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Total Synthesis of Thiangazole, a Novel Naturally Occurring HIV-1 Inhibitor from *Polyangium sp*

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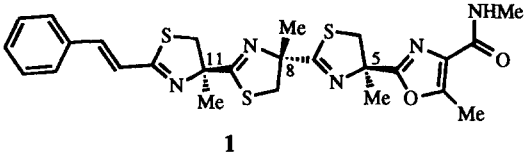
Abstract: The total synthesis of the cinnamyl-oxazole substituted *tris*-thiazoline containing metabolite (-)-thiangazole (**1**) is described. The synthesis is based on elaboration of the *R*-2-methylcysteine derived *bis*-thiazoline nitrile (**5**) and oxazole (**6**) intermediates, followed by a cyclocondensation reaction between (**5**) and (**6**), and treatment of the resulting *tris*-thiazoline oxazole ester (**16**) with methylamine.

Thiangazole (**1**), together with the related tantazoles, *eg* tantazole B (**2**), and mirabazoles, *eg* mirabazole C (**3**), constitute a unique and novel family of cytotoxic alkaloids, which show structures based on the linear fusion of four or five successive 2,4-disubstituted thiazole/oxazole rings terminating in a 2-cinnamyl or 2-isopropyl thiazoline.[1,2] The alkaloid was isolated in 1992 from the gliding bacterium *Polyangium* sp,[1] and it has been shown to be one hundred percent effective against HIV-1 at 4.7 pM and shows no cell toxicity at 4.7 mM; it is also highly selective for HIV-1 over HIV-2. The structure and stereochemistry of thiangazole have been firmly established by chemical degradation, spectroscopy, and by X-ray crystallographic analysis.[3] In this paper we describe a concise total synthesis of (-)-thiangazole (**1**).[4,5]



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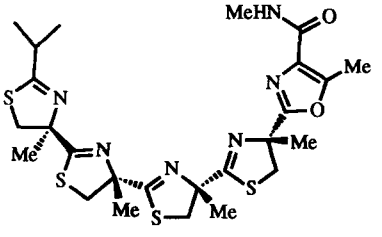

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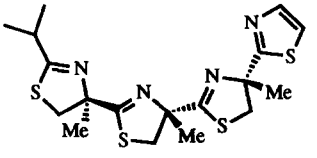
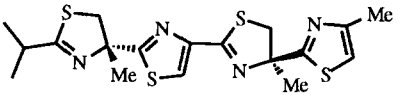


3

Our strategy for the synthesis of 5*R*, 8*S*, 11*S*-thiangazole (**1**) was based on a cyclocondensation reaction between the *R*-2-methylcysteine-derived *bis*-thiazoline nitrile (**5**) and the oxazole (**6**) as a key step (Scheme 1). In contemporaneous studies of the total synthesis of (-)-didehydromirabazole (**4**), produced by the blue green alga *Scytonema mirabile*, [5g,6] we had not only established a useful synthetic route to *R*-2-methylcysteine methyl ester (**7**)[7], but also demonstrated its use in cyclocondensation reactions with nitriles leading to chiral 4-methylthiazolines of the type shown in compound (**5**). Thus, based on this precedent, a cyclocondensation



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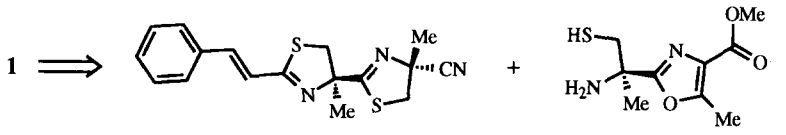
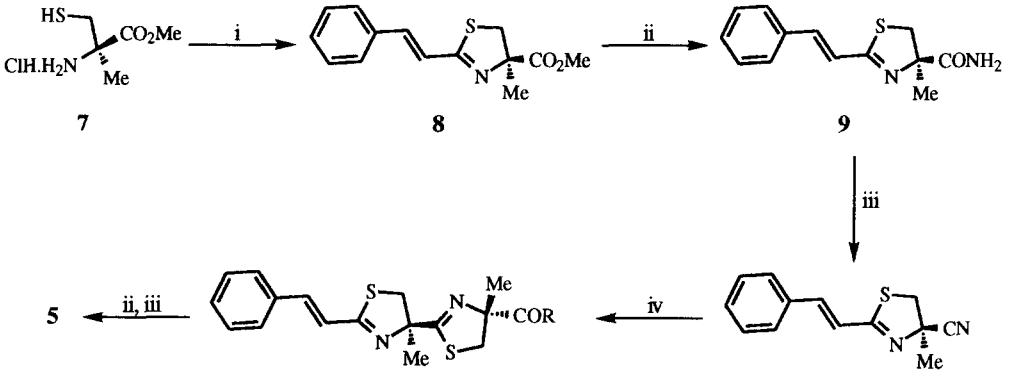


5 **6**

Scheme 1

reaction between *R*-2-methylcysteine methyl ester hydrochloride (**7**) and cinnamonitrile first led to the cinnamyl substituted 4-methylthiazoline ester (**8**)[8] as a pale yellow semi-solid in 39% yield. The ester (**8**) was next converted into the nitrile (**11**) *via* the corresponding amide (**9**)[9], and a second cyclocondensation reaction



7 **8** **9** **10** **11**

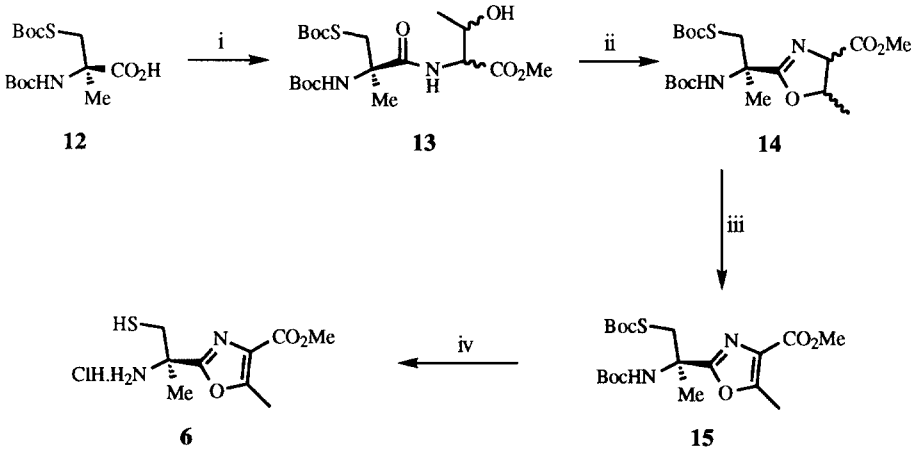
a R=OMe; *b* R=NH_2

Reagents : i, PhHC=CHCN, Et_3N, MeOH, Δ (39%); ii, EtOH-aq NH_3, 25°C (71%); iii, PPh_3, CCl_4, THF, 50°C (74%); iv, **7**, Et_3N, MeOH, Δ (54%)

Scheme 2

between (**11**) and (**7**) then produced the *bis*-thiazoline (**10*a***) as colourless crystals in 54% yield (Scheme 2). The *bis*-thiazoline ester (**10**) was finally converted into the central nitrile intermediate (**5**) *via* the corresponding amide (**10*b***), in readiness for coupling to the substituted oxazole (**6**).

The 2-methylcysteine-derived oxazole (**6**) was synthesised from *bis*-Boc protected *R*-2-methylcysteine (**12**)[10] as outlined in Scheme 3. Thus, a coupling reaction between (**12**) and (±)-threonine methyl ester hydrochloride in the presence of pyBOP[11] first led to the amide (**13**), which was next converted into a 1:1 mixture of diastereomers of the oxazoline (**14**) in 70% yield following treatment with Burgess' reagent (*ie* methoxycarbonylsulphamoyl-triethylammonium hydroxide).[12] Oxidation of the oxazoline (**14**) using nickel peroxide, or better, using *t*-butylperoxybenzoate in the presence of copper (I) bromide,[13] next produced the oxazole (**15**) as a colourless oil in 34% yield. Deprotection of (**15**) in the presence of anhydrous hydrochloric acid in ether finally led to the *R*-2-methylcysteine derived oxazole (**6**) which was produced as a colourless solid.

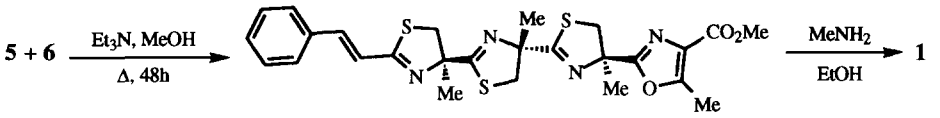


12 **13** **14** **15** **6**

Reagents: i, pyBOP,[11] Et_3N, CH_2Cl_2, then (±)-Thr-HCl, Et_3N, 25°C (68%); ii, Burgess' reagent,[12] THF (70%); iii, $^tBuOCOOPh$, Cu(I)Br, C_6H_6, Δ, (34%); iv, HCl-Et_2O (68%)

Scheme 3

With the two key intermediates in hand, a cyclocondensation reaction between the nitrile (**5**) and the substituted cysteine (**6**) next produced the *tris*-thiazoline oxazole (**16**), which, on treatment with methylamine followed by crystallisation finally led to thiangazole (**1**). The synthetic thiangazole was obtained as colourless crystals, mp and mixed mp 141°C with natural thiangazole (mp 142°C), and the two compounds showed identical pmr, cmr, ir and uv spectroscopic data. Natural thiangazole shows an optical rotation of $[\alpha]_D$ - 287 (c 0.1 in MeOH), where our synthetic material had $[\alpha]_D$ - 275 (c 0.1 in MeOH).



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EXPERIMENTAL

For general experimental details see reference 6.

(4R)-4-Methoxycarbonyl-4-methyl-2-cinnamyl-Δ^2-thiazoline (**8**). - Cinnamonitrile (97 µl, 0.774 mmol) was added in one portion to a stirred solution of *R*-2-methylcysteine methyl ester hydrochloride (143 mg, 0.774 mmol)[7] and triethylamine (108 µl, 0.774 mmol) in methanol (5 ml), and the mixture was then heated under reflux for 48h in a nitrogen atmosphere. The cooled solution was diluted with ethyl acetate (20 ml), then washed with water (20 ml), dried, and evaporated *in vacuo* to leave a yellow solid. Column chromatography on silica gel using 25% ethyl acetate-light petroleum as eluant gave the *thiazoline* (75 mg, 39%) as a yellow semi-solid; $[\alpha]_D$ 29.6 (c 1.55 in CH_2Cl_2); λ_{max} (EtOH) 222 (12 577), 287 (25 840) nm; ν_{max} (film) 2951, 1732, 1634, 1581, 1117, 962, 754 and 691 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 7.43-7.39 (2H, m, 2xCH), 7.37-7.24 (3H, m, 3xCH), 7.07 (1H, d, *J* 16.2 Hz, CH), 7.00 (1H, d, *J* 16.2 Hz, CH), 3.77 (1H, d, *J* 11.3 Hz, C*H*H), 3.75 (3H, s, OCH_3), 3.16 (1H, d, *J* 11.3 Hz, CH*H*), 1.54 (3H, s, CH_3); δ_C (67.8 MHz; $CDCl_3$) 173.75 (s, CO), 167.62 (s, SC:N), 141.80 (d, PhCH=CH), 134.99 (s), 129.63 (d, CH), 128.84 (d, CH), 127.49 (d, CH), 122.39 (d, PhCH=CH), 83.88 (s, $C(CO_2CH_3)CH_3$), 52.92 (q, OCH_3), 40.70 (t, CH_2), 23.97 (q, CH_3); m/z (EI) 261.0830 (M^+, 1%, $C_{12}H_{15}N_2O_2S$ requires 261.0824), 202 (100), 130 (17) and 73 (69).

(4R)-4-Methyl-4-carboxamide-2-cinnamyl-Δ^2-thiazoline (**9**). - Aqueous ammonia solution (3 ml) was added in one portion to a stirred solution of the methyl ester (**8**) (254 mg, 0.973 mmol) in ethanol (5 ml) at room temperature. The solution was stirred overnight at room temperature, and then the solvents were evaporated *in vacuo*. Brine (10 ml) was added to the residue, which was then extracted with ether (4x10 ml). The combined organic extracts were dried and evaporated *in vacuo* to leave an oil which was purified by column chromatography on silica gel using 50% ethyl acetate-light petroleum as eluant to give the *amide* (160 mg, 71%) as a white solid which was recrystallised from ethyl acetate to afford white crystals; m.p. 172-4°C; $[\alpha]_D$ -98.0 (c 0.66 in CH_2Cl_2); (Found C, 63.04; H, 5.83; N, 11.28; $C_{13}H_{14}N_2OS$ requires C, 63.39; H, 5.73; N, 11.37); λ_{max} (EtOH) 222 (13 899), 287 (27 925) nm; ν_{max} (KBr disc) 3442, 2929, 1690, 1645, 1581, 759 and 695 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 7.51-7.47 (2H, m, 2xCH), 7.40-7.34 (3H, m, 3xCH), 7.16 (1H, d, *J* 16.2 Hz, CH), 6.98 (1H, d, *J* 16.2 Hz, CH), 6.82 and 6.34 (2H, 2xbrd, NH_2), 3.76 (1H, d, *J* 11.4 Hz, C*H*H), 3.28 (1H, d, *J* 11.4 Hz, CH*H*), 1.59 (3H, s, CH_3); δ_C (67.8 MHz; $CDCl_3$) 177.98 (s, CO), 168.46 (s, SC:N), 142.30 (d, PhCH=CH), 135.26 (s), 130.19 (d, CH), 129.29 (d, CH), 127.94 (d, CH), 122.46 (d, PhCH=CH), 84.73 (s, $C(CONH_2)CH_3$), 41.06 (t, CH_2), 25.27 (q, CH_3); m/z (EI) 246.0867 (M^+, 1%, $C_{13}H_{14}N_2OS$ requires 246.0827), 202 (100), 102 (30) and 73 (50).

(4R)-4-Methyl-4-nitrile-2-cinnamyl-Δ^2-thiazoline (**11**). - A solution of the amide (**9**) (1.45 g, 5.9 mmol) in dry THF (10 ml) was added dropwise over 10 min to a stirred solution of triphenylphosphine (3.09 g, 11.8 mmol) in dry carbon tetrachloride (10 ml), and the mixture was then heated at 45-55°C for 2h in an atmosphere of nitrogen. The solvents were evaporated *in vacuo*, and the residue was then taken up in ether (40 ml). The ether solution was washed with water (20 ml), then dried and evaporated *in vacuo* to leave a yellow residue. The residue was purified by column chromatography on silica gel using 30% ethyl acetate-light petroleum as eluant to give the *nitrile* (988 mg, 74%) as a yellow oil; $[\alpha]_D$ 20.0 (c 0.07 in CH_2Cl_2); λ_{max} (EtOH) 223 (13 010), 290 (26 439) nm; ν_{max} (film) 2920, 2241, 1632, 1579, 754 and 691 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 7.45-7.18 (5H, m, 5xCH), 7.12 (1H, d, *J* 16.2 Hz, CH), 6.91 (1H, d, *J* 16.2 Hz, CH), 3.70 (1H, d, *J* 11.5 Hz, C*H*H), 3.28 (1H, d, *J* 11.5 Hz, CH*H*), 1.72 (3H, s, CH_3); δ_C (67.8 MHz; $CDCl_3$) 170.55 (s, SC:N), 143.43 (d, PhCH=CH), 135.50 (s), 130.14 (d, CH), 128.93 (d, CH), 127.69 (d, CH), 121.26 (d, PhCH=CH), 120.32 (s, CN), 73.05 (s, C(CN)CH_3), 42.82 (t, CH_2), 25.20 (q, CH_3); m/z (EI) 228.0718 (M^+, 36%, $C_{13}H_{12}N_2S$ requires 228.0721), 227 (100), 200 (96), 161 (48) and 129 (92).

(4S)-4-Methyl-4-[2'(4'R)-4'-methoxycarbonyl-4'-methyl)-Δ^2-thiazoline]-2-cinnamyl-Δ^2-thiazoline (**10*a***). - The thiazoline-nitrile (**11**) (988 mg, 3.77 mmol) was added in one portion to a stirred solution of *R*-2-methylcysteine methyl ester hydrochloride (910 mg, 4.89 mmol)[7] and triethylamine (683 µl, 4.89 mmol) in methanol (20 ml), and the mixture was then heated under reflux for 48h in a nitrogen atmosphere. The cooled solution was diluted with ethyl acetate (50 ml), and the organic solution was then washed with water (30 ml), dried and evaporated *in vacuo* to leave a yellow oil. Column chromatography on silica gel using 25% ethyl acetate-light petroleum as eluant gave the *ester* (726 mg, 54%) as an off white solid which was recrystallised from ethyl acetate to afford white crystals; mp 120-4°C, $[\alpha]_D$ -168.8 (c 2.47 in CH_2Cl_2); (Found C, 59.67; H, 5.74; N, 7.65; $C_{18}H_{21}N_2S_2O_2$ requires C, 59.81; H, 5.86; N, 7.75); λ_{max} (CH_2Cl_2) 231 (12 768), 288 (14 257) nm; ν_{max} ($CHCl_3$) 2923, 1722, 1167 and 754 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 7.57-7.53 (2H, m, 2xCH), 7.45-7.39 (3H, m, 3xCH), 7.04 (1H, d, *J* 16.2 Hz, CH), 6.94 (1H, d, *J* 16.2 Hz, CH), 3.90 (1H, d, *J* 11.2 Hz, C*H*H), 3.85 (3H, s, OCH_3), 3.79 (1H, d, *J* 11.2 Hz, C*H*H), 3.45 (1H, d, *J* 11.2 Hz, C*H*H), 3.18 (1H, d, *J* 11.2 Hz, CH*H*), 1.73 (3H, s, A4-CH_3), 1.60 (3H, s, B4-CH_3); δ_C (67.8 MHz; $CDCl_3$) 177.42 (s, CO), 173.67 (s), 167.30 (s), 142.43 (d, PhCH=CH), 134.91 (s), 129.83 (d, CH), 128.86 (d, CH), 127.65 (d, CH), 122.05 (d, PhCH=CH), 83.97 and 83.04 (2xs, A2 and B2), 52.85 (q, OCH_3), 42.28 and 41.42 (2xt, 2xCH_2), 25.82 and 23.81 (2xq, 2xCH_3); m/z (FAB) 361 (MH^+, 22%), 360 (3), 149 (65), 136 (47) and 81 (44).

(4S)-4-Methyl-4-[2'(4'S)-4'-carboxamide-4'-methyl)-Δ^2-thiazoline]-2-cinnamyl-Δ^2-thiazoline-(**10*b***). - Aqueous ammonia solution (5 ml) was added in one portion to a stirred solution of the *bis*-ester (**10*a***) (292 mg, 1.12 mmol) in ethanol (5 ml). The solution was stirred overnight at room temperature, and then the solvents were evaporated *in vacuo*. Brine (10 ml) was added to the residue, which was then extracted with ether (4x10 ml). The combined organic extracts were dried and evaporated *in vacuo* to leave an oil which was purified by column chromatography on silica gel using 25% ethyl acetate-light petroleum as eluant to give the *bis-amide* (180 mg, 65%) as a white solid; m.p. 137-140°C (ether-light petroleum); $[\alpha]_D$ -185.4 (c 6.99 in CH_2Cl_2); λ_{max}

(CH_2Cl_2) 231 (11 984), 290 (31 196) nm; ν_{max} (KBr disc) 3438, 2924, 1674, 1626, 751 and 690 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 7.55-7.40 (5H, m, 5xCH), 7.21 (1H, d, *J* 16.2 Hz, CH), 7.11 (1H, d, *J* 16.2 Hz, CH), 7.00 and 6.80 (2H, 2xbrd, NH_2), 3.85 (1H, d, *J* 11.2 Hz, C*H*H), 3.72 (1H, d, *J* 11.2 Hz, C*H*H), 3.39 (1H, d, *J* 11.2 Hz, C*H*H), 3.27 (1H, d, *J* 11.2 Hz, CH*H*), 1.72 (3H, s, A4-CH_3), 1.57 (3H, s, B4-CH_3); δ_C (67.8 MHz; $CDCl_3$) 177.80 (s, CO), 174.64 (s), 167.67 (s), 141.83 (d, Ph*C*H=CH), 134.74 (s), 129.51 (d, CH), 128.61 (d, CH), 127.71 (d, CH), 122.12 (d, PhCH=*C*H), 84.01 and 83.15 (2xs, A2 and B2), 42.10 and 40.86 (2xt, 2xCH_2), 25.66 and 24.48 (2xq, 2xCH_3); m/z (EI) 345.0991 (M^+, 26%, $C_{17}H_{19}N_3OS_2$ requires 345.0969), 301 (77), 202 (100), 172 (49) and 73 (83).

(4S)-4-Methyl-4-[2'(4'R)-4'-nitrile-4'-methyl)-Δ^2-thiazoline-]-2-cinnamyl-Δ^2-thiazoline (**5**). - A solution of the *bis*-amide (**10*b***) (150 mg, 0.434 mmol) in dry THF (2 ml) was added dropwise over 5 min to a stirred solution of triphenylphosphine (228 mg, 0.870 mmol) in dry carbon tetrachloride (2 ml), and the mixture was then heated at 45-55°C for 2h in an atmosphere of nitrogen. The solvents were evaporated *in vacuo*, and the residue was then taken up in ether (15 ml), washed with water (10 ml), dried and evaporated *in vacuo* to leave a yellow residue. The residue was purified by column chromatography on silica gel using 30% ethyl acetate-light petroleum as eluant to give the *bis-nitrile* (22 mg, 15%) as a viscous oil; $[\alpha]_D$ -158.9 (c 2.14 in CH_2Cl_2); λ_{max} (EtOH) 223 (12 001), 288 (23 787) nm; ν_{max} (film) 2980, 2928, 2243, 1632, 1608, 733 and 690 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 7.45-7.42 (2H, m, 2xCH), 7.33-7.27 (3H, m, 3xCH), 7.08 (1H, d, *J* 16.2 Hz, CH), 6.96 (1H, d, *J* 16.2 Hz, CH), 3.72 (1H, d, *J* 11.2 Hz, C*H*H), 3.65 (1H, d, *J* 11.2 Hz, C*H*H), 3.29 (1H, d, *J* 11.2 Hz, CH*H*), 3.22 (1H, d, *J* 11.2 Hz, CH*H*), 1.62 (3H, s, A4-CH_3), 1.61 (3H, s, B4-CH_3); δ_C (67.8 MHz; $CDCl_3$), 180.86 (s), 168.50 (s), 142.35 (d, Ph*C*H=CH), 134.90 (s), 129.85 (d, CH), 128.90 (d, CH), 127.62 (d, CH), 122.09 (d, PhCH=*C*H), 120.61 (s, CN), 83.29 and 73.07 (2xs, A2 and B2), 43.13 and 42.09 (2xt, 2xCH_2), 25.93 and 25.03 (2xq, 2xCH_3); m/z (EI) 327.0868 (M^+, 43%, $C_{17}H_{17}N_3S_2$ requires 327.0864), 281 (49), 202 (100), 115 (27) and 73 (31).

N,S-Bis-tert-butoxycarbonyl-R-2-methylcysteine (**12**). - Di-*tert*-butyl dicarbonate (10.0 ml, 43.5 mmol) was added dropwise over 10 min to a stirred solution *R*-2-methylcysteine hydrochloride (5.0 g, 29.1 mmol)[7] and triethylamine (16.2 ml, 116 mmol) in THF (50 ml) and water (50 ml) at 0°C under a nitrogen atmosphere. The resulting solution was allowed to warm to room temperature and then stirred at this temperature for 48h. Ether (100 ml) was added, and the organic phase was then extracted with 10% triethylamine in water (3x100 ml). The combined aqueous extracts were carefully acidified with citric acid, and then extracted with ether (4x100 ml). The combined organic extracts were washed with aqueous citric acid (0.5 M; 50 ml), and water (50 ml), then dried and evaporated *in vacuo* to leave the *acid* (8.42 g, 86%) as a white solid; m.p. 60-62°C; $[\alpha]_D$ -3.41 (c 1.05 in $CHCl_3$); ν_{max} ($CHCl_3$) 3419, 2932, 1713, 1493, 1456, 1369, 1310 and 1130 cm^{-1}; δ_H (250MHz; $CDCl_3$) 5.69 (1H, brd, NH), 3.52 (1H, d, *J* 14.3 Hz, C*H*H), 3.37 (1H, d, *J* 14.3 Hz, CH*H*), 1.50 (9H, s, $SCO_2(CH_3)_3$), 1.46 (3H, s, CH_3), 1.45 (9H, s, $NHCO_2(CH_3)_3$); δ_C (67.8 MHz; $CDCl_3$) 176.37 (s, CO_2H), 173.24 (s, SCO_2), 156.17 (s, $NHCO_2$), 85.68 (s, $C(CH_3)CO_2H$), 61.39 (s, $SCO_2C(CH_3)_3$), 60.84 (s, $NHCO_2C(CH_3)_3$), 43.66 (t,

CH_2), 28.67 (q, $SCO_2C(CH_3)_3$), 28.42 (q, $NHCO_2C(CH_3)_3$), 23.02 (q, CH_3); m/z (FAB) 336 (MH^+, 12%), 280 (30), 204 (34), 180 (84) and 134 (36).

N,S-Bis-tert-butoxycarbonyl-R-2-methylcysteinethreonine methyl ester (**13**). - Benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (1.94 g, 3.73 mmol) was added in one portion to a stirred solution of the acid (**12**) (1.00 g, 2.98 mmol) and triethylamine (520 µl, 3.73 mmol) in dry dichloromethane (50 ml) at 0°C under a nitrogen atmosphere and the resulting solution was then stirred at 0°C for 30 min. A solution of *DL*-threonine methyl ester (595 mg, 4.47 mmol) in dry dichloromethane (20 ml) was added dropwise over 5 min, and the resulting solution was stirred at room temperature for 12h. The solvents were evaporated *in vacuo* to leave an oily residue which was purified by column chromatography on silica gel using 50% ethyl acetate-light petroleum as eluant to give the *β-hydroxyamide* (918 mg, 68%), (1:1 mixture of diastereoisomers) as a white solid; m.p. 106-108°C; ν_{max} (KBr) 3425, 2935, 1694, 1489, 1457, 1370 and 1129 cm^{-1}; δ_H (250MHz; $CDCl_3$) 7.15 (1H, d, *J* 9.0 Hz, NH), 5.31 (1H, brd, NH), 4.58 (1H, dd, *J* 9.0, 2.3 Hz, C*H*(CO_2CH_3), 4.52 (1H, m, C*H*(OH)CH_3), 3.78 and 3.77 (3H, 2xs, CO_2CH_3), 3.62 (1H, d, *J* 14.2 Hz, C*H*H), 3.45 (1H, d, *J* 14.2 Hz, CH*H*), 2.52 and 2.45 (1H, 2xd, *J* 5.2 Hz, OH), 1.69 and 1.62 (3H, 2xs, CH_3), 1.52 and 1.50 (9H, 2xs, $SCO_2(CH_3)_3$), 1.44 (9H, s, $NHCO_2(CH_3)_3$), 1.26 and 1.25 (3H, 2xd, *J* 6.3 Hz, CH(OH)C*H*$_3$); δ_C (67.8 MHz; $CDCl_3$) 173.55 (s), 173.28 (s), 170.82 (s), 170.62 (s), 169.09 (s), 168.68 (s), 154.07 (s), 84.84 (s), 84.49 (s), 67.53 (d), 67.32 (d), 59.89 (d), 59.37 (d), 59.07 (s), 57.41 (s), 51.84 (q), 37.34 (t), 36.41 (t), 29.13 (q), 28.65 (q), 27.77 (q), 27.62 (q), 22.77 (q), 22.28 (q), 14.72 (q), 13.68 (q); m/z (FAB) 451 (MH^+, 18%), 395 (10), 339 (24), 295 (61), 134 (47) and 90 (21).

N,S-Bis-tert-butoxycarbonyl-R-2-methylcysteine-5′-methyl-Δ^2-oxazoline-4′-methyl ester (**14**). - Burgess' reagent (510 mg, 2.14 mmol) was added in one portion to a stirred solution of N,S-bis-*tert*-butoxycarbonyl-*R*-2-methylcysteinethreonine methyl ester (**13**) (918 mg, 2.04 mmol) in dry THF (100 ml), and the resulting solution was then heated under reflux for 12h under a nitrogen atmosphere. The solvents were evaporated *in vacuo* to leave an oily residue which was partitioned between brine (20 ml) and ether (50 ml). The separated aqueous layer was extracted with ether (3x50 ml), and the combined organic extracts were then dried and evaporated *in vacuo* to leave an oil. The oil was purified by column chromatography on silica gel using 25% ethyl acetate-light petroleum as eluant to give the *oxazoline* (620 mg, 70%) (1:1 mixture of diastereoisomers) as a clear oil; ν_{max} (film) 2979, 1719, 1660, 1499, 1448, 1368, 1252, 1200, 1171, 1129 and 1051 cm^{-1}; δ_H (270 MHz; $CDCl_3$) first eluted isomer, 5.59 (1H, brd, NH), 4.90 (1H, m, OC*H*(CH)CH_3), 4.74 (1H, d, *J* 10.2 Hz, C*H*(CO_2CH_3)), 3.69 (3H, s, OCH_3), 3.63 (1H, d, *J* 14.0 Hz, C*H*H), 3.41 (1H, d, *J* 14.0 Hz, CH*H*), 1.58 (3H, s, CH_3), 1.41 (9H, s, $SCO_2(CH_3)_3$), 1.35 (9H, s, $NHCO_2(CH_3)_3$), 1.21 (3H, d, *J* 6.6 Hz, OCH(CH)C*H*$_3$); second eluted isomer, 5.75 (1H, brd, NH), 4.85 (1H, m, OC*H*(CH)CH_3), 4.65 (1H, d, *J* 9.9 Hz, C*H*(CO_2CH_3)), 3.68 (3H, s, OCH_3), 3.60 (1H, d, *J* 14.0 Hz, C*H*H), 3.33 (1H, d, *J* 14.0 Hz, CH*H*), 1.62 (3H, s, CH_3), 1.40 (9H, s, $SCO_2(CH_3)_3$), 1.35 (9H, s, $NHCO_2(CH_3)_3$), 1.23 (3H, d, *J* 6.4 Hz, OCH(CH)C*H*$_3$); δ_C (67.8 MHz; $CDCl_3$) 170.67 (s), 169.27 (s), 169.22 (s), 168.28 (s), 168.10 (s), 153.41 (s), 84.27 (s), 84.15 (s), 78.83 (d), 78.35 (d),

70.60 (d), 70.37 (d), 55.02 (s), 54.86 (s), 51.59 (q), 51.39 (q), 37.22 (t), 36.93 (t), 27.82 (q), 27.64 (q), 22.97 (q), 22.59 (q), 15.44 (q), 15.33 (q); m/z (FAB) 433 (MH^+, 9%), 321 (11), 134 (11) and 95 (16).

N,S-Bis-tert-butoxycarbonyl-R-2-methylcysteine-5'-methyloxazole-4'-methyl ester (**15**). - *tert*-Butylperoxybenzoate (397 µl, 2.08 mmol) was added dropwise over 5 min to a stirred solution of N,S-bis-*tert*-butoxycarbonyl-*R*-2-methylcysteine-5'-methyl-Δ^2-oxazoline-4'-methyl ester (**14**) (600 mg, 1.39 mmol) and copper (I) bromide (216 mg, 1.53 mmol) in dry benzene (50 ml) under a nitrogen atmosphere. The resulting suspension was heated under reflux for 5h, and then the solvents were evaporated *in vacuo* to leave a solid residue. The residue was partitioned between ether (50 ml) and a saturated solution of ammonium chloride (10 ml). The separated aqueous layer was extracted with ether (3x10 ml), and the combined organic extracts were then washed with water (20 ml), dried and evaporated *in vacuo* to leave a residue. The residue was purified by column chromatography on silica gel using 20% ethyl acetate-light petroleum as eluant to give the *oxazole* (205 mg, 34%) as a colourless oil; $[\alpha]_D$ -1.5 (c 0.80 in $CHCl_3$); λ_{max} (EtOH) 202 (2176), 226 (2157) nm; ν_{max} ($CHCl_3$) 2954, 1716, 1493, 1456, 1369, 1316 and 1130 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 5.61 (1H, brd, NH), 3.81 (3H, s, OCH_3), 3.77 (1H, d, *J* 11.2 Hz, C*H*H), 3.52 (1H, d, *J* 11.2 Hz, CH*H*), 2.54 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.36 (9H, s, $SCO_2(CH_3)_3$), 1.32 (9H, s, $NHCO_2(CH_3)_3$); δ_C (67.8 MHz; $CDCl_3$) 168.37 (s), 163.05 (s), 162.53 (s), 156.64 (s), 153.98 (s), 130.06 (s), 128.39 (s), 127.20 (s), 85.14 (s), 55.67 (q), 38.89 (t), 28.14 (q), 27.91 (q), 24.01 (q), 11.92 (q); m/z (FAB) 431 (MH^+, 17%), 375 (9), 319 (46) and 134 (23).

R-2-Methylcysteine-5'-methyloxazole-4'-methyl ester hydrochloride (**6**). - An ethereal solution of HCl (0.5 M, 50 ml) was added in one portion to N,S-bis-*tert*-butoxycarbonyl-*R*-2-methylcysteine-5'-methyloxazole-4'-methyl ester (**15**) (200 mg, 0.465 mmol), and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 12h. The solvent was removed *in vacuo* to leave a solid residue which was partitioned between water (10 ml) and ether (10 ml). The separated aqueous phase was evaporated *in vacuo* to leave the *oxazole* (84 mg, 68%) as a white solid which was recrystallised from ether-light petroleum; m.p. 153°C (decomp.); $[\alpha]_D$ 5.2 (c 1.3 in EtOH); λ_{max} (EtOH) 217 (5889) nm; ν_{max} (KBr disc) 2924, 2853, 1719, 1618, 1448, 1373, 1138 and 1025 cm^{-1}; δ_H (250 MHz; CD_3OD) 3.97 (3H, s, OCH_3), 3.63-3.25 (2H, m, CH_2), 2.72 (3H, s, CH_3), 1.93 (3H, s, CH_3); δ_C (67.8 MHz; CD_3OD) 163.97 (s), 163.05 (s), 159.87 (s), 129.88 (s), 58.56 (s), 53.06 (q), 33.39 (t), 23.05 (q), 12.72 (q); m/z (FAB) 239 (5%), 154 (17), 149 (11), 136 (16), 102 (100) and 57 (37).

(4S)-4-Methyl-4-[2'(4'S)-4'-methyl-4'(2"-(4"R)-4"-methyl-4"-(2"'-(4"'-methoxycarbonyl-5"'-methyl)oxazole)-Δ^2-thiazoline-)-Δ^2-thiazoline]-2-cinnamyl-Δ^2-thiazoline (**16**). - Triethylamine (10 µl, 67.0 µmol) was added dropwise over 2 min to a stirred solution of cinnamyl-4-methyl-Δ^2-thiazoline-4-*R*-4'-methyl-Δ^2-thiazoline-4-*R*-nitrile (**5**) (22 mg, 63.7 µmol) and *R*-2-methylcysteine-5'-methyloxazole-4'-methyl ester hydrochloride (**6**) (17 mg, 63.7 µmol) in methanol (5 ml), and the resulting solution was heated under reflux for 4 days. The solvent was evaporated *in vacuo* to leave a solid residue which was partitioned between brine (2 ml) and dichloromethane (5 ml). The separated aqueous phase was extracted with dichloromethane (3x5 ml), and the

combined organic extracts were then dried and evaporated *in vacuo* to leave an oily residue. The residue was purified by column chromatography on silica gel using 50% ethyl acetate-light petroleum as eluant to give the *tetrakis-ester* (10 mg, 30%) as a colourless oil; $[\alpha]_D$ -230.5 (c 0.8 in $CHCl_3$); λ_{max} (EtOH) 223 (30 348), 289 (29 577) nm; ν_{max} ($CHCl_3$) 2928, 2853, 1722, 1621, 1580, 1450, 1352, 1116 and 1093 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.52-7.50 (2H, m, 2xCH), 7.39-7.37 (3H, m, 3xCH), 7.16 (1H, d, *J* 16.1 Hz, PhC*H*=CH), 7.07 (1H, d, *J* 16.1 Hz, PhCH=C*H*), 3.95 (1H, d, *J* 11.5 Hz, C*H*H), 3.92 (3H, s, OCH_3), 3.81 (1H, d, *J* 11.3 Hz, C*H*H), 3.78 (1H, d, *J* 11.3 Hz, C*H*H), 3.38 (1H, d, *J* 11.3 Hz, CH*H*), 3.29 (1H, d, *J* 11.5 Hz, CH*H*), 3.27 (1H, d, *J* 11.3 Hz, CH*H*), 2.65 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.61 (3H, s, CH_3); δ_C (100.8 MHz; $CDCl_3$) 178.25 (s), 178.06 (s), 167.99 (s), 163.71 (s), 162.80 (s), 157.35 (s), 142.06 (d), 135.18 (s), 129.78 (d), 128.98 (d), 127.69 (d), 127.44 (s), 122.54 (d), 83.76 (s), 83.59 (s), 79.44 (s), 52.11 (q), 43.24 (t), 42.54 (t), 42.16 (t), 26.22 (q), 25.78 (q), 24.36 (q), 14.20 (q); m/z (EI) 540.1295 (M^+, 1%, $C_{26}H_{28}N_4O_3S_3$ requires 540.1324), 525 (7), 494 (7), 301 (39), 260 (44), 202 (100) and 73 (76).

(-) -Thiangazole (**1**). - Methylamine (33% solution in EtOH, 1 ml) was added to the *tetrakis*-ester (**16**) (8 mg, 14.8 μmol) in one portion at 0°C under a nitrogen atmosphere, and the resulting solution was stirred at room temperature for 4h. The solvents were evaporated *in vacuo* to leave a solid residue which was purified by column chromatography on silica gel using 60% ethyl aceate-light petroleum as eluant to give *thiangazole* (6 mg, 75%) as a white solid. Recrystallisation from acetone gave *thiangazole;* m.p. 141°C ; (mixed m.p. 141°C with natural material) $[\alpha]_D$ -275.0 (c 0.1 in MeOH) (Lit[1] $[\alpha]_D$ -285.0 (c 0.1 in MeOH); λ_{max} (EtOH) 223 (49 774), 289 (41 640) nm; ν_{max} ($CHCl_3$) 3698, 2928, 2853, 1722, 1660, 1634, 1580, 1568, 1454, 1368, 1337, 1104, 1000 and 962 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.52-7.50 (2H, m, 2xCH), 7.39-7.37 (3H, m, 3xCH), 7.16 (1H, d, *J* 16.2 Hz, PhC*H*=CH), 7.07 (1H, d, *J* 16.2 Hz, PhCH=C*H*), 6.93 (1H, brd, NH), 3.88 (1H, d, *J* 11.4 Hz, C*H*H), 3.85 (1H, d, *J* 11.2 Hz, C*H*H), 3.76 (1H, d, *J* 11.4 Hz, C*H*H), 3.39 (1H, d, *J* 11.2 Hz, CH*H*), 3.29 (1H, d, *J* 11.4 Hz, CH*H*), 3.23 (1H, d, *J* 11.4 Hz, CH*H*), 2.95 (3H, d, *J* 5.0 Hz, NHC*H*$_3$), 2.66 (3H, s, CH_3), 1.71 (3H, s, CH_3), 1.69 (3H, s, CH_3), 1.62 (3H, s, CH_3); δ_C (100.8 MHz; $CDCl_3$) 178. 34 (s, 10), 177.50 (s, 7), 167.47 (s, 13), 163.26 (s, 4), 162.50 (s, 1), 153.50 (s, 3), 142.33 (d, 15), 136.03 (s, 16), 130.53 (s, 2), 130.52 (d, 19), 129.74 (d, 18), 128.50 (d, 17), 123.23 (d, 14), 84.52 (s, 11), 84.36 (s, 8), 80.06 (s, 5), 43.25 (t, 9), 42.77 (t, 6), 42.20 (t, 12), 26.30 (q, 8-CH_3), 26.01 (q, 11-CH_3), 25.55 (q, N-CH_3), 24.08 (q, 5-CH_3), 11.45 (q, 3-CH_3); m/z (EI) 524.1241 (M^+-Me, 6%, $C_{25}H_{26}N_5O_2S_3$ requires 524.1249), 337 (9), 301 (21), 260 (22), 202 (31), 149 (33), and 69 (100).

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