Naturally Occurring Linear Fused Thiazoline-Thiazole Containing Metabolites: Total Synthesis of (−)-Didehydromirabazole A, a Cytotoxic Alkaloid from Blue–Green Algae

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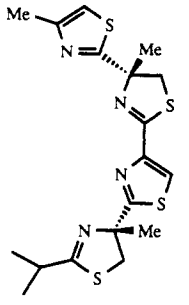
A concise total synthesis of the thiazoline-thiazole containing metabolite didehydromirabazole A **1** is described. The synthesis uses the unusual amino acid (*R*)-2-methylcysteine **20** in sequential cyclocondensations with imino ethers as key steps, *viz* **22** → **32** and **37** → **38**.

Didehydromirabazole A **1** is a member of a unique family of cytotoxic alkaloids, known as 'mirabazoles' and 'tantazoles', which have recently been isolated from the terrestrial blue–green alga *Scytonema mirabile*.[1,2] Other members include tantazole A **2**, mirabazole C **3** and tantazole I **4**, and they all show structures which are based on the linear fusion of four or five successive 2,4-disubstituted thiazoline/thiazole/oxazole rings terminating in a 2 isopropyl thiazoline.† The extensive studies of Moore *et al.* have shown the presence of three other classes of cytotoxins in *S. mirabile*, *viz* scytophycins,[3] mirabimides[4] and mirabilene isonitriles.[5] Several of these compounds, including the tantazoles and mirabazoles show pronounced solid tumour selective toxicity.



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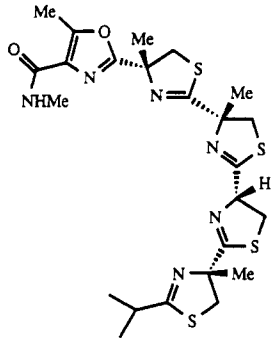

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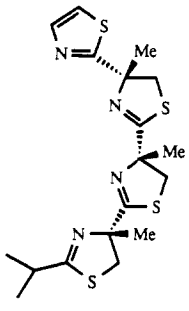

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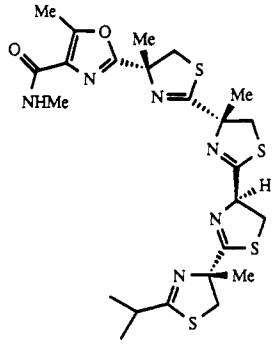

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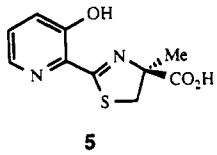
Although the presence of a 2-thiazoline ring in natural products is not uncommon, *e.g.* luciferin,[6] pyochelin,[7] anguibactin,[8] cyclothiazomycin,[9] bacitracin,[10] lissoclinamide,[11] althiomycin,[12] the mirabazoles and tantazoles represent the first family of natural products to have been isolated whose biosynthesis ostensibly uses 2-methylcysteine. To our knowledge, the only other natural products which accommodate a 2-methylcysteine unit are the siderophore desferrithiocin **5**,[13] and thiangazole **6**,[14] a novel inhibitor of HIV-1, which was reported in 1992 from *Polyangium* sp. The combination of unique structural and novel biological properties of the tantazoles and mirabazoles has enticed us to investigate synthetic routes to this class of compound. In this paper we describe a total synthesis of natural (−)-didehydromirabazole A **1** which uses a route easily adaptable to access other members of the mirabazole-tantazole, and thiangazole, families of natural products.[15]



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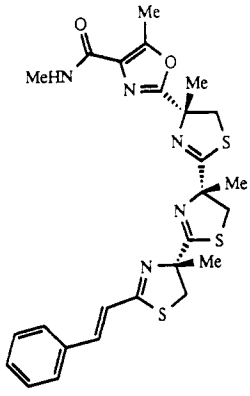

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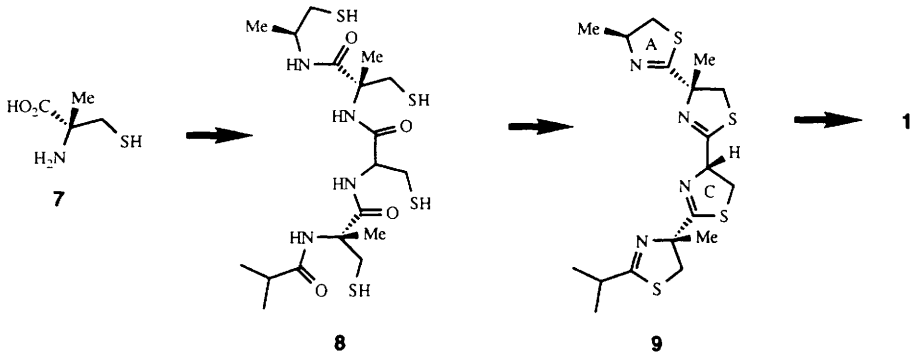
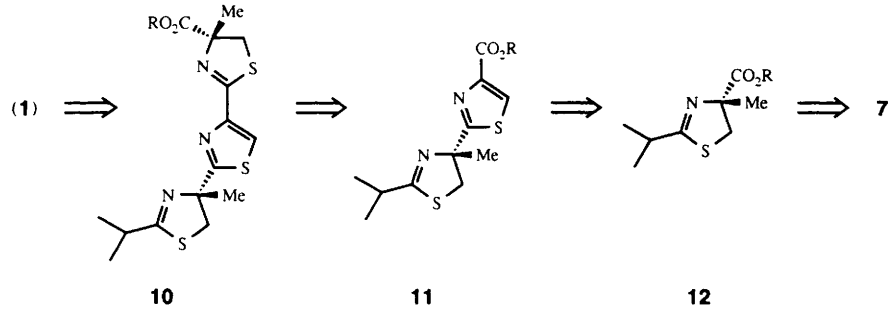
The linear thiazole-thiazoline ring system in didehydromirabazole A **1** is most likely derived in Nature from an appropriately substituted (*R*)-cysteine-(*R*)-2-methylcysteine tetrapeptide intermediate **8**, following successive cyclodehydrations to elaborate the tetracycle **9** and then enzymatic oxidations of the A and C 2-thiazoline rings in **9**[16] (Scheme 1). Indeed in contemporaneous studies, Walker and Heathcock[17] have used this 'biomimetic' strategy in a synthesis of (−)-mirabazole C **3**. We chose to approach a synthesis of (−)-didehydromirabazole A **1** in a linear fashion, by building the terminal thiazoline ring **12** first, then proceeding to the target *via* the thiazoline-thiazole **11** and the thiazoline-thiazole-thiazoline **10** intermediates (Scheme 2). It is clear from this design that we first needed a plentiful supply of (*R*)-2-methylcysteine **7**, and a concise synthesis of chiral 4-methyl-2-thiazolines.

2-Thiazolines can be prepared quite conveniently from cysteine esters following cyclocondensations with nitriles or with imino ethers, *e.g.* **13** → **14**.[18] They are also available from a variety of cyclisations involving thioamide precursors, *e.g.* **15** → **16**,[19] and from cyclocondensations between thioamides and α-bromoacrylic acids, *e.g.* **17** → **18**[20] (Scheme 3).

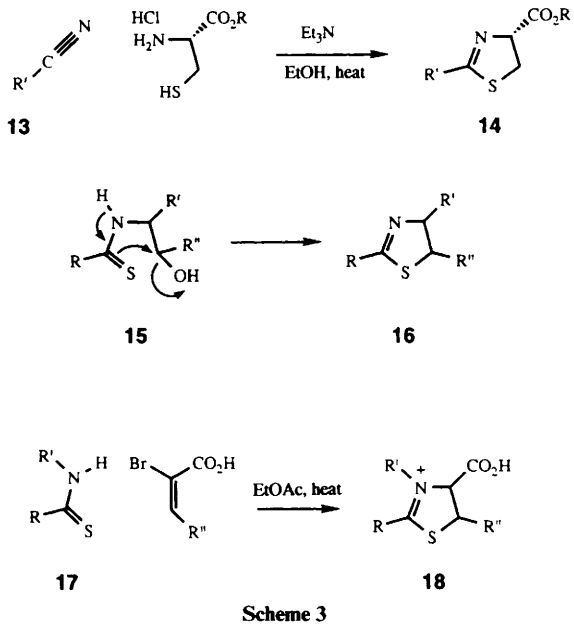
† The name thiazoline has been used, for convenience, throughout the Discussion section; in the Experimental section, however, for nomenclature purposes, the IUPAC-approved name dihydrothiazole has been used.



Scheme 1

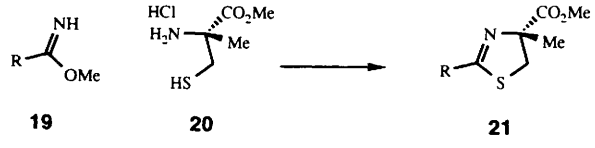


Scheme 2



Scheme 3

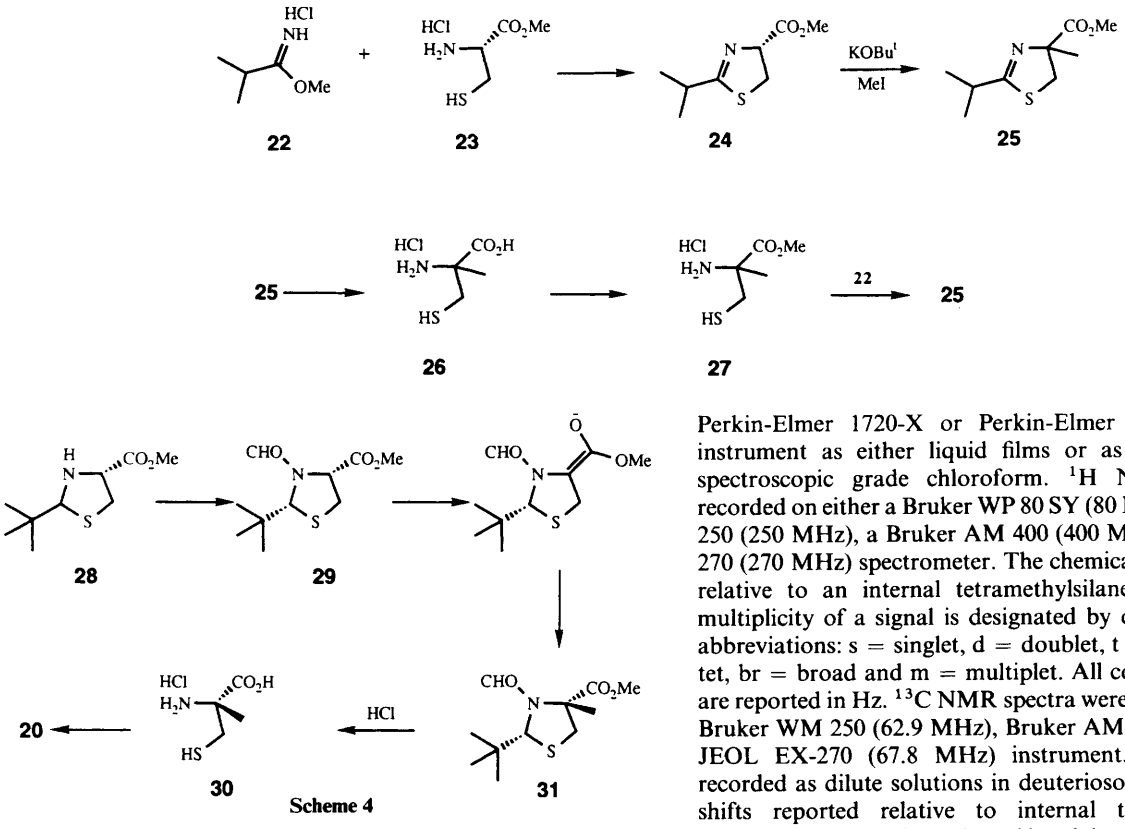
Following model studies, we decided that the most practical approach to the synthesis of the 2-thiazoline rings **21** in didehydromirabazole A **1** would be from cyclocondensations between methyl (*R*)-2-methylcysteine hydrochloride **20** and imino ether precursors **19**. Indeed we had used this overall



strategy to: (a) synthesise the 2-thiazoline **24** from the imino ether hydrochloride **22** and cysteine methyl ester hydrochloride **23**, and next used **24** to prepare the 4-methyl-2-thiazoline **25** following deprotonation and methylation.[21] Acid hydrolysis of **25** then led to a simple route to (±)-2-methylcysteine **26**[22] and (b) synthesise the (±)-4-methyl-2-thiazoline **25** from a condensation involving methyl (±)-2-methylcysteine HCl **27** and the imidate **22**. To pursue the synthesis of (−)-didehydromirabazole A **1** based on the model work, we now required a practical, large-scale synthesis of (*R*)-2-methylcysteine **7**.

Although Schöllkopf and co-workers[23] have applied their method based on metallation and alkylation of bis-lactim ethers derived from (*S*)-valine to synthesise *S*-benzyl- and *S*-butyl-(*S*)-2-methylcysteine methyl esters, this method is somewhat lengthy and not totally practical for large-scale preparations of optically pure 2-methylcysteine.[24] We succeeded in synthesising (*R*)-2-methylcysteine hydrochloride in large quantities and in excellent yield and enantiomeric purity by a modification of Seebach's 'self-regeneration of chirality' protocol[25] (Scheme 4). Thus, treatment of the *N*-formyl derivative **29** of the thiazolidine adduct **28** derived from (*R*)-cysteine methyl ester HCl and pivalaldehyde with lithium diisopropylamide in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (DMPU) at −90 °C, followed by reaction with iodomethane first produced the corresponding methylated thiazoline **31** containing the methyl and *tert*-butyl groups exclusively *anti* to each other. Hydrolysis of **31** in the presence of hydrochloric acid then afforded (*R*)-2-methylcysteine hydrochloride **30** which is best stored as the corresponding methyl ester **20**.[26]

With a practical synthesis of large quantities of methyl (*R*)-2-methylcysteine hydrochloride **20** we were now in a position to pursue our synthesis of (−)-didehydromirabazole A **1** (Scheme 5). Thus, cyclocondensation of **20** and the imino ether hydrochloride **22** derived from isobutyronitrile in the presence of triethylamine first led to the corresponding thiazoline **32** as a colourless oil in 58% yield. The application of chiral HPLC and chiral solvating agents in ^{1}H NMR studies showed that **32** was produced with an ee >95%. The thiazoline ester **32** was next converted into the corresponding thioamide **34** following treatment with aqueous ammonia (to **33**) and then Lawesson's



Scheme 4

reagent. When a solution of **34** in ethanol was heated overnight with ethyl α-bromopyruvate, the thiazoline–thiazole **35** was secured in 55% yield. The ester group in the bicycle **35** was next elaborated to the corresponding imino ether **37** *via* the amide **36** in readiness for conversion into the tricyclic ester **38**. A second cyclocondensation reaction using methyl (*R*)-2-methylcysteine hydrochloride **20** and the imino ether **37** then led to the linear fused tricyclic ester **38** as a single isomer in 34% yield. Interestingly, the same tricyclic ester **44** could be produced as a 1 : 1 mixture of diastereoisomers by a different route as outlined in Scheme 6. Thus, a cycloaddition between the thioamide **41** derived from **36**, and 2-bromoacrylic acid first led to the 2-thiazolinecarboxylic acid **42** which was then converted into **44** following esterification to **43**, deprotonation and methylation with methyl iodide.

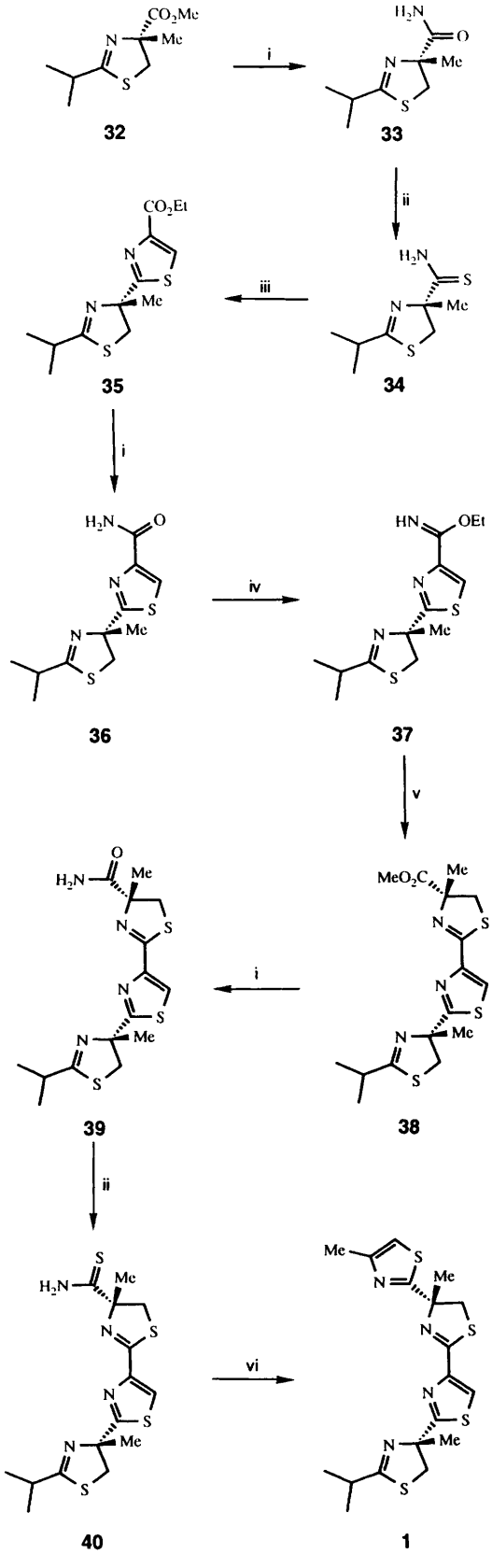
Finally, conversion of the homochiral tricyclic ester **38** into the corresponding thioamide **40**, followed by reaction with 2-chloroacetone in hot ethanol led to (−)-dihydromirabazole A **1** as a viscious oil in 62% yield. Likewise, the 1 : 1 mixture of diastereoisomers of **44** could be converted into a 1 : 1 mixture of dihydromirabazole A diastereoisomers, using identical chemistry. The synthetic (−)-didehydromirabazole A displayed ^{1}H NMR and ^{13}C NMR spectroscopic data which were superimposable on those of naturally derived material. The specific rotation of the synthetic material $[\alpha]_D$ −289 (*c* 1.78 $CHCl_3$) is at variance with that reported for the natural product $[\alpha]_D$ −26 (*c* 0.44 $CHCl_3$); this discrepancy may be due, in part, to the difference in concentrations of the measurements.

Experimental

General Details.—All m.p.s were determined on a Köfler hot-stage apparatus and are uncorrected. Optical rotations were measured on a JASCO DIPA-370 polarimeter; $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}; UV spectra were recorded on a Philips PU 8700 spectrophotometer as solutions in spectroscopic grade ethanol. IR spectra were obtained using a Perkin-Elmer 1720-X or Perkin-Elmer 1600 series FT-IR instrument as either liquid films or as dilute solutions in spectroscopic grade chloroform. ^{1}H NMR spectra were recorded on either a Bruker WP 80 SY (80 MHz), a Bruker WM 250 (250 MHz), a Bruker AM 400 (400 MHz) or a JEOL EX-270 (270 MHz) spectrometer. The chemical shifts are recorded relative to an internal tetramethylsilane standard and the multiplicity of a signal is designated by one of the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, br = broad and m = multiplet. All coupling constants, *J*, are reported in Hz. ^{13}C NMR spectra were recorded on either a Bruker WM 250 (62.9 MHz), Bruker AM 400 (100.6 MHz) or JEOL EX-270 (67.8 MHz) instrument. The spectra were recorded as dilute solutions in deuteriosolvents with chemical shifts reported relative to internal tetramethylsilane or chloroform standard on a broad band decoupled mode, and the multiplicities obtained using a DEPT sequence. The following symbolisms are used for the multiplicities in ^{13}C spectra: q = primary methyl, t = secondary methylene, d = tertiary methine and s = quaternary. Mass spectra were recorded on a AE1 MS-902 or a MM-701CF spectrometer using electron ionisation (EI) or fast atom bombardment (FAB) techniques.

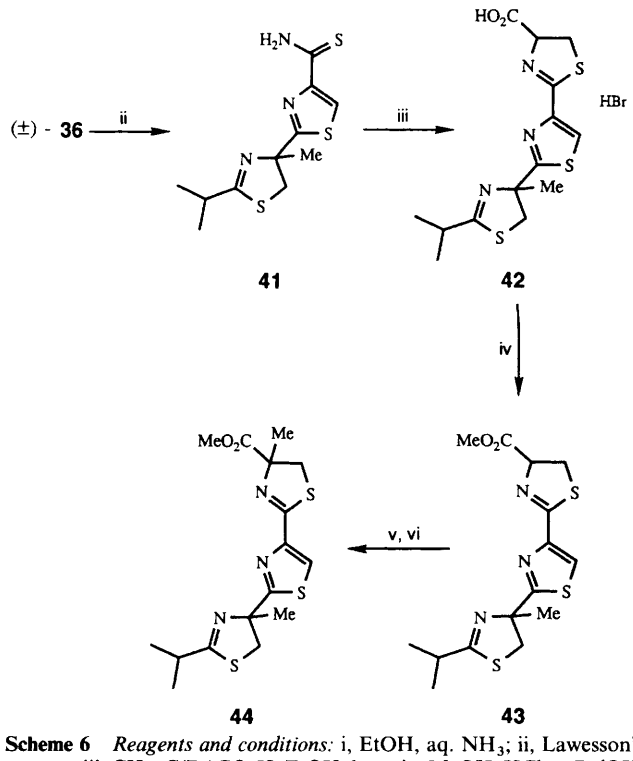
(±)-*Methyl 2-Isopropyl-4,5-dihydrothiazole-4-carboxylate* **24**.—Lawesson's reagent (12.77 g, 31.57 mmol) was added to a stirred solution of isobutyramide (5.00 g, 57.39 mmol) in THF (100 cm^3) under a nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 12 h, after which the solvent was evaporated under reduced pressure to leave a residue which was partitioned between aqueous $NaHCO_3$ (200 cm^3) and ether (100 cm^3). The separated aqueous layer was extracted with ether (3 × 100 cm^3) and the combined extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 20% ethyl acetate–light petroleum as eluent to give isobutyrothioamide (4.02 g, 68%) as a white solid, m.p. 39–40 °C; $\nu_{max}(CHCl_3)$/cm^{-1} 3490, 3375, 2937, 1604, 1382, 1305 and 946; δ_H(270 MHz; $CDCl_3$) 8.53 and 7.61 (2 H, 2 brd, NH_2), 2.92 [1 H, septet, *J* 6.9, C*H*(CH_3)$_2$] and 1.25 [6 H, d, *J* 6.9, CH(C*H*$_3$)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 216.24 (s, C=S), 42.52 [d, *C*H(CH_3)$_2$] and 22.09 [q, CH(*C*H$_3$)$_2$].

A solution of α-bromoacrylic acid (8.95 g, 59.3 mmol) and isobutyrothioamide **17** (R=Pr^i, R′=H) (4.08 g, 39.54 mmol) in ethyl acetate (60 cm^3) was heated under reflux for 4 h. The precipitated white hydrobromide was filtered off, washed with ethyl acetate and dried. Acetyl chloride (10 cm^3) was added dropwise to methanol (100 cm^3) over 10 min at 0–5 °C under a nitrogen atmosphere and the solution was stirred at room temperature for 1 h. The above hydrobromide was then added to it in one portion and the mixture stirred overnight. The solvent was evaporated under reduced pressure and the residue was then partitioned between aqueous $NaHCO_3$ (200 cm^3) and ether (100 cm^3). The aqueous layer was separated and extracted



Scheme 5 *Reagents and conditions:* i, EtOH, aq. NH_3; ii, Lawesson's reagent, THF, room temp.; iii, ethyl bromopyruvate, EtOH, heat; iv, $Et_3O^+PF_6^-$, CH_2Cl_2, heat; v, compd. **20**, CH_2Cl_2, room temp.; vi, $AcCH_2Cl$, EtOH, heat

with ether (3 × 100 cm^3) and the combined extracts were then dried, and evaporated under reduced pressure to leave an oil.



Scheme 6 *Reagents and conditions:* i, EtOH, aq. NH_3; ii, Lawesson's reagent; iii, CH_2=C(Br)CO_2H, EtOH, heat; iv, MeOH, HCl; v, Bu^{t}OK, THF, 78 °C; vi, MeI

This was purified by chromatography on silica gel using 10% ethyl acetate–light petroleum as eluent to given the title compound (4.65 g, 63%) as a colourless oil (Found: C, 51.0; H, 7.2; N, 7.5. $C_8H_{13}NO_2S$ requires C, 51.3; H, 7.0; N, 7.5); λ_{max}(EtOH)/nm 234 (2298) and 247 (2295); ν_{max}($CHBr_3$)/cm^{-1} 2967, 1737, 1614, 1464, 1436, 1233, 1206 and 1046; δ_H(250 MHz; $CDCl_3$) 5.05 [1 H, app. t, *J ca.* 9.5, C*H*(CO_2CH_3)], 3.80 (3 H, s, CO_2CH_3), 3.54–3.42 (2 H, m, CH_2), 2.94–2.83 [1 H, m, C*H*(CH_3)$_2$], 1.24 [3 H, *d*, *J* 7.0, CH(C*H*$_3$)$_2$] and 1.23 [3 H, d, *J* 7.0, CH(C*H*$_3$)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 180.86 (s, CO), 171.41 (s, SC=N), 77.59 [d, *C*H(CO_2CH_3)], 52.63 (q, CO_2*C*H$_3$), 34.76 (t, CH_2), 34.04 [d, *C*H(CH_3)$_2$] and 21.15 and 21.10 [2 × q, CH(*C*H$_3$)$_2$]; *m*/*z* (CI) 188 (MH^+, 100%) and 156 (10%).

(4R)-*Methyl 2-Isopropyl-4,5-dihydrothiazole-4-carboxylate* **24**.—Hydrogen chloride (65 g, 1.45 mol) was bubbled through a stirred solution of isobutyronitrile (100 g, 1.45 mol) in methanol (64.4 cm^3, 1.59 mol) and light petroleum (525 cm^3) at 0–5 °C for 3 h. The mixture was then stirred for a further 1 h to give a white crystalline precipitate. The mixture was stoppered and left at 0 °C for 2.5 days after which the product was filtered off and dried to give methyl isobutyrimidate hydrochloride (196 g, 98%), as a white solid, m.p. 104–106 °C; ν_{max}($CHCl_3$)/cm^{-1} 3158, 2825, 1652, 1109 and 898; δ_H(270 MHz; $CDCl_3$) 12.39 and 11.54 (2 H, 2 × br d, NH_2), 4.32 (3 H, s, OCH_3), 3.26 [1 H, septet, *J* 6.9, C*H*(CH_3)$_2$] and 1.31 [6 H, d, *J* 6.9, CH(C*H*$_3$)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 183.84 (s, C=NH), 60.84 (q, OCH_3), 33.14 [d, *C*H(CH_3)$_2$] and 18.99 [q, CH(*C*H$_3$)$_2$].

Triethylamine (3.35 cm^3, 24.0 mmol) was added dropwise over 5 min to a stirred solution of (*R*)-cysteine methyl ester hydrochloride (4.29 g, 25.0 mmol) and methyl isobutyrimidate hydrochloride (3.44 g, 25.0 mmol) in dichloromethane (25 cm^3). The mixture was stirred for 3 days at room temperature and then diluted with water (30 cm^3). The aqueous layer was separated and extracted with dichloromethane (3 × 30 cm^3) and the combined organic extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by

chromatography on silica gel using 10% ethyl acetate–light petroleum as eluent to give the title comound (3.71 g, 83%) as a colourless oil; $[\alpha]_D$ +101 (*c* 0.774 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 5.06 [1 H, app. t, *J ca.* 9.2, C*H*(CO_2CH_3)], 3.81 (3 H, s, CO_2CH_3), 3.57–3.45 (2 H, m, CH_2), 2.96–2.85 [1 H, m, C*H*(CH_3)$_2$] and 1.24 [6 H, d, *J* 6.9 CH(C*H*$_3$)$_2$]; δ_C(100.6 MHz; $CDCl_3$) 180.37 (s, CO), 170.65 (s, SC=N), 76.79 [d, *C*H(CO_2CH_3)], 51.92 (q, CO_2*C*H$_3$), 34.06 (t, CH_2), 33.32 [d, *C*H(CH_3)$_2$] and 20.46 and 20.40 [2 × q, CH(*C*H$_3$)$_2$].

(±)-*Methyl 2-Isopropyl-4-methyl-4,5-dihydrothiazole-4-carboxylate* **25**.—*Method* (*a*) A solution of potassium *tert*-butoxide (1.0 mol dm^{-3}) in THF (24.7 cm^3, 24.7 mmol) was added dropwise to a stirred solution of the ester **24** (4.40 g, 23.5 mmol) in THF (70 cm^3) at −78 °C under a nitrogen atmosphere. The solution was stirred at −78 °C for 0.5 h and then methyl iodide (1.75 cm^3, 28.2 mmol) was added dropwise to it over 5 min. The resulting solution was stirred for 1 h at −78 °C and then warmed to room temperature. The solvent was removed under reduced pressure to leave an oily residue which was partitioned between brine (100 cm^3) and ether (100 cm^3). The aqueous layer was separated and extracted with ether (3 × 100 cm^3), and the combined ether extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel, using 10% ethyl acetate–light petroleum as eluent to give the title compound (3.94 g, 83%) as a colourless oil (Found: C, 53.5; H, 7.3; N, 7.0. $C_9H_{15}NO_2S$ requires C, 53.7; H, 7.5; N, 7.0%); λ_{max}(EtOH)/nm 232 (2392) and 247 (2339); ν_{max}($CHBr_3$)/cm^{-1} 2968, 1729, 1613, 1463, 1454, 1435, 1235 and 1204; δ_H(250 MHz; $CDCl_3$) 3.79 (3 H, s, CO_2CH_3), 3.72 (1 H, d, *J* 11.3, C*H*H), 3.12 (1 H, d, *J* 11.3, CH*H*), 2.94–2.83 [1 H, m, C*H*(CH_3)$_2$]; 1.53 (3 H, s, CH_3), 1.24 [3 H, d, *J* 6.9, CH(C*H*$_3$)$_2$] and 1.22 [3 H, d, *J* 6.9, CH(C*H*$_3$)$_2$]; δ_C(100.6 MHz; $CDCl_3$) 173.70 and 178.07 (2 × s, CO and SC=N), 83.52 [s, *C*(CH_3)CO_2CH_3], 52.54 (q, CO_2*C*H$_3$), 40.90 (t, CH_2), 33.77 (d, CH), 23.66 (q, CH_3), 21.02 and 20.93 [2 × q, CH(*C*H$_3$)$_2$]; *m*/*z* (EI) 201 (M+, 4%), 142 (100), 100 (84) and 73 (100).

Method (*b*). Triethylamine (1.20 cm^3, 8.6 mmol) was added dropwise over 5 min to a stirred solution of methyl (±)-2-methylcysteine hydrochloride **27** (1.45 g, 7.8 mmol) and methyl isobutyrimidate hydrochloride (1.29 g, 9.4 mmol) in dichloromethane (25 cm^3). The mixture was stirred for 3 days at room temperature and then diluted with water (30 cm^3). The aqueous layer was separated and extracted with dichloromethane (3 × 30 cm^3) and the combined extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 10% ethyl acetate–light petroleum as eluent to give the title compound (918 mg, 58%) as a colourless oil, which showed spectroscopic properties identical with those described under method (a).

(4R)-*Methyl 2-Isopropyl-4-methyl-4,5-dihydrothiazole-4-carboxylate* **32**.—Triethylamine (3.22 cm^3, 23.1 mmol) was added dropwise over 5 min to a stirred solution of methyl (*R*)-2-methylcysteine hydrochloride (3.9 g, 21.0 mmol)[26] and methyl isobutyrimidate hydrochloride (3.46 g, 25.2 mmol) in dichloromethane (25 cm^3). The mixture was stirred for 3 days at room temperature and then diluted with water (30 cm^3). The aqueous layer was separated and extracted with dichloromethane (3 × 30 cm^3), and the combined organic extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 10% ethyl acetate–light petroleum as eluent to give the title compound (2.44 g, 58%) as a colourless oil; $[\alpha]_D$ −4.4 (*c*. 1.44 in $CHCl_3$); λ_{max}(EtOH)/nm 232 (119) and 247 (116); ν_{max}($CHBr_3$)/cm^{-1} 2968, 1729, 1613, 1463, 1454, 1435, 1235 and 1204; δ_H(250 MHz; $CDCl_3$) 3.79 (3 H, s, OCH_3), 3.72 (1 H, d, *J* 11.3, C*H*H), 3.12 (1 H, d, *J* 11.3 CH*H*), 2.93–2.82 (1 H, m, CH), 1.52 (3 H, s CH_3), 1.23 [3 H, d, *J* 6.9, CH(C*H*$_3$)$_2$] and 1.22 [3 H, d, *J* 7.0, CH(C*H*$_3$)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 178.07 and 173.70 (2 × s, CO and SC=N), 83.52 (s, *C*(CH_3)CO_2CH_3], 52.54 (q, OCH_3), 40.90 (t, CH_2), 33. 77 (d, CH), 23.66 (q, CH_3) and 21.02 and 20.93 [2 × q, CH(*C*H$_3$)$_2$]; *m*/*z* (EI) 201 (M$^+$, 4%), 142 (100) and 100 (84).

(4R)-2-*Isopropyl-4-methyl-4,5-dihydrothiazole-4-carboxamide* **33**.—Aqueous ammonia (40 cm^3) was added in one portion to a stirred solution of the ester **32** (4.28 g, 21.26 mmol) in ethanol (20 cm^3). The solution was stirred at room temperature overnight, after which the ethanol was evaporated under reduced pressure. Brine (50 cm^3) was added to the residue which was then extracted with ether (4 × 50 cm^3). The ether extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 40% ethyl acetate–light petroleum as eluent gave the *title compound* (3.46 g, 87%) which was recrystallised from ether–light petroleum; it had m.p. 53–54 °C; $[\alpha]_D$ −181.6 (*c* 0.75 in $CHCl_3$) (Found: C, 51.4; H, 7.8; N, 15.0. $C_8H_{14}N_2OS$ requires C, 51.6; H, 7.6; N, 15.0%; λ_{max}(EtOH)/nm 232 (2679) and 255 (2421); ν_{max}($CHCl_3$)/cm^{-1} 3510, 3389, 2934, 1685, 1620 and 1564; δ_H(250 MHz; $CDCl_3$) 6.73 and 6.00 (2 H, 2 × br d, NH_2), 3.64 (1 H, d, *J* 11.5, C*H*H), 3.19 (1 H, d, *J* 11.5, CH*H*), 2.78 (1 H, septet, *J* 6.9, CH), 1.49 (3 H, s, CH_3), 1.22 [6 H, d, *J* 6.9, CH(C*H*$_3$)$_2$]; δ_C(62.9 MHz; $CDCl_3$) 177.82 and 177.45 (2 × s, CO and SC=N), 83.80 [s, *C*(CO_2CH_3)CH_3], 40.54 (t, CH_2), 33.54 (d, CH), 24.43 (q, CH_3) and 20.77 and 20.59 [2 × q, CH(*C*H$_3$)$_2$]; *m*/*z* (CI) 205 (MNH_4^+, 90%) and 187 (MH^+, 100%).

(4R)-2-*Isopropyl-4-methyl-4,5-dihydrothiazole-4-thiocarboxamide* **34**.—Lawesson's reagent (3.91 g, 9.7 mmol) was added to a stirred solution of the amide **33** (3.27 g, 17.6 mmol) in THF (60 cm^3) under a nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 14 h, after which the solvent was evaporated under reduced pressure to leave a residue. This was partitioned between aqueous $NaHCO_3$ (100 cm^3) and ether (50 cm^3). The separated aqueous layer was extracted with ether (3 × 50 cm^3) and the combined extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 50% ethyl acetate–light petroleum as eluent to give the title compound (2.57 g, 72%) as a white solid which was recrystallised from ethyl acetate–light petroleum, m.p. 122 °C; $[\alpha]_D$ −276.2 (*c* 0.78 in $CHCl_3$) (Found: C, 47.2; H, 7.2; N, 14.0. $C_8H_{14}N_2S_2$ requires C, 47.5; H, 7.0; N, 13.8%); λ_{max}(EtOH)/nm 269 (10 349); ν_{max}($CHCl_3$)/cm^{-1} 3468, 3326, 2935, 1618 and 1572; δ_H(250 MHz; $CDCl_3$) 8.59 and 7.82 (2 H, 2 × br d, NH_2), 3.74 (1 H, d, *J* 11.7, C*H*H), 3.42 (1 H, d, *J* 11.7, CH*H*), 2.77 (1 H, septet, *J* 6.9, CH), 1.58 (3 H, s, CH_3) and 1.22 [6 H, d, *J* 6.9, CH(C*H*$_3$)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 212.43 (s, CS), 178.36 (s, SC=N), 89.04 [s, *C*(CO_2CH_3)CH_3], 43.41 (t, CH_2), 34.1 (d, CH), 27.35 (q, CH_3) and 21.17 and 20.97 [2 × q, CH(*C*H$_3$)$_2$]; *m*/*z* (EI) 202.0649 (*M*$^+$, $C_8H_{14}N_2S_2$ requires 202.0598).

(4R)-4-(4′-*Ethoxycarbonylthiazole-2′-yl*)-2-*isopropyl-4-methyl-4,5-dihydrothiazole* **35**.—Ethyl bromopyruvate (2.0 cm^3, 16.0 mmol) was added dropwise to a solution of the thioamide **34** (2.4 g, 11.9 mmol) in ethanol (40 cm^3) over 1 min, and the resulting solution was then heated under reflux overnight in a nitrogen atmosphere. The solvent was evaporated under reduced pressure to leave a residue which was then partitioned between aqueous $NaHCO_3$ and ether. The aqueous layer was separated and extracted with ether, and the combined extracts were dried, and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 10% ethyl acetate–light petroleum as eluent

to give the title compound (1.95 g, 55%) as a colourless oil; $[\alpha]_D$ −218.7 (*c* 2.03 in $CHCl_3$); λ_{max}(EtOH)/nm 237 (9790); ν_{max}($CHCl_3$)/cm^{-1} 2936, 1724, 1613, 1484, 1370 and 1101; δ_H(250 MHz; $CDCl_3$) 8.06 (1 H, s, SCH=), 4.42 (2 H, q, *J* 7.1, CH_2CH_3), 3.84 (1 H, d, *J* 11.4, CHH), 3.51 (1 H, d, *J* 11.4, CHH), 2.88 [1 H, septet, *J* 6.9, $CH(CH_3)_2$], 1.79 (3 H, s, CH_3), 1.40 (3 H, t, *J* 7.1, CH_2CH_3) and 1.27 [6 H, d, *J* 6.9, $CH(CH_3)_2$]; δ_C(67.8 MHz; $CDCl_3$) 179.62 (s) and 177.52 (s), 161.46 (s, CO), 147.19 (s), 127.31 (d), 83.40 (s), 61.30 (t, CH_2CH_3), 44.06 (t), 34.00 [d, $CH(CH_3)_2$], 27.82 (q, CH_3), 21.13 and 21.01 [2 × q, $CH(CH_3)_2$, 14.34 (q, CH_2CH_3); *m/z* 299.0883 (M^+, $C_{13}H_{18}N_2O_2S_2$ requires 299.0888).

(4R)-4-[(4′-*Aminocarboxythiazole*-2′-*yl*]-2-*isopropyl*-4-*methyl*-4,5-*dihydrothiazole* **36**.— Aqueous ammonia (30 cm^3) was added in one portion to a stirred solution of the ester **35** (1.80 g, 6.03 mmol) in ethanol (20 cm^3). The solution was stirred at room temperature overnight, after which the ethanol was evaporated under reduced pressure. Brine (50 cm^3) was added to the residue which was then extracted with ether (4 × 50 cm^3). The ether extracts were dried and evaporated under reduced pressure to leave a solid. This was purified by chromatography on silica gel using 50% ethyl acetate–light petroleum as eluent to give the amide (1.22 g, 75%) which recrystallised from ether–light petroleum, m.p. 97–98 °C; $[\alpha]_D$ −228 (*c* 1.07 in $CHCl_3$) (Found: C, 49.0; H, 5.7; N, 15.4. $C_{11}H_{15}N_3OS_2$ requires C, 49.0; H, 5.6; N, 15.6%); λ_{max}(EtOH)/nm 232 (10 349) and 293 (858); ν_{max}($CHCl_3$)/cm^{-1} 3520, 3400, 2933, 1682, 1614, 1574, 1366 and 908; δ_H(270 MHz; $CDCl_3$) 8.05 (1 H, s, SCH=), 7.16 and 6.03 (2 H, 2 × br d, NH_2), 3.76 (1 H, d, *J* 11.5, CHH), 3.44 (1 H, d, *J* 11.5, CHH), 2.88 [1 H, septet, *J* 6.9, $CH(CH_3)_2$], 1.76 (3 H, s, CH_3) and 1.28 [6 H, d, *J* 6.9, $CH(CH_3)_2$]; δ_C(67.8 MHz; $CDCl_3$) 179.51 (s) and 176.82 (s), 163.20 (s, CO), 149.32 (s), 124.20 (d), 83.25 (s), 44.13 (t), 34.05 [d, $CH(CH_3)_2$], 27.89 (q, CH_3), 21.17 and 21.04 [2 × q, $CH(CH_3)_2$]; *m/z* (CI) 270 (MH^+, 100%) and 252 (34).

(±)-(4′-*Aminothiocarbonylthiazol*-2′-*yl*)-2-*isopropyl*-4-*methyl*-4,5-*dihydrothiazole* **41**.—Treatment of the ester **35** with aqueous ethanolic ammonia, using the procedure described for the corresponding chiral ester derivative, gave (±)-4-(4′-aminocarbonylthiazol-2′-yl) 2-isopropyl-4-methyl-4,5-dihydrothiazole (840 mg, 77%), m.p. 110–111 °C; which showed spectroscopic data identical with those of **36** (Found: C, 49.1; H, 5.7; N, 15.6. $C_{11}H_{15}N_3OS_2$ requires C, 49.0; H, 5.6; N, 15.6%). Lawesson's reagent (1.94 g, 4.9 mmol) was added to a stirred solution of the amide (2.40 g, 8.91 mmol) in THF (40 cm^3) under a nitrogen atmosphere. The resulting solution was stirred at ambient temp. for 16 h, after which the solvent was evaporated under reduced pressure to leave a residue which was partitioned between aqueous $NaHCO_3$ (100 cm^3) and ether (50 cm^3). The aqueous layer was separated and extracted with ether (3 × 50 cm^3), and the combined ether extracts were dried and evaporated under reduced pressure to leave a yellow oil. This was purified by chromatography on silica gel to give the thioamide (2.18 g, 86%) as a viscous oil (Found: C, 46.2; H, 5.2; N, 14.5. $C_{11}H_{15}N_3S_3$ requires C, 46.3; H, 5.3; N, 14.7%); λ_{max}(EtOH)/nm 255 (14 620) and 315 (7803); ν_{max}($CHBr_3$)/cm^{-1} 3473, 3345, 2970, 1610, 1581 and 1378; δ_H(250 MHz; $CDCl_3$) 8.62 and 7.62 (2 H, 2 × br d, NH_2), 8.35 (1 H, s, SCH=), 3.74 (1 H, d, *J* 11.3, CHH), 3.43 (1 H, d, *J* 11.3, CHH), 2.88 [1 H, septet, *J* 6.8, $CH(CH_3)_2$], 1.75 (3 H, s, CH_3) and 1.28 [6 H, d, *J* 6.8, $CH(CH_3)_2$]; δ_C(67.8 MHz; $CDCl_3$) 190.7 (s, C=S), 179.8 (s) and 176.6 (s), 153.0 (s), 127.6 (d, SCH=), 83.2 (s), 44.1 (t, CH_2), 34.1 [d, $CH(CH_3)_2$], 27.8 (q, CH_3) and 21.2 and 21.0 [2 × q, $CH(CH_3)_2$]; *m/z* (CI) 286 (MH^+, 85%) and 252 (100).

4-[(4′-(4″-*Methoxycarbonyl*)4,5-*dihydrothiazol*-2″-*yl*)*thiazol*-2′-*yl*]-4-*methyl*-2-*isopropyl*-4,5-*dihydrothiazole* **43**.—A solution of α-bromoacrylic acid (1.67 g, 11.0 mmol) and the thioamide **41** (2.10 g, 7.36 mmol) in ethyl acetate (30 cm^3) was heated under reflux overnight to give a brown precipitate, of the corresponding hydrobromide salt. This was filtered off, washed with ethyl acetate and dried. Acetyl chloride (2 cm^3) was added dropwise to methanol (20 cm^3) over 10 min at 0–5 °C under a nitrogen atmosphere. The solution was stirred at room temperature for 1 h and then the crude hydrobromide salt was added in one portion. The mixture was stirred overnight after which the solvent was evaporated under reduced pressure and the residue partitioned between aqueous $NaHCO_3$ (50) and ether (50 cm^3). The aqueous layer was separated and extracted with ether (3 × 50 cm^3), and the combined extracts were dried and evaporated under reduced pressure to leave an oil This was purified by chromatography on silica gel using 10% ethyl acetate–light petroleum as eluent to give the title compound (882 mg, 32%) as a viscous oil (1 : 1 mixture of diastereoisomers) (Found: C, 48.6; H, 5.2; N, 11.4. $C_{15}H_{19}N_3O_2S_3$ requires C, 48.8; H, 5.2; N, 11.4%); λ_{max}(EtOH)/nm 212 (19 359) and 252 (13 726; ν_{max}($CHBr_3$)/cm^{-1} 2969, 1734, 1608, 1435, 1233, 1205 and 1024; δ_H(250 MHz; $CDCl_3$) 7.91 (1 H, s, SCH=), 5.29 (1 H, t, *J* 9.3, $CHCO_2CH_3$), 3.84 (1 H, d, *J* 11.2, CHH), 3.82 (3 H, s, CO_2CH_3), 3.72–3.56 (2 H, m, CH_2), 3.47 (3.46) (1 H, d, *J* 11.2, CHH), 2.87 [1 H, septet, *J* 6.9 $CH(CH_3)^2$], 1.77 (1.76) (3 H, s, CH_3) and 1.27 [6 H, d, *J* 6.9, $CH(CH_3)_2$]; δ_C(62.9 MHz; $CDCl_3$) 179.64 (s), 177.07 (s), 171.22 (s), 166.11 (s), 148.47 (s), 121.47 (121.41) (d, SCH:), 83.32 (s), 78.31 (d), 52.73 (q, OCH_3), 44.11 (44.02) (t), 34.94 (t), 33.98 [d, $CH(CH_3)_2$], 27.97 (27.84 [q, $C(CH_3)$] and 21.10 and 20.98 [2 × q, $CH(CH_3)_2$]; *m/z* (CI) 370 (MH^+, 100%).

2-*Isopropyl*-4-[4′-(4″-*methoxycarbonyl*-4″-*methyl*-4″,5″-*dihydrothiazol*-2″-*yl*)*thiazol*-2′-*yl*]-4-*methyl*-4,5-*dihydrothiazole* **44**.—A solution of potassium *tert*-butoxide (1.0 mol dm^{-3}) in THF (2.06 cm^3, 2.06 mmol) was added dropwise to a stirred solution of the dihydrothiazole **43** (725 mg, 1.96 mmol) in THF (10 cm^3) at −78 °C under a nitrogen atmosphere. The deep red solution was stirred at −78 °C for 0.5 h after which iodomethane (146 mm^3, 2.35 mmol) was added dropwise to it over 5 min. The resulting solution was stirred for 1 h at −78 °C and then warmed to room temperature. The solvent was removed under reduced pressure to leave an oily residue which was partitioned between brine (30 cm^3) and ether (30 cm^3). The aqueous layer was separated and extracted with ether (3 × 20 cm^3), and the combined ether extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 20% ethyl acetate–light petroleum as eluent to give the title compound (410 mg, 54%) as a colourless oil (1 : 1 mixture of diastereoisomers); λ_{max}(EtOH)/nm 211 (19 769) and 252 (14 039); ν_{max}(film)/cm^{-1} 2971, 2931, 1737, 1609, 1436 and 1173; δ_H(270 MHz; $CDCl_3$) 7.93 (1 H, s, SCH=), 3.86 (1 H, d, *J* 11.5, CHH), 3.86–3.81 (1 H, m, CHH), 3.81 (3 H, s, OCH_3), 3.47 (1 H, d, *J* 11.2, CHH), 3.26 (1 H, d, *J* 11.5, CHH), 2.86 [1 H, septet, *J* 6.9, $CH(CH_3)_2$], 1.77 (3 H, s, CH_3), 1.66 (1.65) (3 H, s, CH_3), 1.27 [6 H, d, *J* 6.9, $CH(CH_3)_2$]; δ_C(67.8 MHz; $CDCl_3$) 179.49 (179.44) (s), 176.76 (s), 173.71 (s), 163.39 (s), 148.66 (s), 121.17 (121.13) (d), 84.53 and 83.36 (2 × s), 52.87 (q, OCH_3), 44.15 (44.10) and 41.28 (2 × t), 34.00 [d, $CH(CH_3)_2$], 28.01 (27.94) and 24.04 (23.99) [2 × q, 2x $C(CH_3)$] and 21.15 and 21.02 [2 × q, $CH(CH_3)_2$]; *m/z* (EI) 383 (M^+, 15%), 368 (20), 326 (18), 325 (20), 324 (100) and 255 (55).

(4R)-2-*Isopropyl*-4-{4′-[(4″R)-4″-*methoxycarbonyl*-4″-*methyl*-4″,5″-*dihydrothiazol*-2″-*yl*]*thiazol*-2′-*yl*}-4-*methyl*-4,5-*dihydrothiazole* **38**.—Triethyloxonium hexafluorophosphate

(1.30 g, 4.68 mmol) was added in one portion to a stirred solution of the amide **36** (900 mg, 3.34 mmol) in dichloromethane (25 cm^3) under an atmosphere of nitrogen. The resulting solution was heated under reflux for 48 h and then washed with aqueous $NaHCO_3$ (30 cm^3). The aqueous layer was separated and extracted with dichloromethane (3 × 30 cm^3) and the combined organic extracts were dried and evaporated under reduced pressure to leave the crude imino ether **37** as a brown oil. Methyl (*R*)-2-methylcysteine hydrochloride (1.24 g, 6.68 mmol) was added to the crude imino ether in dichloromethane (18 cm^3) and the resulting suspension was stirred for 72 h at ambient temperature. It was then diluted with water (20 cm^3) and the aqueous layer separated and extracted with dichloromethane (3 × 30 cm^3). The combined extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 20% ethyl acetate–light petroleum as eluent to give the tricycle (439 mg, 34%) as a colourless oil; $[\alpha]_D$ −192 (*c* 1.12 in $CHCl_3$); λ_{max}(EtOH)/nm 211 (21 669) and 252 (15 255); ν_{max}($CHCl_3$)/cm^{-1} 2971, 2930, 1738, 1614, 1436, 1286, 1234, 1173, 1118 and 1016; δ_H(270 MHz; $CDCl_3$) 7.92 (1 H, s, SCH=), 3.86 (1 H, d, *J* 11.5, C*H*H), 3.83 (1 H, d, *J* 11.2, CH*H*) 3.81 (3 H, s, OCH_3), 3.46 (1 H, d, *J* 11.2, C*H*H), 3.26 (1 H, d, *J* 11.5, C*H*H), 2.87 [1H, septet, *J* 6.9, C*H*(CH_3)$_2$], 1.78 (3 H, s, CH_3), 1.66 (3 H, s, CH_3), 1.27 [6 H, d, *J* 6.9, CH(CH_3)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 179.6 (s), 176.8 (s), 173.8 (s), 163.4 (s), 148.7 (s), 121.1 (d), 84.6 and 83.4 (2 × s), 52.9 (q, OCH_3), 44.2 and 41.3 (2 × t), 34.0 (d, *C*H[CH_3)$_2$], 28.0 and 24.1 [2 × q, 2 × C(*C*H_3)], 21.2 and 21.0 [2 × q, CH(*C*H_3)$_2$]; *m*/*z* (EI) 383.0783 (M^+, $C_{16}H_{21}N_3O_2S_3$ requires 383.0796).

(4R)-4-{4′-[(4″R)-4″-*Aminocarbonyl*-4″-*methyl*-4″,5″-*dihydrothiazol*-2″-*yl*]*thiazol*-2′-*yl*}-2-*isopropyl*-4-*methyl*-4,5-*dihydrothiazole* **39**.—Aqueous ammonia (5 cm^3) was added in one portion to a stirred solution of the tricyclic ester **38** (400 mg, 1.04 mmol) in ethanol (5 cm^3). The solution was stirred at room temperature overnight after which the ethanol was evaporated under reduced pressure. Brine (15 cm^3) was added to the residue which was then extracted with ether (4 × 20 cm^3). The extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 50% ethyl acetate–light petroleum as eluent to give the corresponding amide (189 mg, 0.51 mmol) as a gummy solid; $[\alpha]_D$ −303 (*c* 0.89 in $CHCl_3$); λ_{max}(EtOH)/nm 210 (18 882) and 253 (14 808); ν_{max}($CHCl_3$)/cm^{-1} 3510, 3389, 2933, 1688, 1610, 1565, 1464, 1368, 1134 and 994; δ_H(270 MHz; $CDCl_3$) 7.87 (1 H, s, SCH=), 6.83 and 6.22 (2 H, 2 × br d, NH_2), 3.82 (1 H, d, *J* 11.6, C*H*H), 3.79 (1 H, d, *J* 11.2, CH*H*), 3.47 (1 H, d, *J* 11.2, C*H*H), 3.32 (1 H, d, *J* 11.6, CH*H*), 2.87 [1 H, septet, *J* 6.9, C*H*(CH_3)$_2$], 1.77 (3 H, s, CH_3), 1.63 (3 H, s, CH_3) and 1.27 [6 H, d, *J* 6.9, CH(CH_3)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 179.59 (s), 177.46 (s), 177.03 (s), 163.59 (s), 148.70 (s), 121.01 (d), 84.88 and 83.27 (2 × s), 44.06 and 40.94 (2 × t), 33.95 [d, *C*H(CH_3)$_2$], 27.84 and 24.89 [2 × q, 2 × C(*C*H_3)], 21.08 and 20.97 [2 × q, CH(*C*H_3)$_2$]; *m*/*z* (FAB) 369 (MH^+, 100%), 324 (32), 300 (27) and 255 (31).

Treatment of the (4*RS*,4″*RS*)-tricyclic ester **38** with aqueous ethanolic ammonia using the procedure described for the chiral ester derivative gave the corresponding tricyclic amide (81 mg, 73%) as an oil (1:1 mixture of diastereoisomers); λ_{max}(EtOH)/nm 211 (18 365) and 252 (14 446); ν_{max}($CHCl_3$)/cm^{-1} 3510, 3390, 2933, 1686, 1610 and 1595; δ_H(270 MHz; $CDCl_3$) 7.87 (1 H, s, SCH=), 6.82 and 6.18 (2 H, 2 × br d, NH_2), 3.83 (3.82) (1 H, d, *J* 11.2, C*H*H), 3.79 (1 H, d, *J* 11.6, CH*H*), 3.47 (1 H, d, *J* 11.2, CH*H*), 3.32 (1 H, d, *J* 11.6, C*H*H), 2.87 [1 H, septet, *J* 6.9, C*H*(CH_3)$_2$], 1.78 (3 H, s, CH_3), 1.63 (1.62) (3 H, s, CH_3) and 1.27 [6 H, d, *J* 6.9, CH(CH_3)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 179.60 (179.55) (s), 177.45 (s), 177.09 (177.05) (s), 163.59 (s), 148.68 (s), 121.10 (121.02) (d), 84.89 and 83.27 (2 × s), 44.06 (43.97) and 40.94 (2 × t), 33.95 [d, *C*H(CH_3)$_2$], 27.96 (27.85) and 24.89 (24.85) [2 × q, 2 × C(*C*H_3)] and 21.08 and 20.97 [2 × q, CH(*C*H_3)$_2$]; *m*/*z* (FAB) 369 (MH^+, 91%), 324 (24), 300 (43) and 255 (56).

(4R)-4-{4′-[(4″R)-4″-*Aminothiocarbonyl*-4″-*methyl*-4″,5″-*dihydrothiazol*-2″-*yl*]*thiazol*-2′-*yl*}-2-*isopropyl*-4-*methyl*-4,5-*dihydrothiazole* **40**.—Lawesson's reagent (91 mg, 0.22 mmol) was added to a stirred solution of the tricyclic amide **39** (150 mg, 0.41 mmol) in THF (2 cm^3) under a nitrogen atmosphere. The resulting solution was stirred at ambient temperature for 14 h after which the solvent was evaporated under reduced pressure to leave a residue which was partitioned between aqueous $NaHCO_3$ (10 cm^3) and ether (10 cm^3). The aqueous layer was separated and extracted with ether (3 × 10 cm^3) and the combined extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 20% ethyl acetate–light petroleum as eluent to give the thioamide (143 mg, 91%) as a viscous oil; $[\alpha]_D$ −351 (*c* 0.70 in $CHCl_3$); λ_{max}(EtOH)/nm 208 (21 829) and 262 (21 621); ν_{max}($CHCl_3$)/cm^{-1} 3467, 3332, 1610, 1572, 1366, 1119, 994 and 899; δ_H(270 MHz; $CDCl_3$) 8.66 and 7.76 (2 H, 2 × br d, NH_2), 7.90 (1 H, s, SCH=), 3.93 (1 H, d, *J* 11.9, C*H*H), 3.82 (1 H, d, *J* 11.2, CH*H*), 3.55 (1 H, d, *J* 11.9, CH*H*), 3.47 (1 H, d, *J* 11.6, C*H*H), 2.89 [1 H, septet, *J* 6.9, C*H*(CH_3)$_2$], 1.78 (3 H, s, CH_3), 1.73 (3 H, s, CH_3) and 1.27 [6 H, d, *J* 6.9, CH(C*H*$_3$)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 212.18 (s, C=S), 179.85 and 177.21 (2 × s), 163.70 (s), 148.68 (s), 121.33 (d), 89.86 and 83.32 (2 × s), 44.13 and 43.54 (2 × t), 34.03 [d, *C*H(CH_3)$_2$], 27.91 and 27.57 [2 × q, 2 × C(*C*H_3)] and 21.17 and 21.04 [2 × q, CH(*C*H_3)$_2$]; *m*/*z* (FAB) 385 (MH^+, 100%), 324 (49), 270 (39), 255 (33) and 223 (37).

Treatment of the (4*RS*,4″*RS*)-amide **39** with Lawesson's reagent, using the same procedure described for the chiral amide derivative gave the corresponding tricyclic thioamide (57 mg, 67%) as a viscous oil (1:1 mixture of diastereoisomers); λ_{max}(EtOH)/nm 210 (21 402) and 263 (21 967); ν_{max}($CHCl_3$)/cm^{-1} 3468, 3330, 1610, 1572, 1366, 1118 and 900 cm^{-1}; δ_H(270 MHz; $CDCl_3$) 8.68 and 8.06 (2 H, 2 × br d, NH_2) 7.87 (1 H, s, SCH=), 3.91 (1 H, d, *J* 11.6, C*H*H), 3.82 (3.81) (1 H, d, *J* 11.2, C*H*H), 3.55 (1 H, d, *J* 11.6, CH*H*), 3.47 (1 H, d, *J* 11.2, CH*H*), 2.87 [1 H, septet, *J* 6.9, C*H*(CH_3)$_2$], 1.77 (3 H, s, CH_3), 1.72 (3 H, s, CH_3), 1.27 [6 H, d, *J* 6.9, CH(C*H*$_3$)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 212.00 (s, C=S), 179.69 (179.66) and 177.21 (177.18) (2 × s), 163.54 (s), 148.62 (s), 121.33 (121.29) (d), 89.91 and 83.29 (83.25) (2 × s), 44.06 (43.97) and 43.49 (2 × t), 33.96 [d, *C*H(CH_3)$_2$], 27.98 (27.84) and 27.50 [2 × q, 2 × C(*C*H_3)] and 21.10 and 20.97 [2 × q, CH(*C*H_3)$_2$]; *m*/*z* (FAB) 385 (MH^+, 22%), 324 (18) and 270 (13).

(−)-*Didehydromirabazole A* **1**.—Chloroacetone (124 mm^3, 1.56 mmol) was added in one portion to a solution of the (−)-thioamide **40** (120 mg, 0.31 mmol) in ethanol (2.5 cm^3), and the resulting solution was then heated under reflux overnight in a nitrogen atmosphere. The solvent was evaporated under reduced pressure to leave a residue which was then partitioned between aqueous $NaHCO_3$ (10 cm^3) and ether (10 cm^3). The aqueous layer was separated and extracted with ether (2 × 10 cm^3) and the combined extracts were dried and evaporated under reduced pressure to leave an oil. This was purified by chromatography on silica gel using 10% ethyl acetate–light petroleum as eluent to give the mirabazole (81 mg, 62%) as a viscous oil; $[\alpha]_D$ −289 (*c* 1.78 in $CHCl_3$); λ_{max}(EtOH)/nm 212 (21 830) and 253 (17 213); ν_{max}($CHCl_3$) 2929, 1607 and 1162 cm^{-1}; δ_H(400 MHz; $CDCl_3$) 7.98 (1 H, s, =CH), 6.76 (1 H, s, =CH), 3.89 (1 H, d, *J* 11.3, C*H*H), 3.83 (1 H, d, *J* 11.3, C*H*H), 3.58 (1 H, d, *J* 11.3, CH*H*), 3.46 (1 H, d, *J* 11.3 Hz, CH*H*), 2.87

[1 H, septet, J 6.9, C*H*(CH_3)$_2$], 2.45 (3 H, s, CH_3), 1.86 (3 H, s, CH_3), 1.79 (3 H, s, CH_3), 1.27 [6 H, d, J 6.9, CH(C*H*$_3$)$_2$]; δ_C(100.6 MHz; $CDCl_3$) 179.60 (s), 176.91 (s), 175.50 (s), 163.95 (s), 152.81 (s), 149.03 (s), 120.99 (d), 113.35 (d), 84.14 (s), 83.52 (s), 44.31 (t), 4.24 (t), 34.14 [d, *C*H(CH_3)$_2$], 28.10 (q, CH_3), 27.92 (q, 4-CH_3), 21.24 and 21.13 [2 × q, CH(*C*H$_3$)$_2$] and 17.35 (q, CH_3); m/z (EI) 422.0726 (M^+, $C_{18}H_{22}N_4S_4$ requires 422.0727).

Treatment of the (4*RS*,4″*RS*)-thioamide **40** with chloroacetone, using the procedure described for the chiral thioamide derivative, gave (4*RS*,4″*RS*)-didehydromirabazole A (36 mg, 58%) as a viscous oil (1:1 mixture of diastereoisomers); λ_{max}(EtOH)/nm 212 (23 611) and 253 (18 578); ν_{max}($CHCl_3$)/cm^{-1} 2900, 1608, 1465, 1309, 1138 and 995; δ_H(400 MHz; $CDCl_3$) 7.98 (1 H, s, =CH), 6.76 (1 H, s, =CH), 3.88 (1 H, d, J 11.3, C*H*H), 3.85 (3.83) (1 H, d, J 11.6, C*H*H), 3.58 (1 H, d, J 11.3, CH*H*), 3.47 (3.46) (1 H, d, J 11.6, CH*H*), 2.87 [1 H, septet, J 6.9, C*H*(CH_3)$_2$], 2.45 (3 H, CH_3), 1.86 (1.85) (3 H, s, CH_3), 1.79 (1.77) (3 H, s, CH_3) and 1.27 [6 H, d, J 6.9, CH(C*H*$_3$)$_2$]; δ_C(67.8 MHz; $CDCl_3$) 179.51 (179.46) (s), 176.78 (s), 175.36 (s), 163.84 (163.77) (s), 152.67 (s), 148.88 (s), 120.95 (120.89) (d), 113.24 (d), 83.97 (s), 83.36 (s), 44.17 (t), 44.10 (t), 34.00 [d, *C*H(CH_3)$_2$], 27.98 (q, CH_3), 27.78 (27.73) (q, CH_3), 21.13 and 21.00 [2 × q, CH(*C*H$_3$)$_2$] and 17.24 (q, CH_3); m/z 422.0687 (M^+, $C_{18}H_{22}N_4S_4$ requires 422.0727).

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References

1 S. Carmeli, R. E. Moore, G. M. L. Patterson, T. H. Corbett and F. A. Valeriote, *J. Am. Chem. Soc.*, 1990, **112**, 8195.
2 S. Carmeli, R. E. Moore and G. M. L. Patterson, *Tetrahedron Lett.*, 1991, **32**, 2593.
3 (*a*) R. E. Moore, *Pure Appl. Chem.*, 1982, **54**, 1919; (*b*) M. Ishibashi, R. E. Moore, G. M. L. Patterson, C. Xu and J. Clardy, *J. Org. Chem.*, 1986, **51**, 5300; (*c*) S. Carmeli, R. E. Moore and G. M. L. Patterson, *J. Nat. Prod.*, 1990, **53**, 1533.
4 S. Carmeli, R. E. Moore and G. M. L. Patterson, *Tetrahedron*, 1991, **47**, 2087.
5 S. Carmeli, R. E. Moore, G. M. L. Patterson, Y. Mori and M. Suzuki, *J. Org. Chem.*, 1990, **55**, 4431.
6 E. H. White, F. McCapra, G. F. Field and W. D. McElroy, *J. Am. Chem. Soc.*, 1961, **83**, 2402.
7 C. D. Cox and R. Graham, *J. Bacteriol.*, 1979, **137**, 357.
8 M. A. F. Jalal, M. B. Hossain, D. van der Helm, J. Sanders-Loehr, L. A. Actis and J. H. Crosa, *J. Am. Chem. Soc.*, 1989, **111**, 292.
9 M. Aoki, T. Ohtsuka, Y. Itezono, K. Yokose, K. Furihata and H. Seto, *Tetrahedron Lett.*, 1991, **32**, 217.
10 See Y. Ariyoshi, T. Shiba and T. Kaneko, *Bull. Chem. Soc. Jpn.*, 1967, 1709 and references cited therein.
11 B. M. Degnan, C. J. Hawkins, M. F. Lavin, E. J. McCaffrey, D. L. Parry, A. L. van den Brenk and D. J. Watters, *J. Med. Chem.*, 1989, **32**, 1349.
12 H. Yamaguchi, Y. Nakayama, K. Takeda, K. Tawara, T. Takeuchi and H. Umezawa, *J. Antibiotics*, 1957, 195; K. Inami and T. Shiba, *Tetrahedron Lett.*, 1984, **25**, 2009.
13 H. U. Naegeli and H. Zähner, *Helv. Chim. Acta*, 1980, **63**, 1400.
14 R. Jansen, B. Kunze, H. Reichenbach, E. Jurkiewicz, G. Hunsmann and G. Höfle, *Liebigs Ann. Chem.*, 1992, 357.
15 Preliminary publication: G. Pattenden and S. M. Thom, *Synlett*, 1992, 533.
16 *cf.* D. K. Minster, U. Jordis, D. L. Evans and S. M. Hecht, *J. Org. Chem.*, 1978, **43**, 1624; see also K. Linderstrøm-Lang and C. F. Jacobsen, *J. Biol. Chem.*, 1941, **137**, 443.
17 M. A. Walker and C. H. Heathcock, *J. Org. Chem.*, 1992, **57**, 5566.
18 H. Baganz and L. Domaschke, *Chem. Ber.*, 1962, **95**, 1842.
19 (*a*) See G. C. Barrett and A. R. Khokhar, *J. Chem. Soc. C*, 1969, 1117 and references cited therein; (*b*) N. Galéotti, C. Montagne, J. Poncet and P. Jouin, *Tetrahedron Lett.*, 1992, **33**, 2807.
20 A. Eidem, K. Undheim and K. R. Reistad, *Acta Chem. Scand.*, 1971, **25**, 1.
21 S. Nakatsuka, H. Tanino and Y. Kishi, *J. Am. Chem. Soc.*, 1975, **97**, 5010.
22 G. L. Schmir, *J. Am. Chem. Soc.*, 1965, **87**, 2743 and references cited therein.
23 U. Groth and U. Schöllkopf, *Synthesis*, 1983, 37.
24 For other syntheses of 2-methylcysteine derivatives see ref. 17 and also O. W. Griffith, *J. Biol. Chem.*, 1983, **258**, 1591.
25 See A. Jeanguenat and D. Seebach, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2291.
26 G. Pattenden, S. M. Thom and M. Jones, *Tetrahedron*, 1993, **49**, 2131.

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