Synthesis and establishment of stereochemistry of the unusual polyoxazole–thiazole based cyclopeptide YM-216391 isolated from *Streptomyces nobilis*

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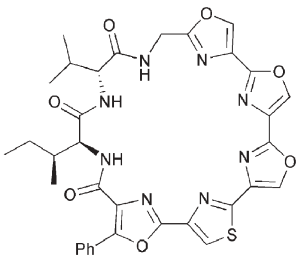
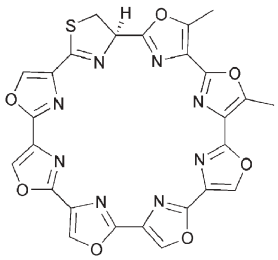
Received (in Cambridge, UK) 28th October 2004, Accepted 19th November 2004
First published as an Advance Article on the web 23rd December 2004
DOI: 10.1039/b416530f

A concise total synthesis of the unusual oxazole-based cyclopeptide structure YM-216391, which also establishes the stereochemistry of the natural product *i.e.* 1, is described.

The unusual polyoxazole–thiazole-based cyclopeptide **1**, designated YM-216391, was recently isolated from *Streptomyces nobilis*.[1] It shares both a structural and biological homology with the potent telomerase inhibitor telomestatin **2** which is showing promise in cancer chemotherapy.[2] The structure of YM-216391 comprises a continuum of five azoles which have their origins in serine, cysteine and phenylalanine, linked *via* a glycine–valine–isoleucine tripeptide tether. The complete stereochemical assignment of YM-216391 has not been established. In this *communication* we describe a concise total synthesis of the cyclopeptide, which not only confirms its unique structure but also allows the assignment of its stereochemistry, shown in formula **1**.



1



2

Thus, the 2,4-disubstituted oxazoles **3** and **4** and the trisubstituted oxazole **5** were first elaborated from their constituent amino acids using methodology which is well-precedented in the literature.[3] A coupling reaction between **3** and **4** in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole (HOBt) and 4-methylmorpholine (NMM)[4] next led to the amide **6** which was then converted into the trisoxazole **8a**, *via* **7**, in three straightforward steps (Scheme 1). Saponification of **8a**, followed by coupling the resulting carboxylic acid **8b** with the oxazole substituted amine **5** (EDC, HOBt, NMM; 87%) next led to the tetraoxazole amide **9**. The amide **9** was then

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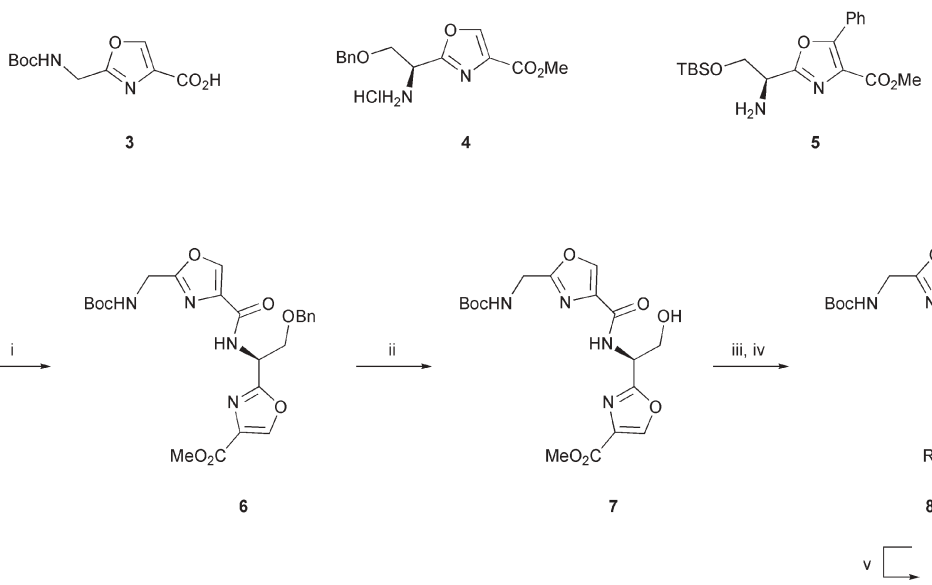
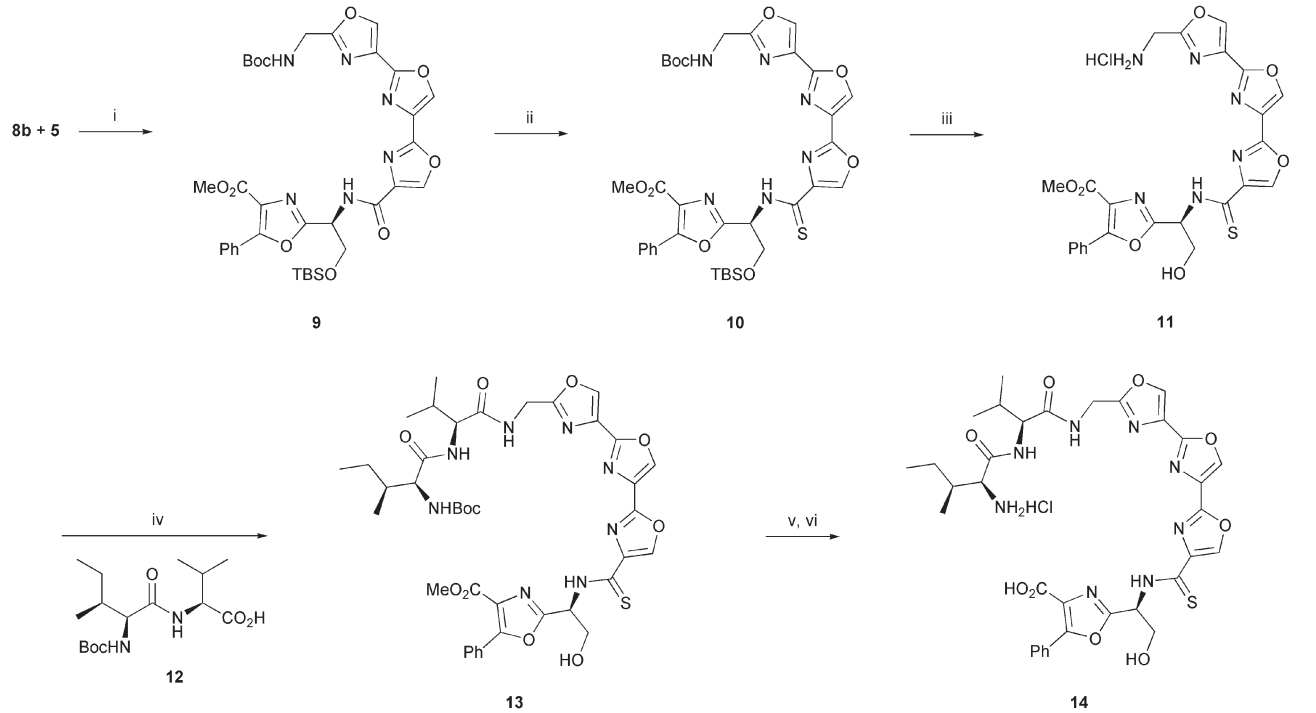
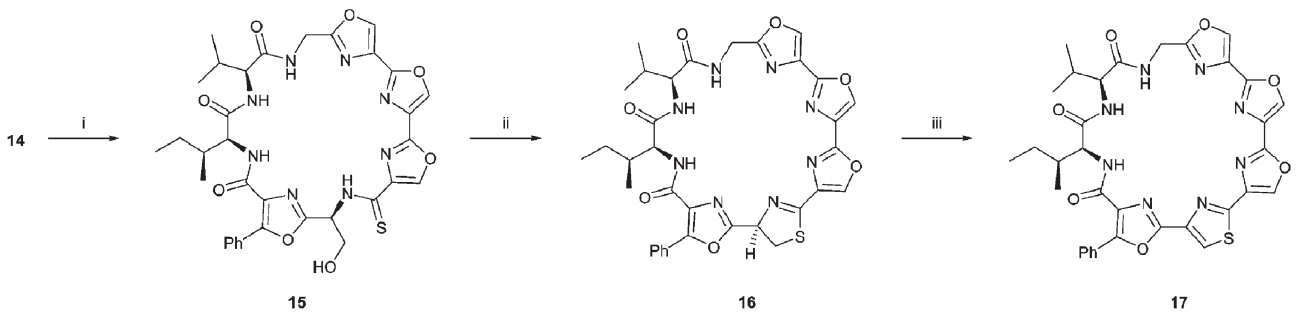


Scheme 1 *Reagents and conditions*: i, EDC, HOBt, NMM, CH_2Cl_2, 0 °C → rt, 24 h, 56%; ii, H_2, 20% $Pd(OH)_2$/C, MeOH–THF (2 : 1), rt, 81%; iii, DAST, CH_2Cl_2, −78 °C, 1.5 h; iv, $BrCCl_3$, DBU, CH_2Cl_2, 0 °C → rt, 24 h, 57% over two steps; v, NaOH, THF, H_2O, rt, 24 h, 88%.



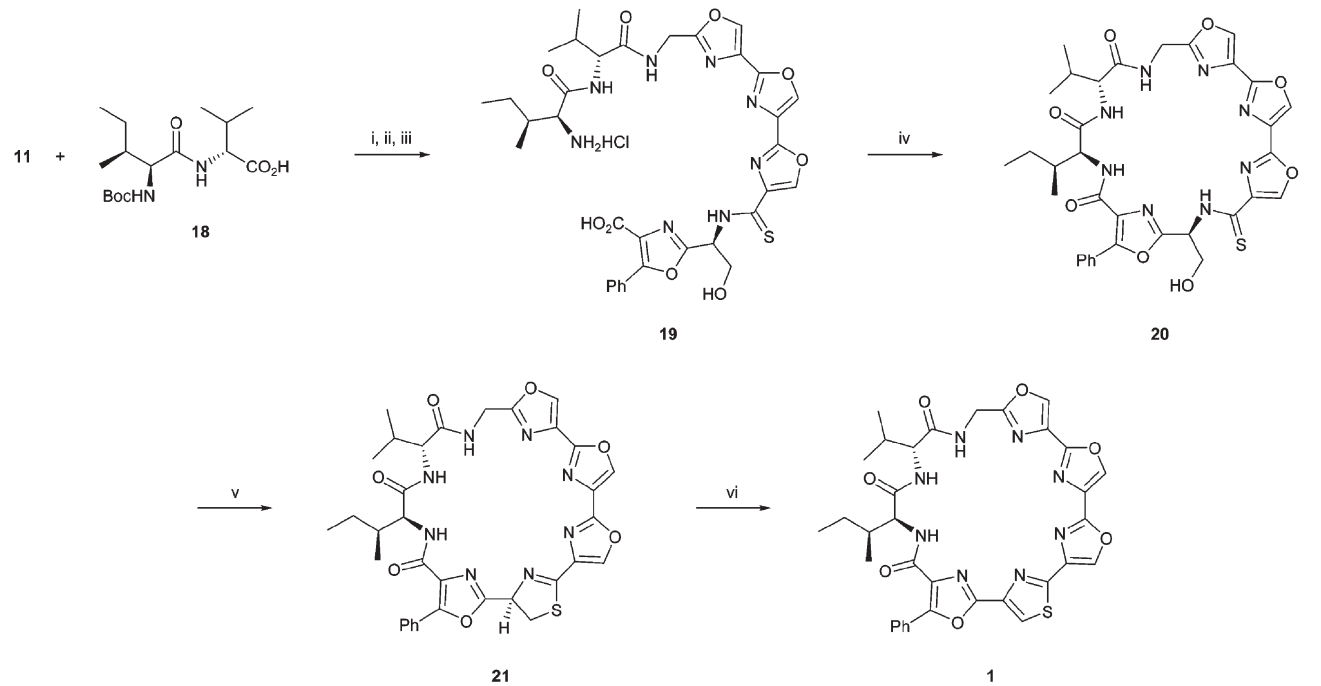
Scheme 2 *Reagents and conditions*: i, EDC, HOBt, NMM, CH_2Cl_2, 0 °C → rt, 24 h, 87%; ii, Lawesson's reagent, THF, reflux, 18 h, 50%; iii, 4.0 M HCl solution in dioxane, rt, 24 h, 91%; iv, EDC, HOBt, NMM, CH_2Cl_2, 0 °C → rt, 48 h, 68%; v, NaOH, THF, H_2O, rt, 24 h; vi, 4.0 M HCl solution in dioxane, rt, 18 h, 65% over two steps.



Scheme 3 *Reagents and conditions*: i, HATU, NMM, CH_2Cl_2–DMF (2:1), 0 °C → rt, 72 h, 88%; ii, DAST, CH_2Cl_2, −78 °C, 2 h, 88%; iii, MnO_2, CH_2Cl_2, rt, 48 h, 27%.

converted into the corresponding thioamide **10**, using Lawesson's reagent,[5] which was then deprotected leading to the amine hydrochloride salt **11** (Scheme 2).

Believing that the tripeptide tether in naturally occurring YM-216391 had its origins in the 'natural' amino acids L-isoleucine and L-valine, the azole-based amine **11** was next condensed with the protected dipeptide **12** derived from L-isoleucine and L-valine leading to the advanced precursor **13**. The methyl ester and the *N*-Boc protecting groups in **13** were then removed, in sequence, producing the amino acid **14**, which underwent smooth macrolactamisation in the presence of *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU)[4a,6] and NMM at 0 °C to room temperature leading to the cyclopeptide **15** in an agreeable 88% yield (Scheme 3). Finally, the thioamide unit in **15** was converted into the corresponding thiazoline **16** using (diethylamino)sulfur trifluoride (DAST) in CH_2Cl_2 at −78 °C, which then underwent oxidation in the presence of MnO_2 at room temperature to produce the YM-216391 structure with the stereochemistry shown in formula **17**. Comparison of the ^{1}H NMR spectroscopic data for synthetic **17**[7] with those recorded for natural YM-216391, showed that although there were close similarities, the two structures were not identical. We surmised that the two structures differed in their stereochemistry at the valine residue, and that the natural product was most likely derived from D- rather than L-valine. Accordingly, we re-synthesised the dipeptide **12** using D-valine and L-isoleucine (*cf.* **18**), and then reproduced the sequence of reactions, shown in Schemes 2 and 3, producing the cyclopeptide intermediate **20**, which differs from **15** only according to its stereochemistry at the isopropyl bearing carbon centre (Scheme 4). Conversion of the intermediate **20** into the thiazoline **21**, followed by oxidation with MnO_2 in CH_2Cl_2 then gave the cyclopeptide **1**, whose NMR



Scheme 4 *Reagents and conditions*: i, EDC, HOBt, NMM, CH_2Cl_2, 0 °C → rt, 48 h, 82%; ii, NaOH, THF, H_2O, rt, 24 h; iii, 4.0 M HCl solution in dioxane, rt, 18 h, 70% over two steps; iv, HATU, NMM, CH_2Cl_2–DMF (2:1), 0 °C → rt, 72 h, 75%; v, DAST, CH_2Cl_2, −78 °C, 2 h, 89%; vi, MnO_2, CH_2Cl_2, rt, 48 h, 55%.

spectroscopic data[8] were identical to those described for the natural product YM-216391 produced by *S. nobilis*.

A concise synthesis of the novel anti-tumour cyclopeptide **1** has therefore been achieved which has also established its stereochemistry.

We thank the EPSRC for a studentship (to JD) and Dr Y. Takebayashi (Yamanouchi Pharmaceutical Co. Ltd., Ibaraki, Japan) for helpful correspondence and for supplying relevant NMR spectroscopic data on natural YM-216391. We also thank David Evans for his contribution to the early part of this project.

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7 δ_H (500 MHz, DMSO-d_6) 9.15 (1H, s), 9.05 (1H, s), 8.95 (1H, s), 8.71 (1H, s), 8.58 (1H, d, J = 8.4 Hz), 8.47 (2H, d, J = 7.1 Hz), 8.47–8.40 (1H, m), 7.98 (1H, d, J = 5.6 Hz), 7.62–7.49 (3H, m), 5.13 (1H, dd, J = 17.2 and 8.9 Hz), 4.68 (1H, dd, J = 8.4 and 5.5 Hz), 4.20–4.08 (2H, m), 2.18–2.07 (1H, m), 2.06–1.98 (1H, m), 1.68–1.53 (1H, m), 1.29–1.13 (1H, m) and 1.02–0.71 (12H, m) ppm.
8 Synthetic YM-216391 (**1**): $[\alpha]_D^{20}$ –56 (c = 0.50, $CHCl_3$); δ_H (500 MHz, DMSO-d_6) 9.12 (1H, s), 9.02 (1H, s), 8.93 (1H, s), 8.71 (1H, dd, J = 9.1 and 2.5 Hz), 8.68 (1H, s), 8.58 (1H, d, J = 9.0 Hz), 8.39 (2H, d, J = 7.3 Hz), 8.26 (1H, d, J = 7.2 Hz), 7.61–7.47 (5H, m), 5.04 (1H, dd, J = 16.6 and 9.1 Hz), 4.78 (1H, dd, J = 7.2 and 4.4 Hz), 4.61 (1H, dd, J = 9.0 and 4.6 Hz), 4.22 (1H, d, J = 16.6 Hz), 2.18–2.07 (2H, m), 1.73–1.64 (1H, m), 1.18–1.09 (1H, m) and 0.98–0.76 (12H, m) ppm; δ_C (125 MHz, DMSO-d_6) 171.3, 170.3, 163.5, 160.6, 158.0, 155.9, 155.5, 154.6, 151.3, 141.5, 140.2, 140.0, 139.8, 136.1, 131.2, 130.6, 130.4, 129.6, 129.1(×2), 127.9(×2), 127.2, 122.9, 58.2, 57.8, 38.5, 35.6, 32.1, 25.3, 20.3, 17.9, 15.5 and 12.4 ppm; *m/z* (ESI) found: 719.2043, $C_{34}H_{32}N_8O_7SNa$ [$(M + Na)^+$] requires 719.2012.