Total synthesis of (−)-ulapualide A, a novel *tris*-oxazole macrolide from marine nudibranchs, based on some biosynthesis speculation†

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A new, second generation, total synthesis of ulapualide A (**1**), whose stereochemistry was recently determined from X-ray analysis of its complex with the protein actin, is described. The synthesis is designed and based on some speculation of the biosynthetic origin of the contiguous *tris*-oxazole unit in ulapualide A, alongside that of the related co-metabolites that contain only two oxazole rings, *e.g.* **6** and **7**. The mono-oxazole carboxylic acid **67b** and the mono-oxazole secondary alcohol **55b** which, together, contain all of the 10 asymmetric centres in the natural metabolite, were first elaborated using a combination of contemporary asymmetric synthesis protocols. Esterification of **67b** with **55b** under Yamaguchi conditions gave the ester **77** which was then converted into the ω-amino acid **18a** following simultaneous deprotection of the *t*-butyl ester and the *N*-Boc protecting groups. Macrolactamisation of **18a**, using HATU, now gave the key intermediate macrolactam **17**, containing two of the three oxazole rings in ulapualide A (**1**). A number of procedures were used to introduce the third oxazole ring in ulapualide A from **17**, including: a) cyclodehydration to the oxazoline **78a** followed by oxidation using nickel peroxide leading to **76**; b) dehydration to the enamide **79**, followed by conversion into the methoxyoxazoline **78b**, *via* **80**, and elimination of methanol from **78b** using camphorsulfonic acid. The *tris*-oxazole macrolide **76** was next converted into the aldehyde **82b** in four straightforward steps, which was then reacted with *N*-methylformamide, leading to the *E*-alkenylformamide **83**. Removal of the TBDPS protection at C3 in **83** finally gave (−)-ulapualide A, whose ^{1}H and ^{13}C NMR spectroscopic data were indistinguishable from those obtained for naturally derived material. It is likely that the *tris*-oxazole unit in ulapualide A (**1**) is derived in nature from a cascade of cyclodehydrations from an acylated *tris*-serine precursor, *e.g.* **9**, followed by oxidation of the resulting *tris*-oxazoline intermediate, *i.e.* **10**. It is also plausible to speculate that the biosynthesis of metabolites related to ulapualide A, *e.g.* the *bis*-oxazole **6** and the imide **7**, involve cyclisations of just two of the serine units in **9**. These speculations were given some credence by carrying out pertinent interconversions involving the *bis*-oxazole amide **24**, the enamide **25**, the imide **26**, the oxazoline **27** and the *tris*-oxazole **30** as model compounds. An alternative strategy to the *tris*-oxazole macrolide intermediate **76** was also examined, involving preliminary synthesis of the aldehyde **73**, containing a shortened (C25–C34) side chain from **67b** and **47b**. A Wadsworth–Emmons olefination reaction between **73** and the phosphonate ester **74** led smoothly to the *E*-alkene **75**, but we were not able to reduce selectively the conjugated enone group in **75** to **76** without simultaneous reduction of the oxazole alkene bond, using a variety of reagents and reaction conditions.

Introduction

The "ulapualides" are a unique family of macrolides isolated from sponges and nudibranchs (sea slugs). They show structures which feature three contiguously linked oxazoles embedded within the macrocycle, and a substituted polyol side chain terminated by an unusual *N*-formyl enamine unit. Ulapualide A (**1**) was the first of their number to be characterised[1], and the family now includes the mycalolides, *e.g.* **2**, kabiramides **3**, halishigamides **4** and halichondramides **5**,[2–4] together with a number of congeners where the *tris*-oxazole unit has been severed, *e.g.* **6**, or modified as an imide, *e.g.* **7**.[5] The ulapualides show antifungal activity and ichthyotoxic properties, together with modest activity against L1210 leukemia cells.

At the time ulapualide A was isolated in the late 1980s, oxazoles had rarely been reported as secondary metabolides, let alone those containing contiguously linked oxazoles. The burgeoning family of polyoxazole-based secondary metabolites now includes the phorboxazoles,[6] hennoxazoles,[7] diazonamide A,[8] several azole-based cyclic peptides[9], the tetraoxazole YM-216391,[10] and the intriguing hepta-oxazole telomestatin.[11]

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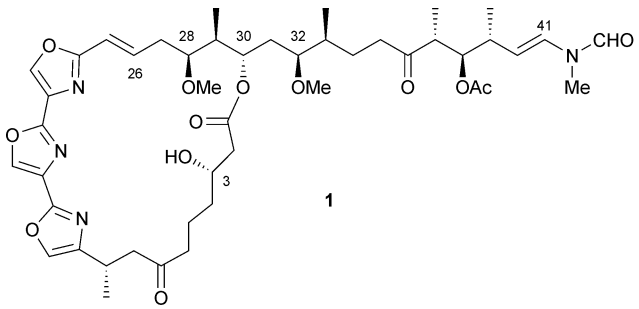
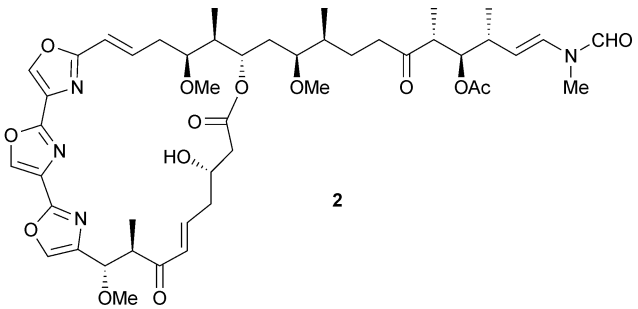
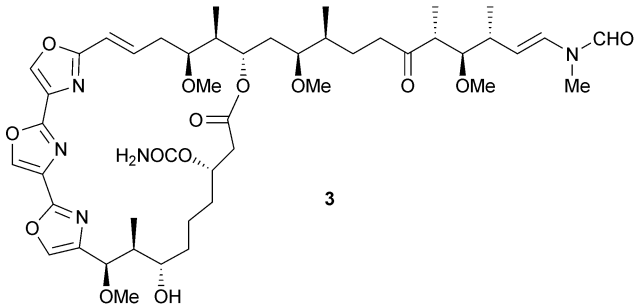
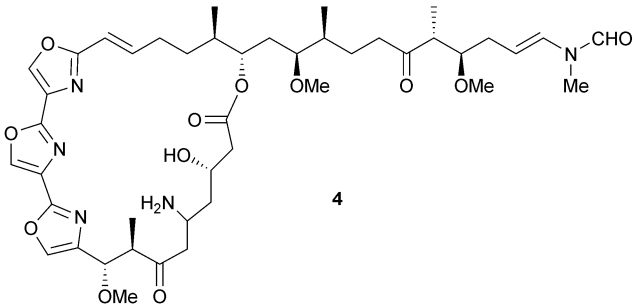
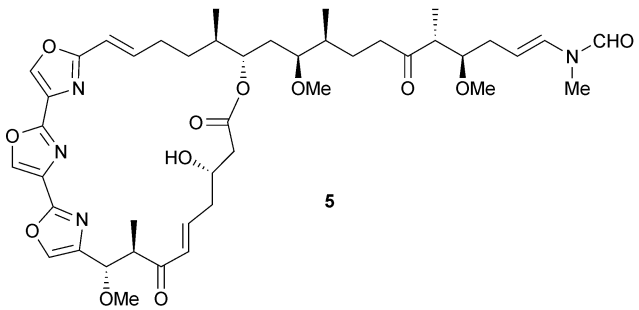
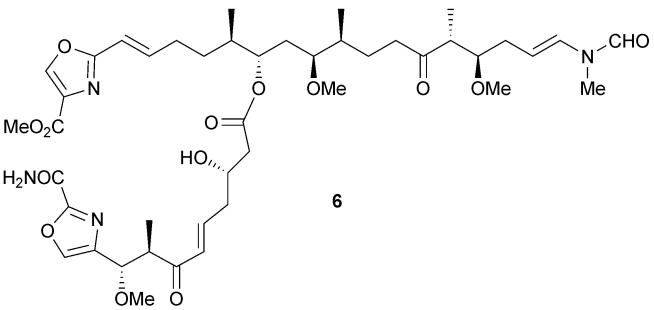


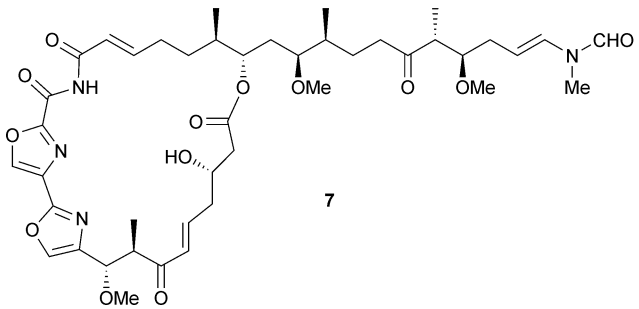


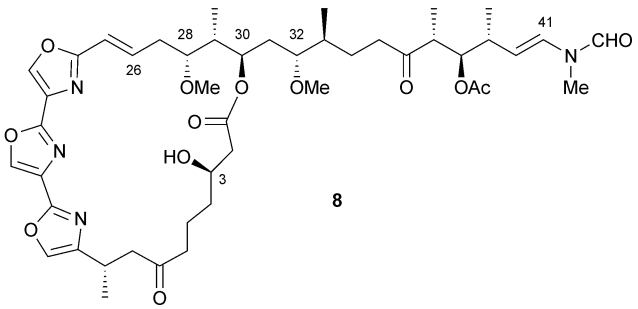












The juxtaposition of several nitrogen and oxygen ligand-binding sites in the ulapualides encouraged us earlier to carry out a molecular mechanics study of a hypothetical metal-chelated complex of ulapualide A.[12] This study led us to assign the relative stereochemistry shown in structure **8** for ulapualide A,[13] and in 1998 we described a total synthesis of this compound. Much to our chagrin, although the synthetic ulapualide A showed identical chromatographic behaviour, as well as chiroptical and ^{1}H NMR spectroscopic data, with those of the natural product, very small differences were observed in the ^{13}C NMR spectra, associated with the C32–C34 portions, of the structures. We therefore concluded that we had synthesised a diastereoisomer of natural ulapualide A, which, apart from other features, was almost certainly epimeric at C32. Contemporaneously, Panek and Fusetani,[14] and their collaborators, using a combination of degradation studies, together with reconnective and total synthesis, established that the related metabolite mycalolide A had the stereochemistry shown in the structure **2**. The stereochemistry established for mycalolide A differed from the one we had tentatively assigned to ulapualide A at no less than five stereocentres, *i.e.* C28, C29, C30, C32 and C3. This was uncanny, even somewhat bewildering, in view of the close similarity of much of the NMR spectroscopic data recorded for our synthetic and natural ulapualide A. To cap it all, in 2004, Rayment *et al.*[15] presented an X-ray crystal structure of ulapualide A bound to the protein actin which showed that the metabolite had the stereochemistry shown in structure **1**. Thus, ulapualide A (**1**) and

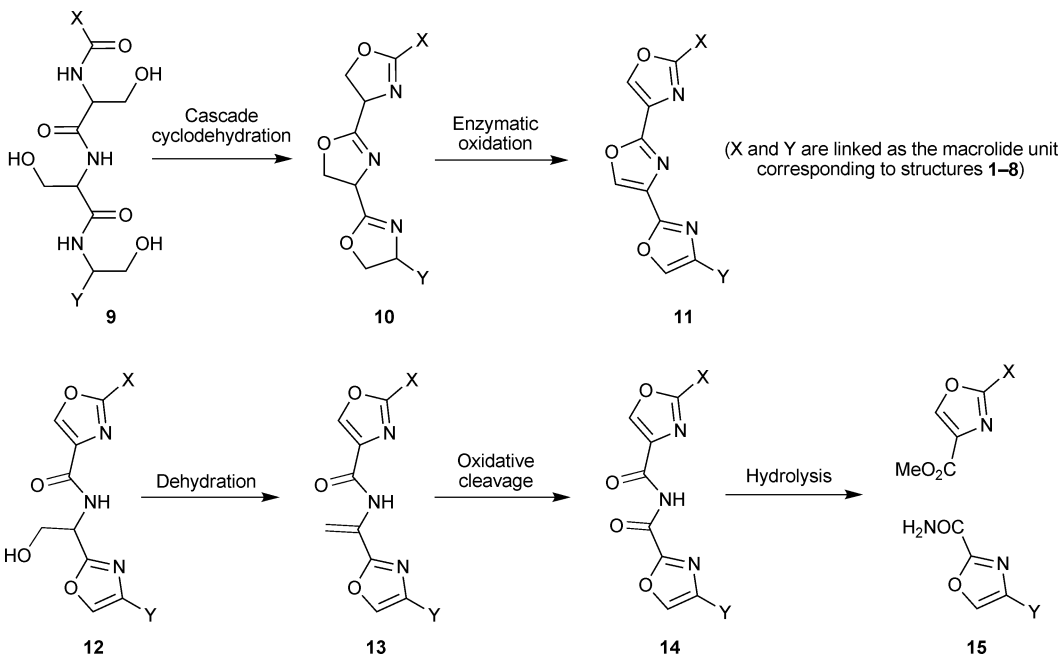
mycalolide A (**2**) have identical stereochemistries at C3, and along their C28–C33, and indeed C37–C39, side chains. As synthetic chemists, driven by curiosity and desirous of completeness, it became imperative for us to undertake a new, second generation, total synthesis of ulapualide A. This paper presents full details of these new synthetic endeavours,[16] which are interweaved with an exploration of the biosynthetic interrelationship between the contiguously linked *tris*-oxazole containing metabolites **1**–**5** and those congeners, **6** and **7**, with incomplete *tris*-oxazole motifs.

Discussion and synthetic strategy

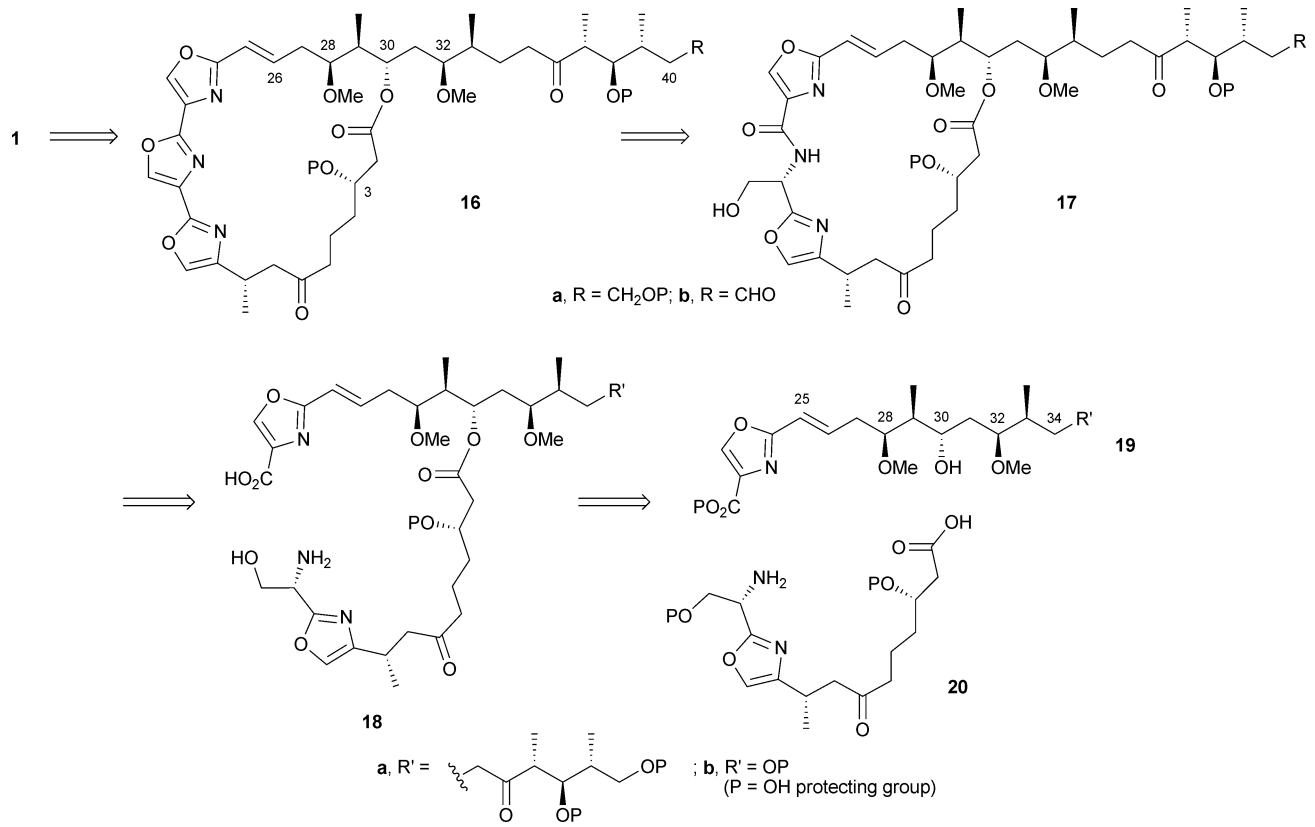
In the absence of biosynthetic studies, it is likely that the *tris*-oxazole unit **11** in the ulapualides is derived from a cascade of cyclodehydrations from an acylated *tris*-serine precursor, *e.g.* **9**, followed by oxidation of the resulting *tris*-oxazoline intermediate **10**.[17] It is also plausible that a similar cyclodehydration–oxidation process involving just two of the serine units in **9** would lead to the *bis*-oxazole amide **12** (Scheme 1). The amide **12** could then act as precursor to the *tris*-oxazole **11**, and also to the enamide **13**, and then to the open-chain ester-amide **15**, by a sequence involving oxidation to the imide **14** and hydrolysis. Indeed, based on this speculation we designed our second generation synthesis of ulapualide A (**1**) involving macrolactamisation of an ω-amino acid intermediate, *viz.* **18a**, as a key step, followed by elaboration of the central oxazole ring in the natural product from a macrolide-macrolactam, *viz.* **17a**,[18] as a late step in the overall synthesis. This approach required a synthesis of the ester **18a** from the carboxylic acid **20a** and the alcohol **19**, which, together, contain all of the ten stereocentres in ulapualide A. The terminal formyl enamine unit in **1** would be introduced as a late step in the synthesis, following manipulation of the functionality and the protecting groups in the *tris*-oxazole macrolide **16a**, leading to the aldehyde **16b**, and treatment of the latter with *N*-methylformamide. Before discussing this total synthesis of ulapualide A (**1**) in detail, however, we first describe some complementary synthetic interconversions with some model substrates, which give credence to the speculation regarding the biosynthetic relationships between the ulapualides **1**–**5**, and their congeners, **6** and **7**, having modified *tris*-oxazole units.[18]

Using the truncated *tris*-oxazole **30**, together with the *bis*-oxazole amide **24** and the oxazoline *bis*-oxazole **27**, as model compounds, we first prepared the known substituted oxazoles **21** and **22a**[18] starting from readily available derivatives of serine. The oxazole-oxazolidine **21** was next doubly deprotected, using 4 M HCl in dioxane, and the resulting secondary amine **23** was then acylated with the acid chloride **22b**, produced from **22a**, leading to the *bis*-oxazole serine amide derivative **24** (Scheme 3).

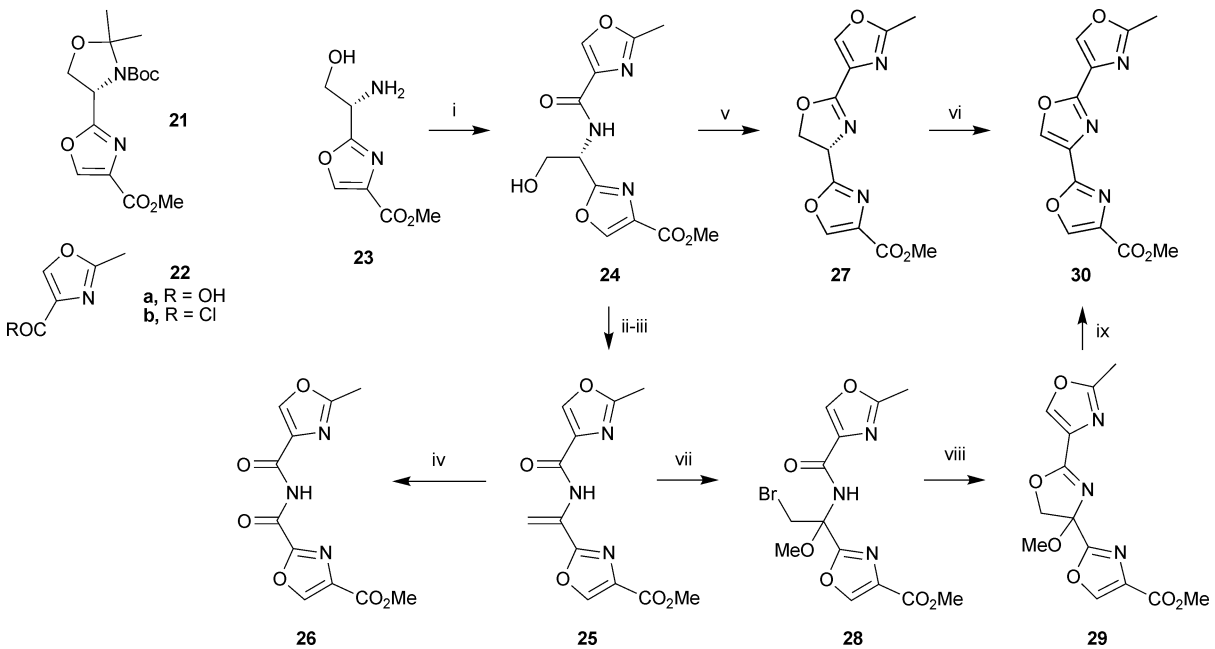
Treatment of **24** with $SOCl_2$ in DCM next gave the corresponding alkyl chloride, which underwent dehydrochlorination in the presence of DBU to produce the enamide **25** (Scheme 3). Oxidative cleavage of the alkene bond in **25**, using catalytic RuO_2 and $NaIO_4$ then gave the imide **26**, *cf.* the natural product **7**. In a separate sequence, the *bis*-oxazole serine amide **24** underwent cyclodehydration when treated with DAST,[19] producing the *bis*-oxazole oxazoline **27** in 99% yield. Oxidation of the oxazoline **27** in the presence of NiO_2 in hot benzene,[20] or better, using $BrCCl_3$–DBU,[21] then led to the contiguously linked *tris*-oxazole **30**. The same *tris*-oxazole **30** was also produced from the enamide **25** following conversion to the methoxy-substituted oxazoline **29** *via* the methoxy-bromide **28**, and treatment with camphorsulfonic acid in toluene (Scheme 3).[22] The aforementioned synthetic interconversions, involving the amide **24**, the enamide **25**, the imide **26**, together with the oxazolines **27** and **29** and the *tris*-oxazole **30**, not only provide a plausible biogenetic link between the ulapualide natural products **1**–**7**, but also set some precedent for the more demanding synthetic work towards ulapualide A that we were about to embark upon.



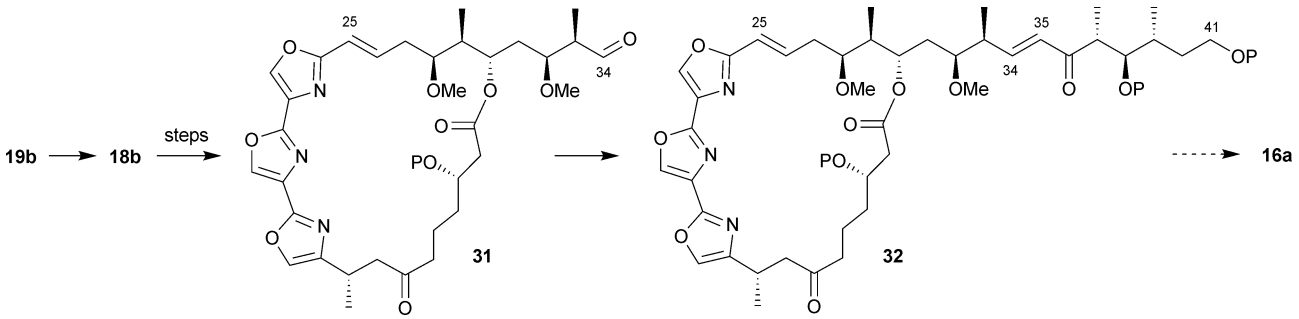
Scheme 1



Scheme 2



Scheme 3 *Reagents and conditions:* i, **22**, **23**, DCM, 87%; ii, $SOCl_2$, DCM, 98%; iii, DBU, DCM, 99%; iv, RuO_2, $NaIO_4$, CCl_4, H_2O, MeCN, 50%; v, DAST, DCM, −78 °C, 99%; vi, NiO_2, benzene, reflux, 40% or $BrCCl_3$, DBN, 81%; vii, NBS, MeOH, 96%; viii, Cs_2CO_3, dioxane, 88%; ix, CSA, toluene, Dean–Stark, 95%.



Scheme 4

Synthesis of the oxazole-substituted C25–C41 (55) and C25–C34 (47) side chains

In our synthesis of the diastereoisomer **8** of ulapualide A, we applied a range of contemporary synthetic methods in asymmetric synthesis, and examined a variety of OH protecting groups to prepare the C26–C41 (top chain) portion in **8**. Pertinent to these studies was the use of methoxymethyl, *t*-butyldimethylsilyl and *t*-butyldiphenylsilyl ether protecting groups at C30, C38 and C41 respectively, and their sequential and selective deprotection using Me_2BBr (for $MeOCH_2O$–), Me_3SiOTf (for C38, *sec*-OH), HF–C_5H_5N (for C41, primary OH).

We investigated two separate approaches to the advanced intermediate **16a** *en route* to ulapualide A. In the first of these approaches we planned to synthesise the *tris*-oxazole based macrolide **31** containing a shortened (C25–C34) side chain, derived ultimately from **19b** and **20**, *via* **18b**, and then to elaborate **31** to **16a** *via* an olefination reaction, producing **32**, followed by selective reduction of the C34–C35 alkene bond (Scheme 4). In the second, more convergent, approach we proposed incorporating the entire C25–C41 top chain in the natural product at an earlier stage in the overall synthesis, *i.e.* starting with the oxazole substituted intermediate **19a**.

The (shortened) C25–C34 side chain **47** was synthesised starting from 3-benzyloxypropanal **33**, (*R*)-2-benzyl-3-propionyl-2-oxazolidinone **34**, and the (*R*)-pentenoyloxazolidin-2-one **40**, using conventional Evans aldol chemistry[23] to introduce the *syn* stereochemistry at C32–C33 (*i.e.* **34** → **35**) and the *anti*- stereochemistry at C29–C30 (*i.e.* **40** → **41**), and by applying Brown's allylboration chemistry[24] to install the β-orientated hydroxyl group at C28 (*viz.* **43** → **44a**) (Scheme 5). Protection of the hydroxyl group in **44a** as its methyl ether **44b**, followed by oxidative cleavage of the alkene bond, next gave the corresponding aldehyde **45**. A Wittig reaction between the aldehyde **45** and the phosphorus ylide, derived *in situ* from the oxazolemethyl bromide **46a**[25] and Bu_3P, using DBU as base, gave the *E*-vinyloxazole **47a** with the C25–C34 side chain present in ulapualide A. The methyl ether group in **47a** was then converted into the corresponding alcohol in two steps leading to **47b** in readiness for coupling to the carboxylic acid **20** *en route* to the macrolide **31**.

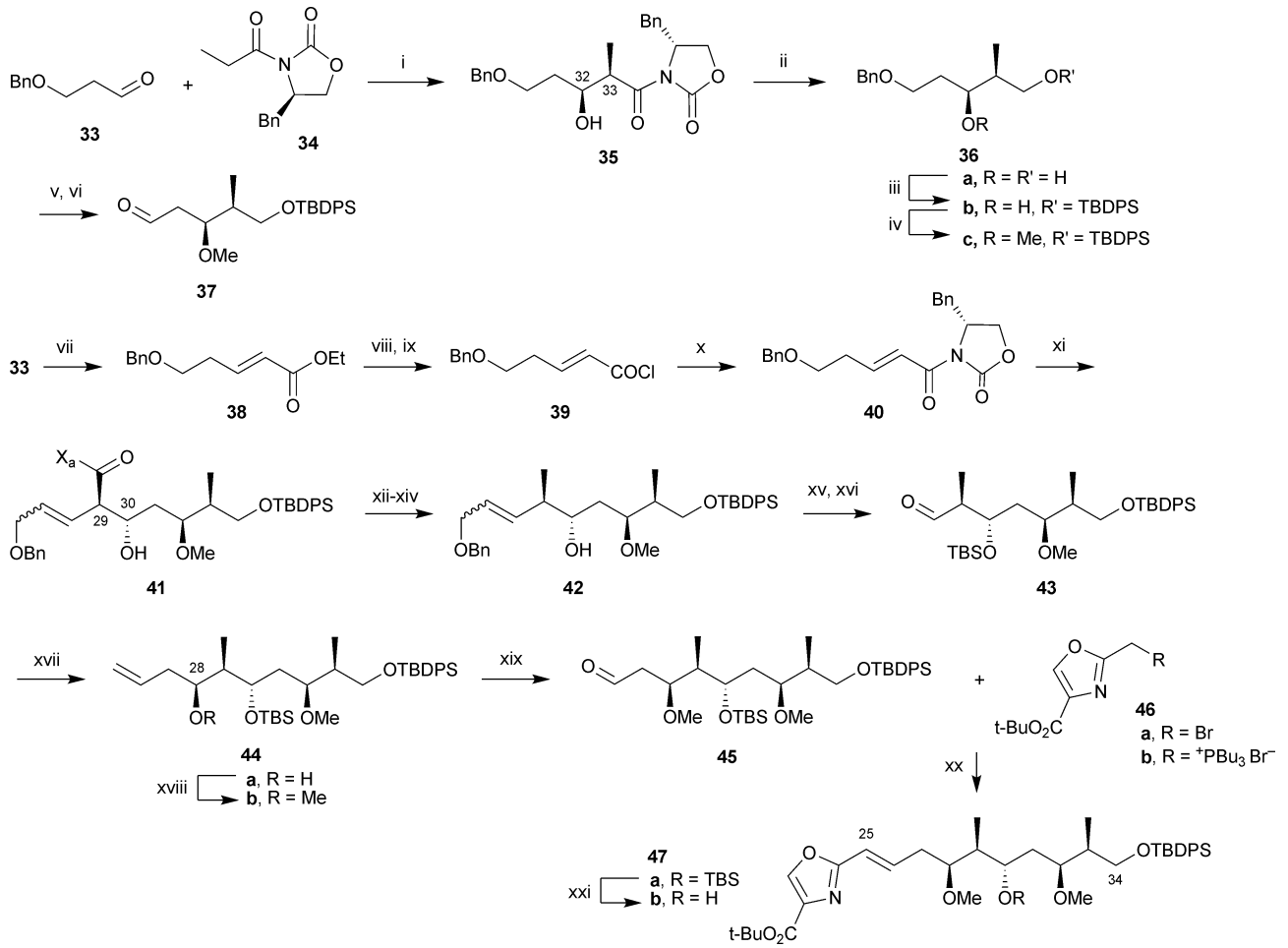
The oxazole-substituted compound **55b**, containing the entire C25–C41 top chain in ulapualide A, was also synthesised from the intermediate **44b** following exchange of TBS for MOM, oxidative cleavage of the alkene bond in **48b** and protection of the resulting aldehyde as the corresponding dimethylacetal **49b** (Scheme 6). The absolute stereochemistry of the dimethylacetal **49b** was established by X-ray crystallography.[26] Deprotection of the silyl ether in **49b** and oxidation of the resulting alcohol, using TPAP, next gave the aldehyde **50b**. A Wadsworth–Emmons reaction between the aldehyde **50** and the phosphonate ester **51** we had used in our synthesis of the diastereoisomer of ulapualide A,[13] using $Ba(OH)_2$ as base[27] then gave the *E*-alkene **52**, which, in one step was converted into the alcohol **53a** following hydrogenation/hydrogenolysis in the presence of Pearlman's catalyst[28] The primary alcohol in **53a** was now protected as its TBDPS ether **53b**, and the dimethylacetal group was then unmasked selectively using Me_2BBr at −78 °C[29] to give the aldehyde **54** in excellent yield (Scheme 6). Finally, a straightforward Wittig reaction between **54** and the phosphonium salt **46b**, under the same conditions as those used to synthesise **47a** from **45**, led to the *E*-2-alkenyloxazole **55a**, which was selectively deprotected using Me_2BBr in CH_2Cl_2 at −78 °C to provide the corresponding C30-alcohol **55b**.

Synthesis of the oxazole-substituted carboxylic acid 20

In our (first generation) synthesis of the diastereoisomer **8** of ulapualide A we introduced the methyl group at C9 as a late step in the overall synthesis using a 1,4-addition reaction of methylcopper lithium to an C8,9-unsaturated enone precursor. This conjugate addition showed poor selectivity (3:2, α:β) and accordingly we examined an alternative strategy to synthesise the C9(*S*)-methyl, C3(*S*) oxy-protected carboxylic acid **20** (Scheme 2).[30] This synthesis was based on a little-used chromium-mediated coupling reaction between the C4 (*S*) oxy-protected alkyl iodide **59** and the C3(*S*) methyl substituted aldehyde **65**, in the presence of vitamin B_{12}.[31]

Thus, asymmetric reduction of the known β-keto ester **56a**[32] using (*S*)-Ru[BINAP][33] first gave the (*S*)-hydroxy ester **57a** (97% ee), which was next selectively protected as its C6-TBS, C3-TBDPS *bis*-silyl ether **58a** (Scheme 7). The absolute stereochemistry of **57a** was confirmed by comparison with the same compound prepared from **56b** using Noyori's asymmetric hydrogenation protocol, followed by hydrogenolysis of the benzyl ether protecting group ($[\alpha]_D$ +21.9; $[\alpha]_D$ +22.7 synthetic).[34] Selective deprotection of the TBS group in **58a**, using camphorsulfonic acid in MeOH, followed by iodination of the resulting primary alcohol **58a** then gave the (*S*)-iodide **59** in 83% overall yield over two steps.

The substituted aldehyde **65** was prepared from Garner's aldehyde starting with an *E*-selective Wittig reaction, leading to the α,β-unsaturated ester **60**,[35] followed by chelation-controlled *syn*-addition of lithium dimethylcuprate producing the adduct **61a** (9:1 *syn* selectivity).[35] Successive functional group interconversions



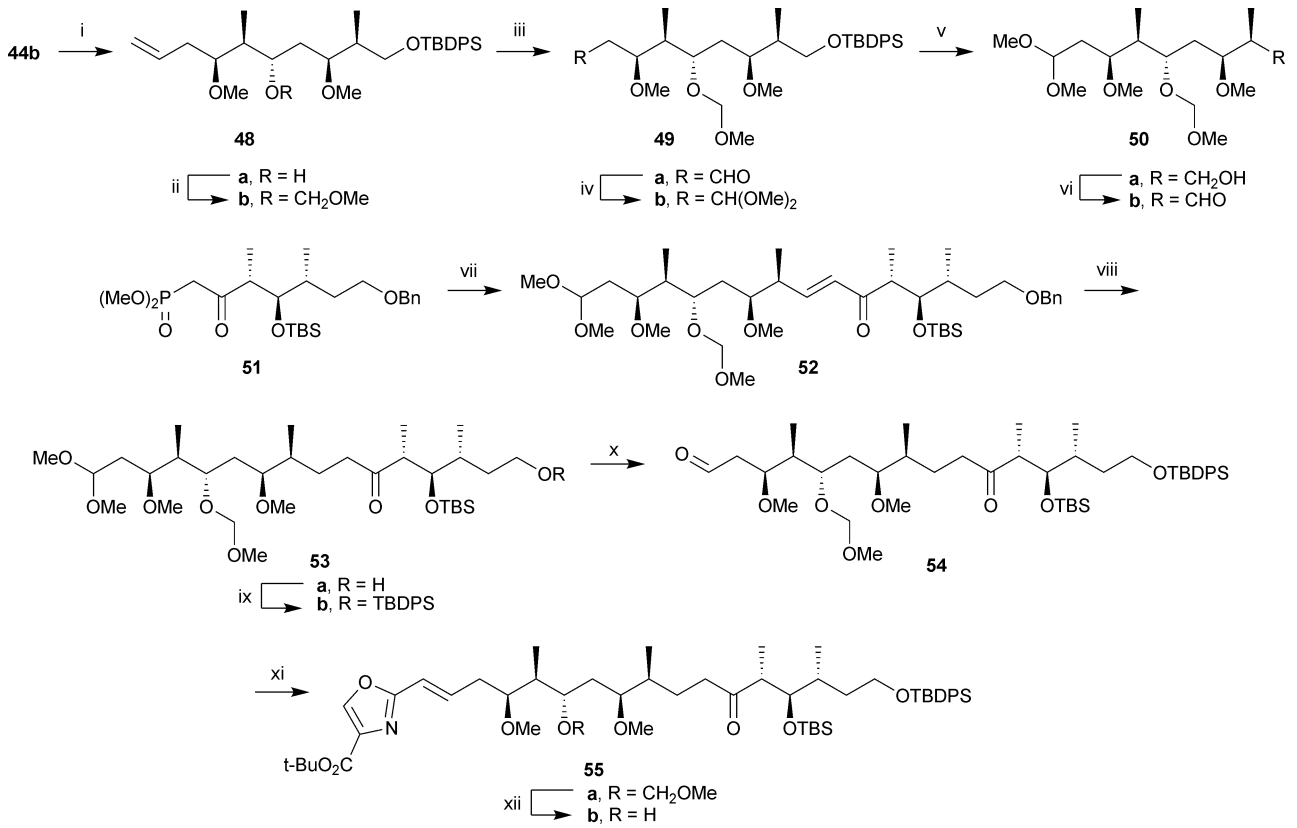
Scheme 5 *Reagents and conditions:* i, Bu_2BOTf, Et_3N, DCM, −78 °C, 72%; ii, $LiBH_4$–MeOH, THF; iii, TBDPS-Cl, imidazole, DMF, 94%; iv, NaHMDS, MeI, THF, 0 °C, 90%; v, $Pd(OH)_2/C$, H_2, EtOAc, 92%, vi, DMSO, $(COCl)_2$, DCM, Et_3N, −78 °C, 96%; vii, ethoxycarbonylmethylenetriphenylphosphorane, DCM, 68%; viii, LiOH, THF, H_2O, 95%; ix, $(COCl)_2$, DMF, DCM, 99%; x, *n*-BuLi, 4-phenylmethyl-2-oxazolidone, −78 °C, 95%; xi, **37**, Bu_2BOTf, Et_3N, DCM, −78 °C, 58%, xii, $LiBH_4$–MeOH, THF, 99%; xiii, MsCl, DIPEA, DCM, −40 °C; xiv, $LiBH_4$–MeOH, THF, 85%; xv, TBSOTf, 2,6-lutidine, DCM, 85%; xvi, O_3, DCM, PPh_3, −78 °C, 93%; xvii, allylmagnesium bromide, Et_2O, −78 °C, (−)-*B*-chlorodiisopinocamphenylborane, 91%; xviii, NaHMDS, MeI, THF, −15 °C, 91%; xix, O_3, DCM, PPh_3, −78 °C, 94%; xx, PBu_3, then **45**, DBU, DMF, 0 °C, 91%; xxi, HF–pyridine, THF, pyridine, 91%, then TBDPSCl, imidazole, DMF, 63%.

next led to the amino alcohol **62**, which was then reacted with Garner's acid[36] to deliver the corresponding amide **63** (Scheme 8). Oxidation of the primary OH group in **63** followed by a Robinson–Gabriel cyclisation[37] of the resulting keto-aldehyde gave the substituted oxazole **64**, which was then elaborated to the C7-aldehyde **65** in two straightforward steps.

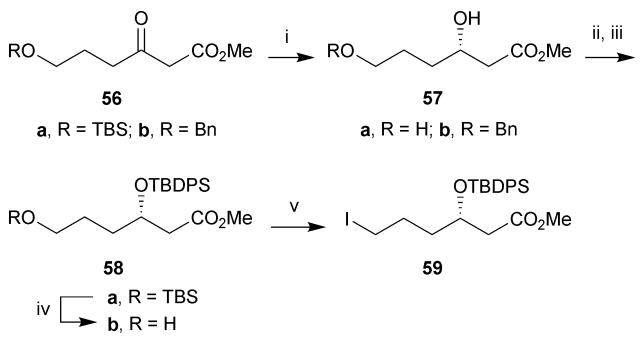
The oxazole-substituted aldehyde **65** was coupled to the iodide **59** in degassed DMF in the presence of chromium chloride and vitamin B_{12} to give a 1:1 mixture of C7 epimers of the alcohol **66** in 88% yield. Finally, oxidation of the alcohol **66** using Swern conditions, followed by saponification of the ester group in the resulting 6-ketoester **67a**, using LiOH/MeOH, gave the carboxylic acid **67b**.

Synthesis of the *tris*-oxazole macrolide 72a containing a C25–C34 side chain

With concise syntheses of the oxazole-containing carboxylic acid **67b** and the oxazole-containing C30 alcohol **47b**, we were now in a position to examine their combination and conversion to the *tris*-oxazole macrolide **72**. The esterification of the carboxylic acid **67b** with the alcohol **47b** proceeded smoothly under Yamaguchi conditions[38] to give the ester **68** in an excellent 96% yield (Scheme 9). The *t*-butyl ester and the *N*-Boc protecting groups in **68** were then removed simultaneously using TMSOTf in the presence of Et_3N[39] to give the amino acid **69**, which was immediately treated with DPPA and iPr_2NEt[40] in DMF at room temperature, leading to the macrolactam **70** in 50–70% yield over two steps. When the macrolactam **70** was treated with DAST at −78 °C it underwent smooth cyclodehydration and gave the corresponding oxazoline **71** in 92% yield. The oxidation of the oxazoline **71** to the *tris*-oxazole macrolide **72** however did not turn out to be straightforward. Where most oxidants such as DDQ, MnO_2 and activated NiO_2 worked reasonably well with model systems, both DDQ or MnO_2 failed to oxidise **71** to **72**, and NiO_2 needed to be used in considerable excess (60 equiv), with recovery and recycling of unoxidised oxazoline, before a respectable 55% yield of the *tris*-oxazole macrolide **72a** could be realised.



Scheme 6 *Reagents and conditions:* i, PPTS, EtOH, reflux, 77%; ii, MOM-Cl, DIPEA, DCM, reflux, 95%; iii, O_3, DCM, PPh_3, −78 °C, 99%; iv, trimethylorthoformate, MeOH, *p*TSA, 89%; v, TBAF, THF 99%; vi, TPAP, NMO, DCM, 78%; vii, **50b**, $Ba(OH)_2$, THF, H_2O, 68%; viii, $Pd(OH)_2/C$, H_2, EtOAc, 96%; ix, TBDPS-Cl, imidazole, DMF, 93%; x, Me_2BBr, DCM, −78 °C, 98%; xi, **46a**, PBu_3, then **54**, DBU, DMF, 75%; xii, Me_2BBr, Et_2O, −78 °C, 79%.



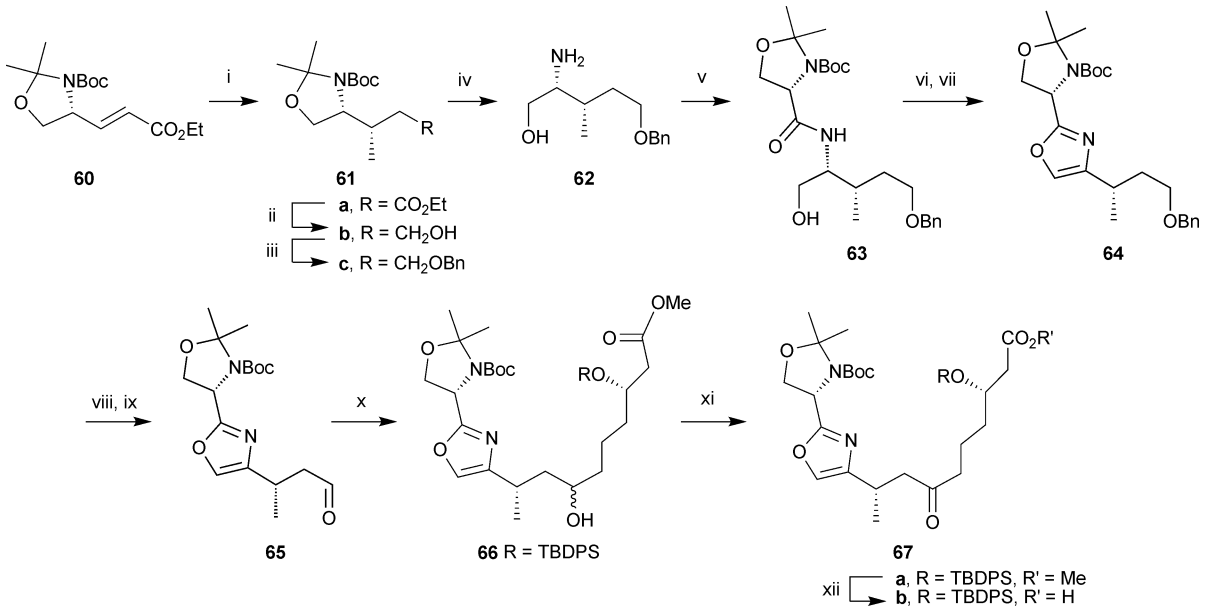
Scheme 7 *Reagents and conditions:* ia, *S*-Ru[BINAP], MeOH, H_2, 80 bar, 92%; ib, S-Ru[Binap], MeOH, H_2, 80 bar, 86%; ii, TBS-Cl, imidazole, DMF, 81%; iii, TBDPS-Cl, imidazole, DMF, 90%; iv, CSA, MeOH, DCM, 97%; v, PPh_3, I_2, imidazole, DCM, 0 °C, 86%.

Synthesis of the *tris*-oxazole macrolide 16a containing the entire C25–C41 top chain and its C34–C35 dehydro analogue 75, and completion of the total synthesis of ulapualide A (1)

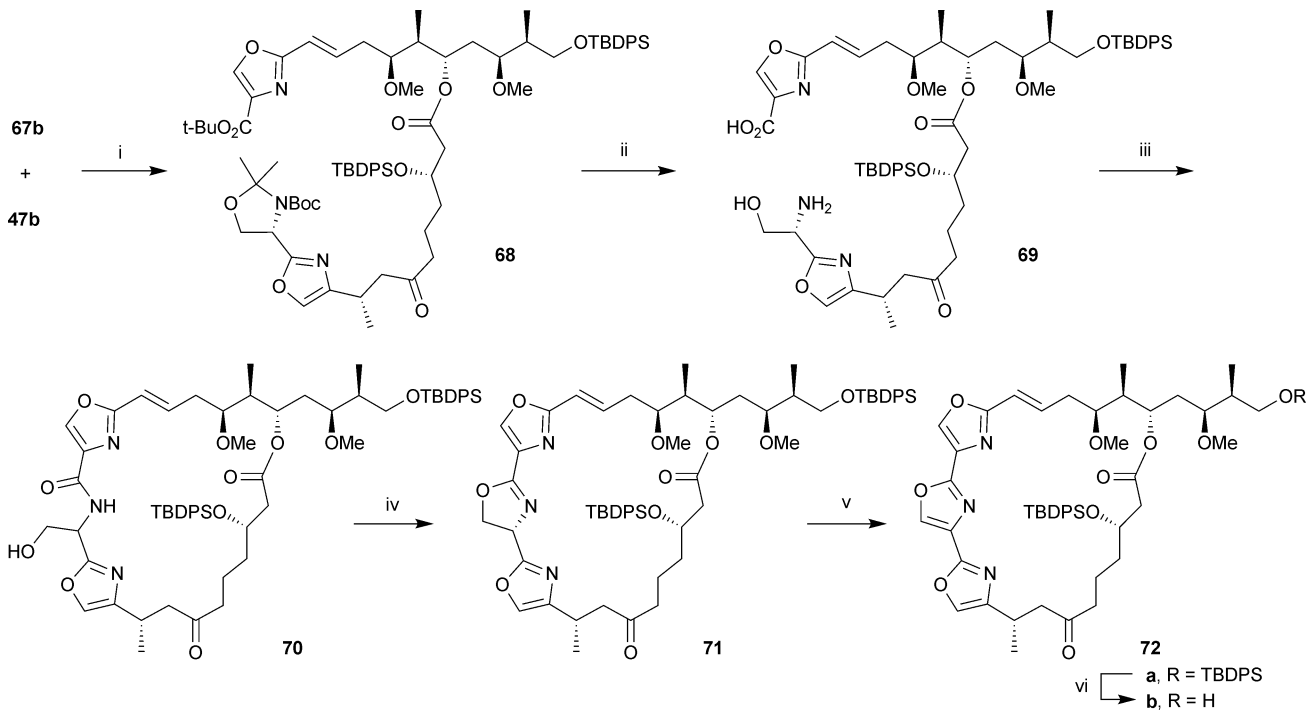
In our first approach to the advanced intermediate **16a** *en route* to ulapualide A (Scheme 2), we planned to elaborate the aldehyde **73**, containing a shortened C25–C34 side chain, to the corresponding alkene **75** using an olefination reaction with the substituted phosphonate ester **74**, and then to effect a regioselective reduction of the C34–C35 alkene in **75** in the presence of the C25–C26 (vinyloxazole) double bond, leading to **76** (Scheme 10).

Thus, selective deprotection of the TBDPS ether of the primary alcohol group in **72a** using HF–pyridine, followed by oxidation of the resulting alcohol **72b** with Dess–Martin periodinane,[41] first gave the aldehyde **73**. A Wadsworth–Emmons reaction between the aldehyde **73** and the phosphonate ester **74**, produced in two steps from **51** using $Ba(OH)_2$ as base, next gave the *E*-alkene **75** in 60% yield over two steps.

Selective reduction of the conjugated enone alkene, at C34–C35 in the presence of the vinyloxazole alkene at C25–C26 in **75**, leading to the target **76** (*cf.* **16a**), was not straightforward. A plethora of methods for selective 1,4-reductions of enones abound in the literature, with transition-metal-catalysed hydrosilylations and "copper hydride" reductions amongst the most attractive. Using model systems alongside the substrate **75**, we investigated the scope for $(PPh_3{\cdot}CuH)_6$ and $PhSiH_3$,[42] Red-Al® and CuBr or CuI,[43] $Mo(Co)_6$ and Ph_3SiH_3,[44] H_2 and $Pd(OH)_2$ on C,[28] and CuCl, Bu_4NF, PPh_3 with $PhMe_2SiH$.[45] To our chagrin, in all cases, we either recovered starting material or observed simultaneous reduction of both conjugated enone and vinyloxazole alkene bonds in **75**. At this stage therefore we abandoned our first approach to the advanced intermediate **76** (*cf.* **16a**) towards ulapualide A (**1**), and instead focused on our second approach, *i.e.* incorporating the entire C25–C41 top chain in the natural



Scheme 8 *Reagents and conditions*: i, Me_2CuLi, TMS-Cl, THF, 81%; ii, DIBAL-H, THF, 100%; iii, NaH, BnBr, TBAI, THF, 78%; iv HCl, dioxane; v, Garner's acid, EDC, 4-methylmorpholine, THF, HOBt, 79%; vi DMSO, $(COCl)_2$, Et_3N, DCM, −78 °C, 97%; vii PPh_3, 1,2 dibromotetrachloroethane, 2,6-di-*t*-butylpyridine, DCM, DBU, MeCN, 72%; viii, Pd/C, EtOAc, H_2, 81%; ix, DMSO, $(COCl)_2$, Et_3N, DCM, −78 °C, 87%; x, **59**, vitamin B_{12}, $CrCl_2$, DMF, 88%; xi, DMSO, $(COCl)_2$, Et_3N, DCM, −78 °C, 85%; xii, LiOH, MeOH, H_2O, 88%.

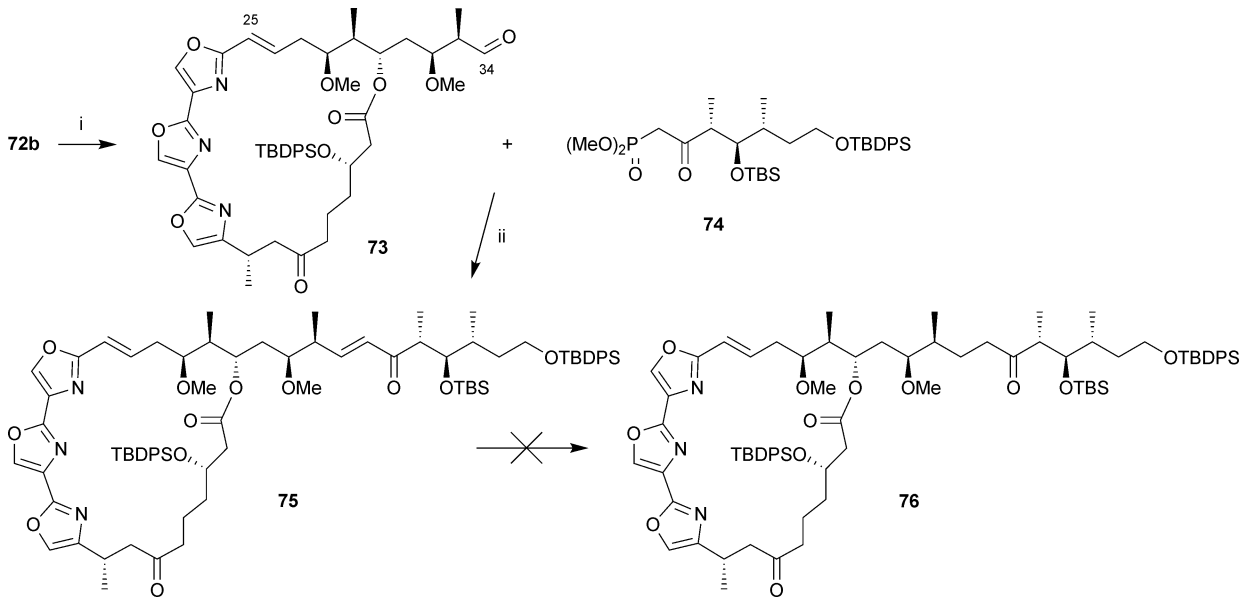


Scheme 9 *Reagents and conditions*: i, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, DMAP, 0 °C, 96%; ii, TMSOTf, Et_3N, DCM, 0 °C; iii, DIPEA, DPPA, DMF, 68%; iv, DAST, DCM, −78 °C, 92%; v, NiO_2, benzene, reflux, 55%; vi, HF–pyridine, THF, pyridine, 45%.

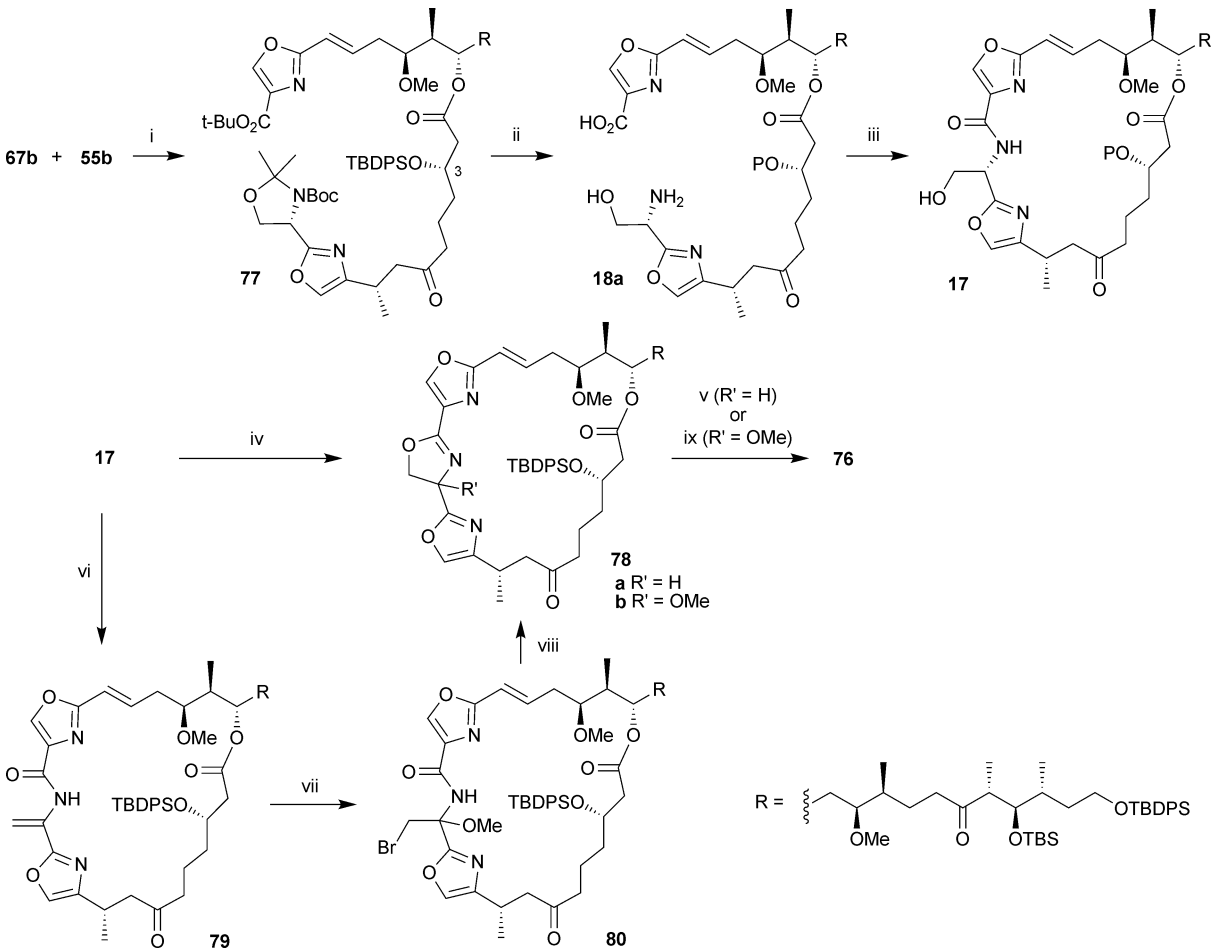
product, starting from the already synthesised oxazole-substituted C30 alcohol **55b**.

The synthesis of **76** from the C30 alcohol **55b** and the carboxylic acid **67b** was relatively straightforward and proceeded along a pathway essentially identical to that followed in our synthesis of the ester **68** and the macrolide **71** with a shorter side chain, from **47b** and **67b**.

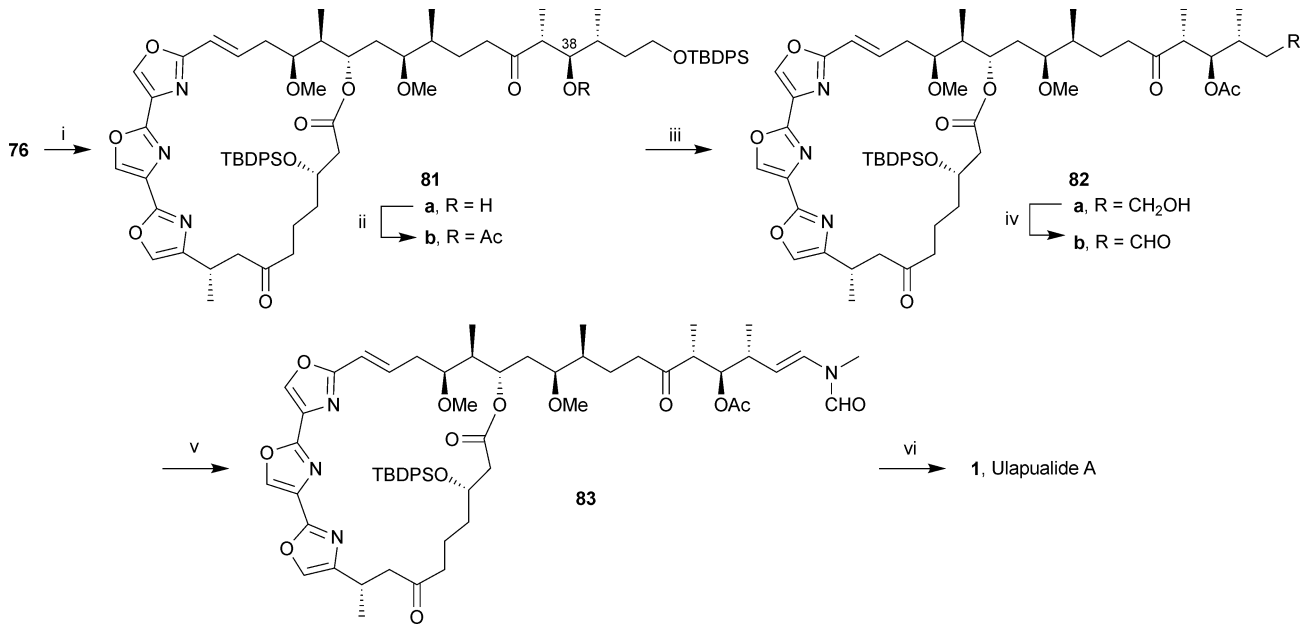
Thus, esterification of the carboxylic acid **67b** with the alcohol **55b**, using Yamaguchi's conditions, followed by removal of the *t*-butyl ester and *N*-Boc protecting groups in the product **77**, first gave the corresponding ω-amino acid **18a** (Scheme 11). Instead of DPPA–iPr_2NEt used in the macrolactamisation of the analogue **69** to **70**, we treated **18a** with HATU[46] at 0 °C, which resulted in an equally efficient macrolactamisation and gave **17** in an



Scheme 10 *Reagents and conditions*: i, $NaHCO_3$, Dess–Martin periodinane, DCM; ii, $Ba(OH)_2{\cdot}8H_2O$, THF, H_2O, 36% over two steps.



Scheme 11 *Reagents and conditions*: i, 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, DMAP, 0 °C, 93%; ii, TMSOTf, Et_3N, DCM, 0 °C; iii, HATU, Et_3N, DCM, 0 °C, 67%; iv, DAST, DCM, −78 °C, 89%; v, NiO_2, benzene, reflux, 25%; vi, MsCl, DIPEA, DCM, DBU, 0 °C, 75%; vii NBS, MeOH, DCM, 92%; viii, Cs_2CO_3, dioxane, 60 °C, 92%; ix, CSA, benzene, 5 Å mol. sieves, reflux, 58%.



Scheme 12 *Reagents and conditions*: i, TMSOTf, DCM, −78 °C, 85%; ii, acetic anhydride, DMAP, DCM, pyridine, 84%; iii, HF–pyridine, DCM, pyridine, 61%; iv, Dess–Martin periodinane, DCM, 80%; v, *N*-methylformamide, PPTS, benzene, reflux, 40%; vi, HF–pyridine, THF, 60%.

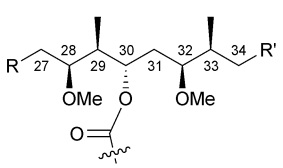
agreeable 67% yield (over 2 steps). Treatment of **17** with DAST at −78 °C next gave the oxazoline **78a** (89%), but the subsequent oxidation of **78a** to the corresponding *tris*-oxazole **76** (*cf.* **16a**), using NiO_2 in benzene under reflux, was unreliable and seldom gave yields above 25%. A more reliable route to **76** from **17** was *via* the enamide **79**, and based on our earlier model studies with **25** (Scheme 3). Thus, mesylation of **17** followed by elimination of $MeSO_2H$ from the intermediate mesylate in the presence of DBU first gave the enamide **79** in 75% yield over two steps. Treatment of **79** with NBS in MeOH next led to the methoxybromide **80**, which underwent dehydrobromination in the presence of Cs_2CO_3[22] producing the methoxyoxazoline **78b**. Finally, treatment of **78b** with camphorsulfonic acid in benzene, heated under reflux, gave the same *tris*-oxazole macrolide **76** to that obtained using the NiO_2 oxidation route.

The final six steps in the synthesis of ulapualide A (**1**) from the *tris*-oxazole macrolide **76** had already been established in our first generation total synthesis of the diastereoisomic ulapualide A (**8**). Thus, selective deprotection of the TBS group in **76** using TMSOTf at −78 °C, followed by acetylation of the resulting secondary alcohol **81a** first led to the C38-acetate **81b** (Scheme 12). A second, selective deprotection of the TBDPS ether of the C41 primary alcohol, using HF–pyridine (1.5 h only) next gave the alcohol **82a**, which was then oxidised to the aldehyde **82b** using Dess–Martin periodinane. Although not without some difficulties, when a solution of the aldehyde **82b** in benzene was heated under reflux with *N*-methylformamide) (22 equiv.) in the presence of PPTS (0.25 equiv) for 6–10 h (t.l.c. monitoring with further additions of *N*-methylformamide) workup and chromatography gave the *E*-alkenyl formamide **83** which was isolated as a 3:2 mixture of rotamers, in 25–40% yield. Finally, removal of the TBDPS protection at C3 in **83**, using HF–pyridine in THF (12 h), gave (−)-ulapualide A as a colourless viscous oil, in 60% yield.

The synthetic ulapualide A had $[\alpha]_D^{26}$ −52.8 (*c* 0.11 in MeOH) (lit. $[\alpha]_D$ −42.9 (*c* 0.16 in MeOH)) and displayed ^1H and ^{13}C NMR spectroscopic data which were indistinguishable from those obtained for naturally derived material.[1] Significantly, chemical shift data for the C32, C34 and C33-Me carbon atoms in synthetic **1** were superimposable on those obtained for natural ulapualide A.

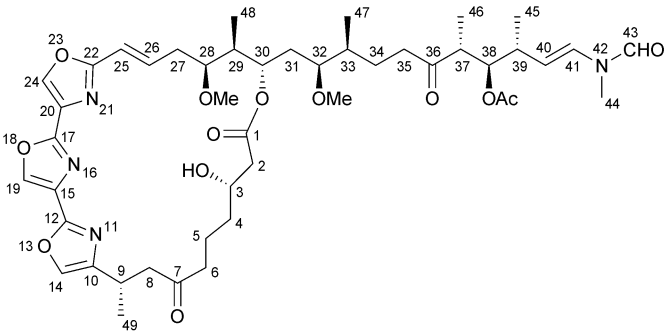
This is in contrast to the synthetic diastereoisomer **8** which displayed small differences in the chemical shifts of these same three carbon atoms in its ^{13}C NMR spectrum (Table 1) yet closely

Table 1 ^{13}C NMR data (δ_C in ppm) for the C32–C34 unit in synthetic and natural ulapualide A, and in the synthetic diastereoisomer **8**



Carbon atom	Natural ulapualide A	Synthetic ulapualide A	Diastereoisomer **8** of ulapualide A
32	81.8	81.8	81.0
34	27.6	27.7	26.6
C33-Me	15.5	15.6	14.2

Table 2 ^{13}C NMR data (δ_C in ppm) for natural and synthetic ulapualide A



Carbon atom	Natural ulapualide A	Synthetic ulapualide A	Carbon atom	Natural ulapualide A	Synthetic ulapualide A
1	172.6	172.6	32	81.8	81.8
2	43.0	43.0	33	40.4	40.5
3	68.4	68.6	34	27.6	27.7
4	37.2	37.3	35	39.8	39.9
5	20.8	20.8	36	211.8	211.7
6	43.9	43.9	37	48.6	48.7
7	210.5	210.5	38	77.3	77.6
8	48.1	48.3	39	37.0	37.0
9	28.2	27.9	40	112.2	112.2
10	146.5	146.5		110.5	110.5
12	154.2	154.3	41	129.6	129.6
14	133.5	133.5		125.5	125.6
15	131.7	131.8	43	162.2	162.2
17	156.2	156.3		161.0	161.0
19	137.4	137.4	44	33.1	33.1
20	130.2	130.4	45	19.5	19.5
22	162.7	162.8	C38-O*C*OMe	170.1	170.1
24	137.8	137.8	C38-OCO*Me*	20.9	21.0
25	117.2	117.3	46	13.4	13.4
26	139.9	139.8	47	15.5	15.6
27	33.7	33.6	C32-O*Me*	58.1	58.2
28	80.0	80.0	48	9.1	9.1
29	34.6	34.6	C28-O*Me*	57.8	57.8
30	73.0	73.0	49	18.9	18.9
31	32.1	32.2			

similar chemical shift data for all other carbon atoms.[13] The ^{13}C NMR spectroscopic data for synthetic (−)-ulapualide A (**1**) and naturally derived material, recorded on the same spectrometer during the same period of time, are collected in Table 2.

Summary and comment

Our total synthesis of (−)-ulapualide A complements the recent X-ray studies made by Rayment *et al.*[15] on an actin–ulapualide A complex. The synthesis also emphasises how vigilant and cautious synthetic chemists should be in relying on NMR spectroscopy when comparing data for complex natural products and their synthetic counterparts. Our present studies have shown that profound changes in the stereochemistry of a natural product (compare structures **1** and **8** which differ at five stereocentres) are not always adequately reflected in a significant way in their NMR spectroscopic, and other, data.[47] It could be argued that apart from the usual comparisons of mass spectrometric, chiroptical, and chromatography data, the unambiguous proof of identity of a complex natural product with a synthetic compound should always be ascertained by recording "mixed" ^1H and ^{13}C NMR spectra. This proposition assumes of course, that there are sufficient quantities (*i.e.* 0.5–1 mg) of both natural and synthetic materials to "sacrifice" in the exercise! This concept of "mixed" NMR spectra is akin to mixed melting point measurements which, after all, were used routinely and with great accuracy for decades by our synthetic chemistry ancestors!

Experimental

General details

^1H NMR spectra were recorded on Bruker DPX 360 (360 MHz), Varian Inova 400 (400 MHz), or Bruker DRX 500 (500 MHz) spectrometers. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane, and the spectra are referenced to residual protonated solvent (δ 7.27 for $CDCl_3$ and 7.15 for C_6D_6). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), app (apparent) and br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. ^{13}C NMR spectra were recorded on Bruker DPX 360 (360 MHz), Varian Inova 400 (400 MHz) or Bruker DRX 500 (500 MHz) spectrometers. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane, and spectra are referenced to residual protonated solvent (δ 77.1 for $CDCl_3$, 128.6 for C_6D_6); multiplicities were determined using a DEPT sequence.

Abbreviations used in the description of resonances are: s (singlet, quaternary), d (doublet, CH), t (triplet, CH_2), q (quartet CH_3). Where required, ^1H–^1H COSY and ^1H–^{13}C COSY were recorded on Bruker DPX 360 (360 MHz), Varian Inova 400 (400 MHz) or Bruker DRX 500 (500 MHz) spectrometers.

Infra-red spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer as a dilute solution in chloroform. Absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}).

Mass spectra were recorded on VG Autospec, MM-701CF, or Micromass LCT spectrometers, using electron ionisation (EI) or electrospray (ES) techniques. High-resolution mass spectra were calculated from the molecular formula corresponding to the observed signal using the lowest atomic weights of isotopes of each element, to 4 decimal places.

Optical rotations were recorded on a JASCO DIP 370 polarimeter. $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on a Stuart Scientific SMP3 apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on Merck DC-Alufolien $60PF_{254}$ 0.2 mm precoated plates. Product spots were visualised by the quenching of UV fluorescence (λ_{max} = 254 nm) and subsequently developed using vanillin solution, molybdophosphoric acid solution, or potassium permanganate solution, as appropriate. Flash column chromatography was carried out on silica gel (Merck silica gel 60 (230–400 mesh ASTM)).

Unless stated otherwise, reactions requiring anhydrous conditions were conducted in an inert atmosphere of nitrogen in flame-dried or oven-dried apparatus. Combined solvent extracts were dried over $MgSO_4$ prior to evaporation, unless stated otherwise.

Several reagents were purified prior to use. Triethylamine, pyridine and diisopropylethylamine were distilled from calcium hydride. Dimethylboron bromide was prepared according to the procedure of Guindon *et al.*[29] and stored as a solution in dry dichloromethane at −20 °C. Nickel peroxide was reactivated according to the procedure of Konaka *et al.*[48] The concentrations of alkylation reagents were determined by titration against 1,3-diphenylacetone *p*-tosylhydrazone. Molecular sieves were stored in a warm oven before use. All other commercially available reagents were used as received.

When necessary, solvents were dried prior to use. Benzene, toluene, diethyl ether and tetrahydrofuran (THF) were distilled from sodium and benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Methanol was distilled from magnesium methoxide and ethanol was distilled from magnesium ethoxide. Anhydrous dimethylformamide was obtained from Aldrich.

2-{1-[(2-Methyloxazole-4-carbonyl)amino]vinyl}-2,3-dihydrooxazole-4-carboxylic acid methyl ester (25)

Thionyl chloride (320 µl, 4.40 mmol) was added dropwise over 5 min to a stirred solution of the hydroxy amide **24** (144 mg, 0.49 mmol) in dry dichloromethane (3.5 ml) at 0 °C under a nitrogen atmosphere. The solution was stirred at room temperature for 12 h and then concentrated *in vacuo.* Ethyl acetate (36 ml) and water (20 ml) were added to the residue and the separated aqueous phase was then extracted with ethyl acetate (2 × 20 ml). The combined organic extracts were dried ($MgSO_4$) and then concentrated *in vacuo* to leave the corresponding *alkyl chloride* (160 mg, 98%) as a yellow oil: ν_{max} (soln, $CHCl_3$)/cm^{-1} 3398, 1737 and 1682; ^1H NMR (360 MHz, $CDCl_3$) δ 2.50 (3H, s, CH_3CN), 3.93 (3H, s, CH_3O), 4.04 (1H, dd, *J* 11.3, 4.7 Hz, C*H*H), 4.12 (1H, dd, *J* 11.3, 4.7 Hz, CH*H*), 5.78 (1H, app dt, *J* 8.7, 4.7 Hz, CONHC*H*), 7.73 (1H, d, *J* 8.7 Hz, NH), 8.13 (1H, s, C*H*CCONH), 8.25 (1H, s, $CHCCO_2Me$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 13.9 (q), 45.2 (t), 48.3 (d), 52.4 (q), 133.8 (s), 135.2 (s), 141.6 (d), 144.7 (d), 160.4 (s), 161.3 (s), 161.5 (s), 161.7 (s); *m/z* (EI) 336.0393 (M^+ + Na), $C_{12}H_{12}ClN_3O_5$ + Na requires 336.0363.

1,8-Diazabicyclo[5.4.0]undec-7-ene (485 µl, 3.20 mmol) was added dropwise over 5 min to a stirred solution of the alkyl chloride (1.18 g, 3.20 mmol) in dry dichloromethane (13 ml) at room temperature under a nitrogen atmosphere. The orange mixture was stirred at room temperature for 3 h and then concentrated *in vacuo.* Ethyl acetate (100 ml) and 2 M hydrochloric acid (80 ml) were added to the residue and the separated organic phase was then washed with 2 M hydrochloric acid (2 × 80 ml), dried ($MgSO_4$), and concentrated *in vacuo.* The residue was recrystallised from ethyl acetate–light petroleum (bp 40–60 °C) to give the *enamide* (0.88 g, 99%) as colourless crystals, mp 150–151 °C: ν_{max} (soln, $CHCl_3$)/cm^{-1} 3366, 1747 and 1689; (found, C, 51.8%; H, 3.9%; N, 15.0%; $C_{12}H_{11}N_3O_5$ requires C, 52.0%; H, 4.0%; N, 15.2%); ^1H NMR (360 MHz, $CDCl_3$) δ 2.53 (3H, s, CH_3CN), 3.95 (3H, s, CH_3O), 5.86 (1H, s, CC*H*H), 6.64 (1H, s, CCH*H*), 8.15 (1H, s, C*H*CCONH), 8.24 (1H, s, $CHCCO_2Me$), 9.29 (1H, s, NH); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 13.9 (q), 52.4 (q), 105.1 (t), 127.9 (s), 134.0 (s), 136.0 (s), 141.5 (d), 144.5 (d), 158.9 (s), 159.7 (s), 161.3 (s), 161.7 (s); *m/z* (EI) 278.0754 (M^+ + H), $C_{12}H_{11}N_3O_5$ + H requires 278.0777.

2-[(2-Methyloxazole-4-carbonyl)carbamoyl]oxazole-4-carboxylic acid methyl ester (26)

Ruthenium(IV) oxide hydrate (2.3 mg, 0.02 mmol) and sodium periodate (618 mg, 2.89 mmol) were added sequentially to a stirred solution of the enamide **25** (200 mg, 0.72 mmol) in carbon tetrachloride (7.3 ml), water (7.3 ml) and acetonitrile (0.4 ml) at room temperature. The mixture was stirred vigorously for 30 min, then chloroform (10 ml) and water (10 ml) were added. The separated aqueous phase was extracted with chloroform (2 × 10 ml) and the combined organic extracts were then washed with saturated aqueous sodium thiosulfate solution (10 ml) and brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (3:2) as eluent to give the *imide* (99 mg, 50%), which recrystallised from ethyl acetate–light petroleum (bp 40–60 °C) as colourless crystals, mp 254–256 °C: ν_{max} (soln, $CHCl_3$)/cm^{-1} 1764; ^1H NMR (360 MHz, $CDCl_3$) δ 1.58 (3H, s, CH_3CN), 3.98 (3H, s, CH_3O), 8.31 (1H, s, C*H*CCONH), 8.44 (1H, s, $CHCCO_2Me$), 10.80 (1H, s, NH); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 13.9 (q), 52.8 (q), 134.4 (s), 134.8 (s), 143.8 (d), 147.3 (d), 151.4 (s), 154.1 (s), 157.8 (s), 160.4 (s), 162.1 (s); *m/z* (EI) 280.0567 (M^+ + H), $C_{11}H_9N_3O_5$ + H requires 280.0570.

Methyl 2-(2-(2-methyloxazol-4-yl)oxazol-4-yl)oxazole-4-carboxylate (30)

Procedure A. A solution of the oxazoline **27** (2.5 mg, 0.009 mmol) in dry degassed benzene (1 ml) was heated under

reflux in the presence of nickel peroxide (30 mg, 0.33 mmol) and 4 Å molecular sieves (10 mg) for 30 min. The mixture was filtered through celite and the filter cake was washed with ethyl acetate (3 × 5 ml). The combined ethyl acetate washings were concentrated *in vacuo* and the residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:1) as eluent to give the *tris*-oxazole (1 mg, 40%) as a crystalline solid.

Procedure B. Bromotrichloromethane (99 μl, 1.0 mmol) was added to a stirred solution of the oxazoline **27** (90 mg, 0.32 mmol) in dry dichloromethane (3 ml) at 0 °C under a nitrogen atmosphere and the mixture was stirred at 0 °C for 10 min. 1,8-Diazabicyclo[5.4.0]undec-7-ene (150 μl, 1.0 mmol) was added dropwise over 5 min and the mixture was allowed to warm to room temperature overnight. The mixture was concentrated *in vacuo* and the residue was then partitioned between ethyl acetate (5 ml) and 10% aqueous citric acid solution (5 ml). The separated organic extract was washed with saturated sodium bicarbonate solution (5 ml), then dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:1) as eluent to give the *tris*-oxazole (70 mg, 81%) as a solid, which recrystallised from ethyl acetate–light petroleum (bp 40–60 °C) as colourless crystals, mp 217–220 °C.

Procedure C. A solution of the oxazoline **29** (13 mg, 0.04 mmol) and CSA (10 mg, 0.04 mmol) in dry toluene (10 ml) was heated under reflux using a Dean–Stark apparatus for 12 h. The mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:1) as eluent to give the *tris*-oxazole (12 mg, 95%), which recrystallised from ethyl acetate–light petroleum (bp 40–60 °C) as colourless crystals, mp 216–219 °C; ν_{max} (soln, $CHCl_3$)/cm^{-1} 1732, 1655 and 1586; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.57 (3H, s, CH_3CN), 3.95 (3H, s, CH_3O), 8.26 (1H, s, C*H*OCCH$_3$), 8.33 (1H, s, CHCCNCCO$_2$Me) 8.42 (1H, s, CHCCO$_2$Me); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 13.9 (q), 52.4 (q), 129.7 (s), 130.9 (s), 134.5 (s), 139.3 (d), 139.3 (d), 143.9 (d), 155.6 (s), 156.4 (s), 161.4 (s), 163.1 (s); *m*/*z* (EI) 276.0618 (M$^+$ + H), 298.0499 (M$^+$ + Na), $C_{12}H_9N_3O_5$ + H requires 276.0620.

Methyl 2-(1-(2-methyloxazole-4-carboxamido)-2-bromo-1-methoxyethyl)oxazole-4-carboxylate (28)

N-Bromosuccinimide (14 mg, 0.08 mmol) was added in one portion to a stirred solution of the enamide **25** (20 mg, 0.07 mmol) in dry methanol (2 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 15 h whereupon a colourless solid precipitated. The solid was filtered and washed with cold methanol to leave the *bromide* (26 mg, 96%) which recrystallised from ethyl acetate–light petroleum (bp 40–60 °C) as colourless crystals, mp 140–142 °C: ν_{max} (soln, $CHCl_3$)/cm^{-1} 3374, 1732 and 1693; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.53 (3H, s, CH_3CN), 3.24 (3H, s, C*H*$_3$OCNH), 3.95 (3H, s, CH_3O_2C), 4.11 (1H, d, *J* 10.7 Hz, C*H*HBr), 4.82 (1H, d, *J* 10.7 Hz, CH*H*Br), 8.13 (1H, s, C*H*CCONH), 8.34 (1H, s, CHCCO$_2$Me), 8.35–8.42 (1H, br, NH); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 13.9 (q), 33.1 (t), 52.5 (q), 52.5 (q), 85.4 (s), 133.3 (s), 135.5 (s), 141.8 (d), 145.6 (d), 160.2 (s), 160.5 (s), 161.1 (s), 161.7 (s); *m*/*z* (EI) 409.9965 (M$^+$ + Na) 355.9899 (M$^+$ − MeOH + H), $C_{13}H_{14}BrN_3O_6$ + Na requires 409.9964.

Methyl 2-(4,5-dihydro-4-methoxy-2-(2-methyloxazol-4-yl)oxazol-4-yl)oxazole-4-carboxylate (29)

Caesium carbonate (18 mg, 0.06 mmol) was added in one portion to a stirred solution of the bromide 28 (11 mg, 0.03 mmol) in dry dioxane (1 ml) at 60 °C under a nitrogen atmosphere. The mixture was stirred at 60 °C for 12 h and then concentrated *in vacuo.* Dichloromethane (10 ml) and 10% aqueous citric acid solution (10 ml), were added and the separated aqueous phase was then extracted with dichloromethane (2 × 5 ml). The combined organic extracts were dried (Na_2SO_4) and then concentrated *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:1) as eluent to give the *oxazoline* (7.4 mg, 88%) as a solid, which recrystallised from ethyl acetate–light petroleum (bp 40–60 °C) as colourless crystals, mp 135–137 °C: ν_{max} (soln, $CHCl_3$)/cm^{-1} 1743, 1725, 1674 and 1584; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.53 (3H, s, CH_3CN), 3.45 (3H, s, C*H*$_3$OCH$_2$), 3.92 (3H, s, CH_3O_2C), 4.67 (1H, d, *J* 10.5 Hz, C*H*HO), 5.05 (1H, d, *J* 10.5 Hz, CH*H*O), 8.15 (1H, s, C*H*CCONH), 8.28 (1H, s, CHCCO$_2$Me); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 13.8 (q), 51.6 (q), 52.3 (q), 74.8 (t), 99.6 (s), 129.7 (s), 133.3 (s), 142.4 (d), 145.0 (d), 161.3 (s), 162.2 (s), 162.5 (s), 162.9 (s); *m*/*z* (EI) 308.0861 (M$^+$ + H), 330.0674 (M$^+$ + Na), 276.0614 (M$^+$ − MeOH + H), $C_{13}H_{13}N_3O_6$ + H requires 308.0883.

(*S*)-4-[(1*S*,7*S*)-7-(*tert*-Butyldiphenylsilanyloxy)-3-hydroxy-8-methoxycarbonyl-1-methyloctyl]-2′,2′-dimethyl-4′,5′-dihydro-[2,4′]bioxazolyl-3′-carboxylic acid *tert*-butyl ester (66)

A solution of the aldehyde **65** (500 mg, 1.5 mmol) and the iodide **59** (3 g, 5.9 mmol) in dry dimethylformamide (12 ml) was added dropwise over 15 min to a stirred suspension of chromium chloride (1.8 g, 14.7 mmol) and vitamin B_{12} (160 mg, 0.12 mmol) (both weighed in a glove bag under an argon atmosphere), in dry dimethylformamide (21 ml) at room temperature with argon bubbling through the solution. The mixture was stirred at room temperature for 3 days and then diluted with water (40 ml) and diethyl ether (210 ml). The separated organic extract was washed with water (3 × 40 ml) and brine (62 ml), then dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by chromatography on silica using diethyl ether–light petroleum (bp 40–60 °C) (1:1 to 1:0) as eluent to give a 1:1 mixture of diastereoisomers of the *alcohol* (760 mg, 72%) as a colourless oil: $[\alpha]_D^{22}$ −21.2 (*c* 1.03 in $CHCl_3$); ν_{max} (soln, $CHCl_3$)/cm^{-1} 3368, 1732 and 1699; ^{1}H NMR (360 MHz; C_6D_6, 333 K) δ 1.16–1.30 (16H, m, (CH$_3$)$_3$CSi, C*H*$_3$CH, C*H*$_2$C*H*$_2$CHOH), 1.36 (9H, s, (CH$_3$)$_3$CO), 1.39–1.64 (7H, m, CH$_3$C, C*H*$_2$CHOSi, C*H*$_2$CHCH$_3$), 1.87 (3H, s, CH$_3$C), 2.52 (1H, dd, *J* 14.9, 4.6 Hz, C*H*HCO$_2$Me), 2.54 (1H, dd, *J* 14.9, 6.8 Hz, CH*H*CO$_2$Me), 2.95 (1H, ddq, *J* 7.0, 6.9, 6.8 Hz, C*H*CH$_3$), 3.33 (3H, s, CH$_3$O), 3.42–3.52 (1H, m, C*H*OH), 3.76 (1H, dd, *J* 8.8, 6.7 Hz, C*H*HCHN), 3.88 (1H, dd, *J* 8.8, 2.6 Hz, CH*H*CHN), 4.37 (1H, app pentet, *J* 5.8 Hz, CHOSi), 4.79–4.91 (1H, m, CHN), 6.99 (1H, s, CHCN), 7.24–7.28 (6H, m, ArH), 7.78–7.83 (4H, m, ArH); ^{13}C NMR (90.6 MHz; C_6D_6, 333 K) δ 19.9 (q), 20.7 (s), 21.7 (t), 25.0 (q), 26.0 (q), 27.7 (3q), 28.7 (3q), 28.8 (d), 38.0 (t), 38.3 (t), 42.5 (t), 45.1 (t), 51.2 (q), 56.0 (d), 67.9

(t), 69.3 (d), 71.5 (d), 80.3 (s), 95.5 (s), 128.2 (2d), 128.3 (2d), 130.3 (2d), 133.8 (d), 135.0 (s), 135.2 (s), 136.7 (4d), 146.6 (s), 151,9 (s), 162.2 (s), 171.7 (s); *m/z* (EI) 723.4001 (M^+ + H), 745.3893 (M^+ + Na), $C_{40}H_{58}N_2O_8Si$ + H requires 723.4041.

(*S*)-4-[(1*S*,7*S*)-7-(*tert*-Butyldiphenylsilanyloxy)-8-methoxycarbonyl-1-methyl-3-oxooctyl]-2′,2′-dimethyl-4′,5′-dihydro-[2,4′]bioxazolyl-3′-carboxylic acid *tert*-butyl ester (67a)

DMSO (2.1 ml, 29.5 mmol) was added dropwise over 10 min to a stirred solution of oxalyl chloride (1.55 ml, 17.8 mmol) in dry dichloromethane (10 ml) at −78 °C under a nitrogen atmosphere. The solution was stirred at −78 °C for 15 min and then a solution of the alcohol **66** (984 mg, 11.8 mmol) in dry dichloromethane (10 ml) was added dropwise over 15 min. The mixture was stirred at −78 °C for 1.5 h, then triethylamine (9.4 ml, 67.3 mmol) was added dropwise over 15 min. The mixture was allowed to warm to room temperature, then diluted with water (10 ml). The separated aqueous phase was extracted with dichloromethane (2 × 20 ml) and the combined dichloromethane extracts were then dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by chromatography on silica using diethyl ether–light petroleum (bp 40–60 °C) (1:1) as eluent to give the *ketone* (869 mg, 87%) as a colourless oil: $[\alpha]_D^{22}$ −69.4 (*c* 1.90 in $CHCl_3$); ν_{max} (soln, $CHCl_3$)/cm^{-1} 1731 and 1699; (Found: C, 66.8; H, 7.8; N, 3.9; $C_{40}H_{56}N_2O_8Si$ requires C, 66.6; H, 7.8; N, 3.9%); ^{1}H NMR (400 MHz; C_6D_6, 333 K) δ 1.10–1.16 (12H, m, $(CH_3)_3CSi$, CH_3CH), 1.34 (9H, s, $(CH_3)_3CO$), 1.41–1.48 (4H, m, CH_2CH_2CHOSi), 1.58 (3H, s, CH_3C), 1.81–1.91 (5H, m, $CH_2COCH_2CHCH_3$, CH_3C), 2.13–2.22 (1H, m, $CHHCHCH_3$), 2.37 (1H, dd, *J* 14.9, 5.7 Hz, $CHHCO_2Me$), 2.51 (1H, dd, *J* 14.9, 6.6 Hz, $CHHCO_2Me$), 2.57 (1H, dd, *J* 16.5, 6.2 Hz, $CHHCHCH_3$), 3.23 (1H, ddq, *J* 6.8, 6.7, 6.6 Hz, $CHCH_3$), 3.33 (3H, s, CH_3O), 3.81 (1H, dd, *J* 8.9, 6.5 Hz, $CHHCHN$), 3.89 (1H, dd, *J* 8.9, 3.3 Hz, $CHHCHN$), 4.32 (1H, app pentet, *J* 5.4 Hz, CHOSi), 4.84–5.01 (1H, m, CHN), 6.98 (1H, s, CHCN), 7.23–7.27 (6H, m, ArH), 7.74–7.80 (4H, m, ArH); ^{13}C NMR (90.6 MHz; C_6D_6, 333 K) δ 19.3 (t), 19.5 (q), 19.5 (s), 24.7 (q), 25.6 (q), 27.3 (3q), 27.4 (d), 28.3 (3q), 36.9 (t), 41.9 (t), 42.7 (t), 48.5 (t), 50.9 (q), 55.7 (d), 67.6 (t), 70.7 (d), 79.8 (s), 95.1 (s), 127.8 (2d), 127.9 (2d), 129.9 (2d), 133.3 (d), 134.5 (s), 134.6 (s), 136.2 (2d), 136.3 (2d), 145.8 (s), 151,5 (s), 163.3 (s), 171.1 (s), 207.0 (s); *m/z* (EI) 721.3845 (M^+ + H), 745.3893 (M^+ + Na), $C_{40}H_{56}N_2O_8Si$ + H requires 721.3884.

The *bis*-oxazole ester (68)

The ester was prepared from the carboxylic acid **67b** (150 mg, 0.212 mmol) and the alcohol **47b** (118 mg, 0.18 mmol) under Yamaguchi conditions, using the procedure described for the synthesis of the ester **75** from **55b** and **67b**. It was purified by chromatography on silica, using diethyl ether–light pretroleum (bp 40–60 °C) (1:1 to 1:3) as eluent, and was obtained as an oil (96%), which showed, $[\alpha]_D^{22}$ −21.3 (c 1.50 in $CHCl_3$); ν_{max} (soln, $CHCl_3$, cm^{-1}) 1717, 1703; ^{1}H NMR (360 MHz, $CDCl_3$) (rotamers) δ 0.88 (3H, d, *J* 6.6 Hz, CH_3 CH), 0.90 (3H, d, *J* 6.7 Hz, CH_3CH), 1.05 (9H, $SiCMe_3$), 1.07 (9H, $SiCMe_3$), 1.21 (3H, d, *J* 6.6 Hz, CH_3 CH), 1.27–1.65 (27H, m), 1.68–1.93 (5H, m), 2.13 (2H, t, *J* 7.6 Hz, CH_2CH_2CO), 2.36–2.58 (5H, m), 2.73 (1H, dd, *J* 17.0 and 5.7 Hz, $CHHCO$), 3.11–3.27 (3H, m), 3.24 (3H, OMe), 3.26 (3H, OMe), 3.57 (1H, dd, *J* 10.0 and 6.2 Hz, $CHHOSi$), 3.67 (1H, dd, *J* 10.0 and 6.1 Hz, CHH OSi), 4.03–4.27 (3H, m), 4.98 (0.7H, dd, *J* 6.2 and 3.4 Hz, CHN), 5.04–5.15 (1.3H, m, CHN and CH.OC=O), 6.4 (1H, d, *J* 16 Hz, CH=$CHCH_2$), 6.78 (1H, dt, J 16 and 7.5 Hz, CH=$CHCH_2$), 7.27 (0.3H, OCH=CHMe), 7.31 (0.7H, OCH=CHMe), 7.36–7.47 (12H, m), 7.65–7.72 (8H, m, ArH), 8.01 (1H, OCH=); ^{13}C NMR (90 MHz, $CDCl_3$)(rotamers) 9.3 (q), 12.2 (q), 18.7 (q), 19.2 (s), 19.3 (s), 19.3 (q), 24.3 (q), 25.1 (q), 26.7 (d), 26.9 (q), 28.1 (q), 28.2 (q), 28.3 (q), 32.9 (t),34.9 (t), 36.0 (t), 38.7 (d), 40.1 (d), 41.7 (t), 42.8 (t), 48.2 (t), 55.2 (d), 57.7 (q), 58.6 (q), 65.0 (t), 67.4 (t), 69.5 (d), 72.9 (d), 78.5 (d), 80.1 (s), 80.8 (d), 82.0 (s), 94.4 (s), 94.9 (s), 118.2 (d), 127.6 (2 × d), 129.6 (d), 129.7 (2 × d), 133.1 (d), 133.3 (d), 133.7 (2 × s), 133.9 (s), 135.3 (s), 135.5 (2 × d), 135.8 (d), 135.9 (d), 137.7 (d), 142.5 (d), 145.0 (s), 151.2 (s), 151.9 (s), 160.5 (s), 161.2 (s), 162.6 (s), 162.8 (s), 170.6 (s), 208.5 (s), 208.8 (s). *m/z* (ESI) 1354.7366 (M^+ + H), $C_{77}H_{108}N_3O_{14}Si_2$ requires 1354.7370.

The *bis*-oxazole macrolactam (70)

The macrolactam was prepared from the ester **68** using TMSOTf–Et_3N in CH_2Cl_2 at 0 °C to give, first, the corresponding amino acid **69**. The amino acid was then treated with DPPA–Et_3N in DMF at 0 °C (*cf.* HATU–Et_3N in CH_2Cl_2 used in the synthesis of **17** from **75**), to give the macrolactam (68%) as a viscous oil, $[\alpha]_D^{22}$ +2.2 (c 0.55 in $CHCl_3$); ν_{max} (soln, $CHCl_3$, cm^{-1}) 3646, 3398, 1718, 1670; ^{1}H NMR (360 MHz, $CDCl_3$), 0.81 (3H, d, *J* 6.9 Hz, CH_3 CH), 0.84 (3H, d, *J* 6.9 Hz, CH_3CH), 1.03 (9H, CMe_3), 1.04 (9H, CMe_3), 1.24 (3H, d, *J* 7.0 Hz, CH_3CH), 1.38–162 (6H, m), 1.77–1.86 (2H, m), 2.08–2.26 (2H, m), 2.36 (1H, dd, *J* 16.2 and 5.1 Hz, $CHHC$=O), 2.4–2.59 (4H, m), 2.86 (1H, dd, *J* 16.2 and 9.2, CH*H*.C=O), 3.06–3.15 (2H, m, 2 × $CHOMe$), 3.2 (3H, OMe), 3.28 (3H, OMe), 3.27–3.34 (1H, m), 3.41 (1H, brt, *J* 5.8 Hz, O*H*), 3.54 (1H, dd, *J* 9.9 and 6.3 Hz, $CHHOSi$), 3.62 (1H, dd, *J* 9.9 and 6.0 Hz, CHH OSi), 3.99–4.13 (3H, m), 5.0–5.06 (1H, m), 5.35 (1H, dt, *J* 8.1 and 3.9 Hz, $CHNH$), 6.34 (1H, d, *J* 16 Hz, CH=CH.CH_2), 6.81 (1H, dt, *J* 16 and 7.5, =$CHCH_2$), 7.32–7.46 (13H, m), 7.64–7.69 (8H, m, ArH), 7.88 (1H, d, *J* 8.1 Hz, NH), 8.09 (1H, OCH=). ^{13}C NMR (90 MHz, $CDCl_3$), 9.4 (q), 12.0 (q), 18.6 (q), 19.2 (2 × s), 19.9 (q), 26.9 (d), 26.9 (2 × q), 32.4 (t), 33.7 (t), 35.6 (t), 38.7 (d), 39.7 (d), 42.0 (t), 43.2 (t), 48.3 (t), 49.0 (d), 57.4 (q), 58.6 (q), 64.2 (t), 64.9 (t), 69.5 (d), 72.4 (d), 78.4 (d), 80.6 (d), 118.1 (d), 127.6 (d), 129.6 (2 × d), 129.7 (2 × d), 133.7 (2 × s), 133.8 (s), 133.9 (s), 134.5 (d), 135.5 (d), 135.6 (d), 135.8 (d), 136.1 (s), 137.3 (d), 140.5 (d), 144.1 (s), 160.8 (s), 161.1 (s), 170.1 (s), 209.6 (s). *m/z* (ESI) 1140.5806 (M^+ + H), $C_{65}H_{86}N_3O_{11}Si_2$ requires 1140.5801.

The oxazoline *bis*-oxazole macrolide (71)

The oxazoline was prepared from the macrolactam **70** using DAST in CH_2Cl_2, and following the procedure described for the synthesis of the analogous oxazoline **76a** from **17**. It was purified by chromatography on silica, using diethyl ether–light petroleum (bp 40–60 °C) (1:1 to 1:99) as eluent, and was obtained as a viscous oil (92%) which showed $[\alpha]_D^{22}$ + 64.5 (c 0.4 in $CHCl_3$); ν_{max} (soln, $CHCl_3$, cm^{-1}) 1716, 1679; ^{1}H NMR (360 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.9 Hz, $CHMe$), 0.89 (3H, d, *J* 7.0 Hz, $CHMe$), 1.02 (9H,

CMe_3), 1.08 (9H, CMe_3), 1.18–1.23 (1H, m), 1.23 (3H, d, *J* 7.0 Hz, CH*Me*), 1.35–1.56 (5H, m), 1.67–1.77 (2H, m), 1.79–1.94 (2H, m), 2.19 (1H, dd, J 16.4 and 4.3 Hz, C*H*H.C=O), 2.37 (2H, d, *J* 6.2 Hz, CH_2 CO_2), 2.46–2.64 (2H, m, =CHCH_2), 2.85 (1H, dd, *J* 16.5 and 9.5 Hz, C*H*HC=O), 3.07 (1H, td, *J* 6.3 and 2.8 Hz, C*H*OMe), 3.31–3.18 (2H, m), 3.31 (3H, OMe), 3.34 (3H, OMe), 3.58 (1H, dd, *J* 10.1 and 6 Hz, C*H*HOSi), 3.64 (1H, dd, *J* 10.1 and 6.2 Hz, CH*H* OSi), 3.97–4.05 (1H, m), 4.68 (1H, dd, *J* 9.5 and 8.8 Hz, C*H*HCHN), 4.98 (1H, dd, *J* 8.7 and 4.4 Hz, C*H*.OC=O), 5.05 (1H, dd, *J* 6.7 and 8.8 Hz, CH*H*.CHN), 5.43 (1H, dd, *J* 9.9 and 6.4 Hz, CHN), 6.43 (1H, d, *J* 16.2 Hz, C*H*=CH.CH_2), 6.85 (1H, ddd, *J* 16.2, 8.1 and 6.5 Hz, CH_2C*H*=CH), 7.35 (1H, C*H*=), 7.35–7.50 (12H, m), 7.62–7.75 (8H, m), 8.01 (1H, OC*H*=); ^{13}C NMR (90 MHz, $CDCl_3$) 9.1 (q), 12.1 (q), 18.3 (t), 19.3 (2 × s), 26.4 (q), 26.5 (d), 26.8 (q), 26.9 (q), 32.1 (t), 32.5 (t), 35.6 (t), 38.6 (q), 39.1 (q), 41.5 (t), 43.2 (t), 47.8 (t), 57.2 (q), 59.2 (q), 63.3 (d), 65.0 (t), 69.3 (d), 7.10 (t), 72.0 (d), 78.5 (d), 81.6 (d), 118.9 (d), 237.5 (d), 127.6 (d), 129.6 (d), 129.8 (d), 130.8 (s), 133.7 (2 × 5), 133.8 (s), 134.0 (s), 134.2 (d), 135.5 (d), 135.6 (d), 135.8 (d), 135.9 (d), 136.4 (d), 140.2 (d), 144.3 (s), 159.4 (s), 161.9 (s), 162.7 (s), 169.9 (s), 209.7 (s); *m/z* (ESI) 1122.5674 (M^+ + H) $C_{65}H_{84}N_3O_{10}Si_2$ requires 1122.5695.

The *tris*-oxazole macrolide (72b)

The *tris*-oxazole **72a** was produced by oxidation of the oxazoline *bis*-oxazole **71**, using NiO_2 in benzene, following the procedure described for the preparation of the analogous *tris*-oxazole **76** from **78a**. Recovered **78a** was continuously recycled to produce the *tris-oxazole* (55%) as an oil, which showed $[\alpha]_D^{22}$ +14.5 (c 0.24 in $CHCl_3$); ν_{max} (soln, $CHCl_3$, cm^{-1}) 1728, 1714; ^{1}H NMR (500 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.9 Hz, CH*Me*), 0.85 (3H, d, *J* 6.9 Hz, CH*Me*), 1.02 (9H, CMe_3), 1.04 (9H, CMe_3), 1.29 (3H, d, *J* 6.9 Hz, CH*Me*), 1.46 (1H, ddd, *J* 14.4, 10.0 and 1.9 Hz, C*H*H.CHOMe), 1.58 (1H, ddd, *J* 14.4, 10.3 and 1.7 Hz, CH*H*.CHOMe), 1.65–1.79 (4H, m), 1.83–1.91 (2H, m), 2.27–2.30 (1H, m), 2.35 (1H, d, *J* 6.1 Hz, C*H*H.CO), 2.38 (1H, d, *J* 5.7, C*H*H.CO), 2.46 (1H, app, dt, *J* 15.1 and 8.3 Hz, C*H*H.CH=), 2.50 (1H, dd, J 15.9 and 6.9 Hz, C*H*H.CO_2), 2.57 (1H, dd, *J* 15.9 and 5.2 Hz, CH*H*.CO_2), 2.59–2.66 (1H, m), 3.14 (1H, dd, *J* 16.6 and 7.7 Hz, C*H*H.CO), 3.2–3.24 (1H, m), 3.25 (3H, OMe), 3.27 (3H, OMe), 3.40 (1H, app. sex, *J* 6.7 Hz, CH_3C*H*CH_2C=O), 3.52 (1H, dd, *J* 10.0 and 6.5 Hz, C*H*HOSi), 3.63 (1H, dd, *J* 10.0 and 6.2 Hz, CH*H*OSi), 4.29 (1H, app. qn, *J* 5.4 Hz, CH_2C*H*OSi), 5.06 (1H, ddd, *J* 8.0, 5.7 and 2.3 Hz, C*H*O.C=O), 6.35 (1H, d, *J* 15.9 Hz, CH_2CH=C*H*), 7.10 (1H, ddd, *J* 15.9, 8.6 and 6.0 Hz, CH_2C*H*=), 7.30–7.43 (13H, m), 7.63–7.73 (8H, m), 8.05 (2H, OC*H*=); ^{13}C NMR (125 MHz, $CDCl_3$) 8.70 (q), 12.0 (q), 19.2 (s), 19.3 (s), 19.4 (t), 19.7 (q), 26.9 (q) 27.0 (q and d), 33.0 (2 × t), 36.2 (t), 39.0 (d), 41.5 (t), 44.0 (t), 47.5 (t), 57.3 (q), 58.8 (q), 65.1 (t), 69.6 (d), 72.8 (t) 78.4 (d), 80.5 (d), 117.3 (d), 127.5 (d), 127.6 (d), 129.5 (d), 130.5 (s), 131.8 (s), 133.4 (d), 133.8 (2 × s), 134.1 (s), 134.2 (s), 135.5 (d), 135.6 (d), 135.8 (d), 135.9 (d), 136.9 (d), 137.2 (d), 138.7 (d), 146.5 (s), 154.1 (s), 156.4 (s), 162.3 (s), 170.5 (s), 210.5 (s). *m/z* (ESI) 1120.5569 (M^+ + H). $C_{65}H_{82}N_3O_{10}Si_2$ requires 1120.5539.

The corresponding alcohol **72b** was prepared from the silyl ether **72a**, using HF–pyridine complex in dry THF, following the procedure described for the deprotection of **47a** to **47b**. It was purified by chromatography on silica, using diethyl ether–ethyl acetate (1:1, then 1:99) as eluent, and was obtained as a viscous oil which was used immediately in the next step.

The *tris*-oxazole macrolide conjugated enone (75)

Powdered sodium hydrogencarbonate (7.1 mg, 84 μ mol) and Dess–Martin periodinane (7.4 mg, 17 μmol) were added to a solution of the alcohol **72b** (7.4 mg, 8.4 μmol) in dichloromethane (800 μ) at room temperature and the mixture was stirred for 2h. More Dess–Martin periodinane (3.7 mg) was added and the mixture was stirred at room temperature for a further 1h. Saturated sodium thiosulfate (500 μl) and saturated sodium hydrogencarbonate (500 μl), followed by ether (2 ml), were added and the separated aqueous phase was then extracted with diethyl ether (3 × 2 ml). The combined organic extracts were washed with brine (1 ml) then dried and evaporated in vacuo. The residue containing the aldehyde **73** was reacted with the β-ketophosphonate **74** (5.3 mg, 11 μmol) in THF-H_2O (180 μl) in the presence of $Ba(OH)_2{\cdot}8H_2O$ (2.8 mg, 9 μl), using the procedure described for the synthesis of the conjugated enone **52** from **50b** and **51**. Chromatography on silica, using diethyl ether as eluent, gave the *enone* (4.1 mg, 36%) as an oil, $[\alpha]_D^{22}$ −27.3 (c 0.41 in $CHCl_3$); ν_{max} (soln, $CHCl_3$, cm^{-1}) 1732, 1709; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.10 (3H, SiMe), 0.04 (3H, SiMe), 0.80 (3H, d, *J* 7.0 Hz, CH_3 CH), 0.81 (9H, CMe_3), 0.87 (3H, d, *J* 6.8 Hz, CH_3CH), 0.97 (3H, d, *J* 7.5 Hz, CH_3CH), 0.99 (3H, d, *J* 7.4 Hz, CH_3CH), 1.03 (9H, CMe_3), 1.05 (9H, CMe_3), 1.28 (3H, d, *J* 6.9 Hz, CH_3CH), 1.41–1.53 (3H, m), 1.70–1.80 (5H, m), 1.83–1.93 (2H, m), 2.24–2.36 (2H, m), 2.39 (1H, dd, *J* 16.7 and 5.6 Hz, C*H*H.CO), 2.40–2.47 (1H, m), 2.54 (1H, dd, *J* 15.6 and 6.4 Hz, C*H*H.CO_2), 2.59 (dd, *J* 15.6 and 5 Hz, CH*H* CO_2), 2.57–2.7 (2H, m), 2.98 (1H, app. qn, *J* 7.5 Hz, CH_3CH.C=O), 3.04 (1H, ddd, *J* 9.9, 4.1 and 2.1 Hz, CH_2C*H* OMe), 3.15 (1H, dd, *J* 16.7 and 7.7 Hz, CH*H*CO), 3.16–3.20 (1H, m), 3.28 (3H, OMe), 3.31 (3H, OMe), 3.4 (1H, app. sx, *J* 6.7 Hz, CH_3C*H*.CH_2C=O), 3.64 (1H, app. dt, *J* 9.1 and 5.6 Hz, C*H*H.OSi), 3.75 (1H, ddd, *J* 10.4, 7.6 and 5.3 Hz, CH*H*.OSi), 3.92 (1H, dd, *J* 8.1 and 2.2 Hz, CH_2OTBS), 4.29 (2H, app. qn, *J* 5.3 Hz, CH_2C*H*OSi), 5.10 (1H, dd, *J* 9.6, 7.0 and 2.0, C*H*OC=O), 6.17 (1H, dd, *J* 16.0 and 1.0 Hz, CH.C=O), 6.34 (1H, d, *J* 15.9 Hz, CH_2CH =C*H*), 6.87 (1H, dd, *J* 15.9 and 6.5 Hz, C*H*=CH.C=O), 7.07 (1H, ddd, *J* 15.7, 8.4 and 6.2 Hz, CH_2C*H*=), 7.30–7.46 (13H, m), 7.65–7.73 (8H, m, ArH), 8.05 (1H, OC*H*=), 8.05 (1H, OC*H*=); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.3 (q), −4.0 (q), 8.6 (q), 14.3 (q), 14.6 (q), 16.6 (q), 18.4 (s) 19.2 (s), 19.4 (s), 19.5 (t), 19.7 (q), 26.2 (q), 26.9 (q), 27.1 (q), 32.6 (t), 32.7 (d), 33.1 (t), 33.5 (t), 36.3 (t) 38.3 (d), 39.3 (d), 41.4 (t), 44.1 (t), 47.6 (t), 48.4 (d), 57.4 (q), 58.1 (q), 62.2 (q), 69.7 (d), 72.6 (d), 78.5 (d), 80.4 (d), 80.9 (d), 117.2 (d), 127.6 (d), 127.7 (d), 129.6 (d), 130.4 (d), 130.6 (s), 131.9 (s), 133.5 (d), 134.0 (s), 134.1 (s), 134.2 (s), 135.6 (d), 135.9 (d), 136.0 (d), 137.0 (d), 137.3 (d), 138.8 (d), 146.5 (s), 147.8 (d), 154.2 (s), 156.5 (s), 162.4 (s), 170.4 (s), 203.2 (s), 210.4 (s); *m/z* 1405.7489 (M^+ + H_2O). $C_{80}H_{111}O_{13}N_3Si_2$ requires 1405.7425.

The *bis*-oxazole macrolactam (17) (P = TBDPS; P′ = TMS)

Trimethylsilyl trifluromethanesulfonate (258 μl, 1.42 mmol), was added dropwise over 5 min to a stirred solution of the acetonide **77** (117 mg, 0.072 mmol) and triethylamine (229 μl, 1.64 mmol) in dry dichloromethane (14 ml) at 0 °C under a nitrogen atmosphere.

The solution was allowed to warm to room temperature and stirred at this temperature for 48 h. Saturated aqueous ammonium chloride solution (700 μl) and diethyl ether (250 ml) were added and the mixture was stirred vigorously at room temperature for 30 min. The separated organic phase was dried (Na_2SO_4) and then concentrated *in vacuo* to leave the crude *amino alcohol* **18a** (P′ = TBS) as an oil.

HATU (36 mg, 0.095 mmol) was added in one portion to a stirred solution of crude amino alcohol and triethylamine (13 μl, 0.095 mmol) in dry dichloromethane (35 ml) at 0 °C, under a nitrogen atmosphere. The solution was allowed to warm to room temperature and stirred at this temperature for six days. Saturated aqueous sodium bicarbonate solution (10 ml) was added and the separated aqueous phase was then extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried (Na_2SO_4) and then concentrated *in vacuo.* The residue was purified by chromatography on silica using diethyl ether–light petroleum (bp 40–60 °C) (1:1 to 0:1) as eluent to give the *macrocycle* (68 mg, 67%) as a colourless oil, which crystallised from diethyl ether, light petroleum (bp 40–60 °C) as colourless crystals, mp 57–59 °C: $[\alpha]_D^{31}$ −6.4 (*c* 1.0 in $CHCl_3$); ν_{max} (soln, $CHCl_3$)/cm^{-1} 3399, 2931, 2857, 1715, 1671 and 1596; (Found: C, 68.0; H, 8.4; N, 2.9 $C_{80}H_{115}N_3O_{13}Si_3$ requires C, 68.1; H, 8.2; N, 3.0%); ^{1}H NMR (400 MHz, $CDCl_3$) δ− 0.04 (3H, s, CH_3Si), 0.07 (3H, s, CH_3Si), 0.77 (3H, d, *J* 6.8 Hz, CH_3-29), 0.84 (3H, d, *J* 7.3 Hz, CH_3-39), 0.88 (9H, s, $(CH_3)_3CSi(CH_3)_2$), 0.90 (3H, d, *J* 7.2 Hz, CH_3-33), 0.95 (3H, d, *J* 7.0 Hz, CH_3-37), 1.07 (9H, s, $(CH_3)_3CSi(Ph)_2$), 1.08 (9H, s, $(CH_3)_3CSi(Ph)_2$), 1.25 (3H, d, *J* 6.9 Hz, CH_3-9), 1.33–1.38 (1H, m, C*H*H H-40), 1.40–1.48 (4H, m, H-31, H-4), 1.53–1.63 (2H, m, H-5), 1.68–1.89 (5H, m, CH*H* H-40, H-33, H-29, H-34), 1.95 (1H, m, H-39), 2.11–2.29 (2H, m, H-6), 2.37 (1H, dd, *J* 16.3, 5.0 Hz, C*H*H H-8), 2.47 (2H, app d, *J* 6.4 Hz, H-2), 2.51 (2H, t, *J* 7.6 Hz, H-35), 2.55–2.64 (2H, m, H-27), 2.74–2.85 (2H, m, H-37, H-32), 2.88 (1H, dd, *J* 16.3, 9.2 Hz, CH*H* H-8), 3.13 (1H, m, H-28), 3.24 (3H, s, CH_3OC-32), 3.30–3.35 (1H, m, H-9), 3.34 (3H, s, CH_3OC-28), 3.60–3.70 (1H, m, C*H*H H-41), 3.72–3.79 (1H, m, CH*H* H-41), 3.82 (1H, dd, *J* 8.1, 2.3 Hz, H-38), 4.00–4.15 (1H, m, H-3), 4.02 (1H, dd, *J* 11.3, 3.9 Hz, C*H*H H-19), 4.06–4.14 (1H, m, CH*H* H-19), 5.03–5.13 (1H, m, H-30), 5.35 (1H, app dt, *J* 8.1, 3.9 Hz, H-15), 6.34 (1H, d, *J* 16.0 Hz, H-25), 6.82 (1H, dt, *J* 16.0, 7.2 Hz, H-26), 7.35–7.49 (13H, m, ArH & H-14), 7.65–7.73 (8H, m, ArH), 7.88 (1H, d, *J* 8.1 Hz H-16), 8.12 (1H, s, H-24); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.4 (q), −1.1 (q), 9.5 (q), 14.1 (q), 15.6 (q), 16.2 (q), 18.4 (s), 18.6 (t), 19.2 (s), 19.3 (s), 19.9 (q), 24.4 (t), 26.2 (3q), 26.9 (3q), 27.0 (3q), 30.8 (t), 33.1 (d), 33.8 (2t), 34.1 (d), 35.6 (t), 39.8 (d), 42.0 (t), 42.5 (t), 43.3 (t), 48.4 (t), 49.1 (d), 50.0 (d), 57.5 (q), 57.9 (q), 62.1 (t), 64.3 (t), 69.6 (d), 72.5 (d), 78.6 (d), 80.6 (d), 81.7 (d), 118.2 (d), 125.6 (d), 127.7 (8d), 129.6 (2d), 129.8 (2d), 133.8 (s), 134.9 (2 s), 134.0 (2 s), 134.6 (d), 135.6 (4d), 135.9 (2d), 135.9 (2d), 136.2 (s), 137.5 (d), 140.6 (d), 144.2 (s), 160.9 (s), 161.2 (s), 170.1 (s), 209.7 (s), 214.0 (s); *m*/*z* (EI) 1410.7807 (M^+ + H), 1432.7594 (M^+ + Na), $C_{80}H_{115}N_3O_{13}Si_3$ + H requires 1410.7816.

The oxazoline *bis*-oxazole macrolide (78a)

(Diethylamino)sulfur trifluoride (7 μl, 0.053 mmol) was added in one portion to a stirred solution of the macrocycle **17** (48 mg, 0.035 mmol) in dry dichloromethane (1 ml) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for 2 h, then allowed to warm to room temperature and stirred at this temperature for a further 10 min. The mixture was quenched with saturated sodium bicarbonate solution (2 ml) and the separated organic phase was then dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by chromatography on silica using diethyl ether–light petroleum (bp 40–60 °C) (2:3) as eluent to give the *oxazoline* (43 mg, 89%) as a colourless oil: $[\alpha]_D^{26}$ +22.9 (*c* 2.9 in $CHCl_3$); ν_{max} (soln, $CHCl_3$)/cm^{-1} 2931, 2858, 1714, 1679 and 1598; ^{1}H NMR (400 MHz, $CDCl_3$) δ−0.03 (3H, s, CH_3Si), 0.09 (3H, s, CH_3Si), 0.76 (3H, d, *J* 7.2 Hz, CH_3-29), 0.80 (3H, d, *J* 6.8 Hz, CH_3-39), 0.82–0.90 (3H, m, CH_3-33), 0.86 (9H, s, $(CH_3)_3CSi(CH_3)_2$), 0.95 (3H, d, *J* 6.8 Hz, CH_3-37), 1.00 (9H, s, $(CH_3)_3CSi(Ph)_2$), 1.05 (9H, s, $(CH_3)_3CSi(Ph)_2$), 1.20 (3H, d, *J* 7.2 Hz, CH_3-9), 1.24–1.49 (7H, m, C*H*H H-40, H-31, H-4, H-5), 1.62–1.92 (6H, m, CH*H* H-40, H-39, H-33, H-29, H-34), 2.17 (1H, dd, *J* 16.5, 4.3 Hz, C*H*H H-6), 2.22–2.31 (1H, m, C*H*H H-8), 2.31–2.40 (1H, m, CH*H* H-2), 2.37 (1H, dd, *J* 9.2, 6.3 Hz, C*H*H H-2), 2.41–2.63 (5H, m, CH*H* H-6, H-27, H-35), 2.70–2.81 (1H, m, H-37), 2.81–2.87 (2H, m, H-32, CH*H* H-8), 3.08 (1H, app dt, *J* 6.4, 2.9 Hz, H-28), 3.21–3.41 (1H, m, H-9), 3.30 (3H, s, CH_3OC-32), 3.35 (3H, s, CH_3OC-28), 3.59–3.69 (1H, m, C*H*H H-41), 3.71–3.79 (1H, m, CH*H* H-41), 3.85 (1H, dd, *J* 8.0, 2.4 Hz, H-38), 3.97 (1H, dddd, *J* 5.3, 5.2, 5.1, 5.0 Hz, H-3), 4.65 (1H, dd, *J* 10.0, 8.4 Hz, C*H*H H-19), 4.97 (1H, ddd, *J* 4.7, 4.6, 4.5 Hz, H-30), 5.03 (1H, dd, *J* 8.4, 6.4 Hz, CH*H* H-19), 5.40 (1H, dd, *J* 10.0, 6.4 Hz, H-15), 6.40 (1H, d, *J* 16.2 Hz, H-25), 6.82 (1H, dt, *J* 16.2, 6.4 Hz, H-26), 7.33 (1H, s, H-14), 7.35–7.52 (12H, m, ArH), 7.61–7.75 (8H, m, ArH), 8.01 (1H, s, H-24); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ −4.2 (q), −4.1 (q), 9.31 (q), 14.2 (q), 15.7 (q), 16.2 (q), 18.3 (t), 18.4 (s), 19.3 (s), 19.3 (s), 20.5 (q), 24.4 (t), 26.2 (3q), 26.6 (3q), 26.9 (3q), 30.1 (t), 32.6 (t), 33.1 (d), 33.8 (t), 34.2 (d), 35.6 (t), 38.8 (d), 41.5 (t), 42.5 (t), 43.3 (t), 47.8 (t), 50.1 (d), 57.3 (q), 58.3 (q), 62.2 (t), 63.4 (d), 69.5 (d), 71.0 (t), 72.1 (d), 78.6 (d), 81.6 (d), 82.1 (d), 118.9 (d), 127.6 (d), 127.7 (8d), 129.6 (3d), 129.9 (d), 130.8 (s), 133.8 (2 s), 134.0 (2 s), 134.1 (s), 134.3 (d), 135.6 (4d), 135.9 (2d), 136.1 (2d), 136.7 (d), 140.3 (d), 144.3 (s), 159.5 (s), 162.0 (s), 170.0 (s), 209.8 (s), 214.0 (s); *m*/*z* (EI) 1414.7398 (M^+ + Na), $C_{80}H_{113}N_3O_{12}Si_3$ + Na requires 1414.7530.

The *tris*-oxazole macrolide (76)

Procedure A. A solution of the oxazoline **78a** (14 mg, 0.01 mmol), nickel peroxide (34 mg, 0.38 mmol) and 4 Å molecular sieves (20 mg) in dry degassed benzene (1 ml) was heated under reflux for 12 h. The mixture was filtered through celite and the filter cake was washed with ethyl acetate (3 × 5 ml). The combined ethyl acetate washings were concentrated *in vacuo* and the residue was then purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:9 to 2:3) as eluent to give the *tris-oxazole* (3.6 mg, 25%), which recrystallised from ethyl acetate–light petroleum (bp 40–60 °C) as colourless crystals, mp 72–75 °C: $[\alpha]_D^{26}$–24.8 (*c* 1.0 in $CHCl_3$); ν_{max} (soln, $CHCl_3$)/cm^{-1} 2931, 2858 and 1713; ^{1}H NMR (400 MHz, $CDCl_3$) δ-0.07 (3H, s, CH_3Si), 0.04 (3H, s, CH_3Si), 0.78 (3H, d, *J* 6.8 Hz, CH_3-29), 0.82–0.86 (3H, m, CH_3-39), 0.85 (9H, s, $(CH_3)_3CSi(CH_3)_2$), 0.87 (3H, d, *J* 7.0 Hz, CH_3-33), 0.94 (3H, d, *J* 7.0 Hz, CH_3-37), 1.03 (9H, s, $(CH_3)_3CSi(Ph)_2$), 1.05 (9H, s, $(CH_3)_3CSi(Ph)_2$), 1.25–1.40 (1H, m, C*H*H H-40), 1.28 (3H, d, *J* 7.0 Hz, CH_3-9), 1.38–1.62 (5H, m, C*H*H H-4, H-31, H-33, C*H*H H-34), 1.65–1.82 (5H, m, CH*H*

H-4, H-5, CH*H* H-34, CH*H* H-40), 1.83–1.95 (2H, m, H-29, H-39), 2.21–2.46 (2H, m, H-6), 2.38 (1H, dd, *J* 16.6, 5.5 Hz, C*H*H H-8), 2.44–2.54 (3H, m, C*H*H H-27, H-35), 2.57 (2H, app dd, *J* 5.4, 3.7 Hz, CH*H* H-2), 2.65 (1H, ddd, *J* 16.9, 6.4, 4.1 Hz, CH*H* H-27), 2.75 (1H, dq, *J* 8.0, 7.0 Hz, H-37), 2.88–2.96 (1H, m, H-32), 3.15 (1H, dd, *J* 16.6, 7.8 Hz, CH*H* H-8), 3.18–3.25 (1H, m, H-28), 3.28 (3H, s, CH_3OC-32), 3.32 (3H, s, CH_3OC-28), 3.41 (1H, app q, *J* 7.0 Hz, H-9), 3.64 (1H, ddd, *J* 14.5, 9.8, 4.5 Hz C*H*H H-41), 3.74 (1H, ddd, *J* 9.8, 6.4, 4.4 Hz, CH*H* H-41), 3.83 (1H, dd, *J* 8.0, 2.4 Hz, H-38), 4.29 (1H, dddd, *J* 5.5, 5.4, 5.3, 5.2 Hz, H-3), 5.11 (1H, ddd, *J* 9.0, 6.2, 1.2 Hz, H-30), 6.35 (1H, d, *J* 15.3 Hz, H-25), 7.09 (1H, ddd, *J* 15.3, 8.6, 6.4 Hz, H-26), 7.30–7.49 (13H, m, ArH, H-14), 7.64–7.76 (8H, m, ArH), 8.05 (2H, s, H-19, H-24); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ-4.4 (q), -4.1 (q), 8.8 (q), 14.1 (q), 15.7 (q), 16.2 (q), 18.4 (s), 19.2 (t), 19.4 (q), 19.5 (s), 19.8 (s), 24.5 (t), 26.2 (3q), 26.9 (3q), 27.1 (3q), 27.1 (d) 31.6 (t), 33.0 (d), 33.1 (t), 33.8 (t), 34.2 (d), 36.3 (t), 39.3 (d), 41.5 (t), 42.6 (t), 44.1 (t), 47.6 (t), 50.0 (d), 57.4 (q), 58.0 (q), 62.2 (t), 69.8 (d), 72.8 (d), 78.6 (d), 80.5 (d), 81.9 (d), 117.3 (d), 127.6 (4d), 127.7 (4d), 129.6 (4d), 130.6 (s), 131.8 (s), 133.5 (d), 134.0 (2 s), 134.2 (2 s), 135.6 (4d), 135.9 (2d), 136.0 (2d), 137.0 (d), 137.3 (d), 138.9 (d), 146.5 (s), 154.2 (s), 156.5 (s), 162.4 (s), 170.5 (s), 210.5 (s), 214.0 (s); *m/z* (EI) 1412.7352 (M^+ + Na), 1444.7628 (M^+ + MeOH + Na), $C_{80}H_{111}N_3O_{12}Si_3$ + Na requires 1412.7373.

Procedure B. A solution of the oxazoline **78b** (124 mg, 0.087 mmol), CSA (105 mg, 0.45 mmol) and 5 Å molecular sieves (100 mg) in dry benzene (15 ml) was heated under reflux using a Dean–Stark apparatus for 22 h. The mixture was filtered through celite and the filter cake was washed with ethyl acetate (3 × 5 ml). The combined ethyl acetate washings were diluted with saturated aqueous sodium bicarbonate solution (10 ml) and the separated aqueous phase was then extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried (Na_2SO_4) and then concentrated *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:9 to 2:3) as eluent to give the *tris-oxazole* (70 mg, 58%), which showed analytical and spectroscopic data which were identical to those obtained by procedure A.

The *bis*-oxazole enamide (79)

N,*N*-Diisopropylethylamine (49 µl, 0.28 mmol), and methanesulfonyl chloride (10 µl, 0.13 mmol) were added sequentially to a stirred solution of the alcohol **17** (177 mg, 0.13 mmol) in dry dichloromethane (4.5 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h, then quenched with 1 M aqueous potassium carbonate solution (30 ml) and stirred at room temperature for 10 min. The separated aqueous phase was extracted with dichloromethane (3 × 30 ml) and the combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to leave the corresponding *methanesulfonate* as an oil, which was used without further purification.

1,8-Diazabicyclo[5.4.0]undec-7-ene (19 µl, 0.13 mmol) was added dropwise over 5 min to a stirred solution of the crude methanesulfonate (187 mg, 0.13 mmol) in dry dichloromethane (10 ml) at 0 °C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature, stirred for 2 h and then diluted with water (40 ml) and ethyl acetate (40 ml). The separated aqueous phase was extracted with ethyl acetate (2 × 40 ml) and the combined organic extracts were washed with 1 M hydrochloric acid (40 ml) and saturated aqueous sodium bicarbonate solution (40 ml), then dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:5 to 1:1) as eluent to give the *enamide* (131 mg, 75%) as a colourless oil: $[\alpha]_D^{23}$ −8.4 (*c* 1.0 in $CHCl_3$); ν_{max} (soln, $CHCl_3$)/cm^{-1} 3364, 2932, 2858, 1715, 1675 and 1588; ^{1}H NMR (400 MHz, $CDCl_3$) δ−0.06 (3H, s, CH_3Si), 0.05 (3H, s, CH_3Si), 0.75 (3H, d, *J* 6.8 Hz, CH_3-29), 0.86 (3H, d, *J* 6.3 Hz, CH_3-39), 0.87 (9H, s, $(CH_3)_3CSi(CH_3)_2$), 0.88 (3H, d, *J* 7.2 Hz, CH_3-33), 0.95 (3H, d, *J* 7.0 Hz, CH_3-37), 1.03 (9H, s, $(CH_3)_3CSi(Ph)_2$), 1.06 (9H, s, $(CH_3)_3CSi(Ph)_2$), 1.14–1.24 (1H, m, C*H*H H-34), 1.27 (3H, d, *J* 6.9 Hz, CH_3-9), 1.30–1.45 (1H, m, C*H*H H-40), 1.46–1.58 (4H, m, H-31, H-4), 1.58–1.83 (6H, m, H-5, H-29, H-33, CH*H* H-34, CH*H* H-40), 1.89 (1H, app dp, *J*, 6.3, 3.5 Hz, H-39), 2.35 (2H, t, *J* 6.8 Hz, H-6), 2.36 (1H, dd, *J* 16.4, 6.6 Hz, C*H*H H-8), 2.41–2.55 (5H, m, H-2, C*H*H H-27, H-35), 2.59 (1H, ddd, *J* 11.6, 7.8, 5.1 Hz, CH*H* H-27), 2.73–2.83 (2H, m, H-32, H-37), 2.92 (1H, dd, *J* 16.4, 7.3 Hz, CH*H* H-8), 3.16 (1H, ddd, *J* 8.9, 5.1, 1.1 Hz, H-28), 3.25 (3H, s, CH_3OC-32), 3.32 (3H, s, CH_3OC-28), 3.37 (1H, app dd, *J* 13.7, 6.9 Hz, H-9), 3.64 (1H, ddd, *J* 10.0, 8.9, 5.6 Hz, C*H*H H-41), 3.75 (1H, ddd, *J* 10.0, 6.3, 4.2 Hz, CH*H* H-41), 3.84 (1H, dd, *J* 8.1, 2.5 Hz, H-38), 4.04–4.13 (1H, m, H-3), 5.07 (1H, ddd, *J* 9.9, 6.5, 1.5 Hz, H-30), 5.70 (1H, s, CH*H* H-19), 6.39 (1H, d, *J* 16.0 Hz, H-25), 6.51 (1H, s, CH*H* H-19), 6.82 (1H, dt, *J* 16.0, 7.8 Hz, H-26), 7.30–7.47 (13H, m, ArH, H-14), 7.62–7.71 (8H, m, ArH), 8.15 (1H, s, H-24), 9.45 (1H, s, H-16); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ-4.3 (q), -4.1 (q), 10.0 (q), 14.2 (q), 15.7 (q), 16.2 (q), 18.5 (s), 19.3 (q), 19.3 (s), 19.4 (t), 19.4 (s), 24.4 (t), 26.2 (3q), 27.0 (3q), 27.0 (3q), 27.2 (d), 31.5 (t), 33.1 (d), 33.8 (t), 34.1 (d), 34.2 (t), 36.0 (t), 39.9 (d), 42.5 (t), 42.6 (t), 43.5 (t), 48.1 (t), 50.1 (d), 57.6 (q), 57.9 (q), 62.2 (t), 69.5 (d), 72.7 (d), 78.6 (d), 80.8 (d), 81.8 (d), 102.2 (t), 118.4 (d), 127.7 (8d), 128.6 (s), 129.7 (2d), 129.8 (2d), 133.7 (2 s), 134.0 (2 s), 134.6 (d), 135.6 (4d), 135.9 (4d), 137.0 (s), 137.8 (d), 140.7 (d), 145.9 (s), 157.8 (s), 159.5 (s), 160.7 (s), 170.1 (s), 209.7 (s), 214.0 (s); *m/z* (EI) 1392.7658 (M^+ + H), 1414.7449 (M^+ + Na), $C_{80}H_{113}N_3O_{12}Si_3$ + H requires 1392.7710.

The *bis*-oxazole (80)

N-Bromosuccinimide (16 mg, 0.09 mmol) was added in one portion to a stirred mixture of the enamide **79** (126 mg, 0.09 mmol) and 4 Å molecular sieves (40 mg) in dry methanol (7 ml) and dry dichloromethane (7 ml) at 0 °C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature over 15 h, and then filtered through celite. The filter cake was washed with ethyl acetate (3 × 15 ml) and the combined ethyl acetate washings were then diluted with saturated aqueous sodium thiosulfate solution (10 ml). The separated aqueous phase was extracted with ethyl acetate (2 × 30 ml) and the combined organic extracts were washed with brine (10 ml), then dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:5 to 1:1) as eluent to give the *bromide* (134 mg, 92%) as a colourless oil and a mixture of diastereoisomers: $[\alpha]_D^{24}$ −9.8 (*c* 3.7 in $CHCl_3$); ν_{max} (soln, $CHCl_3$)/cm^{-1} 3364, 2932, 2858, 1714, 1675 and 1591; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.06 (6H, s, CH_3Si), 0.05 (6H, s, CH_3Si), 0.75 (6H, d, *J* 6.6 Hz, CH_3-29), 0.82–0.87 (6H, m, CH_3-39), 0.87

(18H, s, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$), 0.88 (6H, d, *J* 7.3 Hz, CH$_3$-33), 0.96 (6H, d, *J* 6.9 Hz, CH$_3$-37), 1.02 (18H, s, (CH$_3$)$_3$CSi(Ph)$_2$), 1.06 (18H, s, (CH$_3$)$_3$CSi(Ph)$_2$), 1.29 (6H, d, *J* 6.9 Hz, CH$_3$-9), 1.15–1.25 (2H, m, C*H*H H-34), 1.33–1.60 (10H, m, H-4, H-31, C*H*H H-40), 1.61–1.84 (12H, m, H-5, H-29, H-33, CH*H* H-34, CH*H* H-40), 1.84–1.95 (2H, m, H-39), 2.31–2.55 (14H, m, H-2, H-6, C*H*H H-8, H-35), 2.55–2.69 (4H, m, H-27), 2.73–2.84 (4H, m, H-32, H-37), 2.93 (2H, dd, *J* 16.4, 7.9 Hz, CH*H* H-8), 3.13–3.20 (2H, m, H-28), 3.11 (3H, s, CH$_3$OC-15), 3.14 (3H, s, CH$_3$OC-15), 3.25 (6H, s, CH$_3$OC-32), 3.31 (3H, s, CH$_3$OC-28), 3.33 (3H, s, CH$_3$OC-28), 3.34–3.45 (2H, m, H-9), 3.64 (2H, ddd, *J* 10.1, 7.1, 4.0 Hz, C*H*H H-41), 3.75 (2H, ddd, *J* 10.1, 6.3, 4.4 Hz, CH*H* H-41), 3.84 (2H, dd, *J* 8.0, 2.2 Hz, H-38), 3.98 (1H, d, *J* 10.4 Hz, CH*H* H-19), 4.00 (1H, d, *J* 10.4 Hz, CH*H* H-19), 4.01–4.11 (2H, m, H-3), 4.91 (1H, d, *J* 10.4 Hz, CH*H* H-19), 4.96 (1H, d, *J* 10.4 Hz, CH*H* H-19), 5.07 (2H, ddd, *J* 10.3, 6.3, 1.9 Hz, H-30), 6.39 (1H, d, *J* 16.0 Hz, H-25), 6.40 (1H, d, *J* 16.0 Hz, H-25), 6.73–6.92 (2H, m, H-26), 7.30–7.48 (24H, m, ArH), 7.51 (2H, s, H-14), 7.61–7.74 (16H, m, ArH), 8.16 (2H, s, H-24), 8.74 (1H, s, H-16), 8.76 (1H, s, H-16); ^{13}C NMR (90.6 MHz, CDCl$_3$) δ −4.3 (2q), −4.1 (2q), 9.8 (q), 10.0 (q), 14.2 (2q), 15.7 (q), 16.2 (2q), 18.4 (2 s), 19.0 (q), 19.2 (t), 19.3 (2 s), 19.4 (2 s), 19.5 (t), 19.5 (2q), 24.4 (2t), 26.2 (6q), 26.9 (6q), 27.0 (6q), 27.4 (2d), 31.3 (t), 31.7 (2t), 32.6 (t), 33.0 (2t), 33.1 (2d), 33.8 (2t), 33.9 (d), 34.0 (d), 34.1 (t), 34.2 (t), 36.0 (2t), 39.8 (d), 39.9 (d), 42.5 (t), 42.6 (t), 43.5 (t), 43.7 (t), 48.1 (t), 48.2 (t), 50.1 (2d), 52.4 (2q), 57.5 (2q), 57.9 (2q), 62.1 (t), 62.2 (t), 69.5 (d), 69.6 (d), 72.8 (2d), 78.6 (2d), 80.7 (d), 80.8 (d), 81.7 (2d), 85.8 (2 s), 118.3 (d), 118.4 (d), 127.7 (16d), 129.6 (4d), 129.8 (4d), 133.6 (4 s), 134.0 (4 s), 135.6 (8d), 135.9 (8d), 136.0 (s), 136.1 (s), 137.7 (2d), 137.9 (2d), 141.0 (2d), 144.6 (s), 145.0 (s), 159.0 (s), 159.1 (s), 160.2 (2 s), 160.8 (2 s), 170.0 (s), 170.1 (s), 209.5 (s), 209.6 (s), 214.0 (2 s); *m*/*z* (EI) 1524.6863 (M$^+$ + Na), $C_{81}H_{116}BrN_3O_{13}Si_3$ + Na requires 1524.6897.

The methoxyoxazoline *bis*-oxazole macrolide (78b)

Caesium carbonate (176 mg, 0.49 mmol) was added in one portion to a stirred solution of the α-methoxy bromide **80** (250 mg, 0.016 mmol) in dry dioxane (25 ml) at 60 °C under a nitrogen atmosphere. The mixture was stirred at 60 °C for 5 h and then concentrated *in vacuo.* Ethyl acetate (20 ml) and 10% aqueous citric acid solution (10 ml), were added and the separated aqueous phase was then extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried (Na_2SO_4) and then concentrated *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:2 to 1:1) as eluent to give the *oxazoline* (196 mg, 92%) as a colourless foam and a mixture of diastereoisomers: $[\alpha]_D^{24}$ +0.8 (*c* 2.5 in CHCl$_3$); ν_{max} (soln, CHCl$_3$)/cm^{-1} 2931, 2857, 1714 and 1676; ^{1}H NMR (400 MHz, CDCl$_3$) δ −0.06 (6H, s, CH$_3$Si), 0.05 (6H, s, CH$_3$Si), 0.77 (3H, d, *J* 7.1 Hz, CH$_3$-29), 0.79 (3H, d, *J* 7.7 Hz, CH$_3$-29), 0.80 (3H, d, *J* 7.2 Hz, CH$_3$-39), 0.81 (3H, d, *J* 6.8 Hz, CH$_3$-39), 0.85 (18H, s, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$), 0.88 (6H, d, *J* 7.1 Hz, CH$_3$-33), 0.95 (3H, d, *J* 6.9 Hz, CH$_3$-37), 0.96 (3H, d, *J* 6.9 Hz, CH$_3$-37), 1.00 (9H, s, (CH$_3$)$_3$CSi(Ph)$_2$), 1.03 (9H, s, (CH$_3$)$_3$CSi(Ph)$_2$), 1.05 (18H, s, (CH$_3$)$_3$CSi(Ph)$_2$), 1.16–1.28 (2H, m, C*H*H H-34), 1.21 (3H, d, *J* 6.9 Hz, CH$_3$-9), 1.24 (3H, d, *J* 6.9 Hz, CH$_3$-9), 1.29–1.56 (14H, m, H-4, H-5, H-31, C*H*H H-40), 1.63–1.82 (6H, m, H-33, CH*H* H-34, CH*H* H-40), 1.83–1.94 (4H, m, H-29, H-39), 2.07 (2H, t, *J* 10.0 Hz, H-6), 2.08 (2H, t, *J* 10.0 Hz, H-6), 2.20 (1H, dd, *J* 16.6, 5.2 Hz, C*H*H H-8), 2.21–2.30 (1H, m, C*H*H H-8), 2.36 (2H, dd, *J* 9.4, 7.0 Hz, C*H*H H-2), 2.39 (2H, dd, *J* 7.0, 1.5 Hz, CH*H* H-2), 2.47–2.62 (4H, m, H-27, H-35), 2.72–2.95 (6H, m, CH*H* H-8, H-32, H-37), 3.08 (2H, ddd, *J* 8.8, 6.8, 3.8 Hz, H-28), 3.21–3.30 (2H, m, H-9), 3.26 (3H, s, CH$_3$OC-32), 3.31 (3H, s, CH$_3$OC-32), 3.32 (3H, s, CH$_3$OC-28), 3.33 (3H, s, CH$_3$OC-28), 3.47 (3H, s, CH$_3$OC-15), 3.49 (3H, s, CH$_3$OC-15), 3.61–3.69 (2H, m, C*H*H H-41), 3.75 (2H, ddd, *J* 9.7, 5.9, 4.0 Hz, CH*H* H-41), 3.84 (2H, dd, *J* 8.1, 2.3 Hz, H-38), 3.95–4.08 (2H, m, H-3), 3.49 (1H, d, *J* 9.9 Hz, CH*H* H-19), 4.54 (1H, d, *J* 9.9 Hz, CH*H* H-19), 4.75 (1H, d, *J* 9.9 Hz, CH*H* H-19), 4.99 (2H, ddd, *J* 10.6, 4.5, 1.2 Hz, H-30), 5.03 (1H, d, *J* 9.9 Hz, CH*H* H-19), 6.38 (1H, d, *J* 16.0 Hz, H-25), 6.43 (1H, d, *J* 16.0 Hz, H-25), 6.88 (2H, ddd, *J* 16.0, 6.9, 6.8 Hz, H-26), 7.31–7.49 (26H, m, ArH, H-14), 7.59–7.76 (16H, m, ArH), 8.06 (1H, s, H-24), 8.08 (1H, s, H-24); ^{13}C NMR (90.6 MHz, CDCl$_3$) δ −4.4 (2q), −4.2 (2q), 9.6 (q), 9.2 (q), 14.1 (2q), 15.6 (q), 15.7 (q), 16.2 (2q), 18.4 (2 s), 18.5 (t), 19.1 (t), 19.2 (2 s), 19.3 (2 s), 19.9 (2q), 24.4 (2t), 26.2 (6q), 26.3 (3q), 26.6 (3q), 26.9 (3q), 27.1 (3q), 27.3 (2d), 30.1 (t), 30.4 (t), 32.6 (t), 33.0 (2d), 33.2 (t), 33.8 (2t), 34.2 (2d), 35.4 (t), 35.6 (t), 38.8 (d), 39.2 (d), 41.4 (t), 41.5 (t), 42.5 (2t), 43.2 (t), 43.6 (t), 47.9 (t), 48.0 (t), 50.1 (2d), 52.0 (q), 52.1 (q), 57.2 (q), 57.3 (q), 58.1 (q), 58.3 (q), 62.0 (t), 62.1 (t), 69.5 (d), 69.8 (d), 72.1 (d), 72.5 (d), 74.7 (t), 75.3 (t), 77.3 (d), 78.6 (d), 81.3 (d), 81.6 (d), 81.8 (d), 82.0 (d), 100.2 (s), 100.3 (s), 118.3 (d), 118.8 (d), 127.6 (8d), 127.7 (8d), 129.6 (2d), 129.7 (2d), 129.8 (2d), 130.6 (2 s), 133.7 (2 s), 133.8 (2 s), 133.9 (2 s), 134.0 (2 s), 134.3 (d), 134.8 (d), 135.6 (8d), 135.9 (4d), 136.0 (4d), 137.0 (2d), 137.7 (2d), 141.2 (d), 141.3 (d), 144.4 (s), 145.5 (s), 160.9 (s), 161.3 (s), 161.6 (s), 161.7 (s), 162.1 (s), 162.2 (s), 169.9 (s), 170.1 (s), 209.8 (s), 210.2 (s), 214.0 (2 s); *m*/*z* (EI) 1444.7632 (M$^+$ + Na), $C_{81}H_{115}N_3O_{13}Si_3$ + Na requires 1444.7635.

The C3 TBDPS ether of ulapualide A (83)

Pyridinium *p*-toluenesulfonate (0.8 mg, 0.003 mmol) and *N*-methylformamide (17 µl, 0.29 mmol) were added sequentially to a stirred solution of the aldehyde **82b** (14 mg, 0.013 mmol) in dry benzene (30 ml) and the mixture was then heated under reflux for 4 h in a nitrogen atmosphere. The solution was cooled to room temperature and another portion of *N*-methylformamide (12 µl, 0.21 mmol) was added, and the mixture was heated under reflux for a further 6 h. The mixture was cooled to room temperature, and then diluted with ethyl acetate (10 ml) and water (5 ml). The separated organic phase was washed with brine (5 ml), then dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (1:1 to 3:1) as eluent to give the *N-methyl-N-alkenyl formamide* (5.6 mg, 40%), as a colourless oil, which was used without further purification; ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.78 (3H, d, *J* 6.7 Hz, CH$_3$-33), 0.83 (3H, d, *J* 6.8 Hz CH$_3$-29), 1.00–1.04 (3H, m, CH$_3$-39), 1.02 (9H, s, (CH$_3$)$_3$CSi(Ph)$_2$), 1.07 (3H, d, *J* 6.9 Hz, CH$_3$-37), 1.17–1.25 (1H, m, C*H*H H-34), 1.28 (3H, d, *J* 7.0 Hz, CH$_3$-9), 1.37–1.59 (4H, m, H-4, H-31), 1.65–1.77 (4H, m, H-5, H-33, CH*H* H-34), 1.84–1.93 (1H, m, H-29), 2.00 (3H, s, CH$_3$CO), 2.20–2.35 (2H, m, H-6), 2.38 (1H, dd, *J* 16.5, 5.4 Hz, C*H*H H-8), 2.43–2.57 (4H, m, C*H*H H-27, H-35, H-39), 2.60–2.64 (2H, m, H-2), 2.64–2.69 (1H, m CH*H* H-27), 2.71–2.80 (1H, m, H-37), 2.88–2.93 (1H, m, H-32), 3.08 (3.04) (3H, s, NCH$_3$), 3.13

(1H, dd, *J* 16.5, 8.2 Hz, CH*H* H-8), 3.18–3.24 (1H, m, H-28), 3.26 (3H, s, CH_3OC-32), 3.31 (3H, s, CH_3OC-28), 3.35–3.44 (1H, m, H-9), 4.24–4.32 (1H, m, H-3), 4.98 (1H, dd, *J* 14.4, 9.2 Hz, H-40), 5.05–5.11 (1H, m, H-30), 5.14 (2H, dd, *J* 8.9, 3.8 Hz, H-38), 6.35 (1H, d, *J* 15.7 Hz, H-25), 7.01–7.13 (1H, m, H-26), 7.17 (6.50) (1H, d, *J* 14.4 Hz, H-41), 7.29–7.44 (7H, m, ArH, H-14), 7.65–7.75 (4H, m, ArH), 8.05 (2H, s, H-19, H-24), 8.29 (8.08) (1H, s, CHO); *m/z* (EI) 1141.5544 (M^+ + Na), $C_{60}H_{79}N_3O_{13}Si$ + Na requires 1141.5545.

Ulapualide A (1)

A 70% solution of hydrogen fluoride in pyridine (0.5 ml) was added dropwise over 5 min to a stirred solution of the TBDPS ether **83** (4 mg, 0.004 mmol) in dry tetrahydrofuran (0.5 ml) and dry pyridine (0.5 ml) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 12 h, and then diluted with ethyl acetate (10 ml) and quenched by the careful addition of saturated aqueous sodium bicarbonate solution (5 ml). The separated organic phase was washed with saturated aqueous copper sulfate solution (2 × 5 ml) and brine (5 ml), then dried (Na_2SO_4) and concentrated *in vacuo.* The residue was purified by chromatography on silica using ethyl acetate–light petroleum (bp 40–60 °C) (3:1 to 1:0) as eluent to give ulapualide A (1.8 mg, 60%), as a colourless oil; $[\alpha]_D^{26}$ −52.8 (*c* 0.11 in MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* 6.8 Hz, CH_3-33), 0.91 (3H, d, *J* 6.9 Hz CH_3-29), 1.05 (3H, d, *J* 6.8 Hz, CH_3-39), 1.08 (3H, d, *J* 7.0 Hz, CH_3-37), 1.27–1.31 (1H, m, C*H*H H-34), 1.33 (3H, d, *J* 7.0 Hz, CH_3-9), 1.46–1.63 (4H, m, H-4, H-31), 1.67–1.87 (5H, m, H-5, H-29, H-33, CH*H* H-34), 2.02 (3H, s, CH_3CO), 2.43–2.57 (9H, m, H-2, H-6, C*H*H H-8, C*H*H H-27, H-35, H-39), 2.63–2.71 (1H, m CH*H* H-27), 2.71–2.80 (1H, m, H-37), 2.95–2.99 (1H, m, H-32), 2.99 (1H, dd, *J* 15.0, 7.2 Hz, CH*H* H-8), 3.08 (3.04) (3H, s, NCH_3), 3.28–3.34 (1H, m, H-28), 3.32 (3H, s, CH_3OC-32), 3.39 (3H, s, CH_3OC-28), 3.39–3.48 (1H, m, H-9), 4.20–4.29 (1H, m, H-3), 4.46–4.52 (1H, br, OH), 4.95–5.03 (1H, m, H-40), 5.14 (2H, dd, *J* 8.8, 3.7 Hz, H-38), 5.25–5.30 (1H, m, H-30), 6.41 (1H, d, *J* 16.1 Hz, H-25), 6.97–7.05 (1H, m, H-26), 7.17 (6.50) (1H, d, *J* 14.3 Hz, H-41), 7.41 (1H, s, H-14), 8.06 (2H, s, H-19, H-24), 8.30 (8.09) (1H, s, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.1 (q), 13.4 (q), 15.6 (q), 18.9 (q), 19.5 (q), 20.8 (t), 21.0 (q), 27.7 (t), 27.9 (d), 32.2 (t), 33.1 (q), 33.6 (t), 34.6 (d), 37.0 (d), 37.3 (t), 39.9 (t), 40.5 (d), 43.0 (t), 43.9 (t), 48.3 (t), 48.7 (d), 57.8 (q), 58.2 (q), 68.6 (d), 73.0 (d), 77.6 (d), 80.0 (d), 81.8 (d), 110.5 (d), 112.2 (d), 117.3 (d), 125.6 (d), 129.6 (d), 130.4 (s), 131.8 (s), 133.5 (d), 137.4 (d), 137.8 (d), 139.8 (d), 146.5 (s), 154.3 (s), 156.3 (s), 161.0 (d), 162.2 (d), 162.8 (s), 170.1 (s), 172.6 (s), 210.5 (s), 211.7 (s); *m/z* (EI) 903.4385 (M^+ + Na), $C_{46}H_{64}N_4O_{13}$ + Na requires 903.4368.

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