13. Azole-based Cyclic Peptides, and their Association and Binding with Metals

In 1993 Joe Michael and myself published a review with the somewhat provocative title "*Marine Metabolites and Metal Ion Chelation. The Facts and the Fantasies*".[1] In the review we drew attention to the potential for marine organisms to sequester and transport metal ions, and we then posed a number of questions:

1) How widespread is the evidence for marine natural product – metal congruence ?

2) What structural features in marine metabolites are required for metal complexation and transport ?

3) What are the biological roles of the metal ions in these associations ?

4) Could metal ions be involved in the assembly of marine metabolites *in vivo* ?

Finally, we asked: could answers to the aforementioned questions be exploited in synthetic studies with certain marine natural products? It was at this point, in 1993, that we entered the arena of:

a) synthetic studies of azole-based cyclic peptides and, later

b) the assembly of cyclic peptides from azole-based amino acids, including metal-templated assemblies.

Our last publication in the latter area was in 2007 and in the same year, with Anna Bertram, we presented a second review entitled "*Marine Metabolites: Metal Binding and Metal Complexes of Azole-based Cyclic Peptides of Marine Origin*" which brought up-to-date the literature and, at the same time, answered some of the questions posed in our earlier review.[2] We will now summarise our contributions in this ever-expanding area of research.

Ascidians ("sea squirts") of the genus *Lissoclinum* and *Didemnum*, in particular, are a prolific source of unusual cyclic peptides which contain both *D*- and *L*- amino acids, many modified in the form of thiazole, oxazole, thiazoline or oxazoline rings. Representative examples include lissoclinamide 4 (**1**) and lissoclinamide 5 (**2**) produced by *L. patella*, cyclodidemnamide **3** and mollamide **4** from *Didemnum molle*, and trunkamide **5** from *Lissoclinum sp*. Closely related azole-based cyclic peptides have also been isolated from cyanobacteria, *eg.* raocyclamide A (**6**) from *Oscillatoria raoi*, dendroamide **7** from *Stigonema dedroideum*, and nostocyclamide **8** (Figures 1 and 2). When we entered this arena, cyclic peptides of similar structure to those of **1**–**8** had received prominence as a result of their important biological properties and, not surprisingly therefore, some synthetic studies within the family had already been made. However, these studies had shown that in several instances the structures assigned needed significant revision. Above all, the correct assignment of chiral centres adjacent to the azole rings in these structures was particularly problematic. Given the importance of these chiral centres in determining cytotoxicity, and to our longer term aims of answering at least some of the questions we had already posed regarding cyclic peptide-metal congruence, we decided that it was important, at the outset, to confirm the stereochemistries of the cyclic peptides **1**–**8** by total synthesis. This time and effort was not wasted !

Thus, in 1994, we completed our first synthesis of a cyclic peptide, *i.e.* lissoclinamide 5 (**2**), only to find that its stereochemistry had been misassigned.[3] A year later we synthesised lissoclinamide 4 (**1**) and also found that its stereochemistry was incorrect![4] Again, a few years later we synthesised cyclodidemnamide **3**[5] and raocyclamide A (**6**),[6] and also concluded that their stereochemistries were not correct. As if we needed demonstrations of the importance of total synthesis in structure assignments, here they were !

Our strategy for the synthesis of the structure **2** proposed for lissoclinamide 5 was quite straightforward and is shown in Scheme 1. Thus, we first synthesised the enantiopure amino acid-based thiazoles **9** and **11**, and next converted them into the tri- and tetra-peptides **10** and **12** respectively. These peptides were then coupled at the proline-threonine amide bond, leading to **13**. Removal of the protecting groups in **13** and macrolactamisation of the resulting amino acid next gave the cyclopeptide **14**. Finally, cyclodehydration of **14** using precedent established by Shiori and others produced the structure **2** proposed for lissoclinamide 5.

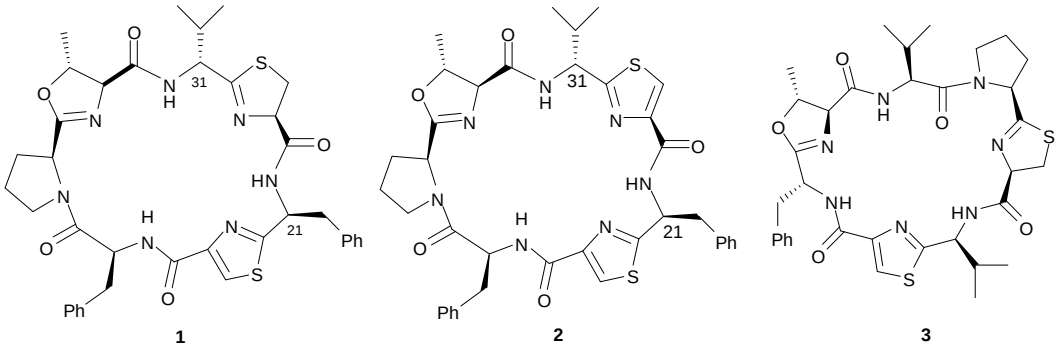


Figure 1. Some azole-based cyclic peptides isolated from ascidians (sea squirts).

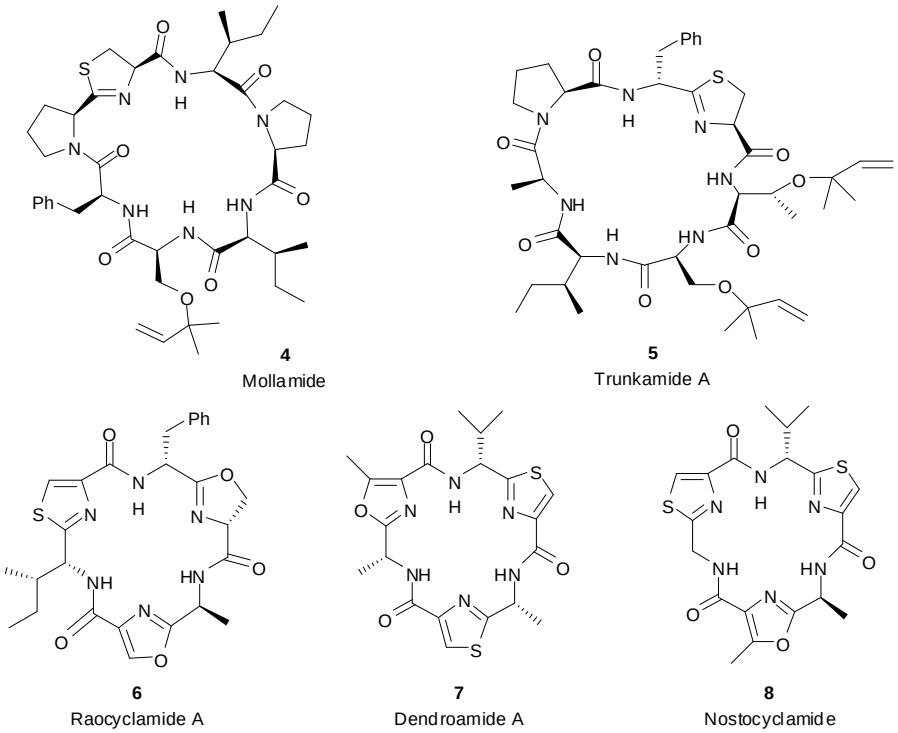
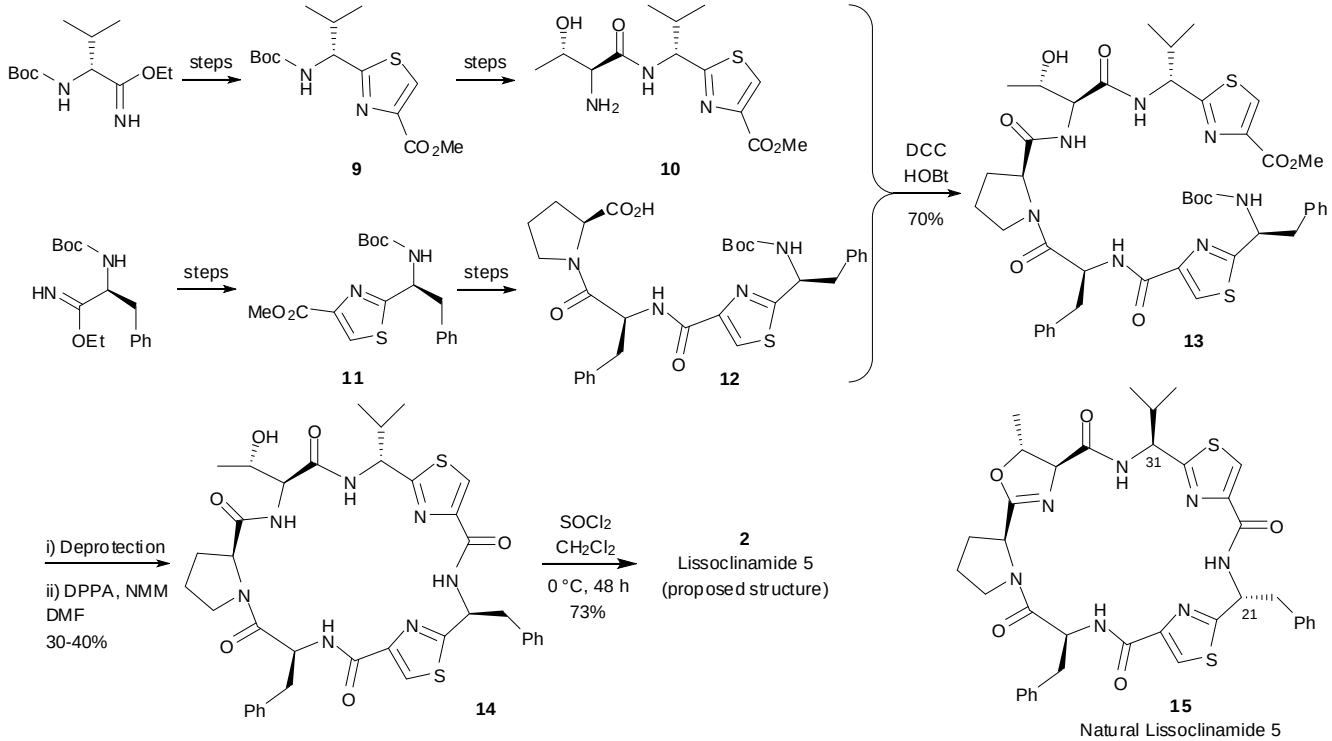


Figure 2. Mollamide **4** and trunkamide A (**5**) from sea squirts and the azole-based cyclic peptides **6**-**8** isolated from cyanobacteria.

The spectroscopic data for synthetic **2** did not match those published for the natural product however, and after careful examination of the data we re-assigned the stereochemistry of natural lissoclinamide 5 to that shown in structure **15,** *i.e.* having the (21*S*,31*S*) stereochemistry**.** We then repeated the aforementioned synthesis, starting with *S*-valine and *R*-phenyalanine, instead of their enantiomers, and in this way produced the stereostructure **15** (Scheme 2). Gratifyingly, this structure was shown to be identical with natural lissoclinamide 5, isolated from *L. patella*.[7]



Scheme 1. Total synthesis of lissoclinamide 5 (**2**) and revision of its stereochemistry to **15**

Lissoclinum patella; source of lissoclinamides **1** and **2**.
Image from https://commons.wikimedia.org/wiki/File:Lissoclinum_patellum.jpg

Didemnum molle (sea squirt); source of cyclodidemnamide **3** and mollamide **4**
http://reefguide.org/didemnummolle.html

Oscillatoria raoi (cyanobacterium); source of raocyclamide A (**6**)
Image from http://www.britannica.com/science/Oscillatoria

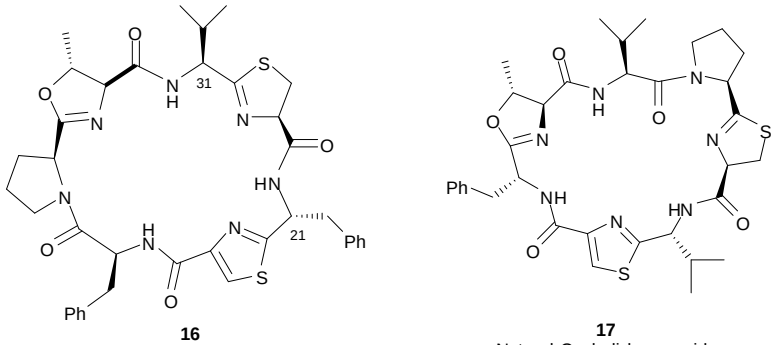
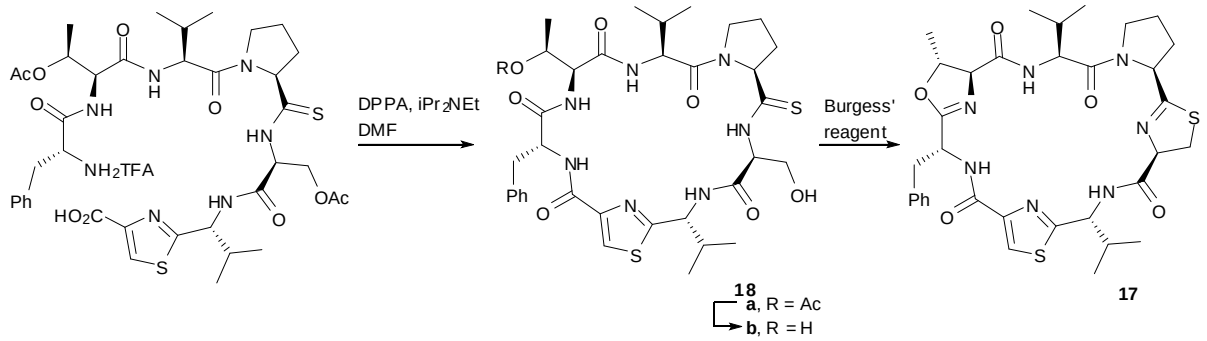


Figure 3. Revision of stereochemistries of lissoclinamide 4 (**16**), *cf.* structure **1**, and cyclodidemnamide **17,** *cf.*structure **3**



Scheme 2. Total synthesis of cyclodidemnamide **17** using a double cyclodehydration sequence to produce the chiral thiazoline and oxazoline rings in **17** from **18b**.

The same outcome emerged when we synthesised the thiazoline-based cyclopeptides lissoclinamide 4 and cyclodidemnamide , *i.e.* the assigned structures **1** and **3** were incorrect, and we modified them to **16** and **17** respectively (Figure 3).[7,8] To overcome the problems associated with the sensitivity of enantiopure amino acid-substituted thiazolines towards epimerisation, our syntheses of lissoclinamide 4 and cyclodidemnamide each featured a novel double-cyclodehydration and sequential formation of their chiral azoline rings from a preformed cyclopeptide intermediate, as key steps. This synthetic approach is shown in Scheme 2 for the case of cyclodidemnamide **17,** whereby treatment of the cyclopeptide intermediate **18b,** with Burgess' reagent resulted in simultaneous formation of the chiral thiazoline and oxazoline rings in the natural product, in one step.

The structures assigned to the oxazole-thiazole based cyclic peptides raocyclamide A (**6**) and raocyclamide B (**20**) were also shown to be incorrect by synthesis. Following our syntheses, using correct chiral amino acid starting materials, their structures were modified to **19** and **21** respectively (Figure 4).[6]

Mollamide **4** and trunkamide A (**5**) are examples of unusual reverse prenyl-substituted cyclic peptides isolated from sea-squirts. Although both structures displayed toxicity against a range of cell lines, trunkamide A was reported to have particularly promising antitumour activity. The structure of mollamide was established by X-ray crystallography by Bruce Bowden *et al*. in 1994. We described its synthesis a few years later, using a strategy which not only further illustrated our

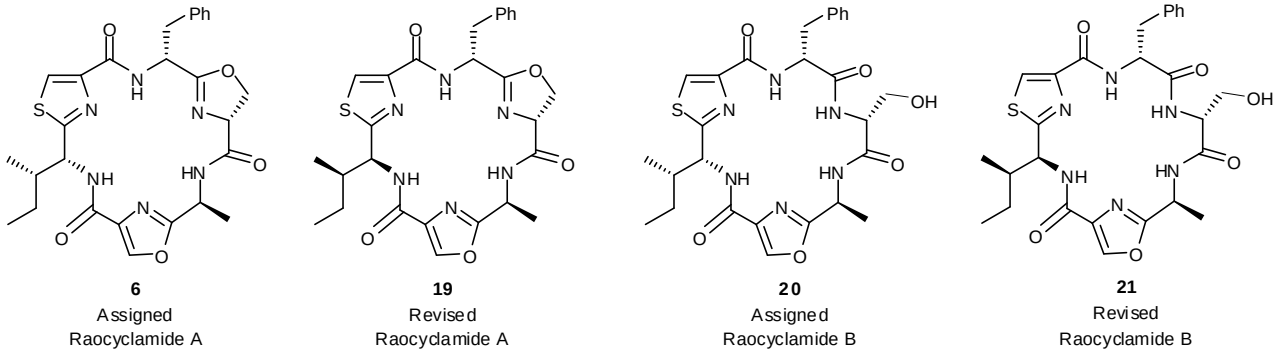
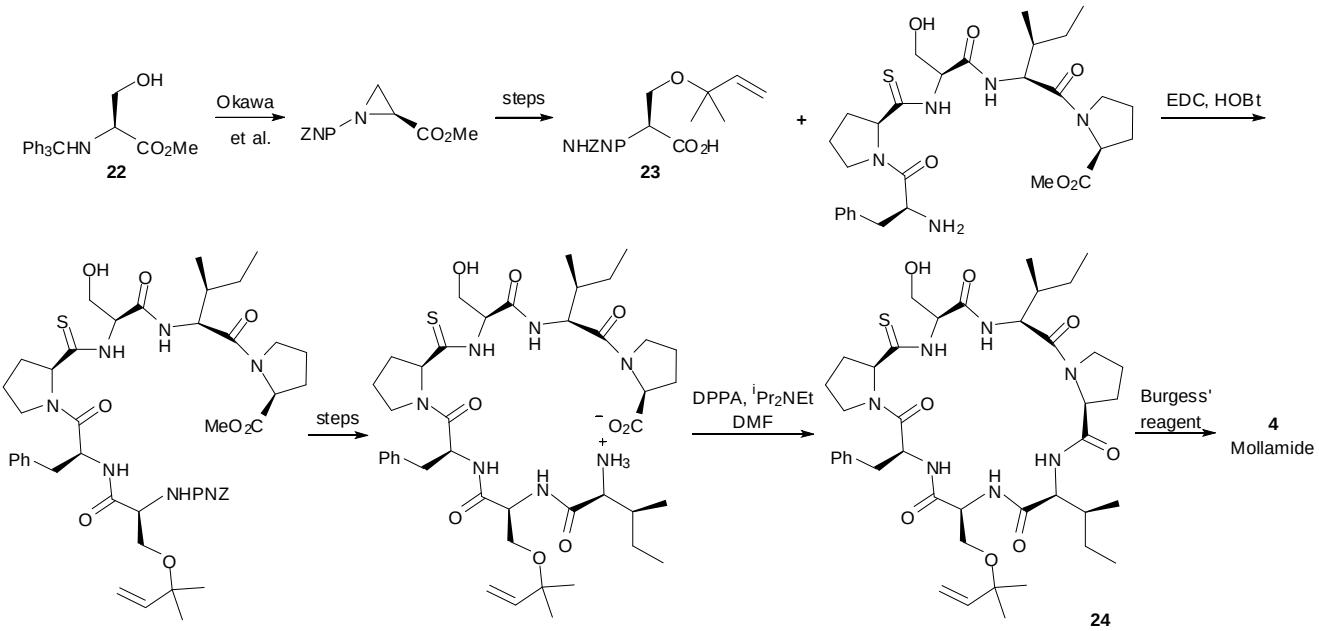


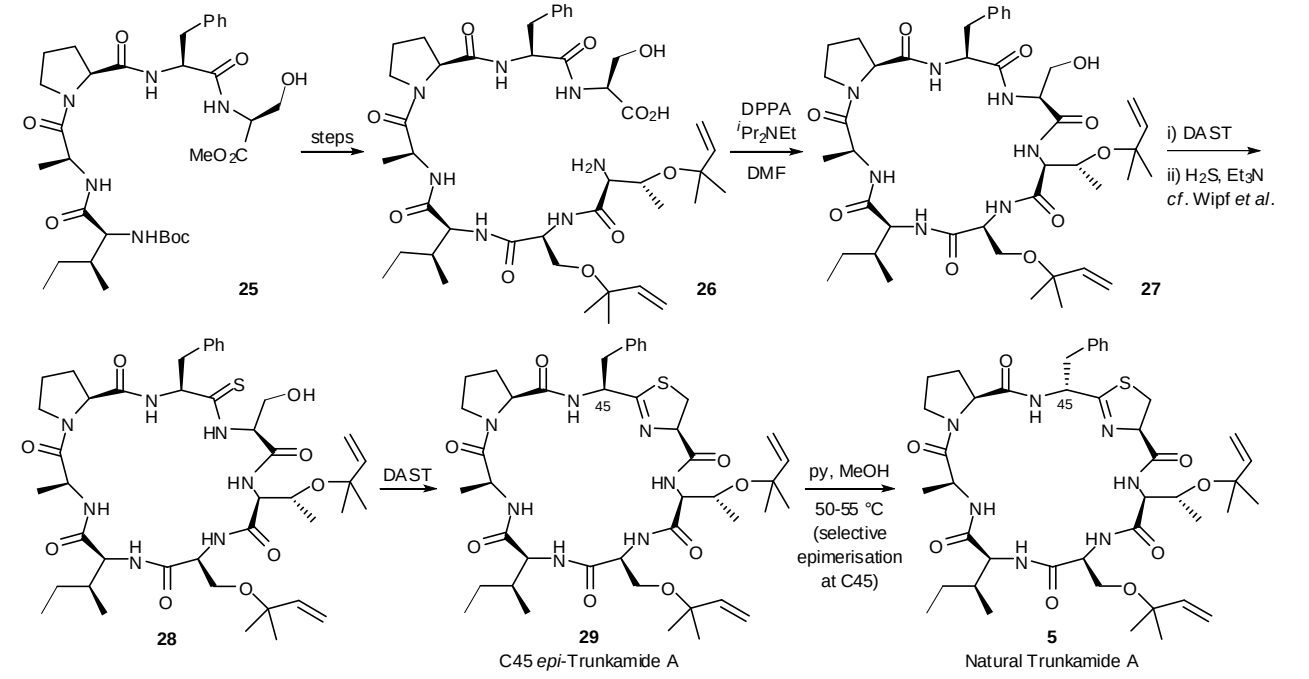
Figure 4. Assigned and revised stereostructures of raocyclamide A (**6**-v-**19**) and raocyclamide B (**20**-v-**21**).



Scheme 3. Total synthesis of the reverse prenyl-substituted cyclopeptide mollamide **4**.

concise method for the incorporation of a sensitive thiazoline ring in a complex cyclopeptide, *i.e.* **24** → **4**, but also illustrated the scope for the method of Okawa *et al.* for synthesising the reverse prenylated amino acid **23** from amino acid derivatives, *viz* **22** (Scheme 3).[9]

The structure of trunkamide A (**5**) accommodates two reverse prenyl groups as well as a sensitive thiazoline ring within its macrocycle. We experienced more problems synthesising trunkamide A than we had with mollamide, but some contemporaneous synthetic investigations by Peter Wipf *et al.* came to our assistance. Thus, we first synthesised the pentapeptide **25** from the relevant amino acids, and then introduced the two reverse prenyl groups leading to the heptapeptide **26** (Scheme 4). After removal of the protecting groups in **26**, macrolactamisation next gave the cyclopeptide **27**. Cyclodehydration of **27** to the corresponding oxazoline and subsequent thiolysis (to **28**) using H_2S, followed by thiazoline ring formation, using a strategy described by Wipf. then gave the trunkamide structure **29**. This structure was identical with *epi*-trunkamide synthesised earlier by Wipf *et al.* but not with naturally-derived trunkamide A. Wipf *et al.* later showed that the correct stereochemistry of trunkamide A was as shown in structure **5**, *i.e.* the "benzyl" epimer of our synthetic trunkamide



Scheme 4. Total synthesis of the unusual cyclopeptide trunkamide A (**5**), involving a novel selective epimerisation of the C45 centre in the epimer **29.**

Lissoclinum sp.; source of trunkamide A (**5**)
Image from http://www.kudalaut.eu/en/dph/4962/Photos-Sale/Compound-ascidian

Stigonema dendroideum (terrestrial blue-green alga); source of dendroamide A (**7**)
Image from http://protist.i.hosei.ac.jp/pdb/images/Prokaryotes/Stigonemataceae/sp_16.html

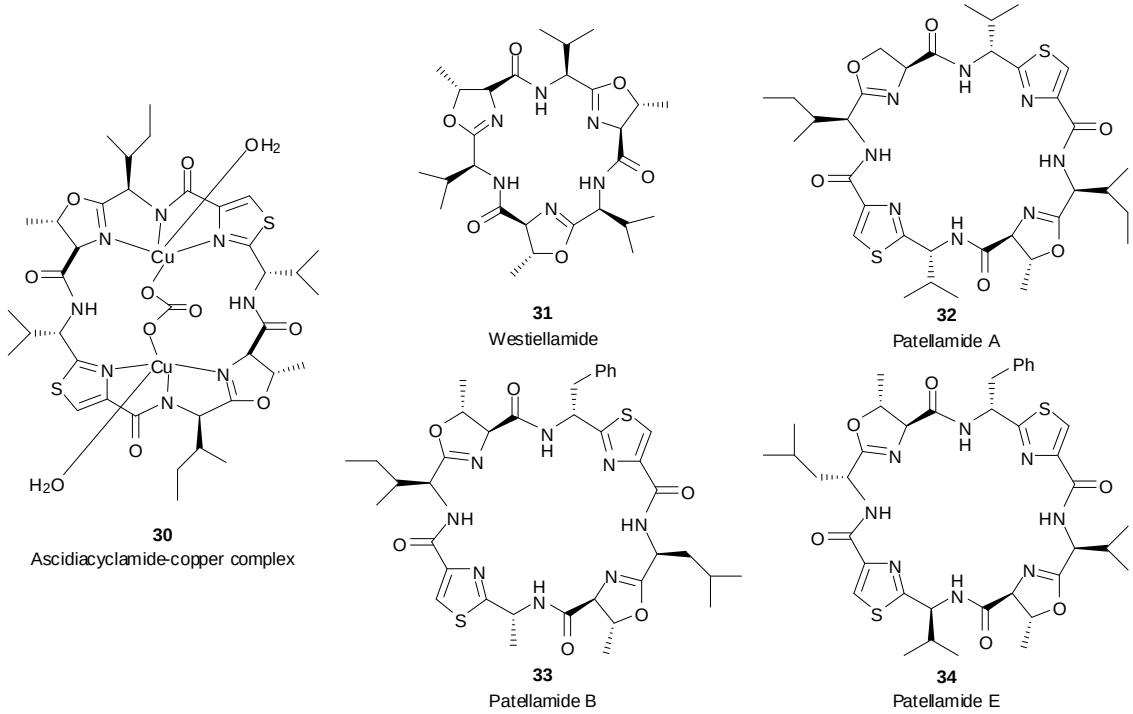


Figure 5. Cycic peptides whose metal complexes have been characterised by X-ray crystallography, *eg.* **30** and **31**, and by CD studies, *i.e.* the patellamides **32-34**.

A. We were reluctant to carry out an entirely new synthesis of natural trunkamide A, and instead took a risk of attempting to selectively epimerise the stereocentre at C45 in **29**. Fortunately, Ben McKeever found he could achieve this objective by treating **29** with methanolic pyridine at 50 ^{o}C which slowly led to its conversion into natural trunkamide A (**5**).[10]

At about this time we had had enough of synthesising azole-based cyclopeptides and correcting their assigned stereochemistries, and decided to move on to aspects of their assembly using a different method. The similarity of structural features in azole-based cyclic peptides to macrocyclic ligands such as porphyrins and crown ethers, supports the notion that they are tailor-made for association and binding to metal ions. However, before we published our review in 1993, there had been only scarce mention of ligand-metal congruence in cyclic peptides found in sea-squirts.[1] This situation was all to change over the ensuing 10 – 15 years, and we now have a much deeper appreciation of the binding of metals to cyclic peptides of the constitution already mentioned in the marine milieu. A summary of this 'evolution', up to 2007, was given in our second review, published during the same year.[2] In this review, we drew attention to the pioneering studies of Bruce Gaham *et al.* and Peter Wipf *et al.*, and their characterisations of the *bis*–copper(II) complex **30** of ascidiacyclamide and the silver complex of westiellamide **31** respectively, by X-ray crystallography. We also summarised our own studies of the variable temperature CD spectra of the patellamides **32** – **34**, and their Cu^{2+} and Zn^{+} complexes in the same review (Figure 5). Thus, in line with earlier NMR spectroscopic studies made by Ishida and others, our CD studies demonstrated that the cyclic peptides **32** – **34** can each bind two metals per molecule and the conjugates could all be correlated with the "square form" conformation of the cyclic peptides, *cf.* the *bis*–Cu^{2+} complex **30** of ascidiacyclamide.[11] Later studies by Marcel Jaspars *et al.* and Comba *et al.* endorsed these findings, but these authors greatly extended the scope of our preliminary findings. It seemed clear from all these studies that copper is the "chosen" metal by the patellamides in sea squirts, and indeed, it was suggested that these conjugates may actually have evolved as special enzymes for specific oxidations and electron transfer processes in the marine environment

The difficulties we had in the somewhat tedious assemblage of azole-based cyclic peptides (*i.e.* from macrolactamisations of peptide chains followed by elaboration of the azole rings by sequences of cyclodehydrations and oxidations), prompted us to consider producing the same cyclic peptide constructs from the assembly of pre-formed azole-based amino acids, *i.e.* **35** or of peptidyl – azoles, *viz* **36** and **37**. In this way, we also imagined that metal ions in the seas and oceans might act as templates, bringing together the azole units in a coordinated fashion (Figure 6).

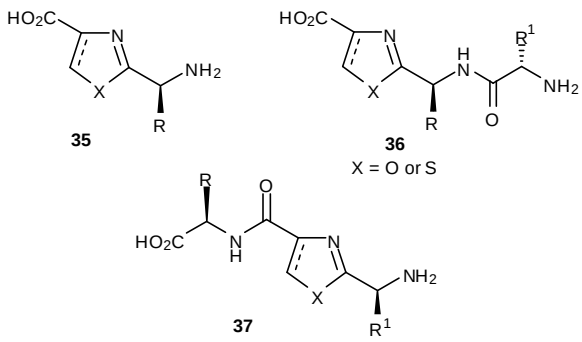
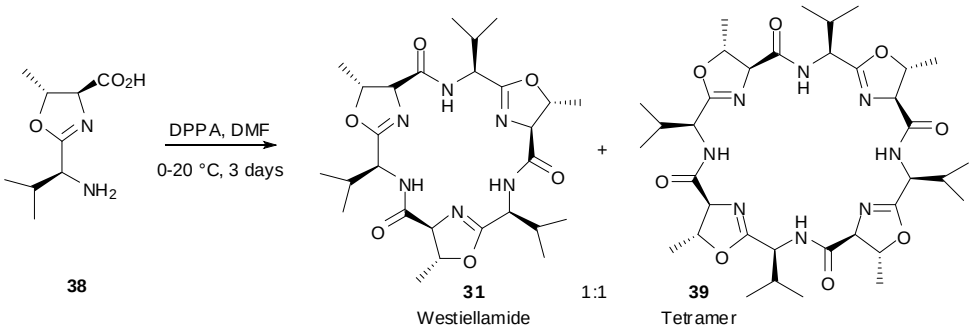
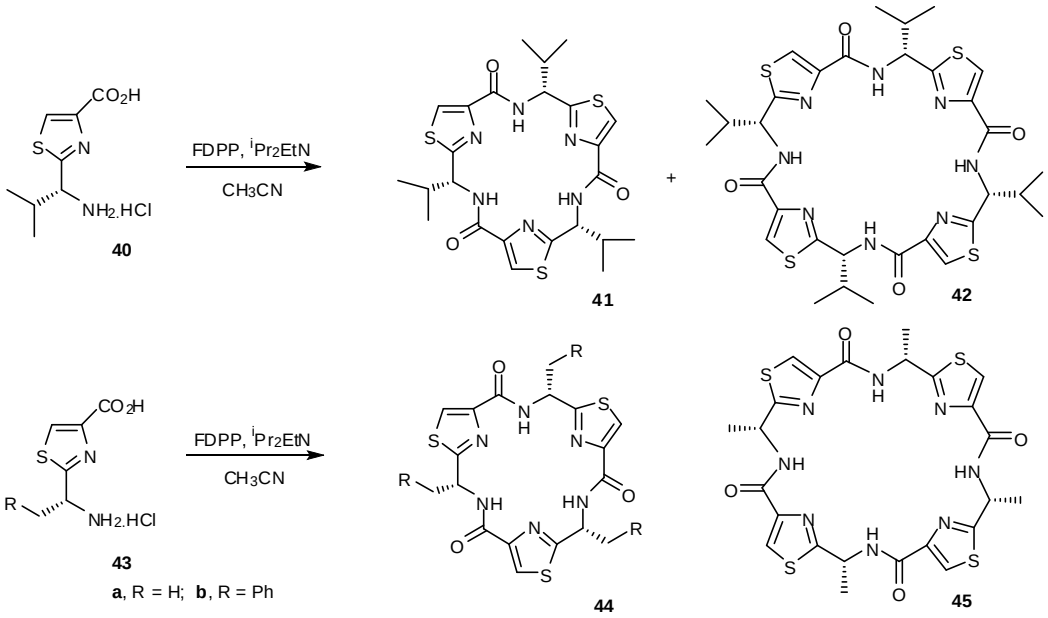


Figure 6. Azole–based amino acid monomers used in cyclooligomerisation studies



Scheme 5. Cyclooligomerisation of the oxazoline-based amino acid **38** to westiellamide **31**, by Wipf *et al*.



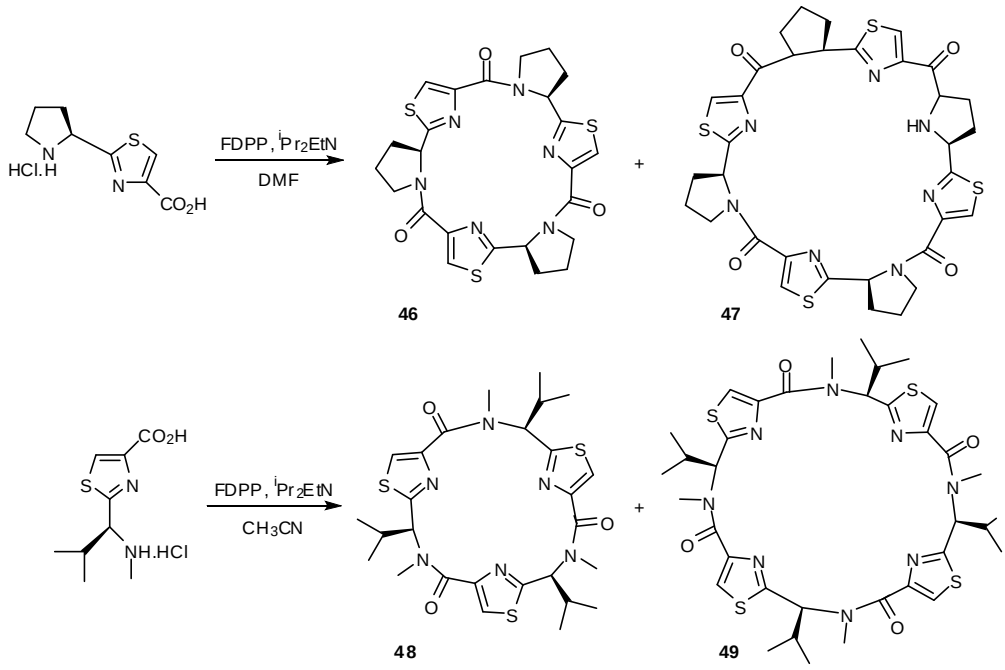
Scheme 6. Cyclooligomerisations of the amino acid-derived thiazoles **40, 43a** and **43b,** in the absence and in the presence of metal ions, leading to differing ratios of cyclic trimers and tetramers, *i.e*. **41** and **42**, **44a** and **45,** exclusively **44b** respectively.

We therefore decided to investigate the cyclooligomerisations of a range of peptidyl-azoles and examine the selectivites of these processes both in the absence, and in the presence of metal ions. We were not alone with these ideas however, and as early as 1992, Peter Wipf and his group had already established precedent for this concept when they treated the oxazoline-based amino acid **38** with DPPA in DMF at 0-20^{o}C for 3 days and produced a 1:1 mixture of westiellamide **31** and the cyclic tetramer **39** in 40% yield (Scheme 5).

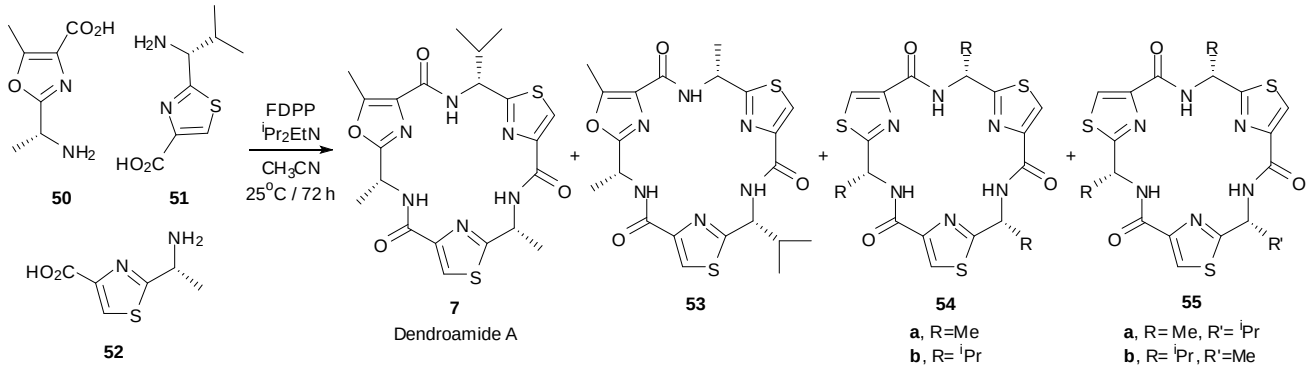
Spurred on by the observation of Wipf *et al.* we carried out a systematic study of the oligomerisations of a range of azole-based amino acids. Thus, in our first studies we showed that the *D*-valine derived thiazole **40** underwent cyclooligomerisation in the presence of FDPP and Hunig's base to give a 5:2 mixture of the cyclic trimer **41** and the cyclic tetramer **42** in a combined yield of 80 – 90% (Scheme 6).[12] In other studies, the oligomerisation of the alanine-derived thiazole **43a** gave a 9:2 mixture of the trimer **44a** and the tetramer **45**, and a similar cyclooligomerisation with the phenylalanine-derived thiazole **43b** produced exclusively the trimer **44b**. These latter reactions supported the notion that as the size of the substituent on the thiazole amino acid precursor **43** increases, *i.e.* H to isopropyl to benzyl, unfavourable transannular interactions during the oligomerisations favour the formation of the trimer over the tetramer (Scheme 6).[13]

In complementary studies, we found that the presence of metals ions influenced the relative amounts of the cyclic trimer **41** and the cyclic tetramer **42** produced from the alanine thiazole-based amino acid **40**. Thus, larger metal ions, *eg.* Cd^{2+} enhanced the formation of the tetramer **42**, whereas the smaller alkali metal ions favoured the formation of the trimer **41** (Scheme 6).[14] We carried out a whole raft of cyclooligomerisations with various amino acid-based thiazoles to produce libraries of novel, non-natural cyclopeptides including the trimers **46** and **48** and the tetramers **47** and **49** (Scheme 7).[15]

In other studies Anna Bertram examined cyclooligomerisation reactions with mixtures of thiazole and oxazole-based amino acids, and in this manner even succeeded in preparing various cyclic peptide natural products ! For example, when a 1:1:1 mixture of the oxazole amino acid **50** and the thiazole amino acids **51** and **52** was reacted with FDPP-DIPEA a reasonably selective assembly of the amino acids ensued, producing natural dendroamide A(**7**)



Scheme 7. Cyclooligomerisations of unusual amino acid-based thiazoles, leading to libraries of non-natural cyclopeptides, *i.e.* **46-49.**



Scheme 8. Synthesis of dendroamide A(**7**) by cyclooligomerisation of a mixture of the oxazole and thiazole-based amino acids **50, 51** and **52.**

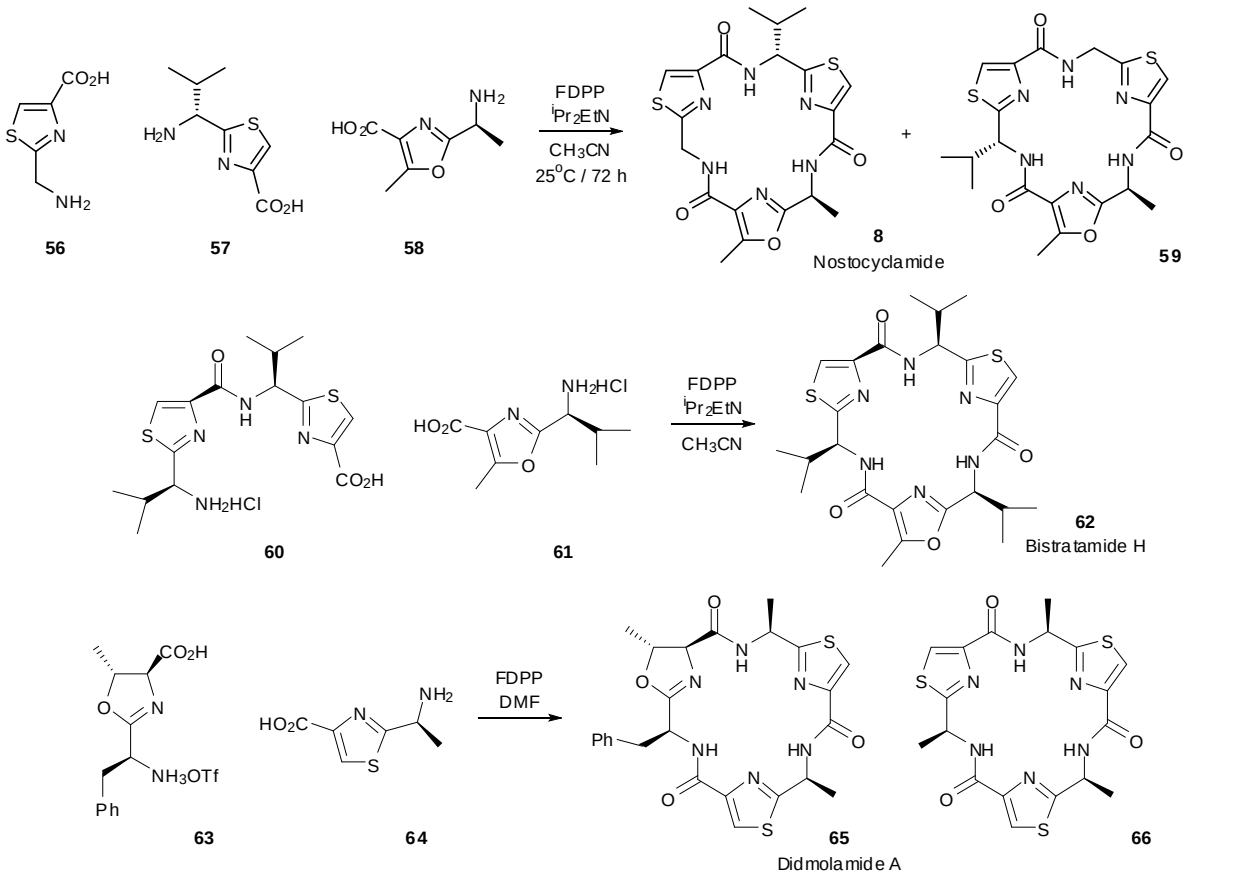
in 23% yield (Scheme 8).[16] The positional isomer **53** of dendroamide A was produced in a similar yield (22%) together with the four cyclic trimers **54a**, **54b**, **55a**, and **55b** (30%). In likewise manner, natural nostocyclamide **8**, alongside the isomeric trimer **59**, was produced when a mixture of **56**, **57** and **58** was treated with FDPP – DIPA,[17] and bistratamide H (**62**) found in *L.bistratum* was produced in 36% yield when the oxazole amino acid **61** was reacted with the *bis*-thiazole amino acid **60** (Scheme 9).[18]

Coupling reactions involving oxazoline amino acids and thiazole amino acids were less successful however, and only a 2% yield of didmolamide A (**65**) found in *Didemnum molle* was realised when a mixture of the phenylalanine-based oxazoline amino acid **63** and two equivalents of the thiazole amino acid **64** was treated with FDPP in DMF. In this instance the major product was the cyclic trimer **66**.

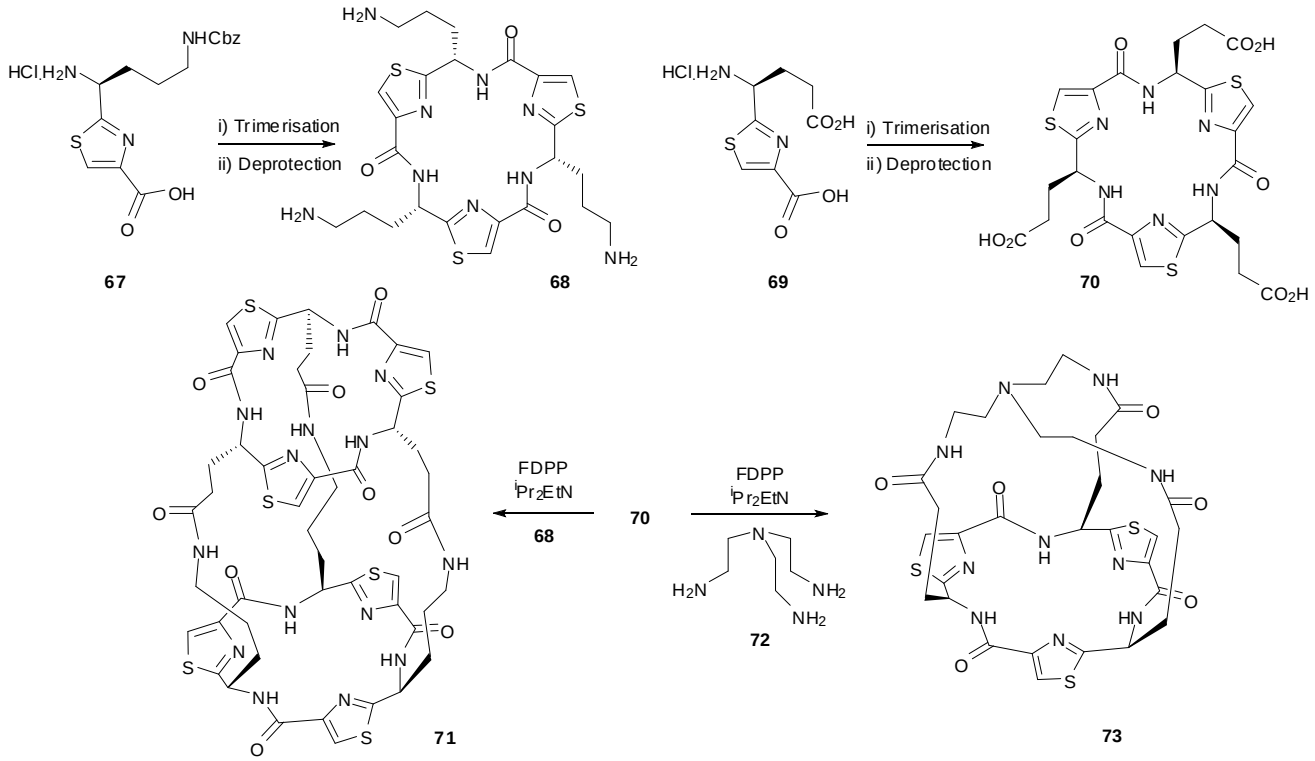
In contemporanious studies both David Fairlie *et al.* and ourselves developed the scope for cyclooligomerisations of azole-based amino acids in the synthesis of tubular and cage structures which, at the time, we felt could have applications as membrane ion channel mimics or as scaffolds for protein mimics. Thus, our own group prepared the *L*-ornithine and *L*-glutamic acid thiazole amino acids **67** and **69** respectively. After each amino acid had been treated separately with FDPP, $^{i}Pr_2NEt$, the resulting cyclic trimers were then deprotected to give the corresponding *tris*-amine **68** and *tris*-carboxylic acid **70** respectively. When these two compounds were mixed and treated with FDPP-$^{i}Pr_2$ NEt, the spectacular C3-symmetric "tubular" structure **71** was obtained in 30% yield. Furthermore, a corresponding reaction between the *tris*–carboxylic acid **70** and *tris*- (aminoethyl)amine **72** led to the novel "cage" structure **73** in 40% yield (Scheme 10).[19]

Lissoclinum bistratum; source of bistratamide H (**62**)
Image from http://www.kudalaut.eu/en/dph/4996/Photos-Sale/Compound-ascidian

Nostoc sp. 31 (cyanobacteria); source of nostocyclamide **8**
Image from http://protist.i.hosei.ac.jp/pdb/images/Prokaryotes/Nostocaceae/Nostoc/sp_09.html



Scheme 9. Syntheses of nostocyclamide **8,** bistratamide H (**62**) and didmolamide A (**65**) from coupling reactions involving mixtures of thiazole, oxazole, and oxazoline-based amino acids.

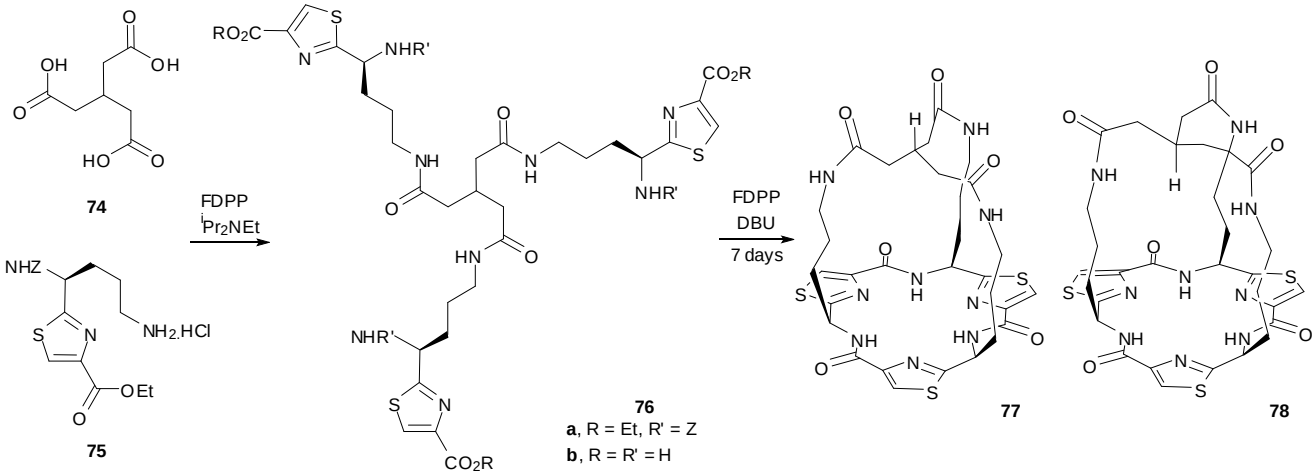


Scheme 10. Synthesis of the "tubular" and "cage" structures **71** and **73**, from the ornithine and glutamic acid thiazole-based amino acids **67** and **69** *via* the corresponding cyclotrimers **68** and **70** respectively.

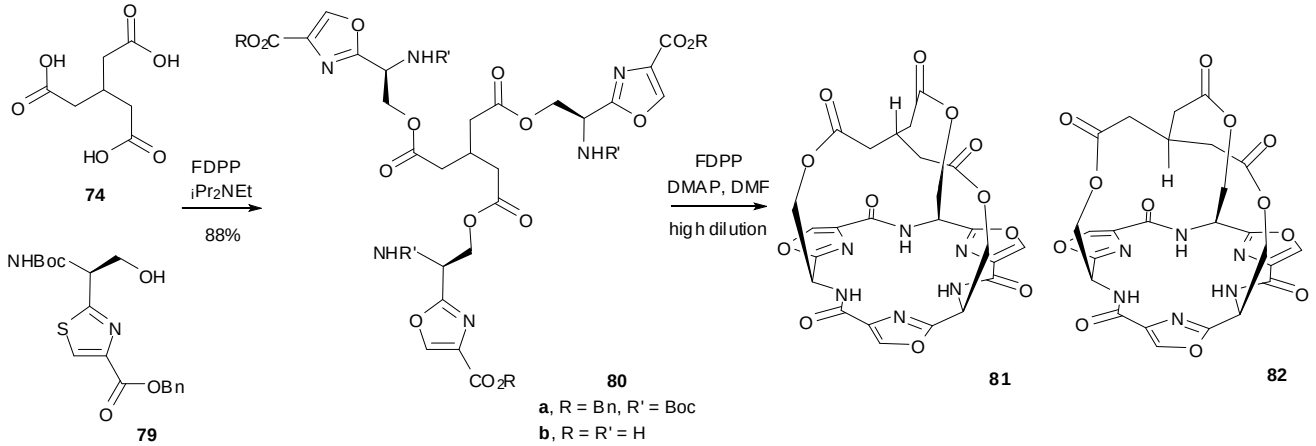
We then took forward the idea of forming novel thiazole peptide-based cage structures, by using the *tris* – carboxylic acid linker **74** to control the assembly and cyclooligomerisation reactions. Thus, the thiazole-substituted amine salt **75** was first reacted with the *tris*–carboxylic acid **74** leading to the *tris*–amide **76a**. Saponification of the ester groups in **76a** and removal of the Z-carbamate protecting groups next produced the corresponding trimeric thiazole amino acid **76b**. Treatment of this amino acid **76b** with FDPP and DBU over 7 days, then resulted in a controlled cyclooligomerisation and the formation of the unusual isomeric cage cyclopeptides **77** and **78** (ratio 2:3) in a combined yield of 19% (Scheme 11). Finally, we prepared the oxazole-substituted alcohol **79** related to the thiazole **75**, but containing a shorter carbon chain to that present in the latter. We then esterified the *tris*-carboxylic acid **74** with the alcohol **79** which led to the *tris*–ester **80a**. Removal of the protecting groups in **80a** followed by a "scaffolded cyclooligomerisation" of the resulting amino acid **80b**, under high dilution, then resulted in the formation of a 9:5 diastereoisomeric mixture of the novel trimeric cage cyclopeptides **81** and **82** in a combined yield of 19% (Scheme 12).[20]

These latter pieces of work, leading to the tubular and cage structures **71**, **73**, **77**, **78**, **81** and **82**, were the last contributions we made to the synthesis of novel structures based on cyclooligomerisations of azole-based amino acids (*i.e.* in 2002). We had intended to develop this chemistry in molecular recognition phenomena, but this did not happen! I was therefore pleased when Kate Joliffe, a former Post-doctoral Fellow in my group, took up this area when she started her independent academic career in Australia.

We should not close this Chapter without briefly discussing our complementary synthetic studies with the poly-oxazole based cyclopeptides telomestatin **83** and YM-216391 (**84**),which were both isolated from *Streptomyces* sp during the early part of the 2000s (Figure 7). Telomestatin **83** is the best known of these metabolites, since it is a potent inhibitor of telomerase, interacting specifically with the G-quadruplex and not affecting DNA polymerases or reverse transcripterases. It has since shown considerable promise in cancer therapy.

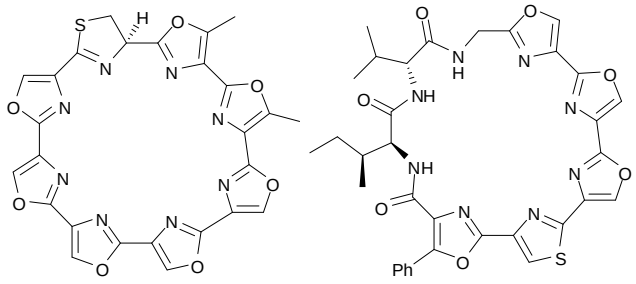


Scheme 11. Syntheses of the thiazole-based "cage" cyclopeptides **77** and **78** from intramolecular macrolactamisation of the trimeric amino acid **76b.**



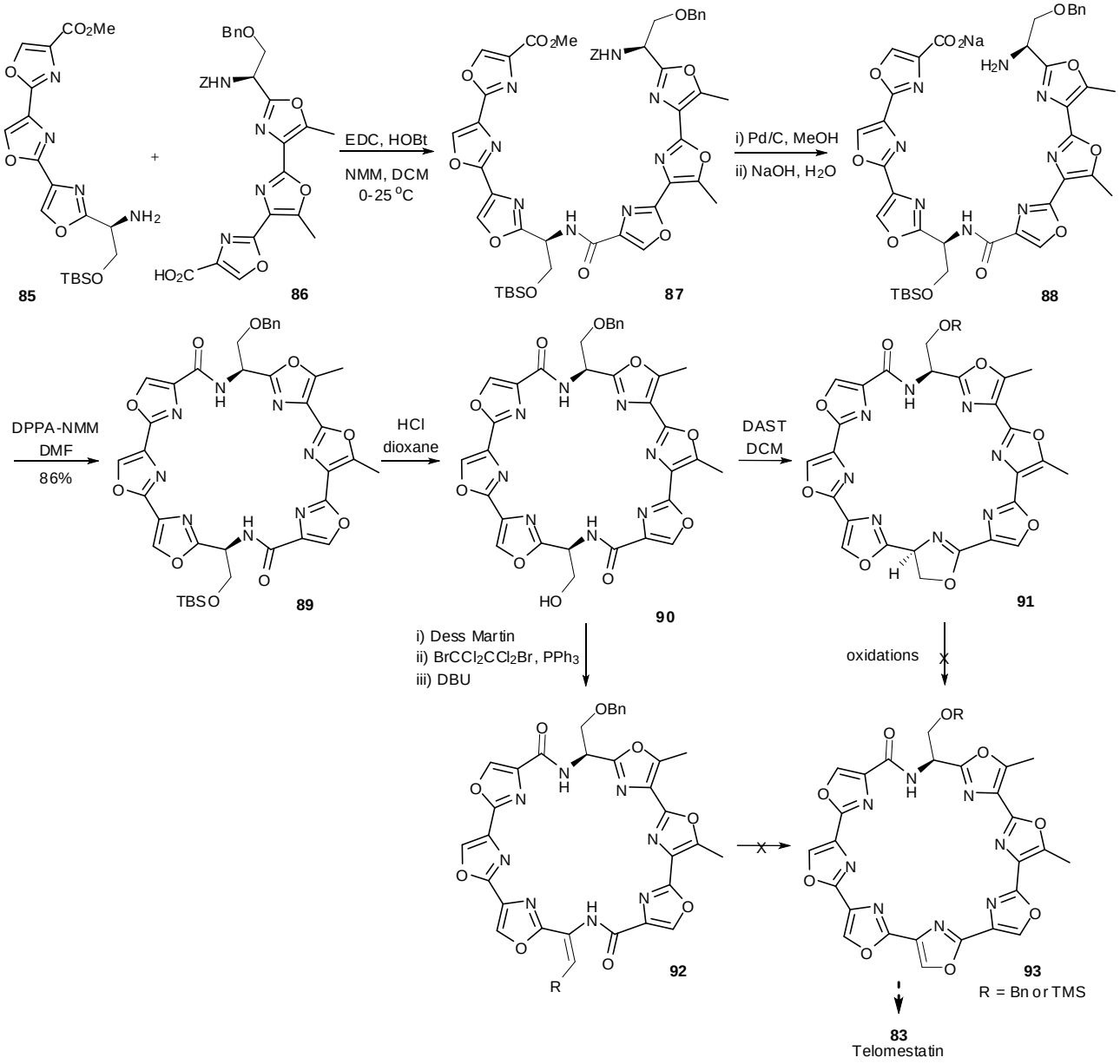
Scheme 12. Syntheses of the oxazole-based "cage" cyclopeptide structures **81** and **82** from intramolecular macrolactamisation of the trimeric amino acids **80b.**

Thus, in one of our approaches to telomestatin, we first developed concise synthetic routes to the contiguously linked *tris*-oxazole units **85** and **86**, and then linked these units together producing the hexa-oxazole **87** (Scheme 13). Manipulation of the protecting groups in **87** next gave the sodium salt **88**, which was then cyclised to the macrocyclic structure **89**. Although we were able to elaborate **89** to the corresponding oxazoline and enamide structures **91** and **92** respectively, *via* the common intermediate **90**, we failed in all our attempts to convert these advanced intermediates to the penultimate precursor **93** to telomestatin **83**.[21] We left this project at this point, only to find that within a short period of time Takahashi *et al*. patented a synthesis of telomestatin which, for all intents and purposes was as close to our approach as it could be. It seemed that we were simply unlucky with our choice of reaction conditions when we had earlier tried to elaborate the key intermediate **93** from the *hexa* oxazole-based compound **90**. Full details of Takahashi's synthesis of telomestatin were published in 2006, and this remains the only synthesis of this novel compound to date.



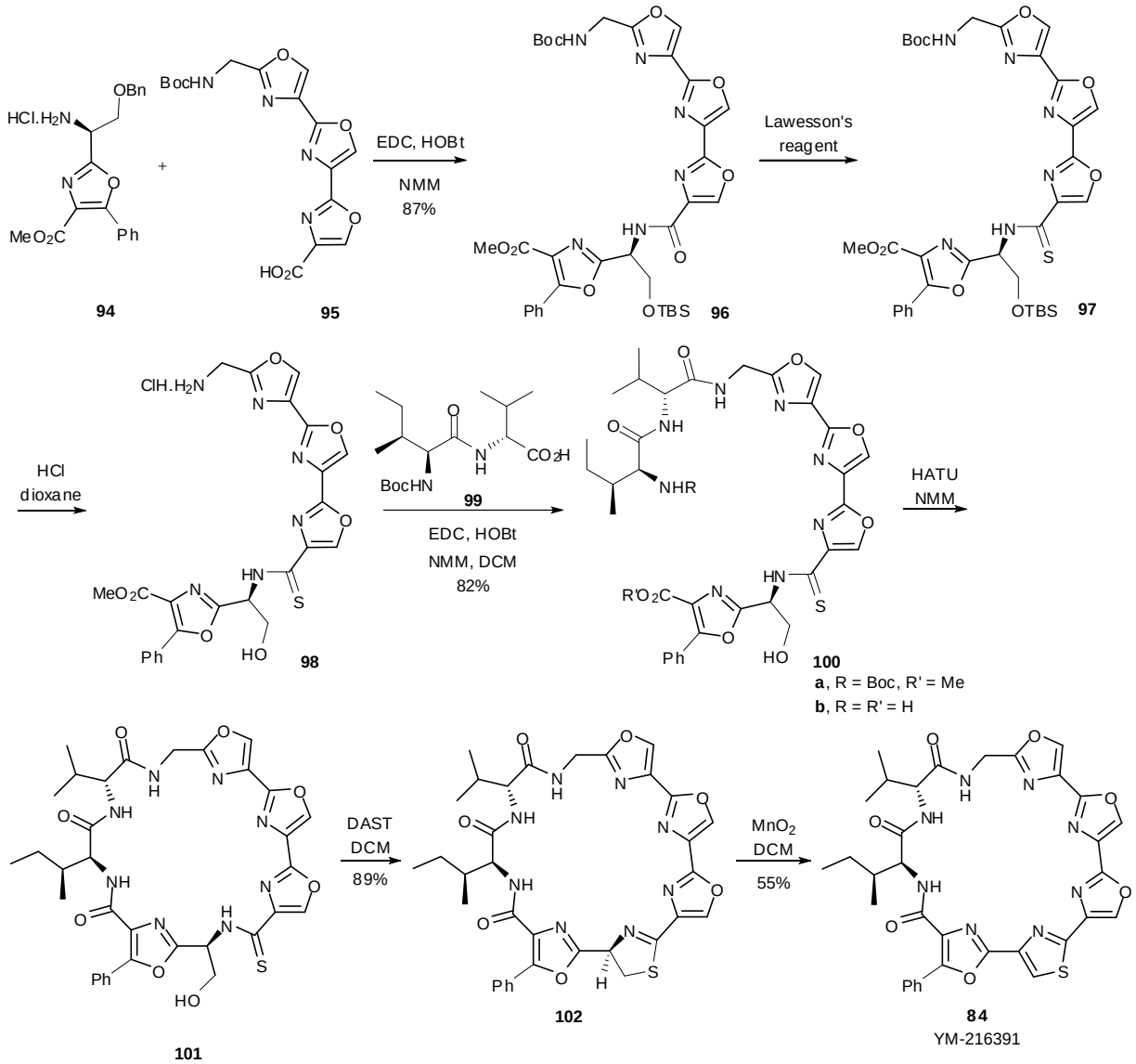
83 Telomestatin **84** YM-216391

Figure 7. The polyoxazole-based cyclopeptides telomestatin **83** and YM-216391 (**84**).



Scheme 13. Synthesis of the advanced macrocyclic intermediates **91** and **92** towards telomestatin **83**.

Our synthesis of YM-216391(**84**) was more straightforward than our efforts to synthesise telomestatin, although at the outset of our studies neither the relative or absolute stereochemistry of this metabolite were known. Thus, we first combined the oxazole-substituted amine **94** with the *tris*-oxazole carboxylic acid **95** and then elaborated the amide product **96** to the corresponding thioamide **97** (Scheme 14). Deprotection of **97** next gave the amine salt **98**, which was then combined with the dipeptide carboxylic acid **99** leading to **100a**. Macrolactamisation of the ω-amino acid **100b** derived from **100a** proceeded smoothly and gave the cyclic peptide **101** in 75% yield. The thioamide group in **101** was then cyclised to the corresponding thiazoline **102** which,on oxidation gave (-)-YM-216391(**84**).[21,22] The synthetic cyclopeptide showed NMR spectroscopic data which were identical with those of the natural product isolated from *Streptomyces nobilis*. After we had completed our synthesis Sohda *et al*. published full details of the isolation and structure of YM-216391, including its optical rotation which was found to be equal but opposite to the figure we had obtained for our synthetic material. These comparisons therefore allowed us to establish that the mirror image of structure **84** represents the absolute stereochemistry of naturally occurring YM-216391.



Scheme14. Total synthesis of the polyoxazole-based cyclopeptide YM-216391 (**84**).

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