Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supplementary Material

Experimental

(1'*S*)-2-(1-{[2-(1'*S*-{[2-(1'-*tert*-Butoxycarbonylamino-2'-methyl-propyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carbonyl]-amino}-2'-methyl-propyl)-thiazole-4-carboxylic acid ethyl ester 30.

Using General Procedure A, the *bis*-thiazole carboxylic acid **27** (40 mg, 0.32 μmol) was coupled to the thiazole hydrochloride salt **24b**[10b] (50 mg, 0.12 mmol) to give the *tripeptide* (56 mg, 71 %) as a colourless solid; $[\alpha]_D^{23}$ – 36.7 (*c* 1.0 in $CHCl_3$); ν_{max} (soln: $CHCl_3$)/cm^{-1} , 1721, 1682, 1666; δ_H (360 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.7, $CHCH_3CH_3$), 1.01 (3H, d, *J* 6.7, $CHCH_3CH_3$), 1.03 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.05 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.30 (3H, t, *J* 6.8, OCH_2CH_3), 1.43 (9H, s, Bu^t), 1.62 (3H, d, *J* 6.8, CH_3CH), 2.84–2.86 (2H, m, (2 x C*H* $(CH_3)_2$), 4.29 (2H, q, *J* 6.8, OCH_2CH_3), 5.06–5.07 (1H, m, N*H*Boc), 5.24–5.28 (2H, m, (2 x C*H*CH $(CH_3)_2$)), 5.49 (1H, dq, *J* 6.5, 4.9, C*H*CH_3), 7.65 (1H, d, *J* 8.2, N*H*CO), 7.85 (1H, d, *J* 8.2, N*H*CO), 7.98 (1H, s, C*H*S), 8.01 (2H, s, (2 x C*H*S)), 8.04 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 14.3 (q), 17.7 (q), 17.9 (q), 19.4 (q), 19.6 (q), 21.0 (q), 28.2 (q), 29.6 (d), 32.9 (d), 33.1 (d), 56.1 (d), 56.4 (d), 61.3 (t), 80.3 (s), 123.6 (d), 123.8 (s), 126.9 (s), 147.4 (s), 149.3 (s), 154.9 (s), 160.7 (s), 160.8 (s), 161.2 (s), 171.6 (s), 171.7 (s); *m*/*z* (FAB) Found 687.2011 ($[M + Na]^+$ $C_{29}H_{40}N_6NaO_6S_3$ requires: 687.2069).

(1'*S*)-2-(1-{[2-(1'*S*-{[2-(1'-Amino-2'-methyl-propyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carbonyl]-amino}-2'-methyl-propyl)-thiazole-4-carboxylic acid hydrochloride 31.

Using General Procedure B, the *tris*-thiazole ethyl ester **30** (30 mg, 45 μmol) was converted into the corresponding carboxylic acid. The acid was then stirred with a solution of hydrogen chloride in 1,4-dioxane (90 μL, 4 M) at room temperature under an atmosphere of nitrogen for 4 h. The solvent was removed *in vacuo* by azeotroping with toluene to leave the *carboxylic acid hydrochloride* (13 mg, 51 %) as a viscous oil; $[\alpha]_D^{23}$ – 40.3 (*c* 0.1 in CH_3CN); δ_H (360 MHz, CD_3OD) 0.95 (3H, d, *J* 6.8, $CHCH_3CH_3$), 0.97 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.00 (3H, d, *J* 7.0, $CHCH_3CH_3$), 1.02 (3H, d, *J* 7.0, $CHCH_3CH_3$), 1.58 (3H, d, *J* 6.8, CH_3CH), 2.45–2.46 (1H, m, C*H* $(CH_3)_2$), 2.84–2.86 (1H, m, C*H* $(CH_3)_2$), 5.28–5.29 (1H, m, C*H*CH $(CH_3)_2$), 5.35–5.37 (1H, m, C*H*CH $(CH_3)_2$), 5.49 (1H, dq, *J* 6.8, 5.3, C*H*CH_3), 8.11 (2H, s, C*H*S), 8.24 (1H, s, C*H*S); δ_C (90.5 MHz, CD_3OD) 18.8 (q), 19.1 (q), 19.8 (q), 19.9 (q), 20.3 (q), 34.4 (d), 34.5 (d), 34.6 (d), 58.1 (d), 58.3 (d), 125.8 (d), 127.5 (d), 129.5 (d), 147.2 (s), 149.9 (s), 150.0 (s), 162.4 (s), 162.8 (s), 167.2 (s), 169.1 (s), 172.4 (s), 172.6 (s); *m*/*z* (FAB) Found 537.1385 $[MH - Cl]^+$ $C_{22}H_{29}N_6O_4S_3$ requires: 537.1412).

Cyclic-*bis*-(*S*)-valine-thiazole-(*S*)-alanine-tris-thiazole 17.

Using General Procedure C, the ω-amino acid **31** (30mg, 52 μmol) was converted into the cyclic peptide (17 mg, 63 %) which was obtained as a colourless powder; mp 264-266 ºC (from CH_2Cl_2 /diethyl ether); $[\alpha]_D^{23}$ – 132 (*c* 0.1 in CH_3CN); λ_{max} (CH_3CN)/nm 237.8 (ε / $dm^3\ mol^{-1}\ cm^{-1}$ 22500); ν_{max} (soln: $CHCl_3$)/cm^{-1} 3699, 2927, 1666, 1602; δ_H (500 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.04 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.06 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.12 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.75 (3H, d, *J* 6.8, CH_3CH), 2.24-2.37 (2H, m, (2 x $CH(CH_3)_2$), 5.40 (1H, dd, *J* 6.1, 8.9, $CHCH(CH_3)_2$), 5.51 (1H, dd, *J* 5.3, 9.4, $CHCH(CH_3)_2$), 5.61-5.69 (1H, m, $CHCH_3$), 8.13 (2H, s, (2 x CHS)), 8.10 (1H, s, CHS), 8.47 (1H, d, *J* 8.9, NHCO), 8.51 (1H, d, *J* 9.4, NHCO), 8.59 (1H, d, *J* 7.6, NHCO); δ_C (125 MHz, $CDCl_3$) 20.3 (q), 27.3 (q), 28.6 (q), 28.8 (q), 29.7 (q), 30.3 (d), 30.7 (d), 35.2 (d), 35.3 (d), 36.0 (d), 123.4 (d), 128.6 (d), 130.5 (d), 136.3 (s), 144.2 (s), 149.5 (s), 155.7 (s), 159.8 (s), 159.9 (s), 169.1 (s), 177.0 (s), 180.9 (s); *m*/*z* (FAB) Found 541.1092 ($[M + Na]^+$ $C_{22}H_{26}N_6NaO_3S_3$ requires 541.1126).

(1'*S*)-2-(1-{[2-(1'-*tert*-Butoxycarbonylamino-ethyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carboxylic acid ethyl ester 34.

Using General Procedure A, the L-alanine thiazole acid **33** (318 mg, 1.2 mmol) was coupled to the L-alanine thiazole amine **24** (250 mg, 1.1 mmol) to give the *dipeptide* (370 mg, 68 %) as a colourless solid; mp 150-152 ºC (from petroleum (40-60 ºC) /diethyl ether); $[\alpha]_D^{23}$ – 50.5 (*c* 1.0 in $CHCl_3$); ν_{max} (soln: $CHCl_3$)/cm^{-1}, 3398, 2965, 1716, 1673; δ_H (360 MHz, $CDCl_3$) 1.41 (3H, t, *J* 7.1, OCH_2CH_3), 1.44 (9H, s, Bu^t), 1.74 (3H, d, *J* 6.6, CH_3CH), 1.80 (3H, d, *J* 7.0, CH_3CH), 4.47 (2H, q, *J* 7.1, OCH_2CH_3), 5.24 (1H, m, NHBoc), 5.35 (1H, m, $CHCH_3$), 5.63 (1H, dq, *J* 7.0, 7.0, $CHCH_3$), 7.89 (1H, d, *J* 7.9, NHCO), 8.09 (1H, s, CHS), 8.14 (1H, s, CHS); δ_C (90.5 MHz, $CDCl_3$) 14.4 (q), 21.6 (q), 21.8 (q), 29.7 (q), 47.2 (d), 48.8 (d), 61.5 (t), 80.4 (s), 123.9 (d), 127.5 (d), 147.2 (s), 149.05 (s), 155.0 (s), 160.6 (s), 161.3 (s), 173.2 (s), 174.6 (s); *m*/*z* (FAB) Found 477.1237 ($[M + Na]^+$ $C_{19}H_{26}N_4NaO_5S_2$ requires 477.1242).

(1'*S*)-2-(1-{[2-(1'-*tert*-Butoxycarbonylamino-ethyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carboxylic acid hydrochloride 35.

Using General Procedure B, the thiazole ester **34** (60 mg, 0.13 mmol) was saponified to the *thiazole acid* (47 mg, 86 %) which crystallised as a cream powder; mp 193-195 ºC (from petroleum 40-60 ºC /diethyl ether); $[\alpha]_D^{23}$ – 32.2 (*c* 1.0 in $CHCl_3$); ν_{max} (soln: $CHCl_3$)/cm^{-1} 3302, 2964, 1665, 1724; δ_H (360 MHz, $CDCl_3$) 1.46 (9H, s, Bu^t), 1.74 (3H, d, *J* 6.9, CH_3CH), 1.81 (3H, d, *J* 6.9, CH_3CH), 5.09 (2H, app d, *J* 6.9, (2 x $CHCH_3$), 5.63 (1H, m, NHBoc), 7.90 (1H, d, *J* 7.9, NHCO), 8.07 (1H, s, CHS), 8.20 (1H, s, CHS); δ_C (90.5 MHz, $CDCl_3$) 20.8 (q),

21.6 (q), 28.3 (q), 47.2 (d), 48.8 (d), 80.5 (s), 124.3 (d), 128.7 (d), 146.7 (s), 148.8 (s), 155.1 (s), 160.8 (s), 163.8 (s), 173.3 (s), 174.8 (s); *m/z* (FAB) Found 449.0906 ($[M + Na]^+$ $C_{17}H_{22}N_4NaO_5S_2$ requires 449.0929).

(1'*S*)-2-(1-{[2-(1'-Amino-2'-methyl-propyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carboxylic acid ethyl ester hydrochloride 26b.

Using Procedure D, the Boc amine **26a** (100 mg, 0.21 mmol), was converted into the *amine hydrochloride* (80 mg, 92 %) which was obtained as an amorphous solid; $[\alpha]_D^{23}$ – 22.0 (*c* 1.0 in $CHCl_3$); ν_{Max} (soln: $CHCl_3$)/cm^{-1} 3019, 2400, 1667, 1541; δ_H (360 MHz, CD_3OD) 0.96 (3H, d, *J* 7.4, CH CH_3CH_3), 0.99 (3H, d, *J* 7.4, $CHCH_3CH_3$), 1.38 (3H, t, *J* 8.2, OCH_2CH_3), 1.94 (3H, d, *J* 7.4, CH_3CH), 2.39 (1H, m, C*H* $(CH_3)_2$), 4.36 (2H, q, *J* 8.2, OCH_3CH_2), 5.00 (1H, m, C*H*CH $(CH_3)_2$), 5.43 (1H, m, C*H*CH_3), 8.00 (1H, s, C*H*S), 8.06 (1H, s, C*H*S); δ_C (90.5 MHz, CD_3OD) 13.6 (q), 16.8 (q), 23.3 (q), 36.8 (d), 61.7 (d), 59.1 (t), 58.3 (d), 118.6 (d), 143.2 (s), 157.5 (s), 166.0 (s), 167.9 (s); m/z (FAB) (Found: 383.1206 $[MH-Cl]^+$, $C_{16}H_{23}N_4O_3S_2$ requires: 383.1212).

(1'*S*)-2-(1-{[2-(1'*S*-{[2-(1'-{[2-(1'-*tert*-Butoxycarbonylamino-ethyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carbonyl]-amino}-2'-methyl-propyl)-thiazole-4-carboxylic acid ethyl ester 36.

Using General Procedure A, the *bis*-thiazole acid **35** (35 mg, 82 μmol) was coupled to the *bis*-thiazole hydrochloride salt **26b** (53 mg, 0.12 mmol) to give the *tetrapeptide* (46 mg, 61 %) which was obtained as a colourless solid; mp 273.5-274 ºC (from petroleum 40-60 ºC /diethyl ether); $[\alpha]_D^{23}$ – 47.4 (*c* 0.1 in $CHCl_3$); ν_{max} (soln: $CHCl_3$)/cm^{-1} 1718, 1602; δ_H (360 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.9, $CHCH_3CH_3$), 0.95 (3H, d, *J* 6.9, $CHCH_3CH_3$), 1.10 (3H, d, *J* 7.4, CH CH_3), 1.12 (3H, d, *J* 7.4, $CHCH_3$), 1.38 (3H, t, *J* 6.8, OCH_2CH_3), 1.40 (9H, s, Bu^t), 1.62-174 (3H, d, 6.9, CH_3CH), 2.64-2.66 (1H, m, C*H* $(CH_3)_2$), 4.35 (2H, q, *J* 6.8, OCH_2CH_3), 5.20-5.22 (1H, m, N*H*Boc), 5.35-5.37 (1H, m, C*H*CH $(CH_3)_2$), 5 .38 – 5.42 (1H, m, C*H*CH_3), 5.47-5.59 (2H, br m, C*H*CH_3), 7.80 (1H, d, *J* 9.2, N*H*CO), 7.82 (1H, d, *J* 9.2, N*H*CO), 7.90 (1H, d, *J* 9.2, N*H*CO), 7.99 (1H, s, C*H*S), 8.01 (1H, s, C*H*S), 8.02 (1H, s, C*H*S), 8.04 (1H, s, C*H*S); δ_C (90.5 MHz, $CDCl_3$) 14.3 (q), 17.7 (q), 17.9 (q), 19.4 (q), 19.6 (q), 21.0 (q), 27.9 (q), 28.2 (q), 29.6 (d), 32.9 (d), 33.1 (d), 56.1 (d), 56.2 (d), 56.4 (d), 61.3 (t), 80.3 (s), 123.6 (d), 123.8 (s), 126.9 (s), 147.4 (s), 149.3 (s), 154.9 (s), 160.7 (s), 160.8 (s), 161.2 (s), 171.6 (s), 171.7 (s); *m/z* (FAB) Found 813.1920 ($[M + Na]^+$ $C_{33}H_{42}N_8NaO_7S_4$ requires 813.1957).

(1'*S*)-2-(1'*S*-{[2-(1'-*tert*-Butoxycarbonylamino-2'-methyl-propyl)-thiazole-4-carbonyl]-amino}-2'-methyl-propyl)-thiazole-4-carboxylic acid ethyl ester 38a.

Using the procedure described previously,[9b,10b] 4-methylmorpholine (0.12 ml, 2.6 mmol) was added dropwise over 5 minutes to stirred solution of the (*L*)-valine thiazole acid **25** (700 mg, 2.3 mmol) in anhydrous dichloromethane (18 ml) at 0 ºC under a nitrogen atmosphere. 1-Hydroxybenzotriazole (290 mg, 2.6 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (498 mg, 2.6 mmol) were added consecutively in one portion and the mixture was then stirred at 0 ºC for 40 min. A precooled solution of the L–valine thiazole amine **24b** (685 mg, 2.6 mmol) and 4-methylmorpholine (0.12 ml, 2.6 mmol) in CH_2Cl_2 (6 ml) was added dropwise over 10 min and the mixture was stirred at 0 ºC for 4 h and then at room temperature for 20 h. Water (*ca.* 30 ml) was added and the separated aqueous extract was extracted with CH_2Cl_2 (3 x 40 ml). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (3 x 30 ml), 10 % aqueous citric acid (3 x 30 ml), and brine (3 x 20 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with pentane / ethyl acetate (1:1) to give the *dipeptide* (995 mg, 85 %) as a colourless solid; mp 57-60 °C; $[\alpha]_D^{23}$ – 28.9 (*c* 1.0 in $CHCl_3$); (Found C, 53.1; H, 6.6; N, 11.0. $C_{22}H_{34}N_4O_5S_2$ requires C, 53.1; H, 6.8; N, 11.0 %); δ_H (360 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.7, $CHCH_3CH_3$), 0.99 (3H, d, *J* 6.7, $CHCH_3CH_3$), 1.00 (3H, d, *J* 6.7, $CHCH_3CH_3$), 1.03 (3H, d, *J* 6.7, $CHCH_3CH_3$), 1.39 (3H, t, *J* 7.1, OCH_2CH_3), 1.46 (9H, s, Bu^t), 2.37 (1H, m, $CH(CH_3)_2$), 2.64 (1H, m, $CH(CH_3)_2$), 4.41 (2H, q, *J* 7.1, OCH_2CH_3), 4.86 (1H, br m, $CHCH(CH_3)_2$), 5.29 (1H, dd, *J* 9.2, 6.8, $CHCH(CH_3)_2$), 5.39 (1H, d, *J* 8.1, NHBoc), 7.89 (1H, d, *J* 9.2, NHCO), 8.08 (1H, s, CHS), 8.54 (1H, s, CHS); δ_C (90.5 MHz, $CDCl_3$) 14.3 (q), 17.3 (q), 18.0 (q), 19.3 (q), 19.7 (q), 28.3 (q), 33.0 (d), 33.2 (d), 56.5 (d), 58.0 (d), 61.3 (t), 80.2 (s), 123.4 (d), 127.0 (d), 147.5 (s), 149.2 (s), 155.4 (s), 160.8 (s), 161.3 (s); *m*/*z* (FAB) Found 533.1822 ($[M + Na]^+$ $C_{23}H_{34}N_4NaO_5S_2$ requires 533.1868).

(1'*S*)-2-(1'*S*-{[2-(1'-Amino-hydrochloride-2'-methyl-propyl)-thiazole-4-carbonyl]-amino}-2'-methyl-propyl)-thiazole-4-carboxylic acid ethyl ester 38b.[9c]

Using the procedure described previously,[9c] a solution of hydrogen chloride in 1,4-dioxane (0.5 ml, 4 M) was added to the Boc amine **26b** (248 mg, 0.49 mmol), the mixture was stirred at room temperature under a nitrogen atmosphere for 8 h. The dioxane was evaporated *in vacuo,* using toluene (*ca* 5 ml) as an azeotrope. The residue was diluted with ether whereupon a precipitate formed that was purified by trituration with hot diethyl ether and gave the *amine hydrochloride* (213 mg, 98 %) as a hygroscopic solid; mp 137-139 °C; $[\alpha]_D^{23}$– 11.5 (*c* 1.0 in $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.8, $CHCH_3CH_3$), 0.97 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.03 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.05 (3H, d, *J* 6.8, $CHCH_3CH_3$), 1.38 (3H, t, *J* 7.1, OCH_2CH_3), 2.38 (1H, m, $CH(CH_3)_2$), 2.85 (1H, m, $CH(CH_3)_2$), 4.37 (2H, q, *J* 7.1, OCH_3CH_2), 5.18 (1H, d, *J* 6.8, $CHCH(CH_3)_2$), 5.47 (1H, dd, *J* 8.7, 6.8,

C*H*CH (CH_3)$_2$), 7.98 (1H, d, *J* 8.9, N*H*CO), 8.17 (1H, s, C*H*S), 8.24 (1H, s, C*H*S), 9.64 (2H, br s, CHNH_2); δ_C (90.5 MHz, $CDCl_3$) 14.4 (q), 18.8 (q), 19.5 (q), 19.9 (q), 29.7 (q), 32.0 (d), 32.8 (d), 58.3 (d), 58.4 (d), 61.7 (t), 124.3 (d), 127.2 (d), 146.6 (s), 148.8 (s), 161.3 (s), 162.4 (s), 173.6 (s); *m*/*z* (FAB) Found 411.1496 ($[MH - Cl]^+$ $C_{18}H_{27}N_4O_3S_2$ requires 411.1525).

(1'*S*)-2-(1-{[2-(1'*S*-{[2-(1-{[2-(1'-*tert*-Butoxycarbonylamino-ethyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carbonyl]-amino}-2'-methyl-propyl)-thiazole-4-carbonyl]-amino}-2'-methyl-propyl)-thiazole-4-carboxylic acid ethyl ester 39.

Using General Procedure A, the *bis*-thiazole acid **35** (50 mg, 0.12 mmol) was coupled to the *bis*-thiazole hydrochloride salt **38** (53 mg, 0.12 mmol) to give the *tetrapeptide* (73 mg, 75 %) which was obtained as a colourless solid; mp 243-245 ºC (from CH_2Cl_2 /diethyl ether); $[\alpha]_D^{23}$ – 48.3 (*c* 0.1 in CH_3CN); λ_{max} (CH_3CN)/nm 234 (ε / dm^3 mol^{-1} cm^{-1} 19800); ν_{max} (soln: $CHCl_3$)/cm^{-1} 3429, 2961, 1710, 1603; δ_H (500 MHz, $CDCl_3$) 1.04 (6H, d, *J* 6.8, (2 x CH_3CH_3CH)), 1.07 (6H, d, *J* 6.8, (2 x CH_3CH_3CH)), 1.35 (3H, t, *J* 7.0, OCH_2CH_3), 1.42 (9H, s, Bu^t), 1.78 (3H, d, *J* 7.1, CH_3CH), 1.80 (3H, d, *J* 7.1, CH_3CH), 2.38 (2H, m, (2 x C*H* (CH_3)$_2$), 4.41 (2H, q, *J* 7.0, OCH_2CH_3), 5.28 (1H, m, C*H*CH(CH_3)$_2$), 5.49 (1H, m, C*H*CH_3), 5.51 (1H, m, C*H*CH_3), 6.98 (1H, m, N*H*Boc), 8.00 (1H, s, C*H*S), 8.09 (2H, m, (2 x C*H*S)), 8.12 (1H, s, C*H*S), 8.46 (1H, m, N*H*CO), 8.63 (2H, m, (2 x N*H*CO)); δ_C (125 MHz, $CDCl_3$) 14.4 (q), 18.8 (q), 23.2 (q), 29.7 (q), 35.5 (d), 47.3 (d), 51.4 (d), 55.8 (d), 60.6 (d), 60.2 (d), 70.6 (s), 124.1 (d), 148.9 (s), 159.7 (s), 167.3 (s), 168.0 (s), 170.4 (s); *m*/*z* (FAB) Found 819.2411 ($[M + H]^+$ $C_{35}H_{46}N_8O_7S_4$ requires 819.2451).

(1'*S*)-2-(1-{[2-(1-{[2-(1'*S*-{[2-(1'-*tert*-Butoxycarbonylamino-ethyl)-thiazole-4-carbonyl]-amino}-2'-methyl-propyl)-thiazole-4-carbonyl]-amino}-2'-methyl-propyl)-thiazole-4-carbonyl]-amino}-2'-methyl-propyl)-thiazole-4-carboxylic acid ethyl ester 40.

Using General Procedure A, the *bis*-thiazole acid **27** (70 mg, 0.15 mmol) was coupled to the *bis*-thiazole hydrochloride salt **38** to give the *tetrapeptide* (80 mg, 63 %) which was obtained as a colourless solid; mp 275-277 ºC (from CH_2Cl_2 /diethyl ether); $[\alpha]_D^{25}$ – 39.9 (*c* 0.1 in CH_3CN); λ_{max} (CH_3CN)/nm 237 (ε / dm^3 mol^{-1} cm^{-1} 24300); ν_{max} (soln: $CHCl_3$)/cm^{-1} 2940, 1643; δ_H (500 MHz, $CDCl_3$) 0.96 (6H, d, *J* 6.8, (2 x CH_3CH_3CH)), 0.98 (6H, d, *J* 6.8, (2 x CH_3CH_3CH)), 1.04 (3H, d, *J* 7.1, CH_3CH_3CH), 1.07 (3H, d, *J* 7.1, CH_3CH_3CH), 1.38 (3H, t, *J* 6.8, OCH_2CH_3), 1.40 (9H, s, Bu^t), 1.83 (3H, d, *J* 6.9, CH_3CH), 2.41–2.44 (3H, m, 3 x C*H*(CH_3)$_2$), 4.45 (2H, q, *J* 6.8, OCH_2CH_3), 5.25–5.33 (3H, br m, (3 x C*H*CH(CH_3)$_2$)), 5.56 (1H, m, C*H*CH_3), 7.98 (1H, d, *J* 8.2 , N*H*Boc), 8.02 (1H, s, C*H*S), 8.17 (2H, m, (2 x C*H*S)), 8.20 (1H, s, C*H*S), 8.48–8.56 (2H, br m, (2 x N*H*CO)), 8.72 (1H, d, *J*

7.8, N*H*CO); δ_C (125 MHz, $CDCl_3$) 13.6 (q), 14.8 (q), 19.2 (q), 23.2 (q), 29.4 (q), 34.7 (d), 47.5 (d), 51.8 (d), 55.8 (d), 58.6 (d), 60.8 (d), 70.5 (s), 124.6 (d), 149.1 (s), 158.2 (s), 168.2 (s), 169.7 (s), 171.2 (s).

2-((*S*)-1-Amino-2-methyl-propyl)-1,5-dimethyl-1*H*-imidazole-4-carboxylic acid hydrochloride 41a

The known imidazole had: mp 178-180 °C (Lit.[13] mp 182 °C); $[\alpha]_D^{25}$ -9.3 (*c* 1, MeOH); δ_H (360 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.2 Hz, -CH(C*H*$_3$)(CH$_3$)), 1.11 (3H, d, *J* 6.2 Hz, -CH(CH$_3$)(C*H*$_3$)), 2.26 (1H, m, -C*H*(CH$_3$)$_2$), 2.72 (3H, s, Imid-C*H*$_3$), 3.38 (3H, s, -NC*H*$_3$), $^+$), 4.92 (1H, d, *J* 9.8 Hz, -C*H*NH$_3$); δ_C (125 MHz, CD_3OD) 10.2, 19.0, 19.3, 33.0, 34.1, 52.6, 123.0, 139.9, 143.6, 160.3; *m*/*z* (FAB) Found 212.1392 ([M + Na]$^+$ $C_{10}H_{18}N_3O_2$ requires 212.1399).

2-((*S*)-1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-1,5-dimethyl-1*H*-imidazole-4-carboxylic acid, 41b.

The known imidazole carboxylic acid had: mp 102-104 °C (Lit.[13] mp 99-102 °C); $[\alpha]_D^{25}$ -54.5 (*c* 1, $CHCl_3$); δ_H (360 MHz, acetone-d$_5$) 0.85 (3H, d, *J* 6.7 Hz, -CH(C*H*$_3$)(CH$_3$)), 1.10 (3H, d, *J* 6.7 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.37 (9H, s, -C(C*H*$_3$)$_3$), 2.12 (1H, m, -C*H*(CH$_3$)$_2$), 2.67 (3H, s, Imid-C*H*$_3$), 3.98 (3H, s, -NC*H*$_3$), 4.84 (1H, app t, *J* 9.4 Hz, -C*H*NHBoc), 7.72 (1H, d, *J* 8.4 Hz, -N*H*Boc), 11.2 (1H, br s, -COO*H*); δ_C (125 MHz, acetone-d$_5$) 9.8, 19.2, 19.5, 28.4 (x3), 32.6, 33.0, 53.4, 79.8, 122.2, 137.6, 149.7, 156.6, 160.5; *m*/*z* (FAB) Found 312.1918 ([M + Na]$^+$ $C_{15}H_{26}N_3O_4$ requires 312.1923).

2-((*S*)-1-Amino-2-methyl-propyl)-1,5-dimethyl-1*H*-imidazole-4-carboxylic acid methyl ester hydrochloride salt, 41c.

The known imidazole had: mp 69-71 °C (Lit.[13] mp 67 °C); $[\alpha]_D^{25}$ -13.7 (*c* 2, $CHCl_3$); δ_H (360 MHz, CD_3OD) 1.00 (3H, d, *J* 6.2 Hz, -CH(C*H*$_3$)(CH$_3$)), 1.33 (3H, d, *J* 6.2 Hz, -CH(CH$_3$)(C*H*$_3$)), 2.73 (3H, s, Imid-C*H*$_3$), 2.76 (1H, m, -C*H*(CH$_3$)$_2$), 3.38 (3H, s, -NC*H*$_3$), 4.04 (3H, s, -CO$_2$C*H*$_3$), 5.00 (1H, d, *J* 9.8 Hz, -C*H*NH$_3^+$); δ_C (125 MHz, CD_3OD) 10.3, 19.0, 19.4, 33.1, 34.2, 52.5, 53.5, 121.9, 140.2, 144.0, 159.6; *m*/*z* (FAB) Found 226.1562 ([M]$^+$ $C_{11}H_{20}N_3O_2$ requires 226.1556).

2-((*S*)-1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-5-methyl-1*H*-imidazole-4-carboxylic acid methyl ester, 41d.[1]

The substituted imidazole was prepared as described in the literature and had: $[\alpha]_D^{25}$ -45.1 (*c* 1, $CHCl_3$); mp 115-117 °C (Lit.[13] mp 130 °C) ; δ_H (360 MHz, $CDCl_3$) 0.59 (3H, d, *J* 6.7 Hz, -CH(C*H*$_3$)(CH$_3$)), 0.77 (3H, d, *J* 6.7 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.49 (9H, s, -C(C*H*$_3$)$_3$), 1.99 (1H, m, -C*H*(CH$_3$)$_2$), 2.79 (3H, s, Imid-C*H*$_3$), 3.41 (3H, s, -NC*H*$_3$), 3.60 (3H, s, -CO$_2$C*H*$_3$), 4.31 (1H, app t, *J* 9.1 Hz, -C*H*NHBoc), 5.31 (1H, d, *J* 9.6 Hz, -N*H*Boc); δ_C (125 MHz,

$CDCl_3$) 9.7, 18.0, 19.1, 27.8 (x3), 29.9, 32.6, 50.8, 51.7, 78.8, 127.0, 135.5, 148.0, 155.3, 163.7; *m/z* (FAB) Found 348.1896 (([M + Na]$^+$ $C_{16}H_{27}N_3O_4Na$ requires 348.1899).

2-((*S*)-1-Amino-2-methyl-propyl)-oxazole-4-carboxylic acid, 42a.

The oxazole carboxylic acid had : $[\alpha]_D^{25}$ -9.6 (*c* 0.5, MeOH); δ_H (360 MHz, CD_3OD) 1.03 (3H, d, *J* 6.5 Hz, -CH(C*H*$_3$)(CH$_3$)), 1.16 (3H, d, *J* 6.5 Hz, -CH(CH$_3$)(C*H*$_3$)), 2.47 (1H, m, -C*H*(CH$_3$)$_2$), 4.57 (1H, d, *J* 6.2 Hz, Oxaz-C*H*), 8.67 (1H, s, Oxaz-*H*); δ_C (125 MHz, CD_3OD) 18.0, 18.6, 32.4, 55.3, 135.0, 147.1, 161.4, 163.7; *m/z* (FAB) Found 185.0929 ([M]$^+$ $C_8H_{13}N_2O_3$ requires 185.0926).

2-((*S*)-1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-oxazole-4-carboxylic acid, 42b.

The known oxazole had: mp 120-122 °C (Lit.[7e] 154-155 °C) ; $[\alpha]_D^{25}$ -53.2 (*c* 0.5, MeOH) (lit. -28.9 (*c* 1.5, $CHCl_3$)); δ_H (360 MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.5 Hz, -CH(C*H*$_3$)(CH$_3$)), 0.90 (3H, d, *J* 6.5 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.32 (9H, s, -C(C*H*$_3$)$_3$), 2.17 (1H, m, -C*H*(CH$_3$)$_2$), 4.78 (1H, dd, *J* 9.4, 6.8 Hz, -C*H*NHBoc), 6.33 (1H, d, *J* 9.7 Hz, -N*H*Boc), 8.24 (1H, s, Oxaz-*H*), 10.93 (1H, br s, -COO*H*); δ_C (125 MHz, $CDCl_3$) 18.0, 18.6, 28.0 (x3), 32.6, 54.4, 79.8, 133.0, 144.4, 155.8, 163.4, 166.5; *m/z* (FAB) Found 307.1260 ([M + Na]$^+$ $C_{13}H_{20}N_2O_5Na$ requires 307.1270).

2-((*S*)-1-Amino-2-methyl-propyl)-oxazole-4-carboxylic acid methyl ester hydrochloride salt, 42c.

The oxazole had: $[\alpha]_D^{25}$ -3.4 (*c* 0.5, MeOH); δ_H (360 MHz, $CDCl_3$) 9.28 (3H, br s, -N*H*$_3^+$), 8.29 (1H, s, Oxaz-*H*), 4.57 (1H, dd, *J* 7.6, 6.1 Hz, -C*H*NH$_3^+$), 3.89 (3H, s, -CO$_2$C*H*$_3$), 2.62 (1H, m, -C*H*(CH$_3$)$_2$), 1.18 (3H, d, *J* 6.8 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.03 (3H, d, *J* 6.8 Hz, -CH(C*H*$_3$)(CH$_3$)); δ_C (125 MHz, $CDCl_3$) 18.6, 19.2, 32.9, 52.3, 58.6, 128.4, 143.0, 159.1, 163.9; *m/z* (FAB) Found 199.1030 ([M + Na]$^+$ $C_9H_{15}N_2O_3$ requires 199.1083).

2-((*S*)-1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-oxazole-4-carboxylic acid methyl ester, 42d.

The oxazole had: mp 117-119 °C; $[\alpha]_D^{25}$ -36.4 (*c* 0.5, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.8Hz, -CH(C*H*$_3$)(CH$_3$)), 0.93 (3H, d, *J* 6.8 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.43 (9H, s, -C(C*H*$_3$)$_3$), 2.19 (1H, m, -C*H*(CH$_3$)$_2$), 3.92 (3H, s, -OC*H*$_3$), 4.80 (1H, dd, *J* 9.2, 6.1 Hz, -C*H*NHBoc), 5.29 (1H, d, *J* 8.6 Hz, -N*H*Boc), 8.18 (1H, s, Oxaz-*H*); δ_C (125 MHz, $CDCl_3$) 17.4, 27.7 (x3), 32.2, 51.5, 53.7, 79.1, 132.5, 143.6, 154.8, 161.0; *m/z* (FAB) Found 299.1616 ([M]$^+$ $C_{14}H_{23}N_2O_5$ requires 299.1607).

2-((*S*)-1-Amino-2-methyl-propyl)-thiazole-4-carboxylic acid hydrochloride salt, 43a.

The thiazole amino acid had: mp: 194-196 °C; $[\alpha]_D^{25}$ -10.4 (*c* 0.5, MeOH); δ_H (360 MHz, CD_3OD) 1.03 (3H, d, *J* 6.5 Hz, -CH(C*H*$_3$)(CH$_3$)), 1.18 (3H, d, *J* 6.5 Hz, -CH(CH$_3$)(C*H*$_3$)), 2.48 (1H, m, -C*H*(CH$_3$)$_2$), 4.74 (1H, d, *J* 6.2 Hz,

Thiaz-C*H*), 8.54 (1H, s, Thiaz-*H*); δ_C (90 MHz, CD_3OD) 18.6, 19.0, 33.6, 58.7, 131.1, 148.0, 163.8, 166.6; *m*/*z* (FAB) Found: m/z 223.0548 ($[M]^+$ $C_8H_{12}N_2O_2SNa$ requires 223.0517).

2-((*S*)-1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-thiazole-4-carboxylic acid, 43b.

The thiazole carboxylic acid had: m.p.: 106-108 °C (lit.[2] 153-156 °C); $[\alpha]_D^{25}$ -23.5 (*c* 1, $CHCl_3$) (lit. -37.6 (c, 1.03, $CHCl_3$)); δ_H (360 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.5 Hz, -CH(C*H*$_3$)(CH$_3$)), 0.87 (3H, d, *J* 6.5 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.39 (9H, s, -C(C*H*$_3$)$_3$), 2.26 (1H, m, -C*H*(CH$_3$)$_2$), 4.78 (1H, app t, *J* 7.2 Hz, -C*H*NHBoc), 5.95 (1H, d, *J* 8.6 Hz, -N*H*Boc), 7.99 (1H, s, Oxaz-*H*), 11.10 (1H, br s, -COO*H*); δ_C (125 MHz, $CDCl_3$) 17.6, 19.1, 27.9 (x3), 32.6, 57.6, 79.2, 125.6, 149.5, 155.2, 165.8, 172.0; *m*/*z* (FAB) Found 323.0998 ($[M + Na]^+$ $C_{13}H_{20}N_2O_4SNa$ requires 323.1041).

2-((S)-1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-thiazole-4-carboxylic acid ethyl ester, 43 (R = Et, R′ = Boc).

The known thiazole had: m.p.: 110-112 °C (lit.[3] 101-103 °C); $[\alpha]_D^{25}$: 10.9 (*c* 1, $CHCl_3$) (lit. 28.5 (c, 0.5, MeOH)); δ_H (360 MHz, $CDCl_3$) 0.65 (3H, d, *J* 7.1 Hz, -CH(C*H*$_3$)(CH$_3$)), 0.72 (3H, d, *J* 7.1 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.12 (3H, t, *J* 7.2 Hz, -OCH$_2$C*H*$_3$), 1.17 (9H, s, -C(C*H*$_3$)$_3$), 2.17 (1H, m, -C*H*(CH$_3$)$_2$), 4.14 (2H, q, *J* 7.2 Hz, -OC*H*$_2$CH$_3$), 4.66 (1H, dd, *J* 7.6, 6.1 Hz, -C*H*NHBoc), 5.41 (1H, d, *J* 7.2 Hz, -N*H*Boc), 7.89 (1H, s, Thiaz-*H*); δ_C (125 MHz, $CDCl_3$) 13.8, 16.8, 18.2, 27.1 (x3), 32.7, 57.6, 60.7, 79.2, 126.5, 146.7, 155.0, 160.7, 173.0; *m*/*z* (FAB) Found 351.1344 ($[M + Na]^+$ $C_{15}H_{24}N_2O_4SNa$ requires 351.1354).

2-((S)-1-Amino-2-methyl-propyl)-thiazole-4-carboxylic acid ethyl ester hydrochloride salt, 43 (R = Et, R′ = H)

The thiazole carboxylic acid had: $[\alpha]_D^{25}$ 13.9 (*c* 1, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 0.95 (3H, d, *J* 7.1 Hz, -CH(C*H*$_3$)(CH$_3$)), 1.16 (3H, d, *J* 7.1 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.34 (3H, t, *J* 7.2 Hz, -OCH$_2$C*H*$_3$), 2.57 (1H, m, -C*H*(CH$_3$)$_2$), 4.33 (2H, q, *J* 7.2 Hz, -OC*H*$_2$CH$_3$), 4.71 (1H, dd, *J* 7.6, 6.1 Hz, -C*H*NH_3^+), 8.19 (1H, s, Thiaz-*H*), 9.21 (3H, br s, -NH_3^+); δ_C (125 MHz, $CDCl_3$) 14.2, 18.4, 19.1, 32.6, 58.6, 61.8, 129.3, 146.2, 161.4, 165.6; *m*/*z* (FAB) Found 229.1014 ($[M + Na]^+$ $C_{10}H_{17}N_2O_2S$ requires 229.1011).

2-((*S*)-1-{[2-((*S*)-1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-1,5-dimethyl-1*H*-imidazole-4-carbonyl]-amino}-2-methyl-propyl)-1,5-dimethyl-1*H*-imidazole-4-carboxylic acid methyl ester, 44.

The protected *bis*-imidazole was prepared from the acid **41b** and the amine **41c**, and had: mp: 82-84 °C (lit.[13] 84 °C); δ_H (360 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.6 Hz, -CH(C*H*$_3$)(CH$_3$)), 0.81 (3H, d, *J* 6.6 Hz, -CH(C*H*$_3$)(CH$_3$)), 0.90 (3H, d, *J* 6.6 Hz, -CH(CH$_3$)(C*H*$_3$)), 0.99 (3H, d, *J* 6.6 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.34 (9H, s, -CH(*CH*$_3$)$_3$), 2.06 (1H, m,

-C*H*(CH_3)$_2$), 2.44 (6H, s, 2 x Imid-C*H*$_3$ overlapped), 2.47 (1H, m, -C*H*(CH_3)$_2$), 3.41 (3H, s, -NC*H*$_3$), 3.57 (3H, s, -NC*H*$_3$), 3.80 (3H, s, -OC*H*$_3$), 4.82 (1H, dd, *J* 9.3, 7.7 Hz, Imid-C*H*), 4.91 (1H, app t, *J* 9.9 Hz, Imid-C*H*), 5.24 (1H, d, *J* 10.7 Hz, -N*H*Boc), 7.57 (1H, d, *J* 9.9 Hz, -C(O)N*H*-); δ_C (90 MHz, $CDCl_3$) 9.5, 9.9, 17.9, 18.9, 19.1, 19.9, 20.0, 29.7 (x3), 30.1, 32.0, 32.9, 49.5, 51.0, 51.5, 79.1, 127.3, 128.9, 132.1, 135.8, 146.2, 148.2, 155.3, 163.2, 164.1; HRMS: $[M+H]^+$ m/z 519.3272 (calcd for $C_{26}H_{43}N_6O_5$ 519.3295).

2-((*S*)-1-{[2-((*S*)-1-Amino-2-methyl-propyl)-1,5-dimethyl-1*H*-imidazole-4-carbonyl]-amino}-2-methyl-propyl)-1,5-dimethyl-1*H*-imidazole-4-carboxylic acid, 45.[13]

The *bis*-imidazole had: m.p.: 126-128 °C; $[\alpha]_D^{25}$ 17.6 (*c* 0.5, MeOH); δ_H (360 MHz, CD_3OD) 0.98 (3H, d, *J* 5.4 Hz, -CH(C*H*$_3$)(CH_3)), 1.03 (3H, d, *J* 5.4 Hz, -CH(C*H*$_3$)(CH_3)), 1.23 (3H, d, *J* 5.4 Hz, -CH(CH_3)(C*H*$_3$)), 1.31 (3H, d, *J* 5.4 Hz, -CH(CH_3)(C*H*$_3$)), 2.60 (3H, s, Imid-C*H*$_3$), 2.64 (2H, m, 2 x -C*H*(CH_3)$_2$ overlapped), 2.69 (3H, s, Imid-C*H*$_3$), 3.81 (3H, s, -NC*H*$_3$), 4.02 (3H, s, -NC*H*$_3$), 4.74 (1H, d, *J* 7.2 Hz, Imid-C*H*), 5.13 (1H, d, *J* 9.5 Hz, $^+H_3$N-C*H*); δ_C (90 MHz, CD_3OD) 9.9, 10.0, 18.8, 18.9, 19.3, 20.2, 32.2, 32.5, 33.2, 33.3, 53.0, 53.4, 116.1, 120.4, 121.6, 130.3, 138.9, 149.1, 158.4, 160.4; HRMS: $[M]^+$ m/z 405.2603 (calcd for $C_{20}H_{33}N_6O_3$ 405.2614).

2-((S)-1-{[2-((S)-1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-oxazole-4-carbonyl]-amino}-2-methyl-propyl)-oxazole-4-carboxylic acid methyl ester, 46.

Using General Procedure A, the oxazole acid **42b** (410 mg, 1.44 mmol) was coupled to the oxazole amine **42c** (377 mg, 1.61 mmol) to give the *bis*-oxazole (648 mg, 97 %); mp: 92-94 °C; $[\alpha]_D^{25}$ -32.8 (*c* 0.5, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 0.85 (3H, d, *J* 6.8 Hz, -CH(C*H*$_3$)(CH_3)), 0.88 (3H, d, *J* 6.8 Hz, -CH(C*H*$_3$)(CH_3)), 0.91 (3H, d, *J* 6.8 Hz, -CH(CH_3)(C*H*$_3$)), 0.99 (3H, d, *J* 6.8 Hz, -CH(CH_3)(C*H*$_3$)), 1.41 (9H, s, -CH(*CH*$_3$)$_3$), 2.13 (1H, m, -C*H*(CH_3)$_2$), 2.30 (1H, m, -C*H*(CH_3)$_2$), 3.87 (3H, s, -OC*H*$_3$), 4.73 (1H, dd, *J* 9.0, 6.2 Hz, Oxaz-C*H*), 5.20 (1H, dd, *J* 9.3, 7.2 Hz, Oxaz-C*H*), 5.21 (1H, d, *J* 9.7 Hz, -N*H*Boc), 7.42 (1H, d, *J* 9.4 Hz, -C(O)N*H*-), 8.10 (1H, s, Oxaz-*H*), 8.17 (1H, s, Oxaz-*H*); δ_C (90 MHz, $CDCl_3$) 18.0, 18.5, 18.6, 18.7, 28.3 (x3), 32.7, 32.8, 52.2, 52.3, 54.2, 80.1, 133.3, 135.4, 141.3, 143.8, 155.3, 160.2, 161.5, 163.9, 164.3; HRMS: $[M+Na+2H_2O]^+$ m/z 523.2402 (calcd for $C_{22}H_{36}N_4NaO_9$ 523.2380).

2-((S)-1-{[2-((S)-1-Amino-2-methyl-propyl)-oxazole-4-carbonyl]-amino}-2-methyl-propyl)-oxazole-4-carboxylic acid hydrochloride salt, 47.

Using General Procedures B and D, the protected *bis*-oxazole **46** (640 mg, 1.38 mmol) gave the free dipeptide (503 mg, 95%); m.p.: 121-123 °C; $[\alpha]_D^{25}$: -24.0 (*c* 0.5, MeOH); δ_H (360 MHz, CD_3OD) 0.98 (3H, d, *J* 6.4 Hz, -CH(C*H*$_3$)(CH_3)), 1.05 (3H, d, *J* 6.4 Hz, -CH(C*H*$_3$)(CH_3)), 1.09 (3H, d, *J* 6.4 Hz, -CH(CH_3)(C*H*$_3$)), 1.18 (3H, d, *J* 6.4 Hz, -CH(CH_3)(C*H*$_3$)), 2.47 (2H, m, 2 x -C*H*(CH_3)$_2$ overlapped), 4.62 (1H, m, Oxaz-C*H*), 5.15 (1H, m, $^+H_3$N-

C*H*), 8.58 (1H, s, Oxaz-*H*), 8.65 (1H, s, Oxaz-*H*); δ_C (90 MHz, CD_3OD) 18.2, 18.9, 19.1, 19.4, 32.4, 32.8, 54.3, 55.3, 134.4, 136.8, 144.6, 146.1, 161.0, 161.9, 163.7, 165.3; HRMS: $[M]^+$ m/z 351.1676 (calcd for $C_{16}H_{23}N_4O_5$ 351.1668).

2-((S)-1-{[2-((S)-1-*tert*-Butoxycarbonylamino-2-methyl-propyl)-thiazole-4-carbonyl]-amino}-2-methyl-propyl)-thiazole-4-carboxylic acid ethyl ester, 48.

The *bis*-thiazole had: $[\alpha]_D^{25}$ -22.4 (*c* 0.5, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.9 Hz, -CH(C*H*$_3$)(CH_3)), 0.98 (3H, d, *J* 6.9 Hz, -CH(C*H*$_3$)(CH_3)), 0.99 (3H, d, *J* 6.9 Hz, -CH(CH_3)(C*H*$_3$)), 1.01 (3H, d, *J* 6.9 Hz, -CH(CH_3)(C*H*$_3$)), 1.38 (3H, t, *J* 7.1 Hz, -OCH$_2$C*H*$_3$), 1.44 (9H, s, -CH(*CH*$_3$)$_3$), 2.36 (1H, m, -C*H*(CH_3)$_2$), 2.62 (1H, m, -C*H*(CH_3)$_2$), 4.40 (2H, q, *J* 7.1 Hz, -OC*H*$_2$CH$_3$), 4.87 (1H, dd, *J* 8.1, 5.7 Hz, Thiaz-C*H*), 5.22 (1H, d, *J* 8.7 Hz, -N*H*Boc), 5.30 (1H, dd, *J* 9.0, 7.1 Hz, Thiaz-C*H*), 7.92 (1H, d, *J* 9.2 Hz, -C(O)N*H*-), 8.01 (1H, s, Thiaz-*H*), 8.07 (1H, s, Thiaz-*H*); δ_C (90 MHz, $CDCl_3$) 14.4, 17.4, 18.1, 19.4, 19.8, 28.3 (x3), 33.0, 33.2, 56.5, 57.9, 61.4, 80.3, 123.4, 127.0, 147.5, 149.1, 155.4, 160.9, 161.3, 171.8, 172.6; HRMS: $[M+Na]^+$ m/z 533.1861 (calcd for $C_{23}H_{34}N_4NaO_5S_2$ 533.1868).

2-((*S*)-1-{[2-((*S*)-1,2-Dimethyl-propyl)-thiazole-4-carbonyl]-amino}-2-methyl-propyl)-thiazole-4-carboxylic acid hydrochloride salt, 49.

The *bis*-thiazole amino acid had: mp: 156-158 °C; $[\alpha]_D^{25}$ -5.6 (*c* 0.5, MeOH); δ_H (360 MHz, CD_3OD) 0.99 (3H, d, *J* 6.3 Hz, -CH(C*H*$_3$)(CH_3)), 1.08 (3H, d, *J* 6.3 Hz, -CH(C*H*$_3$)(CH_3)), 1.16 (3H, d, *J* 6.3 Hz, -CH(CH_3)(C*H*$_3$)), 1.18 (3H, d, *J* 6.3 Hz, -CH(CH_3)(C*H*$_3$)), 2.53 (1H, m, -C*H*(CH_3)$_2$), 2.63 (1H, m, -C*H*(CH_3)$_2$), 4.87 (1H, br s, Thiaz-C*H*), 5.15 (1H, br d, *J* 6.8 Hz, $^+H_3$N-C*H*), 8.45 (1H, s, Thiaz-*H*), 8.55 (1H, s, Thiaz-*H*); δ_C (90 MHz, CD_3OD) 18.4, 18.7, 19.4, 19.8, 33.4, 34.1, 58.2, 58.6, 127.6, 130.3, 145.4, 149.3, 162.3, 162.5, 166.1, 175.8; HRMS: $[M]^+$ m/z 383.1230 (calcd for $C_{16}H_{23}N_4O_3S_2$ 383.1212).

Thiazole / *bis*-Imidazole based Cyclic Trimer 55

Using General Procedure C, the *bis*-imidazole amino acid **45** (56 mg, 0.127 mmol) was reacted with the thiazole amino acid **43a** (30 mg, 0.127 mmol) to give i) the *cyclic trimer* (39 mg, 54 %)**;** mp 116-118 °C; $[\alpha]_D^{25}$ -100.6 (*c* 1, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 0.97-1.08 (9H, m, 3 x -CH(C*H*$_3$)(CH_3) overlapped), 0.97-1.08 (9H, m, 3 x -CH(CH_3)(C*H*$_3$) overlapped), 2.09 (1H, m, -C*H*(CH_3)$_2$), 2.06-2.27 (2H, m, 2 x -C*H*(CH_3)$_2$ overlapped), 2.52 (3H, s, Imid-C*H*$_3$), 2.53 (3H, s, Imid-C*H*$_3$), 3.48 (3H, s, -NC*H*$_3$), 3.51 (3H, s, -NC*H*$_3$), 5.10 (1H, app. t, *J* 7.1 Hz, Het-C*H*), 5.16 (1H, app. t, *J* 7.8 Hz, Het-C*H*), 5.34 (1H, app. t, *J* 7.5 Hz, Het-C*H*), 8.00 (1H, s, Thiaz-*H*), 8.38-8.47 (3H, m, 3 x -C(O)N*H* overlapped); δ_C (90 MHz, $CDCl_3$) 9.7 (x2), 17.9, 18.0, 18.4, 19.2, 19.3, 19.6, 30.3, 34.8,

35.0 (x2), 35.4, 49.7, 50.3, 54.9, 122.9, 129.4, 129.7, 132.3, 132.5, 146.1, 146.9, 149.3, 160.2, 163.1, 163.3, 169.5; HRMS $[M+H]^+$ m/z 569.3022 (calcd for $C_{28}H_{40}N_8O_3S$ 569.3034), and ii) the known cyclic tetramer **56** (14 %).[18]

Oxazole / *bis*-Thiazole based Cyclic Trimer 58

Using General Procedure C, the *bis*-thiazole **49** (60.0 mg, 0.143 mmol) was reacted with the oxazole **42a** (31.5 mg, 0.143 mmol) to give i) the *cyclic trimer* (28 mg, 37 %): δ_H (360 MHz, $CDCl_3$) 1.03 (3H, d, *J* 6.8 Hz, -CH(CH_3)(C*H*$_3$)), 1.05 (3H, d, *J* 6.8 Hz, -CH(CH_3)(C*H*$_3$)), 1.08 (3H, d, *J* 6.8 Hz, -CH(CH_3)(C*H*$_3$)), 1.09 (3H, d, *J* 6.8 Hz, -CH(C*H*$_3$)(CH_3)), 1.11 (3H, d, *J* 6.8 Hz, -CH(C*H*$_3$)(CH_3)), 1.13 (3H, d, *J* 6.8 Hz, -CH(C*H*$_3$)(CH_3)), 2.22-2.40 (2H, m, 2 x -C*H*(CH_3)$_2$ overlapped), 2.37 (1H, m, -C*H*(CH_3)$_2$), 5.25 (1H, dd, *J* 8.6, 5.0 Hz, Het-C*H*), 5.33 (1H, dd, *J* 9.3, 5.3 Hz, Het-C*H*), 5.43 (1H, dd, *J* 9.7, 6.5 Hz, Het-C*H*), 8.09 (1H, s, Thiaz-*H*), 8.12 (1H, s, Thiaz-*H*), 8.20 (1H, s, Oxaz-*H*), 8.37 (1H, d, *J* 9.7 Hz, -C(O)N*H*), 8.40 (1H, d, *J* 9.3 Hz, -C(O)N*H*), 8.44 (1H, d, *J* 8.6 Hz, -C(O)N*H*); δ_C (90 MHz, $CDCl_3$) 18.2, 18.4, 18.6 (x2), 18.7, 19.1, 33.8, 35.3, 35.4, 53.0, 55.5, 55.9, 123.4, 124.0, 135.4, 141.4, 148.8, 149.4, 159.4, 159.8, 160.3, 163.8, 168.3, 168.7; HRMS $[M+Na]^+$ m/z 553.1600 (calcd for $C_{24}H_{30}N_6NaO_4S_2$ 553.1668, and ii) the known cyclic tetramer **11b** (10 %), and iii) the cyclic trimer **59** (3 %).

Thiazole / *bis*-Oxazole Cyclic Trimer 62

Using General Procedure C, the *bis*-oxazole **47** (52.4 mg, 0.135 mmol) was reacted with the thiazole **43a** (31.9 mg, 0.135 mmol) to give i) the *cyclic trimer* (16 mg, 23 %): δ_H (360 MHz, $CDCl_3$) 1.03-1.11 (9H, m, 3 x -CH(C*H*$_3$)(CH_3) overlapped), 1.03-1.11 (9H, m, 3 x -CH(CH_3)(C*H*$_3$) overlapped), 2.22-2.43 (3H, m, 3 x -C*H*(CH_3)$_2$ overlapped), 5.12 (1H, dd, *J* 7.7, 4.6 Hz, Het-C*H*), 5.28 (1H, dd, *J* 8.7, 5.4 Hz, Het-C*H*), 5.35 (1H, dd, *J* 8.7, 5.8 Hz, Het-C*H*), 8.12 (1H, s, Thiaz-*H*), 8.19 (1H, s, Oxaz-*H*), 8.21 (1H, s, Oxaz-*H*), 8.33 (3H, br d, *J* 8.3 Hz, 3 x -C(O)N*H* overlapped); δ_C (90 MHz, $CDCl_3$) 18.3, 18.4, 18.5, 18.6 (x2), 18.8, 33.5, 34.0, 35.4, 53.0, 53.4, 55.8, 123.9, 135.3, 135.7, 141.1, 141.7, 149.1, 159.3, 159.9, 160.1, 163.7, 163.8, 168.4; HRMS $[M+Na]^+$ m/z 537.1859 (calcd for $C_{24}H_{30}N_6NaO_5S$ 537.1896), ii) the cyclic tetramer **63** (11 mg, 12 %): δ_H (360 MHz, $CDCl_3$) 0.99 (12H, d, *J* 6.7 Hz, 4 x -CH(C*H*$_3$)(CH_3)), 1.09 (12H, d, *J* 6.7 Hz, 4 x -CH(CH_3)(C*H*$_3$)), 2.38 (4H, m, 4 x -C*H*(CH_3)$_2$), 5.27 (4H, app. t, *J* 9.7 Hz, 4 x Het-C*H*), 7.30 (4H, d, *J* 9.8 Hz, 4 x -C(O)N*H*), 8.16 (4H, s, 4 x Oxaz-*H*); ^{13}C NMR (90 MHz, $CDCl_3$) δ: 18.7 (x4), 19.0 (x4), 32.9 (x4), 51.7 (x4), 135.7 (x4), 141.7 (x4), 159.8 (x4), 163.8 (x4); HRMS $[M+H]^+$ m/z 665. 3022 (calcd for $C_{32}H_{41}N_8O_8$ 665.3047), and iii) the cyclic trimer **10b** (5 %).

Imidazole / *bis*-Oxazole based Cyclic Trimer 64

Using General Procedure C, the *bis*-oxazole **47** (44.2 mg, 0.114 mmol) was reacted with the imidazole **41b** (28.3 mg, 0.114 mmol) to give i) the *cyclic trimer* (18 mg, 30 %): δ_H (360 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.7 Hz, -

CH(C*H*$_3$)(CH$_3$)), 1.04 (3H, d, *J* 6.7 Hz, -CH(C*H*$_3$)(CH$_3$)), 1.07 (3H, d, *J* 6.7 Hz, -CH(C*H*$_3$)(CH$_3$)), 1.11 (3H, d, *J* 6.7 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.17 (3H, d, *J* 6.7 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.23 (3H, d, *J* 6.7 Hz, -CH(CH$_3$)(C*H*$_3$)), 2.16 (1H, m, -C*H*(CH$_3$)$_2$), 2.28 (1H, m, -C*H*(CH$_3$)$_2$), 2.38 (1H, m, -C*H*(CH$_3$)$_2$), 2.56 (3H, s, Imid-C*H*$_3$), 3.52 (3H, s, -NC*H*$_3$), 5.04-5.16 (2H, m, 2 x Het-C*H* overlapped), 5.21 (1H, dd, *J* 8.8, 5.3 Hz, Het-C*H*), 8.15 (1H, s, Oxaz-*H*), 8.17 (1H, s, Oxaz-*H*), 8.27 (1H, d, *J* 8.8 Hz, -C(O)N*H*), 8.31 (1H, d, *J* 8.3 Hz, -C(O)N*H*), 8.33 (1H, d, *J* 7.5 Hz, -C(O)N*H*); δ_C (90 MHz, CDCl$_3$) 9.8, 18.1, 18.3, 18.4 (x2), 18.8, 19.4, 30.5, 33.6, 34.0, 35.1, 50.6, 52.3, 53.3, 129.5, 133.1, 135.5 (x2), 140.9, 141.4, 146.0, 159.5, 160.0, 163.3, 163.6, 164.6; HRMS $[M+H]^+$ m/z 526.2716 (calcd for $C_{26}H_{36}N_7O_5$ 526.2778), ii) the *cyclic tetramer* **65** (8 mg, 8 %): δ_H (360 MHz, CDCl$_3$) 0.89 (3H, d, *J* 6.6 Hz, -CH(C*H*$_3$)(CH$_3$)), 0.92 (3H, d, *J* 6.6 Hz, -CH(C*H*$_3$)(CH$_3$)), 0.95 (3H, d, *J* 6.6 Hz, -CH(C*H*$_3$)(CH$_3$)), 0.96 (6H, d, *J* 6.6 Hz, -CH(CH$_3$)(C*H*$_3$) and -CH(C*H*$_3$)(CH$_3$) overlapped), 1.12 (3H, d, *J* 6.6 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.13 (3H, d, *J* 6.6 Hz, -CH(CH$_3$)(C*H*$_3$)), 1.15 (3H, d, *J* 6.6 Hz, -CH(CH$_3$)(C*H*$_3$)), 2.35 (1H, m, -C*H*(CH$_3$)$_2$), 2.35-2.45 (2H, m, 2 x -C*H*(CH$_3$)$_2$ overlapped), 2.48 (3H, s, Imid-C*H*$_3$), 2.50 (3H, s, Imid-C*H*$_3$), 2.52 (1H, m, -C*H*(CH$_3$)$_2$), 3.60 (3H, s, -NC*H*$_3$), 3.65 (3H, s, -NC*H*$_3$), 4.94 (1H, app. t, *J* 9.3 Hz, Het-C*H*), 5.00 (1H, app. t, *J* 9.5 Hz, Het-C*H*), 5.13 (1H, app. t, *J* 9.1 Hz, Het-C*H*), 5.28 (1H, app. t, *J* 9.5 Hz, Het-C*H*), 7.84-7.99 (4H, m, 4 x -C(O)N*H* overlapped), 8.10 (1H, s, Oxaz-*H*), 8.11 (1H, s, Oxaz-*H*); δ_C (90 MHz, CDCl$_3$) 9.9 (x2), 17.9 (x2), 18.1, 18.3 (x2), 18.4, 18.5, 18.9, 30.4, 32.8, 33.0, 34.2, 34.9, 35.8, 49.9, 50.3, 52.9, 53.6, 129.2, 129.4, 131.9, 133.0, 134.8, 135.0, 140.8, 141.1, 146.1, 147.4, 159.3, 160.0, 161.4, 163.5, 163.7, 165.2; HRMS $[M+H]^+$ m/z 719.3952 (calcd for $C_{36}H_{51}N_{10}O_6$ 719.3993), and iii) traces of the cyclic tetramer **56**.

Boc-*L*-phenylalanine-*L*-threonine-methyl ester, 69a.

N-Methylmorpholine (5.0 mL, 45.6 mmol) followed by HOBt (6.2 g, 45.6 mmol) and then EDC.HCl (8.7 g, 45.6 mmol) were added, each in one portion to a stirred solution of Boc-*L*-phenylalanine (11.0 g, 41.5 mmol) in dry THF (415 mL) at 0 °C under a nitrogen atmosphere. The suspension was stirred at 0 °C for 0.5 h and then a precooled suspension of *L*-threonine-methyl ester.HCl (7.7 g, 45.6 mmol) and NMM (5.0 mL, 45.6 mmol) in dry DMF (2 mL) was added dropwise over 5 minutes. The mixture was stirred at 0 °C for 1.5 h and then allowed to warm to room temperature over 19 h. Water (200 mL) was added and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed successively with saturated aqueous NaHCO$_3$ (2 x 100 mL), H$_2$O (2 x 100 mL) and brine (2 x 100 mL) and then evaporated *in vacuo* to leave the dipeptide (14 g, 88 %) as a yellow foam, $[\alpha]_D^{29}$ -6.6 (*c* 1.0, CHCl$_3$); (Found : C, 59.9; H, 7.5; N, 7.4; $C_{19}H_{28}N_2O_6$ requires: C, 60.0; H, 7.4; N, 7.4 %); ν_{max} (soln, CHCl$_3$) 3612, 3427, 2979, 2933, 1681 cm^{-1}; δ_H (360 MHz, CD$_3$Cl) 1.16 (3H, d, *J* 6.5, C*H*$_3$CHOH), 2.77 (1H, br. s, O*H*), 1.40 (9H, s, ^{t}Bu), 3.04 (1H, dd, *J* 13.5, *J* 6.2, C*H*$_2$Ph), 3.14 (1H, dd. *J* 13.5, *J* 6.2, C*H*$_2$Ph), 3.73 (3H, s, C*H*$_3$O), 4.23-4.32 (1H, m, C*H*OH), 4.38-4.46 (1H, m, C*H*NHBoc), 4.58 (1H, dd, *J* 8.7, *J* 2.7, C*H*COO), 5.11 (1H, app. d, *J* 7.9, N*H*Boc), 6.79 (1H, app. d, *J* 8.7, N*H*CO), 7.21-7.32 (5H, m, Ar*H*); δ_C

(100.6 MHz, CD_3Cl) 19.8 (q), 28.3 (q), 38.0 (t), 52.6 (q), 55.9 (d), 57.3 (d), 68.3 (d), 80.4 (s), 126.9 (d), 128.6 (d), 129.4 (d), 136.5 (s), 155.4 (s), 171.1 (s), 171.9 (s); *m/z* (EI) 403.1824 (M^+ + Na, $C_{19}H_{28}N_2O_6$ + Na requires 403.1845).

***tert*-Butyl(*S*)-1-((4*S*,5*S*)-4-(methoxycarbonyl)-4,5-dihydro-5-methyloxazol-2-yl)-2-phenylethylcarbamate, 70a**

Deoxo-fluor (1.1 mL, 2.6 mmol) was added dropwise over 10 minutes to a stirred solution of the dipeptide **69a** (1.0 g, 2.6 mmol) in anhydrous DCM at -20 °C under a nitrogen atmosphere. The mixture was stirred at -20 °C for 1.5 hours, then quenched with saturated aqueous $NaHCO_3$ (20 mL) and stirred at -20 °C for 5 min. The mixture was allowed to warm to room temperature, then diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with $CHCl_3$ (3 x 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by chromatography, eluting with ethyl acetate/petroleum ether (3:7) to give the *cis-oxazoline* (0.68 g, 71 %) as pale yellow oil, $[\alpha]_D^{25}$ +26.4 (*c* 1.0, $CHCl_3$); ν_{max} (soln, $CHCl_3$) 3435, 2979, 2950, 1714, 1666 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.5, C*H*$_3$CH(O)), 1.36 (9H, s, ^{t}Bu), 3.02 (1H, dd, *J* 13.6, *J* 6.4, C*H*$_2$Ph), 3.14 (1H, dd, *J* 13.6, *J* 6.4, C*H*$_2$Ph), 3.69 (3H, s, C*H*$_3$O), 4.63 (1H, dd, *J* 13.6, *J* 6.4, C*H*NHBoc), 4.75 (1H, dd, *J* 10.3, *J* 1.4, C*H*COOCH$_3$), 4.85-4.97 (1H, m, C*H*(O)CH$_3$), 5.28 (1H, app. d, *J* 8.4, N*H*Boc), 7.19-7.28 (5H, m, Ar*H*) ; δ_C (100.6 MHz, CD_3Cl) 16.0 (q), 28.1 (q), 38.8 (t), 49.8 (d), 51.5 (q), 70.3 (d), 78.2 (d), 79.3 (s), 126.6 (d), 128.2 (d), 129.3 (d), 136.2 (s), 154.9 (s), 169.6 (s), 169.8 (s); *m/z* (EI) 385.1737 (M^+ + Na, $C_{19}H_{26}N_2O_5$ + Na requires 385.1739).

(4S,5S)-2-(1-Amino-2-phenyl-ethyl)-5-methyl-4,5-dihydro-oxazole-4-carboxylic acid triflate 71a

Using General Procedure B, the oxazoline ester **70a** (0.4 g, 1.1 mmol) was converted into the corresponding carboxylic acid (151 mg, 78 %) which was obtained as a colourless solid, mp 125-126 °C (Et_2O/petroleum ether); $[\alpha]_D^{23}$ -0.4 (*c* 0.5, $CHCl_3$); ν_{max} (soln, $CHCl_3$) 3429, 2932, 1687 cm^{-1}; δ_H (360 MHz, CD_3OD) 1.36 (9H, s, ^{t}Bu), 1.41 (3H, d, *J* 6.8, C*H*$_3$CH), 3.13-3.23 (1H, m, C*H*$_2$Ph), 2.79-2.86 (1H, m, C*H*$_2$Ph), 4.07-4.10 (1H, m, C*H*CH$_2$), 4.34-4.38 (1H, m, C*H*(O)CH$_3$), 4.41 (1H, d, *J* 7.2, C*H*COOH), 5.47-5.49 (1H, m, N*H*Boc), 7.18-7.23 (5H, m, Ar*H*); δ_C (90.6 MHz, CD_3OD) 19.5 (q), 28.6 (q), 38.1 (t), 59.6 (d), 71.5 (d), 80.7 (d), 127.7 (d), 129.4 (d), 130.4 (d), 138.6 (s), 158.0 (s), 170.9 (s), 172.3 (s), 174.4 (s); *m/z* (EI) 349.1770 (M^+ + H, $C_{18}H_{24}N_2O_5$ + H requires 349.1763).

Trimethylsilyl triflate (1.12 mmol, 0.2 mL) was added to a stirred solution of the *N*-Boc protected carboxylic acid (0.13 g, 0.4 mmol) in dry DCM (10 mL) at 0 °C under a nitrogen atmosphere and the mixture was stirred at 0 °C for 1.5 h. The mixture was allowed to warm to RT, then diluted with DCM (2 mL) and evaporated *in vacuo*. The

solid residue was washed with petroleum ether to leave the *triflate salt* (127mg, 85 %) as a colourless solid which was used in the next step without further purification.

(2S,3S)-2-((S)-2-Amino-3-phenyl-propionylamino)-3-hydroxy-butyric acid hydrochloride salt, 72.

Using General Procedures B and D, the protected dipeptide **69a** (410 mg, 1.08 mmol) was converted into the corresponding carboxylic acid (0.31 g, 78 %), mp 86-87 °C (Et_2O/petrol); $[\alpha]_D^{29}$ -0.6 (*c* 1.0, $CHCl_3$); ν_{max} (soln, $CHCl_3$) 3424, 2933, 1711, 1681 cm^{-1}; δ_H (360 MHz, CD_3Cl) 1.36 (3H, d, *J* 6.2, C*H*$_3$CHOH), 1.36 (9H, s, ^{t}Bu), 2.82-2.98 (1H, m, C*H*$_2$Ph), 3.10-3.29 (1H, m, C*H*$_2$Ph), 4.38-4.49 (1H, m, C*H*OH), 4.47 -4.67 (1H, m, C*H*COOH), 4.68-4.71 (1H, m, C*H*CH_2Ph), 5.70 (2H, br. s, 2 x O*H*), 6.35 (1H, br. s, N*H*CO), 7.10 -7.37 (5H, m, Ar*H*); δ_C (90.6 MHz, $CDCl_3$) 19.4 (q), 28.3 (q), 38.3 (t), 55.5 (d), 57.4 (d), 68.0 (d), 80.7 (s), 126.9 (d), 128.6 (d), 129.4 (d), 136.4 (s), 156.0 (s), 172.7 (s), 173.5 (s); *m/z* (EI) 389.1689 (M^+ + Na, $C_{18}H_{26}N_2O_6$ + Na requires 389.1689), and then into the *amine salt*, which was used immediately in the next step.

2-(1-Amino-2-methyl-propyl)-5-methyl-oxazole-4-carboxylic acid hydrochloride salt 73b

The known oxazoline **70b** (300 mg, 0.95 mmol) in anhydrous DCM (10 ml) was cooled to 0 °C. $BrCCl_3$ (0.283 ml, 2.87 mmol) was added and the mixture was stirred at 0 °C for 10 minutes. DBU (0.427 ml, 2.87 mmol) was added dropwise over 10 minutes and the mixture was then stirred. The volatiles were removed under reduced pressure and the residue was then taken up into ethyl acetate and treated with 1N HCl. The separated aqueous layer was extracted with ethyl acetate, and the combined organic extracts washed with sat. aq. $NaHCO_3$, then dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography (50% ethyl acetate in petroleum ether) to give the corresponding oxazole (276 mg, 93%), mp 80-82 °C; $[\alpha]_D^{25}$ -28.2 (*c* 0.5, $CHCl_3$); δ_H (360 MHz, $CDCl_3$) 0.74 (3H, d, *J* 6.7 Hz, -CH(C*H*$_3$)(CH_3)), 0.76 (3H, d, *J* 6.7 Hz, -CH(CH_3)(C*H*$_3$)), 1.25 (9H, s, -C(C*H*$_3$)$_3$), 2.00 (1H, m, -C*H*(CH_3)$_2$), 2.44 (3H, s, Oxaz-C*H*$_3$), 3.73 (3H, s, -CO_2C*H*$_3$), 4.56 (1H, app t, *J* 7.6 Hz, -C*H*NHBoc), 5.24 (1H, d, *J* 7.3 Hz, -N*H*Boc); δ_C (90 MHz, $CDCl_3$) 11.7, 17.7, 18.5, 28.0 (x3), 32.5, 51.6, 53.9, 79.5, 127.0, 155.1, 156.0, 161.9, 162.3; HRMS $[M+Na+2H_2O]^+$ m/z 371.1811 (calcd for $C_{15}H_{28}N_2NaO_7$ 371.1794).

The oxazole (250 mg, 0.80 mmol) was saponified according to the general procedure B to give the crude carboxylic acid which was then BOC deprotected using general procedure D to give the amino acid (182 mg, 97%), $[\alpha]_D^{25}$ -9.2 (*c* 0.5, MeOH); δ_H (360 MHz, CD_3OD) 1.03 (3H, d, *J* 6.8 Hz, -CH(C*H*$_3$)(CH_3)), 1.16 (3H, d, *J* 6.8 Hz, -CH(CH_3)(C*H*$_3$)), 2.43 (1H, m, -C*H*(CH_3)$_2$), 2.70 (3H, s, Oxaz-C*H*$_3$), 4.47 (1H, d, *J* 6.4 Hz, Oxaz-C*H*); δ_C (90 MHz, CD_3OD) 12.1, 18.1, 18.8, 32.3, 55.2, 129.2, 158.6, 158.9, 164.6; HRMS: $[M]^+$ m/z 199.1102 (calcd for $C_9H_{15}N_2O_3$ 199.1083).

(1'*S*)-2-(1-{[2-(1-Amino-ethyl)-thiazole-4-carbonyl]-amino}-ethyl)-thiazole-4-carboxylic acid hydrochloride, 74.

A solution of hydrogen chloride in 1, 4-dioxane (0.1 ml, 4 M) was added to the Boc amine **35** (50 mg, 0.11 mmol) and the mixture was then stirred at room temperature for 8h under a nitrogen atmosphere. The dioxane was evaporated *in vacuo,* using toluene (*ca* 0.5 ml) as an azeotrope to leave the *amine hydrochloride* (40 mg, 93 %) as a hygroscopic solid; mp 147-149 ºC (from CH_3CN /diethyl ether); $[\alpha]_D^{23}$ – 26.2 (*c* 1.0 in CH_3CN); ν_{max} (soln: $CHCl_3$)/cm^{-1} 3397, 2933, 2873, 1694, 1543; δ_H (360 MHz, $CDCl_3$) 1.34 (2H, t, *J* 6.7, OCH_2CH_3), 1.63 (3H, d, *J* 6.6, CH_3CH), 1.80 (3H, d, *J* 6.8, CH_3CH), 4.33 (2H, q, *J* 6.7, OCH_2CH_3), 5.03 (1H, m, $CHCH_3$), 5.55 (1H, m, $CHCH_3$), 7.91 (1H, s, CHS), 8.32 (1H, s, CHS); δ_C (90.5 MHz, $CDCl_3$) 19.9 (q), 20.5 (q), 49.3 (d), 53.5 (d), 125.1 (d), 127.5 (d), 146.5 (s), 148.8 (s), 160.6 (s), 161.5 (s), 166.9 (s), 174.4 (s); *m*/*z* (FAB) Found 377.0689 ($[MNa - HCl]^+$ $C_{14}H_{18}N_4NaO_3S_2$ requires 377.0718).

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