# Synthesis of Chiral Vinylogous Sulfonamidopeptides (vs-Peptides)

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Chiral vinylogous amino sulfonic acids (vs-amino acids) were synthesized starting from either L- or D-α-amino acids via *N*-Boc−α-amino aldehydes. Wittig-Horner reaction with methyl (or ethyl) diethylphosphoryl methanesulfonate and *n*BuLi gave the corresponding α,β-unsaturated sulfonates in high yield and complete (*E*) stereoselectivity. Cleavage of the methyl (ethyl) ester was effected by treatment of the sulfonates with $n$Bu$_4$NI in refluxing acetone. Treatment of the $n$Bu$_4$N$^+$ sulfonate salts with $SO_2Cl_2/PPh_3/CH_2Cl_2$ gave the corresponding sulfonyl chlorides as stable chromatographable compounds. The synthetic sequence proved successful not only starting from α-amino acids carrying unfunctionalized side-chains (Ala, Val, Phe, Leu, Pro), but also with functionalized α-amino acids (Ser, Tyr, Gln) provided that the side chains were suitably protected. The sulfonyl chlorides were coupled with the amine salts to give vs-dipeptides. Amine hydrochlorides were prepared from *N*-Boc derivatives by treatment with HCl in methanol or ethyl acetate. The process was further iterated to give vs-tripeptides and vs-tetrapeptides. The above procedure was also used to synthesize "mixed" peptides, which incorporate both proteinogenic α-amino acids and vs-amino acids. Proteinogenic α-amino acids were incorporated at both the C-terminal and the N-terminal position.

## Introduction

Peptides are attractive targets for drug discovery because of their affinities and specificities toward biological receptors and the simplicity with which large peptide libraries can be synthesized in a combinatorial format. However, the poor bioavailability and rapid enzymatic degradation of peptides in vivo have generally limited their therapeutic application. One approach toward overcoming this obstacle has been the development of non-natural biopolymer scaffolds (carbamates, peptoids, ureas, sulfonamides, β-peptides, etc.)[1] which may show improved pharmacological properties relative to peptides.

The ability to efficiently assemble large synthetic oligomers also offers 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 lead to new classes of folded polymers with novel properties.[1k][1l][1m][1n][1o]

Although massive work has been devoted during the past two decades to the replacement of the scissile peptide bond with mimetic groups,[2] relatively little is known about pseudopeptides characterized by the presence of the sulfonamido bond.[1h][1i][3] This modification creates a peptide bond surrogate with significant changes in polarity, H-bonding capability and acid-base character ($RSO_2$-NHR′, p$K_a$ = 10−11). Furthermore, the sulfonamido bond should show enhanced metabolic stability and structural similarity to the tetrahedral transition state involved in the amide bond enzymatic hydrolysis,[3a][3b][3c] thus making sulfonamidopeptides interesting candidates in the development of protease inhibitors and new drugs.[4] The oligomers and the polymers should also be interesting molecular scaffolds, with specific secondary structures enforced by hydrogen bonding.

The synthesis of α-sulfonamidopeptides **1**, i.e. the direct substitution of the carboxylic acid of natural α-amino acids with a sulfonic acid, remained an elusive goal because α-aminosulfonamides are unstable and immediately decompose via fragmentation.[5] Our group at Milano has recently described the synthesis of β-sulfonamidopeptides **2** via an iterative process, both in solution and in the solid phase (Figure 1).[6]

The conformational preferences of chiral vinylogous amino sulfonic acids (vs-amino acids) and of the corresponding oligomers **3** (vs-peptides)[7] were recently investigated by a combination of X-ray crystallography, variable temperature (VT) $^1$H-NMR spectroscopy, FT-IR spectroscopy, and n.O.e. experiments.[8a] Vs-peptides **3** are a sort of "dipeptide mimetic", being however characterized by 5 atoms in the backbone (instead of the usual 6 atoms in proteinogenic dipeptides, Figure 1). Intramolecular dipolar attraction, including hydrogen bonding, was shown to be a principal driver force for folding in these systems.[8a] In collaboration with C. W. Still at Columbia University and H. P. Nestler at Cold Spring Harbor Laboratory, we re-

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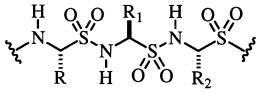
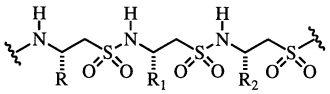
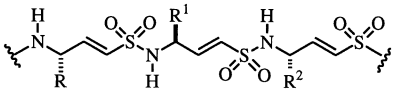
Figure 1. α-Sulfonamidopeptides (**1**), β-sulfonamidopeptides (**2**), and vinylogous sulfonamidopeptides (vs-peptides) (**3**)



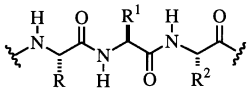
α-Sulfonamidopeptides (**1**)



β-sulfonamidopeptides (**2**)



vinylogous sulfonamidopeptides (vs-peptides) (**3**).



proteinogenic peptides

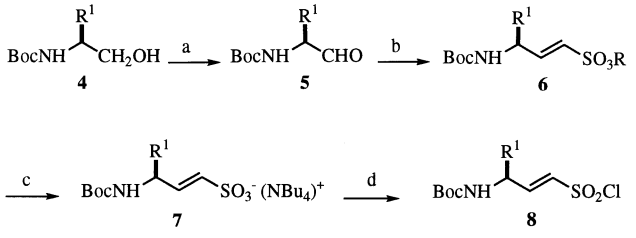
cently described the binding of tweezer-like molecular receptors based on vs-peptides to an encoded combinatorial tripeptide library, showing not only that vs-peptide based receptors bind oligopeptides, but also that the binding selectivity is just as high as that of receptors built with α-amino acids.[8b][8c]

Here we describe the synthesis of chiral vinylogous amino sulfonic acids (vs-amino acids)[7] starting from natural α-amino acids, the development of a straightforward protection-deprotection-coupling chemistry for the sulfonamido bond, and the synthesis of vinylogous sulfonamidopeptides (vs-peptides) **3** via an iterative process.[9a][9b]

## Results and Discussion

A representative sequence is outlined in Scheme 1. (*S*)-*N*-Boc−α-amino aldehydes[10][11] **5** (Boc = *tert*-butoxycarbonyl) were prepared from naturally occurring L-α-amino acids carrying unfunctionalized side-chains (Ala, Val, Phe, Leu, Pro) via reduction to α-amino alcohols, Boc protection to *N*-Boc−α-amino alcohols **4**, and Swern oxidation (90−97%).[12] In a few cases (Phe, Pro), the (*R*)-enantiomers were synthesized starting from the corresponding D-α-amino acids. The *N*-protected α-amino aldehydes **5** were used immediately after preparation, avoiding silica gel chromatography, due to their instability and tendency to racemization.[13] Wittig-Horner reaction with methyl (or ethyl) diethylphosphoryl methanesulfonate[14][15] and *n*BuLi at −78°C gave the corresponding α,β-unsaturated sulfonates **6** in good yield (75−85%) and complete (*E*) stereoselectivity.[14c][16] Cleavage of the methyl (ethyl) ester was effected by treatment of sulfonates **6** with $n$Bu$_4$NI in refluxing acetone (100%).[15b][15c][15d][17a] This cleavage is a $S_N2$ type reaction and therefore the alkyl group of the sulfonic ester plays a major role with regard to the rate of displacement (Me > Et). This deprotection offers several advantages over related reactions leading to different sulfonate salts (e.g. $Na^+$, $NH_4^+$, $NHEt_3^+$)[15b][15c][15d]: a) the $Bu_4N^+$ salts **7** are easily handleable and soluble in organic solvents, b) they are the most suitable starting material for the next step. The activation step required extensive search for appropriate reagents and conditions. After screening several different methods, we found that $SO_2Cl_2/PPh_3$ in dichloromethane[17] gives the corresponding sulfonyl chlorides **8** cleanly and in high yield (85−87%) as stable chromatographable compounds, while other protocols [e.g. $(Cl_3C-O)_2C=O$/cat. DMF/$CH_2Cl_2$,[18] $PCl_5/CHCl_3$,[19] $POCl_3$[20]] were less efficient.

Scheme 1. Synthesis of vinylogous amino sulfonyl chlorides (**8**) from *N*-Boc−α-amino alcohols (**4**). a) $(COCl)_2$, DMSO, $CH_2Cl_2$, −63°C; $Et_3N$, $CH_2Cl_2$, −63°C, 90−97%. − b) $(EtO)_2PO\text{-}CH_2SO_3R$ (R = Me, Et), *n*BuLi, THF, −78°C, 30 min, 75−85%. − c) $n$Bu$_4$NI, acetone, reflux, 10−16 h, 100%. − d) $SO_2Cl_2$, $Ph_3P$, $CH_2Cl_2$, 3-Å molecular sieves, from 0 to + 25°C, 3 h, 85−87%.

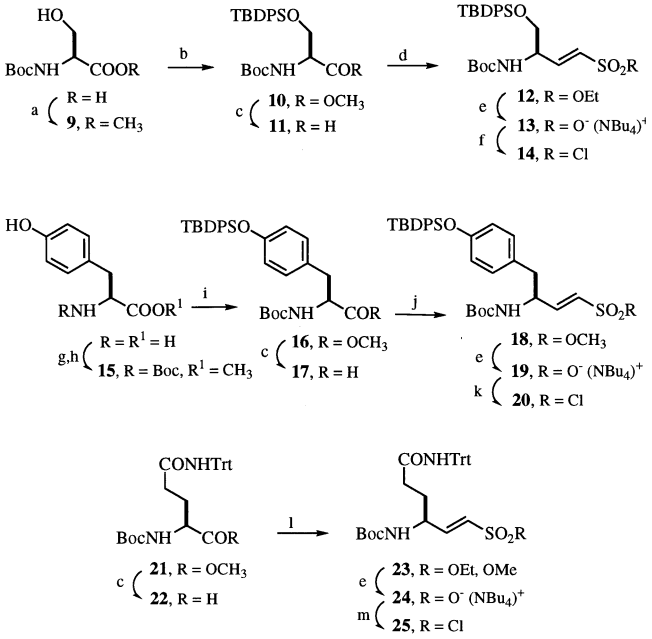


The transformation of functionalized α-amino acids into vinylogous amino sulfonyl chlorides was somehow more problematic due to the presence of the functionalized side-chains. The side-chain functional groups need the introduction of the proper protective groups which should be stable during all the steps of the synthesis, including final Boc deprotection for iterative coupling. The transformation into vs-derivatives was successfully performed on serine, tyrosine, and glutamine (Ser, Tyr, Gln). In this case, the three α-amino aldehydes were synthesized from the corresponding acids via reduction of the methyl esters with diisobutylaluminium hydride (Dibal-H).[21] In the case of serine and tyrosine we found *tert*-butyl diphenylsilyl (TBDPS) to be a suitable OH protective group,[22] stable during the synthesis and easily removable at the end of the iterative process (vide infra). In the case of glutamine, the trityl (Trt) protection proved to be compatible with most synthetic operations, but not with Boc deprotection (vide infra). The synthetic approaches to (*S*)-*N*-Boc−vsSer(TBDPS)−Cl **14**, (*S*)-*N*-Boc−vsTyr(TBDPS)−Cl **20**, and (*S*)-*N*-Boc−vsGln-(Trt)−Cl **25** are reported in Scheme 2.

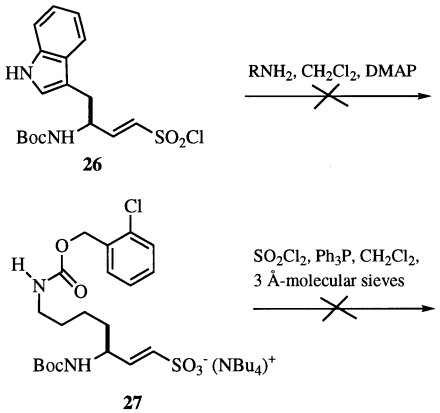
The synthesis of vinylogous amino sulfonyl chlorides was attempted also on (*S*)-tryptophan and (*S*)-lysine (Trp, Lys). However, although successfully synthesized, (*S*)-*N*-Boc−vsTrp−Cl **26** turned out to be surprisingly inert to our standard coupling conditions with free amines, and (*S*)-*N*-Boc−vsLys(2-Cl−Cbz)−$O^-(NBu_4)^+$ **27** could not be transformed into the corresponding sulfonyl chloride (Scheme 3).

Coupling of the sulfonyl chlorides **8** was first investigated using an excess of commercially available free nucleophilic amines [$R^1R^2NH$; $R^1 = R^2 = H$; $R^1$ = Bn $R^2 = H$; $R^1$ = Et $R^2 = H$; $R^1 = i$Pr $R^2 = H$; $R^1$, $R^2 = -(CH_2)_4-$] to give sulfonamides **28** (Scheme 4). Apart from the highly reactive $NH_3$ (78%, 2 h), all the other primary and secondary amines required a stoichiometric amount of 4-dimethylami-

Scheme 2. Synthesis of (*S*)-*N*-Boc−vsSer(TBDPS)−Cl (**14**), (*S*)-*N*-Boc−vsTyr(TBDPS)−Cl (**20**), and (*S*)-*N*-Boc−vsGln(Trt)−Cl (**25**). a) $K_2CO_3$, $CH_3I$, DMF, 100%. − b) TBDPS-Cl, imidazole, DMF, 77%. − c) DIBAL-H, toluene, THF, −78°C, 95%. − d) $(EtO)_2PO$-$CH_2SO_3Et$, *n*BuLi, THF, −78°C, 30 min, 46%. − e) $nBu_4NI$, acetone, reflux, 10−16 h, 100%. − f) $SO_2Cl_2$, $Ph_3P$, $CH_2Cl_2$, 3-A molecular sieves, from 0°C to + 25°C, 3 h, 74%. − g) 2,2-dimethoxypropane, conc. HCl, 100%. − h) $Boc_2O$, $NaHCO_3$, $CH_2Cl_2$, 93%. − i) TBDPS-Cl, imidazole, $CH_2Cl_2$, 89%. − j) $(EtO)_2PO$-$CH_2SO_3Me$, *n*BuLi, THF, −78°C, 30 min, 63%. − k) $SO_2Cl_2$, $Ph_3P$, $CH_2Cl_2$, 3 Å-molecular sieves, from 0°C to + 25°C, 3 h, 70%. − l) $(EtO)_2PO$-$CH_2SO_2R$, *n*BuLi, THF, −78°C, 30 min, R = OEt 56%, R = OMe 60%. −m) $SO_2Cl_2$, $Ph_3P$, $CH_2Cl_2$, 3-A molecular sieves, from 0°C to + 25°C, 3 h, 75%.

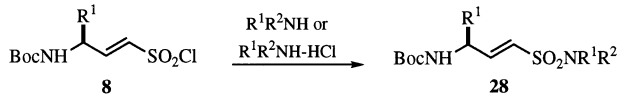



Scheme 3. Unsuccessful coupling of (*S*)-*N*-Boc−vsTrp−Cl (**26**) with amines. Unsuccessful transformation of (*S*)-*N*-Boc−vsLys(2-Cl−Cbz)−$O^-(NBu_4)^+$ (**27**) into the corresponding sulfonyl chloride




nopyridine (DMAP) for obtaining good yields (60−76%) and reasonably fast reaction times (3 h). When an amine hydrochloride ($HCl{\cdot}HNMe_2$) was used, besides the presence of DMAP, the assistance of another tertiary amine was needed to free the nuclephilic amine and scavenge the HCl developed from the reaction. Among the various tertiary amines tryed, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and *N*-methylmorpholine (NMM) allowed a reasonable stability of the sulfonyl chlorides and good coupling yields (52−66%).

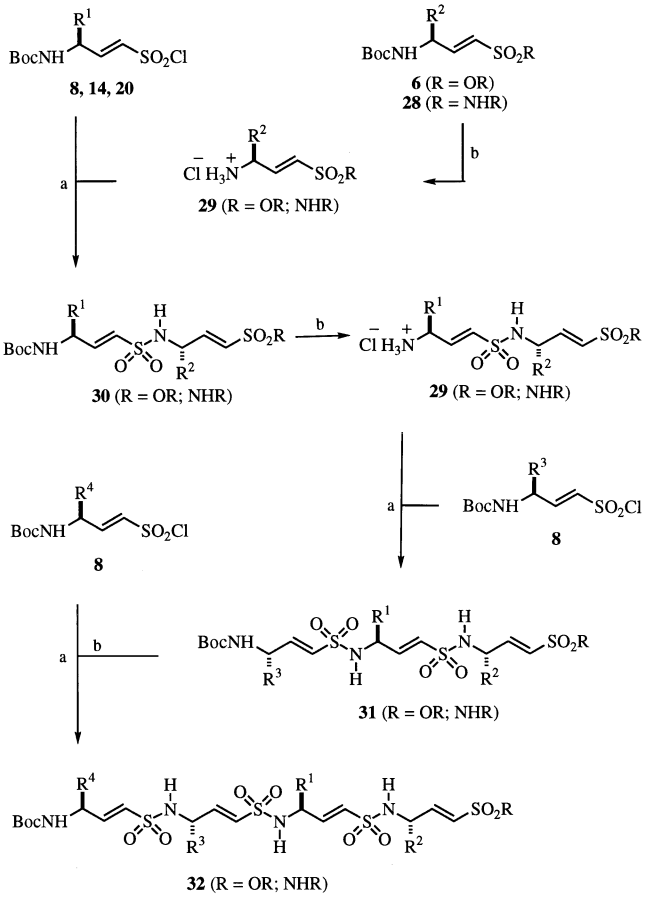
Scheme 4. Synthesis of sulfonamides (**28**). a) $R^1R^2NH$; $R^1$ = $R^2$ = H, $Et_2O$, 78%. − b) $R^1R^2NH$; $R^1$ = Bn $R^2$ = H; $R^1$ = Et $R^2$ = H; $R^1$ = *i*Pr $R^2$ = H; $R^1$, $R^2$ = $-(CH_2)_4-$, $CH_2Cl_2$, DMAP, 60−76%. − c) $R^1R^2NH$-HCl; $R^1$ = $R^2$ = Me, $CH_2Cl_2$, DMAP, DBU, 52−66%.



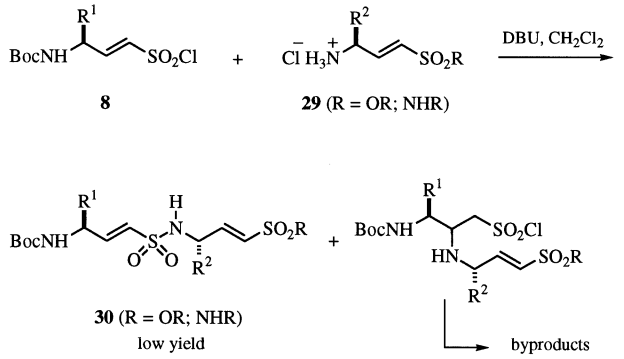

Excess sulfonyl chlorides (**8**, **14**, **20**) were coupled in the presence of DMAP and DBU with the amine salts **29** to give vs-dipeptides **30** in fair to good yields (25−65%) (Scheme 5).

The presence of a stoichiometric amount of DMAP proved absolutely necessary for obtaining good yields in the coupling reactions. In the absence of DMAP the coupling process was slower and less clean, with erratic formation of by-products like the Michael adducts between the α,β-unsaturated sulfonyl chlorides and the free amines (Scheme 6).

Scheme 5. Synthesis of vinylogous sulfonamidopeptides (vs-peptides). a) $CH_2Cl_2$, DBU, DMAP, 25°C, 25−65%. − b) HCl in MeOH or EtOAc, from 0°C to + 25°C, 3 h, 100%.



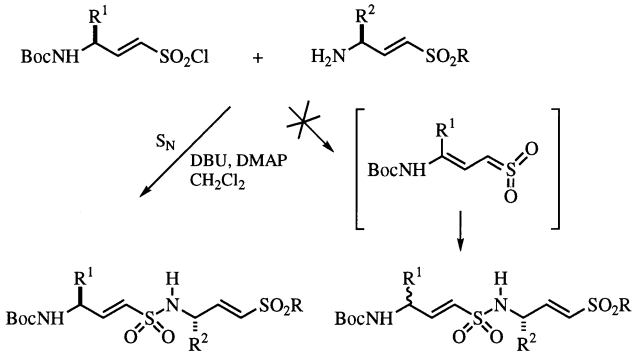
Scheme 6. Coupling reactions between α,β-unsaturated sulfonyl chlorides and amines in the absence of DMAP




Amine hydrochlorides **29** were prepared from *N*-Boc derivatives **6** and **28** in 100% yield by treatment with 3 M HCl in MeOH (room temp., 3 h) or with a saturated HCl solution in ethyl acetate (room temp., 30 min).[22] Boc deprotections were carried out with HCl rather than with the usual trifluoroacetic acid in dichloromethane to avoid partial trifluoroacetylation of the products[23] during the coupling step.

The stereochemical integrity was checked a) via α-methoxy-α-trifluoromethyl(phenyl)acetic acid (MTPA) derivatization[24] of hydrochlorides **29** and NMR analysis ($^1$H, $^{13}$C, $^{19}$F),[25] and b) via $^{13}$C-NMR analysis of vs-dipeptides **30**.[26] The sulfonamide bond is formed from the sulfonyl chloride and the amine via a nucleophilic substitution at the four-coordinated sulfur.[27a] The alternative sequence involving an elimination-addition reaction via an achiral unsaturated sulfene,[27b] is not likely to occur as it would lead to a mixture of two diasteromeric dimers (Scheme 7).[26]

Scheme 7. Alternative mechanisms for sulfonamide bond formation: nucleophilic substitution at the four coordinated sulfur or elimination-addition reaction via sulfene




The process was further iterated to give vs-tripeptides **31** (27−60%) and vs-tetrapeptides **32** (30−60%). Many different vs-peptides were prepared following the above route and are described in the Experimental Section.

The above procedure is also useful for synthesizing "mixed" peptides, which incorporate both proteinogenic α-amino acids and vs-amino acids. Proteinogenic α-amino acids were incorporated at both the C-terminal [(*S*)-*N*-Boc−vsAA−Gly−OMe **33** (51−80%), (*S*)-*N*-Boc−vsAA−(*S*)-vsAA−Gly−OMe **34** (25−41%)] and the N-terminal position [(*S*)-*N*-Boc−Ala−(*S*)-vsAA−R (R = OR, NHR) **35**, coupling conditions: 1-hydroxybenzotriazole (HOBt), TEA, DMAP, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in dichloromethane, 46−87%].

Boc deprotection (sat. HCl solution in EtOAc)[22] and coupling chemistry occurred uneventfully for sulfonamidopeptides containing vsSer(TBDPS) and vsTyr(TBDPS). Final treatment with *n*Bu$_4$NF gave the side-chain deprotected sulfonamidopeptides containing free vsSer and vsTyr (**36**) in good yields (70−94%). In the case of (*S*)-*N*-Boc−vsGln(Trt)−Gly−OMe all the acidic conditions used to deprotect the main chain nitrogen from the Boc group removed also the trityl group from the side chain nitrogen, causing the production of various by-products.

### Summary and Outlook

In summary, we have developed a straightforward approach for the iterative synthesis of sulfonamido-pseudopeptides based on chiral vinylogous amino sulfonic acids (vs-amino acids). The functionalization of the α,β-double bond (Michael additions), the base mediated *N*-alkylations of the sulfonamide group, the extension of these chemistries to solid-phase synthesis and the preparation of combinatorial libraries (split and pool) are under active investigation and will be the subject of a future paper. An entire new array of chiral unnatural polymers is now potentially available, with biological properties to be discovered.

The authors wish to thank Dr. *A. Williams* for running some preliminary experiments on the synthesis of sulfonamido-pseudopeptides based on β-aminosulfonamides in the early stage of this project and Mr. *S. Scotti* for his help during the synthesis of the functionalized vinylogous sulfonamidopeptides. *Pharmacia & Upjohn* (Milano) postdoctoral fellowship to Dr. B. S., postgraduate fellowships to Ms. C. L. and Mr. S. R., and generous financial support are gratefully acknowledged. We thank the *Commission of the European Union* (Fixed Contribution Contract for Training through Research ERB FMB ICT 960586) for financial support and for a postdoctoral fellowship to Dr. A. M.

## Experimental Section

*General:* Nuclear magnetic resonance spectra were recorded with Bruker AC-200, AC-300, AC-500, Varian XL-200 and XL-400 instruments. Optical rotations were determined using a Perkin-Elmer 141 polarimeter. − IR spectra were recorded with a Perkin-Elmer 457 and a FT-IR Varian spectrometers. − All products were purified by flash chromatography using 230−400 mesh silica gel (Merck). − TLC analyses were performed with 0.25 mm 60 $F_{254}$ silica plates (Merck). − All solvents were distilled over drying agents under 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 atmosphere. Organic extracts were dried over $Na_2SO_4$. − *N*-Boc−α-amino alcohols **4** were either purchased from Aldrich or synthesized according to ref.[28]. *N*-Boc−α-amino aldehydes **5** were synthesized according to ref.[12].

*Synthesis of α,β-Unsaturated Sulfonates* (**6**)

*(S)-N-Boc−vsAla−OEt* (**6**, R$^1$ = Me): A solution of ethyl (diethylphosphoryl)methanesulfonate (5.0 g, 19.2 mmol) in THF (72.0

ml) was treated at −78°C, under nitrogen, with a 1.6 M solution of *n*BuLi in *n*-hexane (13.2 ml, 21.1 mmol). After 20 min stirring at −78°C, a solution of (*S*)-*N*-Boc−alaninal[12][13] (3.3 g, 19.2 mmol) in THF (5.0 ml) was added. After 30 min pH 7 phosphate buffer was added and the aqueous phase extracted with ethyl ether. The combined organic extracts were dried, and the solvent evaporated under vacuum. The crude mixture was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) and crystallized (*n*-hexane/ethyl acetate, 8:2) to give the desired sulfonate (4.18 g, 78% yield), m.p. = 69−71°C. − $[\alpha]_D$ = −18.1 (*c* = 0.98, $CHCl_3$). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.33 (3 H, d, C*H*$_3$CH, *J* = 6.9 Hz), 1.39 (3 H, t, C*H*$_3$CH$_2$OSO$_2$, *J* = 7.2 Hz), 1.46 [9 H, s, $(CH_3)_3$C], 4.18 (2 H, q, CH$_3$C*H*$_2$OSO$_2$, *J* = 7.2 Hz), 4.44 (1 H, m, CH$_3$C*H*N), 4.6 (1 H, broad, NH), 6.30 (1 H, dd, CH=C*H*SO$_3$, *J* = 15.1, *J* = 1.6 Hz), 6.83 (1 H, dd, C*H*=CHSO$_3$, *J* = 15.1, *J* = 5.0 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 14.65 ($CH_3$), 19.58 ($CH_3$), 28.13 ([$CH_3$]$_3$), 47.14 (CH-N), 66.85 ($CH_2$), 123.86 (CH=), 149.61 (CH=). − $C_{11}H_{21}NO_5S$ (279.4): calcd. C 47.30, H 7.58, N 5.01; found C 47.24, H 7.65, N 4.97.

*(S)-N-Boc−vsVal−OEt* (**6**, R$^1$ = *i*Pr): Following the above procedure the desired product was obtained in 77% yield after flash chromatography (*n*-hexane/ethyl acetate, 7:3) and crystallization (*n*-hexane), m.p. = 53−55°C. − $[\alpha]_D$ = + 3.2 (*c* = 1.0, $CHCl_3$). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.96 (3 H, d, C*H*$_3$CH, *J* = 6.4 Hz), 0.98 (3 H, d, C*H*$_3$CH, *J* = 6.4 Hz), 1.36 (3 H, t, C*H*$_3$CH$_2$OSO$_2$, *J* = 7.5 Hz), 1.44 [9 H, s, $(CH_3)_3$C], 1.88 [1 H, m, $(CH_3)_2$C*H*, *J* = 6.4 Hz], 4.15 (2 H, q, CH$_3$C*H*$_2$OSO$_2$, *J* = 7.5 Hz), 4.20 (1 H, m, CHN), 4.55 (1 H, broad, NH), 6.32 (1 H, dd, CH=C*H*SO$_3$, *J* = 14.6 Hz, *J* = 1.9 Hz), 6.80 (1 H, dd, C*H*=CHSO$_3$, *J* = 14.6 Hz, *J* = 4.9 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 14.69 ($CH_3$), 17.95 ($CH_3$), 18.74 ($CH_3$), 28.14 [$(CH_3)_3$], 31.78 [$(CH_3)_2$*C*H], 56.38 (CHN), 66.81 ($CH_2$), 125.16 (CH=), 147.63 (CH=). − $C_{13}H_{25}NO_5S$ (307.4): calcd. C 50.79, H 8.20, N 4.56; found C 50.71, H 8.25, N 4.52.

*(S)-N-Boc−vsAla−OMe* (**6**, R$^1$ = Me): Following the above procedure but using methyl (diethylphosphoryl )methanesulfonate, the desired product was obtained in 75% yield after flash chromatography (*n*-hexane/ethyl acetate, 75:25) and crystallization (*n*-hexane/ethyl acetate, 7:3), m.p. = 89−91°C. − $[\alpha]_D$ = −22.3 (*c* = 1.0, $CHCl_3$). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.33 (3 H, d, C*H*$_3$CH, *J* = 7.0 Hz), 1.45 [9 H, s, $(CH_3)_3$C], 3.82 (3 H, s, CH$_3$OSO$_2$), 4.45 (1 H, m, CH$_3$C*H*N), 4.61 (1 H, d, NH, *J* = 4.4 Hz), 6.27 (1 H, dd, CH=C*H*SO$_3$, *J* = 15.1 Hz, *J* = 1.6 Hz), 6.86 (1 H, dd, C*H*=CHSO$_3$, *J* = 15.1 Hz, *J* = 5.0 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 19.61 ($CH_3$), 28.15 [$(CH_3)_3$], 46.75 (CHN), 56.16 ($OCH_3$), 122.71 (CH=), 150.66 (CH=). − $C_{10}H_{19}NO_5S$ (265.3): calcd. C 45.27, H 7.22, N 5.28; found C 45.21, H 7.28, N 5.25.

*(S)-N-Boc−vsVal−OMe* (**6**, R$^1$ = *i*Pr): Following the above procedure the desired product was obtained in 83% yield after flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.90 (3 H, d, C*H*$_3$CH, *J* = 6.8 Hz), 0.92 (3 H, d, C*H*$_3$CH, *J* = 6.7 Hz), 1.4 [9 H, s, $(CH_3)_3$C], 1.85 [1 H, m, $(CH_3)_2$C*H*, *J* = 6.7 Hz], 3.75 (3 H, s, CH$_3$OSO$_2$), 4.15 (1 H, m, CHN), 4.85 (1 H, broad, NH), 6.25 (1 H, dd, CH=C*H*SO$_3$, *J* = 15.2 Hz, *J* = 1.0 Hz), 6.8 (1 H, dd, C*H*=CHSO$_3$, *J* = 15.2 Hz, *J* = 5.4 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 17.95 ($CH_3$), 18.76 ($CH_3$), 28.12 [$(CH_3)_3$], 31.75 ($Me_2$*C*H), 56.12 ($CH_3$), 56.38 (CHN), 123.9 (CH=), 148.79 (CH=), 155.17 (C=O). − $C_{12}H_{23}NO_5S$ (293.4): calcd. C 49.13, H 7.90, N 4.77; found C 49.07, H 7.98, N 4.73.

*(S)-N-Boc−vsPhe−OMe* (**6**, R$^1$ = $CH_2$Ph): Following the above procedure the desired product was obtained in 85% yield after flash chromatography (*n*-hexane/ethyl acetate, 65:35) and crystallization (*n*-hexane/ethyl acetate, 7:3), m.p. = 115−117°C. − $[\alpha]_D$ = +10.8 (*c* = 1.05, $CHCl_3$). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.42 [9 H, s, $(CH_3)_3$], 2.95 (2 H, d, $CH_2$Ph, *J* = 6.63 Hz), 3.73 (3 H, s, CH$_3$OSO$_2$), 4.37 (1 H, m, CHN), 4.47 (1 H, m, NH), 6.24 (1 H, dd, CH=C*H*SO$_3$, *J* = 14.65 Hz, *J* = 1.27 Hz), 6.83 (1 H, dd, C*H*=CHSO$_3$, *J* = 14.65 Hz, *J* = 5.37 Hz), 7.10−7.35 (5 H, m, ArH). − $^{13}$C NMR ($CDCl_3$): δ = 28.84 [$(CH_3)_3$], 40.88 ($CH_2$Ph), 52.71 (CHN), 56.79 ($OCH_3$), 124.64 (CH=), 127.83 (Ar), 129.41 (Ar), 129.87 (Ar), 136.28 (Ar), 149.35 (CH=), 155.40 (CO). − $C_{16}H_{23}NO_5S$ (341.4): calcd. C 56.29, H 6.79, N 4.10; found C 56.35, H 6.82, N 4.07.

*(R)-N-Boc−vsPhe−OMe:* Following the above procedure the desired product was obtained in 75% yield after flash chromatography (*n*-hexane/ethyl acetate, 65:35). − $[\alpha]_D$ = −11.2 (*c* = 1.05, $CHCl_3$). − $C_{16}H_{23}NO_5S$ (341.4): calcd. C 56.29, H 6.79, N 4.10; found C 56.34, H 6.83, N 4.05.

*(S)-N-Boc−vsLeu−OMe* (**6**, R$^1$ = *i*Bu): Following the above procedure the desired product was obtained in 85% yield after flash chromatography (*n*-hexane/ethyl acetate, 80:20) and crystallization (*n*-hexane/ethyl acetate, 95:5), m.p. = 59−61°C. − $[\alpha]_D$ = −15.4 (*c* = 1.0, $CHCl_3$). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.95 [6 H, d, $(CH_3)_2$CH, *J* = 6.6 Hz], 1.40−1.54 (2 H, m, *i*Pr-C*H*$_2$), 1.45 [9 H, s, $(CH_3)_3$C], 1.64 (1 H, m, $Me_2$C*H*), 3.81 (3 H, s, CH$_3$OSO$_2$), 4.40 (1 H, m, CHN), 4.50 (1 H, broad d, NH), 6.28 (1 H, dd, CH=C*H*SO$_3$, *J* = 15.1 Hz, *J* = 1.2 Hz), 6.79 (1 H, dd, C*H*=CHSO$_3$, *J* = 15.1 Hz, *J* = 5.4 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 21.77 ($CH_3$), 22.58 ($CH_3$), 24.56 (CH), 28.18 [$(CH_3)_3$], 42.61 ($CH_2$), 49.42 (CHN), 56.12 ($CH_3$), 122.81 (CH=), 150.30 (CH=). − $C_{13}H_{25}NO_5S$ (307.4): calcd. C 50.79, H 8.20, N 4.56; found C 50.72, H 8.25, N 4.50.

*(S)-N-Boc−vsPro−OMe:* Following the above procedure the desired product was obtained in 85% yield after flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $[\alpha]_D$ = −6.6 (*c* = 1.01, $CHCl_3$). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.44 [9 H, s, $(CH_3)_3$C], 1.76−1.95 (3 H, m, NCHCH*H*C*H*$_2$), 2.2 (1 H, m, NCHC*H*H), 3.43 (2 H, m, NC*H*$_2$CH$_2$), 3.81 (3 H, s, $OCH_3$), 4.5 (1 H, m, NCH), 6.20 (1 H, dd, CH=C*H*SO$_3$, *J* = 15.1 Hz, *J* = 0.9 Hz), 6.8 (1 H, dd, C*H*=CHSO$_3$, *J* = 15.1 Hz, *J* = 5.7 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 20.90 ($CH_2$), 28.22 [$(CH_3)_3$], 31.43 ($CH_2$), 46.31 ($CH_2$), 55.90 (CH), 57.08 ($OCH_3$), 123.13 (CH=), 149.31 (CH=). − $C_{12}H_{21}NO_5S$ (291.4): calcd. C 49.47, H 7.26, N 4.81; found C 49.41, H 7.33, N 4.77.

*(R)-N-Boc−vsPro−OMe:* Following the above procedure the desired product was obtained in 75% yield after flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $[\alpha]_D$ = + 5.5 (*c* = 1.01, $CHCl_3$). − $C_{12}H_{21}NO_5S$ (291.4): calcd. C 49.47, H 7.26, N 4.81; found C 49.40, H 7.36, N 4.80.

*Synthesis of Tetrabutylammonium Sulfonates* (**7**)

A solution of ethyl or methyl α,β-unsaturated sulfonate (3.6 mmol) in HPLC grade acetone (20 ml) was treated with $nBu_4NI$ (recrystallized from ethyl acetate/MeOH, 95:5; 1.33 g, 3.6 mmol), under nitrogen, with stirring. The mixture was refluxed for 16−20 hours monitoring the disappearance of the starting material by TLC (*n*-hexane/ethyl acetate, 6:4). Solvent evaporation at reduced pressure gave the tetrabutylammonium sulfonate quantitatively (100%).

*(S)-N-Boc−vsAla−O$^-$(NBu$_4$)$^+$* (**7**, R$^1$ = Me): $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.0 (12 H, t, [C*H*$_3$CH$_2$CH$_2$CH$_2$)$_4$N$^+$, *J* = 7.6 Hz], 1.20 (3 H, d, C*H*$_3$CHN, *J* = 6.8 Hz), 1.40 [9 H, s, $(CH_3)_3$C], 1.4−1.8 [16 H, m, (CH$_3$C*H*$_2$C*H*$_2$CH$_2$)$_4$N$^+$], 3.3 [8 H, m, (CH$_3$CH$_2$CH$_2$C*H*$_2$)$_4$N$^+$], 4.30 (1 H, m, CH$_3$C*H*N), 4.45 (1 H,

broad, NH), 6.42 (2 H, m, CH=CHSO$_3$). − $C_{25}H_{52}N_2O_5S$ (492.8): calcd. C 60.94, H 10.64, N 6.68; found C 60.86, H 10.74, N 6.62.

*(S)-N-Boc−vsVal−O$^-$(NBu$_4$)$^+$* (**7**, R$^1$ = *i*Pr): $^1$H NMR (200 MHz, CDCl$_3$): δ = 0.87 (3 H, d, C*H*$_3$CHC, *J* = 7.4 Hz), 0.92 (3 H, d, C*H*$_3$CHC, *J* = 7.4 Hz), 1.01 [12 H, t, (C*H*$_3$CH$_2$CH$_2$CH$_2$)$_4$N$^+$, *J* = 7.2 Hz], 1.44 [9 H, s, (CH$_3$)$_3$C], 1.4−1.75 [16 H, m, (CH$_3$C*H*$_2$C*H*$_2$CH$_2$)$_4$N$^+$], 1.82 (1 H, m, Me$_2$C*H*), 3.33 [8 H, m, (CH$_3$CH$_2$CH$_2$C*H*$_2$)$_4$N$^+$], 4.15 (1 H, m, CHN), 4.53 (1 H, d, NH, *J* = *9*.4 Hz), 6.48 (2 H, m, CH=CHSO$_3$). − $C_{27}H_{56}N_2O_5S$ (520.8): calcd. C 62.27, H 10.84, N 5.38; found. C 62.20, H 10.95, N 5.34.

*(S)-N-Boc−vsPhe−O$^-$(NBu$_4$)$^+$* (**7**, R$^1$ = CH$_2$Ph): $^1$H NMR (200 MHz, CDCl$_3$): δ = 1.0 [12 H, t, (C*H*$_3$CH$_2$CH$_2$CH$_2$)$_4$N$^+$, *J* = 7.2 Hz], 1.34 [9 H, s, (CH$_3$)$_3$C], 1.35−1.80 [16 H, m, (CH$_3$C*H*$_2$C*H*$_2$CH$_2$)$_4$N$^+$], 2.92 (2 H, dd, C*H*$_2$Ph, *J* = 5.8 Hz, *J* = 13.6 Hz), 3.32 [8 H, m, (CH$_3$CH$_2$CH$_2$C*H*$_2$)$_4$N$^+$], 4.49 (2 H, m, CHN + NH), 6.49 (2 H, m, CH=CHSO$_3$), 7.17−7.29 (5 H, m, Ar*H*). − $C_{31}H_{56}N_2O_5S$ (568.9): calcd. C 65.45, H 9.92, N 4.92; found C 65.37, H 10.01, N 4.89.

*(R)-N-Boc−vsPhe−O$^-$(NBu$_4$)$^+$:* $C_{31}H_{56}N_2O_5S$ (568.9): calcd. C 65.45, H 9.92, N 4.92; found C 65.39, H 9.99, N 4.90.

*(S)-N-Boc−vsLeu−O$^-$*(NBu$_4$)$^+$ (**7**, R$^1$ = *i*Bu): $^1$H NMR (200 MHz, CDCl$_3$): δ = 0.89 (6 H, (C*H*$_3$)$_2$CH, *J* = 6.6 Hz), 1.00 [12 H, t, (C*H*$_3$CH$_2$CH$_2$CH$_2$)$_4$N$^+$, *J* = 7.1 Hz], 1.32−1.53 [16 H, m, (CH$_3$C*H*$_2$C*H*$_2$CH$_2$)$_4$N$^+$], 1.41 [9 H, s, (CH$_3$)$_3$C], 1.57−1.72 (3 H, m, (CH$_3$)$_2$C*H*C*H*$_2$), 3.30 [8 H, m, (CH$_3$CH$_2$CH$_2$C*H*$_2$)$_4$N$^+$, *J* = 8.0 Hz], 4.30 (1 H, m, CHN), 4.40 (1 H, d, NH), 6.30−6.50 (2 H, m, CH=CH). − $C_{28}H_{58}N_2O_5S$ (534.8): calcd. C 62.88, H 10.93, N 5.24; found C 62.80, H 10.83, N 5.20.

*(S)-N-Boc−vsPro−O$^-$(NBu$_4$)$^+$:* $^1$H NMR (200 MHz, CDCl$_3$): δ = 1.00 [12 H, t, (C*H*$_3$CH$_2$CH$_2$CH$_2$)$_4$N$^+$, *J* = 7.6 Hz], 1.45 [9 H, s, (CH$_3$)$_3$C], 1.4−2.0 [20 H, m, CC*H*$_2$C*H*$_2$C + (CH$_3$C*H*$_2$C*H*$_2$CH$_2$)$_4$N$^+$], 3.30 [8 H, m, (CH$_3$CH$_2$CH$_2$C*H*$_2$)$_4$N$^+$], 3.37 (2 H, m, NC*H*$_2$CH$_2$), 4.30 (1 H, m, NC*H*CH$_2$), 6.33 (2 H, m, CH=C*H*SO$_3$ + C*H*=CHSO$_3$). − $C_{27}H_{54}N_2O_5S$ (518.8): calcd. C 62.51, H 10.49, N 5.40; found C 62.43, H 10.39, N 5.36.

*(R)-N-Boc−vsPro−O$^-$(NBu$_4$)$^+$:* $C_{27}H_{54}N_2O_5S$ (518.8): calcd. C 62.51, H 10.49, N 5.40; found C 62.46, H 10.40, N 5.40.

*Synthesis of Sulfonyl Chlorides* (**8**)

*(S)-N-Boc−vsAla−Cl* (**8**, R$^1$ = Me): Sulfuryl chloride, $SO_2Cl_2$, (180 mg, 0.107 ml, 1.33 mmol) was added to a solution of triphenylphosphine (320 mg, 1.224 mmol) in DCM (1.5 ml) at 0°C, under nitrogen, in the presence of 3 Å molecular sieves. A solution of (*S*)-*N*-Boc−vsAla−O$^-$(NBu$_4$)$^+$ (302 mg, 0.611 mmol) in DCM (2.0 ml) was then added at room temperature, under nitrogen, with stirring. The reaction mixture was stirred at room temp. for 2.5 hours, then the solvent was removed under vacuum and the crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:4) to give the sulfonyl chloride in 85% yield (142 mg). − $^1$H NMR (200 MHz, CDCl$_3$): δ = 1.32 (3 H, d, C*H*$_3$CH, *J* = 7.1 Hz), 1.42 [9 H, s, (CH$_3$)$_3$C], 4.5 (1 H, broad, CH$_3$C*H*N), 5.0 (1 H, broad, NH), 6.80 (1 H, dd, CH=C*H*SO$_2$, *J* = 14.8, *J* = 1.1 Hz), 6.97 (1 H, dd, C*H*=CHSO$_2$, *J* = 14.8 Hz, *J* = 4.4 Hz). − $^{13}$C NMR (CDCl$_3$): δ = 19.36 (CH$_3$), 28.14 [(CH$_3$)$_3$C], 46.49 (CHN), 132.68 (CH=), 150.42 (CH=), 154.65 (C=O). − $C_9H_{16}ClNO_4S$ (269.7): calcd. C 40.07, H 5.98, N 5.19; found C 40.02, H 5.93, N 5.14.

*(S)-N-Boc−vsVal−Cl* (**8**, R$^1$ = *i*Pr): Following the above procedure the sulfonyl chloride was obtained in 87% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, CDCl$_3$): δ = 0.95 (3 H, d, C*H*$_3$CH, *J* = 6.9 Hz), 0.98 (3 H, d, C*H*$_3$CH, *J* = 6.7 Hz), 1.45 [9 H, s, (CH$_3$)$_3$C], 1.93 [1 H, m, (CH$_3$)$_2$C*H*], 4.30 (1 H, m, CHN), 4.8 (1 H, broad, NH), 6.84 (1 H, dd, CH=C*H*SO$_2$, *J* = 14.7 Hz, *J* = 0.8 Hz), 6.99 (1 H, dd, C*H*=CHSO$_2$, *J* = *1*4.7 Hz, *J* = *4*.8 Hz). − $^{13}$C NMR (CDCl$_3$): δ = 17.92 (CH$_3$), 18.70 (CH$_3$), 28.14 [(CH$_3$)$_3$], 31.99 (Me$_2$CH), 57.00 (CHN), 133.90 (CH=), 148.75 (CH=). − $C_{11}H_{20}ClNO_4S$ (297.8): calcd. C 44.37, H 6.77, N 4.70; found C 44.31, H 6.70, N 4.67.

*(S)-N-Boc−vsPhe−Cl* (**8**, R$^1$ = CH$_2$Ph): Following the above procedure the sulfonyl chloride was obtained in 85% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, CDCl$_3$): δ = 1.43 [9 H, s, (CH$_3$)$_3$C], 2.96 (2 H, d, C*H*$_2$Ph, *J* = 6.3 Hz), 4.74 (2 H, broad, CHN + NH), 6.73 (1 H, d, CH=C*H*SO$_2$, *J* = 14.8 Hz), 7.04 (1 H, dd, C*H*=CHSO$_2$, *J* = 14.8 Hz, *J* = 4.4 Hz). − $^{13}$C NMR (CDCl$_3$): δ = 28.13 [(CH$_3$)$_3$], 40.02 (CH$_2$Ph), 127.35 (Ar), 128.85 (Ar), 129.21 (Ar), 135.55 (CH=), 148.82 (CH=). − $C_{15}H_{20}ClNO_4S$ (345.8): calcd. C 52.09, H 5.83, N 4.05; found C 52.03, H 5.78, N 4.02.

*(R)-N-Boc−vsPhe−Cl:* − $C_{15}H_{20}ClNO_4S$ (345.8): calcd. C 52.09, H 5.83, N 4.05; found C 52.05, H 5.70, N 4.00.

*(S)-N-Boc−vsLeu−Cl* (**8**, R$^1$ = *i*Bu): Following the above procedure the sulfonyl chloride was obtained in 85% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, CDCl$_3$): δ = 0.96 [6 H, d, (C*H*$_3$)$_2$CH, *J* = 7.1 Hz], 1.44 [9 H, s, (CH$_3$)$_3$C], 1.35−1.60 (2 H, m, *i*PrC*H*$_2$C), 1.70 (1 H, m, Me$_2$C*H*C), 4.48 (1 H, broad, CHN), 4.69 (1 H, broad, NH), 6.32 (1 H, d, CH=C*H*SO$_2$, *J* = 15.0 Hz), 6.98 (1 H, dd, C*H*=CHSO$_2$, *J* = 15.0 Hz, *J* = 4.9 Hz). − $^{13}$C NMR (CDCl$_3$): δ = 21.69 (CH$_3$), 22.62 (CH$_3$), 24.64 (CH), 28.14 [(CH$_3$)$_3$], 42.67 (CH$_2$), 49.11 (CHN), 132.90 (CH=), 149.99 (CH=). − $C_{12}H_{22}ClNO_4S$ (311.8): calcd. C 46.22, H 7.11, N 4.49; found C 46.18, H 7.04, N 4.45.

*(S)-N-Boc−vsPro−Cl:* Following the above procedure the sulfonyl chloride was obtained in 86% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, CDCl$_3$): δ = 1.47 [9 H, s, (CH$_3$)$_3$C], 1.70−2.05 (3 H, m, CCH*H*C*H*$_2$C), 2.20 (1 H, m, CCH*H*CH$_2$C), 3.50 (2 H, m, NC*H*$_2$CH$_2$), 4.50 (1 H, m, NC*H*CH$_2$), 6.70 (1 H, d, CH=C*H*SO$_2$, *J* = 14.80 Hz), 6.96 (1 H, dd, C*H*=CHSO$_2$, *J* = 14.80 Hz, *J* = 5.40 Hz). − $^{13}$C NMR (CDCl$_3$): δ = 22.96 (CH$_2$), 28.22 [(CH$_3$)$_3$], 31.32 (CH$_2$), 46.46 (CH$_2$), 56.76 (CH), 133.03 (CH=), 149.25 (CH=). − $C_{11}H_{18}ClNO_4S$ (295.8): calcd. C 44.67, H 6.13, N 4.74; found C 44.62, H 6.07, N 4.71.

*(R)-N-Boc−vsPro−Cl:* − $C_{11}H_{18}ClNO_4S$ (295.8): calcd. C 44.67, H 6.13, N 4.74; found C 44.64, H 6.10, N 4.70.

*Synthesis of (S)-N-Boc−vsSer(TBDPS)−Cl* (**14**)

*(S)-N-Boc−Ser−OMe* (**9**): To a solution of (*S*)-*N*-Boc−Ser−OH (9.747 g, 47.5 mmol) in DMF (44.5 ml) was added $K_2CO_3$ (7.214 g, 52.25 mmol). The mixture was stirred under nitrogen at 0°C for 10 minutes, then MeI (13.48 g, 5.9 ml, 95 mmol) was added dropwise. After 30 minutes at 0°C and 2 hours at room temperature the mixture was filtered and the filtrate, diluted with water, was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried and the solvent was evaporated under reduced pressure. The crude compound (100%) was enough pure to be used in the next step. − $^1$H NMR (200 MHz, CDCl$_3$): δ = 1.41 [9 H, s, (CH$_3$)$_3$C], 2.4 (1 H, m, OH), 3.7 (3 H, s, OCH$_3$), 3.8 (2 H, m, CH$_2$O), 4.25 (1 H, m, CHN), 5.65 (1 H, broad, NH). − $C_9H_{17}NO_5$ (219.2): calcd. C 49.31, H 7.82, N 6.39; found C 49.25, H 7.89, N 6.34.

*(S)-N-Boc−Ser(TBDPS)−OMe* (**10**): To a solution of (*S*)-*N*-Boc−Ser−OMe (50 mg, 0.228 mmol) in DMF (1 ml), under nitrogen at room temperature, were added TBDPS-Cl (75.3 mg, 0.274 mmol) and imidazole (38.8 mg, 0.57 mmol). After 30 min water (1 ml) was added, and the water phase was extracted with ethyl acetate. The combined organic extracts were dried and evaporated at reduced pressure. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 9:1) to give the desired product in 77% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.05 [9 H, s, $(CH_3)_3CSi$], 1.45 [9 H, s, $(CH_3)_3CO$], 3.75 (3 H, s, $OCH_3$), 3.90−4.10 (2 H, dd, $OCH_2CH$, *J* = 3.1 Hz, *J* = 8.8 Hz), 4.45 (1 H, m, NHC*H*), 5.45 (1 H, d, NH, *J* = 8.0 Hz), 7.35−7.65 (10 H, m, 2× PhSi).

*(S)-N-Boc−Ser(TBDPS)−H* (**11**): Following the procedure described below for the preparation of aldehyde (**22**), (*S*)-*N*-Boc−Ser(TBDPS)−OMe (**10**) was reduced to give (**11**) in 95% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.1 [9 H, s, $(CH_3)_3CSi$], 1.41 [9 H, s, $(CH_3)_3CO$], 3.7 (2 H, m, $OCH_2CH$), 4.3 (1 H, broad, NHC*H*), 5.3 (1 H, broad, NH), 7.3−7.7 (10 H, m, 2× PhSi), 9.65 (1 H, s, CHO). − $C_{24}H_{33}NO_4Si$ (427.6): calcd. C 67.41 H 7.78, N 3.28; found C 67.32, H 7.86, N 3.25.

*(S)-N-Boc−vsSer(TBDPS)−OEt* (**12**): Following the procedure described above for the α,β-unsaturated sulfonates (**6**), the desired product was obtained in 46% yield after flash chromatography (*n*-hexane/ethyl acetate, 9:1). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.08 [9 H, s, $(CH_3)_3CSi$], 1.36 (3 H, t, $OCH_2CH_3$, *J* = 7.1 Hz), 1.47 [9 H, s, $(CH_3)_3CO$], 3.79 (2 H, m, $OCH_2CH$), 4.17 (2 H, q, $OCH_2CH_3$, *J* = 7.1 Hz), 4.45 (1 H, m, CHN), 4.96 (1 H, d, NH, *J* = 8.3 Hz), 6.39 (1 H, dd, CH=C*H*$SO_3$, *J* = 1.6 Hz, *J* = 15.1 Hz), 6.9 (1 H, dd, C*H*=$CHSO_3$, *J* = 4.7 Hz, *J* = 15.1 Hz), 7.3−7.7 (10 H, m, 2× PhSi). − $^{13}$C NMR ($CDCl_3$): δ = 14.73 ($OCH_2CH_3$), 26.75 [($CH_3$)$_3$CSi], 28.18 [($CH_3$)$_3$CO], 52.62 (CH), 64.71 ($CHCH_2O$), 66.83 ($OCH_2CH_3$), 125.75 (CH=*C*HS), 127.89 (CH=), 130.02 (CH=), 135.45 (CH=), 146.62 (*C*H=CHS). − $C_{27}H_{39}NO_6SSi$ (533.8): calcd. C 60.76, H 7.36, N 2.62; found C 60.69, H 7.43, N 2.60.

*(S)-N-Boc−vsSer(TBDPS)−O$^-$(NBu$_4$)$^+$* (**13**): Following the procedure described above for the tetrabutylammonium sulfonates (**7**), the desired product was obtained in 100% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.95 [12 H, t, $(CH_3CH_2CH_2CH_2)_4N^+$, *J* = 7.1 Hz], 1.02 [9 H, s, $(CH_3)_3CSi$], 1.2−1.8 [16 H, m, $(CH_3CH_2CH_2CH_2)_4N^+$], 1.4 [9 H, s, $(CH_3)_3CO$], 3.3 [8 H, m, $(CH_3CH_2CH_2CH_2)_4N^+$], 3.55 (1 H, dd, C*H*HOTBDPS, *J* = 10.2 Hz, *J* = 7.0 Hz), 3.75 (1 H, dd, CH*H*OTBDPS, *J* = 10.2 Hz, *J* = 4.3 Hz), 4.45 (1 H, m, CHN), 4.60 (1 H, m, NH), 6.43 (1 H, dd, C*H*=$CHSO_3$, *J* = 4.3 Hz, *J* = 15.5 Hz), 6.53 (1 H, d, CH=C*H*$SO_3$, *J* = 15.5 Hz), 7.3−7.7 (10 H, m, 2× PhSi). − $C_{41}H_{70}N_2O_6SSi$ (747.2): calcd. C 65.91, H 9.44, N 3.75; found C 65.83, H 9.35, N 3.73.

*(S)-N-Boc−vsSer(TBDPS)−Cl* (**14**): Following the procedure described above for the sulfonyl chlorides (**8**), the desired product was obtained in 74% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 75:25). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.09 [9 H, s, $(CH_3)_3CSi$], 1.48 [9 H, s, $(CH_3)_3CO$], 3.81 (2 H, m, $CH_2OSi$), 4.56 (1 H, broad, CHN), 4.99 (1 H, d, NH, *J* = 8.5 Hz), 6.89 (1 H, dd, CH=C*H*$SO_2$, *J* = 1.5 Hz, *J* = 14.9 Hz), 7.06 (1 H, dd, C*H*=$CHSO_2$, *J* = 4.0 Hz, *J* = 14.9 Hz), 7.3−7.7 (10 H, m, 2× PhSi). − $^{13}$C NMR ($CDCl_3$): δ = 26.75 [($CH_3$)$_3$], 28.22 [($CH_3$)$_3$], 52.40 (CHN), 64.62 ($CH_2O$), 127.98 (CH=), 130.11 (CH=), 134.45 (CH=), 135.42 (CH=), 147.79 (CH=). − $C_{25}H_{34}ClNO_5SSi$ (524.2): calcd. C 57.29, H 6.54, N 2.67; found C 57.22, H 6.48, N 2.65.

*Synthesis of (S)-N-Boc−vsTyr(TBDPS)−Cl* (**20**)

*(S)-N-Boc−Tyr−OMe* (**15**): To a solution of tyrosine (1.1 g, 6.1 mmol) in 2,2-dimethoxypropane (75 ml) was added conc. HCl (6 ml). After stirring for 24 hours at room temperature the solvent was evaporated under reduced pressure and the crude product was dissolved in methanol. $Et_2O$ was added to this solution to precipitate the methylester hydrochloride, which was filtered and used as a crude (100%) for the next step.

To a solution of HCl·(*S*)-H−Tyr−OMe (600 mg, 2.6 mmol) in DCM (2.6 ml) were added $NaHCO_3$ (2.6 ml, 1 M solution) and $Boc_2O$ (680 mg, 3.12 mmol). After stirring at room temperature for 2 hours the reaction mixture was quenched with water and extracted with DCM. The combined organic extracts were dried and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to give the desired product (93% yield). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.4 [9 H, s, $(CH_3)_3C$], 3.0 (2 H, m, $CHCH_2$-), 3.7 (3 H, s, $CH_3O$), 4.55 (1 H, m, NCHCO), 5.1 (1 H, d, NH, *J* = 8.3 Hz), 6.75 (2 H, d, CH=C-O, *J* = 8.4 Hz), 6.95 (2 H, d, CH=C-C, *J* = 8.4 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 28.18 [($CH_3$)$_3$], 37.42 ($CH_2$), 52.22 ($CH_3O$), 54.55 (CH), 115.45 (CH=), 130.20 (CH=). − $C_{15}H_{21}NO_5$ (295.3): calcd. C 61.00, H 7.17, N 4.74; found C 60.92, H 7.24, N 4.70.

*(S)-N-Boc−Tyr(TBDPS)−OMe* (**16**): To a solution of (*S*)-*N*-Boc−Tyr−OMe (250 mg, 0.846 mmol) in DCM (4.5 ml), under nitrogen at room temperature, were added TBDPS-Cl (581mg, 2.12 mmol) and imidazole (172 mg, 2.54 mmol). After four hours water (5 ml) was added, and the water phase was extracted with DCM. The combined organic extracts were dried and evaporated at reduced pressure. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 9:1) to give the desired product in 89% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.1 [9 H, s, $(CH_3)_3CSi$], 1.4 [9 H, s, $(CH_3)_3CO$], 2.9 (2 H, d, $CH_2CH$, *J* = 5.8 Hz), 3.6 (3 H, s, $OCH_3$), 4.5 (1 H, m, NHC*H*), 4.9 (1 H, d, NH, *J* = 7.9 Hz), 6.7 (2 H, 2× CH=C-O, *J* = 8.5 Hz), 6.9 (2 H, 2× CH=C-C, *J* = 8.5 Hz), 7.3−7.8 (10 H, m, 2× PhSi).

*(S)-N-Boc−Tyr(TBDPS)−H* (**17**): Following the procedure described below for the preparation of aldehyde (**22**), (*S*)-*N*-Boc−Tyr(TBDPS)−OMe (**16**) was reduced to give (**17**) in 95% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.1 [9 H, s, $(CH_3)_3CSi$], 1.4 [9 H, s, $(CH_3)_3CO$], 3.00 (2 H, d, $CH_2C_6H_4$, *J* = 6.5 Hz), 4.35 (1 H, broad, NHC*H*), 4.95 (1 H, broad, NH), 6.7 (2 H, CH=C-O, *J* = 8.6 Hz), 6.9 (2 H, CH=C-C, *J* = 8.6 Hz), 7.3−7.8 (10 H, m, 2× PhSi), 9.55 (1 H, s, CHO). − $C_{30}H_{37}NO_4Si$ (503.7): calcd. C 71.53, H 7.40, N 2.78; found C 71.42, H 7.47, N 2.80.

*(S)-N-Boc−vsTyr(TBDPS)−OMe* (**18**): Following the procedure described above for the α,β-unsaturated sulfonates (**6**), the desired product was obtained in 63% yield after flash chromatography (*n*-hexane/ethyl acetate, 85:15). − $[\alpha]_D$ = +12.1 (*c* = 1.01, $CHCl_3$). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.1 [9 H, s, $(CH_3)_3CSi$], 1.4 [9 H, s, $(CH_3)_3CO$], 2.8 (2 H, d, $CH_2C_6H_4$, *J* = 6.1 Hz), 3.6 (3 H, s, $OCH_3$), 4.55 (1 H, m, CHN), 4.55 (1 H, m, NH), 6.1 (1 H, d, CH=C*H*$SO_3$, *J* = 14.9 Hz), 6.8 (1 H, dd, C*H*=$CHSO_3$, *J* = 14.9 Hz, *J* = 5.0 Hz), 6.72 (2 H, CH=C, *J* = 8.5 Hz), 6.88 (2 H, CH=C, *J* = 8.5 Hz), 7.3−7.7 (10 H, m, 2× PhSi). − $^{13}$C NMR ($CDCl_3$): δ = 26.4 [($CH_3$)$_3$CSi], 28.17 [($CH_3$)$_3$CO], 39.32 ($CH_2$), 52.13 (CH), 56.12 ($OCH_3$), 119.4 (CH=), 123.74 (CH=*C*HS), 127.73 (CH=), 129.90 (CH=),129.99 (CH=), 135.4 (CH=), 148.95 (*C*H=CHS). − $C_{33}H_{43}NO_6SSi$ (609.9): calcd. C 64.99, H 7.11, N 2.30; found C 64.91, H 7.18, N 2.28.

*(S)-N-Boc−vsTyr(TBDPS)−O$^-$(NBu$_4$)$^+$* (**19**): Following the procedure described above for the tetrabutylammonium sulfonates

(**7**), the desired product was obtained in 100% yield. – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.0 [12 H, t, ($CH_3CH_2CH_2CH_2)_4N^+$, *J* = 7.0 Hz], 1.1 [9 H, s, $(CH_3)_3CSi$], 1.2–1.9 [16 H, m, ($CH_3CH_2CH_2CH_2)_4N^+$], 1.32 [9 H, s, $(CH_3)_3CO$], 2.63 (1 H, m, ArC*H*HCH), 2.80 (1 H, dd, ArCH*H*CH, *J* = 12.9 Hz, *J* = 4.7 Hz), 3.3 [8 H, m, ($CH_3CH_2CH_2CH_2)_4N^+$], 4.4 (2 H, m, CHN, NH), 6.46 (2 H, s, CH=$CHSO_3$), 6.64 (2 H, d, CH=C, *J* = 8.4 Hz), 6.90 (2 H, d, CH=C, *J* = 8.4 Hz), 7.3–7.8 (10 H, m, 2× PhSi). – $C_{47}H_{74}N_2O_6SSi$ (823.3): calcd. C 68.57, H 9.06, N 3.40; found C 68.48, H 8.97, N 3.37.

*(S)-N-Boc–vsTyr(TBDPS)–Cl* (**20**): Following the procedure described above for the sulfonyl chlorides (**8**), the desired product was obtained in 70% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 9:1). – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.12 [9 H, s, $(CH_3)_3CSi$], 1.44 [9 H, s, $(CH_3)_3CO$], 2.83 (2 H, m, $CH_2$), 4.62 (2 H, m, CHN, NH), 6.63 (1 H, dd, CH=C*H*$SO_2$, *J* = 14.8 Hz, *J* = 1.3 Hz), 6.9 (1 H, dd, C*H*=$CHSO_2$, *J* = 14.8 Hz, *J* = 4.6 Hz), 6.74 (2 H, CH=C-O, *J* = 8.5), 6.88 (2 H, CH=C-C, *J* = 8.5 Hz), 7.3–7.7 (10 H, m, 2× PhSi). – $^{13}$C NMR ($CDCl_3$): δ = 26.42 [$(CH_3)_3$], 28.17 [$(CH_3)_3$], 39.14 ($CH_2$), 51.72 (CHN), 120.1 (CH=), 127.7 (CH=), 129.9 (CH=), 133.49 (CH=), 135.41 (CH=), 135.41 (CH=), 148.99 (CH=). – $C_{31}H_{38}ClNO_5SSi$ (600.2): calcd. C 62.03, H 6.38, N 2.33; found C 61.97, H 6.32, N 2.32.

*Synthesis of (S)-N-Boc–vsGln(Trt)–Cl* (**25**)

*(S)-N-Boc–Gln(Trt)–H* (**22**): To a solution of (*S*)-*N*-Boc–Gln(Trt)–OMe (**21**) (33 mg, 0.066 mmol) in toluene/THF (1.0 ml, 1:1) at –78°C, under nitrogen, Dibal-H (1.5 M solution in toluene, 4.4 ml, 6.6 mmol) was added dropwise. After 2 hours MeOH (37 ml) and an aqueous solution of potassium and sodium tartrate (223 mg in 619 ml) were added and the mixture was vigorously stirred at room temperature for 30 min. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried and evaporated to give a crude product (95%) which was used without purification for the next step. – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.45 [9 H, s, $(CH_3)_3C$], 1.7 (2 H, m, $CH_2CH_2CO$), 2.4 (2 H, m, $CH_2CO$), 4.3 (1 H, broad, C*H*NH), 5.4 (1 H, broad, NH), 7.15 (1 H, s, N*H*$CPh_3$), 7.2–7.35 (15 H, m, Ar*H*), 9.45 (1 H, s, CHO). – $C_{29}H_{32}N_2O_4$ (472.6): calcd. C 73.71, H 6.83, N 5.93; found C 73.62, H 7.00, N 5.89.

*(S)-N-Boc–vsGln(Trt)–OEt* (**23**, R = OEt): Following the procedure described above for the α,β-unsaturated sulfonates (**6**), the desired product was obtained in 56% yield after flash chromatography (*n*-hexane/ethyl acetate, 65:35). – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.37 (3 H, t, $CH_3CH_2O$, *J* = 7.1 Hz), 1.44 [9 H, s, $(CH_3)_3C$], 1.82–1.94 (2 H, m, $CH_2CH_2CO$), 2.41 (2 H, t, $CH_2CH_2CO$, *J* = 6.7 Hz), 4.15 (2 H, q, $OCH_2CH_3$, *J* = 7.1 Hz), 4.31 (1 H, m, NHC*H*), 5.13 (1 H, d, N*H*CH, *J* = 5.6 Hz), 6.25 (1 H, d, CH=C*H*$SO_3$, *J* = 15.2 Hz), 6.75 (1 H, dd, C*H*=$CHSO_3$, *J* = 5.2 Hz, *J* = 15.2 Hz), 6.8 (1 H, s, N*H*C$Ph_3$), 7.18–7.32 (15 H, m, Ar*H*). – $^{13}$C NMR ($CDCl_3$): δ = 14.70 ($CH_3$), 28.19 [$(CH_3)_3C$], 29.58 ($CH_2$), 33.07 ($CH_2$), 56.76 (CHN), 66.99 ($OCH_2$), 124.87 (CH=), 126.99 (CH=), 127.80 (CH=), 128.53 (CH=), 148.02 (CH=). – $C_{32}H_{38}N_2O_6S$ (578.7): calcd. C 66.41, H 6.62, N 4.84; found C 66.33, H 6.68, N 4.80.

*(S)-N-Boc–vsGln(Trt)–OMe* (**23**, R = OMe): Following the procedure described above for the α,β-unsaturated sulfonates (**6**), the desired product was obtained in 60% yield after flash chromatography (*n*-hexane/ethyl acetate, 65:35). – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.45 [9 H, s, $(CH_3)_3$], 1.65–2.0 (2 H, m, $CH_2CH_2CO$), 2.4 (2 H, t, $CH_2CO$, *J* = 6.9 Hz), 3.8 (3 H, s, $OCH_3$), 4.3 (1 H, broad, C*H*NH), 5.4 (1 H, d, NH, *J* = 8.7 Hz), 6.2 (1 H, d, CH=C*H*$SO_3$, *J* = 15.2 Hz), 6.75 (1 H, dd, C*H*=$CHSO_3$, *J* = 15.2 Hz, *J* = 6.5 Hz), 7.05 (1 H, s, N*H*C$Ph_3$), 7.15–7.45 (15 H, m, Ar*H*). – $^{13}$C NMR ($CDCl_3$): δ = 28.26 [$(CH_3)_3$], 28.43 ($CH_2$), 32.86 ($CH_2CO$), 50.83 (CHN), 56.25 ($OCH_3$), 123.38 (CH=*C*HS), 126.86 (CH=), 127.82 (CH=), 128.63 (CH=), 149.53 (*C*H=CHS). – $C_{31}H_{36}N_2O_6S$ (564.7): calcd. C 65.94, H 6.43, N 4.96; found C 65.86, H 6.49, N 4.92.

*(S)-N-Boc–vsGln(Trt)–O$^-$(NBu$_4$)$^+$* (**24**): Following the procedure described above for the tetrabutylammonium sulfonates (**7**), the desired product was obtained in 100% yield. – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.0 [12 H, t, ($CH_3CH_2CH_2CH_2)_4N^+$, *J* = 7.15 Hz], 1.4 [9 H, s, $(CH_3)_3C$], 1.4–1.8 [16 H, m, ($CH_3CH_2CH_2CH_2)_4N^+$], 1.95 (2 H, m, $CH_2CH_2CO$], 2.35 (2 H, m, $CH_2CH_2CO$), 3.3 [8 H, m, ($CH_3CH_2CH_2CH_2)_4N^+$], 4.28 (1 H, broad, CHN), 4.6 (1 H, broad, d, N*H*CH, *J* = 8.8 Hz), 6.35 (1 H, dd, C*H*=$CHSO_3$, *J* = 4.6 Hz, *J* = 15.4 Hz), 6.48 (1 H, d, CH=C*H*$SO_3$, *J* = 15.4 Hz), 7.1–7.4 (16 H, m, NH + ArH). – $C_{45}H_{67}N_2O_6S$ (764.1): calcd. C 70.74, H 8.84, N 3.67; found C 70.65, H 8.76, N 3.63.

*(S)-N-Boc–vsGln(Trt)–Cl* (**25**): Following the procedure described above for the sulfonyl chlorides (**8**), the desired product was obtained in 75% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1). – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.45 [9 H, s, $(CH_3)_3C$], 1.7–2.5 (4 H, m, $CH_2CH_2$), 4.4 (1 H, broad, C*H*NH), 5.2 (1 H, broad, NH), 6.75 (1 H, d, CH=C*HSO*$_2$, *J* = 15.1 Hz), 6.90 (1 H, dd, C*H*=$SO_2$, *J* = 4.7, *J* = 15.1 Hz), 7.1–7.3 (16 H, m, N*H*C$Ph_3$, NH + 3× Ph). – $^{13}$C NMR ($CDCl_3$): δ = 28.17 [$(CH_3)_3$], 31.46 ($CH_2$), 32.97 ($CH_2CO$), 53.26 (CHN), 127.02 (CH=), 127.88 (CH=), 128.48 (CH=), 133.61 (CH=), 148.76 (CH=). – $C_{30}H_{33}ClNO_5S$ (555.1): calcd. C 64.91, H 5.99, N 2.52; found C 64.84, H 5.93, N 2.51.

*Synthesis of Sulfonamides* (**28**)

*(S)-N-Boc–vsAla–NH$_2$:* (*S*)-*N*-Boc–vsAla–Cl (11.4 mg, 0.042 mmol) was treated with 4 ml of a saturated solution of $NH_3$ in ethyl ether at 0°C, under nitrogen. The mixture was stirred at room temp. for 2 hours, monitoring the disappearance of the starting material by TLC (*n*-hexane/ethyl acetate, 6:4), then the solvent was evaporated at reduced pressure and the crude was purified by flash chromatography (*n*-hexane/ethyl acetate, 3:7) giving the desired product (78%). – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.32 (3 H, d, $CH_3CH$, *J* = 7.0 Hz), 1.5 [9 H, s, $(CH_3)_3C$], 4.4 (1 H, broad, $CH_3CH$), 4.6 (1 H, broad, N*H*CH), 4.8 (2 H, s, $SO_2NH_2$), 6.4 (1 H, dd, CH=C*H*$SO_3$, *J* = 15.6 Hz, *J* = 1.6 Hz), 6.7 (1 H, dd, C*H*=$CHSO_3$, *J* = 15.6 Hz, *J* = 4.0 Hz). – $C_9H_{18}N_2O_4S$ (250.3): calcd. C 43.19, H 7.25, N 11.19; found. C 43.13, H 7.33, N 11.11.

*(S)-N-Boc–vsAla–NHBn:* To a solution of (*S*)-*N*-Boc–vsAla –Cl (100 mg, 0.37 mmol) in DCM (3.7 ml) was added a solution of benzylamine (194.6 mg, 0.74 mmol), and DMAP (45.2 mg, 0.37 mmol) in DCM (1 ml). The mixture was stirred at room temp. for 3 hours then 10% citric acid (1.0 ml) was added; the aqueous phase was extracted with DCM and the combined organic extracts were dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to give the desired product in 70% yield. – $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.25 (3 H, d, $CH_3CH$, *J* = 6.78 Hz), 1.46 [9 H, s, $(CH_3)_3C$], 4.21 (2 H, d, NHC$H_2$Ph, *J* = 6.17 Hz), 4.36 (1 H, m, NC*H*$CH_3$), 4.45 (1 H, d, N*H*CH, *J* = 7.30 Hz), 4.45 (1 H, m, $SO_2NHCH_2$), 6.24 (1 H, dd, CH=C*H*$SO_2$, *J* = 1.30 Hz, *J* = 15.10 Hz), 6.67 (1 H, dd, C*H*=$CHSO_2$, *J* = 4.65 Hz, *J* = 15.1 Hz), 7.35 (5 H, m, Ar*H*). – $C_{16}H_{24}N_2O_4S$ (340.4): calcd. C 56.45, H 7.11, N 8.23; found C 56.43, H 7.16, N 8.20.

*(S)-N-Boc−vsVal−NHBn:* Following the above procedure the sulfonamide was obtained in 75% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.92 (3 H, d, C$H_3$CHCH$_3$, *J* = 5.7 Hz), 0.96 (3 H, d, CH$_3$CHC$H_3$, *J* = 5.7 Hz), 1.46 [9 H, s, (CH$_3$)$_3$C], 1.85 [1 H, m, (CH$_3$)$_2$C*H*], 4.19 (3 H, d, NHC$H_2$Ph + NHC*H*, *J* = 6.1 Hz), 4.55 (1 H, broad, NH), 4.65 (1 H, m, N*H*CH$_2$), 6.28 (1 H, dd, CH=C*H*SO$_2$, *J* = 1.6 Hz, *J* = 15.0 Hz), 6.66 (1 H, dd, C*H*=CHSO$_2$, *J* = 5.5 Hz, *J* = 15.0 Hz), 7.3 (5 H, m, Ar*H*). − $^{13}$C NMR ($CDCl_3$): δ = 18.78 (CH$_3$), 27.95 (CH$_3$), 28.23 [(CH$_3$)$_3$], 31.94 (CH),46.95 (CH$_2$), 56.13 (CH), 96.56 (CH=), 127.30 (CH=), 127.98 (CH=), 128.66 (CH=), 128.74 (CH=), 136.34 (CH=), 144.41 (CH=). − $C_{18}H_{28}N_2O_4S$ (368.5): calcd. C 58.67, H 7.66, N 7.60; found C 58.60, H 7.63, N 7.54.

*(S)-N-Boc−vsAla−NHEt:* Following the above procedure the sulfonamide was obtained in 63% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.2 (3 H, t, C$H_3$CH$_2$, *J* = 7.2 Hz), 1.29 (3 H, d, C$H_3$CH, *J* = 7.0 Hz), 1.4 [9 H, (CH$_3$)$_3$C], 3.08 (2 H, quint, CH$_3$C$H_2$, *J* = 7.2 Hz), 4.4 (2 H, broad, N*H*CH$_2$ + CH$_3$C*H*), 4.6 (1 H, broad, NH), 6.3 (1 H, d, CH=C*H*SO$_2$, *J* = 13.9 Hz), 6.67 (1 H, dd, C*H*=CHSO$_2$, *J* = 13.9 Hz, *J* = 4.9 Hz). − $C_{11}H_{22}N_2O_4S$ (278.4): calcd. C 47.46, H 7.97, N 10.06; found C 47.40, H 8.04, N 9.98.

*(S)-N-Boc−vsAla−NH-iPr:* Following the above procedure the sulfonamide was obtained in 60% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.2 [6 H, d, (C$H_3$)$_2$CH, *J* = 6.5 Hz], 1.3 (3 H, d, C$H_3$CH, *J* = 7.0 Hz), 1.4 [9 H, (CH$_3$)$_3$C], 3.5 [1 H, m, (CH$_3$)$_2$C*H*, *J* = 6.5 Hz], 4.2 (1 H, broad, C*H*CH=), 4.4 (1 H, broad, SO$_2$NH), 4.6 (1 H, broad, N*H*CHCH=), 6.3 (1 H, dd, CH=C*H*SO$_2$, *J* = 15.0 Hz, *J* = 1.4 Hz), 6.7 (1 H, dd, C*H*=CHSO$_2$, *J* = 15.0 Hz, *J* = 5.0 Hz). − $C_{12}H_{24}N_2O_4S$ (292.4): calcd. C 49.29, H 8.27, N 9.58; found C 49.24, H 8.35, N 9.51.

*(S)-N-Boc−vsAla−N[−(CH$_2$)$_5$−]:* Following the above procedure the sulfonamide was obtained in 76% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 8:2). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, C$H_3$CH, *J* = 6.8 Hz), 1.44 [9 H, s, (CH$_3$)$_3$C], 1.5−1.7 [6 H, m, N-CH$_2$(C$H_2$)$_3$], 3.1 (4 H, m, CH$_2$NCH$_2$), 4.3 (1 H, m, NHC*H*), 4.6 (1 H, m, N*H*CH), 6.2 (1 H, d, CH=C*H*SO$_2$, *J* = 15.1 Hz), 6.6 (1 H, dd, C*H*=CHSO$_2$, *J* = 4.1 Hz, *J* = 15.1 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 19.92 (CH$_3$), 23.52 [N(CH$_2$)$_2$C$H_2$], 25.13 (2× NCH$_2$C$H_2$), 28.22 [(C$H_3$)$_3$C], 46.43 (CH$_2$NCH$_2$), 50.00 (CH), 81.00 [(CH$_3$)$_3$*C*], 123.93 (CH=), 147.13 (CH=), 154.55 (C=O). − $C_{14}H_{26}N_2O_4S$ (318.4): calcd. C 52.81, H 8.23, N 8.80; found C 52.75, H 8.31, N 8.72.

*(S)-N-Boc−vsAla−NMe$_2$:* (*S*)-*N*-Boc−vsAla−Cl (150 mg, 0.56 mmol) was dissolved in DCM (5.6 ml), at 0°C, under nitrogen, and a solution of HCl·HNMe$_2$ (92 mg, 1.12 mmol) in DCM (1.0 ml), containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.168 ml, 1.12 mmol) and DMAP (34 mg, 0.28 mmol) was added at once. The mixture was stirred 4 hours at 0°C, then diluted with DCM and treated with a 10% aqueous solution of citric acid (2.0 ml). The aqueous phase was extracted with DCM and the combined organic extracts were dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:4) to give the desired sulfonamide in 52% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, C$H_3$CH, *J* = 6.8 Hz), 1.4 [9 H, s, (CH$_3$)$_3$C], 2.7 [6 H, s, (CH$_3$)$_2$N], 4.4 (1 H, m, CH$_3$C*H*), 4.6 (1 H, broad, N*H*CH), 6.2 (1 H, d, CH=C*H*, *J* = 16.0 Hz), 6.6 (1 H, dd, C*H*=CH, *J* = 4.6 Hz, *J* = 16.0 Hz). − $C_{11}H_{22}N_2O_4S$ (278.4): calcd. C 47.46, H 7.97, N 10.06; found C 47.40, H 8.00, N 10.00.

*(S)-N-Boc−vsVal−NMe$_2$:* Following the above procedure the sulfonamide was obtained in 66% yield after purification by flash chromatography (*n*-hexane/DCM, 2:8). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.95 (3 H, d, C$H_3$CH, *J* = 6.9 Hz), 0.97 (3 H, d, C$H_3$CH, *J* = 6.9 Hz), 1.46 [9 H, s, (CH$_3$)$_3$C], 1.87 [1 H, m, (CH$_3$)$_2$C*H*], 2.7 [6 H, s, (CH$_3$)$_2$N], 4.10 (1 H, m, NHC*H*), 4.60 (1 H, broad, NH), 6.22 (1 H, dd, CH=C*H*, *J* = 1.5 Hz, *J* = 15.1 Hz), 6.63 (1 H, dd, C*H*=CH, *J* = 5.6 Hz, *J* = 15.1 Hz). − $C_{13}H_{26}N_2O_4S$ (306.4): calcd. C 50.96. H 8.55, N 9.14; found C 50.90, H 8.50, N 9.07.

*(S)-N-Boc−vsLeu−NMe$_2$:* Following the above procedure the sulfonamide was obtained in 56% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.91 [3 H, s, (C$H_3$)$_2$CH], 0.94 [3 H, s, (C$H_3$)$_2$CH], 1.43 [9 H, s, (CH$_3$)$_3$C], 1.54−1.69 [3 H, (CH$_3$)$_2$C*H* + CH$_2$], 2.75 [6 H, s, (CH$_3$)$_2$N], 4.30 (1 H, m, NHC*H*), 4.61 (1 H, d, N*H*CH, *J* = 8.0 Hz), 6.20 (1 H, dd, CH=C*H*, *J* = 1.6 Hz, *J* = 15.1 Hz), 6.58 (1 H, dd, CH=CH, *J* = 4.6 Hz, *J* = 15.1 Hz). − $C_{14}H_{26}N_2O_4S$ (318.4): calcd. C 52.81, H 8.23, N 8.80; found C 52.75, H 8.31, N 8.72.

*Amine Hydrochlorides* (**29**). − *Typical Procedures for Boc Cleavage*

*HCl·(S)-H−vsAla−OEt:* (*S*)-*N*-Boc−vsAla−OEt (250 mg, 0.89 mmol) was treated with 3 M HCl in MeOH (5 ml) at 0°C, under nitrogen. The mixture was stirred at room temp. for 3 hours, monitoring the disappearance of the starting material by TLC (*n*-hexane/ethyl acetate, 6:4), then the solvent was evaporated at reduced pressure and the product pumped (0.1 mmHg). The hydrochloride salt (192 mg, 100%) was used in the next reactions without further purification.

*HCl·(S)-H−vsAla−OEt:* (*S*)-*N*-Boc−vsAla−OEt (250 mg, 0.89 mmol) was treated with a saturated HCl solution in ethyl acetate (5 ml) at 0°C, under nitrogen. The mixture was stirred at room temp. for 3 hours, monitoring the disappearance of the starting material by TLC (*n*-hexane/ethyl acetate, 6:4), then the solvent was evaporated at reduced pressure and the product pumped (0.1 mmHg). The hydrochloride salt (192 mg, 100% yield) was used in the next reactions without further purification.

*Synthesis of vs-Dipeptides* (**30**)

*(S)-N-Boc−vsAla−(S)-vsAla−OEt:* (*S*)-*N*-Boc−vsAla−Cl (189 mg, 0.70 mmol) was dissolved in DCM (7.0 ml), at room temp., under nitrogen, and a solution of HCl·(*S*)-H−vsAla−OEt (74.6 mg, 0.35 mmol) in DCM (2.0 ml), containing DBU (0.104 ml, 0.70 mmol) and DMAP (43 mg, 0.35 mmol) was added at once. The mixture was stirred 5 hours at room temperature, then diluted with DCM and treated with a 10% aqueous solution of citric acid (2.0 ml). The aqueous phase was extracted with DCM and the combined organic extracts were dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 1:1) to give the desired disulfonopeptide in 65% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.32 (3 H, d, C$H_3$CH, *J* = 7.1 Hz), 1.39 (3 H, d, C$H_3$CH, *J* = 7.0 Hz), 1.41 (3 H, t, C$H_3$CH$_2$OSO$_2$, *J* = 7.0 Hz), 1.46 [9 H, s, (CH$_3$)$_3$C], 4.15 (1 H, m, CH$_3$C*H*N), 4.22 (2 H, q, CH$_3$C$H_2$OSO$_2$, *J* = 7.0 Hz), 4.36 (1 H, m, CH$_3$C*H*N), 4.75 (2 H, m, 2× NH), 6.30 (1 H, dd, CH=C*H*SO$_2$, *J* = 15.0 Hz, *J* = 1.2 Hz), 6.47 (1 H, dd, CH=C*H*SO$_2$, *J* = 15.1 Hz, *J* = 1.3 Hz), 6.68 (1 H, dd, C*H*=CHSO$_2$, *J* = 15.0 Hz, *J* = 5.4 Hz), 6.82 (1 H, dd, C*H*=CHSO$_2$, *J* = 15.1 Hz, *J* = 5.2 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 15.51 (CH$_3$), 20.30 (CH$_3$), 21.51 (CH$_3$), 28.91 [(CH$_3$)$_3$], 47.40 (CH), 50.23 (CH), 67.91 (OCH$_2$), 126.26 (CH=), 128.61 (CH=), 147.47 (CH=), 148.73 (CH=), 157 (O-C=O). − $C_{15}H_{28}N_2O_7S_2$

(412.5): calcd. C 43.67, H 6.84, N 6.79; found C 43.62, H 6.80, N 6.73.

*(S)-N-Boc−vsAla−(S)-vsVal−OMe:* Following the above procedure the desired disulfonopeptide was obtained in 50% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.98 (3 H, d, C*H*$_3$CHC, *J* = 6.8 Hz), 0.99 (3 H, d, C*H*$_3$CHC, *J* = 6.8 Hz), 1.30 (3 H, d, C*H*$_3$CHN, *J* = 7.1 Hz), 1.45 [9 H, s, $(CH_3)_3C$], 1.94 (1 H, m, $Me_2CHC$), 3.86 (1 H, m, $Me_2CHCHN$), 4.0 (3 H, s, $OCH_3$), 4.39 (1 H, m, $CH_3CHN$), 4.75 (2 H, m, 2× NH), 6.29 (1 H, dd, CH=C*H*SO$_2$N, *J* = 15.1 Hz, *J* = 1.4 Hz), 6.47 (1 H, dd, CH=C*H*SO$_3$Me, *J* = 15.2 Hz, *J* = 1.2 Hz), 6.68 (1 H, dd, C*H*=CHSO$_2$N, *J* = 15.1 Hz, *J* = 5.3 Hz), 6.80 (1 H, dd, C*H*=CHSO$_3$Me, *J* = 15.2 Hz, *J* = 6.0 Hz). − $C_{16}H_{30}N_2O_7S_2$ (426.6): calcd. C 45.05, H 7.09, N 6.57; found C 45.00, H 7.16, N 6.52.

*(S)-N-Boc−vsAla−(S)-vsPro−OMe:* Following the above procedure the desired disulfonopeptide was obtained in 25% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, C*H*$_3$CH, *J* = 7.8 Hz), 1.4 [9 H, s, $(CH_3)_3C$], 2.0 [4 H, m, $NCH_2(CH_2)_2$], 3.5 (2 H, m, $NCH_2$), 3.8 (3 H, s, $OCH_3$), 4.3 (2 H, m, CH + CH), 4.6 (1 H, broad, CHN*H*); 5.25 (1 H, d, CH=C*H*−SO$_2$, *J* = 15.1 Hz), 6.39 (1 H, d, CH=C*H*SO$_2$, *J* = 15.1 Hz), 6.48 (1 H, dd, C*H*=CHSO$_2$, *J* = 15.1 Hz, *J* = 4.8 Hz), 6.85 (1 H, dd, C*H*=CHSO$_2$, *J* = 15.1 Hz, *J* = 4.3 Hz). − $C_{16}H_{28}N_2O_7S_2$ (424.5): calcd. C 45.27, H 6.65, N 6.60; found C 45.23, H 6.71, N 6.54.

*(S)-N-Boc−vsAla−(S)-vsVal−OEt:* Following the above procedure the desired disulfonopeptide was obtained in 60% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.98 (3 H, d, C*H*$_3$CHC, *J* = 6.8 Hz), 0.99 (3 H, d, C*H*$_3$CHC, *J* = 6.8 Hz), 1.30 (3 H, d, C*H*$_3$CHN, *J* = 7.1 Hz), 1.41 (3 H, t, C*H*$_3$CH$_2$OSO$_2$, *J* = 7.1 Hz), 1.45 [9 H, s, $(CH_3)_3C$], 1.94 (1 H, m, $Me_2CHC$), 3.86 (1 H, m, $Me_2CHCHN$), 4.23 (2 H, q, $CH_3CH_2OSO_2$, *J* = 7.1 Hz), 4.39 (1 H, m, $CH_3CHN$), 4.75 (2 H, m, 2× N*H*), 6.29 (1 H, dd, CH=C*H*SO$_2$N, *J* = 15.1 Hz, *J* = 1.4 Hz), 6.47 (1 H, dd, CH=C*H*SO$_3$Et, *J* = 15.2 Hz, *J* = 1.2 Hz), 6.68 (1 H, dd, C*H*=CHSO$_2$N, *J* = 15.1 Hz, *J* = 5.3 Hz), 6.80 (1 H, dd, C*H*=CHSO$_3$Et, *J* = 15.2 Hz, *J* = 6.0 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 14.80 ($CH_3$), 18.04 ($CH_3$), 18.59 ($CH_3$), 27.97 ($CH_3$), 28.21 [$(CH_3)_3$], 32.28 (CH), 46.51 (CHN), 56.19 (CHN), 67.21 ($OCH_2$), 126.91 (CH=), 127.89 (CH=), 146.22 (CH=), 146.67 (CH=), 154.77 (C=O). − $C_{17}H_{32}N_2O_7S_2$ (440.6): calcd. C 46.35, H 7.32, N 6.36; found C 46.40, H 7.39, N 6.31.

*(S)-N-Boc−vsAla−(S)-vsVal−NHBn:* (*S*)-*N*-Boc−vsAla−Cl (75 mg, 0.28 mmol) was dissolved in DCM (2.8 ml), at room temp., under nitrogen, and a solution of HCl·(*S*)-H−vsVal−NHBn (34.9 mg, 0.14 mmol) in DCM (0.55 ml), containing DBU (0.042 ml, 0.28 mmol) and DMAP (17 mg, 0.14 mmol) was added at once. The mixture was stirred 4 hours at room temperature, then diluted with DCM and treated with a 10% aqueous solution of citric acid (2.0 ml). The aqueous phase was extracted with DCM and the combined organic extracts were dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:4) to give the desired disulfonopeptide in 44% yield. The product was cristallized from *n*-hexane/ethyl acetate, 1:1; m.p. 134−136°C. − $[\alpha]_D$ = −7.9 (*c* = 1.01, $CHCl_3$). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.92 (3 H, d, C*H*$_3$CHC, *J* = 6.84 Hz), 0.96 (3 H, d, C*H*$_3$CHC, *J* = 6.84 Hz), 1.21 (3 H, d, C*H*$_3$CHN, *J* = 7.08 Hz), 1.44 [9 H, s, $(CH_3)_3C$], 1.90 (1 H, m, $Me_2CH$), 3.86 (1 H, m, $Me_2CHCHN$), 4.15 (1 H, m, $CH_3CHN$), 4.20 (2 H, d, $NCH_2Ph$, *J* = 5.20 Hz), 4.49 (1 H, d, $Me_2CHCHNH$, *J* = 7.80 Hz), 4.67 (1 H, d, MeCHN*H*, *J* = 5.00 Hz), 5.96 (1 H, t, N*H*CH$_2$Ph, *J* = 5.20 Hz), 6.12 (1 H, d, MeCHCH=C*H*, *J* = 14.65 Hz), 6.31 (1 H, d, $Me_2CHCHCH$=C*H*, *J* = 15.63 Hz), 6.46 (1 H, dd, $Me_2CHCHCH$=CH, *J* = 15.63 Hz, *J* = 5.86 Hz), 6.57 (1 H, dd, MeCHC*H*=CH, *J* = 14.65 Hz, *J* = 4.88 Hz), 7.3−7.4 (5 H, m, Ar*H*). − $^{13}$C NMR ($CDCl_3$): δ = 18.00 ($CH_3$), 18.72 ($CH_3$), 19.54 ($CH_3$), 28.22 [$(CH_3)_3$], 32.36 ($Me_2CH$), 46.52 (CH), 46.95 ($CH_2$), 59.33 (CH), 127.66 (CH=), 127.90 (CH=), 128.27 (CH=), 128.55 (CH=), 130.37 (CH=), 141.99 (CH=), 145.45 (CH=). − $C_{22}H_{35}N_3O_6S_2$ (501.7): calcd C 52.67, H 7.03, N 8.38; found C 52.62, H 7.09, N 8.32.

*(S)-N-Boc−vsAla−(S)-vsAla−NHBn:* Following the above procedure the desired disulfonopeptide was obtained in 60% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.27 (3 H, d, $CH_3$, *J* = 7.08 Hz), 1.32 (3 H, d, $CH_3$, *J* = 7.08 Hz), 1.44 [9 H, s, $(CH_3)_3C$], 4.15 (2 H, broad, 2× CH), 4.2 (2 H, d, C*H*$_2$Ph, *J* = 5.20 Hz), 4.55 (1 H, d, NH, *J* = 4.78 Hz), 4.70 (1 H, d, NH, *J* = 4.78 Hz), 5.9 (1 H, t, SO$_2$N*H*CH$_2$, *J* = 5.20 Hz), 6.15 (1 H, d, CH=C*H*SO$_2$, *J* = 14.30 Hz), 6.3 (1 H, d, CH=C*H*SO$_2$, *J* = 15.73 Hz), 6.45 (1 H, dd, C*H*=CHSO$_2$, *J* = 14.30 Hz, *J* = 4.29 Hz), 6.55 (1 H, dd, C*H*=CHSO$_2$, *J* = 15.73 Hz, *J* = 4.30 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 19.58 ($CH_3$), 20.96 ($CH_3$), 28.19 [$(CH_3)_3$], 47.17 ($CH_2$), 49.64 (CH), 98.92 (CH=), 100.69 (CH=), 127.81 (CH=), 128.05 (CH=), 128.29 (CH=), 128.61 (CH=), 129.71 (CH=), 145.92 (CH=). − $C_{20}H_{31}N_3O_6S_2$ (473.6): calcd. C 50.72, H 6.60, N 8.87; found C 50.66, H 6.66, N 8.80.

*(S)-N-Boc−vsVal−(S)-vsAla−NH$_2$:* (*S*)-*N*-Boc−vsVal−Cl (94 mg, 0.312 mmol) was dissolved in DCM (3.1 ml), at room temp., under nitrogen, and a solution of HCl·(*S*)-H−vsVal−NH$_2$ (0.156 mmol) in DCM (1.5 ml), containing DBU (0.046 ml, 0.312 mmol) and DMAP (19 mg, 0.156 mmol) was added at once. The mixture was stirred 4 hours at room temperature, then diluted with DCM and treated with a 10% aqueous solution of citric acid (2.0 ml). The aqueous phase was extracted with DCM and the combined organic extracts were dried over $Na_2SO_4$ and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 1:1) to give the desired disulfonopeptide in 25% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.89 [3 H, d, $(CH_3)_2CH$, *J* = 6.0 Hz], 0.91 [3 H, d, $(CH_3)_2CH$, *J* = 6.0 Hz], 1.4 (3 H, d, C*H*$_3$CH, *J* = 8.0 Hz), 1.5 [9 H, s, $(CH_3)_3C$], 1.8 [1 H, m, $(CH_3)_2CH$], 4.1 (2 H, m, NHC*H* + NHC*H*), 4.9 (1 H, d, $SO_2NH$, *J* = 8.4 Hz), 5.2 (1 H, d, NH, *J* = 8.1 Hz), 5.6 (2 H, s, $SO_2NH_2$), 6.3−6.7 (4 H, m, 2× CH=CH). − $^{13}$C NMR ($CDCl_3$): δ = 18.65 ($CH_3$), 21.80 ($CH_3$), 28.96 [$(CH_3)_3$], 32.42 [$CH(CH_3)_2$], 50.30 (CHN), 57.1 (CHN), 81.21 [$(CH_3)_3C$], 130.19 (CH=), 132.09 (CH=), 142.68 (CH=), 144.97 (CH=), 156.34 (C=O). − $C_{15}H_{29}N_3O_6S_2$ (411.5): calcd. C 43.78, H 7.10, N 10.21; found C 43.71, H 7.17, N 10.13.

*(S)-N-Boc−vsSer(TBDPS)−(S)-vsAla−NH$_2$:* Following the above procedure the desired disulfonopeptide was obtained in 42% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.0 [9 H, s, $(CH_3)CSi$], 1.3 (3 H, d, $CH_3$, *J* = 6.5 Hz), 1.4 [9 H, s, $(CH_3)_3C$], 3.7 (1 H, dd, OC*H*H, *J* = 4.7 Hz, *J* = 12.0 Hz), 3.8 (1 H, dd, OCH*H*, *J* = 4.3 Hz, *J* = 12.0 Hz), 4.2 (1 H, broad, $OCH_2CH$), 4.4 (1 H, broad, $CH_3CH$), 5.1 (4 H, broad, NH + NH + $NH_2$), 6.3−6.7 (4 H, 2× CH=CH), 7.4−7.7 (10 H, m, 2× PhSi). − $C_{29}H_{43}N_3O_7S_2Si$ (637.9): calcd. C 54.61, H 6.79, N 6.59; found C 54.55, H 6.85, N 6.54.

*(S)-N-Boc−vsPro−(S)-vsAla−NH$_2$:* Following the above procedure the desired disulfonopeptide was obtained in 30% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1).

– $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.4 (3 H, d, $CH_3$, *J* = 7.7 Hz), 1.5 [9 H, s, $(CH_3)_3C$], 1.7–1.9 (4 H, m, NCHC$H_2$C$H_2$), 3.4 (2 H, m, CHNC$H_2$), 4.2 (1 H, m, $CH_3$C*H*), 4.5 (1 H, m, NCH), 4.8 (1 H, d, $SO_2NH$, *J* = 7.3 Hz), 5.7 (2 H, s, $SO_2NH_2$), 6.1–6.6 (4 H, m, 2× CH=CH). – $^{13}$C NMR ($CDCl_3$): δ = 21.20 ($CH_3$), 23.32 ($CH_2$), 28.32 [$(CH_3)_3$], 30.49 ($CH_2$), 46.77 ($CH_2$), 49.78 (CH), 57.02 (CH), 128.90 (CH=), 131.62 (CH=), 141.16 (CH=), 144.40 (CH=). – $C_{15}H_{27}N_3O_6S_2$ (409.5): calcd. C 43.99, H 6.65, N 10.26; found C 43.95, H 6.71, N 10.18.

*(S)-N-Boc–vsVal–(S)-vsPro–NH$_2$:* Following the above procedure the desired disulfonopeptide was obtained in 40% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 2:8). – $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.89 [3 H, d, $(CH_3)_2$CH, *J* = 5.2 Hz], 0.91 [3 H, d, $(CH_3)_2$CH, *J* = 5.2 Hz], 1.4 [9 H, s, $(CH_3)_3C$], 1.6–1.9 [4 H, m, $(CH_3)_2CH$ + $NCH_2CH_2CH$H], 2.5 (1 H, m, NCHCH*H*), 3.3 (2 H, m, $NCH_2$), 3.4 (2 H, s, $NH_2$), 4.2 (3 H, broad, NHCH + NCH), 6.2–6.8 (4 H, m, 2× CH=CH). – $C_{17}H_{31}N_3O_6S_2$ (437.6): calcd. C 46.66, H 7.14, N 9.60; found C 46.60, H 7.20, N 9.52.

*(S)-N-Boc–vsTyr(TBDPS)–(S)-vsAla–NH$_2$:* Following the above procedure the desired disulfonopeptide was obtained in 44% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.1 [9 H, s, $(CH_3)_3$CSi], 1.30 (3 H, d, C$H_3$CH, *J* = 6.5 Hz), 1.39 [9 H, s, $(CH_3)_3C$], 2.74 ( 2 H, m, CHC$H_2$Ar), 4.1 (2 H, m, CH + CH), 4.4 (1 H, m, $NHSO_2$), 4.6 (1 H, m, CONH), 5.4 (2 H, s, $SO_2NH_2$), 6.1–6.6 (4 H, m, 2× CH=CH$SO_2$), 6.7 (2 H, d, CH=C, *J* = 8.4 Hz), 6.9 (2 H, d, CH=C, *J* = 8.4 Hz), 7.3–7.8 (10 H, m, 2× Ph-Si). – $C_{35}H_{47}N_3O_7S_2Si$ (714.0): calcd. C 58.88, H 6.64, N 5.89; found C 58.82, H 6.70, N 5.85.

*MTPA Derivatization of Hydrochlorides* **29**

*Typical Procedure:* A solution of HCl·(*S*)-H–vsAla–OEt (23 mg, 0.107 mmol) in pyridine (0.6 ml) was treated with 4-dimethylaminopyridine (DMAP) (1.3 mg, 0.01 mmol) and (*R*)-(–)-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) (54 mg, 0.214 mmol) at 0°C, under nitrogen. The mixture was stirred at 0°C for 4 hours, monitoring the disappearance of the starting material by TLC (*n*-hexane/ethyl acetate, 7:3), then was diluted with ethyl ether and treated with 1 N HCl. The aqueous phase was extracted with ethyl ether and the combined organic extracts were dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to give the desired Mosher′s amide (31 mg, 72% yield). – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.40 (3 H, t, C$H_3CH_2OSO_2$, *J* = 7.3 Hz), 1.44 (3 H, d, C$H_3$CHN, *J* = 6.7 Hz), 3.37 (3 H, q, $CH_3OC$, *J* = 1.1 Hz, *98.7%*), 3.46 (3 H, q, $CH_3OC$, *J* = 1.1 Hz, *1.3%*), 4.17 (2 H, q, $CH_3CH_2OSO_2$, *J* = 7.3 Hz), 4.78 (1 H, m, $CH_3$C*H*N), 6.31 (1 H, dd, CH=C*H*$SO_3$, *J* = 14.8 Hz, *J* = 1.7 Hz), 6.84 (1 H, dd, C*H*=CH$SO_3$, *J* = 14.8 Hz, *J* = 3.7 Hz), 7.14 (1 H, d, N*H*, *J* = 5.4 Hz), 7.5 (5 H, m, Ar*H*). – $^{13}$C NMR ($CDCl_3$, selected peaks): δ = 14.63 ($CH_3$), 19.38 ($CH_3$), 45.51 (CHN), 54.79; 54.83; 67.30; 124.77; 127.60; 127.64; 128.74; 129.66; 147.56; 165.83 (C=O). – $^{19}$F NMR ($CDCl_3$): δ = –69.0352 ($CF_3$, *98%*), –69.3013 ($CF_3$, *2%*). Starting from non-crystallized (*S*)-*N*-Boc–vsAla–OEt, NMR analysis of the Mosher′s amides revealed a ≥98:2 ratio of diastereoisomers. Starting from recrystallized (*S*)-*N*-Boc–vsAla–OEt, the Mosher′s amides were obtained as single compounds within the limits of NMR detection (> 99:1).

*Synthesis of vs-Tripeptides* (**31**)

*(S)-N-Boc–vsPhe–(S)-vsAla–(S)-vsVal–OEt:* (*S*)-*N*-Boc–vsPhe–Cl (242 mg, 0.70 mmol) was dissolved in DCM (7.0 ml), at room temp., under nitrogen, and a solution of HCl·(*S*)-H–vsAla–(*S*)-vsVal–OEt (131.9 mg, 0.35 mmol) in DCM (1.0 ml), containing DBU (0.104 ml, 0.70 mmol) and DMAP (43 mg, 0.35 mmol) was added at once. The mixture was stirred for 5 hours at room temperature, then diluted with DCM and treated with a 10% aqueous solution of citric acid (2.0 ml). The aqueous phase was extracted with DCM and the combined organic extracts were dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 55:45) to give the desired trisulfonopeptide in 60% yield. – $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.95 (3 H, d, C$H_3$CHC, *J* = 7.5 Hz), 0.97 (3 H, d, C$H_3$CHC, *J* = 7.0 Hz), 1.31 (3 H, d, C$H_3$CHN, *J* = 6.5 Hz), 1.38 [9 H, s, $(CH_3)_3C$], 1.40 (3 H, t, C$H_3CH_2OSO_2$, *J* = 7.0 Hz), 1.88 (1 H, m, $Me_2$C*H*C), 2.82 (1 H, dd, C*H*HPh, *J* = 14.0 Hz, *J* = 7.0 Hz), 3.01 (1 H, broad, d, CH*H*Ph, *J* = 14.0 Hz), 3.90 (1 H, q, $Me_2$C*H*CHN, *J* = 7.5 Hz), 4.13 (1 H, m, $CH_3$C*H*N), 4.23 (2 H, m, $CH_3CH_2OSO_2$), 4.60 (2 H, m, $PhCH_2$C*H*N + MeCHN*H*), 4.65 (1 H, m, $PhCH_2$CHN*H*), 5.76 (1 H, d, $Me_2$CHCHN*H*, *J* = 8.5 Hz), 6.22 (1 H, d, BnCHCH=C*H*, *J* = 15.0 Hz), 6.32 (1 H, d, MeCHCH=C*H*, *J* = 15.4 Hz), 6.398 (1 H, d, *i*PrCHCH=C*H*, *J* = 15.3 Hz), 6.477 (1 H, dd, MeCHC*H*=CH, *J* = 15.4 Hz, *J* = 5.0 Hz), 6.75 (1 H, dd, *i*PrCHC*H*=CH, *J* = 15.3 Hz, *J* = 7.5 Hz), 6.81 (1 H, dd, BnCHC*H*=CH, *J* = 15.0 Hz, *J* = 4.0 Hz), 7.16 (2 H, d, Ar*H*, *J* = 7.0 Hz), 7.24 (1 H, t, Ar*H*, *J* = 6.0 Hz), 7.30 (2 H, t, Ar*H*, *J* = 7.5 Hz). – $^{13}$C NMR ($CDCl_3$): δ = 14.89 ($CH_3$), 18.19 (2× $CH_3$), 18.73 ($CH_3$), 28.19 [$(CH_3)_3$], 32.48 (CH), 39.79 ($CH_2$Ph), 49.23 (CHN), 52.11 (CHN), 59.89 (CHN), 67.09 ($OCH_2$), 126.67 (CH=), 127.01 (Ar), 128.65 (Ar), 128.72 (CH=), 129.20 (Ar), 130.05 (Ar), 143.00 (CH=), 144.87 (CH=), 146.08 (CH=), 155.32 (C=O). – $C_{27}H_{43}N_3O_9S_3$ (649.8): calcd C 49.90, H 6.67, N 6.47; found C 49.80, H 6.70, N 6.46.

*(S)-N-Boc–vsPhe–(S)-vsAla–(S)-vsVal–NHBn:* Following the above procedure the desired trisulfonopeptide was obtained in 32% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 55:45). – $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.95 (3 H, d, C$H_3$CH, *J* = 6.8 Hz), 0.96 (3 H, d, C$H_3$CH, *J* = 6.7 Hz), 1.24 (3 H, d, C$H_3$CH, *J* = 7.0 Hz), 1.40 [ 9 H, s $(CH_3)_3C$], 1.85 (1 H, m, $Me_2$C*H*), 2.82 (1 H, dd, CHC*H*HPh, *J* = 6.9 Hz, *J* = 13.5 Hz), 3.0 (1 H, dd, CHCH*H*Ph, *J* = 4.2 Hz, *J* = 13.5 Hz), 3.8–4.0 (2 H, m, *i*PrC*H*N + MeC*H*N), 4.26 (2 H, d, $NCH_2$Ph, *J* = 6.1 Hz), 4.5–4.7 (2 H, m, BnC*H*N + CHN*H*), 4.85 (1 H, d, N*H*, *J* = 8.6 Hz), 5.4 (1 H, t, N*H*$CH_2$Ph, *J* = 6.1 Hz), 5.65 (1 H, d, N*H*, *J* = 9.0 Hz), 6.2–7.0 (6 H, m, 3× CH=CH), 7.1–7.4 (10 H, m, Ar*H*). – $^{13}$C NMR ($CDCl_3$): δ = 18.01 ($CH_3$), 18.78 ($CH_3$), 28.16 [$(CH_3)_3$], 40.10 ($CH_2$), 46.89 ($NCH_2$Ph), 49.28 (CHN), 126.90 (CH=), 127.80 (CH=), 127.94 (CH=), 128.58 (CH=), 128.66 (CH=), 129.24 (CH=), 130.55 (CH=), 142.09 (CH=), 144.88 (CH=). – $C_{32}H_{46}N_4O_8S_3$ (710.9): calcd C 54.06, H 6.52, N 7.88; found C 54.00, H 6.59, N 7.86.

*(S)-N-Boc–vsVal–(S)-vsPro–(S)-vsAla–NH$_2$:* Following the above procedure the desired trisulfonopeptide was obtained in 30% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 3:7). – $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.9 [6 H, m, $(CH_3)_2$CH], 1.3 (3 H, s, C$H_3$CH), 1.4 [9 H, s, $(CH_3)_3C$], 1.6–1.9 [5 H, m, NCH$(CH_2)_2$ + $(CH_3)_2CH$], 3.4 (2 H, C$H_2$NCH), 4.2 (4 H, m, 3× CH + $SO_2NH$), 4.9 (1 H, broad, BocN*H*), 5.7 (2 H, broad, $NH_2$), 6.3–6.9 (6 H, m, 3× CH=CH). – $C_{21}H_{38}N_4O_8S_3$ (578.8): calcd. C 44.19, H 6.71, N 9.82; found C 44.15, H 6.77, N 9.75.

*(S)-N-Boc–vsAla–(S)-vsSer(TBDPS)–(S)-vsAla–NH$_2$:* Following the above procedure the desired trisulfonopeptide was obtained in 27% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). – $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.0

[9 H, s, $(CH_3)_3CSi$], 1.24 (3 H, d, $CH_3CH$, $J$ = 7.1 Hz), 1.35 (3 H, d, $CH_3CH$, $J$ = 6.9 Hz), 1.45 [9 H, s, $(CH_3)_3C$], 3.67 (1 H, dd, CHHO, $J$ = 4.5 Hz, $J$ = 10.3 Hz), 3.80 (1 H, dd, CHHO, $J$ = 4.2 Hz, $J$ = 10.3 Hz), 4.1 (2 H, m, $CH_2CH$ + $CH_3CH$), 4.3 (1 H, m, $CH_3CH$), 4.6 (1 H, d, $SO_2NH$, $J$ = 6.6 Hz), 5.2 (2 H, s, $NH_2$), 5.3 (1 H, d, NHCH, $J$ = 6.9 Hz), 5.8 (1 H, d, $SO_2NH$, $J$ = 8.4 Hz), 6.2−6.7(6 H, 3× CH=CH), 7.4−7.7 (10 H, m, 2× PhSi). − $^{13}$C NMR ($CDCl_3$): δ = 19.12 ($CH_3$), 21.20 ($CH_3$), 26.80 [$(CH_3)_3CSi$], 28.24 [$(CH_3)_3C$], 46.91 (NCH), 49.83 (NCH), 55.21 (NCH), 65.16 ($CH_2OSi$), 127.42 (CH=), 127.98 (CH=), 130.13 (CH=), 131.06 (CH=), 131.92 (CH=), 132.17 (CH=), 135.51 (CH=), 140.72 (CH=), 142.30 (CH=), 146.73 (CH=). − $C_{33}H_{50}N_4O_9S_3Si$ (771.1) calcd: C 51.41, H 6.54, N 7.27; found C 51.36, H 6.60, N 7.21.

*Synthesis of vs-Tetrapeptides* (**32**)

*(S)-N-Boc−vsLeu−(S)-vsPhe−(S)-vsAla−(S)-vsVal−OEt:* (*S*)-*N*-Boc−vsLeu−Cl (218.3 mg, 0.70 mmol) was dissolved in DCM (7.0 ml), at room temp., under nitrogen, and a solution of HCl·(*S*)-H−vsPhe−(*S*)-vsAla−(*S*)-vsVal−OEt (205.16 mg, 0.35 mmol) in DCM (1.0 ml), containing DBU (0.104 ml, 0.70 mmol) and DMAP (43 mg, 0.35 mmol) was added at once. The mixture was stirred for 12 hours at room temperature, then diluted with DCM and 10% aqueous solution of citric acid (2.0 ml) was added. The aqueous phase was extracted with DCM and the combined organic extracts were dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:4) to give the desired tetrasulfonopeptide in 60% yield. − $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.92 [6 H, t, $(CH_3)_2CHCH_2$, $J$ = 6.9 Hz], 0.96 (3 H, d, $CH_3CHC$, $J$ = 6.5 Hz), 0.97 (3 H, d, $CH_3CHC$, $J$ = 6.8 Hz), 1.32 (2 H, m, $CHCH_2C$), 1.35 (3 H; d, $CH_3CHN$, $J$ = 6.9 Hz), 1.39 (3 H, t, $CH_3CH_2OSO_2$, $J$ = 7.0 Hz), 1.43 [9 H, s, $(CH_3)_3C$], 1.65 (1 H, m, $Me_2CHCH_2$), 1.90 (1 H, m, $Me_2CHC$), 2.77 (1 H, dd, CHHPh, $J$ = 13.9 Hz, $J$ = 8.4 Hz), 3.03 (1 H, dd, CHHPh, $J$ = 13.9 Hz, $J$ = 5.3 Hz), 3.90 (1 H, m, $Me_2CHCHN$), 4.15−4.32 (5 H, m, $CH_3CHN$ + $PhCH_2CHN$ + *i*BuCHN + $CH_3CH_2OSO_2$, $J$ = 7.0 Hz), 4.39 (1 H, d, *i*BuCHNH, $J$ = 7.7 Hz), 4.52 (1 H, d, $PhCH_2CHNH$, $J$ = 5.5 Hz), 4.96 (1 H, d, *i*PrCHNH, $J$ = 8.2 Hz), 5.39 (1 H, d, MeCHNH, $J$ = 7.0 Hz), 5.91 (1 H, d, BnCHCH=CH, $J$ = 15.0 Hz), 6.35 (1 H, d, CH=CH, $J$ = 14.6 Hz), 6.42 (1 H, d, CH=CH, $J$ = 14.0 Hz), 6.44 (1 H, d, *i*PrCHCH=CH, $J$ = 14.8 Hz), 6.53 (1 H, dd, MeCHCH=CH, $J$ = 14.7 Hz, $J$ = 5.9 Hz), 6.59 (1 H, dd, BnCHCH=CH, $J$ = 15.0 Hz, $J$ = 5.1 Hz), 6.63 (1 H, dd, CHCH=CH, $J$ = 15.1 Hz, $J$ = 6.4 Hz), 6.74 (1 H, dd, *i*PrCHCH=CH, $J$ = 14.8 Hz, $J$ = 6.8 Hz), 7.18 (2 H, d, ArH), 7.30 (1 H, t, ArH), 7.35 (2 H, t, ArH). − $^{13}$C NMR ($CDCl_3$): δ = 14.85 ($CH_3$), 18.20 ($CH_3$), 18.63 ($CH_3$), 21.21 ($CH_3$), 21.66 ($CH_3$), 22.83 ($CH_3$), 24.58 (CH), 28.24 [$(CH_3)_3$], 32.39 (CH), 40.37 ($CH_2$), 43.14 ($CH_2$), 49.03 (CHN), 49.57 (CHN), 55.21 (CHN), 59.56 (CHN), 67.27 ($OCH_2$), 126.62 (CH=), 127.24 (CH=), 128.31 (CH=), 128.55 (CH=), 128.81 (CH=), 129.71 (CH=), 129.77 (CH=), 130.33 (CH=), 131.90 (CH=), 132.10 (CH=), 143.48 (CH=), 144.26 (CH=), 146.36 (CH=). − $C_{34}H_{56}N_4O_{11}S_4$ (825.1): calcd: C 49.49, H 6.84, N 6.79; found C 49.43, H 6.90, N 6.73.

*(S)-N-Boc−vsLeu−(S)-vsPhe−(S)-vsAla−(S)-vsVal−NHBn:* Following the above procedure the desired tetrasulfonopeptide was obtained in 30% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 55:45). − $^1$H NMR (300 MHz, $CDCl_3$): δ = 0.92 (3 H, d, $CH_3CHCH_3$, $J$ = 6.6 Hz), 0.93 (3 H, d, $CH_3CHCH_3$, $J$ = 6.7 Hz), 1.25−1.35 (5 H, m, $CH_3CH$ + *i*PrC$H_2$), 1.45 [9 H, s, $(CH_3)_3C$], 1.64 (1 H, m, $Me_2CHCH_2$), 1.83 (1 H, m, $Me_2CH$), 2.72 (1 H, dd, CHCHHPh, $J$ = 9.0 Hz, $J$ = 14.1 Hz), 3.0 (1 H, dd, CHCHHPh, $J$ = 4.9 Hz, $J$ = 14.1 Hz), 3.82 (1 H, m, *i*PrCHN), 4.04 (1 H, m, MeCHN), 4.1−4.3 (2 H, m, BnCHN + *i*BuCHN), 4.2 (2 H, d, $NCH_2Ph$, $J$ = 6.21 Hz), 4.40 (1 H, d, NH, $J$ = 8.0 Hz), 4.65 (1 H, d, NH, $J$ = 8.0 Hz), 4.94 (1 H, d, NH, $J$ = 8.8 Hz), 5.35 (1 H, m, NH), 5.60 (1 H, d, NH, $J$ = 7.3 Hz), 5.94 (1 H, d, CH=CHSO$_2$, $J$ = 15.1 Hz), 6.23 (1 H, d, CH=CHSO$_2$, $J$ = 15.0 Hz), 6.39 (1 H, d, CH=CHSO$_2$, $J$ = 15.1 Hz), 6.45 (1 H, dd, CH=CHSO$_2$, $J$ = 15.1 Hz, $J$ = 6.3 Hz), 6.52 (1 H, dd, CH=CHSO$_2$, $J$ = 15.0 Hz, $J$ = 6.84 Hz), 6.61 (1 H, dd, CH=CHSO$_2$, $J$ = 15.1 Hz, $J$ = 5.0 Hz), 6.64 (1 H, dd, CH=CHSO$_2$, $J$ = 15.1 Hz, $J$ = 5.86 Hz), 7.2−7.4 (10 H, m, ArH). − $^{13}$C NMR ($CDCl_3$): δ = 18.01 ($CH_3$), 18.71 ($CH_3$), 20.94 ($CH_3$), 21.65 ($CH_3$), 22.82 ($CH_3$), 24.58 ($CHCH_2$), 28.22 [$(CH_3)_3C$], 32.53 [$CH(CH_3)_2$], 40.26 ($CH_2Ph$), 43.08 ($CH_2CH$), 46.92 ($NCH_2Ph$), 49.06 (NCH), 49.56 (NCH), 55.21 (NCH), 59.36 (NCH), 126.81 (CH=), 127.27 (CH=), 127.87 (CH=), 127.97 (CH=), 128.68 (CH=), 128.84 (CH=), 129.70 (CH=), 129.90 (CH=), 130.27 (CH=), 130.66 (CH=), 142.02 (CH=), 143.49 (CH=), 143.77 (CH=), 146.48 (CH=). − $C_{39}H_{59}N_5O_{10}S_4$ (886.2): calcd C 52.86, H 6.71, N 7.90; found C 52.80, H 6.79, N 7.85.

*Mixed Peptides (S)-N-Boc−vsAA−Gly−OMe* (**33**)

*(S)-N-Boc−vsPro−Gly−OMe:* (*S*)-*N*-Boc−vsPro−Cl (200 mg, 0.70 mmol) was dissolved in DCM (7.0 ml) and a solution of HCl·H−Gly−OMe (176 mg, 1.40 mmol) in DCM (2.0 ml) containing DBU (0.208 ml, 1.40 mmol) and DMAP (43 mg, 0.35 mmol) was added at once. The mixture was stirred at room temperature for 4 hours, then diluted with DCM and treated with a 10% aqueous solution of citric acid (2.0 ml). The aqueous phase was extracted with DCM and the combined organic extracts were dried over $Na_2SO_4$ and evaporated. The crude product was purified by flash chromatography (*n*-pentane/ethyl acetate, 4:6) to give the desired mixed peptide in 80% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.44 [9 H, s, $(CH_3)_3C$], 1.75 (3 H, m, $NCHCHHCH_2$), 2.15 (1 H, m, NCHCHH), 3.40 (2 H, broad, $NCH_2$), 3.75 (3 H, s, $OCH_3$), 3.80 (2 H, d, $CH_2COOCH_3$, $J$ = 4.3 Hz), 4.40 (1 H, broad, NCH), 4.95 (1 H, t, $NHCH_2COOMe$, $J$ = 4.3 Hz), 6.20 (1 H, dd, CH=CHSO$_2$, $J$ = 15.0 Hz, $J$ = 1.0 Hz), 6.63 (1 H, dd, CH=CHSO$_2$, $J$ = 15.0 Hz, $J$ = 6.5 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 22.70 ($CH_2$, 55%), 23.54 ($CH_2$, 45%), 28.22 [$(CH_3)_3$], 30.37 ($CH_2$, 45%), 31.49 ($CH_2$, 55%), 43.73 ($CH_2CO$), 46.17 ($CH_2$, 55%), 46.54 ($CH_2$, 45%), 52.48 ($OCH_3$), 56.82 (CH), 127.03 (CH=, 55%), 127.48 (CH, 45%), 145.20 (CH=, 55%), 145.63 (CH=, 45%). − $C_{14}H_{24}N_2O_6S$ (348.4): calcd. C 48.26, H 6.94, N 8.04; found C 48.21, H 7.00, N 7.96.

*(S)-N-Boc−vsAla−Gly−OMe:* Following the above procedure the desired mixed peptide was obtained in 51% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, $CH_3CH$, $J$ = 6.9 Hz), 1.43 [9 H, s, $(CH_3)_3C$], 3.78 (3 H, s, $OCH_3$), 3.8 (2 H, d, $CH_2$, $J$ = 5.5 Hz), 4.4 (1 H, m, $CH_3CH$), 4.6 (1 H, broad, $SO_2NH$), 5.1 (1 H, broad, NHCH), 6.3 (1 H, dd, CH=CHSO$_2$, $J$ = 15.1 Hz, $J$ = 1.4 Hz), 6.7 (1 H, dd, CH=CHSO$_2$, $J$ = 4.8 Hz, $J$ = 15.1 Hz). − $C_{12}H_{22}N_2O_6S$ (323.3): calcd. C 44.71, H 6.88, N 8.69; found C 44.66, H 6.94, N 8.62.

*(S)-N-Boc−vsGln(Trt)−Gly−OMe:* Following the above procedure the desired mixed peptide was obtained in 51% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.45 [9 H, s, $(CH_3)_3C$], 1.5−2.0 (2 H, m, $CH_2CH_2CO$), 2.45 (2 H, t, $CH_2CH_2CO$, $J$ = 7.8 Hz), 3.75 (3 H, s, $OCH_3$), 3.8 (2 H, d, $NHCH_2COO$, $J$ = 5.2 Hz), 4.3 (1 H, broad, NHCH), 4.95 (1 H, broad, NH), 5.2 (1 H, broad, NH), 6.3 (1 H, d, CH=CHSO$_2$, $J$ = 15.2 Hz), 6.65 (1 H, dd, CH=CHSO$_2$, $J$ = 15.2 Hz, $J$ = 5.2 Hz), 6.85 (1 H, s, NHCPh$_3$),

7.15−7.4 (15 H, m, Ar*H*). − $C_{33}H_{39}N_3O_7S$ (621.8): calcd: C 63.75, H 6.32, N 6.76; found C 63.68, H 6.38, N 6.70.

*(S)-N-Boc−vsSer(TBDPS)−Gly−OMe:* Following the above procedure the desired mixed peptide was obtained in 64% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.07 [9 H, s, $(CH_3)_3CSi$], 1.46 [9 H, s, $(CH_3)_3CO$], 3.75 (3 H, s, $OCH_3$), 3.65−3.80 (2 H, m, $CH_2OSi$), 3.80 (2 H, d, $NCH_2COO$, *J* = 5.6 Hz), 4.45 (1 H, m, CHN), 4.92 (1 H, d, NH, *J* = 5.3 Hz), 4.96 (1 H, t, N*H*$CH_2$, *J* = 5.6 Hz), 6.38 (1 H, dd, CH=C*H*$SO_2$, *J* = 15.1 Hz, *J* = 1.5 Hz), 6.77 (1 H, dd, C*H*=$CHSO_2$, *J* = 15.1 Hz, *J* = 4.7 Hz), 7.3−7.7 (10 H, m, 2× PhSi). − $^{13}$C NMR ($CDCl_3$): δ = 26.75 [$(CH_3)_3$], 28.22 [$(CH_3)_3$], 43.79 ($NCH_2$), 52.53 ($OCH_3$), 65.01 ($CH_2OSi$), 127.84 (CH=), 128.90 (CH=), 129.95 (CH=), 135.41 (CH=), 143.55 (CH=). − $C_{28}H_{40}N_2O_7SSi$ (576.8): calcd. C 58.31, H 6.99, N 4.86; found C 58.25, H 6.07, N 4.83.

*(S)-N-Boc−vsTyr(TBDPS)−Gly−OMe:* Following the above procedure the desired mixed peptide was obtained in 58% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.1 [9 H, s, $(CH_3)_3CSi$], 1.4 [9 H, s, $(CH_3)_3CO$], 2.75 (2 H, d, $CH_2$, *J* = 5.6 Hz), 3.7 (2 H, d, $NCH_2COO$, *J* = 5.0 Hz), 3.75 (3 H, s, $OCH_3$), 4.6 (1 H, m, CHN), 4.6 (1 H, d, NH, *J* = 6.6 Hz), 5.1 (1 H, t, N*H*$CH_2$, *J* = 5.0 Hz), 6.2 (1 H, d, CH=C*H*$SO_2$, *J* = 15.7 Hz), 6.65 (1 H, dd, C*H*=$CHSO_2$, *J* = 15.7 Hz, *J* = 4.0 Hz), 6.72 (2 H, CH=C-O, *J* = 8.6 Hz), 6.90 (2 H, CH=C-C, *J* = 8.6 Hz), 7.3−7.7 (10 H, m, 2× PhSi). − $^{13}$C NMR ($CDCl_3$): δ = 26.49 [$(CH_3)_3Si$], 28.15 [$(CH_3)_3CO$], 39.59 ($CH_2C_6H_4$), 43.68 ($NCH_2$), 52.58 ($OCH_3$), 119.84 (CH=), 127.67 (CH=), 129.85 (CH=),129.95 (CH=), 135.41 (CH=), 145.43 (CH=). − $C_{34}H_{44}N_2O_7SSi$ (652.9): calcd: C 62.55, H 6.79, N 4.29; found C 62.48, H 6.85, N 4.25.

*Mixed Peptides (S)-N-Boc−vsAA−(S)-vsAA−Gly−OMe* (**34**)

*(S)-N-Boc−vsVal−(S)-vsPro−Gly−OMe:* (*S*)-*N*-Boc−vsVal−Cl (208 mg, 0.70 mmol) was dissolved in DCM (7.0 ml) and a solution of HCl·(*S*)-H−vsPro−Gly−OMe (99.6 mg, 0.35 mmol) in DCM (2.0 ml) containing DBU (0.104 ml, 0.70 mmol) and DMAP (43 mg, 0.35 mmol) was added at once. The mixture was stirred at room temperature for 4 hours, then diluted with DCM and 10% aqueous solution of citric acid (2.0 ml) was added. The aqueous phase was extracted with DCM and the combined organic extracts were dried over $Na_2SO_4$ and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 4:6) to give the desired mixed peptide in 41% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.95 [3 H, d, $(CH_3)_2CH$, *J* = 6.7 Hz], 0.96 [3 H, d, $(CH_3)_2CH$, *J* = 6.7 Hz], 1.44 [9 H, s, $(CH_3)_3C$], 1.83−1.95 [4 H, m, NCHC*H*HC$H_2$ + $(CH_3)_2CH$], 2.02−2.15 (1 H, m, NCHC*H*H), 3.3−3.4 (2 H, m, $NCH_2$), 3.76 (3 H, s, $OCH_3$), 3.87 (2 H, d, NHC$H_2$CO, *J* = 5.5 Hz), 4.08−4.18 [1 H, m, $(CH_3)_2CHCH$], 4.26−4.30 (1 H, m, NCH), 4.75 (1 H, d, BocN*H*, *J* = 8.2 Hz), 5.44 (1 H, t, N*H*$CH_2CO$, *J* = 5.5 Hz), 6.27 (1 H, CH=C*H*$SO_2$, *J* = 15.0 Hz), 6.46 (1 H, d, CH=C*H*$SO_2$, *J* = 15.0), 6.65 (2 H, dd, 2× C*H*=$CHSO_2$, *J* = 5.5 Hz, *J* = 15.0 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 18.18 ($CH_3$), 18.77 ($CH_3$), 23.93 ($CH_2$), 28.17 [$(CH_3)_3$], 31.55 (CH), 31.86 ($CH_2$), 43.83 ($CH_2$), 48.71 ($CH_2$), 52.58 ($OCH_3$), 56.69 (CH), 59.16 (CH), 125.00 (CH=), 128.91 (CH=), 144.35 (CH=), 145.62 (CH=). − High-resolution MS: *m/z*: [M+1$^+$] calcd. 510.1944; found: 510.1956. − $C_{20}H_{35}N_3O_8S_2$ (509.2): calcd. C 47.14, H 6.92, N 8.24; found C 47.09, H 6.98, N 8.18.

*(S)-N-Boc−vsAla−(S)-vsPro−Gly−OMe:* Following the above procedure the desired mixed peptide was obtained in 25% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 1:1). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, C$H_3$CH, *J* = 6.5 Hz), 1.9 [4 H, m, $NCH_2(CH_2)_2$], 3.5 (2 H, m, $NCH_2$), 3.8 (3 H, s, $OCH_3$), 4.3 (2 H, m, NC*H* + NHC*H*), 4.6 (1 H, broad, NH), 6.2 (1 H, d, CH=C*H*$SO_2$, *J* = 15.2 Hz), 6.5 (1 H, d, CH=C*H*$SO_2$, *J* = 15.1 Hz), 6.7 (1 H, dd, C*H*=$CHSO_2$, *J* = 15.2 Hz, *J* = 5.6 HZ), 6.9 (1 H, dd, C*H*=$CHSO_2$, *J* = 15.1 Hz, *J* = 4.7 Hz). − $C_{18}H_{31}N_3O_8S_2$ (481.6): calcd. C 44.89, H 6.49, N 8.73; found C 44.84, H 6.55, N 8.67.

*(S)-N-Boc−vsAla−(S)-vsSer(TBDPS)−Gly−OMe:* Following the above procedure the desired mixed peptide was obtained in 26% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.07 [9 H, s, $(CH_3)_3CSi$], 1.26 (3 H, d, C$H_3$CH, *J* = 7.1 Hz), 1.45 [9 H, s, $(CH_3)_3C$], 3.74 (3 H, s, $OCH_3$), 3.8 (4 H, m, $CH_2$ + $CH_2$), 4.1 (1 H, m, CH), 4.35 (1 H, m, CH), 4.6 (1 H, m, NH), 4.9 (1 H, d, NH, *J* = 7.5 Hz), 6.0 (1 H, m, $SO_2NH$), 6.3−6.7 (4 H, m, 2× CH=CH), 7.65 (10 H, m, Ar-H). − $C_{32}H_{47}N_3O_9S_2Si$ (710.0), calcd. C 54.14, H 6.67, N 5.92; found C 54.08, H 6.73, N 5.88.

*(S)-N-Boc−vsVal−(S)-vsSer(TBDPS)−Gly−OMe:* Following the above procedure the desired mixed peptide was obtained in 36% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.91 (3 H, d, C$H_3$CH, *J* = 6.8 Hz), 0.93 (3 H, d, C$H_3$CH, *J* = 6.8 Hz), 1.07 [9 H, s, $(CH_3)_3CSi$], 1.45 [9 H, s, $(CH_3)_3CO$], 1.86 (1 H, m, $Me_2CH$), 3.73 (3 H, s, $CH_3O$), 3.69 (1 H, dd, NCHC*H*HO, *J* = 10.2 Hz, *J* = 4.6 Hz), 3.82 (1 H, dd, NCHC*H*HO, *J* = 10.2 Hz, *J* = 4.3 Hz), 3.92 (2 H, m, NHC$H_2$COO), 4.1 (2 H, m, 2× NCH), 4.77 (1 H, d, N*H*CH, *J* = 8.9 Hz), 5.12 (1 H, d, N*H*CH, *J* = 7.6 Hz), 6.17 (1 H, t, N*H*$CH_2COO$, *J* = 6.0 Hz), 6.34 (1 H, d, CH=C*H*$SO_2$, *J* = 15.0 Hz), 6.52 (1 H, d, CH=C*H*$SO_2$, *J* = 15.2 Hz), 6.65 (1 H, dd, C*H*=$CHSO_2$, *J* = 15.0 Hz, *J* = 4.7 Hz), 6.67 (1 H, dd, C*H*=$CHSO_2$, *J* = 15.2 Hz, *J* = 4.3 Hz), 7.3−7.7 (10 H, m, 2× PhSi). − $^{13}$C NMR ($CDCl_3$): δ = 18.00 ($CH_3$), 18.77 ($CH_3$), 26.75 [$(CH_3)_3$], 28.21 [$(CH_3)_3C$], 31.86 ($Me_2CH$), 44.03 ($NCH_2COO$), 52.38 ($OCH_3$), 55.14 (CHN), 56.21 (CHN), 65.57 ($CH_2O$), 127.93 (CH=), 129.33 (CH=), 130.05 (CH=), 131.67 (CH=), 135.41 (CH=), 140.05 (CH=), 144.34 (CH=). − $C_{34}H_{51}N_3O_9S_2Si$ (738.0): calcd. C 55.33, H 6.97, N 5.69; found C 55.26, H 7.03, N 5.64.

*(S)-N-Boc−vsVal−(S)-vsTyr(TBDPS)−Gly−OMe:* Following the above procedure the desired mixed peptide was obtained in 36% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.92 (3 H, d, C$H_3$CH, *J* = 6.7 Hz), 0.94 (3 H, d, C$H_3$CH, *J* = 6.7 Hz), 1.1 [9 H, s, $(CH_3)_3CSi$], 1.4 [9 H, s, $(CH_3)_3CO$], 1.9 (1 H, m, $Me_2CH$), 2.78 (1 H, dd, NCHC*H*H, *J* = 3.1 Hz, *J* = 6.2 Hz), 2.81 (1 H, dd, NCHC*H*H, *J* = 3.1 Hz, *J* = 6.2 Hz), 3.7 (3 H, s, $CH_3O$), 3.9 (2 H, m, NHC$H_2$COO), 4.1−4.3 (2 H, m, 2× NCH), 4.4 (1 H, d, N*H*CH, *J* = 5.6 Hz), 4.7 (1 H, d, N*H*CHCH$Me_2$, *J* = 7.1 Hz), 6.0 (1 H, t, N*H*$CH_2COO$, *J* = 6.0 Hz), 6.22 (1 H, d, CH=C*H*$SO_2$, *J* = 15.1 Hz), 6.35 (1 H, d, CH=C*H*$SO_2$, *J* = 15.1 Hz), 6.52 (1 H, dd, C*H*=$CHSO_2$, *J* = 15.1 Hz, *J* = 6.0 Hz), 6.71 (1 H, dd, C*H*=$CHSO_2$, *J* = 15.1 Hz, *J* = 4.0 Hz), 6.72 (2 H, d, CH=C-O, *J* = 8.6 Hz), 6.89 (2 H, d, CH=C-C, *J* = 8.6 Hz), 7.3−7.7 (10 H, m, 2× PhSi). − $^{13}$C NMR ($CDCl_3$): δ = 18.00 ($CH_3$), 18.77 ($CH_3$), 26.40 [$(CH_3)_3$], 28.22 [$(CH_3)_3$], 31.85 ($Me_2CH$), 40.44 ($CH_2Ar$), 43.93 ($NCH_2COO$), 52.43 ($OCH_3$), 54.42 (CHN), 56.26 (CHN), 120.19 (CH=), 127.68 (CH=), 129.24 (CH=), 129.84 (CH=), 130.29 (CH=), 130.50 (CH=), 135.40 (CH=), 144.50 (CH=). − $C_{40}H_{55}N_3O_9S_2Si$ (814.1): calcd. C 59.01, H 6.81, N 5.16; found C 58.94, H 6.88, N 5.12.

*Mixed Peptides (S)-N-Boc−Ala−(S)-vsAA−R (R = OR, NHR)* (**35**)

*(S)-N-Boc−Ala−(S)-vsAla−NHBn:* (*S*)-*N*-Boc−Ala−OH (369 mg, 1.95 mmol) was dissolved in DCM (16 ml), at room temp., under nitrogen, and 1-hydroxybenzotriazole (HOBt) (439 mg, 3.25 mmol) was added. After 10 min, a solution of HCl·(*S*)-H−vsAla −NHBn (448 mg, 1.625 mmol) in DCM (4.0 ml), containing TEA (0.128 ml, 1.625 mmol) and DMAP (40 mg, 0.325 mmol) was added at once. After further 10 min 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (468 mg, 2.44 mmol) was added and the mixture was stirred for 4 hours at room temperature, then diluted with water (5 ml). The aqueous phase was extracted with DCM and the combined organic extracts were dried and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:4) to give the desired sulfonopeptide in 87% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.23 (3 H, d, $CH_3$, *J* = 7.0 Hz), 1.33 (3 H, d, $CH_3$, *J* = 6.6 Hz), 1.42 [9 H, s, $(CH_3)_3C$], 4.1 (1 H, broad, CHCO), 4.2 (2 H, d, C*H*$_2$Ph, *J* = 6.1 Hz), 4.6 (1 H, m, $CH_3CH$), 5.17 (1 H, d, Boc-N*H*, *J* = 7.2 Hz), 5.3 (1 H, broad, N*H*$CH_2$Ph), 6.26 (1 H, d, CH=C*H*$SO_2$, *J* = 15.0 Hz), 6.67 (1 H, broad, NHCO), 6.67 (1 H, dd, C*H*=$CHSO_2$, *J* = 15.0 Hz, *J* = 4.6 Hz), 7.32 (5 H, s, Ph-*H*). − $C_{19}H_{29}N_3O_5S$ (411.5): calcd: C 55.46, H 7.10, N 10.21; found C 55.40, H 7.17, N 10.13.

*(S)-N-Boc−Ala−(S)-vsVal−OMe:* Following the above procedure the desired mixed peptide was obtained in 46% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.0 [6 H, m, $(CH_3)_2CH$], 1.4 (3 H, d, $CH_3CH$, *J* = 6.4 Hz), 1.47 [9 H, s, $(CH_3)_3C$], 1.9 [1 H, m, $(CH_3)_2CH$], 3.8 (3 H, s, $OCH_3$), 4.1 (1 H, m, CHCO), 4.6 (1 H, m, *i*PrC*H*N), 4.8 (1 H, d, N*H*CHCO, *J* = 5.9 Hz), 6.3 (1 H, d, CH=C*H*$SO_2$, *J* = 15.4 Hz), 6.7 (1 H, broad, CONH), 6.8 (1 H, dd, C*H*=$CHSO_2$, *J* = 15.4 Hz, *J* = 4.8 Hz). − $C_{15}H_{28}N_2O_6S$ (364.5): calcd. C 49.43, H 7.74, N 7.69; found C 49.38, H 7.81, N 7.63.

*(S)-N-Boc−Ala−(S)-vsAla−OiPr:* Following the above procedure the desired mixed peptide was obtained in 46% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 2:8). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.2−1.3 (12 H, m 4× $CH_3$), 1.4 [9 H, s, $(CH_3)_3C$], 4.1 (1 H, m, CHCO), 4.8 (1 H, m, $SO_3CH$), 5.0 (1 H, d, N*H*CHCO, *J* = 5.9 Hz), 6.3 (1 H, d, CH=C*H*$SO_3$, *J* = 13.8 Hz), 6.6 (1 H, d, CONH, *J* = 8.0 Hz), 6.8 (1 H, dd, C*H*=$CHSO_3$, *J* = 13.8 Hz, *J* = 4.8 Hz). − $C_{15}H_{28}N_2O_6S$ (364.5): calcd. C 49.43, H 7.74, N 7.69; found C 49.40, H 7.82, N 7.60.

*Cleavage of the TBDPS Side-Chain Protective Group. Synthesis of Sulfonamidopeptides Containing Free vs-Ser and vs-Tyr* (**36**)

*(S)-N-Boc−vsTyr−(S)-vsAla−NH$_2$:* A solution of (*S*)-*N*-Boc−vsTyr(TBDPS)−(*S*)-vsAla−$NH_2$ (12 mg, 0.017 mmol) in THF (0.25 ml), at room temp., under nitrogen, was treated with tetrabutylammonium fluoride (TBAF) (1 M in THF, 0.034 mmol). After 1 hour the solvent was evaporated at reduced pressure and the crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 4:6) to give the desired product in 94% yield. − $^1$H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, $CH_3CH$, *J* = 6.5 Hz), 1.4 [9 H, s, $(CH_3)_3C$], 2.85 (1 H, m, C*H*$_2$Ph), 4.1 (2 H, m, CH + NH), 4.5 (1 H, m, CH), 6.5 (4 H, m, 2× CH=CH), 6.9 (4 H, m, Ar-*H*). − $C_{19}H_{29}N_3O_7S_2$ (475.6): calcd C 47.99, H 6.15, N 8.84; found C 47.92, H 6.21, N 8.77.

*(S)-N-Boc−vsVal−(S)-vsTyr−Gly−OMe:* Following the above procedure the desired product was obtained in 70% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 7:3). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.90 (3 H, d, $CH_3CH$, *J* = 6.1 Hz), 0.91 (3 H, d, $CH_3CH$, *J* = 6.1 Hz), 1.5 [9 H, s, $(CH_3)_3C$], 1.7 (1 H, m, $Me_2CH$), 2.7 (1 H, dd, CH*H*$C_6H_4$, *J* = 13.4 Hz, *J* = 8.5 Hz), 2.96 (1 H, dd, C*H*H$C_6H_4$, *J* = 13.4 Hz, *J* = 5.3 Hz), 3.8 (3 H, s, $OCH_3$), 3.88 (2 H, d, $NCH_2COO$, *J* = 5.3 Hz), 3.9−4.2 (2 H, m, 2× C*H*N), 4.8 (1 H, d, NH, *J* = 9.4 Hz), 5.05 (1 H, d, NH, *J* = 7.3 Hz), 5.9 (1 H, m, N*H*$CH_2$), 5.94 (1 H, d, CH=C*H*$SO_2$, *J* = 15.1 Hz), 6.4−6.8 (2 H, m, 2× C*H*=$CHSO_2$), 6.5 (1 H, d, CH=C*H*$SO_2$, *J* = 15.3 Hz), 6.8 (2 H, d, CH=C-O, *J* = 8.0 Hz), 7.05 (2 H, d, CH=C-C, *J* = 8.0 Hz). − $^{13}$C NMR ($CDCl_3$): δ = 17.74 ($CH_3$), 18.73 ($CH_3$), 28.26 [$(CH_3)_3$], 32.51 ($Me_2CH$), 40.06 ($CH_2Ar$), 43.90 (*C*$H_2$COO), 52.59 ($OCH_3$), 55.31 (CHN), 56.12 (CHN), 116.14 (CH=), 129.09 (CH=*C*H$SO_2$), 129.76 (CH=*C*H$SO_2$), 130.70 (CH=), 143.20 (*C*H=$CHSO_2$), 144.31 (*C*H=$CHSO_2$). − $C_{24}H_{37}N_3O_9S_2$ (575.7): calcd. C 50.07, H 6.48, N 7.30; found C 50.00, H 6.54, N 7.25.

*(S)-N-Boc−vsVal−(S)-vsSer−Gly−OMe:* Following the above procedure the desired product was obtained in 80% yield after purification by flash chromatography (*n*-pentane/ethyl acetate, 2:8). − $^1$H NMR (200 MHz, $CDCl_3$): δ = 0.97 (3 H, d, $CH_3CH$, *J* = 6.7 Hz), 0.98 (3 H, d, $CH_3CH$, *J* = 6.9 Hz), 1.46 [9 H, s, $(CH_3)_3C$], 1.85 (1 H, m, $Me_2CH$), 3.52 (1 H, dd, CH*H*OH, *J* = 6.7 Hz, *J* = 11.7 Hz), 3.78 (3 H, s, $OCH_3$), 3.84 (1 H, dd, C*H*HOH, *J* = 3.8 Hz, *J* = 11.7 Hz), 3.91 (2 H, d, $NCH_2COO$, *J* = 5.9 Hz), 3.9−4.1 (2 H, m, 2× CHN), 4.88 (1 H, d, NH, *J* = 7.5 Hz), 5.42 (1 H, d, NH, *J* = 6.9 Hz), 5.78 (1 H, t, N*H*$CH_2$, *J* = 5.9 Hz), 6.39 (1 H, d, CH=C*H*$SO_2$, *J* = 15.0 Hz), 6.57 (1 H, dd, C*H*=$CHSO_2$, *J* = 6.6 Hz, *J* = 15.0 Hz), 6.65 (2 H, s, C*H*=C*H*$SO_2$). − $^{13}$C NMR ($CDCl_3$): δ = 18.37 ($CH_3$), 18.65 ($CH_3$), 28.22 [$(CH_3)_3$], 31.45 ($Me_2CH$), 43.94 (*C*$H_2$COO), 52.68 ($OCH_3$), 55.86 (CHN), 57.18 (CHN), 63.42 ($CH_2OH$), 129.50 (CH=), 131.06 (CH=), 140.51 (CH=), 143.94 (CH=). − $C_{18}H_{33}N_3O_9S_2$ (499.6): calcd. C 43.27, H 6.66, N 8.41; found C 43.22, H 6.72, N 8.33.

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