CSIRO PUBLISHING

Full Paper

www.publish.csiro.au/journals/ajc

Aust. J. Chem. **2004**, *57*, 747–758

Solution-Phase Synthesis of Linear and Cyclic Peptidomimetics Based on 2-Aminoalkyloxazole-4- or -5-carboxylates

Matthew O. Cox,[A] *Rolf H. Prager*,[A,B] *and Carina E. Svensson*[A]

[A] School of Chemistry, Physics and Earth Sciences, Flinders University of South Australia, Adelaide SA 5001, Australia.

[B] Author to whom correspondence should be addressed (e-mail: rolf.prager@flinders.edu.au).

The solution-phase synthesis of several small linear and cyclic peptidomimetics based on the coupling of BOC-protected 2-aminoalkyloxazole-4- or -5-carboxylic acids is reported. Cyclic amides have been formed both by sequential coupling and cyclization, or by cyclooligomerization.

Manuscript received: 19 September 2003.
Final version: 17 November 2003.

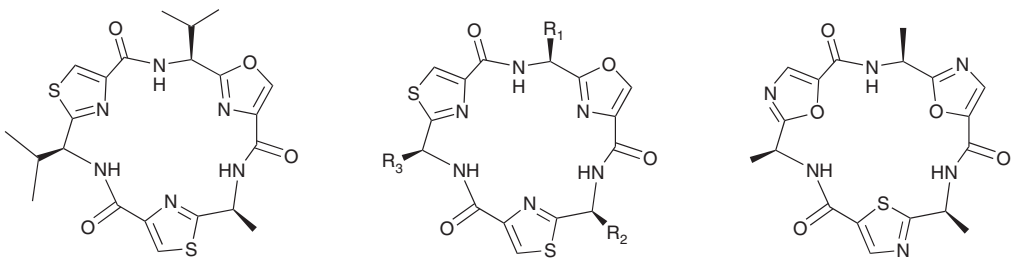
Introduction

A large number of natural and synthetic marine cyclic peptides containing unusual thiazole, thiazoline, oxazole, and oxazoline rings have been isolated from marine invertebrates such as sponges and tunicates,[1] and are possibly produced by symbiotic microorganisms,[2,3] because of the presence of both D-amino acids and unusual amino acids. In sea sponges and squirts it is likely that the production of cyclic peptides is a form of chemical defence.[1] Hydrophobic side chains of cyclic peptides frequently provide a hydrophobic exocyclic surface that protects their amide bonds from peptidases and this also facilitates the crossing of cell membranes.[4]

The 18-membered marine cyclic peptides containing only aromatic heterocycles constitute an interesting class of these peptides, but few have been found to occur in nature. Most oxazole-bearing natural products of both marine and terrestrial origin have the 2,4-disubstitution pattern, which is a consequence of their biogenesis, and the synthesis of the required 2,4-linked thiazole or oxazoles and their coupling have been described by Fairlie et al.,[5] Shioiri et al.,[6] Walker and Heathcock,[7] Wipf and Fritch,[8] and North and Pattenden.[9] These procedures have generally been biomimetic, including cyclodehydration of amides or thioamides, and subsequent dehydrogenation or prior oxidation.

The three-dimensional conformation of one such compound, bistratamide C (**1**, Scheme 1) was investigated by computational techniques.[10] With three aromatic constraints the peptide became nearly flat and the side chains were perpendicular to the plane of the backbone.[10]

The aim of the present work is to synthesize a range of generally unknown structures based upon 2-aminoalkyloxazole carboxylic acids, with the acid functionality at C-4 or C-5, to connect these units with amide bonds, and to selectively orient the ring nitrogen or oxygen atom towards the centre of the macrocycle (e.g. **2** and **3**, Scheme 1). The desired structures would ideally have long side chains derived from unnatural amino acids, to serve as a hydrophobic upper face, to aid penetration into cell membranes (see **4**, Scheme 2). It was our aim to build up the appropriate linear amides in a stepwise manner, followed by cyclization. In addition, cyclotrimerization/cyclotetramerization of the aminoalkyl oxazole carboxylic acid can also be achieved, as shown in



1 **2** **3**

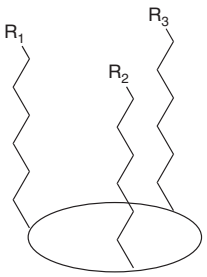
Scheme 1.

 10.1071/CH03250 0004-9425/04/080747

the synthesis of the C_3-symmetrical westiellamide **5** from the oxazoline **6** by Wipf and Miller (Scheme 3).[11]

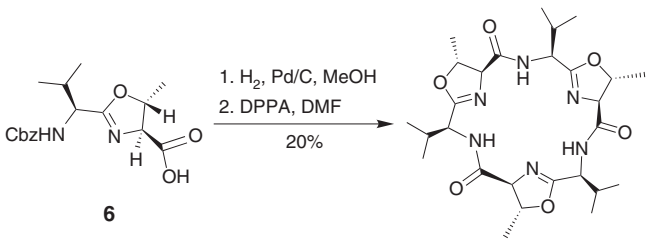
We have reported a new synthesis of oxazoles[12] and thiazoles,[13] and the application to the synthesis of the 2-aminoalkyl-oxazole-4-[14] and -5-carboxylic acids[15] that are capable of being elaborated into the biogenetically 'natural' cyclic amides **2** and their isomeric 'unnatural' cyclic amides, and our initial studies are the subject of this paper.

Boss et al.[16] have recently reported the synthesis of cyclic trimers containing *O*-benzylated serine and lysine oxazole amino acid derivatives via both the cyclooligomerization strategy and the traditional stepwise approach. The 'one-pot' cyclizations of the oxazole derivatives proceeded with yields ranging between 10 and 20%, which is in stark contrast to the high-yielding cyclooligomerization reactions reported for analogous thiazole systems.[17,18] Rebek et al.[19] have also observed low yields for the cyclooligomerization of similar oxazole amino acids.



4

Scheme 2.



6 **5**

Scheme 3.

Discussion

Part 1. Solution-Phase Synthesis by the N-tert-*butoxycarbonyl (BOC) Strategy*

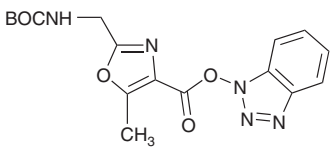
Our initial investigations of the methods for obtaining linear oxazole based amides used the readily available amino ester **7**.[14] *N*-protection gave the ester **8** which was then hydrolyzed to the *N*-protected acid **9** (Scheme 4). Treatment of acid **9** with the amine **7** in the presence of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate[20] (BOP) and triethylamine produced the amide linked bis-oxazole **10**.

The progress of the reaction could be followed by ^{1}H NMR spectroscopy, as the presence of the intermediate activated ester (**11**, Scheme 5) was apparent from its oxazole methyl group, resonating at 2.72 ppm.

After hydrolysis of the ester **10** to the acid **12**, the sequence was repeated, giving the amide-linked tris-oxazole **13** in an overall yield of 26% from **9** (Scheme 6). The compound was analyzed by electrospray mass spectrometry (ESI-MS), giving the $[M + Na]^+$ ion at *m*/*z* 583, with daughter ions appearing at *m*/*z* 527 due to loss of 2-methylpropene, and at *m*/*z* 483 due to further loss of carbon dioxide.

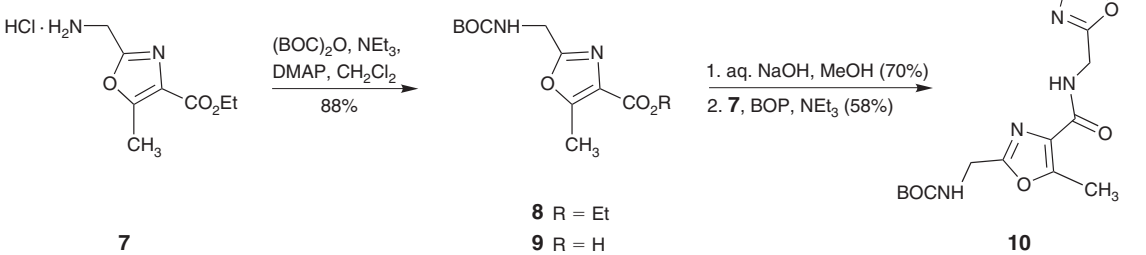
The *C*-terminus was hydrolyzed first to give the acid **14**, then the *N*-terminus was deprotected, either with anhydrous hydrogen chloride or with anhydrous trifluoroacetic acid. The salt of the amine (**15**, $X^- = CF_3CO_2^-$) was obtained in near quantitative yield.

The macrocyclization of **15** was performed in a 1 mM DMF solution with diphenylphosphoryl azide (DPPA) and two equivalents of triethylamine. The resulting product could not be analyzed by NMR spectroscopy, as it was essentially insoluble in a range of solvents, such as chloroform, methanol, dimethylsulfoxide, and water. Upon analysis by electrospray mass spectrometry, a major peak appeared at



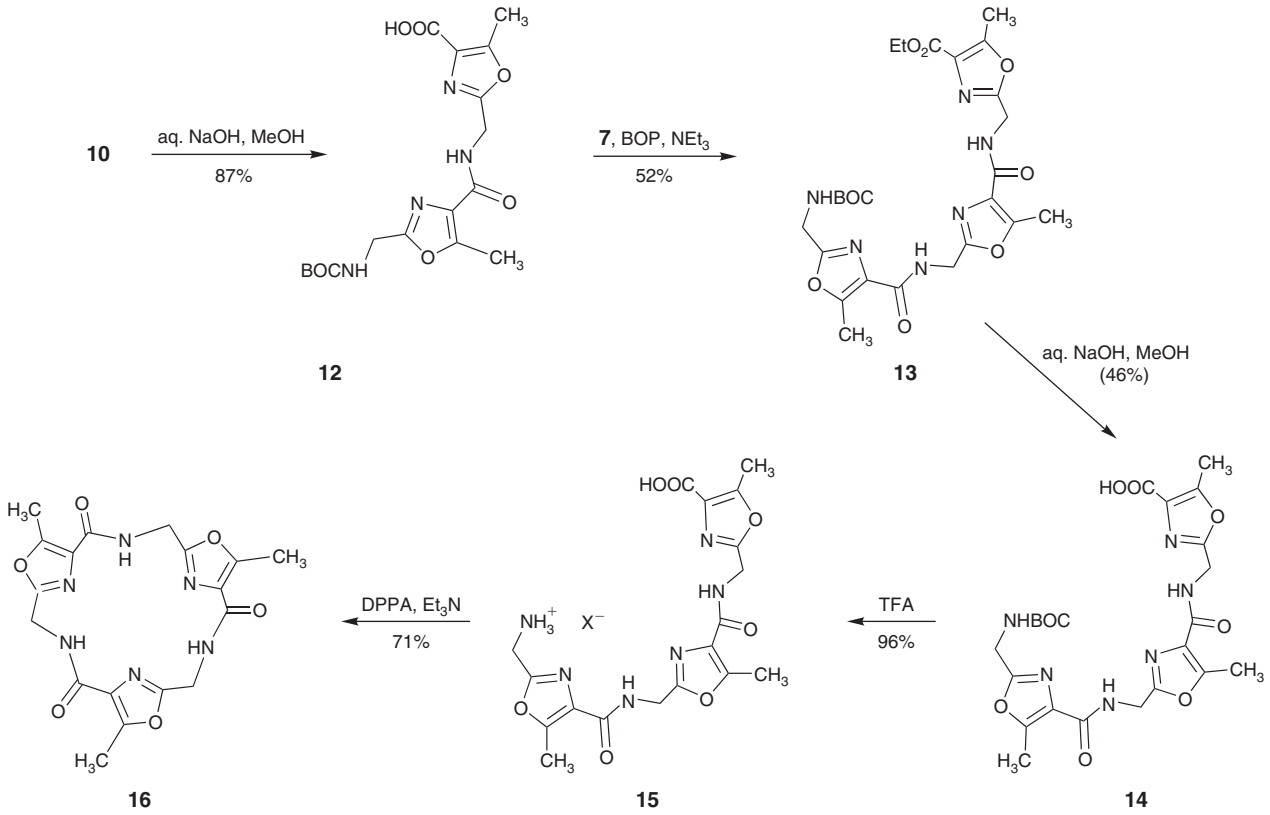
11

Scheme 5.

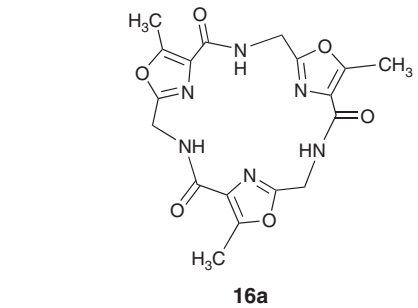


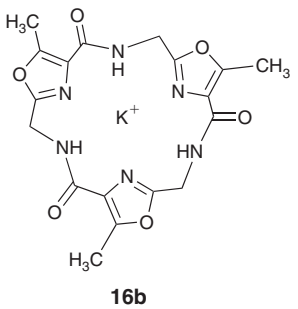
7 **8** R = Et; **9** R = H **10**

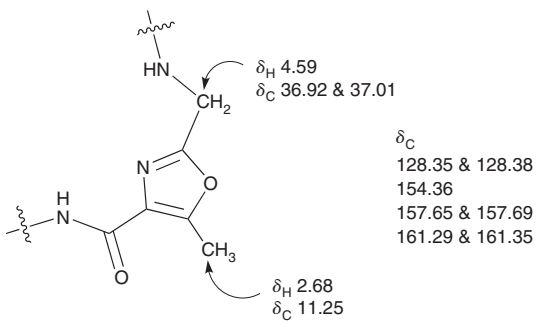
Scheme 4.



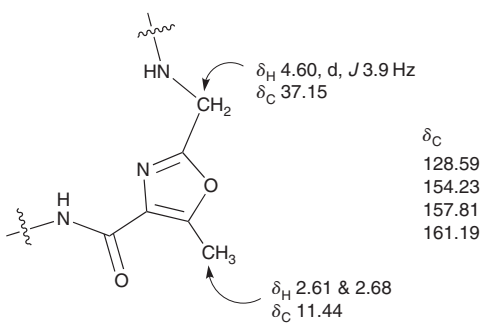
Scheme 6.







Scheme 7. NMR characteristics of **16a**.



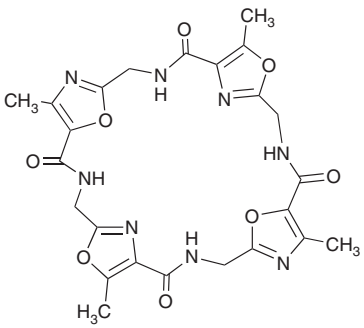
Scheme 8. NMR characteristics of **16b**, K^+ complex.

m/*z* 453, consistent with **16b** (Scheme 8). The presence of the potassium ion is interesting as the reaction mixture had not knowingly been in contact with potassium salts at any stage, although the triethylamine used was dried over potassium carbonate.

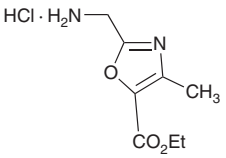
A suspension of this compound in dichloromethane was treated with a solution of hydrogen chloride in dichloromethane at 0–5°C for one hour. The residue, **16a**, was now soluble in a mixture of chloroform and methanol, which made NMR analysis possible. Analysis of this material with ESI-MS showed a $[M + H]^+$ ion, but the $[M + K]^+$ ion was not present. The ^1H NMR spectrum (summarized in Scheme 7) showed a single oxazole methyl peak (9H) and methylene peak (6H), consistent with a planar,

symmetrical molecule. However, the two methylene signals in the ^{13}C NMR spectrum suggest the 'planarity' is probably a consequence of rapid inversion of two conformers.

The mother liquors of the initial product were then washed with aqueous potassium bicarbonate solution to give additional **16b**. The electrospray mass spectrum showed a peak at *m*/*z* 453, again suggesting potassium as the coordinated ion. The ^1H NMR spectrum (summarized in Scheme 8) showed two singlets in the oxazole methyl region (ratio 2 : 1). The nonequivalence of the methyl groups was not expected but may be due to complexation with K^+, inducing a tilted structure where two oxazole units form a plane and the third unit is forced out of the plane, with its methyl group protruding more to the centre of the cavity.



17



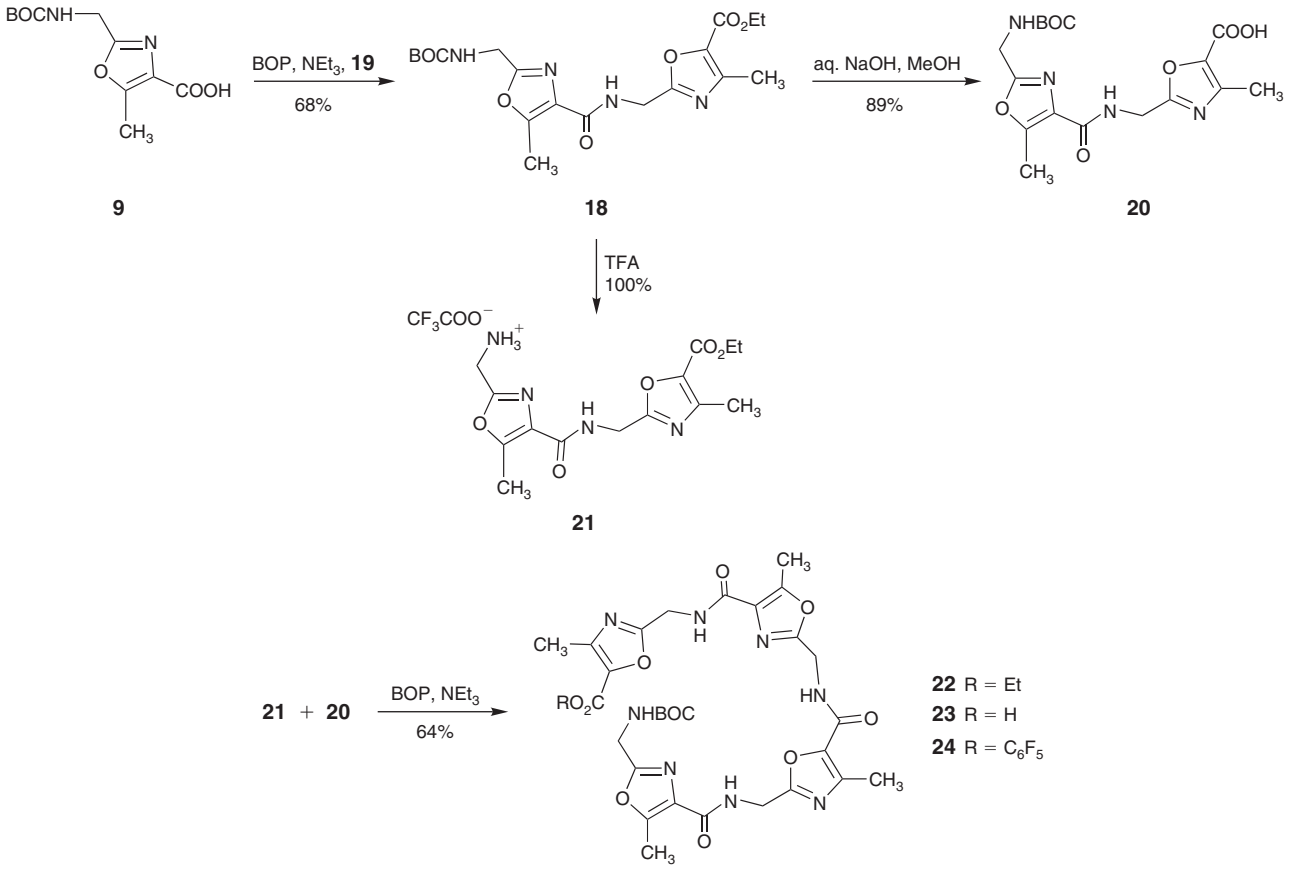
19

Scheme 9.

Since treatment of **16a** with Na_2CO_3 brought about no change, it is possible that the size of the cavity of the cyclic polyamide is suitable for a potassium ion but not for the smaller sodium ion, which was observed as the coordinated ion with the linear polyamide **15**. An unusual potassium-binding cleft has been reported to form after selective acidic hydrolysis of the oxazoline rings of ascidiacyclamide.[5] Unfortunately, attempts to obtain X-ray quality crystals of the product using different solvents and techniques, such as slow evaporation, vapour infusion, and solvent diffusion, were unsuccessful.

Having demonstrated that this procedure could successfully be used to generate the cyclic tris-oxazole **16**, we wished to apply the method to the synthesis of a macrocycle **17** (Scheme 9) consisting of four oxazole units with alternating 4- and 5-ethoxycarbonyl functionality. In that way we hoped to create a cavity suitable for ions or small molecules to bind to the heterocycle nitrogen or oxygen atoms. Dimerization of the amino acid from bisoxazole **18** offered an attractive route to this molecule and a stepwise method of dimerization was chosen, since the alternative approach to cyclization, involving deprotection of both termini, appeared likely to produce polymers or mixtures of ring sizes.

The hydrochloride of the amine **19** was treated with the acid **9**, as above, to give the bis-oxazole **18** (Scheme 10). Half of this material was deprotected on the *N*-terminus in order to obtain the trifluoroacetate **21**, while the other half was hydrolyzed to the acid **20**. In the next step the units were



Scheme 10.

connected, affording the amide-linked linear tetraoxazole **22** in an overall yield of 39% from **9**. The amide-linked oxazoles all gave a prominent $[M + Na]^+$ ion upon ESI-MS analysis, except for compound **21** which appeared as the $[M + H]^+$ ion.

Macrocyclization with DPPA is generally straightforward, but the reaction requires low temperatures and proceeds slowly. Schmidt and Weller[21] have reported the superiority of the pentafluorophenyl ester for the ring closure step over other methods, such as the diphenylphosphorazidate or the trichlorophenyl ester applications. It has been suggested that cyclization of the pentafluorophenyl esters is the most appropriate method for peptides whose linear precursors are conformationally biased against cyclization, since the higher temperatures can overcome the conformational constraints.[3] While cyclization using the pentafluorophenyl ester[22] requires an additional step, the formation of an activated ester, this in situ cyclization step is reported to be much faster at the elevated temperatures (50–100°C).

Consequently, compound **22** was hydrolyzed to the acid **23**, which was isolated in 54% yield, then converted to the corresponding pentafluorophenyl ester **24** using pentafluorophenyl trifluoroacetate in pyridine. The BOC-protecting group was thereafter removed, and the ring closure reaction was attempted in a stirred mixture of chloroform and 2 M aqueous potassium carbonate solution, but no reaction was observed.

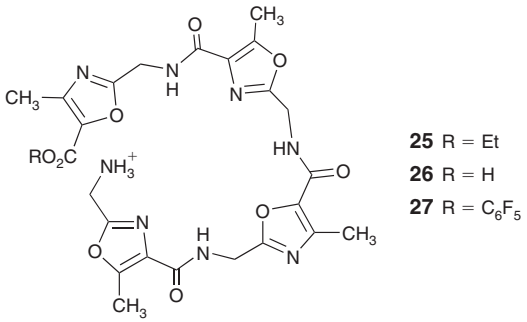
An alternative method for cyclization was demonstrated by Aguilar and Meyers in the synthesis of bistratamide C,[23] in which the amino group reacted directly with the ethyl ester of the *C*-terminus in boiling toluene. This method is suitable for precursors containing only fully aromatic heterocycles, rather than the more sensitive oxazoline and thiazoline moieties. Cyclization of the trifluoroacetate salt of the amine **25** (Scheme 11) was attempted in a similar way. The precursor **22** was deprotected in anhydrous TFA, affording **25**. Compound **25** was heated in toluene at 100°C for 25 h at a concentration of 1 mM, but NMR analysis indicated that no reaction had occurred. Macrocyclization of the acid **26** was attempted in dimethylformamide with excess dicyclohexylcarbodiimide at ambient temperature, but no cyclization occurred using this coupling reagent; the reaction mixture seemed to consist of several compounds, presumably products of different chain lengths.

In further attempts to obtain macrocycles with oxygen atoms within the annulus, the hydrochloride of ethyl 2-(aminomethyl)-1,3-oxazole-5-carboxylate **28**[15] was treated under the same conditions as those discussed previously for the 4-carboxylate **7** and ethyl 2-(aminomethyl)-4-methyl-1,3-oxazole-5-carboxylate **19**, but coupling proceeded considerably slower (Scheme 12), and such reactions were not pursued further.

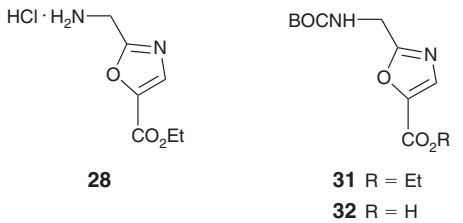
The synthesis of cyclic peptides containing oxazoles with the carboxyl functionality at C-5 only was initiated by BOC protection of the hydrochloride of the amine **28**, followed by hydrolysis of the ester **31**, to give the corresponding acid **32** in 46% yield from **28** (Scheme 13). Unfortunately, recrystallization of the acid was low yielding, and it was not used as the *N*-terminus due to time constraints.

Part 2. Cyclopolymerization

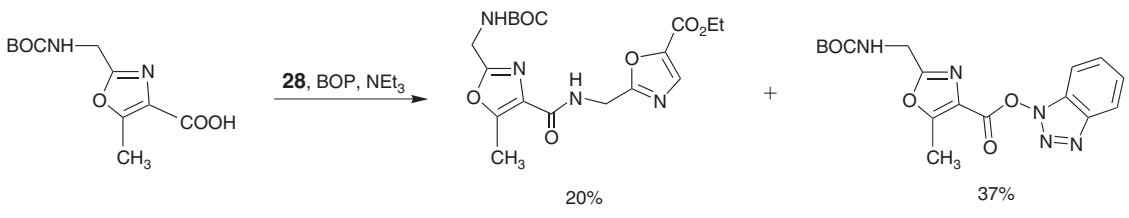
Pattenden et al.[24] investigated the cyclooligomerization reactions of valine- and phenylalanine-derived thiazole amino acids at varying concentrations and with several coupling reagents. Pentafluorophenyldiphenylphosphinate (FDPP) activation was found to give consistently high yields (80–96%) of the desired cyclic products, but the ratios of cyclic trimer and cyclic tetramer were dependent on the concentration.[24] Concentrations within the range 10–50 mM gave the best results. The overall trimer to tetramer ratio was also found to be dependent on both the stereochemistry of the side chain as well as its steric encumbrance.



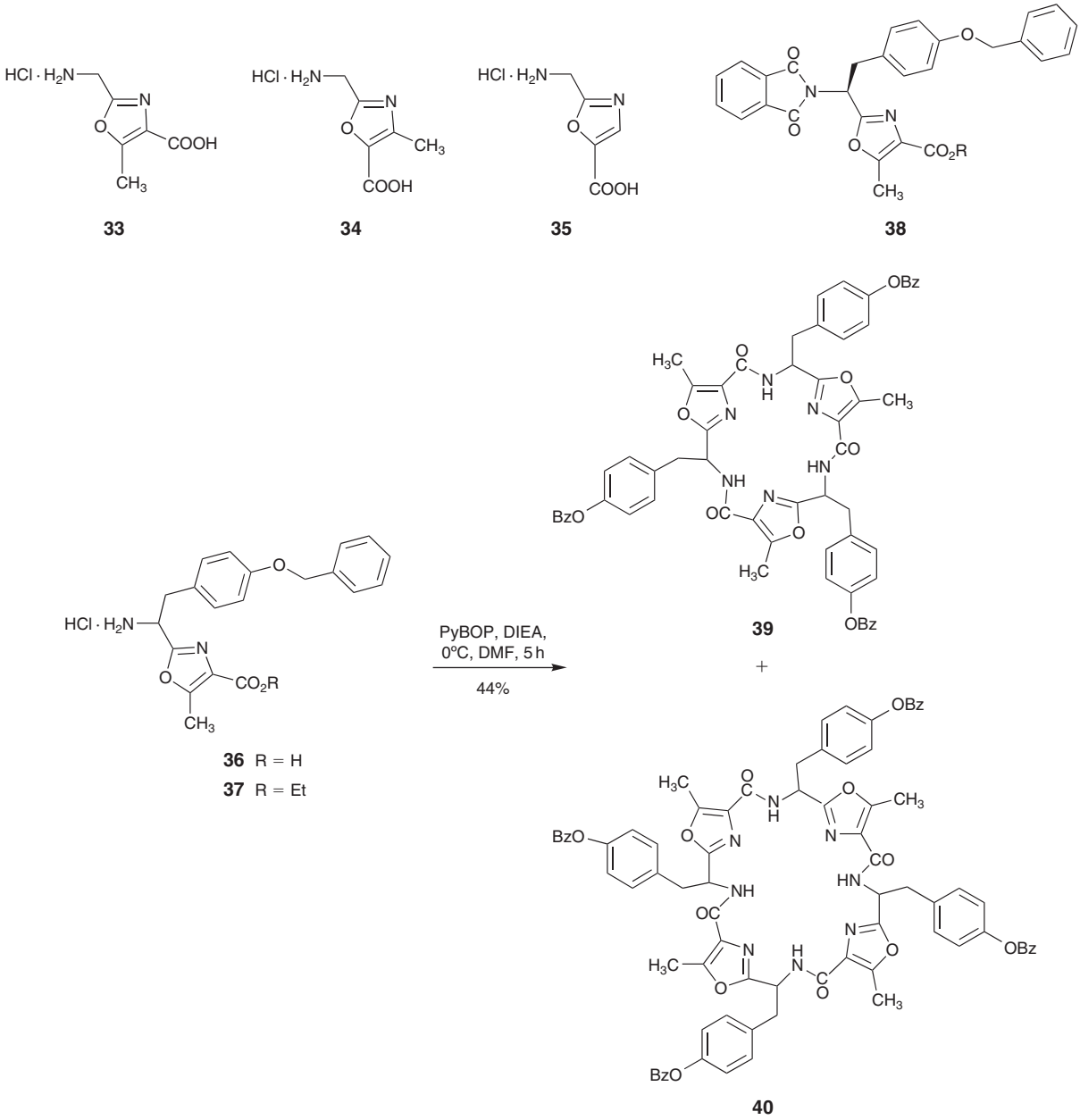
Scheme 11.



Scheme 13.



Scheme 12.

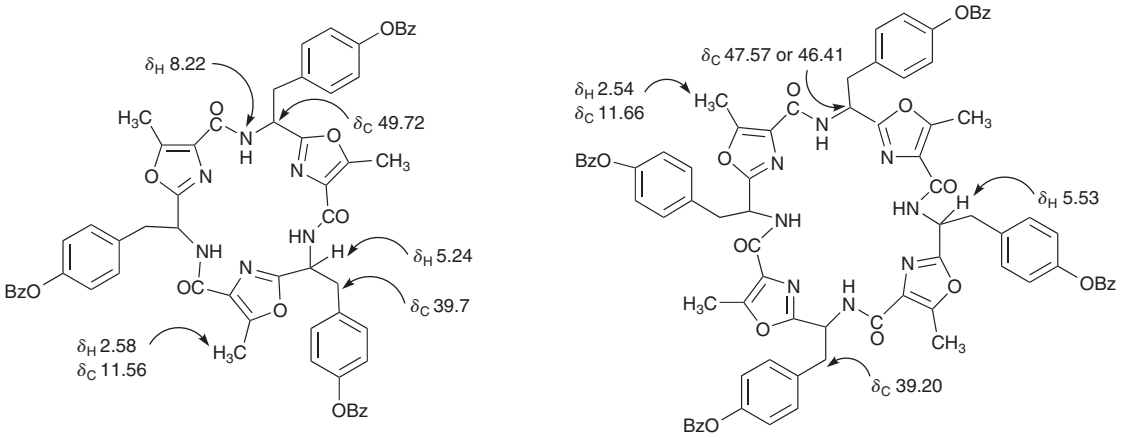


Scheme 14.

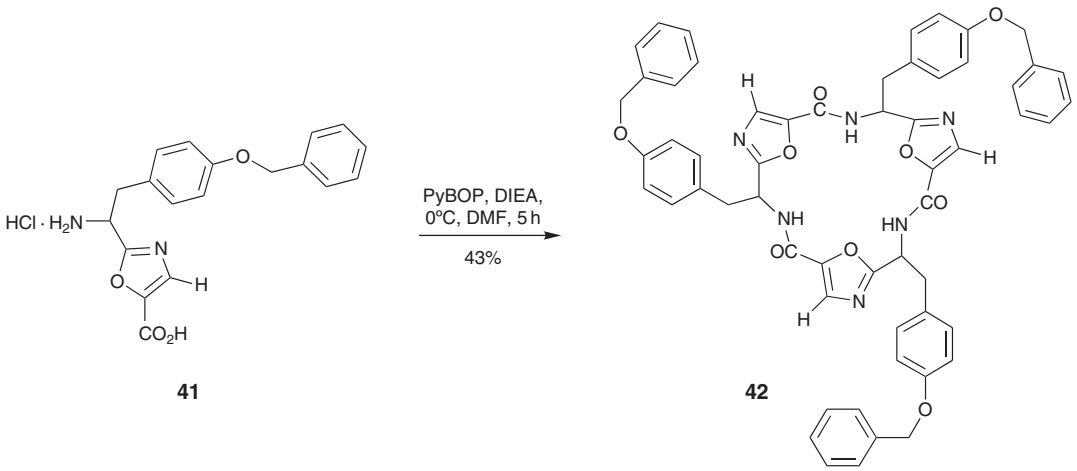
In an extension of this work, Pattenden et al.[25] reported the templating effect of metal ions during the cyclooligomerization reaction. Cyclooligomerization of the thiazole amino acid in the presence of smaller metal ions favoured the formation of the trimer, whereas the cyclic tetramer was favoured with larger metal ions, such as cadmium. Recently, Singh et al.[17] and Pattenden and Thompson[18] reported the synthesis of symmetrical thiazole-containing platforms and their further elaboration into highly constrained chiral cavitands.

In our strategy to create symmetrical cyclic peptides consisting of oxazoles with either 2,4- or 2,5-linking and with unnatural 2-aminoalkyl groups, we initially chose to use the oxazole amino acids **33**–**35** (Scheme 14). Hydrolysis of the 2-aminomethyl 4- and 5-ethoxycarbonyloxazoles (**7**, **19**, **28**) resulted in low yields of the corresponding amino acids in the case of the 5-esters, and thus cyclopolymerizations with these substrates were abandoned. More satisfactory results were obtained with **36**, prepared from the phthalimido ester **38**.[14] Cyclooligomerization of **36** was performed in a 10 mM anhydrous DMF solution with the coupling reagent PyBOP (benzotriazole-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate) reagent and DIEA (diisopropylethylamine). After stirring at 0°C for 5 h, the reaction gave a mixture of the cyclic trimer **39** and cyclic tetramer **40** as a white powder, in a yield of 44%. Unfortunately **39** and **40** could not be separated by chromatography, but neither appeared to complex calcium ions, present as a binder in the chromatography plate.

The ^{1}H and ^{13}C NMR spectra for the cyclic trimer/cyclic tetramer mixture (summarized in Scheme 15) suggested that



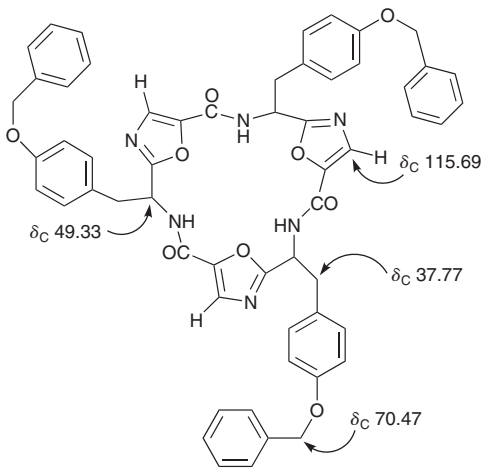
Scheme 15. NMR characteristics of **39** and **40**.



Scheme 16.

the cyclic trimer **39** has high (C_3) symmetry. In addition, the vicinal $^3J_{NHCH}$ value for **39** (6.46 Hz) is comparable to the value of 6.6 Hz observed by Boss et al.[16] in a similar lysine-derived cyclic oxazole trimer. These coupling constants correspond to dihedral angles of $145° < \theta < 155°$ in both macrocycles. In contrast, both Singh et al.[17] and Pattenden and Thompson[18] have reported that the vicinal $^3J_{NHCH}$ values of lysine- and ornithine-derived thiazole-containing cyclic trimers lie between the values of 9.1 and 9.3 Hz, which corresponds to dihedral angles between $165° < \theta < 175°$. We speculate that the decreased dihedral angles observed in the oxazole cyclic trimer may increase the steric congestion between the side chains, and therefore result in a lower yielding cyclooligomerization reaction compared to the thiazole cyclic peptides. Unfortunately, attempts to obtain X-ray quality crystals of the products using different solvents and techniques were unsuccessful.

Having verified that the cyclooligomerization reaction could successfully be applied to the synthesis of both a 2,4-linked cyclic trimer **39** and a cyclic tetramer **40**, we decided to explore its utility to 2,5-linked cyclic oxazole peptides. Cyclooligomerization of **41** using an identical procedure to that outlined above gave the cyclic trimer **42** in 43% yield after purification by radial chromatography (Scheme 16).



Scheme 17. ^{13}C NMR characteristics of **42**.

Interestingly, none of the corresponding cyclic tetramer was isolated from the product mixture.

The C_3-symmetrical nature of **42** was confirmed by the ^{13}C NMR spectrum which indicated one set of resonances for the repeating peptide subunit (summarized in Scheme 17).

Analysis of structure **42** with ESI-MS indicated minor peaks at *m*/*z* 961.3538 and 983.3376, which were consistent

with the $[M + H]^+$ and $[M + Na]^+$ respectively, of the anticipated product. Synthesis of linear polymers was believed to be competing with the cyclooligomerization reaction, hence giving low yields of the desired products.

Conclusions

The procedure for the sequential synthesis of amide linked di-, tri-, and tetra-oxazoles has been outlined. Cyclization to form cyclic tri-oxazoles was successful, but not of tetra-oxazoles. The synthesis of symmetrical cyclic peptides based on both 2-aminoalkyloxazole-4-carboxylic acids and -5-carboxylic acids has been achieved by the cyclooligomerization of their repeatable subunit, in moderate yields. It appears that PyBOP is a valid alternative for the macrocyclizations, having given the desired oxazole peptides in the highest reported yields for the oxazole ring systems. The marked tendency of the linear polyoxazoles to coordinate with sodium contrasted with the observation of the $[M + K]^+$ ion of the cyclic amide linked tris-oxazole.

Experimental

General details have been given in a previous paper.[14] The Attached Proton Test (APT), was used in the assignment of all ^{13}C NMR signals and, where additional information was required, heteronuclear correlation (HETCOR) and homonuclear decoupling experiments were performed.

ESI-MS were recorded on a Finnigan LCQ spectrometer operating under following conditions: spray voltage 5.20 kV; capillary temperature 200°C; capillary voltage 35 V; tube lens offset 55 V. The molecular ion and selected fragment ions are reported as their mass to charge ratio, as their $[M + Na]^+$, $[M + K]^+$, or $[M + H]^+$ ions. The analyses were performed in methanol unless otherwise stated. Additional ESI-MS were recorded at the Central Science Laboratory, University of Tasmania, and these analyses were performed in *m*-nitrobenzyl alcohol (mnba). High-resolution MS were recorded on a Kratos MS25RF spectrometer as above or at the University of Tasmania.

Column chromatography and flash column chromatography used Riedel–de Haën silica gel S 0.032–0.063 mm (31607) (pH 7, pour density 0.4 g mL^{-1}, granulation 32–63 μm [230–400 mesh ASTM]). Centrifugal chromatography was performed with silica gel 60 PF 254 coated glass rotors using a Chromatotron (model 7924T). Analytical thin layer chromatography (TLC) was carried out using Merck Silica gel 60 F_{254} aluminium-backed sheets.

*Ethyl 2-(*N-tert-*Butyloxycarbonylaminomethyl)-5-methyl-1,3-oxazole-4-carboxylate* ***8***

4-Dimethylaminopyridine (25 mg, 0.20 mmol) was added to a mixture of the aminoester **7**[14] (912 mg, 4.13 mmol), di-*tert*-butyl dicarbonate (929 mg, 4.13 mmol), and triethylamine (575 μL, 4.13 mmol) in dichloromethane (8 mL), and the mixture was stirred at rt for 22 h. The reaction was diluted with dichloromethane (25 mL) and extracted with water (2 × 10 mL), then sat. sodium chloride (1 × 10 mL). The organic layer was dried over sodium sulfate, filtered, and reduced under high vacuum, affording the *title compound* (1.029 g, 3.62 mmol, 88%), as an orange solid, mp 90–92°C. (Found: C 54.6, H 7.0, N 9.8%, $M^{+\bullet}$ 284.1398. $C_{13}H_{20}N_2O_5$ requires C 54.9, H 7.1, N 9.85%, $M^{+\bullet}$ 284.1372). ν_{max}/cm^{-1} 3328, 1738, 1683, 1547, 1342, 1294, 1260, 1179, 1101. δ_H 1.39 (3H, t, *J* 6.9), 1.45 (9H, s), 2.61 (3H, s), 4.38 (2H, q, *J* 6.9), 4.43 (2H, d, *J* 6.0), 5.3 (1H, bs, 1H). δ_C 11.8, 14.1, 28.1, 37.6, 60.8, 80.1, 127.6, 155.6, 156.6, 159.3, 162.2. *m*/*z* 284 (M^+, 0.7%), 228 (12%), 57 (100%).

*2-(*N-tert-*Butyloxycarbonylaminomethyl)-5-methyl-1,3-oxazole-4-carboxylic Acid* ***9***

Sodium hydroxide (2.5 M, 3.3 mL) was added dropwise at rt to a solution of the ester **8** (1.020 g, 3.59 mmol) in methanol (6 mL). TLC analysis of the mixture showed the starting material to be absent after 30 min, and the solvent was removed under vacuum. The yellow residue was adjusted to pH 4 by addition of 0.48 M citric acid (18 mL), and the resulting suspension was cooled at 0–5°C overnight. The solid material was collected and washed with citric acid (2 × 4 mL), then ice-cold water (2 × 5 mL) to give an off-white powder. The crude product was suspended in dichloromethane (6 mL), diluted with ether (16 mL), then chilled on ice for several hours, affording the *pure product* as a very fine powder (642 mg, 2.51 mmol, 70%), mp 165–167°C. (Found: C 51.6, H 6.4, N 11.0%, $M^{+\bullet}$ 256.1077. $C_{11}H_{16}N_2O_5$ requires C 51.6, H 6.3, N 10.9%, $M^{+\bullet}$ 256.1059). ν_{max}/cm^{-1} 3349, 1683, 1615, 1524. δ_H ($CDCl_3$/CD_3OD) 1.45 (9H, s), 2.61 (3H, s), 4.13 (1H, bs), 4.39 (2H, bs), 5.92 (1H, bs). δ_C ($CDCl_3$/CD_3OD) 11.6, 28.0, 37.3, 80.1, 127.6, 155.9, 156.7, 159.5, 164.0. *m*/*z* 256 (M^+, 3.6%), 200 ($M - C_4H_8$, 86%), 140 ($C_6H_6NO_3$, 22%), 57 (100%).

N-*(4-Ethoxycarbonyl-5-methyloxazol-2-ylmethyl)-2-(tertbutyloxycarbonylaminomethyl)-5-methyloxazole-4-carboxamide* ***10***

A solution of the hydrochloride of the amine **7** (324 mg, 1.47 mmol) and triethylamine (149 mg, 1.47 mmol) in dichloromethane (10 mL) was added to a mixture of the acid **9** (376 mg, 1.47 mmol), triethylamine (149 mg, 1.47 mmol), and BOP (652 mg, 1.43 mmol) in dichloromethane (10 mL) at rt under N_2, and the reaction was stirred for 20 h. The reaction mixture was extracted with 10% potassium bicarbonate (2 × 10 mL), followed by water (2 × 10 mL), and the solvent was then removed under reduced pressure. The residue was dissolved in ether and extracted with water (3 × 10 mL), the organic layer was dried and the solvent was removed under vacuum, yielding the *product* as a colourless glass (363 mg, 0.859 mmol, 58%). ν_{max}/cm^{-1} (film) 3341, 1716, 1668, 1634, 1519, 1447, 1368, 1342, 1253, 1179, 1097. δ_H 1.37 (3H, t, *J* 7.2), 1.44 (9H, s), 2.55 (3H, s), 2.60 (3H, s), 4.35 (4H, m), 4.71 (2H, d, *J* 5.7), 6.11 (1H, bs, NH), 8.02 (1H, t, *J* 5.7, NH). δ_C 10.9, 11.4, 13.7, 27.8, 35.2, 37.2, 60.4, 79.4, 127.2, 128.2, 153.4, 155.5, 156.2, 158.4, 158.7, 161.6, 161.8. *m*/*z* 366 ([M^+ −56], 25.8%), 314 (10.1%), 183 (25.5%), 41 (100%).

*2-{[2-(*tert-*Butyloxycarbonylaminomethyl)-5-methyloxazol-4-ylcarbamoyl]-methyl}-5-methyloxazole-4-carboxylic Acid* ***12***

Ester **10** (345 mg, 0.817 mmol) was hydrolyzed as for **9** above, yielding the *acid* as a colourless oil, which solidified to a glass (281 mg, 0.713 mmol, 87%), mp 88–89°C. ν_{max}/cm^{-1} 3444 (2 bands), 1716, 1674, 1634, 1588, 1520, 1505, 1322, 1253, 1205, 1162, 1096. δ_H ($CDCl_3$/CD_3OD) 1.45 (9H, s), 2.59 (6H, s), 4.36 (2H, s), 4.68 (2H, s), 5.25 (1H, bs, COOH), 6.36 (1H, t, *J* 5.7, NH), 8.17 (1H, bt, NH). δ_C ($CDCl_3$/CD_3OD) 10.9, 11.2, 27.6, 35.1, 37.0, 79.7, 127.2, 128.1, 153.7, 155.9, 156.6, 158.6, 162.0, 162.1, 163.4. *m*/*z* (ESI) 417.0 ($[M + Na]^+$, $C_{17}H_{22}N_4O_7Na$ requires 417.4), 393.6 ($[M - H]^+$, $C_{17}H_{21}N_4O_7$ requires 393.4).

N-*(4-Ethoxycarbonyl-5-methyloxazol-2-ylmethyl)-2-{[2-(tertbutyloxycarbonylaminomethyl)-5-methyloxazol-4-ylcarbamoyl]-methyl}-5-methyloxazole-4-carboxamide* ***13***

A solution of the amine **7** (159 mg, 0.721 mmol) and triethylamine (75 mg, 0.741 mmol) in dichloromethane (4.6 mL) was added to a mixture of the acid **12** (273 mg, 0.692 mmol), triethylamine (67 mg, 0.662 mmol), and BOP (306 mg, 0.671 mmol) in dichloromethane (5 mL) at rt and the reaction was stirred for 43 h under N_2. The reaction mixture was diluted with dichloromethane (10 mL), extracted with water (10 mL), 10% potassium bicarbonate (2 × 10 mL), and water (5 mL). The solvent was removed under reduced pressure and the residue was dissolved in ether and washed with water (3 × 5 mL). The organic

layer was dried and the solvent was then removed under reduced pressure. The crude product was dissolved in dichloromethane (10 mL) and extracted with 0.48 M citric acid (2 × 5 mL), followed by water (2 × 5 mL). Removal of the solvent under vacuum yielded the *title compound* as a colourless oil (202 mg, 0.360 mmol, 52%). ν_{max}/cm^{-1} 3335, 1718, 1668, 1636, 1520, 1342, 1306, 1261, 1170, 1097. δ_H 1.37 (3H, t, *J* 7.2), 1.44 (9H, s), 2.53 (3H, s), 2.56 (3H, s), 2.57 (3H, s), 4.36 (4H, m), 4.63 (4H, d, *J* 5.7), 5.85 (1H, bt, NH), 7.92 (1H, t, *J* 6.0, NH), 8.07 (1H, bt, NH). δ_C 11.1, 11.6, 14.0, 28.0, 35.4, 35.4, 37.4, 60.6, 79.7, 127.4, 128.4, 128.4, 153.6, 155.5, 156.6, 158.2, 158.5, 158.6, 161.6, 161.7, 161.9. *m/z* (ESI) 583.1 ($[M + Na]^+$ with daughter ions 527 ($[M + Na^+ - 56]$) and 483 ($[M + Na^+ - 100]$), $C_{25}H_{32}N_6O_9Na$ requires 583.6).

*2{[2-(*tert-*Butyloxycarbonylaminomethyl)-5-methyloxazol-4-ylcarbamoyl]-*N-*[2-aminomethyl-5-methyloxazol-4-ylcarbamoyl]}-methyl-5-methyloxazole-4-carboxylic Acid* ***14***

Ester **13** (194 mg, 0.346 mmol) was hydrolyzed as for **9** above, yielding the *product* as a colourless oil (85 mg, 0.160 mmol, 46%). ν_{max}/cm^{-1} 3331, 1713, 1662, 1629, 1520, 1168. δ_H 1.43 (9H, s), 2.56 (9H, bs), 4.37 (2H, d, *J* 4.8), 4.65 (4H, m), 5.74 (1H, bs, NH), 6.55 (1H, bs), 7.87 (1H, bs, NH), 8.06 (1H, bs, NH), 9.7 (1H, bs). δ_C 11.3, 11.7, 28.1, 35.5, 35.6, 37.5, 80.2, 127.2, 128.5, 128.6, 154.1, 155.8, 157.4, 158.3, 158.8, 159.1, 161.9, 162.0, 164.3.

*2{[2-Aminomethyl)-5-methyloxazol-4-ylcarbamoyl}-*N-*[2-aminomethyl-5-methyloxazol-4-ylcarbamoyl]}-methyl-5-methyloxazole-4-carboxylic Acid* ***15***

(*a*) $X^- = CF_3CO_2^-$. The BOC-protected amine **14** (85 mg, 0.160 mmol) was stirred in anhydrous trifluoroacetic acid (2 mL) at rt for 1 h, after which the solvent was removed under vacuum. The residue was dissolved in methanol, and the solvent was removed under vacuum to yield the product as a colourless oil (84 mg, 0.154 mmol, 96%). δ_H (CD_3OD) 2.53 (3H, s), 2.56 (3H, s), 2.58 (3H, s), 3.35 (15H, s), 3.99 (1H, s), 4.38 (2H, s), 4.62 (4H, bs), 5.02 (1H, bs). δ_C (CD_3OD) 11.6, 12.0, 36.8, 37.0, 37.0, 55.3, 128.9, 130.1, 130.6, 155.6, 156.3, 156.8, 158.4, 160.3, 163.8, 164.3, 165.0.

(*b*) $X^- = Cl^-$. The BOC-protected amine **14** (23 mg, 0.043 mmol) was added to a saturated solution of anhydrous hydrogen chloride in dichloromethane (1.2 mL) at 0°C and the reaction was stirred for 2 h at 0–5°C. The mixture was extracted with water, and the aqueous layer was then reduced under vacuum, giving the *product* as a colourless oil, which solidified on standing (10 mg, 0.021 mmol, 49%), mp 214–215°C. ν_{max}/cm^{-1} 3374, 1699, 1667, 1626, 1519, 1307, 1189. δ_H ($CDCl_3/CD_3OD$) 2.59 (3H, s), 2.60 (3H, s), 2.62 (3H, s), 4.31 (2H, s), 4.40 (1H, bs), 4.64 (4H, bs). δ_C ($CDCl_3/CD_3OD$) 10.8, 10.8, 11.3, 35.2, 35.4, 35.5, 127.3, 128.3, 128.8, 154.0, 154.1, 155.0, 156.7, 158.1, 159.0, 161.8, 162.2, 163.5. *m/z* (ESI) 455.1 ($[M + Na]^+$, $C_{18}H_{20}N_6O_7Na$ requires 455.4), 433.1 ($[M + H]^+$, $C_{18}H_{21}N_6O_7$ requires 433.4), 467.2 ($[M + Cl]^-$, $C_{18}H_{20}N_6O_7Cl$ requires 467.8).

Cyclic Trisoxazole ***16***

Diphenylphosphoryl azide (62 μL, 0.288 mmol) was added to a solution of the trifluoroacetate salt of the amine **15** (79 mg, 0.145 mmol) and triethylamine (40 μL, 0.287 mmol) in DMF (145 mL) at −4°C. The temperature was kept at −4 to −10°C for 2 days, at +5°C for a further 3 days, then at 15–16°C for 3 days. The solvent was removed under vacuum below 38°C, dichloromethane (100 mL) was added, and insoluble material was collected by filtration as an off-white powder (50 mg). *m/z* (ESI) 453.0 ($[M + K]^+$, $C_{18}H_{18}N_6O_6K$ requires 453.5).

A suspension of this compound in dichloromethane was treated with gaseous HCl at 0–5°C for 1 h. The solvent was removed under reduced pressure, the residue was dissolved in chloroform (30 mL) and extracted with water (2 × 4 mL), then 10% potassium bicarbonate (2 × 4 mL) followed by water (4 mL). Removal of the organic solvent afforded the *title compound* **16** as a white powder (12 mg, 0.029 mmol, 20%), mp 320–321°C (dec.) (subl. 245–275°). ν_{max}/cm^{-1} 3400, 1683, 1672, 1638, 1592, 1528. δ_H 2.68 (9H, s), 4.59 (6H, s), 8.34 (1H, bs, NH). δ_C 11.2, 36.9, 37.0, 128.3, 128.3, 154.3, 157.6, 157.6, 161.2, 161.3. *m/z* (ESI) ($MeOH/CH_2Cl_2$) 415.1 ($[M + H]^+$ with daughter ion 372.1 ($[M + H^+ - 43]$), $C_{18}H_{19}N_6O_6$ requires 415.4).

The dichloromethane solution above was extracted with 10% potassium bicarbonate (2 × 20 mL) and water (20 mL). The addition of ether allowed an additional amount of the potassium complex **16b** to be collected by filtration as a beige powder (14 mg, 0.034 mmol, 23%), mp 285–286°C. ν_{max}/cm^{-1} 3397, 1683, 1640, 1596, 1528, 1257, 1194, 1144. δ_H 1.74 (1H, bs), 2.62 (3H, s), 2.68 (6H, s), 4.60 (6H, d, *J* 3.9), 8.35 (1H, bt, NH). δ_C 11.4, 37.1, 128.5, 154.2, 157.8, 161.1. *m/z* (ESI) 452.9 ($[M + K]^+$, $C_{18}H_{18}N_6O_6K$ requires 453.5).

N-*(5-Ethoxycarbonyl-4-methyloxazol-2-ylmethyl)-2-(tertbutyloxycarbonylaminomethyl)-5-methyloxazole-4-carboxamide* ***18***

A solution of the hydrochloride of the amine **19**[15] (633 mg, 2.87 mmol) in dichloromethane (3 mL), then triethylamine (400 μL, 2.87 mmol), were added to a mixture of the acid **9** (735 mg, 2.87 mmol), triethylamine (400 μL, 2.87 mmol), and BOP (1.34 g, 2.94 mmol) in dichloromethane (7 mL) at rt, and the reaction was stirred for 16 h under N_2. The reaction mixture was diluted with dichloromethane (10 mL), extracted with water (10 mL), followed by 10% potassium bicarbonate (2 × 5 mL) then water (5 mL). The solvent was removed under reduced pressure and the residue was dissolved in ether (30 mL). The organic layer was extracted with water (3 × 20 mL), dried, and filtered. Removal of the solvent under vacuum yielded the *product* **18** as a slightly yellow oil (821 mg, 1.94 mmol, 68%). ν_{max}/cm^{-1} 3347, 1718, 1670, 1636, 1522, 1334, 1273, 1253, 1171, 1152, 1103. δ_H 1.38 (3H, t, *J* 7.2), 1.44 (9H, s), 2.42 (3H, s), 2.55 (3H, s), 4.37 (4H, m), 4.73 (2H, d, *J* 6.0), 6.08 (1H, bt, NH), 8.03 (1H, t, *J* 6.0, NH). δ_C 11.0, 12.6, 13.8, 27.8, 35.8, 37.2, 60.7, 79.5, 128.2, 137.6, 145.5, 153.6, 155.6, 158.3, 158.5, 161.8, 162.0. *m/z* (ESI) 445.1 ($[M + Na]^{+\bullet}$ with daughter ions 389.0 ($[M + Na^+ - 56]$) and 345.1 ($[M + Na^+ - 100]$), $C_{19}H_{26}N_4O_7Na$ requires 445.4).

*4-[*N-*(5-Ethoxycarbonyl-4-methyloxazol-2-ylmethyl)]carbamoyl (5-methyloxazol-2-yl)methylammonium Trifluoroacetate* ***21***

The protected amine **18** (389 mg, 0.921 mmol) was stirred in anhydrous trifluoroacetic acid (1.5 mL) at rt under N_2 for 1 h. Removal of the solvent under vacuum afforded the *title compound* in quantitative yield (402 mg, 0.921 mmol). ν_{max}/cm^{-1} 3404, 3296, 2700 (br), 1718, 1684, 1654, 1637, 1560, 1541, 1337, 1304, 1205, 1185, 1158, 1139, 1016. δ_H ($CDCl_3/CD_3OD$) 1.39 (3H, t, *J* 7.2), 2.44 (3H, s), 2.63 (3H, s), 3.74 (1H, bs), 4.23 (2H, s), 4.38 (2H, q, *J* 7.2), 4.69 (2H, s). δ_C ($CDCl_3/CD_3OD$) 11.2, 12.7, 13.9, 35.6, 36.0, 61.3, 129.1, 138.1, 145.51, 154.1, 155.3, 158.7, 161.8, 162.6. *m/z* (ESI) 323.1 ($[M + H]^+$, $C_{14}H_{19}N_4O_5$ requires 323.3).

*2-{[2-(*tert-*Butyloxycarbonylaminomethyl)-5-methyloxazol-4-ylcarbamoyl]-methyl}-4-methyloxazole-5-carboxylic Acid* ***20***

Ester **8** (408 mg, 0.966 mmol) was hydrolyzed as above to give the acid as a slightly yellow gum (338 mg, 0.857 mmol, 89%). ν_{max}/cm^{-1} 3346, 2700–2200 br, 1696, 1636, 1622, 1522, 1303, 1275, 1254, 1159, 1100. δ_H 1.44 (9H, s), 2.41 (3H, s), 2.56 (3H, s), 4.36 (2H, s), 4.75 (2H, d, *J* 5.1), 5.84 (1H, bs), 8.03 (1H, bs), 10.06 (1H, bs). δ_C 11.3, 12.6, 28.0, 36.1, 37.4, 80.1, 128.3, 138.1, 146.0, 154.2, 155.8, 158.8, 160.5, 162.1, 162.5. *m/z* (ESI) 417.1 ($[M + Na]^{+\bullet}$ with daughter ions 361.1 ($[M + Na - 56]$) and 317.1 ($[M + Na - 100]$), $C_{17}H_{22}N_4O_7Na$ requires $[M + Na]^{+\bullet}$ 417.4).

N-*(5-Ethoxycarbonyl-4-methyloxazol-2-methyl)-2-[2-(*tert-*butoxycarbonylaminomethyl)-5-methyloxazol-4-ylcarbamoyl-methyl-4-methyloxazol-5-ylcarbamoyl] methyl-4-methyloxazol-5-carboxamide* ***22***

A mixture of the trifluoroacetate of the amine **21** (125 mg, 0.286 mmol) and triethylamine (40 μL, 0.287 mmol) in dichloromethane (1 mL) was added to a mixture of the acid **20** (128 mg, 0.325 mmol), triethylamine (47 μL, 0.337 mmol), and BOP (153 mg, 0.336 mmol) in

dichloromethane (2 mL) at rt, and the reaction was stirred for 48 h under N_2. The reaction mixture was then diluted with dichloromethane (15 mL), extracted with water (2 × 7 mL), followed by 10% potassium bicarbonate (3 × 5 mL) and water (2 × 5 mL). The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (3 mL). Addition of ether (15 mL) then caused excess BOP to precipitate, which was removed by filtration. The organic layer was extracted with water (5 × 10 mL), dried, and evaporated to yield the *product* as a slightly yellow gum which solidified on standing (127 mg, 0.182 mmol, 64%), mp 86–90°C. ν_{max}/cm^{-1} 3332, 3055, 1718, 1701, 1654, 1636, 1559, 1541, 1522, 1508, 1334, 1267, 1168, 1103. δ_H 1.38 (3H, t, *J* 7.2 Hz), 1.43 (9H, s), 2.37 (3H, s), 2.38 (3H, s), 2.50 (3H, s), 2.53 (3H, s), 4.36 (4H, m), 4.59 (2H, d, *J* 6.0), 4.66 (2H, d, *J* 6.0), 4.72 (2H, d, *J* 6.3), 5.84, (1H, bs, NH), 8.05 (1H, bt, NH), 8.20 (1H, bs, NH), 8.44 (1H, bs, NH). δ_C 11.2, 11.3, 12.4, 12.9, 14.1, 28.1, 35.5, 35.8, 36.0, 37.4, 61.2, 80.14, 128.4, 128.5, 137.9, 139.2, 143.1, 145.6, 153.9, 154.0, 155.8, 158.0, 158.2, 158.5, 158.8, 160.2, 162.0, 162.2, 162.2. *m/z* (ESI) 721.2 ($[M + Na]^{+\bullet}$ with daughter ions 665.0 ($[M + Na - 56]$) and 621.2 ($[M + Na - 100]$), $C_{31}H_{38}N_8O_{11}Na$ requires $[M + Na]^{+\bullet}$ 721.7).

*4-[*N*-(2-Aminomethyl-4-methyloxazol-5-ylcarbamoyl)-*N*-(2-aminomethyl-5-methyloxazol-4-ylcarbamoyl)-*N*-(2-aminomethyl-4-methyloxazol-5-ethoxycarbonyl)]-5-methyloxazol-2-ylmethylammonium Trifluoroacetate* ***25***

The protected amine **22** (12 mg) was stirred in anhydrous trifluoroacetic acid (0.1 mL) at rt under N_2 for 1 h. Removal of the solvent under vacuum afforded the title compound, which was used in the next step without further purification. δ_H 1.38 (3H, t, *J* 7.2), 2.42 (3H, s), 2.45 (3H, s), 2.56 (3H, s), 2.58 (3H, s), 4.27 (2H, bs), 4.37 (2H, q, *J* 7.2 Hz), 4.65 (2H, bd), 4.71 (2H, bd), 7.45 (1H, bs), 7.92 (1H, bs), 8.55 (1H, bs).

N-*(5-Carboxy-4-methyloxazol-2-methyl)-2-[2-(*tert-*butoxycarbonylaminomethyl)-5-methyloxazol-4-ylcarbamoyl-methyl-4-methyloxazol-5-ylcarbamoyl] methyl-4-methyloxazol-5-carboxamide* ***23***

Ester **22** (127 mg, 0.182 mmol) was hydrolyzed as above to give the product as a slightly yellow gum. The product precipitated from a mixture of dichloromethane and ether, and was collected after cooling at 0–5°C overnight (66 mg, 0.098 mmol, 54%), mp 143–144°C. ν_{max}/cm^{-1} 3330, 1717, 1701, 1684, 1670, 1654, 1636, 1629, 1559, 1541, 1523, 1508, 1313, 1263, 1160. δ_H ($CDCl_3/CD_3OD$) 1.46 (9H, s), 2.44 (3H, s), 2.47 (3H, s), 2.61 (6H, m), 3.78 (1H, bs), 4.34 (2H, bs), 4.61 (2H, d, *J* 5.7 Hz), 4.66 (4H, m), 8.05 (1H, bs, NH), 8.49 (1H, bs, NH). δ_C ($CDCl_3/CD_3OD$) 11.1, 12.2, 12.5, 27.9, 35.4, 35.5, 35.8, 37.2, 80.2, 128.3, 128.5, 138.4, 139.4, 143.0, 145.5, 154.3, 156.1, 157.9, 158.4, 158.9, 160.1, 160.1, 161.9, 162.2, 162.6. *m/z* (ESI) 693.2 ($[M + Na]^{+\bullet}$ with daughter ions 637.0 ($[M + Na - 56]$) and 593.1 ($[M + Na - 100]$), $C_{29}H_{34}N_8O_{11}Na$ requires $[M + Na]^{+\bullet}$ 693.6).

Attempted Synthesis of ***17***

(*a*) Via **25**. The tetra-oxazole **22** (12.6 mg, 0.018 mmol) was stirred in anhydrous trifluoroacetic acid (0.2 mL) at rt for 1 h, after which excess reagent was removed under vacuum. The residue was dissolved in dichloromethane (0.5 mL), and triethylamine (4 μL) was added. The mixture was stirred for 5 min, then carefully heated during dropwise addition of toluene (18 mL). The reaction mixture was stirred at 100°C for 25 h, and the mixture was analyzed by NMR spectroscopy, which showed that no cyclization had occurred.

(*b*) Via **24** and **27**. Compound **23** (45 mg, 0.0671 mmol) was dissolved in dry pyridine (0.5 mL) at 0°C. Pentafluorophenyl trifluoroacetate (14 μL, 0.0798 mmol) was added, and the reaction mixture was stirred at 0–5°C for 3 h, then at rt for 17 h. Excess reagent was removed under vacuum and the residue was cooled to 0°C, after which anhydrous trifluoroacetic acid (1 mL) was added. The reaction was stirred for 10 min, then at rt for 30 min, after which the excess reagent was removed under vacuum. A mixture of chloroform (3 mL) and 1 M potassium carbonate (1 mL) was added to the residue, and the reaction was stirred rapidly for 10 min. The aqueous layer was extracted twice with chloroform. The combined organic layers were analyzed by ^1H NMR spectroscopy, and it was concluded that no cyclization had occurred.

(*c*) Via **26**. To a crude sample of **25** above (40 mg) was added 1.25 M sodium hydroxide (0.5 mL) at 0°C and the reaction was stirred at 0–5°C for 1 h, after which 3 M HCl was added dropwise to pH 6. The solvent was then removed under vacuum and dimethylformamide (4.5 mL) followed by dicyclohexylcarbodiimide (20 mg, 0.095 mmol) was added and the reaction was stirred at rt for 16 h. TLC analysis indicated that cyclization had not occurred and that the product was probably a mixture of different chain lengths.

N-*(5-Ethoxycarbonyl-oxazol-2-ylmethyl)-2-(*tert-*butyloxycarbonylaminomethyl)-5-methyloxazole-4-carboxamide* ***29***

The hydrochloride of the amine **28**[15] (16 mg, 0.077 mmol) then triethylamine (20 μL, 0.14 mmol) were added to a mixture of the acid **9** (20 mg, 0.078 mmol), triethylamine (14 μL, 0.10 mmol), and BOP (35 mg, 0.077 mmol) in dichloroethane (1 mL) at rt, and the reaction was stirred for 20 h under N_2. The solvent was removed and the residue was dissolved in ether (5 mL) and extracted with water (2 × 5 mL), followed by 10% potassium bicarbonate (2 × 5 mL), then water (5 mL). Removal of the solvent under reduced pressure gave an oil consisting of two products, which were separated by chromatography on silica, eluting with dichloromethane/ethyl acetate (4 : 1). The major product (9 mg) was characterized as methyl 2-(*N-tert*-butyloxycarbonylaminomethyl)-5-methyl-1,3-oxazole-4-carboxylate, apparently formed from traces of methanol adhering to **9**. (Found: $M^{+\bullet}$ 270.1205. $C_{12}H_{18}N_2O_5$ requires $M^{+\bullet}$ 270.1216). δ_H 1.45 (9H, s), 2.61 (3H, s), 3.90 (3H, s), 4.42 (2H, d, *J* 5.4), 5.15 (1H, bs, NH). δ_C 11.8, 28.2, 37.7, 51.9, 80.3, 127.5, 155.6, 157.0, 159.4, 162.7. *m/z* 270 (M^+, 1.3%), 214 ($[M - C_4H_8]$, 100%).

The minor product (20%) was found to be compound **29**. δ_H 1.38 (3H, t, *J* 7.2), 1.47 (9H, s), 2.62 (3H, s), 4.38 (4H, m), 4.76 (2H, d, *J* 6.0), 5.09 (1H, bs), 7.51 (1H, t, *J* 6.0, NH), 7.70 (1H, s).

*2-(*N-tert-*Butyloxycarbonylaminomethyl)-1,3-oxazole-5-carboxylic Acid* ***32***

The hydrochloride of the amine **28** (191 mg, 0.924 mmol) was reacted with di-*tert*-butyl dicarbonate as above to give **31**, which was used in the next step without further purification. δ_H 1.38 (3H, t, *J* 7.2), 1.45 (9H, s), 4.38 (2H, q, *J* 7.2), 4.56 (2H, bd), 5.63 (1H, bt, NH), 7.69 (1H, s). δ_C 13.9, 28.0, 38.0, 61.3, 80.0, 133.8, 142.8, 157.5, 164.5.

The crude ester **31** was hydrolyzed as above to give the crude product **32** as a yellow solid (104 mg, 46% overall). Pure product was obtained by crystallization from ether, but in a poor yield, mp 103–109°C. (Found: $M^{+\bullet}$ 242.0891. $C_{10}H_{14}N_2O_5$ requires $M^{+\bullet}$ 242.0903). ν_{max}/cm^{-1} 3354, 1720, 1677, 1581, 1522, 1297, 1148, 1125. δ_H ($CDCl_3/CD_3OD$) 1.40 (9H, s), 3.26 (1H, s), 4.43 (2H, s), 5.8 (1H, bs, NH), 7.63 (1H, s). δ_H ($CDCl_3/CD_3OD$) 28.0, 37.9, 80.4, 133.9, 143.4, 155.9, 159.3, 164.6. *m/z* 242 (M^+, 1.4%), 186 ($[M - 56]$, 9.0%), 169 (4.7%), 142 (4.6%), 56 (44.9%), 44 (100%).

2-(Aminomethyl)-5-methyl-1,3-oxazole-4-carboxylic Acid Hydrochloride ***33***

Ester **7** (79 mg, 0.36 mmol) was hydrolyzed as above to give the crude product as a brown-orange oil (60 mg, 87%). δ_H ($CDCl_3/CD_3OD$) 2.6 (3H, s), 4.42 (2H, s), 4.65 (1H, s), 8.9 (1H, bs). δ_C ($CDCl_3/CD_3OD$) 11.4, 35.8, 125.6, 132.9, 157.6, 163.5.

2-(Aminomethyl)-4-methyl-1,3-oxazole-5-carboxylic Acid Hydrochloride ***34***

Ester **9** (31 mg, 0.14 mmol) was hydrolyzed as above to give the *title compound* as an orange powder (ca. 5 mg), which was spectroscopically pure. (Found: $M^{+\bullet}$ 156.0534. $C_6H_8N_2O_3$ requires $M^{+\bullet}$ 156.0535). δ_H ($CDCl_3/[D_6]DMSO$) 2.45 (3H, s), 4.22 (2H, s), 9.3 (1H, bs). *m/z* 156 (M^+, 11.9%), 84 (84.7%), 66 (100%).

2-(Aminomethyl)-1,3-oxazole-5-carboxylic Acid Hydrochloride ***35***

Ester **28** (185 mg, 0.895 mmol) was hydrolyzed as above to give the crude product as an orange solid (111 mg), which was recrystallized from methanol/ether to afford the pure *compound* as a beige powder (45 mg, 0.25 mmol, 28%), mp 320°C (dec.). (Found: $M^{+\bullet}$ 142.0381. $C_5H_6N_2O_3$ requires $M^{+\bullet}$ 142.0378). ν_{max}/cm^{-1} 1716, 1598, 1230, 1138. δ_H (D_2O/CD_3OD) 4.53 (2H, s), 4.92 (1H, s), 7.92 (1H, s). δ_H (D_2O/CD_3OD) 35.0, 132.5, 144.2, 158.7, 159.7. *m/z* 142 (M^+, 42.9%), 114 (14.4%), 96 (10.9%), 84 (38.6%), 69 (64.1%).

(S)-Ethyl 2-[1-Amino-2-(4-benzyloxyphenyl)ethyl]-5-methyl-1,3-oxazole-4-carboxylate ***38***

A solution of the phthalimidooxazole **39**[14] (1.8 g, 3.5 mmol) and hydrazine hydrate (720 μL, 16.2 mmol) in ethanol (100 mL) was stirred at 68°C for 3 h. The solvent was evaporated and the residue was extracted with chloroform (3 × 10 mL). The combined organic extracts were filtered and evaporated to give the *title compound* (1.33 g, 99%) isolated as a pale yellow oil, which required no further purification. The *racemate* was also synthesized using the above procedure. (Found: $M^{+\bullet}$ 380.1739. $C_{22}H_{24}N_2O_4$ requires $M^{+\bullet}$ 380.1736). ν_{max}/cm^{-1} 1717, 1655, 1514, 1236, 1095. δ_H 7.29–7.42 (5H, m), 7.05 (2H, d, *J* 8.79), 6.88 (2H, d, *J* 8.79), 5.02 (2H, s), 4.36 (2H, q, *J* 7.0), 4.23 (1H, dd, *J* 5.22, 8.38), 3.15 (1H, dd, *J* 5.22, 13.74), 2.93 (1H, dd, *J* 8.38, 13.74), 2.58 (3H, s), 2.2 (2H, bs, NH_2), 1.37 (3H, t, *J* 7.0 Hz). δ_C 164.3, 162.2, 157.7, 156.1, 136.9, 134.2, 130.2, 129.1, 128.5, 127.8, 123.4, 114.9, 69.1, 60.9, 51.3, 41.1, 14.3, 11.9. *m/z* 380 (M^+, 4%), 226 (5), 198 (9), 183 (100), 137 (33), 110 (6), 91 (27).

(S)-2-[1-Amino-2-(4-benzyloxyphenyl)ethyl]-5-methyloxazole-4-carboxylic Acid Hydrochloride ***36***

Lithium hydroxide hydrate (0.1 g, 2.4 mmol) was added to a solution of (*S*)-ethyl 2-[1-amino-2-(4-benzyloxyphenyl)ethyl]-5-methyloxazole-4-carboxylate **37** (0.45 g, 1.1 mmol) in a mixture of ethanol (1.5 mL), tetrahydrofuran (1.5 mL), and water (3 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 h, when TLC analysis indicated that all of the starting material had been consumed. The mixture was acidified to pH 6 by the careful addition of 1% HCl. The product precipitated as a clean white crystalline powder which was diluted with water (100 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were then washed with water (2 × 30 mL) and evaporated to give the *title compound* **36** as a white crystalline powder (0.37 g, 89%), mp >250°C, $[\alpha]_D^{20}$ +52.3° (*c* 1.5, $CHCl_3$). (Found: $[M+H]^{+\bullet}$ 353.1501. $C_{20}H_{20}N_2O_4$ requires $[M+H]^{+\bullet}$ 353.1501). ν_{max}/cm^{-1} 2932, 1709, 1676, 1616, 1515, 1456, 1177. δ_H ($CDCl_3$/TFA) 2.65 (3H, s), 3.32–3.41 (2H, m), 5.02 (1H, m), 5.04 (2H, s), 6.94 (2H, d, *J* 8.65), 7.03 (2H, d, *J* 8.65), 7.36–7.42 (5H, m), 7.94 (2H, bs, NH_2). δ_C ($CDCl_3$/TFA) 11.8, 36.8, 50.8, 70.4, 116.0, 123.7, 126.5, 127.6, 128.3, 128.7, 130.3, 136.0, 157.7, 158.8, 160.7, 165.7. *m/z* (ESI) 353.1 ($[M+H]^+$, 5%), 335 (23), 307 (2), 262 (13), 246 (12), 91 (100).

Cyclooligomerization of (S)-2-[1-Amino-2-(4-benzyloxyphenyl) ethyl]-5-methyloxazole-4-carboxylic Acid Hydrochloride ***36***

A solution of the oxazole **36** (0.177 g, 0.45 mmol) in anhydrous dimethylformamide (46 mL) was cooled under N_2 to 0°C. PyBOP (0.355 g, 0.68 mmol) was added followed by the dropwise addition of diisopropylethylamine (0.071 g, 0.54 mmol). The reaction mixture was stirred at 0°C for 5 h. The solvent was evaporated under reduced pressure below 38°C to give a milky oil (0.6 g), which was dissolved in ethyl acetate (60 mL) and washed with 3% HCl (2 × 30 mL), water (20 mL), 5% sodium bicarbonate (30 mL), and saturated sodium chloride (30 mL). The organic layer was evaporated to give the crude product (0.32 g) as a yellow oil. The residue was dissolved in a mixture of chloroform (2 mL) and trifluoroacetic acid (0.02 g), and then the mixture was evaporated. The residue was purified by radial chromatography (50% ethyl acetate/light petroleum) to give a mixture of the cyclic trimer **39** and cyclic tetramer **40** (3 : 1, 0.074 g, 44%) which crystallized on standing as a white powder, mp 160–163°C. Cyclic trimer **39**: (Found: $[M+Na]^{+\bullet}$ 1025.3770. $C_{60}H_{54}N_6O_9$ requires $[M+Na]^{+\bullet}$ 1025.3850). Cyclic tetramer **40**: (Found: $[M+Na]^{+\bullet}$ 1359.5150. $C_{80}H_{72}N_8O_{12}$ requires $[M+Na]^{+\bullet}$ 1359.5168). ν_{max}/cm^{-1} 3382, 1673, 1634, 1511, 1454, 1372. δ_H (3 : 1 mixture of **39** and **40**, where an asterisk denotes the cyclic trimer **39**) 2.54 (s), 2.58* (s), 3.12–3.38* (m), 4.96–5.05* (m), 5.24* (dd, *J* 4.59 and 13.65), 5.53 (dd, *J* 7.42 and 14.55), 6.92* (d, *J* 8.79), 6.87* (d, *J* 8.79), 7.0 (d, *J* 8.52, NH), 7.29–7.38* (m), 7.51 (m), 7.87 (bs), 8.22* (d, *J* 6.46, NH). δ_C 11.5*, 11.6, 26.2, 26.3, 29.0, 39.2, 39.7*, 46.4, 47.5, 49.7*, 69.9, 112.5, 114.7*, 114.9, 127.16*, 127.4*, 127.8, 127.9*, 128.2, 128.5*, 128.9*, 130.3, 130.4*, 136.7, 136.8*, 153.7*, 154.1, 157.8*, 157.5, 160.3, 160.3*, 160.8*, 160.9. *m/z* (ESI) 1338.0 ($[M+H]^+$, 1%), 1003.8 ($[M+H]^+$, 15%).

(S)-2-[1-Amino-2-(4-benzyloxyphenyl)ethyl]oxazole-5-carboxylic Acid Hydrochloride ***41***

A solution of (*S*)-ethyl 2-[2-(4-benzyloxyphenyl)-1-phthalimidoethyl] oxazole-5-carboxylate[15] (0.438 g, 0.88 mmol) and hydrazine hydrate (176 μL, 3.96 mmol) in ethanol (20 mL) was stirred at 68°C for 3 h. The solvent was evaporated to leave an orange solid, which was extracted with minimal chloroform (2 × 5 mL) and the combined organic extracts were filtered and evaporated to give *(S)-ethyl 2-[1-amino-2-(4-benzyloxyphenyl)ethyl]-1,3-oxazole-5-carboxylate* (0.3 g, 93%) isolated as an orange oil, which required no further purification. $[\alpha]_D^{20}$ −16.6° (*c* 0.84, $CHCl_3$). (Found: $[M+H]^{+\bullet}$ 367.1655. $C_{21}H_{22}N_2O_4$ requires $[M+H]^{+\bullet}$ 367.1658). ν_{max}/cm^{-1} 3290, 1724, 1511, 1302, 1241, 1145. δ_H 1.38 (3H, t, *J* 7.14), 2.99 (1H, dd, *J* 7.97, 13.59), 3.21 (1H, dd, *J* 5.49, 13.59), 4.01 (2H, bs, NH_2), 4.32 (1H, dd, *J* 5.49, 7.97), 4.38 (2H, q, *J* 7.14), 5.02 (2H, s), 6.88 (2H, d, *J* 8.52), 7.05 (2H, d, *J* 8.52), 7.31–7.43 (5H, m), 7.66 (1H, s). δ_C 14.1, 41.1, 51.6, 61.4, 69.9, 114.9, 127.3, 127.8, 128.5, 128.6, 128.8, 130.2, 133.7, 136.9, 142.4, 157.7, 169.6. *m/z* 367 ($[M+H]^+$, 5%), 322 (10), 294 (12), 276 (2), 260 (4), 91 (100).

The ester above (0.271 g, 0.7 mmol) was hydrolyzed as above with lithium hydroxide to give the *title compound* **41** as a pale brown crystalline powder (0.166 g, 66%), mp >250°C, $[\alpha]_D^{20}$ −30° (*c* 0.16, $CHCl_3$). (Found: $[M+H]^{+\bullet}$ 335.1032. $C_{19}H_{14}N_2O_4$ requires $[M+H]^{+\bullet}$ 335.1035). ν_{max}/cm^{-1} 2935, 1678, 1142. δ_H ($CDCl_3$/TFA) 3.36–3.53 (2H, m), 5.05 (2H, s), 5.17 (1H, m), 6.96 (2H, d, *J* 8.65), 7.04 (2H, d, *J* 8.65), 7.36–7.41 (5H, m), 7.94 (1H, s). δ_C ($CDCl_3$/TFA) 36.9, 51.3, 70.5, 116.2, 123.2, 127.6, 128.4, 128.7, 130.4, 134.5, 135.9, 143.2, 159.0, 160.9, 162.2. *m/z* (ESI) 335.1 ($[M+H]^+$, 5%), 317 (2), 289 (3), 91 (100).

(2,5)-Amide-Linked Cyclic Trimer ***42***

A solution of the oxazole **41** (0.16 g, 0.43 mmol) in anhydrous dimethylformamide (43 mL) was cooled under N_2 to 0°C. PyBOP (0.333 g, 0.64 mmol) was added followed by the dropwise addition of diisopropylethylamine (0.066 g, 0.51 mmol). The procedure used with **36** above gave the crude product (0.299 g) as an orange oil which was purified by radial chromatography (ethyl acetate/light petroleum/TFA 70 : 29 : 1) to give the *cyclic trimer* **42** (0.065 g, 43%) isolated as an orange glass. (Found: $[M+H]^{+\bullet}$ 961.3538, $[M+Na]^{+\bullet}$ 983.3376. $C_{57}H_{48}N_6O_9$ requires $[M+H]^{+\bullet}$ 961.3561, $[M+Na]^{+\bullet}$ 983.3381). ν_{max}/cm^{-1} 3389, 1659, 1511, 1454, 1177. δ_H ($CDCl_3$/TFA) 3.1–3.46 (6H, m), 4.90–5.1 (9H, m), 6.84–7.12 (12H, m), 7.28–7.42 (18H, m), 7.69 (3H, bs, NH). δ_C ($CDCl_3$/TFA) 37.7, 49.3, 70.4, 115.7, 126.0, 127.6, 128.2, 128.6, 130.1, 132.7, 136.1, 158.2, 160–161. *m/z* (ESI) 961.4 ($[M+H]^+$, 10%), 948.6 (29), 924.6 (31), 691.2 (100).

Acknowledgments

M.O.C. acknowledges the award of a Flinders University research scholarship, and C.E.S. is grateful for the award of an OPRS scholarship from Flinders University. We are grateful for financial support from the Australian Research Council.

References

[1] J. R. Pawlik, *Chem. Rev.* **1993**, *93*, 1911.
[2] N. Fusetani, S. Matsunaga, *Chem. Rev.* **1993**, *93*, 1793.
[3] P. Wipf, *Chem. Rev.* **1995**, *95*, 2115.
[4] M. R. Prinsep, R. E. Moore, I. A. Levine, G. M. L. Patterson, *J. Nat. Prod.* **1992**, *55*, 140.
[5] (*a*) D. P. Fairlie, G. Abbenante, D. R. March, *Curr. Med. Chem.* **1995**, *2*, 654.
(*b*) G. Abbenante, D. P. Fairlie, L. R. Gahan, G. R. Hanson, G. K. Pierens, A. L. Van Den Brenk, *J. Am. Chem. Soc.* **1996**, *118*, 10 384. doi:10.1021/JA962260F
[6] (*a*) Y. In, M. Doi, M. Inoue, T. Ishida, Y. Hamada, T. Shioiri, *Chem. Pharm. Bull. (Tokyo)* **1993**, *41*, 1686.
(*b*) Y. Hamada, M. Shibata, T. Sugiura, S. Kato, T. Shioiri, *J. Org. Chem.* **1987**, *52*, 1252.
[7] M. A. Walker, C. H. Heathcock. *J. Org. Chem.* **1992**, *57*, 5566.
[8] P. Wipf, P. C. Fritch, *Tetrahedron Lett.* **1994**, *35*, 5397. doi:10.1016/S0040-4039(00)73509-X
[9] M. North, G. Pattenden, *Tetrahedron* **1990**, *46*, 8267. doi: 10.1016/S0040-4020(01)81482-4
[10] M. P. Foster, G. P. Concepción, G. B. Caraan, C. M. Ireland, *J. Org. Chem.* **1992**, *57*, 6671.
[11] P. Wipf, P. Miller, *J. Org. Chem.* **1993**, *58*, 3604, and references therein.
[12] R. H. Prager, J. A. Smith, B. Weber, C. M. Williams, *J. Chem. Soc., Perkins Trans. 1* **1997**, 2665. doi:10.1039/A700134G
[13] R. H. Prager, M. R. Taylor, C. M. Williams, *J. Chem. Soc., Perkins Trans. 1* **1997**, 2673. doi:10.1039/A700646B
[14] M. Cox, R. H. Prager, C. E. Svensson, *Aust. J. Chem.* **2003**, *56*, 887. doi:10.1071/CH03052
[15] M. Cox, R. H. Prager, C. E. Svensson, *Aust. J. Chem.* **2003**, *56*, 897. doi:10.1071/CH03053
[16] C. Boss, P. H. Rasmussen, A. R. Wartini, S. R. Waldvogel, *Tetrahedron Lett.* **2000**, *41*, 6327. doi:10.1016/S0040-4039(00)01057-1
[17] Y. Singh, N. Sokolenko, M. J. Kelso, L. R. Gahan, G. Abbenante, D. P. Fairlie, *J. Am. Chem. Soc.* **2001**, *123*, 333. doi:10.1021/JA002666Z
[18] G. Pattenden, T. Thompson, *J. Chem. Soc., Chem. Commun.* **2001**, 717. doi:10.1039/B101417J
[19] D. Mink, S. Mecozzi, J. Rebek, *Tetrahedron Lett.* **1998**, *39*, 5709. doi:10.1016/S0040-4039(98)01170-8
[20] B. Castro, J. R. Dormoy, G. Evin, C. Selve, *Tetrahedron Lett.* **1975**, *16*, 1219. doi:10.1016/S0040-4039(00)72100-9
[21] U. Schmidt, D. Weller, *Tetrahedron Lett.* **1986**, *27*, 3495. doi:10.1016/S0040-4039(00)84831-5
[22] U. Schmidt, S. Weinbrenner, *J. Chem. Soc., Chem. Commun.* **1994**, 1003. doi:10.1039/C39940001003
[23] E. Aguilar, A. I. Meyers, *Tetrahedron Lett.* **1994**, *35*, 2473. doi:10.1016/S0040-4039(00)77147-4
[24] A. Bertram, J. S. Hannam, K. A. Jolliffe, F. Gonzalez-Lopez de Turiso, G. Pattenden, *Synlett* **1999**, 1723. doi:10.1055/S-1999-2942
[25] A. J. Blake, J. S. Hannam, K. A. Jolliffe, G. Pattenden, *Synlett* **2000**, 1515. doi:10.1055/S-2000-7640