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Molecular Diversity of Peptidomimetics: Approaches to the Solid-Phase Synthesis of Peptidosulfonamides

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Abstract—In order to use the potential molecular diversity of the peptidosulfonamide peptidomimetics ultimately in libraries, approaches towards the solid-phase synthesis of peptidosulfonamides are a prerequisite. It is shown that peptidosulfonamides can be synthesized by solid-phase synthesis methods using either a Merrifield or a Tentagel® resin. Better and more reproducible results are obtained using the latter resin. The possibility to prepare cyclic peptidosulfonamides was illustrated by the synthesis of cyclo-phenylalanylΨ[$CH_2S(O)_2N$]-glycine. However, translation of synthesis of peptidosulfonamides in solution to a solid-phase method was rather laborious and still requires careful optimization. Copyright © 1996 Elsevier Science Ltd

Peptidomimetics aim at mimicking the favorable biological or structural properties of peptides, while diminishing their unfavorable characteristics, such as poor bioavailability and biodegradation by compounds e.g. proteases. A peptidomimetic consisting of monomeric building blocks can be referred to as a biopolymer mimetic.[1] The construction of such biopolymer mimetics is often advantageously inspired by the well established methods for the preparation of peptides. Recently, several new classes of oligomeric peptidomimetics have been published. These include the increasingly popular peptoids, consisting of N-substituted glycine derivatives,[2,3] the oligo carbamates,[4] the oligo urea peptidomimetics[5a–c] and the hydrazinopeptides,[5d] the oligosulfones[6] and the (α,β-unsaturated)peptidosulfonamides.[7] The modular construction of these biopolymer mimetics has led to the successful implementation of solid-phase approaches, which are a prerequisite for the construction of libraries. Libraries of oligo carbamates and peptoids have been reported[4,8] and the detection of biologically active compounds in a peptoid library[8] illustrates that libraries of peptidomimetics can be extremely useful for lead-finding.

The class of peptidosulfonamides was introduced by us as peptidomimetics containing the sulfonamide transition-state isostere.[7a–c] Two aspects are especially important when one considers the creation of libraries of peptidosulfonamides: first, the presence of 'molecular diversity' and second, the possibilities to prepare peptidosulfonamides by solid-phase synthesis. Clearly, when one considers the possibilities for preparation of all kinds of α- or β-substituted amino ethane sulfonamides, incorporation in oligomers, leading to homo- or hetero biopolymer mimetics as well as the synthesis of cyclic peptidosulfonamides (analogous to diketopiperazine formation) on the solid phase, this requirement of molecular diversity, as is schematically illustrated in Figure 1, is fulfilled. In order to be able to take full advantage of this potential molecular diversity, we describe here approaches to the solid-phase synthesis of peptidosulfonamides.

The obligatory step, before moving to solid-phase synthesis of peptidosulfonamides, viz. the synthesis in solution of various peptidosulfonamides, e.g. the tetrapeptidosulfonamide **1** was described recently.[7c]

For our initial attempts directed to the solid-phase synthesis of peptidosulfonamides, we chose the cheap, widely used Merrifield resin as the solid support.

All reactions were carried out in a vessel with a glass-fritted filter, commonly used in manual solid-phase peptide synthesis. The first amino acid, viz. Boc-Gly-

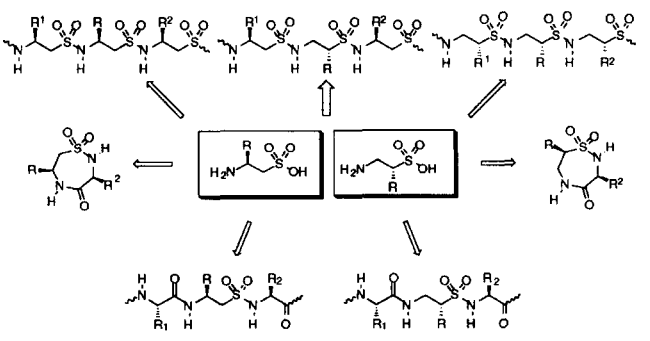

Figure 1. Molecular diversity of peptidosulfonamides.

Key words: biopolymer mimetics, peptidosulfonamides, solid-phase, molecular diversity.

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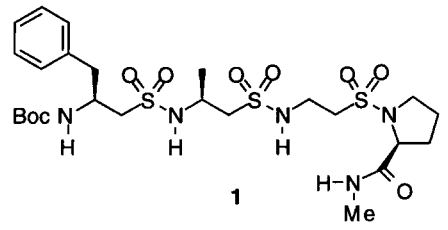

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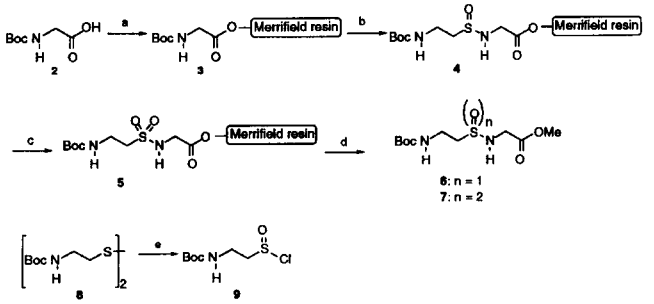
OH **2**, was attached to the resin by reaction of its cesium salt according to a standard procedure[9] to give resin-adduct **3** (0.72 mmol/g resin) as depicted in Scheme 1. Removal of the Boc group by treatment with TFA in dichloromethane and subsequent washing of the resin with triethylamine in dichloromethane afforded Gly linked to the solid support. Boc amino ethanesulfinylchloride **9** (3 equiv), prepared from Boc-protected cystamine by treatment with sulfurylchloride in the presence of acetic anhydride,[7c] was coupled to Gly linked to the resin in the presence of methylmorpholine (NMM). The formed sulfinamide **4** was oxidized by treatment with $NaIO_4/RuCl_3$ using a large excess (3 equiv) of oxidants and a longer reaction time (1 h) than was sufficient for the synthesis of peptidosulfonamides in solution. However sulfinamide **4** was not completely oxidized to the corresponding sulfonamide **5** as was indicated by cleavage of the peptide from the resin by means of a transesterification method using $MeOH/Et_3N$.[10] Both the sulfinamide **6** and the sulfonamide **7** containing peptides were isolated. Moreover, the total yield of cleaved peptide was rather low (30%). The incomplete oxidation might be due to the use of a three-phase system, consisting of an organic layer, a water layer, and the solid support. Therefore, other oxidation systems were attempted, i.e., a homogeneous oxidation system containing $NaIO_4/RuCl_3$ in a mixture of water, DMA, and dichloromethane or tetrapropylammonium perruthenate (TPAP), a well known catalyst for the oxidation of alcohols to aldehydes or ketones, in combination with both *N*-methylmorpholine-*N*-oxide (NMMO) and *n*-Bu_4NIO_4 as a co-oxidant.[11,12] Neither one of these oxidation methods gave rise to complete oxidation of resin-attached sulfinamide **4**. Complexation of the oxidants by the resin (the solid support turned completely black during the oxidation step), as well as the heterogeneous nature of the reaction might be partly responsible for this.



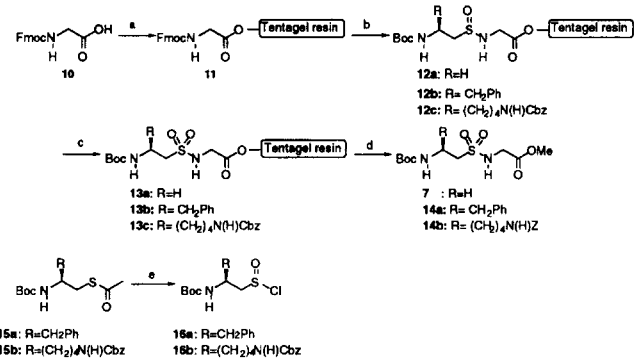
Scheme 1. Solid-phase synthesis of peptidosulfonamides on a Merrifield resin. Reagents: (a) i. Cs_2CO_3 ii. Merrifield resin, DMF, 50 °C; (b) i. TFA/CH_2Cl_2, ii. Et_3N, iii. **9**/NMM; (c) $NaIO_4/RuCl_3$aq; (d) $MeOH/Et_3N$; (e) Ac_2O/SO_2Cl_2, −20 °C

To circumvent these problems, we switched to a resin consisting of polyethylene glycol chains grafted on polystyrene (i.e. Tentagel®). Better results in solid-phase synthesis are often obtained employing this resin, since a better solvation is possible and, consequently, close to homogenous reaction conditions are more likely to be obtained. Instead of **Boc**-Gly-OH, **Fmoc**-Gly-OH was anchored to the resin, since removal of the Fmoc group in a resin sample allows determination of the exact amino acid loading of the resin.

Thus, Fmoc-Gly was attached to Tentagel®S-OH as was described by Sieber,[13] yielding **11**, having a loading 0.18 mmol Fmoc-Gly per gram of resin. The remaining free hydroxyl groups were capped using 5 equiv of acetic anhydride, 5 equiv of triethylamine, and a catalytic amount of DMAP (Scheme 2). After removal of the Fmoc moiety with 20% piperidine in 1-methyl-2-pyrrolidinone (NMP), the amino terminus was sulfinylated in the presence of NMM with 4 equiv of sulfinyl chloride **9**, **16a** or **b**, resulting in sulfinamides **12a**, **b** and **c**, respectively. Sulfinyl chlorides **9**, **16a** or **b** were synthesized as or analogous to procedures described earlier[7a-c] (Schemes 1 and 2). Careful removal of acetyl chloride, liberated at the oxidation step of disulfide **8** or thioacetates **15a**,**b** turned out to be essential. If acetyl chloride was still present, competition between acylation by acetyl chloride and sulfinylation by the sulfinylchlorides decreased the yields of the desired sulfinamides. To ensure completion of the reaction, coupling with the sulfinyl chlorides was carried out twice. After the second coupling reaction, the resin was capped with a mixture of benzoylchloride (5 equiv), triethylamine (5 equiv), and a catalytic amount of DMAP.[14] OsO_4 with NMMO as a co-oxidant is a known oxidation system for converting sulfoxides to sulfones.[15] In addition, oxidation can be carried out with OsO_4 attached to a solid support.[16] Therefore, it should be feasible to oxidize a sulfinamide attached to a solid support to the corresponding sulfonamide using this oxidation mixture. Indeed, oxidation of **12a–c** with 5 mol% OsO_4 and 4 equiv of NMMO as co-oxidant resulted in peptidosulfonamides **13a–c** as was apparent from the formation of peptidosulfonamides **7**, **14a** and **b**, respectively, by a transesterification reaction with methanol in the presence of triethylamine.

Oxidation of the sulfinamides **12a–c** with tetrabutylammonium oxone®[6,17] also resulted, after transesterification with methanol in the presence of triethylamine, in peptidosulfonamides **7**, **14a** and **b**, but the acidity of the oxidation system caused partial removal of the Boc protecting group. For this reason, it was preferred to use OsO_4/NMMO as the oxidation system.

The molecular diversity of peptidosulfonamides was further extended by preparation of cyclic peptidosulfon-

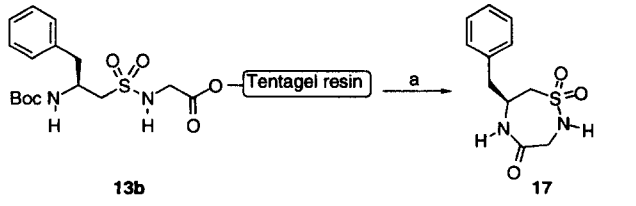


Scheme 2. Solid-phase synthesis of peptidosulfonamides on a Tentagel® resin. Reagents: (a) 2,6-dichlorobenzoylchloride, pyridine, NMP; (b) i. piperidine/NMP, ii. **9**, **16a,b**/NMM; (c) OsO_4/NMMO or *n*-Bu_4N oxone; (d) MeOH/Et_3N; (e) Ac_2O/SO_2Cl_2, −20 °C.

amides analogous to synthesis of diketopiperazines on the solid phase. To this end, the Boc group of sulfonamide **13b** was removed with TFA/CH_2Cl_2, followed by washing with triethylamine. Subsequent heating of the reaction mixture, in the presence of a few drops of triethylamine, resulted in a seven-membered ring compound containing a β-substituted amino ethane sulfonamide moiety (Scheme 3).

In conclusion, in this paper the synthesis of peptidosulfonamides containing a β-substituted amino ethane sulfonamide attached to a solid support is described. Although the desired peptidosulfonamides using a Merrifield resin could be obtained, better results were obtained employing a Tentagel® resin. Oxidation of the sulfinamides was possible using OsO_4/NMMO or with *tetra*-butylammonium oxone®, but the latter method was less attractive for the synthesis of Boc protected dipeptides, since partial deprotection occurred. The potential molecular diversity of peptidosulfonamides was even further increased by the preparation of cyclic peptidosulfonamides by cyclization and simultaneous cleavage from the resin. However, translation of synthesis in solution to solid-phase synthesis was a non-trivial exercise and requires careful monitoring of the reactions and adjustment of the reaction conditions among others for optimization.

Based on these results, the diversity of peptidosulfonamides, as was schematically represented in Figure 1, is now further explored towards obtaining small libraries of homo- and hetero-biopolymer mimetics of peptidosulfonamides, as well as cyclic peptidosulfonamides. In addition, alternative approaches for preparing peptidosulfonamides are under investigation to increase the flexibility of creating molecular diversity of peptidosulfonamides



Scheme 3. Cyclization on the solid phase. Reagents: (a) i. TFA/CH_2Cl_2, ii. THF, cat. Et_3N, reflux.

Experimental

General methods

THF was dried by refluxing on $LiAlH_4$ and distilled prior to use. NMP was stirred on CaH_2 for 16 h and then distilled under reduced pressure. Ethanol free CH_2Cl_2 used for synthesis of the sulfinylchlorides and sulfinamides was purchased from Baker and distilled from CaH_2, prior to use. Acetonitril (MeCN) and *N*-methylmorpholine (NMM) were distilled from CaH_2.

All protected amino acids were purchased from Bachem. The Merrifield polymer (200–400 mesh, 1% divinylbenzene, 1.40 mmol Cl/g resin) was obtained from Fluka, Tentagel®S OH (130 μM) was purchased from Rapp Polymere, Tübingen, Germany.

TLC analysis was performed on Merck pre-coated silicagel 60 F-254 plates. Spots were visualized with UV light, ninhydrin or Cl_2/TDM.[18] Column chromatography was carried out on Merck Kieselgel 60H (5–40 μm) or Kieselgel 60 (63–200 μm).

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Jeol JNM-Fx 200 (200 MHz) spectrometer or a Varian (300.1 MHz) spectrometer. Shifts are given in ppm (δ) relative to TMS or $CDCl_3$ as internal standard.

***N-tert*-Butyloxycarbonyl-glycine-Merrifield resin (3).** Boc-Gly-OH **2** was coupled to the Merrifield resin according to a standard procedure.[9] The weight increase of the resin indicated an incorporation of the used Boc-Gly-OH of 0.72 mmol.g^{-1} resin.

***N-tert*-Butyloxycarbonyl-glycylΨ[$CH_2S(O)N$]-glycine-Merrifield resin (4).** The Boc group of Boc-Gly-OH linked to the Merrifield resin **3** (1.39 g, 1 mmol) was removed analogous to the procedure described by Stewart and Young.[10] The resin was washed with CH_2Cl_2 (3 × 20 mL, 3 min), deprotected in a mixture of TFA:CH_2Cl_2 (1:1, v:v, 20 mL, 30 min), washed with CH_2Cl_2 (6 × 20 mL, 5 min), Et_3N/CH_2Cl_2 (1:9, v:v, 2 × 20 mL, 3 min) and CH_2Cl_2 (6 × 20 mL, 5 min). Subsequently, a solution of sulfinylchloride **9** (3.0 mmol), prepared from Boc-cystamine (**8**) as was described[7a,c] in CH_2Cl_2 (6 mL) was added simultaneously with NMM (0.33 mL, 3.0 mmol) to a suspension of the glycine linked to the Merrifield resin in dry CH_2Cl_2 (10 mL). The mixture was gently rotated overnight, filtered, and washed with CH_2Cl_2 (6 × 20 mL, 5 min).

***N-tert*-Butyloxycarbonyl-glycylΨ[$CH_2S(O)_2N$]-glycine-Merrifield resin (5)**

Method A. A mixture consisting of $NaIO_4$ (0.64 g, 3.0 mmol) and a catalytic amount of $RuCl_3$ hydrate in

CH_2Cl_2 (6 mL), MeCN (6 mL) and H_2O (9 mL) was added to the sulfinamide containing resin **4**. The vessel was gently rotated for 1 h. The resin was subsequently washed with H_2O (20 mL), DMF:H_2O (1:1, v:v, 20 mL, 5 min), DMF:H_2O (2:1, v:v, 20 mL, 5 min), DMF:H_2O (9:1, v:v, 20 mL, 5 min), DMF (20 mL, 5 min), and CH_2Cl_2 (3 × 20 mL, 5 min) and dried over P_2O_5 in vacuo overnight.

A sample of the resin **5** (95 mg, 64 μmol) was suspended in 4 mL dry MeOH, and Et_3N (10 μL, 72 μmol) was added. After stirring overnight, the mixture was filtered, washed with MeOH, and the combined filtrates were concd in vacuo and subjected to column chromatography (7 g silica 60, eluent: EtOAc:MeOH, 95:5, v:v) to give the sulfonamide **7** (R_f(EtOAc:MeOH, 95:5, v:v) = 0.82 as an oil in 16% yield and the sulfinamide **6** (R_f(EtOAc:MeOH, 95:5, v:v) = 0.49 as an oil in 14% yield.

Sulfinamide 6. R_f(EtOAc:MeOH, 95:5, v:v) = 0.49; ^{1}H NMR: δ 1.45 (s, 9H, $C(CH_3)_3$), 2.81–3.09 (m, 2H, CH_2SO), 3.40–3.56 (m, 2H, $C\underline{H}_2CH_2SO_2$), 3.79 (s, 3H, $C(O)OCH_3$), 3.78, 4.01 (two dd, 2H, $CH_2C(O)$, J_{AX} = 5.9 Hz, J_{BX} = 5.4 Hz, J_{AB} = 17.7 Hz), 4.56 (br, 1H, NH), 5.12 (br, 1H, NH).

Sulfonamide 7. R_f(EtOAc:MeOH, 95:5, v:v) = 0.82; NMR data were identical to those described (*vide infra*).

Method B. A mixture consisting of $NaIO_4$ (0.64 g, 3.0 mmol) and a catalytic amount of $RuCl_3$ hydrate in CH_2Cl_2 (9 mL), DMA (9 mL), and H_2O (3 mL) was added to the sulfinamide containing resin **4**. After rotating the vessel for 6 h, the resin was washed according the procedure described for method A. A sample was transesterified with MeOH:Et_3N, as was described above, to give the sulfonamide **7** in 5% yield, whereas no sulfinamide **6** was isolated.

Method C. To a suspension of the sulfinamide containing resin **4** in dry MeCN (15 mL), *n*-Bu_4NIO_4 (0.65 g, 1.5 mmol), NMMO (0.203 g, 1.5 mmol), and a catalytic amount of TPAP were added and the mixture was gently rotated for 2 h. Then another portion of *n*-Bu_4NIO_4 (0.650 g, 1.5 mmol), TPAP (catalytic amount), and NMMO (0.203 g, 1.5 mmol) was added and shaking was continued for 3 h. The resin was washed as described under method A. A sample was transesterified using MeOH:Et_3N to give the sulfonamide **7** in 28% yield and the sulfinamide **6** in 30% yield.

Fmoc-glycine-Tentagel resin (11). Fmoc-Gly-OH **10** was attached to the Tentagel® S OH resin using the procedure of Sieber[13] yielding **11** with a loading of 0.18 mmol g^{-1} (72%), as was determined by Fmoc-cleavage from a resin sample.

***N-tert*-Butyloxycarbonyl-glycylΨ[$CH_2S(O)_2N$]-glycine-Tentagel resin (13a).** Resin **11** (0.17 mmol g^{-1}, 1.01 g) was washed three times with dry CH_2Cl_2 (5 mL) followed by addition of a solution of acetic anhydride (32 μL, 0.35 mmol), Et_3N (50 μL, 0.35 mmol), and a few crystals of DMAP in dry CH_2Cl_2 (5 mL) to cap all remaining hydroxyl functions. For mixing the reactants with the resin, a small flow of N_2 was bubbled through the solution. All washings were performed manually. After 15 min, the resin was washed with CH_2Cl_2 (3 × 5 mL), NMP (3 × 5 mL) and subsequently treated with a solution of 20% piperidine in NMP (5 mL). The Tentagel® resin was washed after 15 min with NMP (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL) followed by addition of freshly prepared sulfinylchloride **9** (0.68 mmol)[7e] and NMM (0.85 mmol, 95 μL) dissolved in CH_2Cl_2 (5 mL). A small N_2 flow was maintained through the solution in order to mix the reaction compounds. After 2.5 h, this coupling procedure was repeated using freshly prepared sulfinylchloride (0.68 mmol) and NMM (0.85 mmol, 95 μL). Capping with a solution of benzoylchloride (98 mL, 0.85 mmol), Et_3N (120 μL, 0.85 mmol), and a few crystals of DMAP in CH_2Cl_2 (5 mL) for 15 min, followed by washing with CH_2Cl_2 (3 × 5 mL) afforded sulfinamide (**12a**) attached to the resin. Oxidation of the sulfinamide to the corresponding sulfonamide was carried out by addition of OsO_4 (85 μL of a 2.5 wt% solution in *t*-BuOH, 5 mol%) and NMMO (78 mg, 0.68 mmol) in a mixture of THF (4 mL) and *t*-BuOH (1 mL), followed by shaking for 16 h. Washing of the resin with THF: *t*-BuOH (4:1, v:v, 3 × 5 mL) and CH_2Cl_2 (3 × 5 mL) followed by drying in vacuo over P_2O_5 resulted in resin **13a**.

Oxidation with tetra *n*-Bu^{4}N oxone®

Sulfinamide **12a** was synthesized as described above starting from 0.99 g of resin **11** (0.20 mmol g^{-1}). After capping of the resin, the beads were washed with CH_2Cl_2 (3 × 5 mL). Subsequently, a solution of *n*-Bu_4N oxone® (0.6 mmol, 0.54 g), dissolved in CH_2Cl_2 (5 mL) was added and the mixture was gently shaken overnight. Washing of the resin with CH_2Cl_2 (3 × 5 mL) and drying in vacuo over P_2O_5 resulted in resin **13a**.

***N-tert*-Butyloxycarbonyl-glycylΨ[$CH_2S(O)_2N$]-glycine methyl ester (7).** Transesterification was carried out by addition of a mixture of MeOH:Et_3N (9:1, v:v, 10 mL) to the resin **13a** and shaking for 16 h followed by washing of the resin with MeOH (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL), evaporation of the filtrate, and purification by silica gel chromatography (silica gel 60H, eluent 45% EtOAc in hexanes) gave **7** (45%, 21.2 mg). R_f(EtOAc) = 0.71; ^{1}H NMR (300 MHz) 1.44 (s, 9H, $C(CH_3)_3$), 3.26 (t, 2H, CH_2SO_2, J = 5.9 Hz), 3.67 (dt, 2H, $C\underline{H}_2CH_2SO_2$, $J_{CH_2NH} = J_{CH_2CH_2} = 5.9$ Hz), 3.78 (s, 3H, $C(O)OCH_3$), 3.97 (d, 2H, $CH_2C(O)$, J = 5.9 Hz), 5.20 (m, 1H, N(H)) and 5.43 (br s, 1H, N(H)); ^{13}C NMR: δ 27.3 ($C(\underline{C}H_3)_3$), 34.6 ($\underline{C}H_2CH_2SO_2$), 43.1 ($\underline{C}H_2C(O)$), 51.6 ($C(O)O\underline{C}H_3$), 52.3 (CH_2SO_2), 79.0 ($\underline{C}(CH_3)_3$), 155.1 (C(O) Boc), and 169.4 ($\underline{C}(O)OCH_3$).

Transesterfication of resin **13a**, treated with *n*-Bu_4N oxone®, followed by purification as described above

resulted in peptidosulfonamide **7** (20.7 mg, 37%). NMR data were identical to those described (*vide supra*).

***N-tert*-Butyloxycarbonyl-phenylalanylΨ[$CH_2S(O)_2N$]-glycine-Tentagel resin (13b).** Compound **13b** was synthesized as described for the preparation of **13a** using sulfinylchloride **16a** using 0.99 g of resin **11**.

***N-tert*-Butyloxycarbonyl-phenylalanylΨ[$CH_2S(O)_2N$]-glycine methyl ester (14a).** Transesterfication of resin **13b** (0.18 mmol g^{-1}, 0.86 g) was carried out as was described for resin **13a**, resulting in **14a** (62%, 33.8 mg) after purification by silica gel chromatography (eluent: 45% EtOAc in hexanes). R_f(EtOAc) = 0.77; ^{1}H NMR (300 MHz): 1.41 (s, 9H, $C(CH_3)_3$), 2.94 (m, 1H, CH_γ-Ph), 2.97 (dd, 1H, CH_βPh, J_{gem} = 13.6 Hz, J_{vic} = 6.6 Hz), 3.16 (dd, 1H, $CH_\alpha SO_2$, J_{gem} = 14.2 Hz, J_{vic} = 8.9), 3.23 (dd, 1H, $CH_\beta SO_2$, J_{gem} = 14.2 Hz, J_{vic} = 4.0), 3.74 (s, 3H, $C(O)OCH_3$), 3.90 (dd, 1H, $CH_\alpha C(O)$, J_{gem} = 18.2 Hz, J_{vic} = 5.0 Hz), 4.01 (dd, 1H, $CH_\beta C(O)$, J_{gem} = 18.2 Hz, J_{vic} = 6.4 Hz), 4.64 (m, 1H, $C\underline{H}CH_2SO_2$), 4.93 (d, 1H, C(O)N(H), J = 9.5 Hz). 5.92 (br s, 1H, $SO_2N(H)$) and 7.20–7.35 (m, 5H, Ph); ^{13}C NMR: δ 28.3 ($C(\underline{C}H_3)_3$), 40.7 ($\underline{C}H_2$Ph), 44.3 ($\underline{C}H_2C(O)$), 48.2 ($\underline{C}HCH_2$), 52.5 ($C(O)O\underline{C}H_3$), 56.3 (CH_2SO_2), 80.3 ($\underline{C}(CH_3)_3$), 127.0, 128.7, and 129.4 (CH Ph), 136.5 (CqPh), 156.0 (C(O) Boc), and 167.5 ($\underline{C}(O)OCH_3$).

***N-tert*-Butyloxycarbonyl-lysyl(Z)Ψ[$CH_2S(O)_2N$]-glycine-Tentagel resin (13c).** Peptidosulfonamide **13c**, attached to the resin was prepared as described for the synthesis of **13a** using resin **11** (1.07 g, 0.19 mmol g^{-1}) and sulfinylchloride **16b**.

***N-tert*-Butyloxycarbonyl-lysyl(Z)Ψ[$CH_2S(O)_2N$]-glycine-methylester (14b).** Transesterification of **13c** was carried out as described for the transesterification of **13a**. Purification by silica gel chromatography (silica gel 60H, eluent 50% EtOAc in hexanes) yielded **14b** (25%, 22.6 mg). Further elution with EtOAc yielded the corresponding sulfinamide (20%, 17.7 mg) which decomposed upon storage. R_f(EtOAc) = 0.66; ^{1}H NMR: δ 1.44 (s, 9H, $C(CH_3)_3$), 1.70 (m, 6H, C^3H_2, C^4H_2 and C^5H_2 Lys), 3.20 (m, 4H, C^6H_2 Lys and CH_2SO_2), 3.74 (s, 3H, $C(O)OCH_3$), 3.91 (dd, 1H, $CH_\alpha C(O)$, J_{gem} = 18.4 Hz, J_{vic} = 4.4 Hz), 4.04 (dd, 1H, $CH_\beta C(O)$, J_{gem} = 18.4 Hz, J_{vic} = 7.0 Hz), 4.33 (br s, 1H, N(H)), 4.88 (m, 2H, C^2H Lys and N(H)), 5.09 (br s, 2H, CH_2 Cbz), 6.01 (br s, 1H, $N(H)SO_2$), 7.35 (m, 5H, Ph): ^{13}C NMR: δ 22.6 (C^4H_2 Lys), 28.3 ($C(\underline{C}H_3)_3$), 29.3 (C^5H_2 Lys), 34.1 (C^3H_2 Lys), 40.4 (C^6H_2 Lys), 44.3 (CH_2 Gly), 46.9 (C^2H Lys), 52.5 ($C(O)O\underline{C}H_3$), 57.8 (CH_2SO_2), 66.7 (CH_2 Cbz), 80.3 ($\underline{C}(CH_3)_3$), 128.1 and 128.5 (CHPh), 136.6 (C_qPh), 156.6 (C(O) Boc and Cbz) and 170.7 ($\underline{C}(O)OCH_3$).

Cyclo-phenylalanylΨ[$CH_2S(O)_2N$]-glycine (17). To resin **13b** (0.88 g, 0.18 mmol g^{-1}) were added CH_2Cl_2 (2.5 mL) and TFA (2.5 mL). After 0.5 h, the resin was washed with CH_2Cl_2 (3 × 5 mL), 10% Et_3N in CH_2Cl_2 (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL). Subsequently, THF (10 mL) was added followed by addition of a few drops of Et_3N until the apparent pH was 10. Refluxing the reaction mixture in an oilbath for 5 days, followed by filtration of the resin, evaporation of the filtrate — as was described for **7** — and purification (silica gel 60H, eluent 10% hexanes in EtOAc) yielded **17** (21%, 7.4 mg). R_f(EtOAc) = 0.39; ^{1}H NMR (300 MHz): 2.91 (dd, 1H, CH_αPh, J_{gem} = 14.2 Hz, J_{vic} = 7.2 Hz), 2.96 (dd, 1H, CH_βPh, J_{gem} = 14.2 Hz, J_{vic} = 6.4 Hz), 3.03 (dd, 1H, $CH_\alpha SO_2$, J_{gem} = 13.9 Hz, J_{vic} = 10.3 Hz), 3.38 (d, 1H, $CH_\beta SO_2$, J_{gem} = 13.9 Hz), 3.68 (dd, 1H, $CH_\alpha C(O)$, J_{gem} = 16.5 Hz, J_{vic} = 0.7 Hz), 4.11 (dd, 1H, $CH_\beta C(O)$, J_{gem} = 16.5 Hz, J_{vic} = 12.1 Hz), 4.22 (m, 1H, $C\underline{H}CH_2$), 5.21 (d, 1H, $N(H)SO_2$, J = 10.3 Hz), 6.10 (br s, 1H, N(H)C(O)) and 7.19–7.40 (m, 5H, Ph); ^{13}C NMR: δ 40.7 ($\underline{C}H_2$Ph), 46.9 ($\underline{C}H_2C(O)$), 49.9 ($\underline{C}HCH_2$), 58.5 (CH_2SO_2), 128.0, 129.0 and 129.4 ($\underline{C}$HPh), 134.4 ($\underline{C}_q$Ph), and 173.0 ($\underline{C}(O)OCH_3$).

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