Sulfahydantoins as Tripeptide Constraints: Synthesis and Structure of Chiral Substituted 3-Oxo-1,2,5-thiadiazolidine 1,1-Dioxides

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A sulfahydantoin (3-oxo-1,2,5-thiadiazolidine 1,1-dioxides) motif is used as a new type of peptidic constraint to lock two consecutive amide nitrogens by a sulfonyl bridge. The 5-membered heterocyclic motif was prepared starting from proteogenic and synthetic amino acids and chlorosulfonyl isocyanate. Constrained dipeptides were obtained under alkaline conditions (methoxide or *tert*-butoxide) by cyclization of symmetric and dissymmetric sulfamides. The absolute configuration of the chiral centers for the derivative L-Phe-D-Ala, a congener of the series, was established by X-ray diffraction crystallographic analysis. In addition, the chemo-, regio-, and stereoselectivities of the reactions were studied. In the acylated derivatives, the sulfahydantoin constraint induces a unique backbone conformation with coplanarity of two consecutive peptide bonds.

Introduction

Many small peptides are key factors in the regulation of a wide variety of biological functions, acting as hormones, neurotransmitters, or enzymatic inhibitors. Major efforts have thus been devoted to the development of agonists or antagonists of these peptides that could be used as drugs with high specificity and low toxicity. The great diversity of biological roles played by peptides is correlated with the huge number of possibilities that exist for their primary sequence and three-dimensional structures. Hence, knowledge of the active conformation of a given bioactive peptide is a major step towards understanding its biological function. The design of conformationally restricted analogs of bioactive peptides is the most common strategy used by medicinal chemists in an effort to firmly establish three-dimensional active structures and to develop new pharmaceutical agents with prolonged action and better therapeutic profiles.[1][2] Although a wealth of physical techniques exist to study polypeptide conformations (e.g. NMR, CD, and X-ray diffraction), a major obstacle in the study of small peptides is their intrinsic flexibility. The number of conformational possibilities for peptides can, however, be reduced by introducing constraints. Indeed, nature uses several such constraints to reduce the flexibility, including the incorporation of cyclic (or macrocyclic) substructures. Reverse turns, α helices and β sheets are the three main classes of secondary structure in proteins that one may want to introduce into a polypeptide chain through the use of a constraint. Thus, reverse turns are ideal sites for receptor recognition because they present side chains in a highly accessible arrangement around a compact fold of the peptide backbone.

Therefore, the cyclization of peptides represents the main strategy in medicinal chemistry to reduce their mobility. This approach for conformational restriction can be considered as a *global* constraint. In this case, the nature and the stereochemistry of the constituent amino acids can be conserved (with specific modifications such as the use of D-enantiomers, cyclic, or *N*-methyl amino acids).

Likewise, a series of inhibitors that incorporates a central constraining element to direct the vectors of functional side chains has also emerged; in the case of such *local* constraint, the peptidic nature is replaced by a rigid bioisosteric structure.

Our goal is to develop a new type of constraint that conserves the peptidic scaffold while inducing a rigid fold that orients the side chain of a tripeptide unit into specific spatial relationships. To do so, we envisioned the linkage of two consecutive amide nitrogens by an SO_2 group to create a sulfahydantoin tripeptide constraint (Figure 1).

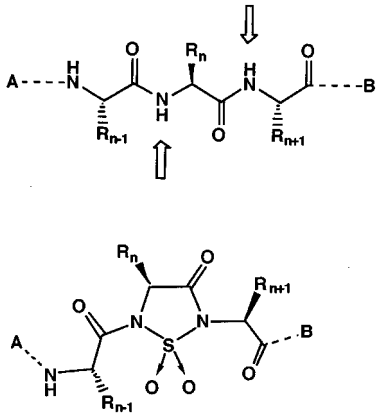

Figure 1. Predictable constraints induced by insertion of a sulfahydantoin motif in a peptidic structure

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  1434–193X/99/0909–2275 $ 17.50+.50/0

As seen with the Ramachandran diagram of the fully protected *sulfonyl* tripeptide derived from Val-Phe-Ala, the values of Φ and ψ angles (Figure 2a), obtained by molecular modelling, are intermediary between those of α-helix and β-sheet conformations of the parent sequence. This centrally constrained conformation can also be considered as a consensus structure between these main chain organization levels (Figure 2b).

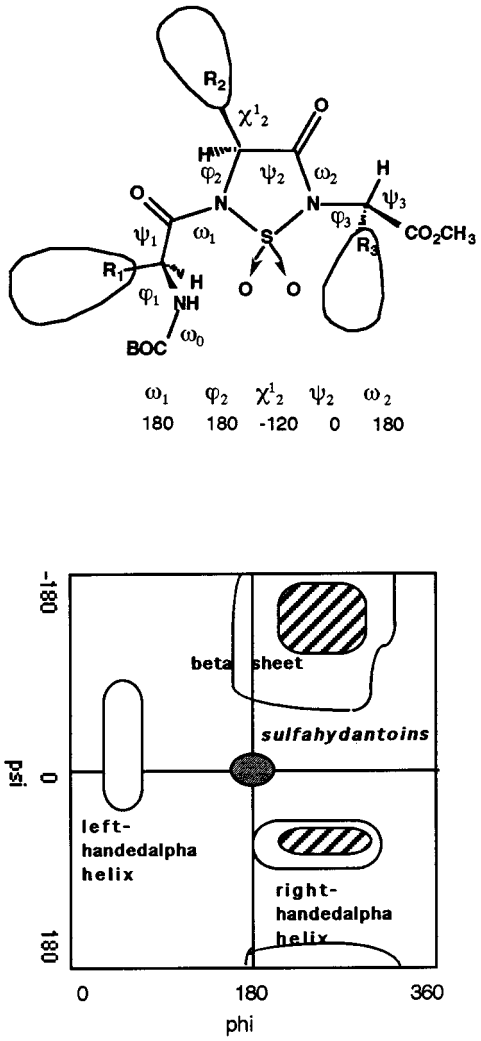


Figure 2. (a, top) Calculated dihedral angles for the sulfonyltripeptide *N*-Boc-L-Val-L-Phe-[SO_2]-D-Ala-OMe (R^1 = *i*Pr; R^2 = Bn; R^3 = Me) see Experimental Section; (b, bottom) Ramachandran plot showing the position of sulfahydantoin-constrained tripeptides relative to that of other secondary structures

The insertion of a sulfahydantoin moiety into the primary sequence can be formally realized by successive selective *N*-2 alkylation and *N*-5 acylation of chiral 3-oxo-1,2,5-thiadazolidine dioxides (sulfahydantoins). The chemistry of this class of heterocycles has been previously described,[3a−3f] and some potential applications were envisaged and/or reported (anticonvulsant,[4] sweetener,[5] antimetabolite[6]). More recently, Groutas et al. have demonstrated that the sulfahydantoin ring is a highly effective peptidomimetic scaffold suitable for inhibition of serine proteinases, especially elastase.[7] Moreover, modelling studies and previous work suggest that the sulfonamide functionality can be exploited as a valuable candidate for the replacement of the amido group in peptidomimetic structures.[8]

Herein we report our results on the development of a general synthetic method to prepare sulfahydantoin-constrained tripeptides that could be adapted to solid phase synthesis.

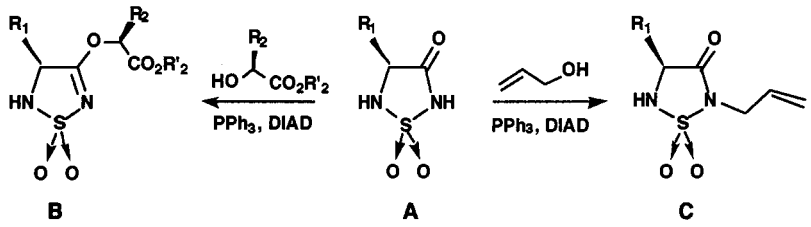
Results and Discussion

General Strategy

Since we have already reported the efficient synthesis of chiral sulfahydantoins derived from amino acids,[3f] we sought to use them as modular units in the construction of constrained tripeptides (Figure 2a). The concept was to exploit the different nucleophilic character of the two nitrogens on the sulfahydantoins. The most nucleophilic sulfonimide nitrogen would be used in a Mitsunobu reaction with α-hydroxy esters to give dipeptide analogs. Then the other nitrogen would be acylated by protected amino acids using conventional peptidic coupling reagents.

However, the alkylation of sulfahydantoins **A** by α-hydroxyesters (i.e. malate, lactate, or glycolate) under Mitsunobu conditions surprisingly gave the *O*-alkylated compound **B** with the hydroxy ester having the same absolute configuration (Scheme 1).[9] This has been proven by X-ray analysis of the *O*-lactim ether and a mechanism has been proposed for the unexpected reaction. In contrast, the use of allylic alcohol under the same conditions gave the expected *N*-alkylated compounds (**C**) (no transposition was observed) in near quantitative yields.[10] These compounds are of interest since they can serve as a precursor of a glycine residue after an oxidative cleavage reaction.

As an alternative approach, we decided to use the cyclization of symmetric and unsymmetrical sulfamides derived from certain amino acid esters under basic conditions. The symmetric derivatives **1**, **3**, **4**, **10** (respectively derived from Gly-OEt, L- and D-Ala-OEt, and L-Phe-OMe) are accessible by a direct treatment of amino acids esters with sulfuryl chloride.[3d] On the other hand, the dissymmetric sulfamides can be obtained by treatment of amino acid esters [Gly-OEt, Ala-OEt, Leu-OMe, Phe-OMe, Asp-$(OMe)_2$, Asp-$(OBn)_2$, and Aib-OMe] with the reagent prepared in situ by the reaction of *t*BuOH and chlorosulfonylisocyanate (CSI) to give first the *N*-Boc-sulfamoyl amino acid esters.[3c] These compounds can be further alkylated under Mitsunobu conditions[11] with α-hydroxyesters (methyl or benzyl glycolate, ethyl or benzyl L-lactate) with inversion of configuration to yield the intermediates ready to be cyclized after a Boc deprotection step with trifluoroacetic acid to the analogs **2**, **5**−**9**, **11**, **12**. The overall yields for the complete process range from 50 to 70%. This type of dissymmetric compound has also been prepared by a sequential disubstitution on catechol sulfate.[3e]



Scheme 1. *O*- versus *N*-alkylation of sulfahydantoins under Mitsunobu conditions

Synthesis of Sulfono-Constrained Dipeptides

All attempts to cyclize the *N*-Boc-sulfamides regioselectively were unsuccessful. However, the cyclization of the deprotected disubstituted sulfamides **1**−**12** was achieved under strongly basic conditions using alkoxides as the base (Scheme 2). These conditions are much more rigorous than those required (NaOH, H_2O/dioxane) to prepare the alkyl-substituted sulfahydantoins **A** (Scheme 1).[4a] Treatment of compounds **1**−**12** with sodium methoxide in methanol gave first the dimethyl esters by transesterification, regardless of their nature, and then cyclization occurred. The formation of bridged diketopiperazines through a dicyclization process was never observed, probably due to the unfavorable conformation of the amide nitrogen that would be required in order for cyclization to occur.

The compounds obtained under these latter conditions are listed in Table 2. Interestingly, starting with compound **8** the reaction furnishes a mixture of regio/stereomers of the sulfonodipeptides **18**−**19** and **22**−**23** and the following observations were made:

(i) When using sodium methoxide or ethoxide as base, the ring closure step of dissymmetric compounds occurs mainly on the most sterically hindered amino acid. *Therefore, the regioselectivity is dependent on the nature of the constituent amino acids.*

(ii) The exocyclic chiral carbon atom undergoes an almost complete epimerization, while the endocyclic one retains its chiral integrity, as demonstrated in earlier studies.[3f]

X-ray structural analysis allowed us to establish the absolute configuration of one derivative obtained, the constrained dipeptide **22** (vide infra). In addition to the four regio/stereoisomers, variable quantities of diastereoisomeric sulfamate dipeptides were isolated (for example **36**−**37**). These compounds result from the nucleophilic opening of the phenylalanine-derived sulfahydantoin by the methoxide anion, as shown in Scheme 2. The structure of these compounds was elucidated with ^{1}H- and ^{15}N-NMR spectroscopy.[12]

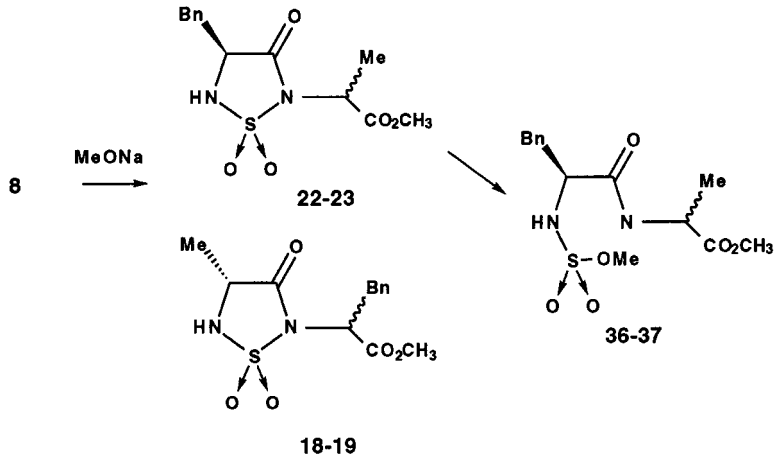
Accordingly, the use of the less nucleophilic and more basic *tert*-butoxide anion avoided transesterification and ring opening processes. Therefore, these conditions allow the preparation of orthogonally protected constrained dipeptides when using differently protected amino acid esters. In this case, the ring closure step is still controlled by the nature of the amino acid constituents. A typical example of this chemical approach is shown in Scheme 3 for the regioselective formation of sulfonodipeptides derived from Asp-Gly **30** and **31**.

Structural Analysis of Derivative 22

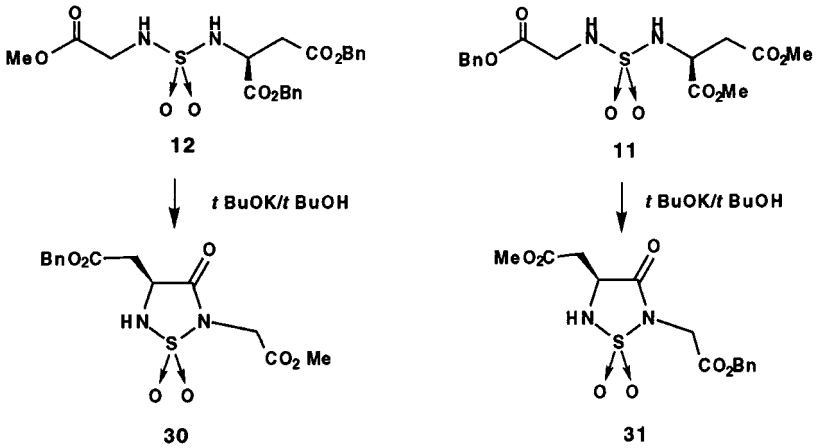
The SO_2-constrained dipeptide **22** was isolated through careful chromatography and recrystallization from the product mixture resulting from the methanolate treatment of the dissymmetric sulfamide **8** (containing L-Phe and D-Ala). Dipeptide **22** is less polar than its epimer **23**. Crystal data and structure refinement are as follows: $C_{13}H_{16}N_2O_5S$;

Xaa / OR1 / O2S / OR2 / Yaa	Xaa Gly OEt	L Ala OEt	D Ala OEt	Aib OMe	L Leu OMe	L Phe OMe	L Asp (OR) OR R= Me R=Bn
Yaa Gly OEt	1						
Gly OMe							12
Gly OBn				5		7	11
L Ala OEt		3					
D Ala OEt	2		4		6	8	
D Ala OBn						9	
L Phe OMe						10	

Table 1. Structure of the acyclic precursors **1**−**12** to the sulfahydantoin constrained dipeptides



Scheme 2. Reactions of disubstitued sulfamides with sodium methoxide



Scheme 3. Regioselectivity of ring closure for dissymmetric sulfamides

M: 312.34, triclinic, *P*1, a = 9.095(3), b = 9.9375(10), c = 10.043(5) Å, α = 109.83(3), β = 114.67(2), γ = 94.94(2)°, V = 748.0(5) Å^3, Z = 2, Dx = 1.387 Mg·m^{-3}, λ(Mo-$K\alpha$) = 0.71073 Å, μ = 2.39 cm^{-1}, F(000) = 328, T = 294 K.[13]

From the X-ray analysis of **22**, it is interesting to note the important difference in the hybridization of the two nitrogens of the sulfahydantoin. Indeed, N2 is sp^2-hybridized, whereas N5 is roughly sp^3-hybridized.[3a] Moreover, the two hydrogens at the N5 and C4 positions are *syn*. On the alanine side, the values of angles φ2 and ψ2 are +76° and +166°, respectively. On the phenylalanine portion, the ψ1 angle of +3.5° is imposed by the heterocyclic structure and

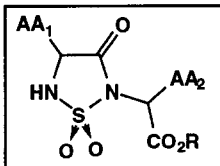
	AA_1 L Ala	D Ala	L Leu	L Phe	L Asp (OBn) (OMe)	Aib
AA_2 D Ala OMe / OEt	**13**	**15**	**20**	**22**		
L Ala OMe / OEt	**14**	**16**	**21**	**23**		
D Ala OBn				**24**		
L Ala OBn				**25**		
Gly OMe / OEt		**17**		**26**	**30**	
Gly OBn				**27**	**31**	**32**
D Phe OMe		**18**		**28**		
L Phe OMe		**19**		**29**		

Table 2. Structure of the constrained sulfonodipeptides **13**−**32**

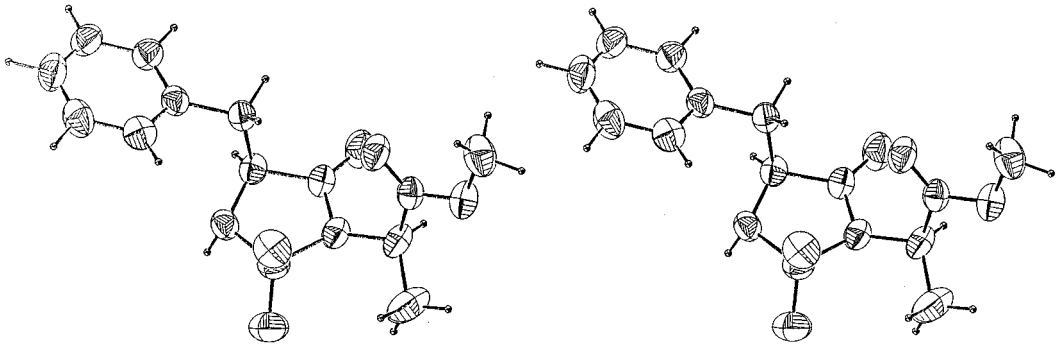


Figure 3: Stereoscopic ORTEP view of (2*R*,4*S*)-4-benzyl-2-[2-(2-methoxycarbonyl)ethyl]-3-oxo-1,2,5-thiadiazolidine 1,1-dioxide (**22**)

the benzyl side chain is characterized by a $\chi 1$ angle of $-61°$. This conformation orients the $CH_{\beta\ pro\text{-}(R)}$ hydrogen above the plane of the heterocycle, *anti* with respect to the CH_α. This characteristic allows its NMR identification as the most shielded proton of the AB protons of the ABX spin system ($\delta = 3.14$; $J_{AB} = -12.40$ Hz; $J_{AX} = 9.10$ Hz). The diastereotopic proton *pro*-(*S*) shows a signal at $\delta = 2.25$ with a vicinal coupling constant of 4.10 Hz. These structural details will be useful in the prediction of the side chain orientations of constrained tripeptides.

Synthesis of Acylated Constrained Dipeptides

AAs models for sulfahydantoin-constrained tripeptides, the N^5-acyldipeptides **38**−**43** were prepared by treatment of the corresponding dipeptides with acetic anhydride in the presence of triethylamine.[14] The most striking consequence of the acylation reaction is the significant epimerization of the endocyclic CHα under the mild basic reaction conditions. This is most probably due to the enhanced lability of the CHα proton, which has been demonstrated by deuterium-exchange NMR experiments (Figure 4). The inversion of the configuration is probably linked to steric decompression involved with the enolization process of the heterocyclic structure.

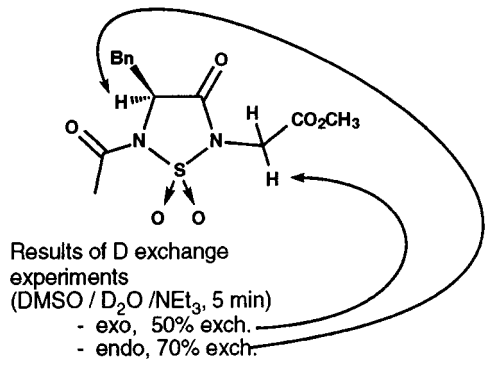


Figure 4. Lability of CHα in alkaline medium

Another feature induced by the acylation reaction on all derivatives is a deshielding effect of 0.7 to 0.8 ppm on the endocyclic CHα proton. In the case of **22**, the signal of the $CH_2\beta$ is also modified. The doublet of doublets having the

AA1 AA2 / Ac SO2 OR	L Phe	Aib	L Asp (OBn)
DL Ala OBn	**38-39**		
Gly OMe	**40**		**43**
Gly OBn	**41**	**42**	

Table 3. Structure of the acyl sulfonoconstrained dipeptides **38**−**43**

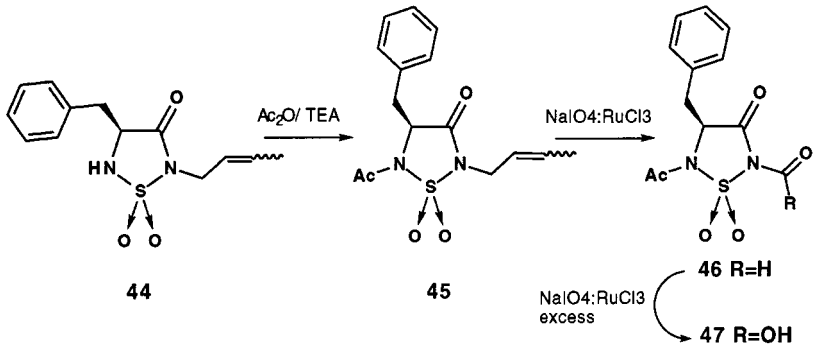
largest ^3J constant corresponds to the most deshielded proton, suggesting a rotation around the Cα−Cβ bond to bring the $\chi 1$ angle roughly equal to $-120°$. This has also been observed with the *O*-alkylated lactim.[9] The change of conformation also affects the signals of the methylenic protons on the N2 in compounds **40** and **41**. Furthermore, the hybridization of the N5 becomes sp^2 and the angle ω of the amide bond created is 180°. In other words, the acyl carbonyl group is antiperiplanar to the N−S bond.[15]

Deprotection of the C-Terminal Group

In order to use the sulfahydantoin-constrained peptide fragments described above as building blocks in solid phase synthesis, it is necessary to deprotect the C-terminal ester. Since the acylated N^5 derivatives are sensitive to basic conditions, we have studied the hydrogenolysis of benzylic ester derivatives such as **41**. Conventional conditions using Pd/C H_2 in ethanol gave the corresponding acid **47**. This compound was also prepared by an oxidative degradation of the acyl derivative **45** using $NaIO_4/RuCl_3$ in a water/acetonitrile mixture (Scheme 4).[16] Interestingly, the aldehyde **46** could be isolated under mild conditions and characterized.

Conclusion

We have devised different synthetic strategies to prepare peptidic structures constrained with a sulfahydantoin motif. We described the preparation of such sulfahydantoin-modified dipeptides from proteogenic and synthetic amino acids. The chemo-, regio-, and stereoselectivities of the reactions in the sequence are predictable and allow the synthesis of several constrained acyldipeptides of desired amino acid se-



Scheme 4. Allylic oxidation of C terminus by $NaIO_4-RuCl_3$ complex

quence. The sulfahydantoin constraint induces a specific backbone conformation with ψ and ϕ angles in between those of α-helical and β-sheet structures. The different reaction steps can possibly be adapted to solid-phase synthesis, which would allow the preparation of libraries of sulfahydantoin-constrained peptides.[17a−17c] Work along these lines is in progress.

Experimental Section

Melting points were determined in open capillary tubes on a thermotechnal apparatus and are uncorrected. − IR spectra were recorded on a Perkin−Elmer spectrophotometer. − Proton Magnetic Resonance spectra were obtained with AC 250 or 400 Bruker spectrometers. Chemical shifts are expressed in parts per million, with TMS as reference. The multiplicity is indicated as: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), l (large), and combinations of these abbreviations. − Fast-atom bombardment mass spectra (FAB-MS) were recorded in positive or negative mode on a JEOL DX 300 spectrometer using either G (glycerol), GT (thioglycerol) or NOBA (nitrobenzyl alcohol) as the matrix. − Thin-layer chromatography (TLC) was performed on silica gel $60F_{254}$ (Merck). Column chromatography was performed with silica gel 60. − All solvents used for the reactions were anhydrous.

Molecular modelling calculations were performed on a Silicon Graphics Indy R 4600 computer with the software MSI Insight-II 97-2 (module discover), with the parameters: forcefield cvff, minimization by steepest descent 200 it., conjugate 300 it. followed by dynamic simulation $T = 800 \rightarrow 300$ K, 8000 steps. The obtained conformation (Figure 2a) shows a good fitting with the geometry of **22** and the NMR data of its acylated derivative. In addition, the proven conformation (X-ray diffraction resol: 1.84 Å) of irreversible inhibitor methoxysuccinyl-Ala-Ala-Pro-Ala-chloromethylketone in the active site of human elastase[18] (E.C.3.4.21.37; entry *1HNE* of Protein Data Bank, Brookhaven) is similar to that in this model.

General Procedure for the Synthesis of the (*N*′-Boc)-*N*-Sulfamoylamino Acid Esters: To a suspension of the amino ester hydrochloride (50 mmol) was added triethylamine (50 mmol in 100 mL of $CHCl_2$). Simultaneously the *tert*-butyl chlorosulfonylcarbamate was prepared by addition of 55 mmol of *tert*-butyl alcohol in CH_2Cl_2 (20 mL) to an ice-cooled solution containing 50 mmol of chlorosulfonyl isocyanate in 20 mL of CH_2Cl_2. The obtained reagent solution was slowly added to the solution of amino acid ester at the same time as 55 mmol of Et_3N. The reaction was monitored by TLC. The mixture was then diluted with CH_2Cl_2 (100 mL) and washed with 2 portions of 1 M HCl (50 mL each) and water. The solution was then dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the pure sulfamide (eluent: CH_2Cl_2/MeOH, 9:1).

General Procedure for the Synthesis of the *N*-Boc-Sulfamides: To a solution containing the Boc-sulfamoylamino acid ester (10 mmol), triphenylphosphane (10 mmol), and α-hydroxyester (10 mmol) in THF was added dropwise diisopropyl diazodicarboxylate (10 mmol). The workup of the reaction consisted of the precipitation of the oxidoreduction product, followed by purification by column chromatography on silica gel (ether/hexane, 8:2) to afford the pure product.

General Procedure for the Synthesis of the *N,N*′-Disubstituted Sulfamides. − (a) Symmetric Derivatives 1, 3, 4, 10: A solution of 5 mmol of sulfuryl chloride in 20 mL of cyclohexane was added dropwise to an ice-cooled, stirred solution of 20 mmol of the amino acid ester in 40 mL of cyclohexane. The reaction mixture was stirred for 15 min and then 100 mL of cold water was added and the reaction mixture stirred for additional 15 min. The mixture was extracted with 120 mL of CH_2Cl_2. The organic phase was washed with 60 mL of 1 M HCl followed by 60 mL of water, dried with Na_2SO_4, and the solvent was removed under reduced pressure to give the crude sulfamide. The aqueous fractions were combined, made basic with 30% (v/v) aqueous NaOH, and extracted with 2 × 60 mL of CH_2Cl_2. The combined organic extracts were washed with 100 mL of water and dried with Na_2SO_4. The solvent was removed under reduced pressure to recover the excess of the amino acid ester.

(b) Dissymmetric Derivatives: The synthesis of this series was carried out by deprotection of Boc-sulfamides under acidic conditions (50% trifluoroacetic acid in CH_2Cl_2). The expected compounds were obtained in quantitative yields.

***N,N*′-*Bis*(ethoxycarbonylmethyl)sulfamide (1):** Yield 30%. − M.p. 56−58°C. − ^{1}H NMR ($CDCl_3$): δ = 1.32 (t, 6 H, *J* = 7.15 Hz, CH_2CH_3), 3.91 (d, 4 H, *J* = 5.83 Hz, $NHCH_2$), 4.25 (q, 4 H, *J* = 7.15 Hz, OCH_2), 5.16 (t, 2 H, N).

***N*-[(2*R*)-2-(Ethoxycarbonyl)ethyl]-*N*′-(ethoxycarbonylmethyl)sulfamide (2):** Yield 95%. Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.31 (2 t, 6 H, CH_2CH_3), 1.46 (d, 3 H, *J* = 7.21 Hz, $CHCH_3$), 3.87 (2 dd, 2 H, $NHCH_2$), 4.10 (q, 1 H, C*H*), 4.14 (2q, 4 H, OCH_2), 5.16 (t, 1 H, *J* = 5.53 Hz, CH_2NH), 5.28 (d, 1 H, *J* = 8.6 Hz, NH).

***N,N*′-Bis[(2*S*)-2-(ethoxycarbonyl)ethyl]sulfamide (3):** Yield: 40%. M.p. 78−79°C. − $[\alpha]_D^{25} = -7$ (*c* = 0.79; CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 1.32 (t, 6 H, *J* = 7.15 Hz, CH_2CH_3), 1.46 (d, 6 H, *J* = 7.22 Hz, $CHCH_3$), 4.11 (q, 2 H, *J* = 7.23 Hz, C*H*), 4.22 (q, 2 H, *J* = 7.12 Hz, OCH_2), 5.21 (d, 2 H, *J* = 8.42 Hz, N*H*).

***N,N′*-Bis[(2*R*)-2-(ethoxycarbonyl)ethyl]sulfamide (4):** $[\alpha]_D^{25} = +7$ ($c = 1$, CH_2Cl_2).

***N*-(Benzyloxycarbonylmethyl)-*N′*-[(2′*S*)-2′-(methoxycarbonyl)propyl]sulfamide (5):** Yield: 90%. Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.57 [s, 6 H, C(CH_3)$_2$], 3.80 (s, 3 H, OCH_3), 3.97 (d, 2 H, J = 5.88 Hz, NHCH_2), 5.23 (s + t, 2 H + 1 H, CO_2CH_2 + CH_2NH), 5.30 (s, 1 H, exch, CN*H*), 7.4 (s, 5 H, Ar*H*).

***N*-[(2*R*)-2-(Ethoxycarbonyl)ethyl]-*N′*-[(2′*S*)-2′-(methoxycarbonyl)-isopentyl]sulfamide (6):** Yield 90%. Oil. − ^{1}H NMR ($CDCl_3$): δ = 0.87 [d, 6 H, J = 6.55 Hz, CH(CH_3)$_2$], 1.23 (t, 3 H, J = 7.12 Hz, CH_2CH_3), 1.33 (d, 3 H, J = 7.14 Hz, CHCH_3), 1.48 (m, 2 H, CHCH_2), 1.73 [m, 1 H, CH(CH_3)$_2$], 3.71 (s, 3 H, OCH_3), 3.96 (m, 2 H, C*H*), 4.16 (q, 2 H, J = 7.11 Hz, OCH_2), 5.17 (s, 2 H, exch, N*H*).

***N*-(Benzyloxycarbonylmethyl]-*N′*-[(2′*S*)-2′-(methoxycarbonyl)-phenethyl]sulfamide (7):** Yield 90%, m.p. 95−98°C. − $[\alpha]_D^{25} = +18$ ($c = 1$, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 3.05, 3.08 (2dd, 2 H, J = −13.8, 7.20, 5.32 Hz, CHCH_2), 3.6 (d, 2 H, J = 5.4 Hz, NHCH_2), 3.75 (s, 3 H, OCH_3), 4.32 (m, 1 H, C*H*), 5.01 (t, 1 H, J = 5.37 Hz, CH_2NH), 5.16 (d, 1 H, J = 9.8 Hz, exch, CHN*H*), 5.18 (s, 2 H, CO_2CH_2), 7.18−7.28 (m, 2 H + 3 H, Ar−*H* Phe), 7.4 (s, 5 H, Ar−*H* Bn).

***N*-[(2*R*)-2-(Ethoxycarbonyl)ethyl]-*N′*-[(2′*S*)-2′-(methoxycarbonyl)-phenethyl]sulfamide (8):** Yield 95%. − M.p. 69−73°C. − $[\alpha]_D^{25}$ = +23 ($c = 1$, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, 3 H, J = 7.13 Hz, CH_2CH_3), 1.33 (t, 3 H, J = 7.19 Hz, CH_2CH_3), 3.05 (d, 2 H, J = 6.05 Hz, CHCH_2), 3.71 (s, 3 H, OCH_3), 3.88 (m, 1 H, CH_3CH), 4.20 (q, 2 H, J = 7.24 Hz, OCH_2), 4.26 (m, 1 H, CH_2CH), 4.92, 4.97 (2d, 2 H, J = 9.0 Hz, exch, N*H*), 7.14−7.27 (m, 2 H + 3 H, Ar−*H*).

***N*-[(2*R*)-2-(Benzyloxycarbonyl)ethyl]-*N′*-[(2′*S*)-2′-(methoxycarbonyl)phenethyl]sulfamide (9):** Yield 95%. Oil. − $[\alpha]_D^{25}$ = +19.9 ($c = 1$, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 1.37 (d, 3 H, J = 7.17 Hz, CHCH_3), 3.03 (d, 2 H, J = 6.11 Hz, CHCH_2), 3.72 (s, 3 H, OCH_3), 3.96 (m, 1 H, C CH_3), 4.30 (m, 1 H, C*H*CH_2), 5.02, 5.09 (2d, 2 H, J = 9.95, 8.89 Hz, exch, N*H*), 5.19 (s, 2 H, OCH_2), 7.12−7.25 [2 m, 2 H + 3 H, Ar−*H* (Phe)], 7.35 [s, 5 H, Ar−*H* (Bn)].

***N,N′*-Bis[(2*S*,2′*S*)-2-(methoxycarbonyl)phenethyl]sulfamide (10):** Yield: 20%. − M.p. 116−118°C. − $[\alpha]_D^{25}$ = +26 ($c = 1$, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 3.01 (d, 4 H, J = 5.65 Hz, CH_2), 3.71 (s, 6 H, OCH_3), 4.23 (m, 2 H, C*H*), 4.88 (d, 2 H, J = 9.29 Hz, exch, N*H*), 7.12−7.30 (2m, 4 H + 6 H, Ar−*H*).

***N*-[(Benzyloxycarbonyl)methyl]-*N′*-[(2′*S*)-1,2-bis(methoxycarbonyl)ethyl]sulfamide (11):** Yield 80%. Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.96, 3.14 (2 dd, 2 H, CHCH_2), 3.73 (s, 3 H, $CH_2CO_2CH_3$), 3.78 (s, 3 H, $CHCO_2CH_3$), 3.96 (m, 2 H, NHCH_2), 4.35 (m, 1 H, C*H*), 5.23 (s, 2 H, ArCH_2), 5.76 (d, 1 H, J = 8.91 Hz, exch, CHN*H*), 7.40 (s, 5 H, Ar*H*).

***N*-(Methoxycarbonylmethyl]-*N′*-[(2′*S*)-1,2-bis(benzyloxycarbonyl)-ethyl]sulfamide (12):** Yield 85%. Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.97, 3.04 (2 dd, 2 H, CHCH_2), 3.67 (s, 3 H, OCH_3), 3.76 [2 d *AB*, J = −18 Hz, 2 H, NCH_2), 4.33 (m, 1 H, C*H*), 5.01 (s, 2 H, Ar CH_2b), 5.06 (s, 2 H, Ar CH_2a), 5.09 (s, 1 H, exch, N*H*), 5.68 (s, 1 H, exch, CHN*H*), 7.25 (m, 10 H, Ar*H*).

General Procedure for the Cyclization of Alkoxycarbonylalkylsulfamides: A solution of 5 mmol of sulfamide and 10 mmol of sodium methoxide in 50 mL of dry methanol was heated under reflux. With potassium *tert*-butoxide (in anhydrous *tert*-butyl alcohol) 5 mmol of base was required, and the reaction temperature was kept at 40°C. The reaction mixture was then acidified with 33% HCl, extracted with 2 × 150 mL portions of CH_2Cl_2, washed with water, dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with ether/hexane (8:2).

(2*R*,4*S*)-, (2*S*,4*S*)-, (2*R*,4*R*)-, and (2*S*,4*R*)-2-[2-(Ethoxycarbonyl)-ethyl]-4-methyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (13, 14, 15, and 16; Equimolar Mixture): Yield 40%. Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.23, 1.24 (2t, 3 H, J = 7.14 Hz, CH_2CH_3), 1.53 (d, 3 H, J = 7.15 Hz, N−CO−CHCH_3), 1.69, 1.70 (2 d, 3 H, J = 7.55, 7.49 Hz, O_2C−CHCH_3), 4.19 (m, 2 H + 1 H, CH_2CH$_3$ + N−CO−C*H*CH$_3$), 4.56, 4.62 (2 q, 1 H, O_2C−C*H*CH$_3$), 5.44 (s b, 1 H, exch, N*H*).

(4*R*)-2-(Ethoxycarbonylmethyl)-methyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (17): Yield 40%. − M.p. 118−121°C. − $[\alpha]_D^{25}$ = +1 ($c = 1$, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 1.31 (t, 3 H, J = 7.15 Hz, CH_2CH_3), 1.60 (d, J = 7.15 Hz, CHCH_3), 4.20−4.42 (m, 5 H, CH_2CH$_3$ + C*H*CH$_3$ + NCH_2), 5.85 (s b, 1 H, N*H*).

(4*S*,2*S*)- and (4*S*,2*R*)-[2-(Methoxycarbonyl)-1-phenylethyl]-4-methyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (18 and 19; Equimolar Mixture): Yield 10%. Oil. − $[\alpha]_D^{25} = -4$ ($c = 1$, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$) δ = 1.49 (d, 3 H, J = 7.07 Hz, CHCH_3), 3.53 (m, 2 H, Ar−CH_2), 3.80 (s, 3 H, OCH_3), 4.17 (2 q, 1 H, Ar−CH_2CH), 4.82 (2 q, 1 H, CH_3CH), 5.16 (s b, 1 H, exch, N*H*), 7.30 (m, 5 H, Ar−*H*).

(4*R*,2*S*)- and (4*R*,2*R*)-2-[2-(Methoxycarbonyl)-1-methylethyl]-4-isobutyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (20 and 21; Equimolar Mixture): Yield 30%. Oil. − $[\alpha]_D^{25}$ = +33 ($c = 1$, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 0.98, 1.01 (2 d, 6 H, J = 5.88, 6.14 Hz, CH_2CHCH_3), 1.76 (d, 3 H, J = 7.46 Hz, NCHCH_3), 1.75−1.82 (m, 2 H + 1 H, CH_2C*H*CH$_3$), 3.79 (s, 3 H, OCH_3), 4.19, 4.25 (2 m, 1 H, NHC*H*), 4.6−4.8 (2 q, 1 H, NC*H*).

(2*R*,4*S*)-2-[2-(Methoxycarbonyl)ethyl]-4-benzyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (22): Yield 15%. − M.p. 103−105°C. − $[\alpha]_D^{25} = -95$ ($c = 1$, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 1.75 (d, 3 H, J = 7.49 Hz, CHCH_3), 3.27 (2 dd, 2 H, ArCH_2), 3.77 (s, 3 H, OCH_3), 4.43 (q, 1 Hz, J = 4.98 Hz, CH_2CH), 4.69 (q, 1 H, J = 7.48 Hz, H_3CCH), 5.0 (s b, 1 H, exch, N*H*), 7.27−7.37 (m, 2 H + 3 H, Ar*H*).

Crystallographic Analysis: The sample (0.37 × 0.24 × 0.22 mm) was studied with an automatic diffractometer (CAD 4 Enraf−Nonius) with graphite-monochromatized Mo-K_α radiation. The cell parameters were obtained by fitting a set of 25 high-theta reflections. The data collection, $2\theta_{max} = 54°$, scan $\omega/2\theta = 1$, t_{max} = 60 s, range *hkl* (limiting indices): $0 \le h \le 11$, $-12 \le k \le 12$, $-12 \le l \le 11$, intensity control without appreciable decay (0.15%) gave 3453 reflections from which 2790 were independent with $I > 2\sigma(I)$. After Lorenz and polarization corrections, the structure was solved with SHELXS-97, which revealed the non-hydrogen atoms of the molecule. After anisotropic refinement, the hydrogen atoms were found with a Fourier difference (between 0.50 and 0.19 eÅ^{-3}). The whole structure was refined by the full-matrix least-square techniques {use of F magnitude; x, y, z, β_{ij} for N, S, C and N atoms and x, y, z fixed for H atoms; 380 variables and 3453 observations; $w = 1/\sigma(F_o)^2 = [\sigma^2(I) + (0.04\ F_o^2)^2]^{-1/2}$} with the resulting R = 0.0369, R_w = 0.0969 and S_w = 1.052 (residual $\Delta\rho \le 0.176$ eÅ^{-3}). The absolute configuration [C endocyclic: (*S*); C exocyclic: (*R*)] was established by the Flack parameter estimated in the final structure factor calculation in the two hypotheses [absolute structure parameter = −0.04(8)]. Atomic scattering factors from International Tables for X-ray Crystallography.[19] The calculations were performed with a Silicon Graphics Indy R 4600 computer with the MolEN package,[20] SHELXS and SHELXS-97.[21a,b]

(2*S*,4*S*)-2-[4-Benzyl-2-(methoxycarbonyl)ethyl]-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (23): Yield 15%. − M.p. 90°C. − $[\alpha]_D^{25} = -70$ (*c* = 1, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 1.76 (d, 3 H, *J* = 7.30 Hz, CHC*H*$_3$), 3.24 (2dd, 2 H, ArC*H*$_2$), 3.76 (s, 3 H, OC*H*$_3$), 4.40 (q, 1 H, *J* = 4.32 Hz, CH_2C*H*), 4.63 (q, 1 H, *J* = 7.50 Hz, H_3CC*H*), 5.0 (sb, 1 H, exch, N*H*), 7.27−7.37 (m, 2 H + 3 H, Ar*H*).

(2*S*,4*S*)- and (2*R*,4*S*)-2-[4-Benzyl-2-(benzyloxycarbonyl)ethyl]-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (24 and 25; Mixture of Diastereoisomers): Yield 55%. − ^{1}H NMR ($CDCl_3$) δ = 1.78, 1.80 (2 d, 3 H, *J* = 7.53, 7.48 Hz, CHC*H*$_3$), 3.10, 3.25 (2 dd, 2 H, ArC*H*$_2$), 4.34 (m, 1 H, CH_2C*H*), 4.74 (m, 1 H + 1 H, N*H* + H_3CC*H*), 5.21, 5.23 (2 s, 2 H, OC*H*$_2$), 7.20−7.38 (m, 2 H + 8 H, Ar*H*).

(4*S*)-4-Benzyl-2-(methoxycarbonyl)methyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (26): Yield 30%. − M.p. 119−121°C. − $[\alpha]_D^{25} = -56$ (*c* = 1, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3226 cm^{-1} (NH), 1747.4 (CO), 1330.2, 1179.2 (SO_2) cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 3.25, 3.28 (2 dd, 2 H, *J* = −14.35, 9.14, 3.83 Hz, ArC*H*$_2$), 3.78 (s, 3 H, OC*H*$_3$), 4.31 (s, 2 H, NC*H*$_2$), 4.49 (dd, *J* = 9.14, 3.83 Hz, C*H*), 5.20 (s b, 1 H, exch, N*H*), 7.35 (m, 5 H, Ar*H*).

(4*S*)-4-Benzyl-2-(benzyloxycarbonyl)methyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (27): Yield 30%. − M.p. 91−93°C. − $[\alpha]_D^{25} = -60$ (*c* = 1, CH_2Cl_2). − IR (KBr): $\tilde{\nu}$ = 3226.4 (NH), 1754.7 (CO), 1354, 1188 (SO_2) cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 3.18, 3.30 (2 dd, 2 H, *J* = −14.30, 9.27, 4.10 Hz, ArC*H*$_2$), 4.36 (s, 2 H, NC*H*$_2$), 4.47 (dd, 1 H, C*H*), 5.20 (s, 2 H, OC*H*$_2$), 7.30−7.50 (m, 10 H, Ar*H*).

(4*S*,2*R*)- and (4*S*,2*S*)-4-Benzyl-2-[2-(methoxycarbonyl)phenethyl]-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (28 and 29: Equimolar Mixture): Yield 30%. − M.p. 132−136°C. − $[\alpha]_D^{25} = -7$ (*c* = 1, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 3.00−3.30 (2 × 2 dd, 2 H, NHCHC*H*$_2$), 3.34−3.65 (2 × 2 dd, 2 H, NCHC*H*$_2$), 3.78, 3.81 (2 s, 3 H + 3 H, OC*H*$_3$), 4.32 (2 dd, 1 H, NHC*H*), 4.66 (s b, 1 H, exch, N*H*), 4.73−4.90 (2 dd, 1 H, NC*H*), 7.10−7.40 (m, 10 H, Ar*H*).

(4*S*)-4-[(Benzyloxycarbonyl)methyl]-2-(methoxycarbonyl)methyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (30): Yield 47%. Oil. − $[\alpha]_D^{25} = -48$ (*c* = 1, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 3.07 (d, 2 H, *J* = 5.88 Hz, CHC*H*$_2$), 3.80 (s, 3 H, OC*H*$_3$), 4.32 (s, 2 H, NC*H*$_2$), 4.68 (t, 1 H, C*H*CH$_2$), 5.20, 5.25 (2 d *AB*, 2 H, *J* = −12.10 Hz, NC*H*$_2$), 5.77 (s b, 1 H, exch, N*H*), 7.40 (m, 5 H, Ar*H*).

(4*S*)-2-[(Benzyloxycarbonyl)methyl]-4-(methoxycarbonyl)methyl]-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (31): Yield 30%. Oil. − $[\alpha]_D^{25} = -39$ (*c* = 1, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 3.00 (m, 2 H, CHC*H*$_2$), 3.79 (s, 3 H, OC*H*$_3$), 4.38 (s, 2 H, NC*H*$_2$), 4.65 (dd, 1 H, *J* = 6.54, 5.34 Hz, C*H*CH$_2$), 5.24 (1 s, 2 H, ArC*H*$_2$), 7.40 (m, 5 H, Ar*H*).

2-[(Benzyloxycarbonyl)methyl]-4,4-dimethyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (32): Yield 60%. − M.p. 62−65°C. − ^{1}H NMR ($CDCl_3$): δ = 1.62 (s, 6 H, *gem* C*H*$_3$), 4.35 (s, 2 H, NC*H*$_2$), 5.23 (s, 2 H, OC*H*$_2$), 7.39 (m, 5 H, Ar−*H*).

Methoxysulfonyl-L-Phe-DL-Phe-OMe (33−34): Yield 7%. − ^{1}H NMR ($CDCl_3$): δ = 3.09 (m, 4 H, ArC*H*$_2$), 3.54 (s, 3 H, SO_3C*H*$_3$), 3.73 (s, 3 H, CO_2C*H*$_3$), 4.11 (m, 1 H, CH_2C*H*), 4.84 (m, 1 H, CH_2C*H*), 5.38 (d, 1 H, *J* = 8.51 Hz, exch, SO_2N*H*), 6.34 (d, 1 H, *J* = 7.87 Hz, exch, CON*H*), 7.27 (m, 10 H, Ar−*H*).

Methoxysulfonyl-L-Phe-Gly-OMe (35): Yield 9%. − M.p. 101−103°C. − IR (KBr): $\tilde{\nu}$ = 3306 (NH), 1740.3 (*CO*−O), 1654.6 (*CO*−N), 1346.9−1174.1 cm^{-1} (SO_2). − $[\alpha]^{25}{}_D = -5$ (*c* = 1, CH_2Cl_2). − ^{1}H NMR ($CDCl_3$): δ = 3.12, 3.15 (2 dd, 2 H, *J* = −14.0, 7.92, 6.34 Hz, ArC*H*$_2$), 3.50 (s, 3 H, SO_3C*H*$_3$), 3.77 (s, 3 H, CO_2C*H*$_3$), 3.90−4.20 (2 dd, 2 H, NHC*H*$_2$), 4.20 (m, 1 H, C*H*CH$_2$), 5.65 (s b, 1 H, exch, SO_2N*H*), 6.65 (t, 1 H, exch, CON*H*), 7.30 (m, 5 H, Ar−*H*). − ^{15}N NMR ($CDCl_3$, internal reference: nitromethane, relaxing agent: Cr (acac)$_3$]: δ (relating to NH_3) = 85.29 (*N*−CO), 66.38 (*N*−SO_2).

Methoxysulfonyl-L-Phe-DL-Ala-OMe (36−37): Yield 8%. − Mass (FAB+, GT) = 345 $[MH]^+$, 285, 214. − ^{1}H NMR ($CDCl_3$): δ = 1.23, 1.36 (2 d, 2 H, *J* = 7.12 Hz, CHC*H*$_3$), 3.04, 3.07 (2 dd, *J* = −12.11, 7.17, 7.36 Hz, ArC*H*$_2$), 3.54 (s, 3 H, SO_3C*H*$_3$), 3.68 (s, 3 H, CO_2C*H*$_3$), 4.07 (q, 1 H, CH_3C*H*), 4.46 (m, 1 H, CH_2C*H*), 5.38, 5.50 (2 d, 1 H, exch, SO_2N*H*), 6.26, 6.40 (2 d, 1 H, exch, CON*H*), 7.25 (m, 5 H, Ar−*H*).

General Procedure for the Synthesis of Acylated Sulfahydantoins: To a solution of 1 mmol of sulfahydantoin in the minimum amount of DMF was added 1.1 mmol of acetic anhydride and 1 mmol of triethylamine. The reaction mixture was extracted with CH_2Cl_2, washed with 0.1 M HCl followed by water, dried with Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The residue was purified by silica gel chromatography [eluent ether/hexane (8:2)].

(2*S*,4*S*)- and (2*R*,4*S*)-5-Acetyl-4-benzyl-2-[2-(benzyloxycarbonyl)-ethyl]-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (38 and 39): Yield 80%. − M.p. 78−83°C. − ^{1}H NMR ($CDCl_3$): δ = 1.68 (d, 3 H, *J* = 7.52 Hz, CHC*H*$_3$), 2.49, 2.55 (2 s, 3 H, COC*H*$_3$), 3.20−3.55 (2 dd, ArC*H*$_2$), 4.43, 4.74 (2 q, 1 H, CH_3C*H*), 5.10 (m, 1 H, CH_2C*H*), 5.23 (2 d *AB*, 2 H, OC*H*$_2$), 7.10, 7.30 (2 m, 2 H + 3 H, Ar*H* Phe), 7.42 (s, 5 H, Ar*H* Bn).

(4*S*)-5-Acetyl-4-benzyl-2-(methoxycarbonyl)methyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (40): Yield 70%. Oil. − $[\alpha]_D^{25} = 0.0$ (racemized). − IR (film): $\tilde{\nu}$ = 1742.0 (*CO*O), 1718.3 (*CO*N), 1364.0, 1172.1 (SO_2) cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 2.53 (s, 3 H, COC*H*$_3$), 3.41, 3.47 (2 dd, 2 H, *J* = −14.0, 3.85, 6.98 Hz, ArC*H*$_2$), 3.81 (s, 3 H, OC*H*$_3$), 4.18, 4.27 (2 d, 2 H, *J* = −17.9 Hz, NC*H*$_2$), 5.23 (dd, 1 H, CH_2C*H*), 7.13, 7.33 (2 m, 2 H + 3 H, Ar*H*).

(4*S*)-5-Acetyl-4-benzyl-2-(benzyloxycarbonyl)-1-methyl]-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (41): Yield 86%. Oil. − IR (film): $\tilde{\nu}$ = 1752.0 (*CO*O), 1719 (*CO*N), 1363.0, 1174 cm^{-1} (SO_2). − ^{1}H NMR ($CDCl_3$): δ = 2.53 (s, 3 H, COC*H*$_3$), 3.30−3.58 (2 dd, 2 H, ArC*H*$_2$), 4.22, 4.32 (2 d *AB*, 2 H, *J* = −17.9 Hz, NC*H*$_2$), 5.20−5.25 (m, 3 H, OC*H*$_2$ + CH_2C*H*), 7.10, 7.32 (2 m, 2 H + 3 H, Ar*H* Phe), 7.40 (m, 5 H, Ar*H* Bn).

5-Acetyl-2-(benzyloxycarbonyl)methyl-4,4-dimethyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (42): Yield 80%. Oil. − ^{1}H NMR ($CDCl_3$): δ = 1.73 [s, 6 H, C(CH_3)$_2$], 2.52 (s, 3 H, COC*H*$_3$), 4.34 (s, 3 H, NC*H*$_2$), 5.17 (s, 2 H, OC*H*$_2$), 7.35 (s, 5 H, Ar*H*).

(4*S*)-5-Acetyl-2-(benzyloxycarbonyl)methyl-4-(methoxycarbonyl)-methyl]-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (43): Yield 92%. Oil. − ^{1}H NMR ($CDCl_3$): δ = 2.57 (s, 3 H, COC*H*$_3$), 3.25, 3.34 (2 dd, 2 H, *J* = −17.1, 3.58, 4.7 Hz, CHC*H*$_2$), 3.83 (s, 3 H, OC*H*$_3$), 4.19, 4.31 (2 d, *AB*, 2 H, *J* = −18 Hz, NC*H*$_2$), 5.05−5.20 (m, 3 H, OC*H*$_2$ + CH_2C*H*), 7.40 (m, 5 H, Ar*H*).

General Procedure for the Synthesis of *N*^{2}-Allyl-Substituted Sulfahydantoins: To a solution of 4-alkyl-3-oxo-1,2,5-thiadiazolidine 1,1-dioxide (5 mmol), triphenylphosphane (5 mmol), and crotyl alcohol (*E*/*Z* mixture of 2-buten-1-ol, 5 mmol) in THF (10 mL) was added dropwise a solution of diisopropyldicarboxylate (5 mmol) in THF. The reaction was monitored by tlc, and after about 30 min the formation of expected *N*-substituted compound was observed. The side products of oxidoreduction were removed by precipitation with diethyl ether, and the organic medium was purified by a column chromatography (silica gel, eluent ether/hexane, 8:2).

(4*S*)-4-Benzyl-2-crotyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (44): Yield 50%. − M.p. 76−79°C. − $[\alpha]_D^{25} = -151$. − IR (KBr): $\tilde{\nu}$ = 3292 (*NH*), 1730 (*CO*), 1330, 1174 cm^{-1} (SO_2). − ^1H NMR ($CDCl_3$): δ = 1.73 (dd, 3 H, ^3J = 6.43, ^4J = 1.24 Hz, CH_3), 3.19, 3.22 (2 dd, 2 H, J = −14.26, 8.94, 3.90 Hz, Ar CH_2), 4.14 (m, 2 H, NCH_2), 4.36 (dd, 1 H, COC*H*), 4.95 (s b, 1 H, exch, N*H*), 5.40−5.60 (m, 1 H, =C*H*−CH_3), 5.70−5.90 (m, =C*H*−CH_2), 7.26, 7.36 (2 m, 2 H + 3 H, Ar*H*).

(4*S*)-5-Acetyl-4-benzyl-2-crotyl-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (45): Yield 95%. − M.p. 97−100°C. − $[\alpha]_D^{25} = 0.0$ (racemized). − IR (KBr): $\tilde{\nu}$ = 1745, 1712 (*CO*−N), 1340, 1174 cm^{-1} (SO_2). − ^1H NMR ($CDCl_3$): δ = 1.71 (dd, 3 H, ^3J = 6.50, ^4J = 1.41 Hz, CH_3), 2.54 (s, 3 H, COCH_3), 3.33, 3.47 (2 dd, 2 H, J = −14.10, 3.10, 5.40 Hz, ArCH_2), 4.08 (m, 2 H, NCH_2), 5.09 (dd, 1 H, J = 3.10, 5.40 Hz, COC*H*), 5.20−5.40 (m, 1 H, =C*H*−CH_3), 5.64−5.85 (m, = C*H*−CH_2), 7.06, 7.31 (2 m, 2 H + 3 H, Ar*H*).

Oxidation of Allylic Compounds: To a solution of N^2-allyl-substituted sulfahydantoin (0.5 mmol) in a mixture of carbon tetrachloride (2 mL), acetonitrile (2 mL), and water (3 mL), was added sodium metaperiodate (2.05 mmol, 4.1 equiv). Into this biphasic medium was then added a catalytic amount of ruthenium trichloride hydrate. The mixture was stirred for 4 h at room temp. The reaction was monitored by tlc, showing initially the formation of the aldehyde, then the formation of the acid derivative. Dichloromethane (15 mL) was added, the organic layer was washed with water, dried and concentrated. The residue was purified by silica gel chromatography.

(4*S*)-5-Acetyl-4-benzyl-2-(formylmethyl)-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (46): Yield 93%. Oil. − ^1H NMR ($CDCl_3$): δ = 2.57 (s, 3 H, COCH_3), 3.35−3.60 (2 dd, 2 H, Ar CH_2), 4.20, 4.28 (2 dd, 2 H, J = −18.69, 0.61 Hz, NCH_2), 5.27 (dd, 1 H, J = 3.43, 5.60 Hz, COC*H*), 7.10, 7.35 (2 m, 2 H + 3 H, Ar*H*), 9.22 (t, 1 H, J = 0.61 Hz, O=C*H*).

(4*S*)-5-Acetyl-4-benzyl-2-(carboxylmethyl)-3-oxo-1,2,5-thiadiazolidine 1,1-Dioxide (47): Yield 80%. − M.p. 54−56°C. − ^1H NMR ($CDCl_3$): δ = 2.52 (s, 3 H, COCH_3), 3.30−3.60 (2 dd, 2 H, Ar CH_2), 4.17, 4.27 (2 d, 2 H, J = −18.0 Hz, NCH_2), 5.22 (dd, 1 H, J = 3.85, 5.89 Hz, COC*H*), 7.12, 7.31 (2 m, 2 H + 3 H, Ar*H*), 9.30 (s b, 1 H, exch, O*H*).

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