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Synthesis of Peptides containing a Sulfinamide or a Sulfonamide Transition-State Isostere

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Abstract: A versatile synthesis of peptides incorporating the sulfinamide or sulfonamide transition-state analogue is described. Apart from the easily accessible Gly-Xxx isosteres used as haptens to elicit catalytic antibodies, other amino acids than Gly can be prepared by α-alkylation of the sulfonamide containing peptides. This is illustrated with the synthesis of a potential HIV-protease inhibitor **27**.

INTRODUCTION

Peptides containing a transition-state analogue of the hydrolysis of the amide bond have received widespread attention in the development of protease inhibitors of e.g. thermolysin[1], renin[2] and pepsin[3]. In addition they have been employed in the development of catalytic antibodies ("abzymes")[4]. A great deal of effort is nowadays devoted towards the incorporation of transition-state analogues in order to obtain inhibitors of HIV-protease[5a-x].

A wide range of transition-state analogues of the hydrolysis of the amide bond has been reported and despite the fact that many of the reported transition-state analogues are only distantly related to the actual transition-state, they often give rise to biologically active compounds[5].

The transition-state analogues which clearly show the best resemblance to the transition-state of the hydrolysis of the amide bond (figure 1a) both from a steric and electronic point of view- are the phosphonamidate (figure 1b) and the sulfonamide moiety (figure 1c). Phosphonamidate and other phosphorus analogues have been used with success to prepare (HIV) protease inhibitors[5k,v]. Surprisingly, the sulfonamide moiety has not been used for this purpose as far as we know. Therefore, we embarked on the synthesis of peptides containing a sulfonamide moiety with the purpose to obtain new and easily accessible transition-state analogues.

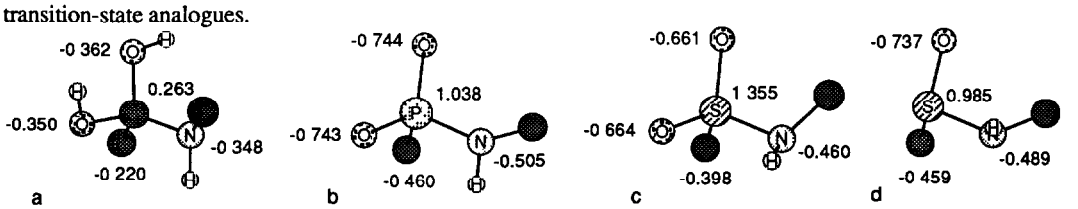
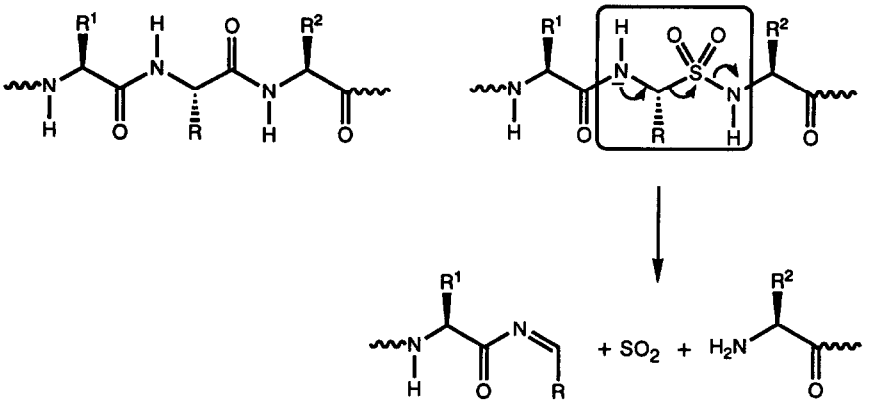


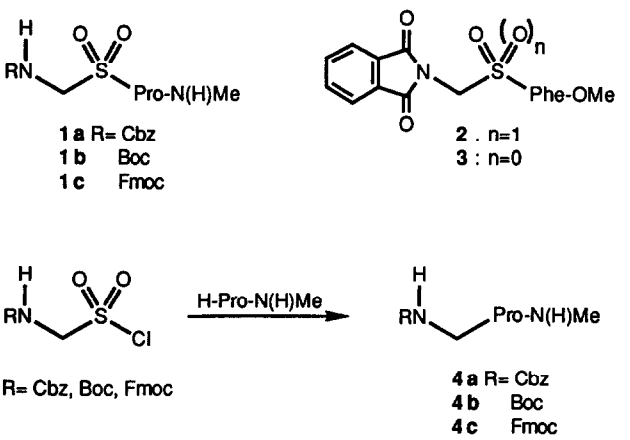
Figure 1 Geometry optimized structures and atomic charges (AMPAC) of the transition-state of amide bond hydrolysis (a), the phosphonamidate (b), the sulfonamide (c) and the sulfinamide (d) transition-state analogues.

The most closely related sulfur-containing transition-state analogue of an α-amino acid incorporated in a peptide is an α-amino **sulfonamide** (scheme 1). However, it is well documented in the literature[6] that these systems tend to fragment as is depicted in scheme 1. Indeed we found that on the attempted synthesis of compounds **1** starting from Cbz-, Boc- or Fmoc-amino-methane sulfonyl chloride (scheme 2) products **4** were formed, which showed NMR data similar to the expected sulfonamides **1**, however FAB mass spectra

and IR indicated that the SO_2 unit was absent. Recently Sammes *et al* [7] reported the synthesis of N-(phthalimidomethylsulfonyl)-L-phenylalaninemethylester **2**. Although this imide is apparently stable, decomposition at the low melting traject (46-49°C) indicated its limitations.



Scheme 1



Scheme 2

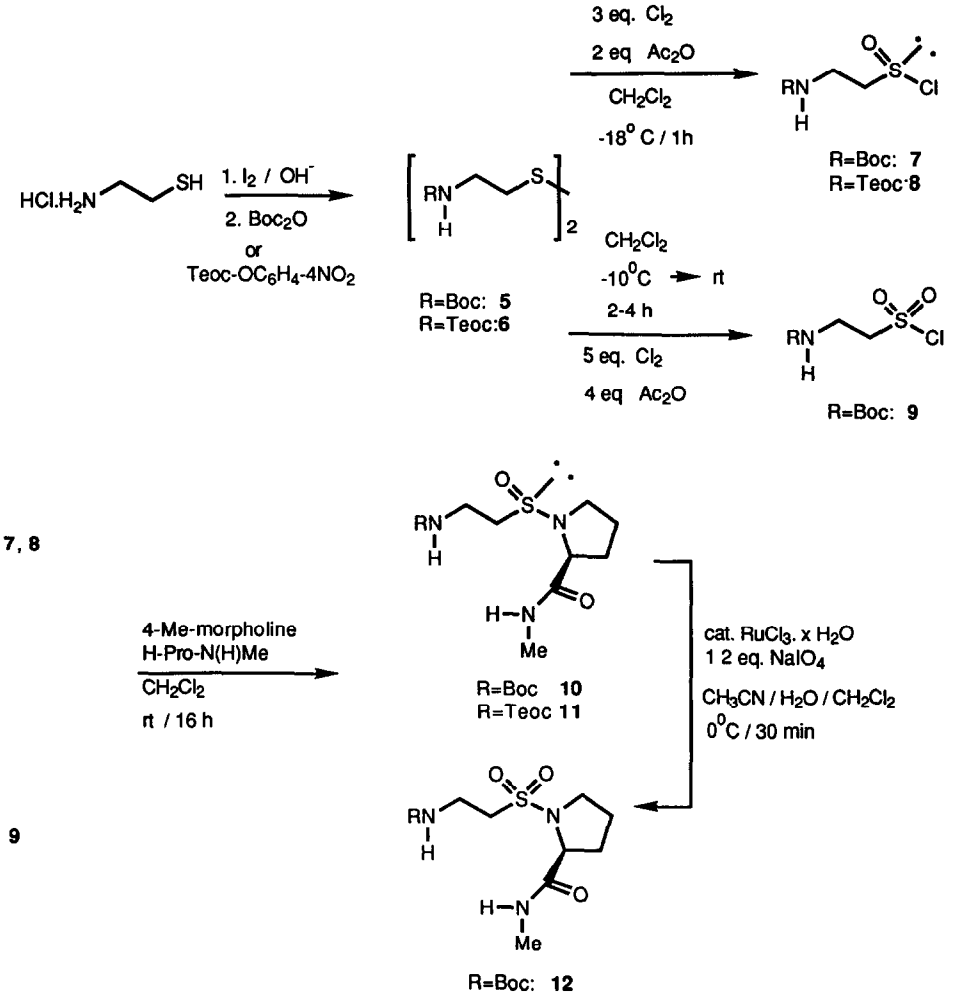
As is expected the corresponding α- amino **sulfinamide** derivative **3** is more stable, because it will be less prone to a similar fragmentation reaction as is shown in scheme 1. However, it was not possible to remove the phthaloyl protecting group in this derivative without decomposition of the sulfinamide moiety[7]. Taking into account the limited stability of the α-amino sulfonamide and sulfinamide compounds, we decided to incorporate β-amino sulfonamide and sulfinamide transition-state analogues into peptides[8].

Only a limited number of examples of peptides containing a β-amino ethane sulfonamide moiety i.e. a taurine residue (Tau) have described in the literature[9]; β-amino ethane sulfonamides derived from cysteine have been described by Aleksiev et al.[10] and Levenson and Meyer[11] in the preparation of potential dihydroorotase inhibitors. A retrosulfonamide peptide analogue was recently described by Lucente et al.[12]. Except for the β-amino ethyl sulfonamides derived from cysteine[10,11], no other substituted taurine derivatives or their incorporation in the backbone of peptides have been reported. To our knowledge, peptides containing a β-amino ethane sulfinamide (hypotaurine) moiety have never been reported thus far.

RESULTS AND DISCUSSION

In this paper we wish to describe the incorporation of a β-amino ethane sulfinamide or a sulfonamide moiety in peptides. These modified peptides can be extended at the N- or the C-terminus, which points to the synthetic possibilities for the preparation of peptides containing these types of transition-state analogues in peptides. Furthermore, we have taken advantage of the electron-withdrawing character of the sulfonamide moiety to alkylate the α-position. This is illustrated with the synthesis of a potential inhibitor of HIV protease.

As a starting target we chose to synthesize a transition-state analogue mimicking the hydrolysis of the Gly(312)-Pro(313) amide bond in a conserved sequence (312-314) i.e. Gly-Pro-Gly in HIV gp120[13]. The target compounds **12** (scheme 3) and **14** (scheme 4), having a sulfonamide with or without the additional Gly(314) were synthesized starting from cysteamine hydrochloride.



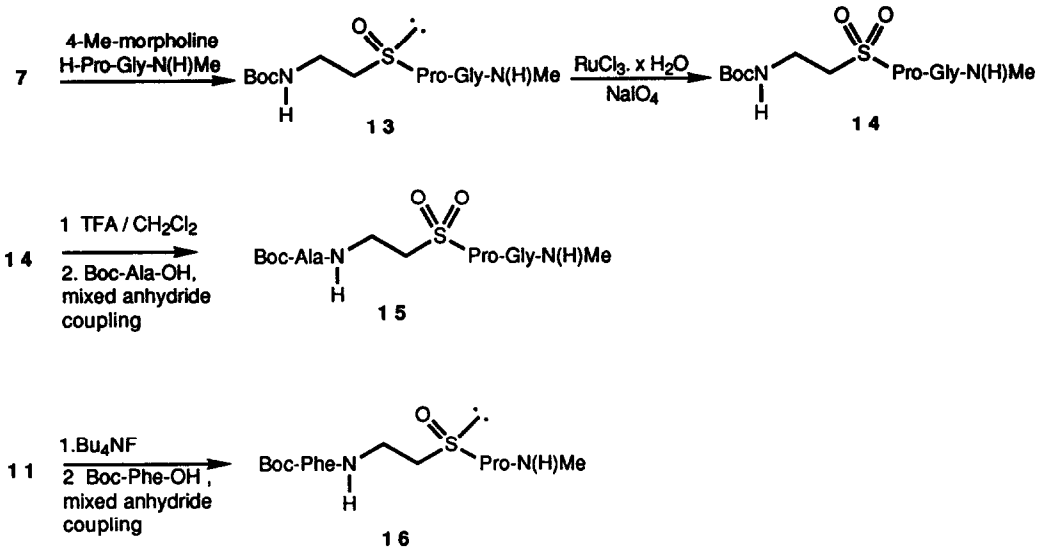
Scheme 3

Oxidation by titration with iodine, followed by protection of the amino group with di-*tert*-butyl dicarbonate or 2-(trimethylsilyl)ethyl-4-nitrophenylcarbonate afforded the disulfides **5** and **6** (88% and 91 % respectively, scheme 3). Originally, we attempted to prepare the sulfonylchloride **9**, using 5 eq. of chlorine in the presence of acetic anhydride[14-16] (4 eq.) analogous to the method of Douglass et al.[14]. However, we found that even after exposure to excess of chlorine for a relatively long period, the sulfonylchloride **9** was invariably contaminated with the sulfinylchloride **7**. This was demonstrated by the finding that a mixture of the sulfonamide **12** as well as the sulfinamide **10** (ratio 2.2/1) was obtained in a combined yield of 61% after treatment of the reaction mixture with proline methyl amide. Fortunately, it was possible to convert the sulfinamide **10** easily and quantitatively into the sulfonamide **12** using $RuCl_3/NaIO_4$[17]. Because we were unable to convert the disulfide **5 completely** to the sulfonylchloride, we decided to prepare the sulfonamide ***via*** the sulfinamide **10** (scheme 3), this will also enable us to study the latter compound as a possible transition-state analogue (figure 1d).

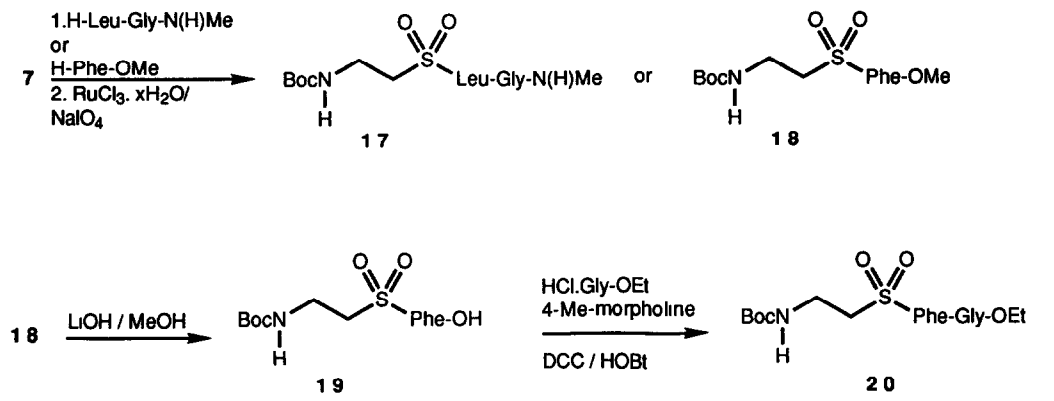
The desired sulfinylchloride **7** was prepared by treatment of the disulfide **5** with 3 eq. of chlorine in the presence of acetic anhydride (2 eq.) analogous to the procedure described for the preparation of α- chloro sulfoxides[18]. The sulfinylchloride was used without further purification for the preparation of the sulfinamides **10** (scheme 3) and **13** (scheme 4). The best overall yields, 72% and 70% respectively were achieved when the sulfinylchloride was reacted with two equivalents of the amine: H-Pro-N(H)Me or H-Pro-Gly-N(H)Me, one equivalent serving as the nucleophile and one equivalent as the base. Using one equivalent of 4-Me-morpholine as a base reduced the yields by approximately 10%, this procedure was preferred to avoid wasting of one equivalent of the amine. The sulfinamides **10** and **13** were isolated as mixtures of diastereomers. The corresponding sulfonamides **12** and **14** were obtained by subsequent oxidation in 92% and 96% yield respectively.

In order to generate (catalytic) antibodies it will be necessary to attach the transition-state analogue containing peptides to a carrier protein. Furthermore, it may be necessary to prepare larger peptides. To show that it is possible to deprotect the amino function, followed by coupling to e.g. linker, we removed the Boc-group in **14** using TFA in dichloromethane. The deprotected amino function was subjected to an amide coupling by the mixed anhydride method using Boc-Ala-OH as a model compound. The resulting tetrapeptide **15** was obtained in a yield of 81% (scheme 4). Applying the same procedure: deprotection followed by coupling, to the sulfinamide **13** gave only a low yield, due to considerable acidolytic cleavage of the sulfinamide. The greater lability of the sulfinamide bond as compared to the sulfonamide bond is also apparent from mass spectra of both compounds. The mass spectrum of **13** showed a large peak due to cleavage of the sulfinamide-amide bond, whereas the mass spectrum of **14** hardly showed a peak due to cleavage of the sulfonamide-amide bond, but a large peak of a fragment without a Boc-group. In order to be able to extend the sulfinamide transition-state analogue containing peptide **11** at the N-terminus to prepare e.g. **16**, the Boc-group was replaced by Teoc-protecting group[19], which can be removed using tetrabutyl ammonium fluoride as is shown in scheme 4. The Teoc-protected peptide derivatives **11** necessary for this conversion were prepared in the same way as the Boc-protected peptide derivative **10** as is shown in scheme 3; the diastereomers could be separated by flash silicagel column chromtography Interestingly, coupling one diastereomer of the deprotected sulfinamide using the DCC/HOBT method gave both the diastereomers of sulfinamide **16**, due to racemization at sulfur, whereas the mixed anhydride method was stereospecific and gave only one diasteromer of **16**.

In addition to proline derivatives, other amino acid or peptide derivatives containing a free amino terminus can be reacted with the sulfinylchloride **7** in the preparation of various sulfonamide transition-state analogue containing peptide as is examplified with the preparation of e.g. **17** and **18** depicted in scheme 5. Finally, extension at the C-terminus in the sulfonamide containing peptides in principle is possible by saponification of the methylester in the sulfonamide transition-state analogue containing peptide **18**, followed by coupling of the thus obtained carboxylic acid **19** with a subsequent amino acid derivative using the DCC/HOBT method. In this case the mixed anhydride method did not give satisfactory results.



Scheme 4



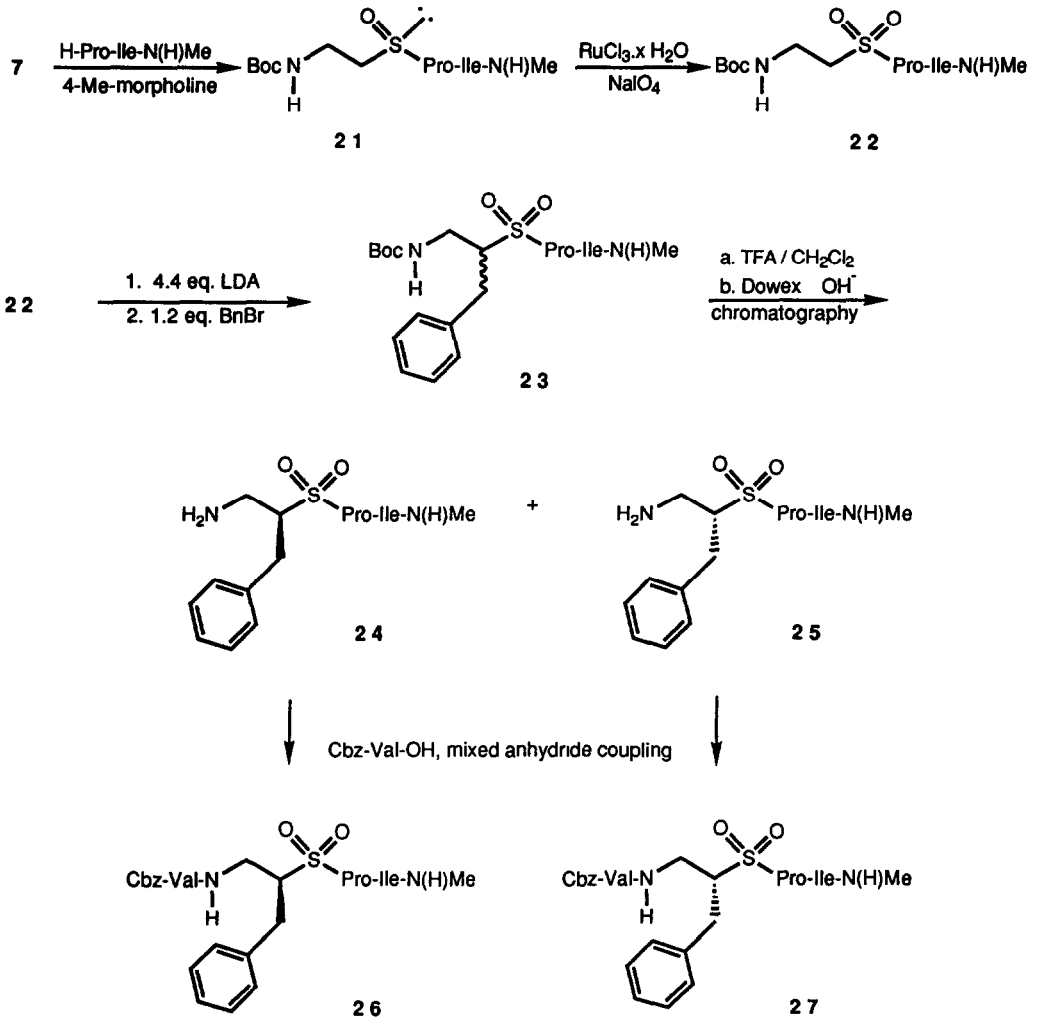
Scheme 5

Another important goal was the incorporation of the sulfonamide transition-state analogue into suitable peptides leading to new potential inhibitors of HIV-protease.

Based on the presently available HIV-protease inhibitors[5a-x], we proposed **27** as a potential inhibitor of HIV-protease. This peptide analogue features the presence of a sulfonamide transition-state analogue of the hydrolysis of the Phe-Pro amide bond, corresponding to the Phe-Pro junction in a HIV precursor polyprotein which is processed by HIV-protease[20]. In addition, hydrophobic N- and C-terminal amino acids are included to ensure a good interaction with the hydrophobic amino acids present in the active site of HIV-protease[21]. The synthesis of **27** is shown in scheme 6. The tripeptide containing the sulfinamide transition-state analogue **21** was synthesized analogous to the earlier synthesized modified peptides (*vide supra*). Oxidation of this sulfinamide **21** to the sulfonamide **22** was followed by alkylation of the latter to a β-amino-phenylalanine

sulfonamide-proline entity as part of the tripeptide derivative **23**. Thus, treatment with 4.4 eq. of LDA leading to abstraction of all N-H-protons as well as the α-sulfonamide proton, followed by treatment with 1.2 eq. of benzylbromide afforded **23** (84%) as a mixture of diastereomers (ratio 3/1, by NMR) which could not be separated by column chromatography[22]. Fortunately, separation of the diastereomers by silicagel chromatography could be accomplished after removal of the Boc-protecting group. Coupling of the thus obtained diastereomers **24** and **25** with Cbz-Val-OH using the mixed-anhydride method gave the potential HIV-protease inhibitor **27** and its diastereomer **26** in a average yield of 85%[23, 24].

Computer-assisted molecular modeling studies revealed that there is virtually no difference between the binding position of this potential inhibitor **27** in the active site of HIV-protease and the position of the inhibitor MVT-101, present in a crystal structure of the HIV-protease MVT101 complex[25,26].



Scheme 6

In summary, we have shown that a novel class of sulfur-based transition-state analogues is now synthetically accessible in a straightforward manner. This has been demonstrated by the synthesis of a sulfinamide or sulfonamide transition-state analogue containing tripeptide derived from a sequence in HIV gp120. By using an amino protecting group which can be removed under neutral conditions, the amino terminus can be extended which opens up the possibility to prepare larger sulfinamide containing peptides. Similarily, either the N-terminus or the C-terminus of sulfonamide containing peptides can be extended. Furthermore, the synthesis of a potential HIV-protease inhibitor containing a sulfonamide transition-state analogue was described. In addition to the incorporation of the sulfonamide analogue into this peptide derivative, we have show that the α-position can be alkylated. Under present investigation is the scope of α-alkylation of sulfonamides transition-state analogues. In addition we are investigating an alternative approach for the preparation of both α-functionalized and β-functionalized sulfonamides[27]. The introduction of α-substituents might be employed for the synthesis of a variety of sulfonamide transition-state analogue containing peptides.

EXPERIMENTAL

General methods: Dioxane and THF were dried by refluxing on $LiAlH_4$ and distilled immediately prior to use. DMF was stirred with CaH_2 for 16 h and then distilled under reduced pressure. Ethanol free dichloromethane used for synthesis of the sulfinylchlorides and sulfinamides was purchased from Baker, dried by refluxing on CaH_2 and distilled directly prior to use. N-methyl morpholine was distilled from calcium hydride, *iso*-butylchloroformate was distilled under Ar.

2-(Trimethylsilyl)ethyl p-nitrophenylcarbonate and LDA.dioxane complex were purchased from Fluka. All monoprotected amino acids were purchased from Bachem.

Melting points were determined on a Büchi Schmelzpunktbestimmungsapparat and are uncorrected. TLC analysis was performed on Merck pre coated silicagel 60 F-254 plates. Spots were visualized with UV light, ninhydrin (after treatment with HCl) or Cl_2-TDM[28]. Column chromatography was carried out on Merck Kieselgel 60 (230-400 Mesh, ASTM). For flash column chromatography Merck kieselgel (60 H) was used.

^1H NMR spectra were recorded on a Jeol NM-Fx 200 (200 MHz) spectrometer or a Bruker WM-300 (300 MHz) spectrometer both interfaced with an ASPECT-2000 computer, operating in the Fourier transform mode and are given in ppm (δ) relative to TMS or TSP as internal standard. ^{13}C NMR spectra were recorded on a Jeol JNM-Fx 200 spectrometer on line with a JEC 980B computer at 50.1 MHz and are given in ppm (δ) relative to $CDCl_3$ as internal standard. The numbering of the carbon atoms in the amino acids is according to IUPAC recommendations[29].

Fast Atom Bombardment (FAB) mass spectometry was carried out using V.G. Micromass ZAB-HFqQ mass spectometer, coupled to a V.G. 11/250 data system. The samples were loaded in a glycerol/thioglycerol/nitrobenzylalcohol (NBA) solution onto a stainless steel probe and bombarded with Xenon atoms wit an energy of 8KeV. During the high resolution FABMS measurements a resolving power of 10,000 (10% valley definition) was used. Glycerol was used to calibrate the mass spectrometer.

N-(Carbobenzyloxycarbonyl)amino-methane-proline-methylamide (**4a**)

To a cooled solution (0°C) of aminomethanesulfonic acid (1.12 g, 10.1 mmol) in 1 N NaOH (10.1 mL) and dioxane (10 mL) were added benzylchloroformate (1.6 mL, 11.07 mmol) in dioxane (5 mL) and 4N NaOH (2.5 mL) simultaneously over a period of 15 min. After stirring for 1.5 h the mixture was concentrated *in vacuo* and partitioned between ether and water. The water layer was washed with ether and concentrated *in vacuo*. The sodium salt of N-(carbobenzyloxycarbonyl)methylsulfonic acid was crystallized from water, dried *in vacuo* over P_2O_5 and obtained in 84% yield. ^1H NMR (D_2O) δ 4.29 (s, 2H, CH_2SO_2), 5.15 (s, 2H, Cbz CH_2), 7.46 (m, 5H, Cbz $H_{arom.}$); ^{13}C NMR (D_2O) δ 57.6 (CH_2SO_2), 67.9 (Cbz CH_2), 128.4, 129.0, 129.4, 136.7 (Cbz, aromatic part), 158.2 (C=O).

To a suspension of the sodium salt (Cbz-N(H)$CH_2SO_3^-$ Na^+) (2.67 g, 1 mmol) in CH_2Cl_2 (5 mL) stirred

under Ar, oxalylchloride (131 μL, 1.50 mmol) and a catalytical amount of DMF were added. After 1.5 h, the reaction mixture was concentrated *in vacuo*, suspended in CH_2Cl_2 (2 mL) followed by addition of a solution of H-Pro-N(H)Me[30] (0.270 g, 2.11 mmol) in CH_2Cl_2 (6 mL) and stirred overnight. Evaporation of the solvent *in vacuo* and silica gel column chromatography (50 g, eluent: EtOAc to EtOAc/MeOH 95/5 v/v) afforded **4a** as an oil in 34% yield. Repeatment of chromatography resulted in 50% product loss, indicating decomposition.

4a R_f 0.29 (eluent EtOAc/MeOH 95/5 v/v); ^1H NMR ($CDCl_3$) δ 1.65-1.81 (m, 2H, Pro-C^4H_2), 1.88-2.04, 2.14 (m (H_a), 11 lines (H_b), 2H, Pro-C^3H_2, J_{BX}= 7.4 Hz, J_{BY}= 10.1 Hz, J_{AB}= 12.6 Hz), 2.53, 3.13 (dt (H_a), 7 lines (H_b), 2H, Pro-C^5H_2, J_{AX}= 6.7 Hz, J_{BX}= 2.8 Hz, J_{BY}= 6.2 Hz, J_{AB}= 9.2 Hz), 2.79 (d, 3H, N(H)$C\underline{H}_3$, J = 4.9 Hz), 3.24 (dd, 1H, Pro-C^2H, J_{AX}= 4.6 Hz, J_{AY} =10.1 Hz), 3.89, 4.19 (two dd, 2H, NCH_2N, J_{AX}= 6.0, J_{BX}= 6.7, J_{AB}=12.8 Hz), 5.09, 5.14 (two d, 2H, Cbz CH_2, J_{AB}=12.2 Hz), 5.59 (br t, 1H, N($\underline{H}$)CH_2), 7.28-7.42 (m, 5H, Cbz $H_{arom.}$), 7.58 (br q, 1H, N($\underline{H}$)CH_3); ^{13}C NMR ($CDCl_3$) δ 24.1 (Pro-C^4), 25.6 (N(H)CH_3), 30.6 (Pro-C^3), 51.5 (Pro-C^5), 59.8 (NCH_2N), 63.4 (Pro-C^2), 66.7 (Cbz CH_2), 127.9, 128.0, 128.4, 136.2 (Cbz, aromatic part), 156.8 (Cbz C=O), 174.8 (C=O); IR (KBr) 3290, 3200 (NH), 1700, 1635 (amide I), 1530 (amide II) cm^{-1}; FABMS m/z 292.2 $(M + H)^+$.

N,N'-di(tert-Butyloxycarbonyl)-cystamine (**5**)

Cysteamine hydrochloride (5.68 g, 50 mmol) dissolved in 2N NaOH (25 mL), was oxidized by titration with a solution of iodine (15.23 g, 60 mmol) in dioxane (25 mL). The resulting cystamine was neutralized with 2 N NaOH (25 mL) and treated with di-*tert*-butyldicarbonate (12.00 g, 55 mmol) in dioxane (25 mL) at 0°C. After stirring for 2.5 h, the reaction mixture was concentrated *in vacuo* and partitioned between EtOAc and water. The organic layer was washed with 10% $Na_2S_2O_3$, 1N $KHSO_4$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Crystallization from EtOAc afforded **5** in 88% yield. M.p. 107.5-108°C. R_f 0.71 (eluent: EtOAc/petroleum ether 40-60 (pet-ether), 1/1 v/v). ^1H NMR ($CDCl_3$) δ 1.45 (s, 18H, Boc $C(CH_3)_3$), 2.80 (t, 4H, CH_2S, J = 6.3 Hz), 3.44 (q, 4H, $C\underline{H}_2N(H)$, J = 6.3 Hz), 5.10 (b, 2H, $CH_2N(\underline{H})$); ^{13}C NMR ($CDCl_3$) δ 28.3 (Boc $C(\underline{C}H_3)_3$), 38.4 (CH_2S), 39.3 ($CH_2N(H)$), 79.5 (Boc $\underline{C}(CH_3)_3$), 155.8 (C=O); IR (KBr) 3340 (NH), 1665 (amide I), 1505 (amide II) cm^{-1}.

N,N'-di(Trimethylsilylethyloxycarbonyl)-cystamine (**6**)

A solution of cystamine hydrochloride (0.568 g, 5.0 mmol) was prepared as described in the prepartion of **5**. After neutralization with 2 M Na_2CO_3 (1.25 mL), a solution of 2-(Trimethylsilyl)ethyl p-nitrophenyl carbonate (1.403 g, 4.95 mmol) in THF (5 mL) and EtOH (10 mL) were added. The reaction was stirred for 5 h, concentrated *in vacuo* and partitioned between ether and water. The organic layer was washed with 25% NH_4OH until complete disappearance of the yellow color, followed by washing with 10% $Na_2S_2O_3$, 1N $KHSO_4$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Silica gel column chromatography (20 g, eluent: pet-ether/ether, 100/0 to 60/40 v/v) gave **6** as an oil in 91% yield. R_f 0.40 (eluent: pet-ether/ether, 1/1 v/v); ^1H NMR ($CDCl_3$ δ 0.04 (s, 18H, Teoc $Si(CH_3)_3$), 0.98 (7 lines, 4H, CH_2Si), 2.81 (t, 4H, CH_2S, J = 6.3 Hz), 3.50 (q, 4H, $C\underline{H}_2N(H)$, J = 6.3 Hz), 4.16 (7 lines, 4H, OCH_2), 5.12 (br t, 2H, $CH_2N(\underline{H})$); ^{13}C NMR ($CDCl_3$) δ -1.8 ($Si(CH_3)_3$), 17.4 (CH_2Si), 37.9 (CH_2S), 39.4 ($CH_2N(H)$), 62.7 (OCH_2), 156.5 (C=O); IR (film) 3320 (NH), 1680 (amide I), 1510 (amide II) cm^{-1}.

N-(tert-Butyloxycarbonyl)amino-ethane-sulfinylchloride (**7**)

To a stirred and cooled (-18°C, ethanol, liquid N_2) solution of disulfide **5** (0.71 g, 2.01 mmol) and Ac_2O (0.38 mL, 4.02 mmol) in CH_2Cl_2 (15 mL) a cooled (-10°C) solution of Cl_2 (ca. 0.6 g, 7.9 mmol, dried over conc. H_2SO_4,) in CH_2Cl_2 (15 mL), was added *via* a glass connecting tube and stirrring was continued for 1hr at -18°C. Concentration and removal of residual solvent and acetylchloride at oilpump vacuum gave the sulfinylchloride, which was used without further purification. ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H, Boc $C(CH_3)_3$), 3.63 (br t, 2H, CH_2SO, J = 5.4 Hz), 3.75 (br q, 2H, $C\underline{H}_2N(H)$, J = 5.4 Hz), 5.21 (br, 1H, $CH_2N(\underline{H})$); ^{13}C NMR ($CDCl_3$) δ 27.9 (Boc, $C(\underline{C}H_3)_3$), 34.5 ($CH_2N(H)$), 64.0 (CH_2SO), 79.6 (Boc

$\underline{C}(CH_3)_3$), 155.7 (C=O).

N-(Trimethylsilylethyloxycarbonyl)amino-ethane-sulfinylchloride (**8**)
The sulfinylchloride **8** was synthesized from **6** analogous to the preparation of the sulfinylchloride **7**.
^1H NMR ($CDCl_3$) δ 0.04 (s, 9H, Teoc $Si(CH_3)_3$), 0.99 (m, 2H, CH_2Si), 2.96 (br, 1H, $CH_2N(\underline{H})$), 3.64 (br t, 2H, CH_2SO, J = 5.3 Hz), 3.83 (br q, 2H, $C\underline{H}_2N(H)$, J = 5.3 Hz), 4.18 (m, 2H, OCH_2); ^{13}C NMR ($CDCl_3$) δ -1.7 ($Si(CH_3)_3$), 17.4 (CH_2Si), 35.0 ($CH_2N(H)$), 63.4, 63.8 (CH_2SO, OCH_2), 156.7 (C=O).

N-(tert-Butyloxycarbonyl)amino-ethane-sulfonylchloride (**9**)
To a stirred and cooled (-10°C, ethanol, liquid N_2) solution of disulfide **5** (0.87 g, 2.46 mmol) and Ac_2O (0.93 mL, 9.82 mmol) in CH_2Cl_2 (20 mL) a cooled (-10°C) solution of Cl_2 (ca. 0.9 g, 12.3 mmol, dried over conc. H_2SO_4,) in CH_2Cl_2 (15 mL) was added *via* a glass connecting tube and stirrring was continued for 4 hr at -0°C. Concentration and removal of residual solvent and acetylchloride at oilpump vacuum gave the sulfonylchloride, which was used without further purification.

N-(tert-Butyloxycarbonyl)amino-ethane-sulfinyl-proline-methylamide (**10**)
A solution of H-ProN(H)Me (0.539 g, 4.20 mmol) in CH_2Cl_2 (10 mL) and N-methyl morpholine (0.44 mL, 4.02 mmol) were added simultaneously to a solution of sulfinylchloride **7** (4.02 mmol) in CH_2Cl_2 (7 mL) at 0°C under Ar. The mixture was stirred overnight at rt, concentrated *in vacuo* and purified by silica gel column chromatography (50 g, eluent: CH_2Cl_2/MeOH 96/4 v/v) to afford **10** as an oil in 64% yield. The diasteromers (ratio 1/1) could not be separated. R_f 0.41 (CH_2Cl_2/MeOH 95/5 v/v); The chemical shifts of the less polar diastereomer are indicated an asterik. ^1H NMR ($CDCl_3$) δ 1.44 (s, 18H, Boc $C(CH_3)_3$, Boc $C(CH_3)_3$*), 1.82-2.00 (m, 4H, Pro-C^4H_2, Pro-C^4H_2*), 2.04-2.36 (m, 4H, Pro-C^3H_2, Pro-C^3H_2*) 2.75, 3.03-3.13 (dt (H_a*), m (H_b*, H_a, H_b), 4H, CH_2SO*, CH_2SO, J_{AX}= 6.0 Hz, J_{AB}= 13.4 Hz), 2.83 (d, 3H, N(H)$C\underline{H}_3$*, J = 4.9 Hz), 2.84 (d, 3H, N(H)$C\underline{H}_3$, J = 4.9 Hz), 3.03-3.13, 3.70 (m (H_a), dt (H_b), 2H, Pro-C^5H_2, J_{BX}= 7.9 Hz, J_{AB}= 9.7 Hz), 3.39-3.59 (m, 6H, N(H)$C\underline{H}_2$, N(H)$C\underline{H}_2$*, Pro-C^5H_2*), 4.21 (dd, 1H, Pro-C^2H, J_{AX}= 3.7 Hz, J_{AY}= 8.3 Hz), 4.45 (dd, 1H, Pro-C^2H*, J_{AX}= 4.4 Hz, J_{AY}= 8.2 Hz), 5.22 (br, 1H, N($\underline{H}$)CH_2*), 5.48 (br, 1H, N($\underline{H}$)CH_2), 6.88 (br, 2H, N($\underline{H}$)CH_3*); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.4 (Pro-C^4, Pro-C^4*), 26.0, 26.1 (N(H)CH_3, N(H)CH_3*), 28.2 (Boc $C(\underline{C}H_3)_3$, Boc $C(\underline{C}H_3)_3$*), 30.9, 31.8 (Pro-C^3, Pro-C^3*), 35.1, 35.2 (N(H)CH_2, N(H)CH_2*), 40.8 (Pro-C^5), 52.6 (Pro-C^5*), 54.1 (CH_2SO), 54.6 (CH_2SO*), 56.7 (Pro-C^2*), 65.9 (Pro-C^2), 79.4 (Boc $\underline{C}(CH_3)_3$, Boc $\underline{C}(CH_3)_3$)*), 155.9 (Boc C=O, Boc C=O*), 172.4, 173.0 (C=O, C=O*); IR (film) 3300 (NH), 1650 (amide I), 1510 (amide II), 1050 (SO) cm^{-1}.

N-(Trimethylsilylethoxycarbonyl)amino-ethane-sulfinyl-proline-methylamide (**11**)
The sulfinamide **11** was prepared analogous to the preparation of **10** from sulfinylchloride **8** (3.32 mmol) and H-ProN(H)Me (0.447 g, 3.48 mmol). Silica gel column chromatography (150 g, eluent: EtOAc/MeOH 95/5 v/v) gave **11** as an oil in 72 % yield. The diasteromers could be separated with flash column chromatography (200 g, eluent: EtOAc/ MeOH 98/2 to 97/3 v/v) and were obtained in a ratio of ca. 1/1. R_f 0.26 (EtOAc/MeOH 9/1 v/v); ^1H NMR ($CDCl_3$) δ 0.00 (s, 9H, Si $(CH_3)_3$), 0.91-0.97 (m, 2H, CH_2Si), 1.79-1.90 (m, 2H, Pro-C^4H_2), 2.01-2.17 (m, 2H, Pro-C^3H_2), 2.73, 2.96-3.05 (dt (H_a), m (H_b), 2 H, CH_2SO, J_{AX}= 5.7 Hz, J_{AB} = 13.3 Hz), 2.79 (d, 3H, N(H)$C\underline{H}_3$, J = 4.9 Hz), 3.34-3.77 (m, 2H, N(H)$C\underline{H}_2$), 3.47 (t, 2H, Pro-C^5H_2, J = 6.7 Hz), 4.08- 4.15 (m, 2H, OCH_2), 4.42 (dd, 1H, Pro-C^2H, J_{AX}= 4.4 Hz, J_{AY}= 8.4 Hz), 5.63 (t, 1H, N($\underline{H}$)CH_2, J = 5.2 Hz), 6.91 (br, 1H, N($\underline{H}$)CH_3); ^{13}C NMR ($CDCl_3$) δ -1.8 (Si $(CH_3)_3$), 17.5 (CH_2Si), 25.4 (Pro-C^4), 26.0 (N(H)CH_3), 31.8 (Pro-C^3), 35.5 (N(H)CH_2), 52.6 (Pro-C^5), 53.9 (CH_2SO), 56.5 (Pro-C^2), 62.9 (OCH_2), 156.7 (Teoc C=O), 173.0 (C=O).
R_f 0.22 (EtOAc/MeOH 9/1 v/v); ^1H NMR ($CDCl_3$) δ 0.00 (s, 9H, Si $(CH_3)_3$), 0.90-0.96 (m, 2H, CH_2Si), 1.80-1.91 (m, 2H, Pro-C^4H_2), 2.01-2.20 (m, 2H, Pro-C^3H_2), 2.78 (d, 3H, N(H)$C\underline{H}_3$, J = 4.9 Hz), 2.93, 2.99-3.08 (8 lines (H_a), m (H_b), 2H, CH_2SO, J_{AX}= 4.7 Hz, J_{AY}= 7.6 Hz, J_{AB}= 13.6 Hz), 2.99-3.08, 3.65 (m (H_a), dt (H_b), 2H, Pro-C^5H_2, J_{BX}= 7.7 Hz, J_{AB}= 9.7 Hz), 3.41, 3.56-3.64 (dq (H_a), m (H_b),

2H, N(H)C$\underline{H}_2$, J_{AX}= 5.8 Hz, J_{AB}= 14.6 Hz), 4.08- 4.13 (m, 2H, OCH_2), 4.15 (dd, 1H, Pro-C^2H, J_{AX}= 4.4 Hz, J_{AY}= 7.9 Hz), 5.96 (t, 1H, N($\underline{H}$)CH_2, J = 6.1 Hz), 6.97 (br, 1H, N($\underline{H}$)CH_3); ^{13}C NMR ($CDCl_3$) δ -1.8 ($Si(CH_3)_3$), 17.4 (CH_2Si), 24.6 (Pro-C^4), 26.0 ($N(H)CH_3$), 31.0 (Pro-C^3), 35.3 ($N(H)CH_2$), 40.7 (Pro-C^5), 54.2 (CH_2SO), 62.8 (OCH_2), 65.6 (Pro-C^2), 156.8 (Teoc C=O), 172.5 (C=O).

N-(tert-Butyloxycarbonyl)amino-ethane-sulfonyl-proline-methylamide (**12**)

Method A: A solution of H-Pro-N(H)Me (1.26 g, 9.83 mmol) in CH_2Cl_2 (10 mL) was added to a stirred, cooled (0°C) suspension of sulfonylchloride **9** (4.92 mmol) in dry CH_2Cl_2 (10 mL). After stirring the mixture overnight at rt under Ar, the HCl.H-Pro-N(H)Me precipitate was filtered and the filtrate concentrated *in vacuo*. Silica gel column chromatography (50 g, eluent: CH_2Cl_2/MeOH, 95/5 v/v) afforded the sulfonamide **12** in 41% yield and the sulfinamide **10** in 19 % yield.

Method B: Sodiumperiodate (0.316 g, 1.48 mmol) and a catalytical amount of $RuCl_3$ monohydrate (8.9 μmol, 2 mg) were added to a cooled (0°C) solution of sulfinamide **10** (0.393 g, 1.23 mmol) in CH_2Cl_2 (3.5 mL), CH_3CN (3.5 mL) and H_2O (5.5 mL). After stirring for 20 min CH_2Cl_2 (40 mL) was added and the separated water layer extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel column chromatography (10 g, eluent: CH_2Cl_2/ MeOH 95/5 v/v) afforded **12** as a white solid in 92 % yield. R_f 0.51 (eluent CH_2Cl_2/MeOH 95/5 v/v); ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H, Boc $C(CH_3)_3$), 1.93-2.01 (m, 2H, Pro-C^4H_2), 2.14, 2.28 (dq (H_a), 12 lines (H_b), 2H, Pro-C^3H_2, J_{AX}= 8.3 Hz, J_{BX} = 3.5 Hz, J_{BY} = 5.6 Hz, J_{AB}= 12.6 Hz), 2.84 (d, 3H, N(H)C$\underline{H}_3$, J = 4.9 Hz), 3.17, 3.25 (8 lines (H_a), 8 lines (H_b), 2H, CH_2SO_2, J_{AX} = 5.1 Hz, J_{AY} = 6.8 Hz, J_{BX} = 5.3 Hz, J_{BX}= 6.9 Hz, J_{AB} = 14.1 Hz), 3.42, 3.48 (two dt, 2H, Pro-C^5H_2, J_{AX}= 5.9 Hz, J_{BX} = 7.4 Hz, J_{AB}= 9.9 Hz), 3.56-3.65 (m, 2H, N(H)C$\underline{H}_2$), 4.26 (dd, 1H, Pro-C^2H, J_{AX} = 3.5 Hz, J_{AY}= 8.3 Hz), 5.59 (br, 1H, N($\underline{H}$)CH_2), 6.70 (br, 1H, N($\underline{H}$)CH_3); ^{13}C NMR ($CDCl_3$) δ 24.9 (Pro-C^4), 26.4 ($N(H)CH_3$), 28.3 (Boc C($\underline{C}H_3$)$_3$), 30.7 (Pro-C^3), 35.1 ($N(H)CH_2$), 49.1 (Pro-C^5, CH_2SO_2), 61.9 (Pro-C^2), 79.8 (Boc $\underline{C}(CH_3)_3$), 155.8 (Boc C=O), 171.9 (C=O); IR (film) 3290 (NH), 1665, 1640 (amide I), 1525 (amide II), 1330, 1130 (SO_2) cm^{-1}.

N-(tert-Butyloxycarbonyl)amino-ethane-sulfinyl-prolinyl-glycine-methylamide (**13**)

The sulfinamide **13** was prepared analogous to the preparation of **10** from sulfinylchloride **7** (8.50 mmol) and H-Pro-Gly-N(H)Me[32] (8.75 mmol). Silica gel column chromatography (280 g, eluent: EtOAc/MeOH 95/5 to 9/1 v/v) gave **13** as a mixture of diasteromers (ratio 1/1) in 69% yield. R_f 0.54 (CH_2Cl_2/MeOH 9/1); The chemical shifts of the less polar diastereomer are indicated an asterik. ^1H NMR ($CDCl_3$) δ 1.44 (s, 18H, Boc $C(CH_3)_3$, Boc $C(CH_3)_3$*), 1.51-2.06 (m, 4H, Pro-C^4H_2, Pro-C^4H_2*), 2.07-2.27 (m, 4H, Pro-C^3H_2, Pro-C^3H_2*), 2.79, 3.02-3.23 (dt (H_a*), m (H_b*, H_a, H_b), 4H, CH_2SO, CH_2SO*, J_{AX}= 6.1 Hz, J_{AB} covered), 2.80 (d, 3H, N(H)C$\underline{H}_3$*, J = 4.7 Hz), 2.81 (d, 3H, N(H)C$\underline{H}_3$, J = 4.7 Hz), 3.02-3.23, 3.72 (m (H_a), dt (H_b), 2H, Pro-C^5H_2, J_{AX}= 7.8 Hz, J_{AB}= 9.8 Hz), 3.47-3.60 (m, 6H, N(H)C$\underline{H}_2$, N(H)C$\underline{H}_2$*, Pro-C^5H_2), 3.84, 4.02, 3.86, 4.09 (four dd, 4H, Gly-C^2H_2, Gly-C^2H_2*, J_{AX}= 4.7 Hz, J_{BX}= 5.9 Hz, J_{AB}= 16.6 Hz), 4.26 (t, 1H, Pro-C^2H, J = 6.3 Hz), 4.52 (dd, 1H, Pro-C^2H*, J_{AX}= 4.1 Hz, J_{AB}= 8.9 Hz), 5.69 (t, 1H, N($\underline{H}$)CH_2*, J = 5.9 Hz), 6.11 (t, 1H, N($\underline{H}$)CH_2, J = 5.8 Hz), 6.95 (br, 2H, N($\underline{H}$)CH_3, N($\underline{H}$)CH_3*), 7.65 (t, 1H, Gly-N($\underline{H}$)*, J = 5.5 Hz), 7.73 (br, 1H, Gly-N($\underline{H}$)); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.4 (Pro-C^4, Pro-C^4*), 25.9 ($N(H)CH_3$, $N(H)CH_3$*), 28.1 (Boc C($\underline{C}H_3$)$_3$, Boc C($\underline{C}H_3$)$_3$*), 30.9, 31.7 (Pro-C^3, Pro-C^3), 35.0, 35.3 ($N(H)CH_2$, $N(H)CH_2$*), 40.8 (Pro-C^5), 42.3 (Gly-C^2, Gly-C^2*), 52.9 (Pro-C^5*), 54.1 (CH_2SO), 54.3 (CH_2SO*), 56.1 (Pro-C^2*), 65.5 (Pro-C^2), 79.2 (Boc $\underline{C}(CH_3)_3$, Boc $\underline{C}(CH_3)_3$*), 155.7, 156.0 (Boc C=O, Boc C=O*), 169.1, 172.5, 173.2 (C=O, C=O*); IR (KBr) 3300 (NH), 1655 (amide I), 1520 (amide II), 1040 (SO) cm^{-1}; exact mass m/z calculated 377.1859, found: 377.1869 $(M + H)^+$.

N-(tert-Butyloxycarbonyl)amino-ethane-sulfonyl-prolinyl-glycine-methylamide (**14**)
The sulfinamide **13** was converted to the sulfonamide **14** analogous to the preparation of **12**. The crude sulfonamide was purified by silica gel column chromatography (10 g, eluent CH_2Cl_2/ MeOH 95/5 v/v) to give **14** as an oil in 97 % yield. R_f 0.37 (EtOAc / MeOH 9/1 v/v); ^1H NMR ($CDCl_3$) δ 1.44 (s, 9H, Boc $C(CH_3)_3$), 1.94-2.07 (m, 2H, Pro-C^4H_2), 2.14, 2.29 (two dq, 2H, Pro-C^3H_2, J_{AX}= 5.1 Hz, J_{BX}= 8.2 Hz, J_{AB}= 12.9 Hz), 2.77 (d, 3H, N(H)$C\underline{H}_3$, J = 4.8 Hz), 3.25, 3.34 (two dt, 2H, CH_2SO_2, J_{AX} = 6.0 Hz, J_{BX} = 6.1 Hz, J_{AB} = 13.6 Hz), 3.45, 3.48 (two dt, 2H, Pro-C^5H_2, J_{AX}= 7.1 Hz, J_{BX} = 6.0 Hz, J_{AB} = 16.0 Hz), 3.58 (m, 2H, N(H)$C\underline{H}_2$), 3.86, 4.03 (two dd, 1H, Gly-C^2H_2, J_{AX} = 5.5 Hz, J_{BX} = 6.6 Hz, J_{AB} = 16.8 Hz), 4.32 (dd, 1H, Pro-C^2H, J_{AX}= 5.1 Hz, J_{AY} = 8.2 Hz), 5.88 (t, 1H, N($\underline{H}$)CH_2, J = 5.9 Hz), 6.90 (q, 1H, N($\underline{H}$)CH_3, J = 4.8 Hz), 7.7 (t, Gly-N($\underline{H}$), J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 24.5 (Pro-C^4), 25.5 (N(H)CH_3), 27.8 (Boc $C(\underline{C}H_3)_3$), 30.6 (Pro-C^3), 34.6 (N(H)CH_2), 42.3 (Gly-C^2), 48.5 (Pro-C^5, CH_2SO_2), 61.2 (Pro-C^2), 79.0 (Boc $\underline{C}(CH_3)_3$), 155.4 (Boc C=O), 169.1, 171.9 (C=O); IR (KBr) 3380 (NH), 1660 (amide I), 1520 (amide II), 1330, 1140 (SO_2) cm^{-1}; exact mass m/z calculated 393.1808, found: 393.1787 $(M + H)^+$.

N-(tert-Butyloxycarbonyl)-alanyl-amino-ethane-sulfonyl-prolinyl-glycine-methylamide (**15**)
TFA (1.4 mL) was added to a cooled (0°C) solution of sulfonamide **14** (0.365 g, 0.93 mmol) in CH_2Cl_2 (1 mL). After stirring for 50 min at rt, the mixture was concentrated *in vacuo* and coevaporated with dry ether (4 x 10 mL). The TFA salt was dissolved in THF (1mL) and neutralized with N-methyl morpholine. To a cooled (-10°C, ethanol, liquid N_2) solution of BocAla-OH (180 mg, 0.95 mmol) in dry THF (3 mL), N-methyl morpholine (0.10 mL, 0.95 mmol) and *iso*-butylchloroformate (0.12 mL, 0.93 mmol) were added. To the mixed anhydride, formed by stirring for 5 min, the THF solution of deprotected **14** was added. After completion of the reaction (ca. 2 hr, -10°C) as indicated by TLC, the mixture was concentrated *in vacuo*. The residue was diluted with EtOAc (40 mL) and washed with 5% $NaHCO_3$ (2 x 5 mL) 5% citric acid (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Silica gel column chromatography (15 g, CH_2Cl_2/MeOH 95/5) afforded **15** as an oil in 81% yield. R_f 0.34 (CH_2Cl_2 / MeOH 9/1 v/v); ^1H NMR ($CDCl_3$) δ 1.36 (d, 3H, Ala-C^3H_3, J = 7.1 Hz), 1.43 (s, 9H, Boc $C(CH_3)_3$), 1.94-2.09 (m, 2H, Pro-C^4H_2), 2.16, 2.28 (two dq, 2H, Pro-C^3H_2, J_{AX}= 5.7 Hz, J_{BX}= 7.9, J_{AB}= 12.4 Hz), 2.80 (d, 3H, N(H)$C\underline{H}_3$, J = 4.8 Hz), 3.20, 3.38 (8 lines (H_a), 8 lines (H_b), 2H, CH_2SO_2, J_{AX}= 4.1 Hz, J_{AY} = 6.5, J_{BX}= 4.3 Hz, J_{BY}= 8.0 Hz, J_{AB}=14.4 Hz), 3.45 (t, 2H, Pro-C^5H_2, J = 6.6 Hz), 3.55-3.64, 3.81 (m (H_a), 12 lines (H_b), 2H, N(H)$C\underline{H}_2$, J_{BX}= 4.3 Hz, J_{BY}= 6.5 Hz, J_{AB}= 14.6 Hz), 3.92, 4.01 (two dd, 2H, Gly-C^2H_2, J_{AX}= 5.7 Hz, J_{BX}= 6.2 Hz, J_{AB}= 16.7 Hz), 4.19 (t, 1H, Ala-C^2H, J_{AX}= 7.1 Hz), 4.36 (dd, 1H, Pro-C^2H, J_{AX}= 5.7 Hz, J_{AY}= 7.9 Hz), 5.27 (br, 1H, Ala-N($\underline{H}$)), 6.66 (b, 1H, N($\underline{H}$)CH_3), 7.41 (br, 1H, Gly-N($\underline{H}$)), 7.74 (b, 1H, N($\underline{H}$)CH_2); ^{13}C NMR ($CDCl_3$) δ 18.7 (Ala-C^3), 25.2 (Pro-C^4), 26.0 (N(H)CH_3), 28.2 (Boc $C(\underline{C}H_3)_3$), 31.1 (Pro-C^3), 34.0 (N(H)CH_2), 42.9 (Gly-C^2), 49.0 (CH_2SO_2), 50.0 (Pro-C^5), 61.6 (Pro-C^2), 79.7 (Boc $\underline{C}(CH_3)_3$), 155.3 (Boc C=O), 169.5, 172.5, 173.5 (C=O); exact mass m/z calculated: 464.2179, found: 464.2192 $(M + H)^+$.

N-(tert-Butyloxycarbonyl)-phenylalanyl-amino-ethane-sulfinyl-proline-methylamide (**16**)
Sulfinamide **11** (R_f 0.22; 135.1 mg, 0.37 mmol) was coevaporated in dioxane (3x 10 mL). To a solution of **11** in dioxane (2 mL) was added a 1.0 M solution of tetrabutylammoniumfluoride in THF (0.37 mL). This mixture was coevaporated in dioxane (3 x 5 mL). This procedure was repeated after addition of another portion of TBAF (0.19 mL). The mixed anhydride of Boc-Phe-OH (101.6 mg, 0.38 mmol) in dry THF (2 mL) was formed at -10°C by stirring for 5 min after addition of N-methyl morpholine (42 µl, 0.38 mmol) and *iso*-butylchloroformate (50 µl, 0.38 mmol). A solution of the deprotected sulfinamide in THF (2 mL) was added and stirring was continued for 7 h, during which the temperature gradually reached rt. The mixture was concentrated *in vacuo* to a small volume and immediately chromatographied (10 g, eluent: CH_2Cl_2/MeOH 95/5). A mixture of **16** and traces of TBAF was isolated, dissolved in *t*BuOH/H_2O 4/1 v/v (10 mL) and stirred with Dowex 50WX4 (Na^+ form, 100-200 mesh). After filtering the Dowex, the sulfinamide was

lyophilized and rechromatographed (10g, eluent: CH_2Cl_2/MeOH 95/5 v/v) to give **16** as an oil in 64% yield. R_f 0.24 (CH_2Cl_2/ MeOH 95/5 v/v); ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H, Boc $C(CH_3)_3$), 1.90 (m, 2H, Pro-C^4H_2), 2.06-2.21 (m, 2H, Pro-C^3H_2), 2.84, 2.94-3.04 (7 lines (H_a), m (H_b), 2H, CH_2SO, J_{AX}= 4.6 Hz, J_{AY}= 8.1 Hz, J_{AB}= 12.7 Hz), 2.85 (d, 3H, N(H)$C\underline{H}_3$, J = 4.8 Hz), 2.98, 3.65 (two dt, 2H, Pro-C^5H_2 , J_{AX}= 6.1 Hz, J_{BX} = 7.6 Hz, J_{AB} = 9.7 Hz), 2.98, 3.09 (two dd, 2H, Phe-C^3H_2, J_{AX}= 6.8 Hz, J_{BX} = 6.4 Hz, J_{AB}= 13.7 Hz), 3.39-3.48, 3.59-3.75 (two m, 2H, N(H)$C\underline{H}_2$), 4.17 (dd, 1H, Pro-C^2H, J_{AX}= 5.2 Hz, J_{AY} = 7.6 Hz), 4.38-4.42 (m, 1H, Phe-C^2H), 5.15 (d, 1H, N($\underline{H}$)-Phe, J = 8.4 Hz), 6.84 (q, 1H, N($\underline{H}$)CH_3, J = 4.8 Hz), 7.19-7.32 (m, 5H, Phe aromatic part), 7.58 (t, 1H, N($\underline{H}$)CH_2, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 25.0 (Pro-C^4), 26.4 (N(H)CH_3), 28.2 (Boc $C(\underline{C}H_3)_3$), 31.9 (Pro-C^3), 33.8 (Phe-C^3), 38.8 (N(H)CH_2), 40.8 (Pro-C^5), 54.0 (CH_2SO), 56.8 (Phe-C^2), 65.9 (Pro-C^2), 80.0 (Boc $\underline{C}(CH_3)_3$), 126.8, 128.5, 129.3, 136.6 (Phe-C arom), 155.2 (Boc C=O), 171.8, 172.8 (C=O); exact mass m/z calculated 467.2328, found: 467.2306 $(M + H)^+$.

N-(tert-Butyloxycarbonyl)amino-ethane-sulfonyl-leucyl-glycine-methylamide (**17**)

The sulfinamide was prepared from sulfinylchloride **7** (5.51 mmol) and H-Leu-Gly-N(H)Me[33] (1.90 g, 5.66 mmol) analogous to the preparation of **10**. However, DMF (7 mL) was used to dissolve the amine H-Leu-Gly-N(H)Me (5.66 mmol, 7 mL). Silica gel column chromatography (200 g eluent: EtOAc/MeOH 97/3 to 9/1 v/v) gave the sulfinamide (R_f 0.35 (CH_2Cl_2/ MeOH 9/1 v/v) which was oxidized to **17** analogous to the preparation of **12**. Silica gel column chromatography (25 g, eluent: EtOAc / MeOH 95/5 v/v) afforded **17** as a white solid in 61% overall yield. R_f 0.38 (EtOAc/ MeOH 95/5); ^1H NMR ($CDCl_3$) δ 0.95, 0.96 (two d, 6H, Leu-C^5H_3, Leu-$C^5'H_3$, J = 6.5 Hz), 1.44 (s, 9H, Boc $C(CH_3)_3$), 1.60 (t, 2H, Leu-C^3H_2, J = 7.2 Hz), 1.80 (7 lines, 1H, Leu-C^4H, J = 6.7 Hz), 2.79 (d, 3H, N(H)$C\underline{H}_3$, J = 4.6 Hz), 3.24 (12 lines, 2H, CH_2SO_2, J_{AX} = 5.8 Hz, J_{BX} = 6.1 Hz, J_{AB} = 14.4 Hz), 3.60 (br q, 2H, N(H)$C\underline{H}_2$), 3.96 (8 lines, 2H, Gly-C^2H_2, J_{AX} = 7.5 Hz, J_{BX} = 5.8 Hz, J_{AB} = 16.1 Hz), 3.94-4.01 (m covered, 1H, Leu-C^2H), 5.44 (t, 1H, N($\underline{H}$)CH_2, J = 6.1 Hz), 6.28 (d, 1H, N($\underline{H}$)-Leu, J = 7.7 Hz), 6.81 (q, 1H, N($\underline{H}$)CH_3, J = 4.6 Hz), 7.47 (t, 1H, N($\underline{H}$)-Gly, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 22.6 (Leu-C^5, Leu-C^5'), 24.2 (Leu-C^4), 25.9 (N(H)CH_3), 28.2 (Boc $C(\underline{C}H_3)_3$), 35.2 (N(H)CH_2), 41.6 (Leu-C^3), 42.7 (Gly-C^2), 52.2 (CH_2SO_2), 55.5 (Leu-C^2), 80.0 (Boc $\underline{C}(CH_3)_3$), 155.8 (Boc C=O), 169.8, 173.4 (C=O); exact mass m/z calculated: 409.2121, found: 409.2173.

N-(tert-Butyloxycarbonyl)amino-ethane-sulfonyl-phenylalanine-methylester (**18**)

The sulfinamide was prepared from sulfinylchloride **7** (10.0 mmol) and HCl.H-Phe-OMe (2.20 g, 10.2 mmol) analogous to the preparation of **10**. However, DMF (7 mL) and CH_2Cl_2 (10 ml) were used to dissolve HCl.H-Phe-OMe, neutralized with N-methylmorpholine (1.12 mL, 10.2 mmol). Silica gel column chromatography (150 g, eluent: EtOAc) gave the sulfinamide (R_f 0.38, 0.48 (EtOAc)) which was oxidized to sulfonamide **18** analogous to the preparation of **12**. Silica gel column chromatography (75 g, eluent: EtOAc/pet-ether 1/1 v/v) afforded **18** as an oil in 63% overall yield. R_f 0.63 (EtOAc/pet-ether 1/1 v/v); ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H, Boc $C(CH_3)_3$), 2.80, 2.91(12 lines (H_a), dt (H_b), 2H, CH_2SO_2, J_{AX} = 4.6 Hz, J_{AY} = 7.1 Hz, J_{BX} = 5.8 Hz, J_{AB} = 14.3 Hz), 2.99, 3.17 (two dd, 2H, Phe-C^3H_2, J_{AX} = 7.9 Hz, J_{BX}= 5.1 Hz, J_{AB}= 13.8 Hz), 3.28-3.45 (m, 2H, N(H)$C\underline{H}_2$), 3.77 (s, 3H, OCH_3), 4.38 (8 lines, 1H, Phe-C^2H, J_{AX} = 5.1 Hz, J_{AY} = 8.0 Hz, J_{AZ} = 9.1 Hz), 5.15 (br, 1H, N($\underline{H}$)CH_2), 5.40 (d, 1H, N($\underline{H}$)-Phe, J = 9.1 Hz), 7.18-7.37 (m, 5H, Phe-arom.); ^{13}C NMR ($CDCl_3$) δ 27.9 (Boc $C(\underline{C}H_3)_3$), 34.8 (N(H)CH_2), 38.6 (Phe-C^3), 52.8 (CH_2SO_2), 52.2 (OCH_3), 57.0 (Pro-C^2), 79.1 (Boc $\underline{C}(CH_3)_3$), 126.8, 128.2, 129.0, 135. 6 (Phe-C arom), 155.4 (Boc C=O), 171.8 (C=O); FABMS m/z 287.1 $(M - Boc)^+$.

N-(tert-Butyloxycarbonyl)amino-ethane-sulfonyl-phenylalanine (**19**)

The methylester **18** (1.13 g, 2.92 mmol) was saponified according to Corey *et al* [34] by dissolving it in 0.25 N LiOH in MeOH (58 mL, 14.5 mmol) and stirring overnight. The reaction mixture was neutralized with 2 N $KHSO_4$, concentrated *in vacuo* and partitioned between EtOAc and water. The pH of the aqueous layer was

adjusted to pH 2 with 2N $KHSO_4$. The water layer was extracted with EtOAc (2x 40 mL). The collected EtOAc layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford **19** as an oil in 99% yield. R_f 0.44 (CH_2Cl_2/ MeOH/ HOAc 90/10/1 v/v); ^1H NMR (MeOD) δ 1.42 (s, 9H, Boc $C(CH_3)_3$), 2.80-2.93 (m partly covered, 2H, CH_2SO_2), 2.91, 3.18 (two dd, 2H, Phe-C^3H_2, J_{AX} = 9.0 Hz, J_{BX} = 5.1 Hz, J_{AB} = 13.7 Hz), 3.25 (t, 2H, N(H)$C\underline{H}_2$, J = 6.7 Hz), 4.23 (dd, 1H, Phe-C^2H, J_{AX} = 5.1 Hz, J_{AY} = 9.0 Hz), 7.13-7.31 (m, 5H, Phe arom.); ^{13}C NMR ($CDCl_3$) δ 28.2 (Boc $C(\underline{C}H_3)_3$), 35.0 ($N(H)CH_2$), 38.8 (Phe-C^3), 52.9 (CH_2SO_2), 57.1 (Pro-C^2), 80.1 (Boc $\underline{C}(CH_3)_3$), 127.2, 128.6, 129.5, 135.8 (Phe C arom.), 156.1 (Boc C=O), 174.3 (C=O).

N-(tert-Butyloxycarbonyl)amino-ethane-sulfonyl-phenylalanyl-glycine-ethylester (**20**)
To a cooled (0°C) solution of **19** (79 mg, 0.481 mmol) in dry THF (6 mL) were added N-methyl morpholine (106 µL, 0.96 mmol), HCl.H-Gly-OEt (69 mg, 0.49 mmol), HOBT (67 mg, 0.49 mmol) and DCC (102 mg, 0.49 mmol). After 1 hr at 0°C, stirring was continued for 3 h at rt. DCU was filtered, the mixture diluted with EtOAc (100 mL) and washed with 5% citric acid (2 x 10 mL), saturated $NaHCO_3$ (2x 10 mL) and brine (1x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Silica gel column chromatography (25 g, eluent: EtOAc / pet-ether, 1/1 v/v) afforded **20** as a white solid in 86% yield, which was crystallized from EtOAc. Mp. 119-120.5°C. R_f 0.41 (EtOAc/ pet-ether 1/1 v/v); ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, $OCH_2C\underline{H}_3$, J = 7.2 Hz), 1.42 (s, 9H, Boc $C(CH_3)_3$), 2.67-2.75, 2.88 (m (H_a), dt (H_b), 2H, CH_2SO_2, J_{BX}= 6.2 Hz, J_{AB}= 14.5 Hz), 3.02, 3.23 (two dd, 2H, Phe-C^3H_2, J_{AX} = 8.4 Hz, J_{BX} = 5.8 Hz, J_{AB} = 13.9 Hz), 3.24-3.32 (m, 2H, N(H)$C\underline{H}_2$), 3.94, 4.09 (two dd, 2H, Gly-C^2H_2, J_{AX}= 5.3 Hz, J_{BX}= 5.6 Hz, J_{AB}= 18.1 Hz), 4.20 (dt, 1H, Phe-C^2H, J_{AX}= 5.8 Hz, J_{AY}= 8.4 Hz), 4.20 (q, 2H, OCH_2, J = 7.2 Hz), 5.06 (t, 1H, N($\underline{H}$)CH_2, J = 6.3 Hz), 5.39 (d, 1H, N(H)-Phe, J = 8.4 Hz), 6.77 (br, 1H, N(H)-Gly), 7.20-7.38 (m, 5H, Phe H arom.); ^{13}C NMR ($CDCl_3$) δ 14.1 ($OCH_2\underline{C}H_3$), 28.3 (Boc $C(\underline{C}H_3)_3$), 35.1 ($N(H)CH_2$), 39.0 (Phe-C^3), 41.4 (Gly-C^2), 52.9 (CH_2SO_2), 58.7 (Pro-C^2), 61.6 (OCH_2), 79.8 (Boc $\underline{C}(CH_3)_3$), 127.4, 128.9, 129.5, 136.3 (Phe-C arom), 155.6 (Boc C=O), 169.6, 171.1 (C=O); IR (KBr) 3380, 3340, 3240 (NH), 1730 (C=O ester), 1675 (amide I), 1515 (amide II), 1315, 1050 (SO_2) cm^{-1}; exact mass m/z calculated 458.1961, found: 458.1929; Anal. Calcd. for $C_{20}H_{31}N_3O_7S$: C 52.39; H 6.81; N 9.16. Found C 52.13; H 6.70; N 8.93.

N-(tert-Butyloxycarbonyl)amino-ethane-sulfonyl-prolinyl-isoleucine-methylamide (**22**)
Sulfinylchloride **7** (9.13 mmol) was coupled with H-Pro-Ile-N(H)Me[35] (2.26 g, 9.40 mmol) analogous the procedure described for the synthesis of **10**. Purification by silica gel column chromatography (150 g, eluent: CH_2Cl_2/MeOH 95/5 v/v) gave the diastereomers **21** as an oil which solidified upon standing. R_f 0.32 (CH_2Cl_2/MeOH 95/5 v/v). Sulfinamide **21** was oxidized to sulfonamide **22** according the procedure described for the synthesis of **12**. Silica gel column chromatography (40 g, eluent: EtOAc / MeOH 97/3 to 95/5 v/v) afforded **22** in 62% overall yield, which was crystallized form EtOAc. Mp. 126-127°C. R_f 0.32 (CH_2Cl_2/MeOH 95/5); ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, Ile-C^5H_3, J = 7.3 Hz), 0.92 (d, 3H, Ile-$C^{3'}H_3$, J = 6.8 Hz), 1.08, 1.26-1.51 (12 lines (H_a), m(H_b), 2H, Ile-C^4H_2, J_{AX}= 6.8 Hz, J_{AY} = 9.7 Hz, J_{AB}= 13.4 Hz), 1.45 (s, 9H, Boc $C(CH_3)_3$), 1.90-2.07 (m, 2H, Pro-C^4H_2), 2.09-2.22 (m, 1H, Ile-C^3H), 2.09-2.22, 2.29 (m (H_a), 11 lines (H_b), 2H, Pro-C^3H_2, J_{BX} = 6.6 Hz, J_{BY} = 9.4 Hz, J_{AB} = 13.1 Hz), 2.79 (d, 3H, N(H)$C\underline{H}_3$, J = 4.8 Hz), 3.21, 3.35-3.40 (8 lines (H_a), m (H_b), 2H, CH_2SO_2, J_{AX}= 4.7 Hz, J_{AY} = 6.6 Hz, J_{AB}= 14.3 Hz), 3.45, 3.54 (6 lines (H_a), 8 lines (H_b), 2H, Pro-C^5H_2, J_{AX}= 6.7 Hz, J_{AY} = 9.1 Hz, J_{BX}= 4.4 Hz, J_{BY}= 6.9 Hz, J_{AB} = 9.8 Hz), 3.57-3.68 (m, 2H, N(H)$C\underline{H}_2$), 4.31 (dd, 1H, Pro-C^2H, J_{AX}= 4.0 Hz, J_{AY} = 8.8 Hz), 4.36 (dd, 1H, Ile-C^2H, J_{AX}= 4.0 Hz, J_{AY} = 8.8 Hz), 5.72 (br, 1H, N($\underline{H}$)CH_2), 6.51 (q, 1H, N($\underline{H}$)CH_3, J = 4.8 Hz), 6.95 (d, N($\underline{H}$)Ile, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 10.8 (Ile-C^5), 15.2 (Ile-$C^{3'}$), 24.2 (Ile-C^4), 24.8 (Pro-C^4), 25.7 (N(H)CH_3), 27.9 (Boc $C(\underline{C}H_3)_3$), 31.0 (Pro-C^3), 35.1 ($N(H)CH_2$), 36.5 (Ile-C^3), 48.9, 49.1 (Pro-C^5, CH_2SO_2), 57.4 (Ile-C^2), 61.3 (Pro-C^2), 79.1 (Boc $\underline{C}(CH_3)_3$), 155.7 (Boc C=O), 171.4, 171.5 (C=O).

N-(tert-Butyloxycarbonyl)amino-2-(S)/(R)-phenyl-ethane-sulfinyl-prolinyl-isoleucine-methylamide (**23**)
Sulfonamide **22** (276 mg, 0.62 mmol) was coevaporated in dioxane (3 x 10 mL) and subsequently dissolved in dry THF (10 mL). The cooled solution (-60°C, acetone, liquid N_2) was stirred under Argon and LDA (1.5M in dioxane, 1.8 mL, 2.7 mmol) was injected. The temperature of the reaction mixture was allowed to rise to - 15°C over an hour, cooled again to - 60°C and benzylbromide (88 µl, 0.74 mmol) was added. After allowing the temperature to rise to -15°C over an hour the reaction mixture was poured into a 1M phosphatebuffer of pH 6 (40 mL) followed by addition of EtOAc (50 mL). The water layer was extracted with EtOAc (50 mL), the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by flash column chromatography (125 g, eluent: EtOAc). The diasteromers (ratio 1/3 by NMR) could not be separated. R_f 0.67 (EtOAc/MeOH 95/5); The chemical shifts of the diastereomer formed in the lowest yield are indicated an asterik. ^1H NMR ($CDCl_3$) δ 0.90 (t, 4H, Ile-C^5H_3, Ile-C^5H_3*, J = 7.3 Hz), 0.91 (d, 4H, Ile-$C^{3'}H_3$, Ile-$C^{3'}H_3$*, J = 6.8 Hz), 1.06-1.13, 1.45-1.52 (two m, 2.7H, Ile-C^4H_2, Ile-C^4H_2*), 1.41 (s, 12H, Boc $C(CH_3)_3$, Boc $C(CH_3)_3$*), 1.93-2.00 (m, 2.7H, Pro-C^4H_2, Pro-C^4H_2*), 2.01-2.13 (m, 3.3H, Pro-C^3H_2, Ile-C^3H, Ile-C^3H*), 2.01-2.13, 2.18-2.30 (m, 0.7H, Pro-C^3H_2*), 2.78 (d, 4H, N(H)$C\underline{H}_3$, N(H)$C\underline{H}_3$*, J = 4.8 Hz), 2.86-2.96, 3.31 (m (H_a), dd (H_b), 2H, Bn CH_2), 2.86-2.96, 3.31 (m (H_a), dd (H_b), 0.7H, Bn CH_2*, J_{BX} = 4.4 Hz, J_{AB} = 14.3 Hz), 3.36 (dd, 1H, Bn CH_b*, J_{BX}= 4.0 Hz, J_{AB} = 15.3 Hz), 3.45-3.60 (m, 5.7H, Pro-C^5H_2, Pro-C^5H_2*, N(H)$C\underline{H}_2$, N(H)$C\underline{H}_2$*, $CHSO_2$*), 3.70-3.73 (m, 1H, $CHSO_2$), 4.32-4.38 (m, 1.3H, Pro-C^2H, Ile-C^2H*), 4.35 (dd, 1H, Ile-C^2H, J_{AX} = 6.0 Hz, J_{AY} = 9.2 Hz), 4.46 (dd, 0.3H, Pro-C^2H*, J_{AX}= 3.8 Hz, J_{AY} = 8.7 Hz), 5.73 (br, 1.3H, N($\underline{H}$)CH_2, N($\underline{H}$)CH_2*) , 6.57 (q, 1H, N($\underline{H}$)CH_3, J = 4.8 Hz), 6.64 (br, 0.3H, N($\underline{H}$)CH_3*), 6.94 (d, 1H, N($\underline{H}$)Ile, J = 9.2 Hz), 6.97 (d, 0.3H, N($\underline{H}$)Ile*, J = 7.4 Hz), 7.21-7.37 (m, 6.7H, Bn arom., Bn arom.*); ^{13}C NMR ($CDCl_3$) δ 11.0 (Ile-C^5, Ile-C^5*), 15.4 (Ile-$C^{3'}$, Ile-$C^{3'}$*), 24.3 (Ile-C^4, Ile-C^4*), 25.0 (Pro-C^4), 25.1 (Pro-C^4*), 25.9 (N(H)CH_3, N(H)CH_3*), 28.1 (Boc $C(\underline{C}H_3)_3$, Boc $C(\underline{C}H_3)_3$*), 31.1 (Pro-C^3), 31.3 (Pro-C^3*), 32.7 (Bn $\underline{C}H_2$, Bn $\underline{C}H_2$*), 36.7 (Ile-C^3), 36.8 (Ile-C^3*), 39.3 (N(H)CH_2, N(H)CH_2*), 49.1 (Pro-C^5), 49.4 (Pro-C^5*), 57.6 (Ile-C^2*), 57.6 (Ile-C^2), 61.6 (Pro-C^2), 62.0 ($CHSO_2$), 62.3 (Pro-C^2*), 63.0 ($CHSO_2$*), 79.2 (Boc $\underline{C}(CH_3)_3$, Boc $\underline{C}(CH_3)_3$*), 126.9, 128.6, 128.9, 136.4, 136.5 (Bn arom.), 155.7 (Boc C=O, Boc C=O*), 171.5, 172.0 (C=O, C=O*); exact mass m/z calculated: 539.2903, found: 539.2948.

Amino-2-(S) and (R)-phenyl-ethane-sulfonyl-prolinyl-isoleucine-methylamide (**24**) *and* (**25**)
TFA (1 mL) was added to a cooled solution (0°C) of sulfonamide **22** (123.5 mg, 0.23 mmol) in dry CH_2Cl_2 (1 mL). After stirring for 40 min at rt, the mixture was concentrated *in vacuo* and coevaporated with dry ether (4 x 10 mL). The TFA salt was dissolved in a mixture of *t*-butanol / water (4/1 v/v) (5 mL) and Dowex 2X8 (OH^- form, 200-400 mesh) was added until the pH of the mixture reached 7 to 8. After removing the Dowex by filtration, the mixture was lyophilized. Flash silicagel column chromatography (75 g, eluent: CH_2Cl_2 /MeOH/Et_3N 95/5/0.1 v/v) afforded 68% yield of the diastereomer **24** with R_f 0.53 and 22 % yield of the diastereomer **25** with R_f 0.68.
R_f 0.53 (CH_2Cl_2/MeOH 9/1); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, Ile-C^5H_3, J = 7.4 Hz), 0.90 (d, 3H, Ile-$C^{3'}H_3$, J = 6.8 Hz), 1.07, 1.45 (13 lines (H_a), 15 lines (H_b), 2H, Ile-C^4H_2, J_{AX}= 7.2 Hz, J_{AY}= 9.4 Hz, J_{BX}= 3.4 Hz, J_{BY} = 7.5 Hz, J_{AB}= 13.3 Hz), 1.85-2.06 (m, 3H, Pro-C^4H_2, Ile-C^3H), 2.12-2.18 (m, 2H, Pro-C^3H_2), 2.78 (d, 3H, N(H)$C\underline{H}_3$, J = 4.8 Hz), 2.87, 3.34 (two dd, 2H, Bn CH_2, J_{AX}= 10.4 Hz, J_{BX}= 3.8 Hz, J_{AB} = 13.5 Hz), 3.05, 3.15 (br dd (H_a), br d (H_b), 1H, N(H)$C\underline{H}_2$, J_{AX}= 6.6 Hz, J_{AB}= 14.1 Hz), 3.35-3.42 (m, 1 H, $CHSO_2$), 3.49, 3.62 (8 lines (H_a), 8 lines (H_b), 2H, Pro-C^5H_2, J_{AX} = 4.2 Hz, J_{AY} = 7.5 Hz, J_{BX}= 7.3 Hz, J_{BY}= 8.2 Hz, J_{AB} = 9.6 Hz), 4.32 (dd, 1H, Ile-C^2H, J_{AX} = 6.8 Hz, J_{AY} = 9.4 Hz), 4.52 (t, 1H, Pro-C^2H, J = 6.0 Hz), 6.70 (q, 1H, N($\underline{H}$)CH_3, J = 4.8 Hz), 7.24-7.36 (m, 5H, Bn arom.), 8.04 (d, N($\underline{H}$)-Ile, J = 9.4 Hz); ^{13}C NMR ($CDCl_3$) δ 11.0 (Ile-C^5), 15.6 (Ile-$C^{3'}$), 24.5 (Ile-C^4), 24.9 (Pro-C^4), 26.0 (N(H)CH_3), 31.3 (Pro-C^3), 32.5 (Bn$\underline{C}H_2$), 36.2 (Ile-C^3), 39.8 (N(H)CH_2), 49.0 (Pro-C^5), 57.7 (Ile-C^2), 62.2 (Pro-C^2), 65.6 ($CHSO_2$), 126.9, 128.7, 128.9, 136.9 (Bn arom.), 171.5, 172.0 (C=O).

R_f 0.68 (CH_2Cl_2/MeOH 9/1); ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, Ile-C^5H_3, J = 7.4 Hz), 0.86 (d, 3H, Ile-$C^3'H_3$, J = 6.7 Hz), 1.07, 1.44 (14 lines (H_a), 16 lines (H_b), 2H, Ile-C^4H_2, J_{AX}= 7.4 Hz, J_{AY}= 9.3 Hz, J_{BX}= 3.4 Hz, J_{BY} = 7.4 Hz, J_{AB}= 13.2 Hz), 1.81-2.07 (m, 5H, NH_2, Pro-C^4H_2, Ile-C^3H), 2.09-2.18, 2.26 (m (H_a), 15 lines (H_b), 2H, Pro-C^3H_2, J_{BX} = 6.8 Hz, J_{BY} = 8.7 Hz, J_{BZ} = 10.3 Hz, J_{AB}= 12.7 Hz) 2.77 (d, 3H, N(H)$C\underline{H}_3$, J = 4.8 Hz), 2.81, 3.38-3.48 (dd (H_a), m (H_b), 2H, Bn CH_2, J_{AX}= 12.5, J_{AB}= 15.4 Hz), 3.11 (br 8 lines, 2H, N(H)$C\underline{H}_2$, J_{AX} = 2.5 Hz, J_{AY} = 7.4 Hz, J_{AB} = 14.4 Hz), 3.38-3.48 (m, 1H, $CHSO_2$), 3.54, 3.71 (8 lines (H_a), 8 lines (H_b), 2H, Pro-C^5H_2, J_{AX} = 4.0 Hz, J_{AY} = 7.4 Hz, J_{BX} = 6.9 Hz, J_{BY} = 8.6 Hz, J_{AB}= 9.6 Hz), 4.32 (dd, 1H, Ile-C^2H, J_{AX}= 7.6 Hz, J_{AY}= 9.5 Hz), 4.62 (dd, 1H, Pro-C^2H, J_{AX}= 3.3 Hz, J_{AY}= 8.7 Hz), 6.71 (q, 1H, N($\underline{H}$)CH_3, J = 4.8 Hz), 7.21-7.38 (m, 5H, Bn arom.), 8.55 (d, N($\underline{H}$)-Ile, J = 9.5 Hz); ^{13}C NMR ($CDCl_3$) δ 11.0 (Ile-C^5), 15.7 (Ile-C^3'), 24.6 (Ile-C^4), 25.2 (Pro-C^4), 26.0 (N(H)CH_3), 31.5 (Pro-C^3), 33.1 (Bn$\underline{C}H_2$), 36.4 (Ile-C^3), 40.4 (N(H)CH_2), 49.5 (Pro-C^5), 57.8 (Ile-C^2), 62.7 (Pro-C^2), 65.8 ($CHSO_2$), 126.9, 128.7, 128.9, 136.7 (Bn arom.), 171.7, 172.1 (C=O).

N-(Carbobenzyloxycarbonyl)-valyl-amino-(S) and (R)-benzyl-ethane-sulfonyl-prolinyl-isoleucyl-methylamide (**26**) *and* (**27**)

To a cooled (-20°C, ethanol, liquid N_2) solution of Cbz-Val-OH (37.6 mg, 0.150 mmol) in dry THF (1 mL) N-methyl morpholine (17 µl, 0.155 mmol) and *iso*-butylchloroformate (20 µl, 0.150 mmol) were added. To the mixed anhydride, formed by stirring for 5 min, amine **24** in THF (2 mL) was added. After completion of the reaction (ca. 2 h ,-10°C) as indicated by TLC, the mixture was diluted with EtOAc (30 mL), washed with 5% citric acid (2 x 5 mL), saturated $NaHCO_3$ (3 x 5 mL), brine (1 x 5 mL,) dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel column chromatography (10 g, eluent: CH_2Cl_2 to CH_2Cl_2/ MeOH 95/5 v/v) afforded **26** as an oil in 84 % yield, which solidified upon standing. R_f 0.52 (CH_2Cl_2/MeOH 9/1 v/v); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, Ile-C^5H_3, J = 7.3 Hz), 0.90 (d, 3H, Ile-$C^3'H_3$, J = 6.8 Hz), 0.90, 0.86 (two d, 6H, Val-C^4H_3, Val-$C^4'H_3$, J = 6.8 Hz), 1.12, 1.50 (11 lines (H_a), 16 lines (H_b), 2H, Ile-C^4H_2, J_{AX}= 6.8 Hz, J_{AY}= 8.7 Hz, J_{BX}= 3.6 Hz, J_{BY}= 7.5 Hz, J_{AB}= 14.1 Hz), 1.81-2.08 (m, 4H, Pro-C^4H_2, Ile-C^3H, Val-C^3H), 1.81-2.08, 2.43 (m (H_a), dq (H_b), 2H, Pro-C^3H_2, J_{BX}= 7.6 Hz, J_{AB}= 12.5 Hz), 2.78 (d, 3H, N(H)$C\underline{H}_3$, J = 4.8 Hz), 2.84, 3.35 (two dd, 2H, Bn CH_2, J_{AX}= 10.0 Hz, J_{BX}= 4.3 Hz, J_{AB}= 14.5 Hz), 3.25, 3.40-3.49 (dq (H_a), m (H_b), 2H, Pro-C^5H_2, J_{AX}= 6.4 Hz, J_{AB}= 9.3 Hz), 3.40-3.49, 3.68 (m (H_a), 8 lines (H_b), 2H, N(H)$C\underline{H}_2$, J_{BX}= 3.0 Hz, J $_{BY}$= 6.0 Hz, J_{AB}= 14.2 Hz), 3.53-3.61 (m, 1H, $CHSO_2$), 4.07 (dd, 1H, Val-C^2H, J_{AX}= 6.3 Hz, J_{AY}= 9.1 Hz), 4.26 (dd, 1H, Ile-C^2H, J_{AX}= 7.1 Hz, J_{AY}= 8.7 Hz), 4.43 (dd, 1H, Pro-C^2H, J_{AX}= 5.4 Hz, J_{AY}= 8.1 Hz), 5.06, 5.10 (two d, 2H, Cbz CH_2, J_{AB} = 12.4 Hz), 5.54 (d, 1H, N($\underline{H}$)Val, J = 9.1 Hz), 6.26 (q, 1H, N($\underline{H}$)CH_3, J = 4.8 Hz), 6.98 (d, N($\underline{H}$)-Ile, J = 7.1 Hz), 7.22-7.38 (m, 10 H, Bn arom.), 7.96 (t, N($\underline{H}$)CH_2, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 11.0 (Ile-C^5), 15.4 (Ile-C^3'), 17.8, 19.3 (Val-C^4, Val-C^4'), 24.6 (Ile-C^4), 25.4 (Pro-C^4), 26.1 (N(H)CH_3), 31.3 (Pro-C^3), 31.3 (Val-C^3), 32.5 (Bn$\underline{C}H_2$), 36.8 (Ile-C^3), 37.9 (N(H)CH_2), 48.9 (Pro-C^5), 58.1 (Val-C^2), 60.3 (Ile-C^2), 61.5 (Pro-C^2), 62.3 ($CHSO_2$), 66.6 (Cbz CH_2), 127.0, 127.7, 128.0, 128.4, 128.7, 128.8, 129.0, 136.3 (Cbz, Bn, arom.), 156.2 (Cbz C=O), 171.6, 171.7, 172.5 (C=O).

27 Was prepared from **25** analogous to the preparation of **26**.

R_f 0.52 (CH_2Cl_2/MeOH 9/1 v/v); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, Ile-C^5H_3, J = 7.2 Hz), 0.90 (d, 3H, Ile-$C^3'H_3$, J = 6.9 Hz), 0.91 (two d, 6H, Val-C^4H_3, Val-$C^4'H_3$, J = 6.8 Hz), 1.12, 1.50 (13 lines (H_a), 12 lines (H_b), 2H, Ile-C^4H_2, J_{AX}= 7.4 Hz, J_{AY}= 9.4 Hz, J_{BX}= 3.6 Hz, J_{BY}= 7.3 Hz, J_{AB}= 13.4 Hz), 1.86-2.18 (m, 5H, Pro-C^4H_2, Ile-C^3H, Val-C^3H), 1.86-2.18, 2.43 (m (H_a), dq (H_b), 2H, Pro-C^3H_2, J_{BX}= 7.5 Hz, J_{AB}= 12.4 Hz), 2.79 (d, 3H, N(H)$C\underline{H}_3$, J = 4.7 Hz), 2.83, 3.36-3.50 (dd (H_a), m (H_b), 2H, Bn CH_2, J_{AX}= 10.4 Hz, J_{AB}= 14.2 Hz), 3.36-3.50, 3.65 (m (H_a), dt (H_b), 2H, Pro-C^5H_2, J_{AX}= 7.0 Hz, J_{AB}= 9.5 Hz), 3.36-3.50 (m, 1H, $CHSO_2$), 3.36-3.50, 3.65-3.81 (two m, 2H, N(H)$C\underline{H}_2$), 3.97 (dd, 1H, Val-C^2H, J_{AX}= 6.4 Hz, J_{AY}= 9.1 Hz), 4.27 (dd, 1H, Ile-C^2H, J_{AX}= 6.5 Hz, J_{AY}= 8.9 Hz), 4.51 (dd, 1H, Pro-C^2H, J_{AX}= 5.2 Hz, J_{AY}= 8.2 Hz), 5.08 (s, 2H, Cbz CH_2), 5.48 (d, 1H, N($\underline{H}$)Val, J = 9.1 Hz), 6.19 (q, 1H, N($\underline{H}$)CH_3, J = 4.7 Hz), 6.95 (d, N($\underline{H}$)-Ile, J = 8.9 Hz), 7.22-7.38 (m, 10 H, Bn arom.), 7.66 (t,

N(H)CH_2, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 11.2 (Ile-C^5), 15.5 (Ile-$C^{3'}$), 17.9, 19.2 (Val-C^4, Val-C^4), 24.6 (Ile-C^4), 25.5 (Pro-C^4), 26.1 (N(H)CH_3), 31.7 (Pro-C^3), 31.1 (Val-C^3), 33.3 (BnCH_2), 37.1 (Ile-C^3), 37.8 (N(H)CH_2), 49.8 (Pro-C^5), 58.0 (Val-C^2), 60.4 (Ile-C^2), 62.6 (Pro-C^2), 63.9 ($CHSO_2$), 66.8 (Cbz CH_2), 127.1, 127.8, 128.1, 128.5, 128.8, 129.0, 136.3, 136.5 (Cbz, Bn, arom.), 156.2 (Cbz C=O),171.3, 171.6, 172.3 (C=O); exact mass m/z calculated: 672. 3471, found: 672.3416.

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15. Chlorine in the presence of water has been used to prepare cysteic acid sulfonylchloride starting from cystine derivatives or cystine containing peptides see ref 10. However, the acid labile Boc-group in **5** and **6** precludes the use of water as an oxygen donor, which is converted to HCl.
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23. The absolute configuration of the α-C atom has been determined by another synthetic route to α-substituted sulfonamides; Moree, W.J.; Van der Marel, G.A.; Liskamp, R.M.J., manuscript in preparation.
24. Disappointingly, a mixture of diastereomers of **26** and **27** does not show inhibition of isolated HIV-protease as was determined by professor D.H. Rich *et al.* (University of Wisconsin, Madison). We are presently investigating longer peptides containing the sulfonamide transition-state analogue to determine if this will improve the inhibitory activity.
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26. Computer assisted molecular modeling studies were carried out using MacroModel (Mohamadi, F.; Richards, N.G.J.; Guida, W.C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W.C. *J. Comp. Chem.* **1990**, *11*, 440-467. In short, a model of the sulfonamide **27** was constructed, energy minimized and fitted on MVT-101 of the HIV-protease MVT-101 complex[23]. Subsequently, the MVT-101 molecule was deleted, followed by a substructure energy minimization of the potential HIV-protease inhibitor **27** and its immediate surrounding i.e. the active site, employing Batchmin of MacroModel. This showed that the active site as well as the position of inhibitor is virtually unchanged as compared tot HIV-protease MVT-101 complex.
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30. Proline-methylamide was prepared from Cbz-Proline: formation of the methylamide by the mixed anhydride method followed by hydrogenolysis of the Cbz-group[36]. ^{1}H NMR ($CDCl_3$) δ 1.61-1.79 (m, 2H, Pro-C^4H_2), 1.91, 2.14 (8 lines (H_a), 11 lines (H_b), 2H, Pro-C^3H_2, J_{AX}= 5.6 Hz, J_{AY}= 6.4 Hz, J_{BX}= 7.4 Hz, J_{BY}= 9.3 Hz, J_{AB}= 12.9 Hz), 2.14 (b, 1H, Pro-N(H), 2.80 (d, 3H, N(H)CH_3, J = 5.0 Hz), 2.89, 3.01 (two dt, 2H, Pro-C^5H_2, J_{AX}= 6.3 Hz, J_{BX}= 6.8 Hz, J_{AB}= 10.1 Hz), 3.74 (dd, 1H, Pro-C^2H, J_{AX}= 5.6 Hz, J_{AY}= 9.3 Hz); ^{13}C NMR ($CDCl_3$) δ 24.5 (N(H)CH_3), 25.1 (Pro-C^4), 29.6 (Pro-C^3), 46.1 (Pro-C^5), 59.5 (Pro-C^2), 174.7 (C=O).
31. Paquet, A. *Can. J. Chem.* **1982**, *60*, 976-980.
32. Proline-Glycine-methylamide was prepared from Boc-Gly-OH in four steps: preparation of the methylamide, removal of the Boc-group followed by coupling with Cbz-Proline and removal of the Cbz-group by hydrogenolysis[36]. ^{1}H NMR (MeOD) δ 1.71-1.90 (m, 2H, Pro-C^4H_2), 1.71-1.90, 1.97-2.22 (two m, 2H, Pro-C^3H_2), 2.73 (s, 3H, N(H)CH_3), 3.00 (10 lines, 2H, Pro-C^5H_2, J_{AX}= 6.5 Hz, J_{AY}= 6.6 Hz, J_{AB}= 10.5 Hz), 3.79 (dd 1H, Pro-C^2H, J_{AX}= 5.6 Hz, J_{AY}= 8.8 Hz), 3.85 (s, 2H, Gly-C^2H_2); ^{13}C NMR ($CDCl_3$) δ 26.1 (N(H)CH_3), 26.1 (Pro-C^4), 30.7 (Pro-C^3), 43.0 (Gly-C^2), 47.2 (Pro-C^5), 60.4 (Pro-C^4), 172.0, 174.3 (C=O).
33. Leucine-Glycine-methylamide was prepared from Boc-Gly-OH and Cbz-Leu-OH as described for Pro-GlyN(H)Me[32]. ^{1}H NMR (D_2O) δ 0.86 (d, 3H, Leu-C^5H_3, J = 6.8 Hz), 0.89 (d, 3H, Leu-C^5'H_3, J = 6.8 Hz), 1.40, 1.48 (8 lines (H_a), dt lines (H_b), 2H, Leu-C^3H_2, J_{AX} = 7.1 Hz, J_{AY} = 7.8 Hz, J_{BX} = 6.8 Hz, J_{AB} = 13.7 Hz), 1.62 (9 lines, 1H, Leu-C^4H, J = 6.7 Hz), 2.71 (s, 3H, N(H)CH_3), 3.44 (dd, 1H, Leu-C^2H, J_{AX}= 6.8 Hz, J_{AY}= 7.8 Hz), 3.82, 3.89 (two d, 2H, Gly-C^2H_2, J_{AB}= 16.8 Hz); ^{13}C NMR (D_2O) δ 22.0, 22.9 (Leu-C^5, Leu-C^5'), 24.8 (N(H)CH_3), 26.4 (Leu-C^4), 42.9 (Leu-C^3), 44.1 (Gly-C^2), 53.6 (Leu-C^2), 172.2, 179.4 (C=O).
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35. Prolinyl-isoleucine-methylamide was prepared from Boc-Ile-OH and Cbz-Pro-OH as described for Pro-GlyN(H)Me[32]. ^{1}H NMR (MeOD) δ 0.90 (t, 3H, Ile-C^5H_3, J = 7.4 Hz), 0.90 (d, 3H, Ile-C^3'H_3, J = 6.8 Hz), 1.13, 1.50 (14 lines (H_a), 16 lines (H_b), 2H, Ile-C^4H_2, J_{AX}= 7.4 Hz, J_{AY}= 9.1 Hz, J_{BX}= 7.4 Hz, J_{BY}= 3.5 Hz, J_{AB}= 13.6 Hz), 1.67-1.87 (m, 3H, Pro-C^4H_2, Ile-C^3H), 1.67-1.87, 2.07-2.14 (two m, 2H, Pro-C^3H_2), 2.72 (d, 3H, N(H)CH_3, J = 4.8 Hz), 2.96 (10 lines, 2H, Pro-C^5H_2, J_{AX}= 5.2 Hz, J_{AB}= 9.0 Hz), 3.68 (dd, 1H, Pro-C^2H, J_{AX}= 5.2 Hz, J_{AY}= 9.0 Hz), 4.15 (d, 1H, Ile-C^2H, J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 11.1 (Ile-C^5), 15.6 (Ile-C^4), 24.6 (Ile-C^3'), 25.9 (N(H)Me), 26.1 (Pro-C^4), 30.8 (Pro-C^3), 36.7 (Ile-C^3), 47.1 (Pro-C^5), 57.2 (Ile-C^2), 60.4 (Pro-C^2), 171.9, 175.4 (C=O).
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