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Radical-Mediated Acyl Thiol-Ene Reaction for Rapid Synthesis of Biomolecular Thioester Derivatives

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The thiol-ene 'click' reaction has emerged as a versatile process for carbon–sulfur bond formation with widespread applications in chemical biology, medicinal chemistry and materials science. Thioesters are key intermediates in a wide range of synthetic and biological processes and efficient methods for their synthesis are of considerable interest. Herein, we report the first examples of acyl-thiol-ene (ATE) for the synthesis of biomolecular thioesters, including peptide, lipid and carbohydrate derivatives. A key finding is the profound effect of the amino acid side chain on the outcome of the ATE reaction. Furthermore, radical generated thioesters underwent efficient S-to-N acyl transfer and desulfurisation to furnish 'sulfur-free' ligation products in an overall amidation process with diverse applications for chemical ligation and bioconjugation.

1. Introduction

The thiol-ene reaction, hydrothiolation of an olefinic substrate *via* a radical chain mechanism, is an archetypal 'click' reaction by virtue of its high atom economy, excellent yields, complete selectivity, fast kinetics (in the order of $10^5\ M^{-1}\ s^{-1}$)[1] and compatibility with aqueous conditions.[2] As a result of its remarkable synthetic utility the reaction is well established throughout the fields of natural product synthesis, bioconjugation[3] and polymerization chemistry.[2] However, these precedents have exclusively described thiol-ene reactions yielding sulfur containing linkages which are problematic for certain applications. Thioether-substituted conotoxin derivatives have been shown to easily oxidize to the sulfoxide, resulting in structural distortion and loss of biological activity.[4] To date, the ubiquity of sulfur in the products of thiol-ene reactions remains something of an 'Achilles' heel' for the methodology. Although still susceptible to oxidation, thioesters are more labile than thioethers and function as key intermediates in a wide range of fundamental biological processes[5–7] as well as in the organic synthesis of valuable heterocyclic molecules and natural products.[8,9] Syntheses of thioesters typically rely on classical methods such as the condensation of activated acyl compounds with thiols, often necessitating strong base, long reaction times or the use of transition metal catalysts.[10] Our group has recently introduced the acyl-thiol-ene (ATE) reaction as an efficient method to furnish thioesters using thioacids under radical-mediated conditions. To date, the methodology has permitted facile access to biologically pertinent thiolactone substrates and has been exploited in both intermolecular and intramolecular processes for the synthesis of thioester derivatives (Figure 1b).[11,12] However, to the best of our knowledge, no examples of ATE reactions involving biomolecular derived thioacids including lipids, carbohydrates or amino acids (AAs), have been reported to date. Herein, we report an important advance in thiol-ene reactivity, exploring radical-mediated formation of biomolecular thioester derivatives *via* ATE chemistry. Furthermore, spontaneous, intramolecular S-to-N acyl transfer and desulfurisation of radical generated thioester intermediates is demonstrated, to furnish desulfurized products in an overall amidation process that offers significant potential for chemical ligation, bioconjugation and protein modification (Figure 1d).

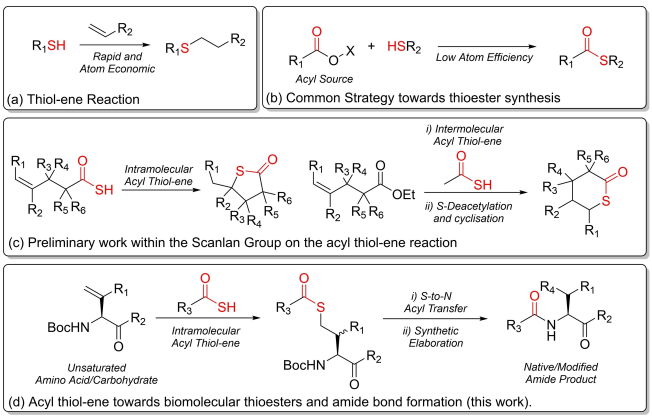

Figure 1. (a) The Thiol-ene "click" reaction towards thioether products; (b) Thio- esterification of thiols; (c) Thiolactone synthesis *via* intra and intermolecular acyl-thiol-ene (ATE) reaction; (d) ATE towards peptidyl/carbohydrate thioesters and amide bond formation (this work).

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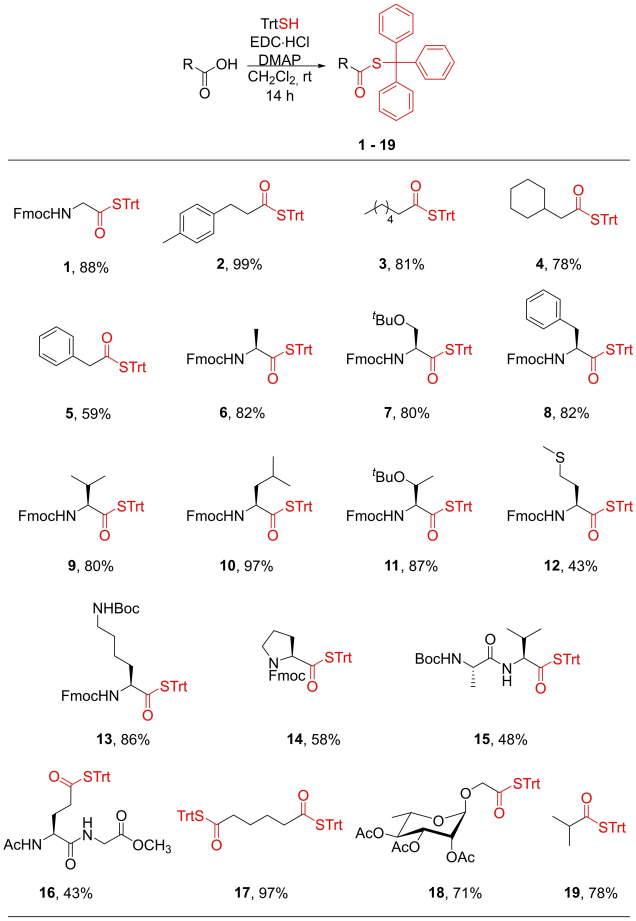
2. Results and Discussion

2.1. Synthesis of Thioacid Surrogates

To investigate the ATE reaction for the synthesis of biomolecular thioesters we focused initially on the family of proteinogenic AAs. AA substrates offered a broad range of functionalities to probe the tolerance of the methodology and the applicability of radical mediated ATE between a thioacid and an alkene in mediating thioester bond formation. This required the synthesis of suitable thioacid and olefinic components for the ATE reaction. Numerous direct thiolation strategies are described in the literature for the preparation of bimolecularly relevant thioacids.[13] The majority rely on *in situ* generation of the thioacid moiety from a suitable activated carboxylic acid precursor prior to immediate reaction. This was not deemed suitable in our case, as this process would preclude effective evaluation of the ATE reaction due to possibility of incomplete thioacid formation and competing side reactions. Coupling of the carboxylic acid derivatives with trityl (Trt) thiol under Steglich conditions as reported by Crich,[14] was found to offer an efficient route to a bench stable thioacid surrogates. The Trt functionality is readily cleaved upon treatment with trifluoroacetic acid (TFA) to quantitatively yield the corresponding thioacid upon concentration of the reaction mixture *in vacuo*, prior to ATE with a suitable olefinic substrate. A range of biomolecule Trt thioesters were synthesized under these conditions from readily available starting materials (Scheme 1).

Moderate to excellent yields were obtained for formation of Trt thioesters. The variation in yields observed for substrates **1**–**19** was primarily dependent on the steric profile of the carboxylic acid employed. The lower yields of Trt thioesters **14**–**16** could be accounted for due to the considerable steric bulk of the carboxylic acid components of the corresponding coupling reactions.

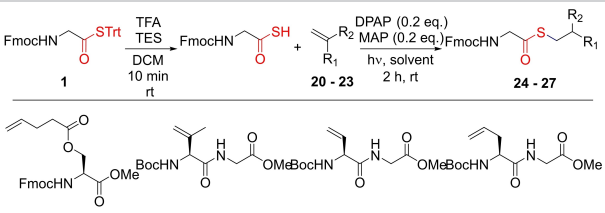


Scheme 1. Thioester formation under Steglich conditions described by Crich[14] for use in ATE reactions.

2.2. Synthesis of Olefinic ATE Substrates and ATE Optimization

Olefinic substrates were required that would prove synthetically accessible, capable of reliably furnishing thioester products and permitting access to biologically relevant amidic products through subsequent S-to-N acyl transfer processes. This approach necessitated the synthesis of a suitable alkene containing peptide substrates through the incorporation of olefinic unnatural amino acids (UAAs) or unsaturated side-chain auxiliaries (Table 1). Our initial approach sought to demonstrate the efficiency of the intermolecular ATE reaction using unsaturated *O*-auxiliaries attached to the side-chain of serine or threonine residues by straightforward acylation of a Fmoc protected amino methyl ester yielding substrates such as **20** (see ESI). Subsequently, the scope of the ATE reaction was explored at substrates more structurally analogous to naturals AAs using unsaturated amino acids β,γ-didehydrovaline, vinylglycine and allylglycine to yield dipeptides **21**–**23**, respectively. Unsaturated targets **21** and **22** were synthesized using

Table 1. Optimisation of Acyl thiol-ene (ATE) reaction of Gly thioacid and alkenes 20–23.



Entry	Alkene	Eq. Thioacid	Solvent	Conc. (M)	Yield [%][a]
i	20	1	DMF	0.05	34
ii.	20	1	DMF	0.10	52
iii.	20	1.5	DMF	0.075	66
iv.	20	3	DMF	0.075	99
v.	20	2	DMF	0.075	76
vi.	20	2	DMF	0.10	93
vii.	21	3	DMF	0.10	67
viii.	21	1.5	EtOAc	0.10	59
ix.	21	3	EtOAc	0.10	93
x.	22	3	EtOAc	0.10	91
xi.	23	3	EtOAc	0.10	91

[a] Isolated yields after silica gel flash chromatography.

strategies inspired by literature precedent[15,16] (see ESI) and were obtained in high overall yields from commercially available precursors in four and six synthetic steps respectively. **23** was synthesized through straightforward amide coupling from commercially available starting materials.

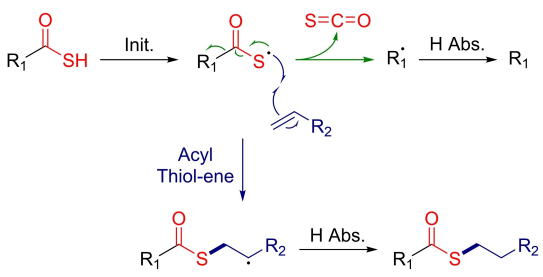
Initial optimization of the ATE reaction was carried out using *N*-fluorenylmethyloxycarbonyl (Fmoc) serine methyl ester **20** as the alkene component and Fmoc-glycine thioacid **1**. Photolysis of **1** in the presence of radical initiator 2,2-dimethoxy-2-phenylacetophenone (DPAP) and photosensitizer 4-methoxyacetophenone (MAP) in dimethylformamide (DMF) at room temperature for 2 hours furnished the thioester product **24** in quantitative yield following optimization of the reaction conditions (Table 1). It was determined that using an excess of the thioacid (2 or 3 equiv.), was required in order to force the reaction to quantitative conversion, due to a competing unimolecular dethiocarboxylation reaction (Scheme 2).[17]

Under these conditions the reaction of Boc-β,γ-didehydrovaline containing dipeptide **21** with Fmoc-glycine thioacid **1** did not reach full conversion to the corresponding thioester, presumably due to the use of the more sterically hindered alkene (Table 1, entry vii). Interestingly, the use of ethyl acetate (EtOAc) as solvent in place of DMF furnished the corresponding thioester in 93% yield (Table 1, entry ix). Equally, EtOAc offered improved yields in the reactions of analogous vinylglycine and allylglycine containing dipeptides **22** and **23**, providing the desired thioester products in high yield in both cases (Table 1, entry x and xi).

2.3. Exploration of ATE Scope

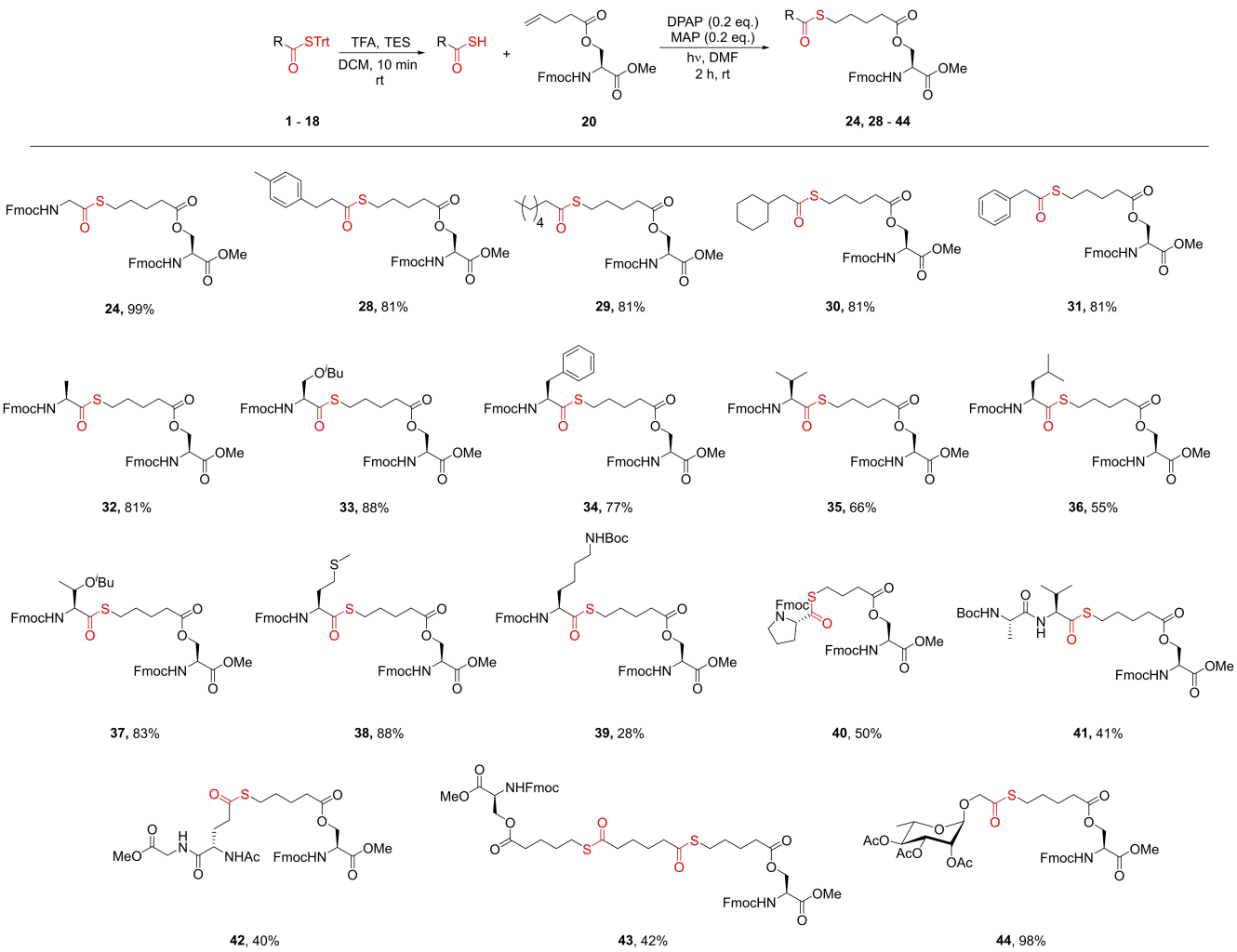
With optimized ATE conditions in hand, the scope of the reaction was investigated for a range of thioacids derived from Trt thioesters **1**–**18** in reaction with alkene **20** (Scheme 3). In the case of the serine *O*-auxiliary alkene **20**, both alkyl and aromatic thioacid substrates underwent thioester formation in excellent yields (**28**–**31**). Alkyl thioester derivative **29** is of particular interest as it closely resembles the lipid thioester derivatives formed as reactive acyl-transfer intermediates in bacterial cell-wall biosynthesis.[18]

A diverse range of amino acid thioacids derived from Trt thioesters **6**–**16** were screened to demonstrate the broad applicability of this methodology (Scheme 3). Importantly, the



Scheme 2. Competing hydrothiolation (blue arrows) and dethiocarboxylation (green arrows) reaction mechanisms.

ATE methodology was found to be compatible with the Fmoc, Boc and ^{t}Bu protecting groups commonly used in synthetic peptide chemistry. In general, amino acids containing a heteroatom in the side chain were highly efficient in the ATE coupling reaction, with the single exception of the Boc protected lysine derivative **39**. Of particular interest was the finding that proline could function as an efficient thioacyl radical derivative in the ligation reaction to yield **40**. Forming a thioester at the *C*-terminus of proline has proven extremely challenging using traditional chemical methods. Formation of the thioester on the side chain of glutamic acid to yield thioester **42** proved successful, albeit in moderate yield. Adipic acid was used as a substrate to furnish **43** to demonstrate that ATE is suitable for thioester formation simultaneously at more than one site. A rhamnosyl thioacid derivative furnished the glycopeptide thioester derivative **44** in excellent yield, offering interesting prospects for the development of carbohydrate acyl transfer reagents and processes. A key finding from the scope study was that the nature of the amino thioacid sidechain appears to have a profound effect on the efficiency of the ATE reaction. Indeed, the relative rate of the competing dethiocarboxylation process is likely contingent on the stability of the *C*-centered radical formed upon elimination of carbonyl sulfide (OCS, Scheme 2). Amino thioacids possessing alkylic sidechains were found to be lower yielding in ATE reactions with alkenes **21**–**23** (Scheme 4), as dethiocarboxylation lead to the formation of comparatively stable secondary carbon radicals. Five equivalents of thioacid were required in order to achieve full conversion to the thioester in cases of increased side-chain steric hindrance and decreased alkene availability (**46**, **47**, **49**, **50**, **52**, **53**). However, in stark contrast, amino thioacids containing a heteroatom in the side chain were highly efficient in ATE coupling reactions, with the exception of the Boc protected lysine thioacid used to furnish **39**. This finding suggests that the heteroatoms in methionine, serine and threonine may assist the radical addition reaction, likely by lowering the rate of competing dethiocaboxylation through diminution of the radical stabilization energy of the *C*-centered radical species formed, as observed in previous studies with similar radical species.[19,20]. The effect of the alkene components of these reactions (**20**–**23**) on thioester yield could also be evaluated through inspection of these results. Thioesters were obtainable in high isolated yields with all four alkenes **20**–**23**. However, the greater steric demands of alkenes **21**–**23** could be observed in that complete conversion of these starting materials to their phenylalanine and valine derived thioester counterparts (**46**, **47**, **49**, **50**, **52**, **53**, respectively) required 5 equivalents of thioacid starting material to reach full reaction conversion. By comparison, the less sterically hindered 4-pentenoyl auxiliary **20** necessitated the use of only 3 equivalents of thioacid to fully consume the alkene starting material to yield thioesters **34** and **35**. To demonstrate more accurately the rate of ATE, the reaction was monitored by NMR spectroscopy using an internal standard (details available in ESI). NMR experiments revealed that complete conversion of alkene to ligated thioester product was achieved within the first 15 minutes of UV irradiation. The scope study demonstrates

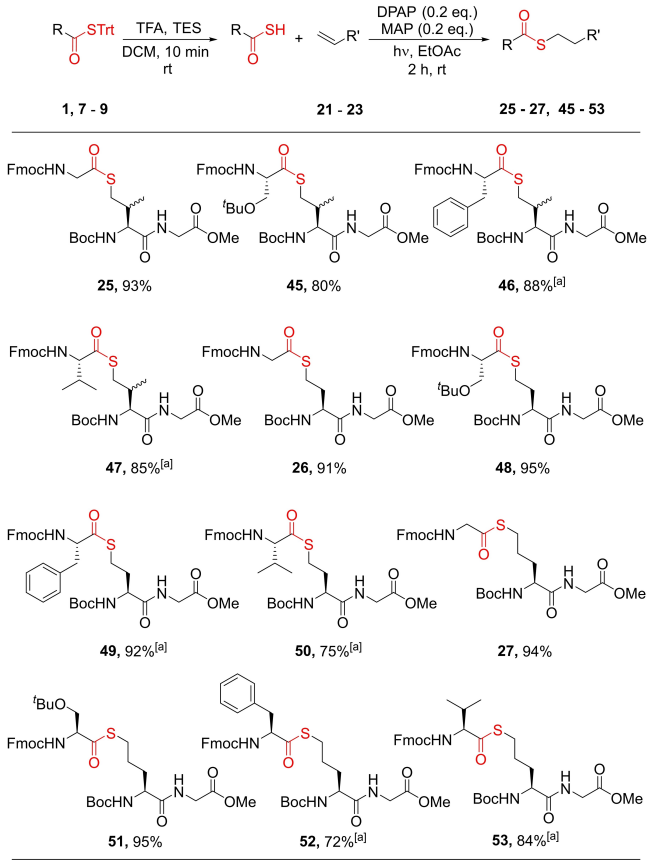


Scheme 3. Scope of the acyl thiol-ene (ATE) reaction utilizing alkene **20** and thioacids derived from the Trt deprotection of Trt thioesters **1**–**18**. (Isolated yields after silica gel column chromatography). Acyl thiol-ene was carried out in dried and degassed dimethylformamide.

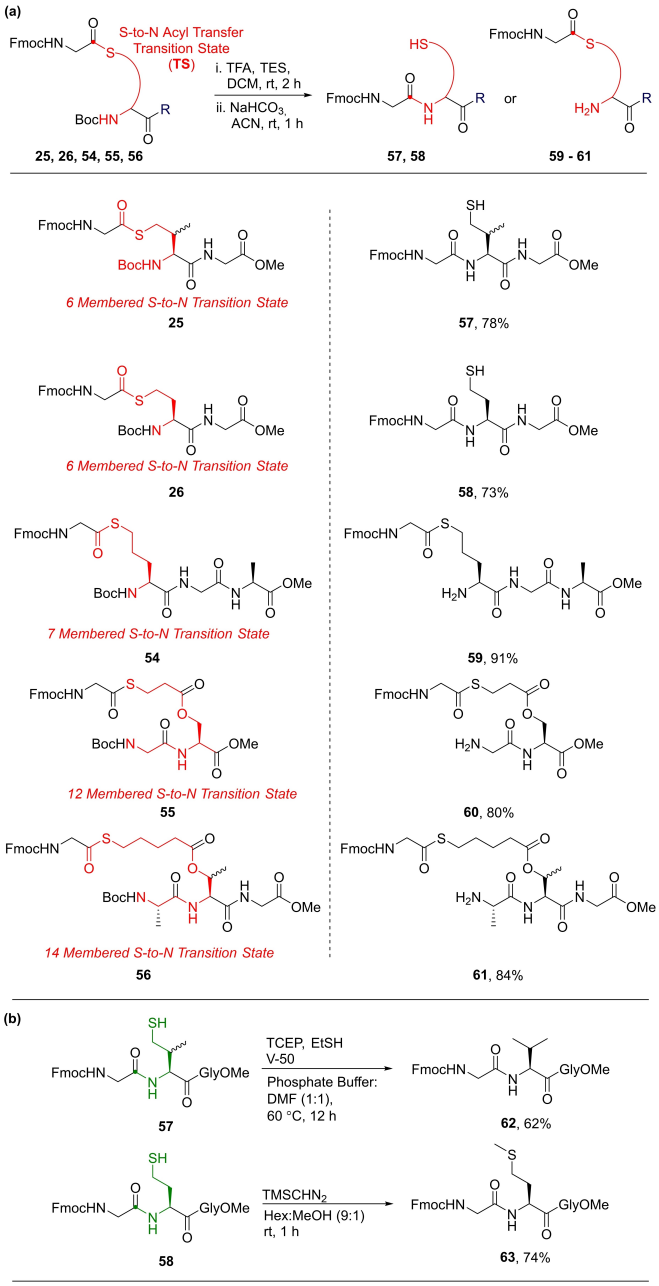
that the ATE reaction provides a robust, facile and rapid means to access a range of thioester substrates that is compatible with a diverse range of alkyl, aromatic, amino acid and carbohydrate derived thioacids and unsaturated ATE substrates.

To access 'thiol-free', amidation products an intramolecular S-to-N acyl transfer step analogous to that in Native Chemical Ligation (NCL) explored. Four intramolecular S-to-N acyl transfer cyclic transitions state (TS) sizes were investigated using thioesters obtained via the ATE reaction of five different unsaturated peptidyl substrates **25**, **26**, **54**, **55** and **56**. (Scheme 5a). The synthesis of unsaturated peptides **55** and **56** was carried out through the esterification of serine and threonine containing starting materials prior to ATE with Gly thioacid **1** (See ESI). The *N*-terminal Boc protecting group of each peptidyl thioester was removed using TFA (20% in DCM) to furnish the corresponding trifluoroacetate ammonium salt quantitatively. The S-to-N acyl transfer reaction was promoted through dissolution of TFA-salts in a saturated solution of $NaHCO_3$ in acetonitrile (ACN). Thioesters investigated whereby the S-to-N acyl transfer occurred over thermodynamically favored 6-membered cyclic TSs (**25** and **26**) permitted isolation of the corresponding thiol-containing tripeptides (**57** and **58**) expeditiously and in high yields, however those employing larger TS sizes (**54, 55, 56**) did not provide the acyl transfer products spontaneously, permitting isolation of free amines **59**, **60** and **61**. These results, coupled to literature precedent,[21] suggest that S-to-N acyl transfers proceeding over large (>6) cyclic TSs are highly substrate dependent and rely on significant substrate preactivation.

Thiol-free compounds could also be obtained from S-to-N acyl transfer products **57** and **58** to yield native peptide substrates. Compounds **57** readily underwent desulfurisation through the metal-free procedure established by Danishefsky and coworkers[22] to provide the desired 'thiol free' product **62** (Scheme 5b). Desulfurisation methodologies are commonly employed in the field of protein ligation and organic synthesis and tolerate a wide range of functionalities having proven capable of dethiolating the β- or γ- positions of fifteen different amino acids to date[23]. Methylation of thiol **58** using trimeth-



Scheme 4. Scope of the acyl thiol-ene (ATE) reaction utilizing alkenes **21**–**23** and thioacids derived from the Trt deprotection of Trt thioesters **1, 7**–**9**. (Isolated yields after silica gel column chromatography). Acyl thiol-ene was carried out in dried and degassed EtOAc. [a] 5 eq. of thioacid used to reach full reaction conversion.



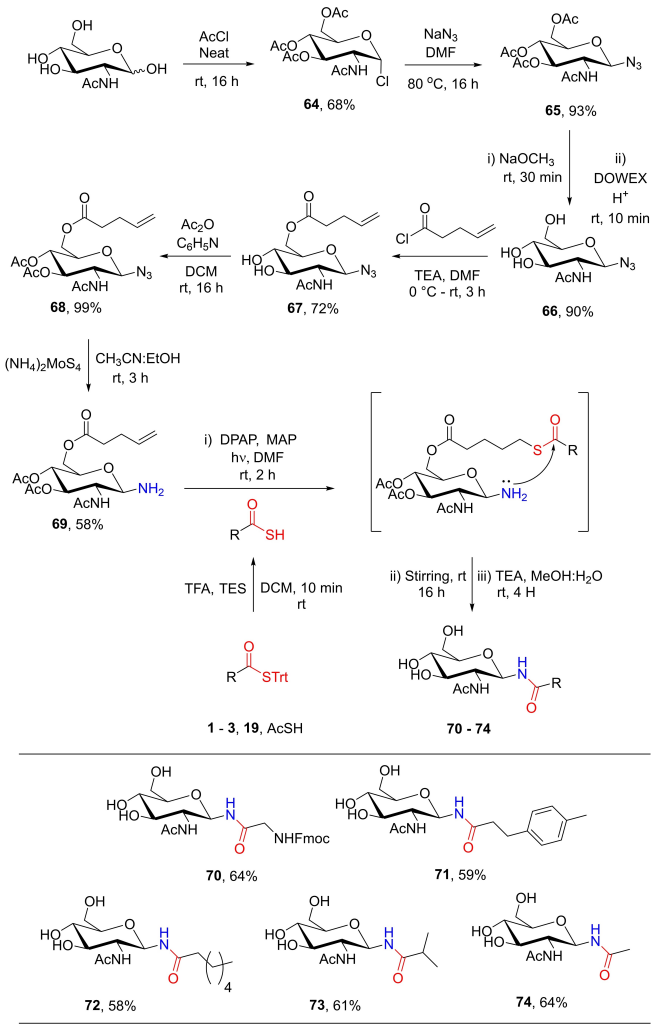
Scheme 5. (a) Isolated Products of deprotection and freebasing of Boc protected thioesters 25, 26, 54, 55, 56. (b) Synthetic elaboration of thiolated peptides 57 and 58 through desulfurisation and methylation, respectively, to yield thiol-free tripeptides 62 and 63 (Isolated yields after silica gel flash chromatography).

ylsilyldiazomethane was also carried out to demonstrate the possibility of further synthetic elaboration if desired, furnishing a methionine residue in tripeptide **63** (Scheme 5b).

2.4. ATE and Sugar Templated S-to-N Acyl Transfer

Sugar templated S-to-N acyl transfer has been observed to offer such preactivation, as demonstrated in the Sugar Assisted Ligation (SAL) developed by Wong and co-workers.[24] Having succeeded in applying ATE reactivity to unsaturated peptide substrates we examined the reactivity of unsaturated amino GlcNAc derivative **69**, capable of S-to-N acyl transfer (Scheme 6). **69** was accessed *via* installation of an azide moiety at the anomeric position of unprotected GlcNAc to yield **65** (Scheme 6). Subsequent protecting group manipulation and esterification with 4-pentenoic chloride yielded unsaturated azido derivative **68**. Reduction of the azide group of **68** yielded the desired ATE substrate **69**.

The one-pot cascade reaction involving (i) ATE, (ii) S-to-N-acyl transfer through a 13-membered ring TS and (iii) ester hydrolysis was successfully demonstrated with protected thioacids which all furnished the desired thiol-free *N*-linked GlcNAc products **70**–**74** after column chromatography in good yields over 3 steps. (Scheme 6). This one pot cascade further demonstrates the applicability of ATE for the synthesis of thiol free amide products, and illustrates the potential for ATE in carbohydrate ligation methodologies.



Scheme 6. Synthesis of unsaturated carbohydrate 69 capable of one pot ATE addition, S-to-N acyl transfer and auxiliary cleavage to yield anomeric amides 70–74 upon reaction with thioacids derived from Trt thioesters 1–3, 19 and thioacetic acid.

3. Conclusion

This work serves as an efficient proof-of-concept, demonstrating the efficiency of the ATE reaction towards the formation of biomolecular thioester derivatives. The methodology demonstrates high tolerance to a range of diversely functionalized biomolecular substrates and common protecting groups, including those derived from the family of natural AA's. The nature of the amino thioacid sidechain has a profound effect on the outcome of the ATE reaction, with AA's containing a heteroatom in the side chain demonstrating highest efficiency in ATE coupling reactions, through supression of the competing CSO elimination pathway. The methodology requires only catalytic quantities of organic photoactivators for ATE and offers an efficient approach to access biomolecular thioester compounds. Unlike the canonical thiol-ene reaction which furnishes thioethers exclusively, products of ATE reactions can undergo chemoselective acyl transfer reactions enabling preparation of 'sulfur-free' products containing a robust amide linkage. This approach represents a new frontier in thiol-ene chemistry with considerable potential for bioconjugation, drug discovery, peptide synthesis and materials chemistry.

Experimental Section

General Experimental Details

All commercial chemicals used were supplied by Sigma Aldrich (Merck), Fluorochem, VWR Carbosynth and Tokyo Chemical Industry and used without further purification unless otherwise stated. Deuterated solvents for NMR were purchased from Sigma Aldrich (Merck) or VWR. Solvents for synthesis purposes were used at GPR grade. Anhydrous DCM, THF, ACN and Et_2O were obtained from a PureSolv MD-4EN Solvent Purification System. All UV reactions were carried out in a Luzchem photoreactor, LZC-EDU (110 V/ 60 Hz) containing 10 UVA lamps centred at 365 nm. Silica gel 60 (Merck, 230–400 mesh) was used for silica gel flash chromatography and all compounds were subject to purification using silica gel, unless otherwise stated. Analytical thin layer chromatography (TLC) was carried out with silica gel 60 (fluorescence indicator F254; Merck) and visualized by UV irradiation or molybdenum staining [ammonium molybdate (5.0 g) and concentrated H_2SO_4 (5.3 mL) in 100 mL H_2O]. NMR spectra were recorded using Bruker DPX 400 (400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR), Bruker AV 600 (600.13 MHz for ^{1}H NMR and 150.90 MHz for ^{13}C NMR), Bruker AV 400 (400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR) or Agilent MR400 (400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR) instruments. Chemical shifts, δ, are in ppm. and referenced to the internal solvent signals. NMR data was processed using Bruker TopSpin software. The assignment of the signals was confirmed by 2D spectra (COSY, HMBC, HSQC). Melting points are uncorrected and were measured with a Stuart SP-10 melting point apparatus. MALDI time of flight (TOF) spectra were acquired using a Waters MALDI Q-Tof Premier in positive or negative mode with DCTB (trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene] malononitrile) as the MALDI matrix. ESI mass spectra were acquired in positive and negative modes as required, using a Micromass TOF mass spectrometer, interfaced to a Waters 2690 HPLC or a Bruker micrOTOF–Q III spectrometer interfaced to a Dionex UltiMate 3000 LC. APCI experiments were carried out on a Bruker micrOTOF–Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe in positive or negative modes. Infrared spectra (IR) spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer.

General Experimental Procedures

Preparation of *S*-trityl thioesters: To a stirred solution of carboxylic acid in anhydrous DCM under Ar was added DMAP (0.1 eq.), triphenylmethanethiol (1.0 eq.) and EDCI·HCl (1.2 eq.). The solution was stirred for 18 h at rt under Ar. The solvent was removed in vacuo and the resulting residue purified by silica gel flash chromatography. Characterisation data for *S*-trityl thioesters 1–19 may be found in the supporting information.

Removal of *S*-trityl protecting groups: To a stirred solution of *S*-trityl thioester in DCM under Ar was added triethylsilane (20.0 eq.). TFA (20 % v/v) was added and the reaction mixture stirred for 5 min at rt, concentrated *in vacuo* and the resulting crude thioacid used directly without further purification.

Intermolecular acyl thiol-ene: To a stirred solution of alkene acceptor in DMF or EtOAc was added DPAP (0.2 eq.), MAP (0.2 eq.)

and thioacid dissolved in a minimum volume of the same solvent. The reaction mixture was subjected to UV irradiation for 2 h, solvent removed in vacuo and the resulting mixture purified by silica gel flash chromatography.

Removal of *N*-Boc protecting groups and freebasing of trifluoroacetate salt: To a stirred solution of Boc protected amine in DCM under Ar was added TES (10.0 eq.). TFA (20% v/v) was added and the reaction mixture stirred for 2 h at rt. Solvent was removed in vacuo to give the corresponding TFA salt. The resulting salt was redissolved in ACN (0.1 M) and a sufficient quantity of $NaHCO_3$ added to saturate the solution. The reaction mixture was stirred for 2 h at rt and following filtration solvent was removed in vacuo and the resulting mixture purified by silica gel flash chromatography.

Thioacid addition, S-to-N-acyl shift and base hydrolysis of unsaturated carbohydrate 70: To a mixture of alkene 70, DPAP (0.1 eq.) and MAP (0.1 eq.) in anhydrous DMF was added the crude thioacid (1.1 or 1.5 eq.) and the reaction mixture irradiated in an UV oven at rt without agitation for 1 h followed by stirring at rt for 16 h outside of the UV oven. The solvent was removed in vacuo and the mixture was re-dissolved in MeOH:H_2O (10 mL, 8:2) and to this was added TEA (25.0 eq.) and the solution was stirred at rt for 4 h. The mixture was neutralised by the addition of DOWEX H+ resin and then filtered. The solvent was removed in vacuo and the reaction mixture was subjected to chromatographic purification.

Characterisation Data for Thioesters 24–54 Synthesized *via* Acyl Thiol-ene Reaction:

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-(((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)thio) pentanoate (24)**: R_f (40% EtOAc:Hex): 0.38. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.2 Hz, 4H, Ar-CH), 7.62 (d, J = 7.2 Hz, 4H, Ar-CH), 7.42 (t, J = 7.2 Hz, 4H, Ar-CH), 7.33 (t, J = 7.2 Hz, 4H, Ar-CH), 5.81 (d, J = 8.2 Hz, 1H, NH), 5.58 (t, J = 6.3 Hz, 1H, NH), 4.70-4.67 (m, 1H, Ser αCH), 4.53-4.41 (m, 6H, Fmoc CHC$\underline{H}_2$, Fmoc CHC$\underline{H}_2$, Ser βCH_2), 4.28-4.23 (dd, J = 7.1 Hz, 2H, Fmoc C$\underline{H}$CH_2, Fmoc C$\underline{H}$CH_2), 4.11 (d, J = 6.0 Hz, 2H, αGly CH_2), 3.80 (s, 3H, OCH_3), 2.92 (t, J = 6.8 Hz, 2H, $CH_2CH_2CH_2C\underline{H}_2S$), 2.37 (2H, t, J = 6.8 Hz, C$\underline{H}_2CH_2CH_2CH_2S$), 1.75-1.61 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2S$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8 (SC=O), 172.7 (C=O), 170.0 (C=O), 156.3 (C=O), 155.8 (C=O), 143.8 (Ar-qC), 143.7 (Ar-qC), 141.3 (Ar-qC), 127.8 (Ar-CH), 127.1 (Ar-CH), 125.1 (Ar-CH), 120.0 (Ar-CH), 67.3 (Fmoc CH$\underline{C}H_2$), 63.9 (Ser βCH_2), 53.4 (Ser αCH), 52.9 (OCH_3), 50.7 (Gly αCH_2), 47.1 (Fmoc $\underline{C}HCH_2$), 33.3 ($CO\underline{C}H_2CH_2CH_2CH_2S$), 28.8 ($COCH_2\underline{C}H_2CH_2CH_2S$), 28.0 ($CH_2S$) 23.8 ($COCH_2CH_2\underline{C}H_2CH_2S$) ppm. HRMS (*m/z*) calculated for $C_{41}H_{40}N_2NaO_9S$ $[M+Na]^+$, calcd. 759.2333, found 759.2347. ν_{max} (film)/cm^{-1}: 3345 (NH), 1712 (C=O).

Methyl *(S)*-(4-(((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)thio)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanoyl)glycinate (25): R_f (50% EtOAc:Hex): 0.35^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.5 Hz, 4H, Ar-CH), 7.64 (d, J = 7.5 Hz, 4H, Ar-CH), 7.42 (t, J = 7.5 Hz, 4H, Ar-CH), 7.34 (t, J = 7.5 Hz, 4H, Ar-CH), 6.94 (bs, 1H, NH), 6.74 (bs, 1H, NH), 5.62 (bs, 1H, NH), 5.57 (bs, 1H, NH), 5.49 (d, J = 8.4 Hz, 1H, NH), 5.29 (d, J = 8.4 Hz, 1H, NH), 4.49–4.44 (m, 4H, Fmoc CHC$\underline{H}_2$), 4.40 (m, 1H, αCH), 4.27 (t, J = 7.0 Hz, 2H, Fmoc C$\underline{H}$CH_2), 4.19–4.00 (m, 9H, Gly αCH_2, Gly αCH_2, αCH), 3.75 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.26 (dd, J = 14.0, 6.6 Hz, 1H, γCH_2), 2.97 (d, J = 6.6 Hz, 2H, γCH_2), 2.79 (dd, J = 14.0, 6.6 Hz, 1H, γCH_2), 2.25 (d, J = 6.2 Hz, 1H, βCH), 1.46 (s, 18H, C(CH_3)$_3$), 1.04 (d, J = 6.9 Hz, 3H, CH_3), 1.00 (d, J = 6.9 Hz, 3H, CH_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.9 (SC=O), 197.7 (SC=O), 171.4 (C=O), 170.8 (C=O), 170.1 (C=O), 170.0 (C=O), 156.4 (C=O), 156.3 (C=O), 155.9 (C=O), 155.7 (C=O), 143.8 (Ar-qC), 143.7 (Ar-qC), 141.3 (Ar-qC), 141.3 (Ar-qC), 127.8 (Ar-CH), 127.1 (Ar-CH), 127.1 (Ar-CH), 125.1 (Ar-CH), 120.0 (Ar-CH), 80.3 (C($\underline{C}$H$_3$)), 67.4 (Fmoc CH$\underline{C}H_2$), 67.3 (Fmoc CH$\underline{C}H_2$), 57.3 (αCH), 56.4 (αCH), 52.4 (OCH_3), 52.4 (OCH_3), 50.8 (Gly CH_2), 50.7 (Gly CH_2), 47.1 (Fmoc $\underline{C}HCH_2$), 47.1 (Fmoc $\underline{C}HCH_2$), 41.2 (Gly CH_2) 41.2 (Gly CH_2), 37.1 (βCH), 36.7 (βCH), 32.3 (γCH_2), 31.3 (γCH_2), 28.3 (C($\underline{C}$H$_3$)), 28.3 (C($\underline{C}$H$_3$)), 16.3 (CH_3), 14.4 (CH_3) ppm. *Isolated as a mixture of diastereoisomers. HRMS (*m/z* APCI +): calculated for $C_{30}H_{38}N_3O_8S$ $[M+H]^+$, calcd. 600.2374, found 600.2375. ν_{max} (film)/cm^{-1}: 3321 (NH), 2978 (C–H), 1682 (C=O).

Methyl *S*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)glycyl)-*N*-(*tert*-butoxycarbonyl)-L-homocysteinylglycinate (26): R_f (50% EtOAc/Hex): 0.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.4 Hz, 2H, Ar-CH), 7.64 (d, J = 7.4 Hz, 2H, Ar-CH), 7.43 (t, J = 7.4 Hz, 2H, Ar-CH), 7.34 (t, J = 7.4 Hz, 2H, Ar-CH), 6.87 (bs, 1H, NH), 5.50 (t, J = 5.5 Hz, 1H, NH), 5.27 (d, J = 7.9 Hz, 1H, NH), 4.47 (d, J = 7.0 Hz, 2H, Fmoc CHC$\underline{H}_2$), 4.27 (m, 2H, Fmoc C$\underline{H}$CH_2, αCH), 4.15 (d, J = 6.0 Hz, 2H, Gly αCH_2), 4.06 (d, J = 5.5 Hz, 2H, Gly αCH_2), 3.75 (s, 3H, OCH_3), 3.11 (dt, J = 14.0, 7.1 Hz, 1H, SC$\underline{H}_2$CH_2), 2.95 (dt, J = 14.0, 7.1 Hz, 1H, SC$\underline{H}_2$CH_2), 2.16 (dt, J = 21.1, 7.1. Hz, 1H, SCH_2C$\underline{H}_2$), 1.94 (dt, J = 21.1, 7.1 Hz, 1H, SCH_2C$\underline{H}_2$), 1.47 (s, 9H, C(CH_3)) ppm.^{13}C NMR (150 MHz, $CDCl_3$) δ 198.1 (SC=O), 171.6 (C=O), 170.0 (C=O), 156.3 (C=O), 155.7 (C=O), 143.7 (Ar-qC), 141.3 (Ar-qC), 127.8 (Ar-CH), 127.1 (Ar-CH), 125.1 (Ar-CH), 120.0 (Ar-CH), 80.5 (C($\underline{C}$H$_3$)), 67.4 (Fmoc CH$\underline{C}H_2$), 53.2 (αCH), 52.4 (OCH_3), 50.7 (Gly αCH_2), 47.1 (Fmoc $\underline{C}HCH_2$), 41.2 (Gly αCH_2), 32.6 (SC$H_2\underline{C}H_2$), 28.3 (C($\underline{C}$H$_3$)), 24.9 (S$\underline{C}H_2CH_2$) ppm. HRMS (*m/z* APCI +): Calculated for $C_{29}H_{36}N_3O_8S$ $([M+H])^+$, Calcd. 586.2145, Found. 586.2225. ν_{max} (film)/cm^{-1}: 3318 (N–H), 2949 (C–H), 1708 (C=O), 1675 (C=O).

Methyl *(S)*-(5-(((((9H-fluoren-9-yl)methoxy)carbonyl)glycyl)thio)-2-((*tert*-butoxycarbonyl)amino)pentanoyl)glycinate (27): R_f (50% EtOAc/Hex): 0.12, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H, Ar-CH), 7.61 (d, J = 7.4 Hz, 2H, Ar-CH), 7.40 (t, J = 7.5 Hz, 2H, Ar-CH), 7.32 (t, J = 7.4 Hz, 2H, Ar-CH), 6.64 (bs, 1H, NH), 5.51 (bs, 1H, NH), 5.07 (bs, 1H, NH), 4.45 (d, J = 7.0 Hz, 2H, Fmoc CHC$\underline{H}_2$), 4.31–4.23 (m, 2H, Fmoc C$\underline{H}$CH_2, αCH), 4.22–4.09 (m, 3H, Gly αCH_2), 3.95 (dd, J = 18.1, 4.4 Hz, 1H, Gly αCH_2), 3.72 (s, 3H, OCH_3), 3.16–3.08 (m, 1H, SC$\underline{H}_2CH_2CH_2$), 2.94–2.88 (m, 1H, SC$\underline{H}_2CH_2CH_2$), 1.89–1.81 (m, 1H, $SCH_2CH_2C\underline{H}_2$), 1.80–1.72 (m, 1H, $SCH_2C\underline{H}_2CH_2$), 1.68–1.60 (m, 2H, $SCH_2C\underline{H}_2C\underline{H}_2$), 1.44 (s, 9H, C($CH_3$)$_3$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.4 (SC=O), 172.3 (C=O), 170.4 (C=O), 156.7 (C=O), 156.4 (C=O), 143.9 (Ar-qC), 141.5 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.2 (Ar-CH), 80.4 (C($\underline{C}$H$_3$)), 67.4 (Fmoc CH$\underline{C}H_2$), 53.4 (αCH), 52.6 (OCH_3), 50.8 (Gly αCH_2), 47.3 (Fmoc $\underline{C}HCH_2$), 41.3 (Gly αCH_2), 31.6 (C$\underline{H}_2$), 31.1 (C$\underline{H}_2$), 28.5 (C($\underline{C}$H$_3$)$_3$), 27.8 (C$\underline{H}_2$), 25.7 (CH_2) ppm. HRMS (*m/z* ESI +): Calculated for $C_{30}H_{38}N_3O_8S$ $[M+H]^+$, Calcd 600.2301, found 600.2305. ν_{max} (film)/cm^{-1}: 3329 (N–H), 2927 (C–H), 1741 (C=O), 1683.92 (C=O).

(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl5-((3-(*p*–tolyl)propanoyl)thio)pentanoate (28): R_f (20% EtOAc:Hex): 0.45, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.4 Hz, 4H, Ar-CH), 7.63 (d, J = 7.4 Hz, 4H, Ar-CH), 7.42 (t, J = 7.4 Hz, 4H, Ar-CH), 7.35 (4H, t, J = 7.4 Hz, 4H, Ar-CH), 7.14–7.06 (m, 4H, Ar-CH), 5.66 (d, J = 7.8 Hz, 1H, NH), 4.69–4.65 (m, 1H, Ser αCH), 4.54–4.39 (m, 4H, Fmoc CHC$\underline{H}_2$, Ser βCH_2), 4.25 (t, J = 6.9 Hz, 1H, Fmoc C$\underline{H}$CH_2), 3.80 (s, 3H, OCH_3), 2.97-2.83 (m, 6H, CH_2, CH_2, CH_2), 2.39-2.33 (m, 5H, CH_2, CH_2, CH_3), 1.73–1.58 (m, 4H, CH_2, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7 (SC=O), 172.8 (C=O), 170.0 (C=O), 155.9 (C=O), 143.8 (Ar-qC), 141.4 (Ar-qC), 137.0 (Ar-qC), 135.9 (Ar-qC), 129.3 (Ar-CH), 128.3 (Ar-CH), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 67.4 (Fmoc CH$\underline{C}H_2$), 64.0 (Ser βCH_2), 53.5 (Ser αCH), 53.0 (OCH_3), 47.2 (Fmoc $\underline{C}HCH_2$), 45.8 (CH_2), 33.4 (CH_2), 31.1 (CH_2), 29.0 (CH_2), 28.4 (CH_2), 23.9 (CH_2), 21.1 (CH_3) ppm. HRMS (*m/z*) calculated for $C_{34}H_{37}NNaO_7S$ $[M+Na]^+$, calcd. 626.2187, found 626.2183. ν_{max} (film)/cm^{-1}: 3357 (NH), 1733 (C=O).

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-(heptanoylthio)pentanoate (29)**: R_f (20% EtOAc:Hex): 0.35, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.5 Hz, 4H, Ar-CH), 7.63

(d, J = 7.5 Hz, 4H, Ar-CH), 7.43 (t, J = 7.5 Hz, 4H, Ar-CH), 7.35 (t, J = 7.5 Hz, 4H, Ar-CH), 5.66 (d, J = 7.9 Hz, 2H, NH), 4.68–4.64 (m, 1H, Ser αCH), 4.53-4.39 (m, 4H, Fmoc CHC$\underline{H}_2$, Ser βCH$_2$), 4.27 (t, J = 6.8 Hz, 1H, Fmoc C$\underline{H}$CH$_2$), 3.82 (s, 3H, OCH$_3$), 2.88 (t, J = 7.1 Hz, 2H, CH$_2$S), 2.55 (t, J = 7.3 Hz, 2H, CH$_2$), 1.75–1.58 (m, 6H, CH$_2$, CH$_2$, CH$_2$), 1.36-1.27 (m, 6H, CH$_2$, CH$_2$, CH$_2$), 0.90 (t, J = 6.8 Hz, 3H, CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ 199.8 (SC=O), 172.9 (C=O), 170.0 (C=O), 155.9 (C=O), 143.8 (Ar-qC), 141.4 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 67.4 (Fmoc CH$\underline{C}$H$_2$), 64.0 (Ser βCH$_2$), 53.5 (Ser αCH), 53.0 (OCH$_3$), 47.2 (Fmoc $\underline{C}$HCH$_2$), 44.3 (CH$_2$), 33.4 (CH$_2$), 31.5 (CH$_2$), 29.1 (CH$_2$), 28.7 (CH$_2$), 28.3 (CH$_2$S), 25.7 (CH$_2$), 23.9 (CH$_2$), 22.5 (CH$_2$), 14.1 (CH$_3$) ppm. HRMS (*m/z*) calculated for $C_{31}H_{39}NNaO_7S$ $[M+Na]^+$, calcd. 592.2344, found 592.2339. ν_{max} (film)/cm^{-1}: 3357 (NH), 1726, 1688 (C=O).

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-((2-cyclohexylacetyl)thio)pentanoate (30)**: R_f (40% EtOc:Hex): 0.35, ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, J = 7.5 Hz, 4H, Ar-CH), 7.62 (d, J = 7.5 Hz, 4H, Ar-CH), 7.43 (t, J = 7.5 Hz, 4H, Ar-CH), 7.35 (t, J = 7.5 Hz, 4H, Ar-CH), 5.65 (d, J = 7.78 Hz, 1H, NH), 4.68-4.64 (m, 1H, Ser αCH), 4.53–4.38 (m, 4H, Fmoc CHC$\underline{H}_2$, Ser βCH$_2$), 4.27 (t, J = 6.9 Hz, 1H, Fmoc C$\underline{H}$CH$_2$), 3.80 (s, 3H, OCH$_3$), 2.88 (t, J = 6.4 Hz, 2H, CH$_2$S), 2.43 (d, J = 6.4 Hz, 2H, CH$_2$), 2.37 (t, J = 6.4 Hz, 2H, CH$_2$), 1.91-1.80 (m, 1H, CH), 1.74-1.58 (m, 9H, CH$_2$, CH$_2$, CH$_2$, CH$_2$, CH$_2$), 1.32-1.14 (m, 3H, CH$_2$, CH$_2$), 1.02-0.92 (m, 2H, CH$_2$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ 199.1 (SC=O), 172.9 (C=O), 170.1 (C=O), 155.9 (C=O), 143.8 (Ar-qC), 141.5 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.2 (Ar-CH), 67.4 (Fmoc CH$\underline{C}$H$_2$), 64.0 (Ser βCH$_2$), 53.6 (Ser αCH), 53.0 (OCH$_3$), 51.9 (CH$_2$) 47.3 (Fmoc $\underline{C}$HCH$_2$), 35.8 (CH), 33.4 (CH$_2$), 33.0, (CH$_2$), 29.2 (CH$_2$), 28.4 (CH$_2$S), 26.2 (CH$_2$), 26.1 (CH$_2$), 24.0 (CH$_2$), ppm. HRMS (*m/z*) calculated for $C_{32}H_{39}NNaO_7S$ $[M+Na]^+$, calcd. 604.2362, found 604.2339. ν_{max} (film)/cm^{-1}: 3335 (NH), 1768 (C=O).

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-((2-phenylacetyl)thio)pentanoate (31)**: R_f (30% EtOAc:Hex): 0.40, ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, J = 7.7 Hz, 4H, Ar-CH), 7.63 (d, J = 7.7 Hz, 4H, Ar-CH), 7.42 (t, J = 7.7 Hz, 4H, Ar-CH), 7.35 (t, J = 7.7 Hz, 4H, Ar-CH), 5.68 (d, J = 8.0 Hz, 1H, NH), 4.68-4.64 (m, 1H, Ser αCH), 4.53-4.38 (m, 4H, Fmoc CHC$\underline{H}_2$, Ser βCH$_2$), 4.26 (t, J = 6.9 Hz, 1H, Fmoc C$\underline{H}$CH$_2$), 3.83 (s, 2H, C$\underline{H}_2$Ph), 3.79 (s, 3H, OCH$_3$), 2.87 (t, J = 7.0 Hz, 2H, CH$_2$S), 2.35 (t, J = 7.0 Hz, 2H, COC$\underline{H}_2$CH$_2$CH$_2$CH$_2$S), 1.73-1.56 (m, 4H, COCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$S) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.6 (SC=O), 172.9 (C=O), 170.1 (C=O), 155.9 (C=O), 143.8 (Ar-qC), 141.4 (Ar-qC), 133.7 (Ar-qC), 129.7 (Ar-CH), 128.8 (Ar-CH), 127.9 (Ar-CH), 127.5 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 67.4 (Fmoc CH$\underline{C}$H$_2$), 64.0 (Ser βCH$_2$), 53.5 (Ser αCH), 53.0 (OCH$_3$), 50.6 (C$\underline{H}_2$Ph), 47.2 (Fmoc $\underline{C}$HCH$_2$), 33.4 (CO$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$S), 28.9, (COCH$_2$$\underline{C}H_2CH_2CH_2$S), 28.8 (CH$_2$S), 23.9 (COCH$_2CH_2$$\underline{C}H_2CH_2$S) ppm. HRMS (*m/z*) calculated for $C_{32}H_{33}NNaO_7S$ $[M+Na]^+$, calcd. 598.1857, found 598.1869. ν_{max} (film)/cm^{-1}: 2950 (NH), 1690 (C=O).

(*S*)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl5-(((((9H-fluoren-9-yl)methoxy)carbonyl)-L-alanyl)thio) pentanoate (32): R_f (40% EtOAc:Hex): 0.32, ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, J = 7.4 Hz, 4H, Ar-CH), 7.62 (d, J = 7.4 Hz, 4H, Ar-CH), 7.42 (t, J = 7.4 Hz, 4H, Ar-CH), 7.33 (t, J = 7.4 Hz, 4H, Ar-CH), 5.69 (d, J = 8.4 Hz, 1H, NH), 5.31 (1H, d, J = 8.0 Hz, 1H, NH), 4.68-4.64 (m, 1H, Ser αCH), 4.52-4.37 (m, 7H, Fmoc CHC$\underline{H}_2$, Fmoc CHC$\underline{H}_2$, Ser βCH$_2$, Ala αCH), 4.28–4.24 (m, 2H, Fmoc C$\underline{H}$CH$_2$, Fmoc C$\underline{H}$CH$_2$), 3.80 (s, 3H, OCH$_3$), 2.91 (t, J = 6.5 Hz, 2H, CH$_2$S), 2.38 (t, J = 6.5 Hz, 2H, COC$\underline{H}_2$CH$_2$CH$_2$CH$_2$S), 1.74-1.61 (m, 4H, COCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$S), 1.43 (d, J = 6.5 Hz, 3H, Ala CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ 201.3 (SC=O), 172.8 (C=O), 170.1 (C=O), 155.9 (C=O), 155.7 (C=O), 144.0 (Ar-qC), 143.9 (Ar-qC), 143.8 (Ar-qC), 141.5 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 67.4 (Fmoc CH$\underline{C}$H$_2$), 67.2 (Fmoc CH$\underline{C}$H$_2$), 64.0 (Ser βCH$_2$), 56.9 (Ala αCH), 53.6 (Ser αCH), 53.1 (OCH$_3$), 47.3 (Fmoc $\underline{C}$HCH$_2$), 47.2 (Fmoc $\underline{C}$HCH$_2$), 33.4 (CO$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$S), 28.9 (COCH$_2$$\underline{C}H_2CH_2CH_2$S), 28.4 (CH$_2$S), 23.9 (COCH$_2CH_2$$\underline{C}H_2CH_2$S), 19.1 (Ala CH$_3$) ppm.. HRMS (*m/z*) calculated for $C_{42}H_{42}N_2NaO_9S$ $[M+Na]^+$, calcd. 773.2521, found 773.2503. ν_{max} (film)/cm^{-1}: 3330 (NH), 1729 (C=O).

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-((*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*O*-(*tert*-butyl)-L-seryl)thio)pentanoate (33)**: R_f (30% EtOAc:Hex): 0.36, ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, J = 7.4 Hz, 4H, Ar-CH), 7.65 (m, 4H, Ar-CH), 7.42 (t, J = 7.4 Hz, 4H, Ar-CH), 7.34 (t, J = 7.4 Hz, 4H, Ar-CH), 5.76 (d, J = 8.8 Hz, 1H, NH), 5.67 (d, J = 8.1 Hz, 1H, NH), 4.67–4.64 (m, 1H, Ser αCH), 4.52–4.36 (m, 7H, Fmoc CHC$\underline{H}_2$, Fmoc CHC$\underline{H}_2$, Ser βCH$_2$, Ser αCH), 4.32–4.24 (m, 2H, Fmoc C$\underline{H}$CH$_2$, Fmoc C$\underline{H}$CH$_2$), 3.92 (dd, J = 2.5 Hz, J = 9.1 Hz, 1H, Ser βCH$_2$), 3.80 (s, 3H, OCH$_3$), 3.56 (dd, J = 2.5 Hz, J = 9.1 Hz, 1H, Ser βCH$_2$), 2.91 (t, J = 6.8 Hz, 2H, CH$_2$S), 2.37 (t, J = 6.8 Hz, 2H, COC$\underline{H}_2$CH$_2$CH$_2$CH$_2$S), 1.73-1.62 (m, 4H, COCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$S), 1.18 (s, 9H, C(CH$_3$)$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.3 (SC=O), 172.9 (C=O), 170.0 (C=O), 156.2 (C=O), 155.9 (C=O), 144.1 (Ar-qC), 143.8 (Ar-qC), 141.4 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 73.7 ($\underline{C}$(CH$_3$)$_3$), 67.4 (Fmoc CH$\underline{C}$H$_2$), 64.0 (Ser βCH$_2$), 62.0 (Ser βCH$_2$), 61.2 (Ser αCH), 53.5 (Ser αCH), 53.1 (OCH$_3$), 47.3 (Fmoc $\underline{C}$HCH$_2$), 47.2 (Fmoc $\underline{C}$HCH$_2$), 33.1 (CO$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$S), 28.8 (COCH$_2$$\underline{C}H_2CH_2CH_2$S), 28.5 (CH$_2$S), 27.4 (C($\underline{C}H_3$)$_3$), 23.9 (COCH$_2CH_2$$\underline{C}H_2CH_2$S) ppm. HRMS (*m/z*) calculated for $C_{46}H_{50}N_2NaO_{10}S$ $[M+Na]^+$, calcd. 845.3082, found 845.3078. ν_{max} (film)/cm^{-1}: 3338 (NH), 1719 (C=O).

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-(((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-phenylalanyl)thio)pentanoate (34)**: R_f (30% EtOAc:Hex): 0.33, ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, J = 7.8 Hz, 4H, Ar-CH), 7.66-7.54 (m, 4H, Ar-CH), 7.44 (t, J = 7.8 Hz, 4H, Ar-CH), 7.38–7.29 (m, 7H, Ar-CH, Phe Ar-CH) 7.25-7.14 (m, 2H, Phe Ar-CH), 5.76 (d, J = 7.8 Hz, 1H, NH), 5.35 (d, J = 8.9 Hz, 1H, NH), 4.78-4.68 (m, 2H, Ser αCH, Phe αCH), 4.55-4.40 (m, 6H, Fmoc CHC$\underline{H}_2$, Fmoc CHC$\underline{H}_2$, Ser βCH$_2$), 4.29-4.20 (m, 2H, Fmoc $\underline{C}$HCH$_2$, Fmoc $\underline{C}$HCH$_2$), 3.81 (s, 3H, OCH$_3$), 3.22 (dd, J = J = 14.0, 5.2 Hz, 1H, Phe βCH$_2$), 3.12–3.04 (m, 1H, βCH$_2$) 2.92 (t, J = 6.8 Hz, 2H, CH$_2$S), 2.38 (t, J = 6.8 Hz, 2H, COC$\underline{H}_2$CH$_2$CH$_2$CH$_2$S), 1.75–1.61 (m, 4H, COCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$S) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.4 (SC=O), 172.7 (C=O), 170.0 (C=O), 155.8 (C=O), 155.7 (C=O), 143.8 (Ar-qC), 143.7 (Ar-qC), 141.3 (Ar-qC), 135.6 (Phe Ar-qC), 129.4 (Phe Ar-CH), 128.8 (Phe Ar-CH), 127.8 (Ar-CH), 127.2 (Phe Ar-CH), 127.1 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 67.3 (Fmoc CH$\underline{C}$H$_2$), 67.2 (Fmoc CH$\underline{C}$H$_2$), 64.0 (Ser βCH$_2$), 61.6 (Phe αCH), 53.5 (Ser αCH), 53.0 (OCH$_3$), 47.1 (Fmoc $\underline{C}$HCH$_2$), 38.4 (Phe βCH$_2$), 33.3 (CO$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$S), 28.7 (COCH$_2$$\underline{C}H_2CH_2CH_2$S), 28.5 (CH$_2$S) 23.8 (COCH$_2CH_2$$\underline{C}H_2CH_2$S), ppm. HRMS (*m/z*) calculated for $C_{48}H_{46}N_2O_9S$ $[M+Na]^+$, calcd. 849.2822, found 849.2816. ν_{max} (film)/cm^{-1}: 3332 (NH), 1728 (C=O).

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-(((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-valyl)thio) pentanoate (35)**: R_f (30% EtOAc:Hex): 0.29 ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, J = 7.4 Hz, 4H, Ar-CH), 7.63 (d, J = 7.4 Hz, 4H, Ar-CH), 7.42 (t, J = 7.4 Hz, 4H, Ar-CH), 7.34 (t, J = 7.4 Hz, 4H, Ar-CH), 5.76 (d, J = 8.0 Hz, 1H, NH), 5.41 (d, J = 9.3 Hz, 1H, NH), 4.68-4.64 (m, 1H, Ser αCH), 4.52-4.36 (m, 7H, Fmoc CHC$\underline{H}_2$, Fmoc CHC$\underline{H}_2$, Ser βCH$_2$, Val αCH), 4.25 (t, J = 7.1 Hz, 2H, Fmoc C$\underline{H}$CH$_2$, Fmoc C$\underline{H}$CH$_2$), 3.80 (s, 3H, OCH$_3$), 2.91 (t, J = 6.9 Hz, 2H, CH$_2$S), 2.36-2.32 (m, 2H, COC$\underline{H}_2$CH$_2$CH$_2$CH$_2$S, Val CH), 1.74-1.59 (m, 4H, COCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$S), 1.02 (d, J = 6.6 Hz, 3H, Val CH$_3$), 0.90 (d, J = 6.6 Hz, 3H, Val CH$_3$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.5 (SC=O), 172.7 (C=O), 170.0 (C=O), 156.3 (C=O), 155.8 (C=O), 143.9 (Ar-qC), 143.7 (Ar-qC), 141.4 (Ar-qC), 141.3 (Ar-qC), 127.8 (Ar-CH), 127.1 (Ar-CH), 125.1 (Ar-CH), 120.1 (Ar-CH), 67.3 (Fmoc CH$\underline{C}$H$_2$), 67.1 (Fmoc CH$\underline{C}$H$_2$), 65.9 (Val αCH), 63.9 (Ser βCH$_2$), 53.5 (Ser αCH), 53.0 (OCH$_3$), 47.3 (Fmoc $\underline{C}$HCH$_2$), 47.1 (Fmoc $\underline{C}$HCH$_2$), 33.3 (CO$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$S), 31.1 (Val βCH), 28.8 (COCH$_2$$\underline{C}H_2CH_2CH_2$S), 28.3 (CH$_2$S), 23.8 (COCH$_2CH_2$$\underline{C}H_2CH_2$S), 19.5

(Val CH_3), 16.9 (Val CH_3) ppm. HRMS (*m/z*) calculated for $C_{44}H_{46}N_2NaO_9S$ $[M+Na]^+$, calcd. 801.2805, found 801.2816. ν_{max} (film)/cm^{-1}:3338 (NH), 1716 (C=O).

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-((((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-leucyl)thio) pentanoate (36)**: R_f (30% EtOAc:Hex): 0.36, ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 4H, Ar-CH), 7.62 (d, *J* = 7.8 Hz, 4H, Ar-CH), 7.42 (t, *J* = 7.8 Hz, 4H, Ar-CH), 7.33 (t, *J* = 7.8 Hz, 4H, Ar-CH), 5.69 (d, *J* = 7.5 Hz, 1H, NH), 5.17 (d, *J* = 7.5 Hz, 1H, NH), 4.68-4.64 (m, 1H, Ser αCH), 4.52-4.38 (m, 7H, Fmoc CHCH_2, Fmoc CHCH_2, Ser βCH_2, Leu αCH), 4.25 (t, *J* = 6.9 Hz, 2H, Fmoc CHCH_2, Fmoc CHCH_2), 3.80 (s, 3H, OCH_3), 2.89 (t, *J* = 6.4 Hz, 2H, CH_2S), 2.37 (t, *J* = 6.4 Hz, 2H, COCH_2CH_2CH_2CH_2S), 1.72–1.60 (m, 7H, $COCH_2CH_2CH_2CH_2S$, Leu βCH_2, Leu γCH), 0.96 (d, *J* = 2.5 Hz, 6H, Leu CH_3, Leu CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6 (SC=O), 172.8 (C=O), 170.1 (C=O), 155.9 (C=O), 155.9 (C=O), 144.0 (Ar-qC), 143.8 (Ar-qC), 141.5 (Ar-qC), 141.4 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 67.4 (Fmoc CHCH_2), 67.1 (Fmoc CHCH_2), 64.0 (Ser βCH_2), 59.7 (Leu αCH), 53.5 (Ser αCH), 53.1 (OCH_3), 47.4 (Fmoc CHCH_2), 47.2 (Fmoc CHCH_2), 41.8 (Leu βCH_2), 33.4 ($COCH_2CH_2CH_2CH_2S$), 28.8 ($COCH_2CH_2CH_2CH_2S$), 28.4 (CH_2S), 24.9 (Leu γCH), 23.9 ($COCH_2CH_2CH_2CH_2S$), 23.2 (Leu CH_3), 21.6 (Leu CH_3) ppm. HRMS (*m/z*) calculated for $C_{45}H_{48}N_2O_9S$ $[M+Na]^+$, calcd. 815.2973, found 815.2972. ν_{max} (film)/cm^{-1}: 3331 (NH), 1724 (C=O).

(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-((((((9H-fluoren-9-yl)methoxy)carbonyl)-L-threonyl) thio)pentanoate (37): R_f (30% EtOAc:Hex): 0.28, M.p. 60–62 °C, ^1H NMR (400 MHz, CDCl3) δ 7.77 (d, *J* = 7.4 Hz, 4H,Ar-CH), 7.65-7.57 (m, 4H, Ar-CH), 7.40 (t, *J* = 7.4 Hz, 4H, Ar-CH), 7.31 (4H, t, *J* = 7.4 Hz, Ar-CH), 5.69 (d, *J* = 7.7 Hz, 0.5H, 0.5xNH), 5.48 (d, *J* = 7.6 Hz, 0.5H, 0.5× NH), 4.67-4.55 (m, 2H, Ser αCH, NH), 4.53-4.36 (m, 8H, Fmoc CHCH_2, Fmoc CHCH_2 Thr αCH, Thr βCH, Ser βCH_2), 4.28-4.17 (m, 2H, Fmoc CHCH_2, Fmoc CHCH_2), 3.78 (s, 3H, OCH_3), 2.87 (t, 2H, *J* = 7.1 Hz, CH_2S), 2.38-2.27 (2H, m, COCH_2CH_2CH_2CH_2S), 1.72-1.60 (m, 4H, $COCH_2CH_2CH_2CH_2S$), 1.43 (s, 12H, $C(CH_3)_3$, Thr CH_3) ppm. ^{13}C NMR (100 MHz, CDCl3) δ 200.9 (SC=O), 172.7 (C=O), 170.0 (C=O), 156.2 (C=O), 155.8 (C=O), 143.8 (Ar-qC), 143.7 (Ar-qC), 141.3 (Ar-qC), 141.3 (Ar-qC), 127.8 (Ar-CH), 127.1 (Ar-CH), 125.1 (Ar-CH), 120.0 (Ar-CH), 79.3 (C$(CH_3)_3$), 67.3 (Thr βCH), 67.1 (Fmoc CHCH_2, Fmoc CHCH_2), 63.9 (Ser βCH_2),60.9 (Thr αCH), 53.4 (Ser αCH), 53.1 (OCH_3), 47.2, 47.2 (Fmoc CHCH_2, Fmoc CHCH_2), 33.3 ($COCH_2CH_2CH_2CH_2S$), 29.7, 28.7 ($COCH_2CH_2CH_2CH_2S$), 28.4 ($C(CH_3)_3$), 28.3 (CH_2S), 23.8 (Thr CH_3) ppm. HRMS (*m/z*) calculated for $C_{43}H_{45}N_2O_{10}S$ $[M+H]^+$, calcd. 781.2779, found 781.2789. ν_{max} (film)/cm^{-1}: 3385 (NH), 1705 (C=O).

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-((((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-methionyl) thio)pentanoate (38)**: R_f (30% EtOAc:Hex): 0.31, M.p. 33–35 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 4H, Ar-CH), 7.62 (d, *J* = 7.4 Hz, 4H, Ar-CH), 7.42 (t, *J* = 7.4 Hz, 4H, Ar-CH), 7.33 (t, *J* = 7.4 Hz, 4H, Ar-CH), 5.69 (d, *J* = 8.3 Hz, 1H, NH), 5.51 (d, *J* = 9.0 Hz, 1H, NH), 4.68-4.64 (m, 1H, Ser αCH), 4.60-4.40 (m, 7H, Fmoc CHCH_2, Fmoc CHCH_2, Ser βCH_2, Met αCH), 4.25 (t, *J* = 6.9 Hz, 2H, Fmoc CHCH_2, Fmoc CHCH_2), 3.80 (s, 3H, OCH_3), 2.90 (m, 2H, CH_2S), 2.58-2.50 (m, 5H, Met CH_3, Met βCH_2), 2.36 (2H, t, *J* = 6.6 Hz, COCH_2CH_2CH_2CH_2S), 2.14-2.09 (2H, m, Met γCH_2), 1.72-1.58 (4H, m, $COCH_2CH_2CH_2CH_2S$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4 (SC=O), 172.8 (C=O), 170.1 (C=O), 155.9 (C=O), 144.0 (Ar-qC), 143.8 (Ar-qC), 141.5 (Ar-qC), 141.4 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 67.4 (Fmoc CHCH_2), 67.2 (Fmoc CHCH_2), 64.0 (Ser CH_2), 60.4 (Met αCH), 53.5 (Ser αCH), 53.1 (OCH_3), 47.3 (Fmoc CHCH_2), 47.2 (Fmoc CHCH_2), 38.5 (Met CH_3), 33.4 ($COCH_2CH_2CH_2CH_2S$), 32.1 (Met βCH_2), 30.1 (Met γCH_2), 28.7 ($COCH_2CH_2CH_2CH_2S$), 28.3 (CH_2S) 23.8 ($COCH_2CH_2CH_2CH_2S$) ppm. HRMS (*m/z*) calculated for $C_{44}H_{46}KN_2O_9S_2$ $[M+K]^+$, calcd. 849.2282, found 849.2534. ν_{max} (film)/cm^{-1}: 3325 (NH), 1726 (C=O).

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-((*N*^{2}-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*^{6}-(*tert*-butoxycarbonyl)-L-lysyl)thio)pentanoate (39)**: R_f (40% EtOAc:Hex): 0.32, ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.75 (d, *J* = 7.7 Hz, 4H, Ar-CH), 7.65-7.61 (m, 4H, Ar-CH), 7.55 (bs, 1H, NH), 7.42 (t, *J* = 7.7 Hz, 4H, Ar-CH), 7.33 (t, *J* = 7.7 Hz, 4H, Ar-CH), 5.72 (d, *J* = 6.9 Hz, 1H, NH), 5.52 (d, *J* = 6.6 Hz, 1H, NH), 4.68–4.64 (m, 1H, Ser αCH), 4.54-4.36 (m, 7H, Fmoc CHCH_2 Fmoc CHCH_2, Ser βCH_2, Lys αCH), 4.25 (t, *J* = 6.9 Hz, 2H, Fmoc CHCH_2, Fmoc CHCH_2), 3.80 (s, 3H, OCH_3), 3.14-3.10 (m, 2H, Lys εCH_2), 2.89 (t, *J* = 6.2 Hz, 2H, CH_2S), 2.33 (t, *J* = 6.2 Hz, 2H, COCH_2CH_2CH_2CH_2S), 1.94-1.86 (m, 1H, Lys βCH_2), 1.73-1.58 (5H, m, Lys βCH_2, $COCH_2CH_2CH_2CH_2S$), 1.54-1.29 (m, 13H, $C(CH_3)_3$, Lys δCH_2, Lys γCH_2,) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1 (SC=O), 172.7 (C=O), 170.0 (C=O), 156.0 (C=O), 155.8 (C=O), 143.7 (Ar-qC), 141.3 (Ar-qC), 127.8 (Ar-CH), 127.1 (Ar-CH), 125.2 (Ar-CH), 120.0 (Ar-CH), 79.4 ($C(CH_3)_3$), 67.3 (Fmoc CHCH_2), 67.1 (Fmoc CHCH_2), 63.9 (Ser βCH_2), 61.0 (Lys αCH), 53.4 (Ser αCH), 52.9 (OCH_3), 47.2 (Fmoc CHCH_2), 47.1 (Fmoc CHCH_2), 40.0 (Lys εCH_2), 33.3 ($COCH_2CH_2CH_2CH_2S$), 32.2 (Lys βCH_2), 29.7 (Lys δCH_2), 28.7 ($COCH_2CH_2CH_2CH_2S$), 23.8 ($COCH_2CH_2CH_2CH_2S$), 28.4 ($C(CH_3)_3$), 28.3 (CH_2S), 22.4 (Lys γCH_2) ppm. HRMS (*m/z*) calculated for $C_{50}H_{57}N_3NaO_{11}S$ $[M+Na]^+$, calcd. 930.3609, found 930.3606. ν_{max} (film)/cm^{-1}: 3351 (NH), 1712 (C=O).

(9*H*-Fluoren-9-yl)methyl *(S)*-2-((*(S)*-1-(9*H*-fluoren-9-yl)-5-(methoxycarbonyl)-3,8-dioxo-2,7-dioxa-13-thia-4-azatetradecan-14-oyl) pyrrolidine-1-carboxylate (40): R_f (40% EtOAc:Hex): 0.36. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.78 (m, 4H, Ar-CH), 7.65-7.61 (m, 4H, Ar-CH), 7.46-7.41 (m, 4H, Ar-CH), 7.38-7.33 (m, 4H, Ar-CH), 5.67 (dd, *J* = 8.0 Hz, *J* = 39.1 Hz, 1H, NH), 4.67-4.62 (m, 1H, Ser αCH), 4.57–4.24 (m, 9H, 2×Fmoc CHCH_2, Fmoc CHCH_2, Fmoc CHCH_2, Fmoc CHCH_2 Ser βCH_2, Pro αCH), 3.79 (s, 3H, OCH_3), 3.71-3.50 (m, 2H, Pro CH_2), 2.92-2.80 (m, 2H, CH_2S), 2.39-2.28 (m, 2H, COCH_2CH_2CH_2CH_2S), 2.26-1.90 (m, 4H, 2×Pro CH_2), 1.72-1.53 (m, 4H, $COCH_2CH_2CH_2CH_2S$) ppm.* ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2 (SC=O), 201.6 (SC=O), 172.9 (C=O), 172.8 (C=O), 170.0 (C=O), 155.9 (C=O), 155.2 (C=O), 154.7 (C=O), 144.2 (Ar-qC), 143.9 (Ar-qC), 141.4 (Ar-qC), 127.9 (Ar-CH), 127.8 (Ar-CH), 127.2 (Ar-CH), 127.1 (Ar-CH), 125.3 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 67.8 (Fmoc CHCH_2), 67.4 (Fmoc CHCH_2), 66.6 (Pro αCH), 66.2 (Pro αCH), 64.0 (Ser βCH_2), 53.5 (Ser αCH), 53.0 (OCH_3), 47.4 (Fmoc CHCH_2), 47.2 (Fmoc CHCH_2), 46.9 (Pro CH_2), 33.4 ($COCH_2CH_2CH_2CH_2S$), 31.9 (Pro CH_2), 30.8 (Pro CH_2), 28.9 ($COCH_2CH_2CH_2CH_2S$), 28.2 (CH_2S), 23.9 ($COCH_2CH_2CH_2CH_2S$), 23.2 (Pro CH_2) ppm.* *multiple signals correspond to an inseparable mixture of *cis/trans* prolyl isomers. HRMS (*m/z*) calculated for $C_{44}H_{44}N_2NaO_9S$ $[M+Na]^+$, calcd. 799.2659, found 799.2642. ν_{max} (film)/cm^{-1}: 3332 (NH), 1704 (C=O).

***(S)*-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl (6*S*,9*S*)-9-isopropyl-2,2,6-trimethyl-4,7,10-trioxo-3-oxa-11-thia-5,8-diazahexadecan-16-oate (41)**: R_f (80% EtOAc:Hex): 0.42.^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 4H, Ar-CH), 7.63 (d, *J* = 7.4 Hz, 4H, Ar-CH), 7.41 (t, *J* = 7.4 Hz, 4H, Ar-CH), 7.32 (t, *J* = 7.4 Hz, 4H, Ar-CH), 6.89 (bs, 1H, NH), 5.68 (d, *J* = 6.7 Hz, 1H, NH), 4.98 (bs, 1H, NH), 4.67–4.59 (m, 2H, Ser αCH, Val αCH), 4.55-4.38 (m, 4H, Fmoc CHCH_2, Ser βCH_2), 4.28-4.20 (m, 2H, Fmoc CHCH_2, Ala αCH), 3.80 (s, 3H, OCH_3), 2.89 (t, *J* = 6.9 Hz, 2H, CH_2S), 2.37-2.30 (m, 3H, COCH_2CH_2CH_2CH_2S, Val βCH), 1.72-1.58 (m, 4H, $COCH_2CH_2CH_2CH_2S$), 1.47 (d, 9H, $C(CH_3)_3$), 1.39 (app. t, *J* = 6.5 Hz, 3H, Ala CH_3), 0.99-0.88 (m, 6H, Val CH_3, Val CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2 (SC=O), 172.9 (C=O), 172.8 (C=O), 170.1 (C=O), 156.0 (C=O), 155.9 (C=O), 143.8 (Ar-qC), 141.5 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.2 (Ar-CH), 80.5 (C$(CH_3)_3$), 67.4 (Fmoc CHCH_2), 64.0 (Ser βCH_2), 63.9 (Ala αCH), 53.5 (Ser αCH), 53.1 (OCH_3), 50.1 (Thr αCH), 47.2 (Fmoc CHCH_2), 33.4 ($COCH_2CH_2CH_2CH_2S$), 31.2 (Thr βCH), 29.8 ($COCH_2CH_2CH_2CH_2S$), 28.5 ($C(CH_3)_3$), 28.4 (CH_2S), 23.9 ($COCH_2CH_2CH_2CH_2S$) 20.1 (Thr CH_3), 19.5 (Thr CH_3), 19.4 (Ala CH_3)

ppm. HRMS (*m/z*) calculated for $C_{37}H_{49}N_3NaO_{10}S$ $[M+Na]^+$, calcd. 750.3045, found 750.3031. ν_{max} (film)/cm^{-1}: 3325 (NH), 1683 (C=O).

(S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-(((S)-4-acetamido-5-((2-methoxy-2-oxoethyl)amino)-5-oxopentanoyl)thio)pentanoate (42): R_f (100% EtOAc): 0.26. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 4H, Ar-CH), 7.632 (d, *J* = 7.4 Hz, 4H, Ar-CH), 7.41 (t, *J* = 7.4 Hz, 4H, Ar-CH), 7.32 (t, *J* = 7.4 Hz, 4H, Ar-CH), 6.90 (d, *J* = 5.7 Hz, 1H, NH), 5.86 (d, *J* = 8.2 Hz, 0.5H, NH), 5.83 (d, *J* = 8.2 Hz, 0.5H, NH), 4.68-4.64 (m, 1H, Ser αCH), 4.58-4.37 (m, 5H, Fmoc CHC$\underline{H}_2$, Ser βCH$_2$, Glu αCH), 4.25 (t, *J* = 6.8 Hz, 1H, Fmoc C$\underline{H}$CH$_2$), 4.01 (d, *J* = 5.7 Hz, 2H, Gly αCH$_2$), 3.80-3.72 (m, 6H, Gly OCH$_3$, Ser OCH$_3$), 2.87 (t, *J* = 6.8 Hz, 2H, CH$_2$S), 2.75-2.65 (m, 2H, Glu γCH$_2$), 2.36 (t, *J* = 6.8 Hz, 2H, CO$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$S), 2.17-2.00 (m, 5H, Glu βCH$_2$, COCH$_3$), 1.70-1.53 (m, 4H, COCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$S) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4 (SC=O), 172.9 (C=O), 171.8 (C=O), 171.2 (C=O), 170.4 (C=O), 170.1 (C=O) 168.3 (C=O), 156.0 (C=O), 143.8 (Ar-qC), 141.4 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 67.4 (Fmoc CH$\underline{C}$H$_2$), 64.0 (Ser βCH$_2$), 53.5 (Ser αCH), 53.0 (Ser OCH$_3$), 52.5 (Gly OCH$_3$), 47.2 (Fmoc $\underline{C}$HCH$_2$), 41.2 (Gly αCH$_2$), 39.9 (Glu γCH$_2$), 33.3 (CO$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$S), 28.9 (COCH$_2$$\underline{C}H_2CH_2CH_2$S), 28.5 (CH$_2$S), 27.9 (Glu βCH$_2$), 23.8 (COCH$_2CH_2$$\underline{C}H_2CH_2$S), 23.0 (CO$\underline{C}H_3$) ppm. HRMS (*m/z*) calculated for $C_{34}H_{41}N_3NaO_{11}S$ $[M+Na]^+$, calcd. 722.2365, found 722.2354. ν_{max} (film)/cm^{-1}: 3306 (NH), 1739, 1660 (C=O).

***(S)*-2-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl 5-(((*S*)-1-(9*H*-fluoren-9-yl)-5-(methoxycarbonyl)-3,8,13-trioxo-2,7-dioxa-12-thia-4-azaoctadecan-18-oyl)thio)pentanoate (43)**: R_f (40% EtOAc:Hex): 0.35. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.5 Hz, 4H, Ar-CH), 7.63 (d, *J* = 7.5 Hz, 4H, Ar-CH), 7.43 (t, *J* = 7.5 Hz, 4H, Ar-CH), 7.34 (t, *J* = 7.5 Hz, 4H, Ar-CH), 5.66 (d, *J* = 8.3 Hz, 2H, NH), 4.68-4.64 (m, 2H, Ser αCH), 4.53-4.39 (m, 8H, Fmoc CHC$\underline{H}_2$, Fmoc CHC$\underline{H}_2$, Ser βCH$_2$, Ser βCH$_2$), 4.27 (t, *J* = 6.8 Hz, 2H, Fmoc C$\underline{H}$CH$_2$, Fmoc C$\underline{H}$CH$_2$), 3.81 (s, 6H, OCH$_3$), 2.88 (t, *J* = 6.8 Hz, 4H, CH$_2$S), 2.55 (t, *J* = 5.7 Hz, 4H, CH$_2$, CH$_2$), 2.37 (t, *J* = 6.8 Hz, 4H, CH$_2$, CH$_2$), 1.73–1.57 (m, 12H, CH$_2$, CH$_2$, CH$_2$, CH$_2$, CH$_2$, CH$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0 (SC=O), 172.9 (C=O), 170.1 (C=O), 155.9 (C=O), 143.8 (Ar-qC), 141.5 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.2 (Ar-CH), 67.4 (Fmoc CH$\underline{C}$H$_2$), 64.0 (Ser βCH$_2$), 53.6 (Ser αCH), 53.1 (OCH$_3$), 47.3 (Fmoc C$\underline{H}$CH$_2$), 43.7 (CH$_2$), 33.4 (CH$_2$), 29.1 (CH$_2$), 28.4 (CH$_2$S), 24.9 (CH$_2$, CH$_2$), 23.9 (CH$_2$) ppm. HRMS (*m/z*) calculated for $C_{54}H_{60}N_2NaO_{14}S_2$ $[M+Na]^+$, calcd. 1047.3378, found 1047.3378. ν_{max} (film)/cm^{-1}: 2949 (NH), 1737, 1682 (C=O).

(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(((*S*)-1-(9*H*-Fluoren-9-yl)-5-(methoxycarbonyl)-3,8,14-trioxo-2,7-dioxa-13-thia-4-azapentadecan-15-yl)oxy)-6-methyltetrahydro-2*H*-pyran-3,4,5-triyl triacetate (44): R_f (40% EtOAc:Hex): 0.33. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 4H, Ar-CH), 7.64-7.60 (m, 4H, Ar-CH), 7.42 (t, *J* = 7.7 Hz, 4H,Ar-CH), 7.34 (t, *J* = 7.7 Hz, 4H, Ar-CH), 5.70 (d, *J* = 8.7 Hz, 1H, NH), 5.42-5.36 (m, 2H, H-3, H-2), 5.11 (t, *J* = 9.7 Hz, 1H, H-4), 4.84 (s, 1H, H-1), 4.68-4.64 (m, 1H, Ser αCH), 4.53-4.39 (m, 4H, Fmoc CHC$\underline{H}_2$, Ser βCH$_2$), 4.28-4.25 (m, 3H, Fmoc C$\underline{H}$CH$_2$, OCH$_2$CO), 3.97-3.90 (m, 1H, H-5), 3.81 (s, 3H, OCH$_3$), 2.92 (t, *J* = 7.2 Hz, 2H, CH$_2$S), 2.38 (t, *J* = 7.2 Hz, 2H, CO$\underline{H}_2$CH$_2$CH$_2$CH$_2$S), 2.17 (s, 3H, COCH$_3$), 2.08 (s, 3H, COCH$_3$), 2.02 (s, 3H, COCH$_3$), 1.75-1.61 (m, 4H, COCH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$S), 1.23 (d, *J* = 6.1 Hz, 3H, H-6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3 (SC=O), 172.8 (C=O), 170.1 (C=O), 155.9 (C=O), 143.8 (Ar-qC), 141.4 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 97.9 (C-1), 71.7 (O$\underline{C}$H$_2$CO), 70.9 (C-4), 69.5 (C-2), 68.9 (C-3), 67.4 (Fmoc CH$\underline{C}$H$_2$), 67.1 (C-5), 64.1 (Ser βCH$_2$), 53.5 (Ser αCH), 53.1 (OCH$_3$), 47.2 (Fmoc $\underline{C}$HCH$_2$), 33.4 (CO$\underline{C}$H$_2$CH$_2$CH$_2$CH$_2$S), 28.9 (COCH$_2$$\underline{C}H_2CH_2CH_2$S), 27.5 (CH$_2$S), 23.9 (COCH$_2CH_2$$\underline{C}H_2CH_2$S) 21.0 (CO$\underline{C}H_3$), 20.9 (CO$\underline{C}H_3$), 20.8 (CO$\underline{C}H_3$), 17.5 (C-6) ppm. HRMS (*m/z*) calculated for $C_{38}H_{45}NNaO_{15}S$ $[M+Na]^+$, calcd. 810.2397, found 810.2402. ν_{max} (film)/cm^{-1}: 3365 (NH), 1741 (C=O).

Methyl ((*S*)-4-((*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*O*-(*tert*-butyl)-L-seryl)thio)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanoyl)glycinate (45): R_f (50% EtOAc:Hex): 0.35. ^{1}H NMR (600 MHz, $CDCl_3$) δ δ 7.79 (bs, 1H, NH) 7.69-7.62 (m, 8H, Ar-CH), 7.40 (t, *J* = 7.4 Hz, 4H, Ar-CH), 7.34-7.28 (m, 4H, Ar-CH), 7.05 (bs, 2H, NH), 6.18 (app. t, 2H, NH), 5.74 (d, *J* = 8.9 Hz, 2H, NH), 5.27-5.18 (m, 2H, NH), 5.26 (d, *J* = 8.5 Hz, 1H, NH), 4.89 (bs, 1H, Ser αCH), 4.73–4.65 (m, 2H, Val αCH, Val αCH), 4.42-4.38 (m, 2H, Fmoc CHC$\underline{H}_2$), 4.16–3.91 (m, 5H, Ser αCH, Fmoc CHC$\underline{H}_2$, Fmoc C$\underline{H}$CH$_2$, Fmoc C$\underline{H}$CH$_2$), 3.85–3.72 (m, 4H, Gly αCH$_2$, Gly αCH$_2$), 3.68-3.66 (m, 6H, OCH$_3$, OCH$_3$), 3.14 (d, *J* = 11.0 Hz, 1H, Val γCH$_2$), 3.06–2.93 (m, 4H, Ser βCH$_2$, Val γCH$_2$, Ser βCH$_2$), 2.86-2.80 (m, 1H Ser βCH$_2$), 2.78-2.71 (m, 2H, Val γCH$_2$), 2.22-2.12 (m, 2H, Val αCH, Val αCH), 1.46-1.44 (m, 18H, C(CH$_3$)$_3$, C(CH$_3$)$_3$), 1.37-1.24 (m, 18H, OC(CH$_3$)$_3$, OC(CH$_3$)$_3$), 1.02-0.95 (m, 6H, Val CH$_3$, Val CH$_3$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.2 (SC=O), 199.9 (SC=O), 171.7 (C=O), 171.1 (C=O), 170.1 (C=O), 170.0 (C=O), 156.9 (C=O), 156.7 (C=O), 156.1 (C=O), 155.8 (C=O), 146.1 (Ar-qC), 146.1 (Ar-qC), 145.8 (Ar-qC), 145.6 (Ar-qC), 139.9 (Ar-qC), 139.9 (Ar-qC), 139.7 (Ar-qC), 139.7 (Ar-qC), 129.8 (Ar-CH), 129.7 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 125.3 (Ar-CH), 124.5, (Ar-CH) 120.3 (Ar-CH), 120.3 (Ar-CH), 82.5 (C(CH$_3$)$_3$), 82.3 (C(CH$_3$)$_3$), 81.1 (C(CH$_3$)$_3$), 81.0 (C(CH$_3$)$_3$), 80.5 (C(CH$_3$)$_3$), 80.4 (C(CH$_3$)$_3$), 70.2 (Fmoc CH$\underline{C}$H$_2$), 70.1 (Fmoc CH$\underline{C}$H$_2$), 58.0 (Ser αCH), 57.6 (Ser αCH), 57.1 (Val αCH), 55.7 (Val αCH), 52.4 (OCH$_3$), 52.4 (OCH$_3$), 41.3 (Fmoc $\underline{C}$HCH$_2$), 41.2 (Fmoc $\underline{C}$HCH$_2$), 41.1 (Gly αCH$_2$), 41.1 (Gly αCH$_2$), 37.6 (Ser βCH$_2$), 37.5 (Ser βCH$_2$), 37.4 (Val βCH$_2$), 36.3 (Val βCH$_2$), 32.6 (Val γCH$_2$), 31.7 (Val γCH$_2$), 28.4 (C($\underline{C}$H$_3$)$_3$), 28.3 (C($\underline{C}$H$_3$)$_3$), 15.8 (Val CH$_3$), 14.8 (Val CH$_3$) ppm. *Isolated as a mixture of diastereoisomers and rotamers at rt. HRMS (*m/z* ESI+): Calculated for $C_{37}H_{44}N_3O_8S$ $[M+H]^+$, Calcd 690.2850, found 690.2844. ν_{max} (film)/cm^{-1}: 3331 (N–H), 2976 (C–H), 1708 (C=O), 1682 (C=O)

Methyl ((*S*)-4-(((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-phenylalanyl)thio)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanoyl)glycinate (46): R_f (50% EtOAc/Hex): 0.35. ^{1}H NMR (600 MHz, $CDCl_3$) δ δ 7.82–7.73 (m, 4H, Ar-CH), 7.61–7.48 (m, 4H, Ar-CH), 7.41 (t, *J* = 7.2 Hz, 4H, Ar-CH), 7.36–7.25 (m, 10H, Ar-CH), 7.19 (t, *J* = 7.2 Hz, 4H, Ar-CH), 6.92-6.72 (m, 2H, NH), 5.45-5.25 (m, 4H, NH), 4.80–4.63 (m, 2H, Phe αCH), 4.51–4.33 (m, 5H, Fmoc CHC$\underline{H}_2$ and Val αCH), 4.25-4.17 (m, 2H, Fmoc C$\underline{H}$CH$_2$), 4.15-3.95 (m, 5H, Gly αCH$_2$, Val αCH), 3.78-3.68 (m, 6H, OCH$_3$), 3.27–3.15 (m, 3H, Phe βCH$_2$, Val γCH$_2$), 3.06 (dt, *J* = 21.7, 10.7 Hz, 2H, Phe βCH$_2$), 2.98–2.89 (m, 2H, Val γCH$_2$), 2.79 (dd, *J* = 13.4, 7.6 Hz, 1H, Val γCH$_2$), 2.29–2.12 (m, 2H, Val βCH), 1.46 (s, 18H, C(CH$_3$)$_3$), 0.99 (dd, *J* = 19.9, 6.7 Hz, 6H, Val γCH$_3$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.7 (SC=O), 200.6 (SC=O), 171.6 (C=O), 171.0 (C=O), 170.1 (C=O), 170.0 (C=O), 156.1 (C=O), 156.3 (C=O), 156.0 (C=O), 155.7 (C=O), 143.9 (Ar-qC), 143.8 (Ar-qC), 143.7 (Ar-qC), 141.4 (Ar-qC), 135.6 (Ar-qC), 129.5 (Ar-CH), 129.4 (Ar-CH), 128.9 (Ar-CH), 128.9 (Ar-CH), 127.8 (Ar-CH), 127.4 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 80.4 (C($\underline{C}$H$_3$)), 80.3 (C($\underline{C}$H$_3$)), 67.4 (Fmoc CH$\underline{C}$H$_2$), 67.3 (Fmoc CH$\underline{C}$H$_2$), 62.0 (Phe αCH), 61.8 (Phe αCH), 57.8 (Val αCH), 56.4 (Val αCH), 52.6 (OCH$_3$), 52.5 (OCH$_3$), 52.4 (OCH$_3$), 47.2 (Fmoc $\underline{C}$HCH$_2$), 47.2 (Fmoc $\underline{C}$HCH$_2$), 41.5 (Gly αCH$_2$) 41.3 (Gly αCH$_2$), 38.4 (Phe βCH$_2$), 38.3 (Phe βCH$_2$), 37.3 (Val βCH), 36.6 (βCH), 32.6 (γCH$_2$), 31.9 (γCH$_2$), 28.4 (C($\underline{C}$H$_3$)), 28.4 (C($\underline{C}$H$_3$)), 16.0 (CH$_3$), 14.4 (CH$_3$) ppm. *Isolated as a mixture of diastereoisomers at rt. HRMS (*m/z* ESI+): Calculated for $C_{37}H_{44}N_3O_8S$ $[M+H]^+$, Calcd 690.2850, found 690.2844. ν_{max} (film)/cm^{-1}: 3323 (N–H), 2963 (C–H), 1731 (C=O), 1690 (C=O).

Methyl ((*S*)-4-(((((9H-fluoren-9-yl)methoxy)carbonyl)-L-valyl)thio)-2-((tert-butoxycarbonyl)amino)-3-methylbutanoyl)glycinate (47): R_f (50% EtOAc/Hex): 0.37. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 4H, Ar-CH), 7.72–7.59 (m, 4H, Ar-CH), 7.45-7.37 (m, 4H, Ar-CH), 7.36–7.28 (m, 4H, Ar-CH), 6.85-6.63 (m, 2H, NH), 5.37-5.15 (m, 4H, NH), 4.55–4.30 (m, 6H, Fmoc CHC$\underline{H}_2$, Fmoc Val αCH and Boc Val αCH), 4.32-4.19 (m, 3H, Fmoc C$\underline{H}$CH$_2$, Fmoc Val αCH), 4.14-3.93 (m,

5H, Gly αCH$_2$, Boc Val αCH), 3.74-3.65 (m, 6H, OCH$_3$), 3.20 (dd, *J*= 13.8, 5.4 Hz, 1H, Boc Val γCH$_2$), 2.91 (d, *J*=6.7 Hz, 2H, Boc Val γCH$_2$), 2.77 (dd, *J*=13.8, 7.6 Hz, 1H, Boc Val γCH$_2$), 2.40–2.08 (m, 1H, Boc Val βCH, Fmoc Val βCH), 1.43 (s, 18H, C(CH$_3$)$_3$), 1.03-0.95 (m, 12H, Boc Val γCH$_3$, Fmoc Val γCH$_3$), 0.90 (dd, *J*=13.3, 6.8 Hz, 6H, Fmoc Val γCH$_3$) ppm. ^{13}C NMR (150 MHz, CDCl$_3$) δ 201.0 (SC=O), 200.8 (SC=O), 171.5 (C=O), 171.0 (C=O), 170.0 (C=O), 169.9 (C=O), 156.6 (C=O), 156.3 (C=O), 156.0 (C=O), 155.7 (C=O), 144.1 (Ar-qC), 143.8 (Ar-qC), 143.7 (Ar-qC), 141.5 (Ar-qC), 127.9 (Ar-CH), 127.3 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 80.3 (C(CH$_3$)), 67.4 (Fmoc CHCH$_2$), 67.3 (Fmoc CHCH$_2$), 66.4 (Fmoc Val αCH), 66.1 (Fmoc Val αCH), 57.9 (Val αCH), 56.4 (Val αCH), 52.5 (OCH$_3$), 52.3 (OCH$_3$), 47.4 (Fmoc CHCH$_2$), 41.3 (Gly αCH$_2$), 37.3 (Boc Val βCH), 36.6 (Boc Val βCH), 32.5 (Boc Val γCH$_2$), 31.8 (Boc Val γCH$_2$), 31.2 (Fmoc Val βCH), 31.0 (Fmoc Val βCH), 28.4 (C(CH$_3$)), 19.6 (CH$_3$), 17.4 (CH$_3$), 17.1 (CH$_3$), 16.0 (CH$_3$), 15.6 (CH$_3$), 14.5 (CH$_3$), 14.3 (CH$_3$) ppm. *Isolated as a mixture of diastereoisomers at rt. HRMS (*m/z* ESI+): Calculated for $C_{33}H_{44}N_3O_8S$ $[M+H]^+$, Calcd 642.2844, found 642.2847. ν_{max} (film)/cm^{-1}: 3323 (N–H), 2927 (C–H), 1670 (C=O)

Methyl *S*-(*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*O*-(tert-butyl)-L-seryl)-*N*-(tert-butoxycarbonyl)-L-homocysteinyl glycinate (48): R$_f$ (50% EtOAc/Hex): 0.35. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 (d, *J*= 7.5 Hz, 2H, Ar-CH), 7.64 (dd, *J*=10.8, 7.6 Hz, 2H,Ar-CH), 7.39 (t, *J*= 7.4 Hz, 2H, Ar-CH), 7.31 (t, *J*=7.4 Hz, 2H, Ar-CH), 6.81 (bs, 1H, NH), 5.75 (d, *J*=8.7 Hz, 1H, NH), 5.20 (d, *J*=7.6 Hz, 1H, NH), 4.57–4.43 (m, 3H, Ser αCH, Fmoc CHCH$_2$), 4.36 (t, *J*=7.1 Hz, 1H, αCH), 4.30-4.11 (m, 3H, Fmoc CHCH$_2$, Gly αCH$_2$), 4.01 (d, *J*=5.3 Hz, 2H, Gly αCH$_2$), 3.87 (dd, *J*=9.1, 3.1 Hz, 1H, Ser βCH$_2$), 3.70 (s, 3H, OCH$_3$), 3.55 (dd, *J*=9.1, 3.1 Hz, 1H, Ser βCH$_2$), 3.05–2.99 (m, 1H, SCH$_2$CH$_2$), 2.91–2.85 (m, 1H, SCH$_2$CH$_2$), 2.13-2.05 (m, 1H, SCH$_2$CH$_2$), 1.88 (dt, *J*=14.3, 7.7 Hz, 1H, SCH$_2$CH$_2$), 1.43 (s, 9H, C(CH$_3$)), 1.15 (s, 9H, OC(CH$_3$)) ppm.* 13C NMR (150 MHz, CDCl$_3$) δ 200.7 (SC=O), 171.8 (C=O), 170.0 (C=O), 156.3 (C=O), 155.8 (C=O) 143.8 (Ar-qC), 141.5 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 80.7 (C(CH$_3$)$_3$), 80.5 (C(CH$_3$)$_3$), 73.9 (Ser αCH), 70.4 (Ser αCH), 67.5 (Fmoc CHCH$_2$), 61.9 (Ser βCH$_2$), 61.4 (αCH), 52.5 (OCH$_3$), 47.3 (Fmoc CHCH$_2$), 41.3 (Gly αCH$_2$), 34.3 (SCH$_2$CH$_2$), 32.0 (SCH$_2$CH$_2$), 28.4 (C(CH$_3$)$_3$), 27.4 (C(CH$_3$)$_3$), 25.5 (SCH$_2$CH$_2$) ppm.* *Multiple signals due to mixture of rotamers at rt. HRMS (*m/z* APCI+): Calculated for $C_{34}H_{46}N_3O_9S$ $[M+H]^+$, Calcd. 672.2949, Found. 672.2949. ν_{max} (film)/cm^{-1}: 3323 (N–H), 2949 (C–H), 1728 (C=O), 1676 (C=O)

Methyl *S*-((((9*H*-fluoren-9-yl)methoxy)carbonyl)-L-phenylalanyl)-*N*-(*tert*-butoxycarbonyl)-L-homocysteinylglycinate (49): R$_f$ (50% EtOAc/Hex): 0.4. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 (d, *J*=7.5 Hz, 2H, Ar-CH), 7.53 (dd, *J*=14.1, 7.5 Hz, 2H, Ar-CH), 7.39 (t, *J*=7.5 Hz, 2H, Ar-CH), 7.33–7.23 (m, 5H, Ar-CH), 7.16 (d, *J*=7.0 Hz, 2H, Ar-CH), 6.90 (bs, 1H, NH), 5.40-5.28 (m, 1H, NH), 4.68 (dd, *J*=13.5, 8.0 Hz, 1H, Phe αCH), 4.38 (d, *J*=7.0 Hz, 2H, Fmoc CHCH$_2$), 4.20 (m, 2H, αCH, Fmoc CHCH$_2$), 4.02 (d, *J*=5.2 Hz, 2H, Gly αCH$_2$), 3.71 (s, 3H, OCH$_3$), 3.19 (dd, *J*=14.1, 5.2 Hz, 1H, Phe βCH$_2$), 3.08–2.98 (m, 2H, Phe βCH$_2$, SCH$_2$CH$_2$), 2.96–2.87 (m, 1H, SCH$_2$CH$_2$), 2.16–2.05 (m, 1H, SCH$_2$CH$_2$), 1.94–1.83 (m, 1H, SCH$_2$CH$_2$), 1.45 (s, 9H, C(CH$_3$)$_3$) ppm. ^{13}C NMR (150 MHz, CDCl$_3$) δ 200.7 (SC=O), 171.8 (C=O), 170.1 (C=O), 155.9 (C=O) 154.8 (C=O), 143.7 (Ar-qC), 141.4 (Ar-qC), 135.6 (Ar-qC), 129.4 (Ar-CH), 128.9 (Ar-CH), 127.8 (Ar-CH), 127.4 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 80.6 (C(CH$_3$)$_3$), 67.3 (Fmoc CHCH$_2$), 61.8 (Phe αCH), 53.4 (αCH), 52.5 (OCH$_3$), 47.2 (Fmoc CHCH$_2$), 41.3 (Gly αCH$_2$), 38.3 (Phe βCH$_2$), 32.6 (SCH$_2$CH$_2$), 28.4 (C(CH$_3$)$_3$), 25.3 (SCH$_2$CH$_2$) ppm. HRMS (*m/z* ESI+): Calculated for $C_{36}H_{41}N_3O_8SNa$ $[M+Na]^+$, Calcd. 698.2507, Found. 698.2507. ν_{max} (film)/cm^{-1}: 2922 (C–H), 1766 (C=O), 1636 (C=O)

Methyl *S*-(((((9H-fluoren-9-yl)methoxy)carbonyl)-L-valyl)-*N*-(*tert*-butoxycarbonyl)-L-homocysteinylglycinate (50): R$_f$ (50% EtOAc/Hex): 0.4. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.81 (d, *J*=7.4 Hz, 2H, Ar-CH), 7.66 (d, *J*=7.4 Hz, 2H, Ar-CH), 7.45 (t, *J*=7.4 Hz, 2H, Ar-CH), 7.36 (t, *J*=7.4 Hz, 2H, Ar-CH), 6.89 (bs, 1H, NH), 5.52 (t, *J*=5.5 Hz, 1H, NH), 5.28 (d, *J*=7.9 Hz, 1H, NH), 4.49 (d, *J*=7.0 Hz, 2H, Fmoc CHCH$_2$), 4.29 (m, 3H, Fmoc CHCH$_2$, Val αCH, αCH), 4.17 4.08 (d, *J*=5.5 Hz, 2H, Gly αCH$_2$), 3.77 (s, 3H, OCH$_3$), 3.13 (dt, *J*=14.0, 7.1 Hz, 1H, SCH$_2$CH$_2$), 2.97 (dt, *J*=14.0, 7.1 Hz, 1H, SCH$_2$CH$_2$), 2.31–2.29 (m, 1H, Val βCH) 2.18 (dt, *J*=21.1, 7.1. Hz, 1H, SCH$_2$CH$_2$), 1.96 (dt, *J*=21.1, 7.1 Hz, 1H, SCH$_2$CH$_2$), 1.49 (s, 9H, C(CH$_3$)$_3$), 1.01-0.88 (m, 6H, Val CH$_3$, Val CH$_3$) ppm.^{13}C NMR (150 MHz, CDCl$_3$) δ 197.9 (SC=O), 171.4 (C=O), 169.8 (C=O), 156.1 (C=O), 155.6 (C=O), 143.5 (Ar-qC), 141.2 (Ar-qC), 127.6 (Ar-CH), 126.9 (Ar-CH), 124.9 (Ar-CH), 119.8.0 (Ar-CH), 80.3 (C(CH$_3$)), 67.2 (Fmoc CHCH$_2$), 58.8 (Val αCH), 53.0 (αCH), 52.2 (OCH$_3$)„ 46.9 (Fmoc CHCH$_2$), 41.0 (Gly αCH$_2$), 32.4 (SCH$_2$CH$_2$), 30.9 (Val βCH), 28.1 (C(CH$_3$)), 24.7 (SCH$_2$CH$_2$), 19.3 (Val CH$_3$) 16.8 (Val CH$_3$) ppm. HRMS (*m/z* ESI+): Calculated for $C_{32}H_{41}N_3O_8SNa$ $[M+Na]^+$, Calcd. 650.2507, Found. 650.2506. ν_{max} (film)/cm^{-1}: 3318 (N–H), 2911 (C–H), 1752 (C=O), 1676 (C=O).

Methyl ((*S*)-5-((*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*O*-(*tert*-butyl)-L-seryl)thio)-2-((*tert*-butoxycarbonyl)amino)pentanoyl) glycinate (51): R$_f$ (50% EtOAc/Hex): 0.17. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.77 (d, *J*=7.6 Hz, 2H, Ar-CH), 7.65 (d, *J*=7.7 Hz, 1H, Ar-CH), 7.63 (d, *J*=7.5 Hz, 1H, Ar-CH), 7.40 (t, *J*=7.6 Hz, 2H, Ar-CH), 7.32 (t, *J*= 7.4 Hz, 2H, Ar-CH), 6.74 (bs, 1H, NH), 5.74 (d, *J*=8.8 Hz, 1H, NH), 5.15 (d, *J*=7.5, 1H, NH), 4.54-4.46 (m, 2H, Ser αCH, Fmoc CHCH$_2$), 4.38-4.34 (m, 1H, Fmoc CHCH$_2$), 4.28 (t, *J*=7.3 Hz, 1H, Fmoc CHCH$_2$), 4.22 (bs, 1H, αCH), 4.00-3.98 (m, 2H, Gly αCH$_2$), 3.89 (dd, *J*=2.3, 9.1 Hz, 1H, Ser βCH$_2$), 3.70 (s, 3H, OCH$_3$), 3.56 (dd, *J*=3.4, 9.1 Hz, 1H, Ser βCH$_2$), 3.02-2.96 (m, 1H, SCH$_2$CH$_2$CH$_2$), 2.93-2.86 (m, 1H, SCH$_2$CH$_2$CH$_2$), 1.92–1.84 (m, 1H, SCH$_2$CH$_2$CH$_2$), 1.76-1.60 (m, 3H, SCH$_2$CH$_2$CH$_2$, SCH$_2$CH$_2$CH$_2$), 1.43 (s, 9H, Boc C(CH$_3$)$_3$), 1.14 (s, 9H, Ser C(CH$_3$)$_3$) ppm. ^{13}C NMR (150 MHz, CDCl$_3$) δ 200.5 (SC=O), 172.3 (C=O), 170.1 (C=O), 156.2 (C=O), 155.8 (C=O), 144.0 (Ar-qC), 141.4 (Ar-qC), 127.9 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 80.2 (Boc C(CH$_3$)$_3$), 73.8 (Ser C(CH$_3$)$_3$), 67.4 (Fmoc CHCH$_2$), 61.9 (Ser-βCH$_2$), 61.2 (Ser-αCH), 53.7 (αCH), 52.4 (OCH$_3$), 47.3 (Fmoc CHCH$_2$), 41.3 (Gly αCH$_2$), 31.6 (CH$_2$), 28.4 (Boc C(CH$_3$)), 28.3 (CH$_2$), 27.4 (Ser C(CH$_3$)$_3$), 25.6 (CH$_2$) ppm. HRMS (*m/z* ESI+): Calculated for $C_{35}H_{48}N_3O_9S$ $[M+H]^+$, Calcd. 686.3106, found 686.3104. ν_{max} (film)/cm^{-1}: 3330 (N–H), 2974 (C–H), 1676 (C=O), 1243 (C–O).

Methyl ((*S*)-5-(((((9H-fluoren-9-yl)methoxy)carbonyl)-L-phenylalanyl)thio)-2-((*tert*-butoxycarbonyl)amino)pentanoyl)glycinate (52): R$_f$ (50% EtOAc/Hex): 0.25, ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 (d, *J*=7.6 Hz, 2H, Ar-CH), 7.55 (d, *J*=7.4 Hz, 1H, Ar-CH), 7.52 (d, *J*= 7.3 Hz, 1H, Ar-CH), 7.40 (t, *J*=7.4 Hz, 2H, Ar-CH), 7.32-7.24 (m, 5H, Ar-CH), 7.15 (d, *J*=7.5 Hz, 2H, Ar-CH), 6.66 (bs, 1H, NH), 5.37 (d, *J*= 8.2 Hz, 1H, NH), 5.08 (bs, 1H, NH), 4.71 (dd, *J*=7.5, 14.0 Hz, 1H, Phe αCH), 4.43-4.35 (m, 2H, Fmoc CHCH$_2$), 4.26 (bs, 1H, αCH), 4.19 (t, *J*= 7.5 Hz, 1H, Fmoc CHCH$_2$), 4.06 (dd, *J*=5.6, 18.5 Hz, 1H, Gly αCH$_2$), 3.97 (dd, *J*=5.0, 18.3 Hz, 1H, Gly αCH$_2$), 3.69 (s, 3H, OCH$_3$), 3.17 (dd, *J*=5.6, 14.3 Hz, 1H, Phe- βCH$_2$), 3.09-2.99 (m, 2H, Phe- βCH$_2$, SCH$_2$CH$_2$CH$_2$), 2.90-2.85 (m, 1H, SCH$_2$CH$_2$CH$_2$), 1.89-1.80 (m, 1H, SCH$_2$CH$_2$CH$_2$), 1.77-1.68 (m, 1H, SCH$_2$CH$_2$CH$_2$), 1.67-1.57 (m, 2H, SCH$_2$CH$_2$CH$_2$), 1.45 (s, 9H, C(CH$_3$)$_3$) ppm. ^{13}C NMR (150 MHz, CDCl$_3$) δ 200.9 (SC=O), 172.2 (C=O), 170.3 (C=O), 155.8 (C=O, C=O), 143.9 (Ar-qC), 141.4 (Ar-qC), 135.7 (Ar-qC), 129.5 (Ar-CH), 128.9 (Ar-CH), 127.9 (Ar-CH), 127.4 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 80.3 (C(CH$_3$)), 67.3 (Fmoc CHCH$_2$), 61.6 (Phe-αCH), 53.5 (αCH), 52.5 (OCH$_3$), 47.3 (Fmoc CHCH$_2$), 41.3 (Gly αCH$_2$), 38.4 (Phe-βCH$_2$), 31.6 (CH$_2$), 28.5 (C(CH$_3$)$_3$), 28.2 (CH$_2$), 25.6 (CH$_2$) ppm. HRMS (*m/z* ESI+): Calculated for $C_{37}H_{44}N_3O_8S$ $[M+H]^+$, Calcd 690.2844, found 690.2840. ν_{max} (film)/cm^{-1}: 3325 (N–H), 2967 (C–H), 1732 (C=O), 1681 (C=O).

Methyl ((*S*)-5-(((((9H-fluoren-9-yl)methoxy)carbonyl)-L-valyl)thio)-2-((*tert*-butoxycarbonyl)amino)pentanoyl)glycinate (53): R$_f$ (50% EtOAc/Hex): 0.27. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.75 (d, *J*=7.6 Hz, 2H, Ar-CH), 7.60 (t, *J*=8.0 Hz, 2H, Ar-CH), 7.39 (t, *J*=7.6 Hz, 2H, Ar-CH),

7.30 (t, $J=7.6$ Hz, 2H, Ar-CH), 6.84 (bs, 1H, NH), 5.51 (bs, 1H, NH), 5.21 (bs, 1H, NH), 4.47-4.40 (m, 2H, Fmoc CHC$\underline{H}_2$), 4.33 (dd, $J=5.0$, 9.3 Hz, 1H, Val αCH), 4.29 (bs, 1H, αCH), 4.23 (t, $J=6.8$ Hz, 1H, Fmoc C$\underline{H}$CH$_2$), 4.22 (bs, 1H, αCH$_2$), 4.04 (dd, $J=4.9$, 18.1 Hz, 1H, Gly αC$\underline{H}_2$), 3.96 (dd, $J=4.7$, 18.3 Hz, 1H, Gly αC$\underline{H}_2$), 3.69 (s, 3H, OCH$_3$), 3.02 (bs, 1H, SC$\underline{H}_2$CH$_2$CH$_2$), 2.91–2.83 (m, 1H, SC$\underline{H}_2$CH$_2$CH$_2$), 2.31-2.21 (m, 1H, Val βCH), 1.89-1.81 (m, 1H, SCH$_2$CH$_2$C$\underline{H}_2$), 1.76–1.67 (m, 1H, SCH$_2$C$\underline{H}_2$CH$_2$), 1.67-1.58 (m, 2H, SCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 1.43 (s, 9H, C(CH$_3$)$_3$), 0.98 (d, $J=6.6$ Hz, 3H, Val CH$_3$), 0.88 (d, $J=6.7$ Hz, 3H, Val CH$_3$) ppm. ^{13}C NMR (150 MHz, CDCl$_3$) δ 201.0 (SC=O), 172.3 (C=O), 170.2 (C=O), 156.4 (C=O), 155.8 (C=O), 144.0 (Ar-qC), 141.4 (Ar-qC), 127.8 (Ar-CH), 127.2 (Ar-CH), 125.2 (Ar-CH), 120.1 (Ar-CH), 80.2 (C(CH$_3$)), 67.2 (Fmoc CH$\underline{C}$H$_2$), 66.0 (Val-α$\underline{C}$H), 53.4 (αCH), 52.4 (OCH$_3$), 47.3 (Fmoc $\underline{C}$HCH$_2$), 41.2 (Gly αCH$_2$), 31.7 (C$\underline{H}_2$), 31.1 (Val-β$\underline{C}$H, 28.4 (C($\underline{C}$H$_3$)$_3$), 28.1 (C$\underline{H}_2$), 25.6 ($\underline{C}$H$_2$), 19.5 (ValCH$_3$, Val CH$_3$) ppm. HRMS (*m/z* ESI+): Calculated for $C_{33}H_{44}N_3O_8S$ $[M+H]^+$, Calcd. 642.2844, found 642.2855. ν_{max} (film)/cm^{-1}: 3313 (N–H), 2964 (C–H), 1736 (C=O), 1685 (C=O).

Characterisation Data for anomeric amides 70–74 synthesized *via* one pot acyl thiol-ene, S-to-N Acyl Transfer and auxiliary cleavage:

(9H-fluoren-9-yl)methyl (2-(((2R,3R,4R,5S,6R)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)amino)-2-oxoethyl)carbamate (70): R_f: 0.34 (CH_2Cl_2:MEOH 90:10). δ_H (600 MHz, MeOD): 7.82 (d, $J=7.5$ Hz, 2H, Ar-CH), 7.71 (dd, $J=11.2$, 7.5 Hz, 2H, Ar-CH), 7.41 (t, $J=7.5$ Hz, 2H, Ar-CH), 7.34 (t, $J=7.5$ Hz, 2H, Ar-CH), 4.97 (d, $J=9.7$ Hz, 1H, H-1), 4.45–4.36 (m, 2H, Fmoc-CH$_2$), 4.28 (t, $J=7.0$ Hz, 1H, Fmoc-CH), 3.89–3.66 (m, 4H, H-2, H-6, H-6′, α-CH$_2$), 3.53–3.46 (m, 1H, H-3), 3.43–3.34 (m, 2H, H-4, H-5), 2.01 (d, $J=10.3$ Hz, 3H, NHC=OC$\underline{H}_3$) ppm. δ_C (151 MHz, MeOD): 174.7 (C=O), 173.1 (C=O), 159.1 (Gly-NH$\underline{C}$=O), 145.4 (qC), 145.2 (qC), 142.6 (qC), 142.6 (qC), 128.8 (Ar-CH), 128.8 (Ar-CH), 128.2 (Ar-CH), 126.3 (Ar-CH), 126.2 (Ar-CH), 120.9 (Ar-CH), 80.8 (C-1), 79.7 (C-5), 76.0 (C-3), 71.9 (C-4), 68.3 (Fmoc-CH$_2$), 62.6 (C-6), 55.9 (C-2), 47.9 (Fmoc-CH), 45.0 (α-CH$_2$), 22.8 (NHC=O$\underline{C}$H$_3$) ppm. HRMS: $C_{14}H_{17}NNaO_5$ requires 302.1004. ESI: Found 302.1009 $[M+Na]^+$. ν_{max} (film)/cm^{-1}: 3600 (OH), 1867 (C=O), 1300 (CH).

N-((2R,3R,4R,5S,6R)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)-3-(p–tolyl)propanamide (71): R_f: 0.32 (CH_2Cl_2:MeOH 90:10). δ_H (600 MHz, DMSO): 8.07 (dd, $J=9.2$, 1.9 Hz, 1H, NH), 7.79 (d, $J=8.9$ Hz, 1H, NH), 7.06 (s, 4H, Ar-CH), 4.81 (m, 1H, H-1), 3.65 (dd, $J=11.8$, 1.9 Hz, 1H, H-6), 3.53 (m, 1H, H-2), 3.42 (dd, $J=11.8$, 5.3 Hz, 1H, H-6), 3.30 (m, H-3), 3.12–2.99 (m, 2H, H-4, H-5), 2.71 (m, 2H, CH$_2$), 2.33 (m, 2H, CH$_2$), 2.24 (s, 3H, CH$_3$), 1.75 (s, 3H, CH$_3$) ppm. δ_C (151 MHz, DMSO): 171.7 (C=O), 169.8 (C=O), 138.1 (qC), 134.7 (qC), 128.8 (Ar-CH), 128.0 (Ar-CH), 78.9 (C-1), 78.7 (C-5), 74.5 (C-3), 70.5 (C-4), 60.9 (C-6), 54.6 (C-2), 37.1 (CH$_2$), 30.3 (CH$_2$), 22.8 (CH$_3$), 20.6 (CH$_3$) ppm. HRMS: $C_{18}H_{26}NNa_2O_6$ requires 389.1689. ESI: Found 389.1708 $[M+Na]^+$ ν_{max} (film)/cm^{-1}: 3301 (NH), 2981 (OH), 2981 (CH), 1655 (C=O).

N-((2R,3R,4R,5S,6R)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)butyramide (72): R_f: 0.3 (CH_2Cl_2:MeOH 91:9). δ_H (400 MHz, CH$_3$OD): 4.97 (d, $J=9.7$ Hz, 1H, H-1), 3.90–3.82 (m, 1H, H-6), 3.77 (t, $J=10.0$ Hz, 1H, H-2), 3.73–3.65 (m, 1H, H-6′), 3.52–3.41 (m, 1H, H-3), 3.36-3.33 (m, 2H, H-4, H-5) 2.27–2.13 (m, 2H, C=OC$\underline{H}_2$), 1.67–1.53 (m, 2H, CH$_2$), 1.32 (m, 6H, 3×CH$_2$), 1.00–0.89 (m, 3H, CH$_3$) ppm. δ_C (101 MHz, CH$_3$OD): 176.8 (C=O), 174.3 (C=O), 80.4 (C-1), 79.8 (C-5), 76.3 (C-3), 71.8 (C-4), 62.7 (C-6), 56.1 (C-2), 37.3(C=OCH$_2$), 32.7 (CH$_2$), 29.9 (CH$_2$), 26.7 (CH$_2$), 23.6 (CH$_2$), 22.8 (C$\underline{H}_2$CH$_3$, NHAc CH$_3$), 14.4 (CH$_2$C$\underline{H}_3$) ppm. HRMS: $C_{15}H_{28}N_2NaO_6$ requires 355.1845. ESI: Found 355.1841 $[M+Na]^+$.ν_{max} (film)/cm^{-1}: 3309 (NH), 2949 (OH), 1654 (C=O).

N-((2R,3R,4R,5S,6R)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)isobutyramide (73): δ_H (600 MHz, DMSO): 4.77 (t, $J=9.4$ Hz, 1H, H-1), 3.66 (dd, $J=11.8$, 1.9 Hz, 1H, H-6), 3.54 (td, $J=9.8$, 8.7 Hz, 1H, H-2), 3.42 (dd, $J=11.8$, 5.3 Hz, 1H, H-6′), 3.33–3.27 (m, 1H, H-3), 3.12–3.01 (m, 2H, H-4, H-5), 2.33 (m, 1H, CH), 1.77 (s, 3H, CH$_3$), 0.95 (dd, $J=6.9$, 3.2 Hz, 6H, 2×CH$_3$) ppm. δ_C (151 MHz, DMSO): 174.4 (C=O), 171.9 (C=O), 79.1 (C-1), 78.8 (C-5), 74.4 (C-3), 70.6 (C-4), 60.9 (C-6), 54.6 (C-2), 33.8 (CH), 22.8 (CH$_3$), 19.7, 18.5 (C$\underline{H}$CH$_3$) ppm. HRMS: $C_{12}H_{21}N_2O_6$ requires 289.1400. ESI: Found 289.1396 $[M-H]^-$ ν_{max} (film)/cm^{-1}: 3301 (NH), 2982 (OH), 1666 (C=O).

***N,N′*-((2R,3R,4R,5S,6R)-4,5-dihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2,3-diyl)diacetamide (74)**: R_f: 0.24 (CH_2Cl_2:MeOH 90:10). δ_H (600 MHz, DMSO): 4.79 (t, $J=9.4$ Hz, 1H, H-1), 3.64 (dd, $J=11.9$, 1.8 Hz, 1H, H-6), 3.51 (m, 1H, H-2), 3.41 (dd, $J=11.8$, 5.0 Hz, 1H, H-6′), 3.32–3.27 (m, 1H, H-3), 3.09–3.03 (m, 2H, H-4. H-5), 1.79 (s, 3H, CH$_3$), 1.78 (s, 3H, CH$_3$) ppm. δ_C (151 MHz, DMSO): 169.8 (C=O), 169.6 (C=O), 78.8 (C-1), 78.7 (C-5), 74.6 (C-3), 70.5 (C-4), 60.9 (C-6), 54.5 (C-2), 22.9 (CH$_3$), 22.8 (CH$_3$) ppm. HRMS: $C_{10}H_{17}N_2O_6$ requires 261.1087. ESI: Found 261.1091 $[M-H]^-$ ν_{max} (film)/cm^{-1}: 3269 (NH), 2924 (OH), 1646 (C=O), 1314 (CH).

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Amides · Click Chemistry · Hydrothiolation · Radical Reactions · Thiol-ene

[1] B. H. Northrop, R. N. Coffey, *J. Am. Chem. Soc.* **2012**, *134*, 13804–13817.
[2] C. E. Hoyle, C. N. Bowman, *Angew. Chem. Int. Ed.* **2010**, *49*, 1540–1573; *Angew. Chem.* **2010**, *122*, 1584–1617.
[3] F. Dénès, M. Pichowicz, G. Povie, P. Renaud, *Chem. Rev.* **2014**, *114*, 2587–2693.
[4] Z. Dekan, I. Vetter, N. L. Daly, D. J. Craik, R. J. Lewis, P. F. Alewood, *J. Am. Chem. Soc.* **2011**, *133*, 15866–15869.
[5] A. Plechanovova, E. G. Jaffray, S. A. McMahon, K. A. Johnson, I. Navratilova, J. H. Naismith, R. T. May, *Nat. Struct. Mol. Biol.* **2011**, *18*, 1052–1059.
[6] C. J. Noren, J. M. Wang, F. B. Perler, *Angew. Chem. Int. Ed.* **2000**, *39*, 450–466; *Angew. Chem.* **2000**, *112*, 458–476.
[7] A. P. A. Hendrickx, J. M. Budzik, S. Y. Oh, O. Schneewind, *Nat. Rev. Microbiol.* **2011**, *9*, 166–176.
[8] T. Fukuyama, S. C. Lin, L. Li, *J. Am. Chem. Soc.* **1990**, *112*, 7050–7051.
[9] T. Mukaiyama, M. Araki, H. Takei, *J. Am. Chem. Soc.* **1973**, *95*, 4763–4765.
[10] M. Kazemi, L. Shiri, *J. Sulfur Chem.* **2015**, *36*, 613–623.
[11] R. McCourt, F. Dénès, G. Sánchez, E. M. Scanlan, *Org. Lett.* **2018**, *20*, 2948–2951.
[12] R. McCourt, E. M. Scanlan, *Org. Lett.* **2019**, *21*, 3460–3464.
[13] N. Narendra, M. Vishwanatha, B. Thimmalapura, B. Hosamani, G. Prabhu, L. Roopesh Kumarb, V. V. Sureshbabu, *Org. Biomol. Chem.* **2018**, *16*, 3524–3552
[14] D. Crich, I. Sharma, *Angew. Chem. Int. Ed.* **2009**, *48*, 2355–2358; *Angew. Chem.* **2009**, *121*, 2391–2394.
[15] A. Afzaliardakani, H. Rapoport, *J. Org. Chem.* **1980**, *45*, 4817–4820.

[16] Y. Yonezawa, K. Shimizu, K. S. Yoon, C. G. Shin, *Synthesis* **2000**, *5*, 634–636.
[17] T. Shimidzu, R. Miyajima, N. Naruse, K. Yamaoka, K. Aihara, A. Shigenaga, A. Otaka, *Chem. Pharm. Bull.* **2016**, *64*, 375–378.
[18] M. Wiktor, D. Weichert, N. Howe, C. Y. Huang, V. Olieric, C. Boland, J. Bailey, L. Vogeley, P. J. Stansfeld, N. Buddelmeiser, M. Wang, M. Caffrey, *Nat. Commun.* **2017**, *8*, 15952.
[19] M. L. Coote, C. Y. Lin, H. Zipse, in *The Stability of Carbon-Centered Radicals*, ed. M. D. E. Forbes, John Wiley and Sons, inc., Hoboken, New Jersey, **2009**, Ch. 5, 83–104.
[20] M. L. Coote, *Macromolecules* **2004**, *37*, 5023–5031.
[21] a) S. S. Panda, C. D. Hall, A. A. Oliferenko, A. R. Katritzky, *Acc. Chem. Res.* **2014**, *47*, 1076–1087. b) J. C. M. Monbaliu, G. Dive, C. V. Stevens, A. R. Katritzky, *J. Chem. Theory Comput.* **2013**, *9*, 927–934.
[22] Q. Wan, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2007**, *46*, 9248–9252; *Angew. Chem.* **2007**, *119*, 9408–9412.
[23] H. M. Burke, L. McSweeney, E. M. Scanlan, *Nat. Commun.* **2017**, *8*, 15655.
[24] a) A. Brik, Y. Y. Yang, S. Ficht, C. H. Wong, *J. Am. Chem. Soc.* **2006**, *128*, 5626–5627 b) Y. Y. Yang, S. Ficht, A. Brik, C. H. Wong, *J. Am. Chem. Soc.* **2007**, *129*, 7690–7701.

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