Synthesis of Combinatorial Libraries of Vinylogous Sulfonamidopeptides (vs-Peptides)

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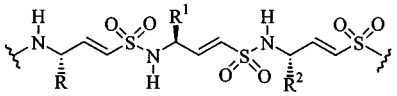
Chiral vinylogous sulfonamidopeptides (vs-peptides) were synthesized on TentaGel resin employing (*S*)- and (*R*)-*N*-Boc-vinylogous sulfonyl chlorides **2a–i** as building blocks. Glycine and two different photocleavable molecules were used as linkers, and the corresponding cleavage conditions were optimized. According to preliminary studies in solution and on solid phase, three libraries were synthesized with the "split-mix synthesis" method. Taking advantage of the acidic character of the sulfonamides (RSO_2–NHR: pK_a = 10–11), mild conditions were developed to alkylate the sulfonamide nitrogen atom so as to reduce the acidity of the monomers and of the oligomers and increase their in vivo bioavailability. This synthetic methodology was employed to increase the diversity in a library of di-*N*-alkylated vs-dipeptides **26**. The electron-withdrawing capability of the sulfonamido group pointed to the use of vinylogous sulfonamidopeptides as Michael acceptors. The sodium enolate of dimethyl malonate was used as nucleophile to obtain *N*-Boc-γ-lactams **35** in moderate yields and good diastereoselectivity.

Introduction

The current goal in drug discovery is to rapidly synthesize as many structurally diverse substances as possible, so that, in combination with high-throughput screening, the search for new lead structures and their optimization can be accelerated. A response to this need is provided by combinatorial chemistry.[1] The vast majority of the presently available combinatorial approaches makes use of SPS (Solid Phase Synthesis), which was first developed and optimized for peptides.[2] However, the poor bioavailability and rapid enzymatic degradation of peptides in vivo have generally limited their therapeutic application. One approach to overcome this obstacle has been the development of non-natural biopolymer scaffolds (carbamates, peptoids, ureas, sulfonamides, β-peptides, β-peptoids, etc.)[3] which may show improved pharmacological properties relative to peptides. As a consequence, research on the solid-phase synthesis of non-natural oligomers and small organic molecules has received increasing attention.[3][4]

At present, several approaches are available for the preparation of peptide isosters[5] and their synthesis on solid support.[6] In particular, sulfonamides[7] should show enhanced metabolic stability and structural similarity to the tetrahedral transition state involved in the enzymatic amide bond hydrolysis,[7a][7b][7c] thus making sulfonamidopeptides interesting candidates in the development of protease inhibitors and new drugs.[8] The synthesis in solution of both β-sulfonamidopeptides[9] and chiral vinylogous sulfonamidopeptides (vs-peptides)[10][11] has been developed by our research group starting from natural α-amino acids by an iterative process based on a straightforward protection-deprotection-coupling chemistry (Figure 1).

Figure 1. Vinylogous sulfonamido peptides (vs-peptides)



vinylogous sulfonamidopeptides (vs-peptides)

Some methods for the SPS of sulfonamides have appeared in the literature;[7e][7g][12] our main effort aimed at the development of SPS of vs-peptides[13] and at the application of these techniques to combinatorial chemistry. In this paper, the successful synthesis of three different vs-peptide libraries is described. Moreover, *post*-synthetic functionalization of vs-peptides was achieved by generating *N*-alkylated oligomers by selective alkylation of the sulfonamide group,[14] and by Michael addition of stabilized enolates to the electrophilic conjugated double bond.[15]

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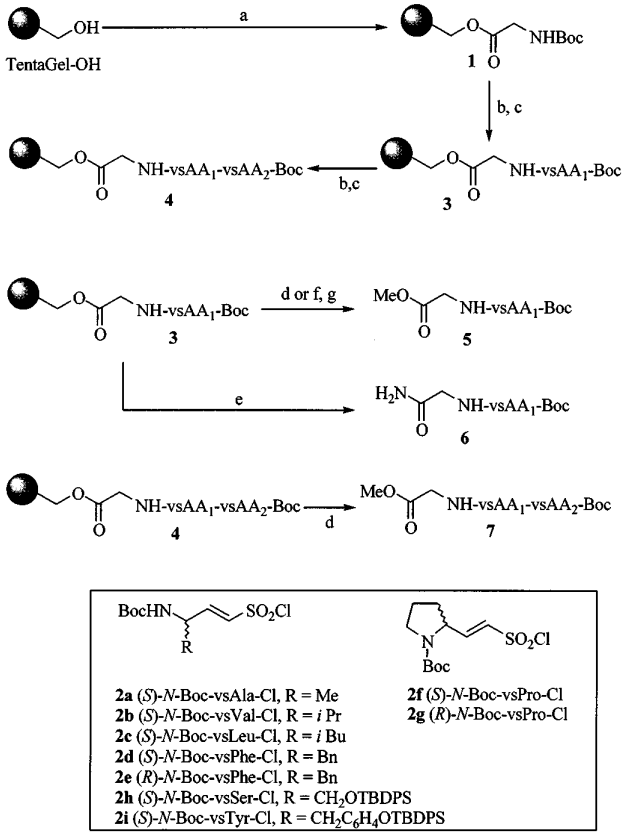
Results and Discussion

Solid Phase Synthesis of vs-Peptides

Two different types of TentaGel resins[16] were employed in the work here outlined: TentaGel-OH[16c] and TentaGel-NH_2[16c] (Scheme 1 and Scheme 2). Boc-glycine was attached as linker to TentaGel-OH resin affording functionalized resin **1**, while photocleavable linkers[17] were employed with TentaGel-NH_2 resin to give functionalized resins **8** [Boc-linker-A-NH-TentaGel (linker A = 4-aminomethyl-3-nitrobenzoic acid)] and **9** [Fmoc-linker-B-NH-Tentagel (linker-B = aminoethyl Photolinker Nova-Syn)[17b]].

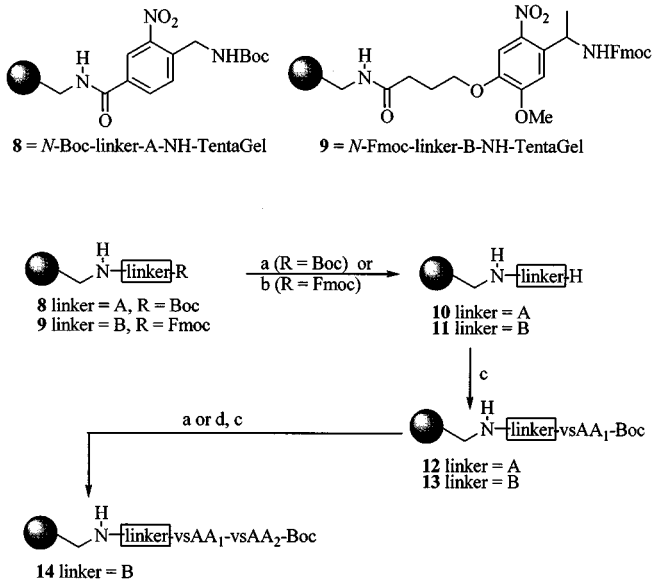
Scheme 1. Solid-phase synthesis of vs-peptides using TentaGel-OH resin and glycine linker



a: Boc-Gly-OH, DMAP, DIPC, DCM; b: i. TFA 25% in DCM; ii. DIPEA 5% in DCM; c: **2a−g**, NMM, DMAP, DCM; d: TEA, MeOH; e: NH_3, MeOH; f: NaOH, MeOH; g: CH_2N_2.

At the beginning of the synthesis, the *tert*-butoxycarbonyl (Boc) group was removed from resins **1** and **8** by treating with 25% trifluoroacetic acid (TFA) in dichloromethane (DCM), and the resulting ammonium salts were neutralized by washing with 5% diisopropylethylamine (DIPEA) in DCM. In the case of resin **9**, the 9-fluorenylmethoxycarbonyl (Fmoc) group was removed with a 20% solution of piperidine in *N,N*-dimethylformamide (DMF) to give free amine **11**.

Scheme 2. Solid-phase synthesis of vs-peptides using TentaGel-NH_2 resin and photocleavable linkers



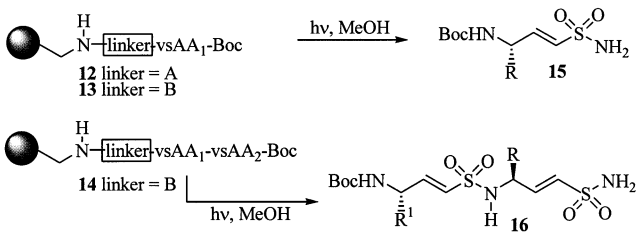
a: i. TFA 25% in DCM; ii. DIPEA 5% in DCM; b: Piperidine 20% in DMF; c: **2a−i**, NMM, DMAP, DCM; d: HCl, EtOAc (to be used when O-TBDPS protective group is present in the vs-peptide sequence, see **2h** and **2i**).

Our SPS of vs-peptides made use of *N*-Boc vinylogous amino sulfonyl chlorides[11a][11b][11c] **2a−i** and followed a Boc-protection-adapted strategy. Contrary to the synthesis in solution,[11a][11b][11c] SPS allows the use of TFA for Boc deprotection, as the ammonium trifluoroacetate salts can be neutralized to free amines, and the risk of obtaining trifluoroacetamides during the subsequent coupling step is thus avoided. The free amines were coupled with *N*-Boc vinylogous amino sulfonyl chlorides[11a][11b][11c] **2a−i** to give vinylogous sulfonamides **3**, **12**, **13**. According to the protocol for the synthesis in solution,[11a][11b][11c] we used 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 4-dimethylaminopyridine (DMAP) to run the coupling reactions on solid support.[13] More recent experiments have demonstrated that DBU leads to partial decomposition of the sulfonyl chlorides because of the long time required by the coupling. Replacement of DBU by 2,6-lutidine, *N*-methylimidazole or triethylamine was not successful either. By employing *N*-methylmorpholine (NMM), in the presence of a substoichiometric amount of DMAP, a reasonable stability of the sulfonyl chlorides was achieved, thus allowing a cleaner coupling to the solid-phase-supported amines in a minor number of cycles. The optimized coupling reactions were performed by treating the resin-bound amines with 0.5 equivalents of DMAP, 1.0 equivalent of NMM and 2.0 equivalents of *N*-Boc vinylogous amino sulfonyl chloride in DCM. The coupling reactions were monitored with bromophenol blue (BPB),[18] while the traditional Kaiser ninhydrin test[19] proved less suitable. Using this protocol, we synthesized vs-dipeptides **4**, **14** on solid support in moderate to good yields and excellent purity, as determined by subsequent cleavage from the resin (see below).

vs-Peptides were cleaved from the solid support (TentaGel-OH resin, glycine linker) by direct ester methanolysis (10% TEA in MeOH) to give the desired glycine methyl ester derivatives **5**, **7** in 20−60% yield after chromatography. Alternatively, the cleavage of the products from the solid support (TentaGel-OH resin, glycine linker) was performed by saponification of the Gly-O-TentaGel ester (NaOH/MeOH) and subsequent esterification (CH_2N_2) of the carboxylic acid to afford the corresponding glycine methyl ester derivatives **5** in good yields (60%). Direct ester ammonolysis (saturated NH_3 in MeOH) gave the glycine carboxyamide derivatives **6** in poor yields (15−20%). The protected vinylogous sulfonyl derivatives of serine [−vsSer(TBDPS)−] and tyrosine [−vsTyr(TBDPS)−] could be inserted into the vs-peptide sequence only when TentaGel-NH_2 and photocleavable linkers were employed (vide infra). In fact, the basic conditions (1 M Bu_4NF in THF) needed for O-TBDPS deprotection also cleaved the Gly-O-TentaGel ester, precluding the use of this kind of support and linker.

Resin-bound vs-peptides **12**, **13**, **14** were cleaved from the solid support [TentaGel-NH_2 resin, photocleavable linkers A and B] by swelling the resin in MeOH and irradiating for 1−4 days at 354 nm, to give **15** and **16** in 30−86% yields. For both photocleavable linkers we observed a peak in the release of the products during the first 10−20 hours of exposure to the light. After that time, the release continued at a much slower rate. From these studies, linker-B was confirmed to be the best of the two,[17a] affording vs-peptides **15** and **16** in higher yields (77−86%) and no by-products (Scheme 3).

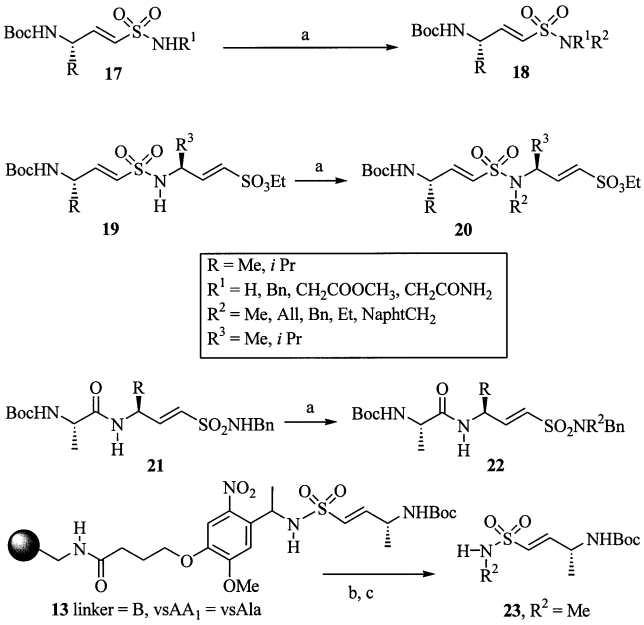
Scheme 3. Photocleavage of vs-peptides from TentaGel-NH_2 resin



N-Alkylation of vs-Peptides in Solution and on Solid Phase

N-Alkylation of the sulfonamide groups seems an effective way to reduce the acidity of vs-peptides and to increase their bioavailability. Several methods are known for *N*-alkylation of amides and sulfonamides, both in solution and on solid phase.[14] Treatment of vs-peptides with diethyl azodicarboxylate (DEAD), triphenylphosphane and alcohols led to no alkylated product, although the Mitsunobu reaction is known to alkylate acidic compounds like phenols and also sulfonamides.[14a][14b][14c][14d][14e] The known methods for amide alkylation in peptide synthesis were not applicable to Boc-protected vs-peptides, since the use of strong bases like NaH or *t*BuOK led to both BocNH and RSO_2NHR alkylation. The use of a milder base (Cs_2CO_3) allowed the selective *N*-alkylation of the more acidic sulfonamide group (RSO_2-NHR: pK_a = 10−11 vs. Boc−NH: pK_a = 15−16) (Scheme 4).

Scheme 4. *N*-Alkylation of vs-peptides in solution and on solid phase



a: R^2X, Cs_2CO_3, THF; b: R^2X, Cs_2CO_3, DMF; c: hν, MeOH.

By treating *N*-Boc protected vs-peptides with Cs_2CO_3 and various alkylating agents [methyl iodide (MeI), ethyl iodide (EtI), benzyl bromide (BnBr), 2-(bromomethyl)-naphthalene ($NaphtCH_2Br$), allyl bromide (AllBr)] in THF, *N*-alkylsulfonamides **18**, **20**, **22** were obtained in moderate to good yields (40−100%). The same reaction was successfully transferred to the solid phase, where it was possible to drive the reaction to completion by repeating the alkylation cycles. In SPS, the use of DMF as solvent, where Cs_2CO_3 is soluble, proved favourable by avoiding the formation of a three-phase system, accelerating the reactions and improving the yields. A representative case is shown in Scheme 4, where compound **23** was obtained as a single product in high purity after photocleavage (50% yield). The *N*-alkylation reactions could be performed only when TentaGel-NH_2 and photocleavable linkers were employed. The basic conditions (Cs_2CO_3, DMF) needed for sulfonamide alkylation also cleaved the Gly-O-TentaGel ester, precluding the use of this kind of support and linker.

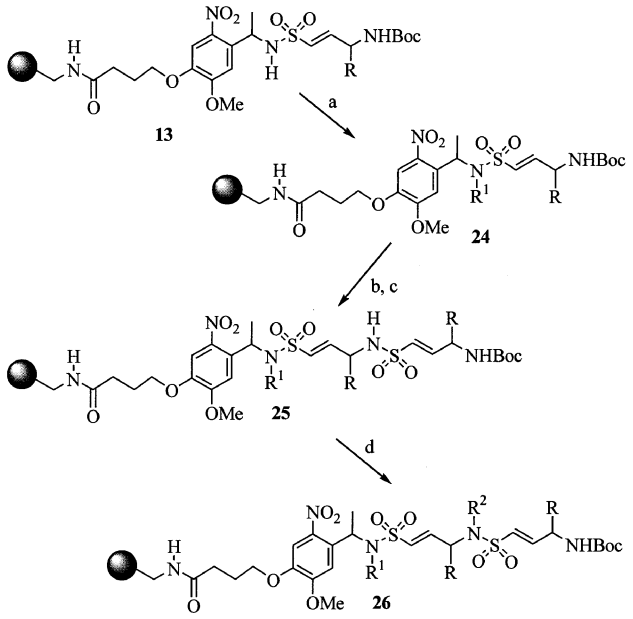
Synthesis of Combinatorial Libraries of vs-Peptides

Once the synthetic strategies had been established, we set out to synthesize three different libraries of sulfonopeptides by the "split-mix synthesis" method, which is the most common approach for the synthesis of compound mixtures.[20]

For the synthesis of a library of di-*N*-alkylated vs-dipeptides, TentaGel-NH_2 resin and the photocleavable linker-B were employed, together with seven sulfonyl chlorides

2a−g, and three alkylating agents [MeI, $PhCH_2Br$ (BnBr), $CH_2{=}CHCH_2Br$ (AllBr)], so as to obtain in principle [7 × 3 × 7 × 3] = 441 di-*N*-alkylated vs-dipeptides (Scheme 5, 6). The general formula of the library is Boc-vsAA_2-*N*(R^2)-vsAA_1-*N*(R^1)-linker-B-resin (**26**), apart from the special case when vsAA_1 = (*L*)- or (*D*)-vsPro (a secondary amine) and the formula then becomes Boc-vsAA_2-vsPro-*N*(R^1)-linker-B-resin, with a reduction of the total number of compounds from 441 to 357.

Scheme 5. Synthesis of the library of 357 di-*N*-alkylated vs-dipeptides



a: R^1X, Cs_2CO_3, DMF (R^1 = Me, Bn, All); b: i. TFA 25% in DCM; ii. DIPEA 5% in DCM; c: **2a−g**, NMM, DMAP, DCM; d: R^2X, Cs_2CO_3, DMF (R^2 = Me, Bn, All).

The resin Fmoc-linker-B-NH-TentaGel (**9**) was split into 7 pools and each pool was treated with 20% piperidine in DMF. In the first library step, each pool suspended in DCM was treated with DMAP, NMM, and sulfonyl chlorides Boc-vsAA_1-Cl (**2a−g**) to give **13**. The mixtures were shaken for 18 hours, and the coupling cycle was repeated 3 times to ensure complete conversion. At the end of each cycle the resin was checked with the BPB test.[18][21] The 7 pools were mixed together in the same flask with DCM and split into 3 pools. In the second library step, each pool suspended in DMF was treated with Cs_2CO_3 and the alkylating agent (AllBr, MeI, and BnBr) to give **24**. The mixtures were shaken for 6 hours, and the alkylating cycle was repeated 4 times to ensure complete conversion. The 3 pools were mixed together in the same flask, the resin was treated with 25% TFA in DCM and then split into 7 pools. In the third library step, each pool suspended in DCM was treated with NMM, DMAP, and sulfonyl chlorides Boc-vsAA_2-Cl (**2a−g**) to give **25**. The mixtures were shaken for 16 hours and the coupling cycle was repeated 3 times. At the end of each cycle the resin was checked with the BPB test.[18][21]

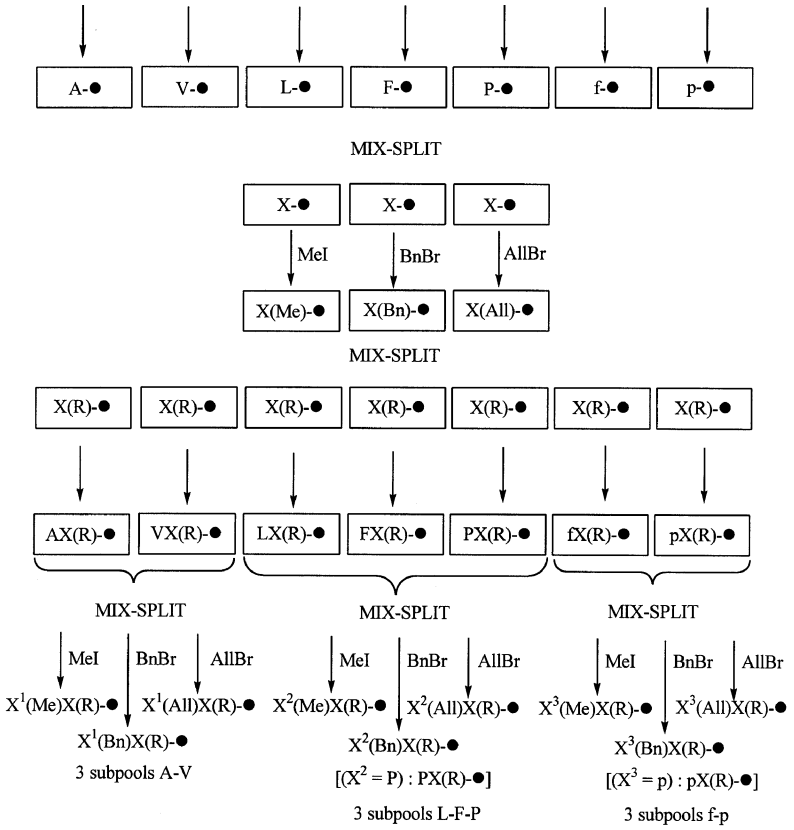
The 7 pools were mixed to form three new pools: the pool A-V (42 *N*-monoalkylated vs-dipeptides), obtained mixing pools A [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*S*)-vsAla] and V [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*S*)-vsVal]; the pool L-F-P (63 *N*-monoalkylated vs-dipeptides), obtained mixing pools L [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*S*)-vsLeu], F [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*S*)-vsPhe] and P [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*S*)-vsPro]; the pool f-p (42 *N*-monoalkylated vs-dipeptides), obtained mixing pools f [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*R*)-vsPhe] and p [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*R*)-vsPro]. Each of these three pools was split into three subpools for the fourth library step. Each subpool A-V, L-F-P, and f-p, suspended in DMF, was treated with Cs_2CO_3 and the alkylating agent (AllBr, MeI, and BnBr) to give **26**. The mixtures were shaken for 6 hours and the alkylating cycle was repeated 4 times. In this way, 9 subpools were generated, each containing a minimum of 42 and a maximum of 63 di-*N*-alkylated vs-dipeptides, for which the last alkylating agent used is known (Scheme 6).

In this way, the number of compounds present in each subpool was mantained relatively low (42−63), so as to make library screening and deconvolution easier. The compounds were released from the resin by photolysis, and the biological activity of the subpools [general formula Boc-vsAA_2-*N*(R^2)-vsAA_1-NH(R^1)] is presently under evaluation, using "recursive deconvolution"[22] in order to identify the structure of "active" compounds in the pools.

The second library was synthesized on TentaGel-NH_2 resin, employing the photocleavable linker-B and nine sulfonyl chlorides **2a−i**, to give a total of [9 × 9 × 9] = 729 vs-tripeptides. Functionalized vs-amino acids[11b] derived from serine [vrSer(TBDPS)] and tyrosine [vrTyr(TBDPS)] were introduced in this library. As the growing vs-peptide chain contained a *tert*-butyl diphenylsilyloxy (TBDPS-O) group [the hydroxy protecting group in −vsSer(TBDPS)− and −vsTyr(TBDPS)−], the Boc cleavage had to be performed with a saturated HCl solution in ethyl acetate to prevent O-TBDPS deprotection.[23] In the last step, the TBDPS group was removed treating the resin with Bu_4NF in THF, according to the protocol successfully employed in solution for serine and tyrosine.[11b] The synthesis of this library [general formula Boc-vsAA_3-vsAA_2-vsAA_1-linker-B-NH-TentaGel (**29**)] is outlined in Scheme 7.

In the synthesis of the third library (first in chronological order) five sulfonyl chlorides **2a−d, 2f**, TentaGel-NH_2 resin and photocleavable linker-A were used, to give a total of [5 × 5 × 5 × 5] = 625 vs-tetrapeptides [general formula Boc-vsAA_4-vsAA_3-vsAA_2-vsAA_1-linker-A-NH-TentaGel (**33**)] (Scheme 8). The synthesis of this library is analogous to the one described above in Scheme 7, the main difference being the use of DBU instead of NMM. The number of coupling cycles necessary in each step of the third library (4−32 cycles) reveals a sharp increase in coupling efficiency for the two libraries outlined above (2−3 cycles). A possible explanation is that DBU is not only aggressive toward sul-

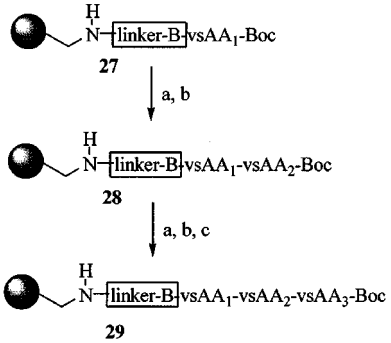
Scheme 6. Library scheme for the 357 di-*N*-alkylated vs-dipeptides



● = TentaGel-NH-linker-B; A = (*S*)-vsAla; V = (*S*)-vsVal; L = (*S*)-vsLeu; F = (*S*)-vsPhe; P = (*S*)-vsPro; f = (*R*)-vsPhe; p = (*R*)-vsPro; x = vsAA; R = Me, Bn, All; X^1 = (*S*)-vsAla or (*S*)-vsVal; X^2 = (*S*)-vsLeu or (*S*)-vsPhe or (*S*)-vsPro; X^3 = (*R*)-vsPhe or (*R*)-vsPro.

fonyl chlorides but can also interfere with the BPB test,[18][21] giving rise to false positives. The new optimized coupling conditions (NMM, DMAP) allow to perform SPS of vs-peptides in high yield and purity with a reasonable number of coupling cycles and do not interfere with the BPB test, which can be used as a reliable method to monitor the conversion at each coupling cycle.[18][21]

Scheme 7. Synthesis of the library of 729 functionalized vs-tripeptides

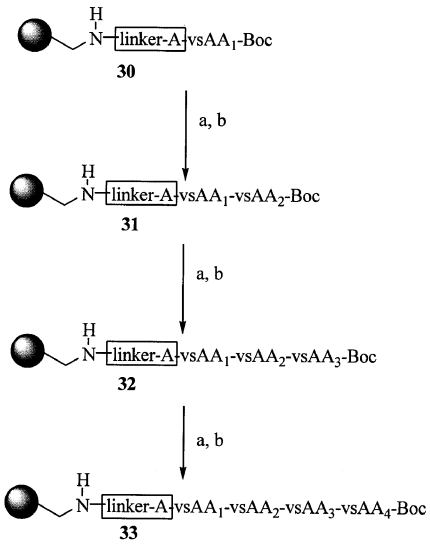


a: i. HCl, EtOAc; ii. DIPEA 5% in DCM; b: **2a−i**, NMM, DMAP, DCM; c: TBAF in THF.

Michael Addition Reactions to vs-Peptides

The sulfonamide group [$-SO_2NR_2$; R = Me; R, R = $-(CH_2)_5-$] confers a low electrophilic character to the con-

Scheme 8. Synthesis of the library of 625 vs-tetrapeptides

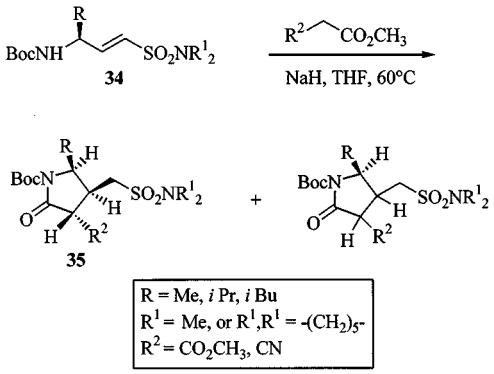


a: i. TFA 25% in DCM; ii. TEA 10% in DCM; b: **2a−d**, **2f**, DBU, DMAP, DCM.

jugated double bond of vs-peptides, and the corresponding Michael addition reactions are sluggish. Diastereoselective Michael addition reactions to optically active trifluoromethylated α,β-unsaturated sulfonamides of lithium or sodium enolates have recently been reported.[15] The strong electron-withdrawing capability of the trifluoromethyl group is responsible for the high reactivity of these substrates.[15]

The Michael addition reaction of various stabilized enolates (derived from 1,3-dicarbonyl compounds) was tested on vs-peptides **34**, and satisfactory results were obtained with dimethyl malonate and NaH in THF at 60°C. The outcome of such reactions is interesting, since no simple addition products were observed: after the addition of the carbon nucleophile to the double bond, attack of the carbamate nitrogen atom onto the methyl ester takes place and γ-lactam products **35** are isolated in poor to moderate yields (20−56%) (Scheme 9). The leaving group on the ester is of particular importance: the use of diethyl malonate did not lead to the cyclic product, and the Michael addition product was not observed either, since the first step is probably reversible. The addition reactions were initially studied on the piperidine derivative of (*S*)-Boc-vs-Ala [**34**; R = Me; R^1, R^1 = $-(CH_2)_5-$]. Two new stereocentres are formed during the addition-ring closure reaction, leading to four possible diastereoisomers.

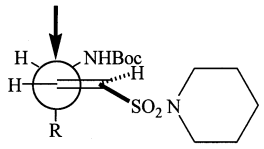
Scheme 9. Michael addition reactions to vs-peptides



The reaction is moderately diastereoselective, and an 85:15 mixture of two products was obtained. On the basis of NOE experiments, the relative stereochemistry was assigned to the major diastereoisomer [**35**; R = Me; R^1, R^1 = $-(CH_2)_5-$; R^2 = CO_2CH_3] as reported in Scheme 9. Four similar "model" structures were optimised with MacroModel force-field calculations,[24] and the corresponding interproton distances were evaluated: only structure **35** fits with the NOE data.

According to the major diastereoisomer formed, the direction of attack of the nucleophile at the α,β-unsaturated sulfonamide possessing a stereogenic centre in the γ position, is probably as shown in Figure 2. This transition-state model is in accordance with that proposed by Yamamoto in the context of conjugate addition of cuprates to γ-alkoxy-α,β-unsaturated esters,[25a][25c] and by Jackson for the nucleophilic epoxidation of γ-alkoxy-α,β-unsaturated sulfones.[25b][25c]

Figure 2. Transition-state model for the Michael addition reaction to vs-peptides



The addition reaction of the sodium enolate of dimethyl malonate to (*S*)-Boc-vs-Val-NMe_2 [**34**; R = *i*Pr; R^1 = Me] gave a single diastereoisomer [**35**; R = *i*Pr; R^1 = Me; R^2 = CO_2CH_3] in good yield (56%). Addition of sodium dimethyl malonate to other substrates (*S*)-Boc-vs-AA-NMe_2 [**34**; R = Me or *i*Bu; R^1 = Me] gave poorer results (20−40%). The use of different nucleophiles, such as sodium dimethyl methylmalonate, or sodium methyl cyanoacetate, also gave low yields of pyrrolidinones.

Conclusions

A feasible route to the solid-phase synthesis of vinylogous sulfonamidopeptides (vs-peptides) was developed on Tentagel resin employing (*S*) and (*R*)-*N*-Boc-vinylogous sulfonyl chlorides **2a−i**. Glycine and two different photocleavable molecules (A and B, Scheme 2) were used to link the substrates to the solid support. The optimal coupling conditions (NMM, DMAP) allowed chain elongation in good yields. Cleavage of vs-peptides from the resin was achieved either by transesterification (glycine linker) or by photolysis (A and B linkers). In the latter case, linker-B proved to be the best choice. Vs-peptides were selectively *N*-alkylated at the sulfonamide group using Cs_2CO_3 as a base. Synthesis of three different vs-peptide libraries was achieved whose potential biological activity is currently under evaluation. vs-Peptides were also subjected to the Michael addition reaction, affording *N*-Boc-γ-lactams in moderate yields and good diastereoselectivity.

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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 an FT-IR Varian spectrometer. − 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 trahydrofuran (THF), Et_2O, benzene, toluene, dichloromethane (DCM), *N,N*-dimethylformamide (DMF), MeOH] for solid-phase synthesis were analytical grade or HPLC grade. THF for Michael addition reactions and vs-peptide *N*-alkylations was distilled from sodium under nitrogen, diisopropylethylamine (DIPEA) and triethylamine (TEA) were distilled from CaH_2 under nitrogen. All solid-phase reactions were carried out with a wrist shaker (Multi-wrist Shaker Lab-line). Organic extracts were dried with Na_2SO_4.

Solid Phase Synthesis: TentaGel-OH Resin and Glycine Linker

Boc-Gly-OTentaGel (**1**): Resin TentaGel-OH (3 g, 0.78 mmol; Rapp Polymere, Tübingen, Germany) in DCM (30 ml) was treated with Boc-Gly-OH (410 mg, 2.34 mmol), diisopropylcarbodiimide (DIC) (295.3 mg, 0.367 ml, 2.34 mmol) and DMAP (9.5 mg, 0.078 mmol). The mixture was shaken for 24 h and then washed with DCM (5 × 30 ml). The coupling cycle was repeated 3 times and at the end of the third cycle the resin was washed with DCM (5 × 30 ml), DMF (3 × 30 ml), MeOH (3 × 30 ml) and DCM (3 × 30 ml).

(S)-Boc-vsAla-Gly-OTentaGel (**3**, $vsAA_1$ = vsAla): The resin Boc-Gly-OTentaGel (**1**, 500 mg, 0.13 mmol) was treated with 25% trifluoroacetic acid (TFA) solution in DCM (3 × 5 ml), washed with DCM (5 × 5 ml), neutralized with 5% DIPEA in DCM (3 × 5 ml) and washed again with DCM (5 × 5 ml). To this resin in DCM (5 ml) were added (*S*)-Boc-vsAla-Cl (**2a**, 70 mg, 0.26 mmol), *N*-methylmorpholine (NMM) (13.1 mg, 0.13 mmol), and DMAP (8 mg, 0.065 mmol). The mixture was shaken for 24 h and then washed with DCM (3 × 5 ml), MeOH (3 × 5 ml) and DCM (5 × 5 ml). The coupling cycle was repeated 3 times, checking at the end of each cycle with the bromophenol blue (BPB) test.[18][21] The resin was suspended in DCM (5 ml) and acetic anhydride (0.50 ml) was added. The mixture was shaken for 12 h and then washed with DCM (5 × 5 ml), DMF (5 × 5 ml) and DCM (5 × 5 ml).

(S)-Boc-vsPhe-(S)-vsAla-Gly-OTentagel (**4**, $vsAA_1$ = vsAla, $vsAA_2$ = vsPhe): The resin (*S*)-Boc-vsAla-Gly-OTentaGel (**3**, $vsAA_1$ = vsAla) (500 mg, 0.13 mmol) was treated with 25% TFA solution in DCM (3 × 5 ml), washed with DCM (5 × 5 ml), neutralized with 5% DIPEA in DCM (3 × 5 ml) and washed again with DCM (5 × 5 ml). To this resin in DCM (5 ml) were added (*S*)-Boc-vsPhe-Cl (**2d**, 90 mg, 0.26 mmol), NMM (13.1 mg, 0.13 mmol) and DMAP (8 mg, 0.065 mmol). The mixture was shaken for 24 h and then washed with DCM (3 × 5 ml), MeOH (3 × 5 ml) and DCM (5 × 5 ml). The coupling cycle was repeated 3 times, checking at the end of each cycle with the BPB test.[18][21] The resin was suspended in DCM (5 ml) and acetic anhydride (0.50 ml) was added. The mixture was shaken for 12 h and then washed with DCM (5 × 5 ml), DMF (5 × 5 ml), DCM (5 × 5 ml).

TentaGel-NH_2 Resin and Photocleavable Linker

Boc-linker-A-NH-TentaGel (**8**): Resin TentaGel-NH_2 (1 g, 0.25 mmol; Rapp Polymere, Tübingen, Germany) in DMF (10 ml) was treated with DIC (69.4 mg, 0.55 mmol), HOBt (186 mg, 1.375 mmol) and after 10 min Boc-4-aminomethyl-3-nitrobenzoic acid (Boc-linker-A; 148 mg, 0.5 mmol). The mixture was shaken for 12 h and then washed with DMF (3 × 5 ml), MeOH (3 × 10 ml) and DCM (5 × 10 ml). The coupling cycle was repeated 6 times, checking at the end of each cycle with the BPB test.[18][21] The resin was suspended in DCM (10 ml) and acetic anhydride (1.00 ml) was added. The mixture was shaken for 12 h and then washed with DCM (5 × 10 ml), DMF (5 × 10 ml) and DCM (5 × 10 ml).

(S)-Boc-vsAla-linker-A-NH-TentaGel (**12**, $vsAA_1$ = vsAla): The resin Boc-linker-A-NH-Tentagel (**8**, 500 mg, 0.125 mmol) was treated with 25% TFA in DCM (3 × 5 ml); the resin was washed with DCM (5 × 5 ml), neutralized with 5% DIPEA in DCM (3 × 5 ml) and washed with DCM (5 × 5 ml). To this resin in DCM (5 ml) were added (*S*)-Boc-vsAla-Cl (**2a**, 67.3 mg, 0.250 mmol), NMM (12.7 mg, 0.125 mmol) and DMAP (7.6 mg, 0.0625 mmol). The mixture was shaken for 24 h and then washed with DCM (3 × 5 ml), MeOH (3 × 5 ml) and DCM (5 × 5 ml). The coupling cycle was repeated twice, checking at the end of each cycle with the BPB test.[18][21] The resin was suspended in DCM (5 ml) and acetic anhydride (0.50 ml) was added. The mixture was shaken for 12 h and then washed with DCM (5 × 5 ml), DMF (5 × 5 ml) and DCM (5 × 5 ml).

(S)-Boc-vsAla-linker-B-NH-TentaGel (**13**, $vsAA_1$ = vsAla): Fmoc-aminoethyl-Photolinker NovaSyn TG resin (Fmoc-linkerB-NH-TentaGel, Novabiochem)[17b] (**9**, 600 mg, 0.138 mmol) was treated with 20% piperidine in DMF (2 × 6 ml); the resin was washed with DMF (3 × 6 ml) and DCM (5 × 6 ml). To this resin in DCM (6 ml) were added (*S*)-Boc-vsAla-Cl (**2a**, 74.4 mg, 0.276 mmol), NMM (14 mg, 0.138 mmol) and DMAP (8.4 mg, 0.069 mmol). The mixture was shaken for 24 h and then washed with DCM (3 × 6 ml), MeOH (3 × 6 ml) and DCM (5 × 6 ml). The coupling cycle was repeated twice, checking at the end of each cycle with the BPB test.[18][21] The resin was suspended in DCM (6 ml) and acetic anhydride (0.60 ml) was added. The mixture was shaken for 12 h and then washed with DCM (5 × 6 ml), DMF (5 × 6 ml) and DCM (5 × 6 ml).

(S)-Boc-vsPhe-(S)-vsAla-linker-B-NH-TentaGel (**14**, $vsAA_1$ = vsAla, $vsAA_2$ = vsPhe): The resin (*S*)-Boc-vsAla-linker-B-NH-TentaGel (**13**, $vsAA_1$ = vsAla) (600 mg, 0.138 mmol) was treated with 25% TFA in DCM (3 × 6 ml); the resin was washed with DCM (5 × 6 ml), neutralized with 5% DIPEA in DCM (3 × 6 ml) and washed with DCM (5 × 6 ml). To this resin in DCM (6 ml) were added (*S*)-Boc-vsPhe-Cl (**2d**, 95.4 mg, 0.276 mmol), NMM (14 mg, 0.138 mmol) and DMAP (8.4 mg, 0.069 mmol). The mixture was shaken for 24 h and then washed with DCM (3 × 6 ml), MeOH (3 × 6 ml) and DCM (5 × 6 ml). The coupling cycle was repeated twice, checking at the end of each cycle with the BPB test.[18][21] The resin was suspended in DCM (6 ml) and acetic anhydride (0.60 ml) was added. The mixture was shaken for 12 h and then washed with DCM (5 × 6 ml), DMF (5 × 6 ml) and DCM (5 × 6 ml).

Cleavage of Sulfonopeptides from TentaGel-OH Resin

(S)-Boc-vsAla-Gly-NH_2 (**6**, $vsAA_1$ = vsAla): The resin (*S*)-Boc-vsAla-Gly-OTentagel (**3**, $vsAA_1$ = vsAla) (500 mg, 0.13 mmol) was treated with 5 ml of a NH_3 saturated MeOH solution. The mixture was shaken for 20 h and then the organic phase was filtered off and evaporated at reduced pressure. The crude product was purified by flash chromatography (ethyl acetate) to give the desired product in 20% yield. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, CH_3CH, *J* = 6.3 Hz); 1.43 (9 H, s, $[CH_3]_3C$); 3.6 (2 H, s, CH_2CO); 4.30 (1 H, m, CHN); 6.3 (3 H, broad, NH + $CONH_2$); 6.39 (1 H, dd, CH=C*H*, *J* = 14.7 Hz, *J* = 1.5 Hz); 6.67 (1 H, dd, C*H*=CH, *J* = 14.7 Hz, *J* = 5.1 Hz).

(S)-Boc-vsVal-(S)-vsPro-Gly-OMe (**7**, $vsAA_1$ = vsPro, $vsAA_2$ = vsVal): The resin (*S*)-Boc-vsVal-(*S*)-vsPro-Gly-OTentagel (**4**, $vsAA_1$ = vsPro, $vsAA_2$ = vsVal) (500 mg, 0.13 mmol) was washed with MeOH (5 × 5 ml) and then treated with 10% TEA in MeOH (8 ml). The mixture was shaken for 24 h and washed with MeOH (5 × 5 ml) at the end of each cycle. The organic fractions were collected and evaporated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:4) to give the desired product in 20% yield. The spectra are identical to those reported for the compound synthesized in solution.[11b]

(S)-Boc-vsAla-Gly-OMe (**5**, $vsAA_1$ = vs Ala): According to the above procedure the desired product was obtained in 52% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). The spectra are identical to those reported for the compound synthesized in solution.[11b]

(S)-Boc-vsAla-Gly-OMe (**5**, $vsAA_1$ = vs Ala): The resin (*S*)-Boc-vsAla-Gly-OTentagel (**3**, $vsAA_1$ = vs Ala) (310 mg, 0.081 mmol) in MeOH (4 ml) was treated with 4 ml of a 0.1 N NaOH solution (0.4 mmol). The mixture was shaken for 20 h and then the solvent was filtered off and evaporated at reduced pressure. The crude product was then dissolved in a solution at pH = 3 (HCl, H_2O), the aqueous phase was exctracted with DCM, and the combined organic extracts were dried and concentrated. The crude product was treated with CH_2N_2 in Et_2O; after 1 h, the solvent was removed at reduced pressure and the product was purified by flash chromatography (*n*-hexane/ethyl acetate, 1:1) giving the pure methyl ester in 60% yield. The spectra are identical to those reported for the compound synthesized in solution.[11b]

Cleavage of Sulfonopeptides from TentaGel-NH_2 Resin

(S)-Boc-vsAla-NH_2 (**15**, R = Me): A suspension of (*S*)-Boc-vsAla-linker-A-NH-TentaGel (**12**, $vsAA_1$ = vsAla) (200 mg, 0.05 mmol) in dry MeOH (5 ml), in a Pyrex reactor, was irradiated for 31 h at 354 nm with a 125-W Hg lamp, under shaking. The solvent was collected and the resin was washed with MeOH (5 × 2 ml). The combined organic fractions were concentrated at reduced pressure. The residue was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:4) to give the desired product in 30% yield. The spectra are identical to those reported for the compound synthesized in solution.[11b]

(S)-Boc-vsAla-NH_2 (**15**, R = Me): A suspension of (*S*)-Boc-vsAla-linker-B-NH-TentaGel (**13**, $vsAA_1$ = vsAla) (109 mg, 0.025 mmol) in dry MeOH (5 ml), in a Pyrex reactor, was irradiated for 100 h at 354 nm with a 125-W Hg lamp, under shaking. The solvent was collected and the resin was washed with MeOH (5 × 2 ml). The combined organic fractions were concentrated at reduced pressure. The residue was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:4) to give the desired product in 77% yield. The spectra are identical to those reported for the compound synthesized in solution.[11b]

(S)-Boc-vsVal-(S)-vsAla-NH_2 (**16**, R = Me, R^1 = *i*Pr). According to the above procedure with the (*S*)-Boc-vsVal-(*S*)-vsAla-linker-B-NH-TentaGel resin (**14**, $vsAA_1$ = vsAla, $vsAA_2$ = vsVal) (200 mg, 0.046 mmol), a crude compound was obtained which was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to give the desired product in 86% yield. The spectra are identical to those reported for the compound synthesized in solution.[11b]

N-Alkylation of vs-Peptides in Solution

(S)-Boc-vsAla-NHMe (**18**, R = Me, R^1 = H, R^2 = Me): A solution of (*S*)-Boc-vsAla-NH_2 (**17**, R = Me, R^1 = H) (10 mg, 0.04 mmol) in THF (0.4 ml) at room temp., under nitrogen, was treated with Cs_2CO_3 (39 mg, 0.12 mmol) and MeI (17 mg, 0.12 mmol). The white suspension was stirred for 3 h then the solvent was evaporated at reduced pressure and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to give the desired product in 40% yield. − ^{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$_3$]$_3$C); 2.7 (3 H, d, C*H*$_3$NH, *J* = 7.0 Hz); 4.2 (1 H, broad, N*H*CH$_3$); 4.4 (1 H, m, C*H*CH$_3$); 4.6 (1 H, broad, N*H*CH); 6.2 (1 H, d, CH=C*H*SO$_2$, *J* = 15.2 Hz); 6.7 (1 H, dd, C*H*=CHSO$_2$, *J* = 4.8 Hz, *J* = 15.2 Hz). − $C_{10}H_{20}N_2O_4S$ (264.3): calcd. C 45.44, H 7.63, N 10.60, O 24.21, S 12.13; found C 45.40, H 7.70, N 10.52.

(S)-Boc-vsVal-N(Me)Bn (**18**, R = *i*Pr, R^1 = Bn, R^2 = Me): According to the above procedure, the desired product was obtained in 100% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 8:2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95 (3 H, d, C*H*$_3$CHCH$_3$, *J* = 6.8 Hz); 0.99 (3 H, d, CH$_3$CHC*H*$_3$, *J* = 6.8 Hz); 1.47 (9 H, s, [CH$_3$]$_3$C); 1.88 [1 H, m, (CH$_3$)$_2$C*H*); 2.69 (3 H, s, CH$_3$N); 4.23 (1 H, m, NHC*H*); 4.25 (2 H, s, NC*H*$_2$Ph); 4.58 (1 H, d, NH, *J* = 6.4 Hz); 6.27 (1 H, dd, CH=C*H*SO$_2$, *J* = 1.2 Hz, *J* = 15.1 Hz); 6.68 (1 H, dd, C*H*=CHSO$_2$, *J* = 5.5 Hz, *J* = 15.1 Hz); 7.35 (5 H, m, Ar*H*). − ^{13}C NMR ($CDCl_3$): δ = 18.01 (CH$_3$); 18.77 (CH$_3$); 28.22 ([CH$_3$]$_3$); 31.81 (CH); 34.03 (CH$_3$N); 53.74 (CH$_2$); 56.46 (CH); 125.70 (CH=); 127.87 (CH=); 128.28 (CH=); 128.59 (CH=); 144.96 (CH=). − $C_{19}H_{30}N_2O_4S$ (382.5): calcd. C 59.66, H 7.91, N 7.32, O 16.73, S 8.38; found C 59.59, H 7.98, N 7.27.

(S)-Boc-vsAla-N(Me)-Gly-OMe (**18**, R = Me, R^1 = CH_2CO_2-CH_3, R^2 = Me): According to the above procedure, the desired product was obtained in 80% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, C*H*$_3$CH, *J* = 6.7 Hz); 1.47 (9 H, s, [CH$_3$]$_3$C); 2.89 (3 H, s, NCH$_3$); 3.76 (3 H, s, OCH$_3$); 4.04 (2 H, s, CH$_2$); 4.5 (2 H, broad, NHC*H* + N*H*CH); 6.3 (1 H, dd, CH=C*H*SO$_2$, *J* = 1.4 Hz, *J* = 15.1 Hz); 6.7 (1 H, dd, C*H*=CHSO$_2$, *J* = 4.6 Hz, *J* = 15.1 Hz). − $C_{13}H_{24}N_2O_6S$ (336.4): calcd. C 46.42, H 7.19, N 8.33, O 28.54, S 9.53; found C 46.37, H 7.26, N 8.27.

(S)-Boc-vsAla-N(Me)-Gly-NH_2 (**18**, R = Me, R^1 = CH_2CO-NH_2, R^2 = Me): According to the above procedure, the desired product was obtained in 60% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 9:1). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, C*H*$_3$CH, *J* = 7.7 Hz); 1.47 (9 H, s, [CH$_3$]$_3$C); 2.7 (3 H, s, CH$_3$N); 3.7 (2 H, s, CH$_2$); 4.4 (1 H, m, CH$_3$C*H*); 6.3 (1 H, broad, N*H*CH); 6.5 (1 H, d, CH=C*H*SO$_2$, *J* = 15.0 Hz); 6.7 (1 H, dd, C*H*=CHSO$_2$, *J* = 15.0 Hz, *J* = 4.7 Hz); 7.0 (2 H, broad, CONH$_2$). − $C_{12}H_{23}N_3O_5S$ (321.4): calcd. C 44.85, H 7.21, N 13.07, O 24.89, S 9.98; found C 44.80, H 7.28, N13.00.

(S)-Boc-vsAla-N(Me)-(S)-vsVal-OEt (**20**, R = Me, R^2 = Me, R^3 = *i*Pr): According to the above procedure, the desired product was obtained in 100% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 8:2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96 (3 H, d, C*H*$_3$CHC, *J* = 6.5 Hz); 1.03 (3 H, d, C*H*$_3$CHC, *J* = 6.5 Hz); 1.3 (3 H, d, C*H*$_3$CHN, *J* = 7.0 Hz); 1.42 (3 H, t, C*H*$_3$CH$_2$OSO$_2$, *J* = 7.2 Hz); 1.45 (9 H, s, [CH$_3$]$_3$C); 1.8 (1 H, m, Me$_2$C*H*C); 2.7 (3 H, s, N-CH$_3$); 4.1 (1 H, m, Me$_2$CHC*H*N); 4.2 (2 H, q, CH$_3$C*H*$_2$OSO$_2$, *J* = 7.2 Hz); 4.4 (1 H, m, CH$_3$C*H*N); 4.7 (1 H, m, N*H*); 6.1 (1 H, dd, CH=C*H*SO$_2$N, *J* = 15 .0 Hz, *J* = 1.5 Hz); 6.45 (1 H, d, CH=C*H*SO$_3$Et, *J* = 15.0 Hz); 6.67 (1 H, dd, C*H*=CHSO$_2$N, *J* = 15.0 Hz, *J* = 4.8 Hz); 6.81 (1 H, dd, C*H*=CHSO$_2$N, *J* = 15.0 Hz, *J* = 8.2 Hz). − $C_{18}H_{34}N_2O_7S_2$ (454.6): calcd: C 47.56, H 7.54, N 6.16, O 24.64, S 14.11; found C 47.51, H 7.61, N 6.11.

(S)-Boc-Ala-(S)-vsAla-N(Me)Bn (**22**, R = Me, R^2 = Me): According to the above procedure, the desired product was obtained in 96% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 4:6). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, C*H*$_3$CH, *J* = 7.4 Hz); 1.4 (3 H, d, C*H*$_3$CH, *J* = 6.5 Hz); 2.7 (3 H, s, NCH$_3$); 4.1 (1 H, m, CHCO); 4.2 (2 H, s, NC*H*$_2$Ph); 4.7 (1 H, m, CH$_3$C*H*CH=); 4.9 (1 H, broad, N*H*CHCO); 6.3 (1 H, d, CH=C*H*SO$_2$, *J* = 15.2 Hz); 6.4 (1 H, d, NHCO, *J* = 6.5 Hz); 6.7 (1 H, dd, C*H*=CHSO$_2$, *J* = 15.2 Hz, *J* = 4.3 Hz); 7.3 (5 H, s, Ph-H). − $C_{20}H_{31}N_3O_5S$ (425.6): calcd: C 56.45, H 7.34, N 9.87, O 18.80, S 7.53; found C 56.39, H 7.41, N 9.80.

(S)-Boc-vsVal-N(Et)Bn (**18**, R = *i*Pr, R^1 = Bn, R^2 = Et). A solution of (*S*)-Boc-vsVal-NHBn (**17**, R = *i*Pr, R^1 = Bn) (14.7 mg, 0.04 mmol) in THF (0.4 ml) at room temp., under nitrogen, was treated with Cs_2CO_3 (39 mg, 0.12 mmol) and ethyl iodide (EtI) (19 mg, 0.12 mmol). The white suspension was stirred for 3 h, the solvent was evaporated at reduced pressure and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate, 8:2) to give the desired product in 100% yield. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (3 H, d, CH_3CHCH_3, *J* = 6.6 Hz); 0.91 (3 H, d, CH_3CHCH_3, *J* = 6.6 Hz); 1.1 (3 H, t, CH_3CH_2, *J* = 7.1 Hz); 1.44 (9 H, s, $[CH_3]_3C$); 1.85 [1 H, m, $(CH_3)_2CH$]; 3.25 (2 H, q, CH_3CH_2N, *J* = 7.1 Hz); 4.15 (1 H, m, NHC*H*); 4.3 (2 H, s, NCH_2Ph); 4.55 (1 H, broad, N*H*); 6.25 (1 H, dd, CH=C*H*SO_2, *J* = 1.2 Hz, *J* = 14.9 Hz); 6.65 (1 H, dd, C*H*=CHSO_2, *J* = 5.5 Hz, *J* = 14.9 Hz); 7.4 (5 H, m, Ar*H*). − $C_{20}H_{32}N_2O_4S$ (396.6): calcd. C 60.58, H 8.13, N 7.06, O 16.14, S 8.09; found C 60.51, H 8.21, N 7.01.

(S)-Boc-vsVal-NBn$_2$ (**18**, R = *i*Pr, R^1 = R^2 = Bn): A solution of (*S*)-Boc-vsVal-NHBn (**17**, R = *i*Pr, R^1 = Bn) (14.7 mg, 0.04 mmol) in THF (0.4 ml) at room temp., under nitrogen, was treated with Cs_2CO_3 (39 mg, 0.12 mmol) and benzyl bromide (BnBr) (20.5 mg, 0.12 mmol). The white suspension was stirred for 3 h, the solvent was evaporated at reduced pressure and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate, 85:15) to give the desired product in 100% yield. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90 (3 H, d, CH_3CHCH_3, *J* = 6.5 Hz); 0.92 (3 H, d, CH_3CHCH_3, *J* = 6.5 Hz); 1.47 (9 H, s, $[CH_3]_3C$); 1.83 [1 H, m, $(CH_3)_2CH$]; 4.15 (1 H, m, NHC*H*); 4.27 (4 H, s, 2 × NCH_2Ph); 4.4 (1 H, broad, NH); 6.1 (1 H, dd, CH=C*H*SO_2, *J* = 1.2 Hz, *J* = 15.0 Hz); 6.6 (1 H, dd, C*H*=CHSO_2, *J* = 5.3 Hz, *J* = 15.0 Hz); 7.3 (10 H, m, 2 × Ar*H*). − $C_{25}H_{34}N_2O_4S$ (458.6): calcd: C 65.47, H 7.47, N 6.11, O 13.95, S 6.99; found C 65.38, H 7.54, N 6.05.

(S)-Boc-vsAla-NHAll (**18**, R = Me, R^1 = H, R^2 = All): A solution of (*S*)-Boc-vsAla-NH_2 (**17**, R = Me, R^1 = H) (20 mg, 0.08 mmol) in THF (0.8 ml) at room temp., under nitrogen, was treated with Cs_2CO_3 (78 mg, 0.24 mmol) and allyl bromide (AllBr) (29 mg, 0.24 mmol). The white suspension was stirred for 3 h, the solvent was evaporated at reduced pressure and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to give the desired product in 40% yield. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, CH_3CH, *J* = 6.9 Hz); 1.45 (9 H, s, $[CH_3]_3C$); 3.66 (2 H, m, $NHCH_2CH$, *J* = 6.0 Hz); 4.4 (2 H, broad, CH_3CH + N*H*SO_2); 4.6 (1 H, d, N*H*CH, *J* = 7.9 Hz); 5.2 (2 H, m, CH=CH_2); 5.85 (1 H, m, CH_2CH=CH_2); 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* = 4.9 Hz, *J* = 15.0 Hz). − $C_{12}H_{22}N_2O_4S$ (290.4): calcd. C 49.64, H 7.64, N 9.65, O 22.04, S 11.04; found C 49.58, H 7.71, N 9.60.

(S)-Boc-vsAla-NHCH$_2$Napht (**18**, R = Me, R^1 = H, R^2 = $NaphtCH_2$): A solution of (*S*)-Boc-vsAla-NH_2 (**17**, R = Me, R^1 = H) (10 mg, 0.04 mmol) in THF (0.4 ml) at room temp., under nitrogen, was treated with Cs_2CO_3 (39 mg, 0.12 mmol) and 2-(bromomethyl)naphtalene ($NaphtCH_2$-Br) (26 mg, 0.12 mmol). The white suspension was stirred for 3 h, the solvent was evaporated at reduced pressure and the residue was purified by flash chromatography (*n*-hexane/ethyl acetate, 7:3) to give the desired product in 40% yield. − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.2 (3 H, d, CH_3CH, *J* = 6.4 Hz); 1.45 (9 H, s, $[CH_3]_3C$); 4.4 (4 H, broad, CHN*H* + C*H*NH + CH_2Naph); 4.6 (1 H, broad, SO_2NH); 6.2 (1 H, d, CH=C*H*SO_2, *J* = 14.3 Hz); 6.7 (1 H, dd, C*H*=CHSO_2, *J* = 14.3 Hz, *J* = 4.6 Hz); 7.4−7.9 (7 H, m, Naph-*H*). − $C_{20}H_{26}N_2O_4S$ (390.5): calcd. C 61.52, H 6.71, N 7.17, O 16.39, S 8.21; found C 61.45, H 6.77, N 7.12.

Solid Phase N-Alkylation of vs-Peptides

(S)-Boc-vsAla-NHCH$_3$ (**23**): The resin (*S*)-Boc-vsAla-linker-B-NH-TentaGel (**13**, $vsAA_1$ = vsAla) (109 mg, 0.025 mmol) in DMF (2 ml) was treated with Cs_2CO_3 (24.4 mg, 0.075 mmol) and MeI (17.7 mg, 0.125 mmol). The mixture was shaken for 20 h and washed with DMF (5 × 2 ml), MeOH (3 × 2 ml) and DCM (5 × 2 ml). The resin was then suspended in dry MeOH (2 ml) and irradiated at 354 nm with a 125 Watt mercury lamp (Pyrex reactor) for 40 h, under shaking. The solvent was collected and the resin was washed with MeOH (5 × 2 ml). The combined organic fractions were evaporated at reduced pressure to give a residue which was purified by flash chromatography (*n*-hexane/ethyl acetate, 6:4) to give the desired compound (**23**) in 50% yield. The spectra are identical to those reported for the compound synthesized in solution.[11b]

Synthesis of a Library of 357 Di-N-alkylated vs-Dipeptides **26**

The resin Fmoc-linker-B-NH-TentaGel (**9**, 2.8 g, 0.56 mmol) was split into 7 pools (400 mg, 0.08 mmol). Each pool was treated with 20% piperidine in DMF (2 × 4 ml) and then washed with DMF (3 × 4 ml) and DCM (5 × 4 ml). In the first library step, each pool (**11**), suspended in 4 ml of DCM, was treated with DMAP (4.9 mg, 0.04 mmol), NMM (8.1 mg, 0.08 mmol) and the sulfonyl chloride, Boc-$vsAA_1$-Cl, [0.16 mmol; (*S*)-Boc-vsAla-Cl (**2a**) 43.0 mg, (*S*)-Boc-vsVal-Cl (**2b**) 47.6 mg, (*S*)-Boc-vsLeu-Cl (**2c**) 49.9 mg, (*S*)-Boc-vsPhe-Cl (**2d**) 55.3 mg, (*R*)-Boc-vsPhe-Cl (**2e**) 55.3 mg, (*S*)-Boc-vsPro-Cl (**2f**) 47.3 mg, and (*R*)-Boc-vsPro-Cl (**2g**) 47.3 mg]. The mixtures were shaken for 18 h and the coupling cycle was repeated 3 times. At the end of each coupling cycle the resin was washed with DCM (3 × 4 ml), MeOH (3 × 4 ml) and DCM (5 × 4 ml) and checked with the BPB test.[18][21]

At the end of the third coupling cycle, a solution of acetic anhydride (0.40 ml) in DCM (4.0 ml) was added. The mixtures were shaken for 19 h and then washed with DCM (5 × 4 ml), DMF (3 × 4 ml) and DCM (3 × 4 ml). At the end of the first library step the pools were dried under vacuum and 100 mg of resin were drawn from each pool for the deconvolution. All the 7 pools were mixed together in the same flask with DCM (30 ml), dried under vacuum and split into 3 pools.

In the second library step, each pool (**13**, 700 mg, 0.14 mmol) suspended in 7 ml of DMF, was treated with Cs_2CO_3 (136.8 mg, 0.42 mmol) and the alkylating agent (0.7 mmol; AllBr 84.7 mg, MeI 99.3 mg, BnBr 119.7 mg). The mixtures were shaken for 6 h and the alkylating cycle was repeated 4 times. At the end of each cycle the resin was washed with DMF (5 × 7 ml) and at the end of the last cycle the resin was washed with DMF (5 × 7 ml), MeOH (3 × 7 ml) and DMF (3 × 7 ml). The pools were then dried under vacuum and 200 mg of resin were drawn from each pool for the deconvolution. All the 3 pools (**24**) were mixed together in the same flask then treated with 25% TFA in DCM (3 × 15 ml), washed with DCM (5 × 15 ml), neutralized with 5% DIPEA in DCM (3 × 15 ml) and finally washed again with DCM (5 × 15 ml). The resin was dried under vacuum and split into 7 pools.

In the third library step, each pool (215 mg, 0.04 mmol), suspended in 2 ml of DCM, was treated with NMM (4 mg, 0.04 mmol), DMAP (2.4 mg, 0.02 mmol) and the sulfonyl chloride, Boc-$vsAA_2$-Cl, [0.08 mmol; (*S*)-Boc-vsAla-Cl (**2a**) 22 mg, (*S*)-Boc-vsVal-Cl (**2b**) 24 mg, (*S*)-Boc-vsLeu-Cl (**2c**) 25 mg, (*S*)-Boc-vsPheCl (**2d**) 28 mg, (*R*)-Boc-vsPheCl (**2e**) 28 mg, (*S*)-Boc-vsProCl (**2f**) 24 mg, and (*R*)-Boc-vsProCl (**2g**) 24 mg]. The mixtures were shaken for 16 h and the coupling cycle was repeated 3 times. At the end

of each cycle the resin was washed with DCM (3 × 2 ml), MeOH (3 × 2 ml) and DCM (5 × 2 ml) and checked with the BPB test.[18][21]

After the third coupling cycle, a solution of acetic anhydride (0.30 ml) in DCM (2.0 ml) was added. The mixtures were shaken for 19 h and then washed with DCM (5 × 2 ml), DMF (3 × 2 ml) and DCM (3 × 2 ml). At the end of the third library step the pools were dried under vacuum and 100 mg of resin were drawn from each pool for the deconvolution.

The 7 pools (**25**) were mixed to form three new pools: the pool A-V (42 *N*-monoalkylated vs-dipeptides), obtained mixing pools A [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*S*)-vsAla] and V [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*S*)-vsVal]; the pool L-F-P (63 *N*-monoalkylated vs-dipeptides), obtained mixing pools L [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*S*)-vsLeu], F [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*S*)-vsPhe] and P [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*S*)-vsPro]; the pool f-p (42 *N*-monoalkylated vs-dipeptides), obtained mixing pools f [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*R*)-vsPhe] and p [21 *N*-monoalkylated vs-dipeptides where the last vs-amino acid added is (*R*)-vsPro]. Each of these three pools was split into three subpools for the fourth library step.

Each subpool A-V and f-p (80 mg, 0.016 mmol), suspended in 1 ml of DMF, was treated with Cs_2CO_3 (15.6 mg, 0.048 mmol) and the alkylating agent (0.08 mmol; AllBr 9.7 mg, MeI 11.3 mg, BnBr 13.7 mg). Each subpool L-F-P (115 mg, 0.023 mmol), suspended in 1 ml of DMF, was treated with Cs_2CO_3 (22.8 mg, 0.07 mmol) and the alkylating agent (0.115 mmol; AllBr 13.9 mg, MeI 16.3 mg, BnBr 19.7 mg). The mixtures were shaken for 6 h and the alkylating cycle was repeated 4 times. At the end of each cycle the resin was washed with DMF (5 × 1 ml) and at the end of the last cycle the resin was washed with DMF (5 × 1 ml), MeOH (3 × 1 ml) and DMF (3 × 1 ml). At the end of the fourth library step the subpools (**26**) were dried under vacuum and the library was used for the biological assays.

Synthesis of a Library of 729 Functionalized vs-Tripeptides **29**

The resin Fmoc-linker-B-NH-TentaGel (**9**, 2.45 g, 0.49 mmol) was split into 9 pools (270 mg, 0.054 mmol). Each pool was treated with 20% piperidine in DMF (2 × 3 ml) and then washed with DMF (3 × 3 ml) and DCM (5 × 3 ml). In the first library step, each pool (**11**) suspended in 3 ml of DCM, was treated with DMAP (3.3 mg, 0.027 mmol), NMM (5.46 mg, 0.054 mmol) and the sulfonyl chloride, Boc-vsAA_1-Cl, [0.108 mmol; (*S*)-Boc-vsAla-Cl (**2a**) 29.1 mg, (*S*)-Boc-vsVal-Cl (**2b**) 32.2 mg, (*S*)-Boc-vsLeu-Cl (**2c**) 33.7 mg, (*S*)-Boc-vsPhe-Cl (**2d**) 37.3 mg, (*R*)-Boc-vsPhe-Cl (**2e**) 37.3 mg, (*S*)-Boc-vsPro-Cl (**2f**) 32.0 mg, (*R*)-Boc-vsPro-Cl (**2g**) 32.0 mg, (*S*)-Boc-vsSer(TBDPS)-Cl (**2h**) 56.6 mg, (*S*)-Boc-vsTyr(TBDPS)-Cl (**2i**) 64.8 mg]. The mixtures were shaken for 18 h and the coupling cycle was repeated twice. At the end of each cycle the resin was washed with DCM (3 × 3 ml), MeOH (3 × 3 ml) and DCM (5 × 3 ml) and checked with the BPB test.[18][21]

After the coupling cycles, a solution of acetic anhydride (0.27 ml) in DCM (3.0 ml) was added. The mixtures were shaken for 4.5 h and then washed with DCM (5 × 3 ml), DMF (3 × 3 ml) and DCM (3 × 3 ml). At the end of the first library step the pools were dried under vacuum and 100 mg of resin were drawn from each pool for the deconvolution. The 9 pools (**27**) were mixed together in the same flask then treated with saturated HCl in ethyl acetate (3 × 15 ml, 3 × 1 h), washed with DCM (3 × 15 ml), neutralized with DIPEA 5% in DCM (3 × 15 ml), and finally washed again with DCM (3 × 15 ml). The resin was dried under vacuum and split into 9 pools.

In the second library step, each pool (170 mg, 0.034 mmol) suspended in 2 ml of DCM, was treated with DMAP (2.1 mg, 0.017 mmol), NMM (3.44 mg, 0.034 mmol) and the sulfonyl chloride, Boc-vsAA_2-Cl, [0.068 mmol; (*S*)-Boc-vsAla-Cl (**2a**) 18.3 mg, (*S*)-Boc-vsVal-Cl (**2b**) 20.2 mg, (*S*)-Boc-vsLeu-Cl (**2c**) 21.2 mg, (*S*)-Boc-vsPhe-Cl (**2d**) 23.5 mg, (*R*)-Boc-vsPhe-Cl (**2e**) 23.5 mg, (*S*)-Boc-vsPro-Cl (**2f**) 20.1 mg, (*R*)-Boc-vsPro-Cl (**2g**) 20.1 mg, (*S*)-Boc-vsSer(TBDPS)-Cl (**2h**) 35.6 mg, (*S*)-Boc-vsTyr(TBDPS)-Cl (**2i**) 40.8 mg]. The mixtures were shaken for 20 h and the coupling cycle was repeated twice. At the end of each cycle the resin was washed with DCM (3 × 2 ml), MeOH (3 × 2 ml) and DCM (5 × 2 ml) and checked with the BPB test.[18][21]

After the coupling cycles, a solution of acetic anhydride (0.17 ml) in DCM (2.0 ml) was added. The mixtures were shaken for 4.5 h and then washed with DCM (5 × 2 ml), DMF (3 × 2 ml) and DCM (3 × 2 ml). At the end of the second library step the pools were dried under vacuum and 100 mg of resin were drawn from each pool for the deconvolution. The 9 pools (**28**) were mixed together in the same flask then treated with saturated HCl in ethyl acetate (3 × 6.5 ml, 3 × 1 h), washed with DCM (3 × 6.5 ml), neutralized with DIPEA 5% in DCM (3 × 6.5 ml), and finally washed again with DCM (3 × 6.5 ml). The resin was dried under vacuum and split into 9 pools.

In the third library step, each pool (70 mg, 0.014 mmol), suspended in 1 ml of DCM, was treated with DMAP (1 mg, 0.007 mmol), NMM (1.4 mg, 0.014 mmol) and the sulfonyl chloride, Boc-vsAA_3-Cl, [0.028 mmol; (*S*)-Boc-vsAla-Cl (**2a**) 7.5 mg, (*S*)-Boc-vsVal-Cl (**2b**) 8.3 mg, (*S*)-Boc-vsLeu-Cl (**2c**) 8.7 mg, (*S*)-Boc-vsPhe-Cl (**2d**) 9.7 mg, (*R*)-Boc-vsPhe-Cl (**2e**) 9.7 mg, (*S*)-Boc-vsPro-Cl (**2f**) 8.2 mg, (*R*)-Boc-vsPro-Cl (**2g**) 8.2 mg, (*S*)-Boc-vsSer(TBDPS)-Cl (**2h**) 14.7 mg, (*S*)-Boc-vsTyr(TBDPS)-Cl (**2i**) 16.8 mg]. The mixtures were shaken for 20 h and the coupling cycle was repeated twice. At the end of each cycle the resin was washed with DCM (3 × 1 ml), MeOH (3 × 1 ml) and DCM (5 × 1 ml) and checked with the BPB test.[18][21]

After the coupling cycles, a solution of acetic anhydride (0.07 ml) in DCM (1.0 ml) was added. The mixtures were shaken for 4.5 h and then washed with DCM (5 × 1 ml), DMF (3 × 1 ml) and DCM (3 × 1 ml).

At the end of the third library step the TBDPS protecting groups were removed by treatment with TBAF (1 M in THF, 0.14 ml, 0.14 mmol) in THF (3 × 0.86 ml, 3 × 1 h). At the end of each cycle the resin was washed with THF (3 × 1 ml) and at the end of the last cycle the resin was washed with THF (1 ml), AcOH 1% in THF (1 ml), THF (3 × 1 ml), MeOH (3 × 1 ml) and DCM (5 × 1 ml). The pools (**29**) were finally dried under vacuum and the library was used for the biological assays.

Synthesis of a Library of 625 vs-Tetrapeptides **33**

The resin Boc-linker-A-NH-TentaGel (**8**, 1 g, 0.2 mmol) was split into 5 pools (200 mg, 0.04 mmol). Each pool was treated with 25% TFA in DCM (3 × 10 ml), washed with DCM (5 × 10 ml), neutralized with 10% TEA in DCM (3 × 10 ml) and then washed with DCM (6 × 10 ml).

In the first library step, each pool (**10**), suspended in 5 ml of DCM, was treated with DMAP (4.9 mg, 0.04 mmol), DBU (6.1 mg, 0.04 mmol) and the sulfonyl chloride, (*S*)-Boc-vsAA_1-Cl, [0.08 mmol; (*S*)-Boc-vsAla-Cl (**2a**) 21.6 mg, (*S*)-Boc-vsVal-Cl (**2b**) 23.8 mg, (*S*)-Boc-vsLeu-Cl (**2c**) 24.9 mg, (*S*)-Boc-vsPhe-Cl (**2d**) 27.7 mg,

(*S*)-Boc-vsPro-Cl (**2f**) 23.6 mg]. The mixtures were shaken for 4 h and the coupling cycle was repeated 4 times. At the end of each cycle the resin was washed with DCM (3 × 5 ml), MeOH (3 × 5 ml) and DCM (5 × 5 ml) and checked with the BPB test.[18][21]

At the end of the first library step the pools were dried under vacuum and 50 mg of resin was drawn from each pool for the deconvolution. The 5 pools (**30**) were mixed together in the same flask then treated with 25% TFA in DCM (3 × 10 ml), washed with DCM (5 × 10 ml), neutralized with 10% TEA in DCM (3 × 10 ml) and finally washed again with DCM (5 × 10 ml). The resin was dried under vacuum and split into 5 pools.

In the second library step, each pool (150 mg, 0.03 mmol), suspended in 5 ml of DCM, was treated with DMAP (4 mg, 0.03 mmol), DBU (4.6 mg, 0.03 mmol) and the sulfonyl chloride, (*S*)-Boc-vsAA$_2$-Cl, [0.06 mmol; (*S*)-Boc-vsAla-Cl (**2a**) 16 mg, (*S*)-Boc-vsVal-Cl (**2b**) 17.9 mg, (*S*)-Boc-vsLeu-Cl (**2c**) 18.7 mg, (*S*)-Boc-vsPhe-Cl (**2d**) 20.7 mg, (*S*)-Boc-vsPro-Cl (**2f**) 17.7 mg]. The mixtures were shaken for 4 h and the coupling cycle was repeated 5 times for (*S*)-Boc-vsAla-Cl (**2a**), (*S*)-Boc-vsLeu-Cl (**2c**) and (*S*)-Boc-vsPro-Cl (**2f**) and 7 times for (*S*)-Boc-vsVal-Cl (**2b**) and (*S*)-Boc-vsPhe-Cl (**2d**). At the end of each cycle the resin was washed with DCM (3 × 5 ml), MeOH (3 × 5 ml) and DCM (5 × 5 ml) and checked with the BPB test.[18][21]

At the end of the second library step the pools were dried under vacuum and 50 mg of resin were drawn from each pool for the deconvolution. The 5 pools (**31**) were mixed together in the same flask then treated with 25% TFA in DCM (3 × 10 ml), washed with DCM (5 × 10 ml), neutralized with 10% TEA in DCM (3 × 10 ml) and finally washed again with DCM (5 × 10 ml). The resin was dried under vacuum and split into 5 pools.

In the third library step, each pool (100 mg, 0.02 mmol), suspended in 5 ml of DCM, was treated with DMAP (2.4 mg, 0.02 mmol), DBU (3 mg, 0.02 mmol) and the sulfonyl chloride, (*S*)-Boc-vsAA$_3$-Cl, [0.04 mmol; (*S*)-Boc-vsAla-Cl (**2a**) 10.8 mg, (*S*)-Boc-vsVal-Cl (**2b**) 11.9 mg, (*S*)-Boc-vsLeu-Cl (**2c**) 12.5 mg, (*S*)-Boc-vsPhe-Cl (**2d**) 13.8 mg, (*S*)-Boc-vsPro-Cl (**2f**) 11.8 mg]. The mixtures were shaken for 4 h and the coupling cycle was repeated 7 times for (*S*)-Boc-vsAla-Cl (**2a**) and (*S*)-Boc-vsLeu-Cl (**2c**) and 14 times for (*S*)-Boc-vsVal-Cl (**2b**), (*S*)-Boc-vsPhe-Cl (**2d**) and (*S*)-Boc-vsPro-Cl (**2f**). At the end of each cycle the resin was washed with DCM (3 × 5 ml), MeOH (3 × 5 ml) and DCM (5 × 5 ml) and checked with the BPB test.[18][21]

At the end of the third library step the pools were dried under vacuum and 50 mg of resin were drawn from each pool for the deconvolution. The 5 pools (**32**) were mixed together in the same flask then treated with 25% TFA in DCM (3 × 10 ml), washed with DCM (5 × 10 ml), neutralized with 10% TEA in DCM (3 × 10 ml) and finally washed again with DCM (5 × 10 ml). The resin was dried under vacuum and split into 5 pools.

In the fourth library step, each pool (23 mg, 0.006 mmol), suspended in 2.5 ml of DCM, was treated with DMAP (0.7 mg, 0.006 mmol), DBU (0.91 mg, 0.006 mmol) and the sulfonyl chloride, (*S*)-Boc-vsAA$_4$-Cl, [0.012 mmol; (*S*)-Boc-vsAla-Cl (**2a**) 3.2 mg, (*S*)-Boc-vsVal-Cl (**2b**) 3.6 mg, (*S*)-Boc-vsLeu-Cl (**2c**) 3.7 mg, (*S*)-Boc-vsPhe-Cl (**2d**) 4.1 mg, (*S*)-Boc-vsPro-Cl (**2f**) 3.5 mg]. The mixtures were shaken for 4 h and the coupling cycle was repeated 11 times for (*S*)-Boc-vsAla-Cl (**2a**) and (*S*)-Boc-vsLeu-Cl (**2c**), 22 times for (*S*)-Boc-vsPhe-Cl (**2d**) and (*S*)-Boc-vsPro-Cl (**2f**) and 32 times for (*S*)-Boc-vsVal-Cl (**2b**). At the end of each cycle the resin was washed with DCM (3 × 2.5 ml), MeOH (3 × 2.5 ml) and DCM (5 × 2.5 ml) and checked with the BPB test.[18][21] At the end of the fourth library step the pools (**33**) were dried under vacuum and the library was used for the biological assays.

Michael Addition Reactions

Pyrrolidinone (**35**; R = Me; R^1, R^1 = $-(CH_2)_5-$; R^2 = CO_2Me): Dimethyl malonate (16.6 mg, 0.126 mmol) was added dropwise to a suspension of NaH (60% oil dispersion, 5 mg, 0.126 mmol) in dry THF (0.32 ml) under nitrogen, at room temperature. After some minutes a solution of (*S*)-Boc-vsAla-N[$-(CH_2)_5-$] [**34**; R = Me; R^1, R^1 = $-(CH_2)_5-$] (20 mg, 0.063 mmol) in dry THF (0.21 ml) was added by cannula. The mixture was stirred at 60°C for 16 h, cooled to room temperature and pH = 7 phosphate buffer (1 ml) was added. The aqueous phase was extracted with DCM and the combined organic extracts were dried and concentrated. The crude product was purified by flash chromatography (*n*-hexane/ethyl acetate, 65:35) to give a mixture of two diastereoisomers (34% overall yield) in the ratio of 85:15. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (3 H, d, C*H*$_3$CH, *J* = 6.5 Hz); 1.5 (9 H, s, [CH$_3$]$_3$C); 1.7 [6 H, m, NCH$_2$(C*H*$_2$)$_3$); 3.05 (3 H, m, CH + CH$_2$SO$_2$); 3.3 (5 H, m, CH$_2$NCH$_2$ + CH); 3.8 (3 H, s, OCH$_3$); 4.1 (1 H, m, CH$_3$C*H*, 15%); 4.6 (1 H, m, CH$_3$C*H*, 85%). – ^{13}C NMR ($CDCl_3$): δ = 14.48 (CH$_3$); 23.57 (N(CH$_2$)$_2$*C*H$_2$); 25.52 (2 × NCH$_2$*C*H$_2$); 27.87 ([CH$_3$]$_3$C); 34.81 (*C*HCH$_2$SO$_2$); 46.56 (*C*H$_2$NCH$_2$); 52.69 (CH$_3$*C*H); 54.04 (*C*HCOO); 83.76 ([CH$_3$]$_3$C); 145.30 (OC(=O)N); 166.09 (*C*OOCH$_3$); 167.70 (NC=O). – $C_{18}H_{30}N_2O_7S$ (418.5): calcd. C 51.66, H 7.23, N 6.69, O 26.76, S 7.66; found C 51.60, H 7.30, N 6.65.

Figure 3. Major diastereomer obtained from the addition of sodium dimethyl malonate to (*S*)-Boc-vsAla-N[$-(CH_2)_5-$] [**34**; R = Me; R^1, R^1 = $-(CH_2)_5-$]

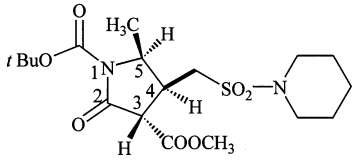

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Table 1. NOE effects observed in structure **36** (s = small effect, m = medium effect, h = high effect, n = no effect)

	5-H	4-H	3-H	5-CH$_3$	4-CH$_2$
5-H	–	s	n	h	n
4-H	s	–	n	n	s
3-H	n	n	–	s	m
5-CH$_3$	h	n	s	–	h
4-CH$_2$	n	s	m	h	–

Pyrrolidinone (**35**; R = *i*Pr; R^1 = Me; R^2 = CO_2Me): According to the above procedure, the product was obtained as a single diastereomer in 56% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (3 H, d, C*H*$_3$CH, *J* = 7.4 Hz); 1.10 (3 H, d, C*H*$_3$CH, *J* = 7.4 Hz); 1.50 (9 H, s, [CH$_3$]$_3$C); 2.20 [1 H, m, (CH$_3$)$_2$C*H*]; 2.9 [6 H, s, (CH$_3$)$_2$N]; 3.05 (1 H, dd, CH*H*SO$_2$, *J* = 5.0 Hz, *J* = 14.0 Hz); 3.15 (1 H, dd ,C*H*HSO$_2$, *J* = 8.0 Hz, *J* = 14.0 Hz); 3.40 (1 H, m, C*H*CH$_2$); 3.50 (1 H, d, CHCO, *J* = 12.0 Hz); 3.8 (3 H, s, CH$_3$O); 4.5 (1 H, m, NC*H*). – ^{13}C NMR ($CDCl_3$): δ = 17.39 (C*H*$_3$CH); 22.09 (C*H*$_3$CH); 27.94 ([CH$_3$]$_3$C); 29.56 (CH); 37.42 ([(CH$_3$)$_2$]N); 47.10 (CH$_2$); 53.26 (OCH$_3$); 54.13 (CH); 61.29 (CH). – $C_{17}H_{30}N_2O_7S$ (406.5): calcd. C 50.23, H 7.44, N 6.89, O 27.55, S 7.89; found C 50.17, H 7.51, N 6.85.

Pyrrolidinone (**35**; R = Me; R^1 = Me; R^2 = CO_2Me): According to the above procedure, the product was obtained in 40% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.3 (3 H, d, C*H*$_3$CH, *J* = 6.4 Hz); 1.5 (9 H, s, [CH$_3$]$_3$C); 2.9 [6 H, s, (CH$_3$)$_2$N]; 3.1 (2 H, d, CH$_2$SO$_2$, *J* = 6.5 Hz); 3.2–3.3 (1 H, m, C*H*CH$_2$SO$_2$); 3.4 (1 H, d, CHCO, *J* = 12.5 Hz); 3.8 (3 H, s, CH$_3$O); 4.5 (1 H, m, CH$_3$C*H*). – $C_{15}H_{26}N_2O_7S$ (378.4): calcd: C 47.61, H 6.92, N 7.40, O 29.59, S 8.47; found C 47.56, H 6.99, N 7.35.

Pyrrolidinone (**35**; R = *i*Bu; R^1 = Me; R^2 = CO_2Me): According to the above procedure, the product was obtained in 20% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (3 H, d, C*H*$_3$CH, *J* = 7.3 Hz); 0.98 (3 H, d, C*H*$_3$CH, *J* = 7.3 Hz); 1.55 (9 H, s, [CH$_3$]$_3$C); 1.6–1.8 [3 H, m, (CH$_3$)$_2$C*H* + NCHC*H*$_2$]; 2.9 (6 H, s, [(CH$_3$)$_2$]N); 3.0–3.2 (3 H, m, C*H*CH$_2$SO$_2$ + CHC*H*$_2$SO$_2$); 3.6 (1 H, broad, CHCO); 3.8 (3 H, s, OCH$_3$); 4.1 (1 H, m, NCH, *J* = 6.6 Hz). – $C_{18}H_{32}N_2O_7S$ (420.5): calcd. C 51.41, H 7.67, N 6.66, O 26.63, S 7.62; found C 51.35, H 7.74, N 6.61.

Pyrrolidinone (**35**; R = *i*Pr; R^1 = Me; R^2 = CN): According to the above procedure, the product was obtained in 15% yield after purification by flash chromatography (*n*-hexane/ethyl acetate, 6:4). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90 (3 H, d, C*H*$_3$CH, *J* = 6.4 Hz); 1.10 (3 H, d, C*H*$_3$CH, *J* = 6.4 Hz); 1.50 (9 H, s, [CH$_3$]$_3$C); 2.20 [1 H, m, (CH$_3$)$_2$C*H*]; 2.9 [6 H, s, (CH$_3$)$_2$N]; 3.2–3.3 (3 H, m, C*H*CH$_2$ + CHC*H*$_2$); 3.6 (1 H, d, CHCN, *J* = 12.5 Hz); 4.6 (1 H, m, NCH). – ^{13}C NMR ($CDCl_3$): δ = 17.40 (C*H*$_3$CH); 22.00 (C*H*$_3$CH); 28.00 ([CH$_3$]$_3$C); 29.00 (CH); 37.40 [(CH$_3$)$_2$N]; 46.00 (CH$_2$); 61.40 (CH); 85.00 ([CH$_3$]$_3$C); 114.80 (CN). – $C_{16}H_{27}N_3O_5S$ (373.5): calcd: C 51.46, H 7.29, N 11.25, O 21.42, S 8.59; found C 51.40, H 7.36, N 11.16.

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[22] According to this approach, pools of compounds are prepared so that each separate pool has defined building blocks at either one or two positions, and all combinations of building blocks are incorporated at the remaining positions. The optimal building blocks at the defined position is selected by determining which pool has the highest biological activity. A second round of synthesis is then performed with the selected building block in place at the initially defined position, in order to prepare pools where the next defined position is introduced. This deconvolution process is then repeated until all the positions are defined. See: C. T. Dooley, N. N. Chung, B. C. Wilkes, P. W. Schiller, J. M. Bidlack, G. W. Pasternak, R. A. Houghten, *Science* **1994**, *266*, 2019−2022.

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