Small Ring Constrained Peptidomimetics. Synthesis of Epoxy Peptidomimetics, Inhibitors of Cysteine Proteases

Mariangela Demarcus,[†] Maria Luisa Ganadu,[†] Giovanni Maria Mura,[†] Andrea Porcheddu,[†] Laura Quaranta,[‡] Gianna Reginato,[‡] and Maurizio Taddei*[,†]

Dipartimento di Chimica, Università degli Studi di Sassari, Via Vienna 2, 07100 Sassari, Italy, and Centro di Studio del CNR Chimica dei Composti Eterociclici e loro Applicazioni, Via G. Capponi 9, 50121 Firenze, Italy

mtad@ssmain.uniss.it

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Different dipeptide analogues containing an oxirane ring in the place of the peptidic bond were prepared starting from naturally occurring amino acids. *N*-Fmoc-amino aldehydes were transformed into the corresponding methoxyvinyl derivatives through a Wittig reaction, and the addition of PhSeCl gave a series of different α-phenylselenyl aldehydes. Mukajiama reaction with silylketene acetals gave an intermediate product that was finally transformed into the desired oxiranyl peptidomimetics. Following this strategy we were able to control three new contiguous stereocenters starting from the enantiomerically pure amino acid. The dipeptide analogues could be used in SPPS on a SASRIN resin as the final epoxides were relatively unstable under acidic conditions. Moreover the synthesis of the single dipeptide mimetics was carried out on solid phase to generate a small library of epoxy peptidomimetics. Some of the products prepared in this work resulted as time-dependent reversible inhibitors of cysteine protease.

The chemistry of peptidomimetics has grown rapidly in the past decade. Starting from the pioneering works where the CO−N bond of an oligopeptide was substituted with a CH_2OH group,[1] several different functions have been introduced in a peptidic sequence to obtain molecules able to mimic a peptidic messenger or recognize different protein structures.[2]

One of the most important fields of action for peptidomimetics has been enzyme inhibition as in, for example, the preparation of protease inhibitors. The most common strategy has been to introduce inside to a peptidic sequence that can be recognized from the enzyme, a functional group that can interact with the reactive center present in the active site. As proteases are nucleophiles, the peptidomimetic inhibitor has been designed as an electrophile. Thus ketones,[3] fluoroketones,[4] aldehydes,[5] hydoxamates,[6] vinyl sulfones,[7] and aziridines[8] have been reported as effective inhibitors of proteases. Epoxides also have been found to be effective protease inhibitors, and several papers reported the synthesis and the biological activity of epoxy peptidomimetics.[9] We communicated the preparation of peptidomimetics containing the oxirane ring where the heterocycle mimics exactly the peptidic bond and the other parts of the molecule remains virtually unaltered.[10] The retrosynthesis of these products is reported in Scheme 1. As they are potentially interesting as enzyme inhibitors or as valuable intermediates for the preparation of other kinds of peptidomimetics, we tried to apply this procedure to the preparation of products suitable for solid-phase peptide synthesis or for the preparation of libraries.

We report here the application of the procedure to the preparation of *N*-Fmoc epoxy acids, their introduction in

* Fax: +39-079-229559.

[†] Università degli Studi di Sassari.

[‡] Centro di Studio del CNR Chimica dei Composti Eterociclici e loro Applicazioni.

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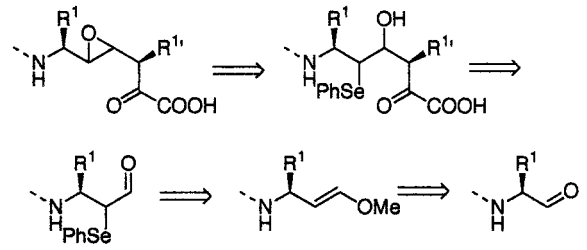
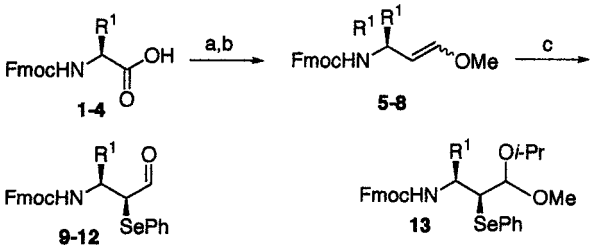
Scheme 1



Scheme 2[a]



1, 5, 9 $R^1 = CH_3$. **2, 6, 10** $R^1 = PhCH_2$. **3, 7, 11** $R^1 = (CH_3)_2CH$-. **4, 8, 12** R1 = $PhCH_2OCH_2$-

[a] (a) 2-Chloro-4,6-dimethoxy[1,3,5]triazine, NMM, DME, followed by H_2 and Pd/C (10%). (b) $MeOCH_2PPh_3Br$, $KN(SiMe_3)_2$, THF, 0 °C. (c) PhSeCl, $Ti(Oi\text{-}Pr)_4$, LiCl, Na_2CO_3, CH_2Cl_2, −78 °C.

a polypeptidic frame, and the solid-supported synthesis of analogous epoxy derivatives for the preparation of a small library.

Two different strategies were possible: build the epoxide on a growing oligopeptide or try to assemble an epoxidic monomer and introduce it as a simple amino acid during the preparation of the peptide. In the first strategy we may have the problem of the chemistries working on the oligopeptidic frame, and in the second case we must to be sure that the epoxide ring would be stable to the conditions of deprotection and couplings. Looking more carefully to the first strategy we thought that a possible intermediate was an oligopeptidic aldehyde. Although the preparation of a peptidic aldehyde has been previously described[11] we observed that during the activation of the carboxylic group a possible racemization of the stereocenter of the amino acid may occur through the generation of an azalactone formed by attack of the amide oxygen to the activated carbonyl. For this reason we decided to follow the other strategy.

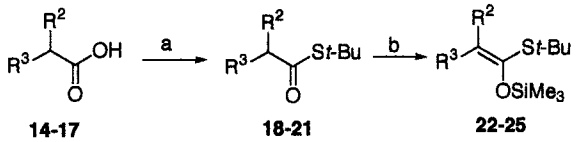
Thus the *N*-Fmoc amino acids **1**−**4** were transformed into the corresponding aldehydes by reduction of the 4,6-dimethoxy[1,3,5]triazin-2-yl esters with H_2 and Pd/C in THF (Scheme 2).[12] The solution obtained from the hydrogenation, filtered from the Pd on carbon, was directly added to the THF solution containing the ylide formed from methoxymethyl triphenylphoshonium bromide and $NaN(SiMe_3)_2$. This addition was carried out at 0 °C; the deep red solution of the ylide discolored rapidly and the products **5**−**8** were obtained as a mixture of E and Z isomers after a hydrolytic workup and filtration of the formed triphenylphosphine oxide. In the case of compounds **5** and **6** it was possible to separate the isomers by column chromatography on silica gel although this effort was unnecessary as the mixture of E and Z isomers gave a single diastereoisomer in the next step.

Table 1. Preparation of Selenyl Aldehydes

starting amino acid	alkene (yield)[a]	selenyl aldehyde (yield)[a] [de][b]
N-Fmoc-Ala-OH	**5** (71%)	**9** (70%) [85%]
N-Fmoc-Phe-OH	**6** (82%)	**10** (73%) [95%]
N-Fmoc-Val-OH	**7** (70%)	**11** (79%) [95%]
N-Fmoc-(OBn)Ser-OH	**8** (66%)	**12** (73%) [90%]

[a] Yields of products isolated after column chromatography. [b] Determined by ^1H NMR (δ 9.0−9.5).

Scheme 3[a]



14, 18, 22 R^2=R^3= Me. **15, 19, 23** R^2=R^3= -$(CH_2)_5$-. **16, 20, 24** R^2 = Me_2CHCH_2-, R^3 = H. **17, 21, 25** R^2 = $PhCH_2OCH_2CH_2$- R^3 = H.

[a] (a) $SOCl_2$, 50 °C, followed by *t*-BuSH, Et_3N, CH_2Cl_2. (b) LDA, THF, −78 °C, Me_3SiCl.

To get a good level of stereoselectivity in the addition of PhSeCl to alkenes **5**−**8**, we coordinated first the starting material with $Ti(Oi\text{-}Pr)_4$ and then added the selenyl chloride at −78 C.[13] To preclude the side formation of the mixed acetal **13** we must add LiCl to the reaction mixture (at least 10 equiv) as a source of nucleophilic chloride to compete with isopropoxyde in the attack to the selenonium intermediate.

When the reaction was carried out without the $Ti(Oi\text{-}Pr)_4$ we obtained a mixture of diastereoisomers as evidenced by the well separated aldehyde signals in the ^1H NMR at δ 9.0−9.5. Consequently the diastereoisomeric purity of products **9**−**12** could be simply determined by comparison of this part of the ^1H NMR spectra. When the reactions were carried out in the presence of the Lewis acid and LiCl, the purity resulted always included between 95% and 85%.

Diastereoisomerically pure aldehydes **9**−**12** were then reacted with silyl thio-ketene acetals **22**−**25** prepared from the acids **14**−**17** as described in Scheme 3.

The aldol-type reaction[14] was carried out in the presence of 1.5 equiv of BF_3OEt_2, and the best results were obtained by precomplexation of the aldehyde with the Lewis acid at −78°, addition of 2.5 equiv of the silyl thioketene acetal, and aqueous workup at −20 °C.

Products **26**−**37** were obtained after column chromatography on silica gel in high diastereoisomeric excess as revealed by ^1H and ^{13}C NMR and HPLC analysis (Scheme 4).[15] Unfortunately attempts to transform compounds **26**−**37** into the corresponding Mosher's esters, to verify the enantiomeric purity, were unsuccessful as

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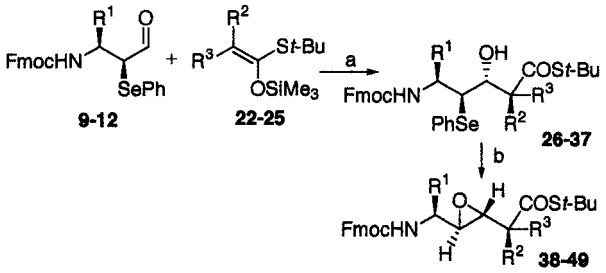
(15) When compound **5** was reacted with PhSeCl, in the absence of $Ti(Oi\text{-}Pr)_4$, aldehyde **9** was obtained as a mixture of two diasteroisomes. When this mixture was submitted to Mukayiama-type reaction, exclusively two isomers were observed for compound **26** (HPLC analysis). When the same reaction was carried out on diastereoisomerically pure **9**, the HPLC trace of **26**, obtained after column chromatography, showed the presence of a predominant peak (at least 95%) that was attributed to a single diastereoisomer.

Table 2. Preparation of *N*-Fmoc-epoxy Peptidomimetics

selenyl aldehyde	silylketene acetal	products: aldol product epoxide	yield[a] [%]	de[b] [%]
9 $R^1 = CH_3$	**22** $R^2 = R^3 = CH_3$	**26**	67	90
		38	74	
9 $R^1 = CH_3$	**23** $R^2 = R^3 = -(CH_2)_5-$	**27**	71	92
		39	78	
9 $R^1 = CH_3$	**24** $R^2 = Me_2CHCH_2CH_2$, $R^3 = H$	**28**	66	91
		40	80	
9 $R^1 = CH_3$	**25** $R^2 = PhCH_2OCH_2CH_2-$, $R^3 = H$	**29**	71	90
		41	81	
10 $R^1 = PhCH_2$	**22** $R^2 = R^3 = CH_3$	**30**	75	90
		42	73	
10 $R^1 = PhCH_2$	**23** $R^2 = R^3 = -(CH_2)_5-$	**31**	77	92
		43	75	
10 $R^1 = PhCH_2$	**24** $R^2 = Me_2CHCH_2CH_2$, $R^3 = H$	**32**	70	89
		44	86	
10 $R^1 = PhCH_2$	**25** $R^2 = PhCH_2OCH_2CH_2-$, $R^3 = H$	**33**	68	91
		45	88	
11 $R^1 = Me_2CH$	**22** $R^2 = R^3 = CH_3$	**34**	75	>95
		46	86	
11 $R^1 = Me_2CH$	**23** $R^2 = R^3 = -(CH_2)_5-$	**35**	65	>95
		47	75	
12 $R^1 = PhCH_2OCH_2$	**22** $R^2 = R^3 = CH_3$	**36**	67	90
		48	80	
12 $R^1 = PhCH_2OCH_2$	**23** $R^2 = R^3 = -(CH_2)_5-$	**37**	71	92
		49	73	

[a] Yields of products isolated after column chromatography. [b] de determined by HPLC analysis of the pure compounds.

Scheme 4[a]



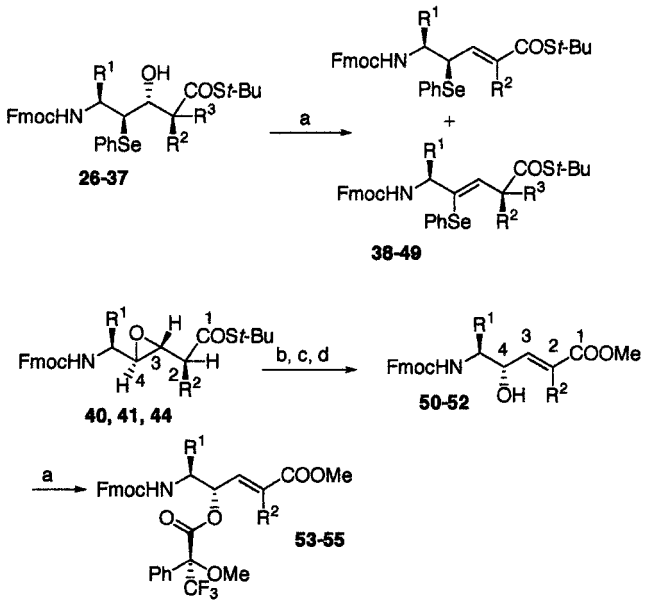
26, 38 $R^1 = R^2 = R^3 = CH_3$. **27, 39** $R^1 = CH_3$, $R^2 = R^3 = -(CH_2)_5-$
28, 40, 50, 53 $R^1 = CH_3$, $R^2 = Me_2CHCH_2$, $R^3 = H$
29, 41, 51, 54 $R^1 = CH_3$, $R^2 = PhCH_2OCH_2-$, $R^3 = H$
30, 42 $R^1 = PhCH_2$, $R^2 = R^3 = CH_3$ **31, 43** $R^1 = PhCH_2$, $R^2 = R^3 = -(CH_2)_5$
32, 44, 52, 55 $R^1 = PhCH_2$, $R^2 = Me_2CHCH_2CH_2$, $R^3 = H$
33, 45 $R^1 = PhCH_2$, $R^2 = PhCH_2OCH_2-$, $R^3 = H$
34, 46 $R^1 = Me_2CH$, $R^2 = R^3 = CH_3$. **35, 47** $R^1 = Me_2CH$, $R^2 = R^3 = -(CH_2)_5-$
36, 48 $R^1 = PhCH_2OCH_2$, $R^2 = R^3 = CH_3$
37, 49 $R^1 = PhCH_2OCH_2$, $R^2 = R^3 = -(CH2)5-$

[a] (a) BF_3OEt_2, CH_2Cl_2, −78 °C. (b) mCPBA, MeOH, Na_2CO_3, −15 °C.

the classical conditions to generate the MTPB esters gave always substantial amounts of the undesired alkenes (see Scheme 5). For this reason we postponed the analysis of the presence of enantiomers to the next step.

The *β*-hydroxyselenyl derivatives were transformed into the desired epoxides **38**−**49** by treatment with MCPBA and K_2CO_3 in MeOH at −15 °C. The *N*-Fmoc group was remarkably stable under this conditions provided that the temperature never exceed −10°. The *trans* arrangement of the epoxide was determined by the value of the coupling constant of the ^1H signal at 2.5−3.2 ppm. In the case of compounds **38**, **39**, **42**, **43**, and **46**−**49** the value could be simply read on the spectrum as the proton is part of an AM system, whereas for the other compounds we must carry out decoupling experiments after a full assignment of all the resonances by COSY experiments.

Scheme 5[a]



[a] (a) (*R*)-MTPA-Cl, pyridine, CCl_4, 50 °C. (b) NaOH 0.2 M, THF, followed by HCl. (c) CH_2N_2, Et_2O, −15 °C. (d) TBAF, THF, 0 °C.

The configuration assignment was performed by transformation of epoxides **40, 41**, and **44** into the alcohols **50**−**52** by treatment with TBAF in THF as reported for analogous compounds.[16] In such transformation the configuration at C4 and the relative stereochemistry of the substituents at C2 and C3 are preserved.[17] As the mechanism proposed for the aldol type reaction is expected to predominantly give the *anti* product (at C2−C3),[14] the resulting alkenes would be the E isomer as confirmed by ^1H and ^{13}C NMR data.[18] Alcohols **50**−**52** were also easily transformed into the MTPA esters to

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verify the enantiomeric integrity of the products prepared, which was always very good.

Finally, the thioesters could be deprotected (aqueous NaOH 0.2 M) to give the corresponding epoxy acids. The acids are mainly solids that are stable if stored as pure compounds but are likely to decompose if stored in $CDCl_3$ solutions. For this reason we decided to store the *tert*-butyl thioesters and prepare the corresponding acids just before the use in the coupling experiments.

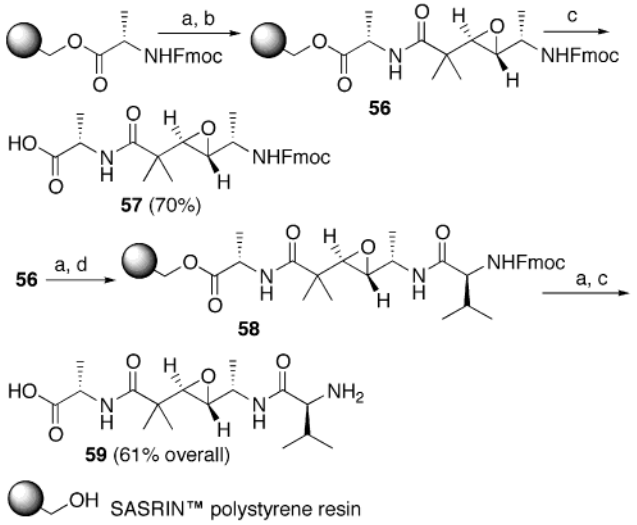
Compounds **38**−**49** can be considered as doubly protected amino acids and we decided to verify if they could be used in solid-phase peptide synthesis (SPPS).

Thus a Wang-type resin was loaded with *N*-Fmoc alanine using standard protocols and subsequently deprotected with piperidine in DMF. The coupling with the acid obtained from **38** was carried out using a classical procedure (PyBOP, HOBT, DIPEA, NMP) and was complete (Kaiser's test)[19] after 1 h. The coupling step of the acid was not particularly troublesome as it could be carried out successfully also using our alternative heterogeneous coupling agent (DMTMM, DIPEA in NMP).[20]

First cleavage of product **56** with TFA/H_2O 95/5 gave a brownish waxy material that we could not identify as the desired product. Better results were obtained using TFA 50% in CH_2Cl_2 in the presence of Et_3SiH. After filtration and evaporation of the solvent under high vacuum, the crude resulted formed by at least four products. After separation by PTLC we could isolate compound **57** in 36% yield**.** A previous deprotection of the *N*-Fmoc group followed by mild acid cleavage was again unsuccessful. The HPLC analysis of the crude showed six peaks and the expected molecular ion was not found in the mass spectra.

As we could imagine from the behavior of compounds **38**−**49** at the prolonged storage in $CDCl_3$, epoxides are not stable in acidic solutions. For SSPS we had to found a linker that could be cleaved under non-acidic conditions. Nevertheless we tried the SASRIN linker (3-methoxy-4-hydroxy-methyl phenol)[21] and we were pleased to find that when the cleavage was carried out under the standard conditions (1% TFA/CH_2Cl_2) followed by neutralization of the filtrate with 2 equiv of Et_3N, compound **57** was recovered in good yield and with an acceptable level of purity (see Experimental Section). Working on SASRIN it was possible to carry out the deprotection of the Fmoc followed by a second coupling (DMTMM, DIPEA) with an amino acid to give a product as **58**. Deprotection of the Fmoc and cleavage from the resin gave product **59** in 61% yield (Scheme 6). With the previously described procedure we demonstrated that our epoxy amino acids could be successfully inserted inside to a peptide sequence as a mimic of a dipeptide frame (as, for example, the protease cleavage site). Moreover compounds **38**−**49** could be used in the preparation of peptide libraries. On the other hand, these compounds have been prepared with a "classical" organic synthesis protocol that limits the possibility to prepare libraries of epoxy acids to test their activity.

Scheme 6[a]



[a] (a) 25% Piperidine in DMF. (b) Acid obtained from **38** in NaOH 0.2 M, THF followed by HCl, DMTMM, DIPEA, NMP. (c) TFA 1% in CH_2Cl_2 followed by Et_3N. (d) *N*-Fmoc-Val-OH, DMTMM, DIPEA, NMP.

To reach this goal we decided to design a possible strategy to prepare the desired epoxy amino acids on a solid support to exploit the potential of a truly solid-phase synthesis for the preparation of libraries. Looking to Scheme 2, the route proposed to build the structure on the carboxylic part of the amino acid is the wrong one in the growing of a peptide-type molecule on a resin. Although the preparation of aldehydes anchored to the resin through the nitrogen have been previously described,[11,22] we excluded this possibility from unsatisfactory previous experiences of our laboratory.

We took advantage of the work of Kobajashi on the preparation of silyl thioketene acetal loaded on a resin[23] to accomplish a synthesis on solid phase. A Merrifield-type resin was loaded with potassium thioacetate, and the thioester obtained was reduced with $LiBH_4$ to give the thiol free resin (positive Ellman's test)[24] that was loaded with the acyl chloride derived from acid **14**. Formation of the thioester was indicated by a negative Ellman's test and by IR spectra showing a strong carbonyl stretching around 1690 cm^{-1}. The silyl thioketene acetal was prepared treating the beads with LDA in THF at −40° followed by Me_3SiCl. After washing the beads with dry NMP and pyridine, the aldol-type reaction with aldehyde **9** was carried out at −40 °C in CH_2Cl_2 and in the presence of TMSOTf (20 mol %). Any other Lewis acid employed gave unsatisfactory results except for $Sc(OTf)_3$, successfully employed by Kobajashi, which gave the same results (in our hands) as TMSOTf. In the presence of BF_3-OEt_2, employed in the homogeneous phase, no reaction at all was observed. The formation of product **63** (Scheme 7) was determined with a visual test for primary alcohols (2,4,6-trichloro[1,3,5]-triazine and Alizarin R, TCT-AliR)

(18) For compounds **50** and **52** we did not observe any NOE effect between CH(4) and the CH_2 of the isobutyl group in position 2 as expected in the case of the Z isomer. Moreover the ^{13}C resonance at C-3 was around δ 131. From reported data[16] the E isomer is expect to have a chemical shift lower than δ 133.

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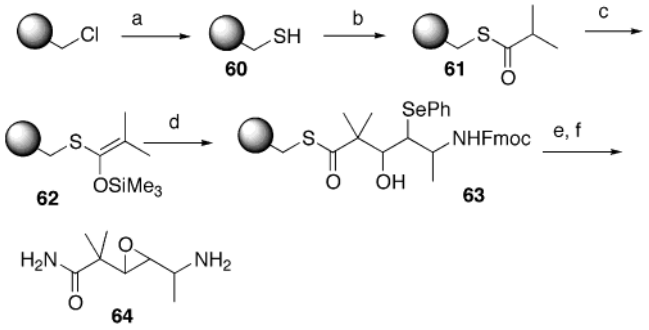
(24) Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70.

Scheme 7[a]



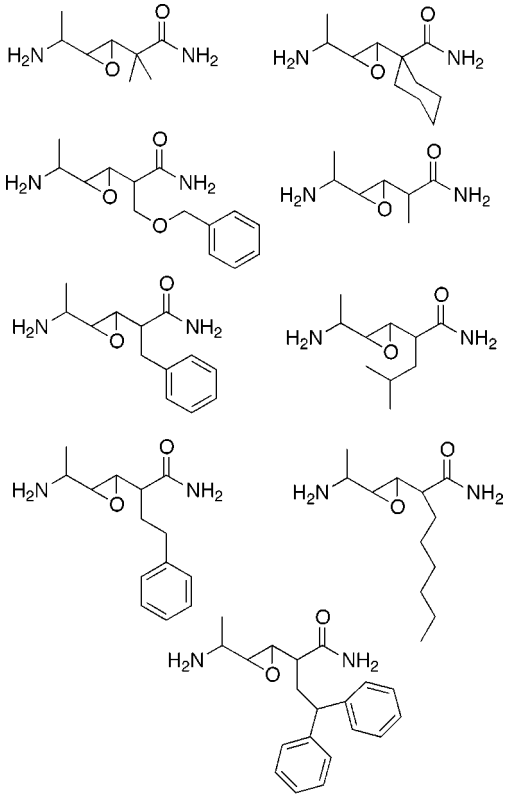
[a] (a) Ref 23 (b) $Me_2CHCOCl$, CH_2Cl_2, DIPEA. (c) LDA, THF, Me_3SiCl, −78 °C. (d) **9**, TMSOTf, CH_2Cl_2, −40 °C. (e) MCPBA, CH_2Cl_2, Na_2CO_3, 0 °C. (f) 25% Piperidine in DMF followed by NH_3 (dry) in MeOH at 50 °C.

developed in our laboratory.[25] After 5 h at −40 °C not all of the beads selected showed a homogeneous red color. Thus the temperature was raised to 0 °C and after 2 h at this temperature, the visual test suggested that the reaction had proceeded further. After several washings with CH_2Cl_2, pyridine, and THF, the epoxidation took place using a solution of MCPBA in DMP/$CsCO_3$. When the beads were clear at the TCT-AliR test, we tried first to cleave the product from the beads using KOH in dioxane/MeOH but we obtained very low yields of the desired acid. Different nucleophilic cleavage conditions with hydroxides were attempted, but results were always disappointing. When we tried to cleave the product with a solution of NH_3 in dry methanol at 50 °C, we obtained an almost complete removal of the organic product from the resin.[26] The crude consisted of a mixture of the Fmoc-protected and deprotected compounds. Thus we carried out first the deprotection of the Fmoc group (piperidine in DMF) and then the cleavage. After evaporation of the solvent product **64** was isolated by separation from diethyl ether in 67% yield and with a purity higher than 80% (HPLC analysis). Analytical samples of the epoxy amides were recovered by PTLC. An accurate ^1H and ^{13}C NMR analysis showed that we obtained product **64** as a mixture of diasteroisomers in approximately a 2/1 ratio.[27]

A small library of epoxy amides were prepared by splitting the resin in nine tubes, adding the acyl chlorides reported in Scheme 8, then mixing together the linked thioester, and finally adding the aldehyde **9**. This small libray of nine compounds was analyzed with a ES-MS and showed an almost equal distribution of the expected molecular ions. To verify if some of the compounds prepared in this work could be considered effective inhibitors of proteases, we tested them as inhibitors of the cysteine protease papain. This enzyme is the most studied cysteine protease and can be considered an easily available model for the search of inhibitors of cysteine proteases involved in different pathologies.[28]

The activity of commercial papain was determined spectrophotometrically following the hydrolysis of L-

Scheme 8



BAPA[29] both in the absence and in the presence of the epoxides at different concentrations, usually in the range from 1 to 500 mM. During the proteolitic assay, described in the Experimental Section, a concentration of papain lower than 10 nmol/min/mL of hydrolyzed L-BAPA was used. The low concentration of papain in the assay allows a reproducible measure of the initial rate of reaction at a practically constant substrate concentration, if the starting L-BAPA concentration (1 mM) is lower than the K_m value of papain for this substrate (2.5 mM, determined in our experimental conditions). Therefore, the initial rate of reaction was calculated with a linear fit, with an error attributable to the substrate disappearance less than 5%.

From the products submitted to the assay, reproducible results were obtained only with the stable thio-esters or with the free amino acids. The values of the inhibition constant were calculated by Dixon plots,. The inhibition of papain was observed with compounds **38**, **39**, **58**, **60**, and **64**.

In Table 3 the inhibition constants calculated for the different compounds are listed. To verify the hypothesis of a slow irreversible reaction between papain and the epoxides, the enzyme was incubated with the different epoxides at a concentration of 200 mM. Aliquots were assayed, after a 20-fold dilution in cuvette, immediately and after 24 and 48 h of incubation at 4 °C. A significant decrease of the papain activity is not evident after 24 and 48 h with respect to the starting of incubation. Therefore, in our conditions, we do not observe irreversible inhibition of papain, neither during the spectrophotometric assay nor after a prolonged incubation.

Although the inhibition potency of our product is poor, these data confirm that the activity is strictly dependent

(25) Attardi, M. E.; Falchi, A.; Taddei, M. *Tetrahedron Lett.* **2000**, *41*, 7395.

(26) We were not able to find the conditions for a hydrolityc clevage from the resin to obtain a carboxylic acid containing the intact epoxide.

(27) The formation of a mixture of diasteroisomers may be expected on the basis of the sterochemical model proposed in ref 14.

(28) Yabe, Y.; Guillaume, D.; Rich, D. H. *J. Am. Chem. Soc.* **1988**, *110*, 4043. Albeck, A.; Fluss, S.; Persky, R. *J. Am. Chem. Soc.* **1996**, *118*, 3591. Otto, H.-H.; Schirmeister, T. *Chem. Rev.* **1997**, *97*, 133.

(29) L-BAPA: benzoylarginyl *p*-nitroanilide.

Table 3. Inhibition Constants for the Non-Time-Dependent Inhibition of Papain

compound	K_i (μM)
38	24 ± 1.
39	106 ± 4
42	>500
43	>500
46	>500
47	>500
48	>500
49	>500
58	48 ± 6
60	298 ± 11
64	2 ± 1
H-Ala-Aib-OH **65**	>500

on the presence of the epoxide as demonstrated by the absence of activity for compound **65**.

We have described an effective stereoselective synthesis of epoxy peptidomimetics that provides *N*-Fmoc-protected fragments that can be successfully employed in SPPS. We also applied the synthesis to the solid-phase preparation of the compounds suitable for the preparation of libraries. Finally the epoxy peptidomimetics obtained were effective inhibitors of papaine, suggesting that an analogous approach can be used for the search for new inhibitors for other proteases involved in important pathologies.

Experimental Section

All solvents employed in this work have been previously dried over activated molecular sieves (4 Å). When THF or ether were used in reactions where a carbanionic species was formed, they were distilled under N_2 over Na and subsequently over $LiAlH_4$ just before the use. All of the reactions in homogeneous phase were carried out under N_2 athmosphere. The reactions on solid phase were carried out in a reactor with a sinter where the mixing was done by bubbling N_2. The reactor had a cooling jacket with inlet and outlet sidearms to allow the cooling (or the heating) of the reaction mixture by connection with a thermostatic circulating bath. Papain from *Carica papaya* (P 3125) and N_a-benzoyl-L-arginine *p*-nitroanilide (L-BAPA) (B 3279) were purchased from Sigma. The NMR spectra were recorded using a 300 MHz spectrometer. The HPLC were carried out using the following general conditions: column C-18-Lichrospher 100, 5 mm, 250 mm × 4 mm, eluent MeCN/H_2O from 80/20 to 20/80 in 35 min. Detector UV lamp, λ 254 nm, flow 1 mL/min.

(*S*,*E*)-(3-Methoxy-1-methyl-allyl)-carbamic Acid 9*H*-Fluoren-9-yl Methyl Ester (5). General Procedure. To a solution of 2-chloro-4,6-dimethoxy-[1,3,5]triazine (1.75 g, 10 mmol) in DME (60 mL) cooled to 0 °C was added *N*-methylmorpholine (1.12 g, 10.8 mmol). A white precipitate was immediately formed and to this mixture was slowly added a solution of (*S*)-*N*-Fmoc alanine (3.1 g, 10 mmol) dissolved in DME (15 mL). After 3 h of stirring at 0 °C, the solid formed was filtered off on Celite and the solution containing the activated ester was transferred into a flask containing Pd/C 10% (0.20 g, 0.1 mmol of active Pd) dispersed in DME (20 mL). The flask was connected with a buret containing H_2. After stirring at room temperature for 3 h (or until TLC analysis showed the disappearance of the activated ester spot, R_f 0.6 with eluent AcOEt/hexane 4/6) the catalyst was filtered on Celite and the solution added to a flask containing methoxymethylene-triphenyl-λ^5-phosphane in THF (50 mL) (prepared from methoxymethy-triphenyl-phpshonium chloride, 3.78 g, 12.1 mmol and NaHMDS, 13 mL of a 1 M solution in THF, 13 mmol) cooled to 0 °C. The mixture was stirred at room temperature for 4 h and then poured into 150 mL of ether. The eventually formed precipitate was filtered off and the solution was washed three times with HCl 1 M and three times with $NaHCO_3$ 5%. The ethereal layer was separated and dried over anhydrous Na_2SO_4. After evaporation of the solvent product **5** (2.3 g, 71% yield) was purified by column chromatography on silica gel. ^{1}H NMR (of the major isomer, $CDCl_3$) δ 1.35 (d, 3H, J = 7 Hz), 3.5 (s, 3H), 4.20−4.3 (m, 2H), 4.70 (dd, J = 16, 7 Hz, 1H), 4.8 (m, 2H7, 6.31 (d, J = 16 Hz, 1H), 6.8 (bd, 1H), 7.20−7.90 (m, 8H). ^{13}C NMR (of the major isomer, $CDCl_3$). 21.6, 37.9, 46.2, 55.4, 73.0, 98.7, 126.8, 128.0, 129.7, 136.5, 140.7, 145.7, 159.9.

(1-Benzyl-3-methoxy-allyl)-carbamic Acid 9*H*-Fluoren-9-yl Methyl Ester 6. ^{1}H NMR (of the major isomer, $CDCl_3$) δ 2.31 (m, 1H), 2.40 (m, 1H), 3.50 (s, 3H), 4.56−4.60 (m, 2H), 4.70 (m, 2H), 4.88 (dd, J = 16, 7 Hz, 1H), 6.40 (d, J 16 Hz, 1H), 6.72 (bd, 1H7, 7.2−7.9 (m, 13 H). ^{13}C NMR (of the major isomer, $CDCl_3$) δ 36.8, 40.6, 51.2, 53.4, 76.7, 95.5, 126−129, 137.3, 141.9, 140.8, 158.8.

(1-Isopropyl-3-methoxy-allyl)-carbamic Acid 9*H*-Fluoren-9-yl Methyl Ester 7. ^{1}H NMR (of the major isomer, $CDCl_3$) δ 1.35 (d, J = 7 Hz, 3H), 1.41 (d, J = 7 Hz, 3H), 2.01 (m, 1H), 3.50 (s, 3H), 4.56−4.60 (m, 2H), 4.65 (m, 2H), 4.80 (dd, J = 16, 7 Hz, 1H,), 6.45 (d, J 16 Hz, 1H), 6.60 (bd, 1H,), 7.3−7.9 (m, 8H,). ^{13}C NMR (of the major isomer, $CDCl_3$) δ 17.8, 18.8, 30.3, 37.7, 53.2, 56.9, 75.5, 99.0, 126−129, 136.5, 140.9, 144.7, 159.6.

(1-Benzyloxymethyl-3-methoxy-allyl)-carbamic Acid 9*H*-Fluoren-9-yl Methyl Ester 8. ^{1}H NMR (of the major isomer, $CDCl_3$) δ 3.50 (m, 3H), 4.4−4.8 (m, 7 H), 5.20 (d-like, 2H), 6.0 (bd, 1H), 6.7 (d, J = 17 Hz, 1H), 7.2−7.9 (m, 13 H). ^{13}C NMR (of the major isomer, $CDCl_3$) δ 37.8, 48.9, 53.9, 74.7, 76.0, 77.1,95.7, 126.1−129, 136.5, 137.0, 141.0, 144.7, 159.8.

(1-Methyl-3-oxo-2-phenylselanyl-propyl)-carbamic Acid 9*H*-Fluoren-9-yl Methyl Ester 9. General Procedure. To a solution of **5** (1 g, 3.0 mmol) in CH_2Cl_2 (30 mL) cooled to −78 °C were added Ti (O*i*-Pr)$_4$ (0.85 g, 3 mmol) and LiCl (1.2 g, 30 mmol). After 3 h of stirring at −78 °C, PhSeCl (0.59 g, 3.1 mmol) was added followed by Na_2CO_3 (0.63 g, 6 mmol). The mixture was vigorously stirred at −78 °C for 2 h and then 10 mL of an aqueous solution of $NaHCO_3$ 10% was added. The mixture was stirred until room temperature was reached and the stirred for and additional 1 h. CH_2Cl_2 was added and the organic layer was separated and washed three times with HCl 1 M and with water. After drying over anhydrous Na_2SO_4, the solvent was evaporated and product **9** (0.97 g, 70% yield) was isolated by column chromatography on silica gel (eluent EtAc/light petroleum 1/6). ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 7 Hz, 3H), 3.21 (dd, J = 9, 2 Hz, 1H), 4.20 (m, 1H), 4.50 (m, 1H), 4.70 (m, 2H), 6.50 (bd, 1H), 7.2−7.9 (m, 13H), 9.73 (d, J = 2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 22.0, 36.7, 37.9, 60.5, 73.9, 126−129, 135.8, 136.9, 141.9, 157.8, 197.4. We were not able to obtain a microanalitical sample of the selenyl aldehydes.

(1-Benzyl-3-oxo-2-phenylselanyl-propyl)-carbamic Acid 9*H*-Fluoren-9-yl Methyl Ester 10. ^{1}H NMR ($CDCl_3$) δ 2.2−2.4 (m, 2H), 3.31 (dd, J = 9, 3 Hz, 1H), 4.29 (m, 1H), 4.51 (m, 1H), 4.70 (m, 2H), 6.50 (bd, 1H), 7.2−7.9 (m, 18H), 9.78 (d, J = 3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ, 35.7, 37.9, 42.8, 61.5, 73.9, 126−129, 135.8, 136.9, 140.5, 141.9, 157.9, 196.4.

(1-Isopropyl-3-oxo-2-phenylselanyl-propyl)-carbamic Acid 9*H*-Fluoren-9-yl Methyl Ester 11. ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 7 Hz, 3H), 1.38 (d, J = 7 Hz, 3H), 2.02 (m, 1H), 3.28 (dd, J = 9, 1 Hz, 1H), 4.16 (m, 1H), 4.51 (m, 1H), 4.77 (m, 2H), 6.00 (bd, 1H), 7.20−7.90 (m, 13H), 9.65 (d, J = 1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 17.3, 17.9, 32.8, 35.7, 37.9, 61.5, 72.9, 126−129, 135.8, 136.9, 141.9, 157.9, 195.4.

(1-Benzyloxymethyl-3-oxo-2-phenylselanyl-propyl)-carbamic Acid 9*H*-Fluoren-9-yl Methyl Ester 12. ^{1}H NMR ($CDCl_3$) δ 3.31 (dd, J = 9, 2 Hz, 1H), 4.06 (m, 1H), 4.50 (m, 1H), 4.60−4.70 (m, 4H), 5.03 (d-like, 2H), 6.35 (bd, 1H), 7.20−7.90 (m, 18H), 9.67 (d, J = 2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 39.7, 40.5, 61.5, 70.7, 71.9, 73.9, 126−129, 135.8, 136.9, 141.9, 143.8, 158.0, 193.0.

(1-*tert*-Butylsulfanyl-2-methyl-propenyloxy)-trimethyl-silane 22. General Procedure. Isobutyryl chloride (2 g, 9.4 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and cooled to 0 °C. *tert*-Butyl thiol (0.9 g, 10 mmol) was added followed by Et_3N (1.5 g, 15 mmol). The mixture was stirred at room temperature overnight. After hydrolytic workup, the organic

layer was dried and the solvent distilled away using a small Vigreaux column (the thioester boils at 60 °C at 25 mmHg). The residue was dried over molecular sieves (4 Å). Product **18** (1.6 g, 10 mmol) was dissolved in dry THF (25 mL) at −78 °C and to this solution was slowly added LDA (11 mL of a 1 M solution in THF) followed, after 20 min, by TMSCl (1.3 g, 12 mmol). The mixture was allowed to reach room temperature under stirring, the solid formed was filtered away using a small Celite pad, and the liquor was evaporated to dryness. To the residue was added dry ether (15 mL) to induce the additional formation of a white precipitate that was filtered off. The filtrate was evaporated again and the addition of ether was repeated until no more precipitate was formed. Evaporation of the solvent gave product **22** sufficiently pure to be used in the next step: 2.12 g, 91% yield. ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 1.45 (s, 9H), 1.76 (s, 3H), 1.80 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 1.0, 18.7, 31.8, 33.7, 89.3, 155.9.

***(tert*-Butylsulfanyl-cyclohexylidene-methoxy)-trimethyl-silane 23.** ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 1.40 (s, 9H), 1.6−2.0 (m, 6H), 2.2−2.4 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 0.9, 26.6, 28.9, 31.9, 34.7, 35.0, 100.7, 153.0.

(1-*tert*-Butylsulfanyl-4-methyl-pent-1-enyloxy)-trimethyl-silane 24. ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 1.08 (d, J = 7 Hz, 3H), 1.12 (d, J = 7 Hz, 3H), 1.40 (s, 9H), 1.80−2.07 (m, 3H), 5.59 (dd, J 7, 4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 0.9, 21.2, 22.0, 28.1, 30.8, 31.8, 33.6, 89.2, 161.9.

(3-Benzyloxy-1-*tert*-butylsulfanyl-propenyloxy)-trimethyl-silane 25. ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 9H), 1.40 (s, 9H), 4.04 (d, J = 7 Hz, 2H), 4.93 (s, 2H), 5.12 (t, J = 7 Hz, 1H), 7.20 (s-like, 5H). ^{13}C NMR ($CDCl_3$) δ 0.7, 31.8, 34.0, 60.8, 76.8, 89.9, 126−127, 139.0, 161.4.

5-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-2,2-dimethyl-4-phenylselanyl-hexanethioic Acid *S*-*tert*-Butyl Ester 26. General Procedure. To a solution of aldehyde **9** (1 g, 2.1 mmol) dissolved in dry CH_2Cl_2 (25 mL) cooled to −78 °C was added BF_3OEt_2 (0.61 g, 4.3 mmol) slowly with a syringe and the mixture stirred at −78 °C for 30 min. Compound **22** (1.21 g, 5.25 mmol) was added and the mixture was stirred at −78 °C for 2 h. Then the temperature was raised to −20° and the mixture was stirred at this temperature for 2 h. A pH 7 phosphate buffer (10 mL) was added and the mixture was warmed to room temperature. Additional CH_2Cl_2 (50 mL) was added and the organic layer was washed several times with saturated solutions of NH_4Cl, $NaHCO_3$, and brine. After evaporation of the solvent, product **26** (0.9 g, 69% yield) was isolated by column chromatography on silica gel (eluent EtAc/light petroleum 1/2). ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J = 7 Hz, 3H), 1.28 (s, 3H), 1.30 (s, 3H), 1.35 (s, 9H), 2.80 (bs, 1H), 3.20 (dd, J = 6, 2 Hz, 1H), 3.73 (bd, 1H), 4.03 (m, 1H), 4.21 (m, 1H), 4.74 (m, 2H), 6.07 (bd, 1H), 7.20−7.90 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 14.6, 16.7, 17.9, 25.8, 38.8, 39.8, 41.1, 43.7, 63.3, 69.8, 75.6, 126−129, 132.6, 138.8, 141.9, 157.2, 200.3. After an additional PTLC: Anal. Calcd for $C_{33}H_{39}NO_4SSe$ (624.69) C, 63.45; H, 6.29; N, 2.24. Found: C, 63.98; H, 6.31; N, 2.19.

1-[3-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-1-hydroxy-2-phenylselanyl-butyl]-cyclohexa-necarbothioic Acid *S*-*tert*-Butyl Ester 27. ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 7 Hz, 3H), 1.35 (s, 9H), 1.61−2.01 (m, 10H), 2.81 (bs, 1H), 3.32 (dd, J = 7, 6 Hz, 1H), 3.70 (bd, 1H), 4.10 (m, 1H), 4.21 (m, 1H), 4.70 (m, 2H), 6.17 (bd, 1H), 7.20−7.90 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 26.7, 29.9, 25.8, 38.8, 38.8, 42.1, 43.8, 61.3, 67.8, 75.9, 126−129, 131.6, 139.8, 141.9, 158.0, 200.7. After an additional PTLC: Anal. Calcd for $C_{36}H_{43}NO_4SSe$ (664.76) C, 65.04; H, 6.52; N, 2.11. Found: C, 65.00; H, 6.50; N, 2.10.

5-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-2-isobutyl-4-phenylselanyl-hexanethioic Acid *S*-*tert*-Butyl Ester 28. ^{1}H NMR ($CDCl_3$) δ 1.03 (d, J = 7 Hz, 3H), 1.10 (d, J = 7 Hz, 3H), 1.22 (d, J = 7 Hz, 3H), 1.35 (s, 9H), 1.71−2.22 (m, 4 H), 2.90 (bs, 1H), 3.30 (dd, J = 8, 2 Hz, 1H), 3.65 (m, 1H), 4.12 (m, 1H), 4.21 (m, 1H), 4.75 (m, 2H), 6.07 (bd, 1H), 7.20−7.90 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 19.6, 22.7, 22.9, 25.8, 29.0, 32.8, 37.9, 38.8, 43.8, 44.1, 56.7, 75.6, 126−129, 135.6, 138.8, 141.9, 158.2, 200.8. After an additional PTLC: Anal. Calcd for $C_{35}H_{43}NO_4SSe$ (652.75) C, 64.40; H, 6.64; N, 2.15. Found: C, 64.54; H, 6.70; N, 2.10.

2-Benzyloxymethyl-5-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-4-phenylselanyl-hexanethioic Acid *S*-*tert*-Butyl Ester 29. ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 7 Hz, 3H), 1.35 (s, 9H), 2.76 (m, 1H), 2.80 (bs, 1H), 3.20 (dd, J = 8, 2 Hz, 1H), 3.60−3.79 (m, 3H), 4.23 (m, 1H), 4.21 (m, 1H), 4.60 (s-like, 2H), 4.77 (m, 2H), 6.17 (bd, 1H), 7.20−7.90 (m, 18H). ^{13}C NMR ($CDCl_3$) δ 22.3, 27.8, 37.8, 39.8, 41.1, 43.7, 60.3, 65.5, 67.8, 74.6, 77.8, 126−129, 132.6, 138.8, 141.9, 142.0, 157.8, 200.0. After an additional PTLC: Anal. Calcd for $C_{39}H_{43}NO_5SSe$ (716.79) C, 65.35; H, 6.05; N, 1.95. Found: C, 66.00; H, 6.03; N, 1.93.

5-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-2,2-dimethyl-6-phenyl-4-phenylselanyl-hexanethioic Acid *S*-*tert*-Butyl Ester 30. ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3H), 1.22 (s, 3H), 1.39 (s, 9H), 2.20 (m, 1H), 2.31 (m, 1H), 2.89 (bs, 1H), 3.06 (dd, J = 6, 4 Hz, 1H), 3.54 (bd, 1H), 4.12 (m, 1H), 4.21 (m, 1H), 4.77 (m, 2H), 6.75 (bd, 1H), 7.20−8.00 (m, 18 H). ^{13}C NMR ($CDCl_3$) δ 17.3, 18.5, 29.0, 36.8, 37.9, 38.9, 59.0, 61.8, 67.6, 69.9, 73.0, 126−129, 136.7, 139.9, 141.0, 158.0, 203.3. After an additional PTLC: Anal. Calcd for $C_{39}H_{43}NO_4SSe$ (700.79) C, 66.84; H, 6.18; N, 2.00. Found: C, 66.76; H, 6.13; N, 2.04.

1-[3-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-1-hydroxy-4-phenyl-2-phenylselanyl-butyl]-cyclohexanecarbothioic Acid *S*-*tert*-Butyl Ester 31. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.62−2.40 (m, 12H), 2.80 (bs, 1H), 3.10 (dd, J = 10, 4 Hz, 1H), 3.55 (bd, 1H), 4.10 (m, 1H), 4.20 (m, 1H), 4.77 (m, 2H), 6.15 (bd, 1H), 7.20−8.00 (m, 18 H). ^{13}C NMR ($CDCl_3$) δ, 24.8, 26.8, 29.0, 30.8, 35.8, 37.7, 38.5, 59.5, 62.8, 67.4, 69.0, 73.2, 126−129, 136.8, 139.2, 140.0, 157.6, 202.9. After an additional PTLC: Anal. Calcd for $C_{42}H_{47}NO_4SSe$ (740.85) C, 68.09; H, 6.39; N, 1.89. Found: C, 68.12; H, 6.38; N, 1.90.

5-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-2-isobutyl-6-phenyl-4-phenylselanyl-hexanethioic Acid *S*-*tert*-Butyl Ester 32. ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 7 Hz, 3H), 1.24 (d, J = 7 Hz), 1.39 (s, 9H), 1.90−2.30 (m, 6H), 2.69 (bs, 1H), 3.09 (dd, J = 7, 2 Hz 1H), 3.64 (m, 1H), 4.09 (m, 1H), 4.21 (m, 1H), 4.77 (m, 2H), 6.75 (bd, 1H), 7.20−8.00 (m, 18 H). ^{13}C NMR ($CDCl_3$) δ 17.3, 18.5, 26.8, 29.0, 34.8, 36.8, 37.9, 38.9, 48.7, 59.0, 67.6, 69.9, 73.0, 126−129, 136.7, 139.9, 141.0, 158.0, 203.3. After an additional PTLC: Anal. Calcd for $C_{41}H_{47}NO_4SSe$ (728.84) C, 67.56; H, 6.50; N, 1.92. Found: C, 67.49; H, 6.45; N, 1.99.

2-Benzyloxymethyl-5-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-6-phenyl-4-phenylselanyl-hexanethioic Acid *S*-*tert*-Butyl Ester 33. ^{1}H NMR ($CDCl_3$) 1.38 (s, 9H), 1.90−2.30 (m, 2H), 2.50 (bs, 1H), 3.08−19 (m, 2H), 3.60 (m, 1H), 4.09 (m, 1H), 4.21−4.40 (m, 5H), 4.77 (m, 2H), 6.70 (bd, 1H), 7.20−8.00 (m, 23 H). ^{13}C NMR ($CDCl_3$) δ, 26.8, 29.0, 34.8, 36.8, 37.9, 38.9, 47.7, 50.8, 58.8, 59.0, 67.6, 69.9, 73.0, 126−129(very intense), 136.8, 139.9, 141.0, 146.8, 158.1, 200.6. After an additional PTLC: Anal. Calcd for $C_{45}H_{47}NO_5SSe$ (792.88) C, 68.17; H, 5.97; N, 1.77. Found: C, 68.00; H, 5.77; N, 1.78.

5-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-2,2,6-trimethyl-4-phenylselanyl-heptanethioic Acid *S*-*tert*-Butyl Ester 34. ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 7 Hz), 1.21 (d, J = 7 Hz, 3H), 1.30 (bs, 6H), 1.35 (s, 9H), 1.90 (m, 1H), 2.64 (bs, 1H), 3.21 (dd, J = 7, 2 Hz, 1H), 3.65 (m, 1H), 4.10 (m, 1H), 4.32 (m, 1H), 4.78 (m, 2H), 6.70 (bd, 1H), 7.20−7.80 (m, 13 H). Anal. Calcd for $C_{35}H_{43}NO_4SSe$ (652.75): C, 64.40; H, 6.64; N, 2.15. Found: C, 64.30; H, 6.70; N, 2.10.

1-[3-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-1-hydroxy-4-methyl-2-phenylselanyl-pentyl]-cyclohexanecarbothioic Acid *S*-*tert*-Butyl Ester 35. ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J = 7 Hz, 3H), 1.21 (d, J = 7 Hz, 3H), 1.35 (s, 9H), 1.4−1.90 (m, 11H), 2.60 (bs, 1H), 3.20 (dd, J = 7, 3 Hz, 1H), 3.40 (m, 1H), 4.11 (m, 1H), 4.30 (m, 1H), 4.78 (m, 2H), 6.70 (bd, 1H), 7.2−7.8 (m, 13H). Anal. Calcd for $C_{38}H_{47}NO_4SSe$ (692.81): C, 65.88; H, 6.84; N, 2.02; Found: C, 65.93; H, 6.80; N, 2.09.

6-Benzyloxy-5-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-2,2-dimethyl-4-phenylselanyl-hexanethioic Acid *S*-*tert*-Butyl Ester 36. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.30 (s, 3H), 1.38 (s, 9H), 2.60 (bs, 1H), 3.19 (dd, J = 7 and 4 Hz, 1H), 3.60−4.20 (m, 6H,) 4.40 (m, 1H,), 4.77 (m, 2H), 6.70 (bd, 1H), 7.20−8.01 (m, 18H). After an additional PTLC: Anal. Calcd for $C_{40}H_{45}NO_5SSe$ (730.82) C, 65.74; H, 6.21; N, 1.92. Found: C, 65.60; H, 6.20; N, 1.90.

1-[4-Benzyloxy-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-1-hydroxy-2-phenylselanyl-butyl]-cyclohexanecarbothioic Acid *S*-*tert*-Butyl Ester 37. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.80−2.20 (m, 10H), 2.60 (bs, 1H), 3.25 (dd, J = 7 and 4 Hz, 1H), 3.60−4.20 (m, 7H) 4.77 (m, 2H), 6.70 (bd, 1H), 7.20−8.00 (m, 18H). After an additional PTLC: Anal. Calcd for $C_{43}H_{49}NO_5SSe$ (770.88) C, 67.00; H, 6.41; N, 1.82. Found: C, 66.97; H, 6.37; N, 1.80.

2-{3-[1-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-ethyl]-oxiranyl}-2-methyl-thiopropionic Acid *S*-*tert*-Butyl Ester 38. General Procedure. To a solution of compound **26** (0.62 g, 1 mmol) dissolved in MeOH (10 mL, cooled to −15 °C, was added K_2CO_3 (0.2 g). After 10 min of stirring at −15 °C, MCPBA (0.34 g of a 60% active sample, 1.2 mmol) was added and the mixture was stirred for 30 min at −15 °C. Water was added followed by diethyl ether. The ethereal layer was separated and washed with a 10% solution of $Na_2S_2O_4$ and a 10% solution of NH_4Cl. After separation and drying (Na_2SO_4) the solvent was evaporated and product **38** was isolated by column chromatography on silica gel (eluent light petroleum/EtOAc 3/1): 0.34 g, 74% yield.^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.21 (s, 3H), 1.30 (d, J = 7 Hz, 3H), 1.41 (s, 9H), 2.33 (d, J = 2 Hz, 1H), 3.03 (dd, J = 9, 2 Hz, 1H), 4.10 (m, 1H), 4.40 (m, 1H), 4.75 (m, 2H), 6.7 (bs, 1H), 7.2−7.8 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 16.3, 19.2, 20.1, 26.3, 37.9, 39.9, 44.3, 53.7, 61.0, 63.2, 75.0, 126.5, 127.9, 128.9, 136.3, 141.7, 157.9, 201.0. Anal. Calcd for $C_{27}H_{33}NO_4S$ (467.62): C, 69.35; H, 7.11; N, 3.00. Found: C. 69.76; H, 7.31; N, 3.09

1-{3-[1-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-ethyl]-oxiranyl}-cyclohexanecarbothioic Acid *S*-*tert*-Butyl Ester 39. ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 7 Hz, 3H), 1.33 (s, 9H), 1.4−1.9 (m, 10H), 2.63 (d, J = 3 Hz, 1H), 3.07 (dd, J = 8, 3 Hz, 1H), 4.16 (m, 1H), 4.51 (m, 1H), 4.71 (m, 2H), 6.71 (bs, 1H), 7.02−7.84 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 16.2, 29.2, 21.5, 27.4, 28.3, 37.9, 38.1, 44.3, 51.7, 58.6, 66.8, 75.2, 126.5, 127.8, 128.9, 136.5, 141.3, 159.9, 201.6. Anal. Calcd for $C_{30}H_{37}NO_4S$ (507.69) C. 70.97; H, 7.35; N, 2.76. Found: C. 70.67; H, 7.30; N, 2.72.

9*H*-Fluoren-9-ylmethoxycarbonylamino)-ethyl]-oxiranyl}-4-methyl-pentanethioic Acid *S*-*tert*-Butyl Ester 40. ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J = 7 Hz, 3H), 1.20 (d, J = 7 Hz, 3H), 1.36 (d, J = 7 Hz, 3H), 1.40 (s, 9H), 1.54−1.80 (m, 3H), 2.60 (m, 1H), 2.78 (dd, J = 8, 2 Hz, 1H), 3.18 (dd J = 9, 2 Hz, 1H), 4.10 (m, 1H), 4.40 (m, 1H), 4.70 (m, 2H), 6.18 (bs, 1H), 7.20−7.80 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 16.7, 22.5, 23.7, 25.6, 29.0, 36.3, 37.0, 39.0, 45.0, 49.4, 54.6, 64.2, 73.2, 126.2, 127.8, 128.3, 136.2, 140.1, 157.8, 200.7. Anal. Calcd for $C_{29}H_{37}NO_4S$ (495.67): C, 70.27; H, 7.52; N, 2.83. Found: C, 70.05; H, 7.42; N, 2.68

3-Benzyloxy-2-{3-[1-(9*H*-fluoren-9-ylmethoxycarbonylamino)-ethyl]-oxiranyl}-thiopropionic Acid *S*-*tert*-Butyl Ester 41. ^{1}H NMR ($CDCl_3$) δ 1.30 (d, J = 7 Hz, 3H), 1.41 (s, 9H), 2.71−2.85 (m, 2H), 3.15 (dd, J = 8, 2 Hz, 1H), 3.70 (d-like, 2H), 4.08 (m, 1H), 4.50−4.80 (m, 5H), 6.38 (bs, 1H), 7.20−7.90 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 16.3, 27.0, 37.2, 39.9, 43.4, 50.6, 53.7, 64.0, 66.9, 73.2, 75.1, 126.5, 127.6, 127.9, 128.4, 128.9, 136.5, 137.2, 141.9, 159.6, 200.1. Anal. Calcd for $C_{33}H_{37}NO_5S$ (559.72): C, 70.81; H, 6.66; N, 2.50. Found: C, 70.58; H, 6.60; N, 2.59.

2-{3-[1-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-2-phenyl-ethyl]-oxiranyl}-2-methyl-thiopropionic Acid *S*-*tert*-Butyl Ester 42. ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 3H), 1.22 (s, 3H), 1.45 (s, 9H), 2.33 (d, J = 2 Hz, 1H), 2.45 (m, 1H), 2.59 (m, 1H), 3.13 (dd, J = 9, 2 Hz, 1H), 4.11 (m, 1H), 4.46 (m, 1H), 4.75 (m, 2H), 6.12 (bs, 1H), 7.20−7.80 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 16.3, 26.3, 38.9, 39.9, 47.3, 53.0, 54.5, 61.0, 64.2, 75.9, 125.3, 126.4, 126.5, 127.9, 128.9, 136.3, 141.7, 157.9, 200.0. Anal. Calcd for $C_{33}H_{37}NO_4S$ (543.72): C, 72.90; H, 6.86; N, 2.58. Found: C, 72.67; H, 6.78; N, 2.45.

1-{3-[1-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-2-phenyl-ethyl]-oxiranyl}-cyclohexanecarbothioic Acid *S*-*tert*-Butyl Ester 43. ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 1.41−1.95 (m, 10H), 2.43 (m, 1H), 2.63 (d, J = 3 Hz, 1H), 2.78 (m, 1H), 3.10 (dd, J = 8, 3 Hz, 1H), 4.26 (m, 1H), 4.50 (m, 1H), 4.77 (m, 2H), 6.21 (bs, 1H), 7.20−7.80 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 18.2, 29.2, 27.4, 28.3, 38.9, 38.0, 45.3, 52.7, 57.9, 58.9, 65.8, 75.0, 125.6, 126.5, 127.8, 128.9, 136.5, 139.9, 141.3, 159.9, 201.9. Anal. Calcd for $C_{36}H_{41}NO_4S$ (583.78): C, 74.07; H, 7.08; N, 2.40. Found: C, 74.20; H, 7.18; N, 2.46.

2-{3-[1-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-2-phenyl-ethyl]-oxiranyl}-4-methyl-pentanethioic Acid *S*-*tert*-Butyl Ester 44. ^{1}H NMR ($CDCl_3$) δ 1.11 (d, J = 7 Hz, 3H), 1.22 (d, J = 7 Hz, 3H), 1.40 (s, 9H), 1.54−1.80 (m, 3H), 2.50−2.80 (m, 3H), 2.70 (dd, J = 8, 2 Hz 1H), 3.11 (dd J = 9, 2 Hz, 1H), 4.20 (m, 1H), 4.43 (m, 1H), 4.71 (m, 2H), 6.34 (bs, 1H), 7.20−7.80 (m, 13H). ^{13}C NMR ($CDCl_3$) δ, 23.5, 24.7, 26.6, 29.9, 36.7, 38.0, 39.4, 44.0, 49.9, 58.6, 59.9, 65.2, 74.2, 125.7, 126.2, 127.8, 128.3, 136.2, 140.1, 141.1, 157.8, 201.7. Anal. Calcd for $C_{35}H_{41}NO_4S$ (571.77): C, 73.52; H, 7.23; N, 2.45. Found: C. 73.65; H, 7.30; N, 2.40

3-Benzyloxy-2-{3-[1-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2-phenyl-ethyl]-oxiranyl}-thiopropionic Acid *S*-*tert*-Butyl Ester 45. ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 2.60−2.80 (m, 4H), 3.10 (dd, J = 8, 2 Hz, 1H), 3.76 (d-like, 2H), 4.09 (m, 1H), 4.50−4.70 (m, 5H), 6.13 (bs, 1H), 7.20−7.90 (m, 18H). ^{13}C NMR ($CDCl_3$) δ, 26.0, 38.2, 39.0, 42.4, 51.6, 52.7, 58.7, 64.8, 67.9, 71.2, 77.1, 125.7, 126.5, 127.6, 127.9, 128.4, 128.9, 136.5, 137.2, 139.9, 141.9, 159.6, 201.1. Anal. Calcd for $C_{39}H_{41}NO_5S$ (635.81): C. 73.67; H, 6.50; N, 2.20. Found: C. 73.6O; H, 6.40; N, 2.12.

2-{3-[1-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-2-methyl-propyl]-oxiranyl}-2-methyl-thiopropionic Acid *S*-*tert*-Butyl Ester 46. ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3H), 1.22 (s, 3H), 1.25−1.28 (m, 6H), 1.40 (s, 9H), 1.93 (m, 1H), 2.39 (d, J = 2 Hz, 1H), 3.13 (dd, J = 8, 2 Hz, 1H), 4.21 (m, 1H), 4.43 (m, 1H), 4.77 (m, 2H), 6.47 (bs, 1H), 7.20−7.80 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 16.3, 18.7, 19.8, 20.0, 25.3, 33.9, 36.7, 38.9, 44.8, 52.7, 60.0, 66.2, 75.7, 126.5, 127.9, 128.9, 136.3, 141.7, 157.9, 200.8. Anal. Calcd for $C_{29}H_{37}NO_4S$ (495.67): C. 70.27; H, 7.52; N, 2.83. Found: C. 70.17; H, 7.58; N, 2.80.

1-{3-[1-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-2-methyl-propyl]-oxiranyl}-cyclohexane-carbothioic Acid *S*-*tert*-Butyl Ester 47. ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J = 7 Hz, 3H), 1.24 (d, J = 7 Hz, 3H), 1.33 (s, 9H), 1.40−1.90 (m, 11H), 2.65 (d, J = 3 Hz, 1H), 3.09 (dd, J = 8, 3 Hz, 1H), 4.21 (m, 1H), 4.65 (m, 1H), 4.74 (m, 2H), 6.79 (bs, 1H), 7.20−7.80 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 17.6, 18.2, 19.9, 29.2, 20.5, 26.4, 28.4, 33.4, 37.0, 39.1, 45.3, 50.7, 58.9, 67.0, 77.2, 126.5, 127.8, 128.9, 136.5, 141.3, 158.9, 200.1. Anal. Calcd for $C_{32}H_{41}NO_4S$ (535.74): C. 71.74; H, 7.71; N, 2.61. Found: C. 71.54; H, 7.67; N, 2.56.

2-{3-[2-Benzyloxy-1-(9*H*-fluoren-9-ylmethoxycarbonylamino)-ethyl]-oxiranyl}-2-methyl-thiopropionic Acid *S*-*tert*-Butyl Ester 48. ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 3H), 1.21 (s, 3H), 1.40 (s, 9H), 2.31 (d, J = 2 Hz, 1H), 3.10 (dd, J = 9, 2 Hz, 1H), 3.95−4.10 (m, 5H), 4.42 (m, 1H), 4.75 (m, 2H), 6.32 (bs, 1H), 7.20−7.80 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 17.3, 19.0, 26.7, 38.9, 38.9, 44.3, 52.7, 60.0, 62.2, 70.3, 74.5, 76.0, 125.5, 126.5, 127.9, 128.9, 136.3, 140.9, 141.7, 159.9, 199.6. Anal. Calcd for $C_{34}H_{39}NO_5S$ (573.74): C. 71.18; H, 6.85; N, 2.44. Found: C. 71.22; H, 6.84; N, 2.44.

1-{3-[2-Benzyloxy-1-(9*H*-fluoren-9-ylmethoxycarbonylamino)-ethyl]-oxiranyl}-cyclohexanecarbo-thioic Acid *S*-*tert*-Butyl Ester 49. ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.40−1.95 (m, 10H), 2.60 (d, J = 3 Hz, 1H), 3.00 (dd, J = 8, 3 Hz, 1H), 4.10−4.61 (m, 6H), 4.76 (m, 2H), 6.65 (bs, 1H), 7.20−7.80 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 16.2, 20.5, 26.4, 28.9, 36.9, 39.8, 42.3, 50.0, 55.6, 61.8, 69.8, 76.8, 77.7, 125.7, 126.5, 127.8, 128.9, 136.5, 141.0, 141.3, 159.0, 200.6. Anal. Calcd for $C_{37}H_{43}NO_5S$ (613.81): C. 72.40; H, 7.06; N, 2.28. Found: C. 72.50; H, 7.11; N, 2.21.

5-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-4-hydroxy-2-isobutyl-hex-2-enoic Acid Methyl Ester 50. To a solution of compound **40** (100 mg, 0.2 mmol) dissolved in dry THF (1 mL) was added 2 mL of a 0.2 M solution of NaOH and the mixture stirred at room temperature until the TLC analysis showed the disappearance of the starting material. Ethyl acetate (10 mL) was added, the mixture was cooled to 0 °C, and HCl 0.5 M was added to red litmus paper. The ethereal layer was separed and dried over anhydrous Na_2SO_4 and the solvent was evaporated. THF (5 mL) was added, the solution was cooled to −15 °C, and a solution containing diazomethane in diethyl ether (prepared using the Diazald kit) was added until persistence of the yellow-green solution. The excess of diazomethane was destroyed adding one drop of acetic acid and a saturated solution of $NaHCO_3$ was added. The mixture was warmed to room temperature and the organic layer separated and washed with water and brine. After drying (Na_2SO_4), to this solution was added TBAF (52 mg, 0.2 mmol) and the mixture was heated gently at 35 °C for 4 h. The solvent was evaporated and product **50** was isolated by PTLC (eluent light petroleum/EtAc 4/1): 35 mg, 80% yield. ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J = 7 Hz, 3H), 1.21 (d, J = 7 Hz, 3H), 1.31 (d, J = 8 Hz, 3H), 1.80 (m, 1H), 1.92 (AB part of an ABX system, 2H), 3.01(bs, 1H), 3.51 (s, 3H), 3.98 (m, 1H), 4.01 (m, 1H), 4.41 (m, 1H), 4.70 (m, 2H), 6.09 (bs, 1H), 6.89 (d, J = 6 Hz, 1H), 7.20−7.80 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 16.2, 22.7, 23.4, 25.7, 36.2, 39.2, 50.2, 56.8, 71.0, 74.2, 126.5, 127.9, 128.9, 131.4, 136.5, 139.8, 143.7, 157.9, 169.9. Anal. Calcd for $C_{26}H_{31}NO_5$ (437.53): C. 71.37; H, 7.14; N, 3.20. Found 71.27; H, 7.10; N, 3.23

2-Benzyloxymethyl-5-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-hydroxy-hex-2-enoic Acid Methyl Ester 51. ^{1}H NMR ($CDCl_3$) δ 1.27 (d, J = 7 Hz, 3H), 3.00 (bs, 1H), 3.65 (s, 3H), 3.89 (m, 1H), 4.06 (AB system, 2H), 4.30−4.70 (m, 6H), 6.60 (bs, 1H), 7.02 (d, J = 9 Hz, 1H), 7.20−7.90 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 15.2, 37.6, 50.8, 56.6, 67.9, 73.2, 74.7, 76.2, 126.5, 127.6, 127.9, 128.4, 128.9, 131.2, 133.3, 136.5, 137.2, 141.9, 157.6, 166.7. Anal. Calcd for $C_{30}H_{31}NO_6$ (501.57): C. 71.84; H, 6.23; N, 2.79. Found: C. 71.75; H, 6.20; N, 2.81.

5-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-4-hydroxy-2-isobutyl-6-phenyl-hex-2-enoic Acid Methyl Ester 52. ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J = 7 Hz, 3H), 1.16 (d, J = 7 Hz, 3H), 1.80 (m, 1H), 1.96 (m, 2H), 2.76 (m, 1H), 2.86 (m, 1H), 3.01 (bs, 1H), 3.60 (s, 3H), 4.00 (m, 1H), 4.30−4.70 (m, 5H), 6.82 (d, J = 8 Hz, 1H), 7.20−7.80 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 22.6, 23.5, 25.8, 35.7, 36.9, 37.9, 50.8, 57.2, 71.2, 73.0, 125.8, 126.5, 127.9, 128.6, 131.4, 134.4, 135.2, 138.8, 141.6, 157.2, 165.0. Anal. Calcd for $C_{32}H_{35}NO_5$ (513.62): C. 74.83; H, 6.87; N, 2.73. Found: C. 74.76; H, 6.90; N, 2.70.

5-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-2-isobutyl-4-(3,3,3-trifluoro-2-methoxy-2-phenyl-propionyloxy)-hex-2-enoic Acid Methyl Ester 53. General Procedure. Product **50** (20 mg, 0.04 mmol) was dissolved in benzene (1 mL) and (*R*)-MTPA-Cl (11 mg, 0.04 mmol) was added followed by pyridine (0.5 mL). The mixture was stirred for 12 h and then filtered through a small pad of silica gel. The solvent was evaporated and the residue submitted to high vacuum (0.01 mmHg) for 3 h. The residue was taken up in $CDCl_3$ and submitted to NMR analysis. The attribution of compounds **53**−**55** was carried out by inspection of the ^{1}H NMR signal of the methoxy (δ = 3.24), the ^{13}C signal of CF_3 (δ = 120.3), and the ^{19}F resonance (δ = 11.0).

2-(2-{3-[1-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-ethyl]-oxiranyl}-2-methyl-propionylamino)-propionic Acid 57. To Fmoc-Ala loaded onto a SASRIN-type resin (250 mg of a 0.75 mmol/g loaded resin, 0.18 mmol) previously swelled in DMF was added piperidine in DMF (5 mL of a 15% solution) and the mixture was bubbled gently with N_2 until a positive Kaiser test. The resin was rinsed several times with DMF and NMP (*N*-methyl pyrrolidinone) and then compound **38** (168 mg, 0.36 mmol) was added followed by DMTMM (87 mg, 0.36 mmol) and DIPEA (0.2 mL). The mixture was stirred (bubbling N_2) for 1 h (Kaiser test negative) and the resin rinsed several time with NMP. The resin was washed with CH_2Cl_2 and treated with a 1% solution of TFA in CH_2Cl_2 (5 mL) for 15 min at 0 °C. After filtration, to the solution Et_3N (50 μL) was added and the solvent evaporated. The residue was dissolved in MeOH and passed through a short column filled with Amberlite X. The solvent was evaporated and product **57** isolated by crystallization from ether: 58 mg, 70% yield. ^{1}H NMR (DMSO-d_6, 45 °C) δ 1.26 (d, J = 7 Hz, 3H), 1.29 (s, 3H), 1.32 (s, 3H), 1.43 (d, J = 6 Hz, 3H), 2.63 (d, J = 2 Hz, 1H), 3.04 (dd, J = 8, 2 Hz, 1H), 4.08 (m, 1H), 4.45−4.75 (m, 4H), 7.20−7.80 (m, 9H), 8.2 (bs, 2H). ^{13}C NMR (DMSO-d_6, 45 °C) δ 15.3, 17.6, 18.9, 19.8, 37.9, 42.0, 44.9, 54.6, 60.7, 63.6, 73.0, 126.5, 127.9, 128.9, 136.2, 141.9, 157.2, 177.0, 184.6.

2-(2-{3-[1-(2-Amino-3-methyl-butyrylamino)-ethyl]-oxiranyl}-2-methyl-propionylamino)-propionic Acid 59. Resin **56** (250 mg) was submitted to an additional series of deprotection (piperidine 15% in DMF) and coupling with Fmoc-Val-OH, DMTMM and DIPEA in NMP (check with Kaiser test). Finally the resin was deprotected with piperidine in DMF and cleaved as previously described to give, after crystallization from acetone, compound **59**: 38 mg, 61% yield. ^{1}H NMR (DMSO-d_6, 45 °C) δ 1.10 (d, J = 7 Hz, 3H), 1.15 (d, J = 7 Hz, 3H), 1.25 (s, 3H), 1.30 (s, 3H), 1.35 (d, J = 6 Hz, 3H), 1.53 (d, J = 7 Hz, 3H), 2.05 (m, 1H), 2.60 (d, J = 2 Hz, 1H), 3.10 (dd, J = 8, 2 Hz, 1H), 3.56 (m, 1H), 4.06 (m, 1H), 4.60 (m, 1H), 7.6−8.0 (series of broad signals, approximately 5 exchangeable H). ES-MS (m/z) 344 ($M^+ + 1$).

2-[3-(1-Amino-ethyl)-oxiranyl]-isobutyramide 64. A thiol resin (derived from a Merrifield resin as described by Kobajashi, 250 mg of an approximately 1 mmol/g, 0.25 mmol) was dispersed in CH_2Cl_2 and isobutyryl chloride (80 mg, 0.75 mmol) was added followed by DIPEA (1 mL). The mixture was stirred (bubbling with N_2) for 2 h (until negative Elman test). The resin was rinsed several time with CH_2Cl_2, DMF, CH_2Cl_2 and THF. Finally the resin was dispersed in THF and cooled to −40°. A solution of LDA (50 mL of a 1 M solution in THF) was added followed by Me_3SiCl (80 mg, 0.75 mmol). The mixture was warmed to room temperature and then rinsed with THF, NMP, pyridine and CH_2Cl_2. The mixture was cooled again to −40 °C and aldehyde **9** (0.23 g, 0.5 mmol) was added followed by TMSOTf (0.111 gr, 0.5 mmol). The mixture was stirred (bubbling N_2) for 5 h at −40° and 2 h at 0 °C (until the TCT-Ali-R test resulted positive). The resin was rinsed with CH_2Cl_2 and DMF and then warmed to room temperature. After additional treatments with CH_2Cl_2, pyridine and CH_2Cl_2, the resin was dried and transferred in a flask having a small mechanical stirrer. MeOH (2 mL) was added, the flask was cooled to 0 °C, and under stirring, Na_2CO_3 (0.05 g) was added followed by MCPBA (85 mg of a 60% active sample, 0.3 mmol). The mixture was stirred at 0 °C for 3 h (until the TCT-AliR test was negative). The mixture was transferred again in the reactor equipped with the sinter and the resin was rinsed with MeOH, DMF, Pyridine and DMF. The Fmoc was deprotected under standard conditions (Kaiser test positive) and the resin was transferred in a sealed flask containing MeOH and NH_3 (obtained bubbling dry NH_3 in MeOH). The flask was gently heated fro 1 h at 50°. The solution was analyzed at the HPLC that showed the presence of several products. After filtration of the residue resin, the solvent was evaporated and the product was dissolved in MeCN and precipitated with diethyl ether. The solid (26 mg, 61% yield overall) was analyzed at the HPLC showing at least 3 peaks where one of the three was about 80%. ES-MS showed that this peak had the expected mass (m/z 173 ($M^+ + 1$)). Product **64** was finally purified by PTLC (eluent EtOH/$CHCl_3$ 1/7). ^{1}H NMR (DMSO-d_6, 45 °C) δ 1.10 (d, J = 7 Hz, 3H), 1.30 (bs, 6H), 2.12 (d, J = 2 Hz, 1H),2.96 (dd, J = 6, 2 Hz, 1H), 3.21 (m, 1H), 5.2−5.8 (large signal containg the exchangeble protons). ^{13}C NMR (DMSO-d_6, 45 °C) δ 18.3, 18.9, 21.1, 42.2, 48.5, 62.2, 64.6, 188.8. MS m/z 172 (M^+).

Library. ES-MS analysis of the library prepared following the procedures described for compound **64**: m/z 158, 172, 200, 212, 228, 234, 248, 264, 324.

Experiments for Inhibiton of Papaine. Papain assay was carried out at 25 °C on a spectrophotometer equipped with the software UV-Visions 1.0 (Hitachi instruments Inc.), according to a previous procedure[9] slightly modified as follows. Epoxide solutions were prepared as 40, 4, and 0.4 mM in

DMSO and directly added to the cuvette. Papain solutions were activated before the kinetic measurements in 50 mM phosphate buffer, pH 6.8, 2 mM EDTA, 2 mM 1,4-dithio-DL-threitol at 25 °C for 30 min (papain concentration, 1.2 mg/mL). The assay mixtures prepared in the same activation buffer contained 1 mM L-BAPA, activated papain 40 mL/mL, 0−0.5 mM epoxides. In all cases the DMSO final concentration was lower than 5%. The papain activity expressed as hydrolyzed L-BAPA was in all cases lower than 10 nmol/min/mL. The absorbance increase at 405 nm was followed and the data were analyzed with the software Microcal Origin 5.0 (Microcal Software Inc.). The inhibition constant values (K_i) were obtained by Dixon plots according to the equation

$$R_{cont}/R_x = 1 + [x]/K_i^{app}$$

corrected to zero substrate concentration with the following formula:

$$K_i = K_i^{app}/(1 + [S]/K_m)$$

The K_m value of papain for L-BAPA, determined in our assay conditions, was 2.5 mM.

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