α-Keto Amide Peptides: A Synthetic Strategy to Resin-Bound Peptide Isosteres for Protease Inhibitor Screening on Solid Support

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A synthetic strategy for the formation of resin-bound internal α-keto amide peptides suitable for protease inhibitor screening on solid support is presented. This general approach is based on the incorporation of α-keto amide building blocks during solid-phase peptide synthesis (SPPS). Such dipeptidyl building blocks were accessible using the acylcyanophosphorane methodology. The acid-labile α-keto carbonyl functionality was protected as a 1,3-dithiolane derivative. This protective group is fully compatible with standard SPPS reaction conditions and can be efficiently removed with *N*-bromosuccinimide in 10% aqueous acetone. The α-keto amide peptides were assembled on SPOCC-1500 resin and were characterized with high-resolution magic angle spinning (HR-MAS) NMR on bead. The methodology was evaluated and tested with a variety of building blocks containing natural and nonnatural amino acid moieties.

Introduction

The functionalization of peptides and proteins by aldehyde or keto groups has become the impetus of intensive research since the discovery of the inhibition properties of activated carbonyl compounds.[1] As inhibitors of serine and cysteine proteases, such peptide isosteres offer low or moderate chemical reactivity and high biochemical specificity, making them promising candidates as therapeutically useful inhibitors of pathological proteolytic events.[2] Several examples are described in the literature, including peptidyl aldehydes,[3] fluorinated ketones,[4] α-keto acids and α-keto esters.[5] Among these isosteric structures, the most potent reversible protease inhibitors are peptidyl aldehydes. The postulated mechanism for inhibition is based on the formation of a covalent, yet fully reversible, transition state intermediate stabilized by the electron-withdrawing effect of the second carbonyl group.[5b,6] Although efficient inhibitors, peptidyl aldehydes have certain limitations. Aldehydes can only be placed on the C-terminal or the N-terminal site of the peptide backbone, thus preventing exploration of the whole binding pocket.

More recently, α-keto amides have displayed significant enhanced potency relative to their parent isosteres. Some examples of the cellular targets which are inhibited by α-keto amides include calpain, a calcium activated cysteine protease[7] that has been implicated in stroke, Alzheimer's disease and muscular distrophy; thrombin, a serine protease that converts fibrinogen to fibrin;[8] and caspase, a cysteine protease that plays a role in apoptosis.[9] α-Keto amide isosteres have also been successfully used as a promising new core for the synthesis of HIV-1 protease inhibitors.[10] In nature, α-keto amide moieties are found in natural products, such as cyclotheonamides,[11] orbiculamide A,[12] and keramamides.[13] α-Keto amides exhibit high activity similar to that of aldehydes; however, by virtue of their chemical constitution they allow spanning of both sides of the active site, and hence, they can potentially fully utilize the active site binding interactions. Moreover, cysteine protease inhibition has often been associated with S′-site recognition, while the presence of binding elements on both sides of the active site appears to be a critical aspect of selectivity.

In previous work, resin-bound N-terminal α-keto amides have been prepared via a copper-ion-catalyzed transamination reaction from peptide precursors on solid support.[14] Internal peptide α-keto amides, however, are not accessible by applying this methodology. In case of transamination from α/β-diamino acids, redox side reaction previously reported for the N-terminal histidine α-keto amide peptides was observed.[14] Therefore, a different strategy for the solid-phase preparation of internal resin-bound α-keto amide peptides had to be developed. Successful approaches in solid-phase organic chemistry comprise more than the simple synthetic routes on solid support. The utilization of building blocks that are synthesized in solution and subsequently incorporated on solid phase allow the introduction of nonpeptidic diversity, for example, in the backbone or side chains of peptides.[15] Most frequently, the functionality introduced by the building block is compatible with peptide coupling conditions; on the other hand, orthogonal protection may be necessary to avoid side reactions when the new functionality is chemically reactive.

Despite the considerable amount of literature on solution-phase synthesis of α-keto amides available,[10a,16] ready access to internal α-keto amides remains problematic. Among the previous synthetic methods available, Wasserman's method utilizing phosphorus ylide chemistry[17] appeared the most attractive, since not only could it introduce the α-keto amide moiety into peptide backbones in a convergent manner under

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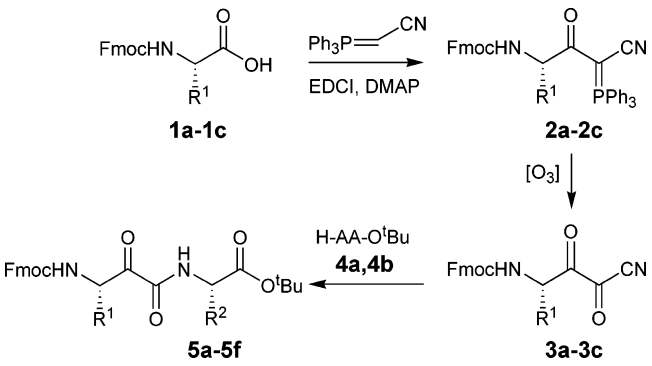
Scheme 1. Synthesis of α-Keto Amide Dipeptidyl Building Blocks.[a]



[a] **1a**−**1c** are converted to the acylcyanophosphoranes **2a**−**2c** by reaction with (cyanomethylene)triphenylphosphorane. Ozonolysis generates the diketo nitriles **3a**−**3c**, which are reacted in situ with C-terminal protected amino acids **4a** and **4b** to form the α-keto amide dipeptides **5a**−**5f**.

mild conditions, but also the reaction was reported to be stereospecific.

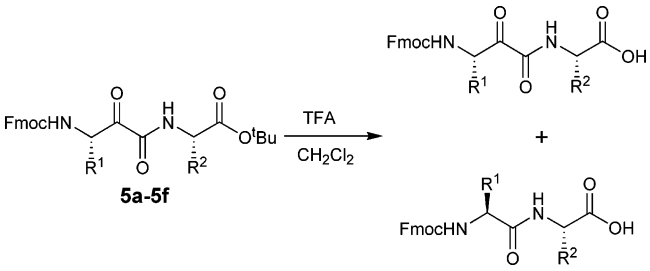
The present work describes the application of this methodology in order to establish a solid-phase synthesis protocol of broader scope and utility. A series of model peptides containing different dipeptidyl α-keto amide building blocks have been prepared on SPOCC-1500 resin.[18] The compatibility and suitability of this strategy to generate resin-bound α-keto amide peptide libraries for protease inhibitor screening on solid support has been investigated using high-resolution MAS NMR techniques.

Results and Discussion

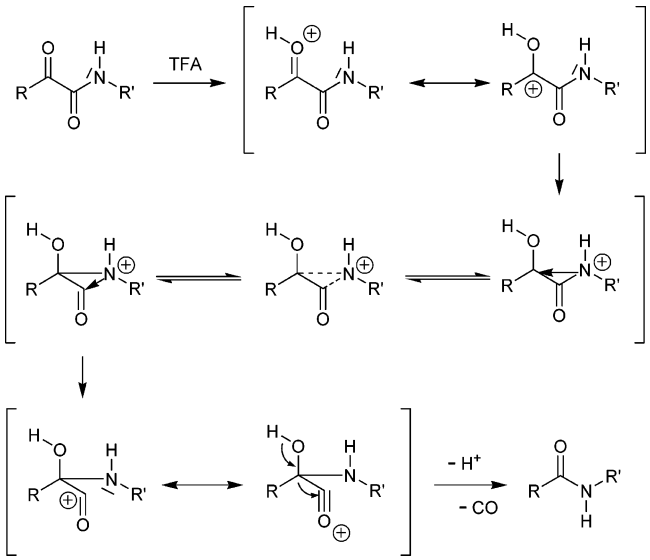
Dipeptidyl α-Keto Amide Building Blocks. The α-keto amide functionality inserted between two amino acid units was accessible by the cyanophosphorane methodology first introduced by Wassermann et al.[17] (Scheme 1). Fmoc-protected amino acids **1a**−**1c** were converted to acylcyanophosphoranes **2a**−**2c** with (cyanomethylene)triphenylphosphorane in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDCI). Ozonolysis generated the corresponding highly electrophilic diketo nitriles **3a**−**3c**, which were reacted in situ with C-terminal-protected amino acids **4a** and **4b** to form α-keto amide dipeptides **5a**−**5f** following treatment with $AgNO_3$ to decompose the intermediate cyanohydrin moiety. The ozonolysis and dipeptide formation was carried out in anhydrous CH_2Cl_2 at −78 °C in order to avoid decomposition of the unstable diketo nitriles **3a**−**3c**. Ag^+ traps CN^- by complexation and causes the reaction to proceed to completion. Three Fmoc-protected amino acids (Ala, Leu, and Phe) were selected and used to generate the cyanoketophosphoranes **2a**−**2c** (79−83% yields), which following oxidation were trapped with leucine and homophenylalanine *tert*-butyl esters, to give the α-keto amide dipeptides **5a**−**5f** in 67−85% yields. In accordance with the literature,[17] this sequence consistently gave stereochemical preservation, as demonstrated by NMR spectroscopy. Homophenylalanine-*tert*-butyl ester **4a** was prepared by transesterification of acetyl-*tert*-butyl ester and homophenylalanine in the presence of TFA and trifluorosulfonic acid.[19]

When removal of the *tert*-butyl ester from the C terminus of the building block **5a**−**5f** was attempted with TFA, partial loss of the α-keto functionality was observed (Scheme 2). HPLC analysis showed a 3:1 ratio of α-keto amide vs decarbonylated product after treatment with TFA for 15 min. The side product appeared at a shorter retention time of ∼1 min, and the structure was confirmed by NMR and ESI-MS. Repeated experiments consistently revealed that the loss of CO is independent of the acid strength as well as the length of the C-terminal peptide chain, thus excluding the possibility of an autocatalytic effect taking place where the C-terminal carboxylic group is involved. Furthermore, the acid-catalyzed decarbonylation side reaction was observed even on resin-bound α-keto amide peptides under moderate conditions. In contrast, the decarbonylation reaction of α-keto esters and α-keto acids via an S_N1 mechanism[20] requires rather harsh reaction conditions; hence, we propose a different mechanism for the CO extrusion reaction of α-keto amides (Scheme 3). It may be assumed that the CO extrusion reaction involves protonation of the oxygen of the α-keto functionality, yielding a carbocation which facilitates rearrangement of the amide nitrogen via a 1,2-nucleophilic shift. Deprotonation and simultaneous loss of CO result in a conventional peptide bond. The amount of the decarbonylated product increases with higher concentrations of acid and prolonged exposure. We assume this side reaction is the reason for the low yields obtained by others when treating α-keto amides with strong acids. For example, M. Tsuda et al. reported a yield of 59% for the deprotection of a *tert*-butyl ester of an α-keto amide tripeptide using TFA for 2 h;[16c] however, the identities of

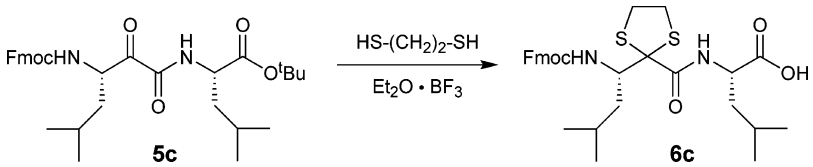
Scheme 2. Treatment of **5a**−**5f** with Acid Results in Cleavage of the C-Terminal *tert*-Butyl Ester and Is Partially Accompanied by CO Extrusion



Scheme 3. Proposed Mechanism for the CO Extrusion Reaction of α-Keto Amides upon Treatment with Acids



Scheme 4. Protection of the α-Keto Functionality with Simultaneous Cleavage of the *tert*-Butyl Ester.[a]



[a] The α-keto amide dipeptide **5c** is converted to the 1,3-dithiolane derivative **6c** by treatment with 1,2-ethanedithiol in the presence of Lewis acid.

the side products were not further investigated. Rademann et al. recently observed loss of CO during the synthesis of α-hydroxyamino acid derivatives that prevented the isolation of an α-keto amide intermediate.[21]

Furthermore, other side reactions had to be considered. In the presence of base under conditions of SPPS, the α-keto carbonyl could undergo Schiff base formation in an inter- or intramolecular fashion. Even though anchoring of the α-keto moiety on the solid support could prevent intermolecular type side reactions, the intramolecular Schiff base formation could still take place, for example, with the free N terminus at the S2 position, a favorable six-membered ring could be formed, thus obstructing further elongation of the peptide.

1,3-Dithiolane Building Block Derivatives. Considering the potential for reactivity of the highly electrophilic α-ketocarbonyl moiety under conditions of SPPS and in view of the acid-catalyzed CO extrusion reaction, masking of the keto functionality was deemed necessary. Because of the acid lability of the present substrates, the protection of the α-ketocarbonyl as a dithioketal seemed to be the most appropriate approach, further substantiated by the fact that the reaction proceeds under mild and essentially neutral conditions. This method has previously been employed for the protection of α-keto esters.[5b] When the α-keto amide dipeptide (**5c**) was treated with 1,2-ethane dithiol in the presence of $BF_3 \cdot Et_2O$ as Lewis acid catalyst, quantitative conversion to the 1,3-dithiolane derivative (**6c**) was observed. The transformation was monitored by HPLC at the wavelengths of 215 and 280 nm, because α-keto amide dipeptides show strong absorption at 280 nm, in contrast to the 1,3-dithiolane product. The 1,3-dithiolane derivative (**6c**) appeared at a slightly shorter retention time of 0.2 min, as compared to the starting material, and formation of the dithioketal was confirmed by ESI-MS and NMR. This reaction not only introduce the protective group for the α-keto functionality, but it also allowed simultaneous deprotection of the *tert*-butyl ester (Scheme 4). The mechanism of the ester cleavage is similar to the one described by Wu et al.[22] using $ZnBr_2$ as Lewis acid for mild deprotection of *tert*-butyl esters. Consequently, α-keto amide dipeptides **5a**−**5f** were transformed into their corresponding 1,3-dithiolane derivatives **6a**−**6f** in excellent yields (96−99%). The ^1H and ^{13}C NMR spectra of the dithioketalized derivatives revealed two sets of signals. A closer investigation indicated two conformers in slow exchange, confirmed by the presence of exchange peaks in a ROESY spectrum (Figure 1). Moreover, the preservation of the stereocenters was established by the absence of additional resonances in the NMR spectra and further verified by the presence of a single peak in the HPLC profile of the 1,3-dithiolane derivatives, thus excluding the possibility of diastereomers.

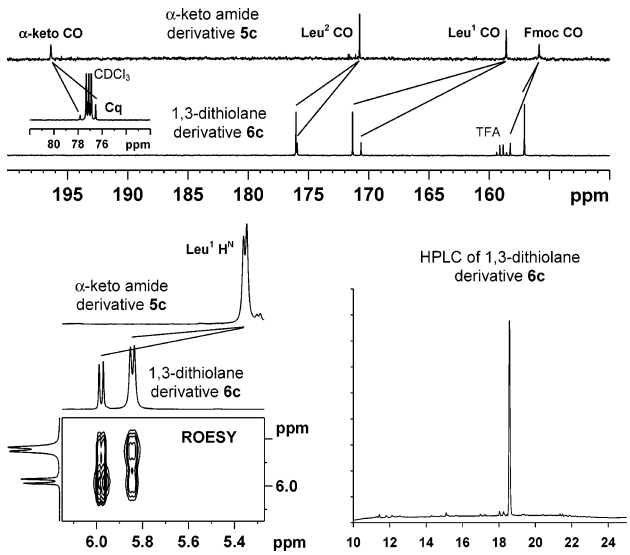
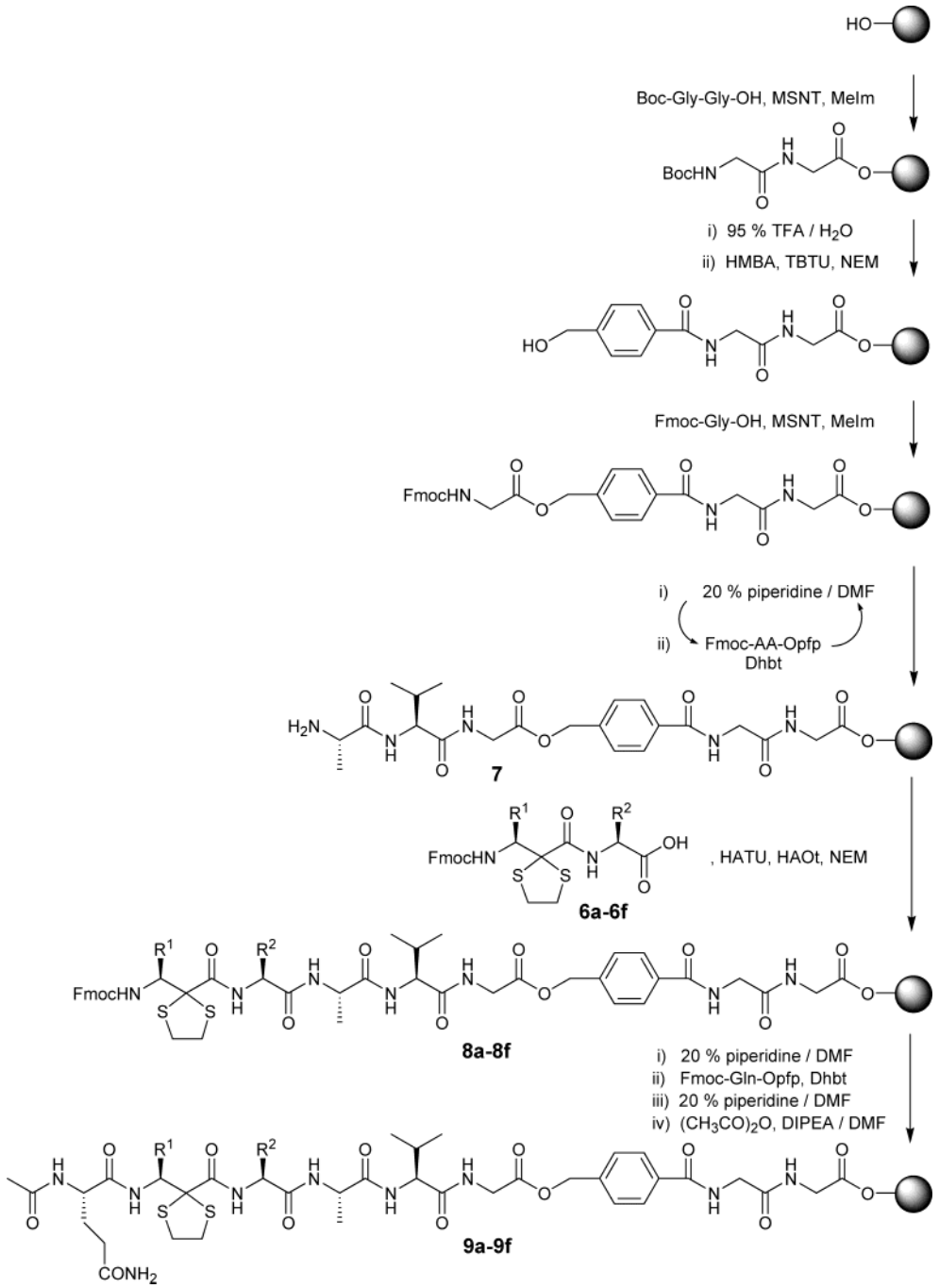


Figure 1. Upper half: excerpts of the carbonyl region of 1D-^{13}C NMR spectra from the α-keto amide dipeptide **5c** (top trace) and 1,3-dithiolane building block **6c** (bottom trace), respectively. The resonances of the 1,3-dithiolane **6c** are split into two sets of signals in a 3:1 ratio due to the presence of two conformers. Lower left: section of the ROESY spectrum of 1,3-dithiolane dipeptide **6c** exhibiting exchange cross-peaks between the Leu^1 H^N signals of the different conformers. For comparison, the ^1H projection of the α-keto amide **5c** is overlaid in the F_2 dimension. Lower right: HPLC profile of product **6c**, clearly displaying a single peak.

Building Block Utilization in Solid-Phase Peptide Synthesis. The 1,3-dithiolane building block incorporation was investigated with peptide **7** on SPOCC-1500,[18] a completely inert resin with only primary ether bonds, which is highly suitable for on-bead NMR experiments using the HR-MAS technology[23] (Scheme 5). Peptide **7** was constructed using standard solid-phase peptide synthesis protocols. To obtain HR-MAS NMR spectra with enhanced resolution, the HMBA linker was elongated with two glycine residues to reduce influence of resin heterogeneity. Boc-Gly-Gly−OH and Fmoc-Gly−OH were esterified onto the resin and the 4-hydroxymethylbenzoic acid (HMBA) linker, respectively, using the condensing agent 1-(2-mesitylenesulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT) in combination with *N*-methylimidazole (MeIm) as catalyst.[24] HMBA assembly and peptide elongation was achieved with TBTU-activated[25] HMBA and Fmoc-protected pentafluorophenyl esters of N^α-protected amino acids (Ala, Val, and Gly) in the presence of Dhbt. The Fmoc-protected 1,3-dithiolane building blocks **6a**−**6f** were introduced onto the resin by activation with HATU,[26] 1-hydroxy-7-azabenzotriazole (HOAt) and *N*-ethyl morpholine (NEM). The progress of the building block coupling reaction was monitored by ^1H HR-MAS NMR on resin, by comparison of the relative area of the Fmoc aromatic protons and that of the methylene protons

Scheme 5. Generation of 1,3-Dithiolane Peptides on SPOCC-1500.[a]



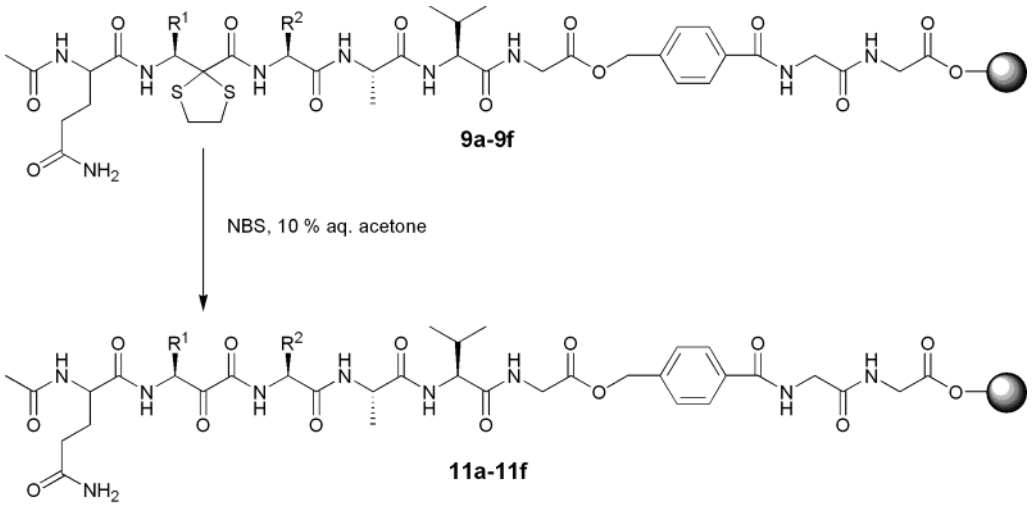
[a] Peptide 7 is synthesized on SPOCC-1500 using standard SPPS protocols. The 1,3-dithiolane building blocks **6a**−**6f** are assembled onto resin 7 to yield **8a**−**8f**. Final Fmoc deprotection followed by acetylation gives **9a**−**9f**.

of the HMBA linker at δ ~5.2. All reactions reached completion within 2−4 h.

In a parallel synthesis fashion, the 1,3-dithiolane peptide derivatives **8a**−**8f** were elongated with the Fmoc-protected pentafluorophenyl ester of glutamine using Dhbt as catalyst, Fmoc-deprotected, and acetylated. Each individual reaction step was monitored by Kaiser test and ^{1}H HR-MAS NMR on the resin. A sample of each resin **9a**−**9f** was cleaved and analyzed by HPLC and ESI-MS. The formation of the expected product **10a**−**10f** was confirmed in all cases, and no byproducts could be detected.

Cleavage of the 1,3-Dithiolane Protection Group. Several methods for cleavage of dithioketals in solution are available;[27] however, to the best of our knowledge, procedures for direct regeneration of carbonyl compounds from dithioketals on solid support have only been reported where ketones were attached onto a resin via a propane-1,3-dithiole linker to form the 1,3-dithianes.[28] Moreover, most of the synthetic methods available involve either harsh or strongly acidic reaction conditions, making them poor candidates for use on solid support. The use of such methods is further hampered as a result of the acid lability of α-keto amides. Among the synthetic methods investigated, a modified protocol of Corey's methodology[29] proved to be the most efficient. Thus, unmasking of the α-keto amide functionality was achieved by treatment of the resin-bound peptides **9a**−**f**

Scheme 6. Deprotection of 1,3-Dithiolane Derivative.[a]



11a: $R^1 = CH_3$ $R^2 = CH_2CH(CH_3)_2$ **11d**: $R^1 = CH_2CH(CH_3)_2$ $R^2 = CH_2CH_2Ph$

11b: $R^1 = CH_3$ $R^2 = CH_2CH_2Ph$ **11e**: $R^1 = CH_2Ph$ $R^2 = CH_2CH(CH_3)_2$

11c: $R^1 = CH_2CH(CH_3)_2$ $R^2 = CH_2CH(CH_3)_2$ **11f**: $R^1 = CH_2Ph$ $R^2 = CH_2CH_2Ph$

[a] The unmasking of the α-keto functionality takes place by treatment of **9a**−**9f** with NBS in 10% aq. acetone yielding **11a**−**11f**.

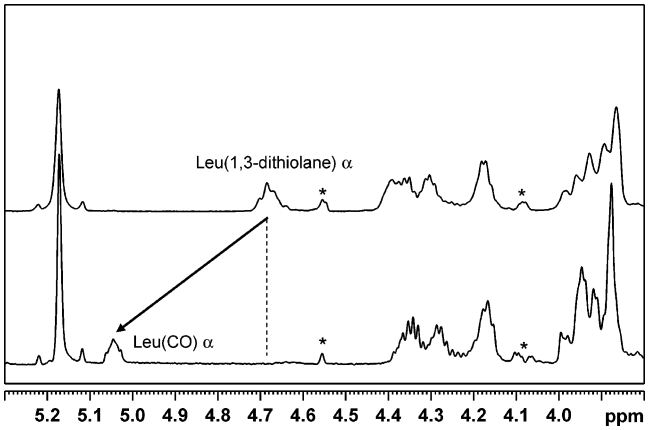


Figure 2. Comparison of the α-proton region of ^{1}H HR-MAS NMR spectra from the 1,3-dithiolane peptide **9c** (upper trace) and α-keto amide peptide **11c** (lower trace) on SPOCC-1500 resin. The quantitative unmasking of the α-keto carbonyl functionality was monitored by the disappearance of the Leu(1,3-dithiolane) α proton resonance (dotted line) and the appearance of the Leu(CO) α signal. Asterisks denote resonances originating from resin impurities.

with *N*-bromosuccinamide in 10% aqueous acetone at ambient temperature, affording pure products **11a**−**f** (Scheme 6) and quantitative conversion, as monitored by ^{1}H HR-MAS NMR (Figure 2).

The congeners **11a**−**f** were characterized on resin by HR-MAS NMR to prevent formation of side products often associated with strong basic conditions that are usually employed for cleavage from the solid support. This was deemed particularly necessary in the case of α-keto amide peptides, since information about purity, stereochemical preservation, and competing equilibria can only be obtained by analysis of the compound still attached onto the solid support. Specific to α-keto amides are intermolecular aldol type reactions, racemization via keto-enol tautomerisation, gem-diol formation, and amide addition reactions. In all ^{13}C NMR spectra, two sets of signals were observed originating from two different conformers, as in the case of the 1,3-dithiolane building blocks **6a**−**6f** discussed earlier. Unfortunately, in the ^{1}H NMR spectra, this splitting is less distinct because of lower dispersion, making it impossible to use ROESY experiments to identify exchange between two conformers. Nevertheless, the presence of conformers can be proven by recording 1D-^{13}C NMR spectra at two different temperatures and observing the change in the ratio of signal intensities between the major and the minor conformer. This effect is illustrated (Figure 3) on selected signals of the ^{13}C spectrum of resin **11c** at 25 °C (upper trace) and 70 °C (lower trace), respectively. For characterization of the product, a complete ^{1}H and ^{13}C assignment of the major conformers of the resin-bound peptides **11a**−**f** at 70 °C using HR-MAS NMR was performed.

Conclusion

A general method for the preparation of resin-bound internal α-keto amide peptides for protease inhibitor screening on solid support has been introduced. The strategy employs α-keto amide building blocks that can be used in SPPS. A protective group strategy for the keto functionality of these building blocks is necessary. A 1,3-dithiolane protective group strategy has been introduced for this reason on α-keto amides on solid support and tested for its compatibility under SPPS conditions with a variety of building blocks. All transformations were studied at high resolution by magic angle spinning NMR on solid support.

Experimental Section

General Procedures. All solution-phase reactions were carried out in oven-dried glassware under N_2. Solvents and reagent solutions were transferred using gastight syringes. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2) under nitrogen. Ozone was generated from dry dioxygen on a Fischer ozonator. Flash chromatography was conducted on silica gel (40−63 μm, Merck Silica Gel 60). Thin-layer chromatography (tlc) was performed on Mach-

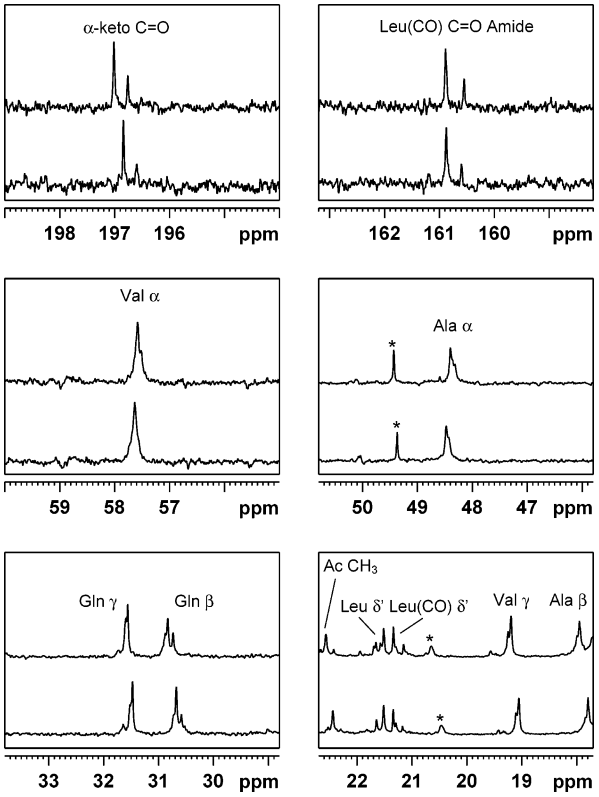


Figure 3. Selected regions of ^{13}C HR-MAS NMR spectra of **11c** recorded at 25 °C (top traces) and 70 °C (bottom traces), respectively. Because of the presence of conformers, the signals are split into two resonances for each carbon. The ratio of the signal intensities is temperature-dependent, favoring the major conformer at higher temperature. Asterisks denote resonances originating from the resin and resin impurities.

erey-Nagel Polygram Sil G/UV_{254} plastic sheets with 0.25 mm of silica gel and with fluorescent indicator UV_{254}. Detection was by fluorescence quenching under 254-nm ultraviolet irradiation or by exposure to iodine vapor where necessary.

Solid-phase peptide chemistry and solid-phase organic chemistry were performed in plastic syringes. Flat-bottom PE syringes were equipped with sintered Teflon filters (50-μm pores), Teflon tubing, and valves for applying suction to the syringes from below. Resin loadings were determined by Fmoc cleavage and optical density measurement at 290 nm and were calculated by employing a calibration curve.

Analysis of all solid-phase reactions was performed by HR-MAS NMR or after product cleavage from a resin sample or both. A small portion of dry resin (1−2 mg) was weighed in an Eppendorf cup and treated with an aqueous 0.1 M solution of NaOH (50 μL, 2 h). The suspension was neutralized with 1 M hydrochloric acid (5 μL). A sample of this solution (20 μL) was examined on an analytical HPLC column (8 × 200 mm C-18 column, Millipore Delta Pack 15 μm) with detection at 215 and 280 nm using a photodiode array detector (Waters M 991). Eluents A (0.1% TFA in water) and B (0.1% TFA in acetonitrile/water, 9:1) were used in a linear gradient (0 → 100% B in 30 min). Collected fractions were analyzed by ESI-MS (Fisons VG Quatro or MALDI-QTOF, Global Ultima (Waters)).

NMR spectra were recorded on a Bruker DRX 600 in standard configuration at 300 K using an inverse 5-mm triple-resonance TXI probe equipped with a three-axis gradient system for liquid-phase spectra. For complete ^1H and ^{13}C assignment $^1H/^{13}C$-1D, COSY,[30] ROESY,[31] HSQC[32], and HMBC[33] spectra were recorded. HR-MAS spectra of swollen resin were obtained with a 4-mm double resonance ($^1H/^{13}C$) HR-MAS probe equipped with a magic-angle gradient system at 323 K. The gradient duration was adjusted to be a multiple of 6 over the spinning speed of 4800 Hz. Suppression of the major ^1H resin signal was performed by 1D-NOESY sequence with presaturation and gradient *z*-filter, and single presaturation was utilized for 2D experiments. ZrO_2 rotors with boron nitride rotor caps and poly(tetrafluoroethylene) (PTFE) spacer containing a sample volume of 50 μL were utilized.

Acylcyanophosphoranes (2a−2c). Fmoc-protected amino acids (**1a**−**1c**) (1 equiv) were dissolved in CH_2Cl_2 (50 mL), and 4-(dimethylamino)pyridine (DMAP) (0.1 equiv) was added, followed by 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDCI) (1.3 equiv). Within 1 min, (cyanomethylene)triphenylphosphorane (1.05 equiv) was added rapidly. The reaction mixtures were stirred at ambient temperature for 18 h, diluted with CH_2Cl_2 (30 mL), and washed consecutively with water (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and water (30 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to leave a pale brown foam. Chromatography (ethyl acetate/light petroleum, 1:1) gave the acylcyanophosphoranes (**2a**−**2c**).

9*H*-9-Fluorenyl *N*-[(2*S*)-4-Cyano-3-oxo-4-(triphenylphosphoranylidene)but-2-yl]-carbamate (2a). Fmoc-Ala-C(PPh$_3$)CN. Fmoc-Ala-OH (2.5 g, 8.03 mmol) was reacted as described above to give 9*H*-9-fluorenyl *N*-[(2*S*)-4-cyano-3-oxo-4-(triphenylphosphoranylidene)but-2-yl]-carbamate (**2a**) as an ivory foam (3.96 g, 83%). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.75 (d, ^3J(H,H) = 7.4 Hz, 2H, Fmoc 4,5), 7.64 (t, ^3J(H,H) = 7.7 Hz, 3H, p Ph), 7.61 (d, ^3J(H,H) = 6.6 Hz, 2H, Fmoc 1,8), 7.60 (d, ^3J(H,H) = 7.7 Hz, 6H, o Ph), 7.53 (dt, ^3J(H,H) = 7.7 Hz, ^4J(H,P) = 3.3 Hz, 6H, m Ph), 7.37 (dd, ^3J(H,H) = 7.4 Hz, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 3,6), 7.29 (dd, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 6.6 Hz, 2H, Fmoc 2,7), 5.84 (d, ^3J(H,H) = 7.0 Hz, 1H, Ala H^N), 5.01 (m_c, 1H, Ala α), 4.35 (m_c, 2H, Fmoc 14), 4.21 (t, ^3J(H,H) = 7.1 Hz, 1H, Fmoc 9), 1.59 (d, ^3J(H,H) = 6.9 Hz, 3H, Ala β); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 194.4 (α-keto C═O), 155.2 (Fmoc C═O), 143.9 (Fmoc 10), 143.8 (Fmoc 13), 141.0 (Fmoc 11,12), 133.3 (^2J(P,C) = 10.0 Hz, o Ph), 133.1 (p Ph), 129.1 (^3J(P,C) = 13.0 Hz, m Ph), 127.4 (Fmoc 3,6), 126.8 (Fmoc 2,7), 125.1 (Fmoc 1), 125.0 (Fmoc 8), 122.4 (^1J(P,C) = 93.3 Hz, iPPh$_3$), 120.6 (^2J(P,C) = 15.5 Hz, CN), 119.7 (Fmoc 4,5), 66.4 (Fmoc 14), 52.3 (^3J(P,C) = 9.0 Hz, Ala α), 47.0 (Fmoc 9), 46.6 (^1J(P,C) = 126.2 Hz, C═P), 19.6 (Ala β). HR-MS: calcd, [MNa^+] ($C_{38}H_{31}N_2O_3$-PNa) = 617.1965; found, *m*/*z* = 617.1950 [MNa^+].

9*H*-9-Fluorenyl *N*-[(3*S*)-5-Methyl-1-cyano-2-oxo-1-(triphenylphosphoranylidene)hex-3-yl] Carbamate (2b). Fmoc-Leu-C(PPh$_3$)CN. Fmoc-Leu-OH (5.0 g, 14.15 mmol) was reacted as described above to give 9*H*-9-fluorenyl *N*-[(3*S*)-5-methyl-1-cyano-2-oxo-1-(triphenylphosphoranylidene)hex-3-yl]-carbamate (**2b**) as a white foam (7.12 g, 79%). ^1H NMR

(600 MHz, $CDCl_3$): δ = 7.75 (d, ^3J(H,H) = 7.5 Hz, 2H, Fmoc 4,5), 7.64 (m, 3H, p PPh), 7.61 (d, ^3J(H,H) = 7.3 Hz, 2H, Fmoc 1,8), 7.60 (m, 6H, o PPh), 7.52 (m, 6H, m PPh), 7.38 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.3 Hz, 2H, Fmoc 3,6), 7.28 (t, ^3J(H,H) = 7.3 Hz, 2H, Fmoc 2,7), 5.49 (d, ^3J(H,H) = 7.9 Hz, 1H, Leu H^N), 5.011 (m_c, 1H, Leu α), 4.35 (d, ^3J(H,H) = 7.2 Hz, 2H, Fmoc 14), 4.23 (t, ^3J(H,H) = 7.2 Hz, 1H, Fmoc 9), 1.83 (m_c, 1H, Leu β), 1.81 (m_c, 1H, Leu γ), 1.53 (m_c, 1H, Leu β'), 1.10 (d, ^3J(H,H) = 4.8 Hz, 3H, Leu δ), 0.99 (d, ^3J(H,H) = 6.2 Hz, 3H, Leu δ'); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.0 (α-keto C═O), 156.0 (Fmoc C═O), 144.2 (Fmoc 10), 144.0 (Fmoc 13), 141.3 (Fmoc 11), 141.2 (Fmoc 12), 133.6 (^2J(P,C) = 10.3 Hz, o PPh), 133.2 (^4J(P,C) = 2.4 Hz, p PPh), 129.2 (^3J(P,C) = 12.6 Hz, m PPh), 127.5 (Fmoc 3,6), 127.0 (Fmoc 2,7), 125.3 (Fmoc 1), 125.3 (Fmoc 8), 122.8 (^1J(P,C) = 94.0 Hz, i PPh), 120.8 (^2J(P,C) = 15.5 Hz, CN), 119.8 (Fmoc 4,5), 66.7 (Fmoc 14), 55.4 (^3J(P,C) = 8.7 Hz, Leu α), 47.3 (Fmoc 9), 47.2 (^1J(P,C) = 126.4 Hz, C═P), 43.2 (Leu β), 25.1 (Leu γ), 23.7 (Leu δ'), 21.6 (Leu δ). HR-MS: calcd, [MNa^+] ($C_{41}H_{37}N_2O_3PNa$) = 637.2615; found, *m*/*z* = 637.2624 [MNa^+].

9*H*-9-Fluorenyl *N*-[(2*S*)-1-Phenyl-4-cyano-3-oxo-4-(triphenylphosphoranylidene)but-2-yl] Carbamate (2c). Fmoc-Phe-C(PPh$_3$)CN. Fmoc-Phe-OH (2.5 g, 6.45 mmol) was reacted as described above to give 9*H*-9-fluorenyl *N*-[(2*S*)-1-phenyl-4-cyano-3-oxo-4-(triphenylphosphoranylidene)but-2-yl] carbamate (**2c**) as a white foam (3.55 g, 82%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.75 (d, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 4,5), 7.64 (m_c, 3H, p PPh), 7.57 (d, ^3J(H,H) = 7.5 Hz, 2H, Fmoc 1,8), 7.56 (m_c, 6H, o PPh), 7.52 (m, 6H, m PPh), 7.38 (dd, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 7.5 Hz, 2H, Fmoc 3,6), 7.28 (t, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 2,7), 7.24 (d, 2H, o Phe), 7.23 (t, 2H, m Phe), 7.23 (t, 1H, p Phe), 5.64 (d, ^3J(H,H) = 8.0 Hz, 1H, Phe H^N), 5.24 (m_c, 1H, Phe α), 4.39 (dd, ^3J(H,H) = 7.0 Hz, ^2J(H,H) = 10.1 Hz, 1H, Fmoc 14), 4.24 (dd, ^3J(H,H) = 7.4 Hz, ^2J(H,H) = 10.1 Hz, 1H, Fmoc 14′), 4.18 (t, ^3J(H,H) = 7.0 Hz, 1H, Fmoc 9), 3.39 (dd, ^3J(H,H) = 5.1 Hz, ^2J(H,H) = 14.2 Hz, 1H, Phe β), 3.15 (dd, ^3J(H,H) = 7.3 Hz, ^2J(H,H) = 14.2 Hz, 1H, Phe β'); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 192.8 (α-keto C═O), 155.4 (Fmoc C═O), 144.1 (Fmoc 10), 144.0 (Fmoc 13), 141.2 (Fmoc 11,12), 136.8 (i Phe), 133.6 (^2J(P,C) = 10.2 Hz, o PPh), 133.3 (p PPh), 129.8 (o Phe), 129.1 (^3J(P,C) = 13.2 Hz, m PPh), 128.1 (m Phe), 127.5 (Fmoc 3,6), 126.9 (Fmoc 2,7), 126.5 (p Phe), 125.243 (Fmoc 1,8), 122.5 (^1J(P,C) = 94.1 Hz, i PPh), 120.9 (^2J(P,C) = 14.8 Hz, CN), 119.8 (Fmoc 4,5), 66.6 (Fmoc 14), 57.2 (^3J(P,C) = 8.6 Hz, Phe α), 48.0 (^1J(P,C) = 125.6 Hz, C═P), 47.2 (Fmoc 9), 38.8 (Phe β). HR-MS: calcd, [MNa^+] ($C_{44}H_{35}N_2O_3PNa$) = 693.2278; found, *m*/*z* = 693.2263 [MNa^+].

2-Amino-4-phenyl-(2*S*)-butyric Acid *tert*-Butyl Ester Hydrochloride (4a). H-homoPhe-O*t*Bu·HCl. To (*S*)-2-amino-4-phenylbutyric acid (5.0 g, 27.90 mmol) was added *tert*-butyl acetate (263.2 mL, 1.953 mol). Trifluoroacetic acid was added until the amino acid was dissolved (21.65 mL, 278.98 mmol), followed by trifluoromethanesulfonic acid (2.96 mL, 33.48 mmol). The reaction mixture was stirred at ambient temperature for 2 days before it was poured slowly into a $NaHCO_3$/Na_2CO_3 buffer (pH 10) and was shaken until there was no more evolution of gas. The two layers were separated, the organic layer was washed again with the buffer solution and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The yellow oil was dissolved in ether, and acidic ether (saturated) was added. A white solid precipitated, which was filtered and dried (4.58 g, 60%). ^{1}H NMR (600 MHz, CD_3OD): δ = 7.30 (t, ^3J(H,H) = 7.6 Hz, 2H, m homoPhe), 7.23 (d, ^3J(H,H) = 7.6 Hz, 2H, o homoPhe), 7.21 (t, ^3J(H,H) = 7.6 Hz, 1H, p homoPhe), 3.91 (t, ^3J(H,H) = 6.3 Hz, 1H, homoPhe α), 2.81 (ddd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 10.7 Hz, ^3J(H,H) = 5.0 Hz, 1H, homoPhe γ), 2.71 (ddd, ^2J(H,H) = 13.8 Hz, ^3J(H,H) = 10.7 Hz, ^3J(H,H) = 6.2 Hz, 1H, homoPhe γ'), 2.19 (m_c, 1H, homoPhe β), 2.12 (m_c, 1H, homoPhe β'), 1.55 (s, 9H, *t*Bu CH_3); ^{13}C NMR (150 MHz, CD_3OD): δ = 169.6 (homoPhe C═O), 141.2 (i homoPhe), 129.8 (m homoPhe), 129.4 (o homoPhe), 127.6 (p homoPhe), 85.3 (*t*Bu qC), 54.0 (homoPhe α), 33.7 (homoPhe β), 32.7 (homoPhe γ), 28.2 (*t*Bu CH_3). HR-MS: calcd, [MH^+] ($C_{14}H_{22}NO_2$) = 236.16505; found, *m*/*z* = 236.1645 [MH^+]; calcd, [MNa^+] ($C_{14}H_{21}NO_2Na$) = 258.14700; found, *m*/*z* = 258.1473 [MNa^+].

α-Keto Amide Dipeptides (5a−5f). The cyano phosphoranes (**2a**−**2c**) (1.05 equiv) were ozonized in CH_2Cl_2 (120 mL) at −78 °C until the reaction mixture turned blue-green. It was then purged with O_2 and N_2 for 4 and 8 min, respectively. To the resulting mixture of α,β-diketo nitrile (**3a**−**3c**) were added solutions of C-terminal-protected amino acids (**4a**, **4b**) (1.0 equiv) in CH_2Cl_2 (10 mL). The mixture was stirred for 1 h before cooling was discontinued. Following concentration, an orange oil was obtained, which was stirred at ambient temperature for 24 h with 58.9 mL of a 1 M solution of silver nitrate in THF/water, 4:1. Water, 100 mL, was added to the dark slurry, followed by CH_2Cl_2 ,and the two phases were separated. The aqueous phase was washed with CH_2Cl_2 (2 × 50 mL), and the combined organic phases were dried (Na_2SO_4). Concentration afforded a greenish oil which was subjected immediately to flash chromatography.

***tert*-Butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-oxobutanoyl)amino]-4-methylpentanoate (5a). Fmoc-Ala-CO-Leu-O*t*Bu.** The cyanophosphorane 9*H*-9-fluorenyl *N*-[(2*S*)-4-cyano-3-oxo-4-(triphenylphosphoranylidene)but-2-yl] carbamate (**2a**) (3.5 g, 5.89 mmol) was reacted with H-Leu-O*t*Bu (**4b**) (1.1 g, 5.60 mmol) as described above to give *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-oxobutanoyl)amino]-4-methylpentanoate (**5a**) as an ivory foam (chromatography: ethyl acetate/light petroleum, 1:1; yield, 2.01 g, 67%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (d, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 4,5), 7.59 (d, ^3J(H,H) = 7.4 Hz, 2H, Fmoc 1,8), 7.40 (dd, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 7.4 Hz, 2H, Fmoc 3,6), 7.32 (t, ^3J(H,H) = 7.4 Hz, 2H, Fmoc 2,7), 7.27 (m_c, 1H, Leu H^N), 5.46 (d, ^3J(H,H) = 6.7 Hz, 1H, Ala H^N), 5.19 (m_c, 1H, Ala α), 4.47 (m_c, 1H, Leu α), 4.39 (m_c, 2H, Fmoc 14), 4.22 (t, ^3J(H,H) = 6.9 Hz, 1H, Fmoc 9), 1.69 (m_c, 1H, Leu β), 1.65 (m_c, 1H, Leu γ), 1.58 (m_c, 1H, Leu β'), 1.47 (d, ^3J(H,H) = 8.5 Hz, 1H, Ala β), 1.47 (s, 9H, *t*Bu CH_3), 0.96 (d, ^3J(H,H) = 6.2 Hz, 3H, Leu δ), 0.95 (d, ^3J(H,H) =

6.2 Hz, 3H, Leu δ'); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.9 (α-keto C═O), 170.7 (Leu C═O), 158.1 (Ala C═O), 155.1 (Fmoc C═O), 143.7 (Fmoc 10,13), 141.2 (Fmoc 11,-12), 127.5 (Fmoc 3,6), 126.9 (Fmoc 2,7), 124.9 (Fmoc 1,8), 119.7 (Fmoc 4,5), 82.1 (*t*Bu qC), 67.0 (Fmoc 14), 51.8 (Ala α), 51.4 (Leu α), 46.8 (Fmoc 9), 41.5 (Leu β), 27.7 (*t*Bu CH_3), 24.7 (Leu γ), 22.2 (Leu δ), 17.8 (Ala β). HR-MS: calcd, [MNa^+] ($C_{29}H_{36}N_2O_6Na$) = 531.2466; found, *m*/*z* = 531.2467 [MNa^+].

***tert*-Butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-oxobutanoyl)amino]-4-phenylbutanoate (5b). Fmoc-Ala-CO-homoPhe-O*t*Bu.** The cyanophosphorane 9*H*-9-fluorenyl *N*-[(2*S*)-4-cyano-3-oxo-4-(triphenylphosphoranylidene)but-2-yl] carbamate (**2a**) (3.47 g, 5.84 mmol) was reacted with H-homoPhe-O*t*Bu (**4a**) (1.3 g, 5.55 mmol) as described above to give *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-oxobutanoyl)amino]-4-phenylbutanoate (**5b**) as a white solid (chromatography: ethyl acetate/light petroleum, 3:7; yield, 2.53 g, 78%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (d, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 4,5), 7.60 (d, ^3J(H,H) = 8.0 Hz, 1H, Fmoc 1), 7.59 (d, ^3J(H,H) = 8.4 Hz, 1H, Fmoc 8), 7.41 (d, ^3J(H,H) = 5.1 Hz, 1H, homoPhe H^N), 7.40 (t, ^3J(H,H) = 7.3 Hz, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 3,6), 7.32 (dd, ^3J(H,H) = 7.3 Hz, ^3J(H,H) = 8.0 Hz, 1H, Fmoc 2), 7.32 (dd, ^3J(H,H) = 7.3 Hz, ^3J(H,H) = 8.4 Hz, 1H, Fmoc 7), 7.28 (dd, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 7.0 Hz, 2H, m homoPhe), 7.20 (t, ^3J(H,H) = 7.6 Hz, 1H, p homoPhe), 7.16 (d, ^3J(H,H) = 7.0 Hz, 2H, o homoPhe), 5.44 (d, ^3J(H,H) = 7.1 Hz, 1H, Ala H^N), 5.19 (m_c, 1H, Ala α), 4.51 (ddd, ^3J(H,H) = 5.1 Hz, ^3J(H,H) = 7,0 Hz, ^3J(H,H) = 7.6 Hz, 1H, homoPhe α), 4.40 (m_c, 2H, Fmoc 14), 4.22 (t, ^3J(H,H) = 7.0 Hz, 1H, Fmoc 9), 2.65 (m_c, 2H, homoPhe γ), 2.23 (m_c, 1H, homoPhe β), 2.05 (m_c, 1H, homoPhe β'), 1.49 (s, 9H, *t*Bu CH_3), 1.47 (d, ^3J(H,H) = 7.1 Hz, 3H, Ala β); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.1 (α-keto C═O), 170.1 (homoPhe C═O), 158.3 (Ala C═O), 155.5 (Fmoc C═O), 143.9 (Fmoc 10), 143.8 (Fmoc 13), 141.3 (Fmoc 11,12), 140.5 (i homoPhe), 128.6 (m homoPhe), 128.3 (o homoPhe), 127.7 (Fmoc 3,6), 127.1 (Fmoc 2,7), 126.3 (p homoPhe), 125.1 (Fmoc 1,8), 120.0 (Fmoc 4,5), 83.0 (*t*Bu qC), 67.0 (Fmoc 14), 52.7 (homoPhe α), 51.9 (Ala α), 47.2 (Fmoc 9), 33.9 (homoPhe β), 31.5 (homoPhe γ), 28.0 (*t*Bu CH_3), 18.0 (Ala β). HR-MS: calcd, [MNa^+] ($C_{33}H_{36}N_2O_2Na$) = 579.2466; found, *m*/*z* = 579.2466 [MNa^+].

***tert*-Butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-oxo-5-methylhexanoyl)amino]-4-methylpentanoate (5c). Fmoc-Leu-CO-Leu-O*t*Bu.** The cyanophosphorane 9*H*-9-fluorenyl *N*-[(3*S*)-5-methyl-1-cyano-2-oxo-1-(triphenylphosphoranylidene)hex-3-yl] carbamate (**2b**) (2.0 g, 3.14 mmol) was reacted with H-Leu-O*t*Bu (**4b**) (0.56 g, 2.98 mmol) as described above to give *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-oxo-5-methylhexanoyl)amino]-4-methylpentanoate (**5c**) as an ivory foam (chromatography: ethyl acetate/light petroleum, 1:1; yield, 1.25 g, 72%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, ^3J(H,H) = 7.5 Hz, 2H, Fmoc 4,5), 7.59 (d, ^3J(H,H) = 7.2 Hz, 1H, Fmoc 8), 7.56 (d, ^3J(H,H) = 7.2 Hz, 1H, Fmoc 1), 7.40 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.2 Hz, 1H, Fmoc 3), 7.39 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.2 Hz, 1H, Fmoc 6), 7.31 (t, ^3J(H,H) = 7.2 Hz, 2H, Fmoc 2,7), 7.25 (d, ^3J(H,H) = 8.4 Hz, 1H, Leu2 H^N), 5.35 (d, ^3J(H,H) = 8.4 Hz, 1H, Leu1 H^N), 5.17 (dd, ^3J(H,H) = 7.9 Hz, ^3J(H,H) = 8.4 Hz, 1H, Leu1 α), 4.46 (ddd, ^3J(H,H) = 8.4 Hz, ^3J(H,H) = 5.5 Hz, 1H, Leu2 α), 4.40 (d, ^3J(H,H) = 7.3 Hz, 2H, Fmoc 14), 4.22 (t, ^3J(H,H) = 7.3 Hz, 1H, Fmoc 9), 1.74 (m_c, 1H, Leu1 γ), 1.72 (m_c, 1H, Leu1 β), 1.68 (m_c, 1H, Leu2 β), 1.63 (m_c, 1H, Leu2 γ), 1.57 (m_c, 1H, Leu2 β'), 1.47 (s, 9H, *t*Bu CH_3), 1.45 (m_c, 1H, Leu1 β'), 1.02 (d, ^3J(H,H) = 6.2 Hz, 3H, Leu1 δ), 0.94 (d, ^3J(H,H) = 6.2 Hz, 3H, Leu2 δ), 0.94 (d, ^3J(H,H) = 6.2 Hz, 3H, Leu2 δ'), 0.94 (d, ^3J(H,H) = 6.2 Hz, 3H, Leu1 δ'); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.4 (α-keto C═O), 170.8 (Leu2 C═O), 158.6 (Leu1 C═O), 155.9 (Fmoc C═O), 143.9 (Fmoc 10), 143.8 (Fmoc 13), 141.3 (Fmoc 11,-12), 127.7 (Fmoc 3,6), 127.1 (Fmoc 2,7), 125.1 (Fmoc 1,8), 120.0 (Fmoc 4,5), 82.5 (*t*Bu qC), 67.0 (Fmoc 14), 55.0 (Leu1 α), 51.5 (Leu2 α), 47.2 (Fmoc 9), 41.6 (Leu2 β), 40.9 (Leu1 β), 28.0 (*t*Bu CH_3), 25.1 (Leu1 γ), 25.0 (Leu2 γ), 23.2 (Leu1 δ'), 22.6 (Leu2 δ), 22.1 (Leu2 δ'), 21.5 (Leu1 δ). HR-MS: calcd, [MNa^+] ($C_{32}H_{42}N_2O_6Na$) = 573.2935; found, *m*/*z* = 573.2940 [MNa^+].

***tert*-Butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-oxo-5-methylhexanoyl)amino]-4-phenylbutanoate (5d). Fmoc-Leu-CO-homoPhe-O*t*Bu.** The cyanophosphorane 9*H*-9-fluorenyl *N*-[(3*S*)-5-methyl-1-cyano-2-oxo-1-(triphenylphosphoranylidene)hex-3-yl] carbamate (**2b**) (5.30 g, 8.324 mmol) was reacted with H-homoPhe-O*t*Bu (**4a**) (1.86 g, 7.908 mmol) as described above to give *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)-amino]-2-oxo-5-methylhexanoyl)amino]-4-phenylbutanoate (**5d**) as an ivory solid (chromatography: ethyl acetate/light petroleum, 1:1; yield, 4.24 g, 85%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 4,5), 7.59 (t, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 3,6), 7.42 (m_c, 1H, homoPhe H^N), 7.41 (m_c, 2H, Fmoc 2,7), 7.32 (m_c, 2H, Fmoc 1,8), 7.28 (dd, ^3J(H,H) = 7.1 Hz, ^3J(H,H) = 7.3 Hz, 2H, m homoPhe), 7.20 (t, ^3J(H,H) = 7.1 Hz, 1H, p homoPhe), 7.16 (d, ^3J(H,H) = 7.3 Hz, 2H, o homoPhe), 5.35 (d, ^3J(H,H) = 8.6 Hz, 1H, Leu H^N), 5.18 (m_c, 1H, Leu α), 4.51 (m_c, 1H, homoPhe α), 4.40 (d, ^3J(H,H) = 6.8 Hz, 2H, Fmoc 14), 4.22 (t, ^3J(H,H) = 6.8 Hz, 1H, Fmoc 9), 2.64 (m_c, 2H, homoPhe γ), 2.23 (m_c, 1H, homoPhe β), 2.05 (m_c, 1H, homoPhe β'), 1.76 (m_c, 1H, Leu γ), 1.74 (m_c, 1H, Leu β), 1.50 (s, 9H, *t*Bu CH_3), 1.45 (m_c, 1H, Leu β'), 1.04 (d, ^3J(H,H) = 5.5 Hz, 3H, Leu δ), 0.96 (d, ^3J(H,H) = 5.8 Hz, 3H, Leu δ'); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 196.2 (α-keto C═O), 170.1 (homoPhe C═O), 158.6 (Leu C═O), 155.9 (Fmoc C═O), 143.9 (Fmoc 10,13), 141.3 (Fmoc 11,-12), 140.5 (homoPhe δ), 128.5 (m homoPhe), 128.3 (o homoPhe), 127.7 (Fmoc 2,7), 127.0 (Fmoc 1,8), 126.3 (p homoPhe), 125.0 (Fmoc 3,6), 119.9 (Fmoc 4,5), 82.9 (*t*Bu qC), 67.0 (Fmoc 14), 54.8 (Leu α), 52.7 (homoPhe α), 47.2 (Fmoc 9), 40.9 (Leu β), 34.0 (homoPhe β), 31.5 (homoPhe γ), 28.0 (*t*Bu CH_3), 25.1 (Leu γ), 23.2 (Leu δ'), 21.5 (Leu δ). HR-MS: calcd, [MNa^+] ($C_{36}H_{42}N_2O_6Na$) = 621.2935; found, *m*/*z* = 621.2948 [MNa^+].

***tert*-Butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-oxo-4-phenylbutanoyl)amino]-4-methyl-**

pentanoate (5e). Fmoc-Phe-CO-Leu-O*t*Bu. The cyanophosphorane 9*H*-9-fluorenyl *N*-[(2*S*)-1-phenyl-4-cyano-3-oxo-4-(triphenylphosphoranylidene)but-2-yl] carbamate (**2c**) (5.0 g, 7.45 mmol) was reacted with H-Leu-O*t*Bu (**4b**) (1.3 g, 7.08 mmol) as described above to give *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-oxo-4-phenylbutanoyl)amino]-4-methylpentanoate (**5e**) as a pale yellow powder (chromatography: ethyl acetate/light petroleum, 3:7; yield, 3.05 g, 70%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (d, ^3J(H,H) = 7.7 Hz, 2H, Fmoc 4,5), 7.54 (d, ^3J(H,H) = 7.3 Hz, 2H, Fmoc 1,8), 7.40 (dd, ^3J(H,H) = 7.7 Hz, ^3J(H,H) = 7.3 Hz, 2H, Fmoc 3,6), 7.31 (t, ^3J(H,H) = 7.3 Hz, 2H, Fmoc 2,7), 7.25 (m_c, 2H, m Phe), 7.24 (m_c, 1H, p Phe), 7.22 (m_c, 1H, Leu H^N), 7.03 (d, ^3J(H,H) = 6.3 Hz, 2H, o Phe), 5.48 (m_c, 1H, Phe α), 5.38 (d, ^3J(H,H) = 7.9 Hz, 1H, Phe H^N), 4.51 (m_c, 1H, Leu α), 4.45 (dd, ^3J(H,H) = 7.7 Hz, ^2J(H,H) = 10.6 Hz, 1H, Fmoc 14), 4.34 (dd, ^3J(H,H) = 7.3 Hz, ^2J(H,H) = 10.6 Hz, 1H, Fmoc 14′), 4.20 (m_c, 1H, Fmoc 9), 3.32 (dd, ^3J(H,H) = 5.1 Hz, ^2J(H,H) = 13.9 Hz, 1H, Phe *β*), 3.23 (dd, ^3J(H,H) = 5.8 Hz, ^2J(H,H) = 13.9 Hz, 1H, Phe *β*′), 1.70 (m_c, 1H, Leu *β*), 1.66 (m_c, 1H, Leu *γ*), 1.60 (m_c, 1H, Leu *β*′), 1.47 (s, 9H, *t*Bu CH_3), 0.99 (d, ^3J(H,H) = 6.3 Hz, 3H, Leu *δ*), 0.99 (d, ^3J(H,H) = 6.3 Hz, 3H, Leu *δ*′);^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.1 (α-keto C═O), 170.7 (Leu C═O), 158.4 (Phe C═O), 155.4 (Fmoc C═O), 143.8 (Fmoc 10), 143.7 (Fmoc 13), 141.3 (Fmoc 11,12), 135.4 (i Phe), 129.4 (o Phe), 128.6 (m Phe), 127.7 (Fmoc 3,6), 127.2 (p Phe), 127.0 (Fmoc 2,7), 125.1 (Fmoc 1), 125.0 (Fmoc 8), 120.0 (Fmoc 4,5), 82.6 (*t*Bu qC), 66.9 (Fmoc 14), 57.0 (Phe α), 51.5 (Leu α), 47.2 (Fmoc 9), 41.6 (Leu *β*), 37.8 (Phe *β*), 27.8 (*t*Bu CH_3), 25.0 (Leu *γ*), 22.8 (Leu *δ*′), 22.0 (Leu *δ*). HR-MS: calcd, [MNa^+] ($C_{35}H_{40}N_2O_6Na$) = 607.2779; found, *m*/*z* = 607.2792 [MNa^+].

***tert*-Butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-oxo-4-phenylbutanoyl)amino]-4-phenylbutanoate (5f). Fmoc-Phe-CO-homoPhe-O*t*Bu.** The cyanophosphorane 9*H*-9-fluorenyl *N*-[(2*S*)-1-phenyl-4-cyano-3-oxo-4-(triphenylphosphoranylidene)but-2-yl] carbamate (**2c**) (5.0 g, 7.45 mmol) was reacted with H-homoPhe-O*t*Bu (**4a**) (1.67 g, 7.08 mmol) as described above to give *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-oxo-4-phenylbutanoyl)amino]-4-phenylbutanoate (**5f**) as a white foam (chromatography: ethyl acetate/light petroleum, 3:7; yield, 3.87 g, 82%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (d, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 4,5), 7.56 (t, ^3J(H,H) = 8.0 Hz, 2H, Fmoc 1,8), 7.42 (d, 1H, homoPhe H^N), 7.41 (t, ^3J(H,H) = 7.6 Hz, 1H, Fmoc 3), 7.40 (dd, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 6.8 Hz, 1H, Fmoc 6), 7.32 (m_c, 2H, Fmoc 2,7), 7.31 (m_c, 2H, m homoPhe), 7.26 (m_c, 1H, p Phe), 7.23 (t, ^3J(H,H) = 7.1 Hz, 2H, m Phe), 7.22 (m_c, 1H, p homoPhe), 7.19 (m_c, 2H, o homoPhe), 7.06 (d, ^3J(H,H) = 7.1 Hz, 2H, o Phe), 5.48 (m_c, 1H, Phe α), 5.38 (d, ^3J(H,H) = 8.0 Hz, 1H, Phe H^N), 4.54 (m_c, 1H, homoPhe α), 4.45 (dd, ^3J(H,H) = 7.6 Hz, ^2J(H,H) = 10.8 Hz, 1H, Fmoc 14), 4.34 (dd, ^3J(H,H) = 7.0 Hz, ^2J(H,H) = 10.8 Hz, 1H, Fmoc 14′), 4.20 (dd, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 7.0 Hz, 1H, Fmoc 9), 3.33 (dd, ^3J(H,H) = 5.4 Hz, ^2J(H,H) = 13.9 Hz, 1H, Phe *β*), 3.20 (dd, ^3J(H,H) = 6.3 Hz, ^2J(H,H) = 13.9 Hz, 1H, Phe *β*′), 2.66 (m_c, 2H, homoPhe *γ*), 2.25 (m_c, 1H, homoPhe *β*), 2.06 (m_c, 1H, homoPhe *β*′), 1.50 (s, 9H, *t*Bu CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.0 (α-keto C═O), 170.0 (homoPhe C═O), 158.5 (Phe C═O), 155.4 (Fmoc C═O), 143.8 (Fmoc 10), 143.7 (Fmoc 13), 141.3 (Fmoc 11,12), 140.5 (i homoPhe), 135.4 (i Phe), 129.4 (o Phe), 128.6 (p Phe), 128.6 (m homoPhe), 128.3 (o homoPhe), 127.7 (Fmoc 3,6), 127.2 (m Phe), 127.1 (Fmoc 2,7), 126.4 (p homoPhe), 125.1 (Fmoc 1), 125.0 (Fmoc 8), 120.0 (Fmoc 4,5), 83.0 (*t*Bu qC), 67.0 (Fmoc 14), 56.9 (Phe α), 52.7 (homoPhe α), 47.2 (Fmoc 9), 37.9 (Phe *β*), 34.1 (homoPhe *β*), 31.6 (homoPhe *γ*), 28.0 (*t*Bu CH_3). HR-MS: calcd, [MNa^+] ($C_{39}H_{40}N_2O_6Na$) = 655.2779; found, *m*/*z* = 655.2763 [MNa^+].

1.3-Dithiolane Dipeptides (6a−6f). To a solution of the α-keto amide dipeptides (**5a**−**5f**) in CH_2Cl_2 (5.0 mL) was added 1,2-ethanedithiol (1.1 equiv) followed by boron trifluoride ethyl etherate (500 *μ*L). The reaction mixture was stirred at ambient temperature until the reaction was complete. Water (50 mL) and CH_2Cl_2 (50 mL) were added. The organic layer was separated, washed with H_2O (2 × 10 mL) and saturated NaCl (30 mL), and dried (Na_2SO_4), and the solvent was evaporated in vacuo.

(2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-butanoyl)amino]-4-methylpentanoic acid (6a). The α-keto amide (**5a**) (2.00 g, 3.932 mmol) was reacted as described above to yield *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-butanoyl)amino]-4-methylpentanoate (**6a**) as a ivory foam (2.02 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 4,5), 7.73 (d, ^3J(H,H) = 7.7 Hz, 1H, Leu H^N), 7.64 (d, ^3J(H,H) = 7.6 Hz, 1H, Fmoc 1), 7.61 (d, ^3J(H,H) = 7.6 Hz, 1H, Fmoc 8), 7.39 (dd, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 7.4 Hz, 2H, Fmoc 3,6), 7.31 (dd, ^3J(H,H) = 7.6 Hz, ^3J(H,H) = 7.4 Hz, 2H, Fmoc 2,7), 6.19 (d, ^3J(H,H) = 10.1 Hz, 1H, Ala H^N), 4.57 (m_c, 1H, Leu α), 4.48 (dd, ^3J(H,H) = 7.0 Hz, ^3J(H,H) = 10.2 Hz, 1H, Fmoc 14), 4.45 (m_c, 1H, Ala α), 4.31 (dd, ^3J(H,H) = 7.7 Hz, ^2J(H,H) = 10.2 Hz, 1H, Fmoc 14′), 4.25 (dd, ^3J(H,H) = 7.7 Hz, ^3J(H,H) = 7.0 Hz, 1H, Fmoc 9), 3.36 (m, 2H, 1,3-dithio CH_2), 3.33 (m, 1H, 1,3-dithio CH_2), 3.27 (m, 1H, 1,3-dithio CH_2), 1.79 (m_c, 1H, Leu *β*), 1.71 (m_c, 1H, Leu *γ*), 1.68 (m_c, 1H, Leu *β*′), 1.29 (d, ^3J(H,H) = 6.6 Hz, 3H, Ala *β*), 0.99 (d, ^3J(H,H) = 6.9 Hz, 3H, Leu *δ*), 0.98 (d, ^3J(H,H) = 6.6 Hz, 3H, Leu *δ*′); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.8 (Leu C═O), 171.3 (Ala C═O), 156.1 (Fmoc C═O), 144.1 (Fmoc 10), 143.9 (Fmoc 13), 141.3 (Fmoc 11), 141.2 (Fmoc 12), 127.6 (Fmoc 3), 127.5 (Fmoc 6), 127.0 (Fmoc 2,7), 125.3 (Fmoc 1), 125.1 (Fmoc 8), 119.8 (Fmoc 4,5), 75.6 (1,3-dithio qC), 66.9 (Fmoc 14), 55.1 (Ala α), 51.5 (Leu α), 47.2 (Fmoc 9), 40.6 (Leu *β*), 40.6 (1,3-dithio CH_2), 39.6 (1,3-dithio CH_2), 25.1 (Leu *γ*), 22.8 (Leu *δ*), 21.7 (Leu *δ*′), 19.3 (Ala *β*). HR-MS: calcd, [MNa^+] ($C_{27}H_{32}N_2O_2S_2Na$) = 551.1644; found, *m*/*z* = 551.1613 [MNa^+].

(2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-butanoyl)amino]-4-phenylbutanoic Acid (6b). The α-keto amide (**5b**) (1.23 g, 2.210 mmol) was reacted as described above to yield *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-

butanoyl)amino]-4-phenylbutanoate (**6b**) as a white foam (1.26 g, 99%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.86 (d, ^3J(H,H) = 7.6 Hz, 1H, homoPhe H^N), 7.76 (d, ^3J(H,H) = 7.5 Hz, 2H, Fmoc 4,5), 7.64 (d, ^3J(H,H) = 7.6 Hz, 1H, Fmoc 1), 7.62 (d, ^3J(H,H) = 8.4 Hz, 1H, Fmoc 8), 7.38 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 6.9 Hz, 2H, Fmoc 3,6), 7.30 (t, ^3J(H,H) = 7.0 Hz, 2H, m homoPhe), 7.29 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.6 Hz, 1H, Fmoc 2), 7.29 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 8.4 Hz, 2H, Fmoc 7), 7.21 (t, ^3J(H,H) = 7.0 Hz, 1H, p homoPhe), 7.19 (d, ^3J(H,H) = 7.0 Hz, 2H, o homoPhe), 6.18 (d, ^3J(H,H) = 10.1 Hz, 1H, Ala H^N), 4.60 (m_c, 1H, homoPhe α), 4.47 (m, 2H, Phe α, Fmoc 14), 4.32 (m, 1H, Fmoc 14′), 4.25 (t, ^3J(H,H) = 6.9 Hz, 1H, Fmoc 9), 3.39−3.21 (m, 4H, 1,3-dithio CH_2), 2.71 (t, ^3J(H,H) = 7.9 Hz, 2H, homoPhe γ), 2.31 (td, J(H,H) = 13.6 Hz, ^3J(H,H) = 7.9 Hz, 1H, homoPhe β), 2.13 (ddd, ^2J(H,H) = 14.7 Hz, ^3J(H,H) = 13.6 Hz, ^3J(H,H) = 7.6 Hz, 1H, homoPhe β′) 1.29 (d, ^3J(H,H) = 6.6 Hz, 3H, Ala β); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.3 (homoPhe C═O), 171.2 (Ala C═O), 156.2 (Fmoc C═O), 144.1 (Fmoc 10), 143.9 (Fmoc 13), 141.3 (Fmoc 11,12), 140.2 (i homoPhe), 128.6 (m homoPhe), 128.4 (o homoPhe), 127.6 (Fmoc 3,6), 127.0 (Fmoc 2,7), 126.4 (p homoPhe), 125.3 (Fmoc 1), 125.2 (Fmoc 8), 119.9 (Fmoc 4,5), 75.5 (1,3-dithio qC), 66.9 (Fmoc 14), 55.1 (Ala α), 52.7 (homoPhe α), 47.2 (Fmoc 9), 40.6 (1,3-dithio CH_2), 39.7 (1,3-dithio CH_2), 33.3 (homoPhe β), 31.6 (homoPhe γ), 19.4 (Ala β). HR-MS: calcd, [MNa^+] ($C_{31}H_{32}N_2O_5S_2$-Na) = 599.1645; found, m/z = 599.1666 [MNa^+].

(2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-5-methylhexanoyl)amino]-4-methylpentanoic Acid (6c). The α-keto amide (**5c**) (2.51 g, 4.558 mmol) was reacted as described above to yield *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-5-methylhexanoyl)amino]-4-methylpentanoate (**6c**) as a pale yellow foam (2.58 g, 99%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (d, ^3J(H,H) = 7.7 Hz, 1H, Leu2 H^N), 7.75 (d, ^3J(H,H) = 7.7 Hz, 2H, Fmoc 4,5), 7.63 (d, ^3J(H,H) = 7.5 Hz, 1H, Fmoc 1), 7.61 (d, ^3J(H,H) = 7.5 Hz, 1H, Fmoc 8), 7.38 (dd, ^3J(H,H) = 7.7 Hz, ^3J(H,H) = 7.2 Hz, 2H, Fmoc 3,6), 7.30 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 7.2 Hz, 2H, Fmoc 2,7), 5.85 (d, 1H, ^3J(H,H) = 10.3 Hz, Leu1 H^N), 4.54 (m_c, 1H, Leu2 α), 4.53 (m_c, 1H, Fmoc 14), 4.40 (m_c, 1H, Fmoc 14′), 4.37 (m_c, 1H, Leu1 α), 4.24 (t, ^3J(H,H) = 7.0 Hz, 1H, Fmoc 9), 3.32−3.22 (m, 4H, 1,3-dithio CH_2), 1.76 (m_c, 1H, Leu2 β), 1.69 (m_c, 1H, Leu2 γ), 1.67 (m_c, 1H, Leu2 β′), 1.62 (m_c, 1H, Leu1 γ), 1.38 (m_c, 1H, Leu1 β), 1.23 (m_c, 1H, Leu1 β′), 0.96 (d, ^3J(H,H) = 7.7 Hz, 3H, Leu2 δ), 0.95 (d, ^3J(H,H) = 6.6 Hz, 3H, Leu2 δ′), 0.91 (d, ^3J(H,H) = 6.6 Hz, 3H, Leu1 δ), 0.86 (d, ^3J(H,H) = 6.6 Hz, 3H, Leu1 δ′); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.0 (Leu2 C═O), 171.3 (Leu C═O), 157.1 (Fmoc C═O), 144.1 (Fmoc 10), 143.7 (Fmoc 13), 141.3 (Fmoc 11,12), 127.7 (Fmoc 3), 127.6 (Fmoc 6), 127.1 (Fmoc 2), 127.1 (Fmoc 7), 125.2 (Fmoc 8), 125.1 (Fmoc 1), 119.9 (Fmoc 4,5), 76.5 (1,3-dithio qC), 66.8 (Fmoc 14), 57.1 (Leu1 α), 51.5 (Leu2 α), 47.4 (Fmoc 9), 40.3 (1,3-dithio CH_2), 39.6 (1,3-dithio CH_2), 42.8 (Leu1 β), 40.8 (Leu2 β), 25.4 (Leu1 γ), 25.1 (Leu2 γ), 23.7 (Leu1 δ′), 22.9 (Leu2 δ), 21.8 (Leu2 δ′), 21.3 (Leu1 δ). HR-MS: calcd, [MNa^+] ($C_{30}H_{38}N_2O_5S_2$-Na) = 593.2114; found, m/z = 593.2088 [MNa^+].

(2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-5-methylhexanoyl)amino]-4-phenylbutanoic Acid (6d). The α-keto amide (**5d**) (2.69 g, 4.493 mmol) was reacted as described above to yield *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-5-methylhexanoyl)amino]-4-phenylbutanoate (**6d**) as a pale yellow foam (2.70 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.83 (d, ^3J(H,H) = 7.7 Hz, 1H, homoPhe H^N), 7.75 (d, ^3J(H,H) = 7.6 Hz, 2H, Fmoc 4,5), 7.65 (d, ^3J(H,H) = 7.6 Hz, 1H, Fmoc 1), 7.62 (d, ^3J(H,H) = 7.6 Hz, 1H, Fmoc 8), 7.38 (t, 2H, ^3J(H,H) = 7.6 Hz, Fmoc 3,6), 7.30 (t, ^3J(H,H) = 7.6 Hz, 1H, Fmoc 2), 7.29 (t, ^3J(H,H) = 7.6 Hz, 1H, Fmoc 7), 7.29 (t, ^3J(H,H) = 7.5 Hz, 2H, m homoPhe), 7.21 (t, ^3J(H,H) = 7.5 Hz, 1H, p homoPhe), 7.19 (d, ^3J(H,H) = 7.5 Hz, 2H, o homoPhe), 5.93 (d, ^3J(H,H) = 10.0 Hz, 1H, H^N Leu), 4.60 (ddd, ^3J(H,H) = 5.3 Hz, ^3J(H,H) = 7.8 Hz, ^3J(H,H) = 7.7 Hz, 1H, homoPhe α), 4.53 (dd, ^3J(H,H) = 6.7 Hz, ^2J(H,H) = 10.8 Hz, 1H, Fmoc 14), 4.38 (dd, ^3J(H,H) = 7.5 Hz, ^2J(H,H) = 10.8 Hz, 1H, Fmoc 14′), 4.38 (m_c, Leu α), 4.25 (dd, ^3J(H,H) = 7.5 Hz, ^3J(H,H) = 6.7 Hz, 1H, Fmoc 9), 3.36−3.20 (m, 4H, 1,3-dithio CH_2), 2.72 (t, ^3J(H,H) = 8.0 Hz, 2H, homoPhe γ), 2.31 (m_c, 1H, homoPhe β), 2.12 (m_c, 1H, homoPhe β′), 1.65 (m_c, 1H, Leu γ), 1.42 (ddd, ^3J(H,H) = 3.6 Hz, ^3J(H,H) = 11.4 Hz, ^2J(H,H) = 14.4 Hz, 1H, Leu β), 1.29 (ddd, ^3J(H,H) = 2.2 Hz, ^3J(H,H) = 10.8 Hz, ^2J(H,H) = 13.6 Hz, 1H, Leu β′), 0.95 (d, ^3J(H,H) = 6.6 Hz, 3H, Leu δ), 0.89 (d, ^3J(H,H) = 6.7 Hz, 3H, Leu δ′); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.4 (homoPhe C═O), 171.3 (Leu C═O), 156.7 (Fmoc C═O), 144.2 (Fmoc 10), 143.8 (Fmoc 13), 141.3 (Fmoc 11), 141.3 (Fmoc 12), 140.2 (i homoPhe), 128.6 (m homoPhe), 128.4 (o homoPhe), 127.5 (Fmoc 3), 127.5 (Fmoc 6), 127.0 (Fmoc 2,7), 126.3 (p homoPhe), 125.2 (Fmoc 1), 125.1 (Fmoc 8), 119.8 (Fmoc 4,5), 75.9 (1,3-dithio qC), 66.6 (Fmoc 14), 57.6 (Leu α), 52.5 (homoPhe α), 47.3 (Fmoc 9), 42.7 (Leu β), 40.5 (1,3-dithio CH_2), 39.6 (1,3-dithio CH_2), 33.3 (homoPhe β), 31.5 (homoPhe γ), 25.4 (Leu γ), 23.7 (Leu δ′), 21.4 (Leu δ). HR-MS: calcd, [MNa^+] ($C_{34}H_{38}N_2O_5S_2Na$) = 641.2114; found, m/z = 641.2119 [MNa^+].

(2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-4-phenylbutanoyl)amino]-4-methylpentanoic Acid (6e). The α-keto amide (**5e**) (1.06 g, 1.813 mmol) was reacted as described above to yield *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-4-phenylbutanoyl)amino]-4-methylpentanoate (**6e**) as a pale yellow foam (1.07 g, 98%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, ^3J(H,H) = 7.8 Hz, 1H, Leu H^N), 7.74 (d, ^3J(H,H) = 8.4 Hz, 2H, Fmoc 4,5), 7.55 (d, ^3J(H,H) = 7.5 Hz, 1H, Fmoc 1), 7.47 (d, ^3J(H,H) = 7.5 Hz, 1H, Fmoc 8), 7.37 (dd, ^3J(H,H) = 8.4 Hz, ^3J(H,H) = 7.4 Hz, 2H, Fmoc 3,6), 7.28 (dd, ^3J(H,H) = 7.4 Hz, ^3J(H,H) = 7.5 Hz, 2H, Fmoc 2,7), 7.24 (d, ^3J(H,H) = 7.0 Hz, 2H, o Phe), 7.21 (t, ^3J(H,H) = 7.0 Hz, 2H, m Phe), 7.13 (t, ^3J(H,H) = 7.0 Hz, 1H, p Phe), 6.08 (d, ^3J(H,H) = 10.7 Hz, 1H, Phe H^N), 4.61 (m_c, 1H, Leu α), 4.61 (m_c, 1H, Phe α), 4.24 (dd, ^3J(H,H) = 7.2 Hz, ^2J(H,H) = 10.2 Hz, 1H, Fmoc 14), 4.18 (dd, ^3J(H,H) = 7.8 Hz, ^2J(H,H) = 10.2 Hz, 1H, Fmoc 14′),

4.08 (dd, ^3J(H,H) = 7.0 Hz, ^3J(H,H) = 7.3 Hz, 1H, Fmoc 9), 3.40 (m_c, 2H, 1,3-dithio CH_2), 3.35 (ddd, ^2J(H,H) = 11.6 Hz, ^3J(H,H) = 5.5 Hz, ^3J(H,H) = 5.3 Hz, 1H, 1,3-dithio CH_2), 3.27 (ddd, ^2J(H,H) = 11.6 Hz, ^3J(H,H) = 5.9 Hz, ^3J(H,H) = 5.8 Hz, 1H, 1,3-dithio CH_2), 3.07 (dd, ^2J(H,H) = 13.7 Hz, ^3J(H,H) = 3.2 Hz, 1H, Phe β), 2.67 (dd, ^2J(H,H) = 13.7 Hz, ^3J(H,H) = 10.8 Hz, 1H, Phe β'), 1.81 (m_c, 1H, Leu β), 1.73 (m_c, 1H, Leu γ), 1.70 (m_c, 1H, Leu β'), 1.01 (d, ^3J(H,H) = 6.2 Hz, 3H, Leu δ), 0.99 (d, ^3J(H,H) = 6.1 Hz, 3H, Leu δ');^{13}C NMR (150 MHz, $CDCl_3$): δ = 176.0 (Leu C═O), 171.4 (Phe C═O), 156.3 (Fmoc C═O), 144.1 (Fmoc 10), 144.0 (Fmoc 13), 141.2 (Fmoc 11,12), 137.6 (i Phe), 129.3 (o Phe), 128.3 (m Phe), 127.5 (Fmoc 3,6), 127.0 (Fmoc 2,7), 126.6 (p Phe), 125.2 (Fmoc 1,8), 119.8 (Fmoc 4,5), 75.2 (1,3-dithio qC), 66.8 (Fmoc 14), 60.8 (Phe α), 51.5 (Leu α), 47.2 (Fmoc 9), 40.8 (1,3-dithio CH_2), 40.8 (Leu β), 39.7 (Phe β), 39.6 (1,3-dithio CH_2), 25.2 (Leu γ), 22.9 (Leu δ), 21.8 (Leu δ'). HR-MS: calcd, [MNa^+] ($C_{33}H_{36}N_2O_5S_2Na$) = 627.1958; found, *m*/*z* = 627.1960 [MNa^+].

(2*S*)-2-[((3*S*)-3[(9*H*-9-Fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-4-phenylbutanoyl)amino]-4-phenylbutanoic Acid (6f). The α-keto amide (**5f**) (1.22 g, 1.928 mmol) was reacted as described above to yield *tert*-butyl (2*S*)-2-[((3*S*)-3[(9*H*-9-fluorenylmethoxycarbonyl)amino]-2-(1,3-dithiolane)-4-phenylbutanoyl)amino]-4-phenylbutanoate (**6f**) as a pale yellow foam (1.21 g, 96%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.86 (d, ^3J(H,H) = 7.8 Hz, 1H, homoPhe H^N), 7.73 (d, ^3J(H,H) = 7.8 Hz, 2H, Fmoc 4,5), 7.55 (d, ^3J(H,H) = 7.8 Hz, 1H, Fmoc 1), 7.47 (d, ^3J(H,H) = 7.8 Hz, 1H, Fmoc 8), 7.37 (t, ^3J(H,H) = 7.8 Hz, 2H, Fmoc 3,6), 7.29 (t, ^3J(H,H) = 7.8 Hz, 2H, m homoPhe), 7.27 (t, ^3J(H,H) = 7.8 Hz, 2H, Fmoc 2,7), 7.23 (d, ^3J(H,H) = 7.1 Hz, 2H, o Phe), 7.21_3 (m_c, 2H, o homoPhe), 7.20_5 (m_c, 1H, p homoPhe), 7.20 (t, ^3J(H,H) = 7.1 Hz, 2H, m Phe), 7.12 (t, ^3J(H,H) = 7.1 Hz, 1H, p Phe), 6.09 (d, 1H, ^3J(H,H) = 10.6 Hz, Phe H^N), 4.63 (m_c, 1H, homoPhe α), 4.60 (m_c, 1H, Phe α), 4.24 (dd, ^2J(H,H) = 10.8 Hz, ^3J(H,H) = 7.1 Hz, 1H, Fmoc 14), 4.19 (dd, ^2J(H,H) = 10.8 Hz, ^3J(H,H) = 7.4 Hz, 1H, Fmoc 14′), 4.08 (dd, ^3J(H,H) = 7.1 Hz, ^3J(H,H) = 7.4 Hz, 1H, Fmoc 9), 3.41−3.23 (m, 4H, 1,3-dithio CH_2), 3.10 (m_c, 1H, Phe β), 2.74 (m_c, 2H, homoPhe γ), 2.68 (dd, ^2J(H,H) = 13.6 Hz, ^3J(H,H) = 10.9 Hz, 1H, Phe β'), 2.34 (m_c, 1H, homoPhe β), 2.16 (m_c, 1H, homoPhe β'); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.1 (homoPhe C═O), 171.4 (Phe C═O), 156.3 (Fmoc C═O), 144.1 (Fmoc 10), 144.0 (Fmoc 13), 141.2 (Fmoc 11,12), 140.2 (i homoPhe), 137.5 (i Phe), 129.3 (o Phe), 128.7 (m homoPhe), 128.4 (m Phe), 128.3 (o homoPhe), 127.5 (Fmoc 3,6), 127.0 (Fmoc 2), 127.0 (Fmoc 7), 126.6 (p Phe), 126.4 (p homoPhe), 125.2 (Fmoc 1,8), 119.8 (Fmoc 4,5), 75.1 (1,3-dithio qC), 66.9 (Fmoc 14), 60.9 (Phe α), 52.7 (homoPhe α), 47.2 (Fmoc 9), 40.8 (1,3-dithio CH_2), 39.7 (Phe β), 33.3 (homoPhe β), 31.6 (homoPhe γ). HR-MS: calcd, [MNa^+] ($C_{37}H_{36}N_2O_5S_2Na$) = 675.1957; found, *m*/*z* = 675.1939 [MNa^+].

H-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$ (7). SPOCC-1500 resin (1.93 g, 0.772 mmol) was treated with a solution of MSNT (0.69 g, 2.316 mmol), Boc-Gly-Gly−OH (0.54 g, 2.316 mmol), and MeIm (138 μL, 1.737 mmol) in CH_2Cl_2 (10 mL) for 2 h. After the resin was washed with dry CH_2Cl_2, the coupling procedure was repeated. Boc cleavage was effected with 95% TFA in water (15 min), and the resin was washed again with CH_2Cl_2 and DMF. The HMBA linker (0.35 g, 2.316 mmol) was coupled onto the resin using TBTU (0.71 g, 2.223 mmol) as condensing agent and NEM (391 μL, 3.088 mmol) in DMF (5 mL). The resin was washed with DMF, followed by CH_2Cl_2, and lyophilized. Fmoc-Gly−OH (0.69 g, 2.316 mmol) was esterified onto the resin using MSNT (0.69 g, 2.316 mmol) and MeIm (138 μL, 1.737 mmol) in CH_2Cl_2 (10 mL). After the resin was washed with dry CH_2Cl_2, the esterification procedure was repeated. Fmoc cleavage was effected with 20% piperidine in DMF (1 × 2 min, 1 × 18 min). The unprotected amine was acylated with 3 equiv of the Fmoc-protected pentafluorophenyl esters of the N^α-protected amino acids of Val and Ala using Dhbt (0.13 g, 0.772 mmol) in DMF (5 mL). Each acylation step was followed by the deprotection procedure as described. Finally, the resin was washed with DMF and CH_2Cl_2 and dried in vacuo. Fmoc cleavage as described in the general procedure section revealed a loading of 0.45 mmol/g. A sample of the resin was subjected to ^{1}H HR-MAS NMR analysis. ^{1}H NMR (600 MHz, DMSO): δ = 8.82 (m_c, 1H, Gly H^N), 8.49 (m_c, 1H, Val H^N), 7.88 (d, ^3J(H,H) = 6.6 Hz, 2H, HMBA 2,6), 7.44 (d, ^3J(H,H) = 6.6 Hz, 2H, HMBA 3,5), 5.18 (s, 2H, HMBA 7), 4.20 (m_c, 1H, Val α), 4.0 (m_c, 1H, Gly α), 3.87 (m_c, 1H, Gly α), 3.30 (q, ^3J(H,H) = 6.2 Hz, 1H, Ala α), 1.99 (m_c, 1H, Val β), 1.13 (d, ^3J(H,H) = 6.2 Hz, 3H, Ala β), 0.85 (d, ^3J(H,H) = 6.2 Hz, 3H, Val γ), 0.81 (d, ^3J(H,H) = 6.7 Hz, 3H, Val γ').

General Procedure for Coupling of 1,3-Dithiolane Dipeptides onto the Resin (7). The Fmoc-protected 1,3-dithiolane dipeptide derivatives (**6a**−**f**) (3.0 equiv) were dissolved in Eppendorf reaction vessels in DMF (500 μL) and activated with HATU (2.85 equiv), HOAt (1.0 equiv), and NEM (3.0 equiv). Each solution was then added to lyophilised resin **7** (50 mg, ∼23 μmol swollen in 200 μL of DMF) and left at ambient temperature for 2 h. The resin samples were washed with dry DMF, and the coupling was repeated for another 2 h prior to washing with DMF and CH_2Cl_2 and drying in vacuo. A sample of each resin was analyzed by ^{1}H HR-MAS NMR. Conversions were above 95% for all samples.

2-[1-(Fmoc-amino)-ethyl]-2-(carboxyl-Leu-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$)-1,3-dithiolane (8a). ^{1}H NMR (600 MHz, DMSO): δ = 8.24 (m_c, 1H, Val H^N), 8.16 (m_c, 1H, Gly H^N), 8.05 (d, ^3J(H,H) = 7.2 Hz, 1H, Ala H^N), 7.89 (d, ^3J(H,H) = 6.9 Hz, 2H, HMBA 2,6), 7.86 (d, ^3J(H,H) = 5.9 Hz, 2H, Fmoc 4,5), 7.73 (m_c, 1H, Leu H^N), 7.71 (d, ^3J(H,H) = 5.9 Hz, 1H, Fmoc 1), 7.69 (d, ^3J(H,H) = 5.9 Hz, 1H, Fmoc 8), 7.45 (d, ^3J(H,H) = 6.9 Hz, 2H, HMBA 3,5), 7.40 (t, ^3J(H,H) = 5.9 Hz, 2H, Fmoc 3,6), 7.31 (t, ^3J(H,H) = 5.9 Hz, 2H, Fmoc 2,7), 7.03 (m_c, 1H, Fmoc-amino H^N), 5.18 (s, 2H, HMBA 7), 4.46 (m_c, 1H, Leu α), 4.37 (m_c, 1H, (Fmoc-amino)-ethyl H(1)), 4.35 (m_c, 1H, Ala α), 4.31 (m_c, 1H, Fmoc 14), 4.20 (m_c, 3H, Val α, Fmoc 9,14′), 3.95 (m_c, 1H, Gly α), 3.87 (m_c, 1H, Gly α), 3.30−3.060 (m, 4H, 1,3-dithiolane CH_2), 1.970 (m_c, 1H, Val β), 1.55 (m, 2H, Leu β, Leu γ), 1.48 (mc, 1H, Leu β'), 1.19 (d, ^3J(H,H) = 6.3 Hz,

3H, Ala β), 1.07 (d, ^3J(H,H) = 5.3 Hz, 3H, (Fmoc-amino)-ethyl H(2)), 0.89−0.79 (m, 12H, Val γ, Leu δ).

2-[1-(Fmoc-amino)-ethyl]-2-(carboxyl-homoPhe-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$)-1,3-dithiolane (8b). ^{1}H NMR (600 MHz, DMSO): δ = 8.33 (m_c, 1H, homoPhe H^N), 8.23 (m_c, 1H, Gly H^N), 8.15 (m_c, 1H, Val H^N), 7.89 (d, ^3J(H,H) = 7.4 Hz, 2H, HMBA 2,6), 7.86 (m_c, 2H, Fmoc 4,5), 7.70 (m_c, 2H, Fmoc 1,8), 7.66 (d, ^3J(H,H) = 7.2 Hz, 1H, Ala H^N), 7.45 (d, ^3J(H,H) = 7.4 Hz, 2H, HMBA 3,5), 7.40 (m_c, 2H, Fmoc 3,6), 7.31 (m_c, 2H, Fmoc 2,7), 7.25 (m_c, 1H, p homoPhe), 7.23 (m_c, 2H, m homoPhe), 7.14 (d, ^3J(H,H) = 7.4 Hz, 2H, o homoPhe), 7.08 (m_c, 1H, Fmoc-amino H^N), 5.17 (s, 2H, HMBA 7), 4.48 (m_c, 1H, (Fmoc-amino)-ethyl H(1)), 4.41 (m_c, 1H, Ala α), 4.38 (m_c, 1H, homoPhe α), 4.26 (m_c, 1H, Fmoc 9), 4.20 (m_c, 2H, Fmoc 14), 4.17 (m_c, 1H, Val α), 3.98 (m_c, 1H, Gly α), 3.88 (m_c, 1H, Gly α), 3.30−3.10 (m, 4H, 1,3-dithiolane CH_2), 2.52 (m_c, 2H, homoPhe γ), 1.97 (m_c, 1H, Val β), 1.94 (m_c, 2H, homoPhe β), 1.19 (d, ^3J(H,H) = 7.4 Hz, 3H, Ala β), 1.10 (d, ^3J(H,H) = 6.6 Hz, 3H, (Fmoc-amino)-ethyl H(2)), 0.87 (d, ^3J(H,H) = 6.2 Hz, 3H, Val γ), 0.82 (d, ^3J(H,H) = 7.4 Hz, 3H, Val γ').

2-[(1-Fmoc-amino)-3-methyl-butyl]-2-(carboxyl-Leu-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$)-1,3-dithiolane (8c). ^{1}H NMR (600 MHz, DMSO): δ = 8.258 (m_c, 1H, Val H^N), 8.148 (m_c, 1H, Gly H^N), 8.024, (d, ^3J(H,H) = 8.11 Hz, 1H, Ala H^N), 7.883 (d, ^3J(H,H) = 7.26 Hz, 2H, HMBA 2,6), 7.850 (d, ^3J(H,H) = 6.51 Hz, 2H, Fmoc 4,5), 7.750 (d, ^3J(H,H) = 7.25 Hz, 1H, Leu H^N), 7.703 (d, ^3J(H,H) = 6.52 Hz, 1H, Fmoc 1), 7.692 (d, ^3J(H,H) = 7.02 Hz, 1H, Fmoc 8), 7.445 (d, ^3J(H,H) = 6.70 Hz, 2H, HMBA 3,5), 7.394 (t, ^3J(H,H) = 6.52 Hz, 2H, Fmoc 3,6), 7.300 (t, ^3J(H,H) = 7.51 Hz, 2H, Fmoc 2,7), 6.880 (m_c, 1H, Fmoc-amino H^N), 5.175 (s, 2H, HMBA 7), 4.419 (m_c, 1H, Leu α), 4.355 (m_c, 1H, (1-Fmoc-amino)-3-methyl-butyl H(1)), 4.319 (m_c, 1H, Ala α), 4.257 (m_c, 2H, Fmoc 14), 4.195 (m_c, 2H, Val α, Fmoc 9), 3.975 (m_c, 1H, Gly α), 3.883 (m_c, 1H, Gly α'), 3.270−3.058 (m, 4H, 1,3-dithio CH_2), 1.966 (m_c, 1H, Val β), 1.549 (m, 3H, Leu β, Leu γ), 1.461 (m_c, 1H, (1-Fmoc-amino)-3-methyl-butyl H(3)), 1.346 (m_c, 1H, (1-Fmoc-amino)-3-methyl-butyl H(2)), 1.198 (m_c, 1H, (1-Fmoc-amino)-3-methyl-butyl H(2)'), 1.192 (d, ^3J(H,H) = 7.02 Hz, 3H, Ala β), 0.890−0.756 (m, 18H, Val γ, (1-Fmoc-amino)-3-methyl-butyl CH_3, Leu δ).

2-[1-(Fmoc-amino)-3-methyl-butyl]-2-(carboxyl-homo-Phe-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$)-1,3-dithiolane (8d). ^{1}H NMR (600 MHz, DMSO): δ = 8.35 (m_c, 1H, homoPhe H^N), 8.24 (m_c, 1H, Val H^N), 8.16 (m_c, 1H, Gly H^N), 8.05 (d, 1H, Ala H^N), 7.89 (d, ^3J(H,H) = 7.4 Hz, 2H, HMBA 2,6), 7.86 (m_c, 2H, Fmoc 4,5), 7.70 (d, ^3J(H,H) = 6.5 Hz, 1H, Fmoc 1), 7.67 (d, ^3J(H,H) = 6.5 Hz, 1H, Fmoc 8), 7.45 (d, ^3J(H,H) = 7.4 Hz, 2H, HMBA 3,5), 7.39 (m_c, 2H, Fmoc 3.6), 7.30 (t, ^3J(H,H) = 6.5 Hz, 2H, Fmoc 2.7), 7.29 (m_c, 1H, p homoPhe), 7.24 (m_c, 2H, m homoPhe), 7.13 (d, ^3J(H,H) = 7.4 Hz, 2H, o homoPhe), 6.94 (m_c, 1H, Fmoc-amino H^N), 5.17 (s, 2H, HMBA 7), 4.44 (m_c, 1H, (1-Fmoc-amino)-3-methyl-butyl H(1)), 4.40 (m_c, 1H, Ala α), 4.35 (m_c, 1H, homoPhe α), 4.26 (m_c, 1H, Fmoc 14), 4.21 (m_c, 2H, Fmoc 9,14), 4.19 (m_c, 1H, Val α), 3.97 (m_c, 1H, Gly α), 3.88 (m_c, 1H, Gly α'), 3.30−3.11 (m, 4H, 1,3-dithiolane CH_2), 2.52 (m_c, 2H, homoPhe γ), 1.97 (m_c, 1H, Val β), 1.95 (m_c, 2H, homoPhe β), 1.54 (m_c, 1H, (1-Fmoc-amino)-3-methyl-butyl H(3)), 1.41 (m_c, 1H, (1-Fmoc-amino)-3-methyl-butyl H(2)), 1.23 (m_c, 1H, (1-Fmoc-amino)-3-methyl-butyl H(2)'), 1.21 (d, ^3J(H,H) = 6.8 Hz, 3H, Ala β), 0.90−0.74 (m 12H, Val γ, (1-Fmoc-amino)-3-methyl-butyl CH_3).

2-[1-(Fmoc-amino)-2-phenyl-ethyl]-2-(carboxyl-Leu-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$)-1,3-dithiolane (8e). ^{1}H NMR (600 MHz, DMSO): δ = 8.29 (m_c, 1H, Val H^N), 8.16 (m_c, 1H, Gly H^N), 8.11, (d, 1H, Ala H^N), 7.88 (d, ^3J(H,H) = 7.1 Hz, 2H, HMBA 2,6), 7.84 (d, ^3J(H,H) = 6.1 Hz, 2H, Fmoc 4,5), 7.72 (d, 1H, Leu H^N), 7.64 (d, ^3J(H,H) = 7.0 Hz, 1H, Fmoc 1), 7.63 (d, ^3J(H,H) = 6.5 Hz, 1H, Fmoc 8), 7.44 (d, ^3J(H,H) = 7.1 Hz, 2H, HMBA 3,5), 7.39 (dd, ^3J(H,H) = 6.1 Hz, ^3J(H,H) = 6.5 Hz, 2H, Fmoc 3,6), 7.30 (dd, ^3J(H,H) = 7.0 Hz, ^3J(H,H) = 6.5 Hz, 1H, Fmoc 2), 7.30 (t, ^3J(H,H) = 6.5 Hz, 1H, Fmoc 7), 7.25 (m_c, 2H, o 2-phenyl-ethyl), 7.18 (m_c, 2H, m 2-phenyl-ethyl), 7.15 (m_c, 1H, p 2-phenyl-ethyl), 7.09 (m_c, 1H, Fmoc-amino H^N), 5.18 (s, 2H, HMBA 7), 4.60 (m_c, 1H, Leu α), 4.46 (m_c, 1H, 1-(Fmoc-amino)-2-phenyl-ethyl H(1)), 4.37 (m_c, 1H, Ala α), 4.36 (m_c, 1H, Fmoc 9), 4.18 (m_c, 2H, Val α, Fmoc 14), 4.06 (m_c, 1H, Fmoc 14'), 3.96 (m_c, 1H, Gly α), 3.89 (m_c, 1H, Gly α'), 3.30−3.10 (m, 4H, 1,3-dithio CH_2), 3.08 (m_c, 1H, 1-(Fmoc-amino)-2-phenyl-ethyl H(2)), 2.62 (m_c, 1H, 1-(Fmoc-amino)-2-phenyl-ethyl H(2)'), 1.97 (m_c, 1H, Val β), 1.60 (m, 2H, Leu β, Leu γ), 1.50 (m_c, 1H, Leu β'), 1.20 (d, ^3J(H,H) = 6.4 Hz, 3H, Ala β), 0.90−0.75 (m, 12H, Val γ, Leu δ).

2-[1-(Fmoc-amino)-2-phenyl-ethyl]-2-(carboxyl-homoPhe-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$)-1,3-dithiolane (8f). ^{1}H NMR (600 MHz, DMSO): δ = 8.35 (m_c, 1H, homoPhe H^N), 8.28 (m_c, 1H, Val H^N), 8.10 (m_c, 1H, Gly H^N), 7.88 (d, ^3J(H,H) = 6.9 Hz, 2H, HMBA 2,6), 7.82 (m_c, 2H, Fmoc 4,5), 7.75 (m_c, 1H, Ala H^N), 7.60 (m_c, 2H, Fmoc 1,8), 7.44 (d, ^3J(H,H) = 6.9 Hz, 2H, HMBA 3,5), 7.38 (m_c, 2H, Fmoc 3,6), 7.29 (m_c, 2H, Fmoc 2,7), 7.27−7.10 (m, 10H, aryl homoPhe, 2-phenyl-ethyl), 7.09 (m_c, 1H, Fmoc-amino H^N), 5.16 (s, 2H, HMBA 7), 4.62 (m_c, 1H, 1-(Fmoc-amino)-2-phenyl-ethyl H(1)), 4.44 (m_c, 1H, Ala α), 4.41 (m_c, 1H, homoPhe α), 4.21 (m_c, 1H, Fmoc 9), 4.18 (m_c, 2H, Val α, Fmoc 14), 4.04 (m_c, 1H, Fmoc 14'), 3.94 (m_c, 2H, Gly α), 3.30−3.11 (m, 4H, 1,3-dithiolane CH_2), 3.08 (m_c, 1H, 1-(Fmoc-amino)-2-phenyl-ethyl H(2)), 2.74 (m_c, 1H, homoPhe γ), 2.65 (m_c, 1H, 1-(Fmoc-amino)-2-phenyl-ethyl H(2)'), 2.57 (m_c, 1H, homoPhe γ'), 2.04 (m_c, 2H, homoPhe β), 1.96 (m_c, 1H, Val β), 1.23 (d, ^3J(H,H) = 6.3 Hz, 3H, Ala β), 0.86 (m_c, 3H, Val γ), 0.83 (m_c, 3H, Val γ').

Ac-Gln-X-(1,3-dithiolane)-Y-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$ (9a−f). Fmoc cleavage from resins (**8a−f**) was effected with 20% piperidine in DMF (1 × 2 min, 1 × 18 min). The unprotected amines were acylated with Fmoc-protected pentafluorophenyl esters of Gln(25.4 mg, 69 μmol) using Dhbt (3.8 mg, 23 μmol) in DMF (500 μL). Each acylation step was followed by a Fmoc deprotection procedure, as described. The peptides were finally acetylated with 10% acetic anhydride and 20% DIPEA in DMF (2 × 15 min). The resin was washed with DMF and CH_2Cl_2 and

lyophilised. A sample of each resin was subjected to HPLC and MS analysis.

2-[1-(Ac-Gln-amino)-ethyl]-2-(carboxyl-Leu-Ala-Val-Gly-OH)-1,3-dithiolane (10a). HPLC: t_R = 10.1 min. ESI-MS: calcd [MNa^+] ($C_{29}H_{49}N_7O_9S_2Na$), 726.3 Da; found [MNa^+], *m*/*z* 726.4.

2-[1-(Ac-Gln-amino)-ethyl]-2-(carboxyl-homoPhe-Ala-Val-Gly-OH)-1,3-dithiolane (10b). HPLC: t_R = 10.6 min. ESI-MS: calcd [MK^+] ($C_{33}H_{49}N_7O_9S_2K$), 791.0 Da; found [MK^+], *m*/*z* 791.2.

2-[1-(Ac-Gln-amino)-3-methyl-butyl]-2-(carboxyl-Leu-Ala-Val-Gly-OH)-1,3-dithiolane (10c). HPLC: t_R = 10.8 min. ESI-MS: calcd [MK^+] ($C_{32}H_{55}N_7O_9S_2K$), 784.3 Da; found [MK^+], *m*/*z* 784.3.

2-[1-(Ac-Gln-amino)-3-methyl-butyl]-2-(carboxyl-homo-Phe-Ala-Val-Gly-OH)-1,3-dithiolane (10d). HPLC: t_R = 11.1 min. ESI-MS: calcd [MNa^+] ($C_{36}H_{55}N_7O_9S_2Na$), 817.3 Da; found [MNa^+], *m*/*z* 817.3.

2-[1-(Ac-Gln-amino)-2-phenyl-ethyl]-2-(carboxyl-Leu-Ala-Val-Gly-OH)-1,3-dithiolane (10e). HPLC: t_R = 10.2 min. ESI-MS: calcd [MNa^+] ($C_{35}H_{53}N_7O_9S_2Na$), 802.3 Da; found [MNa^+], *m*/*z* 802.2.

2-[1-(Ac-Gln-amino)-2-phenyl-ethyl]-2-(carboxyl-homo-Phe-Ala-Val-Gly-OH)-1,3-dithiolane (10f). HPLC: t_R = 11.0 min. ESI-MS: calcd [MNa^+] ($C_{39}H_{53}N_7O_9S_2Na$), 850.3 Da; found [MNa^+], *m*/*z* 850.3.

Cleavage of the 1,3-Dithiolane Protection Group. The resin samples (**9a**−**f**) were treated with *N*-bromosuccinamide (NBS) (16.4 mg, 92 μmol) in 10% aqueous acetone (500 μL) for 2 h. The resins were drained, and the deprotection procedure was repeated for another 2 h. The resins were washed with acetonitrile, DMF, and CH_2Cl_2 and dried in vacuo. The resin-bound α-keto amide peptides (**11a**−**f**) were analyzed by complete ^{1}H and ^{13}C NMR spectral assignment using HR-MAS NMR.

Ac-Gln-Ala-CO-Leu-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$ (11a). ^{1}H NMR (600 MHz, DMSO): δ = 8.27 (m_c, 1H, Gly H^N), 8.23 (m_c, 1H, Ala(CO) H^N), 8.15(m_c, 1H, Leu H^N), 8.15(m_c, 1H, Ala H^N), 7.87 (m_c, 2H, HMBA 2,6), 7.85(m_c, 1H, Gln H^N), 7.54(m_c, 1H, Val H^N), 7.44 (m_c, 2H, HMBA 3,5), 7.22 (s, 1H, Gln $H^N\delta$), 5.18 (s, 2H, HMBA 7), 4.96(m_c, 1H, Ala(CO) α), 4.35(m_c, 1H, Ala α), 4.35 (m_c, 1H, Leu α), 4.28(m_c, 1H, Gln α), 4.18(m_c, 1H, Val α), 3.97 (m_c, 1H, Gly α), 3.88(m_c, 1H, Gly α′), 2.13 (m, 2H, Gln γ), 1.99(m_c, 1H, Val β), 1.89 (m_c, 1H, Gln β), 1.86(s, 3H, Ac), 1.71 (m_c, 1H, Gln β′), 1.64 (m_c, 1H, Leu β), 1.55 (m_c, 1H, Leu γ), 1.49(m_c, 1H, Leu β′), 1.27(d, 3H, Ala(CO) β), 1.22-(d, 3H, Ala β), 0.85(m, 6H, Leu δ), 0.84 (m_c, 6H, Val γ); ^{13}C NMR (150 MHz, DMSO): δ = 196.3 (α-keto C═O), 174.0 (Gln C═O δ), 171.9 (Leu C═O), 171.7 (Ala C═O), 171.5 (Gln C═O), 170.1 (Val C═O), 169.4 (Ac C═O), 169.26 (Gly C═O), 166.4 (HMBA C═O), 160.5 (Ala(CO) C═O amide), 139.1 (HMBA 4), 133.5 (HMBA 1), 127.3 (HMBA 2,6), 127.3 (HMBA 3,5), 65.2 (HMBA 7), 57.8 (Val α), 51.8 (Gln α), 51.2 (Leu α), 49.5 (Ala(CO) α), 48.3 (Ala α), 42.2 (Gly α), 40.9 (Leu β), 31.2 (Gln γ), 30.4 (Gln β), 27.8 (Val β), 24.2 (Leu γ), 22.6 (Leu δ), 22.3 (Ac CH_3), 21.5 (Leu δ′), 18.8 (Val γ), 17.6 (Ala β), 15.4 (Ala(CO) β).

Ac-Gln-Ala-CO-homoPhe-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$ (11b). ^{1}H NMR (600 MHz, DMSO): δ = 8.49 (m_c, 1H, homoPhe H^N), 8.26 (m_c, 1H, Ala(CO) H^N), 8.25 (m_c, 1H, Gly H^N), 8.14 (m_c, 1H, Ala H^N), 7.87 (m_c, 2H, HMBA 2,6), 7.84 (m_c, 1H, Gln H^N), 7.66 (m_c, 1H, Val H^N), 7.42 (m_c, 2H, HMBA 3,5), 7.24 (m_c, 2H, m homoPhe), 7.17 (m_c, 1H, p homoPhe), 7.15 (m_c, 2H, o homoPhe), 6.60 (s, 1H, Gln $H^N\delta$), 5.17 (s, 2H, HMBA 7), 4.96 (m_c, 1H, Ala-(CO) α), 4.38 (m_c, 1H, Ala α), 4.31 (m_c, 1H, homoPhe α), 4.27 (m_c, 1H, Gln α), 4.17 (m_c, 1H, Val α), 3.96 (m_c, 1H, Gly α), 3.87 (m_c, 1H, Gly α′), 2.59 (m_c, 1H, homoPhe γ), 2.53 (m_c, 1H, homoPhe γ′), 2.13 (m, 2H, Gln γ), 2.01 (m_c, 1H, homoPhe β), 1.98 (m_c, 1H, Val β), 1.97 (m_c, 1H, homoPhe β′), 1.89 (m_c, 1H, Gln β), 1.85 (s, 3H, Ac), 1.71 (m_c, 1H, Gln β′), 1.26 (d, 3H, Ala(CO) β), 1.22 (d, 3H, Ala β), 0.82 (m_c, 6H, Val γ); ^{13}C NMR (150 MHz, DMSO): δ = 196.4 (α-keto C═O), 174.2 (Gln C═O δ), 172.1 (homoPhe C═O), 172.0 (Ala C═O), 171.5 (Gln C═O), 170.4 (Val C═O), 169.7 (Ac C═O), 169.5 (Gly C═O), 166.5 (HMBA C═O), 160.8 (Ala(CO) C═O amide), 141.3 (i homoPhe), 139.3 (HMBA 4), 133.7 (HMBA 1), 128.3 (m homoPhe), 128.3 (m homoPhe), 127.5 (HMBA 2,6), 127.5 (HMBA 3,5), 125.9 (p homoPhe), 66.2 (HMBA 7), 57.6 (Val α), 52.5 (homoPhe α), 51.9 (Gln α), 49.6 (Ala(CO) α), 48.5 (Ala α), 42.4 (Gly α), 33.5 (homoPhe β), 31.3 (homoPhe γ), 31.4 (Gln γ), 30.7 (Gln β), 28.1 (Val β), 22.4 (Ac CH_3), 19.1 (Val γ), 17.8 (Ala β), 15.5 (Ala(CO) β).

Ac-Gln-Leu-CO-Leu-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$ (11c). ^{1}H NMR (600 MHz, DMSO): δ = 8.43 (m_c, 1H, Leu H^N), 8.26 (m_c, 1H, Gly H^N), 8.13 (m_c, 1H, Ala H^N), 8.11 (m_c, 1H, Leu(CO) H^N), 7.87 (m_c, 2H, HMBA 2,6), 7.84 (m_c, 1H, Gln H^N), 7.51 (m_c, 1H, Val H^N), 7.43 (m_c, 2H, HMBA 3,5), 7.17 (s, 1H, Gln $H^N\delta$), 6.59 (s, 1H, Gln $H^N\delta'$), 5.17 (s, 2H, HMBA 7), 5.04 (m_c, 1H, Leu(CO) α), 4.33 (m_c, 1H, Ala α), 4.37 (m_c, 1H, Leu α), 4.27 (m_c, 1H, Gln α), 4.16 (m_c, 1H, Val α), 3.96 (m_c, 1H, Gly α), 3.87 (m_c, 1H, Gly α′), 2.13 (m, 2H, Gln γ), 1.98 (m_c, 1H, Val β), 1.89 (m_c, 1H, Gln β), 1.85 (s, 3H, Ac), 1.70 (m_c, 1H, Gln β′), 1.66 (m_c, 1H, Leu(CO) γ), 1.59 (m_c, 1H, Leu β), 1.53 (m_c, 1H, Leu γ), 1.51 (m_c, 1H, Leu β′), 1.47 (m_c, 1H, Leu(CO) β), 1.41 (m_c, 1H, Leu(CO) β′), 1.21 (m_c, 3H, Ala β), 0.86 (m, 6H, Leu(CO) δ), 0.84 (m, 6H, Leu δ), 0.83 (m_c, 6H, Val γ); ^{13}C NMR (150 MHz, DMSO): δ = 196.8 (α-keto C═O), 174.3 (Gln C═O δ), 172.0 (Leu C═O), 171.8 (Ala C═O), 171.5 (Gln C═O), 171.0 (Val C═O), 169.7 (Ac C═O), 169.5 (Gly C═O), 166.6 (HMBA C═O), 160.9 (Leu-(CO) C═O amide), 139.3 (HMBA 4), 133.6 (HMBA 1), 127.6 (HMBA 2,6), 127.5 (HMBA 3,5), 66.2 (HMBA 7), 57.6 (Val α), 52.5 (Leu(CO) α), 52.5 (Gln α), 51.3 (Leu α), 48.5 (Ala α), 42.4 (Gly α), 40.8 (Leu β), 38.5 (Leu(CO) β), 31.5 (Gln γ), 30.7 (Gln β), 28.0 (Val β), 24.7 (Leu(CO) γ), 24.4 (Leu γ), 23.0 (Leu(CO) δ), 22.9 (Leu δ), 22.4 (Ac CH_3), 21.5 (Leu δ′), 21.3 (Leu(CO) δ′), 19.1 (Val γ), 17.8 (Ala β).

Ac-Gln-Leu-CO-homoPhe-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$ (11d). ^{1}H NMR (600 MHz, DMSO): δ = 8.49 (m_c, 1H, homoPhe H^N), 8.25 (m_c, 1H, Gly H^N), 8.17 (m_c, 1H, Ala H^N), 8.13 (m_c, 1H, Leu(CO) H^N), 7.87 (m_c, 2H, HMBA 2,6), 7.84 (m_c, 1H, Gln H^N), 7.66 (m_c, 1H, Val

H^N), 7.42 (m_c, 2H, HMBA 3,5), 7.23 (m_c, 2H, m homoPhe), 7.16 (m_c, 1H, p homoPhe), 7.14 (m_c, 2H, o homoPhe), 6.60 (s, 1H, Gln $H^N\delta$), 5.17 (s, 2H, HMBA 7), 5.05 (m_c, 1H, Leu-(CO) α), 4.36 (m_c, 1H, Ala α), 4.34 (m_c, 1H, homoPhe α), 4.29 (m_c, 1H, Gln α), 4.18 (m_c, 1H, Val α), 3.96 (m_c, 1H, Gly α), 3.85 (m_c, 1H, Gly α′), 2.59 (m_c, 1H, homoPhe γ), 2.52 (m_c, 1H, homoPhe γ′), 2.13 (m, 2H, Gln γ), 2.02 (m_c, 1H, homoPhe β), 1.98 (m_c, 1H, Val β), 1.95 (m_c, 1H, homoPhe β′), 1.90 (m_c, 1H, Gln β), 1.85 (s, 3H, Ac), 1.71 (m_c, 1H, Gln β′), 1.67 (m_c, 1H, Leu(CO) γ), 1.52 (m_c, 1H, Leu(CO) β), 1.43 (m_c, 1H, Leu(CO) β′), 1.22 (m_c, 3H, Ala β), 0.88 (m_c, 6H, Leu(CO) δ), 0.83 (m_c, 6H, Val γ); ^{13}C NMR (150 MHz, DMSO): δ = 196.7 (α-keto C═O), 174.3 (Gln C═O δ), 172.0 (homoPhe C═O), 171.8 (Ala C═O), 171.5 (Gln C═O), 170.4 (Val C═O), 169.7 (Ac C═O), 169.5 (Gly C═O), 166.6 (HMBA C═O), 160.8 (Leu(CO) C═O amide), 141.2 (i homoPhe), 139.3 (HMBA 4), 133.6 (HMBA 1), 128.3 (m homoPhe), 128.3 (o homoPhe), 127.5 (HMBA 2,6), 127.5 (HMBA 3,5), 125.9 (p homoPhe), 66.2 (HMBA 7), 57.6 (Val α), 52.6 (homoPhe α), 52.4 (Leu(CO) α), 52.0 (Gln α), 48.5 (Ala α), 42.4 (Gly α), 38.5 (Leu(CO) β), 33.5 (homoPhe β), 31.3 (homoPhe γ), 31.5 (Gln γ), 30.7 (Gln β), 28.1 (Val β), 24.7 (Leu(CO) γ), 23.0 (Leu(CO) δ), 22.4 (Ac CH_3), 21.3 (Leu(CO) δ′), 19.1 (Val γ), 17.9 (Ala β).

Ac-Gln-Phe-CO-Leu-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$ (11e). ^{1}H NMR (600 MHz, DMSO): δ = 8.39 (m_c, 1H, Leu H^N), 8.26 (m_c, 1H, Gly H^N), 8.14 (m_c, 1H, Ala H^N), 8.14 (m_c, 1H, Phe(CO) H^N), 7.87 (m_c, 2H, HMBA 2,6), 7.83 (m_c, 1H, Gln H^N), 7.52 (m_c, 1H, Val H^N), 7.43 (m_c, 2H, HMBA 3,5), 7.24 (m_c, 2H, o Phe(CO)), 7.17 (m_c, 2H, m Phe(CO)), 7.11 (m_c, 1H, p Phe(CO)), 5.25 (m_c, 1H, Phe-(CO) α), 5.17 (s, 2H, HMBA 7), 4.34 (m_c, 1H, Ala α), 4.36 (m_c, 1H, Leu α), 4.26 (m_c, 1H, Gln α), 4.17 (m_c, 1H, Val α), 3.97 (m_c, 1H, Gly α), 3.87 (m_c, 1H, Gly α′), 3.08 (m_c, 1H, Phe(CO) β), 2.89 (m_c, 1H, Phe(CO) β′), 2.09 (m, 2H, Gln γ), 1.98 (m_c, 1H, Val β), 1.86 (m_c, 1H, Gln β), 1.83 (s, 3H, Ac), 1.68 (m_c, 1H, Gln β′), 1.64 (m_c, 1H, Leu β), 1.50_8 (m_c, 1H, Leu β′), 1.50_6 (m_c, 1H, Leu γ), 1.21 (m_c, 3H, Ala β), 0.84_4 (m, 6H, Leu δ), 0.83_8 (m_c, 6H, Val γ); ^{13}C NMR (150 MHz, DMSO): δ = 195.6 (α-keto C═O), 174.2 (Gln C═O δ), 171.9 (Leu C═O), 171.7 (Ala C═O), 171.5 (Gln C═O), 170.4 (Val C═O), 169.7 (Ac C═O), 169.5 (Gly C═O), 166.6 (HMBA C═O), 160.3 (Phe(CO) C═O amide), 139.3 (HMBA 4), 136.8 (i Phe(CO)), 133.6 (HMBA 1), 129.0_8 (p Phe(CO)), 129.0_7 (m Phe(CO)), 128.3 (o Phe(CO)), 127.5 (HMBA 2,6), 127.5 (HMBA 3,5), 66.4 (HMBA 7), 57.6 (Val α), 55.1 (Phe(CO) α), 52.0 (Gln α), 51.3 (Leu α), 48.5 (Ala α), 42.4 (Gly α), 41.1 (Leu β), 35.7 (Phe(CO) β), 31.4 (Gln γ), 30.7 (Gln β), 27.8 (Val β), 24.3 (Leu γ), 23.0 (Leu δ), 22.4 (Ac CH_3), 21.5 (Leu δ′), 19.0 (Val γ), 17.8 (Ala β).

Ac-Gln-Phe-CO-homoPhe-Ala-Val-Gly-HMBA-Gly-Gly-SPOCC$_{1500}$ (11f). ^{1}H NMR (600 MHz, DMSO): δ = 8.49 (m_c, 1H, homoPhe H^N), 8.26 (m_c, 1H, Gly H^N), 8.19 (m_c, 1H, Ala H^N), 8.17 (m_c, 1H, Phe(CO) H^N), 7.87 (m_c, 2H, HMBA 2,6), 7.83 (m_c, 1H, Gln H^N), 7.66 (m_c, 1H, Val H^N), 7.43 (m_c, 2H, HMBA 3,5), 7.28−7.07 (m, 10H, aryl homoPhe, Phe(CO)), 5.26 (m_c, 1H, Phe(CO) α), 5.17 (s, 2H, HMBA 7), 4.38 (m_c, 1H, Ala α), 4.34 (m_c, 1H, homoPhe α), 4.27 (m_c, 1H, Gln α), 4.19 (m_c, 1H, Val α), 3.96 (m_c, 1H, Gly α), 3.86 (m_c, 1H, Gly α′), 3.10 (m_c, 1H, Phe(CO) β), 2.89 (m_c, 1H, Phe(CO) β′), 2.61 (m_c, 1H, homoPhe γ), 2.53 (m_c, 1H, homoPhe γ′), 2.10 (m, 2H, Gln γ), 2.02 (m_c, 1H, homoPhe β), 1.98 (m_c, 1H, Val β), 1.94 (m_c, 1H, homoPhe β′), 1.87 (m_c, 1H, Gln β), 1.83 (s, 3H, Ac), 1.69 (m_c, 1H, Gln β′), 1.22 (d, 3H, Ala β), 0.82 (m_c, 6H, Val γ); ^{13}C NMR (150 MHz, DMSO): δ = 195.6 (α-keto C═O), 174.2 (Gln C═O δ), 172.1 (homoPhe C═O), 171.7 (Ala C═O), 171.5 (Gln C═O), 170.3 (Val C═O), 169.7 (Ac C═O), 169.5 (Gly C═O), 166.6 (HMBA C═O), 160.4 (Phe(CO) C═O amide), 141.3 (i homoPhe), 139.3 (HMBA 4), 136.9 (i Phe(CO)), 133.7 (HMBA 1), 129.1 (m Phe(CO)), 128.4 (o Phe(CO)), 128.3 (m homoPhe), 128.3 (o homoPhe), 127.9 (p Phe(CO)), 127.6 (HMBA 2,6), 127.5 (HMBA 3,5), 125.9 (p homoPhe), 66.2 (HMBA 7), 57.7 (Val α), 55.1 (Phe(CO) α), 52.6 (homoPhe α), 52.0 (Gln α), 48.6 (Ala α), 42.4 (Gly α), 35.6 (Phe(CO) β), 33.6 (homoPhe β), 31.4 (homoPhe γ), 31.4 (Gln γ), 30.7 (Gln β), 27.8 (Val β), 22.4 (Ac CH_3), 19.1 (Val γ), 17.9 (Ala β).

Note

After submission of this manuscript, an alternative route to resin-bound α-keto amides utilizing 2-iodoxybenzoic acid for the oxidation of resin-bound a-hydroxy amides was published by Basso et al. (Basso, A.; Banfi, L.; Riva, R.; Piaggio, P.; Guanti, G. *Tetrahedron Lett.* **2003**, *44*, 2367−2370).

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References and Notes

(1) Melnyk, O.; Fehrentz, J.-A.; Martinez, J.; Gras-Masse, H. *Biopolymers* **2000**, *55*, 165−186.
(2) (a) Otto, H.-H.; Schirmeister, T. *Chem. Rev.* **1997**, *97*, 133−171. (b) McKerrow, J. H.; James, M. N. G. *Perspect. Drug Discovery Des.* **1996**, *6*, 1−125. (c) Chapman, H. A.; Riese, R. J.; Shi, G.-P. *Annu. Rev. Physiol.* **1997**, *59*, 63−88. (d) Venkatesan, N.; Kim, B. H. *Curr. Med. Chem.* **2002**, *9*, 2243−2270.
(3) (a) Ede, N. J.; Eagle, S. N.; Wickham, G.; Bray, A. M.; Warne, B.; Shoemaker, K.; Rosenberg, S. *J. Pept. Sci.* **2000**, *6*, 11−18. (b) Lynas, J. F.; Harriott, P.; Healy, A.; McKervey, M. A.; Walker, B. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 373−378. (c) Lubisch, W.; Möller, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 373−378.
(4) (a) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813−1817. (b) Imperiali, B.; Abeles, R. H. *Biochemistry* **1986**, *25*, 3760−3767.
(5) (a) Hu, L.-Y.; Abeles, R. H. *Arch. Biochem. Biophys.* **1990**, *281*, 271−274. (b) Li, Z.; Patil, G. S.; Golubski, Z. E.; Hori, H.; Tehrani, K.; Foreman, J. E.; Eveleth, D. D.; Bartus, R. T.; Powers, J. C. *J. Med. Chem.* **1993**, *36*, 3472−3480.
(6) Wassermann, H. H.; Ennis, D. S.; Power, P. L.; Ross, M. J. *J. Org. Chem.* **1993**, *58*, 4785−4787.
(7) Harbeson, S. L.; Abelleira, S. M.; Akiyama, A.; Barrett, R., III; Carroll, R. M.; Straub, J. A.; Tkacz, J. N.; Wu, C.; Musso, G. F. *J. Med. Chem.* **1994**, *37*, 7, 2918−2929.

(8) (a) Di Cera, E.; Dang, Q. D.; Ayala, Y. M. *Cell. Mol. Life Sci.* **1997**, *53*, 701−730. (b) Boatman, P. D.; Ogbu, C. O.; Eguchi, M.; Kim, H. O.; Nakanishi, H. B.; Cao, L.; Shea, J. P.; Kahn, M. *J. Med. Chem.* **1999**, *42*, 1367−1375. (c) St. Charles, R.; Matthews, J. H.; Zhang, E. L.; Tulinsky, A. *J. Med. Chem.* **1999**, *42*, 1376−1383.
(9) (a) Brady, K. D.; Giegel, D. A.; Grinnell, C.; Lunney, E.; Talanian, R. V.; Wong, W.; Walker, N. *Bioorg. Med. Chem.* **1999**, *7*, 621−631. (b) Villa, P.; Kaufmann, S. H.; Earnshaw, W. C. *Trends Biochem. Sci.* **1997**, *22*, 388−393.
(10) (a) Munzo, B.; Gian, C.-Z.; Wong, C.-H. *Bioorg. Med. Chem.* **1994**, *2*, 1085−1090. (b) Sheha, M. M.; Mahfouz, N. M.; Hassan, H. Y.; Youssef, A. F.; Mimoto, T.; Kiso, Y. *Eur. J. Med. Chem.* **2000**, *35*, 887−894.
(11) Fusetani, N.; Matsunaga, S.; Matsumoto, H.; Takebayashi, Y. *J. Am. Chem. Soc.* **1990**, *112*, 7053−7054.
(12) Fusetani, N.; Sugarawa, T.; Matsunaga, S.; Hirota, H. *J. Am. Chem. Soc.* **1991**, *113*, 7811−7812.
(13) Kobayashi, J.; Itagaki, F.; Shigemori, H.; Ishibashi, M.; Takahashi, K.; Ogura, M.; Nagasawa, S.; Nakamura, T.; Hirota, H.; Ohta, T.; Nozoe, S. *J. Am. Chem. Soc.* **1991**, *113*, 7812−7813.
(14) Papanikos, A.; Rademann, J.; Meldal, M. *J. Am. Chem. Soc.* **2001**, *123*, 2176−2181.
(15) (a) Groth, T.; Meldal, M. *J. Comb. Chem.* **2001**, *3*, 34−44. (b) Buchardt, J.; Ferreras, M.; Krog-Jensen, C.; Delaissé, J.-M.; Tækker Foged, N.; Meldal, M. *Chem. Eur. J.* **1999**, *5*, 2877−2884.
(16) (a) Yang, Z.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2002**, *4*, 1103−1105. (b) Banfi, L.; Guanti, G.; Riva, R.; Basso, A.; Calcagno, E. *Tetrahedron Lett.* **2002**, *43*, 4067−4069. (c) Tsuda, M.; Muraoka, Y.; Nagai, M.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 890−899.
(17) (a) Wasserman, H. H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364−4366. (b) Wasserman, H. H.; Petersen, A. K. *J. Org. Chem.* **1997**, *62*, 8972−8973.
(18) Rademann, J.; Grøtli, M.; Meldal, M.; Bock, K. *J. Am. Chem. Soc.* **1999**, *121*, 5459−5466.
(19) Stang, P.; Hanack, M.; Subramanian, L. *Synthesis* **1982**, 85−126.
(20) Ropp, G. A. *J. Am. Chem. Soc.* **1960**, *82*, 842−852.
(21) Weik, S.; Rademann, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2491−2494.
(22) Wu, Y.-Q.; Limburg, D. C.; Wilkinson, D. E.; Vaal, M. J.; Hamilton, G. S. *Tetrahedron Lett.* **2000**, *41*, 2847−2849.
(23) Halkes, K. M.; Gotfredsen, C. H.; Grøtli, M.; Miranda, L. P.; Duus, J. Ø.; Meldal, M. *Chem. Eur. J.* **2001**, *7*, 3584−3591.
(24) Blankemeyer-Menge, B.; Nimtz, M.; Frank, R. *Tetrahedron Lett.* **1990**, *31*, 1701−1704.
(25) Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927−1930.
(26) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.
(27) (a) Bates, G. S.; O'Doherty, J. *J. Org. Chem.* **1981**, *46*, 1745−1747. (b) Chattopadhyaya, J. B.; Rama Rao, A. V. *Tetrahedron Lett.* **1973**, *14*, 3735−3736. (c) Ho, T.-L.; Ho, H. C.; Wong, C. M. *Chem. Commun.* **1972**, 791. (d) Olah, G. A.; Narang, S. C.; Mehrotra, A. K. *Synthesis* **1982**, 965−966.
(28) Bertini, V.; Lucchesini, F.; Pocci, M.; De Munno, A. *J. Org. Chem.* **2000**, *65*, 4839−4842.
(29) (a) Cain, E. N.; Welling, L. L. *Tetrahedron Lett.* **1975**, *16*, 1353−1356. (b) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553−3560.
(30) Derome, A.; Williamson, M. *J. Magn. Reson.* **1990**, *88*, 177−185.
(31) (a) Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *63*, 207−213. (b) Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 3157−3159.
(32) Kay, L. E.; Keifer, P.; Saarinen, T. *J. Am. Chem. Soc.* **1992**, *114*, 10663−10665.
(33) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093−2094.

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