectivity observations. The inhibitors tended to show low to moderate absolute bioavailability with short half-lives. The in vivo data for this class of inhibitors seemed to be highly dependent on the PK profile. Compounds such as **49** and **50** which maintained blood levels above 100 ng/mL for 3 h or more tended to show in vivo activity.

## Experimental Section

All commercial chemicals and solvents are reagent grade and used without further purification unless otherwise specified. The following solvents and reagents have been abbreviated: tetrahydrofuran (THF), ethyl ether ($Et_2O$), dimethyl sulfoxide (DMSO), ethyl acetate (EtOAc), dichloromethane (DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF), methanol (MeOH). All reactions except those in aqueous media were carried out with the use of standard techniques for the exclusion of moisture. Reactions were monitored by thin-layer chromatography on 0.25-mm silica gel plates (60F-254, E. Merck) and visualized with UV light, iodine vapors, or 5% phosphomolybdic acid in 95% ethanol. Final compounds were typically purified either by flash chromatography on silica gel (E. Merck, 40−63 mm) or by preparative reverse-phase high-pressure liquid chromatography (RP-HPLC) using a Waters model 4000 Delta Prep instrument equipped with a Waters Symmetry preparative steel column (C-18, 19 m × 300 mm) as the stationary phase. The mobile phase employed 0.1% formic acid with acetonitrile as the organic modifier. Both isocratic and linear gradient methods were used as appropriate and the flow rate was 20 mL/min. Analytical purity was assessed by RP-HPLC using a Waters 600 system equipped with a diode array spectrometer ($\lambda$ range 200−400 nm). The stationary phase was a Waters Symmetry C-18 column (4.6 mm × 200 mm). The mobile phase employed 0.1% formic acid with acetonitrile as the organic modifier and a flow rate of 1.0 mL/min. Analytical data is reported as retention time, $t_R$, in minutes (% acetonitrile, time, flow rate).

$^1$H NMR spectra were recorded on a Varian Unity-300 instrument. Chemical shifts are reported in parts per million (ppm, $\delta$ units). Coupling constants are reported in units of hertz (Hz). Splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Low-resolution mass spectra (MS) were recorded on a Micromass Platform quadrupole mass spectrometer. Mass spectra were acquired in either the positive or negative ion mode under electrospray ionization (ESI). Combustion analyses were performed internally.

Human synovial proMMP-3 was obtained from Dr. Hideaki Nagase, University of Kansas Medical Center, Kansas City, KS. Human fibroblast proMMP-1, human MMP-9, and human recombinant MMP-7 catalytic domain were obtained from Dr. Howard Welgus, Jewish Hospital, St. Louis, MO. Human recombinant MMP-8 catalytic domain was obtained from Dr. Harald Tschesche, University Bielefeld, Bielefeld, Germany. Human recombinant proMMP-2 was purified from CHO cells as described below. Human recombinant truncated MMP-3 and truncated MMP-1 were purified from *E. coli* cells as described below. Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-$NH_2$ was purchased from Bachem Bioscience, King of Prussia, PA.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*R*)-methanesulfonoxypyrrolidine (2).** The starting alcohol **8** (17.9 g, 57 mmol) was taken in $CH_2Cl_2$ (100 mL) and $Et_3N$ (25 mL) was added. Methanesulfonyl chloride was added dropwise and the resulting mixture was stirred overnight at room temperature. The following the mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to give 24.3 g of solid product which was recrystallized from hexane:EtOAc (∼1:1) to give 18.3 g of pure white solid. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.34 (ddd, $J$ = 14.5, 9.3, 5.1 Hz, 1H), 2.51−2.57 (m, 1H), 2.97, (s, 3H), 3.61 (ddd, $J$ = 11.9, 2.6, 1.1 Hz, 1H), 3.67 (dd, $J$ = 11.9, 4.8 Hz, 1H), 3.74 (s, 3H), 3.88 (s, 3H), 4.56 (dd, $J$ = 9.5, 6.8 Hz, 1H), 5.16 (m, 1H), 7.00 (ddd, $J$ = 9.0, 2.6, 2.6 Hz, 2H), 7.85 (ddd, $J$ = 9.1, 2.6, 2.6 Hz, 2H). CI$^+$ MS: *m*/*z* (rel intensity) 411 ([M + $NH_4$]$^+$, 25), 394 ([M + H]$^+$, 21), 224 (82), 155 (23), 128 (100).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-azidopyrrolidine (3a).** The starting mesylate **2** (4.2 g, 10.7 mmol) was taken in 15 mL of dry DMF in the presence of $NaN_3$ (695 mg, 10.7 mmol). The resulting mixture was heated to 55 °C for 26 h and then partitioned between water and EtOAc. The organic layer was then washed with brine, dried over $MgSO_4$, filtered and evaporated. The resulting crude oil was chromatographed over flash silica with hexane:EtOAc (5:1 to 3:1) to provide 2.87 g (79%) of pale yellow oil which solidified upon standing. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.15−2.21 (m, 2H), 3.39 (ddd, $J$ = 11.2, 3.3, 0.9 Hz, 1H), 3.69 (dd, 11.2, 4.9 Hz, 1H), 3.77 (s, 3H), 3.88 (s, 3H), 4.17−4.23 (m, 1H), 4.27 (ddd, $J$ = 7.3, 7.3, 0.6 Hz, 1H), 7.00 (ddd, 9.0, 2.6, 2.6 Hz, 2H), 7.81 (ddd, $J$ = 9.0, 2.6, 2.6 Hz, 2H). CI$^+$ MS: *m*/*z* (rel intensity) 358 ([M + $NH_4$]$^+$ 50), 341 ([M + H]$^+$, 67), 315 (95), 145 (100).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-aminopyrrolidine (3).** The starting azide **3a** (1.18 g, 3.48 mmol) was taken in 100 mL of EtOH:THF:$HCO_2H$ (5:1:

0.1) and hydrogenated at room temperature under 54 psi of hydrogen in the presence of 100 mg of 10% Pd−C for 16 h. The mixture was then filtered through a pad of Celite, concentrated to an oil and recrystallized from hexane:EtOAc to give 720 mg (58%) of the desired product as the formate salt. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 1.72−1.81 (m, 1H), 2.00 (ddd, $J$ = 13.0, 5.7, 5.7 Hz, 1H), 2.86 (dd, $J$ = 9.7, 5.3 Hz, 1H), 3.46−3.57 (m, 2H), 3.57 (s, 3H), 3.73 (s, 3H), 4.21 (dd, $J$ = 8.2, 6.2 Hz, 1H), 6.86 (br d, $J$ = 9.0 Hz, 2H), 7.66 (br d, $J$ = 9.0 Hz, 2H). CI$^+$ MS: $m/z$ (rel intensity) 315 ([M + H]$^+$, 12), 177 (13), 143 (42), 123 (60), 109 (100).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-propylaminopyrrolidine (4).** The starting amine **3** (810 mg, 2.6 mmol) was dissolved in 8 mL of methanol and stirred for 48 h in the presence of propianaldehyde (206 mL, 2.86 mmol), sodium cyanoborohydride (180 mg, 2.86 mmol), sodium acetate (810, 9.9 mmol) and 25 drops of acetic acid. The mixture was evaporated to dryness and then partitioned between dilute $NaHCO_3$ and EtOAc and the organic layer washed 2× with $NaHCO_3$, 1× with brine, dried over $MgSO_4$, filtered and evaporated. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 0.87 (t, $J$ = 7.4 Hz, 3H), 1.49−1.64 (m, 2H), 2.10−2.22 (m, 1H), 2.31 (ddd, $J$ = 13.2, 7.0, 2.7 Hz, 1H), 2.69−2.80 (m, 2H), 3.28 (dd, $J$ = 10.1, 6.8 Hz, 1H), 3.55 (s, 3M), 3.63−3.86 (m, 2H), 3.76 (s, 3H), 4.35 (dd, $J$ = 9.2, 2.9 Hz, 1H), 6.92 (br d, $J$ = 9.1 Hz, 2H), 7.65 (br d, $J$ = 9.2 Hz, 2H). ESI MS: $m/z$ (rel intensity) 357.3 ([M + H]$^+$, 100).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-methanesulfonylaminopyrrolidine (5).** The primary amine **3** (502 mg, 1.60 mmol) was taken in 5 mL of methylene chloride and 0.5 mL of triethylamine and treated with methanesulfonyl chloride (200 $\mu$L, 2.58 mmol) via syringe. The mixture was stirred for 2 h and then partitioned between 1 N HCl and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to give 684 mg of crude material which was chromatographed over flash silica with hexane:EtOAc (2:1 to 1:1) to give 104 mg (14%) of disulfonylated material **5a** and 393 mg (61%) of monosulfonylated material **5**. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.21 (ddd, $J$ = 13.4, 8.2, 6.4 Hz, 1H), 2.96 (s, 3H), 3.33 (dd, $J$ = 10.4, 4.9 Hz, 1H), 3.65 (dd, $J$ = 10.4, 5.9, Hz, 1H), 3.71 (s, 3H), 3.88 (s, 3H), 4.10−4.20 (m, 1H), 4.49 (dd, $J$ = 8.4, 5.5 Hz, 1H), 4.74 (d, $J$ = 7.9 Hz, 1H), 7.00 (ddd, $J$ = 9.0, 2.6, 2.6 Hz, 2H), 7.82 (ddd, $J$ = 9.0, 2.5, 2.5 Hz, 2H). CI$^+$ MS: $m/z$ (rel intensity) 410 ([M + $NH_4$]$^+$, 15), 393 ([M + H]$^+$, 10), 203 (100).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-*N*-bis(methanesulfonyl)aminopyrrolidine (5a).** $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.23−2.31 (m, 1H), 2.74−2.86 (m, 1H), 3.28 (s, 6H), 3.68 (dd, $J$ = 10.4 Hz, 1H), 3.74 (s, 3H), 3.81 (dd, $J$ = 10.5 Hz, 1H), 3.98 (s, 3H), 4.38 (dd, $J$ = 11.4, 4.2 Hz, 1H), 5.08−5.21 (m, 1H), 7.01 (br d, $J$ = 8.9 Hz, 2H), 7.81 (br d, $J$ = 8.9 Hz, 2H). ESI MS: $m/z$ (rel intensity) 488.3 ([M + $NH_4$]$^+$, 15), 471.3 ([M + H]$^+$, 10).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-*N*-formylaminopyrrolidine (6a).** The free amine **3** (20.2 g, 64 mmol) was converted to 17.5 g (80%) of the title formamide as described by Krishnamurthy.[30] $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.20−2.38 (m, 2H), 3.42 (dd, $J$ = 10.6, 2.9 Hz, 1H), 3.55 (dd, $J$ = 11.0, 5.5 Hz, 1H), 3.71 (s, 3H), 3.89 (s, 3H), 4.52−4.62 (m, 2H), 6.19 (d, $J$ = 6.6 Hz, 1H), 7.01 (ddd, $J$ = 9.0, 2.4, 2.0 Hz, 2H), 7.85 (ddd, $J$ = 9.0, 3.1, 2.0 Hz, 2H), 8.03 (s, 1H). ESI: $m/z$ (rel intensity) 360.1 ([M + $NH_3$]$^+$, 68), 343.1 ([M + H]$^+$, 100).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-*N*-methylaminopyrrolidine (6b).** The formamide **6a** (13.3 g, 342 mmol) was taken in 20 mL of THF and cooled to 0 °C and a solution of $BH_3$·THF (85.8 mL, 1 M in THF, 85.5 mmol) was added via syringe. After 10 min, the solution was heated to 60 °C for 2 h and then cooled to room temperature and quenched with 20 mL of MeOH. An additional 150 mL of MeOH was then added which had been pretreated with 15 mL of $SOCl_2$ and the resulting mixture was heated to 60 °C for 3 h. The resulting solution was then condensed to an oil by rotary evaporation and partitioned between EtOAc and dilute $Na_2CO_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude oil was chromatographed over flash silica with EtOAc:MeOH (20:1 to 4:1) to give 11.5 g (91%) of the title amine. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 1.93 (ddd, $J$ = 12.8, 8.6, 6.6, 1H), 2.16 (ddd, $J$ = 12.8, 5.6, 5.6 Hz, 1H), 2.29 (s, 3H), 3.09 (dd, $J$ = 9.8, 5.3 Hz, 1H), 3.30−3.40 (m, 1H), 3.62 (dd, $J$ = 9.8, 5.6 Hz, 1H), 3.74 (s, 3H), 3.88 (s, 3H), 4.34 (dd, $J$ = 8.4, 5.4 Hz, 1H), 6.99 (ddd, $J$ = 8.9, 3.1, 2.1 Hz, 2H), 7.82 (ddd, $J$ = 9.0, 2.9, 2.2 Hz, 2H). CI$^+$ MS: $m/z$ (rel intensity) 423.5 ([M + $NH_4$]$^+$, 42), 406.5 ([M + H]$^+$, 100).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-*N*-methyl-*N*-methanesulfonylaminopyrrolidine (6).** The title compound was prepared (284 mg, 46%) from amine **6b** (502 mg, 1.47 mmol) as described for compound **5**. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.15−2.33 (m, 2H), 2.74 (s, 3H), 2.82 (s, 3H), 3.33 (dd, $J$ = 9.5, 7.5 Hz, 1H), 3.60 (dd, $J$ = 9.5, 8.2 Hz, 1H), 3.67 (s, 3H), 3.90 (s, 3H), 4.53 (dd, $J$ = 7.9, 3.5 Hz, 1H), 4.64−4.78 (m, 1H), 7.02 (br d, $J$ = 9.0 Hz, 2H), 7.81 (br d, $J$ = 9.0 Hz, 2H). CI$^+$ MS: $m/z$ (rel intensity) 423.5 ([M + $NH_4$]$^+$, 42), 406.5 ([M + H]$^+$, 100).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-*N*-(methanesulfonylpropyl)aminopyrrolidine (7).** The starting amine **4** (783 mg, 2.20 mmol) was converted to the title compound (624 mg, 66%) as described for **7**. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 0.86 (t, $J$ = 7.4 Hz, 3H), 1.51−1.66 (m, 2H), 2.16−2.23 (m, 2H), 2.82 (s, 3H), 2.91 (ddd, $J$ = 13.9, 9.5, 6.0 Hz, 1H), 3.01 (ddd, $J$ = 14.1, 8.1, 4.4 Hz, 1H), 3.24 (dd, $J$ = 8.8, 8.8 Hz, 1H), 3.64 (dd, $J$ = 9.0, 8.2 Hz, 1H), 3.68 (s, 3H), 3.88 (s, 3H), 4.47−4.58 (m, 2H), 7.00 (ddd, $J$ = 9.0, 2.6, 2.6 Hz, 2H), 7.80 (ddd, $J$ = 9.0, 2.6, 2.6 Hz, 2H). ESI MS: $m/z$ (rel intensity) 452 ([M + $NH_4$]$^+$, 25), 435 ([M + H]$^+$, 75), 265 (100), 155 (75), 126 (40).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*R*)-hydroxypyrrolidine (8).** *cis*-Hydroxy-D-proline (**1**; 50 g, 0.38 mol) was dissolved in water:dioxane (1:1, 300 mL) with triethylamine (135 mL, 0.96 mol). 4-Methoxyphenylsulfonyl chloride (87 g, 0.42 mol) was added along with 2,6-(dimethylamino)pyridine (4.6 g, 0.038 mol) and the mixture was stirred 14 h at room temperature. The mixture was then concentrated and diluted with EtOAc. Layers were separated and the organic layer was washed 2× with 1 N HCl, 1× with brine, dried over $MgSO_4$, filtered and evaporated to give 83 g of solid material which was dissolved in MeOH (500 mL). Thionyl chloride (50 mL) was added dropwise and the resulting mixture stirred for 14 h. The mixture was then evaporated to dryness and triturated with $CHCl_3$ to give 85 g (69%) of white solid which was sufficeintly pure to carry forward without purification. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.07 (ddd, $J$ = 14.1, 3.8, 1.6 Hz, 1H), 2.16 (ddd, $J$ = 14.1, 9.5, 4.4 Hz, 1H), 3.31 (dd, $J$ = 10.3, 4.2 Hz, 1H), 3.48−3.54 (m, 2H), 3.76 (s, 3H), 3.89 (s, 3H), 4.28−4.34 (m, 2H), 6.98 (ddd, $J$ = 9.0, 2.5, 2.5 Hz, 2H), 7.79 (ddd, $J$ = 9.1, 2.6, 2.6 Hz, 2H). CI$^+$ MS: $m/z$ (rel intensity) 316 ([M + H]$^+$, 100), 256 (300), 146 (45), 114 (20).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-(3*N*-methylhydanto-1*N*-yl)pyrrolidine (9).** Diethyl azodicarboxylate (1.8 mL, 11.42 mmol) was added to a stirred solution of the starting alcohol **8** (3.0 g, 9.51 mmol), triphenylphosphene (3.74 g, 9.51 mmol), and 1-methylhydantoin (1.3 g, 11.42 mmol) in 30 mL of $CH_2Cl_2$ and stirred for 16 h at room temperature. The mixture was then chromatographed over flash silica with hexane and then hexane:EtOAc (1:1) to give a colorless glass which was recrystallized from methanol to give 3.2 g (82%) of white powder. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.15 (ddd, $J$ = 12.8, 7.5, 2.9 Hz, 1H), 2.83−2.91 (m, 1H), 2.97 (s, 3H), 3.69 (d, $J$ = 8.06 Hz, 2H), 3.77 (s, 3H), 3.79 (s, 2H), 3.90 (s, 3H), 4.50 (dd, $J$ = 9.3, 2.9 Hz, 1H), 4.78−4.89 (m, 1H), 7.02 (ddd, $J$ = 9.2, 2.6 Hz, 2H), 7.83 (ddd, $J$ = 9.2, 2.6 Hz, 2H). ESI MS: $m/z$ (rel intensity) 412.1 ([M + H]$^+$, 100), 429.1 ([M + $NH_4$]$^+$, 45).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-(morpholin-1*N*-yl)pyrrolidine (10).** The starting amine **3** (590 mg, 1.88 mmol) was taken in 4 mL of DMF and 1 mL of $NEt_3$ and treated with 1 mL of 2-bromoethyl ether. The

resulting mixture was then heated to 60 °C for 3 h and partitioned between dilute $NaCO_3$ and EtOAc. The organic layer was then dried over $MgSO_4$, filtered and evaporated. The crude residue was chromatographed over flash silica with EtOAc:MeOH (9:1) to give 348 mg (48%) of the title compound as a white solid. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 1.97 (ddd, $J$ = 12.5, 8.9, 8.9 Hz, 1H), 2.18 (ddd, $J$ = 12.5, 5.7, 2.4 Hz, 1H), 2.34−2.49 (m, 4H), 3.01−3.12 (m, 2H), 3.66 (dd, $J$ = 4.8, 4.8 Hz, 4H), 3.69−3.74 (m, 1H), 3.77 (s, 3H), 3.90 (s, 3H), 4.35 (dd, $J$ = 9.7, 2.4 Hz, 1H), 7.01 (ddd, $J$ = 8.8, 2.6, 2.6 Hz, 2H), 7.82 (ddd, $J$ = 8.8, 2.5, 2.5 Hz, 2H). ESI MS: *m/z* (rel intensity) 385.1 ([M + H]$^+$, 100).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-(γ-chlorosulfonamido)pyrrolidine (11).** The free amine **3** (7.51 g, 23.8 mmol) was taken in 15 mL of methylene chloride in the presence of triethylamine and treated with 3-chloropropylsulfonyl chloride (3.76 mL, 31.0 mmol) at room temperature. The resulting mixture was allowed to stir for 18 h and then it was diluted with 200 mL of methylene chloride, washed with 1 N HCl, dried over $MgSO_4$, filtered and evaporated. The crude material was adsorbed onto silica and then eluted through a column of flash silica with hexane:EtOAc (2:1 to 1:3) to give 7.21 g (67%). $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.20−2.38 (m, 4H), 3.20 (dd, $J$ = 7.4, 7.4 Hz, 2H), 3.38 (dd, $J$ = 10.4, 4.6 Hz, 1H), 3.63−3.72 (m, 2H), 3.72 (s, 3H), 3.90 (s, 3H), 4.11−4.22 (m, 1H), 4.53 (dd, $J$ = 8.4, 5.7 Hz, 1H), 4.72 (d, $J$ = 8.1 Hz, 1H), 7.03 (ddd, $J$ = 8.8, 2.9, 2.0 Hz, 2H), 7.85 (ddd, $J$ = 8.9, 2.9, 2.0 Hz, 2H). ESI MS: *m/z* (rel intensity) 455.0 ([M + H]$^+$, 100), 419.0 ([M − Cl]$^+$, 90).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-(γ-sultam-1*N*-yl)pyrrolidine (12).** The substrate **11** was taken in 20 mL of DMF and treated at room temperature with 1,8-diazabicyclo[5.4.0]undec-7-ene (3 mL, 20.1 mmol). The resulting mixture was stirred for 18 h and then diluted with hexanes:EtOAc (3:1) and washed twice with 1 N HCl, once with brine, dried over $MgSO_4$, filtered and evaporated. The residue was adsorbed onto silica and eluted through a column of flash silica with hexane:EtOAc (1:1 to 1:3) to give 1.28 g (77%). $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 2.26−2.45 (m, 4H), 3.12−3.27 (m, 4H), 3.41 (dd, $J$ = 9.9, 6.6 Hz, 1H), 3.67 (dd, $J$ = 9.7, 6.8 Hz, 1H), 3.70 (s, 3H), 3.89 (s, 3H), 4.07−4.17 (m, 1H), 4.51 (dd, $J$ = 8.6, 4.0 Hz, 1H), 7.01 (ddd, $J$ = 9.0, 2.9, 2.0 Hz, 2H), 7.82 (ddd, $J$ = 9.0, 2.9, 2.1 Hz, 2H). ESI MS: *m/z* (rel intensity) 419.0 ([M + H]$^+$, 100).

**1*N*-*tert*-Butoxycarbonyl-2(*R*)-carbomethoxy-4(*R*)-hydroxypyrrolidine (13).** *cis*-4-Hydroxy-D-proline methyl ester hydrochloride (40 g, 221 mmol) was taken in 250 mL of water:acetone (2:3) in the presence of 60 mL of triethylamine and 1 g of 4-*N*,*N*-dimethylaminopyridine. Di-*tert*-butyl dicarbonate (66 g, 303 mmol) was added slowly in portions and the resulting mixture was allowed to stir for 16 h and then concentrated to one-half of its original volume and then partitioned between EtOAc and dilute $NaH_2PO_4$. The organic layer was washed once with dilute $NaH_2PO_4$, once with brine, dried over $MgSO_4$, filtered and evaporated to give 58 g of material (107%) which was carried forward withput purification. *This compound appears in the $^1$H NMR spectrum as a distinct pair of rotomers.* $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ [1.44 (s), 1.48 (s)] 9H, 2.06−2.16 (m, 1H), 2.27−2.42 (m, 1H), 3.50−3.75 (m, 2H), [3.80 (s), 3.81 (s)] 1H, 4.29−4.42 (m, 2H). ESI MS: *m/z* (rel intensity) 262.9 ([M + $NH_4$]$^+$, 45), 245.9 ([M + H]$^+$, 100), 145.8 ([M − Boc + H]$^+$, 90).

**1*N*-*tert*-Butoxycarbonyl-2(*R*)-carbomethoxy-4(*R*)-methanesulfonylpyrrolidine (14a).** The starting alcohol **13** (58 g, 237 mmol) was converted to the title compound as described for compound **2**. The crude oil was filtered through a plug of silica with hexane:EtOAc (1:1) and concentrated to give 73 g (95%) of pale orange oil. *This compound appears in the $^1$H NMR spectrum as a distinct pair of rotomers.* $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ [1.44 (s), 1.49 (s)] 9H, 2.48−2.60 (m, 2H), 3.03 (s, 3H), 3.75−3.84 (m, 1H), 3.77 (s, 3H), [4.42 (dd, $J$ = 5.9 Hz), 4.53 (dd, $J$ = 7.7, 4.0 Hz)] 1H, 5.21−5.29 (m, 1H).

**1*N*-*tert*-Butoxycarbonyl-2(*R*)-carbomethoxy-4(*S*)-azidopyrrolidine (14b).** The mesylate **14a** (73 g, 226 mmol) was converted and purified as described for compound **3a** to give the title azide (34.5 g, 59%) as a yellow gum. *This compound appears in the $^1$H NMR spectrum as a distinct pair of rotomers.* $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ [1.43 (s), 1.48 (s)] 9H, [2.17 (dd, $J$ = 6.5, 6.5 Hz), 2.21 (dd, 6.4, 6.4 Hz)] 1H, 2.26−2.41 (m, 1H), [3.49 (dd, $J$ = 11.4, 3.5 Hz), 3.60 (dd, $J$ = 11.5, 2.6 Hz)] 1H, 3.70−3.74 (m, 1H), 3.76 (br s, 3H), 4.17−4.24 (m, 1H), [4.35 (dd, $J$ = 7.6, 7.6 Hz), 4.43 (dd, $J$ = 7.1, 7.1 Hz) 1H.

**1*N*-*tert*-Butoxycarbonyl-2(*R*)-carbomethoxy-4(*S*)-aminopyrrolidine (14).** The azide **14b** (26 g, 101 mmol) was hydrogenated and purified as described for compound **3** to give the title amine (15.7 g, 61%) as a pale yellow gum. *This compound appears in the $^1$H NMR spectrum as a distinct pair of rotomers.* $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ [1.35 (s), 1.41 (s)] 9H, 1.75−2.02 (m, 2H), 2.93−3.06 (m, 1H), 3.38−3.50 (m, 2H), [3.62 (s), 1.64 (s)] 3H, 4.20−4.28 (m, 1H). ESI MS: *m/z* (rel intensity) 245.0 ([M + H]$^+$, 55), 144.8 ([M − Boc + H]$^+$, 100).

**1*N*-*tert*-Butoxycarbonyl-2(*R*)-carbomethoxy-4(*S*)-(pyrrolidin-1*N*-yl)pyrrolidine (15).** The starting free amine **14** (7.51 g, 30.7 mmol) was treated with 8 mL of 1,4-dibromobutane to give the title pyrrolidine (6.85 g, 75%) as described for compound **10**. *This compound appears in the $^1$H NMR spectrum as a distinct pair of rotomers.* $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ [1.40 (s), 1.46 (s)] 9H, 1.77−1.89 (m, 4H), 2.10−2.34 (m, 2H), 2.50−2.66 (m, 4H), 2.88−3.05 (m, 1H), 3.25−3.37 (m, 1H), 3.70−3.86 (m, 1H), 3.74 (s, 3H), [4.33 (dd, $J$ = 9.0, 2.2 Hz), 4.43 (dd, $J$ = 8.7, 1.8 Hz)] 1H. ESI MS: *m/z* (rel intensity) 299.0 ([M + H]$^+$, 100), 242.9 (50), 198.9 ([M − Boc + H]$^+$, 5).

**1*N*-(4-Phenoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-(pyrrolidin-1*N*-yl)pyrrolidine (16).** The starting protected amine **15** (1.36 g, 4.56 mmol) was taken in 30 mL of $CH_2Cl_2$ and treated with 2 mL of trifluoroacetic acid. The resulting mixture was allowed to stir for 2 h, evaporated to dryness and tritutated with $CHCl_3$. The residue was then taken in 30 mL of dioxane:water:$Et_3N$ (3:1:2) and treated with 4-phenoxybenzenesulfonyl chloride.[31] The resulting mixture was stirred for 16 h and then partitioned between EtOAc and dilute $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude residue was adsorbed onto silica and eluted through a column of flash silica to give 884 mg (45%) of clear gum which solidified upon standing. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 1.69−1.83 (m, 4H), 2.05 (ddd, $J$ = 12.6, 9.3, 9.3 Hz, 1H), 2.17 (ddd, $J$ = 12.8, 6.0, 3.1 Hz, 1H), 2.38−2.54 (m, 4H), 2.93−3.05 (m, 1H), 3.08 (dd, $J$ = 8.2, 8.2 Hz, 1H), 3.72 (dd, $J$ = 8.2, 6.0 Hz, 1H), 3.78 (s, 3H), 4.33 (dd, $J$ = 9.3, 2.9 Hz, 1H), 7.05 (ddd, $J$ = 8.7, 2.9, 1.8 Hz, 2H), 7.08−7.13 (m, 2H), 7.22−7.29 (m, 1H), 7.40−7.48 (m, 2H), 7.82 (ddd, $J$ = 8.6, 2.9, 1.8 Hz, 2H). ESI MS: *m/z* (rel intensity) 431.0 ([M + H]$^+$, 100).

**1*N*-*tert*-Butoxycarbonyl-2(*R*)-carbomethoxy-4(*S*)-(γ-chlorosulfonamido)pyrrolidine (17a).** The starting amine **14** (4.01 g, 16.4 mmol) was converted to 6.18 g (98%) of the title sulfonamide as a white solid as described for compound **11**. *This compound appears in the $^1$H NMR spectrum as a distinct pair of rotomers.* $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ [1.43 (s), 1.48 (s)] 9H, 2.24−2.36 (m, 4H), 3.24 (dd, $J$ = 7.3, 7.7 Hz, 2H), [3.32 (dd, $J$ = 11.0, 5.9 Hz), 3.42 (dd, $J$ = 10.8, 4.8 Hz)] 1H, 3.70 (dd, $J$ = 6.1, 6.1 Hz, 2H), 3.77 (s, 3H), 3.82−3.92 (m, 1H), 4.08−4.39 (m, 1H), [4.35 (dd, $J$ = 6.6, 7.0 Hz), 4.43 (dd, $J$ = 8.1, 4.2 Hz)] 1H, [4.92 (d, $J$ = 8.4), 5.01 (d, $J$ = 7.7 Hz)] 1H. ESI MS: *m/z* (rel intensity) 285.0 ([M − Boc + H]$^+$, 100).

**1*N*-*tert*-Butoxycarbonyl-2(*R*)-carbomethoxy-4(*S*)-(γ-sultam-1*N*-yl)pyrrolidine (17).** The starting sulfonamide **17a** (6.15 g, 16.0 mmol) was converted as described for compound **12** to give 4.21 g (76%) of the title compound as a white solid. *This compound appears in the $^1$H NMR spectrum as a distinct pair of rotomers.* $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ [1.40 (s), 1.46 (s)] 9H, 2.23−2.45 (m, 3H), 2.54 (ddd, $J$ = 13.5, 8.5, 8.5 Hz, 1H), 3.10−3.34 (m, 4H), 3.42−3.53 (m, 1H), 3.74 (s, 3H), 3.78−3.88 (m, 1H), 3.98−4.15 (m, 1H), [4.36 (dd, $J$ = 8.8, 3.7 Hz), 4.43 (dd, $J$ = 9.2, 3.3 Hz)] 1H. ESI MS: *m/z* (rel intensity) 249.0 ([M − Boc + H]$^+$, 100).

**1*N*-(4-*n*-Propoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-(γ-sultam-1*N*-yl)pyrrolidine (18).** The starting car-

bamate **17** (1.27 g, 3.67 mmol) was deprotected and sulfonylated as described for compound **16** to give 934 mg (57%) of the title sultam as a solid. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 1.07 (t, $J$ = 7.4 Hz, 3H), 1.80−1.93 (m, 2H), 2.27−2.46 (m, 4H), 3.12−3.30 (m, 4H), 3.41 (dd, $J$ = 9.9, 6.8 Hz, 1H), 3.68 (dd, $J$ = 9.7, 6.8 Hz, 1H), 3.70 (s, 3H), 4.08−4.18 m, 1H), 4.51 (dd, $J$ = 8.6, 3.8 Hz, 1H), 7.00 (ddd, $J$ = 9.0, 2.7, 2.0 Hz, 2H), 7.81 (ddd, $J$ = 9.0, 2.7, 2.0 Hz, 2H). ESI MS: $m/z$ (rel intensity) 464 ($[M + NH_4]^+$, 20).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-aminopyrrolidine (19).** The starting ester **3** (500 mg, 1.59 mmol), was taken in 5 mL of MeOH, treated with $NH_2OK$ (1.92 mL, 0.86 M in methanol; solution prepared as described in Fieser and Fieser, Vol 1, p 478) and stirred overnight. The following morning, dry silica (1.5 mL) was added to the mixture and the solvent removed under vacuum. The dry silica was poured on the top of a flash silica gel column which was subsequently eluted with EtOAc:MeOH (4:1 to 3:2) to give 284 mg (56%) of white solid. $^1$H NMR: ($CDCl_3$, 300 MHz) $\delta$ 1.49 (ddd, $J$ = 12.1, 7.9, 7.9 Hz, 1H), 1.85 (ddd, $J$ = 12.3, 4.9, 4.9 Hz, 1H), 2.68 (dd, $J$ = 8.6, 5.9 Hz, 1H), 3.41−3.57 (m, 2H), 3.87 (s, 3H), 3.93 (dd, $J$ = 8.4, 4.4 Hz, 1H), 7.14 (d, $J$ = 8.8 Hz, 2H), 7.80 (d, $J$ = 8.8 Hz, 2H). ESI MS: $m/z$ (rel intensity) 316.1 ($[M + H]^+$, 100). Analysis: C, H, N for $C_{12}H_{17}N_3O_5S \cdot 0.8H_2O$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-hydroxycarboxamido-4(*S*)-aminopyrrolidine (20).** The title compound was prepared as described for compound **19** and then purified further by recrystallizing from water. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.95 (td, $J$ = 7.1, 1.8 Hz, 3H), 1.47 (septet, $J$ = 7.7 Hz, 2H), 1.69−1.88 (m, 4H), 2.67 (dd, $J$ = 7.3 Hz, 1H), 3.48 (ddd, $J$ = 13.6, 13.6, 5.5 Hz, 1H), 3.92 (dd, $J$ = 7.5, 3.3 Hz, 1H), 4.08 (t, $J$ = 6.3 Hz, 2H), 7.13 (br d, $J$ = 8.6 Hz, 2H), 7.77 (br d, $J$ = 8.6 Hz, 2H). ESI MS: $m/z$ (rel intensity) 358 ($[M + H]^+$, 100). Analysis: C, H, N for $C_{15}H_{23}N_3O_5S \cdot 0.2H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-propylaminopyrrolidine (21).** The starting methyl ester **4** (11.3, g, 31.7 mmol) was taken in 30 mL of methanol, treated with $NH_2OK$ (38 mL, 1.25 M in methanol; solution prepared as described in Fieser and Fieser, Vol 1, p 478) and stirred for 16 h. The following morning, dry silica (30 mL) was added to the mixture and the solvent removed under vaccuum. The dry silica was poured on the top of a flash silica gel column which was subsequently eluted with chloroform:methanol (8:2) to give a pale yellow solid which was taken in methanol and stirred for 1 h in the presence of activated charcoal and then filtered through Celite and evaporated to give 2.00 g (18%) of a white solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.74 (t, $J$ = 7.4 Hz, 3H), 1.05−1.25 (m, 2H), 1.58−1.68 (m, 1H), 1.91 (ddd, $J$ = 12.5, 5.7, 5.7 Hz, 1H), 2.13−2.30 (m, 2H), 2.87 (dd, $J$ = 9.7, 5.1 Hz, 1H), 3.22−3.33 (m, 1H), 3.48 (dd, $J$ = 9.9, 5.5 Hz, 1H), 3.86 (s, 3H), 3.93 (dd, $J$ = 8.1, 5.5 Hz, 1H), 7.13 (br d, $J$ = 8.8 Hz, 2H), 7.79 (br d, $J$ = 8.8 Hz, 2H). ESI MS: $m/z$ (rel intensity) 358.2 ($[M + H]^+$, 100), 380.1 ($[M + Na]^+$, 5). Analysis: C, H, N for $C_{15}H_{23}N_3O_5S \cdot HCl$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-(2-phenylethyl)aminopyrrolidine (22).** The title compound was prepared as described for compound **21** and purified over flash silica with EtOAc:MeOH (4:1) to give a white solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.58−1.67 (m, 1H), 1.88−1.94 (m, 1H), 2.37−2.57 (m, 2H), 2.88 (dd, $J$ = 9.7, 5.3 Hz, 1H), 3.48 (dd, $J$ = 10.0, 5.5 Hz, 1H), 3.69−3.87 (m, 1H), 3.85 (s, 3H), 3.94 (dd, $J$ = 7.5, 5.7 Hz, 1H), 7.11−7.10 (m, 5H), 7.82 (br d, $J$ = 9.0 Hz, 2H). ESI MS: $m/z$ (rel intensity) 420.4 ($[M + H]^+$, 100). Analysis: $C_{20}H_{25}N_3O_5S \cdot HCl \cdot 0.5H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-hydroxycarboxamido-4(*S*)-methanesulfonylaminopyrrolidine (23).** The starting ester **5** (354 mg, 0.903 mmol) was converted to the title compound and chromatographed as described for compound **3**. It was then recrystallized from acetonitrile/water to give 261 mg (74%) of pale yellow crystals. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.67 (ddd, $J$ = 12.6, 6.3, 6.3 Hz, 1H), 2.04 (ddd, $J$ = 12.6, 6.2, 2.2 Hz, 1H), 2.86 (dd, $J$ = 8.6, 8.6 Hz, 1H), 2.90 (s, 3H), 3.65 (dd, $J$ = 9.2, 7.1 Hz, 1H), 3.87 (s, 3H), 3.98 (dd, $J$ = 9.0, 2.2 Hz, 1H), 4.01−4.14 (m, 1H), 7.16 (br d, $J$ = 8.61, 2H), 7.23 (d, $J$ = 6.8 Hz, 1H), 7.79 (d, $J$ = 8.8 Hz, 2H), 9.04 (s, 1H), 10.75 (1H). ESI MS: $m/z$ (rel intensity) 394.1 ($[M + H]^+$, 100). Analysis: C, H, N for $C_{13}H_{19}N_3O_7S_2 \cdot 0.3H_2O$.

**1*N*-(4-*n*-Butoxyphenylsulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-methanesulfonylaminopyrrolidine (24).** Compound **24** was prepared as described for compound **23** to give a white solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.95 (t, $J$ = 7.4, 3H), 1.39−1.42 (m, 2H), 1.61−1.79 (m, 3H), 1.98−2.06 (m, 1H), 2.82−2.94 (m, 1H), 2.89 (s, 3H), 3.64 (dd, $J$ = 9.0, 6.8 Hz, 1H), 3.99 (dd, $J$ = 9.2, 2.2 Hz, 1H), 4.02−4.14 (m, 3H), 7.14 (br d, $J$ = 9.0 Hz, 2H), 7.77 (br d, $J$ = 9.0 Hz, 2H). ESI MS: $m/z$ (rel intensity) 453.08 ($[M + NH_4]^+$, 50), 436.05 ($[M + H]^+$, 100). Analysis: C, H, N for $C_{16}H_{25}N_3O_7S_2 \cdot 0.7H_2O$.

**1*N*-(4-Pyridin-4-yloxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-aminopyrrolidine (25).** The title compound was prepared as described for compound **23** to give a white solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.81−1.95 (m, 1H), 2.07 (ddd, $J$ = 12.9, 6.3, 6.3 Hz, 1H), 2.99 (dd, $J$ = 9.7, 4.8 Hz, 1H), 3.53 (dd, $J$ = 9.7, 5.5 Hz, 1H), 3.63 (s, 3H), 4.34 (dd, $J$ = 5.7 8.2 Hz, 1H), 6.80 (m, 2H), 7.12 (d, $J$ = 8.8 Hz, 2H), 7.85 (d, $J$ = 8.8 Hz, 2H), 8.43−8.46 (m, 2H). ESI MS: $m/z$ (rel intensity) 378.1 ($[M + H]^+$, 100). Analysis: $C_{17}H_{20}N_4O_7S_2 \cdot HCl \cdot 0.3H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-hydroxycarboxamido-4(*S*)-*N*-methyl-*N*-methanesulfonylaminopyrrolidine (26).** Compound **24** was prepared as described for compound **23** to give a white solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.81−1.91 (m, 2H), 2.46 (s, 3H), 2.88 (s, 3H), 3.03 (dd, $J$ = 9.4, 8.8 Hz, 1H), 3.57 (dd, $J$ = 9.7, 7.7 Hz, 1H), 3.86 (s, 3H), 4.07 (dd, $J$ = 6.4, 4.4 Hz, 1H), 4.58−4.71 (m, 1H), 7.16 (br d, $J$ = 9.0 Hz, 2H), 7.82 (br d, $J$ = 8.8 Hz, 1H). ESI MS: $m/z$ (rel intensity) 429.3 ($[M + Na]^+$, 15), 425.0 ($[M + NH_4]^+$ 20), 407.4 ($[M + H]^+$, 100). Analysis: C, H, N for $C_{14}H_{21}N_3O_7S_2 \cdot 0.4H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-(3-pyridylmethyl)-*N*-methanesulfonylaminopyrrolidine (27).** The title compound was prepared according to the synthetic sequence described for compound **23**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.87 (dd, $J$ = 12.6, 7.5 Hz, 1H), 2.63 (ddd, $J$ = 12.2, 9.3 Hz, 1H), 2.86 (dd, $J$ = 9.3, 9.3 Hz, 1H), 3.05 (s, 3H), 3.60 (dd, $J$ = 8.5, 8.5 Hz, 1H), 3.90 (s, 3H), 3.98−4.13 (m, 2H), 4.28 (d, $J$ = 17.4 Hz, 2H), 4.58−4.82 (m, 1H), 7.13 (ddd, $J$ = 9.0, 2.0, 2.0 Hz, 2H), 7.35 (dd, $J$ = 7.9, 4.8 Hz, 1H), 7.57 (ddd, $J$ = 7.9, 1.8, 1.8 Hz, 1H), 7.71 (ddd, $J$ = 9.0, 1.8, 1.8 Hz, 2H), 8.32 (d, $J$ = 1.8 Hz, 1H), 8.47 (dd, $J$ = 6.4, 1.7 Hz, 1H), 9.04 (br s, 1H), 10.73 (br s, 1H). ESI MS: $m/z$ (rel intensity) 484.9 ($[M + H]^+$, 100), 506.9 ($[M + NH_4]^+$, 10). Analysis: C, H, N for $C_{19}H_{24}N_4O_7S_2 \cdot H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-methanesulfonyl-*N*-propylaminopyrrolidine (28).** The starting ester **7** (614 mg, 1.41 mmol) was converted to the title compound (448 mg, 73%) as described for **23**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.68 (t, $J$ = 7.3 Hz, 3H), 1.22−1.42 (m, 2H), 1.61−1.74 (m, 1H), 1.93 (dd, $J$ = 12.6, 7.0 Hz, 1H), 2.74 (ddd, $J$ = 14.8, 9.9, 5.7 Hz, 1H), 2.85−2.91 (m, 4H), 3.62 (dd, $J$ = 8.8, 8.8 Hz, 1H), 3.87 (s, 3H), 4.16 (d, $J$ = 9.2 Hz, 1H), 4.55−4.66 (m, 1H), 7.18 (br d, $J$ = 9.0 Hz, 2H), 7.84 (br d, $J$ = 9.0 Hz, 2H). ESI MS: $m/z$ (rel intensity) 452.9 ($[M + NH_4]^+$ 100), 435.8 ($[M + H]^+$, 55). Analysis: C,H,N for $C_{16}H_{25}N_3O_7S_2$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-hydroxycarboxamido-4(*S*)-4-methoxyphenylsulfonylaminopyrrolidine (29).** The desired material was prepared according to the synthetic sequence described for compound **23**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.54 (ddd, $J$ = 12.6, 9.3, 9,3 Hz, 1H), 1.68−1.76 (m, 1H), 2.78 (dd, $J$ = 8.6, 8.6 Hz, 1H), 3.36 (dd, $J$ = 9.2, 6.8 Hz, 1H), 3.73−3.83 (m, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 3.92 (dd, $J$ = 9.0, 2.4 Hz, 1H), 7.12 (ddd, $J$ = 9.0, 2.6, 2.6 Hz, 2H), 7.16 (ddd, $J$ = 9.0, 2.6, 2.6 Hz, 2H), 7.69 (ddd, $J$ = 9.0, 2.6, 2.6 Hz, 2H), 7.74 (ddd, $J$ = 9.0, 2.6, 2.6 Hz, 2H), 8.34 (s, 1H). ESI MS: $m/z$ (rel intensity) 486.3 ($[M + H]^+$, 100). Analysis: C, H, N for $C_{19}H_{23}N_3O_8S_2 \cdot 0.7H_2O$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(1*N*-methylimidazol-4-yl)sulfonylaminopyrrolidine (30).** The desired material was prepared according to the synthetic sequence described for compound **23**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.97 (t, $J$ = 7.4 Hz, 3H), 1.39−1.63 (m, 3H), 1.69−1.87 (m, 3H), 2.76 (dd, $J$ = 8.8, 8.8 Hz, 1H), 3.41 (dd, $J$ = 9.0, 6.8 Hz, 1H), 3.71 (s, 3H), 3.90−4.0 (m, 2H), 4.08 (t, $J$ = 12.8 Hz, 2H), 7.14 (br d, $J$ = 9.0 Hz, 2H), 4.11 (br d, $J$ = 9.0 Hz, 2H), 7.16 (s, 1H), 7.80 (d, $J$ = 0.9 Hz, 1H), 9.05 (br s, 1H), 10.7 (s, 1H). ESI MS: *m*/*z* (rel intensity) 502.2 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{19}H_{27}N_5O_7S_2\cdot H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-hydroxycarboxamido-4(*S*)-[(1,1′-biphenyl)-4-yl]carbonylaminopyrrolidine (31).** The desired material was prepared according to the synthetic sequence described for compound **23**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 2.08 (dd, $J$ = 6.5, 6.5 Hz, 2H), 3.21 (dd, $J$ = 9.9, 5.7 Hz, 1H), 3.64−3.70 (m, 4H), 4.13 (dd, $J$ = 7.0, 7.0 Hz, 1H), 4.44−4.55 (m, 1H), 7.01 (br d, $J$ = 9.0 Hz, 2H), 7.40−7.45 (m, 1H), 7.52 (dd, $J$ = 7.4, 7.4 Hz, 2H), 7.69−7.80 (m, 8H), 8.14 (d, $J$ = 5.7 Hz, 1H). ESI MS: *m*/*z* (rel intensity) 517.8 ([M + Na]$^+$, 15), 513.0 ([M + NH$_4$]$^+$, 60), 496.0 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{25}H_{25}N_3O_6S\cdot 2H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-hydroxycarboxamido-4(*S*)-*N*-methylcarboxaidoaminopyrrolidine (32).** The desired material was prepared according to the synthetic sequence described for comound **23**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.63 (ddd, $J$ = 12.3, 8.8, 8.8 Hz, 1H), 1.93 (ddd, $J$ = 12.6, 6.0, 4.0 Hz, 1H), 2.57 (d, $J$ = 4.8 Hz, 3H), 2.81 (dd, $J$ = 9.0, 7.3 Hz, 1H), 2.52 (dd, $J$ = 9.2, 6.2 Hz, 1H), 3.87 (s, 3H), 3.98 (dd, $J$ = 8.8, 3.7 Hz, 1H), 4.15−4.26 (m, 1H), 5.54 (dd, $J$ = 4.8, 2.0 Hz, 1H), 5.88 (d, $J$ = 6.6 Hz, 1H), 7.15 (d, $J$ = 8.8 Hz, 2H), 7.78 (d, $J$ = 8.8 Hz, 2H), 9.01 (s, 1H), 10.8 (s, 1H). ESI MS: *m*/*z* (rel intensity) 411.0 ([M + K]$^+$, 30), 373.1 ([M + H]$^+$, 100), 316 (32). Analysis: C, H, N for $C_{14}H_{20}N_4O_6S$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-(3-pyridylmethyl)-*N*-isopropylcarbonylaminopyrrolidine (33).** The title compound was prepared according to the synthetic sequence described for compound **23**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.23 (d, $J$ = 6.6 Hz, 6H), 1.68 (dd, $J$ = 11.8, 7.2 Hz, 1H), 2.21−2.96 (m, 3H), 3.51 (dd, $J$ = 9.1, 7.8 Hz, 1H), 3.90 (s, 3H), 4.03−4.31 (m, 3H), 4.48−4.74 (m, 1H), 7.11 (ddd, $J$ = 9.0, 2.0, 2.0 Hz, 2H), 7.33 (dd, $J$ = 7.8, 4.8 Hz, 1H), 7.57 (m, 1H), 7.71 (ddd, $J$ = 9.0, 2.0, 2.0 Hz, 2H), 8.33 (d, $J$ = 1.7 Hz, 1H), 8.49 (dd, $J$ = 6.7, 1.9 Hz, 1H), 9.08 (br s, 1H), 10.25 (br s, 1H). ESI MS: *m*/*z* (rel intensity) 476.9 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{22}H_{28}N_4O_6S\cdot 1.5H_2O$.

**1*N*-(4-*n*-Propoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(1-oxy-2-methoxyethyl)aminopyrrolidine (34).** The title compound was prepared as described for compound **23** to give a white solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.00 (t, $J$ = 7.3 Hz, 3H), 1.72−1.77 (m, 4H), 2.94 (dd, $J$ = 8.2 Hz, 1H), 3.22 (s, 3H), 3.52 (dd, $J$ = 8.8, 6.8 Hz, 1H), 3.65 (s, 2H), 3.98 (dd, $J$ = 8.1, 4.2 Hz, 1H), 4.04 (t, $J$ = 6.2 Hz, 2H), 4.38−4.51 (m, 1H), 7.14 (d, 8.8 Hz, 2H), 7.68 (d, $J$ = 7.1 Hz, 1H), 7.76 (d, $J$ = 8.5 Hz, 2H), 8.70 (br s, 1H), 10.35 (s, 1H). ESI MS: *m*/*z* (rel intensity) 416.1 ([M + H]$^+$, 100), 433.1 ([M + NH$_4$]$^+$, 10). Analysis: C, H, N for $C_{17}H_{25}N_3O_7S$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(1-oxy-2-methoxyethyl)aminopyrrolidine (35).** The title compound was prepared as described for compound **23** to give a white solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.95 (t, $J$ = 7.3 Hz, 3H), 1.39−1.52 (m, 2H), 1.68−1.79 (m, 2H), 1.83−1.96 (m, 2H), 2.94 (dd, $J$ = 9.2, 7.7 Hz, 1H), 3.22 (s, 3H), 3.52 (dd, $J$ = 9.2, 6.6 Hz, 1H), 3.63 (s, 2H), 3.98 (dd, $J$ = 7.7, 4.0 Hz, 1H), 4.07 (t, $J$ = 6.4 Hz, 2H), 4.37−4.51 (m, 1H), 7.14 (br d, $J$ = 9.2 Hz, 2H), 7.68 (d, $J$ = 7.0 Hz, 1H), 7.76 (br d, $J$ = 8.8 Hz, 2H), 9.00 (br s, 1H), 10.68 (s, 1H). ESI MS: *m*/*z* (rel intensity) 430.1 ([M + H]$^+$, 100), 447.1 ([M + NH$_4$]$^+$, 20). Analysis: C, H, N for $C_{18}H_{27}N_3O_7S$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-(1-oxy-2(*R*)-benzyloxypropyl)aminopyrrolidine (36).** The desired material was prepared according to the synthetic sequence described for comound **37** to give a white soild. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.18 (dd, $J$ = 6.6, 2.9 Hz, 3H), 1.75−2.0 (m, 2H), 2.88 (ddd, $J$ = 8.1, 8.1, 7.8 Hz, 1H), 3.55 (dd, $J$ = 8.4, 7.3 Hz, 1H), 3.76 (q, $J$ = 6.8 Hz, 1H), 3.85 (s, 3H), 4.03 (dd, $J$ = 8.4, 2.4 Hz, 1H), 4.14 (d, $J$ = 12.3 Hz, 1H), 4.41−4.56 (m, 1H), 4.45 (d, $J$ = 11.9 Hz, 1H), 7.15 (br d, $J$ = 8.6 Hz, 2H), 7.26−7.39 (m, 5H), 7.80 (br d, $J$ = 8.8 Hz, 2H), 7.84 (dd, $J$ = 7.9, 3.1 Hz, 1H), 8.98 (s, 1H), 10.66 (s, 1H). ESI MS: *m*/*z* (rel intensity) 478.3 ([M + H]$^+$, 100), 500.2 ([M + NH$_4$]$^+$, 12). Analysis: C, H, N for $C_{22}H_{27}N_3O_7S$.

**2(*R*)-Benzyloxy-3-phenylpropionic Acid (37a).** Sodium hydride (2.9 g, 120 mmol) was washed 2× with hexane and covered with 50 mL of DMF. The starting L-3-phenyllactic acid (5 g, 30.1 mmol) was then added in portions and after fizzing ceased, the mixture was heated to 55 °C for 1 h. The mixture was then cooled to 0 °C and benzyl bromide (4.3 mL, 36.1 mmol) was added dropwise. The mixture was heated to 60 °C for 3 h and then partitioned between hexane:EtOAc (1:1) and 1 N HCl. The organic layer was washed with brine, dried over MgSO$_4$, filtered and evaporated. The residue was chromatographed over flash silica with hexane:EtOAc (9:1 to 0:1) to give 4.00 g (52%) of colorless oil. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 3.05 (dd, $J$ = 14.1, 8.4 Hz, 1H), 3.18 (dd, $J$ = 14.1, 4.2 Hz, 1H), 4.20 (dd, $J$ = 8.2, 1H), 4.43 (d, $J$ = 11.7 Hz, 1H), 4.65 (dd, $J$ = 11.5 Hz, 1H), 7.14−7.18 (m, 1H), 7.23−7.33 (m, 4H). ESI MS: *m*/*z* (rel intensity) 274.3 ([M + NH$_4$]$^+$, 100).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-*N*-(1-oxy-2(*R*)-benzyloxy-3-phenylpropyl)aminopyrrolidine (37b).** The starting amine **3** (800 mg, 2.55 mmol) and the starting benzyl lactic acid **37a** (784 mg, 3.06 mmol) were taken in 5 mL of DMF in the presence of 1 mL of *N*-methylmorpholine, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (979 mg, 5.10 mmol) and hydroxybenzotriazole (1.03 mg, 7.65 mmol). The resulting mixture was stirred at room temperature for 16 h and then partitioned between 1 N HCl and EtOAc. The organic layer was then washed 1× with dilute NaHCO$_3$, 1× with brine, dried over MgSO$_4$, filtered and evaporated. The crude residue was then chromatographed with hexane:EtOAc (8:1 to 1:1) to give 1.08 g (57%) of the title compound. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.83−1.93 (m, 1H), 2.02−2.13 (m, 1H), 2.91 (dd, $J$ = 14.1, 6.6 Hz, 1H), 3.10−3.25 (m, 2H), 3.51 (dd, $J$ = 10.8, 5.7 Hz, 1H), 3.72 (s, 3H), 3.86 (s, 3H), 4.07 (dd, $J$ = 6.6, 3.8 Hz, 1H), 4.23 (dd, $J$ = 8.1, 6.4 Hz, 1H), 4.38−4.53 (m, 3H), 6.48 (d, $J$ = 7.1 Hz, 1H), 6.96 (br d, $J$ = 9.0 Hz, 2H), 7.19−7.40 (m, 10H), 7.81 (br d, $J$ = 9.0 Hz, 2H). ESI MS: *m*/*z* (rel intensity) 553.2 ([M + H]$^+$, 100), 570.3 ([M + NH$_4$]$^+$, 18).

**1*N*-(4-Methoxyphenylsulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-(1-oxy-2(*R*)-benzyloxy-3-phenylpropyl)aminopyrrolidine (37).** The starting methyl ester **37b** (700 mg, 1.27 mmol) was taken in 2 mL of methanol, treated with NH$_2$-OK (2.5 mL, 1.25 M in methanol; solution prepared as described in Fieser and Fieser, Vol 1, p 478) and stirred overnight. The following morning, dry silica (3 mL) was added to the mixture and the solvent removed under vaccuum. The dry silica was poured on the top of a flash silica gel column which was subsequently eluted with hexane:EtOAc (1:1 → 0:1) to give 322 mg (46%) of a white foamy solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.67 (dd, $J$ = 14.2, 7.5 Hz, 1H), 1.82−1.91 (m, 1H), 2.72 (dd, $J$ = 8.5, 8.5 Hz, 1H), 2.80 (d, $J$ = 6.0 Hz, 2H), 3.47 (dd, $J$ = 7.8, 7.8 Hz, 1H), 3.82 (s, 3H), 3.89 (dd, $J$ = 6.3, 6.3 Hz, 1H), 3.98 (d, $J$ = 7.3 Hz, 1H), 4.26 (d, $J$ = 12.3 Hz, 2H), 4.38−4.51 (m, 2H), 7.10−7.39 (m, 12 H), 7.77 (d, $J$ = 9.0 Hz, 2H), 7.87 (d, $J$ = 7.3 Hz, 1H), 9.00 (s, 1H), 10.7 (s, 1H). ESI MS: *m*/*z* (rel intensity) 553.3 ([M + H]$^+$, 100), 576.3 ([M + Na]$^+$, 23). Analysis: C, H, N for $C_{28}H_{31}N_3O_7S\cdot 0.2H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-*N*-(1-oxy-2(*R*)-benzyloxypropyl)-*N*-propylaminopyrrolidine (38a).** The starting amine **4** (636 mg, 1.79 mmol) and the starting benzyl lactic acid (390 mg, 2.15 mmol) were taken in 5 mL of DMF in the presence of 1 mL of *N*-methylmorpholine, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (687 mg, 3.58 mmol) and hydroxybenzotriazole (762 mg, 5.37 mmol). The resulting mixture was stirred at room temperature for 16 h and then partitioned between 1 N HCl and EtOAc. The

organic layer was then washed 1× with dilute $NaHCO_3$, 1× with brine, dried over $MgSO_4$, filtered and evaporated. The crude residue was then chromatographed with hexane:EtOAc (8:1 to 1:1) to give 406 mg (44%) of the title compound. *$^1$H NMR indicates two distinct rotamers in a 2:3 ratio which complicates spectral interpretation.* $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.75−0.87 (m, 3H), 1.34−1.51 (m, 5H), 1.95−2.17 (m, 2H), 2.44−2.56, 2.68−2.80 (m, 1H), 2.89−3.20 (m, 2H), 3.34−3.54 (m, 1H), 3.56−3.74 (m, 3H), 3.85, 3.87 (m, 3H), 4.14−4.61, 5.09−5.22 (m, 5H), 7.0 (br d, J − 9.0 Hz, 2H), 7.26−7.38 (m, 5H), 7.73−7.85 (m, 2H). ESI MS: *m/z* (rel intensity) 519.3 ([M + H]$^+$, 100), 536.3 ([M + $NH_3$]$^+$, 60).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-*N*-(1-oxo-2(*R*)-hydroxypropyl)-*N*-propylaminopyrrolidine (38b).** The starting ether **38a** (700 mg, 1.35 mmol) was taken in 25 mL of methanol with catalytic 10% Pd−C and $H_2SO_4$ and hydrogenated for 3 h at 54 psi in a Parr apparatus. The material was then filtered through a pad of Celite, evaporated to dryness and chromatographed over flash silica to give 341 mg (59%) of clear gum. *$^1$H NMR indicates two distinct rotamers in a 2:3 ratio which complicates spectral interpretation.* $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.93−0.96 (m, 3H), [1.28−1.29 (d, $J$ = 7.1 Hz, 2H), 1.50−1.64 (m, 2H), 2.09−2.22 (m, 1H), 2.48−2.62 (m, 1H), 2.95−3.28 (m, 3H), 3.45−3.69 (m, 2H), 3.73 (s, 3H), 3.90 (s, 3H), 4.29−4.66 (m, 3H), 7.02 (br d, $J$ = 8.8 Hz, 2H), 7.83 (br d, $J$ = 8.8 Hz, 2H). ESI MS: *m/z* (rel intensity) 429.3 ([M + H]$^+$, 100), 446.3 ([M + $NH_3$]$^+$, 12).

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-carbomethoxy-4(*S*)-*N*-(1-oxy-2(*R*)-hydroxypropyl)-*N*-propylaminopyrrolidine (38).** The starting methyester **38b** (331 mg, 0.771 mmol) was taken in 1 mL of methanol, treated with $NH_2OK$ (1.23 mL, 1.25 M in methanol; solution prepared as described in Fieser and Fieser, Vol 1, p 478) and stirred overnight. The following morning, dry silica (3 mL) was added to the mixture and the solvent removed under vaccuum. The dry silica was poured on the top of a flash silica gel column which was subsequently eluted with hexane:EtOAc (1:1 → 0:1) to give 300 mg (91%) of a white foamy solid. *$^1$H NMR indicates two distinct rotamers in a 1:1 ratio which complicates spectral interpretation.* $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.60−0.77 (m, 3H), 1.60−1.37 (m, 5H), 1.63−2.04 (m, 2H), 2.70−3.08 (m, 2H), 3.25−3.65 (m, 2H), 3.86 (s, 3H), 4.08−4.40 (m, 2H), 4.56−5.02 (m, 1H), 7.12−7.20 (m, 2H), 7.76−7.86 (m, 2H), 10.75 (s, 1H). ESI MS: *m/z* (rel intensity) 519.3 ([M + H]$^+$, 100), 536.3 ([M + $NH_4$]$^+$, 60). Analysis: C, N, N for $C_{18}H_{27}N_3O_7S\cdot0.3H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-(1-oxo-2(*R*)-hydroxy-3-phenylpropyl)-*N*-propylaminopyrrolidine (39).** The compound was prepared as described for compound **38** to give a white foamy solid. *$^1$H NMR indicates two distinct rotamers in a 2:3 ratio which complicates spectral interpretation.* $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.58−0.66 (m, 3H), 0.78−1.90 (m, 4H), 2.21−2.96 (m, 5H), 3.29−3.61 (m, 2H), 3.33 (s, 3H), 3.85 (s, 3H), 3.95−5.19 (m, 5H), 7.12−7.28 (m, 7H), 7.23−7.83 (m, 3H). ESI MS: *m/z* (rel intensity) 506.3 ([M + H]$^+$, 100), 526.3 ([M + Na]$^+$, 12). Analysis: C, H, N for $C_{24}H_{31}N_3O_7S\cdot0.6H_2O$.

**1*N*-(4-*n*-Propoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-(1-oxy-2(*R*)-hydroxypropyl)aminopyrrolidine (40).** The title compound was described according to the synthetic sequence described for compound **38**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.02 (t, $J$ = 7.1 Hz, 3H), 1.15 (d, $J$ = 6.8 Hz, 3H), 1.69−1.92 (m, 4H), 2.88 (dd, $J$ = 8.4, 8.4 Hz, 1H), 3.53 (dd, $J$ = 7.7, 7.7 Hz, 1H), 3.80−4.17 (m, 4H), 4.40−4.44 (m, 1H), 5.19 (d, $J$ = 5.1 Hz, 1H), 7.15 (br d, $J$ = 8.8 Hz, 2H), 7.72 (d, $J$ = 7.0 Hz, 1H), 7.77 (br d, $J$ = 8.8 Hz, 2H), 9.0 (br s, 1H), 10.75 (br s, 1H). ESI MS: *m/z* (rel intensity) 415.6 (M + H$^+$, 100). Analysis: C, H, N for $C_{17}H_{25}N_3O_7S\cdot0.2H_2O$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-(1-oxy-2(*R*)-hydroxypropyl)aminopyrrolidine (41).** The title compound was described according to the synthetic sequence described for compound **38**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.95 (t, $J$ = 7.2 Hz, 3H), 1.13 (d, $J$ = 6.6 Hz, 3H), 1.38−1.53 (m, 2H), 1.67−1.80 (m, 2H), 1.81−1.94 (m, 2H), 2.86 (dd, $J$ = 8.3, 8.3 Hz, 1H), 3.51 (dd, $J$ = 7.5, 7.5 Hz, 1H), 3.85 (dd, $J$ = 12.8, 6.2 Hz, 1H), 3.98 (dd, $J$ = 7.3, 3.3 Hz, 1H), 4.09 (t, $J$ = 6.1 Hz, 2H), 4.39−4.54 (m, 1H), 5.39 (br s, 1H), 7.14 (br d, $J$ = 8.8 Hz, 2H), 7.71 (d, $J$ = 7.5 Hz, 1H), 7.77 (br d, $J$ = 8.6 Hz, 2H), 9.0 (br s, 1H), 10.74 (s, 1H). ESI MS: *m/z* (rel intensity) 430.1 (M + H$^+$, 100). Analysis: C, H, N for $C_{17}H_{25}N_3O_7S\cdot0.2H_2O$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-(1-oxy-2(*R*)-hydroxy-3-methylbutyl)-aminopyrrolidine (42).** The title compound was described according to the synthetic sequence described for compound **38**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.79 (d, $J$ = 6.8 Hz, 3H), 0.84 (d, $J$ = 6.9 Hz, 3H), 0.95 (t, $J$ = 7.3 Hz, 3H), 1.39−1.53 (m, 2H), 1.68−1.93 (m, 4H), 2.99 (dd, $J$ = 8.6, 8.6 Hz, 1H), 3.34 (s, 3H), 3.51 (dd, $J$ = 7.9 Hz, 1H), 3.58 (dd, $J$ = 4.7, 4.7 Hz, 1H), 3.98 (dd, $J$ = 8.6, 2.4 Hz, 1H), 4.08 (t, $J$ = 6.4 Hz, 2H), 4.44−4.58 (m, 1H), 5.27 (d, $J$ = 5.3 Hz, 1H), 7.13 (d, $J$ = 9.0, 2H), 7.71 (d, $J$ = 7.7 Hz, 1H), 7.77 (d, $J$ = 8.8 Hz, 2H), 8.99 (s, 1H), 10.73 (s, 1H). ESI MS: *m/z* (rel intensity) 474.8 (M + $NH_4$$^+$, 20), 457.8 (M + H$^+$, 100). Analysis: C, H, N for $C_{20}H_{31}N_3O_7S\cdot0.3H_2O$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-*N*-(1-oxy-2(*R*)-hydroxy-4-methylpentyl)-aminopyrrolidine (43).** The title compound was described according to the synthetic sequence described for compound **38**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.84 (br d, $J$ = 6.4 Hz, 6H), 0.95 (t, $J$ = 8.2 Hz, 3H), 1.23−1.39 (m, 2H), 1.39−1.53 (m 2H), 1.64, 1.92 (m, 4H), 2.87 (dd, $J$ = 8.3, 8.3 Hz, 1H), 3.51 (dd, $J$ = 7.7 Hz, 1H), 3.71−3.79 (m, 1H), 3.97 (dd, $J$ = 5.8, 0.8 Hz, 1H), 4.08 (t, $J$ = 6.1 Hz, 2H), 4.39−4.54 (m 1H), 5.30 (d, $J$ = 5.5 Hz, 1H), 7.14 (d, $J$ = 7.9 Hz, 2H), 7.73 (d, $J$ = 8.6 Hz, 1H), 7.76 (d, $J$ = 8.1 Hz, 2H), 9.00 (s, 1H), 10.73 (s, 1H). ESI MS: *m/z* (rel intensity) 489.2 ([M + $NH_4$]$^+$, 10), 472.0 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{21}H_{33}N_3O_7S\cdot0.5H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(piperidin-1*N*-yl)pyrrolidine (44).** The compound was prepared according to the synthetic sequence described for compound **48** to give a pale orange solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.27−1.43 (m, 6H), 1.52 (ddd, $J$ = 12.5, 9.9, 9.9 Hz, 1H), 1.89−1.96 (m, 1H), 2.17−2.31 (m, 4H), 2.74 (dd, $J$ = 8.7, 8.7 Hz, 1H), 2.94−3.08 (m, 1H), 3.63 (dd, $J$ = 8.7, 6.8 Hz, 1H), 3.87 (s, 3H), 3.98 (d, $J$ = 8.7 Hz, 1H), 7.16 (br d, $J$ = 9.0 Hz, 2H), 7.80 (br d, $J$ = 9.0 Hz, 2H). ESI MS: *m/z* (rel intensity) 384 (M$^+$ + H, 100), 406 (M$^+$ + Na, 82), 422 (M$^+$ + K, 65). Analysis: C, H, N for $C_{17}H_{25}N_3O_5S$.

**1*N*-(4-*n*-Propoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(piperidin-1*N*-yl)pyrrolidine (45).** The compound was prepared according to the synthetic sequence described for compound **48** to give a pale orange solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.99 (t, $J$ = 7.4 Hz, 3H), 1.26−1.54 (m, 7H), 1.70−1.83 (m, 2H), 1.90 (dd, $J$ = 12.3, 6.0 Hz, 1H), 2.10−2.29 (m, 4H), 2.69 (dd, $J$ = 8.4 Hz, 1H), 2.88−3.01 (m, 1H), 3.59 (dd, $J$ = 7.5 Hz, 1H), 3.98 (d, $J$ = 9.0 Hz, 1H), 4.05 (t, $J$ = 6.4 Hz, 2H), 7.15 (br d, $J$ = 8.8 Hz, 2H), 7.78 (br d, $J$ = 8.8 hz, 2H), 8.96 (s, 1H), 10.69 (s, 1H). ESI MS: *m/z* (rel intensity) 412.1 (M$^+$ + H, 100). Analysis: C, H, N for $C_{19}H_{29}N_3O_5S$.

**1*N*-(4-*n*-Pentylbenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(piperadin-1*N*-yl)pyrrolidine (46).** The compound was prepared according to the synthetic sequence described for compound **48**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.87 (t, $J$ = 6.6 Hz, 3H), 1.23−1.40 (m, 10H), 1.48 (ddd, $J$ = 12.1, 9.5, 9.5 Hz, 1H), 1.55−1.67 (m, 2H), 1.89 (dd, $J$ = 11.7, 5.5 Hz, 1H), 2.08−2.25 (m, 4H), 2.69 (t, $J$ = 7.7 Hz, 2H), 2.74 (dd, $J$ = 8.6, 8.6 Hz, 1H), 3.60 (dd, $J$ = 7.3, 8.0 Hz, 1H), 3.98 (d, $J$ = 7.69 Hz, 1H), 7.47 (d, $J$ = 7.9 Hz, 2H), 7.76 (d, $J$ = 7.3 Hz, 2H), 8.97 (s, 1H), 10.70 (s, 1H). ESI MS: *m/z* (rel intensity) 424.1 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{21}H_{33}N_3O_4S$.

**1*N*-(4-Phenyloxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(piperadin-1*N*-yl)pyrrolidine (47).** The compound was prepared according to the synthetic sequence described for compound **48**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.25−1.43 (m, 6H), 1.58 (ddd, $J$ = 12.3, 9.9, 9.9 Hz, 1H), 1.92 (dd, $J$ = 12.1, 5.5 Hz, 1H), 2.12−2.29 (m, 4H), 2.78 (dd, $J$ =

8.3, 8.3 Hz, 1H), 2.90−3.02 (m, 1H), 3.61 (dd, $J$ = 8.1, 7.0 Hz, 1H), 3.98 (d, $J$ = 9.2 Hz, 1H), 7.12−7.21 (m, 2H), 7.29 (dd, $J$ = 7.3, 7.3 Hz, 1H), 7.49 (dd, 7.7, 7.7 Hz, 2H), 7.85 (dd, $J$ = 8.8, 1.5 Hz, 2H), 8.97 (s, 1H), 10.70 (s, 1H). ESI MS: *m/z* (rel intensity) 446.1 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{22}H_{27}N_3O_5S\cdot0.3H_2O$.

**1*N*-(4-Methoxyphenylsulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(morpholin-1*N*-yl)pyrrolidine (48).** The starting methyl ester **10** (310 mg, 0.86 mmol) was treated with $NH_2OK$ (2 mL, 1.25 M in methalol) in 4 mL of methanol and stirred overnight at room temperature. The material was then condensed and partitioned between EtOAC and dilute $NaHCO_3$. The organic layer was then dried over $MgSO_4$, filtered and evaporated. The residue was adsorbed onto silica and eluted through a flash silica column with EtOAC:MeOH (1:0 to 4:1) to give 205 mg (66%) of material which was puffed to a white solid under vacuum and not recrystallized. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.53 (ddd, $J$ = 12.5, 8.8, 8.8 Hz, 1H), 1.88−1.96 (m, 1H), 2.17−2.31 (m, 4H), 2.78 (dd, $J$ = 8.4, 8.4 Hz, 1H), 2.90−3.00 (m, 1H), 3.41−3.46 (m, 4H), 3.59 (dd, $J$ = 9.0, 6.4 Hz, 1H), 3.88 (s, 3H), 3.98 (d, $J$ = 6.78 Hz, 1H), 7.16 (br d, $J$ = 9.0 Hz, 2H), 7.81 (br d, $J$ = 9.0 Hz, 2H). ESI MS: *m/z* (rel intensity) 408.1 ([M + $NH_4$]$^+$, 7), 386.1 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{16}H_{23}N_3O_6S\cdot0.6H_2O$.

**1*N*-(4-*n*-Propoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(morpholin-1*N*-yl)pyrrolidine (49).** The compound was prepared according to the synthetic sequence described for compound **48**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.01 (t, $J$ = 7.3 Hz, 3H), 1.55 (ddd, $J$ = 12.6, 6.1, 6.1 Hz, 1H),1.72−1.84 (m, 2H),), 1.93 (ddd, $J$ = 12.5, 6.6, 2.4 Hz, 1H), 2.17−2.32 (m 4H), 2.78 (dd, $J$ = 8.5, 8.5, Hz, 1H), 2.89−3.00 (m, 1H), 3.41−3.48 (m, 4H), 3.60 (dd, $J$ = 8.8, 6.2 Hz, 1H), 3.97 (dd, $J$ = 8.8, 2.2 Hz, 1H), 4.06 (t, $J$ = 6.6 Hz, 2H), 7.16 (d, $J$ = 9.0 Hz, 2h), 7.79 (d, $J$ = 9.0 Hz, 2H), 8.98 (d, $J$ = 1.5 Hz, 1H), 10.71 (d $J$ = 1.5 Hz, 1H). ESI MS: *m/z* (rel intensity) 414.1 ([M + H]$^+$, 100). Analysis: C,H,N for $C_{18}H_{27}N_3O_6S$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(morpholin-1*N*-yl)pyrrolidine (50).** The compound was prepared according to the synthetic sequence described for compound **48** to give material which was puffed to a white solid under vacuum and not recrystallized. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.96 (t, $J$ = 7.4 Hz, 3H), 1.39−1.59 (m, 3H), 1.69−1.77 (m, 2H), 1.87−1.95 (m, 1H), 2.16−2.31 (m, 4H), 2.77 (dd, $J$ = 8.4, 8.4 Hz, 1H), 2.89−3.00 (m, 1H), 3.40−3.46 (m, 4H), 3.58 (dd, $J$ = 8.6, 6.0 Hz, 1H), 3.97 (dd, $J$ = 8.5, 2.5 Hz, 1H), 4.08 (t, $J$ = 6.4 Hz, 2H), 7.14 (br d, $J$ = 8.8 Hz, 2H), 7.78 (br d, $J$ = 8.9 Hz, 2H). ESI MS: *m/z* (rel intensity) 428.08 ([M + H]$^+$, 100), 450.07 ([M + Na]$^+$, 8), 465.99 ([M + K]$^+$, 15). Analysis: C, H, N for $C_{19}H_{29}N_3O_6S\cdot0.1H_2O$.

**1*N*-(4-*n*-Pentylbenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(morpholin-1*N*-yl)pyrrolidine (51).** The compound was prepared according to the synthetic sequence described for compound **48**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.87 (t, $J$ = 6.3 Hz, 3H), 1.22−1.37 (m, 4H), 1.49−1.67 (m, 3H), 1.91 (br d, $J$ = 12.5 Hz, 1H), 2.14−2.29 (m, 4H), 2.69 (dd, $J$ = 7.5, 7.5 Hz, 1H), 2.80−2.99 (m, 2H), 3.36−3.44 (m, 4H), 3.60 (dd, $J$ = 8.2, 6.2 Hz, 1H), 3.98 (d, $J$ = 7.3 Hz, 1H), 7.46 (d, $J$ = 7.2 Hz, 2H), 7.77 (d, $J$ = 7.0 Hz, 2H), 8.98 (s, 1H), 10.71 (s, 1H). ESI MS: *m/z* (rel intensity) 426.1 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{20}H_{31}N_3O_5S$.

**1*N*-(4-Phenyloxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(morpholin-1*N*-yl)pyrrolidine (52).** The compound was prepared according to the synthetic sequence described for compound **48**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.57−1.72 (m, 1H), 1.87−1.98 (m, 1H), 2.16−2.34 (m, 4H), 2.82−3.00 (m, 2H), 3.38−3.50 (m, 4H), 3.56−3.64 (m, 1H), 3.94−4.01 (m, 1H), 7.11−7.20 (m, 4H), 7.28 (ddd, $J$ = 6.9, 6.9, 0.9 Hz, 1H), 7.49 (ddd, $J$ = 7.6, 7.6, 1.1 Hz, 1H), 7.86 (dd, $J$ = 8.6 Hz, 2H), 8.99 (s, 1H), 10.71 (s, 1H). ESI MS: *m/z* (rel intensity) 448.0 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{19}H_{29}N_3O_6S\cdot0.2H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-(2R)-*N*-hydroxycarboxamido-4(*S*)-(4,4-dioxythiomorpholin-1*N*-yl)pyrrolidine (53).** The compound was prepared according to the synthetic sequence described for compound **48** and recrystallized from EtOAC:methanol to white crystals. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.62 (ddd, $J$ = 12.6, 9.3, 9.3 Hz, 1H), 1.91−1.99 (m, 1H), 2.72−2.78 (m, 4H), 2.83 (dd, $J$ = 8.4, 8.4 Hz, 1H), 2.94−2.99 (m, 4H), 3.29−3.39 (m, 1H), 3.62 (dd, $J$ = 8.8, 7.2 Hz, 1H), 3.88 (s, 3H), 3.99 (dd, $J$ = 9.0, 2.4 Hz, 1H), 7.16 (br d, $J$ = 8.6 Hz, 2H), 7.82 (ddd, $J$ = 8.6 Hz, 2H), 9.00 (s, 1H), 10.71 (s, 1H). ESI MS: *m/z* (rel intensity) 434.0 ([M + H]$^+$, 100), 456.0 ([M + Na]$^+$, 32). Analysis: C, H, N for $C_{16}H_{23}N_3O_7S_2$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(4,4-dioxythiomorpholin-1*N*-yl)pyrrolidine (54).** The compound was prepared according to the synthetic sequence described for compound **48** to give material which was puffed to a white solid under vacuum and not recrystallized. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.96 (t, $J$ = 7.3 Hz, 3H), 1.39−1.53 (m, 2H), 1.55−1.67 (m1H), 1.69−1.79 (m, 2H), 1.89−2.00 (m, 1H), 2.72−2.87 (m, 5H), 2.93−3.03 (m, 4H), 3.30−3.40 (m, 1H), 3.61 (dd, $J$ = 8.6, 6.2 Hz, 1H), 3.99 (br d, $J$ = 7.0 Hz), 4.09 (t, $J$ = 6.4 Hz, 2), 7.15 (br d, $J$ = 8.6 Hz, 2H), 7.79 (br d, $J$ = 8.6 Hz, 2H). ESI MS: *m/z* (rel intensity) 476.1 ([M + H]$^+$, 100), 498.1 ([M + Na]$^+$, 22). Analysis: C, H, N for $C_{19}H_{29}N_3O_6S_2$.

**1*N*-(4-*n*-Propoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(1-pyrrolidin-1*N*-yl)pyrrolidine (55).** The compound was prepared according to the synthetic sequence described for compound **57** to give a white solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.99 (t, $J$ = 7.3 Hz, 3H), 1.46−1.56 (m, 4H), 1.63 (ddd, $J$ = 12.1, 8.4, 8.4 hz, 1H), 1.69−1.82 (m, 2H), 1.88 (ddd, $J$ = 13.1, 4.0, 4.0 Hz, 1H), 2.25−2.34 (m, 4H), 2.76−2.70 (m, 2H), 3.46−3.55 (m, 1H), 3.96 (dd, $J$ = 8.4, 4.0 Hz, 1H), 4.03 (t, $J$ = 6.4 Hz, 2H), 7.12 (d, $J$ = 8.8 Hz, 2H), 7.78 (d, $J$ = 8.8 Hz, 2H), 8.97 (br s, 1H), 10.69 (s, 1H). ESI MS: *m/z* (rel intensity) 398.1 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{18}H_{27}N_3O_5S\cdot0.2H_2O$.

**1*N*-(4-Fluorophenoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(pyrrolidin-1*N*-yl)pyrrolidine (56).** The compound was prepared according to the synthetic sequence described for compound **57**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.48−1.58 (m, 4H), 1.73 (ddd, $J$ = 12.5, 7.9, 7.9 Hz, 1H), 1.91 (ddd, $J$ = 12.5, 4.9 Hz, 1H), 2.18−2.36 (m, 4H), 2.80−2.88 (m, 1H), 2.95 (dd, $J$ = 9.3, 6.4 Hz, 1H), 3.53 (dd, $J$ = 9.2, 5.3 Hz, 1H), 3.98 (dd, $J$ = 8.2, 4.4 Hz, 1H), 7.13 (d, $J$ = 8.4 Hz, 2H), 7.23 (dd, $J$ = 8.2, 4.8 Hz, 2H), 7.33 (dd, $J$ = 8.2, 8.2 Hz, 2H), 7.85 (d, $J$ = 7.84 Hz, 2H), 8.97 (s, 1H), 10.71 (s, 1H). ESI MS: *m/z* (rel intensity) 449.9 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{21}H_{24}FN_3O_5S\cdot0.4H_2O$.

**1*N*-(4-Phenyloxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(pyrrolidin-1*N*-yl)pyrrolidine (57).** The starting methyl ester **16** (752 mg, 1.75 mmol) was converted to the title hydroxamic acid as described for compound **48** and purified by recrystallizing from EtOAc:MeOH (∼10:1) to give 320 mg (43%) of white powder. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.50−1.58 (m, 4H), 1.69−1.80 (m, 1H), 1.87−1.75 (m, 1H), 2.19−2.37 (m, 4H), 2.80−2.90 (m, 1H), 2.76 (dd, $J$ = 9.3, 6.2 Hz, 1H), 3.53 (dd, $J$ = 9.5, 6.2 Hz, 1H), 3.88 (dd, $J$ = 7.7, 4.8 Hz, 1H), 7.10−7.19 (m, 4H), 7.29 (ddd, $J$ = 7.3, 7.3, 1.3 Hz, 1H), 7.50 (dd, $J$ = 7.1, 7.1 Hz, 2H), 7.86 (dd, $J$ = 8.6, 1.7 Hz, 2H), 8.99 (br s, 1H), 10.71 (br s, 1H). ESI MS: *m/z* (rel intensity) 432.2 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{21}H_{25}N_3O_5S\cdot0.2H_2O$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(γ-sultam-1*N*-yl)pyrrolidine (58).** Compound **24** was prepared as described for compound **23** to give a white solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.83−2.17 (m, 4H), 2.91−3.03 (m, 2H), 3.06 (dd, $J$ = 9.5, 8.1 Hz, 1H), 3.12−3.22 (m, 2H), 2.79−3.89 (m, 2H), 3.59 (dd, $J$ = 9.7, 6.8 Hz, 1H), 3.87 (s, 3H), 3.92−4.03 (m, 1H), 4.05 (dd, $J$ = 8.4, 2.7 Hz, 1H), 7.17 (br d, $J$ = 9.0 Hz, 2H), 7.82 (br d, $J$ = 9.0 Hz, 2H), 9.02 (s, 1H), 10.81 (s, 1H). ESI MS: *m/z* (rel intensity) 420.0 ([M + H]$^+$, 100), 437 ([M + $NH_4$]$^+$, 20). Analysis: C, H, N for $C_{15}H_{21}N_3O_7S_2$.

**1*N*-(4-*n*-Propoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(γ-sultam-1*N*-yl)pyrrolidine (59).** Com-

pound **24** was prepared as described for compound **23** to give a white solid. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.00 (t, $J$ = 7.4 Hz, 3H), 1.70−1.83 (m, 2H), 1.84−2.15 (m, 4H), 2.91−3.24 (m, 6H), 3.60 (dd, $J$ = 9.7, 6.8 Hz, 1H), 3.92−4.09 (m, 3H), 7.16 (d, $J$ = 9.0 Hz, 2H), 7.80 (d, $J$ = 9.0 Hz, 2H), 9.04 (s, 1H), 10.82 (s, 1H). ESI MS: $m/z$ (rel intensity) 448.0 ([M + H]$^+$, 90), 465.1 ([M + $NH_4$]$^+$, 100). Analysis: C, H, N for $C_{17}H_{25}N_3O_7S_2$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(γ-sultam-1*N*-yl)pyrrolidine (60).** The compound was prepared according to the synthetic sequence described for compound **59**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.95 (t, $J$ = 7.4 Hz, 3H), 1.39−1.52 (m, 2H), 1.68−1.79 (m, 2H), 1.83−2.18 (m, 4H), 2.91−3.23 (m, 6H), 3.59 (dd, $J$ = 9.7, 6.8 Hz, 1H), 3.92−4.12 (m, 3H), 7.15 (br d, $J$ = 9.0 Hz, 2H), 7.80 (br d, $J$ = 9.0 Hz, 2H), 9.04 (s, 1H), 10.81 (d, $J$ = 1.1 Hz, 1H). ESI MS: $m/z$ (rel intensity) 462.0 ([M + H]$^+$, 90), 479.1 ([M + $NH_4$]$^+$, 100). Analysis: C, H, N for $C_{18}H_{27}N_3O_7S_2$.

**1*N*-(4-Methoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-methylhydantoin-1*N*-yl)pyrrolidine (61).** The starting methyl ester **9** (500 mg, 1.22 mmol) was taken in 7 mL of methanol/tetrahydrofuran (1:1), and treated with $NH_2OK$ (2.5 mL, 1.25 M in methanol) and stirred overnight. The following morning, dry silica (1.5 mL) was added to the mixture and the solvent removed under vacuum. The dry silica was poured on top of a flash silica column which was subsequently eluted with ethyl acetate followed with ethyl acetate (9:1) to give a clear glass which was puffed to a foamy solid by slight heating under vacuum. The product was recrystallized from cold methanol to give 428 mg (85%) of white powder. $^1$H NMR: (DMSO-$d_6$, 300 mHz) $\delta$ 1.82−1.88 (m, 1H), 2.39−2.46 (m, 1H), 2.78 (s, 3H), 3.49 (d, $J$ = 3.49 Hz, 2H), 3.81 (s, 2H), 3.85 (s, 3H), 4.10 (d, $J$ = 8.6 Hz, 1H), 4.74−4.80 (m, 1H), 7.16 (d, $J$ = 8.79 Hz, 2H), 7.78 (d, $J$ = 8.8 Hz, 2H), 9.05 (s, 1H). ESI MS: $m/z$ (rel intensity) 413.0 ([M + H]$^+$, 100), 430.0 ([M + $NH_4$]$^+$, 55). Analysis: C, H, N for $C_{16}H_{20}N_4O_7S\cdot 1.1H_2O$.

**1*N*-(4-Ethoxybenzenesulfony)l-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-methylhydantoin-1*N*-yl)pyrrolidine (62).** The title compound was prepared as described for compound **61**. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.37 (t, $J$ = 7.0 Hz, 3H), 1.84 (dd, $J$ = 11.0, 7.3 Hz, 1H), 2.43 (ddd, $J$ = 11.4, 11.4, 10.8 Hz, 1H), 2.78 (s, 3H), 3.47 (s, 1H), 3.49 (s, 1H), 3.80 (s, 2H), 4.08 (d, $J$ = 7.5 Hz, 1H), 4.14 (q, $J$ = 7.0 Hz, 2H), 4.70−4.82 (m, 1H), 7.14 (d, $J$ = 9.0 Hz, 2H), 7.76 (d, $J$ = 9.0 Hz, 2H), 9.03 (br s, 1H), 10.80 (br s, 1H). ESI MS: $m/z$ (rel intensity) 427.0 ([M + H]$^+$, 100), 444.0 ([M + $NH_4$]$^+$, 12), 449.0 ([M + Na]$^+$, 8). Analysis: C, H, N for $C_{17}H_{22}N_4O_7S\cdot 0.2H_2O$.

**1*N*-(4-*n*-Propoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-methylhydantoin-1*N*-yl)pyrrolidine (63).** The title compound was prepared as described for compound **61**. The product was recrystallized from cold methanol to give white powder. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.01 (t, $J$ = 7.4 Hz, 1H), 1.73−1.89 (m, 3H), 2.43 (dd, $J$ = 10.2, 10.2 Hz, 1H), 2.78 (s, 3H), 3.47 (s, 1H), 3.50 (s, 1H), 3.80 (s, 2H), 4.01−4.12 (m, 3H), 4.69−4.82 (m, 1H), 7.14 (d, $J$ = 8.8 Hz, 2H), 7.75 (d, $J$ = 8.8 Hz, 2H), 9.05 (br s, 1H), 10.80 (br s, 1H). ESI MS: $m/z$ (rel intensity) 458.1 ([M + $NH_4$]$^+$, 15), 441.0 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{18}H_{24}N_4O_7S\cdot 0.5H_2O$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-methylhydantoin-1*N*-yl)pyrrolidine (64).** The title compound was prepared as described for compound **61**. The product was recrystallized from cold methanol to give white powder. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.95 (dd, $J$ = 8.2, 1.10 Hz, 3H), 1.46 (dd, $J$ = 14.8, 7.3 Hz, 2H), 1.70−1.87 (m, 2H), 2.39−2.48 (m, 1H), 2.78 (s, 3H), 3.48 (d, $J$ = 8.4 Hz, 2H), 3.80 (s, 2H), 4.00−4.73 (m, 3H), 4.74−4.79(m, 1H), 7.14 (d, $J$ = 8.8 Hz, 2H), 7.76 (d, $J$ = 8.6 Hz, 2H). ESI MS: $m/z$ (rel intensity) 455.0 ([M + H]$^+$, 100), 472.0 ([M + $NH_4$]$^+$, 50). Analysis: C, H, N for $C_{19}H_{26}N_4O_7S\cdot 0.4H_2O$.

**1*N*-(4-Isobutoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-methylhydantoin-1*N*-yl)pyrrolidine (65).** The compound was prepared according to the synthetic sequence described for compound **61** to give a white powder. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.01 (d, $J$ = 6.8 Hz, 6H), 1.84 (dd, $J$ = 11.2, 7.7 Hz, 1H), 2.00−2.13 (m, 1H), 2.44 (ddd, $J$ = 13.0, 9.9, 9.9 Hz, 1H), 2.78 (s, 3H), 3.48 (d, $J$ = 8.2 Hz, 2H), 3.80 (s, 2H), 3.86 (d, $J$ = 6.4 Hz, 2H), 4.08 (d, $J$ = 8.6 Hz, 1H), 4.70−4.83 (m, 1H), 7.15 (br d, $J$ = 8.8 Hz, 2H), 7.76 (br d, $J$ = 8.8 Hz, 2H), 9.12 (br s, 1H), 10.78 (br s, 1H). ESI MS: $m/z$ (rel intensity) 455.1 ([M + H]$^+$, 100), 472.1 ([M$^+$ + $NH_4$]$^+$, 15). Analysis: C, H, N for $C_{19}H_{26}N_4O_7S\cdot 0.7H_2O$.

**1*N*-(4-(2-Methoxyethoxy)benzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-methylhydantoin-1*N*-yl)pyrrolidine (66).** The compound was prepared according to the synthetic sequence described for compound **61**. The product was recrystallized from cold methanol to give a white powder. $^1$H NMR: (DMSO-$d_6$,300 mHz) $\delta$ 1.80−1.87 (m, 1H), 2.37−2.45 (m, 1H), 2.77 (s, 3H), 3.32 (s, 3H), 3.48 (d, $J$ = 8.3, 2H), 3.68−3.71 (m, 2H), 3.79 (s, 2H), 4.11−4.22 (m, 2H), 4.72−4.78 (m, 1H), 7.14−7.17 (m, 2H), 7.74−7.77 (m, 2H). ESI MS: $m/z$ (rel intensity) 457.08 ([M + H]$^+$, 100), 474.09 ([M + $NH_4$]$^+$, 60). Analysis: C, H, N for $C_{18}H_{24}N_4O_8S\cdot 1.2H_2O$.

**1*N*-(4-Phenoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-methylhydantoin-1*N*-yl)pyrrolidine (67).** The compound was prepared according to the synthetic sequence described for compound **61**. The product was recrystallized from cold methanol to give a white powder. $_1$H NMR: (DMSO-$d_6$, 300 mHz) $\delta$ 1.87 (dd, $J$ = 11.5, 6.6 Hz, 1H), 2.36−2.47 (m, 1 H), 2.8 (s, 3H), 3.48 (d, $J$ = 8.9, 2H), 3.83 (s, 2H), 4.18 (br s, 1H), 4.79−4.85 (m, 1H), 7.16−7.19 (m, 4H), 7.26 (t, $J$ = 7.5 Hz, 1H), 7.45−7.50 (m, 2H), 7.8 (d, $J$ = 8.2, 2H). ESI MS: $m/z$ (rel intensity) 475.09 ([M + H]$^+$, 100), 497.07 ([M + $NH_4$]$^+$, 60). Analysis: C, H, N for $C_{21}H_{22}N_4O_7S\cdot 1.9H_2O$.

**1*N*-(4-Pyridin-4-yloxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-(3*N*-methylhydantoin-1*N*-yl)pyrrolidine (68).** The compound was prepared according to the synthetic sequence described for compound **61** to give a white solid. $^1$H NMR: (DMSO-$d_6$, 300 mHz) $\delta$ 1.88 (dd, $J$ = 12.4, 7.1 Hz, 1H), 2.41 (ddd, $J$ = 10.9, 10.9, 10.6 Hz, 1H), 2.80 (s, 3H), 3.46 (dd, $J$ = 8.9, 8.9 Hz, 1H), 5.56 (dd, $J$ = 8.4, 8.4 Hz, 1H), 3.84 (s, 2H), 4.23 (d, $J$ = 8.4 Hz, 1H0, 4.75−4.89 (m, 1H), 7.11 (dd, $J$ = 4.8, 1.7 Hz, 2H), 7.42 (d, $J$ = 8.8 Hz, 2H), 7.93 (d, $J$ = 8.8 Hz, 2H), 8.53 (dd, $J$ = 4.8, 1.5 Hz, 2H), 9.25 (br s, 1H). ESI MS: $m/z$ (rel intensity) 476.0 ([M + H]$^+$, 100). Analysis: C, H, N for $C_{20}H_{21}N_5O_7S\cdot 1.2H_2O$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(4*S*-methylhydantoin-1*N*-yl)pyrrolidine (69).** The compound was prepared according to the synthetic sequence described for compound **61**. The product was recrystallized from cold methanol to give a white powder. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.95 (t, $J$ = 7.3 Hz, 3H), 1.18 (d, $J$ = 6.9 Hz, 3H), 1.46 (dd, $J$ = 15.2, 7.5 Hz, 2H), 1.70−1.88 (m, 3H), 2.41 (m, 1H), 3.33 (s, 3H), 3.48 (d, $J$ = 8.43 Hz, 2H), 3.91−3.96 (m, 1H), 4.07−4.10 (m, 3H), 7.14 (d, $J$ = 9.0 Hz, 2H), 7.76 (d, $J$ = 8.9 Hz, 2H), 8.22 (s,1H). ESI MS: $m/z$ (rel intensity) 455.0 ($M^+$ + H, 100), 472.0 ($M^+$ + $NH_3$, 30). HRMS: calcd for $C_{19}H_{27}N_4O_7S$, 455.1601; found, 455.1600.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(4-dimethylhydantoin-1*N*-yl)pyrrolidine (70).** The compound was prepared according to the synthetic sequence described for compound **61**. The product was recrystallized from cold methanol to give a white powder. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.95 (t, $J$ = 7.36 Hz, 3H), 1.25 (s, 6H), 1.46 (dd, $J$ = 15.2, 7.5 Hz, 2H), 1.70−1.76 (m, 2H), 1.84−1.90 (m, 1H), 2.51−2.52 (m, 1H), 3.34 (s, 3H), 3.46−3.50 (m, 2H), 4.08 (t, $J$ = 6.4, 3H), 7.14 (d, $J$ = 9.0 Hz, 2H), 7.76 (d, $J$ = 9.0 Hz, 2H), 8.31 (s,1H). ESI MS: $m/z$ (rel intensity) 469.0 ([M + H]$^+$, 100), 486.0 ([M + $NH_4$]$^+$, 10). Analysis: C, H, N for $C_{20}H_{28}N_4O_7S\cdot 0.7H_2O$.

**1*N*-(4-*n*-Propoxyphenylsulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-allylhydantoin-1*N*-yl)pyrrolidine (71).** The compound was prepared according to the synthetic sequence described for compound **61** to give a white powder. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.01 (t, $J$ = 7.3 Hz, 3H), 1.74−1.92 (m, 3H), 2.45 (ddd, $J$ = 11.0, 10.7, 10.7 Hz, 1H), 3.50 (d, $J$ = 8.6, 2H), 3.78 (s, 2H), 3.82−3.88 (m, 2H),

4.01−4.12 (m, 3H), 4.72−4.85 (m, 1H), 5.14−5.27 (m, 2H), 5.69−5.83 (m, 1H), 7.15 (dd, $J$ = 9.0, 1.8 Hz, 2H), 7.76 (dd, $J$ = 8.8, 1.8 Hz, 2H), 9.04 (br s, 1H), 10.78 (s, 1H). ESI MS: *m/z* (rel intensity) 467.0 ($[M + H]^+$, 100), 484.0 ($[M + NH_4]^+$, 10). Analysis: C, H, N for $C_{20}H_{26}N_4O_7S \cdot 0.5H_2O$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-allylhydantoin-1*N*-yl)pyrrolidine (72).** The compound was prepared according to the synthetic sequence described for compound **61**. The product was recrystallized from cold methanol to give a white powder. $_1$H NMR: (DMSO-$d_6$,300 mHz) $\delta$ 0.83−0.99 (m, 4H), 1.46 (dd, $J$ = 15.4, 7.7 Hz, 2H), 1.71−1.77 (m, 1H), 2.38−2.45 (m, 1H), 3.50 (d, $J$ = 8.2, 2H), 3.77 (s, 2H), 3.85 (m, 2H), 4.07−4.11 (m, 3H), 5.16−5.25 (m, 2H), 5.72−5.80 (m, 1H), 7.13 (dd, $J$ = 9.0, 2.0 Hz, 2H), 7.76 (dd, $J$ = 9.0, 1.8 Hz, 2H). ESI MS: *m/z* (rel intensity) 481.2 ($[M + H]^+$, 100), 498.2 ($[M + NH_4]^+$, 60). Analysis: C, H, N for $C_{21}H_{28}N_4O_7S$.

**1*N*-(4-(2-Methoxyethoxy)benzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-allylhydantoin-1*N*-yl)-pyrrolidine (73).** The compound was prepared according to the synthetic sequence described for compound **61** to give a white powder. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 1.86 (dd, $J$ = 11.4, 7.3 Hz, 1H), 2.44 (ddd, $J$ = 10.1, 10.1, 9.3 Hz, 1H), 3.34 (s, 3H), 3.48 (d, $J$ = 9.2 Hz, 1H), 3.54 (d, $J$ = 9.3 Hz, 1H), 3.68−3.74 (m, 2H), 3.77 (s, 2H), 3.85 (br d, $J$ = 5.7 Hz, 2H), 4.10 (d, $J$ = 9.0 Hz, 1H), 4.23 (dd, $J$ = 4.4, 4.2 Hz, 2H), 4.72−4.84 (m, 1H), 5.15−5.27 (m, 2H), 5.69−5.83 (m, 1H), 7.17 (d, $J$ = 8.8 Hz, 2H), 7.77 (d, $J$ = 9.0 Hz, 2H), 9.05 (br s, 1H), 10.82 (br s, 1H). ESI MS: *m/z* (rel intensity) 500.1 ($[M + NH_4]^+$, 15), 483.1 ($[M + H]^+$, 100), 391.2 (20). Analysis: C, H, N for $C_{20}H_{28}N_4O_8S \cdot 0.5H_2O$.

**1*N*-(4-*n*-Butoxybenzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-*n*-propylhydantoin-1*N*-yl)pyrrolidine (74).** The compound was prepared according to the synthetic sequence described for compound **61**. The product was recrystallized from cold methanol to give a white powder. $^1$H NMR: (DMSO-$d_6$, 300 mHz) $\delta$ 0.81 (t, $J$ = 7.3 Hz, 3H), 0.95 (t, $J$ = 7.4 Hz, 3H), 1.39−1.53 (m, 4H), 1.69−1.80 (m, 2H), 1.85 (dd, $J$ = 12.4, 7.1 Hz, 1H), 2.38−2.47 (m, 1H), 3.15 (t, $J$ = 7.1 Hz, 2H), 3.43 (d, $J$ = 9.2 Hz, 1H), 3.51 (d, $J$ = 8.8 Hz, 1H), 3.82 (s, 2H), 4.09 (t, $J$ = 5.7 Hz, 2H), 4.50−4.83 (m, 1H), 7.14 (br d, $J$ = 8.2 Hz, 2H), 7.76 (br d, $J$ = 8.4 Hz, 2H), 9.04 (br s, 1H), 10.81 (br s, 1H). ESI MS: *m/z* (rel intensity) 483.1 ($[M + H]^+$, 100), 500.1 ($[M + NH_4]^+$, 60). Analysis: C, H, N for $C_{21}H_{30}N_4O_7S$.

**1*N*-(4-(2-Methoxyethoxy)benzenesulfonyl)-2(*R*)-*N*-hydroxycarboxamido-4(*S*)-1*N*-(3*N*-*n*-propylhydantoin-1*N*-yl)pyrrolidine (75).** The compound was prepared according to the synthetic sequence described for compound **61** to give a white powder. $^1$H NMR: (DMSO-$d_6$, 300 MHz) $\delta$ 0.83 (t, $J$ = 7.4 Hz, 3H), 1.39−1.53 (m, 2H), 1.86 (dd, $J$ = 12.6, 7.7 Hz, 1H), 2.45 (ddd, $J$ = 11.7, 10.2, 10.2 Hz, 1H), 3.15 (t, $J$ = 7.1 Hz, 2H), 3.33 (s, 3H), 3.50 (d, $J$ = 8.4 Hz, 2H), 3.71 (dd, $J$ = 4.8, 3.7 Hz, 2H), 3.83 (s, 2H), 4.10 (d, $J$ = 8.8 Hz, 1H), 4.23 (dd, $J$ = 4.9, 3.3 Hz, 2H), 4.71−4.84 (m, 1H0, 7.17 (br d, $J$ = 8.8 Hz, 2H), 7.77 (br d, $J$ = 8.6 Hz, 2H), 9.06 (br s, 1H), 10.77 (br s, 1H). ESI MS: *m/z* (rel intensity) 485.0 ($[M + H]^+$, 100), 502.0 ($M + NH_4]^+$, 10). Analysis: C, H, N for $C_{20}H_{28}N_4O_8S$.

**MMP Inhibition Assay.** The preparation of the human recombinant MMPs used in these studies has been described previously.[17] MMP inhibitors were tested for their ability to inhibit human MMPs using the quenched fluorescence assay.[21] This assay was modified to fit a 96-well format to increase the throughput. Assays for MMP-1, -3, -7, -8 and -13 employed human recombinant truncated enzymes. The optimal amount of each enzyme to produce significant and reproducible substrate cleavage was determined in preliminary experiments. Assays for MMP-2 and -9 utilized human recombinant full length enzymes. MMP-2 was activated by incubating proMMP-2 with APMA for 45 min. The final concentration of MMP-2 in the assay mixture was 1 nM. ProMMP-9 was activated with MMP-3 (ratio 20:1) for 2 h and diluted to a final assay concentration of 0.75 nM. The final concentration of MMP-3 in the assay was 0.038 nM. The low concentration of MMP-3 in the final MMP-9 dilution did not contribute to the rate of substrate cleavage as assessed by control experiments with 0.038 nM MMP-3. MMP-1, -3, -7, -8, and -13 were used at final concentrations of 8, 16, 2, 4 and 0.5 nM, respectively. The MMP assays was performed using the fluorogenic substrate Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-$NH_2$ at a concentration of 4 $\mu$M at 25 °C. The assay buffer was 50 mM Tris, pH 7.5, 0.2 M NaCl, 5 mM $CaCl_2$ and 0.02% Brij-35. The increase in fluorescence due to cleavage of the substrate (Gly-Leu bond) was monitored kinetically for 30 min with a BMG Fluostar fluorescence plate reader ($\lambda_{ex}$ 328 nm, $\lambda_{em}$ 393 nm). Each 96-well microtiter plate contained 100 $\mu$L of substrate and 50 $\mu$L of enzyme in each well. 50 $\mu$L of MMP inhibitor was added to each well (except for positive control) to give a final volume of 200 $\mu$L/well. MMP inhibitors were tested at 8 different concentrations and an $IC_{50}$ was calculated using the formula: $V_i/V_o = 1/(1 + [I]/IC_{50})$, where $V_i$ is the initial velocity of substrate cleavage in the presence of inhibitor at concentration [I] and $V_o$ is the initial velocity in the absence of inhibitor.

**X-ray Crystallography with Truncated Stromelysin.** A truncated form of stromelysin containing the catalytic domain with residues 83−255 was crystallized as described.[32] 1 mM compound **24** was added to the crystal hanging drop for 4.5 h. Data were then collected at the IMCA beamline at the Advanced Photon Source in the Argonne National Laboratory on a Mar-Research 165-mm CCD detector. These data were processed using the HKL program. The structure was solved and refined to 1.72 Å using CCP4/XPLOR. The stromelysin−**24** complex structure has been deposited with the Protein Data Bank.[24]

**Iodoacetate-Induced Arthritis Model.** Sprague−Dawley male rats weighing 220−230 g (Harlan, Indianapolis, IN) were housed singly in wire cages in sanitary ventilated animal rooms with controlled temperature, humidity and regular light cycles. Rodent chow (Ralston-Purina, Richmond, IN) and water were allowed ad libitum. Animals were acclimated for 1 week before use.

Arthritis was induced by a single intraacticular injection of iodoacetate into the knee joint of rats anesthetized using 3:1 $CO_2/O_2$. A 10 mg/mL concentration of monosodium iodoacetate (MIA) (Aldrich Chemical Co., Milwaukee, WI) was prepared using injectable saline as the vehicle. After appropriate anesthesia, each rat was positioned on their back and the left leg was flexed 90° at the knee. The patellar ligament was palpated below the patella and the injection was made into this region. Each rat received 0.25 mL intraarticular injection into the left knee using a glass gastight syringe with a 27 gauge 0.5-in. needle. Care was taken not to advance the needle in too far into the cruciate ligaments.

Animals were dosed with the inhibitor twice daily at 12-h intervals (b.i.d.) for the first 7 days after iodoacetate injection. Vehicle control and MMP inhibitor treated groups consisted of 15 animals each. Animals were sacrificed 21 days after iodoacetate injection and the left knee joint was immediately disarticulated and fixed in 10% buffered formalin for 24−48 h prior to capturing the image.

After fixation, an image of the tibial cartilage surface was captured using an Optimas image analysis system (Optimas, Media Cybernetics LP, Silver Spring, MA). The tibial plateau was utilized for image analysis because it provided a relatively flat surface compared to the femoral condyles allowing the image analysis camera to focus on the entire cartilage surface. The image was used for grading the severity of damage. Cartilage damage was assessed by three independent observers in a blinded manner using a scale of 0−4 of increasing severity (0 = normal; 4 = maximum severity).

**Statistical Analysis.** Data were analyzed using a nonparametric procedure (Wilcoxon rank sum). The data are expressed as the mean of inhibition of joint damage relative to the vehicle-treated control group. Statistical differences from the vehicle treated control ($p < 0.05$) are denoted with an asterisk.

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