Supporting Information
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A Facile, Inexpensive and Scalable Route to Orthogonally Protected α-Methyl Cysteine

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Supporting Information

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1.1   General methods
All non-aqueous reactions were carried out under an atmosphere of nitrogen using oven-dried glassware that was cooled in a desiccator prior to use. Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without further purification. Toluene, THF, CH2Cl2, and Et2O were dried and purified by passage through activated alumina columns using a Glass Contour Solvent Purification System. Triethylamine was distilled from calcium hydride and stored over molecular sieves under a nitrogen atmosphere. Saturated aqueous solutions of inorganic salts are represented as (volume, sat. aq.). 1H and 13C NMR spectra were obtained on Bruker instruments at the stated frequency. Infra-red spectra were recorded neat on Shimadzu IRAffinity-1 unless otherwise stated. Electrospray (ESI) and fast atom bombardment (FAB) mass spectra were obtained on a Kratos MS50TC mass spectrometer. Melting points were determined on a Gallenkamp Electrothermal Melting Point apparatus and are uncorrected. Flash chromatography was carried out using Merck Kieselgel 60 (Merck 9385) under positive pressure. Eluent compositions are quoted as v/v ratios.
1.2 Synthesis of α-methyl cysteine

(4R)-Ethyl 2-phenyl-4,5-dihydrothiazole-4-carboxylate

(R)-Cysteine ethyl ester hydrochloride 5 (3.12 g, 16.8 mmol) and ethyl benzimidate hydrochloride (2.97 g, 16.0 mmol) were dissolved in MeOH (32 mL) and stirred at rt. Triethylamine (2.34 mL, 16.8 mmol) was added dropwise over 15 min and the reaction mixture was stirred at rt for ~18 h. The reaction mixture was then diluted with H2O (32 mL) and the MeOH removed in vacuo. The remaining aqueous material was extracted with EtOAc (3 × 50 mL) and dried with anhydrous Na2SO4. The product was concentrated in vacuo and the crude product was then purified using column chromatography (EtOAc:hexane, 1:9) to give the desired product (CH3), 19.93 (CH3). 1H and 13C spectroscopic data in good agreement with literature.1

CDCl3 (neat, cm−1) 1738 (C=O), 1661 (C=N), 1595 (Ar), 1575 (Ar), 689 (C–S); IR (neat, cm−1) 1736 (C=O), 1694 (C=N), 1605 (Ar), 1579 (Ar), 1325 (S=O), 1132 (S=O), 685 (C–S); m/z (ESI+, MeOH/DCM) 258 ([M+Na]+, 100%), 236 (41), 185 (18). 1H and 13C spectroscopic data in good agreement with literature.1

(1S)-2,10-N-[(4RS)-2-Phenylthiazoline-4-carbonyl]camphorsultam

Diastereomer A: 1H NMR δ (400 MHz, CDCl3) 7.89–7.81 (2H, m, ArH), 7.51–7.43 (1H, m, ArH), 7.43–7.35 (2H, m, ArH), 5.81 (1H, t, J = 8.9 Hz, CHCH2S), 4.02 (1H, dd, J = 7.5, 5.0 Hz, Sultam), 3.78–3.65 (2H, m, CHCH2S), 3.59 (1H, d, J = 13.8 Hz, Sultam), 3.50 (1H, d, J = 13.8 Hz, Sultam), 2.30–1.84 (5H, m, Sultam), 1.52–1.32 (2H, m, Sultam), 1.27 (3H, s, CCH2), 1.01 (3H, s, CCH2); 13C NMR δ (101 MHz, CDCl3) 171.90 (C), 169.59 (C), 132.78 (C), 131.73 (CH), 128.84 (2 × CH), 128.50 (2 × CH), 78.74 (CH), 65.65 (CH), 53.18 (CH2), 48.88 (C), 47.94 (C), 44.84 (CH), 38.46 (CH2), 35.34 (CH2), 33.02 (CH2), 26.49 (CH2), 21.07 (CH3), 20.00 (CH3).

Diastereomer B: 1H NMR δ (400 MHz, CDCl3) 7.94–7.79 (2H, m, ArH), 7.51–7.44 (1H, m, ArH), 7.44–7.36 (2H, m, ArH), 5.91 (1H, dd, J = 9.4, 8.7 Hz, CHCH2S), 4.07–3.92 (1H, m, Sultam), 3.85 (1H, dd, J = 11.2, 9.4 Hz, CHCH2H2S), 3.56 (1H, d, J = 13.9 Hz, Sultam), 3.52 (1H, d, J = 13.9 Hz, Sultam), 3.47 (1H, dd, J = 11.2, 8.7 Hz, CHCH2H2S), 2.25–1.81 (5H, m, Sultam), 1.50–1.30 (2H, m, Sultam), 1.18 (3H, s, CCH2), 1.00 (3H, s, CCH2); 13C NMR δ (101 MHz, CDCl3) 171.56 (C), 169.28 (C), 132.74 (CH), 131.63 (CH), 128.82 (2 × CH), 128.47 (2 × CH), 78.62 (CH), 65.31 (CH), 53.03 (CH2), 48.82 (C), 47.94 (C), 44.57 (CH), 38.17 (CH2), 37.01 (CH2), 32.76 (CH2), 26.46 (CH2), 20.89 (CH2), 19.93 (CH3). 1H and 13C spectroscopic data in good agreement with literature.1

-S2-
Iodomethane (0.77 mL, 12.4 mmol) was added dropwise to a stirred solution of sultam 8 (1.00 g, 2.47 mmol) and TBAB (79.6 mg, 0.247 mmol) in DCM (15 mL) and stirred for 30 min at rt. The reaction mixture was then chilled to -78 °C and P2-Et (0.82 mL, 2.47 mmol) was added dropwise over 10 min. After stirring for 1 h at -78 °C, the reaction was allowed to return to rt and quenched with NH₄Cl (5 mL; sat aq). The reaction mixture was then diluted with DCM (400 mL), washed with H₂O (2 × 100 mL) and dried with anhydrous MgSO₄. The product was concentrated in vacuo and the crude product was then purified using column chromatography (EtOAc:hexane, 1:9) to give the desired product 9 as a colourless solid (1.02 g, 99%).

Rf (EtOAc:hexane, 1:1) = 0.50; [α]D ≈ 84.0 (c 1.00, MeOH); mp 136-138 °C, lit. 1 mp 138-140 ºC; IR (neat, cm⁻¹) 1736 (C=O), 1672 (C=N), 1624 (Ar), 1595 (Ar), 1344 (S=O), 1151 (S=O), 704 (C–S); 1H NMR δ (400 MHz, CDCl₃) 7.97 (2H, d, J = 7.3 Hz, ArH), 7.49–7.37 (3H, m, ArH), 4.11 (1H, dd, J = 7.4, 5.2 Hz, Sultam), 3.99 (1H, d, J = 11.3 Hz, CHAHS), 3.56 (1H, d, J = 13.6 Hz, Sultam), 3.45 (1H, d, J = 11.3 Hz, CHAHS), 2.20–1.80 (5H, m, Sultam), 1.69 (3H, s, CH₃CN), 1.45–1.31 (2H, m, Sultam), 1.28 (3H, s, CH(CH₃)₂); 13C NMR δ (126 MHz, CDCl₃) δ 173.88 (C), 168.96 (C), 132.96 (C), 131.72 (CH), 129.16 (2 × CH), 128.53 (2 × CH), 86.55 (C), 67.91 (CH), 54.82 (CH₂), 48.25 (C), 47.87 (C), 44.99 (CH), 41.52 (CH₂), 39.44 (CH₂), 33.52 (CH₂), 26.55 (CH₂), 25.05 (CH₃), 21.46 (CH₃), 20.10 (CH₃); m/z (EI+) 419 ([M+H]+, 31%), 234 (13), 229 (16), 178 (83).

LiOH (50 mL, 50 mmol; 1 M aq) was added to a stirred solution of methylated thiazoline 9 (1.07 g, 2.56 mmol) in THF (50 mL) at rt. The reaction mixture was stirred for 30 min and then the THF was removed in vacuo. The remaining aqueous material was extracted with EtOAc (2 × 60 mL) and the combined organic layers were dried with anhydrous MgSO₄. The product was concentrated in vacuo and the crude product was then recrystallised from EtOH to give (1S)-(-)-2,10-camphorsultam 7 as a colourless solid (0.55 g, 89%). The remaining aqueous material was then acidified with HCl (50 mL, 50 mmol; 1 M aq), extracted with EtOAc (3 × 100 mL) and the combined organics were dried with anhydrous MgSO₄. The solvent was removed in vacuo to give the desired product as a pale yellow oil (0.58 g, 91%). Rf (DCM:MeOH, 9:1) = 0.56; [α]D = 30.0 (c 1.00, Acetone); IR (neat, cm⁻¹) 3100-3700 (O–H), 1708 (C=O), 1641 (C=N), 1629 (Ar), 1620 (Ar), 1564 (Ar); 1H NMR δ (500 MHz, CDCl₃) 10.57 (1H, br s, COO), 7.86 (2H, d, J = 7.5 Hz, ArH), 7.50 (1H, t, J = 7.4 Hz, ArH), 7.42 (2H, t, J = 7.6 Hz, ArH), 3.92 (1H, d, J = 11.4 Hz, CH₂(CH₃)₂), 3.36 (1H, d, J = 11.4 Hz, CH₂(CH₃)₂), 1.70 (3H, s, CH₃); 13C NMR δ (126 MHz, CDCl₃) δ 177.28 (C), 171.18 (C), 132.28 (CH), 132.13 (C), 128.74 (2 × CH), 128.73 (2 × CH), 84.07 (C), 41.30 (CH₂), 23.94 (CH₃); m/z (ESI+, MeOH/DCM) 222 ([M+H]+, 93%), 176 (6). 1H and 13C spectroscopic data in good agreement with literature.

Thiazoline (0.58 g, 2.62 mmol) was dissolved in HCl (25 mL; 6 M aq) and the reaction mixture was heated at reflux for 24 h. The reaction was allowed to cool to rt and concentrated in vacuo until ~5 mL of solution remained. Toluene (5 mL) was added and excess water was removed by azeotropic distillation to give the desired product 10 as a colourless solid (0.31 g, 89%). [α]D = +10.0 (c 1.00, H₂O); mp 157-159 ºC, lit. 3 mp 157-159 ºC; IR (neat, cm⁻¹) 3094 (N–H), 2997 (N–H), 2840-2370 (O–H), 1722 (C=O), 1223 (C–O), 634 (C–S); 1H NMR δ (500 MHz, D₂O) 3.20 (1H, d, J = 15.0 Hz, CH₂(CH₃)₂), 2.91 (1H, d, J = 15.0 Hz, CH₂(CH₃)₂), 1.61 (3H, s, CH₃CN); 13C NMR δ (126 MHz, D₂O) 173.37 (C), 61.56 (C), 30.23(CH₂), 21.17 (CH₃); m/z (FAB’) 136 ([M+H]+, 52%), 122 (47), 105 (100). 1H and 13C spectroscopic data in good agreement with literature.
1.3 References


(4R)-Ethyl 2-phenyl-4,5-dihydrothiazole-4-carboxylate
(4R)-Ethyl 2-phenyl-4,5-dihydrothiazole-4-carboxylate
(1S)-2,10-N-[(4RS)-2-Phenylthiazoline-4-carbonyl]camphorsultam
(1S)-2,10-N-[(4RS)-2-Phenylthiazoline-4-carbonyl]camphorsultam
(1S)-2,10-N-[(4R)-4-Methyl-2-phenylthiazoline-4-carbonyl]camphorsultam
(1S)-2,10-N-[(4R)-4-Methyl-2-phenylthiazoline-4-carbonyl]camphorsultam
(4R)-4-Methyl-2-phenyl-4,5-dihydrothiazole-4-carboxylic acid (Crude)
(4R)-4-Methyl-2-phenyl-4,5-dihydrothiazole-4-carboxylic acid (Crude)
(2R)-2-Amino-2-methyl-3-sulfanylpropanoic acid hydrochloride
(2R)-2-Amino-2-methyl-3-sulfanylpropanoic acid hydrochloride
(2R)-2-Amino-2-methyl-3-[(triphenylmethyl)sulfanyl]propanoic acid phosphate salt
(2R)-2-Amino-2-methyl-3-[(triphenylmethyl)sulfanyl]propanoic acid phosphate salt
(2R)-2-Amino-2-methyl-3-[(prop-2-en-1-yl)sulfanyl]propanoic acid
(2R)-2-Amino-2-methyl-3-\{(prop-2-en-1-yl)sulfanyl\}propanoic acid
(2R)-2-Amino-3-(tert-butylsulfanyl)-2-methylpropanoic acid hydrochloride salt
(2R)-2-Amino-3-(tert-butylsulfanyl)-2-methylpropanoic acid hydrochloride salt