

Hydrogen-Bonding Donor/Acceptor Scales in β -Sulfonamidopeptides

Cesare Gennari,* Markus Gude, Donatella Potenza,* and Umberto Piarulli

Abstract: The conformational preferences of β -sulfonamidopeptides in chloroform solution were investigated by variable-temperature ^1H NMR spectroscopy and FT-IR spectroscopy. The following hydrogen-bonding acceptor scale was derived from the experiments: $\text{RCON} \approx t\text{BuOCON} > \text{COOMe} \geq \text{RS-O}_2\text{N}$. An intermolecular study gave

results complementary to those described above: the N–H stretch bands of *N*-methylacetamide and *N*-methyl metha-

Keywords: beta-sulfonamidopeptides • conformational preferences • hydrogen bonds • peptides • sulfonamides

nesulfonamide in chloroform were followed during titration with excess methanesulfonylpyrrolidine and *N,N*-dimethylacetamide. Shifts to lower frequencies were observed which are correlated with the hydrogen-bond strengths and show that the amide is a stronger hydrogen-bond acceptor than the sulfonamide.

Introduction

The attention of organic and medicinal chemists has recently been attracted by unnatural biopolymer scaffolds (carbamates, peptoids, ureas, sulfonamides, β -peptides, β -peptoids, etc.)^[1] because of the affinities and specificities of these compounds towards biological receptors and the simplicity with which large libraries can be synthesized combinatorially. The ability to efficiently assemble large synthetic oligomers also provides an opportunity to generate unnatural polymers with defined secondary and tertiary structures. Such structures should provide increased insight into the relationships between monomer structure and polymer conformation, and may provide new classes of folded polymers with novel properties.^[1m-q, 2] In particular, β -sulfonamidopeptides^[1h,i, 2b-d, 3] are peptide surrogates with increased polarity and hydrogen-bond donation capability. Furthermore, the sulfonamido bond should show enhanced metabolic stability and structural similarity to the tetrahedral transition state involved in the amide bond enzymatic hydrolysis, thus making sulfonamidopeptides interesting candidates in the development of both protease inhibitors and new drugs.^[3b]

β -Sulfonamidopeptides have a covalent framework that should be essential for the formation of well-defined folded structures by intramolecular hydrogen bonding; the repeating backbone structure contains both hydrogen-bond donors (N–H) and hydrogen-bond acceptors (C=O and S=O). β -Sulfonamidopeptides are interesting compounds with which to study the local folding propensities, and the competition between sulfonamide, ester, carbamate, and carboxamide as donor/acceptor groups in the formation of intramolecular hydrogen bonds.

Results and Discussion

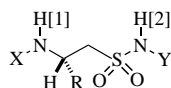
The conformational preferences of β -sulfonamidopeptides in chloroform solution were investigated by variable-temperature ^1H NMR spectroscopy and FT-IR spectroscopy. A (sulfon)amide N–H chemical shift is very sensitive to that proton's hydrogen-bonded status. Typically, it moves upfield as the temperature is raised, which is interpreted as heat-induced disruption of hydrogen bonding. Equilibration between hydrogen-bonded and non-hydrogen-bonded states is fast on the NMR time scale, which means that observed chemical shifts are weighted averages of the chemical shifts of the contributing states.^[2a, 4, 5] In contrast to NMR, hydrogen-bonding equilibria are slow on the IR time scale, giving rise to discrete N–H stretch bands for hydrogen-bonded and non-hydrogen-bonded states of a given secondary (sulfon)amide group.^[2a, 4, 5]

A sulfonamide N–H is more acidic (pK_a is approximately 11–12) and is therefore a stronger hydrogen-bond donor than a carbamate or an amide N–H.^[2a] The hydrogen-bonding

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acceptor scale is much more intriguing, and was derived from the following analysis.

The $\Delta\delta\text{NH}/\Delta T$ values for the sulfonamide protons of **1** (H[1] and H[2], Scheme 1) are similar and also rather small;^[6] for both hydrogens the SO_2N groups act as the hydrogen-bond acceptors. The more conservative conclusion is that both the



- 1** X = CH_3SO_2 ; Y = Bn; R = H
2 X = $t\text{BuOCO}$; Y = Bn; R = H
3 X = CH_3CO ; Y = CH_2COOMe ; R = Et
4 X = CH_3SO_2 ; Y = CH_2COOMe ; R = Et

Scheme 1. Structures of the β -sulfonamidepeptides **1–4**.

eight-membered-ring hydrogen bond involving H2 and the six-membered-ring hydrogen bond involving H1 are relatively unimportant (Table 1). The large temperature dependence of

Table 1. δNH (ppm) at 300 K and $\Delta\delta\text{NH}/\Delta T$ (ppbK⁻¹) values for 1 mM CDCl_3 solutions of β -sulfonamidepeptides **1–4** in the 240–300 K temperature range.^[a, b]

Compound	δH1	δH2	$\Delta\delta(\text{NH}[1])/\Delta T$	$\Delta\delta(\text{NH}[2])/\Delta T$
1	5.00	4.66	–3.8	–5.3
2	5.07	4.81	–1.7	–9.1
3	5.66	5.92	–1.1	–11.0
4	5.29	5.32	–10.8	–2.3

[a] The resonances of N-H protons are resolved at all temperatures studied. These resonances were assigned either by their splitting patterns or by homonuclear decoupling experiments. [b] For all compounds described, NMR experiments show that the N-H proton chemical shifts are independent of concentration at 240–300 K, at or below 5×10^{-3} M, and therefore all experiments were conducted using 1×10^{-3} M solutions.

H2 in compound **2** ($\Delta\delta\text{NH}[2]/\Delta T = -9.1$ ppb/K)^[6] shows that the carbamate is a better hydrogen-bond acceptor (eight-membered-ring hydrogen bond involving H2) than the sulfonamide. In addition, the large temperature dependence of H2 in compound **3** ($\Delta\delta\text{NH}[2]/\Delta T = -11.0$ ppb/K)^[6] shows

Abstract in Italian: *Le preferenze conformazionali dei β -solfonammidopeptidi in soluzione di cloroformio sono state studiate mediante spettroscopia ¹H-NMR a temperatura variabile e spettroscopia FT-IR. Dagli esperimenti è stata ricavata la seguente scala di efficacia come accettore di legame ad idrogeno: $\text{RCON} \approx t\text{BuOCON} > \text{COOMe} \geq \text{RSO}_2\text{N}$. Uno studio intermolecolare ha fornito risultati che sono complementari a quelli descritti qui sopra: le bande di stiramento degli N–H della N-metilacetammide e della N-metil metansolfonammide in cloroformio sono state seguite durante titolazione con eccesso di metansolfonilpirrolidina e N,N-dimetilacetammide. Furono osservati spostamenti a frequenze più basse, che sono correlati alla forza dei legami ad idrogeno, e che mostrano che l'ammide è un accettore di legame ad idrogeno più forte della solfonammide.*

that the amide is a much better hydrogen-bond acceptor (eight-membered-ring hydrogen bond involving H2) than the sulfonamide (six-membered-ring hydrogen bond involving H1) or the methyl ester (nine-membered-ring hydrogen bond involving H1). The IR spectrum of **3** in chloroform (Figure 1 and Table 2) confirms that even at room temperature the

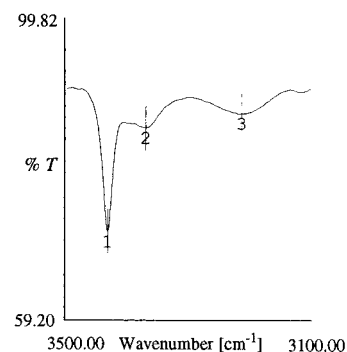


Figure 1. N–H stretch bands (cm^{-1}) for compound **3**. Band 1: 3433 (CONH); band 2: 3370 (SO_2NH); band 3: 3213 (SO_2NH).

Table 2. Stretch band positions (cm^{-1}) for compounds **3–11** in 1 mM CHCl_3 solutions at 298 K.

Compound	$\bar{\nu}\text{N-H}$ (CONH)	$\bar{\nu}\text{N-H}$ (SO_2NH)	$\bar{\nu}\text{C=O}$ (CO-NH)	$\bar{\nu}\text{C=O}$ (O-CO-NH)	$\bar{\nu}\text{C=O}$ (CO-OMe)
3	3433	3370, 3213	1664	–	1752
4	–	3379, 3295	–	–	1748
5	3446	3363, 3252	–	1700	–
6	3428	3370, 3238	–	1693	–
7	3437	3370, 3219	–	1696	1741
8	3436	3381, 3266	1664	–	1742
9	3431	3376, 3315, 3270, 3250	1671	–	–
10	–	3379, 3352, 3307	–	–	1747
11	3428	3381, 3309, 3285	1672	–	–

sulfonamide proton (H2) is largely hydrogen-bonded to the amide carbonyl group.^[7] The large temperature dependence of H1 in compound **4** ($\Delta\delta\text{NH}[1]/\Delta T = -10.8$ ppb/K)^[6] shows that even the methyl ester (nine-membered-ring hydrogen bond involving H1) is a better hydrogen-bond acceptor than the sulfonamide (eight-membered-ring hydrogen bond involving H2) (Figure 2). The IR spectrum of **4** in chloroform at room temperature (Figure 3 and Table 2) shows a hydrogen-bonded $\text{SO}_2\text{N-H}$, a nonhydrogen-bonded $\text{SO}_2\text{N-H}$, and a weakly hydrogen-bonded ester carbonyl group CO-OMe .^[7]

It is worth noting that the above preferences are not consistent with entropic effects (a more negative entropy value is expected for a large-ring formation than for a small-ring formation).

Interpretation of the data for larger molecules **5–11** (Scheme 2) is more difficult since there seem to be many hydrogen-bonding possibilities in these cases. However, some common features are still evident and worthy of comment. Given the relative unimportance of the six- and eight-membered-ring hydrogen bonds involving a sulfonamide as

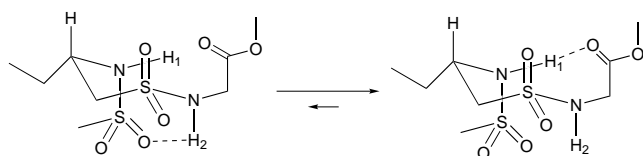


Figure 2. Compound **4**: the methyl ester (nine-membered-ring H-bond involving H[1]) is a better hydrogen-bond acceptor than the sulfonamide (eight-membered-ring H-bond involving H[2]).

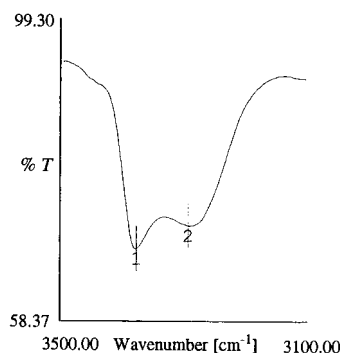
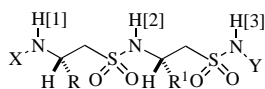


Figure 3. N–H stretch bands (cm^{-1}) for compound **4**. Band 1: 3379 (SO_2NH); band 2: 3295 (SO_2NH).

acceptor, β -sulfonamidopeptides **5–8** (Scheme 2) show a strong preference for a twelve-membered-ring hydrogen



- 5** X = *t*BuOCO; Y = Bn; R = R¹ = H
6 X = *t*BuOCO; Y = Bn; R = R¹ = Bn
7 X = *t*BuOCO; Y = CH₂COOMe; R = R¹ = Bn
8 X = CH₃CO; Y = CH₂COOMe; R = Me; R¹ = Et
9 X = CH₃CO; Y = CH₂CONH[4]Bn; R = Me; R¹ = Et
10 X = CH₃SO₂; Y = CH₂COOMe; R = Me; R¹ = Et
11 X = CH₃SO₂; Y = CH₂CONH[4]Bn; R = Me; R¹ = Et

Scheme 2. The structures of β -sulfonamidopeptides **5–11**.

bond ($\text{H3}-\text{O}=\text{C}$, $\Delta\delta\text{NH}[3]/\Delta T = -8.6 - -19.0$ ppb/K) involving the carbamate or the carboxamide as hydrogen-bond acceptors (Table 3). Sulfonamide protons H2 show a reduced temperature dependence in compounds **5–8**

Table 3. δNH (ppm) at 300 K and $\Delta\delta\text{NH}/\Delta T$ (ppb K^{-1}) values for 1 mM CDCl_3 solutions of β -sulfonamidopeptides **5–11** in the 240–300 K temperature range.^[a, b]

Compound	δH1	δH2	δH3	δH4	$\Delta\delta(\text{NH}[1])/\Delta T$	$\Delta\delta(\text{NH}[2])/\Delta T$	$\Delta\delta(\text{NH}[3])/\Delta T$	$\Delta\delta(\text{NH}[4])/\Delta T$
5	5.04	5.44	5.85	–	–0.7	–4.5	–19.0	–
6	4.62	5.06	5.52	–	0.0	–1.6	–8.6	–
7	4.60	5.92	6.92	–	0.0	–6.0	–13.6	–
8	5.57	5.84	6.63	–	–1.0	–7.3	–14.3	–
9	5.75	6.21	6.52	6.45	–4.4	–10.6	–9.7	–4.1
10	4.91	5.48	5.52	–	–2.3	–9.3	–8.5	–
11	5.13	6.16	5.84	6.36	–6.6	–9.1	–7.0	–8.5

[a] The resonances of N–H protons are resolved at all temperatures studied. These resonances were assigned either by their splitting patterns or by homonuclear decoupling experiments. [b] For all compounds described, NMR experiments show that the N–H proton chemical shifts are independent of concentration at 240–300 K, at or below 5×10^{-3} M, and therefore all experiments were conducted using 1×10^{-3} M solutions.

($\Delta\delta\text{NH}[2]/\Delta T = -1.6 - -7.3$ ppb/K) owing to a less important competing eight-membered-ring hydrogen bond involving the carbamate or the carboxamide as hydrogen-bond acceptors (and/or nine-membered-ring hydrogen bond involving the methyl ester as acceptor in the case of **7** and **8**).

The IR spectra of **5** and **6** in chloroform at room temperature (Table 2) confirm the presence of a sulfonamide proton largely hydrogen-bonded to the carbamate carbonyl group.^[7] The IR spectra of **7** and **8** (Table 2) show a hydrogen-bonded $\text{SO}_2\text{N}-\text{H}$, a non-hydrogen-bonded $\text{SO}_2\text{N}-\text{H}$, a non-hydrogen-bonded $\text{CON}-\text{H}$, a hydrogen-bonded carbamate carbonyl group (**7**), a hydrogen-bonded amide carbonyl group (**8**), and a weakly hydrogen-bonded ester carbonyl group (Figure 4).^[7]

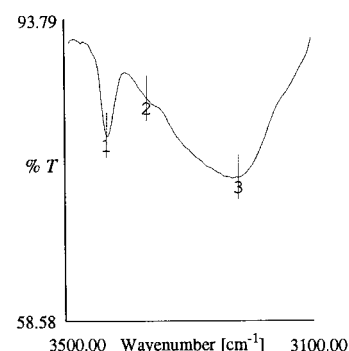


Figure 4. N–H stretch bands (cm^{-1}) for compound **7**. Band 1: 3437 (CONH); band 2: 3370 (SO_2NH); band 3: 3219 (SO_2NH).

The strong temperature dependence of protons H2 and H3 of β -sulfonamidopeptide **9** indicates the preference for a twelve-membered-ring hydrogen bond ($\text{H3}-\text{O}=\text{C}-\text{N}$, $\Delta\delta\text{NH}[3]/\Delta T = -9.7$ ppb/K), a eight- and a nine-membered-ring hydrogen bond ($\text{H2}-\text{O}=\text{C}-\text{N}$, $\Delta\delta\text{NH}[2]/\Delta T = -10.6$ ppb/K), all of which involve carboxamides as hydrogen-bond acceptors.^[6] The IR spectrum of compound **9** (four different N–H groups, two carboxamides and two sulfonamides) shows five different N–H peaks (Table 2 and Figure 5). A tentative attribution is as follows: a non-hydrogen-bonded $\text{CON}-\text{H}$ (3431 cm^{-1}), a non-hydrogen-bonded $\text{SO}_2\text{N}-\text{H}$ (3376 cm^{-1}), a weakly hydrogen-bonded $\text{SO}_2\text{N}-\text{H}$ (3315 cm^{-1}), two differently hydrogen-bonded $\text{SO}_2\text{N}-\text{H}$ ($3270, 3250 \text{ cm}^{-1}$), and a hydrogen-bonded amide carbonyl group (Figure 5).^[7] The 3315 cm^{-1} $\text{SO}_2\text{N}-\text{H}$ is probably

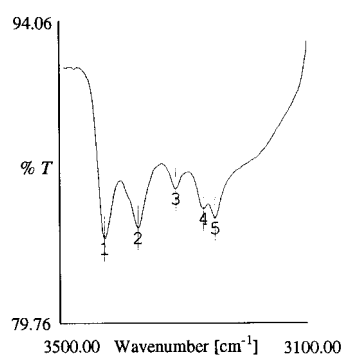


Figure 5. N–H stretch bands (cm^{-1}) for compound **9**. Band 1: 3431 (CONH); band 2: 3376 (SO_2NH); band 3: 3315 (SO_2NH); band 4: 3270 (SO_2NH); band 5: 3250 (SO_2NH).

hydrogen-bonded to a sulfonamide (see the $\text{SO}_2\text{N}-\text{H}$ values in Table 4 and the discussion).

Table 4. N–H stretch bands (cm^{-1}) for *N*-methylacetamide (**12**) and *N*-methylmethanesulfonamide (**13**) in 10 mM CHCl_3 solutions at 298 K: titration experiments.

Compound	$\bar{\nu}\text{N}-\text{H}$	$\bar{\nu}\text{N}-\text{H}$ with excess methanesulfonylpyrrolidine	$\bar{\nu}\text{N}-\text{H}$ with excess <i>N,N</i> -dimethylacetamide
12	3466	3466, 3410	3466, 3342
13	3397	3397, 3307	3397, 3255

Substitution of the terminal acetamide of **8** with a methanesulfonamide gives compound **10**, where both H2 [$\Delta\delta\text{NH}[2]/\Delta T = -9.3$ ppb/K, sulfonamide (eight-membered ring) and ester (nine-membered ring) as acceptors] and H3 [$\Delta\delta\text{NH}[3]/\Delta T = -8.5$ ppb/K, sulfonamide (eight- and twelve-membered rings) as acceptor] exhibit a rather strong temperature dependence. The IR spectrum of **10** in chloroform at room temperature (Table 2) shows three different $\text{SO}_2\text{N}-\text{H}$ peaks [weakly bonded ($3307, 3352\text{ cm}^{-1}$) and non-hydrogen bonded (3379 cm^{-1})], and a weakly hydrogen-bonded ester carbonyl group.^[7] The 3307 and 3352 cm^{-1} $\text{SO}_2\text{N}-\text{H}$ are probably hydrogen-bonded to a sulfonamide or an ester (see the $\text{SO}_2\text{N}-\text{H}$ values in Table 4 and the relevant discussion).

Substitution of the terminal acetamido group of **9** with a methanesulfonamido group yields compound **11**, in which H2 experiences a larger temperature dependence ($\Delta\delta\text{NH}[2]/\Delta T = -9.1$ ppb/K, nine-membered-ring hydrogen-bond involving the carboxamide as acceptor) than H3 ($\Delta\delta\text{NH}[3]/\Delta T = -7.0$ ppb/K, eight- and twelve-membered-ring hydrogen bonds involving the sulfonamide as acceptor).

The $\Delta\delta\text{NH}/\Delta T$ data discussed above may sometimes be difficult to interpret, and should be used cautiously to infer hydrogen-bond strength. In fact it is true that the $\Delta\delta\text{NH}/\Delta T$ values are related to the effect of temperature on the equilibrium between hydrogen-bonded and non-hydrogen-bonded states, which is in turn related to the enthalpy difference between these two states and between alternative folding patterns (at least in weakly polar solvents like chloroform). However, a number of other factors can also

influence the $\Delta\delta\text{NH}/\Delta T$ values. For example, in a flexible molecule small $\Delta\delta\text{NH}/\Delta T$ values can be associated with amide protons that are either completely free of hydrogen bonding (as in our case) or completely locked in an intramolecular hydrogen bond over the temperature range examined. These two extreme possibilities were distinguished by analysis of the IR spectrum, and by observation of the chemical shift value in comparison with the appropriate reference molecules.^[6] Furthermore, the magnitude of $\Delta\delta\text{NH}/\Delta T$ depends on the total difference in chemical shift between fully hydrogen-bonded and completely non-hydrogen-bonded states. Thus, for example, for the same N–H donor, the fully hydrogen-bonded state is not as far downfield when the acceptor is a sulfonamide (or an ester) as when it is an amide, which means that alternative folding patterns involving such systems cannot be directly compared with $\Delta\delta\text{NH}/\Delta T$ values, particularly when numerical differences are small. For these reasons we confirmed our conclusions with an intermolecular study which gave results that are complementary to those described above with the $\Delta\delta\text{NH}/\Delta T$ data. The N–H stretch bands of *N*-methylacetamide (**12**) and *N*-methyl methanesulfonamide (**13**) in chloroform were followed during titration with excess methanesulfonylpyrrolidine and *N,N*-dimethylacetamide (Table 4). Shifts to lower frequencies were observed which are correlated with the hydrogen-bond strengths and show that the amide is a stronger hydrogen-bond acceptor than the sulfonamide.

In summary, the following hydrogen-bonding acceptor scale was derived from the above experiments: $\text{RCON} \approx t\text{BuOCON} > \text{COOMe} \geq \text{RSO}_2\text{N}$. While the position in the scale of the first three functional groups is expected (an ester carbonyl group is known to be a weaker hydrogen-bond acceptor than an amide carbonyl group),^[4a, d] the very poor acceptor ability of the sulfonamide group is more noticeable, and confirms the recent theoretical studies by Houk et al.^[8a] Analysis of a number of X-ray structures also reveals that the N–H–O=S=O hydrogen bond is much weaker than the N–H–O=C hydrogen bond.^[8b, c] Even structures which are intramolecularly hydrogen-bonded in the crystal with the oxygen of RSO_2N as acceptor group^[2a, d] will use different acceptors (for example carbonyls, if available) in chloroform solution.

Experimental Section

General: NMR spectra were recorded on Bruker AC-200, AC-300, AC-500, Varian XL-200 and XL-400 instruments. IR spectra were recorded with a Jasco-FT 300E spectrometer. All products were purified by flash chromatography with a 230–400 mesh silica gel (Merck). TLC analyses were performed with 0.25 mm 60F₂₅₄ silica plates (Merck). All solvents were distilled over drying agents under a nitrogen atmosphere: tetrahydrofuran (THF), Et_2O , benzene, toluene over sodium; dichloromethane (DCM), diisopropylethylamine (DIPEA), triethylamine (TEA), *N,N*-dimethylformamide (DMF) over CaH_2 ; MeOH over BaO. All reactions were carried out under nitrogen. Organic extracts were dried over Na_2SO_4 .

Synthetic procedures: The synthesis of compounds **1**, **2**, **5** (taurine derivatives) followed the guidelines reported in ref. [11]; the synthesis of compounds **6**, **7** followed the guidelines reported in ref. [3e]. The synthesis of compounds **3**, **4**, **8**–**11** was performed on solid-phase support by means of a Fmoc-protection adapted strategy: Fmoc-Gly-OH was attached as a

linker to the polymeric support (Wang–Merrifield resin, P-CH₂OH),^[9] by means of the coupling procedure of Pátek et al.^[10] The loading was determined by Fmoc deprotection (see details below) and quantitative picric acid monitoring,^[11] and was found to be about 0.72 mmol g⁻¹. The resin Fmoc-Gly-OCH₂-P was subjected to an iterative deprotection-(coupling-deprotection)_n scheme (*n* = 1 for compounds **3**, **4**; *n* = 2 for compounds **8**–**11**), followed by final capping and cleavage, as outlined below.

1) Fmoc deprotection: The resin (containing Fmoc-protected amino groups, 0.144 mmol) was treated with 20% piperidine in DMF [1 × 3 mL (3 min), 1 × 3 mL (17 min)], followed by washings with DMF (4 × 3 mL) and DCM (4 × 3 mL).

2) Preparation of (S)-Fmoc-NHCH(Me)CH₂SO₂Cl and (S)-Fmoc-NHCH(Et)CH₂SO₂Cl: The substituted taurines^[3c, 12] [⁺NH₃CH(Me)-CH₂SO₃⁻ and ⁺NH₃CH(Et)CH₂SO₃⁻] (0.50 mmol) and *n*Bu₄NOH · 30H₂O (400 mg, 0.50 mmol) were dissolved in water (0.40 mL). The mixture was stirred for 5 min, cooled to 0 °C, and treated with NaHCO₃ (42 mg, 0.5 mmol) and Fmoc-*O*-succinimide (Fmoc-ONSu) (185 mg, 0.55 mmol). Stirring was continued overnight (0 °C to room temperature), then the reaction mixture was diluted with water (20 mL), and the aqueous phase extracted with DCM (3 × 10 mL). The extracts were combined, washed with brine (2 × 5 mL), and dried. The solvent was removed in vacuo, and the crude product was dissolved in DCM (3.6 mL) and treated with DMF (3.4 mg, 0.046 mmol). The reaction mixture was cooled to 0 °C and a solution of triphosgene (83 mg, 0.31 mmol) in DCM (1 mL) was added dropwise. Stirring was continued for 1 h at 0 °C and 30 min at room temperature. The mixture was purified by flash chromatography (10:1 EtOAc/DCM) to give the desired sulfonyl chloride as a white powder.

(S)-Fmoc-NHCH(Me)CH₂SO₂Cl (95 mg, 50%). ¹H NMR (200 MHz, CDCl₃): δ = 1.50 (d, *J* = 6.5 Hz, 3H, CH₃CH), 3.75–4.60 (m, 3H, CH₂SO₂ + CHN), 4.25 (t, *J* = 6 Hz, 1H, ArCHCH₂O), 4.48 (m, 2H, ArCHCH₂O), 7.30–7.49 (m, 4H, aromatic H), 7.60 (d, *J* = 7.8 Hz, 2H, aromatic H), 7.78 (d, *J* = 8.3 Hz, 2H, aromatic H); ¹³C NMR (CDCl₃): δ = 19.5 (CH₃), 44.4 (CH₂SO₂), 47.1 (CHN), 66.8 (CHCH₂O), 69.3 (CHCH₂O), 119.9 (C=), 124.8 (C=), 127.0 (C=), 127.7 (C=); C₁₈H₁₈ClNO₄S (379.86): calcd C 56.92, H 4.78, N 3.69; found C 56.81, H 4.90, N 3.60.

(S)-Fmoc-NHCH(Et)CH₂SO₂Cl (116 mg, 59%). ¹H NMR (200 MHz, CDCl₃): δ = 1.0 (t, *J* = 7 Hz, 3H, CH₃CH₂), 1.7 (q, *J* = 7 Hz, 2H, CH₂CH₃), 3.9–4.2 (m, 3H, CHN + CH₂SO₂), 4.23 (t, *J* = 6 Hz, 1H, ArCHCH₂O), 4.45 (m, 2H, ArCHCH₂O), 5.06 (m, 1H, NH), 7.38–7.50 (m, 4H, aromatic H), 7.62 (d, *J* = 8 Hz, 2H, aromatic H), 7.79 (d, *J* = 7 Hz, 2H, aromatic H); C₁₉H₂₀ClNO₄S (393.89): calcd C 57.94, H 5.12, N 3.56; found C 57.76, H 5.07, N 3.49.

3) Coupling reactions: A suspension of the resin (containing free amino groups, 0.144 mmol) in dichloromethane (3 mL) was treated with the Fmoc-protected sulfonyl chloride (S)-Fmoc-NHCH(R)CH₂SO₂Cl (0.288 mmol), 1-methoxy-2-methyl-1-trimethylsilyloxypropene^[3c] (100 mg, 0.57 mmol) and 4-dimethylaminopyridine (DMAP) (7 mg, 0.057 mmol). The mixture was shaken for 18 h (wrist-shaker), the resin filtered and washed with DMF (4 × 3 mL) and DCM (4 × 3 mL). The progress of the coupling reactions (absence of free amino groups) was followed with the trinitrobenzenesulfonic acid test.^[13]

4) Capping with mesyl chloride (for compounds **4, **10**, **11**):** A suspension of the resin (0.144 mmol) in DCM (3 mL) was treated with MsCl (0.035 mL, 0.43 mmol), 1-methoxy-2-methyl-1-trimethylsilyloxypropene^[3c] (0.20 mL, 0.86 mmol) and DMAP (8 mg, 0.058 mmol). The mixture was shaken (wrist-shaker) for 18 h, and the resin was filtered and washed with DMF (4 × 3 mL) and DCM (4 × 3 mL). The progress of the capping reactions (absence of free amino groups) was followed with the trinitrobenzenesulfonic acid test.^[13]

5) Capping with acetylimidazole (for compounds **3, **8**, **9**):** A suspension of the resin (0.144 mmol) in DCM (3 mL) was treated with acetylimidazole (160 mg, 1.44 mmol). The mixture was shaken (wrist-shaker) for 18 h, and the resin was filtered and washed with DMF (4 × 3 mL) and DCM (4 × 3 mL). The progress of the capping reactions (absence of free amino groups) was followed with the trinitrobenzenesulfonic acid test.^[13]

6) Cleavage from the resin to give a methyl ester (for compounds **3, **4**, **8**, **10**):** A suspension of the resin (0.144 mmol) in MeOH/NET₃ (9:1 v/v, 3 mL) was shaken (wrist-shaker) for 60 h. The resin was filtered and washed with MeOH/NET₃ (9:1 v/v, 2 × 3 mL), and the combined organic phases were

removed in vacuo. The crude product was purified by flash chromatography (DCM/MeOH 10:1) to give the desired methyl esters in 85–95% yields.

7) Cleavage from the resin to give an acid, and subsequent transformation into a benzylamide (for compounds **9, **11**):** A suspension of the resin (0.144 mmol) in TFA/water (95:5, 4 mL) was shaken (wrist-shaker) for 2.5 h. The resin was filtered and washed with TFA (2 × 3 mL) and DCM (2 × 3 mL), and the combined organic phases were removed in vacuo. The crude product (a white solid) was dissolved in DMF (1.9 mL), cooled to 0 °C, and treated with benzylamine (0.016 mL, 0.144 mmol), 2,4,6-trimethylpyridine (0.039 mL, 0.288 mmol), and *O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (54 mg, 0.144 mL). Stirring was continued for 1 h at 0 °C and for 17 h at room temperature, then the mixture was diluted with water (10 mL), and the aqueous phase extracted with DCM (3 × 3 mL). The organic phase was washed with an aqueous solution of citric acid (2 × 3 mL, pH = 2.5) and dried. The solvent was removed in vacuo, and the crude product was purified by flash chromatography (DCM/MeOH 10:1) to give the desired benzylamides in 65–75% yields.

CH₃SO₂NHCH₂CH₂SO₂NHBn (1): A solution of BocNHCH₂CH₂SO₂NHBn (**2**) (1.335 g, 4.25 mmol; for the preparation of **2**, see details below) in dichloromethane (21.25 mL) was treated with trifluoroacetic acid (21.25 mL) at 0 °C. The mixture was stirred for 20 min, then evaporated under vacuum to give the crude trifluoroacetate salt (1.394 g, 100%). A solution of mesyl chloride (0.487 g, 4.25 mmol) in dichloromethane (10 mL) was cooled to 0 °C and treated with a solution of the above trifluoroacetate salt (1.394 g, 4.25 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.518 mL, 10.19 mmol) in dichloromethane (2.5 mL) by dropwise addition (20 min). The mixture was stirred overnight at room temperature, then diluted with dichloromethane (20 mL), washed with aqueous NH₄Cl sat. soln. (10 mL) and brine (10 mL), and then dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/EtOAc 1:2) to give the desired taurine derivative **1** (0.633 g, 51%), m.p. = 129–130 °C; ¹H NMR (200 MHz, [D₆]acetone): δ = 2.98 (s, 3H, CH₃SO₂), 3.30 (t, *J* = 6.7 Hz, 2H, CH₂SO₂), 3.53 (brt, *J* = 6.7 Hz, 2H, CH₂NHSO₂), 4.33 (d, 2H, NHCH₂Ph), 6.20 (brt, 1H, NH), 6.70 (brt, 1H, NH), 7.25–7.45 (m, 5H, aromatic H); C₁₀H₁₆N₂O₄S₂ (292.4): calcd C 41.08, H 5.52, N 9.58; found C 40.75, H 5.68, N 9.39.

BocNHCH₂CH₂SO₂NHBn (2):^[14] A solution of taurine (4.0 g, 32 mmol) in aqueous NaOH (2.0 M, 16.0 mL, 32 mmol) was treated by dropwise addition with a solution of (Boc)₂O (6.98 g, 32 mmol) in THF (10.0 mL) at room temperature, while being stirred (CO₂ evolved). The mixture was stirred at room temperature for 15 h and the disappearance of (Boc)₂O was monitored by TLC; the resulting mixture was extracted once with ethyl ether (20 mL). The aqueous phase was diluted with water (170 mL), treated with LiOH · H₂O (1.342 g, 32 mmol) and *n*Bu₄NHSO₄ (10.86 g, 32 mmol), and stirred at room temperature for 30 min. The resulting mixture was then extracted with dichloromethane (3 × 120 mL), the organic phase dried and evaporated at reduced pressure, and the product pumped (0.1 mmHg). *N*-Boc-taurine *n*Bu₄N⁺ salt (13.57 g, 91%) was used in the next reactions without further purification. ¹H NMR (200 MHz, CDCl₃): δ = 1.0 [t, *J* = 7.7 Hz, 12H, (CH₃CH₂CH₂CH₂)₄N⁺], 1.40 [s, 9H, (CH₃)₃C], 1.4–1.6 [m, 8H, (CH₃CH₂CH₂CH₂)₄N⁺], 1.6–1.8 [m, 8H, (CH₃CH₂CH₂CH₂)₄N⁺], 2.9 (m, 2H), 3.3 [t, *J* = 7.7 Hz, 8H, (CH₃CH₂CH₂CH₂)₄N⁺], 3.57 (m, 2H), 6.19 (br, 1H, NH).

A solution of *N*-Boc-taurine *n*Bu₄N⁺ salt (3.728 g, 8.0 mmol) in dichloromethane (28 mL) was treated with DMF (0.064 mL, 0.82 mmol) and then with triphosgene (0.952 g, 3.20 mmol) at room temperature, with stirring. The reaction mixture was stirred at room temperature for a further 30 min, then cooled to 0 °C and treated with a solution of DBU (2.5 mL, 16.80 mmol) and benzylamine (1.3 mL, 12.0 mmol) in dichloromethane (4.0 mL) by dropwise addition (20 min). The mixture was stirred overnight at room temperature, then diluted with dichloromethane (28 mL), washed with aqueous NH₄Cl sat. soln. (50 mL) and brine (50 mL), and then dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/EtOAc 1:1) to give the desired *N*-benzyl sulfonamide (**2**) (2.047 g, 81.5%). ¹H NMR (200 MHz, CDCl₃): δ = 1.40 [s, 9H, (CH₃)₃C], 3.1 (t, *J* = 6.6 Hz, 2H, CH₂SO₂), 3.5 (q, *J* = 6.6 Hz, 2H, CH₂NHCO), 4.3 (d, *J* = 6.6 Hz, 2H, NHCH₂Ph), 4.81 (brt, 1H, NH), 5.07 (t, *J* = 6.6 Hz, 1H, NH), 7.3–7.4 (m, 5H, aromatic H); C₁₄H₂₂N₂O₄S (314.4): calcd C 53.48, H 7.05, N 8.91; found C 53.29, H 7.12, N 8.81.

(S)-CH₃CONHCH(Et)CH₂SO₂NHCH₂COOMe (3): This compound was synthesized according to the solid-phase protocol described above in the paragraph synthetic procedures. IR (CHCl₃): $\tilde{\nu}$ = 1664 cm⁻¹ (CO-NH), 1752 (CO-OMe), 3213 (SO₂-NH), 3370 (SO₂-NH), 3433 (CO-NH); ¹H NMR (200 MHz, CDCl₃): δ = 0.98 (t, *J* = 7 Hz, 3H, CH₃), 1.56–1.76 (m, 2H, CH₂), 2.0 (s, 3H, CH₃CO), 3.12 (dd, *J* = 10, 14 Hz, 1H, CH_aH_bSO₂), 3.29 (dd, *J* = 3.5, 14 Hz, 1H, CH_aH_bSO₂), 3.75 (s, 3H, CH₃O), 3.92 (dd, *J* = 5, 19 Hz, 1H, CH_aH_bCO), 4.08 (dd, *J* = 7, 19 Hz, 1H, CH_aH_bCO), 4.59 (m, 1H, CHN), 5.66 (d, *J* = 9 Hz, 1H, NHCH), 5.92 (dd, *J* = 5, 7 Hz, 1H, NHCH₂); ¹³C NMR (CDCl₃): δ = 10.1 (CH₃CH₂), 23.2 (CH₃CO), 27.5 (CH₃CH₂), 44.1 (CH₂SO₂), 47.2 (CHN), 52.4 (CH₃O), 56.7 (CH₂CO); C₉H₁₈N₂O₅S (266.32): calcd C 40.59, H 6.81, N 10.52; found C 40.48, H 6.90, N 10.41.

(S)-CH₃SO₂NHCH(Et)CH₂SO₂NHCH₂COOMe (4): This compound was synthesized according to the solid-phase protocol described above in the paragraph synthetic procedures. IR (CHCl₃): $\tilde{\nu}$ = 1748 cm⁻¹ (CO-OMe), 3295 (SO₂-NH), 3379 (SO₂-NH); ¹H NMR (200 MHz, CDCl₃): δ = 1.0 (t, *J* = 7 Hz, 3H, CH₃), 1.64–1.84 (m, 2H, CH₂), 3.05 (s, 3H, CH₃SO₂), 3.3 (m, 2H, CH₂SO₂), 3.8 (s, 3H, CH₃O), 3.9–4.1 (m, 3H, CH₂CO + CHN), 5.29 (m, 1H, NH), 5.32 (m, 1H, NH); ¹³C NMR (CDCl₃): δ = 9.7 (CH₃CH₂), 29.5 (CH₃CH₂), 41.8 (CH₃SO₂), 44.1 (CH₂SO₂), 51.6 (CHN), 52.7 (CH₃O), 56.7 (CH₂CO); C₈H₁₈N₂O₅S₂ (302.37): calcd C 31.79, H 6.00, N 9.26; found C 31.60, H 6.09, N 9.21.

BocNHCH₂CH₂SO₂NHCH₂CH₂SO₂NHBn (5):^[11] A solution of BocNHCH₂CH₂SO₂NHBn (**2**) (1.335 g, 4.25 mmol) in dichloromethane (21.25 mL) was treated with trifluoroacetic acid (21.25 mL) at 0 °C. The mixture was stirred for 20 min, then evaporated under vacuum to give the crude trifluoroacetate salt (1.394 g, 100%). A solution of *N*-Boc-tyrosine *n*Bu₄N⁺ salt (1.32 g, 2.83 mmol) (see details above in the preparation of **2**) in dichloromethane (10 mL) was treated with DMF (0.025 mL, 0.32 mmol) and then with triphosgene (0.336 g, 1.132 mmol) at room temperature, with stirring. The reaction mixture was stirred at room temperature for 30 min, then cooled to 0 °C and treated with a solution of the above trifluoroacetate salt (1.394 g, 4.25 mmol) and DBU (1.518 mL, 10.19 mmol) in dichloromethane (2.5 mL) by dropwise addition (20 min). The mixture was stirred overnight at room temperature, then diluted with dichloromethane (20 mL), washed with aqueous NH₄Cl sat. soln. (10 mL) and brine (10 mL), and then dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/EtOAc 1:2) to give the desired tyrosine dimer **5** (0.751 g, 63%), m.p. = 132–133 °C; IR (CHCl₃): $\tilde{\nu}$ = 1700 cm⁻¹ (O-CO-NH), 3252 (SO₂-NH), 3363 (SO₂-NH), 3446 (CO-NH); ¹H NMR (200 MHz, CDCl₃): δ = 1.40 [s, 9H, C(CH₃)₃], 3.1 (brt, 2H), 3.2 (t, *J* = 6.3 Hz, 2H), 3.4–3.6 (m, 4H), 4.33 (d, *J* = 5.8 Hz, 2H, NHCH₂Ph), 5.04 (br, 1H, NH), 5.44 (br, 1H, NH), 5.85 (br, 1H, NH), 7.3–7.4 (m, 5H, aromatic H); ¹³C NMR (CDCl₃): δ = 28.960 (3 CH₃), 36.375, 38.717, 47.799, 52.001, 53.034, 81.257, 128.780 (2 CH=), 128.916 (1 CH=), 129.650 (2 CH=), 137.347 (C=), 156.876 (C=O); MS (FAB⁺): *m/z* = 91, 106, 125, 215, 232, 276, 322, 366, 422 (*M*+1); C₁₆H₂₇N₃O₆S₂ (421.5): calcd C 45.59, H 6.46, N 9.97; found C 45.40, H 6.60, N 9.85.

(S,S)-BocNHCH(Bn)CH₂SO₂NHCH(Bn)CH₂SO₂NHBn (6):

a) (*S*)-BocNHCH(Bn)CH₂SO₂Cl: (*S*)-2-benzyltaurine^[8e, 12] [⁺NH₃CH(Bn)CH₂SO₃] (100 mg, 0.46 mmol) and *n*Bu₄NOH · 30H₂O (409 mg, 0.51 mmol) were dissolved in water (0.64 mL). The mixture was stirred for 5 min and a solution of Boc₂O (101 mg, 0.46 mmol) in THF (0.92 mL) was added. Stirring was continued overnight, then the reaction mixture was diluted with water (10 mL) and the aqueous phase extracted with DCM (3 × 5 mL). The extracts were combined, washed with brine (5 mL) and dried. The solvent was removed in vacuo and the crude product was dissolved in DCM (3.6 mL) and treated with DMF (3.4 mg, 0.046 mmol). The reaction mixture was cooled to 0 °C and a solution of triphosgene (83 mg, 0.31 mmol) in DCM (1 mL) was added dropwise. Stirring was continued for 1 h at 0 °C and 30 min at room temperature. The mixture was purified by flash chromatography (10:1 EtOAc/DCM) to give the desired sulfonyl chloride as a white powder (107 mg, 70%). ¹H NMR (200 MHz, CDCl₃): δ = 1.43 [s, 9H, C(CH₃)₃], 3.09 (m, 2H, CH₂Ph), 3.90 (dd, *J* = 5, 15 Hz, 1H, CH_aH_bSO₂), 4.00–4.45 (m, 2H, CH_aH_bSO₂ + CHN), 4.90 (m, 1H, NH), 7.18–7.42 (m, 5H, aromatic H); C₁₄H₂₀ClNO₄S (333.83): calcd C 50.37, H 6.04, N 4.20; found C 50.28, H 6.16, N 4.17.

b) (*S*)-BocNHCH(Bn)CH₂SO₂NHBn: (*S*)-BocNHCH(Bn)CH₂SO₂Cl (50 mg, 0.15 mmol) was dissolved in DCM (2 mL), and a solution of 1-methoxy-2-methyl-1-trimethylsilyloxypropene^[3c] (35 mg, 0.20 mmol) and

benzylamine (11 mg, 0.10 mmol) in DCM (0.5 mL) was added. Stirring was continued for 2 h and the organic phase was washed with an aqueous solution of citric acid (1 mL, pH = 4) and dried. The solvent was removed in vacuo and the crude product was purified by flash chromatography (10:1 EtOAc/DCM) to give the desired product as a white/pale-yellow solid (39 mg, 96%). ¹H NMR (200 MHz, CDCl₃): δ = 1.38 [s, 9H, C(CH₃)₃], 2.81 (m, 2H, CH₂Ph), 2.96 (dd, *J* = 4, 15 Hz, 1H, CH_aH_bSO₂), 3.10 (dd, *J* = 8, 15 Hz, 1H, CH_aH_bSO₂), 4.20 (m, 1H, CHN), 4.23 (d, *J* = 6 Hz, 2H, NCH₂Ph), 4.90 (d, *J* = 9 Hz, 1H, NHCO), 5.60 (m, 1H, NHCH₂), 7.1–7.4 (m, 4H, aromatic H); ¹³C NMR (CDCl₃): δ = 28.2 [C(CH₃)₃], 40.1 (CH₂Ph), 47.2 (CH₂SO₂), 48.1 (CHN), 56.0 (NCH₂), 81.0 [C(CH₃)₃], 127.0, 128.3, 128.9, 130.0, 136.8, 137.0 (6 C =), 155.9 (NCO); C₂₁H₂₈N₂O₄S (404.53): calcd C 62.35, H 6.98, N 6.92; found C 62.15, H 7.07, N 6.88.

c) (*S*)-BocNHCH(Bn)CH₂SO₂NHBn (21.4 mg, 0.053 mmol) was dissolved in a HCl solution (3M) in MeOH (1 mL) and stirred until TLC analysis indicated the absence of starting material (ca. 20 h). The solvent was removed in vacuo and the crude product was dissolved in DCM (1.5 mL). (*S*)-BocNHCH(Bn)CH₂SO₂Cl (27 mg, 0.081 mmol), DMAP (1 mg, 0.008 mmol), and 1-methoxy-2-methyl-1-trimethylsilyloxypropene^[3c] (36 mg, 0.21 mmol) were added and stirring was continued for 6 h. The organic phase was washed with an aqueous solution of citric acid (1 mL, pH = 4) and dried. The solvent was removed in vacuo and the crude product was purified by flash chromatography (10:1 EtOAc/DCM) to give the desired product **6** as a white solid (22 mg, 69%). IR (CHCl₃): $\tilde{\nu}$ = 1693 cm⁻¹ (O-CO-NH), 3238 (SO₂-NH), 3370 (SO₂-NH), 3428 (CO-NH); ¹H NMR (200 MHz, CDCl₃): δ = 1.37 [s, 9H, C(CH₃)₃], 2.5–3.1 (m, 8H, CH₂SO₂ + CH₂-Ph), 2.8–4.1 (m, 3H, NHCH + NCH₂Ph), 4.36 (brs, 1H, NHCH), 4.62 (brs, 1H, NHCO), 5.06 (brs, 1H, SO₂NHCH), 5.52 (brs, 1H, SO₂NHBn), 7.19 (m, 15H, aromatic H); ¹³C NMR (CDCl₃): δ = 28.3 [C(CH₃)₃], 40.0 + 42.0 (CH₂Ph), 47.0 + 48.0 (CH₂SO₂), 51.9 (2 CHN), 56.0 (NCH₂Ph), 81.1 [C(CH₃)₃], 126.8, 127.3, 128.0, 128.2, 128.6, 128.9, 129.5, 129.7, 136.3, 136.7, 136.8 (11 C=), 155.7 (NCO); MS (FAB⁺): *m/z* = 694 [*M*⁺+glycerol+H], 623 [*M*⁺+Na - H], 501 [*M*⁺ - C₅H₈O₂]; C₃₀H₃₅N₃O₆S₂ (601.79): calcd C 59.88, H 6.53, N 6.98; found C 59.70, H 6.61, N 6.91.

(S,S)-BocNHCH(Bn)CH₂SO₂NHCH(Bn)CH₂SO₂NHCH₂CO₂Me (7)

a) (*S*)-BocNHCH(Bn)CH₂SO₂NHCH₂CO₂Me: A solution of (*S*)-BocNHCH(Bn)CH₂SO₂Cl (200 mg, 0.60 mmol) in DCM (6 mL) was treated with glycine methyl ester hydrochloride (75 mg, 0.60 mmol) and DMAP (147 mg, 1.20 mmol). Stirring was continued for 3 h and the solvent was removed in vacuo. The crude product was purified by flash chromatography (10:1 EtOAc/DCM) to give the desired product as a clear syrup (160 mg, 69%). ¹H NMR (200 MHz, CDCl₃): δ = 1.38 [s, 9H, C(CH₃)₃], 2.92 (m, 2H, CH₂Ph), 3.18 (m, 2H, CH₂SO₂), 3.73 (s, 3H, OCH₃), 3.92 (t, *J* = 6 Hz, 2H, CH₂CO), 4.59 (m, 1H, CHN), 4.92 (m, 1H, NH), 5.80 (m, 1H, NH); ¹³C NMR (CDCl₃): δ = 28.2 [C(CH₃)₃], 40.6 (CH₂Ph), 44.2 (CH₂SO₂), 48.2 (CHN), 52.4 (OCH₃), 56.3 (CH₂CO), 80.2 [C(CH₃)₃], 126.9, 128.6, 129.4, 136.4 (4 C=), 155.9 (NCO), 170.5 (COOCH₃); C₁₇H₂₆N₂O₆S (386.47): calcd C 52.83, H 6.78, N 7.25; found C 52.72, H 6.83, N 7.16.

b) (*S*)-BocNHCH(Bn)CH₂SO₂NHCH₂CO₂Me (151 mg, 0.39 mmol) was dissolved in a HCl solution (3M) in MeOH (2 mL) and stirred until TLC analysis indicated the absence of starting material (ca. 20 h). The solvent was removed in vacuo and the crude product was dissolved in DCM (5.8 mL). (*S*)-BocNHCH(Bn)CH₂SO₂Cl (193 mg, 0.58 mmol) and DMAP (95 mg, 0.78 mmol) were added and stirring was continued for 3 h. The organic phase was washed with water (2 mL) and dried. The solvent was removed in vacuo and the crude product was purified by flash chromatography (10:1 EtOAc/DCM) to give the desired product **7** as a white solid (99 mg, 43%). IR (CHCl₃): $\tilde{\nu}$ = 1696 cm⁻¹ (O-CO-NH), 1741 (CO-OMe), 3219 (SO₂-NH), 3370 (SO₂-NH), 3437 (CO-NH); ¹H NMR (200 MHz, CDCl₃): δ = 1.34 [s, 9H, C(CH₃)₃], 2.8–3.1 (m, 4H, CH₂-Ph), 3.2 (m, 4H, CH₂SO₂), 3.70 (s, 3H, CH₃O), 3.86 (dd, *J* = 4, 19 Hz, 1H, CH_aH_bCO), 4.07 (dd, *J* = 9, 19 Hz, 1H, CH_aH_bCO), 4.18 (m, 1H, CHNH), 4.44 (m, 1H, CHNH), 4.60 (d, *J* = 10 Hz, 1H, NHCO), 5.92 (d, *J* = 9 Hz, 1H, CHNH/SO₂), 6.92 (brs, 1H, CH₂NH/SO₂), 7.25 (m, 10H, aromatic H); ¹³C NMR (CDCl₃): δ = 28.2 [C(CH₃)₃], 40.3 + 42.8 (CH₂Ph), 44.2 (CH₂SO₂), 47.4 (CHN), 52.2 (CH₃O), 52.7 (CHN), 55.2 (CH₂SO₂), 56.1 (CH₂CO), 80.3 [C(CH₃)₃], 126.9, 127.1, 128.6, 128.8, 129.6, 129.7, 136.2 (7 C=); MS (FAB⁺): *m/z* = 606 [*M*⁺+Na], 584 [*M*⁺+H], 484 [*M*⁺ - C₃H₇O₂]; C₂₈H₃₇N₃O₆S₂ (583.73): calcd C 53.50, H 6.39, N 7.20; found C 53.48, H 6.60, N 7.13.

(S,S)-CH₃CONHCH(Me)CH₂SO₂NHCH(Et)CH₂SO₂NHCH₂COOMe

(8): This compound was synthesized according to the solid-phase protocol described above in the paragraph synthetic procedures. IR (CHCl₃): $\tilde{\nu}$ = 1664 cm⁻¹ (CO-NH), 1742 (CO-OMe), 3266 (SO₂-NH), 3381 (SO₂-NH), 3436 (CO-NH); ¹H NMR (200 MHz, CHCl₃): δ = 0.95 (t, *J* = 7 Hz, 3H, CH₃CH₂), 1.32 (d, *J* = 7 Hz, 3H, CH₃CH), 1.75 (q, *J* = 7 Hz, 2H, CH₃CH₂), 2.0 (s, 3H, CH₃CO), 3.1–3.3 (m, 4H, CH₂SO₂), 3.75 (CH₃O), 3.95 (m, 1H, CHEt), 3.95 (dd, *J* = 7, 19 Hz, 1H, CH₂H₅CO), 4.10 (dd, *J* = 5, 19 Hz, 1H, CH₂H₅CO), 4.55 (q, *J* = 7 Hz, 1H, CHMe), 5.57 (d, *J* = 8 Hz, 1H, CONHCHMe), 5.84 (d, *J* = 8 Hz, 1H, SO₂NHCHEt), 6.63 (t, *J* = 5, 7 Hz, 1H, SO₂NHCH₂); ¹³C NMR (CDCl₃): δ = 9.2 (CH₃CH₂), 20.3 (CH₃CH), 23.2 (CH₃CO), 29.3 (CH₃CH₂), 41.8 (CHN), 44.1 (CH₂SO₂), 51.7 (CHN), 52.6 (CH₃O), 55.8 (CH₂SO₂), 58.0 (CH₂CO); C₁₂H₂₅N₃O₇S₂ (387.48): calcd C 37.20, H 6.50, N 10.84; found C 37.13, H 6.55, N 10.77.

(S,S)-CH₃CONHCH(Me)CH₂SO₂NHCH(Et)CH₂SO₂NHCH₂CONHBn

(9): This compound was synthesized according to the solid-phase protocol described above in the paragraph synthetic procedures. IR (CHCl₃): $\tilde{\nu}$ = 1671 cm⁻¹ (CO-NH), 3250 (SO₂-NH), 3270 (SO₂-NH), 3315 (SO₂-NH), 3376 (SO₂-NH), 3431 (CO-NH); ¹H NMR (200 MHz, CDCl₃): δ = 0.95 (t, *J* = 7 Hz, 3H, CH₃CH₂), 1.35 (d, *J* = 7 Hz, 3H, CH₃CH), 1.75 (q, *J* = 7 Hz, 2H, CH₂CH₃), 2.0 (s, 3H, CH₃CO), 3.1–3.4 (m, 4H, CH₂SO₂), 3.8–4.1 (m, 3H, CH₂CO + CHEt), 4.45 (d, *J* = 6 Hz, 2H, CH₂Ph), 4.5 (m, 1H, CHMe), 5.75 (d, *J* = 8 Hz, 1H, CONHCHMe), 6.21 (d, *J* = 8 Hz, 1H, SO₂NHCHEt), 6.45 (t, *J* = 6 Hz, 1H, CONHBn), 6.52 (t, *J* = 6 Hz, 1H, SO₂NHCH₂); ¹³C NMR (CDCl₃): δ = 12.5 (CH₃CH₂), 23.1 (CH₃CO), 25.2 (CH₃CH), 32.5 (CH₃CH₂), 42.6 + 45.5 (CHN), 46.5 + 48.8 (CH₂SO₂), 60.2 (CH₂Ph), 61.5 (CH₃CO), 130.7, 130.9, 131.2, 131.7, 131.9, 132.5 (6 C=); C₁₈H₃₀N₄O₆S₂ (462.59): calcd C 46.74, H 6.54, N 12.11; found C 46.65, H 6.59, N 12.07.

(S,S)-CH₃SO₂NHCH(Me)CH₂SO₂NHCH(Et)CH₂SO₂NHCH₂COOMe

(10): This compound was synthesized according to the solid-phase protocol described above in the paragraph synthetic procedures. IR (CHCl₃): $\tilde{\nu}$ = 1747 cm⁻¹ (CO-OMe), 3307 (SO₂-NH), 3352 (SO₂-NH), 3379 (SO₂-NH); ¹H NMR (200 MHz, CDCl₃): δ = 1.0 (t, *J* = 7 Hz, 3H, CH₃CH₂), 1.45 (d, *J* = 7 Hz, 3H, CH₃CH), 1.75 (m, 2H, CH₂CH₃), 3.05 (s, 3H, CH₃SO₂), 3.3–3.5 (m, 4H, CH₂SO₂), 3.8 (s, 3H, CH₃O), 3.9–4.1 (m, 4H, CHMe + CH₂CO + CHEt), 4.91 (d, *J* = 8 Hz, 1H, SO₂NHCHMe), 5.48 (d, *J* = 8 Hz, 1H, SO₂NHCHEt), 5.52 (t, *J* = 6 Hz, 1H, SO₂NHCH₂); ¹³C NMR (CDCl₃): δ = 9.5 (CH₃CH₂), 21.8 (CH₃CH), 29.6 (CH₃CH₂), 41.6 (CH₂SO₂), 44.0 + 56.2 (CH₂SO₂), 46.4 + 51.8 (CHN), 52.8 (CH₃O), 59.6 (CH₂CO); C₁₁H₂₅N₃O₈S₃ (423.53): calcd C 31.20, H 5.95, N 9.92; found C 31.10, H 6.10, N 9.90.

(S,S)-CH₃SO₂NHCH(Me)CH₂SO₂NHCH(Et)CH₂SO₂NHCH₂CONHBn

(11): This compound was synthesized according to the solid-phase protocol described above in the paragraph synthetic procedures. IR (CHCl₃): $\tilde{\nu}$ = 1672 cm⁻¹ (CO-NH), 3285 (SO₂-NH), 3309 (SO₂-NH), 3381 (SO₂-NH), 3428 (CO-NH); ¹H NMR (200 MHz, CDCl₃): δ = 1.0 (t, *J* = 7 Hz, 3H, CH₃CH₂), 1.45 (d, *J* = 7 Hz, 3H, CH₃CH), 1.7 (m, 2H, CH₂CH₃), 3.0 (s, 3H, CH₃SO₂), 3.15–3.45 (m, 4H, CH₂SO₂), 3.90 (m, 3H, CH₂CO + CHEt), 4.05 (m, 1H, CHMe), 4.45 (d, *J* = 6 Hz, 2H, CH₂Ph), 5.13 (d, *J* = 8 Hz, 1H, SO₂NHCHMe), 5.84 (t, *J* = 6 Hz, 1H, SO₂NHCH₂CO), 6.16 (d, *J* = 8 Hz, 1H, SO₂NHCHEt), 6.36 (t, *J* = 6 Hz, 1H, CONHBn); ¹³C NMR (CDCl₃): δ = 9.7 (CH₃CH₂), 21.8 (CH₃CH), 29.0 (CH₃CH₂), 41.6 (CH₂SO₂), 43.6 + 45.6 (CH₂SO₂), 46.4 + 51.6 (CHN), 55.3 (CH₂CO), 59.5 (CH₂Ph), 127.6 + 128.7 (C=); C₁₇H₃₀N₄O₇S₃ (498.64): calcd C 40.95, H 6.06, N 11.24; found C 40.79, H 6.11, N 11.18.

Acknowledgments: We thank the Commission of the European Union for financial support and for a postdoctoral research fellowship to M. Gude (Fixed Contribution Contract for Training through Research ERB FMB ICT 950328), N.A.T.O. (Collaborative Research Grant to C. Gennari and H. P. Nestler, Cold Spring Harbor Laboratory, N.Y., USA) and also Merck (Merck's Academic Development Program Award to C. Gennari, 1996–97) for financial support. We thank Professor S. H. Gellman (University of Wisconsin) for helpful discussions and comments.

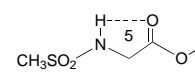
Received: March 9, 1998 [F1041]

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- [6] Reference molecules (1 mM CDCl₃ solutions): CH₃SO₂NHCH₂Ph, δ NH = 4.50 at 300 K, $\Delta\delta$ NH/ Δ T = -2.8 ppb/K;^[2a] *t*BuO-CO-NHCH₂Ph, δ NH = 4.85 at 300 K, $\Delta\delta$ NH/ Δ T = -1.0 ppb/K;^[2a] CH₃SO₂NHCH₂COOCH₃, δ NH = 4.74 at 300 K, $\Delta\delta$ NH/ Δ T = -2.1 ppb/K.
- [7] Reference molecules: CH₃CO-NHCH₃, N-H stretch band at 3466 cm⁻¹, amide I C=O stretch band at 1675 cm⁻¹ in dilute chloroform (Table 4, ref. [4j]). *t*BuO-CO-NHCH₂Ph, N-H stretch band at 3458 cm⁻¹, C=O stretch band at 1730 cm⁻¹ in dilute chloroform;^[2a] CH₃SO₂NHCH₃, N-H stretch band at 3397 cm⁻¹ in dilute chloroform (Table 4); CH₃SO₂NHCH₂COOCH₃, N-H stretch band at 3381 cm⁻¹, ester C=O stretch band at 1750 cm⁻¹ in dilute chloroform [glycine derivatives show weak intramolecular five-membered-ring (C₅-type) hydrogen bonding (ref. [4c], Scheme 3)].
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Scheme 3. Intramolecular five-membered ring (C₅-type) hydrogen bonding.