Design and Synthesis of Matrix Metalloproteinase Inhibitors Guided by Molecular Modeling. Picking the S_1 Pocket Using Conformationally Constrained Inhibitors

Stephen Hanessian,* D. Bruce MacKay, and Nicolas Moitessier

Department of Chemistry, Université de Montréal, C. P. 6128, Succursale Centre-Ville, Montréal, P. Q., Canada H3C 3J7

Received March 3, 2001

Conformationally constrained MMP inhibitors based on a D-proline scaffold were designed using AutoDock as a modeling program. Thus a family of D-proline hydroxamic acids, having differentiated functionality at the site of binding to the S_1 pocket, was synthesized. Biological evaluation showed low nanomolar activity and modest selectivity toward different MMP subclasses, delineating the importance of binding to the S_1 pocket for both activity and selectivity.

Introduction

The matrix metalloproteinases (MMPs) are recognized as promising drug targets as evidenced by the disclosure of several potent inhibitors in recent years.[1] MMP inhibitors can be roughly organized into two categories, namely succinate-type structures, exemplified by Batimastat (**1**)[2] and Ro32-3555 (**2**),[3] and sulfonamides, including CGS 27023A (**3**)[4] and **4**[5] (Figure 1). X-ray crystallography and NMR conformational studies have been used extensively to better understand the binding of inhibitors to these enzymes. For instance, CGS 27023A (**3**) complexed with MMP-3 was studied by NMR,[6] and the tertiary structure of MMP-8 cocrystallized with **1** has been elucidated by X-ray crystallography.[7] Although many broad spectrum MMP inhibitors have been disclosed, selectivity toward specific MMP subtypes remains an important issue. We now report the design, synthesis, and in vitro MMP inhibitory activity of conformationally constrained hydroxamic acids related to D-proline.

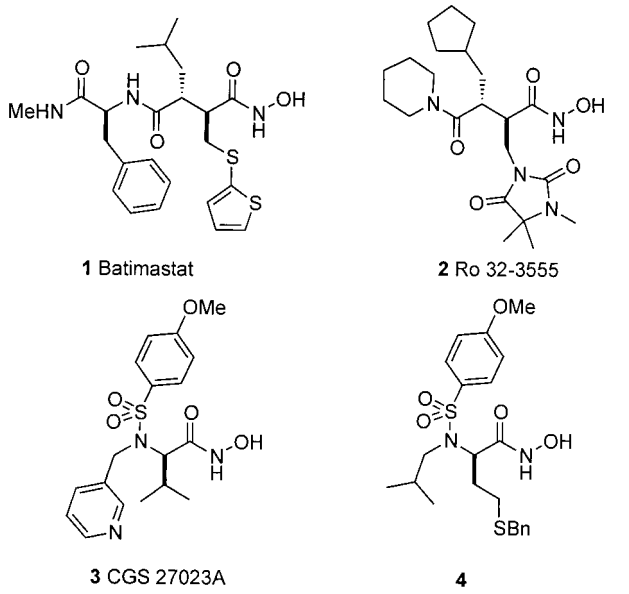


Figure 1. MMP inhibitors.

Results and Discussion

Molecular Modeling and Design. Previous studies have shown that selectivity can be achieved by optimizing the length of the P_1' subsite according to the difference in depth of the S_1' pocket for different MMP subtypes.[8] As observed from X-ray crystal structures,[7,9] the S_1' pocket is long and narrow for MMP-2, MMP-3, and MMP-8, and short and narrow for MMP-1 and MMP-9. By contrast, less information is available concerning the exploitation the S_1 pocket for selectivity purposes.

A survey of reported X-ray crystallographic structures of MMP−inhibitor complexes[7,9] revealed that although the tertiary structures were quite similar, a few mutations of amino acids occurred at the S_1 pocket (Table 1).[10] For example, MMP-1 and MMP-8 featured the same His, Phe, Ser triad of amino acids in this pocket. Similarly, His, Phe, Tyr were found in MMP-2, MMP-9, and MMP-13, while MMP-3 presented a distinct combination of amino acids (His, Tyr, Tyr). It is possible that these differences, which are mainly related to the aromaticity and hydrophobicity of these side chains, could reflect on inhibitor binding and enzymatic activity.

Table 1. Amino Acids Present in the S_1' Pocket of MMPs

MMPs	aa 1	aa 2	aa 3
MMP-1	His-183	Phe-185	Ser-172
MMP-8	His-162	Phe-164	Ser-151
MMP-2	His-166	Phe-168	Tyr-155
MMP-9	His-183	Phe-185	Tyr-172
MMP-13	His-187	Phe-189	Tyr-176
MMP-3	His-166	Tyr-168	Tyr-155

Previous studies in our laboratories were concerned with probing the S_1, S_1', and S_2' pockets with acyclic inhibitors such as **4** and uncovered subnanomolar inhibition of some MMPs.[5] In an effort to further improve our understanding of the bioactive conformation of such acyclic motifs and to validate the potential for selectivity at the S_1 pocket, we turned our attention to a constrained scaffold. Using the AutoDock suite of molecular modeling programs,[11] we designed the D-

* To whom correspondence should be addressed. Fax: (514) 343-5728. Tel: (514) 343-6738. E-mail: stephen.hanessian@umontreal.ca.

10.1021/jm010096n CCC: $20.00
Published on Web 08/14/2001

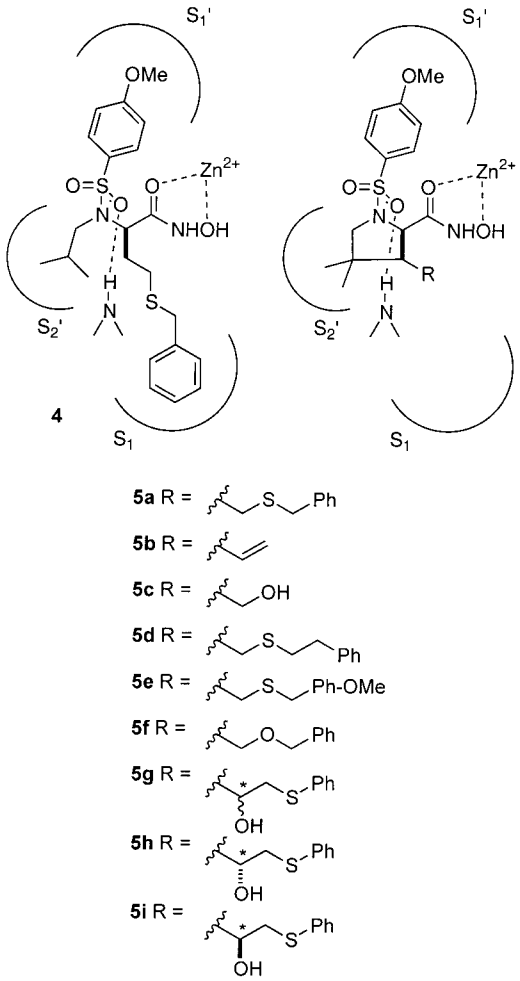


Figure 2. Designed inhibitors.

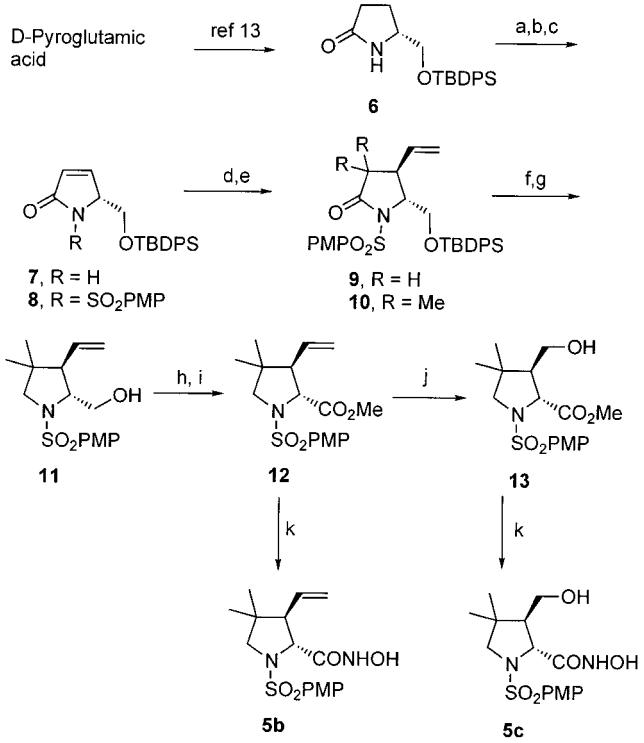
proline-derived analogues represented by structures **5a**−**i** (Figure 2).[12]

AutoDock docking studies confirmed the expected binding mode of **5a** to be similar to that of **4** in MMP-3 (Figure 3, panels a and b). Analogues **5a**, **5d**, and **5f** were involved in hydrophobic interactions with the S_1 pocket through the phenyl moieties. Although the side chain of **5e** was also aromatic, the presence of the methoxy group sterically disfavored a good interaction in this pocket.

Interestingly, AutoDock also revealed the presence of a hydrogen bond formed between the hydroxymethyl analogue **5c** with residue Ala-165 of the protein backbone in MMP-3 (Figure 3, panel c). This interesting feature led us to design compound **5g** in which the hydroxyl *and* the aromatic groups could interact with the protein (Figures 3, panel d).

Synthesis. D-Pyroglutamic acid was converted to the known lactam **6** according to a literature procedure.[13] The sulfonamide functionality was introduced as in **7**, since it was common to all targeted inhibitors and was expected to be compatible with subsequent chemistry. Elimination via the phenylselenyl derivative afforded the α,β-unsaturated lactam **8**, which was subjected to conjugate addition with a vinyl magnesio cuprate to give **9** in good yield and with exclusive stereocontrol. Initially, dimethylation of **9** to give **10** proved quite sluggish, affording the monomethyl product in preponderance. To achieve complete methylation, the reaction had to be repeated on the crude material. Reduction of **10** with $LiAlH_4$ then with Et_3SiH in the presence of $BF_3 \cdot Et_2O$ led to product, which was immediately desilylated to afford **11**. Oxidation[14] and esterification gave **12**, which was subjected to ozonolysis followed by reductive workup using sequential treatment with Me_2S then $NaBH_4$ to give **13** (Scheme 1).

Scheme 1[a]



[a] (a) LiHMDS, $PMPSO_2Cl$, THF, 79%; (b) LDA, THF then PhSeBr; (c) O_3, CH_2Cl_2, 89% (two steps); (d) $(vinyl)_2CuCN(MgBr)_2$, TMSCl, Et_2O, 71%; (e) LiHMDS, MeI, DMPU, THF (two iterations), 69%; (f) $LiAlH_4$, THF; (g) Et_3SiH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 56% (two steps); (h) $NaClO_2$, NaOCl, TEMPO, CH_3CN, aqueous phosphate buffer; (i) CH_2N_2, Et_2O, quant. (two steps); (j) O_3, CH_2Cl_2; then Me_2S; then $NaBH_4$, EtOH, 69%; (k) NH_2OK, NH_2OH, MeOH, 65% (**5b**), 22% (**5c**).

Conversion of the ester functionality of **12** and **13** directly to the hydroxamic acid was effected using NH_2OK in MeOH.[15] Hydroxamic acid **5c** proved to be highly water soluble, and even after extensive extraction with EtOAc from H_2O, only modest amounts of product could be recovered.

Alcohol **13** was transformed to the thioethers **15a**, **15d**, and **15e** (Scheme 2) by reaction of mesylate **14** with preformed thiolates generated from reaction of thiols with NaH in DMF. Although longer reaction times were required compared with literature procedures,[16] the desired thioethers were nevertheless obtained in moderate to excellent yield. Use of DMF was critical for the thiolate substitution, since no reaction was observed in other solvents such as THF, toluene, or acetonitrile. These observations can be rationalized considering the steric hindrance to attack of the thiolates on the mesylate. The alkoxide generated upon treatment of **13** with NaH proved to be unstable, decomposing to a mixture of unidentified products. Performing an in situ quench of the reaction mixture with benzyl bromide at low temperature to afford **16** minimized this decomposi-

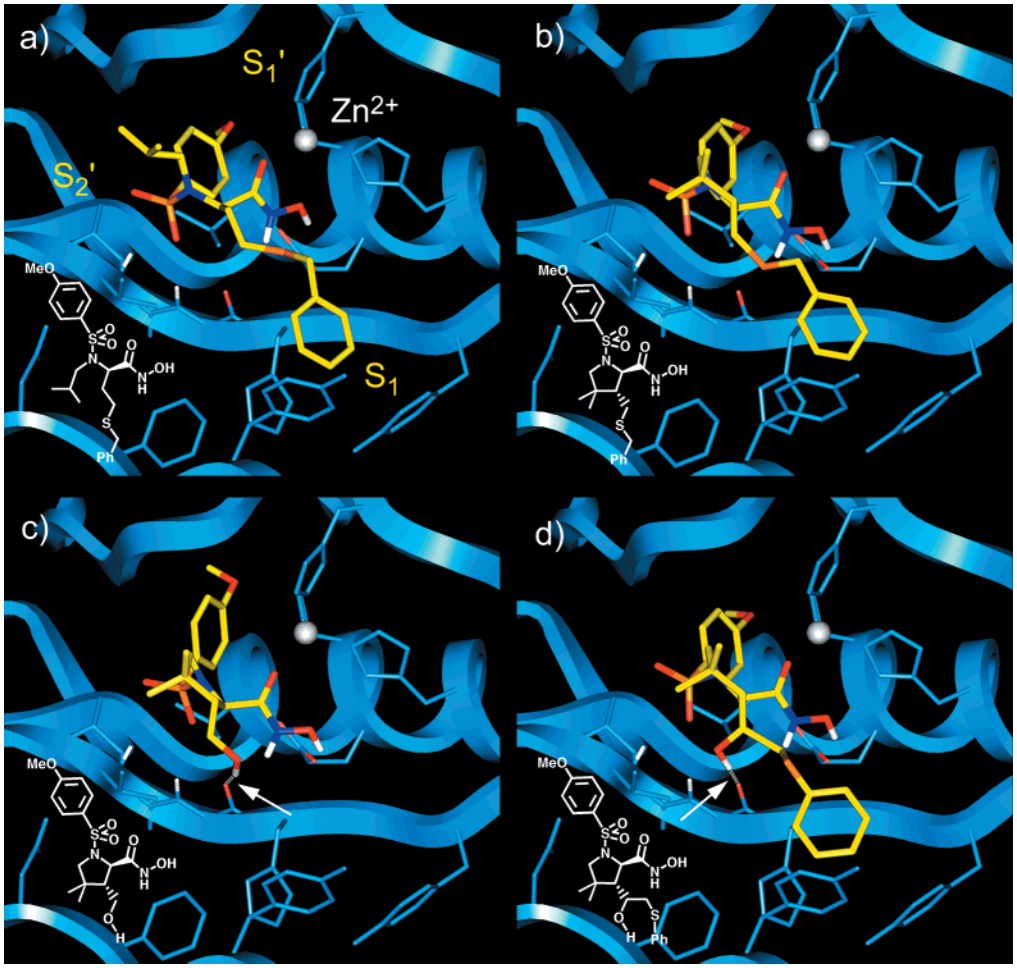
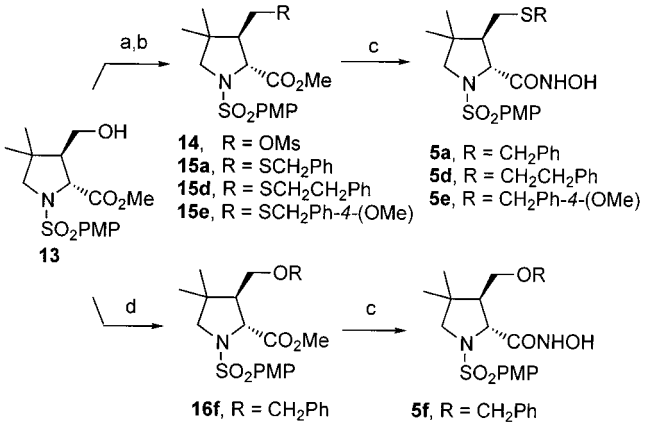


Figure 3. Proposed docked structures for **4** (a), **5a** (b), **5c** (c), and **5h** (d) in the MMP-3 binding site. Arrow in panel d indicates H-bond with residue Ala-165.

Scheme 2[a]

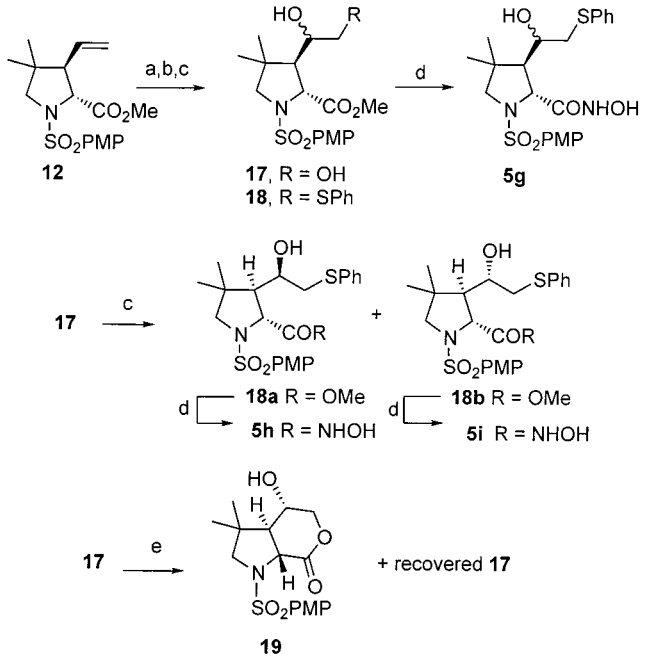


[a] (a) MsCl, Et_3N, CH_2Cl_2, quant.; (b) RSNa, DMF, 92% (**15a**), 49% (**15d**), 55% (**15e**); (c) NH_2OK, NH_2OH, MeOH, 80% (**5a**), 79% (**5d**), 52% (**5e**), 64% (**5f**); (d) NaH, RBr, DMF, 25%.

tion. The final hydroxamic acids **5a**,**d**−**f** were prepared as described above.

Initially, hydroxamic acid **5g** was prepared as a mixture of diastereomers, starting from olefin **12** (Scheme 3). Dihydroxylation of **12** using OsO_4 and NMO for 2 days afforded a 1.3:1 mixture of inseparable diastereomers in excellent yield. As expected, selective tosylation of the primary alcohol and subsequent reaction with sodium benzenethiolate afforded **18** in excellent overall

Scheme 3[a]



[a] (a) OsO_4, NMO, acetone/H_2O, 87%, dr 1.3:1; (b) TsCl, Et_3N, pyridine, CH_2Cl_2; (c) PhSNa, DMF, 84% (2 steps); (d) NH_2OK, NH_2OH, MeOH, 66% (**5g**), 50% (**5h**), 66% (**5i**); (e) Δ, vacuum.

yield. Conversion to hydroxamic acids **5g** proceeded smoothly to give a 1.3:1 mixture of inseparable dia-

Table 2. Inhibitory Activities of Compounds **4** and **5a**−**i**[a]

	IC_{50}, nM				
compd	MMP-1	MMP-2	MMP-3	MMP-9	MMP-13
4	104	0.7	0.7	2.5	12
5a	198	1.64	6.7	0.9	5.5
5b	25710	441	293	138	519
5c	8760	143	136	50	218
5d	654	15.4	6.5	2.8	17.0
5e	458	4.6	16.7	4.4	22.3
5f	1620	32	10.1	9.2	44.2
5h	117	2.5	3.0	0.9	3.7
5i	301	16.2	18.7	3.6	18.1

[a] See Experimental Section for details.

stereomers. The mixture of diastereoisomeric alcohols **18** could be separated by careful flash chromatography to afford the *R*-stereoisomer **18a** and the *S*-stereoisomer **18b**. Conversion of each isomer to the corresponding hydroxamic acid afforded **5h** and **5i** in diastereomerically pure form, as opposed to the original **5g** which consisted of a mixture of the two. Heating **17** in vacuo led to selective cyclization of the *S*-diastereomer to the corresponding lactone **19**, along with recovered **17** which was enriched in the *R*-diastereomer. ^{1}H NMR analysis of **19** showed that the hydroxyl group occupied an equatorial position, judging by the large coupling constant (J = 8.5 Hz) between the methine proton α to the alcohol and the proton at the 3-position of the pyrrolidine ring. On the basis of this NMR data on the lactone **19**, we were able to assign the configuration of the epimeric alcohols **18a** and **18b** as *R*- and *S*- respectively.

Biological Assays. The IC_{50} values of analogues **5a**−**i** compared to the acyclic counterpart **4** on five different MMPs are listed in Table 2.

The initial goal of this work was to constrain the acyclic carbon framework of **4** into the pyrrolidine analogue **5a**. Indeed, both were found to be roughly equally active against four out of five MMPs. The AutoDock model (Figure 3, panel c) showed an additional hydrogen bond between the hydroxyl group in **5c** and the protein backbone of MMP-3. It is of interest that **5c** was between two and three times more active than **5b** (Scheme 2) which lacks this hydroxyl group for all MMPs. A loss of activity of approximately 2 orders of magnitude in going from **5a** to **5b** may be due to the absence of an aromatic P_1 moiety. Lengthening the P_1 subsite as in **5d** resulted in a slightly different orientation of the central core, and for **5e**, the exclusion of the p-methoxyphenyl moiety out of the S_1 pocket of MMP-3. Nevertheless, these analogues did not lose significant inhibitory activity compared to **5a**. Substituting the sulfur atom by oxygen (**5a** to **5f**) resulted in a modest loss of potency. The second generation compound, **5h**, featured both the aromatic ring at the P_1 subsite and the *R*-hydroxyl group that, according to the proposed binding mode (Figure 3, panel d), was involved in a H-bond with Ala-165. Accordingly, **5h** exhibited activities 3−6 times higher than the diastereomer **5i** in inhibiting MMP-3, as well as the other MMPs.

While we succeeded in discovering highly active compounds, the observed selectivity was somewhat disappointing except that activity against MMP-1 was much weaker compared to other MMPs. The low to subnanomolar enzymatic inhibition of the acyclic analogue **4** against MMP-2, MMP-3, MMP-9, and MMP-13, which share the common His, Phe, Tyr or His, Tyr, Tyr triads, compared to MMP-1 (His, Phe, Ser) is of interest in the context of a preferred binding of an arylalkylthio P_1 appendage. The same trend was observed with the constrained analogue **5a**, which encompassed the acyclic skeleton of **4** and approximated its bioactive conformation according to AutoDock modeling, with the same arylalkylthio P_1 substituent. Such a constrained analogue has also proven to be a valuable probe to fine-tune the nature of the S_1−P_1 interaction in the quest for more potent and selective inhibitors. Furthermore, the enhanced activity of the *R*-hydroxy 1-phenylthioethyl analogue **5h** compared to **5i** nicely validates the value of capitalizing on observations based on modeling and showed stereochemical dependence in the P_1 site.

Conclusion

Previously reported acyclic MMP inhibitor **4** was constrained into a D-proline hydroxamic acid. Further design of a series of analogues with the help of a systematic docking study with MMP-3 led to analogues with P_1 appendages of different sizes, hydrophobicities, and shapes. They were prepared from an advanced common chiron derived from D-pyroglutamic acid and subsequently used to probe the S_1 pocket in MMPs. These "designed" compounds exhibited nanomolar activities with a predictable pattern of potencies. Modeling of the complexes with MMP-3 found an extra hydrogen bond in the case of **5c** that could explain its enhanced activity compared to **5b** and was used to modulate the activity of **5a**. On the basis of this observation, we prepared compound **5h** which incorporates a new hydrogen bond donor on the hydrophobic phenylthioethyl P_1 side chain. Compound **5h** proved to be more active than its epimeric analogue **5i**.

Experimental Section

Chemistry. Solvents were distilled under positive pressure of dry argon before use and dried by standard methods; THF and ether, from Na/benzophenone; CH_2Cl_2 and toluene, from CaH_2. All commercially available reagents were used without further purification. All reactions were performed under argon atmosphere. NMR (^{1}H, ^{13}C) spectra were recorded on AMX-300 and ARX-400 spectrometers in $CDCl_3$ or CD_3OD with solvent resonance as the internal standard. Low- and high-resolution mass spectra were recorded on VG Micromass, AEI-MS 902, or Kratos MS-50 spectrometers using fast atom bombardement (FAB). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in a 1 dm cell at ambient temperature. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ precoated silica gel plates. Visualization was performed by UV or by development using $KMnO_4$ or $FeCl_3$ solutions. Flash column chromatography was performed using (40−60 μm) silica gel at increased pressure. All melting points are uncorrected.

(*R*)-5-(*tert*-Butyl-diphenylsilanyloxymethyl)-1-(4-methoxy-benzenesulfonyl)-pyrrolidin-2-one (7). To a solution of lactam **6** (0.80 g, 1.93 mmol) in THF (25 mL) at −25 °C was added LiHMDS (1.0 M in THF, 2.32 mL, 2.32 mmol). The reaction mixture was stirred at −25 °C for 15 min. A solution of $PMPSO_2Cl$ (0.490 g, 2.35 mmol) in THF (4 mL) was added, and the reaction mixture was stirred at −25 °C for 1 h, quenched with H_2O (70 mL), and taken up in EtOAc (40 mL). The phases were separated, and the organic phase was washed with saturated NH_4OH, saturated $NaHCO_3$, and brine (50 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo.

The residue was purified by column chromatography (SiO_2, 20−50% EtOAc in hexanes) to afford sulfonamide **7** (0.89 g, 79%) as a colorless oil, which solidified upon standing and was recrystallized from EtOAc to afford colorless needles: mp 110−112 °C; $[\alpha]_D$ +14.5 (*c* 1.00, $CHCl_3$); TLC $R_f = 0.17$ (20% EtOAc in hexanes); IR (neat liquid): 3074, 1733, 1596, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, $J = 9.0$ Hz, 2H), 7.62−7.55 (m, 4H), 7.46−7.33 (m, 6H), 6.88 (d, $J = 9.0$ Hz, 2H), 4.47−4.38 (m, 1H), 4.02 (dd, $J = 11.0$, 4.0 Hz, 1H), 3.84−3.78 (m, 1H), 3.82 (s, 3H), 2.67 (dt, $J = 20.0$, 10.0 Hz, 1H), 2.36−1.94 (m, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.94, 163.59, 135.49, 135.37, 132.69, 132.30, 130.33, 130.20, 129.84, 129.80, 127.70, 127.67, 113.87, 65.50, 60.49, 55.48, 31.41, 26.68, 22.32, 19.02; HRMS calcd for $C_{28}H_{34}NO_5SiS$ (MH^+) 524.1927, found 524.1912.

(*R*)-5-(*tert*-Butyl-diphenylsilanyloxymethyl)-1-(4-methoxy-benzenesulfonyl)-1,5-dihydro-pyrrol-2-one (8). LDA was prepared as follows: To a solution of diisopropylamine (0.12 mL, 0.86 mmol) in THF (10 mL) at −78 °C was added BuLi (2.5 M in hexanes, 0.340 mL, 0.85 mmol). The solution was allowed to warm by removal of the cooling bath for 5 min and then cooled to −78 °C. To the LDA solution was added a solution of lactam **7** (0.497 g, 0.851 mmol), and the reaction mixture was stirred at −78 °C for 15 min. A solution of PhSeBr (0.250 g, 1.06 mmol) in THF (4 mL) was added dropwise, and the reaction mixture was stirred at −78 °C for 1 h, quenched with H_2O (15 mL), and allowed to warm to room temperature. EtOAc (75 mL) was added, the phases were separated, and the organic phase was washed with 2 N HCl (75 mL), saturated $NaHCO_3$ (75 mL), and brine (75 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (50 mL) and cooled to −78 °C, and the solution was sparged with O_3 until a pale blue color persisted. The reaction mixture was sparged with Ar until the blue color was completely lost from solution, pyridine (1.5 mL) was added, and the reaction mixture was allowed to warm to room temperature by removal of the cooling bath. The reaction mixture was diluted with CH_2Cl_2 (75 mL) and saturated $NaHCO_3$ (75 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 75 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (10−40% EtOAc in hexanes) to afford unsaturated lactam **8** (0.44 g, 89%) as a pale yellow foam: $[\alpha]_D$ +70.6 (*c* 1.26, $CHCl_3$); TLC $R_f = 0.51$ (40% EtOAc in hexanes); IR (neat liquid): 1730, 1595, 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, $J = 9.0$ Hz, 2H), 7.58−7.56 (m, 4H), 7.50−7.33 (m, 6H), 7.11 (d, $J = 6.0$ Hz, 1H), 6.90 (d, $J = 9.0$ Hz, 2H), 6.02 (d, $J = 6.0$ Hz, 1H), 4.79−4.75 (m, 1H), 4.24 (dd, $J = 10.0$, 3.0 Hz, 1H), 3.99 (dd, $J = 10.0$, 6.0 Hz, 1H), 3.83 (s, 3H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.32, 164.00, 150.90, 135.86, 135.74, 132.88, 132.83, 130.47, 130.30, 130.28, 130.21, 128.07, 128.04, 126.68, 114.31, 65.33, 63.42, 55.83, 26.97, 19.39 (1 C missing); HRMS calcd for $C_{28}H_{32}NO_5SiS$ (MH^+) 522.1770, found 522.1762.

(4*R*,5*R*)-5-(*tert*-Butyl-diphenylsilanyloxymethyl)-1-(4-methoxy-benzenesulfonyl)-4-vinyl-pyrrolidin-2-one (9). *Caution*: CuCN is highly toxic and must be handled with due caution. Contact of reaction byproducts with acid must be avoided. To a suspension of CuCN (3.20 g, 35.7 mmol) in Et_2O (100 mL) at −20 °C was added vinylmagnesium bromide (1 M in THF, 73.0 mL, 73.0 mmol) over several minutes. The reaction was stirred for 20 min and then cooled to −78 °C. A solution of lactam **8** (4.83 g, 9.27 mmol) and TMSCl (2.6 mL, 28.0 mmol) in Et_2O (35 mL) was added over 5 min, and the reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of aqueous NH_4OH (15%, 10 mL), warmed to room temperature, and filtered through Celite. The residue was triturated with Et_2O (2 × 150 mL). The combined organic extracts were washed with aqueous NH_4OH (15%, 200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (0−30% EtOAc in hexanes) to afford unsaturated lactam **9** (3.59 g, 71%) as a clear, colorless oil: $[\alpha]_D$ +15.0 (*c* 0.94, $CHCl_3$); TLC R_f = 0.70 (40% EtOAc in hexanes); IR (neat) 1739, 1596, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, $J = 9.0$ Hz, 2H), 7.65−7.56 (m, 4H), 7.46−7.29 (m, 6H), 6.90 (d, $J = 9.0$ Hz, 2H), 5.74−5.13 (m, 1H), 4.92 (dd, $J = 16.0$, 7.0 Hz, 2H), 4.12−4.07 (m, 1H), 4.04−3.82 (m, 2H), 3.78 (s, 3H), 2.93−2.82 (m, 2H), 2.22−2.13 (m, 1H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.02, 163.71, 138.14, 135.56, 135.45, 135.30, 135.34, 132.67, 132.28, 130.38, 129.90, 127.77, 127.70, 115.32, 113.86, 66.14, 64.95, 55.52, 37.93, 36.77, 26.74, 19.09; HRMS calcd for $C_{30}H_{36}NO_5SiS$ (MH^+) 550.2084, found 550.2104.

(4*R*,5*R*)-5-(*tert*-Butyl-diphenylsilanyloxymethyl)-1-(4-methoxy-benzenesulfonyl)-3,3-dimethyl-4-vinyl-pyrrolidin-2-one (10). To a solution of lactam **9** (103.8 mg, 0.189 mmol) in THF (2 mL) at −20 °C was added LiHMDS (1.0 M in THF, 0.40 mL, 0.40 mmol). The solution was stirred for 10 min at −10 °C, DMPU (0.10 mL, 0.826 mmol) was added, and the solution was stirred for 10 min at −10 °C. MeI (0.100 mL, 1.61 mmol) was added, and the reaction mixture was allowed to warm to room temperature over 2.5 h. The reaction mixture was taken up in Et_2O (10 mL), washed with H_2O (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. (Crude NMR at this point shows a mixture of starting material and products from mono- and dialkylation.) The alkylation procedure was repeated exactly for the crude product. The crude product after the second iteration was purified by column chromatography (5−10% EtOAc in hexanes) to afford lactam **10** (74.7 mg, 69%) as a clear, colorless oil: $[\alpha]_D$ +17.1 (*c* 0.97, $CHCl_3$); TLC $R_f = 0.48$ (30% EtOAc in hexanes); IR (neat) 1739, 1596, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, $J = 9.0$ Hz, 2H), 7.48−7.40 (m, 4H), 7.30−7.15 (m, 6H), 6.70 (d, $J = 9.0$ Hz, 2H), 5.37 (dt, $J = 17.0$, 10.0 Hz, 1H), 4.92 (d, $J = 10$ Hz, 1H), 4.63 (d, $J = 10$ Hz, 1H), 4.35 (dd, $J = 11.0$, 3.0 Hz, 1H), 3.78 (m, 1H), 3.65 (s, 3H), 3.58 (d, $J = 9.0$ Hz, 1H), 2.63 (t, $J = 9.0$ Hz, 2H), 0.92 (s, 3H), 0.88 (s, 9H), 0.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.25, 163.62, 135.72, 135.68, 132.98, 132.87, 132.80, 130.46, 130.16, 129.79, 127.83, 127.69, 120.35, 113.88, 62.46, 61.07, 55.55, 48.30, 44.56, 26.89, 22.69, 20.14, 19.37; HRMS calcd for $C_{32}H_{40}NO_5SiS$ (MH^+) 578.2396, found 578.2400.

(2*R*,3*R*)-[1-(4-Methoxy-benzenesulfonyl)-4,4-dimethyl-3-vinyl-pyrrolidin-2-yl]-methanol (11). To lactam **10** (55.0 mg, 0.0958 mmol) at room temperature was added $LiAlH_4$ (1 M in THF, 0.40 mL, 0.40 mmol). The reaction mixture was stirred at room temperature for 30 min, quenched with H_2O (5 mL), extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude lactamol was used immediately without further purification. To a solution of the lactamol in CH_2Cl_2 (2 mL) at 0 °C were added Et_3SiH (100 μL, 0.626 mmol) and $BF_3{\cdot}Et_2O$ (40 μL, 0.33 mmol). The reaction mixture was allowed to warm to room temperature overnight and concentrated in vacuo. The residue was purified by column chromatography (20−60% EtOAc in hexanes) to afford alcohol **11** (17.4 mg, 56% from **10**) as a clear, colorless oil: $[\alpha]_D$ +59.3 (*c* 0.76, $CHCl_3$); TLC $R_f = 0.64$ (60% EtOAc in hexanes); IR (neat) 3501 (br), 1596, 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, $J = 9.0$ Hz, 2H), 6.96 (d, $J = 9.0$ Hz, 2H), 5.37 (dt, $J = 16.5$, 10.0 Hz, 1H), 5.16−5.04 (m, 2H), 3.90−3.80 (m, 1H), 3.86 (s, 3H), 3.56 (dd, $J = 12.0$, 4.5 Hz, 1H), 3.30−3.15 (m, 3H), 2.86 (br s, 1H), 2.24 (t, $J = 10.0$ Hz, 1H), 0.87 (s, 3H), 0.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.13, 147.33, 133.20, 129.50, 120.33, 114.25, 65.59, 63.88, 62.73, 56.25, 55.61, 39.90, 24.12, 20.73; HRMS calcd for $C_{16}H_{24}NO_4S$ (MH^+) 326.1426, found 326.1434.

(2*R*,3*R*)-1-(4-Methoxy-benzenesulfonyl)-4,4-dimethyl-3-vinyl-pyrrolidine-2-carboxylic acid methyl ester (12). A solution of alcohol **11** (0.670 g, 2.06 mmol) and TEMPO (22.6 mg, 0.145 mmol) in CH_3CN (10 mL) and sodium phosphate buffer (0.67 M, pH = 6.5, 7.5 mL) was heated to 35 °C (the heating bath was thermostated to 42 °C). Solutions of $NaClO_2$ (tech. grade, 80%, 0.457 mg, 40.4 mmol) in H_2O (2 mL) and aqueous NaOCl (10.3% available chlorine, 0.05 mL, diluted to 2 mL) were added dropwise over 15 min. (*Note*: the solutions must not be mixed as they are unstable together.) A dark reddish-brown color developed in the reaction mixture during

addition. The reaction mixture was stirred at 35 °C overnight, extracted with EtOAc (3 × 40 mL) from aqueous HCl (0.2 M, 40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude carboxylic acid was taken up in Et_2O (15 mL) and treated at room temperature with CH_2N_2 until a pale yellow color was observed. The reaction mixture was stirred at room temperature for 5 min, titrated with AcOH in Et_2O until the yellow color of CH_2N_2 was lost, and concentrated in vacuo. The residue was purified by column chromatography (10−30% EtOAc in hexanes) to afford ester **12** (0.736 g, quant.) as a clear, colorless oil: $[\alpha]_D$ +85.9 (*c* 0.80, $CHCl_3$); TLC $R_f = 0.33$ (30% EtOAc in hexanes); IR (neat) 1752, 1596, 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, $J = 9.0$ Hz, 2H), 6.94 (d, $J = 9.0$ Hz, 2H), 5.49 (dt, $J = 16.0$, 9.0 Hz, 1H), 5.10 (d, $J = 9$ Hz, 1H), 5.04 (d, $J = 16.0$ Hz, 1H) 3.94 (d, $J = 10.0$ Hz, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.23−3.16 (m, 2H), 2.46 (t, $J = 9.0$ Hz, 1H), 0.87 (s, 3H), 0.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.33, 163.02, 131.64, 129.80, 129.59, 120.12, 114.09, 64.46, 60.99, 58.72, 55.56, 52.32, 41.77, 23.75, 20.34; HRMS calcd for $C_{17}H_{24}NO_5S$ (MH^+) 354.1375, found 354.1375.

(2*R*,3*R*)-3-Hydroxymethyl-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Methyl Ester (13). A solution of olefin **12** (0.736, 2.06 mmol) in CH_2Cl_2 (70 mL) at −78 °C was sparged with O_3 until a faint blue color persisted in solution. The solution was sparged with Ar at −78 °C until all blue coloration was lost from solution. Me_2S (1.0 mL, 14 mmol) was added, and the solution warmed to room temperature over 30 min. $NaBH_4$ (82.2 mg, 2.17 mmol) and EtOH (75 mL) were added, and the reaction mixture was stirred at room temperature for 2 h. The solvents were removed in vacuo. The residue was stirred with 2 N HCl (30 mL) for 15 min, extracted with EtOAc (3 × 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (40−80% EtOAc in hexanes) to afford alcohol **13** (0.5128 g, 69%) as a clear colorless oil, which crystallized upon standing, and was recrystallized (EtOAc/hexanes) to afford **13** as colorless needles: mp 115−117; $[\alpha]_D$ +73.8 (*c* 0.88, $CHCl_3$); TLC $R_f = 0.21$ (50% EtOAc in hexanes); IR (neat liquid): 3528 (br), 1741, 1595, 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, $J = 9.5$ Hz, 2H), 6.96 (d, $J = 9.5$ Hz, 2H), 4.05 (d, $J = 9.0$ Hz, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.72−3.55 (m, 2H), 3.20 (s, 2H), 2.19 (ddd, $J = 9.0$, 7.5, 5.0 Hz, 1H), 1.76 (br s, 1H), 1.05 (s, 3H), 0.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.46, 163.03, 129.96, 129.61, 114.09, 64.21, 61.48, 60.98, 55.86, 55.34, 52.67, 40.37, 25.15, 20.56; HRMS calcd for $C_{16}H_{24}NO_6S$ (MH^+) 358.1324, found 358.1325.

Representative Procedure for Hydroxamic Acid Formation from Esters Using NH_2OK/NH_2OH. (2*R*,3*R*)-1-(4-Methoxy-benzenesulfonyl)-4,4-dimethyl-3-vinyl-pyrrolidine-2-carboxylic Acid Hydroxyamide (5b). Preparation of NH_2OK/NH_2OH solution (*Note*: a blast shield was used for this operation): $NH_2OH{\cdot}HCl$ (0.476 mg, 6.85 mmol) was solubilized in MeOH (2.4 mL) by heating to reflux. Most, but not all of the salt dissolved. The solution was cooled to <40 °C, and a solution of KOH (9.98 mmol) in MeOH (1.4 mL) was added in one portion. The resulting suspension was cooled to room temperature before use and was used without prior removal of precipitated material. A solution of ester **12** (22.0 mg, 0.0622 mmol) in NH_2OK/NH_2OH solution (2 mL) was stirred at room temperature 3 days. The reaction mixture was taken up in dilute aqueous HCl (pH = 3, 20 mL), extracted with EtOAc (3 × 15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (40−100% EtOAc in hexanes) to afford hydroxamic acid **5b** (14.3 mg, 65%) as a white foam: $[\alpha]_D$ +21.3 (*c* 0.30, $CHCl_3$); TLC $R_f = 0.48$ (EtOAc); IR (neat) 3331 (br), 1748, 1693, 1595, 1497 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.86 (d, $J = 9.0$ Hz, 2H), 7.11 (d, $J = 9.0$ Hz, 2H), 5.51 (dt, $J = 16.0$, 9.0 Hz, 1H), 5.16−5.05 (m, 2H), 3.85 (s, 3H), 3.71 (d, $J = 10$ Hz, 1H), 3.27 (s, 2H), 2.58 (t, $J = 9.5$ Hz, 1H), 0.92 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.58, 164.98, 133.26, 130.94, 130.70, 120.96, 115.42, 65.04, 62.53, 60.08, 56.24, 42.50, 24.10, 20.66; HRMS calcd for $C_{16}H_{23}N_2O_5S$ (MH^+) 355.1328, found 355.1332.

(2*R*,3*R*)-3-Hydroxymethyl-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Hydroxyamide (5c). Hydroxamic acid **5c** (4.8 mg, 22%) was prepared from **13** according to the general procedure for preparation of hydroxamic acids from esters, with the following modifications: Extraction was performed using EtOAc (10 × 20 mL EtOAc) from aqueous HCl (1 M, 10 mL), and the product was purified by column chromatography (3−5% MeOH in CH_2Cl_2). Data for **5c**: white foam, $[\alpha]_D$ +94.2 (*c* 0.45, $CHCl_3$); TLC $R_f = 0.08$ (EtOAc); IR (neat) 3280 (br), 1788, 1672, 1596, 1498 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.83 (d, $J = 9.0$ Hz, 2H), 7.11 (d, $J = 9.0$ Hz, 2H), 3.88 (s, 3H), 3.72 (d, $J = 9.5$ Hz, 1H), 3.55−3.43 (m, 2H), 3.27 (d, $J = 9.0$ Hz, 1H), 3.20 (d, $J = 9.0$ Hz, 1H), 2.25−2.17 (m, 1H), 1.84 (br s, 2H), 1.08 (s, 3H), 0.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.49, 164.98, 130.99, 130.56, 115.42, 64.34, 63.27, 60.59, 56.23, 56.16, 41.18, 25.91, 20.80; LRMS: 358 (M^+), 340 ($M - H_2O$)$^+$, 298 (M-CONHOH)$^+$.

(2*R*,3*R*)-3-Methanesulfonyloxymethyl-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Methyl Ester (14). To a solution of alcohol **13** (18.1 mg, 0.0504 mmol) in CH_2Cl_2 (1 mL) at 0 °C were added Et_3N (10 μL, 0.73 mmol) and MsCl (5.0 μL, 0.71 mmol). The reaction was stirred at 0 °C for 1.5 h, taken up in CH_2Cl_2 (10 mL), and washed quickly with saturated NH_4OH (10 mL), 1 M HCl (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mesylate **14** thus formed was used immediately, without further purification. TLC $R_f = 0.36$ (50% EtOAc in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, $J = 9.0$ Hz, 2H), 7.01 (d, $J = 9.0$ Hz, 2H), 4.31−4.14 (m, 2H), 4.05 (d, $J = 9.0$ Hz, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 3.28 (s, 2H), 3.02 (s, 3H), 2.48−2.42 (m, 1H), 1.13 (s, 3H), 0.71 (s, 3H).

Representative Procedure for Conversion of Mesylate 14 to Sulfides. (2*R*,3*R*)-3-Benzylsulfanylmethyl-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Methyl Ester (15a). A solution of BnSNa in DMF was prepared as follows: To NaH (20.9 mg, 0.523 mmol), washed free of oil with hexanes (3 × 3 mL), in DMF (5 mL) was added benzyl mercaptan (50.0 μL, 0.426 mmol). Vigorous gas evolution was observed. The reaction mixture was stirred at room temperature for 5 min and was used immediately afterward. To mesylate **14** (0.0418 mmol) was added BnSNa in DMF (0.50 mL, 0.052 mmol). The reaction was stirred at room temperature for 3 h, after which time TLC indicated a small amount of starting material was still present. A second portion of BnSNa in DMF (0.20 mL, 0.021 mmol) was added, and the reaction mixture was stirred at room temperature a further 30 min. The reaction mixture was taken up in Et_2O (10 mL), washed with H_2O (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (10−50% EtOAc in hexanes) to afford sulfide **15a** (17.9 mg, 92% from alcohol **13**) as a clear, colorless oil: $[\alpha]_D$ +85.9 (*c* 0.95, $CHCl_3$); TLC $R_f = 0.25$ (25% EtOAc in hexanes); IR (neat) 1748, 1596, 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, $J = 9.0$ Hz, 2H), 7.32−7.17 (m, 5H), 6.94 (d, $J = 9.0$ Hz, 2H), 3.86 (d, $J = 9.0$ Hz, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.62 (s, 2H), 3.27−3.16 (m, 2H), 2.43−2.33 (m, 1H), 2.30−2.12 (m, 2H), 0.95 (s, 3H), 0.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.68, 163.02, 154.78, 137.41, 129.63, 128.95, 128.51, 127.17, 114.09, 65.36, 61.42, 55.59, 52.57, 52.43, 40.90, 36.13, 28.57, 24.86, 20.74; HRMS calcd for $C_{23}H_{29}NO_5S_2$ (MH^+) 463.1487, found 463.1478.

(2*R*,3*R*)-1-(4-Methoxy-benzenesulfonyl)-4,4-dimethyl-3-phenethylsulfanylmethyl-pyrrolidine-2-carboxylic Acid Methyl Ester (15d). Sulfide **15d** (20.5 mg, 49% from alcohol **13**) was prepared according to the general procedure for preparation of sulfides from mesylate **14**, modified as follows: the reaction mixture was stirred at room temperature overnight. Data for **15d**: $[\alpha]_D$ +101.1 (*c* 0.83, $CHCl_3$); TLC $R_f = 0.42$ (40% EtOAc in hexanes); IR (neat) 1748, 1596, 1497 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, $J = 9.0$ Hz, 2H), 7.37−7.15 (m, 5H), 7.01 (d, $J = 9.0$ Hz, 2H), 3.94 (d, $J = 8.0$ Hz, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 3.27 (s, 2H), 2.88−2.81 (m, 2H),

2.80−2.67 (m, 2H), 2.65−2.54 (m, 1H), 2.36−2.26 (m, 2H), 1.07 (s, 3H), 0.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.64, 163.02, 140.16, 129.79, 129.64, 128.48, 128.45, 126.43, 114.09, 65.39, 61.32, 55.59, 52.98, 52.55, 40.94, 35.93, 33.98, 30.01, 24.90, 20.31; HRMS calcd for $C_{24}H_{32}NO_5S_2$ (MH^+) 478.1722, found 478.1714.

(2*R*,3*R*)-1-(4-Methoxy-benzenesulfonyl)-4,4-dimethyl-3-(4-methoxy-benzylsulfanylmethyl)-pyrrolidine-2-carboxylic Acid Methyl Ester (15e). Sulfide **15e** (40.2 mg, 55% from alcohol **13**) was prepared according to the general procedure for preparation of sulfides from mesylate **14**. Data for **15e**: $[\alpha]_D$ = +97.6 (*c* 0.51, $CHCl_3$); TLC R_f = 0.37 (40% EtOAc in hexanes); IR (neat) 1748, 1596, 1512 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 9.0 Hz, 2H), 7.15 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 3.87 (d, *J* = 10.0 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.58−3.53 (m, 2H), 3.26−3.16 (m, 2H), 2.43−2.33 (m, 1H), 2.32−2.14 (m, 2H), 0.98 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.43, 161.79, 157.34, 129.98, 129.57, 128.56, 114.06, 113.82, 65.33, 61.39, 55.55, 55.22, 52.51, 40.83, 35.61, 28.14, 24.82, 20.23; HRMS calcd for $C_{24}H_{32}NO_6S_2$ (MH^+) 494.1671, found 494.1630.

(2*R*,3*R*)-3-Benzylsulfanylmethyl-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Hydroxyamide (5a). Hydroxamic acid **5a** (14.4 mg, 80%) was prepared from **15a** according to the general procedure for preparation of hydroxamic acids from esters. Data for **5a**: $[\alpha]_D$ +151 (*c* 1.08, $CHCl_3$); TLC R_f = 0.65 (EtOAc); IR (neat) 3331 (br), 3202 (br), 1667, 1595, 1496 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, *J* = 9.0 Hz, 2H), 7.31−7.25 (m, 4H), 7.25−7.17 (m, 1H), 7.06 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.72 (d, *J* = 8.5 Hz, 1H), 3.65 (s, 2H), 3.28 (d, *J* = 10.0 Hz, 1H), 3.21 (d, *J* = 10.0 Hz, 1H), 2.42−2.35 (m, 2H), 2.16−2.06 (m, 1H), 0.97 (s, 3H), 0.45 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 170.78, 164.94, 149.61, 139.31, 130.91, 130.16, 129.47, 128.01, 115.43, 66.14, 62.83, 56.23, 52.51, 41.75, 36.75, 29.53, 25.48, 20.56; HRMS calcd for $C_{22}H_{29}N_2O_5S_2$ (MH^+) 465.1518, found 465.1534.

(2*R*,3*R*)-1-(4-Methoxy-benzenesulfonyl)-4,4-dimethyl-3-phenethylsulfanylmethyl-pyrrolidine-2-carboxylic Acid Hydroxyamide (5d). Hydroxamic acid **5d** (14.2 mg, 79%) was prepared from **15d** according to the general procedure for preparation of hydroxamic acids from esters. Data for **5d**: $[\alpha]_D$ +108.4 (*c* 0.71, $CHCl_3$); TLC R_f = 0.81 (EtOAc); IR (neat) 3321 (br), 3207 (br), 1667, 1595, 1497 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 (d, *J* = 9.0 Hz, 2H), 7.28−7.10 (m, 5H), 7.09 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 3.73 (d, *J* = 8.5 Hz, 1H), 3.30−3.19 (m, 2H), 2.86−2.80 (m, 2H), 2.75−2.66 (m, 2H), 2.54 (dd, *J* = 13.0, 6.0 Hz, 1H), 2.30 (dd, *J* = 8.0, 6.0 Hz, 1H), 2.21 (dd, *J* = 13.0, 8.0 Hz, 1H), 1.07 (s, 3H), 0.44 (s, 3H): ^{13}C NMR (100 MHz, CD_3OD) δ 171.04, 165.12, 142.06, 131.11, 130.64, 129.79, 129.58, 127.43, 115.61, 66.35, 62.97, 56.40, 53.38, 41.93, 37.19, 34.91, 30.87, 25.72, 20.77; HRMS calcd for $C_{23}H_{31}N_2O_5S_2$ (MH^+) 479.1674, found 479.1685.

(2*R*,3*R*)-1-(4-Methoxy-benzenesulfonyl)-3-(4-methoxy-benzylsulfanylmethyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Hydroxyamide (5e). Hydroxamic acid **5e** (21.1 mg, 52%) was prepared from **15e** according to the general procedure for preparation of hydroxamic acids from esters, modified as follows: the reaction mixture was stirred at room temperature overnight. Data for **5e**: $[\alpha]_D$ +159.0 (*c* 1.05, $CHCl_3$); TLC R_f = 0.69 (EtOAc); IR (neat) 3331 (br), 3197 (br), 1666, 1595, 1511 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, *J* = 9.0 Hz, 2H), 7.18 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 3.71 (d, *J* = 8.0 Hz, 1H), 3.61 (s, 2H), 3.25−3.17 (m, 2H), 2.40−2.32 (m, 2H), 2.14−2.04 (m, 1H), 1.01 (s, 3H), 0.38 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.94, 165.09, 160.34, 131.37, 131.23, 131.07, 130.70, 115.59, 114.99, 66.31, 62.99, 56.39, 55.82, 52.68, 41.89, 36.29, 29.60, 25.69, 20.73; LRMS: 495 (MH^+), 434 (M-CO_2NH_2)$^+$, 373 (M-PMB)$^+$.

(2*R*,3*R*)-3-Benzyloxymethyl-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Methyl Ester (16f). To NaH (60 mg, 60% dispersion in oil, 0.864 mmol), washed free of oil with hexanes (4 × 3 mL) at −78 °C, was added a solution of alcohol **13** (43.4 mg, 0.121 mmol) and benzyl bromide (0.13 mL, 1.0 mmol) in DMF (4 mL). The flask was allowed to warm to −20 °C over 20 min and was stirred at − 20 °C for 1 h. The reaction mixture was taken up in Et_2O (10 mL), washed with H_2O (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (10−50% EtOAc in hexanes) to afford ether **16f** (13.7 mg, 25%) as a clear, colorless oil: $[\alpha]_D$ +21.3 (*c* 0.30, $CHCl_3$); TLC R_f = 0.53 (50% EtOAc in hexanes); IR (neat) 1751, 1596, 1497 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.0 Hz, 2H), 7.39−7.22 (m, 5H), 6.94 (d, *J* = 9.0 Hz, 2H), 4.42 (s, 2H), 4.01 (d, *J* = 10.0 Hz, 1H), 3.86 (s, 3H), 3.68 (s, 3H), 3.51 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.40 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.28−3.20 (m, 2H), 2.40−2.30 (m, 1H), 1.10 (s, 3H), 0.61 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.76, 162.96, 137.84, 129.66, 128.30, 127.60, 127.40, 114.04, 73.23, 68.02, 63.80, 61.63, 55.56, 53.20, 52.40, 40.23, 25.48, 20.73; HRMS calcd for $C_{16}H_{23}N_2O_5S$ (MH^+) 355.1328, found 355.1332.

(2*R*,3*R*)-3-Benzyloxymethyl-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Hydroxyamide (5f). Hydroxamic acid **5f** (7.7 mg, 64%) was prepared from **16f** according to the general procedure for preparation of hydroxamic acids from esters. Data for **5f**: $[\alpha]_D$ +49.9 (*c* 0.39, $CHCl_3$); TLC R_f = 0.60 (EtOAc); IR (neat) 3269 (br), 1667, 1595, 1497 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (d, *J* = 9.0 Hz, 2H), 7.34−7.22 (m, 5H), 7.08 (d, *J* = 9.0 Hz, 2H), 4.47−4.34 (m, 2H), 3.87 (s, 3H), 3.78 (d, *J* = 6.5 Hz, 1H), 3.48−3.33 (m, 2H), 3.19 (d, *J* = 10 Hz, 1H), 2.35 (m, 1H), 1.08 (s, 3H), 0.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.91, 143.65, 139.40, 130.98, 130.42, 129.30, 128.64, 128.56, 115.37, 74.10, 68.73, 64.19, 63.16, 56.19, 54.01, 41.14, 25.95, 21.04; HRMS calcd for $C_{22}H_{29}N_2O_6S$ (MH^+) 449.1746, found 449.1735.

(2*R*,3*R*)-3-(*1*-(*R*,*S*)-1,2-Dihydroxy-ethyl)-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Methyl Ester (17). To a solution of olefin **12** (140.0 mg, 0.396 mmol) and NMO (58.2 mg, 0.496 mmol) in acetone/H_2O (1:1, 5 mL) at room temperature was added OsO_4 (4% aqueous solution, 0.05 mL). The solution was stirred at room temperature 2 days, extracted with EtOAc (3 × 25 mL) from H_2O (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (20−100% EtOAc in hexanes) to afford diol (0.134 g, 87%) as a clear, colorless oil and as a 1.3:1 mixture of diastereomers: $[\alpha]_D$ = +60.0 (*c* 0.57, $CHCl_3$); TLC R_f = 0.16 (50% EtOAc in hexanes); IR (neat) 3470 (br), 1740, 1595, 1498 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 9.0 Hz, 2 × 0.57H), 7.72 (d, *J* = 9.0 Hz, 2 × 0.43H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.27 (d, *J* = 7.0 Hz, 0.57H), 3.91 (d, *J* = 9.0 Hz, 0.43H), 3.84 (s, 3H), 3.78−3.65 (m, 1H), 3.70 (s, 3 × 0.57H), 3.64 (s, 3 × 0.43H), 3.55−3.40 (m, 2H), 3.08−2.83 (m, 2H), 2.22 (apparent t, *J* = 9.0 Hz, 1 × 0.43H), 2.04 (dd, *J* = 7.0, 4.0 Hz, 0.57H), 1.14 (s, 3 × 0.43H), 1.04 (s, 3 × 0.57H), 0.74 (s, 3 × 0.43H), 0.73 (s, 3 × 0.57H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.90, 173.25, 162.92, 162.86, 130.29, 129.58, 129.28, 129.11, 114.00, 113.96, 71.40, 69.64, 65.37, 64.90, 62.13, 61.76, 61.36, 61.32, 55.47, 54.94, 54.48, 52.50, 41.26, 40.44, 26.38, 25.99, 21.15, 20.94; HRMS calcd for $C_{17}H_{26}NO_7S$ (MH^+) 388.1430, found 388.1427.

(2*R*,3*R*)-3-((*R*,*S*)-1-Hydroxy-2-phenylsulfanyl-ethyl)-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Methyl Ester (18). To a solution of diol **17** (44.2 mg, 0.114 mmol) and *p*-TsCl (23.2 mg, 0.125 mmol) in CH_2Cl_2 (2 mL) at 0 °C were added Et_3N (16.5 μL, 0.113 mmol) and pyridine (15.5 μL, 0.112 mmol). The solution was stirred at 0 °C for 3 h, at which time TLC indicated the complete consumption of starting material. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL) from H_2O (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude tosylate was carried on without further purification. A solution of the crude tosylate and PhSNa (29.7 mg, 0.224 mmol) in dry DMF (2 mL) was stirred at room temperature for 2 days, taken up in Et_2O (5 mL), washed with H_2O (3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (20−50% EtOAc in hexanes) to afford sulfide **18** (44.9 mg, 84%) as a

1.3:1 mixture of diastereomers: $[\alpha]_D = +39.4$ (*c* 0.72, $CHCl_3$); TLC $R_f = 0.54$ (50% EtOAc in hexanes); IR (neat) 3508 (br), 1741, 1596, 1498 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, $J = 9.0$ Hz, 2 × 0.43H), 7.75 (d, $J = 9.0$ Hz, 2 × 0.57H), 7.37−7.18 (m, 5H), 6.95 (d, $J = 9.0$ Hz, 2H), 4.30 (d, $J = 6.5$ Hz, 0.43H), 3.93 (d, $J = 9.0$ Hz, 0.57H) 3.84 (s, 3H), 3.76 (s, 3 × 0.43H), 3.70−3.55 (m, 2H), 3.60 (s, 3 × 0.57H), 3.32−3.10 (m, 2H), 3.02 (dd, $J = 14.0$, 4.0 Hz, 0.43H), 2.88 (dd, $J = 14.0$, 10.0 Hz, 0.43H), 2.75 (dd, $J = 14.0$, 10.0 Hz, 0.57H), 2.62 (d, $J = 4.0$ Hz, 0.57H), 2.21 (apparent t, $J = 9.0$ Hz, 0.57H), 1.18 (s, 3 × 0.57H), 1.09 (s, 3 × 0.43H), 0.76 (s, 3 × 0.57H) 0.75 (s, 3 × 0.43H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.33, 172.76, 162.82, 134.00, 130.42, 130.19, 129.77, 129.18, 129.11, 129.07, 127.04, 126.95, 113.93, 113.80, 68.62, 66.79, 62.41, 61.77, 61.07, 60.07, 60.52, 57.04, 56.82, 55.43, 52.43, 41.67, 41.34, 41.08, 40.74, 27.27, 26.05, 21.27, 20.89; HRMS calcd for $C_{23}H_{30}NO_6S_2$ (MH^+) 480.1515, found 480.1526. Diastereomerically pure samples were prepared by a second column chromatography (SiO_2, 40−50% Et_2O in hexanes). Major diastereomer **18a**: $[\alpha]_D = +45.2$ (*c* 0.54, $CHCl_3$); $R_f = 0.22$ (60% Et_2O in hexanes); minor diastereomer **18b**: $[\alpha]_D = +34.7$ (*c* 0.49, $CHCl_3$); $R_f = 0.18$ (60% Et_2O in hexanes).

(3a*R*,4*R*,7a*R*)-4-Hydroxy-1-(4-methoxy-benzenesulfonyl)-3,3-dimethyl-hexahydro-pyrano[3,4-*b*]pyrrol-7-one (19). Diol **17** (35.0 mg, 1.1:1 ratio of diastereomers) was heated to 175 °C in vacuo. After 10 min, the oil was cooled to room temperature. Crude NMR indicated the diastereomeric ratio of the starting diol **17** had increased to 1.3:1. Lactone **19** was the sole reaction product identified by NMR; integration of the aromatic protons showed that the ratio of the major diastereomer of **17** to the combined integration of the minor diastereomer of **17** and the lactone **19** was 1.1:1. An analytical sample of **19** was prepared by concentration of the crude sample and heating for a further 10 min. The resulting oil was cooled to room temperature and purified by column chromatography (20−100% EtOAc in hexanes) to afford lactone **19** as a colorless oil: $[\alpha]_D = +59$ (*c* 0.3, $CHCl_3$); TLC $R_f = 0.33$ (70% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, $J = 9.0$ Hz, 2H), 6.99 (d, $J = 9.0$ Hz, 2H), 4.43 (d, $J = 13.5$ Hz, 1H), 4.26 (d, $J = 13.5$ Hz, 1H), 3.89 (d, $J = 11.5$ Hz, 1H), 3.88 (s, 3H), 3.60 (d, $J = 10.5$ Hz, 1H), 3.20 (m, 1H), 2.98 (d, $J = 10.5$ Hz, 1H), 2.11 (dd, $J = 13.0$, 8.5 Hz, 1H), 1.17 (s, 3H), 1.06 (s, 3H).

(2*R*,3*R*)-3-((*R*,*S*)-1-Hydroxy-2-phenylsulfanyl-ethyl)-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Hydroxyamide (5g). Hydroxamic acid **5g** (8.4 mg, 66%) was prepared from **18** as a 1.3:1 mixture of diastereomers, according to the general procedure for preparation of hydroxamic acids from esters. Data for **5g**: TLC $R_f = 0.51$ (6% MeOH in CH_2Cl_2); ^1H NMR (400 MHz, CD_3OD) δ 7.83 (d, $J = 9.0$ Hz, 2 × 0.43H), 7.79 (d, $J = 9.0$ Hz, 2 × 0.57H), 7.45−7.04 (m, 5H), 7.03 (d, $J = 9.0$ Hz, 2H), 4.21 (d, $J = 9.5$ Hz, 0.57H), 3.88 (s, 3H), 3.81 (d, $J = 9.0$ Hz, 0.43H), 3.68−3.62 (m, 1H), 3.25−3.13 (m, 2H), 3.02 (dd, $J = 13.5$, 6.5 Hz, 0.57H), 2.88 (dd, $J = 14.0$, 7.0 Hz, 0.57H), 2.81 (dd, $J = 13.0$, 10.0 Hz, 0.43H) 2.40 (d, $J = 7.0$ Hz, 1H), 2.39 (apparent t, $J = 8.0$ Hz, 0.45H), 0.95 (s, 3 × 0.57H), 0.46 (s, 3 × 0.57H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.08, 164.84, 137.03, 131.12, 130.70, 130.46, 130.28, 130.06, 127.15, 115.30, 70.51, 66.81, 63.42, 62.84, 60.71, 57.97, 56.57, 56.17, 42.38, 41.54, 41.33, 40.91, 26.84, 26.12, 21.62, 21.41; HRMS calcd for $C_{22}H_{29}N_2O_6S_2$ (MH^+) 481.1467, found 481.1478.

(2*R*,3*R*)-3-((*S*)-1-Hydroxy-2-phenylsulfanyl-ethyl)-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Hydroxyamide (5h). Hydroxamic acid **5h** (6.0 mg, 50%) was prepared from **18a** according to the general procedure for preparation of hydroxamic acids from esters. Data for **5h**: $[\alpha]_D = +69$ (*c* 0.6, $CHCl_3$); TLC $R_f = 0.51$ (6% MeOH in CH_2Cl_2); ^1H NMR (400 MHz, CD_3OD) δ 7.79 (d, $J = 9.0$ Hz, 2H), 7.45−7.04 (m, 5H), 7.03 (d, $J = 9.0$ Hz, 2H), 4.21 (d, $J = 9.5$ Hz, 1H), 3.88 (s, 3H), 3.68−3.62 (m, 1H), 3.25−3.13 (m, 2H), 3.02 (dd, $J = 13.5$, 6.5 Hz, 1H), 2.88 (dd, $J = 14.0$, 7.0 Hz, 1H), 2.40 (d, $J = 7.0$ Hz, 1H), 0.95 (s, 3H), 0.46 (s, 3 × 0.57H); HRMS calcd for $C_{22}H_{29}N_2O_6S_2$ (MH^+) 481.1467, found 481.1478.

(2*R*,3*R*)-3-((*R*)-1-Hydroxy-2-phenylsulfanyl-ethyl)-1-(4-methoxy-benzenesulfonyl)-4,4-dimethyl-pyrrolidine-2-carboxylic Acid Hydroxyamide (5i). Hydroxamic acid **5i** (2.8 mg, 66%) was prepared from **18b** according to the general procedure for preparation of hydroxamic acids from esters. Data for **5i**: $[\alpha]_D = +126$ (*c* 0.35, $CHCl_3$); TLC $R_f = 0.51$ (6% MeOH in CH_2Cl_2); ^1H NMR (400 MHz, CD_3OD) δ 7.83 (d, $J = 9.0$ Hz, 2H), 7.45−7.04 (m, 5H), 7.03 (d, $J = 9.0$ Hz, 2H), 3.88 (s, 3H), 3.81 (d, $J = 9.0$ Hz, 1H), 3.68−3.62 (m, 1H), 3.25−3.13 (m, 2H), 2.81 (dd, $J = 13.0$, 10.0 Hz, 1H) 2.40 (d, $J = 7.0$ Hz, 1H), 2.39 (apparent t, $J = 8.0$ Hz, 1H), 0.95 (s, 3 × 0.57H), 0.46 (s, 3 × 0.57H); HRMS calcd for $C_{22}H_{29}N_2O_6S_2$ (MH^+) 481.1467, found 481.1478.

Molecular Modeling. Molecular modeling studies were performed using software programs from InsightII (Molecular Simulations, 1995, San Diego, CA) using a modified AMBER force field.[17] The starting MMP-3 crystallographic structure, retrieved from the Brookhaven Protein Data Bank (code 1HFS in the PDB). Compounds **4**, **5a**−**i** were docked in the binding site of MMP-3 using AutoDock suite of programs. Grids surrounding the binding site were computed (61 × 61 points, 0.375 Å spacing) with AutoGrid and used for subsequent docking study with AutoDock using Lamarckian genetic algorithm as search protocol. The output from AutoDock was displayed using InsightII.

Biological Assay. Human purified MMPs were purchased or acquired. MMP-2 gelatinase A and MMP-9 gelatinase B were from Boehringer Mannheim (Meylan, France) and MMP-3 stromelysin 1 from Valbiotech (Paris, France). All enzymes were activated by APMA (4-aminophenylmercuric acetate). Inhibition of MMP-3 was quantified by using the peptidomimetic substrate (7-methoxycoumarine-4-yl)-Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met-Lys(Dnp)-NH_2 (Bachem, Bubbendorf, Switzerland) which is cleaved between Ala and Nva. For inhibition studies of the other enzymes, the substrate Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(Nma)-NH_2 (Bachem), which is cleaved between amino acids Gly and Cys, was used. The fluorescent cleavage products were measured with a cytofluorometer (Cytofluor 2350, Millipore, PerSeptive Systems, Voisins le Bretonneux, France) equipped with a combination of 340 and 440 nm filters for excitation and emission, respectively. The IC_{50} values were the average of at least two determinations with a standard deviation of less than ±30%.

Acknowledgment. We thank the NSERC of Canada for financial assistance through the Medicinal Chemistry Chair Program. We thank Dr. G. Tucker, Laboratoires Servier, France, for the biological assays and financial support. We thank Eric Therrien for computational assistance during this work.

References

(1) (a) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. Design and Therapeutic Application of Matrix Metalloproteinase Inhibitors. *Chem. Rev.* **1999**, *99*, 2735−2776. (b) Michaelides, M. R.; Curtin, M. L. Recent Advances in Matrix Metalloproteinase Inhibitors Research. *Curr. Pharm. Des.* **1999**, *5*, 787−820.

(2) Campion, C.; Davidson, A. H.; Dickens, J. P.; Crimmin, M. J. PCT Patent Appl. WO9005719, 1990; *Chem. Abstr.* **1990**, *113*, 212677c.

(3) Broadhurst, M. J.; Brown, P. A.; Lawton, G.; Ballantyne, N.; Bottomley, K. M. K.; Cooper, M. I.; Eatherton, A. J.; Kilford, I. R.; Malsher, P. J.; Nixon, J. S.; Lewis, E. J.; Sutton, B. M.; Johnson, W. H. Design and Synthesis of the Cartilage Protective Agent (CPA, Ro32-3555). *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2299−2303.

(4) MacPherson, L. J.; Bayburt, E. K.; Capparelli, M. P.; Carroll, B. J.; Goldstein, R.; Justice, M. R.; Zhu, L.; Hu, S−i; Melton, R. A.; Fryer, L.; Goldberg, R. L.; Doughty, J. R.; Spirito, S.; Blancuzzi, V.; Wilson, D.; O'Byrne, E. M.; Ganu, V.; Parker, D. T. Discovery of CGS 27023A, a Non-Peptidic, Potent, and Orally Active Stromelysin Inhibitor That Blocks Cartilage Degradation in Rabbits. *J. Med. Chem.* **1997**, *40*, 2525−2532.

(5) Hanessian, S.; Bouzbouz, S.; Boudon, A.; Tucker, G. C.; Peyroulan, D. Picking the S_1, S_1' and S_2' Pockets of Matrix Metalloproteinases. A Niche for Potent Acyclic Sulfonamide Inhibitors. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1691−1696. Hanessian, S.; Moitessier, N.; Gauchet, C.; Viau, M. *N*-Aryl Sulfonyl Homocysteine Hydroxamate Inhibitors of Matrix Metalloproteinases: Further Probing of the S_1, S_1' and S_2' Pockets. *J. Med. Chem.* **2001**, *44*, 3066−3073.

(6) Gonnella, N. C.; Li, Y.-C.; Zhang, X.; Paris, C. G. Bioactive Conformation of a Potent Stromelysin Inhibitor Determined by X-Nucleus Filtered and Multidimensional NMR Spectroscopy. *Bioorg. Med. Chem.* **1997**, *5*, 2193−2201.

(7) Grams, F.; Crimmin, M.; Hinnes, L.; Huxley, P.; Pieper, M.; Tschesche, H.; Bode, W. Structure Determination and Analysis of Human Neutrophil Collagenase Complexed with a Hydroxamate Inhibitor. *Biochemistry* **1994**, *34*, 14012−14020.

(8) Kiyama, R.; Tamura, Y.; Watanabe, F.; Tsuzuki, H.; Ohtani, M.; Yodo, M. Homology Modeling of Gelatinase Catalytic Domains and Docking Simulations of Novel Sulfonamide Inhibitors. *J. Med. Chem.* **1999**, *42*, 1723−1738.

(9) (a) Chen, L.; Rydel, T. J.; Gu, F.; Dunaway, M.; Pikul, S.; McDow Dunham, K.; Barnett, B. L. Crystal Structure of the Stromelysin Catalytic Domain at 2.0 Å Resolution: Inhibitor-induced Conformational Change. *J. Mol. Biol.* **1999**, *293*, 545−557. (b) Lovejoy B.; Welch, A. R.; Carr, S.; Luong, C.; Broka, C.; Hendricks, R. T.; Campbell, J. A.; Walker, K. A. M.; Martin, R.; Van Wart H.; Browner, M. F. Crystal Structures of MMP-1 and MMP-13 Reveal the Structural Basis for Selectivity of Collagenase Inhibitors. *Nature Struct. Biol.* **1999**, *3*, 217. (c) Pikul, S.; McDow Dunham, K. L.; Almstead, N. G.; De, B.; Natchus, M. G.; Anastasio, M. V.; McPhail, S. J.; Snider C. E.; Taiwo, Y. O.; Rydel, T.; Dunaway, C. M.; Gu, F.; Mieling, G. E. Discovery of Potent, Achiral Matrix Metalloproteinase Inhibitors. *J. Med. Chem.* **1998**, *41*, 3568. (d) Esser, C. K.; Bugianesi, R. L.; Caldwell, C. G.; Chapman, K. T.; Durette, P. L.; Girotra, N. N.; Kopka, I. E.; Lanza, T. J.; Levorse, D. A.; MacCoss, M.; Owens, K. A.; Ponpipom, M. M.; Simeone, J. P.; Harrison, R. K.; Niedzwiecki, L.; Becker, J. W.; Marcy, A. I.; Axel, M. G.; Christen, A. J.; McDonnell, J.; Moore, V. L.; Olszewski, J. M.; Saphos, C.; Visco, D. M.; Shen, F.; Colleti, A.; Krieter, P. A.; Hagmann, W. K. Inhibition of Stromelysin-1 (MMP-3) by P_1'-Biphenylethyl Carboxyalkyl Dipeptides. *J Med. Chem.* **1997**, *40*, 1026−1040.

(10) Hanessian, S.; Moitessier, N.; Therrien, E. Design and synthesis of MMP inhibitors guided by molecular modeling. Overview of the available structural data, comparative docking study and design of potentially selective inhibitors. *J. Comput.-Aided Mol. Des.* (in press).

(11) Morris, G. M.; Goodsell, D. S.; Halliday, R. S.; Huey, R.; Hart, W. E.; Belew, R. K.; Olson, A. J. Automated Docking Using a Lamarckian Genetic Algorithm and an Empirical Binding Free Energy Function. *J. Comput. Chem.* **1998**, *19*, 1639−1662.

(12) For proline-based MMP inhibitors, see: (a) Natchus, M. G.; Bookland, R. G.; De, B.; Almstead, N. G.; Pikul, S.; Janusz, M. J.; Heitmeyer, S. A.; Hookfin, E. B.; Hsieh, L. C.; Dowty, M. E.; Dietsch, C. R.; Patel, V. S.; Garver, S. M.; Gu, F.; Pokross, M. E.; Mieling, G. E.; Baker, T. R.; Flotz, D. J.; Peng, S. X.; Bornes, D. M.; Strojnowski, M. J.; Taiwo, Y. O. Development of New Hydroxamate Matrix Metalloproteinase Inhibitors Derived from Functionnalized 4-Aminoprolines. *J. Med. Chem.* **2000**, *43*, 4948−4963. (b) Robinson, R. P.; Laird, E. R.; Blake, J. F.; Bordner, J.; Donahue, K. M.; Lopresti-Morrow, L. L.; Mitchell, P. G.; Reese, M. R.; Reeves, L. M.; Stam, E. J.; Yocum, S. A. Structure-Based Design and Synthesis of a Potent Matrix Metalloproteinase-13 Inhibitor Based on a Pyrrolidinone Scaffold. *J. Med. Chem.* **2000**, *43*, 2293−2296. (c) Cheng, M.; De, B.; Almstead, N. G.; Pikul, S.; Dowty, M. E.; Dietsch, C. R.; Dunaway, C. M.; Gu, F.; Hsieh, L. C.; Janusz, M. J.; Taiwo, Y. O.; Natchus, M. G. Design, Synthesis, and Biological Evaluation of Matrix Metalloproteinase Inhibitors Derived from a Modified Proline Scaffold. *J. Med. Chem.* **1999**, *42*, 5426−5436. (d) Almstead, N. G.; Bradley, R. S.; Pikul, S.; De, B.; Natchus, M. G.; Taiwo, Y. O.; Gu, F.; Williams, L. E.; Hynd, B. A.; Janusz, M. J.; Dunaway, C. M.; Mieling, G. E. Design, Synthesis, and Biological Evaluation of Potent Thiazine- and Thiazepine-Based Matrix Metalloproteinase Inhibitors. *J. Med. Chem.* **1999**, *42*, 4547−4562.

(13) Hanessian, S.; McNaughton-Smith, G. A Versatile Synthesis of a β-turn Peptidomimetics Scaffold: An Approach Towards a Designed Model Antagonist of the Tachykinin NK-2 Receptor. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567−1572 and references therein.

(14) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. Oxidation of Primary Alcohols to Carboxylic Acids with Sodium Chlorite Catalyzed by TEMPO and Bleach. *J. Org. Chem.* **1999**, *64*, 2564−2566. Note that the authors claim substrates bearing an olefin are not suitable for the procedure; however, the terminal olefin of **11** did not interfere.

(15) (a) Fieser, L. F.; Fieser, M. Reagents for Organic Synthesis; J. Wiley and Sons, Inc.: New York, 1967; Vol. 1, pp 478−479. (b) Hauser, C. R.; Renfrow, W. B., Jr. Benzohydroxamic Acid. *Org. Synth. Coll. Vol.* **1943**, *2*, 67−68.

(16) (a) Ono, N.; Miyake, H.; Saito, T.; Kaji A. A Convenient Synthesis of Sulfides, Formaldehyde Dithioacetals, and Chloromethyl Sulfides. *Synthesis* **1980**, 952−953. (b) Reinhard, G.; Soltek, R.; Huttner, G.; Barth, A.; Walter, O. Zsolnai. Chirale Tripodliganden mit Phosphor- und Schwefeldonoren. Synthese und Komplexchemie. *Chem. Ber.* **1996**, *129*, 97−108.

(17) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S., Jr.; Weiner, P. K. A New Force Field for Molecular Mechanical Simulation of Nucleic Acids and Proteins. *J. Am. Chem. Soc.* **1984**, *106*, 765−784. (b) Weiner, S. J.; Kollman, P. A. A Combined Ab Initio Quantum Mechanical and Molecular Mechanical Method for Carrying out Simulations on Complex Molecular Systems: Applications to the CH_3Cl^+ Cl^- Exchange Reaction and Gas Phase Protonation of Polyethers. *J. Comput. Chem.* **1986**, *6*, 718−730.

JM010096N