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

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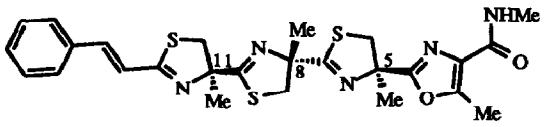
Abstract: A concise total synthesis of the cinnamyl-oxazole substituted *tris*-thiazoline containing metabolite thiangazole **1** is described.

Thiangazole **1**, together with the related tantazoles, e.g. tantazole B **2**, constitute a unique family of biologically interesting alkaloids, which show structures based on the linear fusion of four or five successive 2,4-disubstituted thiazoline/oxazole rings terminating in a 2-cinnamyl or 2-isopropyl thiazoline. Whereas thiangazole has been isolated from the gliding bacterium *Polyangium sp*,[1] the tantazoles are produced by the terrestrial blue-green alga *Scytonema mirabile*.[2] Thiangazole **1** shows a one hundred percent inhibition of HIV-1 infection at 4.7pM, and no cell toxicity at 4.7mM giving a selectivity index of $>10^6$; the compound also discriminates between HIV-1 and HIV-2. The structure of thiangazole was elucidated by spectroscopic methods, and its absolute configuration was derived as shown in **1** by chemical degradation and correlation of CD spectroscopic



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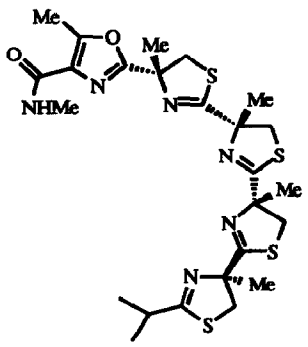

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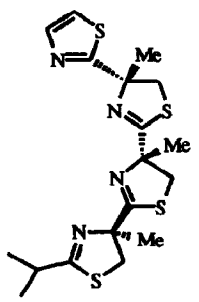
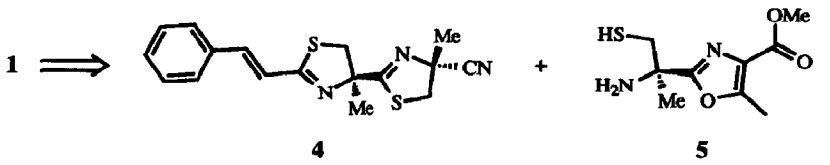


3

data;[2] this stereochemical assignment was more recently confirmed by X-ray crystallographic analysis.[3] Synthetic work by Fukuyama and Xu[4] has shown that the original structure assigned to tantazole B needed to be

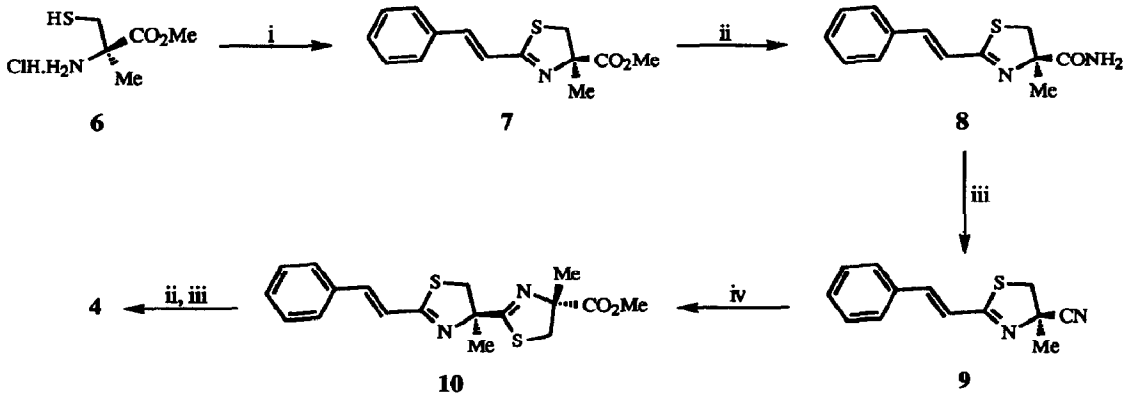
revised to **2**, in which the stereocentre in the isopropyl substituted thiazoline ring has the *R*-(α–methyl), rather than the *S*-(β-methyl) configuration. In contemporaneous structural and synthetic studies with the related mirabazole family of thiazoline/thiazole metabolites, e.g. mirabazole C **3**, from blue-green algae, other researchers[5,6,7] have concluded that all the mirabazoles and tantazoles have the same *R*-configuration at the same stereocentres in their isopropyl substituted thiazoline rings. In this *Letter* we describe a concise total synthesis of 5*R*,8*S*,11*S*-thiangazole **1**, using a strategy based on a cycloeondensation between the *R*-2-methylcysteine derived *bis*-thiazoline nitrile **4** and the oxazole **5** as a key step (Scheme 1).



4 **5**

Scheme 1

Thus, a cyclocondensation reaction between *R*-2-methylcysteine methyl ester hydrochloride **6**[8] and cinnamonitrile (MeOH, Et_3N, reflux, 48h)[9] first led to the cinnamyl substituted 4-methylthiazoline ester **7**, as a pale yellow semi-solid in 40% yield.[10] The ester **7** was next converted into the nitrile **9** *via* the corresponding amide **8** [EtOH-aq NH_3, 25°C, 24h (71%); then Ph_3P-CCl_4, 50°C, 2h (74%)],[11] and a second cyclocondensation reaction between **9** and the methylcysteine **6** then produced the *bis*-thiazoline (**10**; 54%) as a yellow oil, $[\alpha]_D$ -168.8 (c 2.47 in CH_2Cl_2). Elaboration of the ester **10** to the corresponding amide, mp 137-40°C (65%), and then to the nitrile intermediate (**4**; 15%), $[\alpha]_D$ - 158.9 (c 2.14 in CH_2Cl_2), was then carried out using the same procedures that were used to convert **7** into **9** (Scheme 2).

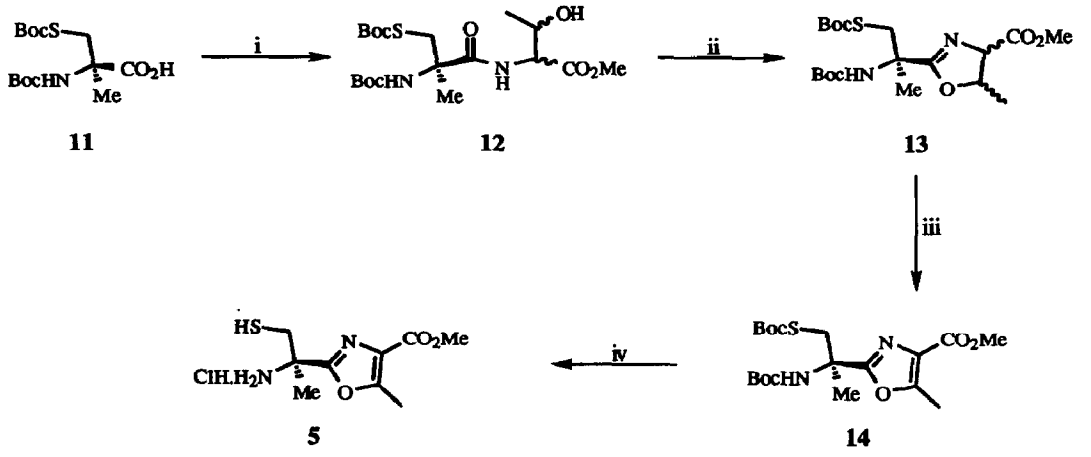


6 **7** **8** **9** **10**

Reagents : i, PhHC=CHCN, Et_3N, MeOH, Δ (40%); ii, EtOH-aq NH_3, 25°C (71%); iii, PPh_3, CCl_4, THF, 50°C (74%); iv, **6**, Et_3N, MeOH, Δ (54%)

Scheme 2

The 2-methylcysteine derived oxazole **5** was synthesised from *bis*-Boc protected 2-methylcysteine **11**[12] as shown in Scheme 3. Thus, a coupling reaction between **11** and (±)-threonine methly ester hydrochloride (pyBOP, Et_3N, CH_2Cl_2, then Thr-HCl, Et_3N, 25°C, 24h)[13] first led to the corresponding amide (**12**; 68%) which was then converted into a mixture of diastereoisomers of the oxazoline **13** in 70% yield following treatment with Burgess reagent (THF, reflux, 12h).[14] Oxidation of **13** using nickel peroxide, or better using t-butylperoxybenzoate in the presence of copper(I) bromide (C_6H_6, reflux, 3h),[15] next produced the oxazole (**14**; 34%) which was then deprotected in the presence of anhydrous hydrochloric acid in ether (reflux 3h) leading to the *R*-2-methylcysteine derived oxazole (**5**; 68%) which was obtained as a white solid, mp 153°C (dec.); $[\alpha]_D$+ 5.2 (c1.3 in EtOH).

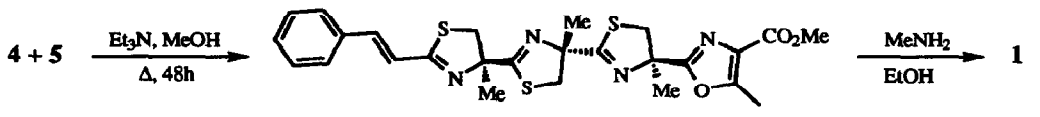


11 12 13 14 5

Reagents: i, pyBOP,[13] Et_3N, CH_2Cl_2, then (±)-Thr-HCl, Et_3N, 25°C (68%); ii, Burgess reagent,[14] THF (70%); iii, $^tBuOCOOPh$, Cu(I)Br, C_6H_6, Δ, (34%); iv, HCl-Et_2O (68%)

Scheme 3

A condensation reaction between the *bis*-thiazoline nitrile **4** and the 2-methylcysteine derived oxazole **5** (Et_3N, MeOH, reflux, 48h) produced the *tris*-thiazoline oxazole [**15**; 35% or 70% based on recovered nitrile **4**] as a yellow oil. Finally, treatment of the ester **15** with methylamine (33% in EtOH, 25°C, 4h) followed by chromatography and crystallisation gave thiangazole (**1**; 75%) as colourless crystals, mp and mixed mp 141°C (from acetone) with natural thiangazole (mp 142°C). The synthetic thiangazole showed an optical rotation of $[\alpha]_D$



15

-275 (c 0.1 in MeOH) [*cf* natural thiangazole has $[\alpha]_D$ -287 (c 0.1 in MeOH)], and its pmr, cmr, ir, and uv spectroscopic data were identical to those obtained for natural thiangazole isolated from *Polyangium sp.*

Acknowledgements

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10. Satisfactory spectroscopic data, together with microanalytical and/or mass spectrometry data were obtained for all new compounds. The *bis*-thiazoline nitrile **4** showed $[\alpha]_D$ -158.9 (c 2.14 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2980, 2928, 2243, 1632, 1608, 733 and 690; 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, CH), 6.96 (1H, d, *J* 16.2, CH), 3.72 (1H, d, *J* 11.2, C*H*H), 3.65 (1H, d, *J* 11.5, C*H*H), 3.29 (1H, d, *J* 11.2, CH*H*), 3.22 (1H, d, *J* 11.5, CH*H*), 1.62 (3H, s, CH_3), 1.61 (3H, s, CH_3); δ_C (67.8 MHz; $CDCl_3$) 180.1 (s), 168.5 (s), 142.3 (d), 134.9 (s), 129.8 (d), 128.9 (d), 127.6 (d), 122.1 (d), 120.6 (s), 83.3 (s), 73.1 (s), 43.1 (t), 42.1 (t), 25.9 (q), 25.0 (q); m/z (EI) 327.0868 (M^+, $C_{17}H_{17}N_3S_2$ requires 327.0864). The oxazole **5** showed m.p. 153°C (dec.); $[\alpha]_D$ +5.2 (c 1.3 in EtOH); λ_{max}(EtOH)/nm 217 (5889); ν_{max}(KBr disc)/cm^{-1} 2924, 2853, 1719, 1618,1448, 1373, 1205 and 1138; 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), 159.87 (s), 129.88 (s), 53.56 (s), 53.06 (q), 33.39 (t), 23.05 (q), 12.72 (q).
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