Pergamon

Tetrahedron Vol. 51, No. 26, pp. 7313-7320, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00355-X

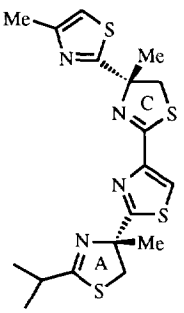
Naturally Occurring 4-Methylthiazolines. A Total Synthesis of (-)-[4*R*, 4*S*']-Didehydromirabazole A

Richard J Boyce and Gerald Pattenden*

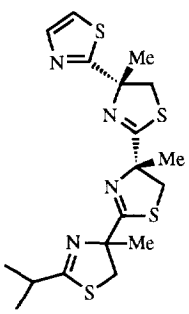
Department of Chemistry, Nottingham University, Nottingham NG7 2RD

The new total synthesis of the 4-methylthiazoline-based natural product didehydromirabazole A, produced by the blue green alga *Scytonema mirabile*, shows that its stereostructure is as shown in formula (**12**).

Didehydromirabazole A (**1**), together with its 'mirabazole', *eg* (**2*a***), and 'tantazole', *eg* (**3*b***), relatives, are a new and interesting family of thiazoline/thiazole/oxazole - based secondary metabolites which have recently been isolated from the blue-green alga *Scytonema mirabile*.[1] Several of their member show pronounced solid tumour selective toxicity and this feature, together with their unique structures, have lured us and several other researchers into investigating synthetic routes to this class of compound. The structures of the mirabazoles and tantazoles were originally assigned as shown in the diagrams, with the ring A stereocentre having an

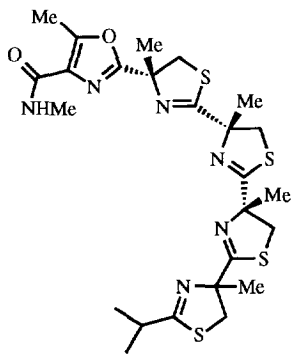


1



2

a, β-Me
b, α-Me



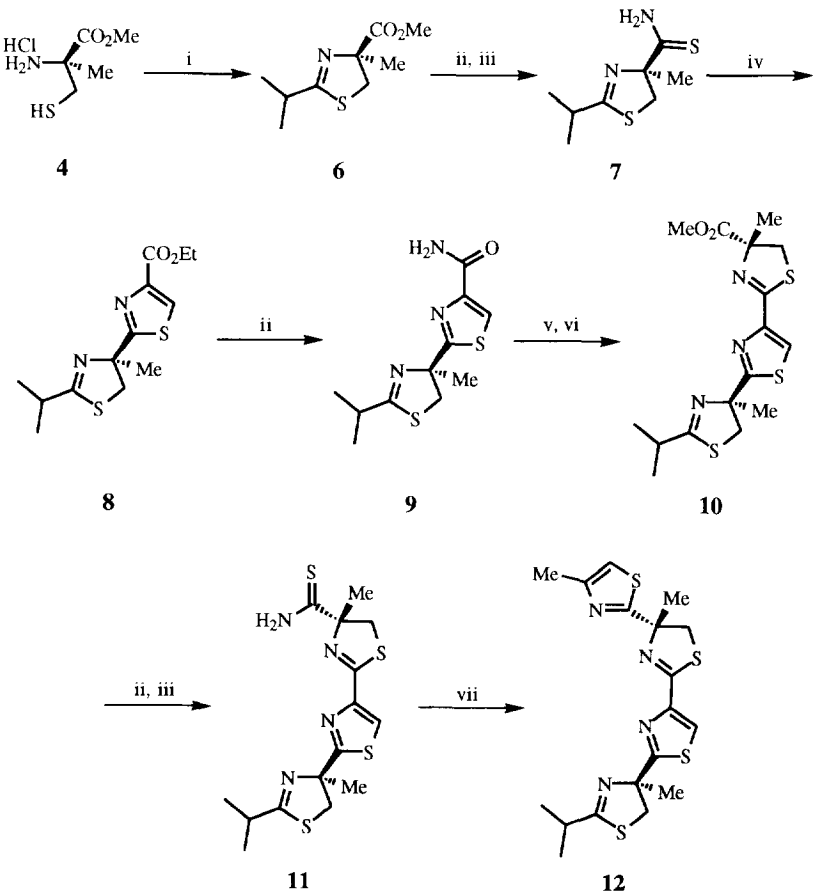
3

a, β-Me
b, α-Me

S-configuration, *ie* (**1**), (**2*a***) and (**3*a***). In 1992 we described a total synthesis of the stereostructure (**1**) and reported that it was identical with natural (-)-didehydromirabazole A according to its nmr data, but that its specific rotation was at variance with that reported for the natural product.[2] Later synthetic work by Fukuyama and Xu[3] showed that tantazole B (**3*a***) has the alternative *R*-configuration at the quaternary centre in ring A, *viz* structure (**3*b***). This finding then led Moore *et al*[4] to re-examine the stereochemistries they had earlier assigned

to several other tantazoles and mirabazoles. In the event they reached the conclusion that all of the naturally occurring tantazoles and mirazoles isolated from *S. mirabile* probably had the alternative *R*-configuration at the stereocentres in their A-ring portions. Indeed, Parsons and Heathcock[5] then confirmed this revised assignment for mirabazole C (**2b**) by total synthesis. These studies have led us to re-examine our earlier synthesis, and conclusions regarding the stereostructure, of didehydromirabazole A. In this paper we report a synthesis of the stereostructure (**12**), the 4*R*, 4*S*'-diastereoisomer of (-)-didehydromirabazole, having the *R*-configuration in ring A and the *S*-configuration in ring C, and a comparison of this stereostructure with the natural metabolite.[6]

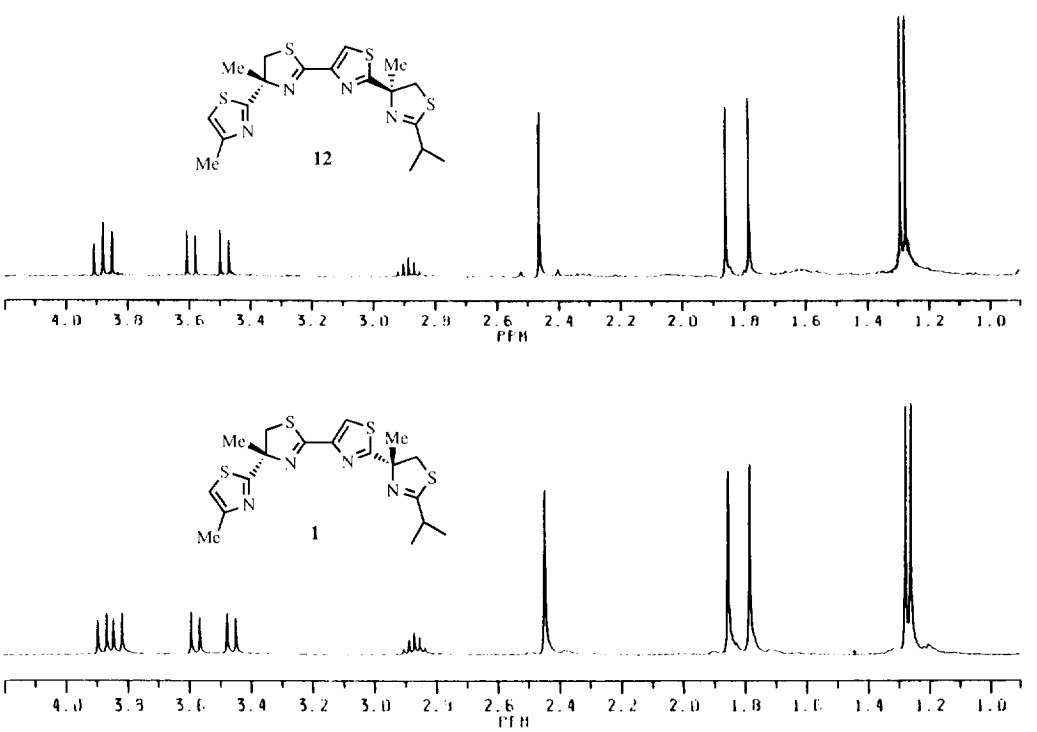
The synthesis of the didehydromirabazole A isomer (**12**) was carried out using the strategy described earlier for the isomer (**1**), but starting from methyl *S*-2-methylcysteine hydrochloride (**4**). The route is



Reagents: i, methyl *iso*butyrimidate hydrochloride (**5**), Et_3N, CH_2Cl_2; ii, EtOH/aq. NH_3; iii, Lawesson's reagent, THF; iv, ethyl bromopyruvate, EtOH, Δ; v, $Et_3O^+PF_6^-$, CH_2Cl_2, Δ; vi, *R*-2-methylcysteine methyl ester hydrochloride, CH_2Cl_2; vii, chloroacetone, EtOH, Δ.

Scheme 1

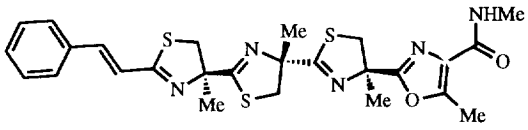
summarised in Scheme 1. Concise syntheses of both the *S*- and the *R*-enantiomers of 2-methylcysteine hydrochloride were achieved by a modification of Seebach's 'self-regeneration of chirality protocol', and this work has been summarised in an earlier publication.[7] A cyclocondensation reaction between methyl *S*-2-methylcysteine hydrochloride (**4**) and the imino ether (**5**) first led to the 4*S*-thiazoline (**6**), whose stereochemical integrity, *ie* ee > 95%, was established using chiral hplc analysis. After conversion of (**6**) into the thioamide (**7**) *via* the corresponding amide, a Hantzsch reaction between (**7**) and ethyl bromopyruvate next produced the thiazoline-thiazole (**8**). The thiazole (**8**) was converted into the amide (**9**), and then into the corresponding imino ether in readiness for a second condensation with *R*-2-methycysteine hydrochloride producing the tricyclic ester (**10**). Finally, elaboration of the ester (**10**) to the thioamide (**11**), *via* the amide, followed by a cyclocondensation reaction with chloroacetone produced 4*R*, 4*S*'-didehydromirabazole (**12**) as a viscous oil. The synthetic compound (**12**) showed nmr spectroscopic data which were identical to those described for natural didehydromirabazole A, and their 500 MHz pmr spectra were superimposable. Finally, the specific rotation of the synthetic mirabazole (**12**) was $[\alpha]_D$ - 26.1 (c 0.41 in $CHCl_3$) where the specific rotation for natural didehydromirabazole A is $[\alpha]_D$ - 26 (c 0.44 in $CHCl_3$). These data thus establish that the stereostructure of didehydromirabazole A from the blue-green alga *S mirabile*, should be revised to (**12**).



P.m.r Spectra (δ 1.0 - 4.0 p.p.m.) of the Synthetic Didehydromirabazoles (12) and (1).

When Professor R.E. Moore kindly compared the proton and carbon nmr spectra of our previously synthesised didehydromirabazole A isomer (**1**) with those of the natural product, they appeared identical. A direct comparison could not be made however since our original pmr spectrum was recorded at 400 MHz; nevertheless all the chemical shifts appeared to be the same. This was in spite of the fact that the optical rotations for the synthetic and natural materials were at variance, *ie* $[\alpha]_D$ - 289 against $[\alpha]_D$ - 26. Clearly there were differences to be seen however in the δ 3.0 - 4.0 ppm regions of the pmr spectra of our synthetic 4*R*, 4*S*' - and 4*R*, 4*R*' - isomers of (-)-didehydromirabazole at 400 MHz, and these spectra are reproduced above.

In the accompanying paper we describe our complementary studies of a total synthesis of thiangazole (**13**),[8] a compound which has a structure based on the linear fusion of three successive 2,4-disubstituted thiazoline/oxazole rings terminating in a 2-cinnamyl thiazoline. This fascinating secondary metabolite, a novel inhibitor of HIV-1, has been isolated from the gliding bacterium *Polyangium sp.*



13

EXPERIMENTAL

For general experimental details see reference 2. Prefixes A,B,C and D in the assignments of cmr chemical shift data refer to the ring numbering system used in formula (**1**).

(4S)-4-Methoxycarbonyl-4-methyl-2-isopropyl-Δ^2-thiazoline (**6**). - Triethylamine (4.57 ml, 32.8 mmol) was added dropwise over 5 min to a stirred solution of methyl (*S*)-2-methylcysteine hydrochloride (**4**) (5.80 g, 29.8 mmol) and methyl *iso*butyrimidate hydrochloride (5.24 g, 35.8 mmol) in dichloromethane (100 ml). The mixture was stirred at room temperature for three days and then water (40 ml) was added. The separated aqueous layer was extracted with dichloromethane (3x30 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 20% ethyl acetate-light petroleum as eluant to give the *thiazoline* (1.92 g, 31%) as a colourless oil; $[\alpha]_D$ 4.2 (c 1.27 in $CHCl_3$); λ_{max} (EtOH) 235 (137), 256 (129) nm; ν_{max} (film) 2969, 1736, 1618, 1458, 1438, 1232 and 1200 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 3.68 (3H, s, OCH_3), 3.62 (1H, d, *J* 11.4 Hz, C*H*H), 3.02 (1H, d, *J* 11.4 Hz, CH*H*), 2.77 (1H, septet, *J* 6.0 Hz, C*H*$(CH_3)_2$), 1.42 (3H, s, CH_3), 1.31 (6H, d, *J* 6.0 Hz, $CH(CH_3)_2$); δ_C (67.8 MHz; $CDCl_3$) 178.00 and 173.94 (2xs, CO and SC:N), 83.74 (s, $C(CH_3)CO_2CH_3$), 52.72 (q, OCH_3), 41.04 (t, CH_2), 33.95 (d, CH), 23.83 (q, CH_3), 21.21 and 21.12 (2xq, $CH(CH_3)_2$); m/z (EI) 201 (M^+, 4%), 142 (25) and 100 (7). Chiral HPLC (100% EtOH, florsil on cellulose triacetate, Merck Col 281) (T_R for 4*R* = 20.4 min, T_R for 4*S* = 24.7 min) showed one enantiomer, *ie* ee > 95%.

(4S)-4-Methyl-4-carboxamide-2-isopropyl-Δ^2-thiazoline . - Aqueous ammonia solution (20 ml) was added in one portion to a stirred solution of (4*S*)-4-methoxycarbonyl-4-methyl-2-*iso*propyl-Δ^2-thiazoline (1.85 g, 8.80 mmol) in ethanol (10 ml). The solution was stirred overnight at room temperature, and then the ethanol was

evaporated *in vacuo*. Brine (20 ml) was added to the residue, which was then extracted with ether (4x25 ml). The combined ether extracts were dried, and then evaporated *in vacuo* to leave an oil. The oil was purified by column chromatography on silica gel using 30% ethyl acetate-light petroleum as eluant to give the *amide* (1.24 g, 76%) as a white solid which was recrystallised from ether-light petroleum to afford white crystals, m.p. 41-42°C; $[\alpha]_D$ 173 (c 1.51 in $CHCl_3$); (Found: C, 51.44; H, 7.74; N, 15.20; $C_8H_{14}N_2OS$ requires C, 51.58; H, 7.58; N, 15.04); λ_{max} (EtOH) 235 (2512), 256 (2384) nm; ν_{max} ($CHCl_3$) 3453, 3295, 2970, 2931, 1682 and 1618 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 6.70 and 6.41 (2H, 2xbrd, NH_2), 3.60 (1H, d, *J* 11.5 Hz, C*H*H), 3.15 (1H, d, *J* 11.5 Hz, CH*H*), 2.75 (1H, septet, *J* 6.9 Hz, C*H*$(CH_3)_2$), 1.46 (3H, s, CH_3), 1.19 (6H, d, *J* 6.9 Hz, CH(CH_3)$_2$); δ_C (67.8 MHz; $CDCl_3$) 178.23 and 177.93 (2xs, CO and SC:N), 84.17 (s, *C*$(CONH_2)CH_3$), 40.92 (t, CH_2), 33.93 (d, CH), 24.82 (q, CH_3), 21.15 and 20.99 (2xq, CH(CH_3)$_2$); m/z (EI) 187.0898 (MH^+, 3%, $C_8H_{15}N_2OS$ requires 187.0905), 142 (100) and 73 (96).

(4R)-4-Methyl-4-thioamide-2-isopropyl-Δ^2-thiazoline (**7**). - Lawesson's reagent (1.31 g, 3.24 mmol) was added to a stirred solution of the above amide (1.20 g, 5.88 mmol) in THF (25 ml) under a nitrogen atmosphere. The resulting solution was stirred overnight at room temperature , then the solvent evaporated *in vacuo* to leave a residue which was partitioned between saturated $NaHCO_3$ solution (40 ml) and ether (20 ml). The separated aqueous layer was extracted with ether (3x20 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 10% ethyl acetate-light petroleum as eluant to give the *thioamide* (0.82 g, 64%) as a white solid which was recrystallised from ethyl acetate to afford white crystals, m.p. 120-121°C; $[\alpha]_D$ 237.2 (c 0.78 in $CHCl_3$); (Found: C, 47.52; H, 7.17; N, 13.88; $C_8H_{14}N_2S_2$ requires C, 47.49; H, 6.97; N, 13.85); λ_{max} 268 (9649) nm; ν_{max}($CHCl_3$) 3274, 2928 and 1604 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 8.54 and 8.08 (2H, 2xbrd, NH_2), 3.67 (1H, d, *J* 11.5 Hz, C*H*H), 3.34 (1H, d, *J* 11.5 Hz, CH*H*), 2.71 (1H, septet, *J* 7.0 Hz, C*H*$(CH_3)_2$), 1.51 (3H, s, CH_3), 1.15 (6H, d, *J* 7.0 Hz, CH(CH_3)$_2$); δ_C (67.8 MHz; $CDCl_3$) 213.07 (s, CS), 178.00 (s, SC:N), 89.15 (s, *C*$(CSNH_2)CH_3$), 43.63 (t, CH_2), 34.13 (d, CH), 27.42 (q, CH_3), 21.17 and 20.95 (2xq, CH(CH_3)$_2$); m/z (EI) 202.0588 (M^+, 1%, $C_8H_{14}N_2S_2$ requires 202.0598), 142 (100) and 73 (38).

(4R)-4-Methyl-4-[2'(4'-ethoxycarbonyl)thiazole]-2-isopropyl-Δ^2-thiazoline (**8**). - Ethyl bromopyruvate (631 µl, 5.02 mmol) was added dropwise to a solution of the thioamide (**7**) (820 mg, 3.72 mmol) in ethanol (20 ml) over 1 min, and the resulting solution was heated under reflux overnight under a nitrogen atmosphere. The solvent was evaporated *in vacuo* to leave a residue which was partitioned between saturated $NaHCO_3$ (20 ml) solution and ether (20 ml). The separated aqueous layer was extracted with ether (3x20 ml), 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 10% ethyl acetate-light petroleum as eluant to give the *bis-ester* (450 mg, 38%) as a colourless oil; $[\alpha]_D$ 96.1 (c 2.08 in $CHCl_3$); λ_{max} 234 (10 021) and 256 (10 090) nm; ν_{max} (film) 2930, 1734, 1614, 1482, 1367 and 1098 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 8.02 (1H, s, SCH:), 4.37 (2H, q, *J* 7.1 Hz, C*H*$_2CH_3$), 3.79 (1H, d, *J* 11.5 Hz, C*H*H), 3.46 (1H, d, *J* 11.5 Hz, CH*H*), 2.82 (1H, septet, *J* 6.9 Hz, C*H*$(CH_3)_2$), 1.74 (3H, s, CH_3), 1.36 (3H, t, *J* 7.1 Hz, CH_2CH_3), 1.23 (6H, d, *J* 6.9 Hz, CH(CH_3)$_2$); δ_C (67.8 MHz; $CDCl_3$) 179.74 and 177.60 (2xs, A2 and B2), 161.44 (s, CO), 61.35 (t, *C*H_2CH_3), 44.96 (t, A5), 33.96 (d, *C*H$(CH_3)_2$), 27.82 (q, CH_3), 21.17 and 21.04 (2xq, CH(CH_3)$_2$), 14.36 (q, CH_2CH_3); m/z (FAB) 299 (MH^+, 100%), 298 (M^+, 6), 184 (45) and 142 (25).

(4R)-4-Methyl-4-[2'(4'-carboxamide)thiazole]-2-isopropyl-Δ^2-thiazoline (**9**). - Aqueous ammonia solution (7 ml) was added in one portion to a stirred solution of the ester (**8**) (450 mg, 1.42 mmol) in ethanol (4 ml), and the resulting solution was stirred overnight at room temperature. The solvent was evaporated *in vacuo* and the solid residue was partitioned between brine (10 ml) and ether (20ml). The separated aqueous layer was extracted with ether (3x20 ml), and the combined organic extracts were dried and evaporated *in vacuo* to leave a solid. The solid residue was purified by column chromatography on silica gel using 40% ethyl acetate-light petroleum as eluant to give the *bis-amide* (340 mg, 84%) as a white solid which was recrystallised from ether to afford white crystals, m.p. 94-96°C; $[\alpha]_D$ 248 (c 0.90 in $CHCl_3$); (Found: C, 49.03; H, 5.67; N, 16.01; $C_{11}H_{15}N_3OS_2$ requires C, 49.05; H, 5.61; N, 15.61); λ_{max} (EtOH) 233 (10 149), 308 (812) nm; ν_{max} ($CHCl_3$) 3282, 2926, 1670, 1616, 1365 and 1023 cm^{-1}; δ_H (270 MHz; $CDCl_3$) 7.97 (1H, s, SCH:), 7.07 and 5.79 (2H, 2xbrd, NH_2), 3.69 (1H, d, *J* 11.1 Hz, C*H*H), 3.36 (1H, d, *J* 11.1 Hz, CH*H*), 2.80 (1H, septet, *J* 6.5 Hz, C*H*(CH_3)$_2$), 1.69 (3H, s, CH_3), 1.20 (6H, d, *J* 6.5 Hz, CH(C*H*$_3$)$_2$); δ_C (67.8 MHz; $CDCl_3$) 179.51 and 176.82 (2xs, A2 and B2), 163.20 (s, CO), 149.32 (s, B4), 124.20 (d, B5), 83.25 (s, A4), 44.13 (t, A5), 34.05 (d, *C*H(CH_3)$_2$), 27.89 (q, CH_3), 21.17 and 21.04 (2xq, CH(*C*H$_3$)$_2$); m/z (EI) 270.0111 (MH^+, 16%, $C_{11}H_{16}N_3OS_2$ requires 270.0173), 254 (39), 236 (87), 199 (100), 156 (77) and 142 (72).

(4R)-4-Methyl-4-[2'(4'-(2"-((4"R)-4"-methoxycarbonyl-4"-methyl))-Δ^2-thiazoline)thiazole]-2-isopropyl-Δ^2-thiazoline (**10**). - Triethyloxonium hexafluorophosphate (462 mg, 1.66 mmol) was added in one portion to a stirred solution of the amide (**9**) (320 mg, 1.19 mmol) in dichloromethane (10 ml) under an atmosphere of nitrogen. The resulting solution was heated under reflux for 48h and then washed with saturated $NaHCO_3$ solution (10 ml). The separated aqueous layer was extracted with dichloromethane (3 x 10 ml), and then the combined organic extracts were dried and evaporated *in vacuo* to leave the crude imino ether as a brown oil. *R*-2-Methylcysteine methyl ester hydrochloride[7] (440 mg, 2.38 mmol) was added to the crude imino ether in dichloromethane (8 ml) and the resulting suspension was stirred at room temperature for 72h. Water (10 ml) was added and the separated aqueous layer was then extracted with dichloromethane (3x10 ml). The combined organic extracts were dried and evaporated *in vacuo* to leave an oil. The oil was purified by chromatography on silica gel using 20% ethyl acetate-light petroleum as eluant to give the *bis-thiazoline* (150 mg, 33%) as a colourless oil; $[\alpha]_D$ 170.2 (c 1.12 in $CHCl_3$); λ_{max} (EtOH) 217 (20 437), 255 (19 965) nm; ν_{max} (film) 2970, 1734, 1609, 1436, 1256, 1232, 1172, 1118 and 1015 cm^{-1}; δ_H (270MHz; $CDCl_3$) 7.85 (1H, s, SCH:), 3.78 (1H, d, *J* 11.2 Hz, C*H*H), 3.76 (1H, d, *J* 11.6 Hz, C*H*H), 3.74 (3H, s, OCH_3), 3.39 (1H, d, *J* 11.6 Hz, CH*H*), 3.18 (1H, d, *J* 11.2 Hz, CH*H*), 2.80 (1H, septet, *J* 6.9 Hz, C*H*(CH_3)$_2$), 1.70 (3H, s, A4-CH_3), 1.58 (3H, s, C4-CH_3), 1.19 (6H, d, *J* 6.9 Hz, CH(C*H*$_3$)$_2$); δ_C (67.8 MHz; $CDCl_3$) 179.64 (s), 176.82 (s), 173.73 (s), 148.54 (s, B4), 121.44 (d, B5), 84.44 and 83.38 (2xs, A4 and C4), 52.92 (q, OCH_3), 44.10 and 41.27 (2xt, A5 and C5), 34.04 (d, *C*H(CH_3)$_2$), 28.02 and 24.01 (2xq, 2xCH_3), 21.15 and 21.04 (2xq, CH(*C*H$_3$)$_2$); m/z (EI) 383.0788 (M^+, 7%, $C_{16}H_{21}N_3O_2S_3$ requires 383.0796), 368 (15), 324 (100), 142 (26) and 73 (57).

(4R)-4-Methyl-4-[2'(4'-(2"-((4"R)-4"-carboxamide-4"-methyl))-Δ^2-thiazoline)thiazole]-2-isopropyl-Δ^2-thiazoline . - Aqueous ammonia solution (2 ml) was added in one portion to a stirred solution of the ester (**10**) (140 mg, 0.365 mmol) in ethanol (2 ml). The solution was stirred overnight at room temperature, and then the ethanol was evaporated *in vacuo*. Brine (5 ml) was added to the residue, which was then extracted with ether (4x10 ml). The combined ether extracts were dried, and evaporated *in vacuo* to leave an oil. The oil was

purified by column chromatography on silica gel using 50% ethyl acetate-light petroleum as eluant to give the *amide* (90 mg, 67%) as a gummy solid; $[\alpha]_D$ 81.0 (c 0.78 in $CHCl_3$); λ_{max} (EtOH) 218 (17 624), 255 (18 971) nm; ν_{max} ($CHCl_3$) 3453, 2971, 2929, 1682, 1608, 1436, 1384 and 1188 cm^{-1}; δ_H (250MHz; $CDCl_3$) 7.87 (1H, s, SCH:), 6.78 and 5.45 (2H, 2xbrd, NH_2), 3.84 (1H, d, *J* 11.6 Hz, C*H*H), 3.79 (1H, d, *J* 11.2 Hz, C*H*H), 3.48 (1H, d, *J* 11.2 Hz, CH*H*), 3.34 (1H, d, *J* 11.6 Hz, CH*H*), 2.88 (1H, septet, *J* 6.9 Hz, C*H*(CH_3)$_2$), 1.78 (3H, s, A4-CH_3), 1.63 (3H, s, C4-CH_3), 1.28 (6H, d, *J* 6.9 Hz, CH(CH_3)$_2$); δ_C (67.8 MHz; $CDCl_3$) 179.75 (s), 177.30 (s), 177.16 (s), 163.72 (s, C2), 148.81 (s, B4), 121.04 (d, B5), 85.00 and 83.36 (2xs, A4 and C4), 44.15 and 41.03 (2xt, A5 and C5), 34.05 (d, *C*H(CH_3)$_2$), 27.94 and 24.96 (2xq, 2xCH_3), 21.17 and 21.06 (2xq, CH(*C*H_3)$_2$); m/z (FAB) 369.0895 (MH^+, 25%, $C_{15}H_{21}N_4OS_3$ requires 369.0878), 324 (6), 255 (9), 135 (13), 109 (23), 83 (50) and 57 (100).

(4R)-4-Methyl-4-[2'(4'-(2"-((4"S)-4"-thioamide-4"-methyl))-Δ^2-thiazoline)thiazole]-2-isopropyl-Δ^2-thiazoline (**11**). - Lawesson's reagent (43 mg, 0.106 mmol) was added to a stirred solution of the corresponding amide (78 mg, 0.212 mmol) in THF (1 ml) under a nitrogen atmosphere. The resulting solution was stirred at room temperature overnight, and then the solvent was evaporated *in vacuo* to leave a residue. The residue was partitioned between saturated $NaHCO_3$ solution (10 ml) and ether (10 ml). The separated aqueous layer was extracted with ether (3x10 ml) and the combined ether extracts were then dried and evaporated *in vacuo* to leave an oil. The oil was purified by column chromatography on silica gel using 20% ethyl acetate-light petroleum as eluant to give the *thioamide* (70 mg, 87%) as a white solid which was recrystallised from ether-light petroleum; m.p. 126°C; $[\alpha]_D$ 37.8 (c 1.28 in $CHCl_3$); (Found: C, 46.69; H, 5.41; N, 14.80; $C_{15}H_{20}N_4S_4$ requires C, 46.85; H, 5.24; N, 14.57); λ_{max} (EtOH) 220 (20 047), 256 (20 049) nm; ν_{max} ($CHCl_3$) 3251, 3180, 2968, 1680, 1184 and 1021 cm^{-1}; δ_H (250MHz; $CDCl_3$) 8.66 and 7.90 (2H, 2xbrd, NH_2), 7.87 (1H, s, SCH:), 3.89 (1H, d, *J* 11.8 Hz, C*H*H), 3.81 (1H, d, *J* 11.3 Hz, C*H*H), 3.54 (1H, d, *J* 11.8 Hz, CH*H*), 3.46 (1H, d, *J* 11.3 Hz, CH*H*), 2.87 (1H, septet, *J* 6.9 Hz, C*H*(CH_3)$_2$), 1.77 (3H, s, A4-CH_3), 1.70 (3H, s, C4-CH_3), 1.26 (6H, d, *J* 6.9 Hz, CH(*C*H_3)$_2$); δ_C (67.8 MHz; $CDCl_3$) 212.24 (s, C:S), 179.89 and 177.20 (2xs, A2 and B2), 163.79 (s, C2), 148.66 (s, B4), 121.37 (d, B5), 89.85 and 83.31 (2xs, A4 and C4), 44.13 and 43.56 (2xt, A5 and C5), 34.04 (d, *C*H(CH_3)$_2$), 27.91 and 27.56 (2xq, 2xCH_3), 21.15 and 21.04 (2xq, CH(*C*H_3)$_2$); m/z (FAB) 324 (M^+, 100%), 183 (9), 142 (15) and 73 (34).

(-)[4R, 4S']-Didehydromirabazole A (**12**). - Chloroacetone (61 µl, 0.761 mmol) was added in one portion to a solution of the thioamide (**11**) (64 mg, 0.152 mmol) in ethanol (2 ml), and the resulting solution was then heated under reflux overnight under a nitrogen atmosphere. The solvent was evaporated *in vacuo* to leave a residue which was then partitioned between saturated $NaHCO_3$ solution (10 ml) and ether (10 ml). The separated aqueous layer was extracted with ether (3x10 ml), and the combined organic extracts were then dried and evaporated *in vacuo* to leave an oil. The oil was purified by column chromatography using 20% ethyl acetate-light petroleum as eluant to give the *title compound* (29 mg, 41%) as a viscous oil; $[\alpha]_D$ -26.1 (c 0.41 in $CHCl_3$); λ_{max} (EtOH) 213 (20 947), 252 (16 475) nm; ν_{max} ($CHCl_3$) 3113, 2971, 2927, 1605 and 1163 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.90 (1H, s, B5), 6.70 (1H, s, D5), 3.81 (1H, d, *J* 11.4 Hz, C5), 3.79 (1H, d, *J* 11.5 Hz, A5), 3.51 (1H, d, *J* 11.4 Hz, C5), 3.40 (1H, d, *J* 11.5 Hz, A5), 2.80 (1H, septet, *J* 7.0 Hz, C*H*(CH_3)$_2$), 2.38 (3H, s, D4-CH_3), 1.78 (3H, s, C4-CH_3), 1.71 (3H, s, A4-CH_3), 1.20 (6H, d, *J* 7.0 Hz, CH(*C*H_3)$_2$); δ_C (100.6 MHz; $CDCl_3$) 179.58 (s, A2), 176.95 (s, B2), 175.52 (s, D2), 163.91 (s, C2), 152.83 (s, D4), 149.02 (s, B4), 121.07

(d, B5), 113.37 (d, D5), 84.15 (s, C4), 83.55 (s, A4), 44.31 (t, A5), 44.22 (t, A5), 34.15 (d, $CH(CH_3)_2$), 28.14 (q, A4-CH_3), 27.87 (q, C4-CH_3), 21.26 and 21.15 (2xq, $CH(CH_3)_2$); m/z (EI) 422.0743 (M^+, 43%, $C_{18}H_{22}N_4S_4$ requires 422.0727), 389 (31), 320 (100), 170 (22) and 73 (40).

ACKNOWLEDGEMENTS

We thank Nottingham University for financial support (to RJB), and Professors R.E. Moore and C.H. Heathcock for helpful correspondence and exchange of pertinent nmr data.

REFERENCES

1 Carmeli, S.; Moore, R.E.; Patterson, G.M.L.; Corbett, T.H.; Valeriote, F.A. *J. Am. Chem. Soc.*, **1990**, *112*, 8195; Carmeli, S.; Moore, R.E.; Patterson, G.M.L. *Tetrahedron Lett.*, **1991**, *32*, 2593.

2 Pattenden, G.; Thom, S.M. *Synlett*, **1992**, 533; Pattenden, G.; Thom, S.M. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1629.

3 Fukuyama, T.; Xu, L. *J. Am. Chem. Soc.*, **1993**, *115*, 8449.

4 Carmeli, S.; Raik, S.; Moore, R.E.; Patterson, G.M.L.; Yoshida, W.Y. *Tetrahedron Lett.*, **1993**, *34*, 6681.

5 Parsons, Jr., R.L.; Heathcock, C.H. *Tetrahedron Lett.*, **1994**, *35*, 1379, *cf Tetrahedron Lett.*, **1994**, *35*, 1383.

6 For preliminary communication see: Boyce, R.J.; Pattenden, G. *Synlett*, **1994**, 587.

7 Pattenden, G.; Thom, S.M.; Jones, M.F. *Tetrahedron*, **1993**, *49*, 2131.

8 Boyce, R.J.; Mulqueen, G.C.; Pattenden, G. *Tetrahedron*, **1995**, Immediately following paper.

(*Received in UK* 19 *April* 1995; *accepted* 5 *May* 1995)