Novel polyoxazole-based cyclopeptides from *Streptomyces sp.* Total synthesis of the cyclopeptide YM-216391 and synthetic studies towards telomestatin†

Jon Deeley, Anna Bertram and Gerald Pattenden*

Received 13th February 2008, Accepted 6th March 2008
First published as an Advance Article on the web 11th April 2008
DOI: 10.1039/b802477d

A convergent, complementary, synthetic approach to the contiguously linked tris-oxazole units **10**, **11** and **12** in telomestatin (**1**) and YM-216391 (**2**) is described. The route involves coupling reactions between oxazole 4-carboxylic acids, *viz* **16a**, **16c**, **16d** and oxazole 2-substituted methylamines, *viz* **16b**, **16e**, **17**, leading to the amides **18** and **21**, followed by cyclodehydrations to the corresponding bis-oxazole oxazolines, *e.g.* **19**, and oxidations of the latter using well-established protocols. The tris-oxazoles **11** and **12** were next converted stepwise into the hexa-oxazole bis-macrolactams **33**. Although the bis-macrolactams **33** (*cf.* **28**) could be converted into the corresponding oxazoline-hexa-oxazoles **34** and to the enamides **35**, neither of these intermediates could be elaborated to the hepta-oxazole **30** *en route* to telomestatin **1**. Likewise, neither the hexa-oxazole **47** or application of an intramolecular Hantzsch oxazole ring-forming reaction from **44b** allowed access to the advanced polyoxazole-macrolactam intermediates **48** and **30a**, respectively, towards telomestatin. Combination of the tris-oxazole based methylamine **70** with the dipeptide carboxylic acid **71** derived from D-valine and L-isoleucine, leads to the corresponding amide which, in two straightforward steps, is converted into the ω-amino acid **78**. Macrolactamisation of **78**, using HATU, next produces the cyclopeptide **79** which is then elaborated to the thiazole and oxazole based cyclopeptide YM-216391 (**2**). The synthetic cyclopeptide **2** is shown to be the enantiomer of the natural product isolated from *Streptomyces nobilis.*

Introduction

Telomestatin (**1**)[1] and YM-216391 (**2**)[2] are members of an ever-expanding family of novel macrocycles, containing contiguously-linked 2,4-disubstituted oxazoles and thiazoles, to be isolated from nature. Other members include ulapualide A (**3**),[3] diazonamide A (**4**)[4] and IB-01211 (**5**).[5] Closely related structures are those cyclic peptides which contain oxazoles, thiazoles, oxazolines and thiazolines linked by several amide bonds, *e.g.* dendroamide A (**6**),[6] patellamide B (**7**)[7] and ascidiacyclamide **8**,[8] and the oxazole-pyridine-thiazole linked cyclopeptide antibiotics, represented by sulfomycin II (**9**).[9]

The contiguously-linked oxazoles **3** and **4**, together with the azole-based cyclic peptides **6**, **7** and **8** are mainly of marine origin, whereas those macrocycles **1**, **2**, **5**, and **9** incorporating thiazole/thiazoline rings have, so far, been isolated from microorganisms, *e.g. Streptomyces* bacteria. Telomestatin **1** is a potent inhibitor of telomerase, interacting specifically with the G-quadruplex, and not affecting DNA polymerases or reverse transcriptases;[10] it is showing promise in cancer therapy. The cyclic polyoxazole IB-01211 (**5**) is toxic against tumour cell lines[11] and, like YM-216391 (**3**) shares a structural homology with telomestatin. Indeed, all of the cyclic polyazole based secondary metabolites **1–9** show a diverse array of interesting biological activities,[12] which has made them attractive targets to synthetic chemists in recent years.[13]

In this paper we describe our synthetic studies towards a variety of contiguously linked tris-, penta- and hepta-azole units present in telomestatin and YM-216391, which have culminated in a total synthesis of YM-216391 (**2**)[14] and the synthesis of several polyoxazole acyclic precursors and macrocyclic intermediates related to telomestatin **1**.[15]

Results and discussion

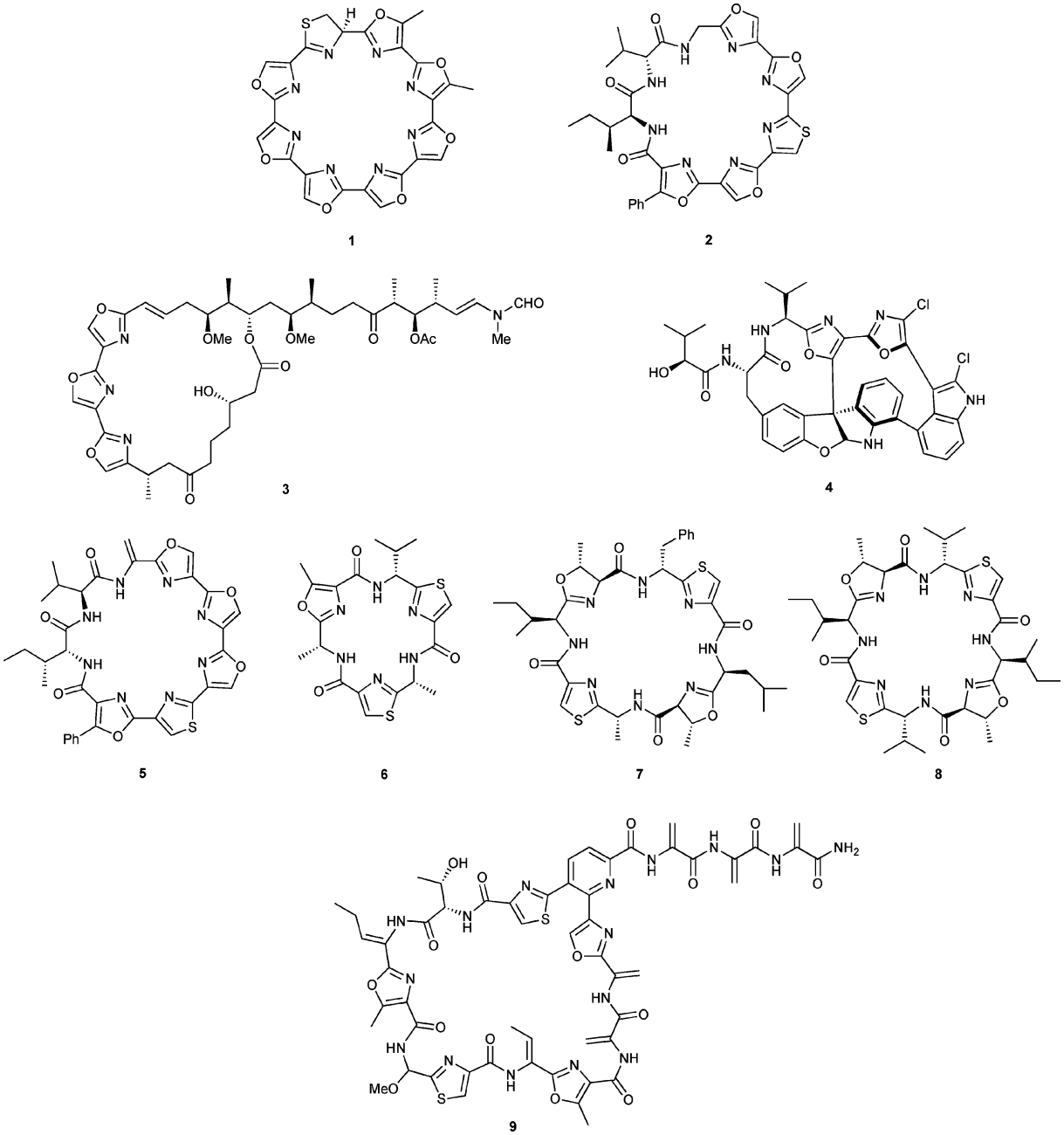
Synthetic strategy, and studies towards arrays of contiguous polyoxazole macrocycles

At the outset of our synthetic studies with telomestatin and YM-216391 only the tris-oxazole based macrolides ulapualide A (**3**) and mycalolide A had succumbed to total synthesis.[16,17] In these syntheses the tris-oxazole units were either elaborated from amide serine precursors by cyclodehydration to oxazoline intermediates followed by oxidation,[18] or by applying iterative Hantzsch oxazole-ring syntheses.[19] Both of these approaches were reliable, robust and high yielding overall. However, the prospect of applying a similar linear approach to the polyazole units in telomestatin or YM-216391 was prohibitive. Other synthetic approaches that have been used to elaborate consecutively linked azoles include: sequential [3 + 2] cycloaddition reactions between rhodium carbenoids and nitriles; Pd(0) catalysed cross coupling reactions; rearrangements of tertiary amides; and base-catalysed cyclisations

School of Chemistry, The University of Nottingham, University Park, Nottingham, UK NG7 2RD

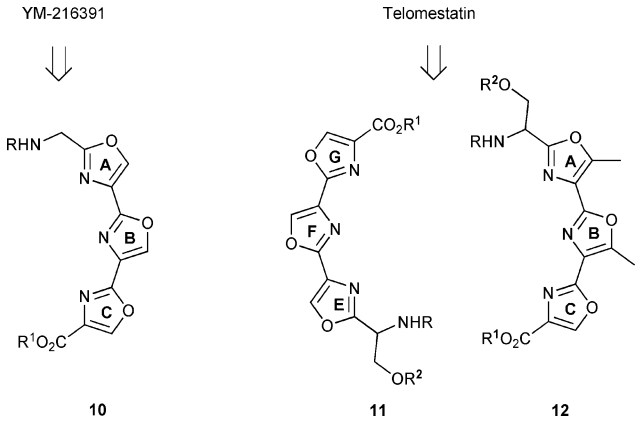
† Electronic supplementary information (ESI) available: Further experimental details for synthesised compounds. See DOI: 10.1039/b802477d

 This journal is © The Royal Society of Chemistry 2008



of alkynyl glycine derivatives.[20,21] To a large degree based on our contemporaneous synthetic studies towards ulapualide A (**3**),[16,18] where we had used a biogenetically-patterned approach to the tris-oxazole unit, *i.e.* making the central oxazole by an initial macrolactamisation from an ω-amino acid precursor, we designed a variety of convergent synthetic approaches to the polyoxazole arrays in **1** and **2**, involving macrolactamisations of bis-, tris- and higher polyoxazoles.

The contiguous tris-oxazole unit **10**, *i.e.* rings A, B, C in YM-216391 (**2**) is directly related to the EFG ring system **11** in telomestatin (**1**). The same ABC tris-oxazole unit **10** in **2** is also analogous to the CBA ring system **12** in telomestatin, except that rings A and B in the latter structure each contain an additional C-2-methyl substituent, *i.e.* the oxazole rings are derived in nature from threonine rather than serine. In our complementary synthetic investigations towards telomestatin and YM-216391, therefore, the closely related substituted tris-oxazoles **10**, **11** and **12** became central synthetic precursors. After examining a range of synthetic strategies we followed a similar convergent approach to each of the tris-oxazoles **10**, **11** and **12**, involving amide coupling reactions between pre-formed oxazole-4-carboxylic acids, *e.g.* **16a/16c**, and oxazole-4-substituted amines, *e.g.* **16b/17c** (Scheme 1). The bis-oxazole amides **18** and **21** were then elaborated to the tris-oxazoles **20** and **22** respectively following cyclodehydrations to the corresponding oxazolines *e.g.* **19** and oxidations of the latter using the procedures and reagents presented in Scheme 2.[22] Saponifications of the methyl ester groups in **22** and **20** then gave the carboxylic acids **23** and **26** respectively. Likewise, removal of the *N*-protecting groups in **20** and **22**, led to the corresponding amines **24** and **25** respectively (Scheme 3).



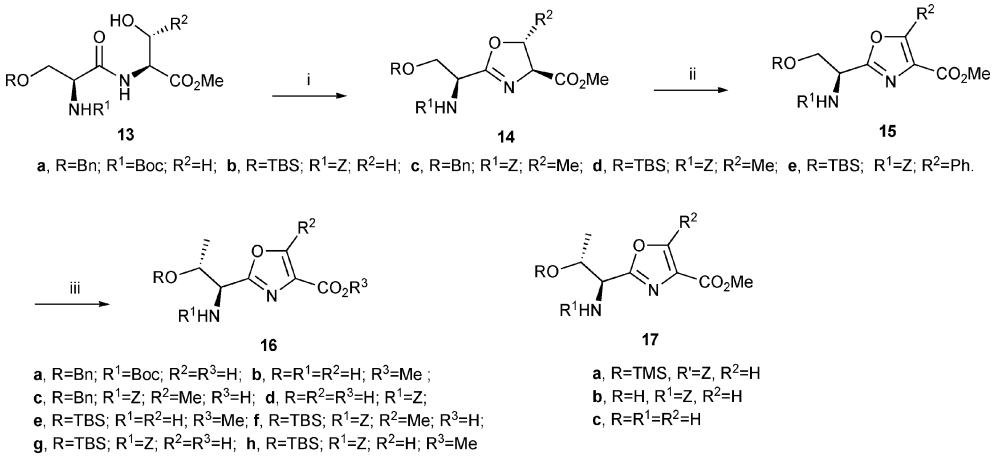
Synthetic studies towards telomestatin 1

With the tris-oxazole-based, and suitably protected, amino acids **23**, **24**, **25** and **26** available, in quantity, *via* the aforementioned synthetic investigations, a number of tactics were considered for their combination, *en route* to telomestatin **1**. In order to allow the greatest conformational flexibility in key macrocyclisation steps, however, we decided to first combine the acids **23**/**26** with the amines **24**/**25**, leading to the respective amides **27**/**29**, and then to effect macrolactamisations from **27**/**29** leading to the corresponding bis-macrolactam **28** as a key intermediate (Scheme 4). Subsequent manipulation of the hydroxyl protecting groups in **28**, accompanied by sequential oxazole/thiazoline ring-forming reactions, *via* intermediates **30**/**31**, would then complete a complementary, convergent synthetic approach to telomestatin. Intuitively, we felt that the tactic of leaving the formation of the thiazoline ring in telomestatin to last *i.e.* proceeding *via* the intermediate **30** was the most prudent. We also felt that the synthesis of **30** starting from **27** would give us the greater number of options to determine at which stage we would introduce a thio ether and/or thioamide unit for thiazoline-ring formation in the natural product.

Thus, a coupling reaction between the amine **24a** and the carboxylic acid **23a**, using EDC–HOBt–NMM[23] first gave the amide **27** in 68% yield. Removal of the *Z*-carbamate group in **27** by hydrogenolysis, followed by saponification of the resulting amino ester **32a** next gave the amino acid salt **32b** (Scheme 5). Macrolactamisation of **32b** in the presence of DPPA–HOBt then gave an excellent yield of the hexa-oxazole-bis-macrolactam **28**. Removal of the silyl ether protecting group in **28** followed by treating the resulting alcohol **33a** with DAST[24] led to the (ring D) oxazoline **34a** in 90% yield. We had hoped that oxidation of the oxazoline ring in **34a** to the corresponding heptaoxazole **30a**, followed by manipulation of the remaining amide unit in **30a** would then provide an expeditious synthesis of telomestatin **1**. How wrong we were! We examined a variety of oxidising agents and conditions, including nickel peroxide,[25] DDQ,[26] and $BrCCl_3$–DBU[22] to convert **34a** into **30a** but all to no avail; on each occasion either starting material was recovered unchanged or intractable material resulted. Furthermore, treatment of the alcohol **33a** with PDC failed to give any of the corresponding aldehyde;[27] hence we were not able to investigate a more direct Robinson Gabriel oxazole-ring forming reaction approach from **33a** to **30a** (Scheme 5). Interestingly, when **33a** was treated with Dess–Martin periodinane followed by immediate treatment with PPh_3, 1,2-dibromotetrachloroethane, di-*tert*-butylpyridine and then with DBU, work-up gave the enamide **35a** resulting from overall dehydration of **33a**. Unfortunately we were not able to convert the enamide **35a** into the corresponding oxazole **30a** following the usual treatment with Br_2–Et_3N, leading to the intermediate vinyl bromide **35b**, and cyclisation of the latter in the presence of Cs_2CO_3.[18,28]

We surmised that a large part of our problem in completing a synthesis of telomestatin **1** from the intermediate bis-macrolactam **28** had its origins in the very poor solubility of **28** and of compounds produced from it, making characterisation inconclusive. In anticipation therefore we changed the protecting groups in the tris-oxazole precursors **20** and **22** and made the alternative silyl/benzyl ether protected bis-macrolactam **37**, *cf.* **28** (Scheme 6). Much to our chagrin, although we could convert **37** into the oxazoline-hexa-oxazole **34b**, we simply could not oxidise this compound to the corresponding hepta-oxazole **30b** and therefore complete a synthesis of telomestatin by this route.

With the persistent problem in attempting to elaborate the ring D oxazole in structure **30** *via* the intermediates **28**, **34**



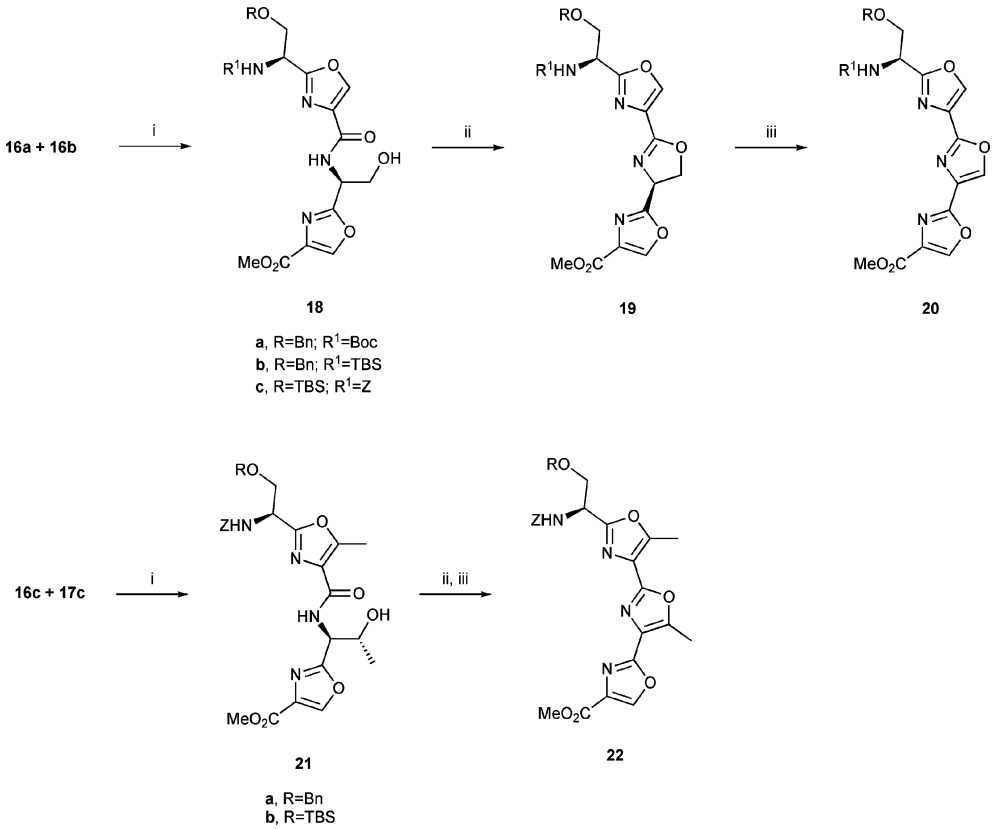
a, R=Bn; R^1=Boc; R^2=H; **b**, R=TBS; R^1=Z; R^2=H; **c**, R=Bn; R^1=Z; R^2=Me; **d**, R=TBS; R^1=Z; R^2=Me; **e**, R=TBS; R^1=Z; R^2=Ph.

a, R=Bn; R^1=Boc; R^2=R^3=H; **b**, R=R^1=R^2=H; R^3=Me ;
c, R=Bn; R^1=Z; R^2=Me; R^3=H; **d**, R=R^2=R^3=H; R^1=Z;
e, R=TBS; R^1=R^2=H; R^3=Me; **f**, R=TBS; R^1=Z; R^2=Me; R^3=H;
g, R=TBS; R^1=Z; R^2=R^3=H; **h**, R=TBS; R^1=Z; R^2=H; R^3=Me

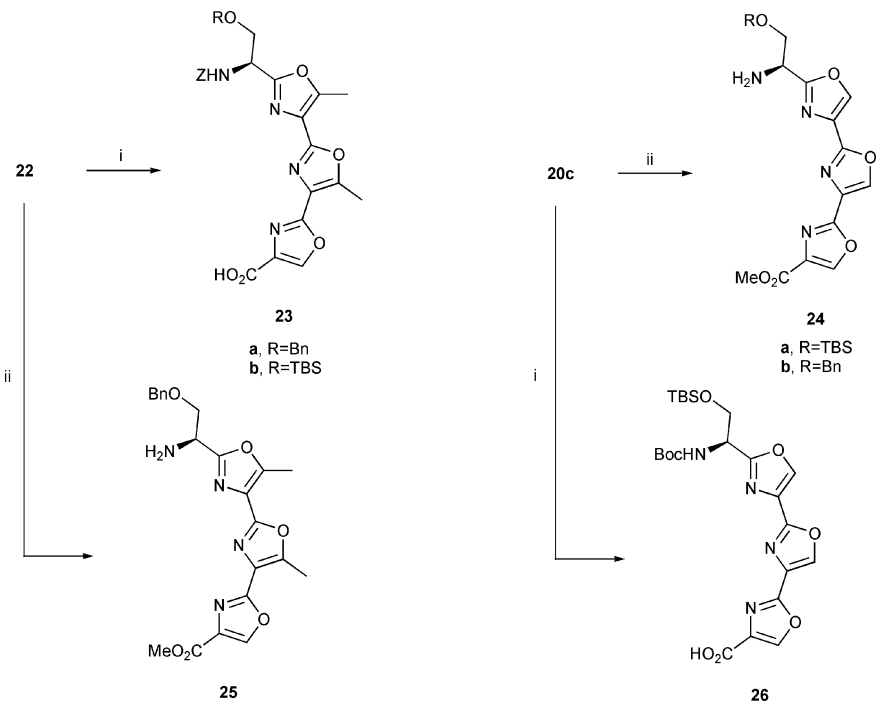
a, R=TMS, R'=Z, R^2=H
b, R=H, R^1=Z, R^2=H
c, R=R^1=R^2=H

Scheme 1 *Reagents and conditions*: i, DAST, DCM, −78 °C, 85–95%; ii, $BrCCl_3$, DBU, DCM, 0–25 °C, 60–70%; iii, sequential and selective deprotections of OR, NHR^1, CO_2Me.

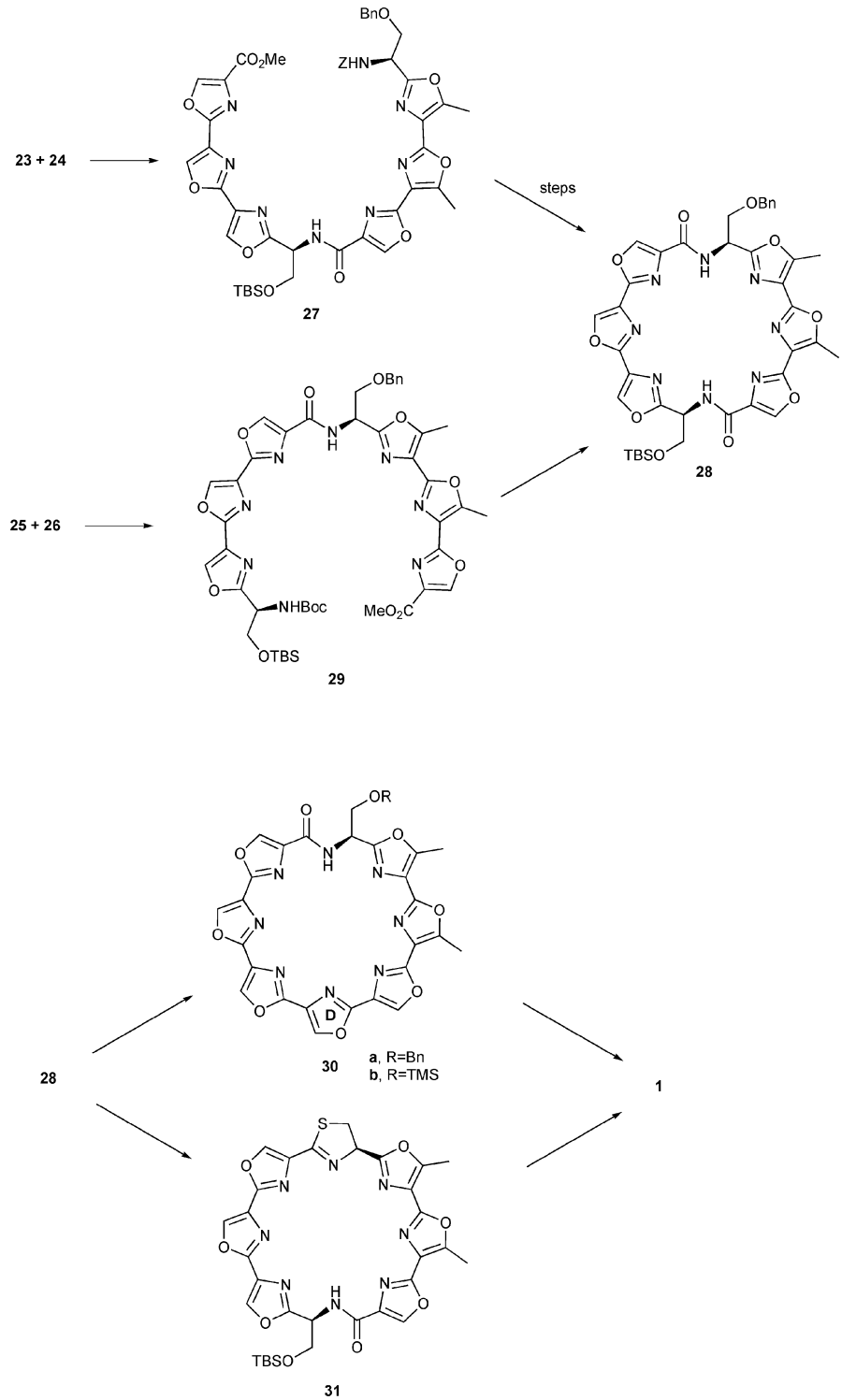
 This journal is © The Royal Society of Chemistry 2008



Scheme 2 *Reagents and conditions*: i, EDC, NMM, HOBt, DCM, 50–70%; ii, DAST, DCM, −78 °C, 85–95%; iii, $BrCCl_3$, DBU, DCM, 0–25 °C, 60–70%.



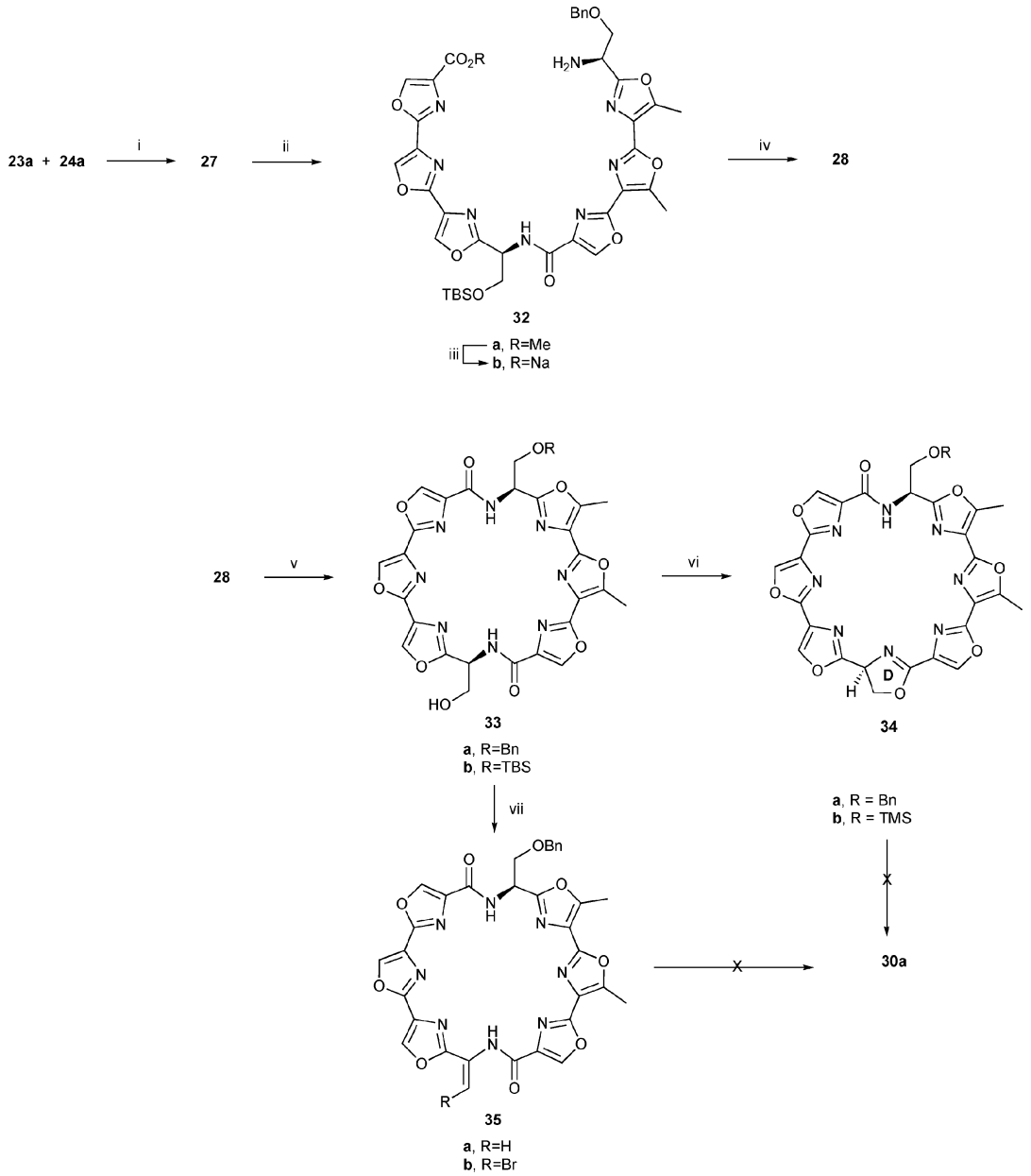
Scheme 3 *Reagents and conditions*: i, NaOH, H_2O, THF, 93–98%; ii, 10% Pd/C in MeOH, ~95% (for **24a** and **25**); HCl–dioxane, 98% (for **24b**).



Scheme 4

and **35**, we decided to examine a more direct macrocyclisation from corresponding α-bromoketone-amide intermediates, *viz.* **44b**, using the classical Hantzsch reaction. The methyl ketone precursor **44a** to **44b** was synthesised in a relatively straightforward manner starting from the tris-oxazole carboxylic acid **41** produced from the mono-oxazole **38** and the oxazole amino-alcohol **16b** *via* the amide **39** and the oxazoline **40** (Scheme 7). A coupling reaction between the tris-oxazole carboxylic acid **41b** and the secondary amine **42** derived from the previously synthesised tris-oxazole intermediate **25** next led to the double amide **43a**, which, in two straightforward steps, was converted into the methyl ketone **44a**. Frustratingly, we were not able to convert the methyl ketone **44a** into the corresponding bromide **44b** as a prelude to investigating the subsequent Hantzsch cyclisation to **30**. The

 This journal is © The Royal Society of Chemistry 2008

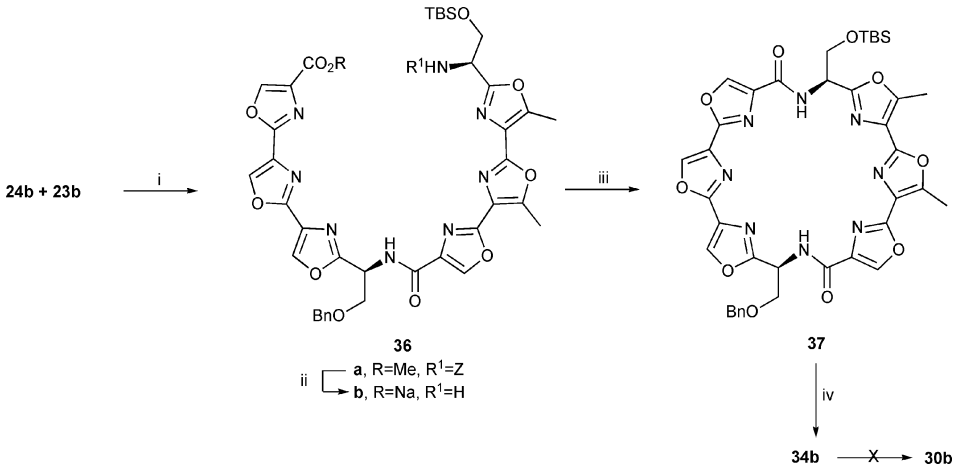


Scheme 5 *Reagents and conditions*: i, EDC, HOBt, NMM, DCM, 0–25 °C, 68%; ii, Pd/C, MeOH–EtOH; iii, NaOH–H_2O, THF, 88% over 2 steps; iv, DPPA, NMM, DMF, 86%; v, HCl–dioxane; vi, DAST, DCM, −78 °C, 90% over 2 steps; vii, Dess–Martin periodinane, DCM, rt, then PPh_3, 1,2-dibromotetrachloroethane, di-*tert*-butyl pyridine, 0 °C–rt, then DBU, rt, 74% over two steps.

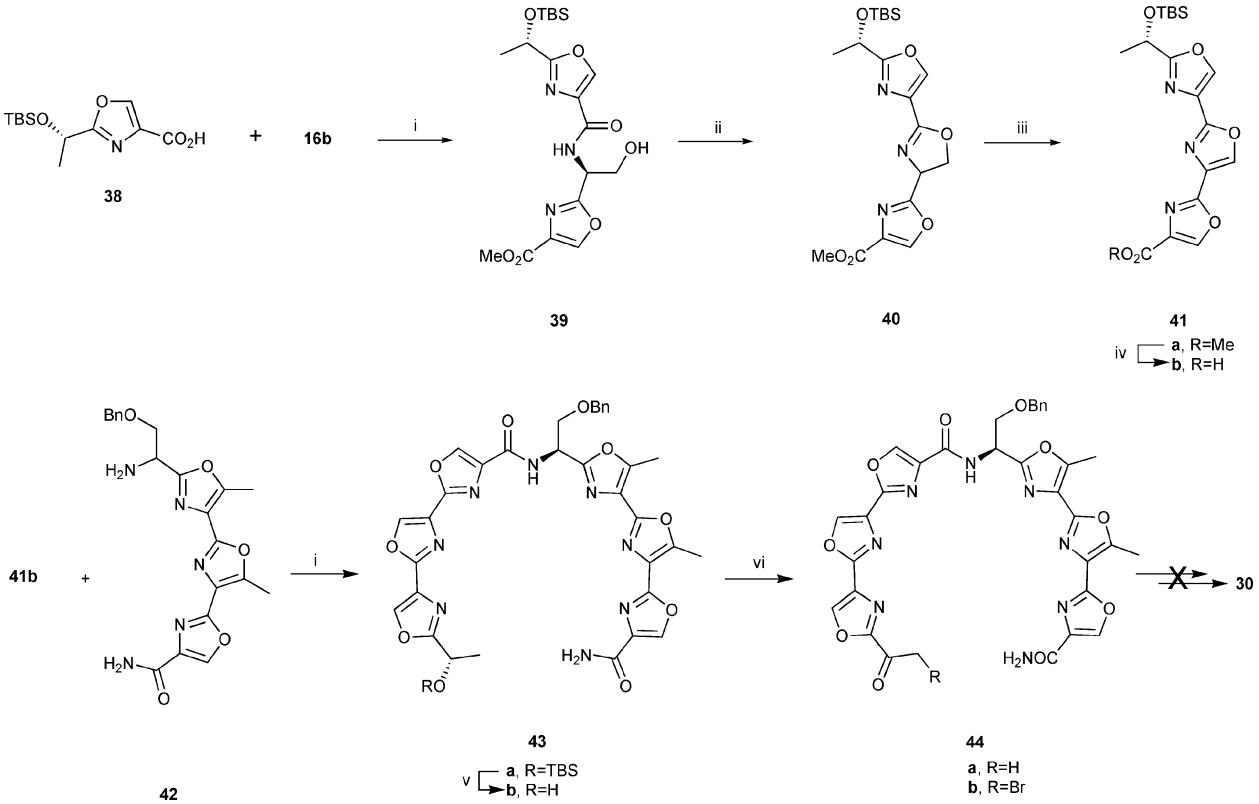
methyl ketone **44a** remained unchanged under all but the harshest conditions for bromination, when extensive decomposition ensued.

At this point in our studies we threw caution to the wind, and planned to make the isomeric hexa-oxazole **47**, corresponding to telomestatin, and study its macrolactamisation to the precursor **48** to the natural product. Thus, following procedures that had already been established in our work, the bis-oxazole amide **45b** was first prepared from the carboxylic acid **15d** and the amine **16d**. A coupling reaction between **45b** and **23** next led to the hexa-oxazole **46** which, in two straightforward steps, was then converted into **47a** (Scheme 8). Manipulation of the protecting groups in **47a** next led to the sodium salt **47b** of the ω-amino acid but, frustratingly, all attempts to form the hexa-oxazole-based macrolactam **48** from **47b** met with failure.

Coincident with the abandonment of our synthetic studies towards telomestatin, Takahashi *et al.*[29] described the first and, so far, only reported total synthesis of this novel telomerase inhibitor. Interestingly, for all intents and purposes, their route was strategically identical with the route we had followed ourselves. Thus, Takahashi *et al.* first prepared the tris-oxazole based carboxylic acid **49** and the amine **50**, and next coupled them to form the amide **51** (Scheme 9). Manipulation of the protecting groups in **51**, followed by macrolactamistation of the resulting ω-amino acid then provided the bis-macrolactam **52** (*cf.* structure **28**). The alcohol residue in **52** was next dehydrated to the enamide



Scheme 6 *Reagents and conditions*: EDC, NMM, HOBt, DCM, 87%; ii, H_2, Pd/C, MeOH, THF then NaOH–H_2O, 76%; iii, HATU, NMM, DMF, DCM, 0–25 °C, 80%; iv, H_2, $Pd(OH)_2$/C, MeOH, THF, then DAST, DCM, −78 °C, 91%.

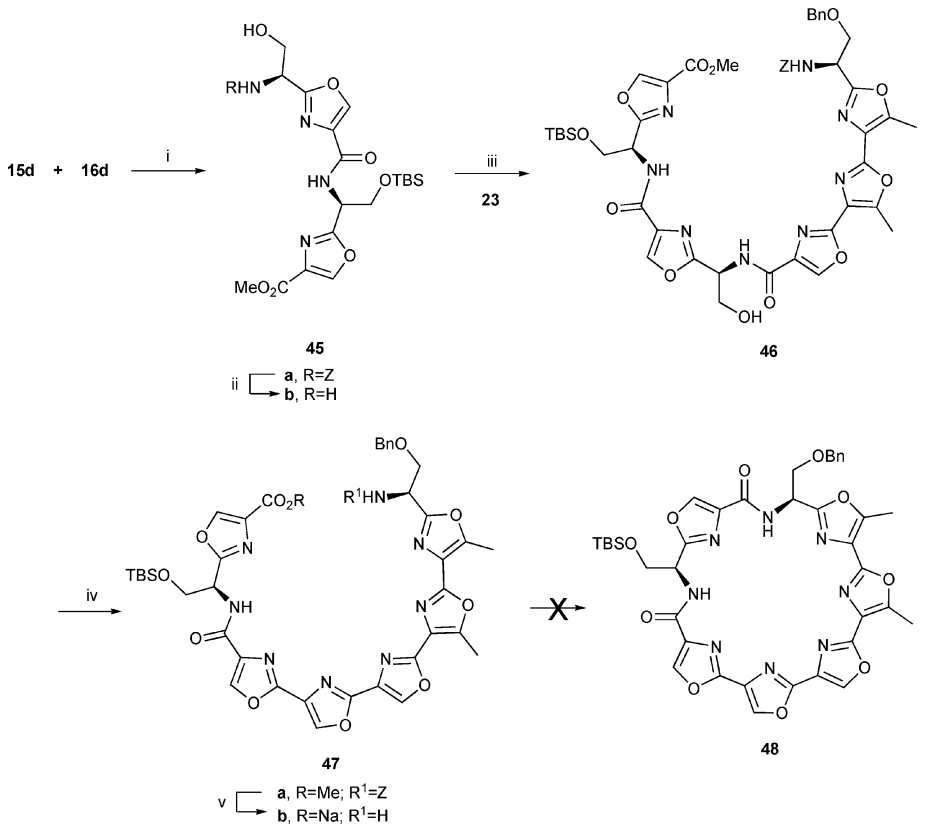


Scheme 7 *Reagents and conditions*: i, EDC, NMM, HOBt, 0–25 °C, 67% for **39**; 76% for **43a**; ii, DAST, DCM, −78 °C; iii, $BrCCl_3$, DBU, DCM, 0–25 °C, 44% over 2 steps; iv, NaOH, THF, H_2O, 25 °C, 85%; v, TBAF, THF, 0–25 °C, 87%; vi, PDC, DCM, 25 °C, 98%.

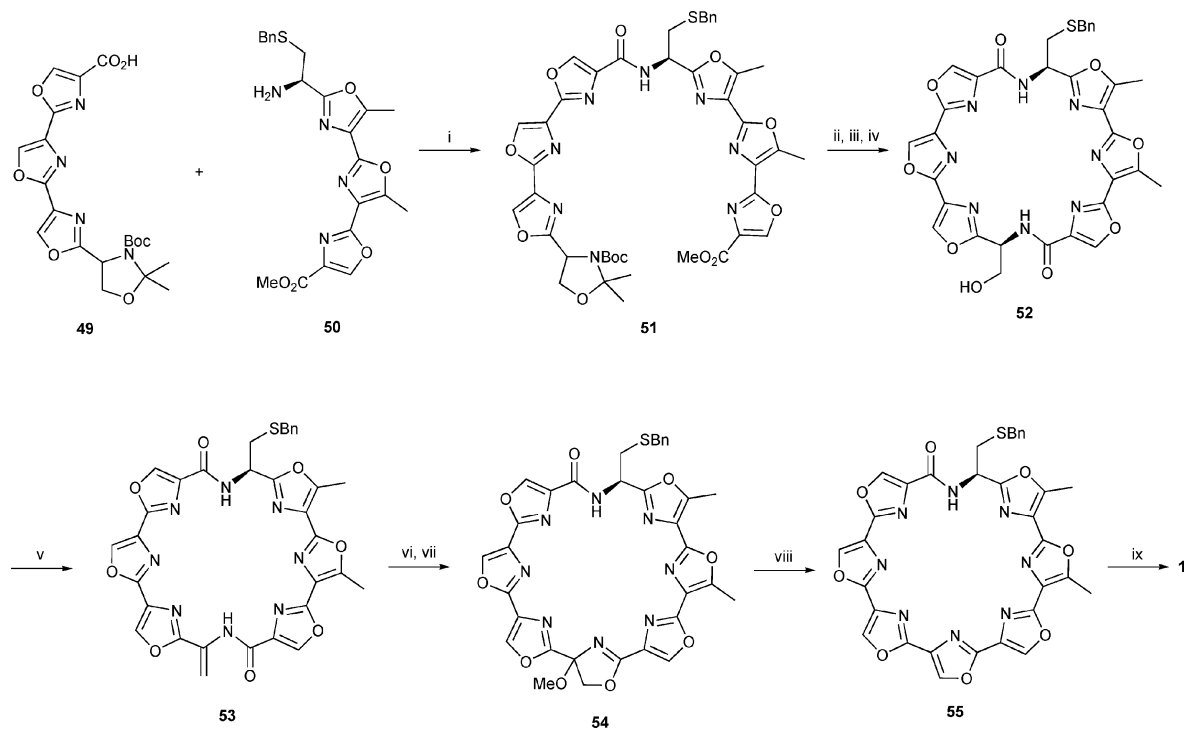
53 (*cf.* structure **35a**), which was then converted into the oxazoline **54** (*cf.* structure **34**) using NBS in MeOH, followed by treatment of the intermediate α-methyl-β-bromo cyclic peptide with K_2CO_3. Elimination of methanol from **54** using camphorosulfonic acid produced the hepta-oxazole **55** which was finally converted into telomestatin, following simultaneous deprotection of the *t*-Bu thio ether and cyclodehydration using Ph_3PO–Tf_2O in CH_2Cl_2[30] at room temperature.

Comparison of the routes to telomestatin followed by Takahashi *et al.* and by ourselves revealed a number of similarities and also some subtle differences in reaction conditions. Thus, whereas we had been able to smoothly convert the hydroxymethyl amide intermediate **33** into the corresponding oxazoline **34** using DAST,[24] Takahashi *et al.* found that treatment of their analogous intermediate **52** with DAST (or Burgess reagent)[31] instead gave the enamide **53**. Takahashi *et al.* were then able to convert the enamide **53** into the hepta-oxazole **55** *via* the oxazoline intermediate **54**, whereas we were not able to convert our enamide **35**, or oxidise the oxazoline **34** into the corresponding hepta-oxazole **30** using a range of conditions. It does seem likely therefore

 This journal is © The Royal Society of Chemistry 2008



Scheme 8 *Reagents and conditions*: i, EDC, NMM, HOBt, DCM, 34%; ii, H_2, Pd/C, MeOH–EtOAc, 55%; iii, **23**, EDC, NMM, HOBt, DCM, 50%; iv, DAST, DCM, −78 °C, then $BrCCl_3$, DBU, 43%; v, H_2, Pd/C, MeOH, 99%.



Scheme 9 *Reagents and conditions*: i, PyBroP, DIEA, DCM, DMF, rt, 85%; ii, 4 M HCl, 1,4-dioxane, rt; iii, LiOH, MeOH–THF–$H_2$0 (3 : 3 : 1); iv, DPPA, HOBt, DIEA, DMAP, DMF, DCM, rt, 48%; v, MsCl, DBU, DCM, 0 °C, 92%; vi, NBS, MS 4 Å, DCM, MeOH, 0 °C, 90%; vii, K_2CO_3, 1,4-dioxane, 60 °C, 79%; viii, camphorsulfonic acid, toluene, MS 5 Å, 70 °C; ix, $Ph_3P(O)$–Tf_2O, anisole, DCM, rt, 20% isolated yield.

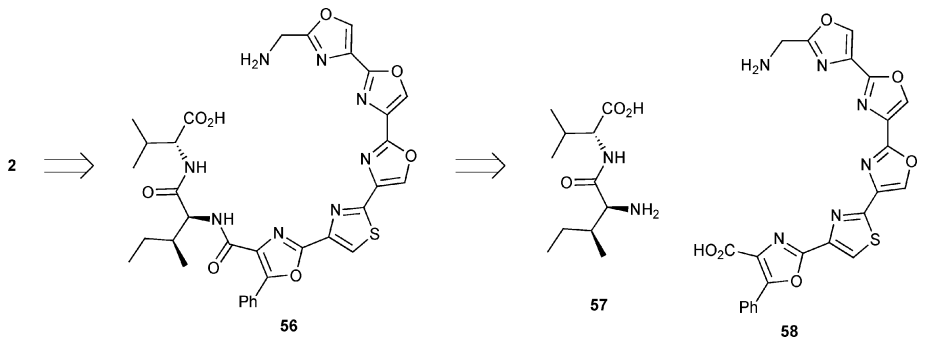
that we were simply unfortunate, at the time, with our choice of reaction conditions attempting to elaborate the hepta-oxazole **30** from the bis-macrolactam intermediate **33**, on the way to telomestatin.

Total synthesis of (−)-YM-216391 (2)

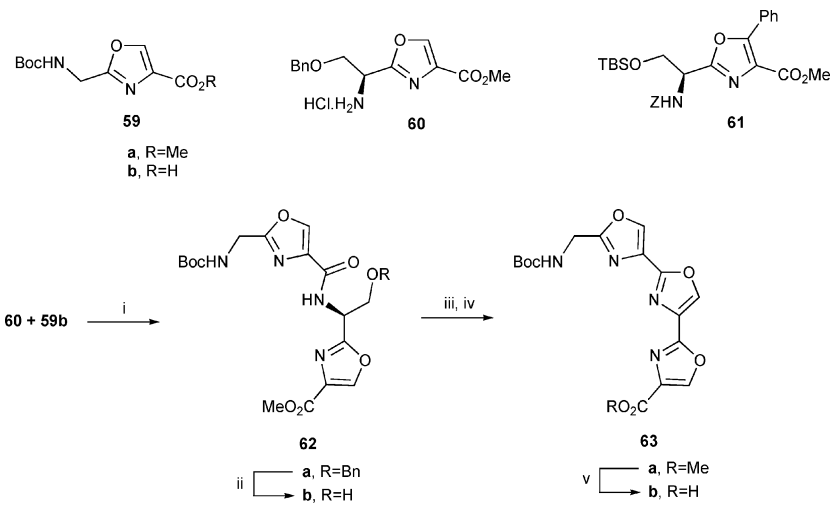
The structure of YM-216391 (**2**), isolated from *Streptomyces nobilis*,[2] consists of a continuum of five azoles which have their origins in serine, cysteine and phenylalanine, linked *via* a glycine-valine-isoleucine tripeptide tether. At the outset of our studies the stereochemical assignment of the valine and isoleucine stereocentres in the natural product had not been established. We therefore chose a synthetic strategy to **2** that would allow us to introduce these two stereocentres as late as possible in the synthesis, and involving a penta-azole intermediate **58** and a valine-isoleucine dipeptide fragment, *i.e.* **57**. Furthermore, we initially decided to effect the key macrolactamistion from the *ω*-amino acid **56**, *i.e.* using the sterically less encumbered glycine amine-valine carboxylic acid amide bond connection (Scheme 10). The penta-azole based *ω*-amino acid **56**, derived from an *L*-(natural) isoleucine-valine dipeptide fragment therefore became our first macrolactamisation precursor.

Thus, the 2,4-disubstituted oxazoles **59** and **60** and the trisubstituted oxazole **61** were first elaborated from their constituent amino acids using methodologies which are well precedented in this paper and in the literature. A coupling reaction between **60** and **59b** in the presence of EDC–HOBt–NMMO[23] led to the amide **62a** which was next converted into the tris-oxazole **63a** *via* **62a**, in three straightforward steps (Scheme 11). Saponification of **63a**, followed by coupling the resulting carboxylic acid **63b** with the amine **61b**, then led to tetra-oxazole amide **64**. Treatment of **64** with Lawesson's reagent[32] gave the thioamide **65** which, after deprotection and reaction with DAST,[24] was cyclised to the thiazoline **66** (Scheme 12). Finally, when the thiazoline **66** was reacted with $BrCCl_3$–DBU[22] it was converted into the corresponding thiazole **67a** which could be saponified to the carboxylic acid **67b**. A coupling reaction between the carboxylic acid **67b** and the L-isoleucine-L-valine dipeptide **68** next gave the substituted penta-azole **69** which, after double deprotection of the ester and *N*-BOC groups gave the ω-amino acid **56**. Attempts to effect macrolactamisation of **56**, using a variety of traditional reagents, however, led to intractable mixtures of polymeric material and none of the anticipated YM-216391 (**2**).

We reasoned that the failure to obtain macrolactamisation from the intermediate ω-amino acid **56** had its origins in poor conformational flexibility, *i.e.* the penta-azole ring system in **56** was too rigid. We therefore decided to examine the thioamide intermediate **73** analogous to **56** in the key macrolactamisation step, with a view to introducing the thiazole ring in the target as the

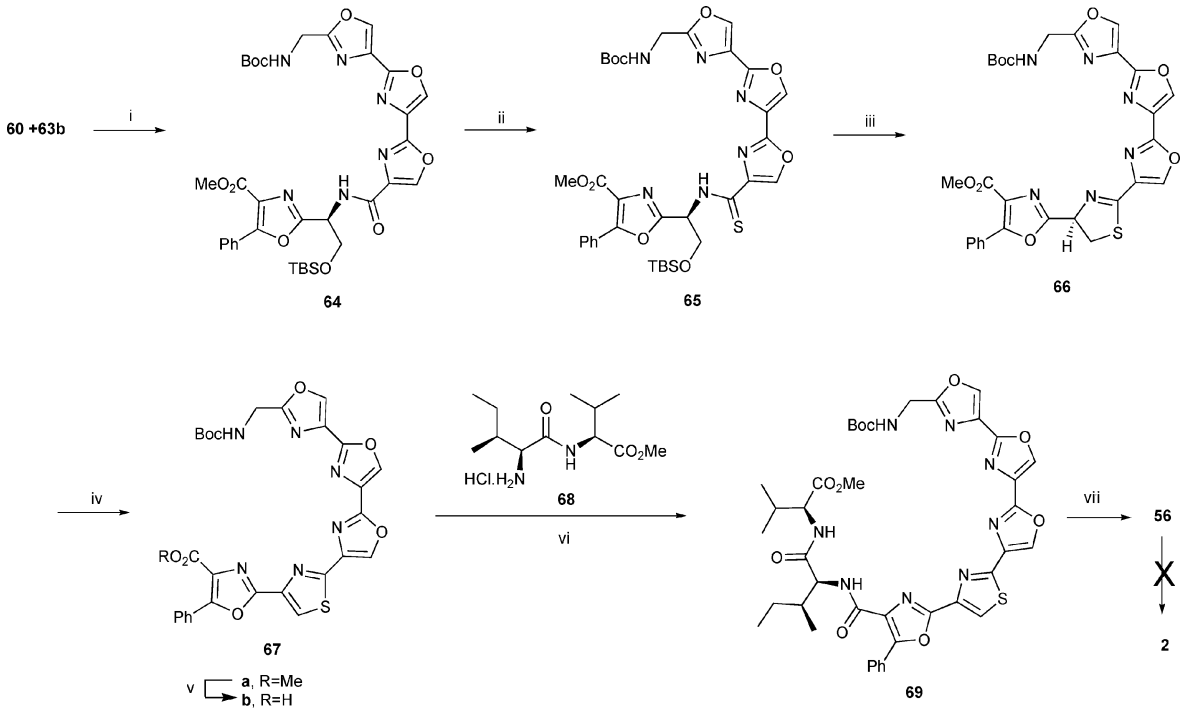


Scheme 10



Scheme 11 *Reagents and conditions*: i, EDC, HOBt, NMM, DCM, 56%; ii, H_2, $Pd(OH)_2/C$, MeOH–THF, 81%; iii, DAST, DCM, −78 °C; iv, $BrCCl_3$, DCM, 57% over two steps; v, NaOH, THF, H_2O, 88%.

 This journal is © The Royal Society of Chemistry 2008



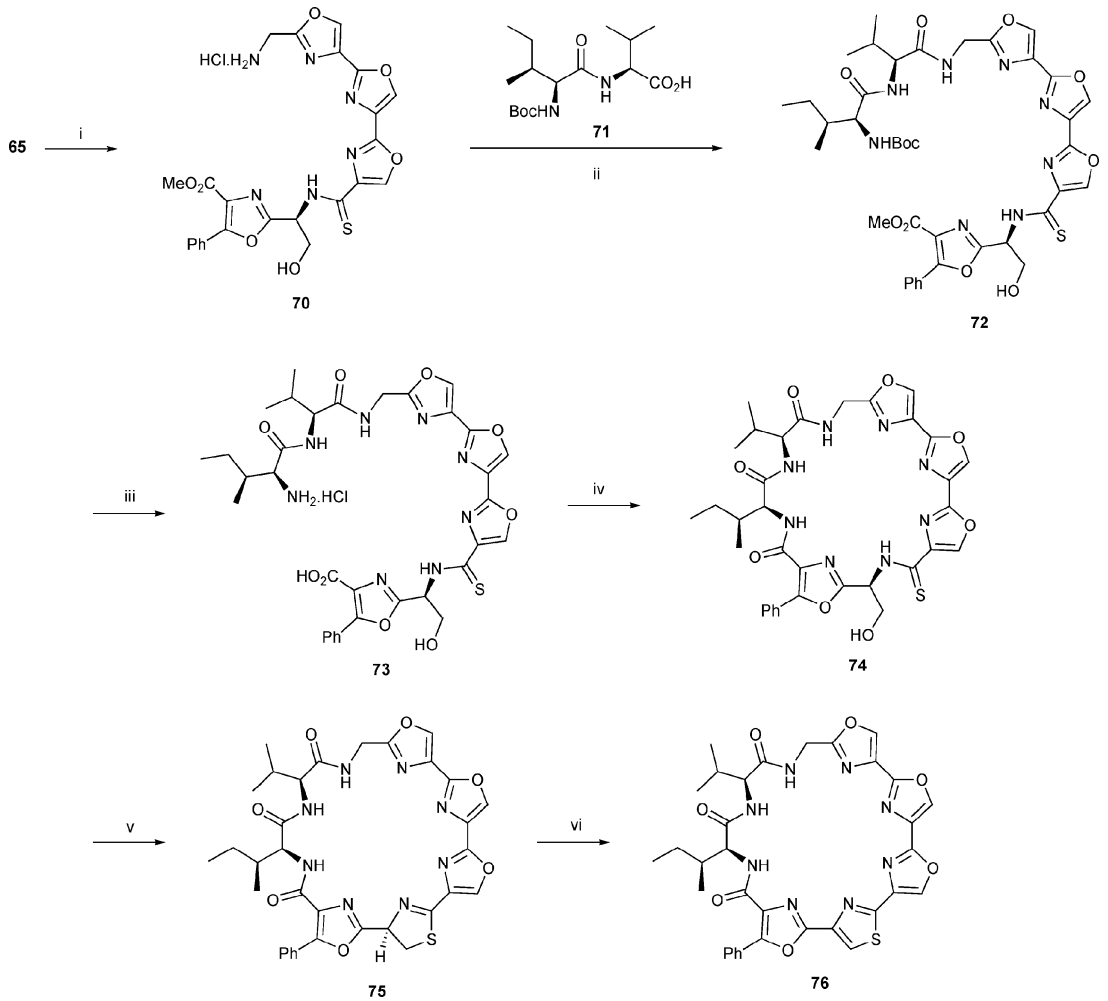
Scheme 12 *Reagents and conditions*: i, EDC, HOBt, NMM, DCM, 87%; ii, Lawesson's reagent, THF, 50%; iii, TBAF, THF, 95%, then DAST, DCM, 59%; iv, $BrCCl_3$, DBU, DCM; v, NaOH, THF–H_2O; vi, EDC, HOBt, NMM, DCM; vii, 4 M HCl in dioxane; then NaOH, THF, H_2O.

final step in the synthesis. The previously synthesised thioamide **65** was therefore first deprotected and the resulting amine **70** was then coupled to the protected dipeptide **71** leading to the intermediate **72**. The methyl ester and the *N*-BOC protecting groups in **72** were next removed, in sequence, producing the ω-amino acid **73**, which underwent smooth macrolactamisation in the presence of HATU[33] leading to the cyclopeptide **74** in 88% yield (Scheme 13). Finally, the thioamide unit in **74** was converted into the corresponding thioazoline **75**, using DAST, which then underwent oxidation, in the presence of MnO_2 to produce the YM-216391 structure with the stereochemistry shown in formula **76**. When we compared the ^{1}H NMR spectroscopic data for **76** with those recorded for natural YM-216391, 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. This situation is perhaps not too surprising, given the prevalence of cyclopeptides such as ascidiacylamide (**8**)[8] and dendroamide A (**6**),[6] which are made up from non-proteinogenic D-amino acids. We therefore re-synthesised the dipeptide **77** using D-valine and L-isoleucine, and then reproduced the sequence of reactions shown in Scheme 13, producing the cyclopeptide intermediate **79** (Scheme 14). The cyclopeptide **79** differs from structure **74** only according to its stereochemistry at the isopropyl bearing carbon centre. Following conversion of the thioamide unit in **79** into the thiazoline **80**, oxidation with MnO_2 in CH_2Cl_2 finally gave the cyclopeptide **81** $[a]_D^{20}$ −56 ($c = 0.5$, $CHCl_3$) whose ^{1}H NMR and ^{13}C NMR spectroscopic data matched very closely those reported for naturally derived YM-216391. Following the completion of our synthesis, which allowed us to establish the relative stereochemistry shown in structure **81** for YM-216391, Sohda *et al.*[34] published details of their investigations of the structure of YM216391 from *Streptomyces nobilis.* The studies of Sohda *et al.* led to the same assignment of relative stereochemistry for YM216391 as we had determined by synthesis, but the natural product showed $[a]_D^{25}$ +48 ($c = 0.1$, CH_3CN), *i.e.* equal and opposite in value to that recorded for our synthetic material. The structural and synthetic studies therefore complemented each other, and established that YM-216391 isolated from *S. nobilis* has the absolute stereochemistry shown in structure **82**.

Summary and Conclusions

A range of robust and efficient methods are available to quickly assemble a variety of amino acid based contiguously linked 2,4-substituted tris-oxazoles, *viz.* **23–26**, and to effect their coupling and cyclisation to hexa-oxazole bis-macrolactam intermediates, *i.e.* **33** and **37**, *en route* to telomestatin **1**. However, the elaboration of these advanced structures to the hepta-oxazole-thiazoline ring systems in telomestatin is thwarted by problems. These problems were associated with the poor solubilities of rotameric mixtures of several intermediates, making characterisations extremely difficult by NMR spectroscopy, and by the important need for proper choices of protecting groups and specific reaction conditions at an advanced stage in the overall synthesis.

By contrast, elaboration of the tris-oxazole based protected amino acid **63** to the cyclic thioamide **74**, followed by its conversion into the naturally occurring thiazole-tetra-oxazole based cyclic peptide YM-216391 (**81**) proved to be trouble-free, and the total synthesis enabled the establishment of the absolute stereochemistry, *i.e.* **82**, of this new metabolite isolated from *Streptomyces nobilis.*



Scheme 13 *Reagents and conditions*: i, 4 M HCl, dioxane, 91%; ii, EDC, HOBt, NMM, DCM, 57%; iii, NaOH, THF, H_2O; then 4 M HCl in dioxane, 77% over two steps; iv, HATU, NMM, DCM, DMF, 88%; v, DAST, DCM, 50%; vi, MnO_2, DCM, 27%.

Experimental

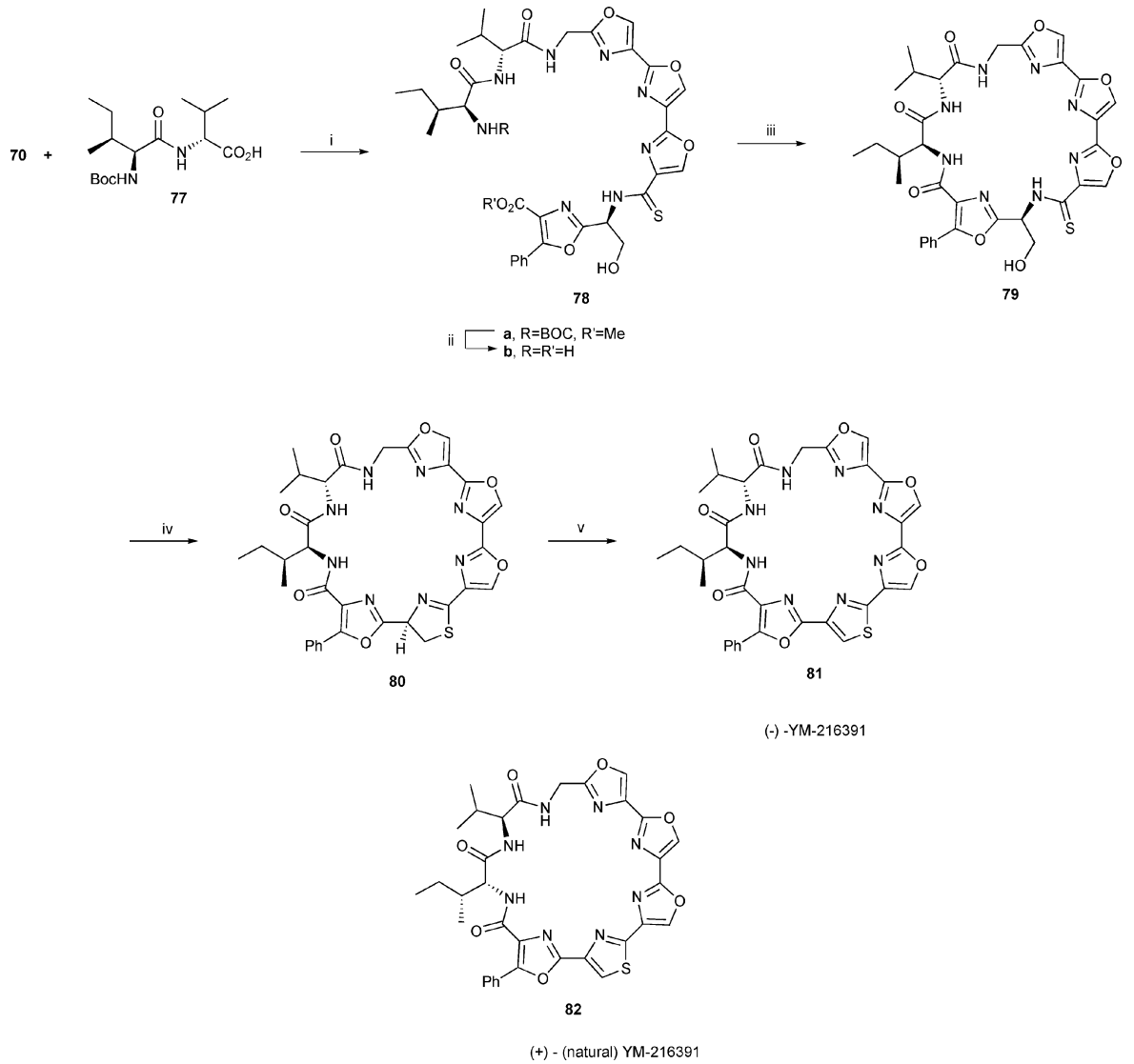
General details

Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Optical rotations were recorded in spectroscopic grade chloroform or ethanol on a Jasco DIP-370 polarimeter at ambient temperature. $[a]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were obtained using a Perkin-Elmer 1600 series FT-IR instrument as dilute solutions in spectroscopic grade chloroform. Proton (^{1}H) NMR spectra were recorded on either a Bruker DPX 360 (360 MHz) or a Bruker DRX 500 (500 MHz) spectrometer as dilute solutions in deuterochloroform, unless stated otherwise. The chemical shifts are quoted in parts per million (ppm) relative to residual chloroform (δ 7.27) as internal standard. The multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad; app, apparent; obs, obscured. All coupling constants are quoted in Hertz. Carbon-13 (^{13}C) NMR spectra were recorded on either a Bruker DPX 360 (90 MHz) or a Bruker DRX 500 (125 MHz) spectrometer as dilute solutions in deuterochloroform, unless otherwise stated. The chemical shifts are quoted in parts per million (ppm) relative to internal chloroform standard (δ 77.0) on a broad band decoupled mode. The multiplicities were determined using a DEPT sequence, and are designated by the following abbreviations: s, quaternary; d, tertiary methine; t, secondary methylene; q, primary methyl. Mass spectra were recorded on a VG Autospec spectrometer using fast atom bombardment (FAB) or chemical ionisation (CI) techniques; a MM-701CF spectrometer using chemical ionisation (CI); or a Micromass LCT spectrometer using electrospray ionistation (ESI). Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

Flash chromatography was performed on Merck silica gel 60 as the stationary phase and the solvents used were of analytical grade or were distilled before use. All reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F_{254} precoated aluminium backed plates which were visualised with ultraviolet light and then developed with either iodine on silica, acidic ninhydrin solution, acidic alcoholic vanillin solution, basic potassium permanganate solution or ethanolic phosphomolybdic acid solution.

Routinely, dry organic solvents were stored under nitrogen and/or over sodium wire. When necessary, commonly used organic solvents were dried prior to use. Tetrahydrofuran (THF),

 This journal is © The Royal Society of Chemistry 2008



Scheme 14 *Reagents and conditions*: i, EDC, HOBt, NMM, DCM, 82%; ii, NaOH, THF, H_2O, then 4 M HCl in dioxane, 70% over two steps; iii, HATU, NMM, DCM, DMF, 75%; iv, DAST, DCM, 89%; v, MnO_2, DCM, 55%.

diethyl ether, benzene and toluene were distilled from sodium benzophenone ketyl or dried by passing through towers of activated alumina. Dichloromethane was distilled from calcium hydride. Anhydrous *N*,*N*-dimethylformamide was obtained from Aldrich. Other organic solvents and reagents were purified by the accepted literature procedures and organic extracts were dried as stated. Petrol refers to petroleum ether (bp 40–60 °C). Solvents were removed on a Büchi rotary evaporator connected to a water pump. Where necessary, reactions requiring anhydrous conditions were performed in flame-dried apparatus under a nitrogen atmosphere.

2-((*S*)-1-{[2-((*S*)-2-Benzyloxy-1-*tert*-butoxycarbonylaminoethyl)-oxazole-4-carbonyl]-amino}-2-hydroxyethyl)-oxazole-4-carboxylic acid methyl ester (18a)

4-Methylmorpholine (0.40 mL, 3.6 mmol) was added to a stirred suspension of the acid **16a** (0.58 g, 1.6 mmol) and 1-hydroxybenzotriazole (0.24 g, 1.8 mmol) in dry dichloromethane (40 mL) at 0 °C under a nitrogen atmosphere. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.35 g, 1.8 mmol) was added and the mixture was then stirred at 0 °C for 10 min. The hydrochloride salt of amine **16b** (0.56 g, 2.5 mmol) was added in one portion, and the mixture was then allowed to warm to room temperature overnight. The reaction was quenched with water (30 mL) and the separated organic layer was washed with 10% aqueous citric acid (3 × 30 mL). The combined aqueous extracts were extracted with dichloromethane (3 × 30 mL) and the combined organic extracts were then washed with saturated sodium bicarbonate solution (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using ethyl acetate as eluent to give the *amide* (1.53 g, 62%) as a colourless foaming solid; $[\alpha]_D^{22}$ −36 ($c = 1.0$, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3444, 3401, 2954, 1714, 1678 and 1598; δ_H(360 MHz, $CDCl_3$) 8.20 (1H, s, oxazole-H), 8.10 (1H, s, oxazole-H), 8.04 (1H, d, *J* 8.6 Hz, CON*H*), 7.35–7.18 (5H, m, 5 × aryl-H), 5.70 (1H, d, *J* 9.2 Hz, BocN*H*), 5.54–5.48

(1H, m, CONHC*H*), 5.09–5.02 (1H, m, BocNHC*H*), 4.53 (1H, d, *J* 12.1 Hz, OCH_aH$_b$Ph), 4.49 (1H, d, *J* 12.1 Hz, OCH$_a$$H_b$Ph), 4.28 (1H, dd, *J* 11.7 and 4.6 Hz, CH_aH$_b$OH), 4.05 (1H, dd, *J* 11.7 and 4.2 Hz, CH$_a$$H_b$OH), 3.88 (3H, s, CO_2CH_3), 3.79 (1H, dd, *J* 9.7 and 4.4 Hz, CH_aH$_b$OBn), 3.73 (1H, dd, *J* 9.7 and 4.6 Hz, CH$_a$$H_b$OBn), 2.62 (1H, br s, O*H*) and 1.46 (9H, s, OC(CH_3)$_3$) ppm; δ_C(90 MHz, $CDCl_3$) 163.1 (s), 162.3 (s), 161.4 (s), 155.2 (s), 150.8 (s), 144.3 (d), 141.7 (d), 137.3 (s), 135.4 (s), 133.0 (s), 128.4 (d), 127.8 (d), 127.5 (d), 80.3 (s), 73.0 (t), 69.8 (t), 62.8 (t), 52.2 (q), 49.3 (d) and 28.2 (q) ppm; *m*/*z* (ESI) found: 553.1865, $C_{25}H_{30}N_4O_9Na$ [(M + Na)$^+$] requires 553.1910.

2″-((*S*)-2-Benzyloxy-1-*tert*-butoxycarbonylaminoethyl)-[2,4′;2′,4″]teroxazole-4-carboxylic acid methyl ester (20a)

(Diethylamino)sulfur trifluoride (0.48 mL, 3.6 mmol) was added dropwise over 1 min to a stirred solution of the bis-oxazole **18a** (1.6 g, 3.0 mmol) in dry dichloromethane (30 mL) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature. The mixture was quenched with saturated sodium bicarbonate solution (20 mL) and the separated organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to leave the crude oxazoline **19a**, which was used immediately without further purification.

Bromotrichloromethane (0.87 mL, 9.0 mmol) was added to a stirred solution of the crude oxazoline in dry dichloromethane (30 mL) at 0 °C under a nitrogen atmosphere and the mixture was stirred at 0 °C for 5 min. 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.4 mL, 9.0 mmol) was added dropwise over 2 min and the mixture was allowed to warm to room temperature overnight. The reaction was quenched with 10% aqueous citric acid (20 mL) and the separated organic extract was then washed with saturated sodium bicarbonate solution (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using dichloromethane–diethyl ether (4 : 1) as eluent to give the tris-oxazole (1.1 g, 72%) as a colourless solid; mp 202–203 °C (from dichloromethane–petrol); $[a]_D^{21}$ −25 (*c* = 1.0, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3441, 3170, 2980, 1715, 1654 and 1579; δ_H(360 MHz, $CDCl_3$) 8.43 (1H, s, oxazole-H), 8.33 (1H, s, oxazole-H), 8.32 (1H, s, oxazole-H), 7.35–7.19 (5H, m, 5 × aryl-H), 5.57 (1H, d, *J* 8.2 Hz, BocN*H*), 5.22–5.13 (1H, m, BocNHC*H*), 4.55 (1H, d, *J* 12.1 Hz, OCH_aH$_b$Ph), 4.51 (1H, d, *J* 12.1 Hz, OCH$_a$$H_b$Ph), 4.00–3.93 (1H, m, C$H_aH_b$OBn), 3.97 (3H, s, CO_2CH_3), 3.85 (1H, dd, *J* 9.6 and 4.4 Hz, CH$_a$$H_b$OBn) and 1.46 (9H, s, OC(CH_3)$_3$) ppm; δ_C(90 MHz, $CDCl_3$) 164.0 (s), 161.2 (s), 156.0 (s), 155.3 (s), 155.1 (s), 143.8 (d), 139.6 (d), 139.3 (d), 137.2 (s), 134.3 (s), 130.7 (s), 129.8 (s), 128.3 (d), 127.8 (d), 127.5 (d), 80.3 (s), 73.2 (t), 70.3 (t), 52.3 (q), 49.4 (d) and 28.2 (q) ppm; *m*/*z* (ESI) found: 533.1658, $C_{25}H_{26}N_4O_8Na$ [(M + Na)$^+$] requires 533.1648.

2″-[(*S*)-1-{[2″-((*S*)-2-Benzyloxy-1-benzyloxycarbonylaminoethyl)-5′,5″-dimethyl-[2,4′;2′,4″]teroxazole-4-carbonyl]-amino}-2-(*tert*-butyldimethylsilanyloxy)-ethyl]-[2,4′;2′,4″]teroxazole-4-carboxylic acid methyl ester (27)

-Methylmorpholine (0.11 mL, 1.0 mmol) was added to a stirred suspension of the carboxylic acid **23a** (0.28 g, 0.5 mmol) and 1-hydroxybenzotriazole (0.14 g, 1.0 mmol) in dry dichloromethane (3 mL) at 0 °C under a nitrogen atmosphere. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.13 g, 0.65 mmol) was added and the mixture was then stirred at 0 °C for 2 min. A solution of the amine **24a** (0.17 g, 0.4 mmol) in dry dichloromethane (4 mL) was added dropwise over 2 min at 0 °C, and the mixture was then allowed to warm to room temperature overnight. The reaction was quenched with water (5 mL) and the separated organic layer was then washed with 10% aqueous citric acid (2 × 5 mL). The combined aqueous extracts were extracted with dichloromethane (2 × 10 mL) and the combined organic extracts were then washed with saturated sodium bicarbonate solution (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using ethyl acetate as eluent to give the *amide* (0.26 g, 68%) as a colourless solid; mp 170–172 °C (from ethyl acetate); $[a]_D^{21}$ −32 (*c* = 1.0, $CHCl_3$); found: C, 59.0; H, 5.2; N, 11.3%. $C_{48}H_{50}N_8O_{13}Si$ requires C, 59.1; H, 5.2; N, 11.5%; $\nu_{max}(CHCl_3)/cm^{-1}$ 3412, 2931, 1724, 1674 and 1596; δ_H(360 MHz, $CDCl_3$) 8.45 (1H, s, oxazole-H), 8.36 (1H, s, oxazole-H), 8.35 (1H, s, oxazole-H), 8.33 (1H, s, oxazole-H), 7.89 (1H, d, *J* 8.7 Hz, CON*H*), 7.43–7.22 (10H, m, 10 × aryl-H), 5.82 (1H, d, *J* 8.5 Hz, ZN*H*), 5.61–5.55 (1H, m, CONHC*H*), 5.23–5.12 (3H, m, CO_2CH_2Ph, ZNHC*H*), 4.58 (1H, d, *J* 12.2 Hz, $CH_2OCH_aH_b$Ph), 4.52 (1H, d, *J* 12.2 Hz, $CH_2OCH_aH_b$Ph), 4.31 (1H, dd, *J* 10.2 and 3.7 Hz, CH_aH$_b$OTBS), 4.13 (1H, dd, *J* 10.2 and 4.4 Hz, CH$_a$$H_b$OTBS), 4.01–3.93 (4H, m, CO_2CH_3, CH_aH$_b$OBn), 3.87 (1H, dd, *J* 9.5 and 4.1 Hz, CH$_a$$H_b$OBn), 2.82 (3H, s, oxazole-CH_3), 2.74 (3H, s, oxazole-CH_3), 0.87 (9H, s, SiC(CH_3)$_3$), 0.08 (3H, s, SiCH_3(CH$_3$)) and 0.02 (3H, s, SiCH$_3$(CH_3)) ppm; δ_C(90 MHz, $CDCl_3$) 163.6 (s), 161.3 (s), 160.9 (s), 156.0 (s), 155.9 (s), 155.4 (s), 154.8 (s), 150.6 (s), 143.8 (d), 141.0 (d), 139.7 (d), 139.3 (d), 137.3 (s), 136.5 (s), 134.4 (s), 130.8 (s), 130.0 (s), 128.5–127.6 (Ar s and d), 125.5 (s), 124.8 (s), 73.2 (t), 70.2 (t), 67.2 (t), 64.1 (t), 52.3 (q), 49.7 (d), 49.2 (d), 25.6 (q), 18.0 (s), 11.8 (q), 11.8 (q), −5.5 (q) and −5.7 (q) ppm; *m*/*z* (ESI) found: 992.3419, $C_{48}H_{52}N_8O_{14}Si$ [(M + H_2O)$^+$] requires 992.3372.

Macrocycle (28)

4-Methylmorpholine (0.10 mL, 0.9 mmol) was added to a stirred suspension of the amino acid **32b** (45 mg, 0.053 mmol) in dry *N*,*N*-dimethylformamide (9 mL) at room temperature under a nitrogen atmosphere. Diphenylphosphoryl azide (46 μL, 0.21 mmol) was added dropwise over 2 min and the mixture was stirred at room temperature for 18 h. The mixture was evaporated to dryness *in vacuo* and the residue was then partitioned between dichloromethane (20 mL) and saturated sodium bicarbonate solution (15 mL). The organic layer was washed with saturated sodium bicarbonate solution (15 mL) and saturated sodium chloride solution (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue partially purified by recrystallisation from dichloromethane–ether–petrol to give the *macrolactam* (37 mg, 86%) as a colourless solid; δ_H(360 MHz, $CDCl_3$) 8.65–8.49 (2H, m, 2 × CON*H*), 8.32–8.40 (4H, m, 4 × oxazole-H), 7.41–7.00 (5H, m, 5 × aryl-H), 5.65–5.30 (2H, m, 2 × CONHC*H*), 4.60–4.40 (2H, m, CH_2OCH_2Ph), 4.83–4.38 (4H, m, CH_2OTBS, CH_2OBn), 2.75 (3H, s, oxazole-CH_3), 2.65 (3H, s, oxazole-CH_3), 0.80 (9H, s, SiC(CH_3)$_3$) and 0.13 to −0.13 (6H, m, SiCH_3(CH$_3$)) ppm.

This journal is © The Royal Society of Chemistry 2008

Desilylated macrocycle (33a)

Hydrogen chloride (4.0 M solution in dioxane) (5 mL) was added to the ether **28** (37 mg, 0.046 mmol) and the mixture was stirred at room temperature for 10 min under a nitrogen atmosphere. The volatiles were evaporated to leave the *alcohol* (32 mg, 100%) as a colourless solid, which was used directly in the next reaction without further purification; δ_H(360 MHz, $CDCl_3$–CD_3OD (1 : 1)) 8.39–8.00 (4H, m, 4 × oxazole-H), 7.12–6.79 (5H, m, 5 × aryl-H), 5.35–5.10 (2H, m, 2 × CONHC*H*), 4.40–4.18 (2H, m, CH_2OCH_2Ph), 3.99–3.60 (4H, m, CH_2OH, CH_2OBn), 2.50 (3H, s, oxazole-CH_3) and 2.42 (3H, s, oxazole-CH_3) ppm.

Oxazole macrocycle 35a

Dess–Martin periodinane (4 mg, 0.008 mmol) was added in one portion to a stirred solution of the macrocycle **33a** (3 mg, 0.004 mmol) in anhydrous dichloromethane (0.5 mL) at room temperature under an atmosphere of nitrogen. The solution was stirred at room temperature for 1.5 h and the volatiles were then removed *in vacuo.* Triphenylphosphine (5 mg, 0.02 mmol), 1,2-dibromotetrachloroethane (6.5 mg, 0.02 mmol) and di-*tert*-butyl pyridine (0.01 mL, 0.04 mmol) were added to the residue in dichloromethane (0.1 mL) at 0 °C under an atmosphere of nitrogen. The mixture was stirred and allowed to gradually warm to room temperature overnight. DBU (0.015 mL, 0.1 mmol) was added and the mixture was stirred at room temperature for a further 3.5 h. Water (2 mL) was added and the separated organic layer was washed with 10% aqueous citric acid solution (3 × 10 mL) and sodium bicarbonate solution (3 × 10 mL), then dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by chromatography on silica using dichloromethane to 4% methanol in dichloromethane as eluent to give the *enamide* (2 mg, 74%) as a colourless solid; δ_H(500 MHz, $CDCl_3$) 9.65 (1H, s, N*H*C=CH_2), 8.58 (1H, d, *J* 7.4 Hz, N*H*CH), 8.34 (1H, S, oxazole-*H*), 8.23 (1H, S, oxazole-*H*), 8.22 (1H, S, oxazole-*H*), 8.19 (1H, S, oxazole-*H*), 5.40–5.45 (1H, m, C*H*NH), 4.55 (1H, d, *J* 12.5 Hz, $CH_2OCH_aH_bPh$), 4.51 (1H, d, *J* 12.5 Hz, $CH_2OCH_aH_bPh$), 3.99 (1H, dd, *J* 11.1 and 4.5 Hz, $CHCH_aH_bOBn$), 3.95 (1H, dd, *J* 11.1 and 5.6 Hz, $CHCH_aH_bOBn$), 2.79 (3H, s, oxazole-CH_3), 2.69 (3H, s, oxazole-CH_3).

Oxazoline macrocycle (34a)

(Diethylamino)sulfur trifluoride (24 μL, 0.18 mmol) was added to a stirred solution of the alcohol **33a** (32 mg, 0.046 mmol) in dry dichloromethane (2 mL) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 3 h and was then allowed to warm to room temperature. The mixture was quenched with saturated sodium bicarbonate solution (2 mL) and the separated aqueous layer was then extracted with dichloromethane (2 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and then concentrated *in vacuo.* The residue was partially purified by recrystallisation from dichloromethane–ethyl acetate–ether to give the *oxazoline* (28 mg, 90%) as a colourless solid; δ_H(360 MHz, $CDCl_3$) 9.29–9.14 (1H, m, CON*H*), 8.61–8.23 (4H, m, 4 × oxazole-H), 7.34–7.05 (5H, m, 5 × aryl-H), 5.83–5.32 (2H, m, CONHC*H*, oxazoline-C*H*), 4.99–4.62 (2H, m, oxazoline-CH_2), 4.59–4.43 (2H, m, CH_2OCH_2Ph), 4.15–3.76 (2H, m, CH_2OBn), 2.75 (3H, s, oxazole-CH_3) and 2.68 (3H, s, oxazole-CH_3) ppm.

2″-[(*S*)-2-Benzyloxy-1-({2″-[(*S*)-1-benzyloxycarbonylamino-2-(*tert*-butyldimethylsilanyloxy)-ethyl]-5′,5″-dimethyl-[2,4′;2′,4″]-teroxazole-4-carbonyl}-amino)-ethyl]-[2,4′;2′,4″]teroxazole-4-carboxylic acid methyl ester (36a)

4-Methylmorpholine (0.28 mL, 2.6 mmol) was added to a stirred suspension of the carboxylic acid **23b** (0.37 g, 0.64 mmol) and 1-hydroxybenzotriazole (0.26 g, 1.9 mmol) in dry dichloromethane (10 mL) at 0 °C under a nitrogen atmosphere. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.25 g, 1.3 mmol) was added and the mixture was then stirred at 0 °C for 10 min. The amine **24b** (0.35 g, 0.78 mmol) was added in one portion, and the mixture was then allowed to warm to room temperature overnight. Dichloromethane (50 mL) was added and the reaction was quenched with water (30 mL). The separated organic layer was washed with 10% aqueous citric acid (2 × 30 mL) and saturated sodium bicarbonate solution (30 mL), then dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by chromatography on silica gel using dichloromethane–ethyl acetate (2 : 1) eluent to give the *amide* (0.54 g, 87%) as a colourless solid; mp 204–205 °C; $[a]_D^{21}$ +14 (*c* = 1.0, $CHCl_3$); found: C, 58.6; H, 5.1; N, 11.3%. $C_{48}H_{50}N_8O_{13}Si$ requires C, 59.1; H, 5.2; N, 11.5%; ν_{max}($CHCl_3$)/cm^{-1} 3412, 2930, 1723, 1674 and 1595; δ_H(360 MHz, $CDCl_3$) 8.43 (1H, s, oxazole-H), 8.34 (1H, s, oxazole-H), 8.33 (1H, s, oxazole-H), 8.30 (1H, s, oxazole-H), 7.86 (1H, d, *J* 8.8 Hz, CON*H*), 7.42–7.22 (10H, m, 10 × aryl-H), 5.77 (1H, d, *J* 8.5 Hz, ZN*H*), 5.71–5.64 (1H, m, CONHC*H*), 5.18 (1H, m, $CO_2CH_aH_bPh$), 5.13 (1H, d, *J* 12.3 Hz, $CO_2CH_aH_bPh$), 5.11–5.03 (1H, m, ZNHC*H*), 4.60 (2H, s, CH_2OCH_2Ph), 4.17–3.93 (4H, m, CH_2OTBS, CH_2OBn), 3.96 (3H, s, CO_2CH_3), 2.79 (3H, s, oxazole-CH_3), 2.72 (3H, s, oxazole-CH_3), 0.81 (9H, s, $SiC(CH_3)_3$), −0.01 (3H, s, $SiCH_3(CH_3)$) and −0.04 (3H, s, $SiCH_3(CH_3)$) ppm; δ_C(90 MHz, $CDCl_3$) 163.0 (s), 161.1 (s), 161.1 (s), 160.1 (s), 155.8 (s), 155.8 (s), 155.7 (s), 155.2 (s), 154.8 (s), 150.7 (s), 150.6 (s), 143.8 (d), 141.0 (d), 139.7 (d), 139.2 (d), 137.1 (s), 136.3 (s), 136.0 (s), 134.2 (s), 130.6 (s), 129.8 (s), 128.3 (d), 128.3 (d), 128.0 (d), 128.0 (d), 127.7 (d), 127.5 (d), 125.3 (s), 124.5 (s), 73.1 (t), 69.6 (t), 67.0 (t), 64.3 (t), 52.2 (q), 51.4 (d), 47.2 (d), 25.5 (q), 17.9 (s), 11.7 (q), 11.6 (q), −5.7 (q) and −5.8 (q) ppm; *m*/*z* (ESI) found: 997.3126, $C_{48}H_{50}N_8O_{13}SiNa$ [(M + Na)$^+$] requires 997.3164.

Macrocycle (37)

4-Methylmorpholine (0.44 mL, 3.8 mmol) was added to a stirred suspension of the amino acid **36b** (0.17 g, 0.19 mmol) in dry dichloromethane (52 mL) and dry *N*,*N*-dimethylformamide (26 mL) at 0 °C under a nitrogen atmosphere. *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (0.15 g, 0.39 mmol) was added and the mixture was stirred at 0 °C for 30 min and then allowed to warm to room temperature and stirred for 18 h. Dichloromethane (60 mL) was added and the reaction was quenched with water (60 mL). The separated organic layer was washed with water (60 mL) and saturated sodium chloride solution (60 mL), then dried ($MgSO_4$) and concentrated *in vacuo.* The residue partially purified by trituration with ether to give the *macrolactam* (0.12 mg, 80%) as a colourless solid; ν_{max}($CHCl_3$)/cm^{-1} 3384, 2928, 1671 and 1597; δ_H(500 MHz, $CDCl_3$) 8.32 (1H, s, oxazole-H), 8.30 (1H, s, oxazole-H), 8.26 (1H, s, oxazole-H), 8.26 (1H, s, oxazole-H), 7.95 (1H, d,

J 8.8 Hz, CONH), 7.89 (1H, d, *J* 8.7 Hz, CONH), 7.37–7.26 (5H, m, 5 × aryl-H), 5.78–5.71 (1H, m, CONHCH), 5.62–5.55 (1H, m, CONHCH), 4.62 (1H, d, *J* 12.3 Hz, $CH_2OCH_aH_bPh$), 4.58 (1H, d, *J* 12.3 Hz, $CH_2OCH_aH_bPh$), 4.30–3.93 (4H, m, CH_2OTBS, CH_2OBn), 2.81 (3H, s, oxazole-CH_3), 2.74 (3H, s, oxazole-CH_3), 0.90 (9H, s, $SiC(CH_3)_3$), −0.08 (3H, s, $SiCH_3(CH_3)$) and −0.03 (3H, s, $SiCH_3(CH_3)$) ppm; *m*/*z* (ESI) found: 831.2527, $C_{39}H_{40}N_8O_{10}SiNa$ [(M + Na)$^+$] requires 831.2534.

2-[(*S*)-1-{[2″-(*tert*-Butoxycarbonylaminomethyl)-[2,4′;2′,4″]-teroxazole-4-carbonyl]-amino}-2-(*tert*-butyldimethylsilanyloxy)-ethyl]-5-phenyloxazole-4-carboxylic acid methyl ester (64)

4-Methylmorpholine (0.77 mL, 7.0 mmol) was added to a stirred suspension of the acid **63b** (0.26 g, 0.70 mmol) and 1-hydroxybenzotriazole (0.47 g, 3.5 mmol) in dry dichloromethane (10 mL) and *N*,*N*-dimethylformamide (5 mL) at 0 °C under a nitrogen atmosphere. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.27 g, 1.4 mmol) was added and the mixture was then stirred at 0 °C for 10 min. A solution of the amine **60** (0.28 g, 0.74 mmol) in dry dichloromethane (5 mL) was added dropwise over 3 min at 0 °C, and the mixture was allowed to warm to room temperature overnight and then quenched with water (20 mL). Dichloromethane (30 mL) was added and the separated organic layer was washed with 10% aqueous citric acid (2 × 15 mL) and saturated sodium bicarbonate solution (15 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography on silica gel using 1 : 1 dichloromethane–ethyl acetate as eluent to give the tetraoxazole amide (0.45 g, 87%) as a colourless solid; mp 96–98 °C (from dichloromethane–petrol); $[\alpha]_D^{27}$ +54 ($c = 1.0$, $CHCl_3$); found: C, 56.9; H, 5.8; N, 11.1%. $C_{35}H_{42}N_6O_{10}Si$ requires C, 57.2; H, 5.8; N, 11.4%; $\nu_{max}(CHCl_3)/cm^{-1}$ 3696, 3605, 3506, 2929, 1719, 1680 and 1595; δ_H(360 MHz, $CDCl_3$) 8.35 (1H, s, oxazole-H), 8.32 (1H, s, oxazole-H), 8.30 (1H, s, oxazole-H), 8.04–8.00 (2H, m, 2 × phenyloxazole-H), 7.83 (1H, d, *J* 8.7 Hz, CONH), 7.49–7.43 (3H, m, 3 × phenyloxazole-H), 5.59–5.52 (1H, m, CONHCH), 5.27 (1H, br s, BocNH), 4.56 (2H, d, *J* 5.8 Hz, $BocNHCH_2$), 4.23 (1H, dd, *J* 10.1 and 4.6 Hz, CH_aH_bOTBS), 4.10 (1H, dd, *J* 10.1 and 5.2 Hz, CH_aH_bOTBS), 3.94 (3H, s, CO_2CH_3), 1.47 (9H, s, $OC(CH_3)_3$), 0.84 (9H, s, $SiC(CH_3)_3$), 0.04 (3H, s, $SiCH_3(CH_3)$) and 0.03 (3H, s, $SiCH_3(CH_3)$) ppm; δ_C(90 MHz, $CDCl_3$) 162.8 (s), 162.3 (s), 160.1 (s), 159.8 (s), 156.0 (s), 155.7 (s), 155.4 (s), 154.3 (d), 141.5 (d), 139.7 (d), 139.0 (d), 136.7 (s), 130.8 (s), 130.3 (d), 129.6 (s), 128.3 (d), 128.2 (d), 126.7 (s), 126.5 (s), 80.2 (s), 64.1 (t), 52.1 (q), 49.1 (d), 37.8 (t), 28.1 (q), 25.6 (q), 18.1 (s), −5.6 (q) and −5.6 (q) ppm; *m*/*z* (ESI) found: 757.2639, $C_{35}H_{42}N_6O_{10}SiNa$ [(M + Na)$^+$] requires 757.2629.

2-[(*S*)-1-{[2″-(*tert*-Butoxycarbonylaminomethyl)-[2,4′;2′,4″]teroxazole-4-carbothioyl]-amino}-2-(*tert*-butyldimethylsilanyloxy)-ethyl]-5-phenyloxazole-4-carboxylic acid methyl ester (65)

Lawesson's reagent (0.45 g, 1.1 mmol) was added in one portion to a stirred solution of the amide **64** (0.45 g, 0.61 mmol) in dry tetrahydrofuran (10 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred at reflux for 21 h and then cooled to room temperature. The mixture was concentrated *in vacuo* and the residue was then partitioned between dichloromethane (80 mL) and saturated sodium bicarbonate solution (80 mL). The aqueous extract was re-extracted with dichloromethane (80 mL) and the combined organic extracts were dried ($MgSO_4$) and then concentrated *in vacuo*. The solid yellow residue was purified by chromatography on silica gel using 6 : 1 dichloromethane–ether as eluent to give the *thioamide* (0.23 g, 50%) as a colourless solid; mp 151 °C (decomp.) (from dichloromethane–petrol); $[\alpha]_D^{22}$ +74 ($c = 1.0$, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3449, 3345, 2930, 1719, 1653 and 1585; δ_H(360 MHz, $CDCl_3$) 9.46 (1H, d, *J* 8.1 Hz, CSNH), 8.43 (1H, s, oxazole-H), 8.34 (1H, s, oxazole-H), 8.32 (1H, s, oxazole-H), 8.03–7.99 (2H, m, 2 × phenyloxazole-H), 7.48–7.42 (3H, m, 3 × phenyloxazole-H), 6.14–6.09 (1H, m, CSNHCH), 5.30 (1H, br s, BocNH), 4.55 (2H, d, *J* 5.9 Hz, $BocNHCH_2$), 4.33 (1H, dd, *J* 10.2 and 4.1 Hz, CH_aH_bOTBS), 4.19 (1H, dd, *J* 10.2 and 5.0 Hz, CH_aH_bOTBS), 3.93 (3H, s, CO_2CH_3), 1.46 (9H, s, $OC(CH_3)_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $SiCH_3(CH_3)$) and 0.03 (3H, s, $SiCH_3(CH_3)$) ppm; δ_C(90 MHz, $CDCl_3$) 185.3 (s), 162.8 (s), 162.3 (s), 159.3 (s), 156.1 (s), 155.9 (s), 154.1 (s), 142.8 (d), 142.0 (s), 139.7 (d), 139.1 (d), 130.9 (s), 130.4 (d), 129.7 (s), 128.4 (d), 128.4 (d), 126.9 (s), 126.6 (s), 80.4 (s), 63.4 (t), 53.7 (d), 52.3 (q), 37.9 (t), 28.2 (q), 25.6 (q), 18.1 (s) and −5.5 (q) ppm; *m*/*z* (ESI) found: 773.2461, $C_{35}H_{42}N_6O_9SSiNa$ [(M + Na)$^+$] requires 773.2401.

4-[(*S*)-2-Hydroxy-1-(4-methoxycarbonyl-5-phenyloxazol-2-yl)-ethylthiocarbamoyl]-[2,4′;2′,4″]teroxazol-2″-ylmethylammonium chloride (70)

Hydrogen chloride (4.0 M solution in dioxane) (3 mL) was added to the carbamate **65** (0.23 g, 0.3 mmol) and the mixture was stirred at room temperature overnight under a nitrogen atmosphere. The mixture was evaporated to leave the *amine hydrochloride salt* (0.16 g, 91%) as a colourless solid; mp 191 °C (decomp.); $[\alpha]_D^{26}$ +80 ($c = 0.2$, CH_2Cl_2–MeOH (3 : 1)); ν_{max}(solid)/cm^{-1} 3350, 1727, 1659 and 1581; δ_H(500 MHz, DMSO-d_6) 10.33 (1H, br s, CSNH), 9.18 (1H, s, oxazole-H), 9.15 (1H, s, oxazole-H), 8.94 (1H, s, oxazole-H), 8.92 (3H, br s, NH_3), 7.99–7.95 (2H, m, 2 × phenyloxazole-H), 7.58–7.52 (3H, m, 3 × phenyloxazole-H), 5.97 (1H, br s, OH), 5.59 (1H, t, *J* 5.9 Hz, CSNHCH), 4.41 (2H, s, NH_3CH_2), 4.15–4.07 (2H, m, CH_2OH) and 3.82 (3H, s, CO_2CH_3) ppm; δ_C(125 MHz, DMSO-d_6) 186.6 (s), 165.4 (s), 163.0 (s), 162.9 (s), 158.8 (s), 158.2 (s), 157.7 (s), 147.7 (d), 145.5 (d), 145.1 (s), 144.9 (d), 134.0 (d), 133.4 (s), 132.6 (s), 132.1 (d), 131.7 (d), 130.0 (s), 129.9 (s), 64.5 (t), 58.0 (d), 55.5 (q) and 38.9 (t) ppm; *m*/*z* (ESI) found: 537.1161, $C_{24}H_{20}N_6O_7S$ [M$^+$] requires 537.1192.

2-{(*S*)-1-[(2″-{[(*R*)-1-((2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-3-methylpentanoylamino)-2-methylpropylamino]-methyl}-[2,4′;2′,4″]teroxazole-4-carbothioyl)-amino]-2-hydroxyethyl}-5-phenyloxazole-4-carboxylic acid methyl ester (78a)

4-Methylmorpholine (59 μL, 0.54 mmol) was added to a stirred suspension of the carboxylic acid **77** (90 mg, 0.27 mmol) and 1-hydroxybenzotriazole (0.11 g, 0.81 mmol) in dry dichloromethane (15 mL) at 0 °C under a nitrogen atmosphere. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.10 g, 0.54 mmol) was added and the mixture was then stirred at 0 °C for 15 min. A pre-cooled (0 °C) solution of the amine **70** (0.16 g, 0.27 mmol) and 4-methylmorpholine (59 μL, 0.54 mmol)

 This journal is © The Royal Society of Chemistry 2008

in dry dichloromethane (5 mL) was added dropwise over 5 min, and the mixture was then allowed to warm to room temperature overnight. The mixture was concentrated *in vacuo* and the residue was then triturated with methanol to leave the *amide* (0.19 g, 82%) as a colourless solid; mp 258 °C (decomp.); $[\alpha]_D^{25}$ +56 (c = 1.0, $CHCl_3$–MeOH (4 : 1)); $\nu_{max}(CHCl_3)/cm^{-1}$ 3343, 2964 and 1692; δ_H(360 MHz, DMSO-d_6) 10.34 (1H, d, J 7.8 Hz, CSN*H*), 9.08 (1H, s, oxazole-H), 8.96 (1H, s, oxazole-H), 8.91 (1H, s, oxazole-H), 8.70 (1H, t, CON*H*CH_2), 8.00–7.91 (3H, m, 2 × phenyloxazole-H, CON*H*-(val)), 7.58–7.49 (3H, m, 3 × phenyloxazole-H), 6.87 (1H, d, J 8.1 Hz, BocN*H*), 6.01–5.94 (1H, m, CONHC*H*-(val)), 5.52 (1H, t, J 5.9 Hz, CSNHC*H*), 4.59–4.43 (2H, m, gly-CH_2), 4.29–4.21 (1H, m, BocNHC*H*), 4.18–4.07 (2H, m, CH_2OH), 3.92 (1H, t, J 7.9 Hz, CH_2O*H*), 3.82 (3H, s, CO_2CH_3), 2.14–2.02 (1H, m, C*H*), 1.76–1.63 (1H, m, C*H*), 1.37 (9H, s, OC(CH_3)$_3$), 1.16–1.03 (2H, m, CH_2) and 0.91–0.75 (12H, m, 3 × CH_3) ppm; δ_C(90 MHz, DMSO-d_6) 188.6 (s), 175.4 (s), 174.9 (s), 174.8 (s), 166.1 (s), 165.4 (s), 163.0 (s), 159.2 (s), 158.1 (s), 157.8 (s), 147.6 (d), 145.1 (s), 144.6 (d), 144.6 (d), 134.0 (d), 133.3 (s), 132.4 (s), 132.1 (d), 131.7 (d), 129.9 (s), 129.9 (s), 81.7 (s), 64.5 (t), 62.5 (d), 60.9 (d), 58.0 (d), 55.4 (q), 39.6 (d), 39.4 (t), 33.5 (d), 31.6 (q), 27.9 (t), 22.7 (q), 21.2 (q), 18.9 (q) and 14.4 (q) ppm; m/z (ESI) found: 871.3130, $C_{40}H_{48}N_8O_{11}SNa$ [(M + Na)$^+$] requires 871.3061.

(1*S*,2*S*)-1-[(*R*)-1-({4-[(*S*)-1-(4-Carboxy-5-phenyloxazol-2-yl)-2-hydroxyethylthiocarbamoyl]-[2,4′;2′,4″]teroxazol-2″-ylmethyl}-carbamoyl)-2-methylpropylcarbamoyl]-2-methylbutylammonium chloride (78b)

A solution of sodium hydroxide (87 mg, 2.2 mmol) in water (5 mL) was added in one portion to a stirred solution of the tetra-oxazole substituted methyl ester **78a** (0.19 g, 0.22 mmol) in tetrahydrofuran (10 mL), and the mixture was stirred at room temperature overnight. Water (20 mL) was added and the mixture was concentrated slowly *in vacuo* to a volume of 20 mL. The aqueous suspension was extracted with dichloromethane–methanol (4 : 1) (5 × 30 mL) and dichloromethane (3 × 30 mL) and the combined organic extracts were then evaporated *in vacuo* to leave the *sodium carboxylate* (0.17 g, 86%) as a colourless solid, which was used directly in the next reaction without further purification.

Hydrogen chloride (4.0 M solution in dioxane) (5 mL) was added to the *sodium carboxylate* (0.17 g, 0.19 mmol) and the mixture was stirred at room temperature overnight under a nitrogen atmosphere. The volatiles were evaporated to leave the *ω-amino acid hydrochloride salt* (0.14 g, 100%) as a colourless solid, which was used without further purification.

(−)-YM-216391 (81)

4-Methylmorpholine (0.28 mL, 2.6 mmol) was added to a stirred suspension of the ω-amino acid (0.14 g, 0.19 mmol) in dry dichloromethane (42 mL) and dry *N*,*N*-dimethylformamide (21 mL) at 0 °C under a nitrogen atmosphere. *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (0.15 g, 0.38 mmol) was added and the mixture was stirred at 0 °C for 5 min and then allowed to warm to room temperature and stirred for 48 h. Dichloromethane (50 mL) was added and the reaction was quenched with water (50 mL). The separated organic layer was washed with 10% aqueous citric acid (40 mL) and saturated sodium bicarbonate solution (40 mL), then dried ($MgSO_4$) and concentrated *in vacuo.* The residue was partially purified by trituration with ether to give the *macrolactam* **79** (95 mg, 75%) as a colourless solid.

(Diethylamino)sulfur trifluoride (35 μL, 0.27 mmol) was added to a stirred solution of the thioamide cyclopeptide **79** (95 mg, 0.13 mmol) in dry dichloromethane (3 mL) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 4 h and then allowed to warm to room temperature. The mixture was quenched with saturated sodium bicarbonate solution (3 mL) and the separated aqueous layer was then extracted with dichloromethane (5 mL). The combined organic extracts were dried ($MgSO_4$) and then concentrated *in vacuo* to leave the corresponding thiazoline **80** (82 mg, 92%) as a yellow solid, which was used directly in the next reaction without further purification.

Activated manganese(IV) oxide (0.2 g, 2.3 mmol) was added to a stirred solution of the thiazoline **80** (82 mg, 0.12 mmol) in dry dichloromethane (10 mL) at room temperature under a nitrogen atmosphere. The mixture was stirred for 48 h and was then filtered through a pad of celite and eluted with dichloromethane–methanol (1 : 1) (100 mL). The filtrate was concentrated *in vacuo* to leave a yellow residue, which was partially purified by trituration with ether to leave the thiazole (55 mg, 66%) as a colourless solid. A portion of this material was further purified by reverse phase HPLC to give the *thiazole* (10 mg) as a colourless solid; mp 240 °C (decomp.); $[\alpha]_D^{20}$ −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 (3H, 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.

Acknowledgements

We thank the EPSRC for a studentship (to JD) and Drs K. Sohda and Y. Takebayashi (Yamanouchi Pharmaceutical Co. Ltd. Tokyo, Japan) for helpful correspondence and for supplying relevant NMR spectroscopic data on natural YM-216391. We also thank Celia Ribes Vidal and David Evans for their contributions to these projects.

References

1 (*a*) K. Shin-ya, K. Wierzba, K. Matsuo, T. Ohtani, Y. Yamada, K. Furihata, Y. Hayakawa and H. Seto, *J. Am. Chem. Soc.*, 2001, **123**, 1262–1263; (*b*) M. Y. Kim, H. Vankayalpati, K. Shin-ya, K. Wierza and L. H. Hurley, *J. Am. Chem. Soc.*, 2002, **124**, 2098–2099.
2 (*a*) K. Sohda, K. Nagai, T. Yamori, K. Suzuki and A. Tanaka, *J. Antibiot.*, 2005, **58**, 27–31; (*b*) K. Hayata, Y. Takebayashi, K. Nagai, and M. Hiramoto, *Jpn. Kokai Tokkyo Koho*, JP11180997-A, 1999.
3 J. A. Roesener and P. J. Scheuer, *J. Am. Chem. Soc.*, 1986, **108**, 846–847.
4 N. Lindquist, W. Fenical, G. D. Van Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1991, **113**, 2303–2304; see also; A. W. G. Burgett, Q. Li,

Q. Wei and P. G. Harran, *Angew. Chem., Int. Ed.*, 2003, **42**, 4961–4966.
5 F. Romero, L. Malet, M. L. Caňedo, C. Cuevas, and F. Reyes, WO 2005/000880 A2, 2005. IB-01211 is also known as merchercharmycin A; see; K. Kanoh, Y. Matsuo, K. Adachi, H. Imagawa, M. Nishizawa and Y. Shizuri, *J. Antibiot.*, 2005, **58**, 289–292.
6 J. Ogino, R. E. Moore, G. M. L. Patterson and C. D. Smith, *J. Nat. Prod.*, 1996, **59**, 581–586.
7 (*a*) C. M. Ireland, A. R. Durso, R. A. Newman and M. P. Hacker, *J. Org. Chem.*, 1982, **47**, 1807–1811; (*b*) F. J. Schmitz, M. B. Ksebati, J. S. Chang, J. L. Wang, M. B. Hossain and D. von der Helm, *J. Org. Chem.*, 1989, **54**, 3463–3472.
8 Y. Hamamoto, M. Endo, M. Nakagawa, T. Nakanishi and K. Mizukawa, *J. Chem. Soc., Chem. Commun.*, 1983, 323–324.
9 H. Abe, K. Kushida, Y. Shiobara and M. Kodama, *Tetrahedron Lett.*, 1988, **29**, 1401–1404 See also: R. A. Hughes and C. J. Moody, *Angew. Chem., Int. Ed.*, 2007, **46**, 7930–7954.
10 M.-Y. Kim, H. Vankayalapati, K. Shin-ya, K. Wierzba and L. H. Hurley, *J. Am. Chem. Soc.*, 2002, **124**, 2098–2099.
11 See D. Hernández, E. Riego, A. Francesch, C. Cuevas, F. Albericio and M. Álvarez, *Tetrahedron*, 2007, **63**, 9862–9870.
12 See also: J. P. Michael and G. Pattenden, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1–24; A. Bertram and G. Pattenden, *Nat. Prod. Rep.*, 2007, **24**, 18–30.
13 For a recent review on polyoxazoles see: E. Riego, D. Hernandez, F. Albericio and M. Álvarez, *Synthesis*, 2005, 1907–1922.
14 Preliminary communication: J. Deeley and G. Pattenden, *Chem. Commun.*, 2005, 797–799. For a synthesis of IB-01211 (merchercharmycin A) see: D. Hernández, G. Vilar, E. Riego, L. M. Caňedo, C. Cuevas, F. Albericio and M. Álvarez, *Org.Lett.*, 2007, **9**, 809–811.
15 For related contemporaneous synthetic studies directed towards telomestatin and its analogues see: S. K. Chattopadhyah, S. Biswas and B. K. Pal, *Synthesis*, 2006, 1289–1294; S. K. Chattopadhyah and S. Biswas, *Tetrahedron Lett.*, 2006, **47**, 7897–7900; M. C. Marson and M. Saadi, *Org. Biomol. Chem.*, 2006, **4**, 3892–3893.
16 (*a*) S. K. Chattopadhyay and G. Pattenden, *Tetrahedron Lett.*, 1998, **39**, 6095–6098; (*b*) S. K. Chattopadhyay and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2429–2454. See also G. Pattenden, N. J. Ashweek, C. A. G. Baker-Glenn, G. M. Walker and J. G. K. Yee, *Angew. Chem.*, 2007, **46**, 4359–4363; G. Pattenden, N. J. Ashweek, C. A. G. Baker-Glenn, J. Kempson, G. M. Walker and J. G. K. Yee, *Org. Biomol. Chem.*, 2008, **6**, 1478–1497.
17 (*a*) P. Liu and J. S. Panek, *J. Am. Chem. Soc.*, 2000, **122**, 1235–1236; (*b*) J. S. Panek and P. Liu, *J. Am. Chem. Soc.*, 2000, **122**, 11090–11097.
18 S. K. Chattopadhyay, J. Kempson, A. McNeil, G. Pattenden, M. Reader, D. E. Rippon and D. Waite, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2415–2428.
19 P. Liu, C. A. Celatka and J. S. Panek, *Tetrahedron Lett.*, 1997, **38**, 5445–5448.
20 For some recent reviews see references 9 and 13.
21 D. C. Palmer, *Oxazoles: Synthesis, Reactions and Spectroscopy; Part A*, John Wiley and Sons Inc., Hoboken, New Jersey, 2003.
22 A. J. Phillips, Y. Uto, P. Wipf, M. J. Reno and D. R. Williams, *Org. Lett.*, 2000, **2**, 1165–1168; G. Pattenden and T. Thompson, *Tetrahedron Lett.*, 2002, **43**, 2459–2461.
23 (*a*) S. V. Downing, E. Aguilar and A. I. Meyers, *J. Org. Chem.*, 1999, **64**, 826–831; (*b*) A. Bertram and G. Pattenden, *Heterocycles*, 2002, **58**, 521–561.
24 G. Burrell, J. M. Evans, G. E. Jones and G. Stemp, *Tetrahedron Lett.*, 1990, **31**, 3649–3652. See also references 21 and 22.
25 D. L. Evans, D. K. Minster, U. Jordis, S. M. Hecht, A. L. Mazzu and A. I. Meyers, *J. Org. Chem.*, 1979, **44**, 497–501.
26 G. J. McGarvey, K. J. Wilson and C. E. Shanholtz, *Tetrahedron Lett.*, 1992, **33**, 2641–2644.
27 (*a*) P. Wipf and S. Lim, *J. Am. Chem. Soc.*, 1995, **117**, 558–559; (*b*) P. Wipf and C. P. Miller, *J. Org. Chem.*, 1993, **58**, 3604–3606.
28 N. Endoh, K. Tsuboi, R. Kim, Y. Yonezawa and C. Shin, *Heterocycles*, 2003, **60**, 1567–1572.
29 T. Doi, M. Yoshida, K. Shin-ya and T. Takahashi, *Org. Lett.*, 2006, **8**, 4165–4167; For an earlier patent see: S. Yamada, K. Shigeno, K. Kitagawa, S. Okajima and T. Asao, WO 200248153 [*Chem. Abs.*, 2002, **137**, 47050].
30 S. You, H. Razavi and J. W. Kelly, *Angew. Chem., Int. Ed.*, 2003, **42**, 83–85.
31 E. M. Burgess, H. R. Penton and E. A. Taylor, *J. Org. Chem.*, 1973, **38**, 26–31. See also reference 27*b*.
32 (*a*) O. E. Jensen and A. Senning, *Tetrahedron*, 1986, **42**, 6555–6564; (*b*) M. P. Cava and M. I. Levinson, *Tetrahedron*, 1985, **41**, 5061–5087; (*c*) G. Lajoie, F. Lépine, L. Maziak and B. Belleau, *Tetrahedron Lett.*, 1983, **24**, 3815–3818; (*d*) K. Clausen, M. Thorsen and S.-O. Lawesson, *Tetrahedron*, 1981, **37**, 3635–3639.
33 (*a*) T. Hu and J. S. Panek, *J. Am. Chem. Soc.*, 2002, **124**, 11368–11378; (*b*) K. J. Hale, J. Cai and G. Williams, *Synlett*, 1998, 149–152; (*c*) L. A. Carpino, A. El-Faham and E. Albericio, *Tetrahedron Lett.*, 1994, **35**, 2279–2282; See also reference 23*a*.
34 K. Sohda, M. Hiramoto, K. Suzumura, Y. Takebayashi, K. Suzuki and A. Tanaka, *J. Antibiot.*, 2005, **58**, 32–36.

 This journal is © The Royal Society of Chemistry 2008