Total synthesis of (+)-nostocyclamide[1]

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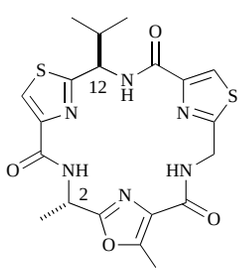
The synthesis of (+)-nostocyclamide from the oxazole 1 and thiazoles 2 and 3 is described. The oxazole amino ester 1b was prepared from *N*-protected alaninamide using a rhodium(II) catalysed N–H insertion reaction as a key step, and the thiazoles 2 and 3 were obtained using a modified Hantzsch reaction. The synthesis was completed in six further steps in which fragments 1 and 2 were coupled using mixed anhydride methodology to give the oxazole–thiazole 13, deprotection of which and coupling to 3 gave the linear bis-thiazole oxazole 15. Macrocyclisation using the pentafluorophenyl ester method gave (+)-nostocyclamide; the synthesis confirms that the natural product is the (+)-enantiomer and has the (2*S*,12*R*) absolute configuration.

Introduction

The nitrogen fixing cyanobacteria of the genus *Nostoc* are a rich source of biologically active substances of diverse structural types.[2–11] In a detailed survey based on antibacterial activity, the major bioactive component of one strain, *Nostoc* sp. 31, was shown to be nostocyclamide, a novel macrocyclic peptide consisting of an 18-membered ring containing two thiazoles and one oxazole.[12] The structure determination was based on extensive ^{1}H and ^{13}C NMR analysis and was confirmed by X-ray crystallography, and, although the absolute configuration could not be assigned with complete certainty, the (2*S*,12*R*)-enantiomer was deemed most likely. In view of our interest in the synthesis of heterocyclic natural products containing oxazoles[13,14] or thiazoles,[15] we now report the details of the first synthesis of (2*S*,12*R*)-nostocyclamide.[1]

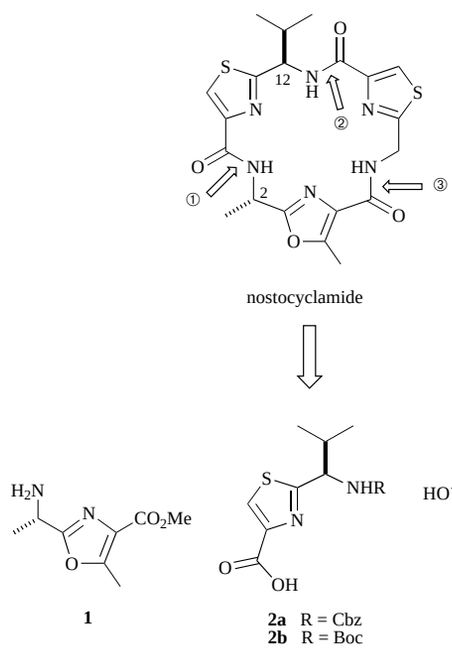


nostocyclamide

Results and discussion

Simple disconnection of the three amide bonds in nostocyclamide as indicated in Scheme 1 revealed an oxazole amino ester **1** and two thiazole derived amino acid derivatives **2** and **3** as suitable precursors to the natural product. Since the absolute configuration of nostocyclamide had not been assigned with complete certainty,[12] we elected to synthesise the 'most likely' (2*S*,12*R*)-enantiomer, thereby dictating that the heterocyclic amino acids **1** and **2** should be derived from (*S*)-alanine and (*R*)-valine respectively. The projected order of coupling of the fragments (Scheme 1) in part dictated the choice of carboxy and amino protecting groups, although two *N*-protecting groups (Cbz and Boc) were considered for the valine-derived thiazole **2**.

The 5-methyloxazole-4-carboxylic acid **1** was readily prepared using our rhodium catalysed N–H insertion reactions of diazo keto esters as described in the preceding paper.[16] Rhodium(II) acetate catalysed reaction of *N*-Cbz-protected alaninamide **4** with methyl diazoacetoacetate resulted in chemoselective N–H insertion to give the keto amide **5**, cyclodehydration of which using the triphenylphosphine–iodine–triethylamine protocol[17] gave the *N*-protected oxazole ester **6**. Finally deprotection by catalytic hydrogenolysis over palladium-on-carbon gave the desired oxazole amino ester **1** (Scheme 2).



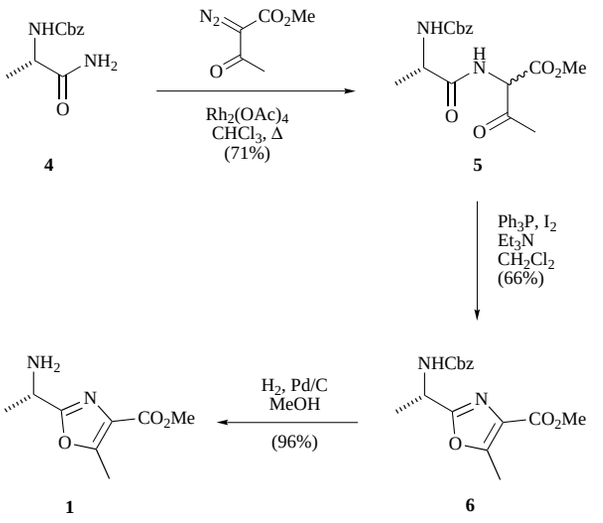
nostocyclamide

1 **2a** R = Cbz **2b** R = Boc **3**

Scheme 1

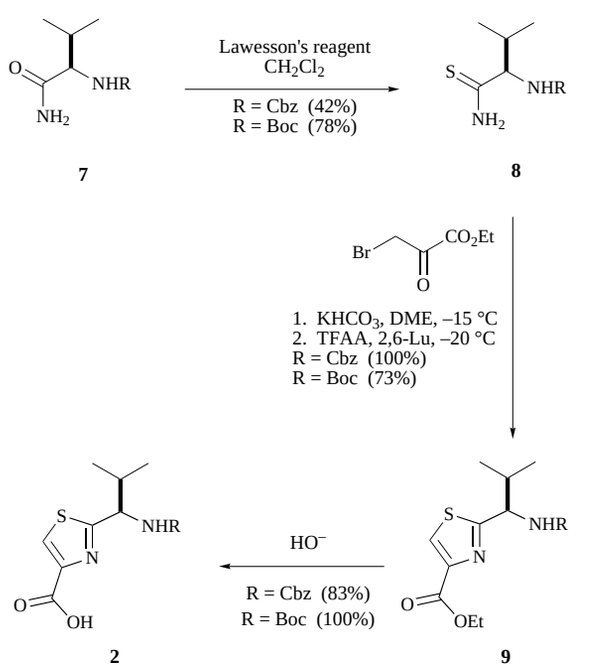
The synthesis of optically active thiazoles has been widely investigated of late.[18–21] In particular, Meyers has reported a modification of the Hantzsch reaction,[22] originally adapted by Holzapfel,[23] as a reliable route to enantiomerically pure thiazole amino acid derivatives, and successfully applied it in his synthesis of bistratamide C,[24] a macrocyclic bis-thiazole–oxazole structurally similar to nostocyclamide. Initially the synthesis of the Cbz-protected thiazole **2a** was investigated. Hence the thioamide **8a**, prepared in modest yield from *N*-Cbz-protected (*R*)-valinamide **7a**, was reacted with ethyl bromopyruvate at −15 °C, followed by dehydration of the resulting hydroxythiazoline with trifluoroacetic anhydride (TFAA) and 2,6-lutidine (2,6-Lu) to give the thiazole-4-ester **9a** in good yield

† A substantial part of this work was carried out by the authors in the Department of Chemistry, Loughborough University, Loughborough, Leics., UK LE11 3TU.



Scheme 2

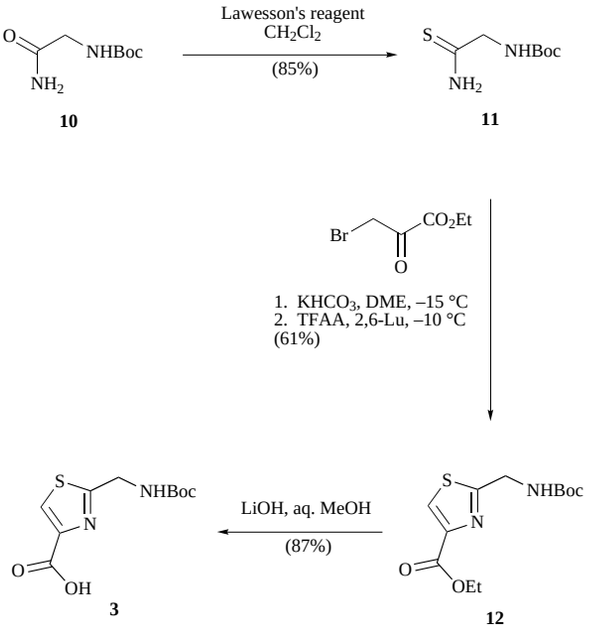
and in 97–98% ee as determined by HPLC analysis on a chiral column [Chiracel OD column, eluting with hexane–propan-2-ol (9:1) at 2.0 ml min^{-1}]. Hydrolysis with sodium hydroxide in aqueous THF gave the required thiazole amino acid **2a** (Scheme 3). However the poor yield in the formation of the



Scheme 3 (**a**, R = Cbz; **b**, R = Boc)

thioamide **8a**, together with difficulties encountered in scaling up the reactions and in subsequent removal of the Cbz-group (see below), led us to investigate the alternative thiazole **2b** in which the side chain nitrogen was protected by a Boc group. The synthesis proceeded as before (Scheme 3), and in general the compounds were easier to purify than the corresponding *N*-Cbz derivatives. The thiazole ester **9b** was formed essentially as a single enantiomer [>99% ee by HPLC; Chiracel OD column, eluting with hexane–propan-2-ol (98:2) at 0.75 ml min^{-1}].[25] Finally alkaline hydrolysis gave the desired thiazole-4-carboxylic acid **26**.[26]

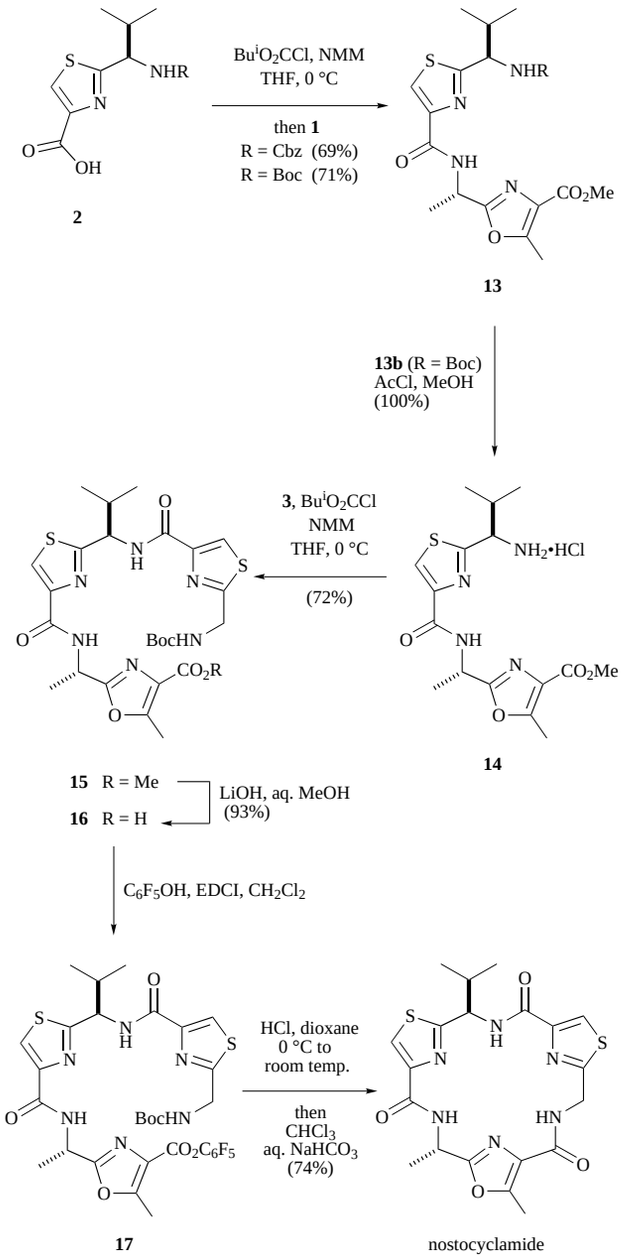
Although racemisation was not an issue in the preparation of the glycine derived thiazole amino acid **3**, a compound previously used in the synthesis of dolastatin,[27] the compound was prepared from *N*-Boc-glycinamide **10** *via* the corresponding thioamide **11** and thiazole ester **12**,[28] in exactly the same way as the valine analogue (Scheme 4).



Scheme 4

The coupling of the heterocyclic amino acid residues to form the linear 'peptide' for macrocyclisation was carried out using the mixed anhydride method (*cf*. ref. 24). Thus reaction of the acid **2a** or **2b** with isobutyl chloroformate in the presence of *N*-methylmorpholine (NMM), followed by addition of the amine **1** gave the *N*-Cbz- or *N*-Boc-protected thiazole–oxazole **13a** and **13b** in 69 and 71% yield respectively (Scheme 5). At this stage the *N*-Cbz-aminoalkyl thiazole series was finally abandoned when we were unable to deprotect the thiazole–oxazole **13a** by catalytic hydrogenolysis over palladium-on-carbon or over Pearlman's catalyst. The *N*-Boc derivative **13b**, however, was cleanly deprotected using methanolic hydrogen chloride, and the resulting amine **14** was coupled to the thiazole acid **3** using the mixed anhydride method to give the terminally protected linear oxazole–bis-thiazole **15** (Scheme 5).

Although there are several methods available for macrolactamisation, the ring closure protocol used by Schmidt and co-workers has consistently given satisfactory results in a number of examples.[29–33] Hence the ester **15** was hydrolysed to the corresponding acid **16**, and converted into the corresponding pentafluorophenyl ester **17** by coupling with pentafluorophenol in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI). The pentafluorophenyl ester **17** was not purified, but underwent deprotection at the *N*-terminus on treatment with HCl in dioxane, and this was followed by macrolactamisation in a two-phase chloroform–aqueous base system to give the macrocyclic peptide nostocyclamide in 74% yield after chromatography. The synthetic material had mp 259–260 °C (decomp.) [lit.,[12] 255.8–256.9 °C (decomp.)], and a specific rotation of $[a]_D^{19}$ +51.3 (*c* 0.84, $CHCl_3$), together with ^1H and ^{13}C NMR spectra consistent with those reported for the natural product, although the published ^{13}C NMR data do not list the resonance for C-8, which was observed at δ 165.6 ($CDCl_3$) in our synthetic material. Subsequent correspondence with the authors of the original paper confirmed that the natural product does exhibit an additional quaternary carbon signal in its ^{13}C NMR spectrum at δ 166.2 ($[^2H_6]$DMSO).[34] Although no rotation was reported for nostocyclamide in the original paper due to lack of material,[12] re-isolation of a small amount of the natural product resulted in material with a (+)-rotation of $[a]_D^{20}$ +25 ($CHCl_3$).[35] In view of the discrepancy in the optical rotations, that of the synthetic material was checked on three different samples on two different polarimeters and found to be consistently +53 (± 2). The lower value for the natural product may be a result



Scheme 5

of the small sample used. Despite the difference in optical rotations, we believe that our synthesis demonstrates that natural (+)-nostocyclamide does indeed have the (2*S*,12*R*).

Experimental

For general experimental points, see the preceding paper.

(*S*)-Methyl 2-(1-aminoethyl)-5-methyloxazole-4-carboxylate 1

A suspension of palladium-on-charcoal (10%; 150 mg) in a solution of (*S*)-methyl 2-[(1-benzyloxycarbonylamino)ethyl]-5-methyloxazole-4-carboxylate **6**[16,36] (0.578 g, 1.82 mmol) in methanol (40 ml) was stirred under H_2 (1 atm) at room temperature for 4 h. The mixture was filtered through a plug of Celite, the plug was washed with ethyl acetate (40 ml) and the filtrates were combined and evaporated *in vacuo* to afford the *title compound* **1** (0.32 g, 96%) as a colourless oil (Found: M^+, 184.0848. $C_8H_{12}N_2O_3$ requires *M*, 184.0848); $[\alpha]_D^{23.5}$ −17.4 (*c* 1.15, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3382, 3320, 1721, 1624, 1581, 1443, 1352, 1197, 1183, 1101 and 1056; δ_H(400 MHz; $CDCl_3$) 4.14 (1H, q, *J* 6.8, NC*H*Me), 3.89 (3H, s, MeO), 2.60 (3H, s, 5-Me), 1.80 (2H, br s, exch. D_2O, NH_2) and 1.49 (3H, d, *J* 6.8, *Me*CH); δ_C(100.6 MHz; $CDCl_3$) 166.55 (C), 163.12 (C), 156.77 (C), 127.42 (C), 52.26 (Me), 45.91 (CH), 21.94 (Me) and 12.30 (Me); *m*/*z* (EI) 185 (MH^+, 27%), 184 (M^+, 18), 169 (45), 168 (18), 137 (30), 110 (20), 58 (20) and 44 (100).

Preparation of thiazole-4-carboxylic acids

(*R*)-2-[1-(Benzyloxycarbonylamino)-2-methylpropyl]thiazole-4-carboxylic acid 2a

(*R*)-*N*^{2}-(Benzyloxycarbonyl)valinamide 7a. Prepared in 69% yield by the method described for the (*S*)-enantiomer in the preceding paper,[16] mp 210–211 °C (methanol–water) [lit.,[37] (*S*)-enantiomer, mp 212 °C]; $[\alpha]_D^{19}$ −25.6° (*c* 0.74, DMF) {lit.,[37] (*S*)-enantiomer $[\alpha]_D^{25}$ 22.6° (*c* 1, DMF)}.

(*R*)-*N*^{2}-(Benzyloxycarbonyl)thiovalinamide 8a. A solution of the above amide **7a** (0.568 g, 2.27 mmol) and Lawesson's reagent (0.505 g, 1.25 mmol) in dry dichloromethane (50 ml) was stirred for 16 h at room temperature. The mixture was evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ether–light petroleum (2:1), to afford the *title compound* **8a** (0.25 g, 42%) as a colourless foam (Found: M^+, 266.1098. $C_{13}H_{18}N_2O_2S$ requires *M*, 266.1089); $[\alpha]_D^{19}$ +39.2° (*c* 2.84, $CHCl_3$); ν_{max}(film)/cm^{-1} 3303, 3195, 3068, 3034, 2965, 2936, 2874, 1699, 1633, 1513, 1454, 1436, 1260, 1229, 1113, 1028, 736 and 696; δ_H(400 MHz; $CDCl_3$) 8.21 (1H, s, exch. D_2O, CSN*H*H), 7.87 (1H, s, exch. D_2O, CSNH*H*), 7.33 (5H, m, PhH), 5.76 (1H, d, *J* 8.1, exch. D_2O, OCONH), 5.10 (1H, d, *J* 12.3, PhC*H*H), 5.05 (1H, d, *J* 12.3, PhCH*H*), 4.29 (1H, m, C*H*NH), 2.11 (1H, m, C*H*Me$_2$) and 0.96 (6H, m, *Me*$_2$CH); δ_C(100.6 MHz; $CDCl_3$) 209.06 (C), 157.05 (C), 136.47 (C), 129.01 (CH), 128.66 (CH), 128.16 (CH), 67.70 (CH_2), 65.86 (CH), 33.85 (CH), 19.89 (Me) and 18.63 (Me); *m*/*z* (EI) 267 (MH^+, 4%), 266 (M^+, 0.2), 206 (15), 162 (13), 155 (8) and 91 (100).

(*R*)-Ethyl 2-[1-(benzyloxycarbonylamino)-2-methylpropyl]-thiazole-4-carboxylate 9a. Potassium hydrogen carbonate (107 mg, 1.07 mmol) and ethyl bromopyruvate (140 μl, 1.12 mmol) were added sequentially to a stirred solution of the above thioamide **8a** (71 mg, 0.27 mmol) in 1,2-dimethoxyethane (1 ml) at −20 °C. The reaction was warmed to −15 °C, stirred for 16 h and filtered through a pad of Celite. The pad was washed with ether (1 ml) and the combined filtrates were evaporated *in vacuo*. The residue was dissolved in 1,2-dimethoxyethane (1 ml), cooled to −20 °C and a solution of trifluoroacetic acid (120 μl, 0.85 mmol) and 2,6-lutidine (210 μl, 1.80 mmol) in 1,2-dimethoxyethane (1 ml) at −20 °C was added. The mixture was stirred for 30 min, evaporated *in vacuo* and partitioned between chloroform (30 ml) and water (30 ml). The organic layer was washed with water (30 ml), dried (Na_2SO_4), evaporated *in vacuo* and purified by flash chromatography on silica, gradient eluting with ethyl acetate–light petroleum (1:4 to 1:2), to afford the *title compound* **9a** (96 mg, 100%) as a pale yellow oil (Found: M^+, 362.1301. $C_{18}H_{22}N_2O_4S$ requires *M*, 362.1300); $[\alpha]_D^{20}$ +26.4° (*c* 1.26, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3435, 3126, 2986, 2971, 2940, 2908, 2875, 1729, 1504, 1392, 1372, 1260, 1098, 1072, 1051, 1021, 910 and 859; δ_H(400 MHz; $CDCl_3$) 7.99 (1H, s, SCH), 7.27 (5H, m, PhH), 5.57 (1H, d, *J* 4.5, exch. D_2O, OCONH), 5.05 (2H, s, PhCH_2), 4.88 (1H, m, C*H*NH), 4.32 (2H, q, *J* 7.1, OC*H*$_2$Me), 2.34 (1H, m, C*H*Me$_2$), 1.32 (3H, t, *J* 7.1, OCH$_2$*Me*), 0.89 (3H, d, *J* 6.8, *Me*CHMe) and 0.85 (3H, d, *J* 6.8, MeCH*Me*); δ_C(100.6 MHz; $CDCl_3$) 172.64 (C), 161.66 (C), 156.46 (C), 147.77 (C), 136.58 (C), 128.91 (CH), 128.57 (CH), 128.44 (CH), 127.26 (CH), 67.54 (CH_2), 61.80 (CH_2), 59.04 (CH), 33.81 (Me), 19.77 (Me), 17.87 (CH) and 14.73 (Me); *m*/*z* (EI) 363 (MH^+, 14%), 362 (M^+, 10), 320 (4), 275 (19), 227 (9), 139 (7) and 91 (100).

(*R*)-2-[1-(Benzyloxycarbonylamino)-2-methylpropyl]thiazole-4-carboxylic acid 2a. Sodium hydroxide (42 mg, 1.05 mmol, 5.2 equiv.) was added in one portion to a stirred solution of the ester **9a** (72 mg, 0.20 mmol) in THF–water (3:1) (6 ml) at room

temperature. The mixture was stirred for 5 h, the THF was evaporated *in vacuo* and the mixture was partitioned between ether (25 ml) and water (25 ml). The aqueous layer was acidified to pH 2 with 1 M aqueous hydrochloric acid and extracted with ethyl acetate (2 × 20 ml). The combined organic extracts were washed with brine (25 ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound **2a** (55 mg, 83%) as a colourless oil; $[\alpha]_D^{24}$ +27.2° (*c* 1.18, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3315, 2965, 2934, 1706, 1516, 1232, 1098, 1026, 753 and 697; δ_H(400 MHz; $CDCl_3$) 8.13 (1H, s, SCH), 7.46 (1H, br s, CO_2H), 7.27 (5H, m, PhH), 6.42 (0.17H, br s, OCONH), 5.67 (0.83H, d, *J* 8.2, exch. D_2O, OCONH), 5.07 (1H, d, *J* 12.5, PhC*H*H), 5.04 (1H, d, *J* 12.5, PhCH*H*), 4.89 (1H, m, C*H*NH), 2.34 (1H, m, C*H*Me_2), 0.89 (3H, d, *J* 6.8, *Me*CHMe) and 0.88 (3H, d, *J* 6.8, MeCH*Me*); δ_C(100.6 MHz; $CDCl_3$) 171.84 (C), 162.90 (C), 155.16 (C), 145.47 (C), 135.10 (C), 127.54 (CH), 127.41 (CH), 127.26 (CH), 127.08 (CH), 66.26 (CH_2), 57.62 (CH), 32.34 (CH), 18.40 (Me) and 16.62 (Me).

(*R*)-2-[1-(*tert*-Butoxycarbonylamino)-2-methylpropyl]thiazole-4-carboxylic acid 26

(*R*)-N^2-(*tert*-Butoxycarbonyl)valinamide 7b. Prepared in 88% yield by the method described for the (*S*)-enantiomer in the preceding paper,[16] mp 162–163 °C (chloroform–light petroleum) [lit.,[38] (*S*)-enantiomer; mp 160–161 °C]; $[\alpha]_D^{24}$ −16.1° (*c* 0.80, DMF) {lit.,[16] (*S*)-enantiomer; $[\alpha]_D^{19}$ 17.7° (*c* 1.33, DMF)}.

(*R*)-N^2-(*tert*-Butoxycarbonyl)thiovalinamide 8b. A solution of the above amide **7b** (0.63 g, 2.90 mmol) and Lawesson's reagent (0.61 g, 1.50 mmol) in dry dichloromethane (50 ml) was stirred for 16 h at room temperature. The mixture was evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ether–light petroleum (1:2), to afford (*R*)-N^2-(*tert*-butoxycarbonyl)thiovalinamide (0.53 g, 78%) as a pale yellow solid. A small portion was recrystallised to afford the title compound **8b** as colourless prisms, mp 101–103 °C (ethyl acetate–light petroleum) [lit.,[38] (*S*)-enantiomer; mp 112–113 °C]; $[\alpha]_D^{22.5}$ +44.0° (*c* 1.02, $CHCl_3$) {lit.,[38] (*S*)-enantiomer; $[\alpha]_D^{25}$ −43.48° (*c* 0.7, $CHCl_3$)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 3480, 3433, 3367, 3306, 3194, 2976, 2935, 2875, 1700, 1606, 1499, 1394, 1369, 1308, 1167, 1089, 1044, 1008 and 871; δ_H(400 MHz; $CDCl_3$) 8.24 (1H, s, exch. D_2O, CSN*H*H), 7.77 (1H, s, exch. D_2O, CSNH*H*), 5.35 (1H, d, *J* 9, exch. D_2O, CHN*H*), 4.22 (1H, m, C*H*NH), 2.15 (1H, m, C*H*Me_2), 1.43 (9H, s, CMe_3) and 0.98 (6H, d, *J* 6, Me_2CH); δ_C(100.6 MHz; $CDCl_3$) 209.42 (C), 156.00 (C), 80.23 (C), 65.09 (CH), 33.32 (CH), 28.32 (Me), 19.47 (Me) and 18.27 (Me); *m*/*z* (EI) 232 (M^+, 17%), 172 (39), 159 (7), 133 (9), 116 (42), 99 (10), 72 (100), 57 (93) and 41 (41).

(*R*)-Ethyl 2-[1-(*tert*-butoxycarbonylamino)-2-methylpropyl]-thiazole-4-carboxylate 9b. Potassium hydrogen carbonate (0.75 g, 7.45 mmol) and ethyl bromopyruvate (1.0 ml, 7.97 mmol) were added sequentially to a stirred solution of the thioamide **8b** (0.43 g, 1.86 mmol, 1.0 equiv.) in 1,2-dimethoxyethane (4 ml) at −40 °C. The reaction was warmed to −20 °C, stirred for 16 h and filtered through a pad of Celite. The pad was washed with ether (4 ml) and the combined filtrates were evaporated *in vacuo*. The residue was dissolved in 1,2-dimethoxyethane (4 ml), cooled to −40 °C and a solution of trifluoroacetic anhydride (0.86 ml, 6.09 mmol, 3.3 equiv.) and 2,6-lutidine (1.50 ml, 12.9 mmol, 6.9 equiv.) in 1,2-dimethoxyethane (2 ml) at −20 °C was added. The mixture was warmed to −20 °C over 10 min, stirred at −20 °C for 30 min, evaporated *in vacuo* and partitioned between chloroform (40 ml) and water (40 ml). The aqueous layer was further extracted with chloroform (20 ml) and the organic extracts were combined, washed with water (40 ml), dried (Na_2SO_4), evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:6), to afford the title compound **9b** (0.49 g, 73%) as colourless needles, mp 118.5–119 °C (from ethyl acetate–light petroleum) (lit.,[25] mp 114–115 °C) (Found: C, 54.6; H, 7.5; N, 8.4. Calc. for $C_{15}H_{24}N_2O_4S$: C, 54.9; H, 7.4; N, 8.5%); $[\alpha]_D^{19}$ +41.6° (*c* 1.06, $CHCl_3$) {lit.,[25] $[\alpha]_D^{25}$ +39.28° (*c* 2.6, MeOH)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 3126, 2982, 2936, 2875, 1716, 1603, 1498, 1393, 1370, 1165, 1098, 1019, 962 and 870; δ_H(400 MHz; $CDCl_3$) 8.07 (1H, s, SCH), 5.31 (1H, d, *J* 8.0, exch. D_2O, CHN*H*), 4.91 (1H, m, C*H*NH), 4.42 (2H, q, *J* 7.2, CH_2Me), 2.45 (1H, m, C*H*Me_2), 1.45 (9H, s, CMe_3), 1.40 (3H, t, *J* 7.2, CH_2Me), 0.98 (3H, d, *J* 6.8, *Me*CHMe) and 0.91 (3H, d, *J* 6.8, MeCH*Me*); δ_C(100.6 MHz; $CDCl_3$) 173.25 (C), 161.38 (C), 155.45 (C), 147.41 (C), 126.78 (CH), 80.10 (C), 61.41 (CH_2), 58.05 (CH), 36.06 (CH), 28.32 (Me), 19.44 (Me), 17.28 (Me) and 14.37 (Me); *m*/*z* (EI) 329 (MH^+, 62%), 328 (M^+, 1.5), 285 (17), 273 (70), 229 (47), 185 (74), 139 (40), 72 (11), 57 (100), 41 (42) and 29 (29).

(*R*)-2-[1-(*tert*-Butoxycarbonylamino)-2-methylpropyl]thiazole-4-carboxylic acid 2b. Lithium hydroxide monohydrate (97 mg, 2.3 mmol) was added in one portion to a stirred solution of the ester **9b** (152 mg, 0.46 mmol) in methanol–water (5:1) (10 ml) at room temperature. The reaction was stirred for 6 h, the methanol was evaporated *in vacuo* and the mixture was partitioned between ether (40 ml) and water (40 ml). The aqueous layer was acidified to pH 4 with 10% aqueous citric acid, extracted with ethyl acetate (2 × 40 ml), acidified to pH 3 with 10% aqueous citric acid and further extracted with ethyl acetate (2 × 40 ml). The combined organic extracts were washed with brine (75 ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound **2b** (0.14 g, quant.) as a colourless solid. A small portion was recrystallised to afford colourless prisms, mp 300–302 °C (lit.,[26] mp not given) (Found: M^+, 300.1146. Calc. for $C_{13}H_{20}N_2O_4S$: *M*, 300.1144); $[\alpha]_D^{20}$ +35.0° (*c* 1.17, $CHCl_3$) {lit.,[26] (*S*)-enantiomer; $[\alpha]_D^{21.5}$ −42.0 (*c* 2.6, $CHCl_3$)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 3440, 3124, 2979, 2934, 2875, 1709, 1496, 1393, 1369, 1341, 1240, 1164, 1097, 1042 and 869; δ_H(400 MHz; $CDCl_3$, 20 °C) 9.50 (1H, br s, exch. D_2O, CO_2H), 8.22 (1H, s, SCH), 6.69 (0.35H, br s, exch. D_2O, CHN*H*), 5.44 (0.65H, m, *J* 8.0, exch. D_2O, CHN*H*), 4.93 (0.65H, m, C*H*NH), 4.88 (0.35H, m, C*H*NH), 2.43 (1H, m, C*H*Me_2), 1.45 (9H, s, CMe_3) and 0.97 (6H, m, Me_2CH); δ_H(400 MHz; $CDCl_3$, 50 °C) 8.13 (1H, s, SCH), 5.15 (1H, m, exch. D_2O, CHN*H*), 4.85 (1H, m, C*H*NH), 2.36 (1H, m, C*H*Me_2), 1.44 (9H, s, CMe_3), 0.99 (3H, d, *J* 6.8, *Me*CHMe) and 0.95 (3H, d, *J* 6.8, MeCH*Me*); δ_C(100.6 MHz; $CDCl_3$) 174.04 (C), 164.70 (C), 155.93 (C), 147.03 (C), 128.68 (CH), 82.42 (C), 58.43 (CH), 33.66 (CH), 28.68 (Me), 19.79 (Me) and 17.79 (Me); *m*/*z* (EI) 301 (MH^+, 2%), 300 (M^+, 0.4), 245 (8), 201 (18), 166 (7), 157 (40), 139 (16), 113 (6), 72 (8), 57 (100) and 41 (68).

2-[*N*-(*tert*-Butoxycarbonyl)aminomethyl]thiazole-4-carboxylic acid 3

***N*^{2}-(*tert*-Butoxycarbonyl)glycinamide 10.** To a stirred solution of *N*-(*tert*-butoxycarbonyl)glycine (7.01 g, 40 mmol) and triethylamine (5.60 ml, 40 mmol) in dry THF (60 ml) was added ethyl chloroformate (3.90 ml, 40 mmol) dropwise at −10 °C. The mixture was stirred for 25 min and aqueous ammonia (35%; 10 ml) was added. The mixture was stirred at −10 °C for 45 min and partitioned between ethyl acetate (75 ml) and water (60 ml). The aqueous layer was extracted with ethyl acetate (50 ml) and the organic extracts were combined, washed sequentially with aqueous sodium hydrogen carbonate (75 ml), brine (2 × 75 ml), dried (Na_2SO_4), evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (4:1), to afford the title compound **10** (1.99 g, 29%) as a colourless solid. A small portion was recrystallised to afford the title compound as colourless prisms, mp 85–86 °C (ethyl acetate–light petroleum) (lit.,[28] mp 94 °C) (Found: C, 48.4; H, 8.3; N, 15.8. Calc. for $C_7H_{14}N_2O_3$: C, 48.3; H, 8.1; N, 16.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3524, 3451, 3410, 2983, 2935, 2872, 1691, 1593, 1576, 1504, 1454, 1394, 1369 and 1164; δ_H(400 MHz; $CDCl_3$) 6.53 (1H, br s, exch. D_2O, CON*H*H), 6.30 (1H, br s, exch. D_2O, CONH*H*), 5.56 (1H, br s, exch. D_2O, CH_2N*H*),

3.81 (2H, d, *J* 4.3, C*H*$_2$NH) and 1.45 (9H, s, CMe$_3$); δ_C(100.6 MHz; CDCl$_3$) 173.13 (C), 156.60 (C), 80.57 (C), 44.18 (CH$_2$) and 28.70 (Me); *m*/*z* (EI) 175 (MH$^+$, 40%), 174 (M$^+$, 0.1), 130 (14), 119 (90), 101 (32), 75 (38), 57 (100), 41 (57) and 30 (98).

***N*^{2}(*tert*-Butoxycarbonyl)thioglycinamide 11.** A solution of the above amide **10** (0.96 g, 5.49 mmol) and Lawesson's reagent (1.16 g, 2.86 mmol) in dry dichloromethane (65 ml) was stirred for 16 h at room temperature. The mixture was evaporated *in vacuo* and purified by flash chromatography on silica, gradient eluting with ether–light petroleum (1:1 to 3:1), to afford the title compound **11** (0.89 g, 85%) as a colourless solid. A small portion was recrystallised to afford colourless prisms, mp 126–127 °C (ethyl acetate–light petroleum) (lit.,[28] mp 124 °C); ν_{max}(CHCl$_3$)/cm^{-1} 3480, 3450, 3364, 2983, 2935, 2874, 1719, 1706, 1606, 1595, 1504, 1422, 1370, 1251, 1162, 1047, 914 and 856; δ_H(400 MHz; CDCl$_3$) 8.52 (1H, br s, exch. D$_2$O, CSN*H*H), 8.30 (1H, br s, exch. D$_2$O, CSNH*H*), 5.89 (1H, br s, exch. D$_2$O, CH$_2$N*H*), 4.10 (2H, d, *J* 7, C*H*$_2$NH) and 1.46 (9H, s, CMe$_3$); δ_C(100.6 MHz; [^{2}H$_6$]DMSO) 204.50 (C), 155.98 (C), 78.77 (C), 50.92 (CH$_2$) and 28.61 (Me); *m*/*z* (EI) 190 (M$^+$, 35%), 135 (51), 134 (50), 117 (19), 75 (47), 57 (100), 41 (62) and 30 (51).

Ethyl 2-[*N*-(*tert*-butoxycarbonyl)aminomethyl]thiazole-4-carboxylate 12. Potassium hydrogen carbonate (0.75 g, 7.45 mmol) and ethyl bromopyruvate (1.0 ml, 7.97 mmol) were added sequentially to a stirred solution of the thioamide **11** (0.43 g, 1.86 mmol) in 1,2-dimethoxyethane (4 ml) at −25 °C. The reaction was warmed to −15 °C, stirred for 16 h and filtered through a pad of Celite. The pad was washed with diethyl ether (4 ml) and the combined filtrates were evaporated *in vacuo*. The residue was dissolved in 1,2-dimethoxyethane (4 ml), cooled to −10 °C and a solution of trifluoroacetic anhydride (0.86 ml, 6.09 mmol) and 2,6-lutidine (1.50 ml, 12.9 mmol) in 1,2-dimethoxyethane (2 ml) at −10 °C was added. The mixture was stirred at −10 °C for 30 min, evaporated *in vacuo* and partitioned between chloroform (35 ml) and water (35 ml). The aqueous layer was further extracted with chloroform (35 ml) and the organic extracts were combined, washed with water (45 ml), dried (Na$_2$SO$_4$), evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:2), to afford the title compound **12** (0.46 g, 61%) as a pale yellow solid. A small portion was recrystallised to afford colourless needles, mp 103–104 °C (ethyl acetate–light petroleum) (lit.,[28] mp 133 °C) (Found: C, 50.4; H, 6.5; N, 9.9. Calc. for C$_{12}$H$_{18}$N$_2$O$_4$S: C, 50.3; H, 6.3; N, 9.8%); ν_{max}(CHCl$_3$)/cm^{-1} 3455, 3125, 2984, 2938, 2873, 1718, 1603, 1503, 1456, 1447, 1370, 1320, 1166, 1099, 1022, 930, 919 and 858; δ_H(400 MHz; CDCl$_3$) 8.13 (1H, s, SCH), 5.94 (1H, m, exch. D$_2$O, CH$_2$N*H*), 4.65 (2H, d, *J* 6.3, C*H*$_2$NH), 4.40 (2H, q, *J* 7.1, C*H*$_2$Me), 1.46 (9H, s, CMe$_3$) and 1.39 (3H, t, *J* 7.1, CH$_2$*Me*); δ_C(100.6 MHz; CDCl$_3$) 170.97 (C), 161.57 (C), 156.16 (C), 147.06 (C), 128.15 (CH), 80.49 (C), 61.69 (CH$_2$), 42.70 (CH$_2$), 28.59 (Me) and 14.80 (Me); *m*/*z* (EI) 287 (MH$^+$, 45%), 286 (M$^+$, 3), 231 (100), 213 (31), 187 (28), 167 (15), 158 (18), 140 (20), 112 (37), 57 (100), 41 (48) and 29 (48).

2-[*N*-(*tert*-Butoxycarbonyl)aminomethyl]thiazole-4-carboxylic acid 3. Lithium hydroxide monohydrate (85 mg, 2.0 mmol) was added in one portion to a stirred solution of the thiazole ester **12** (116 mg, 0.40 mmol) in methanol–water (5:1) (10 ml) at room temperature. The reaction was stirred for 3 h, the methanol was evaporated *in vacuo* and the mixture was partitioned between ether (30 ml) and water (30 ml). The aqueous layer was acidified to pH 3.5 with 10% aqueous citric acid, extracted with ethyl acetate (2 × 30 ml), acidified to pH 2 with 10% aqueous citric acid and further extracted with ethyl acetate (2 × 40 ml). The combined organic extracts were washed with brine (60 ml), dried (Na$_2$SO$_4$) and evaporated *in vacuo* to afford the title compound **3** (91 mg, 87%) as a colourless solid. A small portion was recrystallised to afford colourless prisms, mp 180.5–182 °C (ethyl acetate–light petroleum) (lit.,[28] mp 184 °C) (Found: C, 46.5; H, 5.4; N, 10.7. Calc. for C$_{10}$H$_{14}$N$_2$O$_4$S: C, 46.5; H, 5.5; N, 10.85%); ν_{max}(CHCl$_3$)/cm^{-1} 3455, 3125, 3038, 2984, 2934, 1715, 1506, 1369 and 1165; δ_H(400 MHz; CDCl$_3$, 20 °C) 8.12 (1H, s, SCH), 7.20 (1H, br s, exch. D$_2$O, CO$_2$H), 5.99 (0.2H, br s, exch. D$_2$O, CH$_2$N*H*), 5.75 (0.8H, br s, exch. D$_2$O, CH$_2$N*H*), 4.64 (2H, m, C*H*$_2$NH) and 1.46 (9H, s, CMe$_3$); δ_H(400 MHz; CDCl$_3$, 50 °C) 8.18 (1H, s, SCH), 5.20 (1H, br s, exch. D$_2$O, CH$_2$N*H*), 4.61 (2H, d, *J* 6.3, C*H*$_2$NH) and 1.47 (9H, s, CMe$_3$); δ_C(100.6 MHz; CDCl$_3$) 170.37 (C), 163.32 (C), 156.12 (C), 147.76 (C), 128.08 (CH), 80.57 (C), 42.68 (CH$_2$) and 28.67 (Me); *m*/*z* (EI) 259 (MH$^+$, 19%), 258 (M$^+$, 2), 203 (77), 185 (32), 167 (15), 159 (27), 141 (11), 57 (100), 41 (49) and 29 (24).

Coupling reactions

Methyl 2-[1-({2-[1-(benzyloxycarbonylamino)-2-methylpropyl]-thiazol-4-yl}carbonylamino)ethyl]-5-methyloxazole-4-carboxylate 13a

N-Methylmorpholine (22 μl, 0.20 mmol) and isobutyl chloroformate (26 μl, 0.20 mmol) were added sequentially to a stirred solution of the thiazole carboxylic acid **2a** (52 mg, 0.159 mmol) in dry THF (5 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C, a solution of the oxazole **1** (32 mg, 0.174 mmol) in dry THF (4 ml) was added, the reaction was stirred for 45 min and partitioned between ethyl acetate (30 ml) and water (30 ml). The aqueous layer was further extracted with ethyl acetate (20 ml) and the organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml), dried (Na$_2$SO$_4$), evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:1), to afford the *title compound* **13a** (55 mg, 69%) as a colourless oil (Found: M$^+$, 500.1728. C$_{24}$H$_{28}$N$_4$O$_6$S requires *M*, 500.1729); $[\alpha]_D^{19}$ +36.0° (*c* 1.05, CHCl$_3$); ν_{max}(CHCl$_3$)/cm^{-1} 3436, 3401, 3125, 3091, 3064, 3050, 2967, 2936, 2877, 1723, 1669, 1540, 1505, 1352 and 1100; δ_H(400 MHz; CDCl$_3$) 8.04 (1H, s, SCH), 7.71 (1H, d, *J* 8.5, exch. D$_2$O, CCONH), 7.36 (5H, m, PhH), 5.53 [1H, d, *J* 8.4, exch. D$_2$O, OC(O)NH], 5.45 (1H, dq, *J* 8.5, 7.1, NHC*H*Me), 5.14 (2H, s, PhCH$_2$), 4.94 (1H, dd, *J* 8.4, 5.5, CHC*H*NH), 3.89 (3H, s, OMe), 2.61 (3H, s, Me), 2.35 (1H, m, C*H*Me$_2$), 1.67 (3H, d, *J* 7.1, NHCH*Me*), 0.98 (3H, d, *J* 6.8, *Me*CHMe) and 0.93 (3H, d, *J* 6.9, MeCH*Me*); δ_C(100.6 MHz; CDCl$_3$) 172.02 (C), 162.59 (C), 162.31 (C), 160.27 (C), 156.67 (C), 156.06 (C), 149.41 (C), 136.15 (C), 128.59 (CH), 128.31 (CH), 128.19 (CH), 127.49 (C), 123.59 (CH), 67.31 (CH$_2$), 58.59 (CH), 51.95 (Me), 42.93 (CH), 33.46 (CH), 19.70 (Me), 19.36 (Me), 17.55 (Me) and 12.02 (Me); *m*/*z* (EI) 500 (M$^+$, 7%), 183 (26), 168 (15), 113 (12), 91 (100) and 51 (28).

Methyl 2-[1-({2-[1-(*tert*-butoxycarbonylamino)-2-methylpropyl]-thiazol-4-yl}carbonylamino)ethyl]-5-methyloxazole-4-carboxylate 13b

N-Methylmorpholine (34 μl, 0.31 mmol) and isobutyl chloroformate (40 μl, 0.31 mmol) were added sequentially to a stirred solution of the thiazole carboxylic acid **2b** (75 mg, 0.25 mmol) in dry THF (4 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C, a solution of the oxazole **1** (65 mg, 0.36 mmol) in dry THF (3 ml) was added, the reaction was stirred for 1 h and partitioned between ethyl acetate (30 ml) and water (30 ml). The aqueous layer was further extracted with ethyl acetate (20 ml) and the organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml), dried (Na$_2$SO$_4$), evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (1:2), to afford the *title compound* **13b** (84 mg, 71%) as a colourless oil (Found: MH$^+$, 467.1964. C$_{21}$H$_{30}$N$_4$O$_6$S + H requires 467.1964); $[\alpha]_D^{23}$ +37.7° (*c* 1.10, CHCl$_3$); ν_{max}(CHCl$_3$)/cm^{-1} 3444, 3400, 3124, 2977, 2935, 2876, 1718, 1670, 1623, 1589, 1540, 1494, 1443, 1392, 1369, 1353, 1165 and 1100; δ_H(400 MHz; CDCl$_3$) 8.04 (1H, s, SCH), 7.72 (1H, d,

J 8.5, CCONH), 5.46 (1H, dq, *J* 8.5, 7.1, NHC*H*Me), 5.20 (1H, d, *J* 8.5, exch. D_2O, OCON*H*), 4.87 (1H, m, NHC*H*CHMe$_2$), 3.91 (3H, s, MeO), 2.62 (3H, s, Me), 2.35 (1H, m, C*H*Me$_2$), 1.69 (3H, d, *J* 7.0, NHCH*Me*), 1.47 (9H, s, CMe$_3$), 1.00 (3H, d, *J* 6.7, *Me*CHMe) and 0.93 (3H, d, *J* 6.9, MeCH*Me*); δ_C(100.6 MHz; $CDCl_3$) 173.03 (C), 162.61 (C), 162.32 (C), 160.35 (C), 156.71 (C), 155.45 (C), 149.35 (C), 127.45 (C), 123.45 (CH), 80.27 (C), 58.05 (CH), 51.99 (Me), 42.83 (CH), 33.28 (CH), 28.34 (Me), 19.71 (Me), 19.40 (Me), 17.38 (Me) and 12.04 (Me); *m*/*z* (CI) 323 (8%), 209 (5), 183 (13), 168 (14), 139 (17), 112 (17), 57 (47) and 41 (100).

Methyl 2-(1-{[2-(1-amino-2-methylpropyl)thiazol-4-yl]carbonylamino}ethyl)-5-methyloxazole-4-carboxylate hydrochloride 14

Acetyl chloride (150 μl, 2.11 mmol) was added portionwise over 2.5 h to a stirred solution of the above amide **13b** (84 mg, 0.18 mmol) in dry methanol (2 ml) at room temperature. The reaction was stirred for 2 h and evaporated *in vacuo* to afford the amine hydrochloride **14** (72 mg, 100%) as a colourless foam (Found: [M − HCl]$^+$, 366.1361. $C_{16}H_{22}N_4O_4S$ requires [*M* − HCl]$^+$, 366.1362); $[\alpha]_D^{23}$ +13.1° (*c* 1.29, MeOH); ν_{max}($CHCl_3$)/cm^{-1} 3243, 3123, 2970, 2879, 2674, 1726, 1669, 1623, 1544, 1496, 1444, 1389, 1374, 1353, 1100, 1036, 1011 and 983; δ_H(400 MHz; CD_3OD) 8.82 (1H, s, exch. D_2O, CONH), 8.39 (1H, s, SCH), 5.36 (1H, q, *J* 7.1, NHC*H*Me), 4.72 (1H, d, *J* 6.4, NH_2C*H*CHMe$_2$), 3.89 (3H, s, OMe), 2.62 (3H, s, Me), 2.47 (1H, m, C*H*Me$_2$), 1.69 (3H, d, *J* 7.1, NHCH*Me*), 1.16 (3H, d, *J* 6.9, *Me*CHMe) and 1.05 (3H, d, *J* 6.7, MeCH*Me*); δ_C(100.6 MHz; CD_3OD) 163.03 (C), 160.98 (C), 160.23 (C), 158.89 (C), 154.87 (C), 146.59 (C), 124.68 (C), 124.18 (CH), 55.76 (CH), 49.43 (Me), 46.69 (Me), 41.47 (CH), 30.45 (CH), 15.83 (Me), 15.48 (Me) and 9.05 (Me); *m*/*z* (EI) 366 ([M − HCl]$^+$, 2.5%), 323 (54), 182 (23), 168 (100), 139 (47), 112 (24), 72 (87), 55 (42), 43 (58) and 31 (38).

2-[1-({2-[1-({2-[(*tert*-Butoxycarbonylamino)methyl]thiazol-4-yl}carbonylamino)-2-methylpropyl]thiazol-4-yl}carbonylamino)ethyl]-5-methyloxazole-4-carboxylic acid 16

N-Methylmorpholine (35 μl, 0.32 mmol) and isobutyl chloroformate (21 μl, 0.16 mmol) were added sequentially to a stirred solution of the thiazole carboxylic acid **3** (36 mg, 0.14 mmol) in dry THF (2.5 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C, a solution of the amine hydrochloride **14** (56 mg, 0.14 mmol) in dry THF (2 ml) was added, the reaction was stirred for 45 min and partitioned between ethyl acetate (20 ml) and water (15 ml). The aqueous layer was further extracted with ethyl acetate (20 ml) and the organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate (25 ml) and brine (25 ml), dried (Na_2SO_4), evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (2:1) to afford the ester **15** (60 mg, 72%) as a colourless solid, mp 84.5–86 °C; $[\alpha]_D^{21.5}$ +23.8° (*c* 1.15, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3456, 3399, 3124, 2968, 2935, 2875, 1720, 1670, 1622, 1603, 1538, 1493, 1443, 1392, 1369, 1353, 1166, 1101 and 909; δ_H(400 MHz; $CDCl_3$) 8.00 (1H, s, SCH), 7.98 (1H, s, SCH), 7.81 (1H, d, *J* 9.2, CON*H*CHCH), 7.71 (1H, d, *J* 8.5, CON*H*CHMe), 5.51 (1H, br s, exch. D_2O, OCONH), 5.38 (1H, dq, *J* 8.5, 7.2, NHC*H*Me), 5.25 (1H, dd, *J* 9.2, 6.2, NHC*H*CHMe$_2$), 4.56 (2H, d, *J* 4.9, NHCH_2), 3.83 (3H, s, OMe), 2.55 (3H, s, Me), 2.44 (1H, m, C*H*Me$_2$), 1.62 (3H, d, *J* 7.0, NHCH*Me*), 1.39 (9H, s, CMe$_3$), 0.96 (3H, d, *J* 6.7, *Me*CHMe) and 0.95 (3H, d, *J* 6.8, MeCH*Me*); δ_C(100.6 MHz; $CDCl_3$) 172.79 (C), 171.46 (C), 163.88 (C), 163.64 (C), 162.08 (C), 161.57 (C), 157.96 (C), 157.00 (C), 150.61 (C), 150.32 (C), 128.70 (C), 125.68 (CH), 124.95 (CH), 81.79 (C), 57.64 (CH), 53.27 (Me), 44.10 (CH), 43.66 (CH_2), 34.55 (CH), 29.59 (Me), 20.96 (Me), 20.89 (Me), 19.13 (Me) and 13.34 (Me); *m*/*z* (EI) 606 (M$^+$, 0.1%), 506 (3), 463 (3), 434 (3), 199 (4), 183 (10), 168 (10), 139 (15), 112 (18), 84 (11), 59 (84) and 41 (100).

A solution of lithium hydroxide monohydrate (40 mg, 0.95 mmol) in water (1.5 ml) was added to a solution of peptide **15** (54 mg, 88.5 μmol) in methanol (5 ml) portionwise over 30 h at room temperature. The reaction was stirred overnight, evaporated *in vacuo* and partitioned between water (30 ml) and ether (30 ml). The aqueous layer was separated, acidified to pH 5 with 10% aqueous citric acid, extracted with ethyl acetate (2 × 30 ml), acidified to pH 3 with 10% aqueous citric acid and further extracted with ethyl acetate (2 × 30 ml). The organic layers were combined, washed with brine (60 ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford the *title compound* **16** (49 mg, 93%) as a colourless solid, mp 118.5–120 °C (Found: M$^+$, 592.1807. $C_{25}H_{32}N_6O_7S_2$ requires *M*, 592.1774); $[\alpha]_D^{24}$ +20.3° (*c* 1.01, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3455, 3399, 3124, 2966, 2934, 1715, 1670, 1623, 1603, 1538, 1494, 1454, 1394, 1369, 1167, 1102 and 909; δ_H(400 MHz; $CDCl_3$, 20 °C) 8.12 (1H, s, SCH), 8.10 (1H, s, SCH), 7.94 (2H, m, exch. D_2O, 2 × CCONH), 6.83 (1H, br s, exch. D_2O, CO_2H), 6.63 (0.3H, br s, exch. D_2O, OCONH), 5.61 (0.7H, br s, exch. D_2O, OCONH), 5.47 (1H, m, NHC*H*Me), 5.33 (1H, dd, *J* 9.0, 6.3, NHC*H*-CHMe$_2$), 4.63 (2H, d, *J* 5.2, NHCH_2), 2.63 (3H, s, Me), 2.49 (1H, m, C*H*Me$_2$), 1.69 (3H, d, *J* 7.0, NHCHMe), 1.46 (9H, s, CMe$_3$), 1.03 (3H, d, *J* 6.3, *Me*CHMe) and 1.01 (3H, d, *J* 6.3, MeCH*Me*); δ_H(400 MHz; $CDCl_3$, 50 °C) 8.06 (1H, s, SCH), 8.04 (1H, s, SCH), 7.83 (1H, m, exch. D_2O, CCONH), 7.76 (1H, m, CCONH), 5.40 (1H, m, NHC*H*Me), 5.35 (1H, dd, *J* 9.2, 6.2, NHC*H*CHMe$_2$), 5.29 (1H, br s, exch. D_2O, OCONH), 4.61 (2H, d, *J* 6.0, NHCH_2), 2.62 (3H, s, Me), 2.47 (1H, m, C*H*Me$_2$), 1.67 (3H, d, *J* 7.0, NHCHMe), 1.49 (9H, s, CMe$_3$), 1.05 (3H, d, *J* 6.3, *Me*CHMe) and 1.04 (3H, d, *J* 6.3, MeCH*Me*); δ_C(100.6 MHz; $CDCl_3$) 171.84 (C), 170.64 (C), 165.09 (C), 162.82 (C), 161.32 (C), 160.89 (C), 157.64 (C), 156.20 (C), 149.59 (C), 149.31 (C), 127.73 (C), 125.01 (CH), 124.35 (CH), 80.99 (C), 56.83 (CH), 43.35 (CH), 42.76 (CH_2), 33.76 (CH), 28.70 (Me), 19.98 (Me), 19.94 (Me), 18.26 (Me) and 12.53 (Me); *m*/*z* (EI) 592 (M$^+$, 0.2%), 549 (2), 519 (3), 492 (11), 449 (13), 420 (9), 351 (4), 232 (9), 185 (40), 154 (32), 141 (37), 112 (48), 86 (57) and 84 (100).

(+)-Nostocyclamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (16 mg, 82 μmol) was added to a stirred solution of the carboxylic acid **16** (43 mg, 72 μmol) and pentafluorophenol (16 mg, 87 μmol) in dry dichloromethane (4 ml) at −10 °C. The mixture was warmed slowly to room temperature over 16 h, evaporated *in vacuo* and partitioned between ethyl acetate (20 ml) and brine (20 ml). The aqueous layer was further extracted with ethyl acetate (10 ml) and the organic extracts were combined, dried (Na_2SO_4) and evaporated *in vacuo* to afford crude pentafluorophenyl ester **17** (55 mg) which was used without further purification. A solution of hydrogen chloride in dioxane (4.0 M; 3 ml) was added to a stirred solution of the pentafluorophenyl ester **17** (29 mg, 39 μmol) in dry dioxane (1.5 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and warmed rapidly to room temperature. After stirring for 3.5 h, the mixture was evaporated *in vacuo* and dissolved in chloroform (100 ml). Aqueous potassium hydrogen carbonate (1 M; 100 ml) was added and the mixture was shaken vigorously for 5 min and then separated. The organic layer was dried (Na_2SO_4), evaporated *in vacuo* and purified by flash chromatography on silica, eluting with ethyl acetate–light petroleum (2:1), to afford (+)-nostocyclamide (14 mg, 74%) as a colourless solid, mp 251–252 °C. A small portion was recrystallised to afford colourless crystals, mp 259–260 °C (ethyl acetate–light petroleum) (lit.,[12] mp 255.8–256.9 °C) (Found: M$^+$, 474.1142. $C_{20}H_{22}N_6O_4S_2$ requires *M*, 474.1144); $[\alpha]_D^{19}$ +51.3° (*c* 0.84, $CHCl_3$) {lit.,[35] $[\alpha]_D^{20}$ +25° ($CHCl_3$)}; ν_{max}($CHCl_3$)/cm^{-1} 3397, 3125, 3006, 2966, 2932, 1667, 1642, 1543, 1521, 1497 and 1449; δ_H(400 MHz; $CDCl_3$) 8.56 (1H, d, *J* 5.0, N*H*CHMe), 8.48 (1H, d, *J* 9.0, N*H*CHCH), 8.43 (1H, m, N*H*CH$_2$), 8.11 (1H, s, CH$_2$CSC*H*),

8.08 (1H, s, CHCSC*H*), 5.57 [1H, dd, *J* 9.0, 3.7, NHC*H*-CH(Me)$_2$], 5.07 (1H, dq, *J* 5.0, 6.5, NHC*H*Me), 4.92 (1H, dd, *J* 17.5, 4.8, NHC*H*H), 4.71 (1H, dd, *J* 17.5, 2.9, NHCH*H*), 2.63 (3H, s, Me), 2.25 (1H, m, C*H*Me$_2$), 1.63 (3H, d, *J* 6.5, NHCH*Me*), 0.89 (3H, d, *J* 7.0, *Me*CHMe) and 0.87 (3H, d, *J* 7.0, MeCH*Me*); δ_H(400 MHz; CD_3OD) 8.34 (1H, s, CSCH), 8.32 (1H, s, CSCH), 5.70 (1H, d, *J* 3.6, NHC*H*CHMe$_2$), 5.18 (1H, q, *J* 6.7, NHC*H*Me), 5.05 (1H, d, *J* 17.8, NHC*H*H), 4.81 (1H, d, *J* 17.8, NHCH*H*), 2.68 (3H, s, Me), 2.36 (1H, m, C*H*Me$_2$), 1.69 (3H, d, *J* 6.7, NHCH*Me*), 0.98 (3H, d, *J* 6.9, *Me*CHMe) and 0.94 (3H, d, *J* 6.8, MeCH*Me*); δ_C(100.6 MHz; $CDCl_3$) 169.09 (C), 165.63 (C), 162.00 (C), 161.33 (C), 160.76 (C), 160.21 (C), 154.16 (C), 149.46 (C), 149.33 (C), 128.73 (C), 124.77 (CH), 124.10 (CH), 56.38 (CH), 45.54 (CH), 41.39 (CH_2), 36.82 (CH), 20.58 (Me), 19.00 (Me), 17.77 (Me) and 11.98 (Me); *m*/*z* (EI) 474 (M^+, 3%), 431 ([M − C_3H_7]$^+$, 13), 276 (26), 155 (40), 135 (44), 78 (71), 51 (55), 44 (72) and 31 (100).

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