Investigation of Synthetic Routes towards Derivatives of 3-(Phenylsulfonimidoyl)propanoic Acid

by **Heather Tye*** and **Catharine L. Skinner**

School of Chemical Sciences, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

The synthesis of a range of 3-(phenylsulfonimidoyl)propanoate derivatives is described. A number of strategies for the imination of the key sulfoxide methyl 3-(penylsulfinyl)propanoate are discussed including the use of *O*-(mesitylsulfonyl)hydroxylamine (MSH) and iminoiodane reagents (Ph–I=N–SO_2R). A successful strategy for the preparation of the target compounds was the use of MSH followed by *in situ* coupling with a *N*-Boc-protected amino acid. The pseudo-dipeptides thus formed exhibited interesting conformational properties in $CDCl_3$ solution giving evidence of intramolecular H-bonds in all cases, except for the proline derivative.

Introduction. – As part of an ongoing programme of research into peptidomimetics containing sulfonimide[1]) units for use in protein engineering, we were interested in the preparation of β-carboxylic sulfonimide derivatives **A**, which could potentially be incorporated into normal α-peptide sequences. Since its discovery by *Bentley et al.* in 1949 [1], the sulfonimide unit has seen little use as an amide replacement in peptide chemistry. In 1989, *Mock et al.* employed a sulfonimide-derivatised peptide as a transition-state-analogue inhibitor for carboxypeptidase A [2]. More recently, *Bolm et al.* reported the preparation of a range of pseudopeptides incorporating an α-carboxylic sulfonimide unit **B**. They have shown that these novel compounds appear to adopt a turn conformation in solution and, because of the unusual nature of the sulfonimide unit, they may exhibit resistance to enzymatic degradation [3]. Our expectation is that β-carboxylic sulfonimides will also induce a turn when incorporated into short peptide sequences and may prove useful tools for modifying the stability of turn motifs in protein architectures (*Fig. 1*). To this end, we set about the preparation of a range of β-carboxylic sulfonimide derivatives to be used as building blocks in the synthesis of pseudopeptides. The results of our preliminary synthetic studies are presented herein.

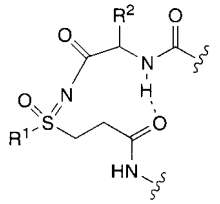


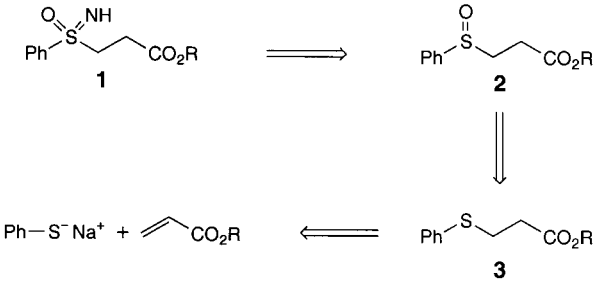
Fig. 1. *H-Bond-turn motif*

[1]) Also known as sulfoximide or sulfoximine.

A **B**

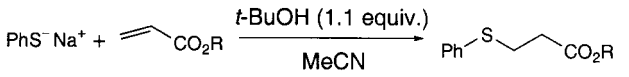
Results and Discussion. – *Preparation of Methyl 3-(Phenylsulfonimidoyl)propanoate* (**1**; R = Me). Retrosynthetic analysis of sulfonimide **1** can follow a variety of paths depending on the point in the synthesis when the sulfonimide group is introduced. Ultimately, it is desirable to achieve an enantioselective synthesis to control the configuration at the S-atom, however, we thought it expedient to develop a racemic synthesis first with a view to return to the issue of stereocontrol later in the project. With this in mind, the simplest synthetic strategy leads back to racemic 3-(phenylsulfinyl)propanoate (**2**) as a key intermediate (*Scheme 1*). It was envisaged that preparation of **2** could be achieved by oxidation of the corresponding sulfide **3**, which results from a conjugate addition of a phenyl thiolate to an acrylate species.

Scheme 1. *Retrosynthetic Analysis of Sulfonimide* **1**

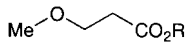


Reaction of PhSNa with methyl acrylate according to the procedure of *Ahern et al.* [4] in MeOH resulted in the formation of the desired sulfide **3** in a disappointing yield. The major product **4** of the reaction was the result of competing addition of MeOH to the electrophile. Formation of **4** could be avoided by performing the reaction in MeCN with *t*-BuOH (1.1 equiv.) acting as a H^+-source (*Scheme 2*). By this method, sulfides **3a**–**c** could be prepared cleanly, although still in relatively poor yield. Many attempts to improve the conversion of this reaction were made, but to no avail.

Scheme 2. *Synthesis of Sulfides* **3a**–**c**



3a R = Me (22%)
b R = Et (21%)
c R = *t*-Bu (37%)



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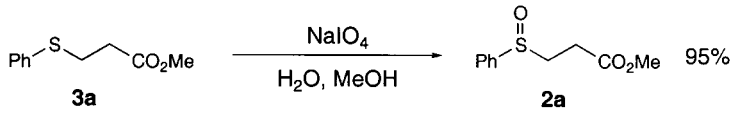
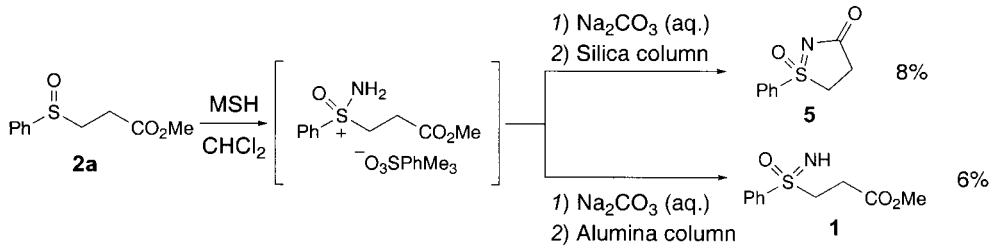
Oxidation of sulfide **3a** could be achieved with either 3-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 or $NaIO_4$ in MeOH/H_2O. When *m*-CPBA was employed, a significant amount of sulfone was also isolated resulting from overoxidation. The reaction with IO_4^- as oxidant proved to be more reliable, providing **2a** in 95% yield as the sole product (*Scheme 3*).

Scheme 3. *Oxidation of Sulfide* **3a**



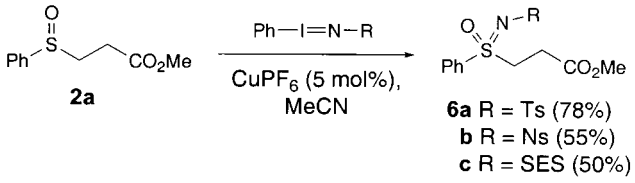
Having prepared the desired sulfoxide intermediate **2a**, we turned our attention to the installation of the sulfonimide functionality. Several methods are available for the introduction of the imide-*N*-atom [5], the most popular being the use of *O*-(mesitylsulfonyl)hydroxylamine (MSH) as an NH_2^+ source [6]. Due to the unstable nature of MSH, it was prepared immediately prior to use. Imination of **2a** with MSH gave disappointing results (*Scheme 4*). At the first attempt, the cyclic derivative **5** was isolated in a poor yield of 8%. This type of lactamisation has been reported previously by *Levenson* and *Meyer* in their work on sulfonimide derivatives of cysteine [7]. This side reaction could be avoided by careful exclusion of acidic conditions during workup with Na_2SO_4 as drying agent and neutral Al_2O_3 for chromatography. Despite this care, sulfonimide **1** was isolated in a pitiful 6% yield, the remaining material being recovered starting material.

Scheme 4. *Direct Imination of* **2a** *with* O-*(Mesitylsulfonyl)hydroxylamine* (MSH)



Alternative Imination Methodology. At this stage, we decided that it might be better to introduce the sulfonimide functionality in a *N*-protected form. A recently reported method for the imination of sulfoxides with the iminoiodane reagent Ph−I=N−Ts [8] appeared to be promising, especially since analogous reagents with more readily removable *N*-protecting groups (nosyl (=2-nitrophenylsulfonyl), 4-nitrophenylsulfonyl [9], and 2-(trimethylsilyl)ethylsulfonyl (SES) [10]) were known to be available. The imination of sulfoxide **2a** by this method proved to be much more successful giving *N*-tosyl sulfonimide **6a** in 78% yield, *N*-nosyl sulfonimide **6b** in 55% yield, and *N*-SES sulfonimide **6c** in 50% yield, respectively (*Scheme 5*). Since a free sulfonimide was required for further synthesis, the deprotection of **6b** and **6c** was then attempted.

Scheme 5. *Imination of* **2a** *with Iminoiodane Reagents*

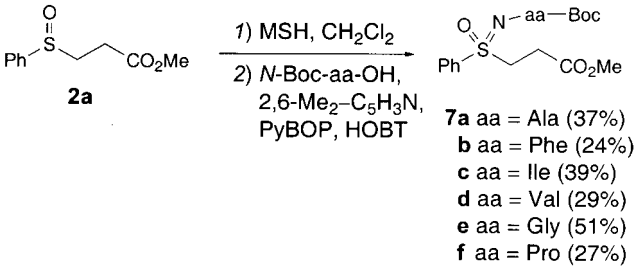


SES = 2-(trimethylsilyl)ethylsulfonyl

Conditions for the removal of the nosyl and SES groups have been developed by us in previous work [11]. Treatment of **6b** with PhSH and Cs_2CO_3 in MeCN resulted in formation of a complex mixture of products. The deprotection of **6c** with Bu_4NF in THF was likewise complicated by the formation of a number of side-product that could not be separated from the desired product **1**.

Imination by MSH with in situ *Peptide Coupling*. Having failed to deprotect the sulfonimide derivatives **6b** and **6c**, we sought an alternative imination strategy. *Yabuchi* and *Kusumi* have previously reported the coupling of a sulfonimide salt (formed with MSH) with a chiral carboxylic acid to determine the enantiomer excess of sulfoxides [12]. Encouraged by their results, we attempted the imination of sulfoxide **2a** and *in situ* coupling of the corresponding sulfonimide salt with an *N*-Boc-amino acid (*Scheme 6*). Treatment of **2a** with MSH in CH_2Cl_2 over a period of 3–7 d (reaction controlled by ^{1}H-NMR) followed by direct coupling with *N*-Boc-L-Ala resulted in the formation of the desired sulfonimide **7a** in 37% yield as a mixture of diastereoisomers. This procedure was repeated with a range of *N*-Boc-amino acids (*Scheme 6*) giving moderate yields in all cases.

Scheme 6. *Imination of* **2a** *by* in situ *Coupling with* N-*Boc-Amino Acids to Pseudodipeptides* **7a**–**f**



HOBT = 1-hydroxybenzotriazol; MSH = *O*-(mesitylsulfonyl) hydroxylamine;
PyBOP = [(1*H*-benzotriazol-1-yl)oxy]tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate

NMR Studies on Sulfonimide Derivatives **7a**–**f**. Analysis of the sulfonimides **7a**–**f** by NMR in $CDCl_3$ was carried out by ^{1}H,^{1}H- and ^{1}H,^{13}C-COSY methods to enable full assignment. The ^{1}H-NMR spectra of the sulfonimides **7a**–**d** appeared to be very similar showing double peaks for the MeO and *t*-Bu groups due to the presence of diastereoisomers (*Fig. 2*). Compound **7e** derived from glycine was also similar but with no peak doubling due to the lack of a second stereocentre. The spectrum of **7f** (*Fig. 2,b*), derived from proline, was very different from the others showing extensive

peak doubling. A series of temperature-variable NMR experiments revealed that this extra doubling was due to a rotamer effect (*Figs. 3* and *4*). Coalescence of signals corresponding to H–C(α)(Pro) and *t*-Bu(Boc) was observed at 331.7 and 346.1 K, respectively, corresponding to a rotation barrier of 17.2 ± 0.2 kcal mol^{-1}. These observations lead us to the conclusion that compounds **7a–e** benefit from an intramolecular H-bond (*Fig. 5*), which gives rise to a single conformation in $CDCl_3$

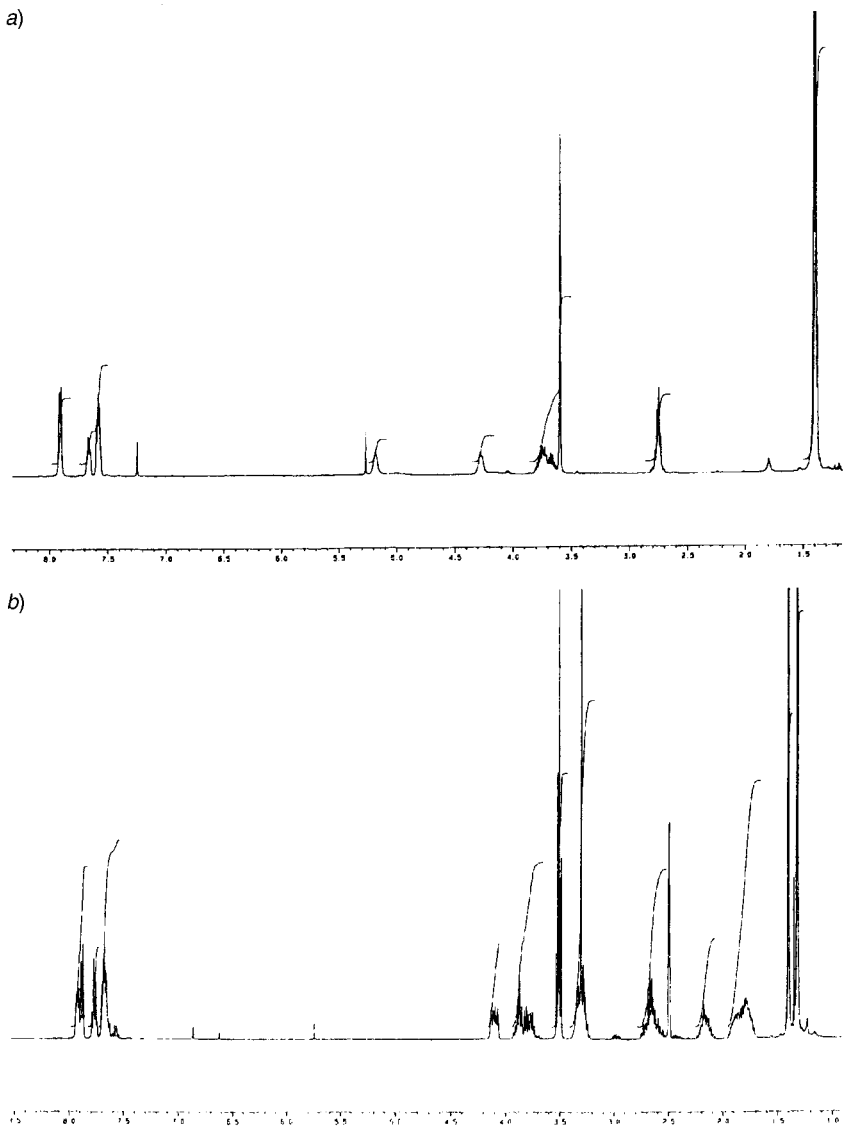


Fig. 2. *^{1}H-NMR Spectra* (500 MHz) *of* a) *alanine derivative* **7a** *and* b) *proline derivative* **7f**

solution, whereas **7f** cannot form a H-bond due to the proline residue and hence exhibits conformational freedom in $CDCl_3$ solution.

Conclusions. – Our synthetic studies have shown that it is possible to prepare a range of methyl 3-(phenylsulfonimidoyl)propanoate derivatives in moderate yield *via* an imination/coupling strategy. The pseudodipeptides thus prepared, except in the case of the proline derivative, are believed to exhibit an intramolecular H-bond resulting, most likely, in a turn conformation adopted in $CDCl_3$ solution. Further NMR studies involving dilution, deuterium-exchange, and titration experiments are underway to confirm this hypothesis. The synthesis of enantiomerically pure derivatives and their incorporation into larger peptide sequences is in progress and will be reported in due course.

We would like to thank Dr. *Neil Spencer* for carrying out the 2-D and temperature-variable NMR experiments. We are grateful to The University of Birmingham, *EPSRC*, and *AstraZeneca* for financial support.

Experimental Part

General. Solvents were purified by standard procedures. TLC: *Merck 60 F_{254}* SiO_2-coated aluminium sheets, 0.2 mm. Flash column chromatography (FC): *Merck 60*, 230–400 mesh, SiO_2; *Aldrich* activated neutral *Brockmann-1*, std. grade CA 150 mesh, Al_2O_3. M.p.: *Electrothermal 9200*, uncorrected. IR: *Perkin-Elmer 1600-FTIR* spectrometer, in $CHCl_3$; $\tilde{\nu}$ in cm^{-1}. NMR: *Bruker AC-300* (300 MHz (^{1}H), 75.5 MHz (^{13}C)), *DRX-500* (500 MHz, (^{1}H)); in $CDCl_3$; chemical shift (δ) in ppm refer to residual C*H*Cl_3 (7.27 ppm (^{1}H)) and *C*DCl_3 (77.0 ppm (^{13}C)); *J* in Hz. MS: *VG ProSpec* spectrometer in EI or ES mode; *m*/*z* (rel. %).

Synthesis of Methyl 3-(Phenylsulfanyl)propanoate (**3a**). PhSNa (5 g, 37.8 mmol) was dissolved in *t*-BuOH (20 ml) and MeCN (10 ml). A soln. of methyl acrylate (3.4 ml, 37.8 mmol) in *t*-BuOH (20 ml) was added at r.t. The resulting soln. was refluxed for 6 h and quenched at r.t. by addition of H_2O. The aq. layer was extracted with $CHCl_3$ (3×50 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude brown oil was purified by FC (Et_2O/hexane 1:4) to afford **3a** (1.42 g, 22%). Colourless oil. IR: 1738.2 (C=O). ^{1}H-NMR (300 MHz): 7.32–7.20 (*m*, 5 arom. H); 3.67 (*s*, MeO); 3.16 (*t*, *J* = 7.3, CH_2S); 2.62 (*t*, *J* = 7.3, CH_2CO). ^{13}C-NMR: 170.5 (CO); 128.4 (arom. C); 127.3 (arom. CH); 124.9 (arom. CH); 121.8 (arom. CH); 50.1 (CH_2); 32.6 (CH_2); 27.4 (Me). EI-MS: 196 (100, M^+), 165 (10), 136 (43), 123 (57), 109 (36), 87 (10), 77 (11), 65 (19), 59 (17), 51 (12), 45 (11), 39 (10).

Synthesis of Ethyl 3-(Phenylsulfanyl)propanoate (**3b**). As described for **3a**, affording **3b** (359 mg, 23%). Colourless oil. IR: 1709.4 (C=O). ^{1}H-NMR (300 MHz): 7.37–7.18 (*m*, 5 arom. H); 4.13 (*q*, *J* = 7.0, MeCH_2); 3.16 (*t*, *J* = 7.3, CH_2S); 2.61 (*t*, *J* = 7.3, CH_2CO); 1.25 (*t*, *J* = 6.6, Me). ^{13}C-NMR: 171.0 (CO); 130.2 (arom. C); 128.4 (arom. CH); 127.4 (arom. CH); 124.9 (arom. CH); 59.0 (CH_2); 32.8 (CH_2); 27.4 (CH_2); 12.6 (Me). EI-MS: 210 (100, M^+), 165 (17), 136 (64), 123 (63), 117 (10), 101 (24), 91 (10), 73 (30), 65 (20), 51 (14), 45 (17), 39 (13).

Synthesis of tert-*Butyl 3-(Phenylsulfanyl)propanoate* (**3c**). As described for **3a** affording **3c** (6.91 g, 36%). Pale yellow oil. ^{1}H-NMR (300 MHz): 7.33–7.20 (*m*, 5 arom. H); 3.13 (*t*, *J* = 7.35, CH_2S); 2.54 (*t*, *J* = 7.35, CH_2CO); 1.45 (*s*, *t*-Bu). ^{13}C-NMR: 171.0 (CO); 135.6 (arom. C); 130 (arom. CH); 129 (arom. CH); 126.4 (arom. CH); 80.9 (Me$_3$*C*); 35.6 (CH_2); 29.2 (CH_2); 28.1 (Me). EI-MS: 238 (100, M^+), 182 (85), 123 (85), 109 (84), 57 (100), 51 (12), 41 (80). HR-MS: 238.103353 ($C_{13}H_{18}O_2S$, calc. 238.102752).

Synthesis of Methyl 3-(Phenylsulfinyl)propanoate (**2a**). Compound **3a** (1.39 g, 7.09 mmol) was dissolved in MeOH (20 ml), and to this $NaIO_4$ (1.51 g, 7.09 mmol) in H_2O (20 ml) was added dropwise at 0°. The resulting white soln. was stirred for 7 h at r.t. The white slurry was filtered and washed with MeOH (50 ml), and the soln. was concentrated to a quarter of the volume. The aq. layer was extracted with CH_2Cl_2 (3×50 ml), and the combined org. phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **2a** (1.42 g, 95%). Pale yellow oil. IR: 1727.6 (C=O), 1050.2 (S=O). ^{1}H-NMR (300 MHz): 7.52–7.36 (*m*, 5 arom. H); 3.53 (*s*, Me); 3.18–3.09 (*m*, 1 H, CH_2); 2.90–2.81 (*m*, 1 H, CH_2); 2.77–2.66 (*m*, 1 H, CH_2); 2.48–2.38 (*m*, 1 H, CH_2). ^{13}C-NMR: 171.5 (CO); 142.9 (arom. C); 131.1 (arom. CH); 129.2 (arom. CH); 124.0 (arom. CH); 52.0 (CH_2); 51.0 (CH_2); 25.8 (Me). ES-MS: 235 (100, $[M+Na]^+$). HR-MS: 235.0414 ($C_{10}H_{12}NaO_3S^+$, calc. 235.0405).

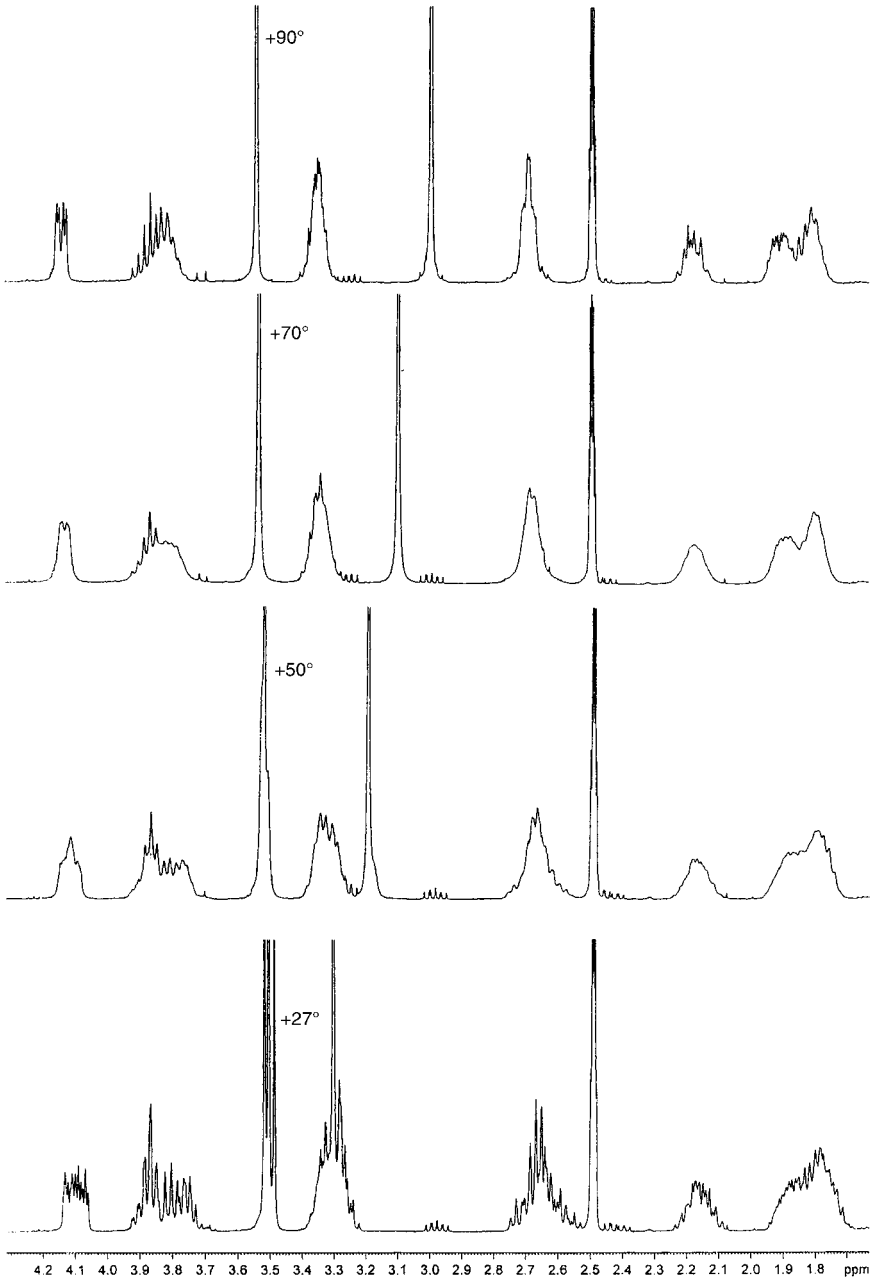


Fig. 3. *Temperature-variable ^{1}H-NMR spectra of* **7f** *showing coalescence of the H–C(α)(Pro) signal*

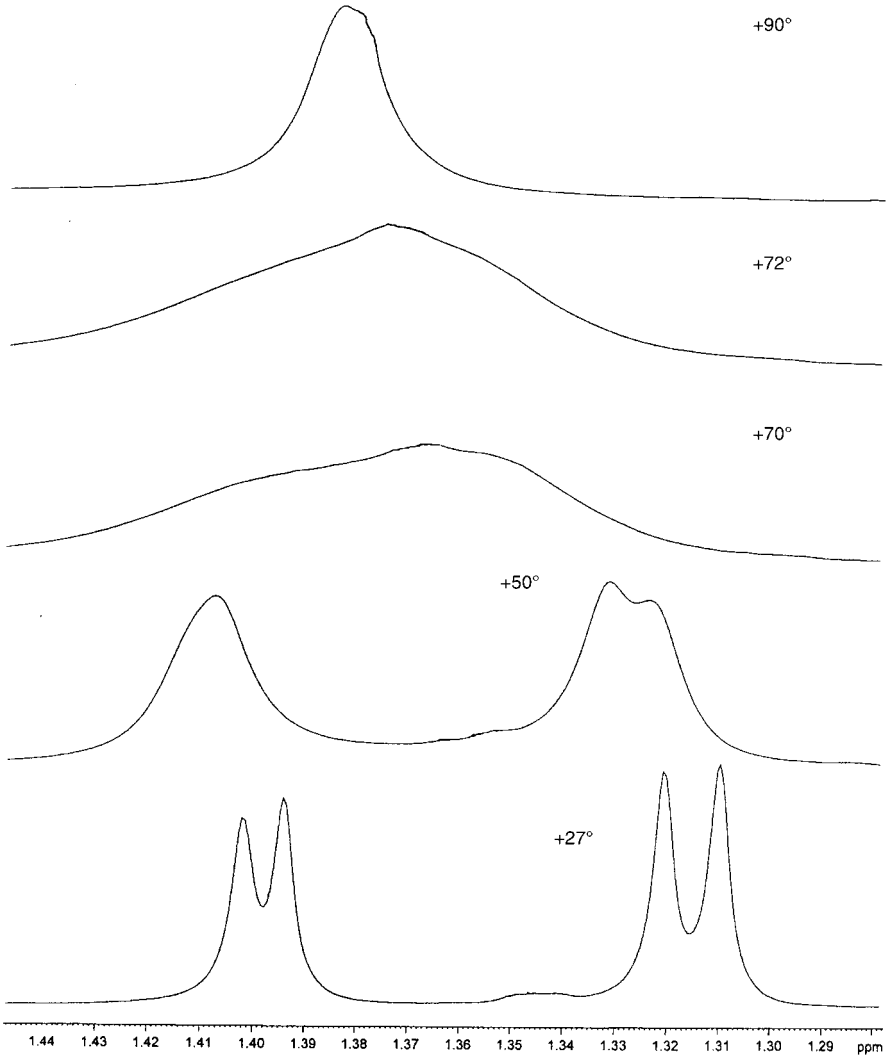
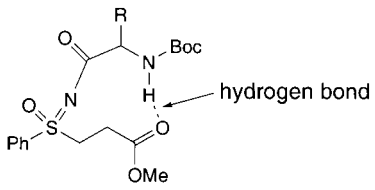


Fig. 4. *Temperature-variable ^{1}H-NMR spectra of* **7f** *showing coalescence of the* t-*Bu(Boc) signal*. Plotted at 2.5 Hz cm^{-1}.



R = H, Me, $PhCH_2$, i-Pr, *s*-Bu

Fig. 5. *Postulated structure of* **7a**–**e** *with intramolecular H-bond*

Synthesis of Methyl 3-(Phenylsulfonimidoyl)propanoate (**1**). Compound **2a** (200 mg, 0.94 mmol) was dissolved in CH_2Cl_2 (7 ml) and stirred at 0°. A soln. of *O*-(mesitylsulfonyl)hydroxylamine (MSH) (1.5 g, 7 mmol) in CH_2Cl_2 (7 ml) was then added, and the resulting soln. was stirred at r.t. for 4 d. The soln. was concentrated to a quarter of the volume, hexane (20 ml) was added, and the soln. was left in the freezer overnight. The pale greasy yellow solid was filtered off and washed with ice-cold hexane (2 × 20 ml). The resulting soln. was taken up in CH_2Cl_2 (20 ml) and washed with 10% aq. Na_2CO_3 soln. (20 ml). The phases were separated and the aq. layer was washed with CH_2Cl_2 (5 × 20 ml). The combined org. extracts were dried ($NaSO_4$), filtered, and the solvent was removed *in vacuo*. Purification by FC (Al_2O_3, AcOEt) gave **1** (13 mg, 6%). Colourless oil. ^{1}H-NMR (300 MHz): 7.93–7.45 (*m*, 5 arom. H); 3.57 (*s*, Me); 3.42 (*t* with fine coupling, $J = 5.8, 1.4$, CH_2); 2.7 (*q* with fine coupling, $J = 5.8, 1.0$, CH_2). ES-MS: 250 (100, $[M + Na]^+$).

*Synthesis of 4,5-Dihydro-1-phenyl-3*H*-1λ⁶-isothiazole-1,3-dione* (**5**). Compound **2a** (400 mg, 1.88 mmol) was dissolved in CH_2Cl_2 (10 ml) and stirred at 0°. A soln. of MSH (1.62 g, 7.55 mmol) in CH_2Cl_2 (10 ml) was then added, and the resulting soln. was stirred at r.t. for 4 d. The soln. was concentrated to a quarter of the volume, hexane (20 ml) was added, and the soln. was left in the freezer overnight. The pale greasy yellow solid was separated by decanting off the solvent and washed with ice-cold hexane (2 × 20 ml). The resulting soln. was taken up in CH_2Cl_2 (20 ml) and washed with 10% aq. Na_2CO_3 soln. (20 ml). The phases were separated, and the aq. layer was washed with CH_2Cl_2 (5 × 20 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. Purification by FC (SiO_2, AcOEt) gave **5** (28 mg, 8%). Colourless oil. M.p. 136–137°. IR: 1697.0 (C=O). ^{1}H-NMR (300 MHz): 7.90–7.45 (*m*, 5 arom. H); 3.77–3.56 (*m*, CH_2); 3.19–3.08 (*m*, 1 H, CH_2); 2.99–2.88 (*m*, 1 H, CH_2). ^{13}C-NMR: 178.8 (CO); 135.0 (arom. C); 133.5 (arom. CH); 128.4 (arom. CH); 126.7 (arom. CH); 52.0 (CH_2); 31.2 (CH_2). ES-MS: 218 (100, $[M + Na]^+$). Anal. calc. for $C_9H_9NO_2S$: C 55.3, H 4.64, N 7.17, S 16.38; found: C 55.4, H 4.65, N 6.81, S 15.83.

*Synthesis of Methyl 3-{*N*-[(4-Methylphenyl)sulfonyl](phenyl)sulfonimidoyl}propanoate* (**6a**). To a stirred soln. of **2a** (400 mg, 1.89 mmol) in MeCN (10 ml) $CuPF_6$ (cat.), and 4-methyl-*N*-(phenyl-λ³-iodanylidene)-benzenesulfonamide (774 mg, 2.07 mmol) were added at 0° under an inert atmosphere. The resulting soln. was stirred overnight, and the solvent was removed *in vacuo*. The resulting green oil was taken up in AcOEt (10 ml), filtered (SiO_2), and washed with AcOEt (3 × 10 ml). The filtrate was concentrated to a quarter of the volume. Crystallization from hexane gave **6a** (0.563 g, 78%). White solid. M.p. 70–71°. IR: 1740.7 (C=O). ^{1}H-NMR (300 MHz): 7.97 (*d*, $J = 4.56$, 2 arom. H); 7.82 (*d*, $J = 5.01$, 2 arom. H); 7.70 (*t*, $J = 4.47$, 1 arom. H); 7.59 (*t*, $J = 4.56$, 2 arom. H); 7.24 (*d*, $J = 4.89$, 2 arom. H); 3.88–3.75 (*m*, CH_2); 3.58 (*s*, MeO); 2.82–2.70 (*m*, CH_2); 2.38 (*s*, Me(Ts)). ^{13}C-NMR: 169.9 (CO); 136.5 (arom. C); 134.6 (arom. CH); 129.7 (arom. CH); 129.2 (arom. CH); 128.4 (arom. CH); 126.6 (arom. CH); 53.5 (CH_2S); 52.3 (MeO); 27.6 (CH_2); 21.5 (Me(Ts)). EI-MS: 381 (8, $[M + Na]^+$), 350 (8), 294 (100), 182 (10), 155 (80), 139 (62), 125 (55), 91 (100), 77 (53), 51 (32), 39 (22).

*Synthesis of Methyl 3-{*N*-[(2-Nitrophenyl)sulfonyl](phenyl)sulfonimidoyl}propanoate* (**6b**). As described for **6a**, with 2-nitro-*N*-(phenyl-λ³-iodanylidene)benzene sulfonamide affording **6b** (212 mg, 55%). White solid. M.p. 70–71°. IR: 1740.7 (C=O). ^{1}H-NMR (300 MHz): 8.37 (*d*, $J = 8.83$, 2 arom. H); 8.03 (*d*, $J = 8.83$, 2 arom. H); 7.94 (*d*, $J = 8.83$, 2 arom. H); 7.86 (*t*, $J = 7.35$, 1 arom. H); 7.71 (*t*, $J = 7.35$, 2 arom. H); 4.17–3.97 (*m*, CH_2); 3.51 (*s*, MeO); 2.74–2.62 (*m*, CH_2). ^{13}C-NMR: 135.3 (arom. C); 135.1 (arom. CH); 129.9 (arom. CH); 128.3 (arom. CH); 127.7 (arom. CH); 124.5 (arom. CH); 52.3 (CH_2S); 52.1 (MeO); 26.8 (CH_2). ES-MS: 435 (100, $[M + Na]^+$).

Synthesis of Methyl 2,2-Dimethyl-5,5,7-trioxo-7-phenyl-5λ⁶,7λ⁶-dithia-6-aza-2-siladec-6-en-10-oate (**6c**). As described for **6a**, with 2-(trimethylsilyl)-*N*-(phenyl-λ³-iodanylidene)ethanesulfonamide affording **6c** (50%). Waxy solid. IR: 3022.1, 2454.2, 1741.1, 1316.5, 1258.1, 1170.3, 1136.8. ^{1}H-NMR (300 MHz): 7.6–8.0 (*m*, 5 arom. H); 4.85 (*m*, CH_2); 3.6 (*s*, MeO); 3.1 (*m*, CH_2); 2.8 (*m*, CH_2); 1.1 (*m*, CH_2); 0.0 (*s*, Me_3Si). ^{13}C-NMR: 169.7 (CO); −1.8 (Me_3Si). 136.1 (arom. C); 10.4 (CH_2); 134.8 (arom. CH); 27.9 (CH_2); 129.8 (arom. CH); 52.5 (Me); 128.5 (arom. CH); 53.5 (CH_2); 53.8 (CH_2). ES-MS: 414.0 (100, $[M + Na]^+$). HR-MS: 414.0826 ($C_{25}H_{25}NNaO_5S_2Si$, calc. 414.0841).

General Procedure for the Synthesis of Pseudodipeptides **7a–f**. Compound **2a** (100 mg, 0.47 mmol) was dissolved in CH_2Cl_2 (5 ml) and stirred at 0°. A soln. of MSH (172 mg, 0.80 mmol) in CH_2Cl_2 (5 ml) was added, and the resulting soln. was stirred at r.t. for 4 d. 2,6-Dimethylpyridine (540 mg, 5.19 mmol), 1-hydroxybenzotriazole (HOBT, 127 mg, 0.94 mmol), [(1*H*-benzotriazol-1-yl)oxy]tris(pyrrolidin-1-yl)phosphonium hexafluorophosphate (PyBOP; 490 mg, 0.94 mmol), and *N*-Boc-protected amino acid (0.94 mmol) were added. The soln. was stirred at r.t. for 18 h and was then diluted with AcOEt (5 ml), washed with 5% HCl (15 ml), sat. aq. $NaHCO_3$ soln. (10 ml), and brine (10 ml). The combined org. phase was dried ($NaSO_4$), filtered, and the solvent removed *in vacuo*.

NOTE: Doubling of signals can be observed in the NMR data due to the formation of diastereoisomers. This is particularly apparent in the ^{13}C-NMR data, but is also seen in the complex multiplicity of signals in the ^{1}H-NMR data. Attention is drawn especially to the signals in the ^{1}H-NMR spectra for the MeO and the *t*-Bu protons. Extra doubling and splitting of signals is observed in the ^{1}H-NMR spectrum of the proline derivative **7f** due to an added rotamer effect.

*Alanine Derivative Methyl (6*S*,9*RS*)-2,2,6-Trimethyl-4,7,9-trioxo-9-phenyl-3-oxa-9λ⁶-thia-5,8-diazadodec-8-en-12-oate* (**7a**). Purification by FC (SiO_2, MeOH/AcOEt 1:4–4:1) gave **7a** (69 mg, 37%). Colourless oil that formed white crystals upon addition of Et_2O. M.p. 68–70°. IR: 3425.9, 3040.6, 2431.9, 1739.4, 1707.2, 1649.7, 1239.9, 1166.1. ^{1}H-NMR (500 MHz): 7.92–7.90 (*m*, 2 arom. H); 7.67–7.66 (*m*, 1 arom. H); 7.60–7.56 (*m*, 2 arom. H); 5.19 (br., NH); 4.29–4.20 (*m*, H–C(α)(Ala)); 3.81–3.64 (*m*, CH_2S); 3.60, 3.59 (2*s*, MeO); 2.78–2.74 (*m*, CH_2CO); 1.41, 1.40 (2*s*, *t*-Bu); 1.38 (*s*, Me(Ala)). ^{13}C-NMR: 181.2 (CO(Ala)); 170.49 (CO_2Me); 154.53 (CO(Boc)); 135.6 (arom. CS); 134.16, 134.13 (arom. CH); 129.7 (arom. CH); 127.89, 127.85 (arom. CH); 79.5 (Me_3C); 52.5 (H–C(α)(Ala)); 52.3 (MeO); 51.4, 51.23 (CH_2S); 28.3 (Me_3C); 27.37, 27.24 (CH_2CO); 19.27, 19.21 (Me(Ala)). ES-MS: 420 (100, $[M+Na]^+$), 320 (60). Anal. calc. for $C_{18}H_{26}N_2O_6S$: C 54.26, H 6.58, N 7.03; found: C 54.21, H 6.61, N 7.01.

*Phenylalanine Derivative Methyl (6*S*,9*RS*)-6-Benzyl-2,2-dimethyl-4,7,9-trioxo-9-phenyl-3-oxa-9λ⁶-thia-5,8-diazadodec-8-en-12-oate* (**7b**). Purification by FC (SiO_2, Et_2O) gave **7b** (69 mg, 24%). Pale yellow oil. IR: 3435.8, 3020.0, 2400.0, 1739.2, 1706.4, 1646.5, 1244.5, 1166.4. ^{1}H-NMR (500 MHz): 7.95–7.88 (*m*, 1 arom. H); 7.83–7.74 (*m*, 1 arom. H); 7.73–7.45 (*m*, 5 arom. H); 7.31–7.16 (*m*, 3 arom. H); 4.90 (br. *s*, NH); 4.00–3.90 (*m*, H–C(α)(Phe)); 3.84–3.65 (*m*, CH_2S); 3.61 (*s*, MeO); 3.26–2.64 (*m*, CH_2(Phe), CH_2CO); 1.42 (*s*, *t*-Bu). ^{13}C-NMR: 179.95, 179.91 (CO(Phe)); 170.04, 169.98 (CO_2Me); 155.36, 155.26 (CO(Boc)); 137.18 (arom. C); 136.17, 136.11 (arom. C); 134.26, 134.15 (arom. CH); 129.79, 129.66 (arom. CH); 129.41, 129.30 (arom. CH); 128.47, 128.29 (arom. CH); 128.18, 127.92 (arom. CH); 79.44, 79.34 (Me_3C); 57.55, 57.46 (H–C(α)(Phe)); 52.37 (MeO); 51.59, 51.37 (CH_2S); 38.91, 38.51 (CH_2(Phe)); 28.34 (Me_3C); 27.33, 27.19 (CH_2CO). ES-MS: 497.1 (100, $[M+Na]^+$). HR-MS: 497.1740 ($C_{24}H_{30}N_2O_6NaS$, calc. 497.1722).

*Isoleucine Derivative Methyl (6*S*,9*RS*)-2,2-Dimethyl-6-(1-methylpropyl)-4,7,9-trioxo-9-phenyl-3-oxa-9λ⁶-thia-5,8-diazadodec-8-en-12-oate* (**7c**). Purification by FC (SiO_2, Et_2O) gave **7c** (122 mg, 39%). Colourless oil. IR: 3435.0, 3011.9, 2478.5, 1739.2, 1709.0, 1644.3, 1257.1, 1169.8. ^{1}H-NMR (500 MHz): 7.93–7.85 (*m*, 2 arom. H); 7.69–7.61 (*m*, 1 arom. H); 7.61–7.51 (*m*, 2 arom. H); 5.11 (br., NH); 4.25–4.16 (*m*, H–C(α)(Ile)); 3.83–3.61 (*m*, CH_2S); 3.59, 3.58 (2*s*, MeO); 2.79–2.69 (*m*, CH_2CO); 1.98–1.82 (*m*, H–C(β)(Ile)); 1.54–1.41 (*m*, 1 H, CH_2(γ)(Ile)); 1.41, 1.39 (2*s*, *t*-Bu); 1.21–1.13 (*m*, 1 H, CH_2(γ)(Ile)); 0.97–0.84 (*m*, 2 Me(Ile)). ^{13}C-NMR: 180.73, 180.60 (CO(Ile)); 170.00, 169.96 (CO_2Me); 155.88, 155.80 (CO(Boc)); 136.34, 136.28 (arom. CS); 134.09, 134.02 (arom. CH); 129.63, 129.57 (arom. CH); 128.07, 127.82 (arom. CH); 79.40, 79.09 (Me_3C); 61.07, 60.87 (H–C(α)(Ile)); 52.25 (Me); 51.48, 51.36 (CH_2S); 38.21, 37.83 (H–C(β)(Ile)); 28.26 (Me_3C); 27.34, 27.14 (CH_2CO); 24.76, 24.48 (CH_2(γ)(Ile)); 15.71, 15.39 (Me(Ile)); 11.71, 11.58 (Me(Ile)). ES-MS: 463.1 (100, $[M+Na]^+$), 363.1 (10). HR-MS: 463.1876 ($C_{21}H_{32}N_2NaO_6S$, calc. 463.1879).

*Valine Derivative Methyl (6*S*,9*RS*)-6-Isopropyl-2,2-dimethyl-4,7,9-trioxo-9-phenyl-3-oxa-9λ⁶-thia-5,8-diazadodec-8-en-12-oate* (**7d**). Purification by FC (SiO_2, Et_2O) gave **7d** (87 mg, 29%). Colourless oil that formed white crystals, which were recrystallized from Et_2O. IR: 3436.3, 3062.0, 2407.0, 1739.7, 1709.3, 1644.0, 1246.1, 1160.2. ^{1}H-NMR (500 MHz): 7.96–7.88 (*m*, 2 arom. H); 7.70–7.54 (*m*, 3 arom. H); 5.08 (*m*, NH); 4.21 (*m*, H–C(α)(Val)); 3.85–3.68 (*m*, CH_2S); 3.61, 3.60 (2*s*, MeO); 2.84–2.70 (*m*, CH_2CO); 2.29–2.20 (*m*, H–C(β)(Val)); 1.41, 1.39 (2*s*, Me_3C); 0.99 (*d*, *J* = 6.6, 1.5 H, Me(γ)(Val)); 0.96 (*d*, *J* = 6.8, 1.5 H, Me(γ)(Val)); 0.88 (*d*, *J* = 6.8, 1.5 H, Me(γ)(Val)); 0.82 (*d*, *J* = 6.6, 1.5 H, Me(γ)(Val)). ^{13}C-NMR: 180.79, 180.61 (CO(Val)); 170.04, 170.00 (CO_2Me); 156.04, 155.97 (CO(Boc)); 136.40, 136.35 (arom. CS); 134.13, 134.07 (arom. CH); 129.70, 129.37 (arom. CH), 128.14, 127.87 (arom. CH); 79.14 (Me_3C); 61.49, 61.41 (H–C(α)(Val)); 52.32, 52.29 (MeO); 51.57, 51.43 (CH_2S); 31.59, 31.45 (H–C(β)(Val)); 28.31 (Me_3C); 27.42, 27.20 (CH_2CO); 19.58, 19.48 (Me(γ)(Val)); 17.27, 17.05 (Me(γ)(Val)). ES-MS: 449.0 (100, $[M+Na]^+$). HR-MS: 449.1739 ($C_{20}H_{30}N_2NaO_6S$, calc. 449.1722).

*Glycine Derivative Methyl (9*RS*)-2,2-Dimethyl-4,7,9-trioxo-9-phenyl-3-oxa-9λ⁶-thia-5,8-diazadodec-8-en-12-oate* (**7e**). Purification by FC (SiO_2, Et_2O) gave **7e** (91 mg, 51%). Colourless oil. IR: 3437.2, 3024.0, 2449.6, 1739.0, 1710.1, 1655.1, 1246.5, 1167.6. ^{1}H-NMR (300 MHz): 7.93–7.91 (*m*, 2 arom. H); 7.71–7.50 (*m*, 3 arom. H); 5.11 (br., NH); 3.97–3.95 (*m*, CH_2(α)(Gly)); 3.84–3.63 (*m*, CH_2S); 3.62 (*s*, MeO); 2.80–2.74 (*m*, CH_2CO); 1.42 (*s*, Me_3C). ^{13}C-NMR: 180.78 (CO(Gly)); 170.0 (CO_2Me); 155.94 (CO(Boc)); 138.47 (arom. CS); 136.59 (arom. CH); 132.13 (arom. CH); 130.25 (arom. CH); 81.66 (Me_3C); 54.70 (MeO); 53.93 (CH_2(α)(Gly)); 48.85 (CH_2S); 30.69 (Me_3C); 29.67 (CH_2CO). ES-MS: 407.2 (100, $[M+Na]^+$). HR-MS: 407.1257 ($C_{17}H_{24}N_2NaO_6S$, calc. 407.1253).

Proline Derivative tert-*Butyl (2*S*)-2-({[(*RS*)-(3-Methoxy-3-oxopropyl)(oxo)phenyl-λ⁶-sulfanylidene]amino}carbonyl)pyrrolidine-1-carboxylate* (**7f**). Purification by FC (SiO_2, Et_2O) gave **7f** (69 mg, 27%). Colourless oil. IR: 3054.1, 2306.2, 1739.8, 1682.2, 1669.4, 1266.4, 1164.1. ^{1}H-NMR (500 MHz): 8.05–7.96 (*m*, 1 arom. H); 7.73–7.84 (*m*, 1 arom. H); 7.74–7.40 (*m*, 3 arom. H); 4.38–4.16 (*m*, H–C(α)(Pro)); 3.89–3.64 (*m*, CH_2S); 3.60, 3.58, 3.56 (3*s*, MeO); 3.56–3.43 (*m*, CH_2(δ)(Pro)); 3.43–3.28 (*m*, CH_2CO); 2.27–1.75 (*m*, CH_2(β)(Pro), CH_2(γ)(Pro)); 1.44, 1.42, 1.41 (3*s*, *t*-Bu). ^{13}C-NMR: 182.29, 182.15 (CO(Pro)); 170.25, 170.20 (CO_2Me); 154.68, 154.53 (CO(Boc)); 136.63, 136.57 (arom. CS); 134.06, 133.97 (arom. CH); 129.59, 129.27 (arom. CH); 128.41, 128.09 (arom. CH); 79.58, 79.20 (Me_3C); 62.84, 62.39 (H–C(α)(Pro)); 52.30, 52.15 (MeO); 51.55, 51.25 (CH_2S); 46.79, 46.45 (CH_2(δ)(Pro)); 30.24, 30.15 (CH_2(β)(Pro)); 28.45, 28.39 (Me_3C); 27.66, 27.44 (CH_2CO); 24.23, 23.41 (CH_2(γ)(Pro)). ES-MS: 447.1 (100, $[M+Na]^+$). HR-MS: 447.1575 ($C_{20}H_{28}N_2NaO_6S$, calc. 447.1566).

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