Towards a total synthesis of ulapualide A. Concise synthetic routes to the *tris*-oxazole ring system and *tris*-oxazole macrolide core in ulapualides, kabiramides, halichondramides, mycalolides and halishigamides

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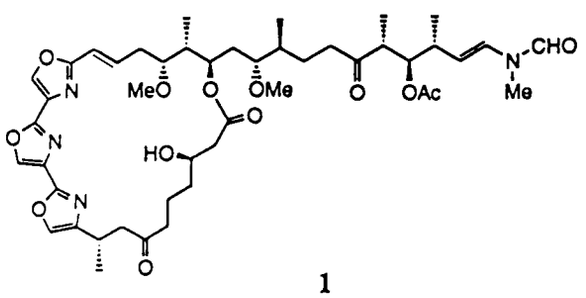
A range of methods for the synthesis of mono-, bis- and tris-2,4-disubstituted oxazoles were evaluated, which led ultimately to a concise synthesis of the three contiguous oxazole ring system **26** in the ulapualide family of 25-membered macrolides, *e.g.* **1**, found in marine organisms. The tris-oxazole macrolide core **30** in ulapualide A (**1**) was also synthesised based on a macrolactamisation strategy from the two functionalised mono-oxazole precursors **28** and **29**, followed by oxazoline **45** and oxazole ring formation, exploiting the methodologies established in the synthesis of linear bis- and tris-oxazoles in the formation of **18** and **26**. The tris-oxazole **26** was converted into the corresponding phosphonium salt **5** in readiness for elaboration to ulapualide A (**1**).

The "ulapualides", which include the halichondramides, kabiramides, mycalolides and halishigamides are a novel family of marine metabolites which show structures based on the presence of three contiguous oxazole rings incorporated in a 25-membered macrolide ring, to which is attached an acyclic side chain that terminates in an *N*-methyl-*N*-alkenyl formamide group.[1–4] The structures, *e.g.* ulapualide A **1**,[1] differ from each other largely according to the oxidation patterns and alkyl group substitutions found in their aliphatic portions, *e.g.* mycalolide B (**2**).[4] Interestingly, other ulapualides are known which contain incomplete tris-oxazole chromophores *e.g.* **3**[3] and **4**.[5]

Although oxazoles are now found quite commonly in nature,[6] the tris-oxazole unit present in the ulapualides remains unprecedented. Indeed, in earlier overtures we have even suggested that some of the unique biological properties of these molecules are associated with their capacity to sequester and transport metal ions, *i.e.* behave as ionophores, using the several oxazole nitrogen and side chain oxygen ligand binding sites present in their structures.[7] The combination of a unique and unprecedented chemical structure with novel biological properties lured us to attempt a total synthesis of the founder member, ulapualide A (**1**), of this intriguing family of marine metabolites.[8] In this paper we focus our attention on the development of suitable synthetic routes to the three contiguous oxazole ring system in the natural product, specifically the doubly functionalised tris-oxazole **5**,[9] and in the accompanying paper we describe the extension of this work culminating in a total



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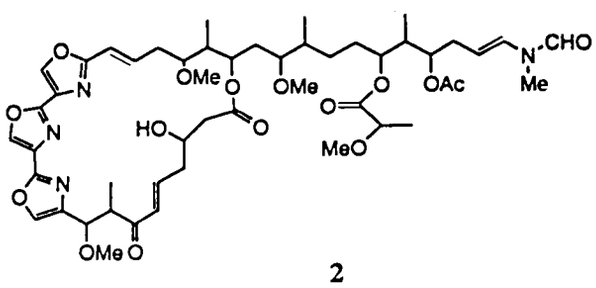

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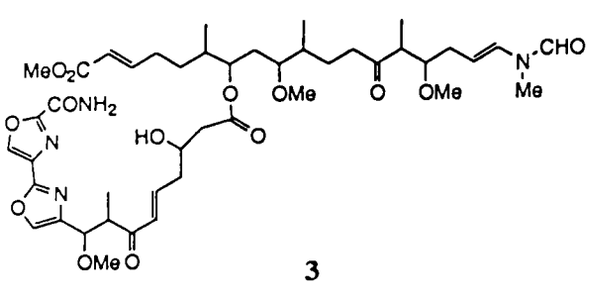

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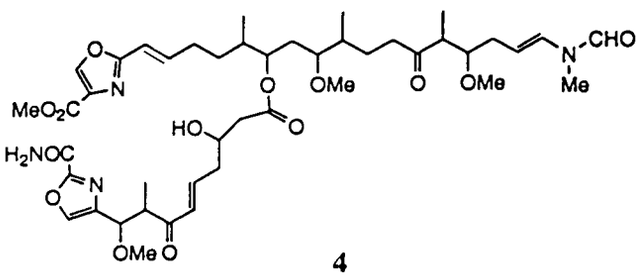

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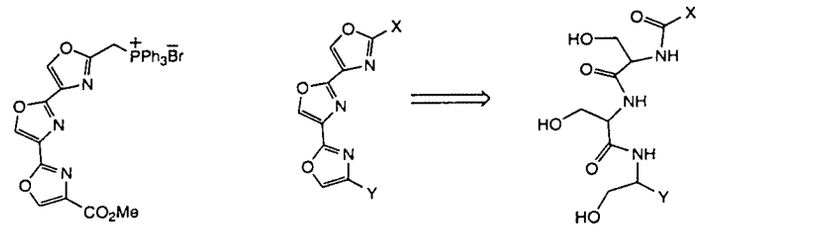

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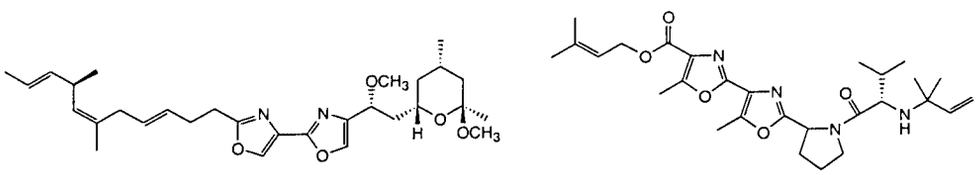

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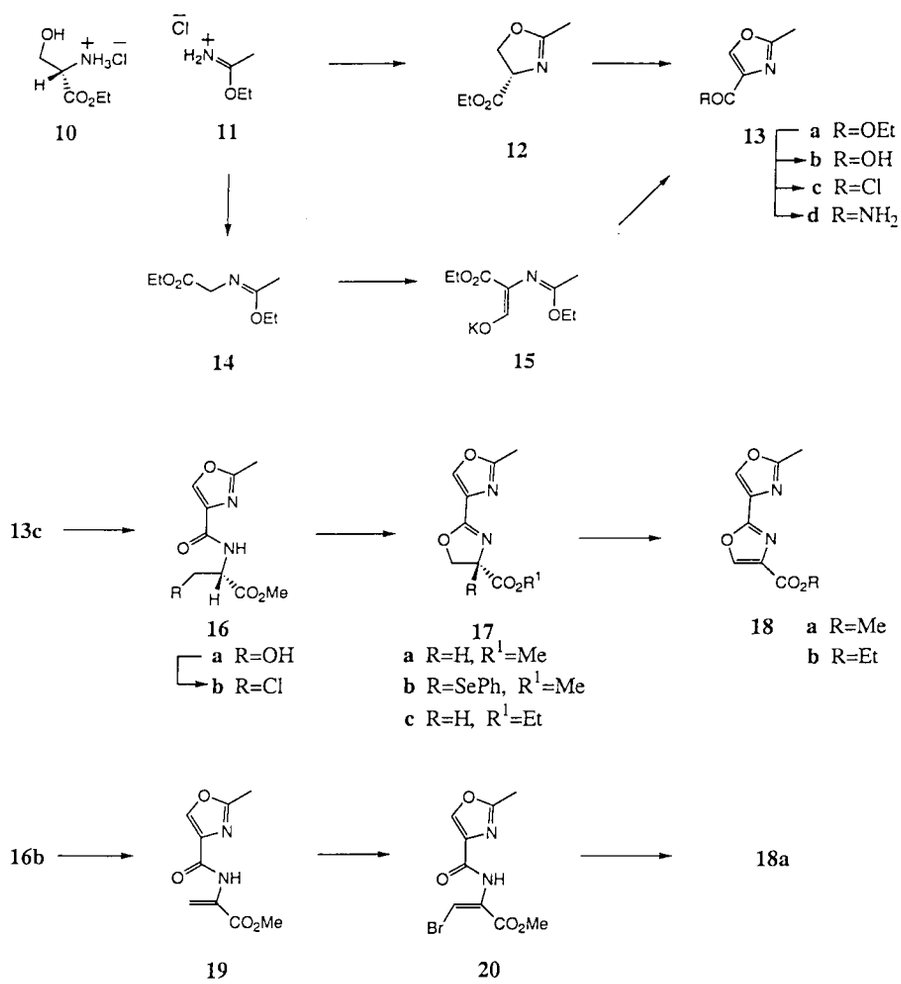
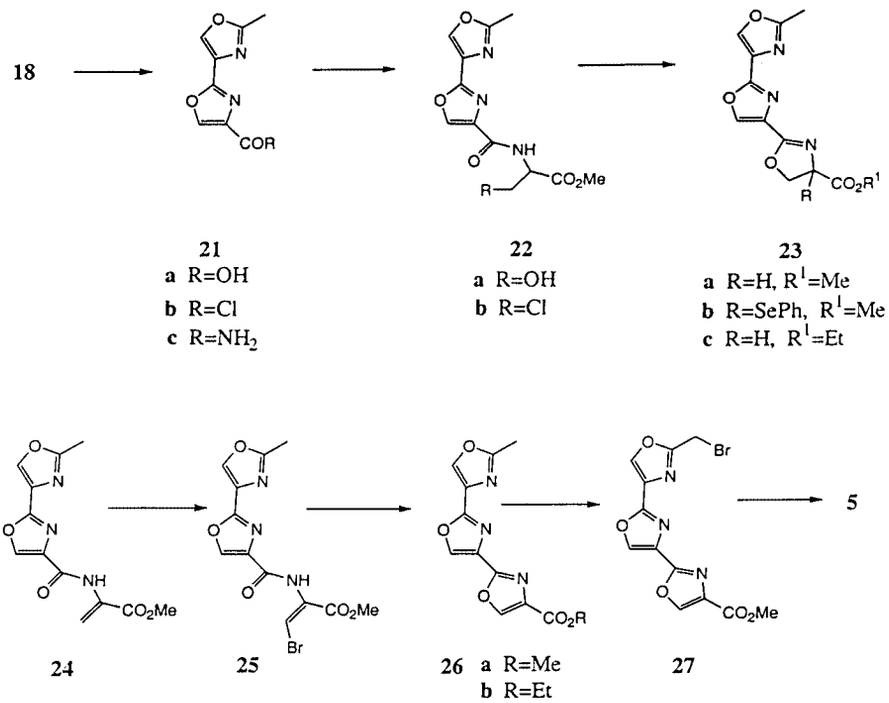
synthesis of ulapualide A, with the relative stereochemistry shown in structure **1**.[10]

The tris-oxazole unit **6** (*cf.* **5**) in the ulapualides is most likely derived in nature by cyclodehydration of an appropriately substituted tris-serine precursor, *e.g.* **7**, leading to the corresponding tris-oxazoline, followed by enzymic oxidation.[11] A related bis-oxazole unit is found in the natural product hennoxazole A **8** isolated from *Polyfibrospongia* sp.,[6] and muscoride A **9** found in the freshwater cyanobacterium *Nostac muscorum*[6] shows a bis-oxazole core which is formally derived from two threonine residues. Our first approach to the differentially functionalised tris-oxazole **5** was indeed based on the aforementioned biogenetic pathway but utilised three molecules of serine in three sequential oxazoline cyclisation–oxidation steps, instead of the more ambitious one-pot, **7**→**6**, approach.[9]

Thus, condensation between serine ethyl ester hydrochloride **10** and ethyl acetimidate hydrochloride **11** in the presence of triethylamine first led to the oxazoline **12** (Scheme 1),[12] which on oxidation with nickel peroxide in hot benzene, according to the method of Meyers *et al.*,[13] gave the mono-oxazole ester **13a**. The same substituted oxazole **13a** could also be obtained from ethyl acetimidate hydrochloride following condensation with glycine ester hydrochloride leading to **14**, followed by formylation (to **15**) and acid-catalysed cyclisation, as described by Cornforth and Cornforth.[14] Saponification of **13a**, followed by conversion of the resulting carboxylic acid **13b** into the corresponding acid chloride **13c** and treatment with a second



Scheme 1



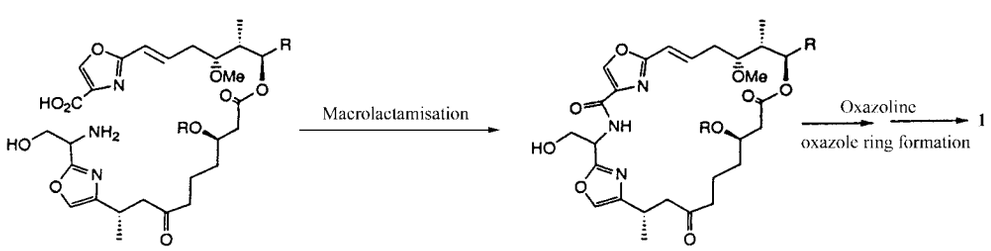
Scheme 2

molecule of serine ester hydrochloride next provided the mono-oxazole serine amide **16a**. Treatment of **16a** with thionyl chloride at 0 °C then led to the alkyl chloride **16b** which could be cyclised to the oxazole-oxazoline **17a** in the presence of 1.2 equivalents of silver triflate.[15] Oxidation of **17a** using nickel peroxide in hot benzene then provided the bis-oxazole **18** as colourless crystals, albeit in only 27% yield. More satisfactory methods for the "oxidation" of **17a** to **18** were either to use *N*-bromosuccinimide with irradiation from a sun lamp,[16] or alternatively to convert **17a** into the corresponding phenylselenyl derivative **17b**, then oxidise the latter to the selenoxide and eliminate the elements of phenylselenic acid.[17] Finally, the same bis-oxazole ester **18** could be produced from the alkyl chloride **16b** following conversion into the alkene **19**, bromination–dehydrobromination of **19** to the vinyl bromide **20**, and cyclisation of the latter in the presence of copper(II) bromide and caesium carbonate.[18]

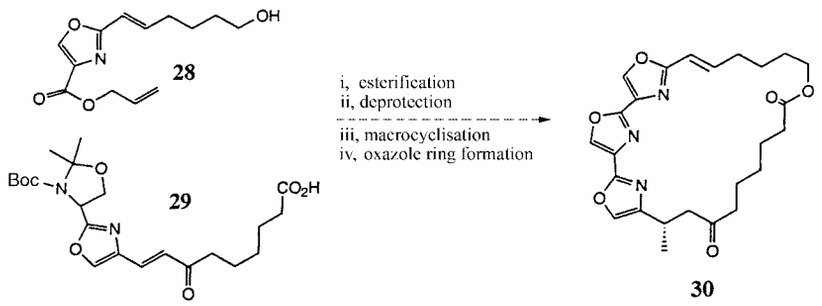
Repetition of the sequences detailed above *i.e.* acid chloride **21b** formation (from **18**), reaction with serine ester hydrochloride (to **22a**), chlorination (to **22b**), cyclisation to **23a** and oxidation (direct or *via* **23b**), or alternatively conversion of **22b** into **24** followed by bromination–dehydrobromination (to **25**) and cyclisation, was then applied to convert the bis-oxazole ester **18** into the target tris-oxazole ester **26** (Scheme 2), which was secured as a white solid, mp 222–224 °C. In a slight modification to the synthesis of **18** and **26** from similar starting materials, the amide **13d** derived from **13c** could be converted into the oxazole-oxazoline **17c** in one step by condensation with serine ethyl ester hydrochloride in the presence of triethyloxonium tetrafluoroborate, and likewise the amide **21c** into **23c** by similar chemistry.

With the tris-oxazole **26** to hand, treatment with *N*-bromosuccinimide and AIBN with irradiation from a 300 W sun lamp at reflux in carbon tetrachloride for 24 h, next led to the corresponding oxazolylmethyl bromide **27** which, on reaction with triphenylphosphine, finally led to the target tris-oxazole phosphonium salt **5** in readiness for elaboration to ulapualide A. These studies are described in the accompanying paper.[10]

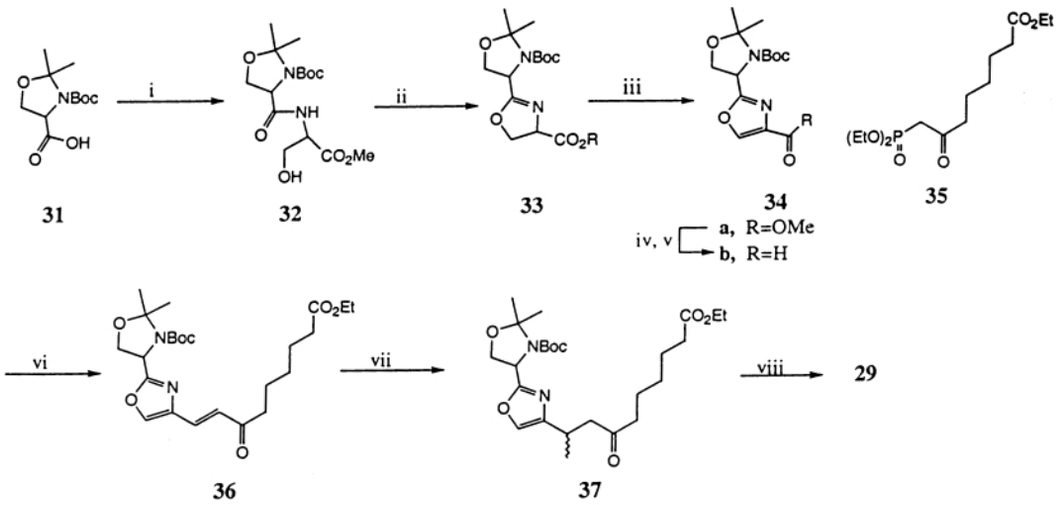
Preliminary details of the aforementioned synthesis of the tris-oxazole unit **26** in the ulapualides were described in 1990.[9] Other approaches to the same unit have been described more recently, which highlight the scope for the Hantzsch oxazole synthesis[19] and for [3 + 2] cycloaddition reactions of acyl carbenes to nitriles[20] in the elaboration of oxazoles. Like our own approach however, these alternative methods are used in a linear, step-wise fashion. A more attractive proposition would be to develop a convergent approach to the tris-oxazole unit in the ulapualides, which would permit the elaboration of the central oxazole ring as a final step and in an intramolecular fashion. We felt this objective could be achieved based on a macrolactamisation strategy from two appropriately functionalised mono-oxazole precursors, followed by oxazoline and oxazole ring formation exploiting the methodologies we had established in the synthesis of the polyoxazoles **18** and **26**; this sequence is shown diagramatically in Scheme 3. Such an approach would offer an attractive alternative strategy for elaboration of the tris-oxazole macrolide core in the ulapualides. Accordingly, we examined the scope for this approach using the substituted mono-oxazoles **28** and **29** as key precursors, with a view to the synthesis of the model tris-oxazole macrolide **30** (Scheme 4).



Scheme 3



Scheme 4



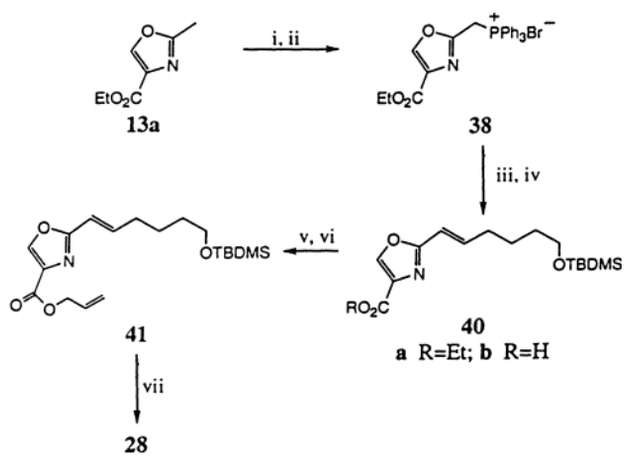
Scheme 5 *Reagents and conditions*: i, SerineOMe·HCl, Et_3N, 0 °C then DCC, 74%; ii, Burgess' reagent, THF, 75%, iii, $BrCCl_3$, DBU, 0–25 °C, 75%; iv, DIBAL-H; v, $PySO_3$ in DMSO, Et_3N, 60%; vi, $Ba(OH)_2{\cdot}8H_2O$, **14**, THF, 71%; vii, Me_2CuLi, Et_2O, −5 °C, 55%; viii, LiOH, THF, H_2O, 98%.

Thus, treatment of the serine-derived oxazolidine carboxylic acid **31** (Garner's acid)[21] with serine methyl ester hydrochloride first gave the corresponding amide **32** which on reaction with Burgess' reagent[22] led to the oxazoline **33** as a mixture of diastereoisomers (Scheme 5). "Oxidation" of this mixture using $BrCCl_3$–DBU[23] then gave the oxazole **34a** which, following reduction to the corresponding aldehyde **34b** and Wadsworth–Emmons olefination using the ketophosphonate **35**,[24] was converted into the *E*-enone **36**. The addition of lithium dimethylcuprate to the enone **36** next led to an unresolved mixture of diastereoisomers of the ketoester **37** which on saponification gave the carboxylic acid **29**, in readiness for esterification with the oxazole substituted primary alcohol **28**.

The oxazole substituted primary alcohol **28** was prepared from the known 2-methyloxazole **13a** following initial conversion into the corresponding phosphonium salt **38**, followed by a Wittig reaction between **38** and 5-*tert*-butyldimethylsilylpentanal **39**[25] using butyllithium as base, to produce the *E*-alkene **40a** almost exclusively. Saponification of **40a** followed by protection of the resulting carboxylic acid **40b** as the corresponding allyl ester **41** and removal of the *tert*-butyldimethylsilyl protection then gave the oxazole substituted primary alcohol **28**, suitably protected at the oxazole carboxylic ester terminus for deprotection under mild palladium(0) catalysis (Scheme 6).[26]

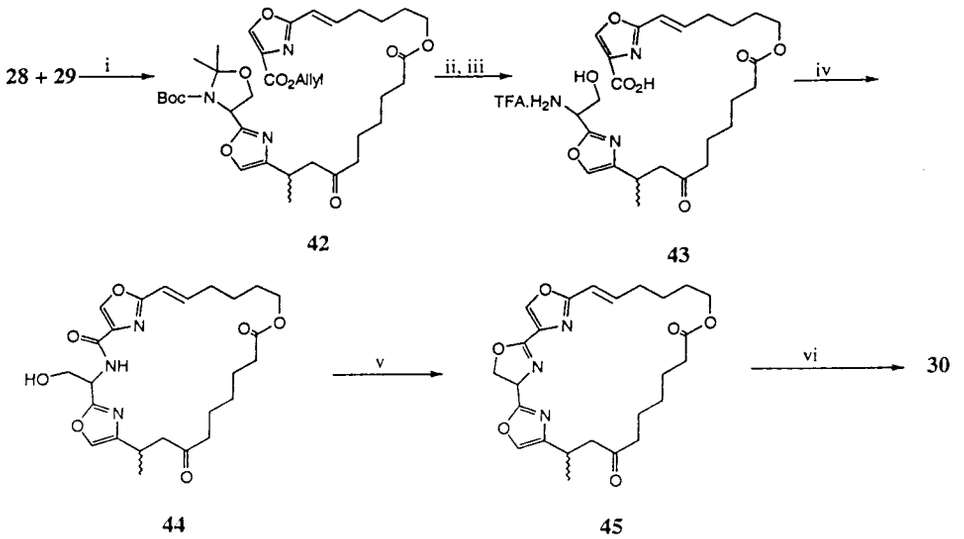
Esterification of the mono-oxazole carboxylic acid **29** with the mono-oxazole alcohol **28** in the presence of l-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride containing 4-(dimethylamino)pyridine next led to the ester **42** in a satisfactory 73% yield (Scheme 7), which was then deprotected sequentially using palladium(0) pyrrolidine (70% to the carboxylic acid) followed by 50% trifluoroacetic acid, leading to the trifluoroacetate salt of the amino acid **43**.

The macrolactamisation of **43** to **44** was accomplished, in an



Scheme 6 *Reagents and conditions*: i, NBS–AIBN, 41%; ii, PPh_3, 82%; iii, BuLi, Et_2O, −78 °C; iv, 5-*tert*-butyldimethylsilylpentanal **39**, 45%; v, LiOH, THF–H_2O, 99%; vi, Allylbromide, $NaHCO_3$, H_2O, 51%; vii, AcOH, THF, H_2O, 91%.

unoptimised 20% yield, by treatment with diphenylphosphoryl azide in the presence of diisopropylethylamine under high dilution.[27] Cyclodehydration of **44** using Burgess' reagent followed by oxidation of the resulting oxazole-oxazoline-oxazole macrolide **45** in the presence of nickel peroxide, finally led to target tris-oxazole macrolide **30** (Scheme 7). This alternative approach to the macrolide core found in the ulapualides, kabiramides, halichondramides, mycalolides, and halishigamides has many attractions over the linear approach to tris-oxazoles used in our total synthesis of the ulapualide A stereostructure **1**. We have plans in place to develop this protocol in a second generation synthesis of the ulapualides, which will be described in due course.



Scheme 7 *Reagents and conditions*: i, EDC·HCl, DMAP, 0 °C, 73%; ii, Pd(0)–pyrrolidine, 70%; iii, 50% TFA solution in CH_2Cl_2; iv, DPPA, DIPEA, DMF, 20%; v, Burgess' reagent, THF; vi, NiO_2, C_6H_6, 46%.

Experimental

General details

[All mps were determined on a Kofler hot stage apparatus and are uncorrected. Optical rotations were measured on a JASCO DIPA-370 polarimeter; $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Ultraviolet spectra were recorded on a Philips PU 8720 spectrophotometer as dilute solutions in spectroscopic grade ethanol; ε values are recorded in units of dm^3 mol^{-1} cm^{-1}. Infrared spectra were obtained using a Perkin-Elmer 1600 series FT-IR instrument as either potassium bromide discs, liquid films or as dilute solutions in spectroscopic grade chloroform. Proton NMR spectra were recorded on either a Bruker WM250 (250 MHz), a Bruker AM400 (400 MHz), a Bruker DRX (500 MHz) or a JEOL EX-270 (270 MHz) spectrometer as dilute solutions in deuterochloroform or d_6-dimethyl sulfoxide. Chemical shifts are recorded relative to a solvent standard and the multiplicity of a signal is designated by one of the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet. All coupling constants, *J*, are reported in Hertz. Carbon-13 NMR spectra were recorded on either a Bruker AM400 (100.6 MHz) or JEOL EX-270 (67.8 MHz) instrument. The spectra were recorded as dilute solutions in deuterochloroform or d_6-dimethyl sulfoxide with chemical shifts reported relative to a solvent standard on a broad band decoupled mode and the multiplicities obtained using a DEPT sequence. The following symbolisms are used for the multiplicities in carbon-13 spectra: q = primary methyl; t = secondary methylene; d = tertiary methine; s = quarternary. Where required, assignment for ^{1}H and ^{13}C NMR spectra were confirmed by two-dimensional homonuclear (^{1}H) and/or heteronuclear (^{1}H/^{13}C) correlation spectroscopy. Matrix dimensions for two dimensional spectra were either 1024 points × 256 columns (homonuclear ^{1}H) or 2048 points × 128 columns (heteronuclear ^{1}H/^{13}C), and were recorded on a JEOL EX-270 instrument. Mass spectra were recorded on a AE1 MS-902, MM-70E or VG Autospec spectrometer using electron ionisation (EI) or fast atom bombardment (FAB) techniques. 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 employed were either of analytical grade or were distilled before use. All reactions were monitored by TLC using Merck silica gel 60 F_{254} precoated plastic backed plates, which were visualised with ultraviolet light and then with either vanillin solution, basic potassium permanganate solution, or phosphomolybdic acid solution.

Commonly used organic solvents were dried by distillation from the following: THF (sodium benzophenone ketyl), dichloromethane (calcium hydride) and methanol (magnesium methoxide). Other organic solvents and reagents were purified by accepted literature procedures. Solvents were removed on a Büchi rotary evaporator using water aspirator pressure. Petrol refers to light petroleum with distillation range 40–60 °C. Where necessary, reactions requiring anhydrous conditions were performed in a flame dried apparatus under a nitrogen atmosphere. A Büchi GKR-50 Kugelröhr apparatus was used for bulb-to-bulb distillations.

2-Methyl-4,5-dihydro-1,3-oxazole-4-carboxylic acid ethyl ester 12

A solution of triethylamine (10.1 g, 100 mmol) in dry CH_2Cl_2 (25 ml) was added dropwise over 30 min to a stirred suspension of ethyl acetimidate hydrochloride (6.2 g, 50 mmol) and L-serine ethyl ester hydrochloride (8.45 g, 50 mmol) in dry CH_2Cl_2 (100 ml) at 25 °C. The mixture was stirred overnight and then the solvents were removed *in vacuo*. The residue was washed with diethyl ether (3 × 25 ml) and the ethereal solution was then dried ($MgSO_4$) and evaporated to dryness. The residue was purified by Kugelröhr distillation under reduced pressure to give the oxazoline (5.89 g, 75%) as a pale yellow oil, bp 100–110 °C at 11 mmHg (lit. bp[12] 98.5–100 °C at 11 mmHg); ν_{max}(film)/cm^{-1} 1735 and 1665; δ_H(250 MHz, $CDCl_3$) 4.8–4.2 (3H, m), 4.21 (2H, q, *J* 7 Hz), 2.0 (3H, s) and 1.35 (3H, t, *J* 7 Hz).

[(1-Ethoxyethylidene)amino]acetic acid ethyl ester 14

Using a modification of the Cornforth procedure,[14] a cooled (0 °C) suspension of ethyl acetimidate hydrochloride **11** (25.0 g, 0.2 mol) in ether (100 ml) was shaken for 5 min in a separating funnel with a cooled (0 °C) solution of potassium carbonate (33.1 g, 0.24 mol) in water (70 ml). The separated aqueous phase was extracted with diethyl ether (30 ml) and a cooled (0 °C) solution of glycine ethyl ester hydrochloride (28.2 g, 0.2 mol) in water (30 ml) was then added to the combined ether extracts with further shaking for 15 min. The separated aqueous layer was once again extracted with diethyl ether (30 ml) and the combined ether phases were washed with water (3 × 30 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow oil which was distilled to give the imino ether (20.7 g, 59%) as a colourless liquid, bp 90 °C at 10 mmHg (lit. bp[14] 85–86 °C at 7.5 mmHg); ν_{max}(film)/cm^{-1} 1745 and 1677; δ_H(250 MHz, $CDCl_3$) 4.24–4.09 (4H, m), 4.04 (2H), 1.88 (:C*Me*) and 1.31–1.24 (6H, m); δ_C(69.2 MHz, $CDCl_3$) 171.2 (q), 164.8

(q), 60.9 (d), 60.8 (d), 51.3 (d), 15.2 (t), 14.2 (t) and 14.2 (t) (Found: *m/z* (EI) 173.1072. $C_8H_{15}NO_3$ requires *M*, 173.1052).

2-Methyl-1,3-oxazole-4-carboxylic acid ethyl ester 13a

(a) Using a modification of the Cornforth procedure,[14] a solution of the imino ether **14** (69.1 g, 0.40 mol) in dry THF (150 ml) was added dropwise over 40 min to a stirred suspension of potassium *tert*-butoxide (49.2 g, 0.44 mol) in dry THF (150 ml) under a nitrogen atmosphere at −10 °C. Ethyl formate (35.5 ml, 0.44 mol) was added sequentially and after stirring at −10 °C for 1 h, dry diethyl ether (100 ml) was added to the brown solution. The mixture was held at this temperature for 1 h and was then evaporated *in vacuo* to leave the potassium enolate salt **15** as a hygroscopic yellow solid. Hot acetic acid (110 ml) was added to the vigorously stirred residue and reflux was maintained for 15 min before the mixture was cooled to room temperature. The resulting orange solid was dissolved in water (500 ml) and the solution was then basified cautiously with solid potassium carbonate before the aqueous mixture was extracted with diethyl ether (3 × 300 ml). The combined organic phases were washed with saturated brine (100 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow liquid. Distillation of the crude material gave the oxazole ester (50.4 g, 81%), as a straw coloured liquid, bp 106–110 °C at 20 mmHg (lit. bp[14] 106–110 °C at 12 mmHg) (Found: C, 54.2; H, 5.8; N, 8.8. $C_7H_9NO_3$ requires C, 54.2; H, 5.8; N, 9.0%); λ_{max}(EtOH)/nm 217 (4760); ν_{max}(film)/cm^{-1} 1738, 1592 and 1109; δ_H(270 MHz, $CDCl_3$) 8.12 (1H, s, 5-H), 4.37 (2H, q, *J* 7 Hz, OCH_2-CH_3), 2.50 (3H, s, 2-Me) and 1.37 (3H, t, *J* 7 Hz, $OCHCH_3$); δ_C(67.8 MHz, $CDCl_3$) 162.0 (s, CO), 160.9 (s, 2-C), 143.4 (d, 5-C), 133.1 (s, 4-C), 60.7 (t, OCH_2CH_3), 13.9 (q, OCH_2CH_3) and 13.4 (q, 2-Me); *m/z* (EI) 155 (M^+, 21%), 126 (2), 110 (57) and 82 (12) (Found: *m/z* 155.0619. $C_7H_9NO_3$ requires *M* 155.0582).

(b) Nickel peroxide (5 × 1 g) was added portionwise over 2 h to a stirred refluxing solution of the oxazoline **12** (5.1 g, 33 mmol) in dry hexane (60 ml) under a nitrogen atmosphere. The mixture was stirred at reflux for a further 2 h and the hot solution was filtered through a Celite pad and then washed with hot ethyl acetate. The combined filtrates were evaporated *in vacuo*, and the residue was purified by distillation to give the oxazole (2.1 g, 41%) as an oil which showed identical spectroscopic data to those described under (a).

2-Methyl-1,3-oxazole-4-carboxylic acid 13b

Using a modification of the Cornforth procedure,[14] a solution of potassium hydroxide (4.34 g, 77 mmol) in water (20 ml) was added in one portion to ethyl 2-methyl-1,3-oxazole-4-carboxylate **13a** (10 g, 64 mmol) and the mixture was then heated under reflux for 1 h. The mixture was cooled to ambient temperature over 1 h and then evaporated *in vacuo*. The residue was acidified with concentrated hydrochloric acid (to pH 1) and then cooled in ice for 30 min. The precipitate was filtered and freeze dried to leave the oxazole acid (5.4 g, 66%) as a white crystalline solid, mp 180–181 °C (water) (lit. mp[14] 183–184 °C) (Found: C, 47.3; H, 4.1; N, 10.9. $C_5H_5NO_3$ requires C, 47.2; H, 4.0; N, 11.0%); λ_{max}(EtOH)/nm 213 (5610); ν_{max}(KBr disc)/cm^{-1} 3436, 1718, 1590, 1164, 1107 and 984; δ_H(270 MHz, d_6-DMSO) 12.96 (1H, br s, CO_2H), 8.58 (1H, s, 5-H) and 2.43 (3H, s, 2-Me); δ_C(67.8 MHz, d_6-DMSO) 162.5 (s, CO_2H), 162.2 (s, 2-C), 145.2 (d, 5-C), 133.5 (s, 4-C) and 13.7 (q, 2-Me); *m/z* (EI) 127 (M^+, 54%), 110 (11) and 82 (7) (Found: *m/z* 127.0287. $C_5H_5NO_3$ requires *M*, 127.0269).

3-Hydroxy-2-[(2-methyl-1,3-oxazol-4-ylcarbonyl)amino]-propionic acid methyl ester 16a

Thionyl chloride (25 ml) was added to the oxazole acid **13b** (5.3 g, 42 mmol) with stirring, and the mixture was then heated under reflux for 4 h. The excess thionyl chloride was removed *in vacuo,* and the residue was then azeotroped with toluene to give the corresponding acid chloride **13c** as a cream solid, which was used immediately without further purification. A solution of the acid chloride in dry dichloromethane (25 ml) was added dropwise over 15 min to a stirred solution of DL-serine methyl ester hydrochloride (7.15 g, 46 mmol) and triethylamine (12.8 ml, 92 mmol) in dry dichloromethane (50 ml) under a nitrogen atmosphere at 0 °C. The mixture was stirred for 20 h at ambient temperature and then evaporated *in vacuo*. The residue was diluted with saturated sodium hydrogen carbonate solution (30 ml), then extracted with ethyl acetate (4 × 30 ml) and the combined organic phases were washed with saturated brine (30 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *oxazole serine derivative* (7.3 g, 77%) as a light brown solid. A small portion was purified by chromatography on silica to give the product as a white crystalline solid, mp 97–98 °C (ethyl acetate–petrol) (Found: C, 47.2; H, 5.4; N, 12.1. $C_9H_{12}N_2O_5$ requires C, 47.4; H, 5.3; N, 12.3%); λ_{max}(EtOH)/nm 222 (3330) and 233sh (3290); ν_{max}($CHCl_3$)/cm^{-1} 3405 br, 1746, 1674, 1601, 1509 and 1106; δ_H(250 MHz, $CDCl_3$) 8.09 (1H, s, 5′-H), 7.70 (1H, br d, *J* 7.4 Hz, N*H*), 4.81 (1H, ddd, *J* 7.4, 3.7 and 3.7 Hz, 4-H), 4.15–3.95 (2H, m, 5-H), 3.81 (3H, s, CO_2Me), 2.91 (1H, br t, *J* 5.6 Hz, O*H*) and 2.48 (3H, s, 2′-Me); δ_C(67.8 MHz, $CDCl_3$) 170.5 (s, 2-C), 161.6 (s, CO_2Me), 160.8 (s, 2′-C), 141.3 (d, 5′-C), 135.3 (s, 4′-C), 62.7 (t, 5-C), 54.3 (d, 4-C), 52.6 (q, CO_2Me) and 13.6 (q, 2′-Me); *m/z* (EI) 210 ($M^+ - H_20$, 4%), 198 (17), 197 (7), 169 (21), 110 (100) and 82 (11) (Found: *m/z* 198.0592 ($M^+ - H_2O$). $C_8H_{10}N_2O_4$ requires *M*, 198.0582).

3-Chloro-2-[(2-methyl-1,3-oxazol-4-ylcarbonylamino]propionic acid methyl ester 16b

Thionyl chloride (3 ml) was added cautiously to the oxazole serine derivative **16a** (1.0 g, 4.4 mmol) under a nitrogen atmosphere at 0 °C and the solution was then stirred at ambient temperature for 12 h. The excess thionyl chloride was evaporated *in vacuo* to leave a residue which was quenched with water (25 ml). The aqueous mixture was extracted with ethyl acetate (3 × 30 ml) and the combined organic extracts were washed with saturated brine (30 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *oxazole serine chloride* (1.04 g, 96%) as a cream solid. A small portion was recrystallised to give a white crystalline solid, mp 104–105 °C (from ethyl acetate–petrol) (Found: C, 43.9; H, 4.6; N, 11.5. $C_9H_{11}ClN_2O_4$ requires C, 43.8; H, 4.5; N, 11.4%); λ_{max}(EtOH)/nm 214 (10240); ν_{max}($CHCl_3$)/cm^{-1} 3401, 1751, 1678, 1600, 1505 and 1107; δ_H(250 MHz, $CDCl_3$) 8.07 (1H, s, 5′-H), 7.64 (1H, br d, *J* 7.8 Hz, N*H*), 5.09 (1H, ddd, *J* 7.8, 3.6 and 3.4 Hz, 4-H), 4.01 (1H, dd, *J* 11.3 and 3.4 Hz, 5-H), 3.90 (1H, dd, *J* 11.3 and 3.6 Hz, 5-H), 3.78 (3H, s, CO_2Me) and 2.44 (3H, s, 2′-Me); δ_C(67.8 MHz, $CDCl_3$) 168.8 (s, 2-C), 161.5 (s, CO_2Me), 160.3 (s, 2′-C), 141.1 (d, 5′-C), 135.3 (s, 4′-C), 52.9 (d, 4-C), 52.6 (q, CO_2Me), 44.8 (t, 5-C) and 13.6 (q, 2′-Me); *m/z* (EI) 211 (M^+ − Cl, 9%), 210 (9), 189 (32), 187 (82), 151 (42), 123 (18) and 110 (100) (Found: *m/z* 194.0283. $C_8H_9N_2O_3$ requires *M*, 194.0275).

2-[(2-Methyl-1,3-oxazol-4-ylcarbonyl)amino]acrylic acid methyl ester 19

1,8-Diazabicyclo[5.4.0]undec-7-ene (4.3 ml, 28.6 mmol) was added dropwise over 10 min to a stirred solution of the serine chloride **16b** (7.1 g, 28.6 mmol) in dry dichloromethane (70 ml) under a nitrogen atmosphere at ambient temperature. The yellow solution was stirred for 3 h, then washed with dilute hydrochloric acid (2 M, 2 × 30 ml) and the separated organic layer was dried ($MgSO_4$) and then evaporated *in vacuo* to leave the *olefin* (1.6 g, 95%) as a white solid; a small sample was recrystallised from 1:1 ether–hexane, mp 128–129 °C (Found: C, 51.3; H, 4.7; N, 13.1. $C_9H_{10}N_2O_4$ requires C, 51.4; H, 4.8; N, 13.3%); λ_{max}(EtOH)/nm 222 (11260) and 259 (11640); ν_{max}($CHCl_3$)/cm^{-1} 3370, 1724, 1685, 1592, 1519 and 1106;

δ_H(250 MHz, $CDCl_3$) 9.19 (1H, br s, N*H*), 8.12 (1H, s, 5′-H), 6.71 (1H, s, 5-H), 5.97 (1H, s, 5-H), 3.89 (3H, s, CO_2Me) and 2.50 (3H, s, 2′-Me); δ_C(67.8 MHz, $CDCl_3$) 163.9 (s, 2-C), 161.3 (s, *C*O_2Me), 159.0 (s, 2′-C), 141.1 (d, 5′-C), 135.9 (s, 4′-C), 130.7 (s, 4-C), 108.9 (t, 5-C), 52.8 (q, CO_2Me) and 13.5 (q, 2′-Me); *m*/*z* (EI) 210 (M^+, 31%), 195 (5), 179 (3), 178 (10), 151 (4) and 110 (100).

3-Bromo-2-[(2-methyl-1,3-oxazol-4-ylcarbonyl)amino]acrylic acid methyl ester 20

A solution of bromine (0.4 ml, 7.7 mmol) in dry dichloromethane (12 ml) was added dropwise over 2 h to a stirred solution of the olefin **19** (1.6 g, 7.7 mmol) in dry dichloromethane (49 ml) under a nitrogen atmosphere at −78 °C. Triethylamine (1.1 ml, 7.7 mmol) was added in one portion and the mixture was then warmed to ambient temperature over 2 h. The mixture was washed with saturated brine (30 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave an orange gum. Purification by chromatography on silica using 2:1 diethyl ether–petrol as eluent gave the *vinyl bromide* (2.1 g, 91%) as a white crystalline solid, mp 107–108 °C (ether–petrol) (Found: C, 37.6; H, 3.2; N, 9.9. $C_9H_9BrN_2O_4$ requires C, 37.4; H, 3.1; N, 9.7%); λ_{max}(EtOH)/nm 222 (4560) and 255 (4570); ν_{max}($CHCl_3$)/cm^{-1} 3376, 1737, 1696, 1625, 1595 and 1111; δ_H(270 MHz, $CDCl_3$) 8.30 (1H, br s, N*H*), 8.15 (1H, s, 5′-H), 7.19 (1H, s, 5-H), 3.83 (3H, s, CO_2Me) and 2.50 (3H, s, 2′-Me); δ_C(67.8 MHz, $CDCl_3$) 162.0 (s, 2-C), 161.4 (s, *C*O_2Me), 157.8 (s, 2′-C), 141.7 (d, 5′-C), 134.7 (s, 4′-C), 131.3 (s, 4-C), 113.3 (d, 5-C), 52.6 (q, CO_2Me) and 13.4 (q, 2′-Me); *m*/*z* (EI) 259, 257 (M^+ − OMe, 2 and 2%), 209 (88), 110 (100) and 82 (20).

2′-Methyl-4,5-dihydro-2,4′-bi(1,3-oxazolyl)-4-carboxylic acid methyl ester 17a

Silver trifluoromethanesulfonate (13.7 g, 53 mmol) was added in one portion to a stirred solution of the oxazole serine chloride **16b** (11.15 g, 45 mmol) in dry benzene (225 ml) at room temperature under a nitrogen atmosphere. The suspension was heated under reflux for 6 h, then cooled to ambient temperature and evaporated *in vacuo*. The residue was partitioned between ethyl acetate (300 ml) and saturated sodium bicarbonate solution (300 ml), with vigorous stirring for 30 min. The separated aqueous layer was extracted with ethyl acetate (3 × 200 ml) and the combined organic phases were then washed with saturated sodium bicarbonate solution (3 × 150 ml). The second aqueous extract was washed further with ethyl acetate (3 × 100 ml) and the combined organic phases were then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *oxazole-oxazoline* (9.50 g, 99%) as a straw coloured oil; ν_{max}($CHCl_3$)/cm^{-1} 2956, 1741, 1675, 1587, 1216 and 1108; δ_H(250 MHz, $CDCl_3$) 8.07 (1H, s, 5′-H), 4.93 (1H, dd, *J* 10.5 and 7.9 Hz, 4-H), 4.68 (1H, dd, *J* 8.6 and 7.9 Hz, 5-H), 4.56 (1H, dd, *J* 10.5 and 8.6 Hz, 5-H), 3.80 (3H, s, CO_2Me) and 2.50 (3H, s, 2′-Me); δ_C(67.8 MHz, $CDCl_3$) 170.1 (s, 2-C), 161.5 (s, *C*O_2Me), 158.9 (s, 2′-C), 140.3 (d, 5′-C), 128.7 (s, 4′-C), 68.6 (t, 5-C), 67.1 (d, 4-C), 51.4 (q, CO_2Me) and 12.4 (q, 2′-Me); *m*/*z* (EI) 210 (M^+, 5%), 151 (61), 126 (100), 110 (25) and 82 (14) (Found: *m*/*z* 210.0651. $C_9H_{10}N_2O_4$ requires *M*, 210.0648).

2′-Methyl-4-phenylselenyl-4,5-dihydro-2,4′-bi(1,3-oxazolyl)-4-carboxylic acid methyl ester 17b

A solution of potassium hexamethyldisilazide in toluene (1.8 ml, 1.5 M, 2.7 mmol) was added dropwise to a stirred solution of the oxazoline ester **17a** (540 mg, 2.6 mmol) in dry THF (5 ml) at −78 °C under an atmosphere of nitrogen. The resulting orange solution was quenched with a solution of phenylselenyl bromide (728 mg, 3.1 mmol) in dry THF (2 ml), and then allowed to warm to ambient temperature. The solvent was evaporated *in vacuo* to leave a brown oil that was purified by column chromatography using hexane–diethyl ether (1:1) as eluent to give the *selenide* (433 mg, 45%) as a yellow oil; ν_{max}(thin film)/cm^{-1} 1729, 1644, 1597 and 1439; δ_H(270 MHz, $CDCl_3$) 8.01 (1H, s), 7.75–7.53 (2H, m), 7.30–7.17 (3H, m), 4.78 (1H, d, *J* 10.6 Hz, CH*H*), 4.56 (1H, d, *J* 10.6 Hz, C*H*H), 3.7 (3H, s, OMe) and 2.42 (3H, 2′-Me); δ_C(67.8 MHz, $CDCl_3$) 169.8 (s), 162.3 (s), 159.8 (s), 143.5 (s), 141.7 (d), 139.2 (s), 137.7 (d), 129.7 (d), 128.9 (d), 126.3 (s), 75.5 (t), 53.0 (q) and 13.7 (q); *m*/*z* (FAB) (Found: *m*/*z* 209 (M^+ − PhSe). $C_9H_9O_4N_2$ requires *M* 209, 20%), 103 (52), 81 (48) and 43 (100). The selenide was found to partially oxidise and eliminate to the bi-oxazole ester **18** upon standing overnight.

2′-Methyl-4,5-dihydro-2,4′-bi(1,3-oxazolyl)-4-carboxylic acid ethyl ester 17c

Triethyloxonium tetrafluoroborate (11 ml of a 1 M solution in CH_2Cl_2, 11 mmol) was added to a suspension of 2-methyloxazole-4-carboxamide[28] (1.26 g, 10 mmol) in dry dichloromethane (25 ml) and the resulting solution was stirred under nitrogen atmosphere for 6 h. L-Serine ethyl ester hydrochloride (1.70 g, 10 mmol) and triethylamine (2.80 ml, 22 mmol) were introduced and the mixture was then stirred overnight at ambient temperature. The mixture was evaporated to dryness *in vacuo* to leave an off-white solid which was preadsorbed onto silica and purified by flash chromatography using 2% methanol in chloroform as eluent to give the product (210 mg, 10%) as a pale yellow oil (starting material (720 mg, 43%) was also recovered); ν_{max}(film)/cm^{-1} 1735, 1670 and 1585; δ_H(400 MHz, $CDCl_3$) 8.08 (1H, s, 5′-H), 4.90 (1H, dd, *J* 11 and 8 Hz, 4-H), 4.66 (1H, dd, *J* 9 and 11 Hz, 5-H), 4.58 (1H, dd, *J* 11 and 9 Hz, 5-H), 4.25 (2H, m, C$H_2$$CH_3$), 2.51 (3H, s, 2′-Me) and 1.31 (3H, t, *J* 7 Hz, CH_2CH_3); δ_C(67.8 MHz, $CDCl_3$) 170.7 (s), 162.4 (s), 159.9 (s), 141.1 (d), 129.9 (s), 69.6 (t), 68.5 (d), 61.7 (t), 14.0 (q) and 13.6 (q) (Found: *m*/*z* 224.0788. $C_{10}H_{12}N_2O_4$ requires *M*, 224.0795).

2′-Methyl-2,4′-bi(1,3-oxazolyl)-4-carboxylic acid methyl ester 18a

(a) Nickel peroxide (5 × 790 mg, Aldrich) was added portionwise over 2.5 h to a stirred refluxing solution of the oxazole-oxazoline **17a** (3.9 g, 18.8 mmol) in dry benzene (25 ml) under a nitrogen atmosphere. The reflux was maintained for a further 2 h and the hot mixture was filtered through a Celite pad which was then washed with hot ethyl acetate (3 × 50 ml). The combined extracts were evaporated *in vacuo* and the residue was then purified by chromatography on silica using ethyl acetate as eluent to give the *bi-oxazole* (0.76 g, 27%) as a white solid, along with some recovered oxazole-oxazoline and the olefin **19** in varying amounts.

(b) Distilled 1,4-dioxane (12.8 ml) was added to a stirred mixture of caesium carbonate (10.4 g, 31.9 mmol), copper(II) bromide (100 mg) and the vinyl bromide **20** (4.6 g, 15.9 mmol) under a nitrogen atmosphere. The slurry was heated to 40 °C for 22 h, next cooled to ambient temperature and ethyl acetate (100 ml) was then added. The mixture was washed with saturated brine (2 × 50 ml). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to leave a residue which was then purified by chromatography on silica using ethyl acetate as eluent to give the *bi-oxazole* (1.35 g, 40%) as a white solid.

(c) *N*-Bromosuccinimide (7.3 g, 41 mmol) was added to a stirred solution of the oxazole-oxazoline **17a** (8.6 g, 41 mmol) in dry benzene (860 ml) under a nitrogen atmosphere at room temperature. The solution was irradiated (sun lamp, 300 W) for 18 h at 25 °C and then evaporated *in vacuo* to leave a brown residue. Purification by chromatography on silica using two columns, the first with ethyl acetate as eluent and the second using 1% methanol–chloroform gave the *bi-oxazole* (4.78 g, 56%) as colourless crystals, mp 130–131 °C (ethyl acetate) (Found: C, 51.6; H, 3.8; N, 13.2. $C_9H_8N_2O_4$ requires C, 51.9; H, 3.9; N, 13.5%); λ_{max}(EtOH)/nm 208 (9990) and 246 (11030);

$\nu_{max}(CHCl_3)/cm^{-1}$ 1744, 1725, 1688, 1641 and 1588; δ_H(270 MHz, $CDCl_3$) 8.28 (1H, s, 5-H), 8.26 (1H, s, 5′-H), 3.94 (3H, s, CO_2Me) and 2.55 (3H, s, 2′-Me); δ_C(67.8 MHz, $CDCl_3$) 162.6 (s, *C*O_2Me), 161.1 (s, 2-C), 155.6 (s, 2′-C), 143.4 (d, 5-C), 139.0 (d, 5′-C), 133.9 (s, 4-C), 129.4 (s, 4′-C), 52.0 (q, CO_2Me) and 13.5 (q, 2′-Me); *m*/*z* (EI) 208 (M^+, 100%), 177 (4), 149 (8) and 110 (75) (Found: *m*/*z* 208.0458. $C_9H_8N_2O_4$ requires *M*, 208.0452).

(d) Pyridine (0.18 ml, 2.2 mmol) and 30% aqueous hydrogen peroxide (0.5 ml, 4.4 mmol) were added sequentially to a stirred solution of the selenide **17b** (404 mg, 1.1 mmol) in dichloromethane (5 ml). The mixture was stirred vigorously for 1 h and then 1 M HCl (5 ml) and chloroform (10 ml) were added sequentially, and the mixture was partitioned. The organic extract was dried and evaporated *in vacuo* to leave an off-white solid which was purified by chromatography on silica using chloroform–methanol (100 : 1) as eluent to give the *bi-oxazole* (216 mg, 94%) as a white solid, mp 130–132 °C (ethyl acetate) which showed identical spectroscopic data to those recorded previously.

2′-Methyl-2,4′-bi(1,3-oxazolyl-4-carboxylic acid ethyl ester 18b

Freshly prepared nickel peroxide (5 × 1g) was added portionwise every 0.5 h to a stirred solution of crude oxazoline **17c** (1.44 g, 6.42 mmol) in dry benzene (25 ml) heated under reflux. The mixture was heated under reflux for a further 2.5 h then cooled and filtered through a Celite pad. The Celite pad was washed with ethyl acetate (3 × 20 ml) and the solvents were then removed *in vacuo* to leave the crude product as an off-white solid. Purification by flash chromatography on silica using 2% methanol in chloroform as eluent afforded unreacted starting material (150 mg, 11%), (eluted second) and the bi-oxazole (0.67 g, 47%) as a white solid, mp 129–130 °C (ethyl acetate–petrol) (Found: C, 54.1; H, 4.5; N, 12.7. $C_{10}H_{10}N_2O_4$ requires C, 54.05; H, 4.5; N, 12.6%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3000, 1730, 1640 and 1580; δ_H(400 MHz, $CDCl_3$) 8.28 (1H, s, 5-H), 8.27 (1H, s, 5′-H), 4.42 (2H, q, *J* 7 Hz, CH_2CH_3), 2.56 (3H, s, 2′-Me) and 1.40 (3H, t, *J* 7 Hz, CH_2CH_3); δ_C(67.8 MHz, $CDCl_3$) 162.8 (s), 161.0 (s), 155.7 (s), 143.5 (d), 139.3 (d), 134.7 (s), 129.8 (s), 61.3 (t), 14.4 (q) and 13.7 (q) (Found: *m*/*z* 222.0651. $C_{10}H_{10}N_2O_4$ requires *M*, 222.0641).

2′-Methyl-2,4′-bi(1,3-oxazolyl)-4-carboxylic acid 21a

A solution of potassium hydroxide (3.4 g, 60 mmol) in water (50 ml) was added to the bi-oxazole **18a** (10.4 g, 50 mmol), and the mixture was heated under reflux for 1 h. The mixture was cooled to ambient temperature, evaporated *in vacuo*, then acidified with concentrated hydrochloric acid (pH 1) and cooled in ice for 30 min. The precipitate was filtered, then washed with water (20 ml) and freeze dried to leave the bi-oxazole acid (6.25 g, 64%) as a cream solid, mp > 210 °C (decomp.) (Found: C, 49.3; H, 3.0; N, 14.4. $C_8H_6N_2O_4$ requires C, 49.2; H, 2.9; N, 14.4%); λ_{max}(EtOH)/nm 208 (6430), 247 (7700) and 254 (7750); ν_{max}(KBr disc)/cm^{-1} 3143, 1681, 1644 and 1122; δ_H(270 MHz, d_6-DMSO) 8.75 (1H, s, 5-H), 8.72 (1H, s, 5′-H) and 2.44 (3H, s, 2′-Me); δ_C(67.8 MHz, d_6-DMSO) 162.6 (s, *C*O_2H), 161.8 (s, 2-C), 155.1 (s, 2′-C), 144.9 (d, 5-C), 140.4 (d, 5′-C), 134.2 (s, 4-C), 129.0 (s, 4′-C) and 13.4 (q, 2′-Me); *m*/*z* (EI) 194 (M^+, 13%), 150 (12), 110 (100) and 82 (10) (Found: *m*/*z* 194.0299. $C_8H_6N_2O_4$ requires *M*, 194.0328).

3-Hydroxy-2-[(2′-methyl-2,4′-bi(1,3-oxazolyl)-4-ylcarbonylamino)propionic acid methyl ester 22a

Thionyl chloride (50 ml) was added to the bi-oxazole acid **21a** (6.25 g, 32 mmol), and the stirred suspension was then heated under reflux for 6 h. The excess thionyl chloride was evaporated *in vacuo* and the residue was next azeotroped with toluene to leave the corresponding acid chloride **21b** as a cream solid which was used immediately without further purification. A solution of the acid chloride in dry dichloromethane (90 ml) was added dropwise over 20 min to a stirred solution of DL-serine methyl ester hydrochloride (5.5 g, 35 mmol) and triethylamine (10 ml, 71 mmol) in dry dichloromethane (62 ml) under a nitrogen atmosphere at 0 °C. The brown solution was stirred at ambient temperature for 14 h, evaporated *in vacuo,* and then diluted with saturated sodium bicarbonate solution (200 ml). The aqueous mixture was extracted with ethyl acetate (4 × 200 ml) and the combined organic extracts were washed with saturated brine (100 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *amide* (8.4 g, 88%) which crystallised as a cream solid, mp 141–142 °C (ethyl acetate) (Found: C, 48.5; H, 4.5; N, 14.2. $C_{12}H_{13}N_3O_6$ requires C, 48.8; H, 4.4; N, 14.2%); λ_{max}(EtOH)/nm 222 (13640), 235 (13380) and 254 (13970); $\nu_{max}(CHCl_3)/cm^{-1}$ 3402 br, 1746, 1676, 1596, 1508 and 1115; δ_H(250 MHz, $CDCl_3$) 8.23 (1H, s, 5′-H), 8.14 (1H, s, 5"-H), 7.80 (1H, br d, *J* 7.9 Hz, N*H*), 4.87 (1H, ddd, *J* 7.9, 3.8 and 3.8 Hz, 4-H), 4.20–3.95 (2H, m, 5-H), 3.81 (3H, s, CO_2Me), 2.80 (1H, br m, O*H*) and 2.57 (3H, s, 2"-Me); δ_C(67.8 MHz, $CDCl_3$) 170.4 (s, 2-C), 163.1 (s, *C*O_2Me), 160.3 (s, 2′-C), 154.9 (s, 2″-C), 141.2 (d, 5′-C), 139.0 (d, 5″-C), 136.5 (s, 4′-C), 129.4 (s, 4″-C), 62.7 (t, 5-C), 54.4 (d, 4-C), 52.5 (q, CO_2Me) and 13.7 (q, 2″-Me); *m*/*z* (EI) 295 (M^+, 7%), 277 (4), 265 (71), 264 (25), 236 (87), 177 (100), 149 (24) and 110 (32) (Found: *m*/*z* 236.0641. $C_{10}H_{10}N_3O_4$ requires *M*, 236.0639).

3-Chloro-2-[2′-methyl-2,4′-bi(1,3-oxazolyl)-4-ylcarbonylamino]propionic acid methyl ester 22b

Thionyl chloride (45 ml) was added cautiously to the bi-oxazole serine derivative **22a** (8.4 g, 28 mmol) under a nitrogen atmosphere at 0 °C. The solution was stirred for 12 h at ambient temperature and the excess thionyl chloride was then evaporated *in vacuo*. The residue was quenched with water (200 ml) and the aqueous layer was then extracted with ethyl acetate (4 × 200 ml). The combined organic phases were washed with saturated brine (100 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *bi-oxazole serine chloride* (8.7 g, 97%) which crystallised as a cream solid, mp 137–138 °C (diethyl ether) (Found: C, 46.0; H, 4.0; N, 13.1; Cl, 11.0. $C_{12}H_{12}ClN_3O_5$ requires C, 46.0; H, 3.9; N, 13.4; Cl, 11.3%); λ_{max}(EtOH)/nm 218 (10440) and 255 (10270); $\nu_{max}(CHCl_3)/cm^{-1}$ 3401, 1748, 1681, 1650 and 1588; δ_H(270 MHz, $CDCl_3$) 8.24 (1H, s, 5′-H), 8.16 (1H, s, 5″-H), 7.75 (1H, br d, *J* 7.9 Hz, N*H*), 5.16 (1H, ddd, *J* 7.9, 4.0 and 3.6 Hz, 4-H), 4.04 (1H, dd, *J* 11.2 and 3.6 Hz, 5-H), 3.93 (1H, dd, *J* 11.2 and 4.0 Hz, 5-H), 3.82 (3H, s, CO_2Me) and 2.56 (3H, s, 2″-Me); δ_C(67.8 MHz, $CDCl_3$) 168.5 (s, 2-C), 162.9 (s, *C*O_2Me), 159.8 (s, 2′-C), 154.9 (s, 2″-C), 141.2 (d, 5′-C), 139.0 (d, 5″-C), 136.1 (S, 4′-C), 129.4 (s, 4″-C), 52.7 (d, 4-C), 52.7 (q, CO_2Me), 44.4 (t, 5-C) and 13.5 (q, 2″-Me); *m*/*z* (EI) 315 (M^+, 1.5%), 3.3 (4), 278 (15), 256 (41), 254 (88), 177 (100), 149 (21) and 110 (28) (Found: *m*/*z* 313.4532. $C_{12}H_{12}ClN_3O_5$ requires *M*, 313.4528).

2-[2′-Methyl-2,4′bi(1,3-oxazolyl)-4-ylcarbonylaminoacrylic acid methyl ester 24

1,8-Diazabicyclo[5.4.0]undec-7-ene (900 μl, 6 mmol) was added dropwise to a stirred solution of the chloride **22b** (1.87 g, 6 mmol), in dry dichloromethane (20 ml), at room temperature under a nitrogen atmosphere. The mixture was stirred for 3 h and then washed with 2 M hydrochloric acid (2 × 10 ml) and the layers were separated. The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave the *olefin* (1.52 g, 92%) as an off-white solid. A small portion was recrystallised from diethyl ether–hexane (1 : 1) and had mp 148–149 °C (Found: C, 52.0; H, 4.06; N, 15.5. $C_{12}H_{13}N_3O_6$ requires C, 52.0; H, 4.0; N, 15.2%); $\nu_{max}(CHCl_3)$ cm^{-1} 3383, 1715, 1694, 1582, 1515 and 1203; δ_H(270 MHz, $CDCl_3$) 9.12 (1H, br s, N*H*), 8.20 (1H, s, 5-H), 8.12 (1H, s, 5′-H), 6.66 (1H, s, *E*=C*H*), 5.94 (1H, d, *J* 1 Hz, *Z*=C*H*), 3.82 (3H, s, CO_2*Me*) and 2.49 (3H, s,

2-*Me*); δ_C(67.8 MHz, $CDCl_3$) 164.2 (s, CO), 163.2 (s, CO), 158.9 (s, 2-C), 154.7 (s, 2′-C), 141.6 (d, 5-C), 139.3 (d, 5′-C), 137.3 (s, 4-C), 130.9 (s, 4′-C), 129.9 (s, *C*CO_2Me), 110.1 (t, C*C*H_2), 53.1 (q, CO_2*Me*) and 13.9 (q, 2-*Me*); *m*/*z* (EI) 277 (M^+, 51%) and 177 (100).

3-Bromo-2-[2′-methyl-2,4′-bi(1,3-oxazolyl)-4-ylcarbonylamino-acrylic acid methyl ester 25

A solution of the alkene **24** (1.52 g, 5.5 mmol) in dry dichloromethane (50 ml) was cooled to −78 °C under a nitrogen atmosphere and then a solution of bromine (282 µl, 5.5 mmol) in dry dichloromethane (3.0 ml) was slowly added dropwise. Triethylamine (840 µl, 5.5 mmol) was added and the resulting mixture was then allowed to warm to room temperature over 2 h. The mixture was washed with brine (15 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The semi-solid residue was purified by flash chromatography on silica gel using ether–petrol (1:1) as eluent to give the *vinyl bromide* (1.73 g, 88%) as a white crystalline solid, mp 140 °C (Found: C, 40.4; H, 2.8; N, 11.55; Br, 22.3. $C_{12}H_{10}BrN_3O_5$ requires C, 40.45; H, 2.8; N, 11.8; Br, 22.5%); ν_{max}($CHCl_3$)/cm^{-1} 3367, 1730, 1691, 1587, 1470 and 1113; λ_{max}(EtOH)/nm 221.5 (1602), 235.2 (1562) and 256.1 (1667); δ_H(250 MHz, $CDCl_3$) 8.30 (1H, br s, N*H*), 8.22 (1H, s, 5-H), 8.09 (1H, s, 5-H), 7.20 (1H, d, *J* 1 Hz, C*H*Br), 3.70 (3H, s, 2-*Me*) and 2.44 (3H, s, C2-*Me*); δ_C(67.8 MHz, $CDCl_3$) 163.2 (s, CO), 162.2 (s, CO), 157.8 (s, 2-C), 155.5 (s, 2′-C), 141.9 (d, 5-C), 139.2 (d, 5′-C), 136.1 (s, 4-C), 131.2 (s, 4′-C), 129.5 (s, *C*CO_2Me), 115.1 (d, *C*HBr), 52.9 (q, CO_2*Me*) and 13.8 (q, 2-*Me*); *m*/*z* (EI) 358 and 356 (M^+, 0.6%), 326 and 324 (M^+ − OMe, 3) and 276 (M^+ − Br, 100).

2′′-Methyl-4,5-dihydro-2,4′:2′,4″-ter(1,3-oxazole)-4-carboxylic acid methyl ester 23a

Silver trifluoromethanesulfonate (12.5 g, 49 mmol) was added in one portion to a stirred solution of the bi-oxazole serine chloride **22b** (10.0 g, 41 mmol) in dry benzene (100 ml) under a nitrogen atmosphere, and the slurry was then heated under reflux for 6 h. The mixture was cooled to ambient temperature, evaporated *in vacuo,* and then the grey residue was slurried in ethyl acetate (300 ml) and saturated sodium bicarbonate (200 ml) with vigorous stirring for 30 min. The separated aqueous layer was extracted with ethyl acetate (3 × 100 ml) and the combined organic phases were washed with sodium hydrogen carbonate (3 × 100 ml). The second aqueous extract was washed with further ethyl acetate (3 × 100 ml) and the total combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to leave the *bi-oxazole-oxazoline* (5.3 g, 62%) which crystallised as a pale yellow solid, mp 181–182 °C (ethyl acetate); λ_{max}(EtOH)/nm 240 (13520) and 255 (13940); ν_{max}($CHCl_3$)/cm^{-1} 1742, 1682, 1639, 1586 and 1113; δ_H(250 MHz, $CDCl_3$) 8.26 (1H, s, 5′-H), 8.22 (1H, s, 5″-H), 4.95 (1H, dd, *J* 10.6 and 7.9 Hz, 4-H), 4.71 (1H, dd, *J* 8.7 and 7.9 Hz, 5-H), 4.60 (1H, dd, *J* 10.6 and 8.7 Hz, 5-H), 3.80 (3H, s, CO_2Me) and 2.54 (3H, s, 2″-Me); δ_C(67.8 MHz, $CDCl_3$) 170.9 (s, 2-C), 162.6 (s, *C*O_2Me), 159.6 (s, 2′-C), 155.8 (s, 2″-C), 141.0 (d, 5′-C), 139.2 (d, 5″-C), 130.9 (s, 4′-C), 129.5 (s, 4″-C), 69.7 (t, 5-C), 68.3 (d, 4-C), 52.5 (q, CO_2Me) and 13.6 (q, 2″-Me); *m*/*z* (EI) 277 (M^+, 14%), 218 (100), 208 (24), 190 (78), 177 (37), 149 (11) and 110 (35) (Found: *m*/*z* 277.0653. $C_{12}H_{11}N_3O_5$ requires *M*, 277.0699).

2″-Methyl-4-phenylselenyl-4,5-dihydro-2,4′:2′,4″-teroxazole-4-carboxylic acid methyl ester 23b

A 1.5 M solution of potassium hexamethyldisilazide in toluene (0.54 ml, 0.8 mmol) was added dropwise to a stirred solution of the oxazoline ester **23a** (215 mg, 0.8 mmol) in dry THF (5 ml) at −78 °C under an atmosphere of nitrogen. The resulting orange solution was immediately quenched with a solution of phenylselenyl bromide (275 mg, 1.2 mmol) in dry THF (3 ml), and then allowed to warm to room temperature. The solvent was then evaporated *in vacuo* to leave the *selenide* as a brown oil (145 mg, 43%) which was used directly without purification.

2″-Methyl-2,4′:2′,4″-ter(1,3-oxazole)-4-carboxylic acid methyl ester 26a

(a) Solid *N*-bromosuccinimide (3.6 g, 20 mmol) was added to a stirred solution of the bi-oxazole-oxazoline **23a** (5.7 g, 20 mmol) in dry benzene (565 ml) under a nitrogen atmosphere at room temperature. The solution was irradiated for 23 h (sun lamp, 300 W) at 25 °C before the solvent was evaporated *in vacuo* to leave a brown residue. Purification by chromatography on silica using 1% methanol–chloroform as eluent gave the *ter-oxazole* (2.8 g, 50%) which crystallised as colourless needles, mp 217–218 °C (ethyl acetate–petrol) (Found: C, 51.9; H, 3.2; N, 15.2. $C_{12}H_9N_3O_5$ requires C, 52.3; H, 3.3; N, 15.3%); λ_{max}(EtOH)/nm 202 (10010), 249 (13130) and 255 (13600); ν_{max}($CHCl_3$)/cm^{-1} 1747 (CO), 1654, 1605, 1588 and 1115; δ_H(250 MHz, $CDCl_3$) 8.41 (1H, s, 5-H), 8.31 (1H, s, 5′-H), 8.25 (1H, s, 5″-H), 3.94 (3H, s, CO_2Me) and 2.56 (3H, s, 2″-Me); δ_C(67.8 MHz, $CDCl_3$) 163.0 (s, *C*O_2Me), 161.3 (s, 2-C), 156.3 (s, 2′-C), 155.5 (s, 2″-C), 143.8 (d, 5-C), 139.2 (s, 5′-C), 134.4 (s, 5″-C), 130.7 (s, 4-C), 129.6 (2 × s, 4′ and 4″-C), 52.3 (q, CO_2Me) and 13.8 (q, 2″-Me); *m*/*z* (EI) (Found: M^+, 275.0491. $C_{12}H_9N_3O_5$ requires *M*, 275.0542, 100%), 244 (10), 216 (2), 149 (11), 124 (3) and 110 (63). This same ter-oxazole was produced from the same oxazoline **23a** using nickel peroxide in 40% yield according to the procedure described for the preparation of the bi-oxazole **18**.

(b) Distilled 1,4-dioxane (800 µl) was added to a mixture of caesium carbonate (348 mg, 1.1 mmol), copper(II) bromide (2 mg, 0.006 mmol) and the vinyl bromide **25** (190 mg, 0.5 mmol), under an atmosphere of nitrogen and the mixture was then heated to 40 °C for 22 h. The mixture was cooled to room temperature, then diluted with ethyl acetate (10 ml) and washed with 1 M hydrochloric acid (2 × 5 ml). The separated aqueous washings were back extracted with ethyl acetate (3 × 10 ml), and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to leave the crude product as a pale orange solid. Purification by flash chromatography on silica gel using ethyl acetate as eluent afforded the *ter-oxazole* as a white solid (76 mg, 62%), mp 217–218 °C, which showed identical spectroscopic properties to those described earlier.

(c) Pyridine (0.04 ml, 0.5 mmol) and hydrogen peroxide (0.11 ml, 1.1 mmol) were added sequentially to a stirred solution of the selenide **23b** (106 mg, 0.2 mmol) in dichloromethane (5 ml). The mixture was stirred vigorously for 1 h and then 1 M HCl (5 ml) and chloroform (10 ml) were added sequentially and the mixture was partitioned. The organic extract was dried and evaporated *in vacuo* to leave an off-white solid which was purified by chromatography on silica using chloroform–methanol (100:1) as eluent to give the *ter-oxazole* (48 mg, 71%) as a white solid, mp 218–220 °C (ethyl acetate–petrol), which showed identical spectroscopic data to those recorded previously.

2′-Methyl-2,4′-bi(1,3-oxazolyl)-4-carboxylic acid amide 21c

Liquid ammonia (2 ml) was added to a cooled (−20 °C) solution of the bi-oxazole ester **18** (0.11 g, 0.5 mmol) in methanol and the reaction flask was then lightly stoppered, allowed to warm to room temperature over *ca.* 2 h, and then left to stand overnight. The solution was evaporated to dryness *in vacuo* to leave the *amide* (96 mg, 99%) which recrystallised from ethyl acetate–petrol as white needles, mp 224–230 °C (decomp.) (Found: C, 49.5; H, 3.6; N, 21.8. $H_7N_3O_3$ requires C, 49.7; H, 3.6; N, 21.8%); ν_{max}(Nujol)/cm^{-1} 3480, 3410, 3200, 1660, 1610, 1585, 1400 and 1100; δ_H(400 MHz, $CDCl_3$ + CD_3OD) 8.45 (2H, br s) and 2.6 (3H, s) (Found: *m*/*z* 193.0522. $C_8H_7N_3O_3$ requires *M*, 193.0557).

2″-Methyl-4,5-dihydro-2,4′ : 2′,4″-ter(1,3-oxazole)-4-carboxylic acid ethyl ester 23c

(a) Silver trifluoromethanesulfonate (1.19 g, 4.62 mmol) was added to a stirred solution of the ethyl ester corresponding to the chloride **22b** (0.69 g, 2.10 mmol) in dry benzene (25 ml), under a nitrogen atmosphere, and the resulting solution was then stirred and heated under reflux for 6 h. The solution was cooled to 25 °C and the solvent was then removed *in vacuo*. The residual grey sticky solid was dissolved in ethyl acetate (50 ml) and the solution was then washed with saturated aqueous sodium bicarbonate (3 × 25 ml) and saturated brine (3 × 25 ml). The aqueous washings were re-extracted separately with ethyl acetate (3 × 25 ml), and the combined organic extracts were then dried and evaporated *in vacuo* to leave the crude product (0.60 g, 98%) as a yellow solid. Chromatography on silica using ethyl acetate as eluent gave the *bi-oxazole-oxazoline* as a white solid, mp 157–158 °C (ethyl acetate); ν_{max}(KBr)/cm^{-1} 3105, 3070, 1725, 1670, 1640 and 1590; δ_H(400 MHz, $CDCl_3$) 8.21 (1H, s), 8.17 (1H, s), 4.88 (1H, dd, *J* 11 and 9 Hz), 4.64 (1H, t, *J* 9 Hz), 4.55 (1H, dd, *J* 11 and 9 Hz), 4.20 (2H, m), 2.49 (3H, s) and 1.26 (3H, t, *J* 7 Hz); δ_C(67.8 MHz, $CDCl_3$) 170.6 (s), 162.8 (s), 159.8 (s), 156.0 (s), 141.2 (d), 139.4 (d), 131.1 (s), 129.7 (s), 69.9 (t), 68.6 (d), 61.9 (t), 14.1 (q) and 13.8 (q) (Found: *m*/*z* 291.0833. $C_{13}H_{13}N_3O_5$ requires *M*, 291.0854).

(b) Triethyloxonium tetrafluoroborate (1.1 ml of a 1 M solution in DCM, 1.1 mmol) was added to a suspension of the bi-oxazole amide **21c** (0.1 g, 1 mmol) in dry dichloromethane (10 ml) and the resulting solution was stirred under an atmosphere of nitrogen for 6 h. L-Serine ethyl ester hydrochloride (0.19 g, 1.1 mmol) and triethylamine (0.31 ml, 2.2 mmol) were introduced and the mixture was then stirred overnight at ambient temperature. The mixture was evaporated to dryness *in vacuo* to leave an off-white solid which was preadsorbed onto silica and purified by flash chromatography using 2% methanol in chloroform as eluent to give the product (35 mg, 12%) as a pale yellow oil. Starting material (74 mg, 39%) was also recovered. The product showed identical spectroscopic properties to those described above.

2″-Methyl-2,4′ : 2′,4″-ter(1,3-oxazole)-4-carboxylic acid ethyl ester 26b

Freshly prepared nickel peroxide (5 × 3.55 g) was added portionwise every 0.5 h to a stirred solution of the bi-oxazole-oxazoline **23c** (2.70 g, 9.28 mmol) in dry benzene (100 ml) heated under reflux. The mixture was heated under reflux for a further 2.5 h then cooled and filtered through a Celite pad. The Celite pad was washed with ethyl acetate (3 × 30 ml) and the solvents were then removed *in vacuo* to leave the crude product as an off-white solid. Purification by flash chromatography on silica using 2% methanol in chloroform as eluent gave unreacted starting material (41 mg, 15%) (eluted second) and the *ter-oxazole* (1.02 g, 38%) as a white solid, mp 222–224 °C (ethyl acetate–petrol); λ_{max}(EtOH)/nm 244; ν_{max}($CHCl_3$)/cm^{-1} 3170, 2920, 1725, 1645 and 1575; δ_H(400 MHz, $CDCl_3$) 8.41 (1H, s), 8.31 (1H, s), 8.27 (1H, s), 4.43 (2H, q, *J* 7 Hz), 2.57 (1H, s) and 1.41 (3H, t, *J* 7 Hz); δ_C(67.8 MHz, $CDCl_3$) 162.6 (s), 160.6 (s), 156.0 (s), 155.1 (s), 143.4 (d), 138.9 (2 × d), 134.3 (s), 130.5 (s), 129.3 (s), 61.1 (t), 13.8 (q) and 13.5 (q) (Found: *m*/*z* 289.0685. $C_{13}H_{11}N_3O_5$ requires *M*, 289.0697).

2″-Bromomethyl-2,4′ : 2′,4″-ter(1,3-oxazole)-4-carboxylic acid methyl ester 27

A stirred solution of the ter-oxazole **26a** (0.89 g, 3.2 mmol), *N*-bromosuccinimide (633 mg, 3.6 mmol) and AIBN (45 mg) in distilled carbon tetrachloride (178 ml) was irradiated (sun lamp, 300 W) under reflux for 23 h in a nitrogen atmosphere. The mixture was cooled to ambient temperature, then evaporated *in vacuo*, and the residue was purified by chromatography on silica eluting with 7 : 1 dichloromethane–diethyl ether and then with 1% methanol–chloroform to give the *methyl bromide* (202 mg, 46% based on recovered starting material) as a white solid (methanol), mp > 230 °C (decomp.) (Found: C, 40.9; H, 2.3; N, 11.9. $C_{12}H_8BrN_3O_5$ requires C, 40.7; H, 2.3; N, 11.9%); λ_{max}-(EtOH)/nm 245 (17345) and 255 (19310); ν_{max}($CHCl_3$)/cm^{-1} 1729, 1654, 1577, 1114 and 1100; δ_H(400 MHz, $CDCl_3$) 8.43 (1H, s, 5-H), 8.37 (1H, s, 5′-H), 8.32 (1H, s, 5″-H), 4.52 (2H, s, CH_2Br) and 3.95 (3H, s, CO_2Me); δ_C(67.8 MHz, d_6-DMSO) 161.1 (s, *C*O_2Me), 161.0, 155.4 and 155.0 (3 × s, 2, 2′ and 2″-C), 145.9, 142.3 and 141.3 (3 × d, 5, 5′ and 5″-C), 133.5, 130.2 and 129.8 (3 × s, 4, 4′ and 4″-C), 52.2 (q, CO_2Me) and 21.1 (t, *C*H_2Br); *m*/*z* (EI) (Found: *m*/*z* 354.9656, (16%). $C_{12}H_8BrN_3O_5$ requires *M*, 354.9627, 353 (17), 274 (100) and 242 (5).

4″-Methoxycarbonyl-4,2′ : 4′,2″-ter(1,3-oxazolyl)-2-ylmethyltriphenylphosphonium bromide 5

A stirred solution of the oxazole bromide **27** (159 mg, 0.45 mmol) and triphenylphosphine (236 mg, 0.90 mmol) in distilled benzene (20 ml) was heated under reflux for 17 h in a nitrogen atmosphere. The mixture was cooled to ambient temperature and the precipitate was then filtered off and washed with dry diethyl ether (50 ml). The residue was dried *in vacuo* to give the *phosphonium salt* (210 mg, 76%) as a hygroscopic, cream powder; δ_H(400 MHz, $CDCl_3$) 8.35 (1H, s, 5-H), 8.30 (1H, s, 5′-H), 8.21 (1H, s, 5″-H), 7.94 (6H, m, Ar), 7.80 (3H, m, Ar), 7.68 (6H, m, Ar), 6.20 (2H, d, *J* 14.9 Hz, CH_2P) and 3.94 (3H, s, CO_2Me); δ_C(67.8 MHz, $CDCl_3$) 162.2 (s, *C*O_2Me), 155.3 and 155.2 (3 × s, 2, 2′ and 2″-C), 143.9, 142.1 and 139.4 (3 × d, 5, 5′ and 5″-C), 135.4 (d, Ar), 134.4 and 130.8 (3 × s, 4, 4′ and 4″-C), 134.2 (d, Ar), 134.1 (d, Ar), 130.5 (d, Ar), 130.3 (d, Ar), 117.7 (s, Ar), 116.9 (s, Ar), 52.3 (q, CO_2Me) and 26.6 (CH_2, d, $J_{P\text{-}C}$ 54 Hz, *C*H_2P) which was used directly without further purification.

4-(2-Hydroxy-1-methoxycarbonylethylcarbamoyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylic acid *tert*-butyl ester 32

Triethylamine (1.81 ml, 13.0 mmol) was added dropwise, over 2 min, to a stirred solution of serine methyl ester hydrochloride (0.58 g, 3.7 mmol) in dry dichloromethane (15 ml) at 0 °C under a nitrogen atmosphere. A solution of Garner′s acid **31**[21] (0.91 g, 3.7 mmol) in dry dichloromethane (5 ml) was added in one portion followed by HOBt (0.54 g, 4.0 mmol) and the resulting suspension was then stirred at room temperature for 15 min. A solution of DCC (0.83 g, 4.0 mmol) in dry dichloromethane (5 ml) was added to the suspension over 10 min and the mixture was then stirred at room temperature for 17 h. The mixture was evaporated *in vacuo* to leave a solid which was taken up in ethyl acetate (20 ml), washed with saturated aqueous sodium bicarbonate solution (3 × 15 ml), 10% aqueous citric acid solution (3 × 15 ml) and brine (2 × 10 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to leave a residue which was purified by chromatography on silica using a 3 : 1 ethyl acetate–petrol as eluent to give the *amide* (0.9 g, 74%) as a straw coloured oil; ν_{max}($CHCl_3$)/cm^{-1} 3423, 2980, 1743, 1681, 1456, 1368, 1094 and 1053; δ_H (360 MHz, d_6-DMSO at 80 °C) 7.81 (1H, dd, *J* 24.4 and 7.6 Hz, NH), 4.87 (1H, br s, OH), 4.46–4.39 (2H, m, 2-H and 2′-H), 4.15–4.08 (1H, m, 1′-H), 3.93–3.87 (1H, m, 1-H), 3.81–3.72 (1H, m, 1-H), 3.68–3.63 (1H, br m, 1-H), 3.68 (3H, s, OCH_3), 1.58 (3H, s, CH_3), 1.48 (3H, s, CH_3) and 1.41 (9H, s, ^{t}Bu); δ_C(100 MHz, $CDCl_3$) 177.0 (175.4), 153.0 (151.3), 95.3 (94.8), 81.8 (80.8), 66.2 (65.7), 60.5 (59.2), 28.3 26.2, 25.0, 24.9 and 24.4; *m*/*z* (FAB) (Found: M^+ + 1, 347.1813 (35%). $C_{15}H_{27}O_7N_2$ requires *M*, 347.1818).

2′,2′-Dimethyl-2′,3′,4′,5′-tetrahydro-2,4′-bi(1,3-oxazolyl)-4,3′-dicarboxylic acid 3′-*tert*-butyl ester 4-methyl ester 34a

A solution of Burgess′ reagent (0.77 g, 3.2 mmol)[22] in dry THF (10 ml) was added to a solution of the amide **32** (0.96 g, 2.8 mmol) in dry THF (20 ml) and the mixture was heated under

reflux for 2 h in a nitrogen atmosphere. The mixture was evaporated to dryness *in vacuo* and the residue was purified by chromatography on silica using 1:1 petrol (bp 40–60 °C)–ethyl acetate as eluent to give the corresponding *oxazoline* **33** (6.1 g, 61%) as an oil; δ_H(360 MHz, $CDCl_3$ at 50 °C, single diastereomer) 4.83–4.79 (1H, m, 2′-H), 4.61–4.56 (2H, m, 1′-H and 2-H), 4.43 (1H, dd, *J* 10.4 and 8.8 Hz, 1′-H), 4.16 (1H, dd, *J* 9.1 and 6.9 Hz, 1-H), 4.04 (1H, dd, *J* 9.0 and 3.2 Hz, 1-H), 3.78 (3H, s, CO_2Me) and 1.67–1.44 (15H, m, 2 × Me and ᵗBu); δ_C(125 MHz, $CDCl_3$, single diastereomer) 171.4, 169.1, 151.3, 106.4, 95.2, 80.4, 70.2, 68.3, 66.7, 55.0, 52.8, 52.4, 28.4, 25.2 and 24.3; *m*/*z* (EI) (Found: $M^+ - CH_3$, 313.1395 (11%). $C_{14}H_{21}N_2O_6$ requires *M*, 313.1400).

DBU (0.53 ml, 3.5 mmol) was added dropwise, over 2 min, to a stirred solution of the oxazoline (1.04 g, 3.2 mmol) in dry dichloromethane (30 ml) at 0 °C under a nitrogen atmosphere. Bromotrichloromethane (0.34 ml, 3.5 mmol) was added dropwise over 10 min and the mixture allowed to warm to room temperature over 24 h.[23] The mixture was quenched with saturated ammonium chloride (2 × 20 ml), and the separated aqueous phase was then extracted with ethyl acetate (2 × 20 ml). The combined organic extracts were dried ($MgSO_4$), and then evaporated *in vacuo* to leave a residue which was purified by chromatography on silica using 1:1 petrol–ethyl acetate as eluent to give the *oxazole* (0.8 g, 75%) as a mixture of rotamers; ν_{max}($CHCl_3$)/cm^{-1} 2980, 1703, 1368, and 1110; δ_H(360 MHz, $CDCl_3$, major rotamer) 8.21 (1H, s), 5.20–5.07 (1H, m, 2-H), 4.29–4.09 (2H, m, 1-H), 3.93 (3H, s, CO_2Me), 1.75 (3H, s, CH_3), 1.60 (3H, s, CH_3) and 1.30 (9H, s, ᵗBu); δ_C(125 MHz, $CDCl_3$, major rotamer) 164.0 (s), 161.3 (s), 150.9 (s), 143.6 (d), 133.4 (s), 95.1 (s), 80.5 (s), 67.4 (t), 55.0 (d), 52.1 (q), 28.0 (q), 25.1 (q) and 23.9 (q); *m*/*z* (FAB) (Found: $M^+ + 1$, 327.1531 (11%). $C_{15}H_{23}N_2O_6$ requires *M*, 327.1556).

4-Hydroxymethyl-2′,2′-dimethyl-,2′,3′,4′,5′-tetrahydro-2,4′-bi(1,3-oxazolyl)-3′-carboxylic acid *tert*-butyl ester

A solution of DIBAL-H (1.5 M in toluene, 5.1 ml) was added dropwise, over 30 min, to a stirred solution of the oxazole ester **34a** (1.0 g, 3.06 mmol) in dry dichloromethane (10 ml) at 0 °C under a nitrogen atmosphere and the mixture was stirred at 0 °C for 4 h. The mixture was quenched with methanol (20 ml) followed by magnesium sulfate (20 g) and the filtered suspension was evaporated *in vacuo* to leave a viscous yellow residue. The residue was added to a saturated solution of potassium sodium tartrate and the mixture was stirred vigorously for 2 h. The mixture was extracted with ethyl acetate (2 × 200 ml), and the combined organic extracts were then dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica using 1:1 petrol–ethyl acetate as eluent to give the *oxazole alcohol* (0.55 g, 61%) as a yellow oil; δ_H(360 MHz, $CDCl_3$, major rotamer) 7.55 (1H, s), 5.13–4.98 (1H, m, 2-H), 4.58 (2H, br s, CH_2OH), 4.26–4.04 (3H, m, 1-H), 2.78 (1H, br s, OH), 1.73 (3H, s, CH_3), 1.59 (3H, s, CH_3) and 1.29 (9H, s, ᵗBu); δ_C(125 MHz, $CDCl_3$) 163.7 (s), 151.2 (s), 140.6 (s), 134.9 (d), 95.0 (s), 80.4 (s), 67.4 (t), 56.7 (t), 55.1 (d), 28.1 (q), 25.2 (q) and 24.2 (q); *m*/*z* (EI) (Found: M^+, 298.1535 (1.26%) $C_{14}H_{22}N_2O_5$ requires *M*, 298.1529).

4-Formyl-2′,2′-dimethyl-2′,3′,4′,5′-tetrahydro-2,4′-bi(1,3-oxazolyl)-3′-carboxylic acid *tert*-butyl ester 34b

A solution of pyridine–sulfur trioxide complex (0.87 g, 5.49 mmol) in DMSO (5 ml) was added dropwise, over 2 min, to a stirred solution of the alcohol (from above) (0.50 g, 1.7 mmol), DMSO (5 ml) and triethylamine (4.71 ml, 33.8 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 h and then quenched with a 10% solution of potassium hydrogen sulfate (10 ml). The separated aqueous layer was extracted with diethyl ether (3 × 25 ml) and the combined organic extracts were then dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by chromatography on silica using ethyl acetate as eluent to give the *oxazole aldehyde* (0.4 g, 79%) as a colourless oil. δ_H(360 MHz, $CDCl_3$, major rotamer) 9.95 (1H, s), 8.24 (1H, s), 5.20–5.07 (1H, m), 4.31–4.12 (2H, m), 1.76 (3H, s), 1.58 (3H, s) and 1.31 (9H, s), which was used without further characterisation.

8-(Diethoxyphosphoryl)-7-oxooctanoic acid ethyl ester 35

A solution of *n*-butyllithium (2.35 M in hexane, 14.4 ml) was added dropwise, over 10 min to a stirred solution of dimethyl methylphosphonate in dry THF (80 ml) under a nitrogen atmosphere at −78 °C. The mixture was stirred at −78 °C for 30 min and a solution of diethyl pimelate (5.0 g, 23.1 mmol) in dry THF (40 ml) was then added. The mixture was stirred at −78 °C for 2 h and then quenched with saturated ammonium chloride solution (100 ml). The separated aqueous layer was extracted with diethyl ether (2 × 50 ml) and the combined organic phases were washed with saturated brine (50 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using ethyl acetate as eluent to give the *β-ketophosphonate* (1.6 g, 24%) as a straw coloured oil; ν_{max}($CHCl_3$)/cm^{-1} 3477, 2953, 1730, 1259 and 1185; δ_H (360 MHz, $CDCl_3$) 4.08 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.77 (3H, s, $POCH_3$), 3.74 (3H, s, $POCH_3$), 3.05 (2H, d, $J_{P\text{-}H}$ 22.7 Hz, 8-H), 2.59 (2H, t, *J* 7.2 Hz, 6-H), 2.26 (2H, t, *J* 7.5 Hz, 2-H), 1.64–1.53 (4H, m, 4-H and 5-H), 1.34–1.25 (2H, m, 3-H) and 1.22 (3H, t, *J* 7.1 Hz, OCH_2CH_3); δ_C(90 MHz, $CDCl_3$) 201.3 (s), 201.2 (s), 173.1 (s), 59.7 (t), 52.6 (q), 52.5 (q), 43.4 (t), 40.8 (d), 33.6 (t), 27.9 (t), 24.2 (t), 22.5 (t) and 13.8 (q); *m*/*z* (EI) 294 (M^+, 2%), 249 ($M^+ - OEt$, 15%) and 231 ($M^+ - (OMe)_2$, 26%).

4-(8-Ethoxycarbonyl-3-oxooct-1-enyl)-2′,2′-dimethyl-2′,3′,4′,5′-tetrahydro-2,4′-bi(1,3-oxazolyl)-3′-carboxylic acid *tert*-butyl ester 36

Barium hydroxide octahydrate (0.4 g, 1.4 mmol) was added in one portion to a stirred solution of the *β*-ketophosphonate **35** (0.4 g, 1.4 mmol) in dry THF (8 ml) under a nitrogen atmosphere at room temperature. The suspension was stirred for 30 min and a solution of the aldehyde **34b** (0.4 g, 1.4 mmol) in 40:1 THF–H_2O (2 ml) was then added in one portion. The mixture was stirred at room temperature for 3 h then quenched with saturated sodium bicarbonate solution (20 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to leave a viscous oil. Purification by chromatography on silica using 2:1 petrol–ethyl acetate as eluent gave the *alkene* (0.5 g, 71%) as a yellow oil; ν_{max}($CHCl_3$)/cm^{-1} 2936, 1698, 1627, 1379, 1368 and 1097; δ_H(360 MHz, $CDCl_3$, major rotamer) 7.77 (1H, s, 14-H), 7.36 (1H, d, *J* 15.6 Hz, 9-H), 6.91 (1H, d, *J* 15.6 Hz, 8-H), 5.15–5.00 (1H, m, 15-H), 4.29–4.22 (1H, m, 19-H), 4.15–4.09 (1H, br m, 19-H), 4.12 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 2.64–2.60 (2H, m, 6-H), 2.30 (2H, t, *J* 7.4 Hz, 2-H), 1.76–1.54 (9H, m, 3-H, 4-H, 5-H and OCH_2CH_3) and 1.49–1.21 (15H, m, 2 × CH_3 and ᵗBu); δ_C(125 MHz, $CDCl_3$) 200.0 (s), 173.8 (s), 160.2 (s), 151.3 (s), 139.4 (s), 137.7 (s), 129.3 (s), 127.3 (s), 95.3 (s), 81.3 (s), 67.3 (t), 60.2 (t), 55.1 (d), 41.5 (t), 34.1 (t), 28.7 (t), 28.1 (q), 25.2 (q), 24.7 (t), 24.2 (q), 23.7 (t) and 14.2 (q).

4-(8-Ethoxycarbonyl-1-methyl-3-oxooctyl)-2′,2′-dimethyl-2′,3′,4′,5′-tetrahydro-2,4′-bi(1,3-oxazolyl)-3′-carboxylic acid *tert*-butyl ester 37

A solution of methyllithium (1.6 M in diethyl ether, 6.7 ml, 10.7 mmol) was added dropwise over 20 min to a stirred suspension of copper iodide (1.0 g, 5.4 mmol) in dry diethyl ether (20 ml) at −5 °C under an argon atmosphere and the resulting yellow solution was stirred at −5 °C for 30 min. A solution of the enone **36** (300 mg, 0.65 mmol) in dry diethyl ether (15 ml) was

added dropwise over 10 min to the cuprate solution at −5 °C and the mixture was stirred at −5 °C for 3 h. The mixture was quenched with a 1:1 mixture of saturated ammonium chloride–ammonium hydroxide solution (20 ml) and the separated aqueous layer was then extracted with diethyl ether (2 × 30 ml). The combined organic phases were washed with saturated brine (30 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 1:1 petrol–ethyl acetate as eluent to give the 3-*methyl ketone* (168 mg, 55%) as a viscous oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1696; δ_H(360 MHz, $CDCl_3$) 7.30 (1H, s, 14-H), 5.29–4.95 (1H, m, 15-H), 4.22–4.16 (1H, m, 19-H), 4.13–4.02 (1H, br m, 19-H), 4.11 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.30–3.24 (1H, m, 9-H), 2.83 (1H, dd, *J* 6.0 and 16.9 Hz, 8-H), 2.51 (1H, dd, *J* 8.1 and 17.2 Hz, 8-H), 2.36 (2H, t, *J* 7.3 Hz, 6-H), 2.27 (2H, t, *J* 7.4 Hz, 2-H), 1.72–1.41 (9H, m, 3-H, 4-H, 5-H and OCH_2CH_3) and 1.31–1.09 (18H, m, 2 × CH_3, ^{t}Bu and 9-CH_3); δ_C(90 MHz, $CDCl_3$) 209.2 (s), 173.6 (s), 162.8 (s), 151.2 (s), 133.1 (s), 94.9 (s), 80.1 (s), 67.5 (t), 60.2 (t), 55.2 (d), 48.3 (t), 42.9 (t), 34.1 (t), 28.6 (t), 28.1 (q), 26.8 (d), 25.1 (q), 24.6 (t), 24.5 (q), 23.1 (t), 19.4 (q) and 14.2 (q); *m/z* (FAB) (Found: $M^+ + 1$, 481.2944 (10%). $C_{25}H_{41}O_7N_2$ requires *M*, 481.2915).

4-(8-Carboxy-3-oxooct-1-enyl)-2′,2′-dimethyl-2′,3′,4′,5′-tetrahydro-2,4′-bi(1,3-oxazolyl)-3′-carboxylic acid *tert*-butyl ester 29

Lithium hydroxide (22 mg, 0.5 mmol) was added in one portion to a solution of the ester **37** (60 mg, 0.17 mmol) in a 3:1 mixture of THF–H_2O (4 ml), and the mixture was then stirred at ambient temperature for 2 h. Water (2 ml) was added, followed by ethyl acetate (10 ml) and the mixture was then acidified to pH 1 with 2 M HCl (0.5 ml added dropwise). The separated aqueous layer was extracted with ethyl acetate (3 × 10 ml), and the combined organic extracts were then washed with brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to leave the *carboxylic acid* (20 mg, 99%) as a viscous oil; δ_H(360 MHz, $CDCl_3$) 7.32 (1H, s, 14-H), 5.12–4.98 (1H, m, 15-H), 4.24–4.15 (1H, m, 19-H), 4.13–4.03 (1H, m, 19-H), 3.32–3.26 (1H, m, 9-H), 2.88–2.82 (1H, m, 8-H), 2.58–2.46 (1H, m, 8-H), 2.40–2.27 (4H, m, 2-H and 6-H) and 1.73–1.12 (18H, m, 2 × CH_3, ^{t}Bu and 9-CH_3).

4-Ethoxycarbonyl-1,3-oxazol-2-ylmethyltriphenylphosphonium bromide 38

Solid *N*-bromosuccinimide (6.9 g, 39 mmol) and AIBN (400 mg, 20% w/w) were added to a stirred solution of the oxazole ester **13a** (2.0 g, 13 mmol) in carbon tetrachloride (40 ml) and the suspension was then heated under reflux in a nitrogen atmosphere for 17 h. The mixture was cooled to room temperature, then evaporated to dryness *in vacuo* to leave a solid residue. Purification by chromatography on silica using 1:1 toluene–ethyl acetate as eluent gave the corresponding *bromomethyloxazole* (1.23 g, 41%) as a yellow oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1726, 1580, 1317, 1114 and 664; δ_H(360 MHz, $CDCl_3$) 8.25 (1H, s, 5-H), 4.49 (2H, s, CH_2Br), 4.39 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 1.40 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C(67.5 MHz, $CDCl_3$) 160.5 (CO), 159.9 (2-C), 144.7 (5-C), 134.1 (4-C), 61.3 (OCH_2CH_3), 19.3 (CH_2Br) and 14.0 (OCH_2CH_3); *m/z* (EI) 235, 233 (M^+, 6, 6%), 190, 188 (15, 15), 154 (91), 110 (4) and 82 (7). A solution of triphenylphosphine (2.4 g, 9.2 mmol) in dry diethyl ether (17 ml) was added to a solution of the bromomethyloxazole (1.1 g, 4.6 mmol) in dry diethyl ether (5 ml) under a nitrogen atmosphere and the solution was then stirred at room temperature for 24 h. The mixture was evaporated to dryness *in vacuo* to leave a yellow solid which was triturated in pentane (3 × 30 ml). The residue was evaporated to dryness *in vacuo* to leave the *phosphonium salt* (1.9 g, 82%) as a pale yellow solid, mp >300 °C (decomp.); δ_H(360 MHz, $CDCl_3$), 8.07 (1H, s, 5-H), 7.94–7.53 (15H, m, 3 Ar), 6.10 (2H, d, $J_{P\text{-}H}$ 14.9 Hz, CH_2P), 4.28 (2H, q, *J* 7.1 Hz, OCH_2CH_3) and 1.32 (3H, t, *J* 7.1 Hz, OCH_2CH_3), which was used without further characterisation.

2-[6-(*tert*-Butyldimethylsilyloxy)hex-1-enyl]-1,3-oxazole-4-carboxylic acid ethyl ester 40a

A solution of butyllithium (2.35 M) in hexane (1.68 ml, 2.69 mmol) was added dropwise over 10 min to a stirred suspension of the phosphonium salt **38** (1.67 g, 2.69 mmol) in dry THF (40 ml) at −30 °C under a nitrogen atmosphere. The deep red solution was stirred at room temperature for 30 min, and was then cooled to −78 °C. A solution of 5-*tert*-butyldimethylsilylpentanal **39** (0.87 g, 4.04 mmol) in dry THF (9 ml) was added dropwise over 5 min to the ylide solution at −78 °C and the mixture was allowed to warm to room temperature overnight. The mixture was quenched with saturated aqueous ammonium chloride solution (20 ml) and the separated aqueous layer was then extracted with diethyl ether (2 × 30 ml). The combined organic phases were washed with saturated brine (20 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 5:1 petrol–ethyl acetate as eluent to give the *olefin* (0.4 g, 41%) as a viscous oil (Found: C, 60.9; H, 9.3; N, 3.9. $C_{18}H_{31}O_4NSi$ requires C, 61.1; H, 8.9; N, 4.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1664, 1318 and 1114; δ_H(360 MHz, $CDCl_3$) 8.12 (1H, s, 5-H), 6.85 (1H, dt, *J* 16.0 and 7.0 Hz, 2′-H), 6.32 (1H, d, *J* 16.0 Hz, 1′-H), 4.39 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.65–3.61 (2H, m, 6′-H), 2.30–2.28 (2H, m, 3′-H), 1.58–1.54 (4H, m, 4′ and 5′-H), 1.39 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 0.90 (9H, s, ^{t}Bu) and 0.05 (6H, s, 2, CH_3); δ_C(67.5 MHz, $CDCl_3$) 161.6 (CO), 160.4 (2-C), 142.9 (5-C), 142.5 (2′-C), 133.3 (4-C), 115.8 (1′-C), 62.7 (6′-C), 61.2 (OCH_2CH_3), 32.5 (3′-C), 32.1 (5′-C), 25.9 (^{t}Bu), 24.7 (4′-C), 18.3 (q-C), 14.3 (OCH_2CH_3) and −5.3 (Si-Me); *m/z* (FAB) (Found: $M^+ + 1$, 354.2119 (77%) $C_{18}H_{32}O_4NSi$ requires *M*, 354.2101).

2-[6-(*tert*-Butyldimethylsilyloxy)hex-1-enyl]-1,3-oxazole-4-carboxylic acid 40b

Lithium hydroxide (22 mg, 0.51 mmol) was added in one portion to a solution of the ester **40a** (60 mg, 0.17 mmol) in a 3:1 mixture of THF–H_2O (4 ml), and the mixture was then stirred at room temperature for 2 h. Water (2 ml) was added, followed by ethyl acetate (10 ml) and the mixture was cooled to 0 °C and then acidified to pH 1 with 2 M HCl (0.5 ml added dropwise). The separated aqueous layer was extracted with ethyl acetate (3 × 10 ml) and the combined organic extracts were then washed with saturated brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to leave the *carboxylic acid* (20 mg, 99%) as a white solid, mp 210–212 °C (from ethanol); $\nu_{max}(CHCl_3)/cm^{-1}$ 3697, 2930, 1716, 1601 and 1110; δ_H(360 MHz, $CDCl_3$) 8.21 (1H, s, 5-H), 6.89 (1H, dt, *J* 16.0 and 7.0 Hz, 2′-H), 6.33 (1H, dt, *J* 16.0 and 1.4 Hz, 1′-H), 3.66–3.63 (2H, m, 6′-H), 2.32–2.30 (2H, m, 3′-H), 1.59–1.56 (4H, m, 4′ and 5′-H), 0.90 (9H, s, ^{t}Bu) and 0.06 (6H, s, 2 × CH_3); δ_C(67.5 MHz, $CDCl_3$) 165.3 (CO_2H), 162.5 (2-C), 144.3 (5-C), 143.6 (2′-C), 133.9 (4-C), 116.0 (1′-C), 63.2 (6′-C), 32.9 (3′-C), 32.6 (5′-C), 26.4 (^{t}Bu), 25.1 (4′-C), 18.8 (q-C) and −4.9 (Si-Me); *m/z* (ES) (Found: *m/z* ($M^+ + 1$), 326.2583. $C_{16}H_{28}O_4NSi$ requires ($M^+ + 1$) 326.1787).

2-[6-(*tert*-Butyldimethylsilyloxy)hex-1-enyl]-1,3-oxazole-4-carboxylic acid allyl ester 41

A solution of tricarpylmethylammonium chloride (77 mg, 0.2 mmol) and allyl bromide (23 mg, 0.2 mmol) in dichloromethane (0.3 ml) was added in one portion to a stirred suspension of the carboxylic acid **40b** (62 mg, 0.2 mmol) and sodium hydrogen carbonate (16 mg, 0.2 mmol) in water (0.3 ml) at room temperature. The mixture was stirred vigorously at room temperature for 24 h, and then extracted with dichloromethane (3 × 10 ml).

The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 5:1 petrol–ethyl acetate as eluent to give the *olefin* (35 mg, 51%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1731, 1664, 1578, 1462, 1369, 1317, 1092 and 989; δ_H(360 MHz, $CDCl_3$) 8.14 (1H, s, 5-H), 6.85 (1H, dt, *J* 16.0 and 7.0 Hz, HC=C*H*CH_2), 6.32 (1H, d, *J* 16.0 Hz, C*H*=$CHCH_2$), 6.01 (1H, ddt, *J* 17.1, 10.4 and 5.9 Hz, CH_2C*H*=CH_2), 5.39 (1H, dd, *J* 17.2 and 1.4 Hz, =C*H*H), 5.29 (1H, dd, *J* 10.4 and 1.1 Hz, =CH*H*), 4.82 (2H, d, *J* 5.9 Hz, CH_2=CH), 3.66–3.61 (2H, m, 6′-H), 2.31–2.28 (2H, m, 3′-H), 1.57–1.42 (4H, m, 4′ and 5′-H), 0.89 (9H, s, ′Bu) and 0.05 (6H, s, 2 × CH_3); δ_C(67.5 MHz, $CDCl_3$) 161.7 (CO), 161.0 (2-C), 143.0 (5-C), 142.6 (2′-C), 133.7 (4-C), 131.7, 119.0, 115.8 (1′-C), 65.7, 62.7 (6′-C), 32.5 (3′-C), 32.1 (5′-C), 25.9 (′Bu), 24.7 (4′-C), 18.3 and −5.4 (Si-Me); *m*/*z* (FAB) (Found: M^+ + 1, 366.2094 (66%). $C_{19}H_{32}O_4NSi$ requires *M*, 366.2101).

2-(6-Hydroxyhex-1-enyl)-1,3-oxazole-4-carboxylic acid allyl ester 28

A solution of the silyl ether **41** (115 mg, 0.3 mmol) in a 3:1:1 mixture of AcOH–THF–H_2O (3.0 ml) was stirred at room temperature for 2 h. The mixture was basified with saturated sodium hydrogen carbonate solution and the separated aqueous phase was then extracted with dichloromethane (3 × 10 ml). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 5:1 petrol–ethyl acetate as eluent to give the corresponding *alcohol* (70 mg, 91%) as a straw coloured oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2936, 1732, 1664, 1316, 1116, 990 and 663; δ_H(360 MHz, $CDCl_3$) 8.14 (1H, s 5-H), 6.85 (1H, dt, *J* 16.0 and 7.0 Hz, 2′-H), 6.32 (1H, d, *J* 16.0 Hz, 1′-H), 6.01 (1H, ddt, *J* 17.1, 10.4 and 5.9 Hz, CH_2C*H*=CH_2), 5.39 (1H, dd, *J* 17.2 and 1.4 Hz, =C*H*H), 5.29 (1H, dd, *J* 10.4 and 1.1 Hz, =CH*H*), 4.82 (2H, d, *J* 5.9 Hz, CH_2CH=CH_2), 3.66–3.61 (2H, m, 6′-H), 2.31–2.28 (2H, m, 3′-H) and 1.57–1.42 (4H, m, 4′ and 5′-H); δ_C(90 MHz, $CDCl_3$) 161.8 (CO), 161.0 (2-C), 143.1 (5-C), 142.2 (2′-C), 133.9 (4-C), 131.7, 119.1, 116.0 (1′-C), 65.8, 62.5 (6′-C), 32.5 (3′-C), 32.0 (5′-C) and 24.6 (4′-C).

4-{8-[6-(4-Allyloxycarbonyl-1,3-oxazol-2-yl)hex-5-enyloxycarbonyl]-1-methyl-3-oxooctyl}-2′,2′-dimethyl-2′,3′,4′,5′-tetrahydro-2,4′-bi(1,3-oxazolyl)-3′-carboxylic acid *tert*-butyl ester 42

1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (37 mg, 0.19 mmol) was added in one portion to a stirred solution of the acid **29** (77 mg, 0.18 mmol) and the alcohol **28** (50 mg, 0.20 mmol) in dichloromethane (6 ml) at 0 °C containing 4-(dimethylamino)pyridine (11 mg, 0.09 mmol). The mixture was stirred at 0 °C for 2 h and then at room temperature overnight before it was evaporated to dryness *in vacuo.* The residue was diluted with ethyl acetate (10 ml) and water (2 ml), and the organic layer was then separated, washed with saturated sodium bicarbonate (15 ml) and water (15 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 1:1 petrol–ethyl acetate as eluent to give the *ester* (89 mg, 73%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3156, 2253, 1793, 1730, 1720, 1368, 1096 and 889; δ_H(360 MHz, $CDCl_3$) 8.14 (1H, s, 9-H), 7.31 (1H, s, 30-H), 6.83 (1H, dt, *J* 16.0 and 7.0 Hz, 11-H), 6.33 (1H, d, *J* 16.0 Hz, 10-H), 6.01 (1H, ddt, *J* 17.1, 10.4 and 5.9 Hz, CH_2C*H*=CH_2), 5.37 (1H, dd, *J* 10.4 and 1.4 Hz, =C*H*H), 5.27 (1H, dd, *J* 10.4 and 1.1 Hz, =CH*H*), 5.08–4.96 (1H, m, 31-H), 4.82 (2H, dt, *J* 5.6 and 1.3 Hz, 3-H), 4.23–4.03 (4H, m, 32-H and 15-H), 3.31–3.26 (1H, m, 24-H), 2.83 (1H, dd, *J* 16.8 and 5.8 Hz, 23-H), 2.51 (1H, dd, *J* 16.9 and 7.8 Hz, 23-H), 2.40–2.27 (6H, m, 12-H, 17-H and 21-H), 1.73–1.55 (10H, m, 13-H, 14-H and 2 × CH_3), 1.48–1.08 (15H, m, 18-H, 19-H, 20-H and ′Bu) and 0.90–0.80 (3H, m, 25-H); δ_C(360 MHz, $CDCl_3$) 210.5 (s), 173.6 (s), 162.8 (s), 161.7 (s), 160.9 (s), 151.2 (s), 144.9 (s), 143.1, 141.8, 133.8 (s), 133.1, 131.7, 119.0 (t), 116.1, 94.9 (s), 80.1 (s), 67.4 (t), 65.7 (t), 63.8 (t), 55.1, 48.3 (t), 42.9 (t), 34.0 (t), 32.2 (t), 29.6 (t), 28.6 (t), 28.2, 28.1, 28.0 (t), 26.8, 25.0, 24.7 (t), 24.6, 24.2, 23.1 (t), 19.3 (q); *m*/*z* (FAB) (Found: M^+ + 1, 686.3677 (100%). $C_{36}H_{52}O_{10}N_3$ requires *M*, 686.3654).

Bis-oxazole amino acid ester 43

Pyrrolidine (33.1 μl, 0.4 mmol) was added in one portion to a stirred solution of the ester (**42**) (0.18 g, 0.3 mmol), tetrakis-(triphenylphosphine)palladium (18 mg, 0.016 mmol) and triphenylphosphine (4.1 mg, 0.016 mmol) in dichloromethane (2 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 4 h, diluted with dichloromethane (10 ml) and then washed with 1 M HCl (3 ml). The separated organic layer was then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 9:1 dichloromethane–methanol as eluent to give the acid (0.11 g, 70%) as an opaque oil. A 50% solution of trifluoroacetic acid in dichloromethane (1 ml) was added to the acid (20 mg, 0.03 mmol) and the resulting mixture was stirred at room temperature for 1 h. The mixture was then evaporated *in vacuo* to leave the TFA salt which was not purified further.

4-Hydroxymethyl-9-methyl-6,18,26-trioxa-3,28,29-triazatricyclo[23.2.1.1^{5,8}]nonacosa-1(27),5(29),7,23,25(28)-pentaene-2,11,17-trione 44

Diisopropylethylamine (37 mg, 0.29 mmol) was added in one portion to a stirred solution of the salt **43** (51 mg, 0.08 mmol) in dry DMF (16 ml) under a nitrogen atmosphere at 0 °C. The solution was stirred at 0 °C for 15 min and then diphenylphosphoryl azide (0.034 g, 0.12 mmol) was added and the mixture was stirred for a further 3 min and then left at room temperature for 5 days. The mixture was diluted with ethyl acetate (20 ml) and poured into ice-cold water. The separated aqueous layer was extracted with ethyl acetate (3 × 20 ml) and the combined organic extracts were washed with water (6 × 30 ml) and brine (30 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using ethyl acetate as eluent to give the *amide* (14 mg, 36%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3399, 1715, 1688 and 1596; δ_H(500 MHz, $CDCl_3$, major rotamer) 8.20 (1H, s, 29-H), 8.02 (1H, d, *J* 7.4 Hz, NH), 7.45 (1H, s, 21-H), 6.93 (1H, dt, *J* 16.2 and 6.8 Hz, 2-H), 6.37 (1H, m, 1-H), 5.46–5.42 (1H, m, 22-H), 4.27–4.10 (4H, m, 23-H and 6-H), 3.42–3.37 (1H, m, 15-H), 3.03 (1H, dd, *J* 16.7 and 11.0 Hz, 14-H), 2.62–2.56 (1H, m, 14-H), 2.54–2.35 (6H, m, 12-H, 8-H and 3-H), 1.84–1.61 (4H, m, 4-H and 5-H), 1.50–1.22 (6H, m, 9-H, 10-H and 11-H) and 0.97–0.91 (3H, m, 16-H); δ_C(125 MHz, $CDCl_3$) 209.5 (s), 173.6 (s), 161.0 (s), 160.8 (s), 145.3 (s), 144.4 (s), 141.7 (d), 140.5 (d), 136.1 (s), 134.2 (d), 132.1 (d), 128.6 (d), 116.0 (d), 64.6 (t), 63.8 (t), 48.3 (t), 43.0 (t), 34.4 (t), 31.9 (t), 29.7 (t), 28.6 (t), 27.8 (t), 24.7 (t), 23.4 (t), 19.4 (q); *m*/*z* (EI) (Found: $M^+ - H_2O$, 469.2223 (100%). $C_{25}H_{31}O_6N_3$ requires *M*, 469.2167).

The oxazole-oxazoline-oxazole macrolide 45

A solution of Burgess' reagent (4.5 mg, 0.02 mmol) in dry THF (0.2 ml) was added to a solution of the amide **44** (8 mg, 0.02 mmol) in dry THF (0.4 ml) and the mixture was heated under reflux for 2 h in a nitrogen atmosphere. The cooled mixture was evaporated to dryness *in vacuo* and the residue was purified by chromatography on silica using 1:1 petrol–ethyl acetate as eluent to give the *oxazoline* (5.5 mg, 72%); δ_H(360 MHz, $CDCl_3$) 8.01 (1H, d, *J* 8.8 Hz, 8-H), 7.33 (1H, d, *J* 14.6 Hz, 14-H), 6.98–6.84 (1H, m, 5-H), 6.29 (1H, d, *J* 15.9 Hz, 6-H), 5.48–5.35 (1H, m, 12-H), 4.77–4.58 (2H, m, 2 × 11-H), 4.16–3.98 (2H, m, 1-H), 3.40 (1H, apparent d, *J* 4.8 Hz, 16-H), 3.33–3.25 (1H, m, 18-H), 2.96–2.87 (1H, m, 18-H), 2.46–2.15 (6H, m, 20-H, 24-H and 4-H), 1.87–1.35 (4H, m, 2-H and 3-H), 1.29–1.03 (6H, m, 23-H, 22-H and 21-H) and 0.90–0.76 (3H, m, 17-H).

The ter-oxazole macrolide 30

Freshly prepared nickel peroxide (150 mg) was added in three portions to a refluxing solution of the *oxazoline* **45** (50 mg) in dry benzene (3 ml) at one hour intervals. The mixture was heated under reflux for 2 h, and then filtered through Celite. The filtrate was concentrated *in vacuo* to leave a viscous mass. Purification by chromatography on silica using ethyl acetate as eluent gave the *ter-oxazole macrolide* as a white solid mp 140–142 °C (EtOAc); λ_{max}(EtOH)/nm 263 (1888); ν_{max}($CHCl_3$)/cm^{-1} 3019, 2929, 1715 and 1215; δ_H(500 MHz, $CDCl_3$) 8.07 and 8.06 (2 × 1H, s, 8 and 11-H), 7.40 (1H, s, 14-H), 7.19 (1H, dt, *J* 15.9 and 7.1 Hz, 5-H), 6.31 (1H, dt, *J* 15.9 and 1.5 Hz, 6-H), 4.08 (2H, 2 × dt, *J* 22.0 and 10.8 Hz, 1-H), 3.43–3.39 (1H, m, 16-H), 3.29 (1H, dd, *J* 17.2 and 6.0 Hz, 18-H), 2.63–2.57 (1H, m, 18-H), 2.49–2.35 (6H, m, 20-H, 24-H and 4-H), 1.80–1.60 (4H, m, 2-H and 3-H), 1.46–1.16 (6H, m, 23-H, 22-H and 21-H) and 0.93–0.78 (3H, m, 17-H); δ_C(125 MHz, $CDCl_3$) 210.25 (s), 173.86 (s), 162.77 (s), 156.57 (s), 154.26 (s), 146.65 (s), 143.23 (d), 137.27 (d), 137.02 (d), 133.40 (d), 131.76 (s), 130.39 (s), 115.21 (d), 65.86 (t), 48.08 (t), 43.64 (t), 34.58 (t), 31.13 (t), 29.70 (t), 29.15 (t), 27.44 (d), 26.88 (t), 25.06 (t), 24.45 (t) and 18.96 (q); *m*/*z* (FAB) (Found: $M^+ + 1$, 468.2154 (7%). $C_{25}H_{30}O_6N_3$ requires *M*, 468.2134).

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