Mild and highly chemoselective oxidation of thioethers mediated by Sc(OTf)₃

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Supporting Information

General informations: Phenyl methyl sulfide, *p*-bromophenyl methyl sulfide, *p*-methoxyphenyl methyl sulfide and 1-cyclohexyl-3-(2-morpholino-ethyl)carbodiimide metho-*p*-toluenesulfonate were purchased from Aldrich. Sulfones *3a*¹, *3b*², *3c*³, *3d*^{3,4} are described in the literature. Scandium(III) trifluoromethanesulfonate hydrate was purchased by Lancaster. Amino acids and Fmoc-OSu were purchased from Novabiochem. Amino acids are abbreviated using the standard-3-letter code and are of configuration L. H₂O₂ was used as a 60% solution in water (*d* = 1.19 g mL⁻¹), supplied by Fisher. CH₂Cl₂ was distilled from calcium hydride and stored over Type 3A molecular sieves. GC were run in a GC Varian 3300/3400 equipped with a flame ionization detector and a capillary column (DBWAX) , 30mx0.53mm. Run conditions: initial temperature: 50 C for 2 minutes; temperature increase rate: 20 C/min; final temperature: 220 C. GC-CIMS were run on a ThermoQuest TraceMS gas chromatography mass spectrometer, ionisation technique: chemical ionisation. RP-HPLC analysis were carried out with a Hewlett Packard Chemstation HP1100 Chemstation. Conditions 1) Column-C₁₈ ODS, i.d. 150mm x 3mm (Analytical, flow 0.5 mLmin⁻¹). Gradient: 0.1% TFA/H₂O to 0.1% TFA/MeCN over 20 min. Conditions 2) Column-C₁₈ ODS, i.d. 4.6mm x 3mm (Analytical, flow 1 mLmin⁻¹). Gradient: 0.1% TFA/H₂O to 0.1% TFA/MeCN over 5 minutes. Detection by UV (220 and 254 nm) and ELS detectors. ¹H NMR spectra were recorded on Bruker AC300 or Bruker DPX 400 MHz spectrometers, ¹³C NMR spectra were recorded on Bruker AC300 (75 MHz) or Bruker DPX 400 MHz (100 MHz) spectrometers and reported in units of (ppm) relative to solvents (CDCl₃ 7.27,

DMSO-d₆ 2.50, D₂O 4.79 for ¹H NMR and CDCl₃ 77.16, DMSO-d₆ 40.45 for ¹³C NMR). ⁴⁵Sc NMR spectra were recorded on Bruker DPX 400 MHz (97 MHz) spectrometer and are reported in ppm using Sc(NO₃)₃ in D₂O/H₂O as external standard (0.0). ES mass spectra were recorded by using a VG Platform Quadrupole Electrospray Ionisation mass spectrometer, measuring monoisotopic masses. HRMS were run on a Bruker APEX3. Infra-red spectra were recorded on a BIORAD Golden Gate FTS 135. All samples were run neat as solids or liquids. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

Abbreviations: CMC: 1-cyclohexyl-3-(2-morpholino-ethyl)carbodiimide metho-*p*-toluenesulfonate; HMPA: hydroxymethylphenoxyacetic acid; HOBt: 1-hydroxybenzotriazole; NMM: *N*-methyl morpholine; Sc(OTf)₃: scandium trifluoromethanesulfonate; TFA: trifluoroacetic acid; TIS: triisopropyl silane.

Synthesis of thioethers.

Phenyl prenyl sulfide (1a).⁵ Yield: 83%; *R*_f: 0.32 (200/1, hexanes/EtOAc); ¹H-NMR (CDCl₃, 400 MHz): 7.35-7.13 (m, 5H), 5.30 (m, 1H), 3.53 (d, 2H, *J* = 8 Hz), 1.70 (s, 3H), 1.58 (s, 3H); ¹³C-NMR (CDCl₃, 100.6 MHz): 137.2, 136.6, 130.0, 129.0, 126.2, 119.7, 32.5, 25.9, 18.0; GC-CIMS: rt 10.78 min, *m/z*: 179 (M+H)⁺; HPLC (λ₂₅₄): 13.5 min (conditions 1).

H-Cys(Me)-OMe HCl.⁶ An adapted literature protocol for the formation of amino acid methyl esters was used.⁷ H-Cys(Me)-OH (5 g, 37 mmol) was suspended in 2,2-dimethoxypropane (150 mL) and conc. hydrochloric acid (15 mL) added. The reaction was stirred overnight. The mixture was concentrated *in vacuo*; the residue, dissolved in a minimum amount of MeOH (25 mL), was added dropwise to cold Et₂O (500 mL). The resulting white precipitate was collected by filtration and dried under vacuum.

mp: (145-146) °C (lit. 143-144) °C⁸; ¹H-NMR (CDCl₃, 300 MHz): 4.38 (dd, *J* = 10, 6 Hz, 1H, *H*), 3.83 (s, 3H, OCH₃), 3.17 (dd, *J* = 20, 6 Hz, 1H, *HH*₂), 3.04 (dd, *J* = 20, 10 Hz, 1H, *HH*₂), 2.12 (s, 3H, SCH₃); ¹³C-NMR (CDCl₃, 75.5 MHz): 172.0 (CO₂Me), 56.4 (OCH₃), 54.4 (C), 36.0 (C), 17.3 (SCH₃).

Fmoc-Cys(Me)-OMe (4a). H-Cys(Me)-OMe HCl (1.25 g, 8.4 mmol, 1 equiv) was dissolved in 10% Na₂CO₃ in water (19 mL). The solution was cooled to 0 °C in an ice

bath and dioxane (19 mL) was added. Fmoc-OSu (3.40 g, 10 mmol, 1.2 equiv) was added and the solution allowed to warm to room temperature and stirred for 1 hour. The mixture was then diluted with water (to *ca.* 80 mL) and extracted with EtOAc (2x100 mL). The extracts were dried (Na₂SO₄), filtered and the solvent removed *in vacuo*. Column chromatography (silica gel, hexanes/EtOAc, 7/3) gave a white solid which was recrystallised from EtOH/EtOAc to afford the desired compound (2 g, 64%). *R*_f: 0.50 (hexanes/EtOAc); mp: (117-120) °C; IR (neat): ν_{max} : 3322, 1754, 1736, 1685 cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz): 7.79 & 7.61 (2d, *J* = 7 Hz, 4H, Fmoc-*H*_{1,4,5,8}), 7.42 & 7.33 (2t, *J* = 7 Hz, 4H, Fmoc-*H*_{2,3,6,7}), 5.67 (d, *J* = 8 Hz, 1H, *NH*), 4.70-4.60 (m, 1H, Cys(Me)-*H*), 4.43 (d, *J* = 7 Hz, 2H, Fmoc-CH₂), 4.25 (t, *J* = 7 Hz, 1H, Fmoc-CH), 3.80 (s, 3H, OCH₃), 2.99 (m, 2H, Cys(Me)-*H*₂), 2.12 (s, 3H, Cys(Me)-SCH₃); ¹³C-NMR (CDCl₃, 75.5 MHz): 171.5 (CO₂Me), 155.8 (OCONH), 143.8 (Fmoc-C_{8a,9a}), 141.4 (Fmoc-C_{4a,4b}), 127.8 (Fmoc-C_{1,8}), 127.2 (Fmoc-C_{4,5}), 125.2 (Fmoc-C_{2,7}), 120.1 (Fmoc-C_{3,6}), 67.3 (Fmoc-CH₂), 53.5 (Cys(Me)-C), 52.8 (OCH₃), 47.2 (Fmoc-CH), 36.8 (Cys(Me)-C), 16.4 (Cys(Me)-SCH₃); ES-MS: *m/z*: 394.2 (M+Na)⁺, 765.4 (2M+Na)⁺; HRMS (ES⁺): calcd for C₂₀H₂₁NO₄SNa (M+Na)⁺ 394.1090, found 394.1083; HPLC (λ₂₅₄): 12.4 min (conditions 1).

H-Cys(Trt)-OMe HCl.⁹ Yield: 98%; *R*_f: 0.60 (CHCl₃/5%MeOH); mp: (70-75) °C (lit. 78 °C); IR (neat): ν_{max} : 1743 cm⁻¹; ¹H-NMR (DMSO-d₆, 400 MHz): 8.90 (br s, 3H, NH₃⁺), 7.42-7.20 (m, 15H, Ar*H*), 3.83-3.75 (m, 1H, *H*), 3.70 (s, 3H, OCH₃), 2.76 (dd, 1H, *J* = 13, 6 Hz, *HH*), 2.63 (dd, 1H, *J* = 13, 6 Hz, *HH*); ¹³C-NMR (DMSO-d₆, 100.6 MHz): 169.0 (CO₂Me), 144.5 (Ar-*ipso*C), 129.9 (ArCH), 129.1 (ArCH), 127.9 (ArCH), 67.5 (Ar₃C), 53.9 (OCH₃), 51.9 (C), 32.2 (C); ESMS: *m/z*: 378.3 (M+H)⁺, 755.6 (2M+H)⁺; HPLC (ELS): 9.4 min (conditions 1).

Boc-Phe-Cys(Me)-OH. Preparation according to a literature procedure.¹⁰ Yield: 93 %; *R*_f: 0.62 (CHCl₃/5%MeOH/1%AcOH); mp: (43-50) °C; IR (neat): ν_{max} : 3303, 1713, 1643 cm⁻¹; ¹H-NMR (DMSO-d₆, 400 MHz): 12.92 (br s, 1H, CO₂H), 8.25 (d, 1H, *J* = 8 Hz, Phe-*NH*), 7.39-7.18 (m, 5H, Ar*H*), 6.93 (d, 1H, *J* = 9 Hz, Cys(Me)-*NH*), 4.49 (m, 1H, Phe-*H*), 4.26 (m, 1H, Cys(Me)-*H*), 3.04 (dd, 1H, *J* = 14, 4 Hz, Cys(Me)-*HH*), 2.93 (dd, 1H,

$J = 14, 5 \text{ Hz}$, Phe- HH), 2.84 (dd, 1H, $J = 14, 5 \text{ Hz}$, Phe- HH), 2.77 (dd, 1H, $J = 14, 11 \text{ Hz}$, Cys(Me)- HH), 2.14 (s, 3H, Cys(Me)- SCH_3), 1.33 (s, 9H, $C(CH_3)_3$); ^{13}C -NMR (DMSO- d_6 , 100.6 MHz): 172.9 & 172.7 (CO_2Me & CONH), 156.1 (OCONH), 139.0 (*ipso*-ArC), 130.1 & 128.9 (*o* & *m*-ArC), 127.1 (*p*-ArC), 79.0 ($C(CH_3)_3$), 56.5 (Cys(Me)-C), 52.8 (Phe-C), 38.3 (Phe-C), 36.0 (Cys(Me)-C), 29.0 ($C(CH_3)_3$), 16.4 (Cys(Me)- SCH_3); ESMS: m/z : 381.3 (M-H^-), 763.5 (2M-H^-); HRMS (ES^+): calcd for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_5\text{SNa}$ (M+Na^+), 405.1454, found 405.1458; HPLC (ELS): 9.9 min (conditions 1).

Boc-Phe-Cys(Me)-Cys(Trt)-OMe (4b). NMM (0.29 mL, 2.61 mmol, 2 equiv) was dissolved in dry CH_2Cl_2 (15 mL). H-Cys(Trt)-OMe HCl (0.84 g, 1.96 mmol, 1.5 equiv) in dry CH_2Cl_2 (30mL) was added followed by Boc-Phe-Cys(Me)-OH (0.50 g, 1.31 mmol, 1 equiv) and HOBT (0.212 g, 1.57 mmol, 1.2 equiv). The mixture was cooled to 0 °C and CMC (0.83 g, 1.96 mmol, 1.5 equiv) added. The mixture was allowed to warm up to room temperature and left stirring for 3 hrs. It was then diluted with CH_2Cl_2 (18 mL), washed with sat. NaHCO_3 (20 mL), 1M HCl (10 mL x 3), aqueous NaHCO_3 (5%, 10 mL x 3), brine (10 mL x 2), dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. Purification by column chromatography (silica gel, hexanes/EtOAc 4/6) gave the desired compound as a white foam (0.63 g, 65%). R_f : 0.54 (hexanes/EtOAc); mp: (61-75) °C; IR (neat): ν_{max} : 3282, 1735, 1686, 1643 cm^{-1} ; ^1H -NMR (CDCl_3 , 400 MHz): 7.28-7.01 (m, 20H, ArH), 6.76 (d, 1H, $J = 7 \text{ Hz}$, NH), 6.71 (d, 1H, $J = 7 \text{ Hz}$, NH), 4.79 (br s, 1H, NH), 4.34-4.17 (m, 3H, 3H), 3.55 (s, 3H, OCH_3), 2.94 (m, 2H, Phe- H_2), 2.73 (dd, 1H, $J = 14, 4 \text{ Hz}$, Cys(Me)- HH), 2.59-2.49 (m, 3H, Cys(Me)- HH & Cys(Trt)- H_2), 1.98 (s, 3H, Cys(Me)- SCH_3), 1.25 (s, 9H, $C(CH_3)_3$); ^{13}C -NMR (CDCl_3 , 100.6 MHz): 171.5, 170.6, 170.1 (CO_2Me & CONH), 155.8 (OCONH), 144.6 (Cys(Trt)-*ipso*-ArC), 136.7 (Phe-*ipso*-ArC), 129.9, 128.6, 129.1, 128.4, 127.4, 127.3 (ArC), 80.8 ($C(CH_3)_3$), 67.4 (Cys(Trt)-Ar₃C), 53.0 (OCH_3), 52.2 & 52.1 (3C), 38.4 (Phe-C), 36.4 (Cys(Me)-C), 33.7 (Cys(Trt)-C), 28.6 ($C(CH_3)_3$), 16.2 (Cys(Me)- SCH_3); ESMS: m/z : 764.4 (M+H^+); HRMS (ES^+): calcd for $\text{C}_{41}\text{H}_{47}\text{N}_3\text{O}_6\text{S}_2\text{Na}$ (M+Na^+), 764.2804, found 764.2798; HPLC (ELS): 14.3 min (conditions 1).

H-Ala-OAll (tosylate salt).¹¹ Alanine (3 g, 33.7 mmol, 1 equiv), allyl alcohol (22.9 mL, 33.7 mmol, 1 equiv) and *p*-toluene sulfonic acid (7.7 g, 40.4 mmol, 1.2 equiv) were refluxed in benzene (270 mL) under Dean and Stark conditions for 24 hours. The solution was evaporated to 20 mL and precipitated in cold Et₂O to give a brownish powder (8.5 g, 89%). *R*_f: 0.33 (CH₂Cl₂/10%EtOH); mp: (79-80) °C; IR (neat): ν_{max} : 1774 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz): 8.18 (br s, 3H, NH₃⁺), 7.73 (d, 2H, *J* = 8 Hz, Ar*H*), 7.14 (d, 2H, *J* = 8 Hz, Ar*H*), 5.79 (ddt, 1H, *J* = 17, 11, 6 Hz, CH=CH₂), 5.25 (dd, 1H, *J* = 17, 1 Hz, CH=CH*H*_{trans}), 5.18 (dd, 1H, *J* = 11, 1 Hz, CH=CH*H*_{cis}), 4.57 (dd, 1H, *J* = 13, 6 Hz, CHH-CH=CH₂), 4.50 (dd, 1H, *J* = 13, 6 Hz, CHH-CH=CH₂), 4.12-3.98 (m, 1H, Ala-*H*), 2.35 (s, 3H, ArCH₃), 1.47 (d, 3H, *J* = 7 Hz, Ala-CH₃); ¹³C-NMR (CDCl₃, 100.6 MHz): 169.7 (CO₂All), 141.3 (*ipso*-ArC), 140.7 (*ipso*-ArC), 131.2 (CH=CH₂), 129.0 & 126.2 (*o* & *m*-ArC), 119.1 (CH=CH₂), 66.8 (CH₂-CH=CH₂), 49.3 (Ala-C), 21.5 (ArCH₃), 16.0 (Ala-CH₃); ESMS: *m/z*: 170.9 (M+H+MeCN)⁺.

Boc-Phe-Cys(Me)-Ala-OAll (4c). NMM (0.69 mL, 6.28 mmol, 2 equiv) was dissolved in dry CH₂Cl₂ (35 mL). *H-Ala-OAll (tosylate salt)* (1.42 g, 4.71 mmol, 1.5 equiv) in dry CH₂Cl₂ (70 mL) was then added followed by Boc-Phe-Cys(Me)-OH (1.20 g, 3.14 mmol, 1 equiv) and HOBt (0.509 g, 3.76 mmol, 1.2 equiv). The mixture was then cooled to 0 °C and CMC (1.99 g, 4.71 mmol, 1.5 equiv) added and allowed to warm up to room temperature and left stirring for 3 hrs. The mixture was then diluted with CH₂Cl₂ (40 mL), washed with sat. NaHCO₃ (45 mL), 1M HCl (25 mL x 3), aqueous NaHCO₃ (5%, 25 mL x 3), brine (25 mL x 2), dried (Na₂SO₄), filtered and the solvent removed *in vacuo*. Purification by precipitation from CH₂Cl₂/hexanes afforded a white solid (1.21 g, 78%). *R*_f: 0.19 (Et₂O/30%hexanes); mp: (83-86) °C; IR (neat): ν_{max} : 3308, 1746, 1692, 1662, 1641 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz): 7.40-7.20 (m, 5H, Phe-Ar*H*), 6.98 (d, 1H, *J* = 8 Hz, NH), 5.96 (ddt, 1H, *J* = 17, 10, 6 Hz, CH=CH₂), 5.38 (dd, 1H, *J* = 17, 1 Hz, CH=CH*H*_{trans}), 5.30 (dd, 1H, *J* = 10, 1 Hz, CH=CH*H*_{cis}), 5.02 (d, 1H, *J* = 7 Hz, NH), 4.75-4.63 (m, 2H, CH₂-CH=CH₂), 4.62-4.53 (m, 2H, Cys(Me)-*H* & Ala-*H*), 4.43 (m, 1H, Phe-*H*), 3.19 (dd, 1H, *J* = 14, 6 Hz, Phe-*HH*), 3.10 (dd, 1H, *J* = 14, 8 Hz, Phe-*HH*), 3.02 (m, 1H, Cys(Me)-*HH*), 2.78 (dd, 1H, *J* = 14, 8 Hz, Cys(Me)-*HH*), 2.17 (s, 3H, Cys(Me)-SCH₃), 1.48 (d, 3H, *J* = 7 Hz, Ala-CH₃), 1.45 (s, 9H, C(CH₃)₃); ¹³C-NMR

(CDCl₃, 100.6 MHz): 172.1 (CO₂All), 171.3 (Phe-CO), 169.7 (Cys(Me)-CO), 155.8 (OCONH), 136.4 (*ipso*-ArC), 131.7 (CH=CH₂), 129.3 & 128.9 (*o* & *m*-ArCH), 127.3 (*p*-ArCH), 118.8 (CH=CH₂), 80.8 (C(CH₃)₃), 66.1 (CH₂-CH=CH₂), 56.1 (Phe-C), 52.0 (Cys(Me)-C), 48.6 (Ala-C), 38.0 (Phe-C), 36.1 (Cys(Me)-C), 28.4 (C(CH₃)₃), 18.1 (Ala-CH₃), 15.9 (Cys(Me)-SCH₃); ESMS: *m/z*: 494.3 (M+H)⁺, 516.3 (M+Na)⁺; HRMS (ES⁺): calcd for C₂₄H₃₅N₃O₆SNa (M+Na)⁺, 516.2139, found 516.2136; HPLC (ELS): 11.2 min (conditions 1).

Boc-Phe-Cys(Me)-Ser(^tBu)-O^tBu (4d). NMM (0.27 mL, 2.49 mmol, 2 equiv) was dissolved in dry CH₂Cl₂ (14 mL). H-Ser(^tBu)-O^tBu HCl (0.475 g, 1.87 mmol, 1.5 equiv) in dry CH₂Cl₂ (28 mL) was then added followed by Boc-Phe-Cys(Me)-OH (0.477 g, 1.25 mmol, 1 equiv) and HOBt (0.202 g, 1.5 mmol, 1.2 equiv). The mixture was then cooled to 0 °C and CMC (0.793 g, 1.87 mmol, 1.5 equiv) added. The mixture was allowed to warm up to room temperature and left stirring for 3 hrs. It was then diluted with CH₂Cl₂ (17 mL), washed with sat. NaHCO₃ (20 mL), 1M HCl (10 mL x 3), aqueous NaHCO₃ (5%, 10 mL x 3), brine (10 mL x 2), dried (Na₂SO₄), filtered and the solvent removed *in vacuo*. A slightly yellow powder (0.58 g, 80%) was obtained which did not need further purification. *R*_f: 0.52 (Et₂O/30%hexanes); mp: (52-62) °C; IR (neat): ν_{max} : 3278, 1736, 1687, 1642 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz): 7.31-7.17 (m, 5H, Phe-ArH), 7.14 (d, 1H, *J* = 8 Hz, NH), 6.98 (d, 1H, *J* = 7 Hz, NH), 4.96 (d, 1H, *J* = 7 Hz, Phe-NH), 4.54-4.46 (m, 2H, Cys(Me)-H & Ser(^tBu)-H), 4.46-4.32 (m, 1H, Phe-H), 3.78 (dd, 1H, *J* = 9, 3 Hz, Ser(^tBu)-HH), 3.53 (dd, 1H, *J* = 9, 3 Hz, Ser(^tBu)-HH), 3.12 (dd, 1H, *J* = 14, 6 Hz, Phe-HH), 3.08 (dd, 1H, *J* = 14, 6 Hz, Phe-HH), 2.88 (dd, 1H, *J* = 14, 5 Hz, Cys(Me)-HH), 2.77 (dd, 1H, *J* = 14, 8 Hz, Cys(Me)-HH), 2.17 (s, 3H, Cys(Me)-SCH₃), 1.46 (s, 9H, C(CH₃)₃), 1.38 (s, 9H, C(CH₃)₃), 1.15 (s, 9H, C(CH₃)₃); ¹³C-NMR (CDCl₃, 100.6 MHz): 171.3 (Phe-CONH), 169.7 & 169.0 (Cys(Me)-CONH & Ser(^tBu)-CONH), 155.5 (OCONH), 136.6 (*ipso*-ArC), 129.5 & 128.8 (*o* & *m*-ArCH), 127.1 (*p*-ArCH), 82.1, 80.4, 73.3 (C(CH₃)₃), 62.0 (Ser(^tBu)-C), 55.8 (Phe-C), 53.8 (Ser(^tBu)-C), 52.2 (Cys(Me)-C), 38.4 (Phe-C), 36.6 (Cys(Me)-C), 28.4, 28.1, 27.5 (C(CH₃)₃), 15.9 (Cys(Me)-SCH₃); ESMS: *m/z*: 582.3 (M+H)⁺, 604.3 (M+Na)⁺; HRMS (ES⁺): calcd for

C₂₉H₄₇N₃O₇SNa (M+Na)⁺, 604.3027, found 604.3031; HPLC (ELS): 13.3 min (conditions 1); Anal. Calcd for C₂₉H₄₇N₃O₇S: C, 59.87; H, 8.14; N, 7.22; S, 5.51. Found: C, 59.60; H, 8.34; N, 6.93; S, 5.21.

General procedure for the oxidation of thioethers

Without Sc(OTf)₃

To the thioether (0.1 mmol, 1 equiv) dissolved in CH₂Cl₂/10%EtOH (1 mL), 60% H₂O₂ (5.7 or 23.8 L, 1.2 or 5 equiv) was added under stirring. (Tables 1 and 2 show conversions of thioethers to sulfoxides under uncatalyzed conditions).

Table 1. Oxidation of sulfides **1a-d** in the absence of Sc(OTf)₃

thioether	60% H ₂ O ₂ (equiv)	time (h)	Yield ^a (% sulfoxide)
1a	1.2	24	43
1a	5	24	76
1b	1.2	24	39
1b	5	24	53
1c	1.2	24	76
1c	5	20	> 98
1d	1.2	24	29 ^b
1d	5	24	60 ^c

^a Determined by ¹H NMR; ^b 0.4% of sulfone formed; ^c 2% of sulfone formed.

Table 1. Oxidation of thioethers **4a-d** in the absence of Sc(OTf)₃

thioether	60% H ₂ O ₂ (equiv)	time (h)	Yield ^{a, b} (% sulfoxide)
4a	1.2	6	15
4a	5	5	66
4b	1.2	7.25	71
4b	5	1.5	85
4c	1.2	6	91
4c	5	2	97

4d	1.2	11	87
4d	5	2	91

^a Determined by RP-HPLC (ELS). ^b No sulfone was observed.

With Sc(OTf)₃ (Phenyl prenyl sulfide)

Sc(OTf)₃ (9.8 mg, 0.02 mmol, 0.2 equiv) was suspended in CH₂Cl₂/10%EtOH (0.4 mL) and 60% H₂O₂ (5.7 or 23.8 mL, 1.2 or 5 equiv) was added under stirring. After 1 minute the substrate was also added (17.8 mg, 0.1 mmol, 1 equiv) dissolved in CH₂Cl₂/10%EtOH (0.3 mL). The vial in which the substrate was weighed was further washed with the solvent mixture (0.3 mL) and added to the reaction mixture.

With Sc(OTf)₃ (all other thioethers)

Sc(OTf)₃ (9.8 mg, 0.02 mmol, 0.2 equiv) was suspended in CH₂Cl₂/10%EtOH (1 mL) and 60% H₂O₂ (5.7 or 23.8 mL, 1.2 or 5 equiv) was added under stirring. After 5 minutes the substrate was also added (0.1 mmol, 1 equiv).

Quantification of conversions.

Oxidations were monitored by TLC and HPLC. Conversions were evaluated via ¹H-NMR (CDCl₃) and HPLC (ELS detector).

Work-up procedure.

The reaction mixture was diluted with CH₂Cl₂, poured in a separating funnel containing water and extracted. The organic phase was washed again with water, dried (MgSO₄) and the solvent removed *in vacuo*.

Phenyl prenyl sulfoxide (2a).¹² A liquid was obtained (96%) which did not need further purification. *R*_f: 0.41 (CHCl₃/10%EtOAc); IR (neat): 1044 (SO st) cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz): 7.62-7.41 (m, 5H), 5.07 (tt, 1H, *J* = 8, 2 Hz), 3.56 (dd, 1H, *J* = 13, 8 Hz), 3.50 (dd, 1H, *J* = 13, 8 Hz), 1.71 (s, 3H), 1.41 (s, 3H); ¹³C-NMR (CDCl₃, 100.6 MHz): 143.7, 142.3, 136.6, 131.1, 129.0, 124.5, 111.2, 56.8, 26.0, 18.1; ESMS: *m/z*: 195 (M+H)⁺, 217 (M+Na)⁺, 236 (M+H+CH₃CN)⁺, 258 (M+Na+CH₃CN)⁺, 389 (2M+H)⁺, 411 (2M+Na)⁺, 452 (2M+Na+CH₃CN)⁺; HPLC (λ₂₅₄): 9.2 min (conditions 1).

p-Bromophenyl methyl sulfoxide (2b).¹³ An off-white solid was obtained (95%) which did not need further purification. IR (neat): 1048 (SO st) cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz):

7.68 (m, 2H), 7.53 (m, 2H), 2.72 (s, 3H, CH₃); ¹³C-NMR (CDCl₃, 100.6 MHz): 145.0, 132.7, 125.5, 125.2, 44.1; GC-CIMS: rt: 12.29 min; *m/z*: 219 + 221 (M)⁺; HPLC (₂₅₄): 3.0 min (conditions 2).

p-Methoxyphenyl methyl sulfoxide (2c)¹⁴. The residue was purified by column chromatography (silica gel, hexanes/EtOAc 6/4) to give a clear liquid (97%). IR (neat): 1045 (SO st) cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz): 7.58 (d, *J* = 9 Hz, 2H), 7.02 (d, *J* = 9 Hz, 2H), 3.84 (s, 3H), 2.68 (s, 3H); ¹³C-NMR (CDCl₃, 100.6 MHz): 162.1, 136.8, 125.5, 115.0, 55.6, 44.1; GC-CIMS: rt: 12.09 min; *m/z*: 171 (M+H)⁺.

Phenyl methyl sulfoxide (2d).⁴ The crude liquid was purified by column chromatography (silica gel, CHCl₃) to give a liquid (61%). *R_f*: 0.17 (CHCl₃); IR (neat): _{max}: 1041 (SO st) cm⁻¹; ¹H-NMR (CDCl₃, 300 MHz): 7.68-7.60 (m, 2H, Ar-CH), 7.66-7.45 (m, 2H, Ar-CH), 2.71 (s, 3H, CH₃); ¹³C-NMR (CDCl₃, 75.5 MHz): 145.7 (*ipso*-ArC), 131.1, 129.4, 123.5 (ArCH), 44.0 (CH₃); GC-CIMS: rt 7.01 mins, *m/z*: 141 (M+H)⁺, 158 (M+NH₄)⁺; GC: 7.01 min; HPLC (Daicel OD-H, UV detector (₂₅₄), flow rate 0.5 mL min⁻¹, hexane/2-propanol 9/1): 23.74 + 26.93 min.

Fmoc-Cys((O)Me)-OMe (5a). The crude was purified by column chromatography (silica gel, EtOAc) to give a white solid (91%). *R_f*: 0.40 (chloroform/10%MeOH); mp: (152-153) °C; IR (neat): _{max}: 3302, 1738, 1692, 1083, 1020 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz): 7.77 & 7.61 (2d, *J* = 7 Hz, 4H, Fmoc-H_{1,4,5,8}), 7.41 & 7.33 (2t, *J* = 7 Hz, 4H, Fmoc-H_{2,3,6,7}), 6.09-5.95 (m, 1H, NH), 4.85-4.67 (m, 1H, Cys((O)Me)-H), 4.52-4.34 (m, 2H, Fmoc-CH₂), 4.30-4.19 (m, 1H, Fmoc-CH), 3.83 & 3.82 (2s, 3H, OCH₃), 3.42-3.15 (m, 2H, Cys((O)Me)-H₂), 2.68-2.67 (2s, 3H, Cys((O)Me)-SCH₃); ¹³C-NMR (CDCl₃, 100.6 MHz): 170.5 & 170.3 (CO₂Me), 156.1 & 155.9 (OCONH), 143.8 & 143.7 (Fmoc-C_{8a,9a}), 141.48 & 141.47 (Fmoc-C_{4a,4b}), 128.0 & 127.9 (2Fmoc-C_{1,8}), 127.3 (Fmoc-C_{4,5}), 125.3 (Fmoc-C_{2,7}), 120.18 & 120.16 (Fmoc-C_{3,6}), 67.5 (Fmoc-CH₂), 56.0 & 55.1 (Cys((O)Me)-C), 53.3 & 53.2 (OCH₃), 50.8 & 50.3 (Cys((O)Me)-C), 47.2 (Fmoc-CH), 39.5 & 39.2 (Cys((O)Me)-SCH₃); ESMS: *m/z*: 388.2 (M+H)⁺, 410.1 (M+Na)⁺, 775.3 (2M+H)⁺, 797.3 (2M+Na)⁺; HRMS (ES⁺): calcd for C₂₀H₂₁NO₅SNa (M+Na)⁺, 410.10327, found 410.10326; HPLC (₂₅₄): 9.5 min (conditions 1).

Boc-Phe-Cys((O)Me)-Cys(Trt)-OMe (5b). A white foam (96%) was obtained which did not need further purification. *R_f*: 0.43 (CHCl₃/3%MeOH); mp: (68-75) °C; IR (neat): ν_{max} : 3282, 1744, 1656, 1021 cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz): 8.16 (d, 1H, *J* = 8 Hz, Cys(Trt)-NH), 7.76 (d, 1H, *J* = 8 Hz, Cys(Trt)-NH), 7.75-7.63 (br s, 1H, Cys((O)Me)-NH), 7.43-7.12 (m, 40H, ArH), 4.96 (br s, 2H, Phe-NH), 4.92-4.80 (m, 2H, Cys((O)Me)-H), 4.41-4.26 (m, 2H, Phe-H), 4.25-4.16 (m, 2H, Cys(Trt)-H), 3.6435 & 3.6334 (s, 6H, CO₂CH₃), 3.36 (dd, 1H, *J* = 14, 8 Hz, Cys((O)Me)-HH), 3.23-2.90 (m, 5H, 3Phe-HH & 2Cys((O)Me)-H₂), 2.84 (s, 3H, Cys((O)Me)-SCH₃), 2.85-2.74 (m, 2H, Phe-HH & Cys((O)Me)-HH), 2.70-2.53 (m, 4H, Cys(Trt)-H₂), 2.60 (s, 3H, Cys((O)Me)-SCH₃), 1.38 & 1.37 (2s, 18H, C(CH₃)₃); ¹³C-NMR (CDCl₃, 100.6 MHz): 171.7, 171.3, 170.5, 169.7, 169.1, 169.0 (2CO₂Me & 4CONH), 155.8 & 155.6 (OCONH), 144.5 & 144.4 (Cys(Trt)-*ipso*-ArC), 136.5 & 136.4 (Phe-*ipso*-ArC), 129.8, 129.7, 129.3, 128.9, 128.1, 128.0, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2, 126.9 (ArCH), 80.7 (C(CH₃)₃), 67.3 (Cys(Trt)-Ar₃C), 56.5 (Phe-C), 55.0 (Cys((O)Me)-C), 52.7 (OCH₃), 52.6 (OCH₃), 52.5 (Cys(Trt)-C), 51.7 (Cys((O)Me)-C), 50.1 (Cys((O)Me)-C), 47.2 (Cys((O)Me)-C), 39.5 (Cys((O)Me)-SCH₃), 38.0 (Phe-C), 37.8 (Cys((O)Me)-SCH₃), 33.3 (Cys(Trt)-C), 33.2 (Cys(Trt)-C), 28.4 (C(CH₃)₃); ESMS: *m/z*: 780.3 (M+Na)⁺; HRMS (ES⁺): calcd for C₄₁H₄₈N₃O₇S₂ (M+H)⁺, 758.2928, found 758.2922; calcd for C₄₁H₄₇N₃O₇S₂Na (M+Na)⁺, 780.2747, found 780.2731; calcd for C₄₁H₄₇N₃O₇S₂K (M+K)⁺, 796.2487, found 796.2469; HPLC (ELS): 13.0 min (conditions 1).

Boc-Phe-Cys((O)Me)-Ala-OAll (5c). A white solid was obtained which was purified by precipitation from CH₂Cl₂/hexanes (92%). *R_f*: 0.44 (CHCl₃/1%MeOH); mp: (115-120) °C; IR (neat): ν_{max} : 3288, 1739, 1689, 1645, 1024 (SO st) cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz): 8.24 (d, 1H, *J* = 8 Hz, Ala-NH), 8.01-7.84 (br s, 1H, Cys²((O)Me)-NH), 7.86 (d, 1H, *J* = 7 Hz, Ala-NH), 7.45 (d, 1H, *J* = 6 Hz, Cys¹((O)Me)-NH), 7.36-7.13 (m, 10H, Phe-ArH), 5.90 (m, 2H, CH=CH₂), 5.35 (m, 1H, CH=CHH), 5.31 (m, 1H, CH=CHH), 5.26 (m, 1H, CH=CHH), 5.23 (m, 1H, CH=CHH), 5.10-4.91 (m, 3H, 2Boc-NH & Cys²((O)Me)-H), 4.87 (td, 1H, *J* = 7, 3 Hz, Cys¹((O)Me)-H), 4.65-4.59 (m, 4H, CH₂-CH=CH₂), 4.57-4.42 (m, 2H, Ala-H), 4.41-4.27 (m, 2H, Phe-H), 3.46 (dd, 1H, *J* = 14, 8

Hz, Cys¹((O)Me)-HH), 3.32-3.22 (m, 1H, Cys²((O)Me)-HH), 3.19 (dd, 1H, *J* = 14, 5 Hz, Phe-HH), 3.13 (dd, 1H, *J* = 14, 6 Hz, Phe-HH), 3.08-2.90 (m, 2H, Cys²((O)Me)-HH & Phe-HH), 2.96 (dd, 1H, *J* = 14, 9 Hz, Phe-HH), 2.86 (s, 3H, Cys((O)Me)-CH₃), 2.85 (dd, 1H, *J* = 14, 3 Hz, Cys¹((O)Me)-HH), 2.63 (s, 3H, Cys((O)Me)-CH₃), 1.45 (d, 3H, *J* = 8 Hz, Ala-CH₃), 1.43 (d, 3H, *J* = 7 Hz, Ala-CH₃), 1.393 (s, 9H, C(CH₃)₃), 1.386 (s, 9H, C(CH₃)₃); ¹³C-NMR (CDCl₃, 100.6 MHz): 172.1, 172.0, 171.7, 171.3 (CO₂Al & Phe-CONH), 169.0 & 168.9 (Cys((O)Me)-CO), 156.0 & 155.5 (OCONH), 136.4 (*ipso*-ArC), 131.9 & 131.8 (CH=CH₂), 129.32, 129.28, 128.94, 128.86 (*o* & *m*-ArCH), 127.2 (*p*-ArCH), 118.8 & 118.6 (CH=CH₂), 80.8 & 80.6 (C(CH₃)₃), 66.0 & 65.9 (CH₂-CH=CH₂), 56.4 & 56.0 (Phe-C), 54.9 (Cys²((O)Me)-C), 51.7 (Cys¹((O)Me)-C), 50.4 (Cys²((O)Me)-C), 48.7 (Ala-C), 47.2 (Cys¹((O)Me)-C), 39.6 (Cys((O)Me)-CH₃), 38.1 (Phe-C), 37.7 (Cys((O)Me)-CH₃), 28.4 (C(CH₃)₃), 17.50 & 17.35 (Ala-CH₃); ESMS: *m/z*: 510.1 (M+H)⁺, 1018.9 (2M+H)⁺; HRMS (ES⁺): calcd for C₂₄H₃₅N₃O₇SNa (M+Na)⁺, 532.2088, found 532.2080; HPLC (ELS): 9.6 min (conditions 1).

Boc-Phe-Cys((O)Me)-Ser(^tBu)-O^tBu (5d). A white solid (92%) was obtained which did not need further purification. *R*_f: 0.50 (CHCl₃/1%MeOH); mp: (58-65) °C; IR (neat): ν_{max} : 3282, 1735, 1710, 1681, 1647, 1020 (SO st) cm⁻¹; ¹H-NMR (CDCl₃, 400 MHz): 7.99 (d, 1H, *J* = 8 Hz, Ser(^tBu)-NH), 7.62 (d, 1H, *J* = 7 Hz, Cys²((O)Me)-NH), 7.59 (d, 1H, *J* = 9 Hz, Ser(^tBu)-NH), 7.37 (d, 1H, *J* = 7 Hz, Cys¹((O)Me)-NH), 7.33-7.14 (m, 10H, ArH), 5.04-4.86 (m, 4H, Phe-NH & Cys²((O)Me)-H & Cys¹((O)Me)-H), 4.49 (m, 2H, Ser(^tBu)-H), 4.48-4.32 (m, 2H, Phe-H), 3.77 (dd, 2H, *J* = 9, 4 Hz, Ser(^tBu)-H₂), 3.54 (dd, 1H, *J* = 10, 3 Hz, Ser(^tBu)-HH), 3.52 (dd, 1H, *J* = 10, 3 Hz, Ser(^tBu)-HH), 3.45 (dd, 1H, *J* = 14, 7 Hz, Cys¹((O)Me)-HH), 3.22-3.03 (m, 4H, Phe-H₂ , Cys²((O)Me)-H₂), 3.11-2.92 (m, 2H, Phe-H₂), 2.85 (dd, 1H, *J* = 14, 7 Hz, Cys¹((O)Me)-HH), 2.84 (s, 3H, Cys((O)Me)-SCH₃), 2.63 (s, 3H, Cys((O)Me)-SCH₃), 1.47 (s, 18H, C(CH₃)₃), 1.38 (s, 18H, C(CH₃)₃), 1.16 (s, 18H, C(CH₃)₃); ¹³C-NMR (CDCl₃, 100.6 MHz): 171.7, 171.2, 169.0, 168.97, 168.92 (CO₂^tBu & Phe-CONH & Cys((O)Me)-CONH), 155.4 (OCONH), 136.6 & 136.5 (*ipso*-ArC), 129.5, 129.4, 128.8 (*o* & *m*-ArCH), 127.15 & 127.10 (*p*-ArCH), 81.95, 81.92, 80.4, 73.34, 73.31 (C(CH₃)₃), 61.81 & 61.75 (Ser(^tBu)-C), 55.9

(Phe-C), 55.4 (Cys²((O)Me)-C), 54.1 & 54.0 (Ser(^tBu)-C), 52.8 (Cys¹((O)Me)-C), 49.7 & 47.1 (Cys¹((O)Me)-C & Cys²((O)Me)-C), 39.6 (Cys((O)Me)-SCH₃), 38.3 (Phe-C), 38.2 (Cys((O)Me)-SCH₃), 28.4, 28.2, 27.4 (C(CH₃)₃); ESMS: *m/z*: 620.2 (M+Na)⁺; HRMS (ES⁺): calcd for C₂₉H₄₇N₃O₈SNa (M+Na)⁺, 620.2976, found 620.2974 ; HPLC (ELS): 11.6 min (conditions 1)

Solid phase synthesis

Fmoc-Cys(Me)-OH was loaded on HMPA-PS resin (1% DVB) (HMPA linker was synthesised according to literature protocol¹⁵ and loaded onto amino methyl polystyrene resin using standard ester bond formation conditions) using standard solid-phase synthesis protocols.¹⁶ The loading was evaluated by Fmoc test (experimental 0.80 mmolg⁻¹, calcd 0.89 mmolg⁻¹).

Treatment of polymer supported Fmoc-Cys(Me)-OH with H₂O₂ and catalytic Sc(OTf)₃. Sc(OTf)₃ (9.8 mg, 0.02 mmol, 0.2 equiv) was suspended under stirring in CH₂Cl₂/10%EtOH (0.4mL) in HPLC vials. 60% H₂O₂ (21.3 L, 0.5 mmol, 5equiv) was then added. After 1 minute, the mixture was added to the pre-swollen (in CH₂Cl₂/10%EtOH) resin (100mg, 0.089 mmol based on calcd loading). The vial was then washed with CH₂Cl₂/10%EtOH (2 x 0.3 mL) and the washings added to the resin. The mixture was shaken in a rotatory wheel for 10 min. The resin was washed with CH₂Cl₂/10%EtOH (3 x 1mL), CH₂Cl₂ (3 x 1mL), MeOH (3 x 1mL), Et₂O (3 x 1mL) and dried. The resin was then swollen again in CH₂Cl₂ before treatment with TFA/CH₂Cl₂/water (95/3/2, 1mL) for 1.5 hr. Resin was washed with the cleavage cocktail (4 x 0.5 mL). The combined cleavage and washings solutions were evaporated to dryness and the residue analysed by RP-HPLC comparing the retention times with known samples of 6 and 7 the preparation of which is detailed below.

Fmoc-Cys((O)Me)-OH (6).¹⁷ Fmoc-Cys(Me)-OH (100 mg, 0.28 mmol, 1 equiv) was dissolved in MeOH (2.5 mL) and the resulting solution cooled in an ice bath. Sodium periodate (65.8 mg, 0.31 mmol, 1.1 equiv) in water (1 mL) was then added dropwise and the resulting mixture allowed to warm up to room temperature and left stirring for 1.5 hrs. After this time, the MeOH was evaporated and the aqueous mixture transferred into a separating funnel containing brine acidified at pH = 1 (10 mL). The mixture was extracted with EtOAc (5 x 40 mL) (problems were encountered to the the low solubility

of the product in most organic solvents, large volumes of solvents were therefore used). The organic phases were then put together, dried (Na₂SO₄), filtered and the solvent removed *in vacuo*. The resulting powder was triturated with EtOH (15 mL), Et₂O (15 mL) and dried (99 mg, 95%). *R_f*: 0.37 (9 CH₂Cl₂:1 MeOH: 0.1 AcOH); mp: higher than 230 °C; IR (neat): ν_{max} : 3327, 1733, 1688, 1044 (SO st) cm⁻¹; ¹H-NMR (DMSO-d₆, 400 MHz): 8.01 & 7.94 (2d, 2H, *J* = 8 Hz, NH), 7.89 & 7.71 (2d, 8H, *J* = 7 Hz, Fmoc-H_{1,4,5,8}), 7.41 & 7.33 (2t, 8H, *J* = 7 Hz, Fmoc-H_{2,3,6,7}), 4.50-4.16 (m, 8H, Fmoc-CH₂ & H & Fmoc-CH), 3.25 (dd, 1H, *J* = 13, 6 Hz, *H*), 3.15-2.96 (m, 3H, *H*), 2.505 & 2.500 (2s, 6H, CH₃); ¹³C-NMR (DMSO-d₆, 100.6 MHz): 172.3 & 171.9 (CO₂H), 156.0 & 155.8 (OCONH), 143.8 (Fmoc-C_{8a,9a}), 140.8 (Fmoc-C_{4a,4b}), 127.7 (Fmoc-C_{1,8}), 127.2 (Fmoc-C_{4,5}), 125.3 (Fmoc-C_{2,7}), 120.2 (Fmoc-C_{3,6}), 65.8 (Fmoc-CH₂), 54.2 (C), 54.1 (C), 48.8 (C), 48.1 (C), 46.6 (Fmoc-CH), 38.5 (CH₃), 38.2 (CH₃); HRMS (ES⁺): calcd for C₁₉H₁₉N₁O₅S₁Na (M+Na)⁺, 396.0882, found 396.0876; HPLC (ELS): 8.8 min (conditions 1)

Fmoc-Cys((O₂)Me)-OH (7). Fmoc-Cys(Me)-OH (100 mg, 0.28 mmol, 1 equiv) was dissolved in MeOH (2.5 mL) and the resulting solution cooled in an ice bath. OXONE (516 mg, 0.84 mmol, 3 equiv) in water (1 mL) was then added dropwise and the resulting mixture allowed to warm up to rt and left stirring for 1.5 hrs. After this time, the MeOH was evaporated and the aqueous mixture transferred into a separating funnel containing brine acidified to pH = 1 (10 mL). The mixture was extracted with EtOAc (2 x 5 mL). The organic phases were then put together, dried (Na₂SO₄), filtered and the solvent removed *in vacuo* to give a white powder (105 mg, 96%) which did not need further purification. *R_f*: 0.52 (CH₂Cl₂:MeOH:AcOH 9:1:0.1); mp: (185-190) °C; IR (neat): ν_{max} : 3302, 1742, 1701, 1313 (SO₂ st as), 1124 (SO₂ st s) cm⁻¹; ¹H-NMR (DMSO-d₆, 400 MHz): 7.93 (d, 1H, *J* = 9 Hz, NH), 7.89 & 7.70 (2d, 4H, *J* = 7 Hz, Fmoc-H_{1,4,5,8}), 7.42 & 7.32 (2t, 4H, *J* = 7 Hz, Fmoc-H_{2,3,6,7}), 4.46 (m, 1H, *H*), 4.39-4.27 (m, 2H, Fmoc-CH₂), 4.24 (t, 1H, *J* = 7 Hz, Fmoc-CH), 3.60-3.46 (m, 2H, *H*), 2.96 (s, 3H, CH₃); ¹³C-NMR (DMSO-d₆, 100.6 MHz): 171.1 (CO₂H), 155.7 (OCONH), 143.7 (Fmoc-C_{8a,9a}), 140.7 (Fmoc-C_{4a,4b}), 127.6 (Fmoc-C_{1,8}), 127.1 (Fmoc-C_{4,5}), 125.2 (Fmoc-C_{2,7}), 120.1 (Fmoc-

C_{3,6}), 65.8 (Fmoc-CH₂), 54.5 (C), 48.8 (C), 49.2 (C), 46.6 (Fmoc-CH), 41.5 (CH₃); ESMS: *m/z*: 501.9 (M+TFA-H)⁻; HRMS (ES⁺): calcd for C₁₉H₁₉NO₅SNa (M+Na)⁺, 412.0825, found 412.0840; HPLC (ELS): 9.8 min (conditions 1).

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