Articles

Design and Synthesis of Pyrrolidine-5,5-*trans*-lactams (5-Oxohexahydropyrrolo[3,2-*b*]pyrroles) as Novel Mechanism-Based Inhibitors of Human Cytomegalovirus Protease. 2. Potency and Chirality

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The stereospecific synthesis of a series of α-methylpyrrolidine-5,5-*trans*-lactam inhibitors of human cytomegalovirus (HCMV) protease is described. Examination of the SAR in this series has defined the size and chirality of the α-substituent, optimized the acyl substituent on the lactam nitrogen, and defined the steric constraint of this functionality. The SAR of the functionality on the pyrrolidine nitrogen of the *trans*-lactam has been investigated, and this has led to the discovery of potent serine protease inhibitors that are highly selective for the viral enzyme over the mammalian enzymes elastase, thrombin, and acetylcholine esterase. The mechanism of action of our lead compounds has been established by mass spectrometry, and enzymatic degradation of HCMV δAla protease acylated with these inhibitors showed that Ser 132 is the active site nucleophile. The crystal structure of HCMV protease was obtained and used to model the conformationally restricted, chiral (*S*)-proline-α-methyl-5,5-*trans*-lactams into the active site groove of the enzyme, enabling us to direct and rationalize the SAR in this series. The activity against HCMV δAla protease is the greatest with inhibitors based on the dansyl-(*S*)-proline α-methyl-5,5-*trans*-lactam template, which have low nanomolar activity against the viral enzyme.

Introduction

Human herpes viruses cause a range of diseases: HSV-1 (cold sores), HSV-2 (genital herpes), VZV (chicken pox, shingles), and HCMV (retinitis, pneumonitis). The current treatment of these diseases uses nucleoside (acyclovir, ganciclovir) and phosphate (PFA) substrate analogues. Because of the toxicity associated with PFA and ganciclovir, together with the emergence of mutants resistant to acyclovir, there is a need for a new class of antiherpes compounds based on a novel mechanism.

Human herpes viruses encode a serine protease, which is essential for viral replication.[1] Recent X-ray structures of the serine proteases of HCMV, HSV-1, HSV-2, and VZV revealed that these enzymes belong to a novel class of serine proteases where the active site is composed of the His, His, Ser triad.[3–6] Substrate cleavage sites across all the herpes virus family are unique and highly conserved, and these enzymes have become attractive molecular targets for the design of novel antiviral drugs.[1,2] We recently reported on the
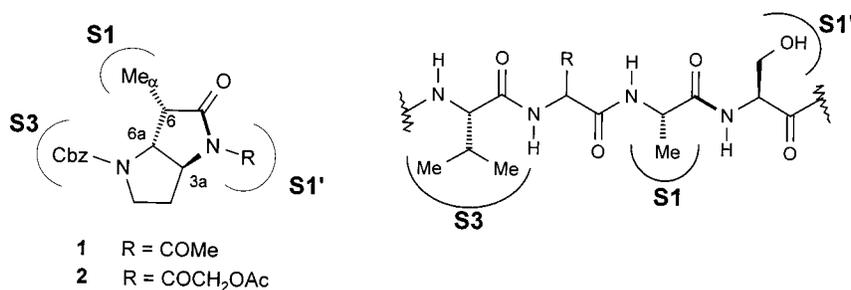
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Scheme 1

1	R = COMe
2	R = COCH$_2$OAc

design and synthesis of a novel class of mechanism-based inhibitors of human cytomegalovirus protease,[7,8] based on the α-methylpyrrolidine-5,5-*trans*-lactam template incorporating the natural substrate requirements of the consensus sequence of HCMV protease (Scheme 1). ESI-MS studies have shown that these inhibitors can bind covalently and reversibly in a time-dependent manner by a mechanism that is consistent with acylation of HCMV δAla protease at the active site nucleophile Ser 132.[7] SAR in this series of pyrrolidine-5,5-*trans*-lactams has defined the relative stereochemistry of the methyl substituent adjacent to the lactam carbonyl and the trend in activity of the functionality on the lactam nitrogen as acyl > ester > sulfonyl > carbamate against HCMV δAla protease.

We now report on work to define further the requirements of the substituent adjacent to the lactam carbonyl that accesses the S1 pocket and on work to exploit the substituents on the nitrogen atoms of this template that have the potential to access the conserved S1′ and S3 pockets of the protease that has given inhibitors with low nanomolar potency against the HCMV δAla protease.

Chemistry

We previously reported[7] that an α-methyl group at the 6 position and a carbonyl function on the nitrogen at the 2 position was optimal for maximum potency in the novel pyrrolidine-5,5-*trans*-lactam inhibitors (**1** and **2**) of HCMV protease (Scheme 1). To investigate the absolute configuration at the 6 position, the racemic mixture **1** was separated by chiral HPLC into the isomers **3** (RSR**)** and **4** (SRS), and their structures were confirmed by synthesis (Scheme 2). The racemic amine **5** was resolved using (+)-di-*O,O′*-*p*-toluyl-D-tartaric acid. The (*S*)-amine salt **6** was crystallized from the mixture of diastereomeric salts in ethanol and then recrystallized from ethanol, and the free amine was regenerated by base to give **7** in 98% yield. The amino ester **7** had previously been synthesized[9] from L-glutamine, confirming the chirality of the primary amine as (*S*). Cyclization of the amino ethyl ester **7** using *tert*-butylmagnesium chloride in THF gave the translactam **8** in 78% yield and 96% ee. Boc protection and methylation followed by deprotection gave **11** in 55% overall yield. Acylation of **11** with acetyl chloride gave **4** in 81% yield and 96% ee and was shown by chiral HPLC to be identical to the active isomer obtained by separation of the enantiomers. Similarly acylation of **11** with acetoxyacetyl chloride gave **12** in 75% yield.

We have introduced the larger allyl group into **13** using the same methodology developed for the methyl group. This proceeded in a lower yield (49%) to give **14** and was taken forward to the acetoxyacetyl derivative **16** via **15** in the usual manner (Scheme 3).

We recently showed that the *gem*-dimethyl-*trans*-lactam **19** could be prepared by alkylation of the β-methyl isomer **18** but not by alkylation of the corresponding α-isomer **20**.[18] Deprotection of **19** with TFA followed by acylation of **21** with acetyl chloride or acetoxyacetyl chloride gave **22** and **23** in 76% and 82% yield, respectively (Scheme 4).

Functionalized acyl derivatives on the lactam nitrogen in the α-methyl-5,5-*trans*-lactam series (Scheme 5) were prepared in 40−87% yield by acylating the anion of lactam **24**, with the corresponding mixed anhydride or acid chloride. The extended hydroxyethyl analogue **37** was similarly prepared via the silyl-protected derivative **36**. The formyl compound **25** was prepared in 54% yield by reacting **24** with sodium hydride followed by addition of DMF in ethylene glycol dimethyl ether in the presence of triflic anhydride.

Compounds with functionality other than ketones and amides were prepared by reacting the anion, generated by treating the lactam **24** with LHMDS, with a variety of electophiles (Scheme 6). Thus, 1,2-epoxy-3-phenoxypropane gave alcohol **38** in 41% yield and 2,4-dinitrofluorobenzene gave the dinitrophenyl derivative **39** in 70% yield. The *N*-pyrrole amide **40** was similarly prepared in 72% yield by reacting the lactam anion with pyrrole-1-carboxylic acid anhydride.[10] The phosphonate derivative **41** and the methylthio analogue **42** were also prepared by treating the lactam anion with dimethyl chlorophosphate and methyl methanethiolsulfonate, respectively. However, the corresponding reactions with diethyl chlorophosphate and dimethylphosphinic chloride failed. The conjugated ketone **43** was prepared in 30% yield by reaction of vinyl methyl ketone with lactam **24** in the presence of a Pd catalyst (PdCl$_2$(MeCN)$_2$) under an atmosphere of oxygen,[11] while alcohol **44** was prepared in 67% yield by treating **24** with paraformaldehyde in THF in the presence of potassium carbonate at room temperature.

Exploration of the substituents on the pyrrolidine nitrogen required to access the S2−S3 space has been done with a variety of linkers, namely, methyl ketone, sulfonamide, ketoamide, and amide (Scheme 7). The sulfonamide **46** was prepared in 53% yield by reacting the pyrrolidine **45** with the corresponding phenethylsulfonyl chloride at room temperature in the presence of triethylamine, whereas the reaction of pyrrolidine **45** with benzyl bromomethyl ketone required heating under reflux in acetonitrile to furnish the benzyl ketone **47** in 29% yield. The majority of amides were prepared using

Scheme 2[a]
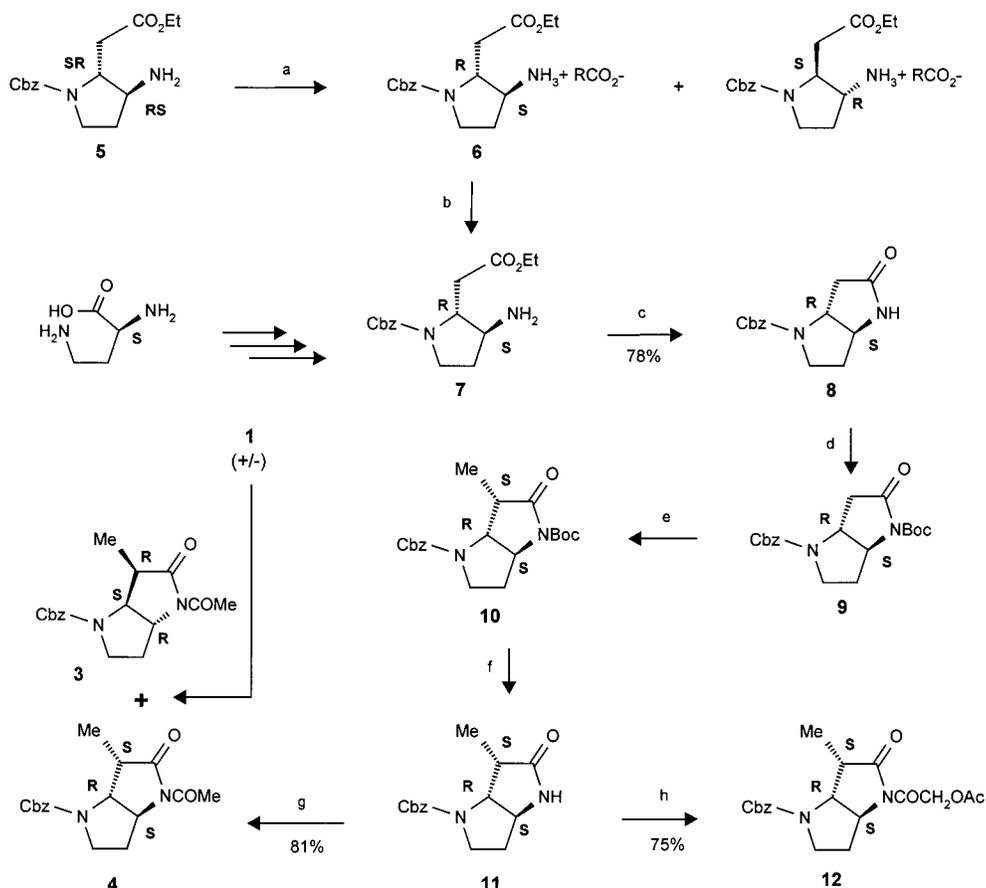
[a] Reagents and conditions: (a) RCO₂H = (+)-di-*O,O′-p*-toluyl-D-tartaric acid, ethanol; (b) aqueous K₂CO₃, EtOAc; (c) Bu^{t}MgCl, THF; (d) LHMDS (1.2 equiv)/THF, −78 °C, then 0 °C, 20 min, then (Boc)₂O (2.8 equiv)/THF, −78 °C; (e) LHMDS (1.3 equiv)/THF, −78 °C, then MeI (17 equiv); (f) TFA, 1 h, room temp; (g) LHMDS (1.2 equiv)/THF, −78 °C, then 0 °C, 30 min, then MeCOCl, −78 °C; (h) LHMDS (1.2 equiv)/THF, −78 °C, then 0 °C, 30 min, then MeCO₂CH₂COCl, −78 °C.
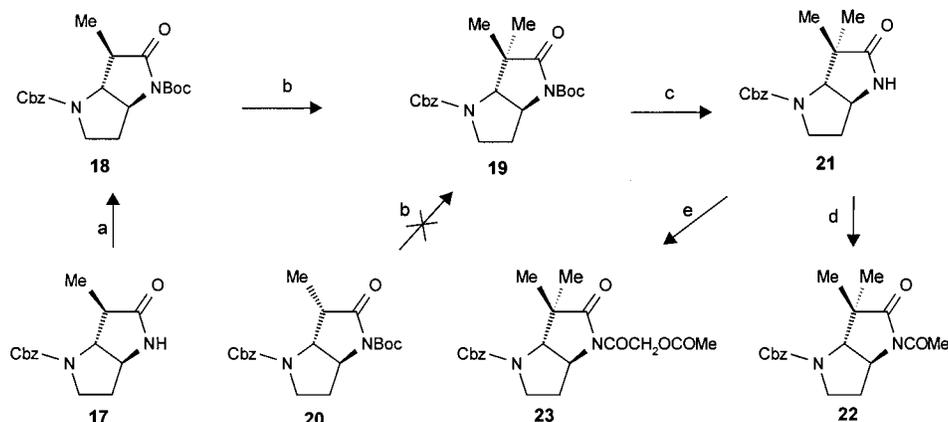
Scheme 3[a]
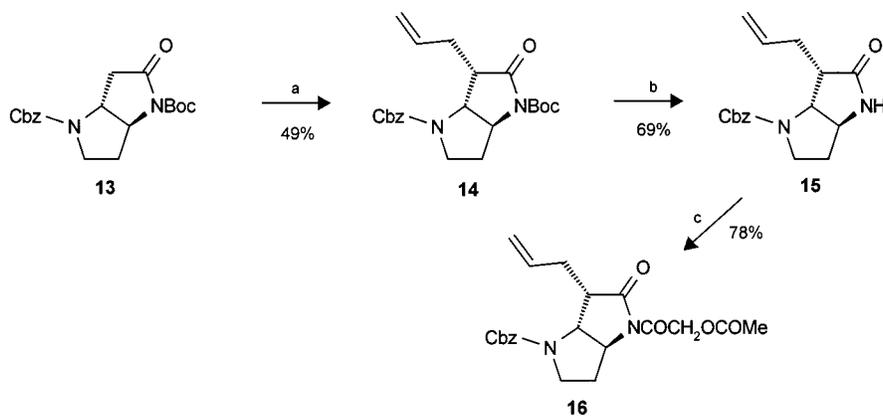
[a] Reagents and conditions: (a) LHMDS (1.3 equiv)/THF, −78 °C, then allyl I (17 equiv); (b) TFA, 2 h, room temp; (c) LHMDS (3 equiv)/THF, −78 °C, then MeCO₂CH₂COCl.

the coupling conditions *O*-benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate/1-hydroxybenzotriazole (TBTU/HOBT) in DMF at room temperature. Reacting racemic **45** with tosyl-(*S*)-proline gave the (S-*SRS*) amide **51** (38%) and the (S-*RSR*) diastereoisomer **52** (30%). Similarly, reaction of racemic **45** with benzoyl-(*S*)-proline or dansyl-(*S*)-proline gave the corresponding diastereoisomers **53** and **54**, or **55** and **56**, respectively.

The phenoxyacetamide **48**, the ketoamide **50**, the indolacetamide **49**, and the nitrophenylsulfonyl-(*S*)-proline **57** derivatives were similarly prepared in 51%, 45%, 56%, and 23% yield, respectively.

Reacting the racemic Boc-protected *trans*-lactam **58** with dansyl-(*S*)-proline gave the two diastereoisomers **59** and **60** in 30% and 38% yield, respectively (Scheme 8).

Scheme 4[a]

[a] Reagents and conditions: (a) LiHMDS (3 equiv)/THF, −78 °C then (Boc)$_2$O; (b) LiHMDS (1.3 equiv)/THF, −78 °C, then MeI ((17 equiv); (c) TFA, 2 h, room temp; (d) LHMDS (1.2 equiv)/THF, −78 °C, then 0 °C, 30 min, then MeCOCl, −78 °C; (e) LHMDS (1.2 equiv)/THF, −78 °C, then 0 °C, 30 min, then MeCO$_2$CH$_2$COCl, −78 °C.

Scheme 5[a]
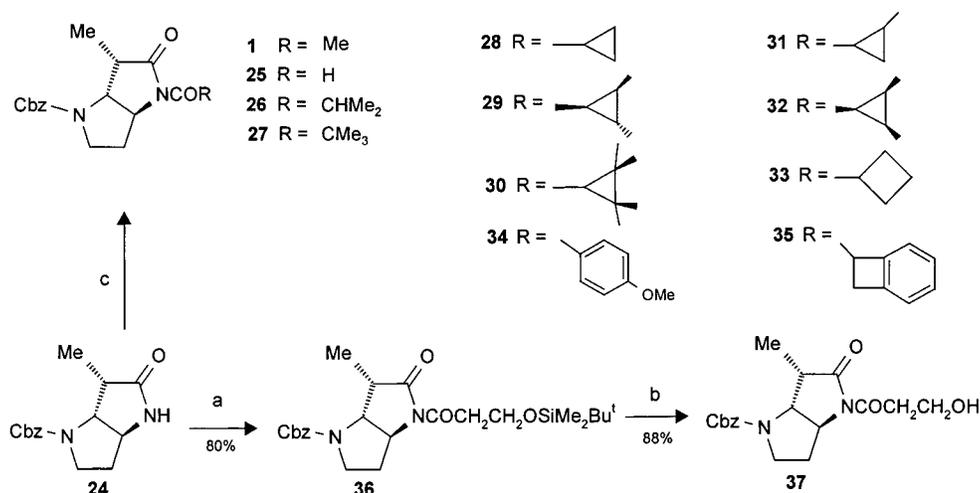
[a] Reagents and conditions: (a) LHMDS (1.4 equiv)/THF, −78 °C, then Me$_3$CCO$_2$COCH$_2$CH$_2$OSiMe$_2$Bu^t; (b) AcOH/H$_2$O/THF, 10/3/1, room temp, 8 h; (c) LHMDS (1.4 equiv)/THF, −78 °C, then RCOCl or RCO$_2$COCMe$_3$.

Deprotection of **60** with TFA gave the lactam **61** in 95% yield, which reacted with cyclopropane carbonyl chloride in the presence of LHMDS to give **62** in 80% yield. Comparison of the CD spectra of **62** and **4** showed that the configuration of the *trans*-lactam ring was the same (*SRS*) in both compounds.

Deprotection of **28** with hydrogen in the presence of palladium gave the amine, which was isolated as the hydrochloride **63** in quantitative yield. Reaction of **63** with dansylsarcosine in the presence of TBTU/HOBT and DIPEA gave the amide **64**. Similarly, reaction of **63** with dansyl-(*S*)-alanine and (*R,S*)-pipecolic acid gave, after separation from their corresponding diastereoisomers, the (S-*SRS*) isomers **65** and **66** in 30% and 14% yield, respectively (Scheme 9). Reaction of racemic **63** with Cbz-(*S*)-proline gave a diastereomeric mixture of amides from which the (S-*SRS*) amide **67** was isolated in 38% yield. Hydrogenolysis of **67** gave the amine **68** in quantitative yield. Reaction of **68** with 3-[(dimethylamino)carbonyl]benzenesulfonyl chloride, 3-(1-methylethoxy)benzenesulfonyl chloride, and 3-[(dimethylamino)carbonyl]benzenemethanesulfonyl chloride in the presence of triethylamine gave the chiral sulfonamides **69**, **70**, and **71** in 32%, 43%, and 22% yield, respectively.

Results and Discussions

The chromogenic assay developed earlier[12,17] based on the 7-mer peptide *p*-nitroanilide (RESYVKA-*p*NA) of the release site and HCMV δAla protease has been developed further into a microtiter assay and is comparable to the HPLC assay used previously[7] (Table 1). IC$_{50}$ data for compounds are determined by preincubating the enzyme with inhibitor for 15 min. We showed recently[7] that the preferred stereochemistry of the methyl group adjacent to the lactam carbonyl was α for activity against HCMV δAla protease. We have investigated the steric space at this position by making the α-allyl derivative **16** (Scheme 2) and the *gem*-dimethyl analogues **23** and **22** (Scheme 3). The α-allyl derivative **16** was less active (51% inhibition at 500 μM) than the methyl derivative **1** (96% inhibition at 500 μM) with the same stereochemistry. The *gem*-dimethyl analogues **23** and **22** were virtually inactive in this series with 2% and 8% inhibition, respectively, at 500 μM. Thus, we are confident that we have defined the stereochemistry and size of the substituent at S1.

To define the chirality of the preferred substituent at S1, both enantiomers (**4**-*SRS* and **3**-*RSR*) of **1** were
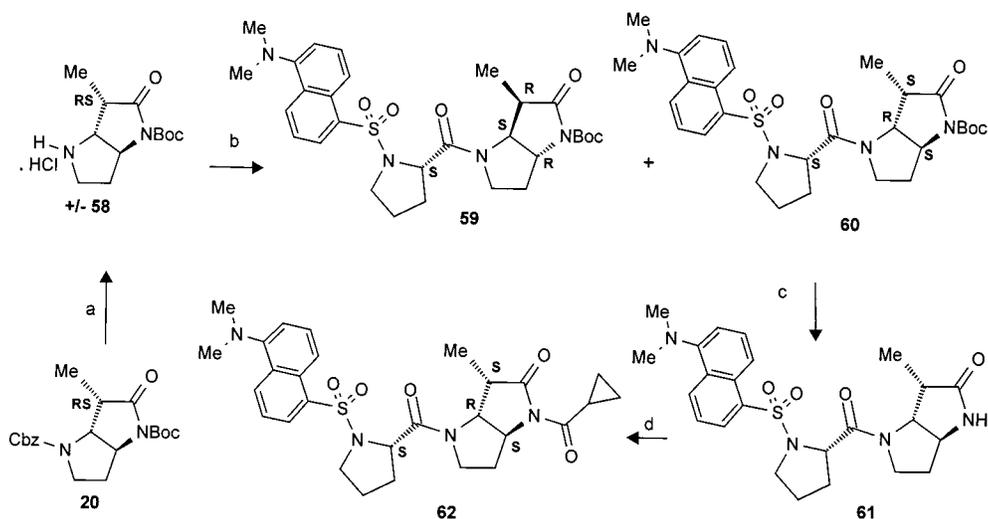
Scheme 6[a]
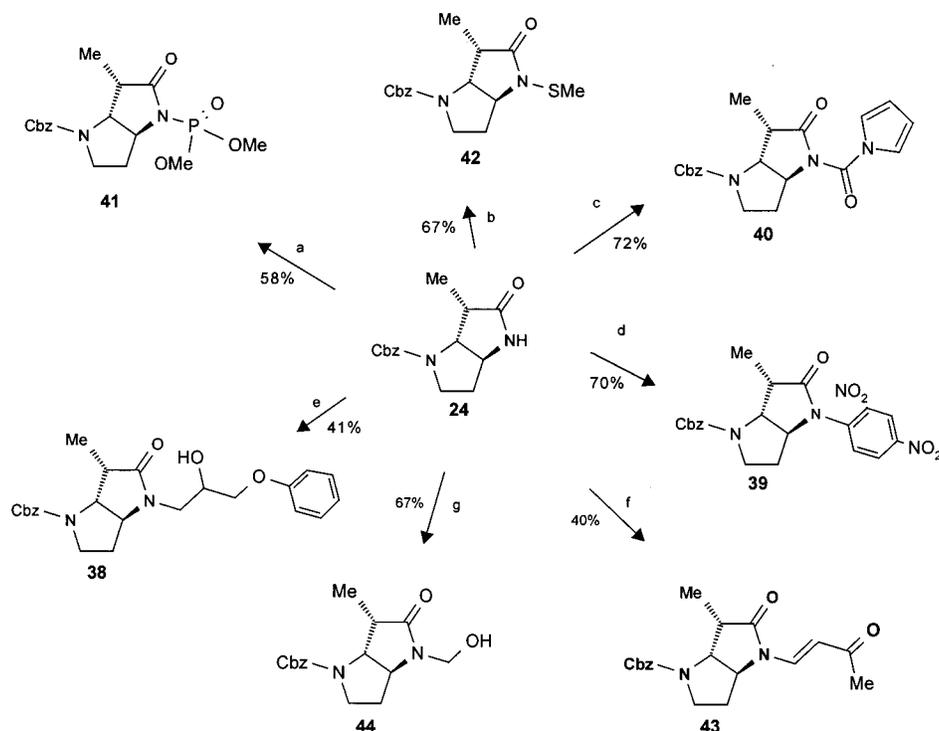
[a] Reagents and conditions: (a) LHMDS (1.4 equiv)/THF, −78 °C, then ClP(O)OMe$_2$; (b) LHMDS (1.5 equiv)/THF, −78 °C, then MeSSO$_2$Me (2 equiv) −78 to 0 °C, 2 h; (c) LHMDS (1.1 equiv)/THF, −78 °C, then (pyrrole-CO)$_2$O; (d) LHMDS (1.4 equiv)/THF, −78 °C, then FC$_6$H$_3$(NO$_2$)$_2$; (e) LHMDS (1.5 equiv)/THF, −78 °C, then 2-epoxy-3-phenoxypropane (1.5 equiv); (f) CuCl, DME, PdCl$_2$(MeCN)$_2$, O$_2$, MeCOCH=CH$_2$; (g) (CH$_2$O)$_n$, K$_2$CO$_3$, THF, room temp.

Scheme 7[a]
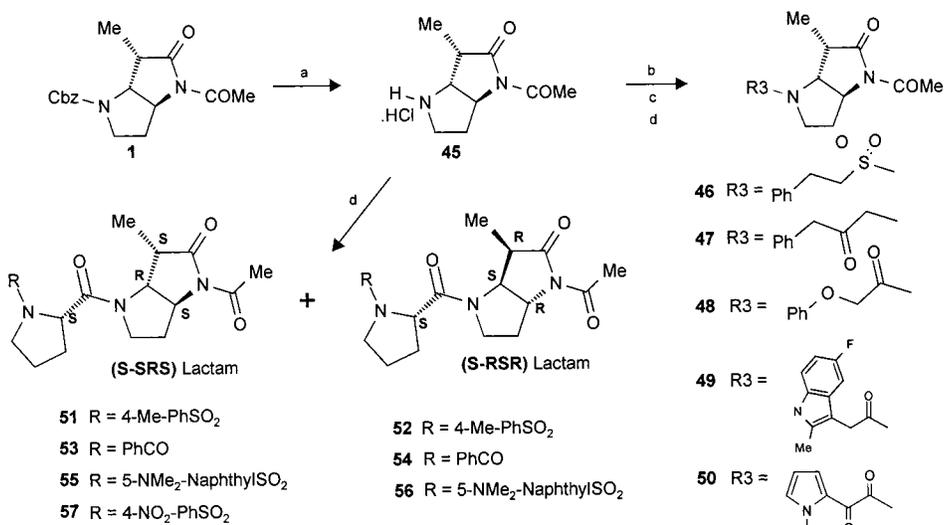
[a] Reagents and conditions: (a) H$_2$, Pd/C, i-PrOH, room temp, then HCl/ether; (b) RSO$_2$Cl (1.1−1.5 equiv), Et$_3$N, MeCN, room temp; (c) PhCH$_2$COCH$_2$Br (1.5 equiv) Et$_3$N, MeCN, reflux; (d) RCO$_2$H, TBTU, HOBT, i-Pr$_2$EtN, DMF, room temp.

separated by chiral HPLC. Only one of these (**4**-*SRS*) was shown to be active against HCMV δAla protease (Table 1). The activity was predicted to be in the isomer where the Me group was the same configuration (*S*) as the Ala side chain of the natural peptide substrate for HCMV protease (Scheme 10). This was confirmed by synthesis (Scheme 2). The corresponding acetoxyacetyl analogue (**12**-*SRS*) was also prepared and found to be more active than the racemate **2** our previous lead compound (Table 1).

Additional acyl derivatives were prepared in an effort to increase potency in this series (Table 2). The hydroxyethylcarbonyl compound **37** was prepared in an attempt to mimic the Ser hydroxyl at S1′, but it did not show any improvement over the acetyl compound **1** in terms of potency. Increasing the size of this acyl functionality to the isopropyl and tertiary butyl analogues **26** and **27**, respectively, caused a loss in potency (Table 2), indicating that the steric bulk adjacent to the carbonyl at the S1′ site is not tolerated.

Scheme 8[a]

[a] Reagents and conditions: (a) H$_2$, Pd/C, i-PrOH, room temp, then HCl/ether; (b) dansyl-(*S*)-proline, TBTU, HOBT, i-Pr$_2$EtN, DMF, room temp; (c) TFA, 2 h, room temp; (d) LHMDS (1.4 equiv)/THF, −78 °C, then cyclopropyl-COCl.

Scheme 9[a]
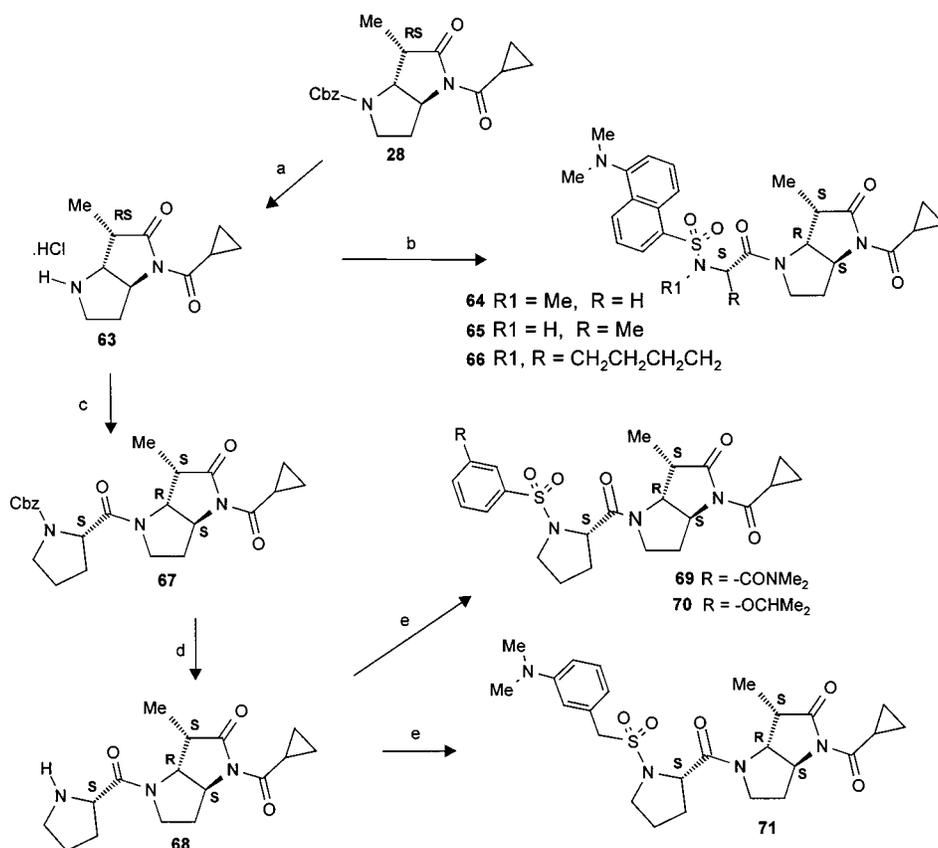
[a] Reagents and conditions: (a) H$_2$, Pd/C, i-PrOH, room temp, then HCl/ether; (b) R'CO$_2$H, TBTU, HOBT, i-Pr$_2$EtN, DMF, room temp; (c) Cbz-proline, TBTU, HOBT, i-Pr$_2$EtN, DMF, room temp; (d) H$_2$, Pd/C, i-PrOH, room temp, then HCl/ether; (e) R'SO$_2$Cl, (1.1−1.5 equiv), Et$_3$N, MeCN, room temp.

Interestingly, some bulk is allowed in that both the cyclopropylcarbonyl compound **28** and the cyclobutyl-carbonyl compound **33** are more active than the acetyl compound **1**. Additional cyclic acyl derivatives were prepared in an attempt to increase potency further in this class. Increasing the steric bulk on the cyclopropyl ring showed a decrease in potency from the monomethyl derivative **31** via the dimethyl derivative **32** to the tetramethyl derivative **30**. While the monomethyl de-

rivative **31** is equipotent to the cyclopropylcarbonyl compound **28**, the tetramethyl derivative **30** is essentially inactive. Interestingly the *cis*-(*Z*)-2,3-dimethyl derivative **32** is more active than the *trans*-(*E*)-2,3-dimethyl derivative **29**, showing the subtle steric requirements at this position. The arylcarbonyl compound **34** is essentially inactive; however, the benzocyclobutane compound **35** with an aryl ring more distant from the carbonyl function is as active as the acetyl compound
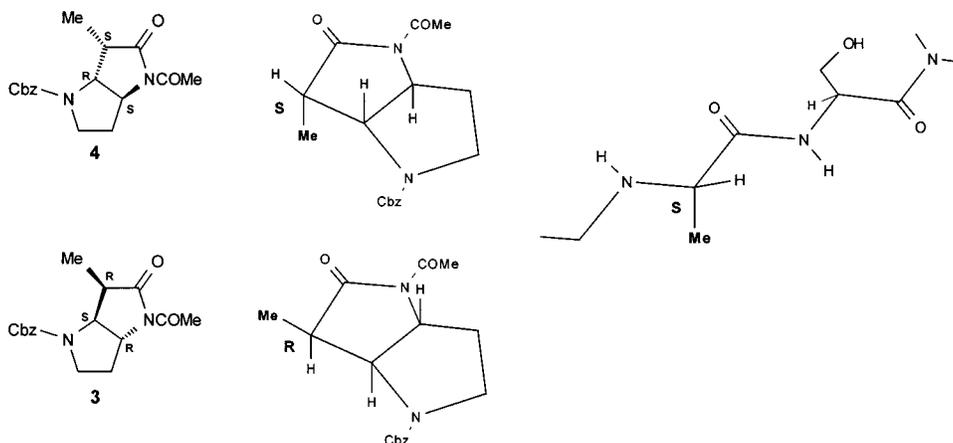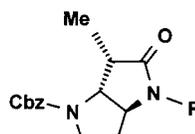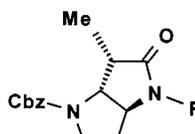
Scheme 10

Table 1

		HCMV protease	
		HPLC assay[7]	*p*NA assay[12]
compd	R	protease IC$_{50}$, μM	protease IC$_{50}$, μM
1	*rac-* COMe	110	40
3	*RSR* COMe	>1000	
4	*SRS* COMe	79	
2	*rac-* COCH$_2$OCOMe	13	11
12	*SRS* COCH$_2$OCOMe	6	

Table 2 [12]

	HCMV protease	
compd	R	IC$_{50}$, μM
2	COCH$_2$OCOMe	11
37	COCH$_2$CH$_2$OH	133
1	COMe, log *P* = 2.21	40
26	COCHMe$_2$	126
27	COCMe$_3$	>500
33	CO-cyclobutyl	32
35	CO-benzocyclobutyl	11.5
28	CO-cyclopropyl	9
31	CO-2-Me-cyclopropyl	10
32	CO-(*Z*)-2,3-diMe-cyclopropyl	72
29	CO-(*E*)-2,3-diMe-cyclopropyl	>100
30	CO-*tetra*-Me-cyclopropyl	>500
34	CO-C$_6$H$_4$-4OMe	>500

1, indicating again that the bulk adjacent to this functionality is not tolerated.

A series of other S1′ substituents was also prepared in an effort to improve activity and to mimic the serine hydroxyl at this position in the natural substrate (Table 3). Both alcohols **38** and **44** were inactive as were the vinyl ketone **43**, the dimethylphosphonate **41**, and the thiomethyl analogue **42**. However, the dinitrophenyl derivative **39** showed some activity at ~500 μM and the formyl compound **25** and acyl pyrrole **40** were weakly active.

Having optimized the S1 and S1′ positions, we turned our attention to the other conserved pocket in this

Table 3 [12]
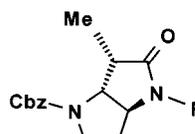
	HCMV protease	
compd	R	IC$_{50}$, μM
40	CO-*N*-pyrryl	250
25	CHO	398
44	CH$_2$OH	>500
38	CH$_2$CH(OH)CH$_2$OPh	>500
43	CH=CHCOCH$_3$	>500
41	PO(OMe)$_2$	>500
42	SMe	>500
39	C$_6$H$_3$-2,4-(NO$_2$)$_2$	~500

enzyme at the S3 position. Comparison of several compounds bearing linkages of a phenyl group three atoms from the pyrrolidine nitrogen of **1**, **47**, **48**, and **46** indicate that none has a particular advantage in terms of potency (Table 4).

In an effort to increase the potency of **1**, we have used array technology to make a wide range of substituents on the pyrrolidine nitr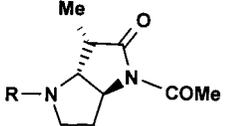ogen to thoroughly span the S2–S3 space, incorporating an isopropyl group and other functionality to mimic the conserved valine required for S3 in the natural substrate. This produced three lead compounds with increased potency, the 2-methyl-5-fluoroindole-3-acetamide **49**, *N*-methylpyrrole-2-keto-amide **50**, and the *N*-tosyl-(*S*)-proline derivative **51** (Table 4). Replacing the ketocarbonyl of the *N*-meth-ylpyrrole-2-ketoamide **50** with methylene, changing the heterocycle, or removing the *N*-methyl function resulted in lost activity, as did replacing the fluorine substituent and changing the heterocycle in the 2-methyl-5-fluoro-indole-3-acetamide **49**. Lead optimization of the proline derivative **51** was successful and showed that this arylsulfonyl derivative is more active than the arylcar-bonyl analogue **53** (Table 5). Also both the (S-*SRS*) isomers **51** and **53** are more active than the correspond-ing (S-*RSR*) isomers **52** and **54**. While the *p*-nitro analogue **57** has a potency similar to that of the *p*-methyl analogue **51**, both of these monocyclic deriva-tives are less active than the bicyclic dansyl-(*S*)-proline analogue **55** (IC$_{50}$ = 0.54 μM). The corresponding cyclopropyldansyl-(*S*)-proline analogue **62** is even more potent (IC$_{50}$ = 0.34 μM), and both are ~2 orders of

Table 4 [12]

	HCMV protease	IC$_{50}$,
compd	R	μM
1	PhCH$_2$OCO	40
47	PhCH$_2$COCH$_2$	79
48	PhOCH$_2$CO	63
46	PhCH$_2$CH$_2$SO$_2$	45
50	*N*-Me-2-pyrrolyl-COCO	5
49	5-F-2-Me-3-indolyl-CH$_2$CO	6
51	*N*-tosyl-(*S*)-prolinyl	14

Table 5 [12]
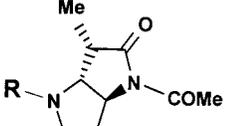
	HCMV protease	
compd	R	IC$_{50}$, μM
51	4-MePhSO$_2$N-pyrrolidine-2-CO (S-*SRS*)	14
52	4-MePhSO$_2$N-pyrrolidine-2-CO (S-*RSR*)	159
53	PhCON-pyrrolidine-2-CO (S-*SRS*)	50
54	PhCON-pyrrolidine-2-CO (S-*RSR*)	>500
57	4-NO$_2$PhSO$_2$N-pyrrolidine-2-CO (S-*RSR*)	11
55	5-NMe$_2$-naph-SO$_2$N-pyrrolidine-2-CO (S-*SRS*)	0.54
56	5-NMe$_2$-naph-SO$_2$N-pyrrolidine-2-CO (S-*RSR*)	>500

Table 6 [12]
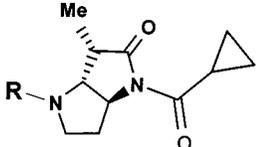
	HCMV protease	
compd	R	IC$_{50}$, μM
62	5-NMe$_2$-naph-SO$_2$N-pyrrolidine-2-CO (S-*SRS*)	0.34
64	5-NMe$_2$-naph-SO$_2$NMe-CH$_2$CO (*SRS*)/(*RSR*)	>100
65	5-NMe$_2$-naph-SO$_2$NH−CHMeCO (S-*SRS*)	7
66	5-NMe$_2$-naph-SO$_2$N-piperidine-2-CO (S-*SRS*)	13
69	3-NMe$_2$COPhSO$_2$N-pyrrolidine-2-CO (S-*SRS*)	1.4
71	3-NMe$_2$PhCH$_2$SO$_2$N-pyrrolidine-2-CO (S-*SRS*)	2.2
70	3-Me$_2$CHOPhSO$_2$N-pyrrolidine-2-CO (S-*SRS*)	65

magnitude more potent than Cbz compound **1**. The corresponding (S-*RSR*) diastereoisomer **56** of **55** is inactive, again indicating that the stereochemistry of the translactam ring is crucial for activity.

To see if the dansyl-(*S*)-proline was essential for good activity, several other (*S*) amino acid linkers and partial structures of the dansyl ring in the dansyl-(*S*)-proline cyclopropyl analogue **62** were prepared (Table 6). However, the partial proline structures of the glycine **64** and alanine **65** analogues were much less active, as was the six-membered pipecolic analogue **66**, indicating that the rigid (*S*)-proline ring was optimal for activity.

Compounds **69**−**71** (Table 6), containing partial structures of the dansyl ring, have less activity than **62**. It seems that both chiral dansyl-(*S*)-proline analogues **55** and **62** are conformationally restricted, semirigid compounds, where both the (*S*)-proline ring and the bicyclic

Table 7

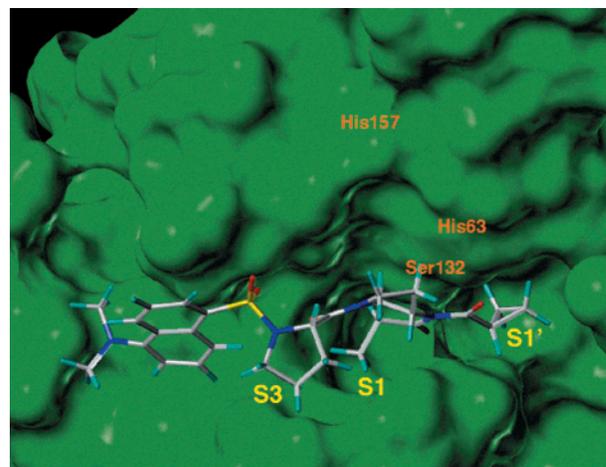|	thrombin	acetylcholine	elastase	HCMV protease	
compd	IC$_{50}$, μM	esterase IC$_{50}$, μM	IC$_{50}$, μM	IC$_{50}$, μM	K_i, nM
55	>200	>100	>10	0.54	34
62	>200	>100	>10	0.34	20

Figure 1.

dansyl function are important for potent activity against HCMV δAla protease. These two dansyl-(*S*)-proline derivatives **55** and **62** are the most active compounds of this series (Tables 5 and 6), having potencies of K_i = 34 and 20 nM, respectively, and show selectivity for the viral HCMV protease over acetylcholine esterase and the mammalian proteases elastase and thrombin (Table 7).

X-ray crystal structures of various HCMV protease mutants are known.[3−6] We have crystallized the recombinant HCMV protease mutant (V141Y, V207Y, and A209N) and determined its X-ray crystal structure at 2.2 Å resolution.[13] We have used the X-ray coordinates of this HCMV protease in a modeling study[14] with the semirigid *trans*-lactam **62** and compared it to a similarly docked substrate analogue model. Figure 1 shows a view of the active site of (V141Y, V207Y, and A209N) HCMV protease incorporating **62** in what could be considered as an initial binding complex. The α-Me in the (*S*) configuration extends into the S1 specificity pocket as expected from the substrate requirements of a conserved alanine at this position for this enzyme. The C-1 *trans*-lactam carbonyl is situated in the oxyanion pocket formed by the backbone amide NH of arginine 165 and arginine 166 and is in position for attack by the hydroxyl of serine 132, which is part of the active site catalytic triad formed by serine 132, histidine 63, and histidine 157. The lactam substituent extends into the prime sites of the enzyme. The model shows that α-Me in the (*S*) configuration is easily accommodated in the S1 pocket and allows us to visualize why the (*R*) configuration for the α-Me is less favorable. There is clearly insufficient room for the (*R*) configuration to fit *and* preserve the complementarity of the other portions of the molecule to the active site. The α-allyl in the (*S*) configuration found in **16** is also unable to access the S1 pocket.

The (*S*)-proline carbons C-4′ and C-5′ fit into the S3 pocket, and the rigidity of the proline ring can be seen as important because the flexibility of the partial
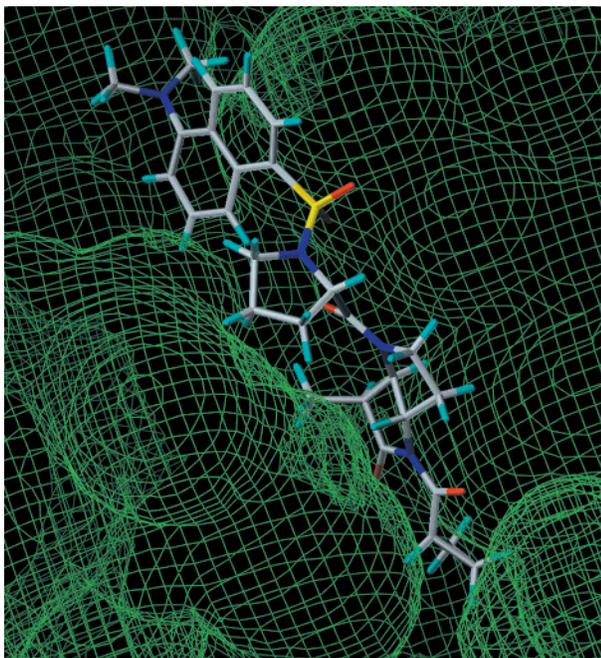
Figure 2. Me probe of HCMV protease active site and inhibitor **62**.

structures **64** and **65** and the more flexible six-membered ring **66** do not allow access to this pocket and they are all >10-fold less active. Also, in the rigid (*S*)-proline analogue **62,** the dansyl ring is held in a position to make a favorable hydrophobic interaction with the enzyme, which is less efficiently accessed with the more flexible partial structures. Both rings of the dansyl function are necessary for this hydrophobic interaction because the more flexible partial structures **71** and **69**, which make less of an interaction, are much less active.

While only one sulfonamide oxygen is located within hydrogen-bonding distance of the backbone amide NH of Ser 135, both sulfonamide oxygens are within hydrogen-bonding distance of this residue in the tetrahedral transition state, which might explain some of the beneficial effects of the sulfonamide over the amide at this position.

The cyclopropylcarbonyl function extends into the S′ prime sites of the enzyme. However, while the cyclo-

propyl ring substituted with one methyl group **31** is tolerated, increasing this to two adjacent methyls (**32** and **29**) was less well tolerated and the tetramethyl analogue **30** is essentially inactive because of unavoidable clashes with the enzyme regardless of what conformation this functionality takes up.

The semirigid nature of **62** prearranges the molecule in a conformation that mimics the shape adopted by peptide substrates bound in serine proteases, allowing the inhibitor to fit snugly in the active site channel/groove (Figure 2). This has been shown by a comparison of our docked molecules with a model of a substrate analogue iodo-Y-V-N-A-S-aldehyde recently shown[3] in an X-ray crystal structure bound in the active site of HCMV protease. We see good register between the α-Me groups in P1, and also between the valine side chain of the substrate analogue and the proline ring carbons of **62** residing in P3.

To investigate the mechanism of action of the dansyl-(*S*)-proline-derived *trans*-lactam **55** interaction with δAla, HCMV protease was studied by liquid chromatography (LC) coupled to electrospray ionization mass spectrometry (ESI-MS). The complexes formed between the enzyme and the compound were analyzed over a time course, aliquots taken initially at 20 min and 1, 2, 4, and 48 h, to enable assessment of the potency and duration of inhibition as a result of any covalent modification (Figure 3). In a detailed study additional time points were introduced, 30 s and 1, 2, 3, 5, 8, 12, and 18 min, specifically to investigate the early stages of interaction. Once acylation of the enzyme had been confirmed, the key residues in the catalytic triad were identified using LC−ESI-MS and ESI-MS−MS techniques in conjunction with enzymatic degradation of the acylenzyme species, as previously described.[12]

The HCMV δAla protease, unmodified average molecular weight (M_{av}) determined as 27 824 Da, was fully acylated after only 1 min of incubation with compound **55**. The M_{av} of the complex was determined as 28 336 Da for **55**, corresponding to the M_{av} of the enzyme plus the molecular weight of the inhibitor. Further to this, complete acylation was preserved for at least 4 h following addition. Samples analyzed after 48 h contained only unmodified HCMV δAla protease, indicating
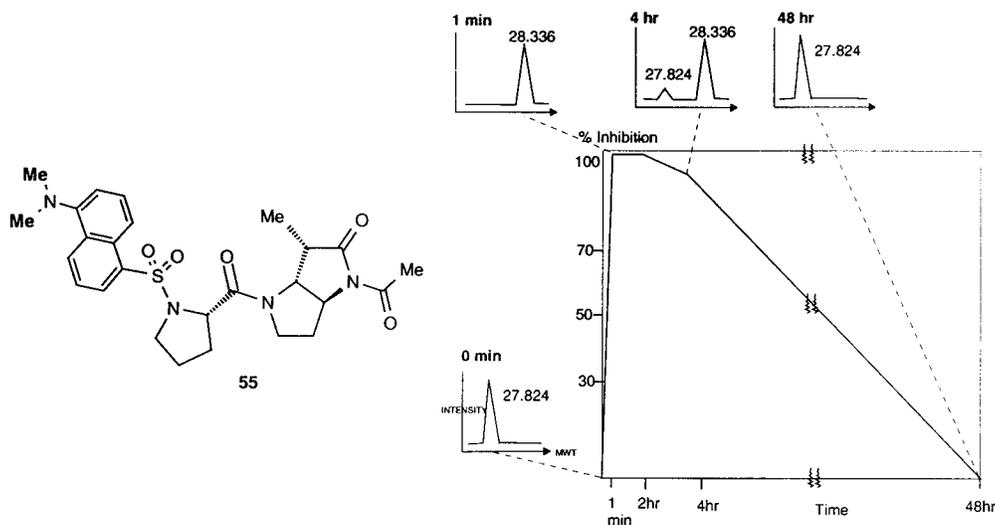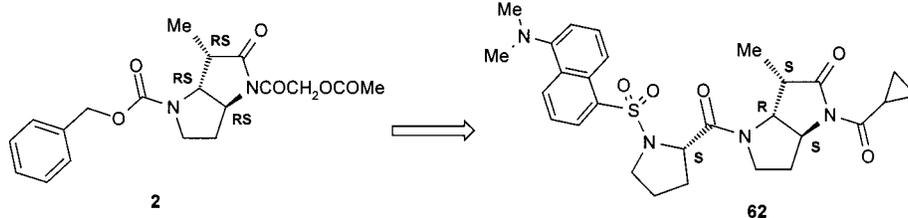

Figure 3. MS characterization of the acylation of HCMV δAla protease by α-methyl- pyrrolidine-5,5-*trans*-lactams.

Figure 4.

turnover of the compound within this period. LC−ESI-MS analysis of the products of a tryptic digestion of the acylated complex formed with the enzyme and **55** revealed a peptide having an increased mass relative to that expected, which corresponded to the molecular weight of peptide plus **55**. ESI-MS−MS analysis of this peptide revealed serine 132 to be the active site hydroxyl nucleophile. This is in agreement with published crystal structures[3−6] and site-directed mutagenesis and affinity labeling studies.[2,15]

Conclusions

Having previously defined the stereochemistry[7] of the substituent next to the lactam carbonyl (for accessing the S1 specificity site) required for activity against HCMV δAla protease, we have now defined its size and shape and have shown the preferred chirality of this α-Me substituent to be (*S*). A stereospecific synthesis has been developed for the chiral (*SRS*)-α-methylpyrrolidine-5,5-*trans*-lactam template required for potent inhibitors of human cytomegalovirus (HCMV) protease. Optimization of the substituent on the lactam nitrogen has shown that activity against HCMV δAla protease is in the order CO-cyclopropyl > COMe > CO$_2$Me > SO$_2$-Me > CONHMe. Optimization of the functionality on the pyrrolidine nitrogen gave the highly potent dansyl-(*S*)-proline derivatives **55** and **62** (with K_i's in the low nanomolar range against HCMV δAla protease), which are highly selective over the mammalian enzymes elastase, thrombin and acetylcholine esterase. Mechanism of action studies using ESI-MS together with enzymatic degradation of the acylated HCMV protease showed that these inhibitors acylate HCMV protease at the active site serine (Ser 132) in a time-dependent and reversible manner. The crystal structure of HCMV protease was obtained and used to model the conformationally restricted, chiral (*S*)-proline-α-methyl-5,5-*trans*-lactams into the active site groove of the enzyme, enabling us to direct and rationalize the SAR in this series. In summary, using SAR, we have developed the racemic defined template **2** (Figure 4) with micromolar activity against HCMV protease into the chiral proline *trans*-lactam **62** with low nanomolar potency against the viral enzyme.

Experimental Section

General Procedures. Melting points were obtained using an electrothermal digital melting point apparatus and are uncorrected. All purifications by flash chromatography were performed using Kieselgel 60, Merck 9385 silica gel. Monitoring of reactions by TLC used Merck 60 F$_{254}$ silica gel glass backed plates (5 cm × 10 cm), and the products were eluted with mixtures of ethyl acetate and cyclohexane and visualized by UV light, followed by heating with aqueous phosphomolybdic acid. Analytical HPLC measurements were run on a Hewlett-Packard 1090 HPLC instrument equipped with an

Intersil M column ODS2. Standard conditions were eluent system A (H$_2$O, 0.1% H$_3$PO$_4$) and system B (95% MeCN/H$_2$O, 0.1% H$_3$PO$_4$): gradient was 0% B at 2 min, 0−100% B at 40 min, 100% B at 10 min; flow rate was 1 mL/min; λ = 215 nm. Retention times (t_R) are given in minutes. All NMR spectra were run on a Bruker 250 MHz instrument generally as solutions in CDCl$_3$ unless otherwise stated. IR spectra were recorded on a Bio-rad FTS7 spectrometer from thin films on NaCl plates, from a KBr mix, or from solutions in the solvent specified. Mass spectra were run by an electrospray Hewlett-Packard 5989B instrument. CD spectra were recorded in acetonitrile on a Jasco J-720A spectropolarimeter. Optical rotations were taken with a Perkin-Elmer model 241 polarimeter. Enantiomeric excess (% ee) was determined by chiral HPLC analysis using a Chiracel OJ or Chiral Pak AD464 column with a UV detector at λ = 215 nm and with eluents and flow rates as indicated in each case. Final organic solutions were dried over MgSO$_4$ before filtration and evaporation using a Buchi rotavapor. Ambient temperature was 20 °C. All solvents used were Fisons analytical reagents except for pentane (Aldrich Chemical Co.) and anhydrous THF (Fluka Sureseal). All other reagents were obtained from Aldrich, Fluka, or Lancaster. Elemental microanalyses were determined by the Microanalytical Laboratory, GlaxoSmithKline Stevenage.

(2*R*,3*S*)-3-Amino-2-ethoxycarbonylmethylpyrrolidine-1-carboxylic Acid Benzyl Ester (2*S*,3*S*)-Bis(4-methyl-*O*-benzyloxy)succinate Salt (6). To a solution of *trans*-3-amino-2-ethoxycarbonylmethylpyrrolidine-1-carboxylic acid benzyl ester[7] **5** (168.9 g, 0.55 mol) in ethanol (2500 mL) was added a solution of (+)-di-*O*-*p*-toluyl-D-tartaric acid (213 g, 0.55 mol) in ethanol (2500 mL), and the solution was allowed to stand overnight. The resulting solid was collected by filtration, washed with ethanol, and then recrystallized from boiling ethanol (3500 mL) to give the **6** as a white solid, 93.7 g. A further recrystallization gave a white solid, mp 184−185 °C. HPLC analysis using a Chiracel OJ column showed it to be 97.5% ee (ethanol/heptane (3:7), flow rate = 1 mL/min, λ = 215 nm, t_R = 7.7 min)). Anal. (C$_{36}$H$_{40}$N$_2$O$_{12}$·0.2EtOH) C, H, N.

(2*R*,3*S*)-3-Amino-2-ethoxycarbonylmethylpyrrolidine-1-carboxylic Acid Benzyl Ester (7). The intermediate salt **6** (131.8 gm, 190 mmol) was suspended in water/ethyl acetate (1:1) (1500 mL), and solid potassium carbonate was added (63 g, 457 mmol). After 15 min, the phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 200 mL). The organic portions were combined and washed with water and brine, dried, and evaporated to give **7** as a colorless oil (57.8 g, 98%): ^{1}H NMR (CDCl$_3$) δ 7.37 (5H, m, C$_6$H$_5$), 5.15 (2H, m, PhCH$_2$), 4.15 (2H, m, CO$_2$CH$_2$CH$_3$), 3.91 (d, J = 9.4 Hz, 1H) and 3.67 (m, 1H) and 3.49 (m, 2H) (CH$_2$CHNH$_2$, CH$_2$-NCbz and CHNCbz), 2.99 (d, J = 16.3 Hz, 0.5H) and 2.79 (d, J = 16.3 Hz, 0.5H) (EtOCOCH$_2$), 2.33 (dd, J = 10.0 Hz, J = 15.7 Hz, 1H, EtOCOCH$_2$), 2.10 (m, 1H, CH$_2$CH$_2$HCHNH$_2$), 1.70 (m, 1H, CH$_2$CH$_2$CHNH$_2$), 1.38 (s, 2H, NH$_2$), 1.25 (m, 3H, CH$_3$); MS (thermospray) m/z 307 (MH$^+$), 613 (2M + H$^+$); [α]$_D$ −11.3° (*c* 1.33, MeOH). Anal. (C$_{16}$H$_{22}$N$_2$O$_4$) C, H, N.

(3a*S*,6a*R*)-5-Oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (8). To **7** (52.9 g, 173 mmol) in tetrahydrofuran (550 mL), under nitrogen and in an ice-salt bath was added dropwise a solution of *tert*-butylmagnesium chloride (554 mL of a 1 M solution in tetrahydrofuran, 554 mmol), keeping the temperature at <1 °C. The mixture was warmed to room temperature over 1 h and 15 min, then

quenched with saturated ammonium chloride while cooling in an ice bath. The phases were separated, and the aqueous phase was extracted with ethyl acetate. The combined organics were washed with water and brine, dried, and evaporated to give the title compound as a cream solid, 43.5 g (97%). A portion of the solid was purified by flash column chromatography using ethyl acetate as the eluting solvent to give the lactam **8** as a white solid, mp 157−159 °C: IR (KBr) 3277, 1699, 1690 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.35 (m, 5H, C$_6$H$_5$), 5.99 (s, 1H, N*H*), 5.12 (ABq, *J* = 12.5 Hz, 2H, PhC*H$_2$*), 3.87 (dd, *J* = 10.4 Hz, *J* = 12.4 Hz, 1H, NC*H*HCH$_2$), 3.71 (m, 1H, NCH*H*CH$_2$), 3.34 (m, 2H, NC*H*CH$_2$ and NC*H*CH$_2$CO), 2.81 (m, 1H, C*H*HCO), 2.45 (m, 1H, CH*H*CO), 2.23 (m, 1H, NCH$_2$C*H*H), 1.87 (m, 1H, NCH$_2$CH*H*); HPLC 97.5% (t_R = 18.56 min); MS (thermospray) *m/z* 261 (MH$^+$), 278 (MNH$_4^+$); [α]$_D$ −68.4° (*c* 1.28, MeOH); chiral HPLC (Chiral Pak AD464) 95.9% ee (propan-2-ol/heptane (1:4), flow rate = 1 mL/min, t_R = 9.42 min (3a*S*,6a*R*), t_R = 8.47 min (3a*R*,6a*S*). Anal. (C$_{14}$H$_{16}$N$_2$O$_3$·0.05CH$_2$Cl$_2$) C, H, N.

(3a*R*,6a*S*)-2-Oxohexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic Acid 4-Benzyl Ester 1-*tert*-Butyl Ester (9). To **8** (43.2 g, 166 mmol) in tetrahydrofuran (1200 mL) at −75 °C under nitrogen was added 1 M LHMDS solution in tetrahydrofuran (216 mL, 216 mmol) dropwise, keeping the temperature at −70 °C. After 10 min, a solution of di-*tert*-butyl dicarbonate (54.3 g, 249 mmol) in tetrahydrofuran (350 mL) was added, keeping the temperature at −70 °C. The reaction mixture was stirred at −75 °C for 2.5 h, and then the reaction was quenched with saturated ammonium chloride. Then the mixture was allowed to warm to room temperature, water was added, and the phases were separated. The aqueous phase was extracted with ethyl acetate, and the combined organic phase was washed with water and brine, dried, and evaporated to give the title compound as an orange-red semisolid. This residue was purified by trituration under diethyl ether to give the title compound **9** (42.5 gm, 71%) as a pale-cream solid. A sample was crystallized from diethyl ether to give a white solid: mp 101−103 °C: IR (KBr) 1791, 1765, 1713 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.35 (s, 5H, C$_6$H$_5$), 5.12 (ABq, *J* = 12.5 Hz, 2H, PhC*H$_2$*), 3.86 (m, 1H, NC*H*HCH$_2$), 3.75 (m, 1H, NCH*H*CH$_2$), 3.46 (m, 1H, NC*H*CH$_2$), 3.33 (m, 1H, NC*H*CHMe), 2.93 (m, 1H, C*H*HCO), 2.55 (m, 2H, NCH$_2$C*H*H and C*H*HCO), 2.01 (m, 1H, NCH$_2$CH*H*), 1.54 (s, 9H, C(CH$_3$)$_3$); MS (thermospray) *m/z* 378 (MNH$_4^+$); HPLC 100% (t_R = 27.2 min); [α]$_D$ −45.6° (*c* 1.13, MeOH); chiral HPLC (Chiral Pak AD464) 96.0% ee (propan-2-ol/heptane (2:5), flow rate = 1 mL/min, t_R = 9.54 min (3a*S*,6a*R*), t_R = 6.79 min (3a*R*,6a*S*). Anal. (C$_{19}$H$_{24}$N$_2$O$_5$) C, H, N.

The following compounds were similarly prepared.

***rel*-(3*R*,3a*R*,6a*S*)-3-Methyl-2-oxohexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic Acid 4-Benzyl Ester 1-*tert*-Butyl Ester (18).** Compound **17**[7] was reacted with 1 M LHMDS and then treated with di-*tert*-butyl dicarbonate as described for **9** to give **18** (93%) as a white solid: mp 69−71 °C: ^{1}H NMR (CDCl$_3$) δ 7.35 (m, 5H, C$_6$H$_5$), 5.13 (m, 2H, PhC*H$_2$*), 3.91−3.66 (m, 1H, NC*H$_2$*CH$_2$), 3.51−3.38 (m, 1H, NC*H*CH$_2$), 3.05−2.94 (m, 1H, NC*H*CHMe), 2.71−2.45 (m, 2H, C*H*Me and NCH$_2$C*H*H), 2.02−1.83 (m, 1H, NCH$_2$CH*H*), 1.56−1.32 (m, 12H, C(CH$_3$)$_3$ and CH$_3$); IR (KBr) 1787, 1766, 1713 cm^{-1}; MS (thermospray), *m/z* 392 (MNH$_4^+$), 375 (MH$^+$); HPLC 99.53% (29.46 min). Anal. (C$_{20}$H$_{26}$N$_2$O$_5$·0.5H$_2$O) C, H, N.

(3*S*,3a*R*,6a*S*)-3-Methyl-2-oxohexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic Acid 4-Benzyl Ester 1-*tert*-Butyl Ester (10). Compound **9** (606 mg, 1.68 mmol) was dissolved in tetrahydrofuran (6 mL) and cooled, under nitrogen, to −75 °C. A 1 M LHMDS solution in tetrahydrofuran (2.2 mL, 2.2 mmol) was added, keeping the temperature below −70 °C. After 10 min, methyl iodide was added (1.8 mL, 28.9 mmol). After the mixture was stirred for a further 45 min, the reaction was quenched with saturated aqueous ammonium chloride and then the mixture was allowed to warm to room temperature. Water was added, and then the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with water and brine, dried (MgSO$_4$), and evaporated to give

a golden oil. The crude residue was purified by flash column chromatography, eluting with cyclohexanes/ethyl acetate (3:1) to yield **10** (526 mg, 83%) as a white foam: IR (KBr) ν_{max} 1789, 1765, 1712 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.35 (s, 5H, C$_6$H$_5$), 5.12 (m, 2H, PhC*H$_2$*), 3.87 (m, 1H, NC*H*HCH$_2$), 3.68 (m, 2H, NCH*H*CH$_2$ and NC*H*CH$_2$), 3.44 (dd, *J* = 6.6 Hz, *J* = 11 Hz, 1H, NC*H*CHMe), 3.05 (br m, 1H, CHMe), 2.51 (m, 1H, NCH$_2$C*H*H), 1.99 (m, 1H, NCH$_2$CH*H*), 1.54 (s, 9H, C(CH$_3$)$_3$), 1.12 (bs, 3H, CH$_3$); MS (thermospray) *m/z* 375 (MH$^+$); HPLC 99.5% (t_R = 28.27 min); [α]$_D$ −88.6° (*c* 1.1, MeOH); chiral HPLC (Chiral Pak AD 464) 96.1% ee (propan-2-ol/heptane (2:23), flow rate = 1 mL/min, t_R = 20.85 min (3*S*,3a*R*,6a*S*), t_R = 3.71 min (3*R*,3a*S*,6a*R*). Anal. (C$_{20}$H$_{26}$N$_2$O$_5$) C, H, N.

The following compounds were similarly prepared.

***rel*-(3*S*,3a*R*,6a*S*)-3-Allyl-2-oxohexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic Acid 4-Benzyl Ester 1-*tert*-Butyl Ester (14).** Compound **13** was reacted with allyl iodide as described for **10** to give **14** (40%) as a white foam: ^{1}H NMR (CDCl$_3$) δ 7.35 (s, 5H, C$_6$H$_5$), 5.9−5.7 (bs, 1H, CH$_2$C*H*=CH$_2$), 5.3−4.9 (m, 4H, PhC*H$_2$* and CH$_2$CH=C*H$_2$*), 3.90−3.60 (m, 3H, NC*H$_2$*CH$_2$ and NC*H*CH$_2$), 3.50 (dd, *J* = 6.6 Hz, *J* = 11 Hz, 1H, NC*H*CHAllyl), 3.2−2.7 (br m, 1H, C*H*allyl), 2.6−2.2 (m, 3H, C*H$_2$*CH=CH$_2$ and NCH$_2$C*H*H), 2.00 (m, 1H, NCH$_2$CH*H*), 1.6 (s, 9H, C(CH$_3$)$_3$); MS (thermospray) *m/z* 419 (MNH$_4^+$), 401 (MH$^+$); HRMS calcd for C$_{22}$H$_{28}$N$_2$O$_5$ (MH$^+$) 401.207 647, found 401.207 134; HPLC 98% (t_R = 30.64 min).

***trans*-3,3-Dimethyl-2-oxohexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic Acid 4-Benzyl Ester 1-*tert*-Butyl Ester (19).** Compound **18** was reacted with methyl iodide as described for **10** to give **19** (72%) as a white solid: IR (KBr) ν_{max} 1790, 1764, 1713 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.35 (s, 5H, C$_6$H$_5$), 5.15 (q, 2H, PhC*H$_2$*), 3.9 (m, 1H, NC*H*HCH$_2$), 4.0−3.6 (m, 3H, NC*H$_2$*CH$_2$ and NC*H*CH$_2$), 3.15 (d, *J* = 10 Hz, 1H, NC*H*CMe$_2$), 2.55 (m, 1H, NCH$_2$CH*H*), 1.95 (m, 1H, NCH$_2$CH*H*), 1.6 (s, 9H, C(CH$_3$)$_3$), 1.2 (bs, 6H, 2CH$_3$); IR (KBr) 1790, 1764, 1713 cm^{-1}. MS (thermospray), *m/z* 406 (MNH$_4^+$), 389 (MH$^+$); HPLC 99.67% (30.72 min). Anal. (C$_{21}$H$_{28}$N$_2$O$_5$) C, H, N.

(3a*S*,6*S*,6a*R*)-6-Methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (11). To **10** (486 mg, 1.3 mmol) was added trifluoroacetic acid (6 mL), and the mixture was stirred at room temperature for 40 min and then evaporated to give a brown oil. This was dissolved in ethyl acetate (6 mL) and was washed with saturated sodium bicarbonate solution (2 × 3 mL), water (3 mL), and brine (3 mL), dried (MgSO$_4$), and evaporated to give **11** (340 mg, 95%) as a pale-beige solid. The solid was recrystallized from diethyl ether to give a white solid (202 mg, 56%), mp 112−113 °C: IR (CDCl$_3$) 3273, 1710, 1698 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.35 (s, 5H, C$_6$H$_5$), 5.98 (bs, 1H, N*H*), 5.13 (ABq, *J* = 12.5 Hz, 2H, PhC*H$_2$*), 3.89 (br m, 1H, NC*H*HCH$_2$), 3.60 (m, 3H, NCH*H*CH$_2$, NC*H*CH$_2$, and NC*H*CHMe), 2.90 (br m, 1H, C*H*Me), 2.22 (m, 1H, NCH$_2$C*H*H), 1.86 (m, 1H, NCH$_2$CH*H*), 1.10 (br s, 3H, CH$_3$); MS (thermospray) *m/z* 275 (MH$^+$); HPLC 100% (t_R = 19.82 min); chiral HPLC (Chiral Pak AD 464) 96.00% ee (propan-2-ol/heptane (2:25), flow rate = 1 mL/min, t_R = 20.91 min (3a*S*,6*S*,6a*R*), t_R = 18.85 min (3a*R*,6*R*,6a*S*). Anal. (C$_{15}$H$_{18}$N$_2$O$_3$) C, H, N.

The following compounds were similarly prepared.

***rel*-(3a*S*,6*S*,6a*R*)-6-Allyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (15).** Compound **14** was reacted with trifluoroacetic acid as described for **11** to give **15** (69%) as a white foam: ^{1}H NMR (CDCl$_3$) δ 7.40 (s, 5H, C$_6$H$_5$), 6.1 (bs, 1H, N*H*), 5.9−5.7 (bs, 1H, CH$_2$C*H*=CH$_2$), 5.2−4.9 (m, 4H, PhC*H$_2$*, CH$_2$CH=C*H$_2$*), 3.90 (m, 1H, NC*H*HCH$_2$), 3.7−3.5 (m, 3H, NCH*H*CH$_2$, NC*H*CH$_2$, and NC*H*CHallyl), 3.0−2.7 (bm, 1H, C*H*allyl), 2.5−2.2 (m, 3H, C*H$_2$*CH=CH$_2$, NCH$_2$C*H*H), 1.85 (m, 1H, NCH$_2$CH*H*); MS (thermospray) *m/z* 318 (MNH$_4^+$), 301 (MH$^+$); HRMS calcd for C$_{17}$H$_{20}$N$_2$O$_3$ (MH$^+$) 301.155 218, found 301.155 627; HPLC 98.13% (t_R = 22.21 min).

***trans*-6,6-Dimethyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (21).** Compound **19** was reacted with trifluoroacetic acid as described for **11** to give

21 (90%) as a white solid, mp 170 °C: ^{1}H NMR (CDCl$_3$): δ 7.35 (m, 5H, C$_6$H$_5$), 6.00 (s, 1H, N*H*), 5.14 (ABq, *J* = 12 Hz, 2H, PhC*H*$_2$), 3.88 (br t, 1H, *J* = 10.4 Hz, NC*H*HCH$_2$), 3.70 (m, 1H, NCH*H*CH$_2$), 3.46 (m, 1H, NC*H*CH$_2$), 3.20 (br d, *J* = 10 Hz, NC*H*CMe$_2$), 2.21 (m, 1H, NCH$_2$CH*H*), 1.81 (m, 1H, NCH$_2$C*H*H), 1.7–1.0 (br m, 6H, 2CH$_3$); MS (thermospray) *m/z* 289 (MH$^+$), 577 (2M + H$^+$); HPLC 99.5% (t_R = 21.85 min). Anal. (C$_{16}$H$_{20}$N$_2$O$_3$) C, H, N.

(3*S*,3a*R*,6a*S*)-4-[((2*S*)-1-{[5-(Dimethylamino)-1-naphthyl]-sulfonyl}pyrrolidin-2-yl)carbonyl]-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2-one (61). Deprotection of **60** (1.12 g, 1.96 mmol) with trifluoroacetic acid, using the same procedure as for the preparation of **11**, afforded **61** (870 mg, 95%): IR (KBr) ν_{max} 3280, 1713, 1666 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.53 (d, *J* = 8.5 Hz, 1H, dansyl-2*H*), 8.42 (d, *J* = 8.5 Hz, 1H, dansyl-4*H*), 8.28 (dd, *J* = 1.2 Hz, *J* = 7.3 Hz, 1H, dansyl-8*H*), 7.60–7.48 (m, 2H, dansyl-3*H*, dansyl-7*H*), 7.18 (d, *J* = 7.3 Hz, 1H, dansyl-6*H*), 5.79 (s, 1H, CON*H*), 4.74 (dd, *J* = 4.3 Hz, *J* = 7.9 Hz, 1H, NC*H*CO), 4.29 (t, *J* = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.85–3.74 (m, 1H, NCH*H*CH$_2$CH$_2$), 3.65–3.34 (m, 4H, NC*H*$_2$-CH$_2$, NC*H*CH$_2$, NC*H*CHMe), 3.10–2.98 (m, 1H, C*H*Me), 2.87 (s, 6H, N*Me*$_2$), 2.33–1.84 (m, 6H, NCH$_2$C*H*$_2$CH$_2$, NCH$_2$C*H*$_2$), 1.06 (d, *J* = 7.3 Hz, 3H, CHC*H*$_3$); ^{13}C NMR (CDCl$_3$) δ 179.5, 155.8, 136.2, 128.6, 128.2, 128.0, 67.2, 63.4, 60.5, 49.3, 39.6, 27.7; MS (thermospray) *m/z* 471 (MH$^+$); HPLC: 99.2% (t_R = 18.3 min). Anal. (C$_{24}$H$_{30}$N$_4$O$_4$ S·0.4EtOAc) C, H, N, S.

(3a*S*,6*S*,6a*R*)-4-Acetyl-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (4). The lactam **11** (50 mg, 0.18 mmol) in tetrahydrofuran (2.5 mL) stirred under nitrogen at −75 °C was treated with 1 M LHMDS solution in tetrahydrofuran (0.22 mL, 0.22 mmol). The solution was stirred and allowed to warm to −15 °C over 15 min, recooled to −75 °C, and treated with acetyl chloride (39 μL, 0.55 mmol). The solution was stirred and allowed to warm to −15 °C over 1.5 h, and then the reaction was quenched with saturated aqueous ammonium chloride (2.5 mL). After warming to room temperature over 1 h, the mixture was diluted with water (2.5 mL) and extracted with ethyl acetate (3 × 2.5 mL). The combined organic extracts were washed with brine (2.5 mL), dried, and evaporated to give a yellow gum (62 mg). This gum was purified by flash column chromatography over silica using cyclohexanes/ethyl acetate 2:1 as the eluting solvent to give **4** (47 mg, 81%) as a white foam: IR (KBr) ν_{max} 1747, 1712, 1698 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.36 (s, 5H, C$_6$H$_5$), 5.13 (ABq, *J* = 11 Hz, 2H, PhC*H*$_2$), 3.87–3.62 (m, 3H, NC*H*$_2$-CH$_2$ and NC*H*CH$_2$), 3.45 (dd, *J* = 7.5 Hz, *J* = 12 Hz, 1H, NC*H*CHMe), 3.10 (br m, 1H, C*H*Me), 2.74 (m, 1H, NCH$_2$C*H*H), 2.46 (s, 3H, COC*H*$_3$), 1.97 (m, 1H, NCH$_2$CH*H*), 1.13 (br m, 3H, C*H*$_3$CH); HPLC 99.48% (t_R = 24.72 min); MS (thermospray) *m/z* 317 (MH$^+$); circular dichroism (CH$_3$CN) λ_{max} 211.2 nm, dE −25.20, E16538, λ_{max} 238.2 nm, dE 18.10, E1538; chiral HPLC (Chiral Pak AD464) 96.2% ee (ethanol/heptane (2:5), flow rate = 1 mL/min, t_R = 12.12 min (3a*S*,6*S*,6a*R*), t_R = 19.6 min (3a*R*,6*R*,6a*S*). Anal. (C$_{17}$H$_{20}$N$_2$O$_4$) C, H, N.

(3a*S*,6*S*,6a*R*)-4-Acetyl-6-methyl-5-oxohexahydropyrrolo-[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (4) and (3a*R*,6*R*,6a*S*)-4-Acetyl-6-methyl-5-oxohexahydropyrrolo-[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (3). The racemic *trans*-lactam **1**[7] was separated by preparative chiral HPLC into the two enantiomers of **4**: chiral HPLC (Chiral Pak AD464) 99.5% (t_R = 12.12 min), identical in all respects to compound **4** above and **3**; IR (KBr) ν_{max} 1747, 1712, 1697 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.37 (s, 5H, C$_6$H$_5$), 5.14 (q, *J* = 11 Hz, 2H, PhC*H*$_2$), 3.86 and 3.7 (m, 3H, NC*H*$_2$CH$_2$ and NC*H*CH$_2$), 3.45 (dd, *J* = 7.5 Hz, *J* = 12 Hz, 1H, NC*H*CHMe), 3.1 (bm, 1H, C*H*Me), 2.74 (m, 1H, NCH$_2$C*H*H), 2.46 (s, 3H, COC*H*$_3$), 1.97 (m, 1H, NCH$_2$CH*H*), 1.14 (br, 3H, C*H*$_3$CH); HRMS calcd for C$_{17}$H$_{20}$N$_2$O$_4$ (MH$^+$) 317.150 132, found 317.150 109; chiral HPLC (Chiral Pak AD464) 99.8% (t_R = 19.6 min); circular dichroism (CH$_3$CN) λ_{max} 211.0 nm, dE 25.40, E17153, λ_{max} 238.2 nm, dE −18.30, E1946.

Preparation of 12, 16, 22, 23, 26, 28, 33, 34, and 62. By use of essentially the same procedure as for the preparation

of **4**, the following compounds listed in Schemes 2−5 and 8 were prepared from **11**, **15**, **21**, **24**, or **61**.

trans-4-Acetyl-6,6-dimethyl-5-oxohexahydropyrrolo-[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (22). 22 was derived from **21** and acetyl chloride to give a pale-yellow gum (76%): ^{1}H NMR (CDCl$_3$) δ 7.35 (m, 5H, C$_6$H$_5$), 5.13 (ABq, *J* = 12 Hz, 2H, PhC*H*$_2$), 3.87 (m, 1H, NC*H*HCH$_2$), 3.75–3.55 (m, 2H, NC*H*CH$_2$ and NC*H*CH$_2$), 3.15 (br d, *J* = 10 Hz, NC*H*-CMe$_2$), 2.90 (m, 1H, NCH$_2$CH*H*), 2.70 (m, 1H, NCH$_2$C*H*H), 2.45 (s, 3H, COC*H*$_3$), 1.5–1.0 (br m, 6H, 2C*H*$_3$); MS (thermospray) *m/z* 331 (MH$^+$); HPLC 99.4% (t_R = 27.43 min). Anal. (C$_{18}$H$_{22}$N$_2$-O$_4$·0.1C$_6$H$_{12}$·0.1EtOAc) C, H, N.

(3a*S*,6*S*,6a*R*)-4-Acetoxyacetyl-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (12). 12 was derived from **11** and acetoxyacetyl chloride to give a white gum (75%): IR (CDCl$_3$) ν_{max} 1750, 1715, 1706 cm^{-1}; ^{1}H NMR (CHCl$_3$) δ 7.36 (m, 5H, C$_6$H$_5$), 5.13 (ABq, *J* = 11 Hz, 2H, PhC*H*$_2$), 5.01 (m, 2H, COC*H*$_2$O), 3.95–3.62 (m, 3H, NC*H*$_2$-CH$_2$ and NC*H*CH$_2$), 3.51 (dd, 1H, NC*H*CHMe), 3.10 (br m, 1H, COC*H*CH$_3$), 2.72 and 2.02 (2m, 2H, NCH$_2$C*H*$_2$), 2.18 (s, 3H, COC*H*$_3$), 1.18 (br m, 3H, CHC*H*$_3$); HPLC 98.86% (t_R = 25.41 min); MS (thermospray) *m/z* 375 (MH$^+$); chiral HPLC (Chiral Pak AD464) 96.3% ee (propan-2-ol/heptane (2:5), flow rate = 1 mL/min, t_R = 10.56 min (3a*S*,6*S*,6a*R*), t_R = 3.015 min (3a*R*,6*R*,6a*S*)). Anal. (C$_{19}$H$_{22}$N$_2$O$_6$·0.1 cyclohexane) C, H, N.

rel-(3a*S*,6*S*,6a*R*)-4-Acetoxyacetyl-6-allyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (16). 16 was derived from **15** and acetoxyacetyl chloride to give a white foam (78%): ^{1}H NMR (CDCl$_3$) δ 7.40 (s, 5H, C$_6$H$_5$), 5.9–5.6 (bs, 1H, CH$_2$C*H*=CH$_2$), 5.2–4.9 (m, 6H, PhC*H*$_2$, C*H*$_2$-OAc, and CH$_2$CH=C*H*$_2$), 3.90 (m, 1H, NC*H*HCH$_2$), 3.78 (m, 1H, NC*H*CH$_2$), 3.70 (m, 1H, NCH*H*CH$_2$), 3.60 (m, 1H, NC*H*-CHAllyl), 3.3–2.9 (bm, 1H, C*H*allyl), 2.77 (m, 1H, NCH$_2$C*H*H), 2.50 (bs, 1H, CH*H*CH=CH$_2$), 2.35–2.15 (bs, 1H, C*H*HCH=CH$_2$), 2.20 (s, 3H, OAc), 2.00 (m, 1H, NCH$_2$CH*H*); MS (thermospray) *m/z* 418 (MNH$_4$$^+$), 401 (MH$^+$); HRMS calcd for C$_{21}H_{24}N_2O_6$ (MH$^+$) 401.171 262, found 401.171 325; HPLC 94% (t_R = 27.93 min).

trans-4-Acetoxyacetyl-6,6-dimethyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (23). 23 was derived from **21** and acetoxyacetyl chloride to give a white solid (82%), mp 108−109 °C: ^{1}H NMR (CDCl$_3$): δ 7.35 (m, 5H, C$_6$H$_5$), 5.20−4.95 (m, 4H, PhC*H*$_2$ and COC*H*$_2$O), 4.95−3.60 (m, 3H, NC*H*$_2$CH$_2$ and NC*H*CH$_2$), 3.20 (br d, NC*H*CMe$_2$), 2.70 (m, 1H, NCH$_2$CH*H*), 1.97 (m, 1H, NCH$_2$C*H*H), 1.7−1.0 (br, 9H, 3C*H*$_3$); MS (thermospray) *m/z* 389 (MH$^+$), 406 (MNH$_4$$^+$); HPLC 99.2% ($t_R$ = 27.9 min). Anal. (C$_{20}$H$_{24}$N$_2$O$_6$·0.12C$_6$H$_{12}$) C, H, N.

rel-(3a*S*,6*S*,6a*R*)-4-Isobutyryl-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester 26. 26 was derived from **24** and isobutyryl chloride to give a gum (57%): ^{1}H NMR (CDCl$_3$) δ 7.45 (s, 5H, C$_6$H$_5$), 5.2 (ABq, *J* = 11 Hz, 2H, PhC*H*$_2$), 4.0−3.4 (3m, 5H, (CH$_3$)$_2$C*H*, NC*H*$_2$CH$_2$, NC*H*CH$_2$, and NC*H*CHMe), 3.3−2.8 (2bm, 1H, C*H*Me), 2.74 (dt, *J* = 6 Hz, 1H, NCH$_2$C*H*H), 1.97 (2t, *J* = 11 Hz, 1H, NCH$_2$-CH*H*), 1.3−1.0 (m, 3H, (C*H*$_3$)$_2$CH); MS (thermospray) *m/z* 345 (MH$^+$); HPLC 95% (t_R = 29.84 min). Anal. (C$_{19}$H$_{24}$N$_2$O$_4$·0.4H$_2$O) C, H, N.

rel-(3a*S*,6*S*,6a*R*)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (28). 28 was derived from **24** and cyclopropanecarbonyl chloride to give as an oil (87%) that crystallized to a white solid on standing, mp 101−102 °C: IR (KBr) ν_{max} 1747, 1713, 1704, 1693, 1681 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.35 (s, 5H, C$_6$H$_5$), 5.15 (AB q, *J* = 12.5 Hz, 2H, PhC*H*$_2$), 4.0−3.60 and 3.50 (m, 4H, NC*H*$_2$CH$_2$, NC*H*CH$_2$, and NC*H*CHMe), 3.2 and 3.0 (br d, 1H, C*H*Me), 2.92 (br, 1H, COC*H*CH$_2$CH$_2$), 2.70 (m, 1H, NCH$_2$CH*H*), 1.95 (m, 1H, NCH$_2$C*H*H), 1.3−0.9 (m, 7H, COCHC*H*$_2$C*H*$_2$ and C*H*$_3$CH); MS (thermospray) *m/z* 343 (MH$^+$); HPLC 99.4% (t_R = 28.7 min). Anal. (C$_{19}$H$_{22}$N$_2$O$_4$) C, H, N.

**(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-4-[((2*S*)-1-{[5-(dimethylamino)-1-naphthyl]sulfonyl}pyrrolidin-2-yl)carbonyl]-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2-

one (62). 62 was derived from **61** and cyclopropanecarbonyl chloride (3 equiv) to give 62 (80%) as a green-yellow foam: IR (KBr) ν_{max} 1747, 1689, 1682, 1667, 1651 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 8.54 (d, $J = 8.5$ Hz, 1H, dansyl-2*H*), 8.42 (d, $J = 8.5$ Hz, 1H, dansyl-4*H*), 8.28 (dd, $J = 1.2$ Hz, $J = 7.3$ Hz, 1H, dansyl-8*H*), 7.61−7.49 (m, 2H, dansyl-3*H*, dansyl-7*H*), 7.18 (d, $J = 7.3$ Hz, 1H, dansyl-6*H*), 4.75 (dd, $J = 4.9$ Hz, $J = 7.9$ Hz, 1H, NC*H*CO), 4.25 (t, $J = 9.5$ Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.87−3.36 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H*$_2$CH$_2$, NC*H*CHMe, NC*H*CHMe), 3.27 (m, 1H, C*H*Me), 2.99−2.83 (m, 7H, N*Me*$_2$, COC*H*CH$_2$CH$_2$), 2.81−2.68 (m, 1H, NCH$_2$C*H*H), 2.29−1.81 (m, 5H, NCH$_2$C*H$_2$*-C*H$_2$*, NCH$_2$CH*H*), 1.28−0.87 (m, 7H, CH*Me*, COCHC*H$_2$*C*H$_2$*); MS (thermospray) m/z 539 (MH$^+$), 471 (MH−CO-cyclopropyl$^+$); HPLC 100% (t_R = 26.3 min). Anal. (C$_{28}$H$_{34}$N$_4$O$_5$S·0.5H$_2$O) C, H, N.; circular dichroism λ_{max} 200.8 nm, dE 0.01, λ_{max} 217.8 nm, dE −23.80, λ_{max} 238.4 nm, dE 15.10.

***rel*-(3a*S*,6*S*,6a*R*)-4-(Cyclobutylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester) (33).** 33 was derived from **24** and cyclobutanecarbonyl chloride to a colorless gum (82%): IR (KBr) ν_{max} 1749, 1710, 1694 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.37 (m, 5H, C$_6$H$_5$), 5.13 (ABq, $J = 12.5$ Hz, 2H, PhC*H$_2$*), 3.88 and 3.71 (2m, 4H, NC*H$_2$*CH$_2$, NC*H*CH$_2$, and CH$_2$CH$_2$C*H*CO), 3.45 (dd, $J = 7.5$ Hz, $J = 12$ Hz, 1H; NC*H*CHMe), 3.06 (br d, 1H, C*H*Me), 2.75 and 1.95 (2m, 4H, NCH$_2$C*H$_2$* and CH$_2$C*H$_2$*CH$_2$), 2.26 (m, 4H, C*H$_2$*CH$_2$C*H$_2$*), 1.12 (br, 3H, CH$_3$); MS (thermospray) m/z 357 (MH$^+$); HPLC 99.6% (t_R = 30.24 min). Anal. (C$_{20}$H$_{24}$N$_2$O$_4$·0.1EtOAc) C, H, N.

***rel*-(3a*S*,6*S*,6a*R*)-4-(4-Methoxybenzoyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (34).** 34 was derived from **24** and 4-methoxybenzoyl chloride to give a clear oil (54%): IR (KBr) ν_{max} 4199, 1753, 1747 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.75 (d, $J = 9$ Hz, 2H, COCC*H*), 7.5−7.3 (m, 5H, C$_6$H$_5$), 6.92 (d, $J = 9$ Hz, 2H, MeOCC*H*), 5.15 (m, 2H, PhC*H$_2$*), 4.1 (s, 3H, *Me*O), 4.0−3.75 (br m, 1H, NC*H*HCH$_2$), 3.7−3.4 (m, 3H, NCH*H*CH$_2$, NC*H*CH$_2$, and NC*H*-CHMe), 3.2−2.7 (br m, 1H, C*H*Me), 2.8−2.6 (br m, 1H, NCH$_2$C*H*H), 2.1−1.8 (br m, 1H, NCH$_2$CH*H*), 1.3−1.0 (br, 3H, C*H$_3$*); HPLC 99.2% (t_R = 28.9 min). Anal. (C$_{23}$H$_{24}$N$_2$O$_5$·0.2CHCl$_3$) C, H, N.

***rel*-(3a*S*,6*S*,6a*R*)-4-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}-propanoyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (36).** To a solution of 3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propanoic acid[16] (0.257 g, 1.3 mmol) in tetrahydrofuran (7 mL), cooled in an ice bath, was added triethylamine (0.168 mL, 1.2 mmol) and trimethylacetyl chloride (0.148 mL, 1.2 mmol). The resulting white suspension of mixed anhydride was stirred under nitrogen for 3 h. Meanwhile, to a solution of *trans*-lactam **24** (0.113 g, 0.41 mmol) in anhydrous tetrahydrofuran (7 mL) cooled to −78 °C under nitrogen was added 1 M LHMDS solution in tetrahydrofuran (0.494 mL, 0.49 mmol) over ca. 2 min. The solution was stirred at −78 °C for 20 min, then stirred at 0 °C for 10 min and then recooled to −78 °C. The suspension of mixed anhydride was added to the *trans*-lactam solution, keeping the temperature below −70 °C, and the solution was stirred at −70 °C for a further 35 min. Saturated aqueous ammonium chloride (20 mL) was added, the cooling bath was removed, and the mixture was stirred for 10 min. Ethyl acetate (75 mL) and water (40 mL) were added to the stirred mixture, and the organic phase was separated. The aqueous phase was re-extracted with ethyl acetate (40 mL). The combined organic phase was washed with saturated ammonium chloride solution (40 mL) and brine (40 mL), dried (MgSO$_4$), and evaporated to give a yellow oil. This was purified by flash column chromatography using cyclohexanes/ethyl acetate as the eluting solvent to give **36** as a pale-yellow gum (111 mg, 59%): IR (KBr) ν_{max} 1749, 1712 cm^{-1}; ^{1}HNMR (CDCl$_3$) δ 7.3 (s, 5H, C$_6$H$_5$), 5.1 (m, 2H, PhC*H$_2$*), 3.9−3.7 (m, 3H, NC*H$_2$*CH$_2$, NC*H*CH$_2$), 3.7−3.6 (m, 2H, NC*H*CHMe, C*H*HOSiMe$_2$Bu^t), 3.4 (m, 1H, CH*H*OSiMe$_2$Bu^t), 3.1−2.9 (m, 3H, C*H*Me, C*H$_2$*CO-(CH$_2$)$_2$), 2.7 (m, 1H, NCH$_2$C*H*H), 1.9 (m, 1H, NCH$_2$CH*H*), 1.2−1.0 (m, 3H, CH*Me*), 0.82 (s, 9H, *t*-BuSi), 0.06 (s, 6H, *Me$_2$*Si);

MS (thermospray) m/z 461 (MH$^+$) , 483 (MNa$^+$); HPLC 95% (t_R = 37 min). Anal. (C$_{24}$H$_{36}$N$_2$O$_5$Si) C, H, N.

***rel*-(3a*S*,6*S*,6a*R*)-4-(3-Hydroxypropanoyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (37).** The *trans*-lactam **36** (75 mg, 0.16 mmol) was treated with acetic acid/water/tetrahydrofuran (10:3:1, 7 mL), and the solution was stirred at room temperature. After 8 h, solid NaHCO$_3$ was added and the reaction mixture was diluted with ethyl acetate (15 mL) and water (10 mL). The organic phase was washed with saturated sodium hydrogen carbonate solution until the solution was neutral and then was washed with water (3 × 15 mL) and then dried (MgSO$_4$). Evaporation of the solvent in vacuo gave a yellow oil (54 mg) that was purified by flash column chromatography using cyclohexanes/ethyl acetate as the eluting solvent to give **37** as a colorless gum (49 mg, 88%): IR (KBr) ν_{max} 1749, 1705, 1700 cm^{-1}; ^{1}NMR (CDCl$_3$) δ 7.4 (s, 5H, C$_6$H$_5$), 5.1 (d, 2H, PhC*H$_2$*), 4.0−3.8 (m, 3H, NC*H$_2$*CH$_2$, NC*H*CH$_2$), 3.8−3.6 (m, 2H, NC*H*CHMe, C*H*HOH), 3.5 (m, 1H, CH*H*OH), 3.3−2.9 (m, 3H, C*H*Me, COC*H$_2$*), 2.7 (m, 1H, NCH$_2$C*H*H), 2.4 (m, 1H, O*H*), 1.99 (m, 1H, NCH$_2$CH*H*), 1.2 (br s, 3H, C*H$_3$*); MS (thermospray) m/z 347 (MH$^+$); HRMS calcd for C$_{18}$H$_{22}$N$_2$O$_5$ (MH$^+$) 347.160 697, found 347.160 451; HPLC 98% (t_R = 21.6 min).

***rel*-(3a*S*,6*S*,6a*R*)-4-Formyl-6-methyl-5-oxohexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (25).** To a stirred solution of *trans*-lactam **24** (52 mg, 0.19 mmol) in dry dimethylformamide (22.6 mL) and dry dimethoxyethane (1.3 mL) at 0 °C under nitrogen was added sodium hydride (60% dispersion in mineral oil; 12.5 mg, 0.31 mmol). After 30 min, the reaction mixture was cooled to −78 °C and trifluoromethanesulfonic anhydride (96 μL, 0.57 mmol) was added. After 3 min, the reaction mixture was rapidly warmed to room temperature. The reaction was quenched by addition of a saturated ammonium chloride solution and extracted with ethyl acetate (3 × 25 mL). The combined organic extract was washed with saturated sodium hydrogen carbonate solution (20 mL) and brine (20 mL) and dried over MgSO$_4$. The solvent was evaporated to give a pale-yellow gum (63 mg), which was purified by flash column chromatography using cyclohexane/ethyl acetate as the eluting solvent to give **25** as a colorless gum (31 mg, 54%): IR (KBr) ν_{max} 1759, 1699 cm^{-1}; ^{1}NMR (CDCl$_3$) δ 9.1 (s, 1H, C*H*O), 7.4 (s, 5H, C$_6$H$_5$), 5.1 (d, 2H, PhC*H$_2$*), 4.0−3.9 (br.m, 1H, NC*H*HCH$_2$), 3.8−3.6 (m, 2H, NCH*H*CH$_2$, NC*H*CH$_2$), 3.5 (dd,1H, NC*H*CHMe), 3.3−2.9 (br.s, 1H, C*H*Me), 2.7 (m, 1H, NCH$_2$C*H*H), 2.1 (m, 1H, NCH$_2$CH*H*), 1.2 (m, 3H, CH*Me*); MS (thermospray) m/z 320 (MNH$_4^+$), 303 (MH$^+$). Anal. (C$_{16}$H$_{18}$N$_2$O$_4$) C, H, N.

Preparation of 27, 29−32, 35. By use of essentially the same procedure as for the preparation of **36**, the following compounds listed in Scheme 5 were prepared from **24**.

***rel*-(3a*S*,6*S*,6a*R*)-4-(2,2-Dimethylpropanoyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (27).** 27 was derived from **24** and the mixed anhydride prepared from 2,6-dimethylbenzoic acid and trimethylacetyl chloride to give a white solid (70%): IR (KBr) ν_{max} 1747, 1712, 1683 cm^{-1}; ^{1}H NMR (CHCl$_3$) δ 7.36 (m, 5H, C$_6$H$_5$), 5.13 (q, $J = 11$ Hz, 2H, PhC*H$_2$*), 3.92−3.60 (m, 3H, NC*H$_2$*CH$_2$ and NC*H*CH$_2$), 3.49 (dd, $J = 7.5$ Hz, $J = 12$ Hz, 1H; NC*H*CHMe), 3.06 (br d, 1H, C*H*Me), 2.65 and 1.81 (2m, 2H, NCH$_2$C*H$_2$*), 1.30 (s, 9H, Bu^t), 1.13 (br, 3H, CH$_3$); MS (thermospray) m/z 359 (MH$^+$); HPLC 99.7% (t_R = 32.07 min). Anal. (C$_{20}$H$_{26}$N$_2$O$_4$) C, H, N.

***rel*-(3a*S*,6*S*,6a*R*)-6-Methyl-4-[(2-methylcyclopropyl)-carbonyl]-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid Benzyl Ester (31).** 31 was derived from **24** and the mixed anhydride prepared from 2-methylcyclopropanecarboxylic acid and trimethylacetyl chloride to give a white solid (73%): IR (KBr) ν_{max} 1747, 1708, 1685 cm^{-1}; ^{1}H NMR (CHCl$_3$) δ 7.36 (m, 5H, C$_6$H$_5$), 5.13 (ABq, $J = 12.5$ Hz, 2H, PhC*H$_2$*), 3.95−3.60 (m, 3H, NC*H$_2$*CH$_2$, NC*H*CH$_2$), 3.48 (m, 1H, NC*H*CHMe), 3.10 (br m, 1H, C*H*Me), 2.67 and 1.95 (2m, 3H, COC*H*CH$_2$CH$_2$ and NCH$_2$C*H$_2$*), 1.50, 1.31 and 0.84 (3m, 3H, COCHC*H$_2$*C*H*Me), 1.16 (m, 6H, 2 × C*H$_3$*); MS (thermospray) m/z 357 (MH$^+$); HPLC 98.4% (t_R = 29.74 min); chiral HPLC

(run in ethanol/heptane (2:3), 1 mL/min, room temp), t_R = 5.415 min 16.36%, t_R = 5.656 min, 22.13%, t_R = 5.844 min, 29.86%, t_R = 6.173 min, 29.14%; chiral HPLC (run in ethanol/heptane (3:97), 0.5 mL/min, temp of 40 °C), t_R = 29.487 min, 20.06%, t_R = 31.162 min, 50.5%, t_R = 34.396 min, 23.1%. Anal. ($C_{20}H_{24}N_2O_4$·0.1EtOAc) C, H, N.

rel-(3aS,6S,6aR)-4-(cis-2,3-Dimethylcyclopropanecarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (32). 32 was derived from **24** and the mixed anhydride prepared from *cis*-2,3-dimethylcyclopropane carboxylic acid and trimethylacetyl chloride to a colorless gum (40%): IR (KBr) ν_{max} 1746, 1713, 1682 cm^{-1}; ^{1}H NMR (CHCl$_3$) δ 7.36 (m, 5H, C$_6$H$_5$), 5.13 (ABq, J = 12.5 Hz, 2H, PhCH$_2$), 3.93−3.58 (m, 3H, NCH$_2$CH$_2$, NCHCH$_2$), 3.48 (m, 1H, NCHCH), 3.08 (br m, 1H, CHMe), 2.82 (m, 1H, COCH-CHMeCHMe), 2.70 and 1.91 (2m, 2H, NCH$_2$CH$_2$), 1.61 (m, 2H, CHMeCHMe), 1.30 and 1.18 (2m, 9H, 3 × CH$_3$); MS (thermospray) m/z 371 (MH$^+$). HRMS calcd for $C_{21}H_{26}N_2O_4$ (MH$^+$) 371.197 083, found 371.197 289.

rel-(3aS,6S,6aR)-4-(trans-2,3-Dimethylcyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (29). 29 was derived from **24** and the mixed anhydride prepared from *trans*-2,3-dimethylcyclopropanecarboxylic acid and trimethylacetyl chloride to give a colorless gum (69%): ^{1}H NMR (CHCl$_3$) δ 7.36 (m, 5H, C$_6$H$_5$), 5.13 (ABq, J = 12.5 Hz, 2H, PhCH$_2$), 3.96−3.58 (m, 3H, NCH$_2$CH$_2$, NCHCH$_2$), 3.47 (m, 1H, NCHCH), 3.09 (br m, 1H, CHMe), 2.83 and 2.46 (2m, 2 × 0.5 H, COCHCHMeCHMe), 2.71 and 1.94 (2m, 2H, NCH$_2$CH$_2$), 1.54−1.02 (m, 11H, COCHCHMeCHMe and 3 × CH$_3$); MS (thermospray) m/z 371 (MH$^+$); HRMS calcd for $C_{21}H_{26}N_2O_4$ (MH$^+$) 371.197083, found 371.197412; HPLC 97.86% (t_R = 30.77 min).

rel-(3aS,6S,6aR)-6-Methyl-5-oxo-4-(2,2,3,3-tetramethylcyclopropylcarbonyl)hexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (30). 30 was derived from **24** and the mixed anhydride prepared from 2,2,3,3-tetramethylcyclopropanecarboxylic acid and trimethylacetyl chloride to give a white solid (66%): IR (KBr) ν_{max} 1745, 1714, 1683 cm^{-1}; ^{1}H NMR (CDCl$_3$ δ 7.5−7.3 m, 5H, C$_6$H$_5$), 5.15 (m, 2H, PhCH$_2$), 4.0−3.75 (br m, 1H, NCHHCH$_2$), 3.7−3.4 (m, 3H, NCHHCH2, NCHCH2 and NCHCHMe), 3.2−2.8 (br m, 1H, CHMe), 2.7 (br m, 1H, NCH$_2$CHH), 2.33 (s, 1H, COCHCMe$_2$CMe$_2$), 2.1−1.8 (br m, 1H, NCH$_2$CHH), 1.4−1.0 (br, 15H, 5 x CH$_3$); MS (thermospray) m/z 399 (MH$^+$); HPLC 93% (t_R = 34 min). Anal. ($C_{23}H_{30}N_2O_4$) C, H, N.

rel-(3aS,6S,6aR)-4-(Bicyclo[4.2.0]octa-1,3,5-trien-7-yl-carbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (35). 35 was derived from **24** and the mixed anhydride prepared from 1-benzocyclobutene carboxylic acid and trimethylacetyl chloride to give a colorless gum (61%): IR (KBr) ν_{max} 1749, 1706, 1696 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.37 (s, 5H, C$_6$H$_5$), 7.28−7.00 (m, 4H, C$_6$H$_4$), 5.23−5.01 (m, 3H, PhCH$_2$, cyclobutaneCH), 3.9−3.4 (m, 6H, NCH-CHMe, NCHCH$_2$, NCH$_2$CH$_2$, cyclobutaneCH$_2$), 3.3−3.0 (br m, 1H, CHMe), 2.79−2.65 (m, 1H, NCH$_2$CHH), 2.07−1.85 (m, 1H, NCH$_2$CHH), 1.2 (br d, 3H, CH$_3$); MS (thermospray) m/z 405 (MH$^+$); HPLC 99% (t_R = 32.2 min). Anal. ($C_{24}H_{24}N_2O_4$·0.4EtOAc) C, H, N.

Preparation of 38−42. By use of essentially the same procedure as for the preparation of **4**, the following compounds listed in Scheme 6 were prepared from **24**.

rel-(3aS,6S,6aR)-4-(2,4-Dinitrophenyl)-6-methyl-5-oxohexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (39). 39 was derived from **24** and 2,4-dinitrofluorobenzene (3 equiv) to give a yellow foam (70%): IR (KBr) ν_{max} 1711, 1605, 1542, 1531 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.83 (d, J = 2.4 Hz, 1H, C$_6$H$_3$(NO$_2$)$_2$), 8.49 (dd, J = 2.4 Hz, J = 9.2 Hz, 1H, C$_6$H$_3$(NO$_2$)$_2$), 7.43−7.35 (m, 6H, C$_6$H$_5$ and C$_6$H$_3$(NO$_2$)$_2$), 5.23−5.11 (ABq, J = 12.2 Hz, 2H, PhCH$_2$), 4.18−3.96 (m, 2H, NCH$_2$CH$_2$), 3.89−3.74 (m, 2H, NCHCH$_2$, NCHCHMe), 3.4−3.0 (br d, 1H, CHMe), 2.47−2.35 (m, 1H, NCH$_2$CHH), 2.17−1.98 (m, 1H, NCH$_2$CHH), 1.30−1.10 (br m, 3H, CH$_3$); MS (thermospray) m/z 458 (MNH$_4$$^+$), 442 (MH$^+$); HPLC 100% ($t_R$ = 29.2 min). Anal. ($C_{21}H_{20}N_4O_7$) C, H, N.

rel-(3aS,6S,6aR)-4-(Dimethoxyphosphoryl)-6-methyl-5-oxohexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (41). 41 was derived from **24** and dimethyl chlorophosphate (3.5 equiv) to give a colorless gum 45%): IR (KBr) ν_{max} 1739, 1709 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.36 (s, 5H, C$_6$H$_5$), 5.20−5.05 (ABq, J = 12.2 Hz, 2H, PhCH$_2$), 3.96−3.45 (br m, 10H, NCH$_2$CH$_2$, NCHCH$_2$, NCHCHMe, 2 × OCH$_3$), 3.30−2.75 (br m, 1H, CHMe), 2.59−2.47 (m, 1H, NCH$_2$CHH), 2.10−1.85 (m, 1H, NCH$_2$CHH), 1.27−1.05 (br m, 3H, CH$_3$); MS (thermospray) m/z 400 (MNH$_4$$^+$), 383 (MH$^+$); HPLC 92% ($t_R$ = 22.2min). Anal. ($C_{17}H_{23}N_2O_6P$) C, H, N.

rel-(3aS,6S,6aR)-4-(2-Hydroxy-3-phenoxypropyl)-6-methyl-5-oxohexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (38). 38 was derived from **24** and 1,2-epoxy-3-phenoxypropane (1.3 equiv) to give a white solid (41%): IR (KBr) ν_{max} 3420, 2930, 1701−1682 cm^{-1}; ^{1}H NMR (CDCl$_3$) shows rotamers, δ 7.40 − 7.25 (m, 7H, aryl), 7.03 − 6.85 (m, 3H, aryl), 5.20−5.05 (m, 2H, PhCH$_2$O), 4.23−3.30 (m, 10H, PhOCH$_2$, CHOH, NCH$_2$CH$_2$, NCHCH$_2$, NCHCHMe, NCH$_2$CHOH, OH), 3.20−2.80 (2m, 1H, CHMe), 2.32−2.17 (n, 1H, NCH$_2$CHH), 1.98−1.70 (m, 1H, NCH$_2$CHH), 1.30−1.00 (m, 3H, CHMe); MS (thermospray) 425 (MH$^+$); HPLC 99% (t_R = 26.4 min). Anal. ($C_{24}H_{28}N_2O_5$) C, H, N.

rel-(3aS,6S,6aR)-6-Methyl-4-(methylthio)-5-oxohexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (42). 42 was derived from **24** and methyl methanethiolsulfonate (1.3 equiv) to give a clear oil (67%): IR (KBr) ν_{max} 2961, 1715, 1454 cm^{-1}; ^{1}H NMR (CDCl$_3$) shows rotamers, δ 7.35 (s, 5H, C$_6$H$_5$), 5.20−5.05 (m, 2H, PhCH$_2$O), 3.99−3.82 (m, 1H, NCHHCH$_2$), 3.73−3.40 (m, 3H, NCHHCH$_2$, NCHCH$_2$, and NCHCHMe), 3.20−2.85 (2m, 1H, CHMe), 2.42−2.30 (m, 4H, SMe, NCH$_2$CHH), 2.00−1.80 (m, 1H, NCH$_2$CHH), 1.20−1.00 (m, 3H, CHMe); MS (thermospray) 321 (MH$^+$); HPLC 100% (t_R = 24.68 min). Anal. ($C_{16}H_{20}N_2O_3S$) C, H, N, S.

rel-(3aS,6S,6aR)-6-Methyl-5-oxo-4-(1H-pyrrol-1-ylcarbonyl)-hexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (40). 40 was derived from **24** and pyrrole-1-carboxylic acid anhydride[10] (2 equiv) to give a white foam (72%): IR (KBr) ν_{max} 1769, 1719,1701, 1686 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 7.37 (s, 5H, C$_6$H$_5$), 7.20−7.16 (m, 2H, NCH=CH), 6.32−6.27 (m, 2H, NCH=CH), 5.23−5.07 (ABq, J = 12.2 Hz, 2H, PhCH$_2$), 4.07−3.61 (m, 4H, NCH$_2$CH$_2$, NCHCH$_2$, and NCHCHMe), 3.35−2.93 (br m, 1H, CHMe), 2.63−2.51 (m, 1H, NCH$_2$CHH), 2.01−1.81 (m, 1H, NCH$_2$CHH), 1.32−1.10 (br m, 3H, CH$_3$); MS (thermospray) m/z 368 (MH$^+$), 385 (MNH$_4$$^+$); HPLC 100% ($t_R$ = 29.91 min). Anal. ($C_{20}H_{21}N_3O_4$) C, H, N.

rel-(3aS,6S,6aR)-4-(Hydroxymethyl)-6-methyl-5-oxohexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (44). To a solution of the *trans*-lactam **24** (50 mg, 0.18 mmol) in dry THF (3 mL) was added paraformaldehyde (56 mg, 1.9 mmol) and potassium carbonate (25 mg, 0.18 mmol). The heterogeneous reaction mixture was stirred at room temperature for 43 h, more potassium carbonate (9 mg, 0.065 mmol) was added, and the mixture wasstirred for a further 3 h. Saturated ammonium chloride solution (40 mL) was added, and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extract was washed with water (25 mL) and dried, and the solvent was evaporated to give a white residue (50 mg), which was purified by flash column chromatography using cyclohexanes/ethyl acetate as the eluting solvent to give **44** as a colorless gum (37 mg, 67%): IR (KBr) ν_{max} 1721, 1710, 1910, 1679 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.36 (s, 5H, C$_6$H$_5$), 5.20−5.05 (m, 3H, PhCH$_2$, NCHHOH), 4.58−4.45 (br m, 1H, NCHHOH), 4.02−3.85 (br m, 1H, NCHHCH$_2$), 3.77−3.63 (m, 2H, NCHHCH$_2$ and NCHCHMe), 3.53−3.43 (m, 1H, NCHCH$_2$), 3.15−2.77 (br m, 1H, CHMe, OH), 2.38−2.25 (m, 1H, NCH$_2$CHH), 1.97−1.77 (m, 1H, NCH$_2$CHH), 1.20−1.00 (br m, 3H, CH$_3$); MS (thermospray) m/z 305 (MH$^+$), 610 (2MH$^+$); HPLC 98% (t_R = 19.4 min). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N.

rel-(3aS,6S,6aR)-6-Methyl-5-oxo-4-[(1E)-3-oxobut-1-enyl]hexahydropyrrolo[3,2-b]pyrrole-1-carboxylic Acid Benzyl Ester (43). A mixture of PdCl$_2$(MeCN)$_2$ (24 mg, 0.09 mmol), CuCl (10 mg, 0.09 mmol), and **24** (500 mg, 1.82 mmol)

was stirred in dry dimethylformamide (5 mL) under an atmosphere of oxygen at 60 °C. Methyl vinyl ketone (450 μL, 5.4 mmol) was added in portions over 4 h to the reaction mixture, and then stirring at 60 °C was continued for 17 h. The reaction mixture was diluted with ether at room temperature and then filtered. The filtrate was evaporated, and the residue was purified by flash column chromatography, eluting with ethyl acetate/cyclohexane (2:1) to give **43** (188 mg, 33%) as a solid: IR (KBr) ν_{max} 3000, 1741, 1705 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.89 (d, J = 15 Hz, 1H, NCH=CH), 7.37 (m, 5H, C$_6H_5$), 5.75 (d, J = 15 Hz, 1H, NCH=CH), 5.21–5.07 (ABq, J = 12 Hz, 2H, PhCH_2), 4.05–3.90 (br m, 1H, NCHHCH$_2$), 3.84–3.56 (m, 3H, NCHHCH$_2$, NCHCH$_2$, and NCHCHMe), 3.34–2.90 (br m, 1H, CH$_3$CH), 2.64–2.53 (br m, 1H, NCH$_2$CHH), 2.28 (s, 3H, CH_3CO), 2.21–2.04 (br m, 1H, NCH$_2$CHH), 1.28–1.06 (br, m, 3H, CHCH_3); MS (thermospray) 343 (MH$^+$). Anal. (C$_{19}$H$_{22}$N$_2$O$_4$·0.4EtOAc) C, H, N.

rel-(3*S*,3a*R*,6a*S*)-1-Acetyl-3-methylhexahydropyrrolo-[3,2-*b*]pyrrol-2-one (45). A solution of **1** (3.4 g, 10.7 mol) in 2-propanol (150 mL) containing 1 M HCl in ether (13 mL, 13 mmol) was added to the palladium catalyst (10% Pd/C, Degussa type, E101, NE/W, 50% H$_2$O, 1.5 g) under an atmosphere of nitrogen. The resulting mixture was then stirred vigorously under an atmosphere of hydrogen for 3.5 h, filtered, and evaporated to give **45** (2.369 g, 99%) as a white foam: IR (KBr) ν_{max} 1754 cm^{-1}; ^{1}H NMR (MeOD): δ 3.97–3.66 (m, 3H, NCH_2CH$_2$ and NCHCH$_2$), 3.61–3.51 (m, 1H, NCHCHMe), 3.11–2.97 (m, 1H, CHMe), 2.81–2.68 (m, 1H, NCH$_2$CHH), 2.44 (s, 3H, MeCO), 2.18–1.96 (m, 1H, NCH$_2$CHH), 1.30 (d, J = 7.3 Hz), 1.14 (d, J = 6.1 Hz) (3H, CHCH_3); MS (thermospray) m/z 183 (MH – HCl$^+$); HPLC 97.2% (t_R = 3.45 min). Anal. (C$_9$H$_{14}$N$_2$O$_4$·HCl·H$_2$O·0.5C$_3$H$_8$O$_2$) C, H, N.

The following compounds were similarly prepared.

rel-(3*S*,3a*R*,6a*S*)-3-Methyl-2-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid *tert*-Butyl Ester Hydrochloride (58). Compound **20**[7] was deprotected with hydrogen in the presence of Pd/C as described for **45** to give **58** (88%) as a white solid: IR (KBr) ν_{max} 2974, 2697, 1786 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.44 (br.s, 1H, NH), 3.93–3.29 (m, 4H, NCH_2CH$_2$, NCHCH$_2$, NCHCHMe), 2.91–2.75 (m, 1H, CHMe), 2.46–2.30 (m, 1H, NCH$_2$CHH), 2.12–1.92 (m, 1H, NCH$_2$CHH), 1.46 (s, 9H, Bu^t), 1.20 (d, J = 7.3 Hz), 1.04 (d, J = 6.1 Hz) (3H, CHCH_3); MS (thermospray) m/z 241 (MH$^+$), 481 (2MH$^+$), 258 (MNH$_4^+$); HPLC 98.6% (t_R = 8.94 min). Anal. (C$_{12}$H$_{20}$N$_2$O$_3$·HCl·0.25C$_3$H$_8$O) C, H, N.

rel-(3a*S*,6*S*,6a*R*)-1-Cyclopropanecarbonyl-3-methyl-hexahydropyrrolo[3,2-*b*]pyrrol-2-one hydrochloride (63). Compound **28** was deprotected with hydrogen in the presence of Pd/C as described for **45** to give **63** (91%) as a white solid: ^{1}H NMR (MeOD) δ 3.86–3.40 (m, 4H, NCH_2CH$_2$, NCHCH$_2$, and NCHCHMe), 3.03–2.97 (m, 2H, NCH$_2$CHH and COCHCH$_2$-CH$_2$), 2.65–2.53 (m, 1H, CHMe), 2.00–1.81 (m, 1H, NCH$_2$-CHH), 1.21 (d, J = 7.3 Hz, 3H, CH_3), 1.02–0.85 (m, 4H, COCHCH_2CH_2); MS (thermospray) m/z 209 (MH$^+$); HRMS calcd for C$_{11}$H$_{16}$N$_2$O$_2$ (MH$^+$) 209.129 003, found 209.129 312; HPLC 93% (t_R = 7.3 min).

rel-(3*S*,3a*R*,6a*S*)-1-(Cyclopropylcarbonyl)-3-methyl-4-[(2*S*)-pyrrolidin-2-ylcarbonyl]hexahydropyrrolo[3,2-*b*]-pyrrol-2-one Hydrochloride (68). Compound **67** was deprotected with hydrogen in the presence of Pd/C as described for **45** to give **68** (94%) as a white foam: ^{1}H NMR (MeOD) δ 4.56–4.48 (m, 1H, NCHCO), 4.06–3.77 (m, 4H, NCH_2CH$_2$CH$_2$ and NCH_2CH$_2$), 3.68–3.60 (m, 1H, NCHCH$_2$), 3.53–3.14 (m, 7H, NCHCHMe and CHMe + H$_2$O), 3.01–2.88 (m, 1H, COCHCH$_2$-CH$_2$), 2.79–2.67 (m, 1H, NCH$_2$CHH), 2.61–2.45 (m, 1H, NCH$_2$-CHH), 2.19–1.90 (br m, 4H, NCH$_2$CH_2CH$_2$ and NCH$_2$-CH$_2$CH_2), 1.20–0.95 (m, 7H, CHMe and COCHCH_2CH$_2$); MS (thermospray) m/z 306 (MH$^+$); HRMS calcd for C$_{16}$H$_{23}$N$_3$O$_3$ (MH$^+$) 306.181 767, found 306.181 634; HPLC 98% (t_R = 10.8 min).

rel-(3*S*,3a*R*,6a*S*)-1-Acetyl-3-methyl-4-[(2-phenylethyl)-sulfonyl]hexahydropyrrolo[3,2-*b*]pyrrol-2-one (46). A solution of the phenethylsulfonyl chloride (44 mg, 0.22 mmol) in acetonitrile (1 mL) was added to a solution of hydrochloride

45 (30 mg, 0.14 mmol) and triethylamine (78 uL, 56.6 mg, 0.56 mmol) in acetonitrile (2 mL) under nitrogen. The resulting mixture was stirred at room temperature for 18 h, the solvent was evaporated, and the residue was partitioned between ethyl acetate (5 mL) and 1 N HCl (5 mL). The aqueous phase was separated and extracted with ethyl acetate (2 × 5 mL), and the combined organic phase was washed with water (5 mL) and brine (5 mL) and dried over MgSO$_4$. The residue (33 mg) was purified by flash column chromatography, eluting with cyclohexanes/ethyl acetate (2:1) to give the title compound **46** (25 mg, 51%) as a solid, mp 147–149 °C: IR (KBr) ν_{max} 1749, 1700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.41–7.17 (s, 5H, C$_6H_5$), 3.90–3.70 (m, 2H, NCH_2CH$_2$), 3.64–3.40 (m, 2H, NCHCH$_2$ and NCHCHMe), 3.32–3.31 (m, 2H, PhCH$_2$CH_2), 3.21–3.12 (m, 2H, PhCH_2), 3.12–2.95 (m, 1H, CHMe), 2.83–2.69 (m, 1H, NCH$_2$CHH), 2.47 (s, 3H, COCH_3), 2.14–1.92 (m, 1H, NCH$_2$-CHH), 1.28 (br, 3H, CH_3CH). Anal. (C$_{17}$H$_{22}$N$_2$O$_4$S·0.1Et$_2$O) C, H, N, S.

rel-(3*S*,3a*R*,6a*S*)-1-Acetyl-3-methyl-4-(2-oxo-3-phenyl-propyl)hexahydropyrrolo[3,2-*b*]pyrrol-2-one (47). To a solution of the *trans*-lactam **45** (30 mg, 0.137 mmol) in anhydrous acetonitrile (2.5 mL) was added triethylamine (19 μL, 0.138 mmol), followed by a solution of the benzyl bromo-methyl ketone (34.4 mg, 0.204 mmol) in anhydrous acetonitrile (0.25 mL). The reaction mixture was stirred at room temperature for almost 3 h, heated at 88 °C for 2 h, and then was to stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (20 mL) and was washed with saturated sodium hydrogen carbonate (10 mL). The aqueous layer was re-extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine (10 mL) and dried, and the solvent was evaporated. The yellow residue that was purified by flash column chromatography using cyclohexanes/ethyl acetate as the eluting solvent gave **47** (12 mg, 29%) d as a yellow gum: ^{1}H NMR (CDCl$_3$) δ 7.4–7.2 (m, 5H, C$_6H_5$), 3.8–3.5 (m, 4H, PhCH_2, NCHHCH$_2$, NCHCH$_2$), 3.5 (m, 1H, NCHHCH$_2$), 3.2 (m, 1H, NCHCHMe), 2.8–2.5 (m, 4H, NCH$_2$-CHH, COCH_2, CHMe), 2.4 (s, 3H, COCH), 2.9–1.8 (m, 1H, NCH$_2$CHH), 1.1 (m, 3H, CHMe); MS (thermospray) m/z 315 (MH$^+$); HRMS calcd for C$_{18}$H$_{22}$N$_2$O$_3$ (MH$^+$) 315.170 868, found 315.170 765.

(3*S*,3a*R*,6a*S*)-1-Acetyl-4-{[(2*S*)-1-benzoylpyrrolidin-2-yl]carbonyl}-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1H)-one (53) and (3*R*,3a*S*,6a*R*)-1-Acetyl-4-{[(2*S*)-1-benzoylpyrrolidin-2-yl]carbonyl}-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2-one (54). To a stirred solution of the *N*-benzoyl-(*S*)-proline (30 mg, 0.14 mmol) in dimethylformamide (1 mL) at room temperature was added a solution of TBTU (36 mg, 0.11 mmol) in dimethylformamide (0.25 mL) and a solution of HOBT·H$_2$O (18 mg, 0.12 mmol) in dimethylformamide (0.25 mL). The reaction mixture was stirred at room temperature for 20 min before addition of diisopropylethylamine (38 μL, 218 μmol) and the pyrrolidine **45** (31 mg, 0.14 mmol) in a solution of acetonitrile/dimethylformamide (1:1) (0.6 mL). The reaction mixture was left at room temperature for 20 h before it was diluted with dichloromethane (10 mL) and washed with water (7 mL). The aqueous phase was back-extracted with dichloromethane (10 mL), and the combined organic extract was washed with 2 N HCl (10 mL), water (10 mL), and saturated sodium hydrogen carbonate (10 mL). It was then dried, and the solvent was evaporated to give a yellow residue (44 mg). This was purified by flash column chromatography using cyclohexanes/ethyl acetate as the eluting solvent to give the less polar diastereomer **53** (15 mg, 28%) as an off-white foam: IR (KBr) ν_{max} 1747, 1699, 1661, 1627 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.62–7.52 (m, 2H, C$_6H_5$) 7.46–7.35 (m, 3H, C$_6H_5$), 4.75–4.67 (m, 1H, NCHCO), 4.66–4.56 (m, 1H, NCHHCH$_2$CH$_2$), 3.92–3.66 (m, 3H, NCH_2CH$_2$, NCHCH$_2$), 3.63–3.52 (m, 2H, NCHCHMe and NCHHCH$_2$CH$_2$), 3.38–3.22 (m, 1H, NCH$_2$CHH), 2.88–2.76 (m, 1H, NCH$_2$CHH), 2.48 (s, 3H, COCH_3), 2.36–1.81 (m, 5H, NCH$_2$CH_2CH$_2$ and CHMe), 1.16 (d, J = 7.3 Hz, 3H, CHMe); MS (thermospray) m/z 384 (MH$^+$); HRMS calcd for C$_{21}$H$_{25}$N$_3$O$_4$ (MH$^+$) 384.192 332, found 384.192 158; HPLC 96% (t_R = 19.0 min).

Further elution with cyclohexanes/ethyl acetate gave the more polar diastereomer **54** (18 mg, 34%) as an off-white foam: ^{1}H NMR (CDCl$_3$) shows rotameric forms present, δ 7.62−7.52 (m, 2H, C$_6$H$_4$), 7.46−7.35 (m, 3H, C$_6$H$_4$), 4.75−4.09 (3m, 2H, NC*H*CO and NC*H*HCH$_2$CH$_2$), 3.91−3.44 (m, 5H, NC*H$_2$*CH$_2$, NC*H*CH$_2$, NC*H*CHMe, and NCH*H*CH$_2$CH$_2$), 3.37−3.24 (m, 1H, NCH$_2$CH*H*), 2.97−2.68 (m, 1H, NCH$_2$CH*H*), 2.48 (s, 3H, COCH$_3$), 2.35−1.81 (m, 5H, NCH$_2$*CH$_2$CH$_2$* and C*H*Me), 1.30 and 1.22 (2d, *J* = 7.3 Hz, 3H, CH*Me*); MS (thermospray) *m/z* 384 (MH$^+$); HRMS calcd for C$_{21}$H$_{25}$N$_3$O$_4$ (MH$^+$) 384.192 332, found 384.192 019; HPLC 99% (t_R = 18.0 min.).

The following compounds were similarly prepared.

(3*S*,3a*R*,6a*S*)-1-Acetyl-3-methyl-4-({(2*S*)-1-[(4-nitrophenyl)sulfonyl]pyrrolidin-2-yl}carbonyl)hexahydropyrrolo[3,2-*b*]pyrrol-2-one (57). Similarly prepared as **53** using 1-[(4-nitrophenyl)sulfonyl]-(*S*)-proline, the less polar diastereomer **57** (23%) was isolated as a white solid: IR (KBr) $ν_{max}$ 1749, 1694, 1656, 1539 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.39−8.32 (m, 2H, C$_6$H$_4$), 8.14−8.07 (m, 2H, C$_6$H$_4$), 4.69 (dd, *J* = 4.9 Hz, *J* = 7.9 Hz, 1H, NC*H*CO), 4.24 (t, *J* = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.90−3.22 (m, 6H, NC*H$_2$*CH$_2$, NC*H*CH$_2$, NC*H*CHMe, NCH*H*CH$_2$CH$_2$, and NCH$_2$C*H*H), 2.92−2.80 (m, 1H, NCH$_2$CH*H*), 2.49 (s, 3H, COCH$_3$), 2.31−1.89 (m, 5H, NCH$_2$*CH$_2$CH$_2$*, +C*H*Me), 1.12 (d, *J* = 7.3 Hz, 3H, CH$_3$); MS (thermospray) *m/z* 465 (MH$^+$) 482 (MNH$_4$$^+$); HPLC 97% ($t_R$ = 23.3 min). Anal. (C$_{20}$H$_{24}$N$_4$O$_7$S·0.2H$_2$O) C, H, N.

***rel*-(3*S*,3a*R*,6a*S*)-1-Acetyl-3-methyl-4-[(1-methyl-1*H*-pyrrol-2-yl)(oxo)acetyl]hexahydropyrrolo[3,2-*b*]pyrrol-2-one (50).** Similarly prepared as **53**, 1-methyl-pyrrole-2-glyoxylic acid was used to give **50** (45%) as a white foam: IR (KBr) $ν_{max}$ 1748, 1702, 1654, 1650, 1629 cm^{-1}; ^{1}H NMR (CDCl$_3$) shows rotameric forms present, δ 7.23−7.20 and 7.08−7.05 (2m, 1H, pyrrole-4*H*), 6.98 (br s, 1H, pyrrole-3*H*), 6.22 (dd, *J* = 2.4 Hz, *J* = 4.3 Hz, 1H, pyrrole-5*H*), 4.17−3.34 (m, 7H, NCH$_3$, NC*H$_2$*CH$_2$, NC*H*CH$_2$, and NC*H*CHMe), 2.96−2.75 (m, 2H, NCH$_2$C*H*H and C*H*Me), 2.50 and 2.47 (2s, 3H, COCH$_3$), 2.15−1.92 (m, 1H, NCH$_2$CH*H*), 1.32 and 0.93 (2d, *J* = 7.3 Hz, 3H, CH*Me*); MS (thermospray) *m/z* 318 (MH$^+$); HPLC 98% (t_R = 19.4 min). Anal. (C$_{16}$H$_{19}$N$_3$O$_4$·0.1CH$_2$Cl$_2$) C, H, N,

***rel*-(3*S*,3a*R*,6a*S*)-1-Acetyl-4-[2-(5-fluoro-2-methyl-1*H*-indol-3-yl)acetyl]-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2-one (49).** Similarly prepared as **53**, 2-(5-fluoro-2-methyl-1*H*-indol-3-yl)acetic acid was used to give **49** (56%) as a white amorphous solid: IR (CHBr$_3$) $ν_{max}$ 1751, 1708 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.91 (bs, 1H, NH), 7.21−7.09 (m, 2H, indolyl-*H*4 and *H*-7), 6.90−6.80 (m, 1H, indolyl-*H*6), 3.94−3.42 (m, 6H, NC*H$_2$*CH$_2$, NC*H*CH$_2$, indolylC*H$_2$*, and NC*H*CHMe), 3.38−3.23 (m, 1H, C*H*Me), 2.85−2.70 (m, 1H, NCH$_2$C*H*H), 2.47 (s, 3H, COC*H$_3$*), 2.40 (s, 3H, indolylC*H$_3$*), 2.12−1.93 (m, 1H, NCH$_2$CH*H*), 1.16 (d, *J* = 7.3 Hz, 3H, C*H$_3$*CH); TLC R_f = 0.63 (ethyl acetate); MS (thermospray) *m/z* 372 (MH$^+$); HPLC 98.1% (t_R = 22.69 min). Anal. (C$_{20}$H$_{22}$FN$_3$O$_3$·2H$_2$O·0.4C$_4$H$_8$O$_2$) C, H, N, F.

***rel*-(3*S*,3a*R*,6a*S*)-1-Acetyl-3-methyl-4-(phenoxyacetyl)hexahydropyrrolo[3,2-*b*]pyrrol-2-one (48).** Similarly prepared as **53**, phenoxyacetic acid was used to give **48** (51%) as a pale-yellow gum: IR (KBr) $ν_{max}$ 1748, 1698, 1673 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.38−7.24 (m, 2H, phenoxy-2*H*, phenoxy-6*H*), 7.08−6.88 (m, 3H, phenoxy-3*H*, phenoxy-4*H*, and phenoxy-5*H*), 4.64 (bs, 2H, PhOC*H$_2$*CO), 3.95 (m, 2H, NC*H$_2$*CH$_2$), 3.55 (m, 2H, NC*H*CH$_2$ and NC*H*CHMe), 3.32 (m, 1H, C*H*Me), 2.81 (m, 1H, NCH$_2$C*H*H), 2.47 (s, 3H, COC*H$_3$*), 2.06 (m, 1H, NCH$_2$CH*H*), 1.11 (m, 3H, C*H$_3$*CH); TLC R_f = 0.63 (ethyl acetate); MS (thermospray) *m/z* 317 (MH$^+$); HPLC 97.4% (t_R = 20.74 min). Anal. (C$_{17}$H$_{20}$N$_2$O$_4$) C, H, N. HRMS calcd for C$_{17}$H$_{20}$N$_2$O$_4$ (MH$^+$) 317.150 132, found 317.150 142.

(3*S*,3a*R*,6a*S*)-1-Acetyl-3-methyl-4-({(2*S*)-1-[(4-methylphenyl)sulfonyl]pyrrolidin-2-yl}carbonyl)hexahydropyrrolo[3,2-*b*]pyrrol-2-one (51) and (3*R*,3a*S*,6a*R*)-1-Acetyl-3-methyl-4-({(2*S*)-1-[(4-methylphenyl)sulfonyl]pyrrolidin-2-yl}carbonyl)hexahydropyrrolo[3,2-*b*]pyrrol-2-one (52). Similarly prepared as **53**, using *N*-tosyl-(*S*)-proline, the less polar diastereomer **51** (38%) was isolated as a white solid, mp 213.7−215.3 °C: IR (KBr) $ν_{max}$ 1751, 1738, 1693, 1658 cm^{-1};

^{1}H NMR (CDCl$_3$) δ 7.76 (d, *J* = 7.9 Hz, 2H, tosyl-2*H*, 6*H*), 7.31 (d, *J* = 7.9 Hz, 2H, tosyl-4*H*, 5*H*), 4.52 (dd, *J* = 4.3 Hz, *J* = 7.3 Hz, 1H, NC*H*CO), 4.30 (t, *J* = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.93−3.24 (m, 6H, NC*H$_2$*CH$_2$, NC*H*CH$_2$, NC*H*CHMe, and NCH*H*CH$_2$CH$_2$), 2.90−2.78 (m, 1H, NCH$_2$CH*H*), 2.49 (s, 3H, COCH$_3$), 2.43 (s, 3H, tosylCH$_3$), 2.20−1.73 (m, 5H, NCH$_2$*CH$_2$CH$_2$* and C*H*Me), 1.13 (d, *J* = 7.3 Hz, 3H, CH$_3$); MS (thermospray) *m/z* 434 (MH$^+$), 392 (M − COCH$_3$$^+$); HPLC 100% ($t_R$ = 23.3 min). Anal. (C$_{21}$H$_{27}$N$_3$O$_5$S·0.2CH$_2$Cl$_2$) C, H, N, S.

The more polar diastereomer **52** (30%) was isolated as a white solid: IR (KBr) $ν_{max}$ 1751, 1702, 1663 cm^{-1}; ^{1}H NMR (CDCl$_3$) shows rotamers present, δ 7.76 and 7.66 (2d, *J* = 7.9 Hz, 2H, tosyl-2*H*, 6*H*), 7.31 (d, *J* = 7.9 Hz, 2H, tosyl-4*H*, 5*H*), 4.47−4.20 (2m, 1H, NC*H*CO), 4.10−3.23 (m, 7H, NC*H$_2$*CH$_2$CH$_2$, NC*H$_2$*CH$_2$, NC*H*CH$_2$, NC*H*CHMe, and NCH$_2$C*H*H), 2.95−2.70 (2m, 1H, NCH$_2$CH*H*), 2.48 (s, 3H, COCH$_3$), 2.43 (s, 3H, tosylC*H$_3$*), 2.18−1.71 (m, 5H, NCH$_2$*CH$_2$CH$_2$* and C*H*Me), 1.21 and 1.17 (2d, *J* = 7.3 Hz, 3H, CH$_3$); MS (thermospray) *m/z* 434 (MH$^+$), 392 (M − COCH$_3$$^+$); HPLC 95% ($t_R$ = 22.9 min). Anal. (C$_{21}$H$_{27}$N$_3$O$_5$S·0.15CH$_2$Cl$_2$) C, H, N, S.

(3*S*,3a*R*,6a*S*)-1-Acetyl-4-[((2*S*)-1-{5-(dimethylamino)-1-naphthyl]sulfonyl}pyrrolidin-2-yl)carbonyl]-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (55) and (3*R*,3a*S*,6a*R*)-1-Acetyl-4-[((2*S*)-1-{5-(dimethylamino)-1-naphthyl]sulfonyl}pyrrolidin-2-yl)carbonyl]-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1*H*)-one (56). Similarly prepared as **53**, using dansyl-(*S*)-proline, the less polar diastereomer **55** (26%) was obtained as a yellow-green foam: IR (KBr) $ν_{max}$ 1749, 1700, 1687 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.54 (d, *J* = 8.5 Hz, 1H, dansyl-2*H*), 8.42 (d, *J* = 8.5 Hz, 1H, dansyl-4*H*), 8.28 (dd, *J* = 1 Hz, *J* = 7.3 Hz, 1H, dansyl-8*H*), 7.61−7.47 (m, 2H, dansyl-3*H*, dansyl-7*H*), 7.18 (d, *J* = 7.3 Hz, 1H, dansyl-6*H*), 4.74 (dd, *J* = 4.9 Hz, *J* = 7.9 Hz, 1H, NC*H*CO), 4.27 (t, *J* = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.89−3.17 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H$_2$*CH$_2$, NC*H*CH$_2$, NC*H*CHMe), 2.91−2.74 (m, 8H, N*Me$_2$*, NCH$_2$C*H*H, C*H*Me), 2.47 (s, 3H, COC*H$_3$*), 2.30−1.82 (m, 5H, NCH$_2$*CH$_2$CH$_2$*, NCH$_2$CH*H*), 1.11 (d, *J* = 7.3 Hz, 3H, CHC*H$_3$*); TLC R_f = 0.37 (ethyl acetate/cyclohexane, 7:3); MS (thermospray) *m/z* 513 (MH$^+$), 471 (M − COCH$_3$$^+$); HPLC 100% ($t_R$ = 23.54 min). Anal. (C$_{26}$H$_{32}$N$_4$O$_5$S·0.2H$_2$O) C, H, N, S.

The more polar diastereomer **56** (30%) was isolated as a yellow foam: ^{1}H NMR (CDCl$_3$) δ 8.54 (d, *J* = 8.5 Hz, 1H, dansyl-2*H*), 8.41 (d, *J* = 8.5 Hz, 1H, dansyl-4*H*), 8.27 (broad d, *J* = 7.3 Hz, 1H, dansyl-8*H*), 7.60−7.46 (m, 2H, dansyl-3*H*, dansyl-7*H*), 7.18 (d, *J* = 7.3 Hz, 1H, dansyl-6*H*), 4.01−3.14 (m, 7H, NC*H*CO, NC*H*HCH$_2$CH$_2$, NCH*H*CH$_2$CH$_2$, NC*H$_2$*CH$_2$, NC*H*CH$_2$, NC*H*CHMe), 2.93−2.76 (m, 8H, N*Me$_2$*, NCH$_2$C*H*H, C*H*Me), 2.45 (s, 3H, COC*H$_3$*), 2.34−1.88 (m, 5H, NCH$_2$*CH$_2$CH$_2$*, NCH$_2$CH*H*), 0.93 (d, *J* = 7.3 Hz, 3H, CHC*H$_3$*); TLC R_f = 0.22 (ethyl acetate/cyclohexane, 7:3); MS (thermospray) *m/z* 513 [MH]$^+$, 471 (M − COCH$_3$$^+$); HRMS calcd for C$_{26}H_{32}N_4O_5$S (MH$^+$) 513.217 167, found 513.217 025; HPLC 97% (t_R = 23.41 min).

(3*S*,3a*R*,6a*S*)-4-[((2*S*)-1-{5-(Dimethylamino)-1-naphthyl]sulfonyl}pyrrolidin-2-yl)carbonyl]-3-methyl-2-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid *tert*-Butyl Ester (60) and (3*R*,3a*S*,6a*R*)-4-[((2*S*)-1-{5-(Dimethylamino)-1-naphthyl]sulfonyl}pyrrolidin-2-yl)carbonyl]-3-methyl-2-oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic Acid *tert*-Butyl Ester (59). Similarly prepared as **53**, using dansyl-(*S*)-proline and **58**, the less polar (3*S*,3a*R*,6a*S*) diastereomer **60** (38%) was isolated as a yellow foam: IR (KBr) $ν_{max}$ 1787, 1665 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.55 (d, *J* = 8.5 Hz, 1H, dansyl-2*H*), 8.42 (d, *J* = 8.5 Hz, 1H, dansyl-4*H*), 8.28 (d, *J* = 7.3 Hz, 1H, dansyl-8*H*), 7.61−7.47 (m, 2H, dansyl-3*H*, dansyl-7*H*), 7.18 (d, *J* = 7.3 Hz, 1H, dansyl-6*H*), 4.74 (dd, *J* = 4.3 Hz, *J* = 7.9 Hz, 1H, NC*H*CO), 4.28 (t, *J* = 9.5 Hz, 1H, NC*H*HCH$_2$CH$_2$), 3.89−3.12 (m, 5H, NCH*H*CH$_2$CH$_2$, NC*H$_2$*CH$_2$, NC*H*CH$_2$, NC*H*CHMe), 2.88 (s, 6H, N*Me$_2$*), 2.64−2.51 (m, 1H, C*H*Me), 2.28−1.82 (m, 6H, NCH$_2$*CH$_2$CH$_2$*, NCH$_2$C*H$_2$*), 1.54 (s, 9H, CO$_2$C(*CH$_3$*)$_3$), 1.11 (d, *J* = 7.6 Hz, 3H, CHC*H$_3$*); ^{13}C NMR (CDCl$_3$) δ 179.5, 155.8, 136.2, 128.6, 128.2, 128.0, 67.2, 63.4, 60.5, 49.3,

39.6, 27.7; MS (thermospray) m/z 571 (MH$^+$) 417 (M − Boc$^+$); HPLC 99.98% (t_R = 27.53 min). Anal. (C$_{29}$H$_{38}$N$_4$O$_6$S·0.3EtOAc) C, H, N, S.

The more polar (3R,3aS,6aR) diastereomer **59** (30%) was isolated as a yellow foam: ^{1}H NMR (CDCl$_3$) δ 8.54 (d, J = 8.3 Hz, 1H, dansyl-2H), 8.40 and 8.31 (2d, J = 8.5 Hz, 1H, dansyl-4H), 8.28 and 8.17 (2d, J = 7.3 Hz, 1H, dansyl-8H), 7.59−7.48 (m, 2H, dansyl-3H, dansyl-7H), 7.18 (d, J = 7.5 Hz, 1H, dansyl-6H), 4.71−4.66 and 4.38−4.34 (2m, 1H, NCHCO), 4.04−3.34 (m, 6H, NCH_2CH$_2$CH$_2$, NCH_2CH$_2$, NCHCH$_2$, NCHCHMe), 3.23−3.14 (m, 1H, CHMe), 2.87 (s, 6H, NMe_2), 2.62−1.80 (m, 6H, NCH$_2$CH_2CH$_2$, NCH$_2$CH_2), 1.53 (s, 9H, CO$_2$C(CH_3)$_3$), 1.10 and 0.96 (2d, J = 7.3 Hz, 3H, CHCH_3); MS (thermospray) m/z 571 (MH$^+$), 417 (M − Boc$^+$). Anal. (C$_{29}$H$_{38}$N$_4$O$_6$S·0.1CHCl$_3$) C, H, N.

N-{(1***S***)-2-[***rel***-(3a***S***,6***S***,6a***R***)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2H)-yl]-1-methyl-2-oxoethyl}-5-(dimethylamino)naphthalene-1-sulfonamide (65).** Compound **63** was reacted with dansyl-(*S*)-alanine as described for **53** to give **65** (30%) as a pale-yellow foam: ^{1}H NMR (CDCl$_3$) shows rotamers, δ 8.59−8.49 and 8.32−8.20 (2m, 2H, dansyl-2H, dansyl-4H), 7.65−7.46 and 7.29−7.15 (2m, 4H, dansyl-8H, dansyl-3H, dansyl-7H, dansyl-6H), 5.76−5.65 (m, 1H, NH), 4.10−2.60 (m, 14H, NCH(Me)-CO, NCH_2CH$_2$, NCHCHMe, NCHCH$_2$, NMe_2, COCHCH$_2$CH$_2$, CHMe, NCH$_2$CHH), 1.93−1.75 (m, 1H, NCH$_2$CHH), 1.34−0.92 and 0.39−0.33 (2m, 10H, NCH(*Me*)CO, CH*Me*, COCHCH_2CH_2); MS (thermospray) m/z 513 (MH$^+$); HRMS calcd for C$_{26}$H$_{32}$N$_4$O$_5$S (MH$^+$) 513.217 214, found 513.216 973; HPLC 97% (t_R = 24.3 min).

N-{2-[rel-(3a***S***,6***S***,6a***R***)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2***H***)-yl]-2-oxoethyl}-5-(dimethylamino)-***N***-methylnaphthalene-1-sulfonamide (64).** Compound **63** was reacted with dansylsarcosine as described for **53** to give **64** (9%) as a yellow foam: ^{1}H NMR (CDCl$_3$) shows rotamers, δ 8.59−8.53 and 8.37−8.23 (2m, 3H, dansyl-2H, dansyl-4H, dansyl-8H), 7.60−7.49 (m, 2H, dansyl-3H, dansyl-7H), 7.20−7.15 (m, 1H, dansyl-6H), 4.20−3.18 (m, 6H, N(Me)CH_2CO, NCH_2CH$_2$, NCHCHMe, NCHCH$_2$), 3.01−2.73 (m, 12H, CHMe, NMe_2, NMe, COCHCH$_2$CH$_2$, NCH$_2$CHH), 2.12−1.92 (m, 1H, NCH$_2$CHH), 1.30−0.82 (m, 7H, CH*Me*, COCHCH_2CH_2); MS (thermospray) m/z 513 (MH$^+$); HRMS calcd for C$_{26}$H$_{32}$N$_4$O$_5$S (MH$^+$) 513.217 214, found 513.217 167; HPLC 98% (t_R = 25.7 min).

rel-(3***S***,3a***R***,6a***S***)-1-(Cyclopropylcarbonyl)-4-[(1-{[5-(dimethylamino)-1-naphthyl]sulfonyl}piperidin-2-yl)carbonyl]-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2(1H)-one (66).** Compound **63** was reacted with D,L-pipecolic acid as described for **53** to give **66** (14%) as a yellow foam: ^{1}H NMR (CDCl$_3$) shows rotamers, δ 8.58−8.49, 7.60−7.47 and 7.30−7.14 (3m, 6H, dansyl-2H, -4H, -8H, -3H, -7H, -6H), 4.87−4.65 and 4.10−2.66 (2m, 16H, NCHCO, NCH_2CH$_2$CH$_2$CH$_2$, NCH_2CH$_2$, NCHCHMe, NCHCH$_2$, CHMe, NMe_2, COCHCH$_2$CH$_2$, NCH$_2$CHH), 2.07−0.80 (m, 14H, NCH$_2$CHH, CH*Me*, NCH$_2$CH_2CH$_2$, COCHCH_2CH_2); MS (thermospray) m/z 553 (MH$^+$); HRMS calcd for C$_{29}$H$_{36}$N$_4$O$_5$S (MH$^+$) 553.248 468, found 553.248 712; HPLC 100% (t_R = 29.4 min).

Benzyl (2*S***)-2-{[(3a***S***,6***S***,6a***R***)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2***H***)-yl]carbonyl}pyrrolidine-1-carboxylate (67).** Compound **63** was reacted with Cbz-(*S*)-proline as described for **53** to give **67** (37%) as a white amorphous solid: IR (KBr) ν_{max} 1747, 1701, 1664 cm^{-1}; ^{1}H NMR (CDCl$_3$) shows rotamers, δ 7.38−7.27 (m, 5H, C$_6$H$_5$), 5.20−4.95 (m, 2H, PhCH_2O), 4.48−4.44 and 4.37−4.29 (2m, 2H, NCHCO, NCHHCH$_2$CH$_2$), 3.81−3.49 (m, 5H, NCHHCH$_2$, NCH_2CH$_2$, NCHCHMe, NCHCH$_2$), 3.37−3.20 (m, 1H, CHMe), 3.08−1.82 (m, 7H, COCHCH$_2$CH$_2$, NCH$_2$CH_2CH$_2$, NCH$_2$CH_2), 1.21−0.95 (m, 7H, CHMe, COCHCH_2CH_2); HPLC 100% (t_R = 24.9 min); MS (thermospray) m/z 440 (MH$^+$); Anal. (C$_{24}$H$_{29}$N$_3$O$_5$·0.3H$_2$O) C, H, N.

3-[((2*S***)-2-{[(3a***S***,6***S***,6a***R***)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2***H***)-yl]carbonyl}pyrrolidin-1-yl)sulfonyl]-***N***,***N***-dimethylbenzamide (69).** To a solution of the *trans*-lactam **68** (35 mg, 0.1

mmol) in dry acetonitrile (1.6 mL) was added triethylamine (0.032 mL, 0.23 mmol) followed by a solution of 3-[(dimethylamino)carbonyl]benzenesulfonyl chloride[19] (44 mg, 0.18 mmol) in acetonitrile (0.5 mL). After 45 min, the reaction was quenched with 2-propanol (0.01 mL) and evaporated to dryness. The residue was partitioned between water (15 mL) and ethyl acetate (20 mL). The organic phase was washed with water (15 mL), saturated sodium hydrogen carbonate solution (15 mL), and water (15 mL) and dried (MgSO$_4$). The solvent was evaporated to give a colorless gum, which was purified by preparative TLC on silica gel, eluting with ethyl acetate to give **69** (20 mg, 38%) as white solid: IR (KBr) ν_{max} 1747, 1666, 1634 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.99−7.91 (m, 2H, C$_6$H$_4$), 7.70−7.54 (m, 2H, C$_6$H$_4$), 4.55 (dd, J = 4.9 Hz, J = 7.9 Hz, 1H, NCHCO), 4.25 (t, J = 9.8 Hz, 1H, NCHHCH$_2$CH$_2$), 3.89−2.73 (m, 14H, NCHHCH$_2$CH$_2$, NCH_2CH$_2$, NCHCH$_2$, NCHCHMe, CHMe, NMe_2, COCHCH$_2$CH$_2$, NCH$_2$CHH), 2.22−1.77 (m, 5H, NCH$_2$CHH, NCH$_2$CH_2CH$_2$), 1.31−0.95 (m, 7H, CHMe, COCH-CH_2CH_2); MS (thermospray) m/z 517 (MH$^+$); HRMS calcd for C$_{25}$H$_{32}$N$_4$O$_6$S (MH$^+$) 517.212 108, found 517.212 135; HPLC 98% (t_R = 21.1 min).

The following compounds were similarly prepared.

(3*S***,3a***R***,6a***S***)-1-(Cyclopropylcarbonyl)-4-({(2***S***)-1-[(3-isopropoxyphenyl)sulfonyl]pyrrolidin-2-yl}carbonyl)-3-methylhexahydropyrrolo[3,2-*b*]pyrrol-2-one (70).** Similarly prepared as **69**, using 3-(1-methylethoxy)benzenesulfonyl chloride as the sulfonylating agent, product **70** was obtained as a white solid (43%): IR (KBr) ν_{max} 1754, 1674, 1661 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.44−7.36 (m, 3H, C$_6$H$_4$), 7.11−7.04 (m, 1H, C$_6$H$_4$), 4.68−4.49 (m, 2H, OCHMe$_2$, NCHCO), 4.29 (t, J = 9.2 Hz, 1H, NCHHCH$_2$CH$_2$), 3.90−3.22 (m, 6H, NCHHCH$_2$-CH$_2$, NCH_2CH$_2$, NCHCHMe, NCHCH$_2$, CHMe), 3.0−2.9 (m, 1H, COCHCH$_2$CH$_2$), 2.84−2.72 (m, 1H, NCH$_2$CHH), 2.20−1.76 (m, 5H, NCH$_2$CHH, NCH$_2$CH_2CH$_2$), 1.36 and 1.34 (2d, J = 6.1 Hz, 6H, OCH*Me*$_2$), 1.20−0.96 (m, 7H, CH*Me*, COCHCH_2-CH_2); MS (thermospray) m/z 504 (MH$^+$); HPLC 100% (t_R = 28.3 min). Anal. (C$_{25}$H$_{33}$N$_3$O$_6$S·0.2CH$_2$Cl$_2$) C, H, N, S.

3-{[((2*S***)-2-{[(3a***S***,6***S***,6a***R***)-4-(Cyclopropylcarbonyl)-6-methyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrol-1(2***H***)-yl]carbonyl}pyrrolidin-1-yl)sulfonyl]methyl}-***N***,***N***-dimethylbenzamide (71).** To a suspension of 3-(dimethylamino)benzenemethanesulfonic acid (43 mg, 0.175 mmol) in dichloromethane (2 mL) stirred at room temperature under nitrogen was added DMF (0.003 mL) followed by triphosgene (38 mg, 0.127 mmol) and triethylamine (0.024 mL, 0.175 mmol). The solution was stirred at room temperature for 2 h before a solution of the *trans*-lactam **68** (30 mg, 0.088 mmol) and DBU (0.026 mL, 0.175 mmol) in dichloromethane (2 mL) was added. The mixture was stirred for 1.5 h at room temperature before the reaction was quenched with 2-propanol (0.01 mL) and the mixture was evaporated to dryness in vacuo. The residue was partitioned between ethyl acetate (20 mL) and water (15 mL), and the organic phase was washed with saturated sodium hydrogen carbonate solution (15 mL) and brine (15 mL) and dried (MgSO$_4$). The solvent was evaporated in vacuo to give a white residue that was purified by preparative TLC on silica gel, eluting with chloroform/methanol (95:5) to give **71** (10 mg, 22%) as a white solid: IR (KBr) ν_{max} 1747, 1688, 1681, 1661, 1651, 1633 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.7−7.6 (m, 2H, C$_6$H$_4$), 7.5−7.4 (2H, m, C$_6$H$_4$), 4.7−4.3 (m, 3H, PhCH_2, NCHCO), 4.1−3.9 (m, 2H, NCH_2CH$_2$CH$_2$), 3.8−3.3 (m, 5H, NCH_2CH$_2$, NCHCHMe, NCHCH$_2$, CHMe), 3.2−2.9 (7H, m, NMe_2, COCHCH$_2$-CH$_2$), 2.86−2.74 (m, 1H, NCH$_2$CHH), 2.4−1.8 (m, 5H, NCH$_2$-CHH, NCH$_2$CH_2CH$_2$), 1.4−0.8 (m, 7H, CH*Me*, COCHCH_2CH_2); MS (thermospray) m/z 531 (MH$^+$); HPLC 98% (t_R = 21.2 min). Anal. (C$_{26}$H$_{34}$N$_4$O$_6$S) C, H, N, S.

References

(1) Gibson, W.; Welch, A. R.; Hall, M. R. T. Assemblin, a herpesvirus serine maturational proteinase and a new molecular target for antivirals. *Perspect. Drug Discov. Des.* **1994**, *2*, 413−426.

(2) (a) Holwerda, B. C. Herpesvirus proteases: targets for novel antiviral drugs. *Antiviral Res.* **1997**, *35*, 1−21. (b) Qiu, X. Y.; Abdelmeguid, S. S. Human Herpes Proteases. In *Proteases of*

Infectious Agents; Dunn, B. M., Ed.; Academic Press: San Diego, CA, 1999; Chapter 3, pp 93−115. (c) Waxman, L.; Darke, P. L. The herpes proteases as targets for antiviral chemotherapy. *Antiviral Chem. Chemother.* **2000**, *11*, 1−22.

(3) Chen, P.; Tsuge, H.; Almassy, R. J.; Gribskov, C. L.; Katoh, S.; Vanderpool, D. L.; Marbosiak, S. A.; Pinko, C.; Matthews, D. A.; Kan, C. C. Structure of the Human Cytomegalovirus Protease Catalytic Domain Reveals a Novel Serine Protease Fold and Catalytic Triad. *Cell* **1996**, *86*, 835−843.

(4) Tong, L.; Qian, C. G.; Massariol, M. J.; Bonneau, P. R.; Cordingley, M. G.; LaGace, L. A. A New Serine−Protease Fold Revealed by the Crystal Structure of Human Cytomegalovirus Protease. *Nature* **1996**, *383* (N6597), 272−275.

(5) Qiu, X. Y.; Culp, J. S.; Dilella, A. G.; Hellmig, B.; Hoog, S. S.; Janson, C. A.; Smith, W. W.; Abdelmeguid, S. S. Unique Fold and Active Site in Cytomegalovirus Protease. *Nature* **1996**, *383* (N6597), 275−279.

(6) Shieh, H. S.; Kurumbail, R. G.; Stevens, A. M.; Stegeman, R. A.; Sturman, E. J.; Pak, J. Y.; Wittwer, A. J.; Palmier, M. O.; Wiegand, R. C.; Holwerda, B. C.; Stallings, W. C. Three Dimensional Structure of Human Cytomegalovirus Protease. *Nature* **1996**, *383* (N6597), 279−282.

(7) Borthwick, A. D.; Angier, S. J.; Crame, A. J.; Exall, A. M.; Haley, T. M.; Hart, G. J.; Mason, A. M.; Pennell, A. M. K.; Weingarten, G. G. Design and Synthesis of Pyrrolidine 5,5-*trans*-Lactams (5-Oxo-hexahydro-pyrrolo[3,2-b]pyrroles) as Novel Mechanism-Based Inhibitors of Human Cytomegalovirus Protease. 1. The α-Methyl-*trans*-lactam Template. *J. Med. Chem.* **2000**, *43*, 4452−4464.

(8) Borthwick, A. D.; Crame, A. J.; Davies, D. E.; Exall, A. M.; Jackson, D. L.; Mason, A. M.; Pennell, A. M. K.; Weingarten, G. G. Stereoselective Synthesis of α-Methyl and β-Methyl-5,5-pyrrolidine-*trans*-lactam (5-Oxo-hexahydro-pyrrolo[3,2-b]pyrrole) and Stereoselective Alkylation of the Strained Pyrrolidine-5,5-*trans*-lactam Ring System. *Synth. Lett.* **2000**, 504−508.

(9) Box, D. S.; Holman, S.; Pritchard, J. M.; Youds, P. M. Unpublished work. Modification of the amino acid route is in ref 7.

(10) Boger, D. L.; Patel, M. Activation and Coupling of Pyrrole-1-carboxylic Acid in the Formation of Pyrrole N-Carbonyl Compounds: Pyrrole-1-carboxylic Acid Anhydride. *J. Org. Chem.* **1987**, *52*, 2319.

(11) Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S.-I. Palladium(II)-Catalysed Amination of Alkenes. *Tetrahedron Lett.* **1992**, *33*, 6643.

(12) Haley, T. M.; Angier, S. J.; Borthwick, A. D.; Montogomery, D. S.; Purivs, I. J.; Smart, D. H.; Bessant, C.; Van Wely, C.; Hart, G. J. Investigation of the Covalent Modification of the Catalytic Triad of Human Cytomegalovirus Protease by Pseudo-reversible β-Lactam Inhibitors and a Peptide Chloromethylketone. *J. Mass Spectrom.* **1998**, *33*, 1246−1255.

(13) Recombinant HCMV protease mutant (V141Y, V207Y, and A209N) was expressed in *E. coli* and purified by two consecutive ion-exchange chromatography steps at 4 °C in a manner similar to that of the previously described HCMV δAla protease.[12] The protein was concentrated to 30 mg/mL and crystallized by vapor diffusion by mixing 2 μL of protein with 2 μL of 15−20% PEG 3.4K, 10% glycerol, 5% *tert*-butyl alcohol, 0.1 M MES buffer at pH 6.0. Tetragonal bipyramid crystals grew in 10 days at 20 °C. The crystals belonged to space group $p4_12_12$ with cell dimensions of $a = b = 76.45$ Å and $c = 170.72$ Å. X-ray data were collected from cryocooled crystals at 100 K, and the enzyme structure was solved to 2.2 Å resolution by mid-IR using data from terpyridinylplatinate-derivatized crystals.

(14) The enzyme−ligand structural modeling was done with Sybyl (version 6.3), and the geometry optimization of the ligands within the context of a rigid enzyme was done using the standard Sybyl force field.

(15) Cox, G. A.; Wakulchik, M.; Sassmannshausen, L. M.; Gibson, W.; Villarreal, E. C. Human cytomegalovirus protease: candidate glutamic acid identified as third member of putative active-site triad. *J. Virol.* **1995**, *69*, 4524−4528.

(16) Hungerbuhler, E.; Lang, M.; Scartazzini, R. European Patent (to Ciba-Geigy) 297042 A1, 1988.

(17) Borthwick, A. D.; Weingarten, G. G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yeun, L.; Mansour, T. S. Design and Synthesis of Monocyclic β-Lactams as Mechanism-Based Inhibitors of Human Cytomegalovirus Protease. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365−370.

(18) Borthwick, A. D.; Crame, A. J.; Exall, A. M.; Jackson, D. L.; Mason, A. M.; Pennell, A. M. K.; Weingarten, G. G. Stereoselective Synthesis of the *gem*-Dimethyl-5,5-pyrrolidine-*trans*-lactam (5-Oxo-hexahydro-pyrrolo[3,2-b]pyrrole). *Tetrahedron Lett.* **2001**, *42*, 6933−6935.

(19) Barr, C. R.; Salminen, I. F.; Weissberger, A. The Reaction of 3-Chlorosulfonylbenzoyl Chloride with Amines. *J. Am. Chem. Soc.* **1951**, *73*, 4131−4133.