# A NEW APPROACH TO THE MARINE NATURAL PRODUCT ULAPUALIDE A

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A Thesis Submitted to the University of Nottingham for the degree of Doctor of Philosophy

**November 2000**

# *Contents*

## DECLARATION

I declare that the substance of this thesis has not been submitted, nor is concurrently being submitted in candidature for any other degree. I also declare that the work embodied in this thesis is the result of my own investigations. Where the work of other investigators has been used, this has been fully acknowledged in the text.

J. Kempson

G. Pattenden

*Dedicated to Mum, Dad and Claire for their constant love and support.*

## ACKNOWLEDGEMENTS

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Thanks go to all the technical staff at the University of Nottingham for all their help and support, and also to the GP group members for making my life in laboratory C13 such an enjoyable one. Thanks especially to Paul Little and Dave Millan for proof reading this thesis.

Finally, I would like to thank Anna for her never ending support and much needed artistic flair in poster design!

## ABSTRACT

This thesis describes synthetic studies directed towards a second generation total synthesis of ulapualide A. Ulapualide A is an extraordinary bioactive *tris*-oxazole based macrolide which was isolated from the egg masses of the marine sponge *Hexabranchus sanguineus* and exhibits potent antifungal activity with inhibition of leukaemia cell proliferation.

The ***Introduction*** to this thesis includes an overview of natural product chemistry and draws attention to the 'ulapualide' family of secondary metabolites including their isolation, biological activity, biosynthesis and structural determination. Also included is a summary of a total synthesis of ulapualide A by our research group in Nottingham, together with a review of oxazole containing natural products.

The ***Results and Discussion*** section of this thesis details our general strategy for an alternative design for the synthesis of the *tris*-oxazole based macrolide core of ulapualide A. A synthesis of a model system exemplifying this strategy is then described, together with a detailed discussion of polyoxazole ring formation. This is followed by application of the model study to ulapualide A itself, and includes a total synthesis of the polyol C26-C41 side-chain of ulapualide A. The section concludes by describing our synthetic efforts towards the remaining chiral fragment of this natural product, the bottom-chain.

The thesis concludes with an ***Experimental*** section containing full details of the preparative work completed and listing spectroscopic and analytical data for all new compounds synthesised during the study.

An ***Appendix*** contains a description of contemporaneous synthetic studies carried out by Panek *et al* during the course of my PhD studies. X-ray crystallographic and spectroscopic data, together with reprints of publications resulting from our work are also included.

## ABBREVIATIONS

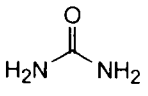
| | |
|---|---|
| Ac | acetyl |
| AIBN | azoisobutyronitrile |
| Bu | butyl |
| Bu$^{i}$ | isobutyl |
| Bu$^{s}$ | *sec*-butyl |
| Bu$^{t}$ | *tert*-butyl |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| BINOL | 1,1'-bi-2-naphthol |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| Bz | benzoyl |
| CAN | cerium (IV) ammonium nitrate |
| CSA | camphorsulfonic acid |
| DAST | diethylaminosulfur trifluoride |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | 1,3-dicyclohexylcarbodiimide |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| de | diasteromeric excess |
| DEAD | diethyl azodicarboxylate |
| DIBAL-H | diisobutylaluminium hydride |
| DMAP | 4-dimethylaminopyridine |
| DMF | *N,N*-dimethylformamide |
| DMPU | 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one |
| DMS | dimethyl sulfide |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| EDTA | ethylenediaminetetraacetic acid |
| ee | enantiomeric excess |
| Et | ethyl |
| HMPA | hexamethylphosphoramide |
| HMPT | hexamethylphosphorus triamide |

| | |
|---|---|
| HOBT | 1-hydroxybenzotriazole |
| LAH | lithium aluminium hydride |
| LDA | lithium diisopropylamide |
| MCPBA | *m*-chloroperbenzoic acid |
| Me | methyl |
| MEM | (2-methoxyethoxy)methyl |
| MOM | methoxymethyl |
| Ms | methylsulfonyl (mesyl) |
| NBS | *N*-bromosuccinimide |
| NMO | 4-methylmorpholine *N*-oxide |
| nmr | nuclear magnetic resonance |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| Ph | phenyl |
| PPTS | pyridinium toluene-*p*-sulfonate |
| PTSA | toluene-*p*-sulfonic acid |
| Pr | propyl |
| $Pr^i$ | isopropyl |
| PyBOP | benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate |
| RNA | ribonucleic acid |
| RT | room temperature |
| TBAF | tetrabutylammonium fluoride |
| TBDMS/TBS | *tert*-butyldimethylsilyl |
| TBDPS/TPS | *tert*-butyldiphenylsilyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| TMANO | trimethylamine-*N*-oxide |
| TMOF | trimethylorthoformate |
| TMS | trimethylsilyl *or* trimethylsilane |
| TPAP | tetrapropylammonium perruthenate |

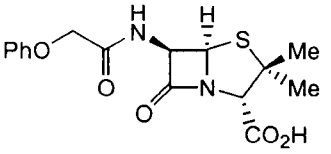
# INTRODUCTION

## *1.1 Total Synthesis – the Past, Present and the Future.*

The synthesis of urea **1** way back in 1828 signaled the birth of organic synthesis. [1] Ever since this time, the field of total synthesis has grown tremendously with today's chemical literature overflowing with countless examples of natural products that have fallen to the synthetic organic chemist.



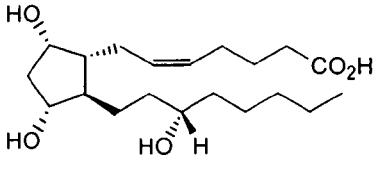
**1**



**2**

Penicillin **2**, discovered in 1928 by Alexander Fleming, was a highly prized synthetic target in the mid-nineteenth century. [2] Its unique molecular structure with a fragile β-lactam ring, together with its remarkable antibacterial properties which saved so many lives in World War II, finally led to the first total synthesis of penicillin V in 1957.[3]

The prostaglandins with their potent and important biological activities and their potential applications in medicine[4] have also been an important natural product target. E. J. Corey's first total synthesis of prostaglandin $F_{2\alpha}$ **3** in 1969[5] led the way for a myriad of prostaglandin analogues. With these syntheses came important developments in the field of catalyst design which included a set of chiral aluminium- and boron-based catalysts for the Diels-Alder reaction[6] and the oxazaborolidine (CBS) catalyst to generate chiral alcohols from ketones. [7]



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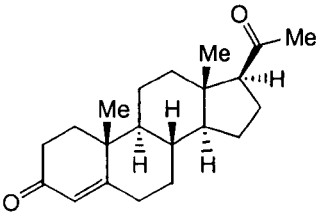
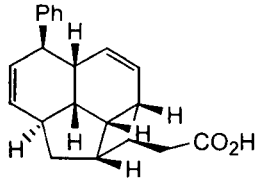


**4**

Progesterone **4** is another important target and belongs to the steroid class of compounds that are so ubiquitous in nature. Its linearly fused polycyclic carbon framework is characteristic of numerous natural products of steroidal and triterpenoid structure and it was W. S. Johnson, in 1971, who employed a polyolefinic ring-closing cascade to generate progesterone's skeleton in just one step. [8]

The 'cascade theme' is very much continued in the endiandric acids **5-7**; a fascinating group of natural products discovered in the early 1980s in the Australian plant *Endiandra introsa*. [9] Here, a direct one-step strategy involving an $8\pi$ electron electrocyclisation, a $6\pi$ electrocyclisation, and a Diels-Alder [4+2] cycloaddition reaction installed the polycyclic skeletons of the endiandric acids. [10]

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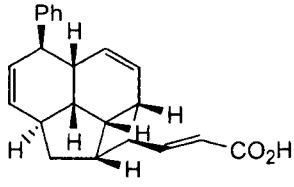
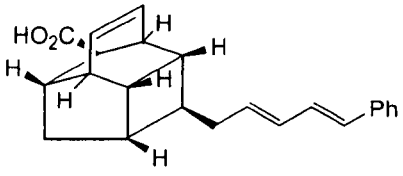


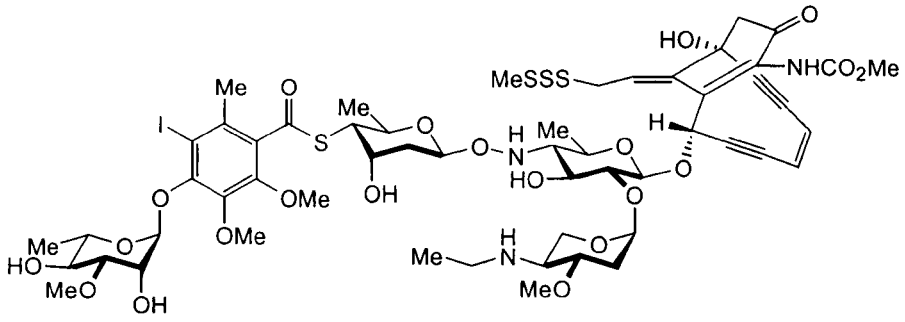

**6**




**7**

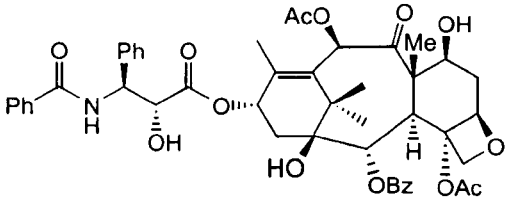
As with all of these examples, the development of new synthetic methods was very much the driving force and natural product synthesis provided ideal opportunities with which to test these new methods and theories. Indeed, by the early 1990s the organic chemist had conquered most of the known structural types of secondary metabolites: prostaglandins, steroids, β-lactams, macrolides, polyene macrolides, polyethers, alkaloids, endiandric acids; all were synthesised by the organic chemist. So where was total synthesis heading?

Most significantly, total synthesis has looked deeper into biology with synthetic chemists now being driven, not only by novel molecular architectures, but also by their modes of biological action. The enediyne anticancer antibiotics, in particular calicheamicin $\gamma'_1$ **8**, was one of the first new challenges to the organic chemist. [11] This natural product provided a unique opportunity for discovery and invention in the areas of chemistry, biology and medicine. Its novel molecular structure is responsible for its powerful biological properties, which include strong binding to DNA, double-strand cleavage of the genetic material by formation of a benzenoid diradical, and – as a consequence – potent antitumour and antibiotic activity. By the mid-1990s, two groups had achieved the challenging total synthesis, K. C. Nicolaou[12] and S. J. Danishefsky. [13]



**8**

The tubulin binding agents taxol **9**, [14, 15] epothilone A **10**[16-18] and eleutherobin **11**[19, 20] commanded much attention in the 1990s. Each of these natural products included in their structure a number of unique features – taxol exhibiting its notoriously well known 6,8,6 ring-fused system; epothilone A with its macrolide structure and eleutherobin containing an oxygen-bridged 10-membered ring. The study of all three of these natural products by the organic chemist has contributed immensely in both delivering scarce natural substances for biological investigations and in our treatment of cancer.



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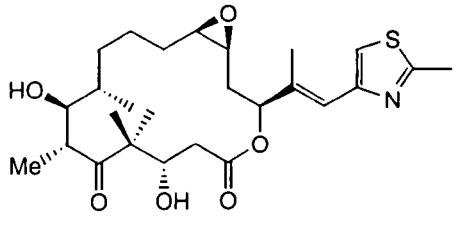

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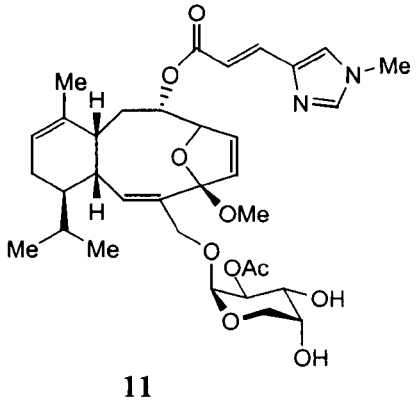
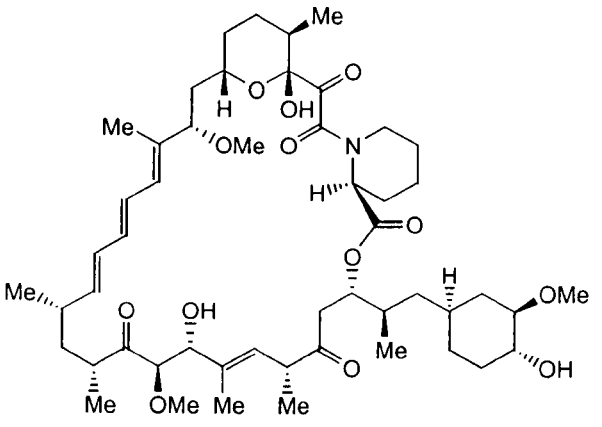


**11**

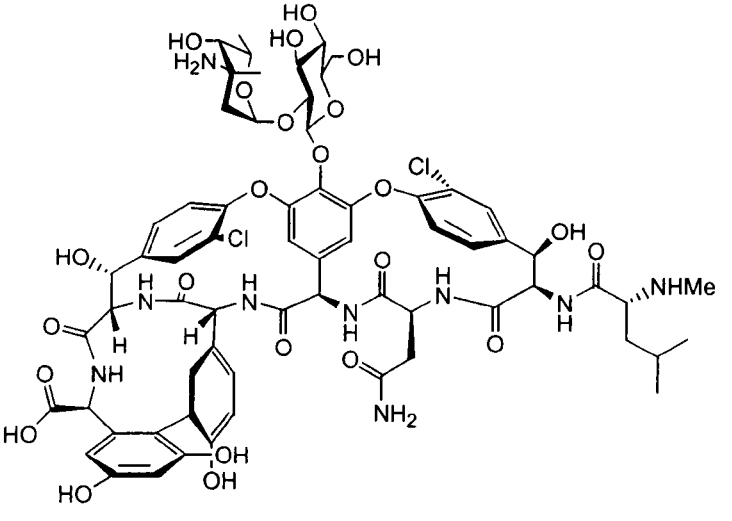
The 29-membered ring natural product rapamycin **12** has been an important target in the field of immunosuppression, so much so, that by the end of 1995, no fewer than four research groups had reported its total synthesis. [21-24] This natural product also highlighted the recent advances made in organometallic chemistry with Stille's

methodology allowing the conjugated triene system to be formed concurrently with the macrocyclic portion of the molecule.



**12**

One of the most recent milestones of the organic chemist has come with the glycopeptide class of antibiotics. [25] Vancomycin **13** in particular has been used over the last four decades as a weapon to combat bacterial disease, and with the first total synthesis of vancomycin in 1999, [26, 27] new achievements in organic synthesis were realised.



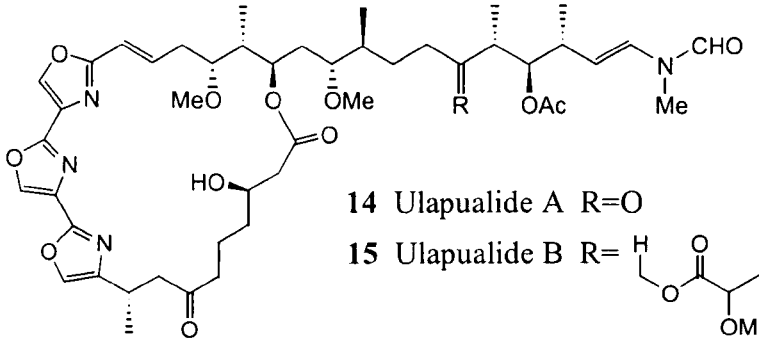
**13**

The field of total synthesis in the 21st century promises to be an exciting one. The pursuit for targeting even more complex structures will demand both new analytical techniques with which to isolate and identify these structures, together with more effective reactions in terms of accomplishing bond constructions and functional group transformations. Furthermore, with the advent of solid phase and combinatorial

chemistry techniques, natural products and their analogues will be the subject of increased biological screening.

### *1.2 The Ulapualides and Related Metabolites*

As part of the ongoing challenge, and inspired by the wealth of biologically active natural products to be isolated from nature, we were lured to the 'ulapualide' family of secondary metabolites whose structures tantalise the imagination regarding their biosynthetic origin and mode of action *in vivo*.




Ulapualides A **14** and B **15**, [28] together with kabiramide C **16**, [29] were the first members of this extraordinarily unique family of *tris*-oxazole based macrolides to be isolated from nature. The ulapualides derive their name from the Hawaiian words 'ula' meaning red and 'pua' meaning flower, since they were both isolated from the striking rosebud-like egg masses deposited by the nudibranch *Hexabranchus sanguineus* on ledges in underwater caves off the coast of Hawaii. Simultaneously in 1986, kabiramide C was isolated from the egg masses of an unidentified nudibranch collected at Kariba Bay in the Ryukyus Islands. Once again, this compound shows the three contiguous oxazole ring based macrolide structure found in the ulapualides.

Later, isolation and characterisation of the structurally similar halichondramide **17** from a species of the sponge *Halichondria*[30] was reported. Dihydrohalichondramide **18**, isohalichondramide **19**, the acid **20**, the imide **21** and the ester **22** are further examples of similar metabolites which were also isolated from a second specimen of the same sponge. The family of metabolites is further extended by mycalolides A-C **23-25** which were isolated from a sponge of the genus *Mycale*.[31] The molecules **14-19** and **23-25** show structures based on a 25-membered macrocyclic lactone which

incorporates a novel *tris*-oxazole unit, and to which is attached a C11-oxygenated side chain terminating in an unusual formyl enamine residue. The members differ from each other largely according to the oxidation patterns and the level of alkyl group substitutions found in the aliphatic portions of their structures. More recently however, the structurally related halishigamides A-D **26-29** from the Okinawan marine sponge *Halichondria*[32] have added to this strikingly unusual family of secondary metabolites; with their incomplete *tris*-oxazole chromophores contained within these molecules intriguing questions about their biosynthesis are posed.

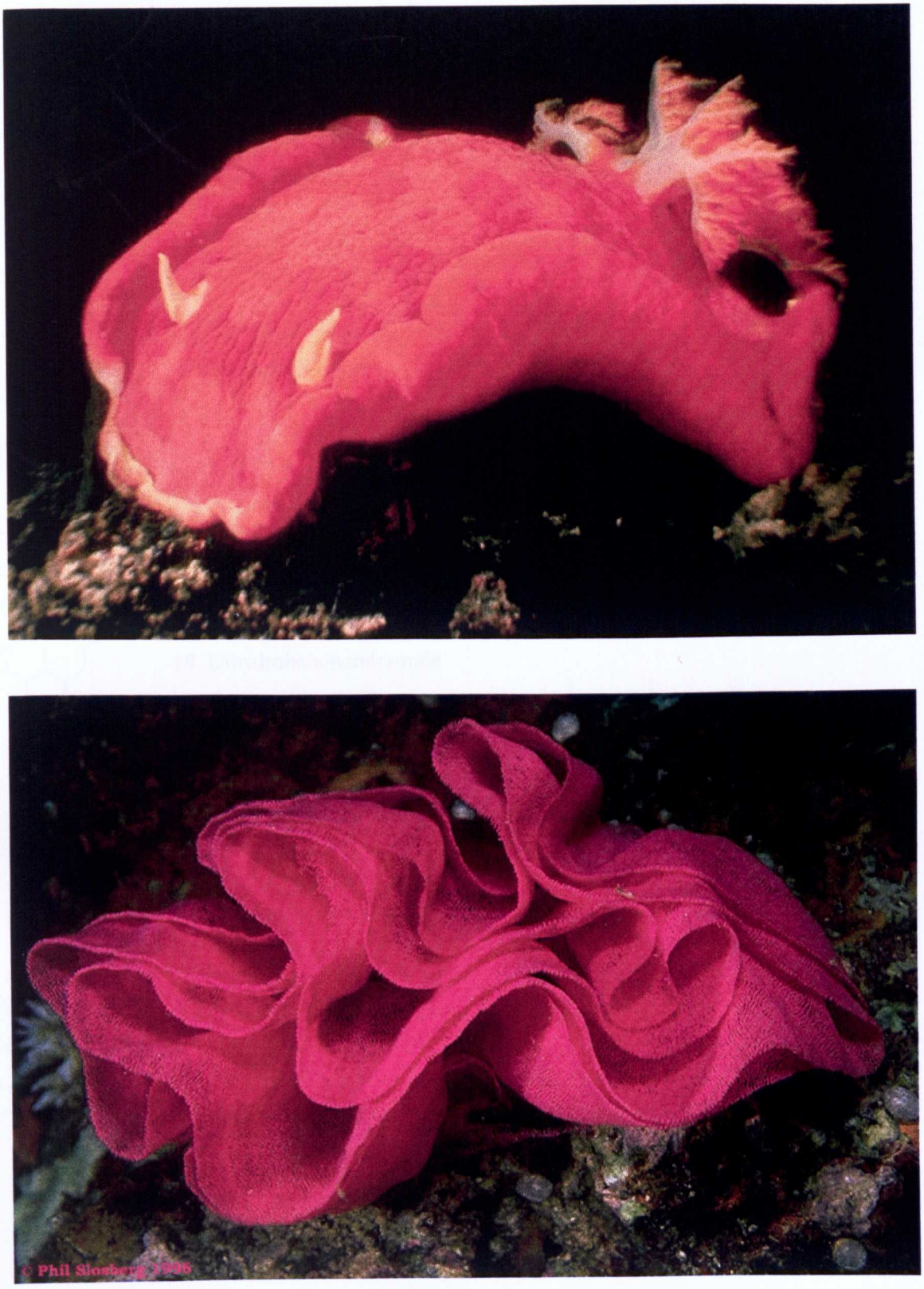
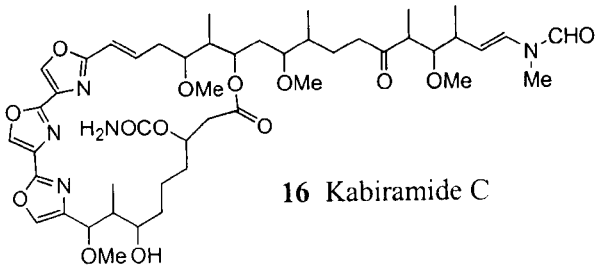


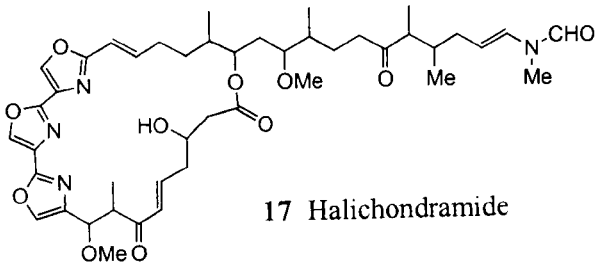

**Figure 1.2.1**

*Top: The sea slug Hexabranchus sanguineus.*

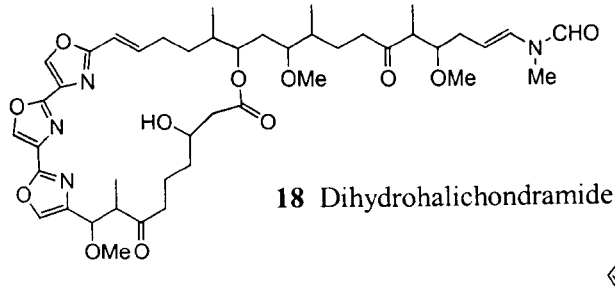
*Bottom: The rosebud-like egg mass from which ulapualide A is isolated.*



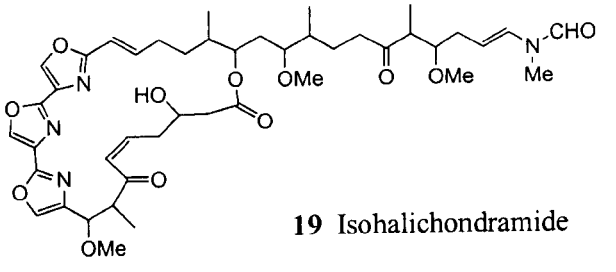
**16** Kabiramide C



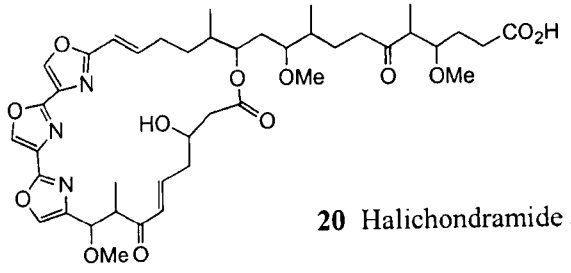
**17** Halichondramide



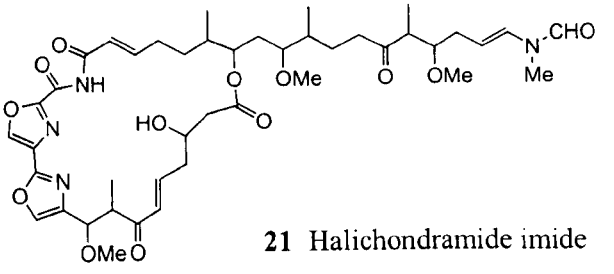
**18** Dihydrohalichondramide



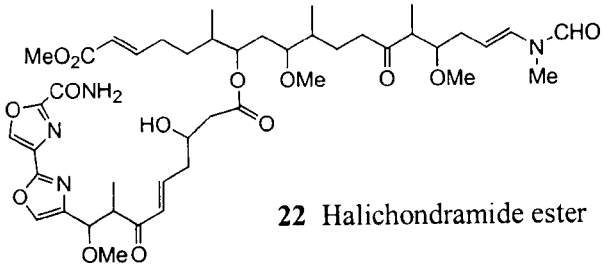
**19** Isohalichondramide



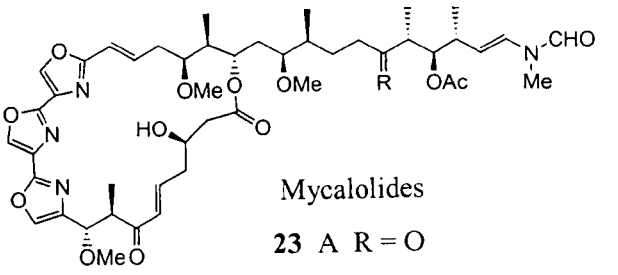
**20** Halichondramide acid



**21** Halichondramide imide

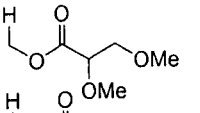


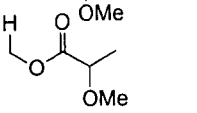
**22** Halichondramide ester

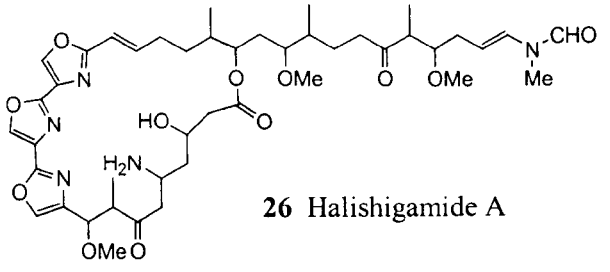


Mycalolides

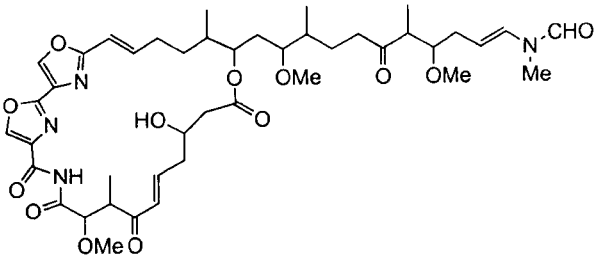
**23** A R = O

**24** B R = 

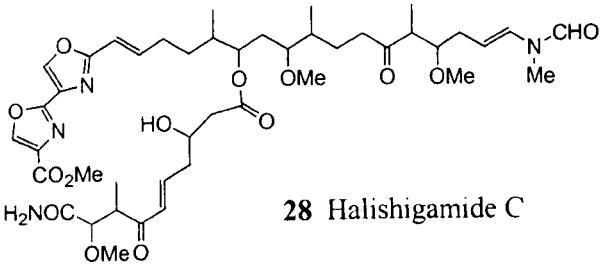
**25** C R = 



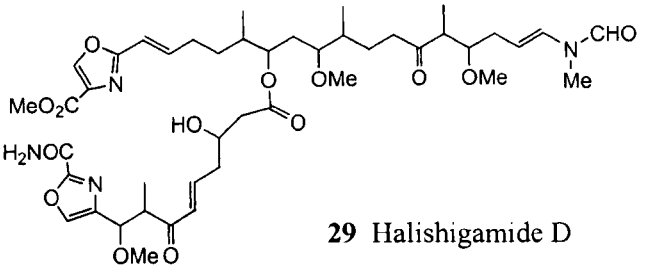
**26** Halishigamide A



**27** Halishigamide B



**28** Halishigamide C

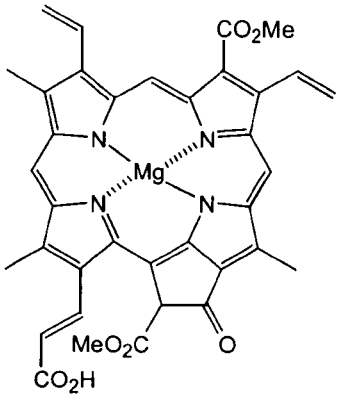


**29** Halishigamide D

### *1.3 Metal Ion Chelation in Nature*

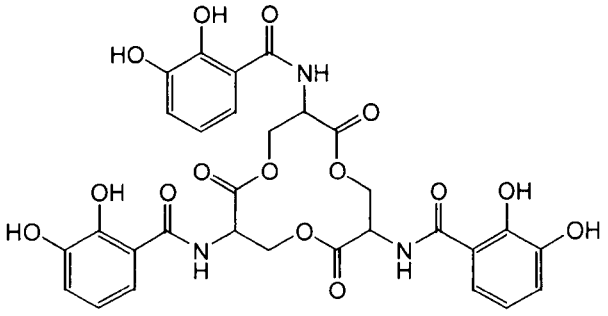
Metal ions are essential for all life forms with each organism of a living cell nothing more than a highly tuned multimetal multiligand system. Transition metal ions perform many functions in nature and it is of paramount importance that these essential elements (a) be delivered to the right biological compartments, (b) that they be present in the desired forms of oxidation state and co-ordination geometry required to carry out their selective functions, and (c) that the organism is able to control the amounts of each of these elements and distinguish between them. All of these requirements can be, and are, achieved by selective *chelation*. Indeed, without chelation as a control, any free transition metal ions would indiscriminantly bind to a range of biological molecules with concomitant physiological disorders!

The discovery of metal-porphyrin complexes provided some of the first evidence for the importance of metal ions in nature. Perhaps the most common examples are the magnesium containing chlorophyls found in plants and green algae, and one of the more recent is chlorophyl $C_3$ **30**, isolated from the algae *Emiliana huxleyi*.[33]




**30**

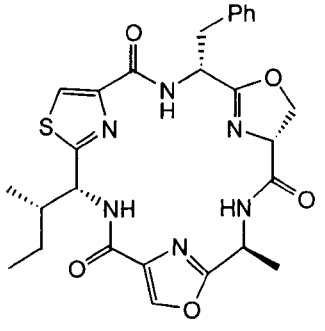
Further intrigue within the terrestrial based environment is found within the siderophores which are iron chelators possessing either hydroxamate or catecholate chelating groups. Enterobactin **31**,[34] a cyclic depsipeptide derived from *L*-serine has three covalently linked catechol groups which form an $Fe^{(III)}$ complex having the largest known metal binding constant (*ca.* $10^{52}$) of any known $Fe^{(III)}$ complex. So strong in fact are these complexes that they have been known to leach iron from stainless steel vessels!!



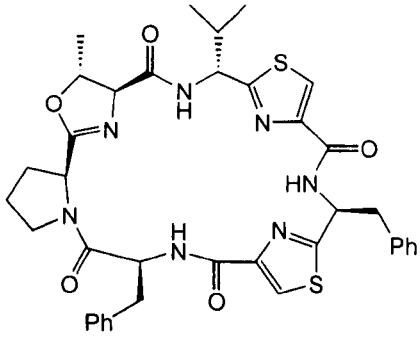
**31**

The marine environment too contains a wealth of life, but despite the rich availability of carbon, relatively few organisms other than algae can utilise photosynthesis to exploit this source. In spite of the inhospitable nature of the marine environment however, marine flora and fauna produce metabolites which show an incredibly diverse range of molecular architectures. Many of these metabolites contain structural features which would enable them to behave as ionophores, incorporating a macrocyclic cavity with which to encapsulate a metal, with the potential for chelation from polar functional groups.

For example, metabolites such as **32**[35] and **33**[36] have been isolated from nudibranches, sponges, ascidians and algae. The structures of these cyclic metabolites are reminiscent of the structures of porphyrins and similar ligands capable of metal complexation. It is this similarity to ligands that has led to the suggestion that marine metabolites may be capable of metal complexation and that such a complexation may be responsible for either metal transport, biological assembly of the metabolites or even the biological activity exhibited by a number of these compounds.

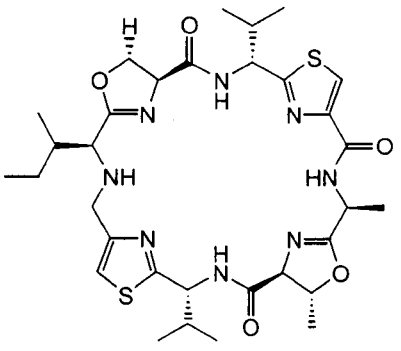


**32**



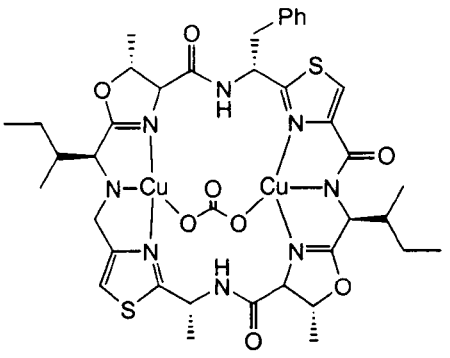
**33**

The 'patellamide' family of cyclic peptides,[37] *viz* patellamide A, **34**, is characterised by the presence of two thiazole and two oxazoline rings which form part of a conformationally restrained 24-azacrown-8 macrocyclic framework.

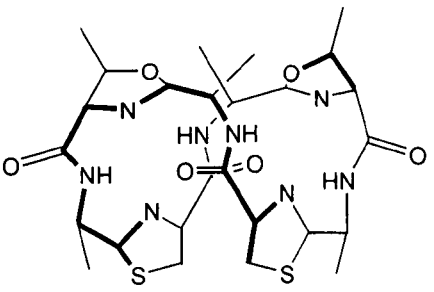


**34**

The organism, *Lissoclinum patella*, from which they have been isolated, has been found to concentrate several metals, including copper, to ten thousand times the concentration found in the local marine environment. A number of synthetic studies[38] have been carried out to establish the relative stereochemistries of these cyclic peptides. $^1$H-nmr studies have also been used to determine the conformation in solution, while X-ray studies determined the solid state conformation. These investigations, taken together, have shown that the $C_2$-symmetric patellamides have predominantly a 'square form' conformation, *viz* **35**, the presence of a bridging carbonate group between the two metal ions leading to the suggestion that such complexes may be responsible for $CO_2$ transport in biological systems. The non-$C_2$ symmetric patellamides assume largley twisted 'figure-eight like' conformations, *viz* **36**. As a result of these studies, relationships can be drawn between chemical structure, conformation and biological activity and how metal ions may contribute in one or other of these factors.

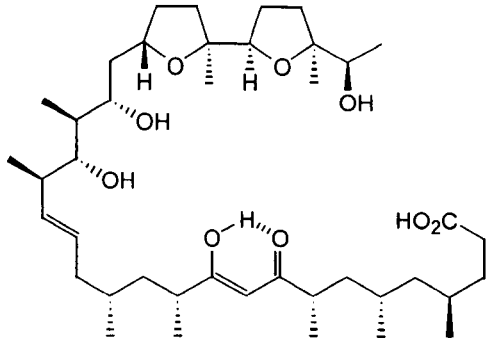


**35**



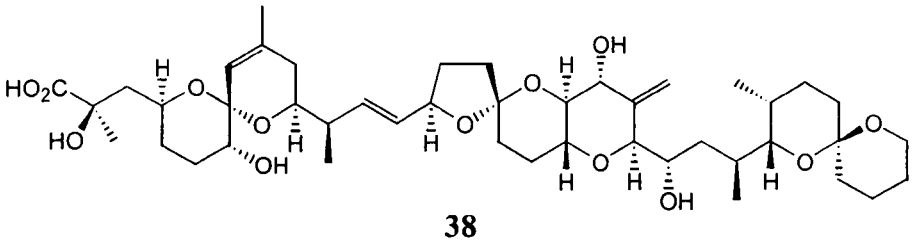
**36**

In complete contrast to the cyclic peptides, the polyether antibiotics have commanded much interest in the scientific world with regard to their biological function and ability to chelate various cations in a transport process. Ionomycin **37** was isolated in 1978 from the organism *Streptomyces conlobactus* as its hexane soluble calcium complex and further studies showed a specificity for divalent cations.[39] The ability to facilitate cation transport across membrane barriers has produced a wide range of biological responses in this and other members of the polyether family.



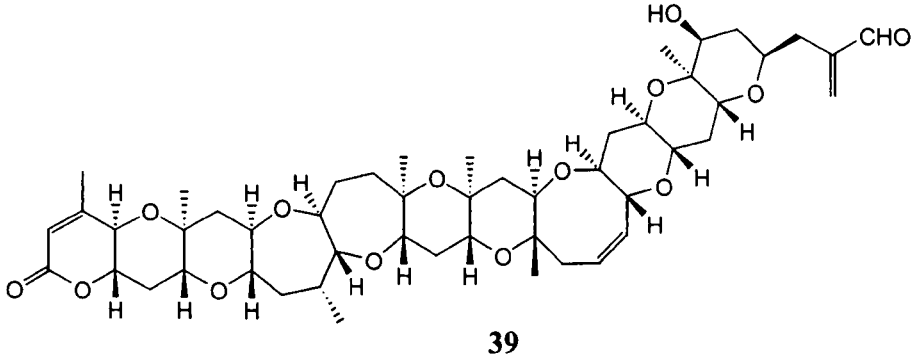
**37**

Other studies with okadaic acid **38**, isolated from the dinoflagellate *Prorcentrum lima*, have predicted its conformation in solution producing reports of an unspecified 'metal complex'.[40]



**38**

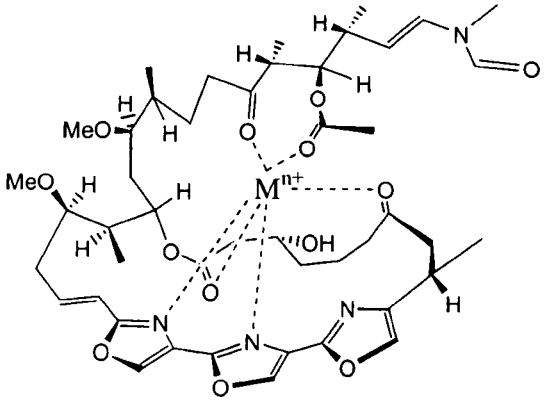
In additon to compounds of this type, brevetoxin B **39**, with its incredible molecular structure, must be included.[41] The biological activity of this compound rests on its potent neurotoxicity and marked interference with the function of the sodium channels contained within neurons.



**39**

### *1.4 Biological Profile and Stereochemical Prediction*

The 'ulapualide' family *viz* **14-29** of marine natural products possess marked biological activity, with all structures showing pronounced antifungal activity. The ulapualides together with the kabiramides and dihydrohalichondramides inhibit leukaemia cell proliferation, and all the metabolites inhibit cell division in the fertilised sea urchin egg assay. Also, kabiramide C and some of the halichondramides have shown ichthyotoxic properties. This biological activity could be due in part to the *tris*-oxazole moiety incorporated within the macrolide ring. Indeed, it was our supposition that the several nitrogen and oxygen ligation sites present within the macrolide ring could play host to a metal ion, with retention of the ion made possible by the use of the pendant side chain to wrap over and 'cap' the complex **40**.[42]

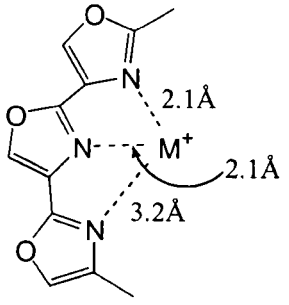


**40**

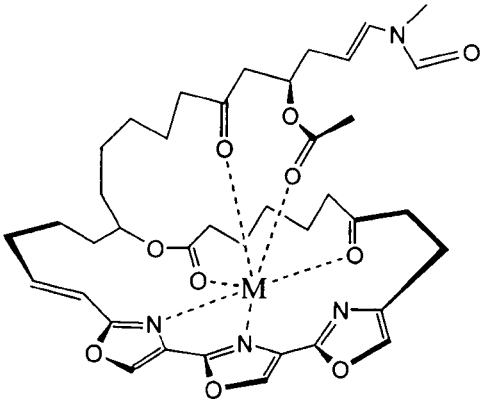
Pursuing the assumption that the biological properties of ulapualide A stem from the ability of the metabolite to act as an ionophore, a metal ion chelation model of the molecule was designed with the intention of predicting the most likely stereochemistry of the ten asymmetric centres contained within ulapualide A.

The donor atoms available in ulapualide A for metal complex formation are both numerous and mixed in type. The oxazole aza-nitrogen centres are expected to be 'soft' donors, and in common with other heterocyclic aza donors are likely to show selectivity for transition metal ion sequestration. The remaining carbonyl, ether and amide oxy atom donors are more typical of the familiar terrestrial ionophores, which are known to express a preference for alkali and alkali-earth metals. The initial study however, focussed on the use of a 'dummy' metal atom for complexation and this

indicated that only two of the three possible oxazole nitrogen centres could complex at one time.

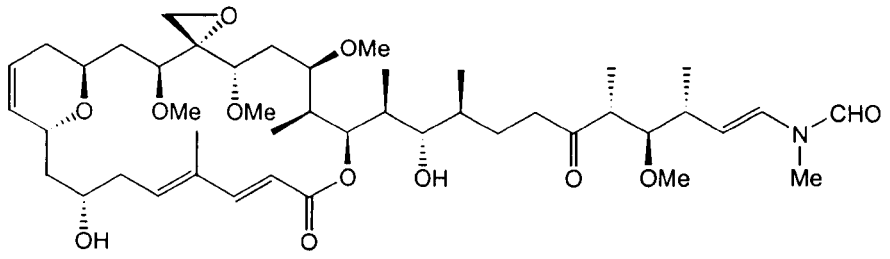



Complex formation was achieved, incorporating structural features common to both the ulapualides and halichondramides, to produce a somewhat arbitrarily chosen octahedral complex **41** using two oxazole aza-nitrogen centres and four carbonyl oxygen donors.



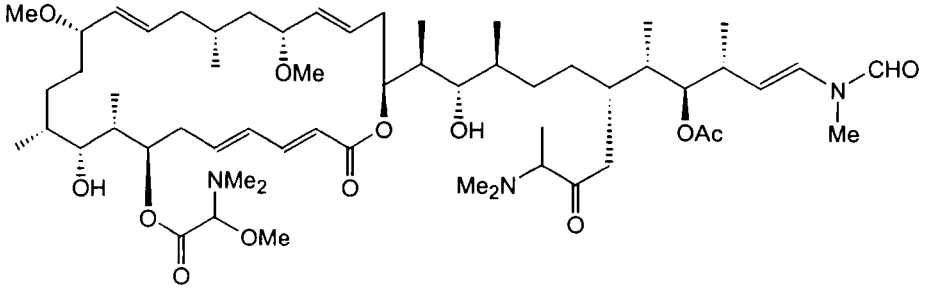

**41**

Having obtained this complex **41**, the various side chain substituents in ulapualide A were added to the complex, one at a time. As each substituent was added, both of the epimers were then considered and energy minimised and in each case the epimer of higher energy was discarded. The outcome of this study was interesting, since the relative stereochemistry of a major part of the polyol side chain in ulapualide A correlated with the corresponding chiral centres in scytophycin B **42**, a related metabolite whose structure had been established by X-ray crystallography measurements.[43]



**42**

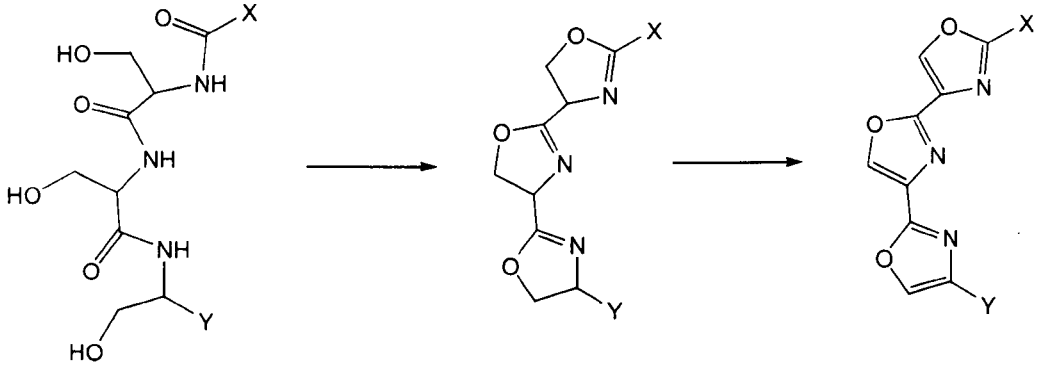
The more recent disclosure of the existance of an additional marine natural product, *viz* aplyronine **43**, [44] which also shows remarkable similarity to our predicted stereochemistry for ulapualide A, added further evidence for our stereochemical model.



**43**

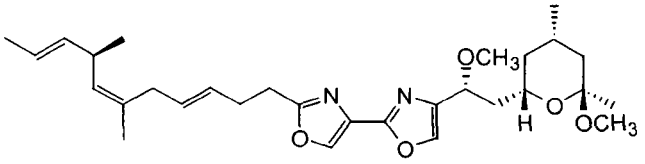
## *1.5 Biosynthesis of the tris-Oxazole Unit in the Ulapualides*

The biosynthesis of the three contiguous oxazole rings found in ulapualide A and other members of this family of marine metabolites is open to some debate. The cyclisation of a *tris*-serine moiety **44**, leading to the corresponding *tris*-oxazoline **45**, followed by enzymic oxidation to **46** is a common suggestion for the biosynthesis of the *tris*-oxazole moiety. [19, 45]

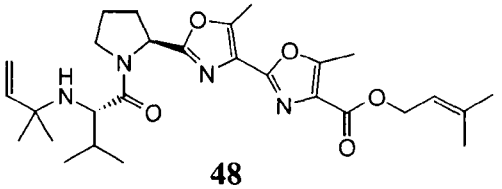


**44** **45** **46**

This is supported by the related *bis*-oxazole unit found in the natural product hennoxazole A **47**, isolated from *Polyfibrospongia sp.*,[46a] and muscoride A **48**, found in the freshwater cyanobacterium *Nostac muscorum*,[46b] displaying a *bis*-oxazole core which is formally derived from two threonine residues.

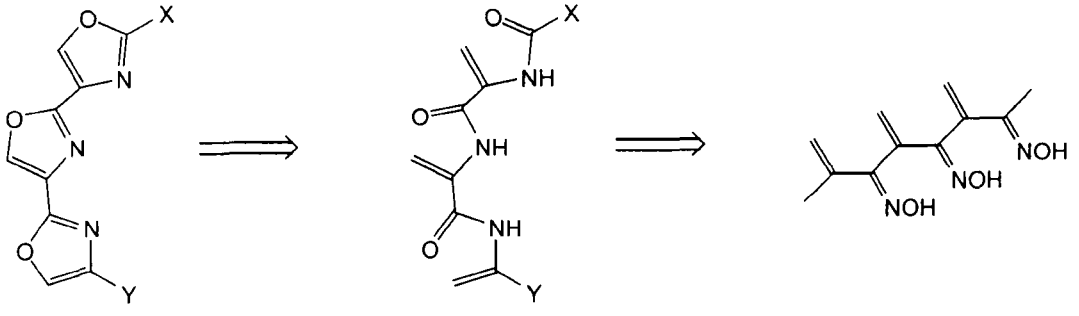



**47**




**48**

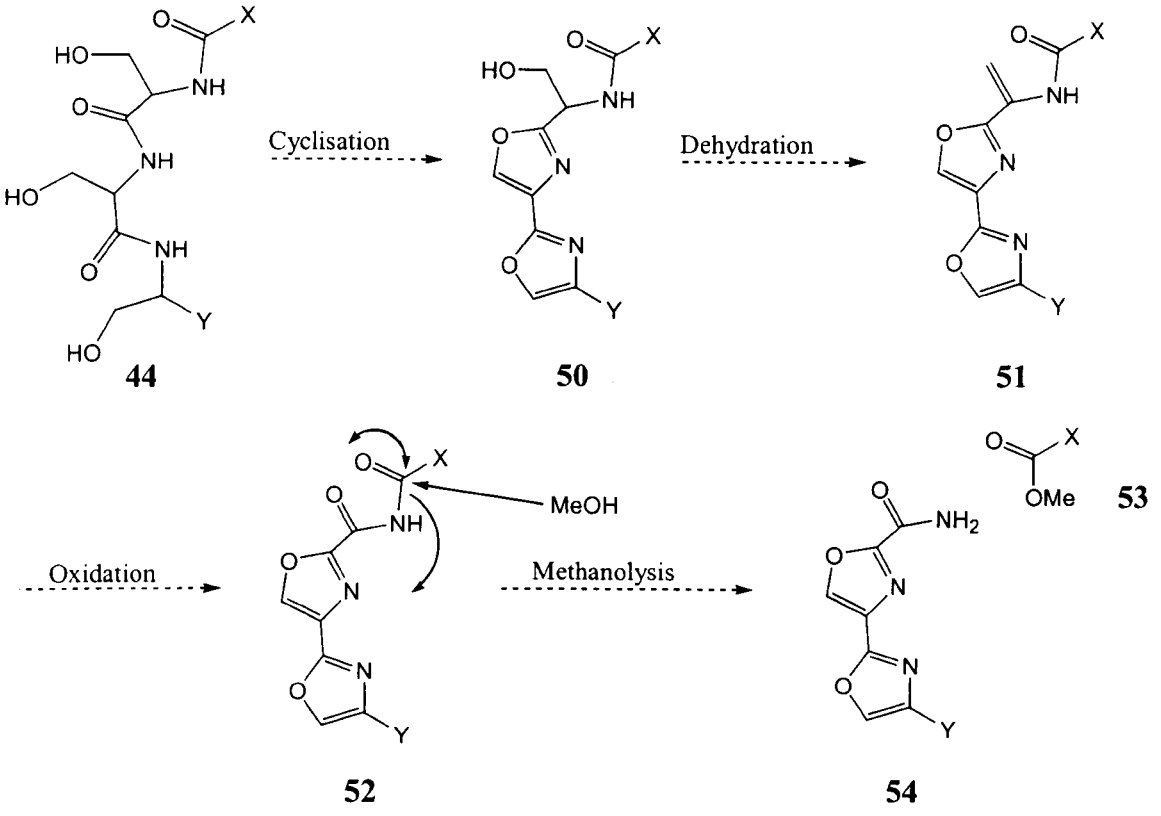
Alternatively, Moore[47] has suggested a polyketide precursor which leads to the *tris*-oxazole unit **46** *via* an intramolecular Beckmann rearrangement of a *tris*-oxime intermediate **49**. This route seems to be particularly attractive due to the ubiquity of 1,2-shifts in nature.




**46** **49**

However, strong evidence of a third biosynthetic route to these metabolites comes from the recent publication by Kobayashi *et al* who isolated the four new oxazole containing compounds, halishigamides A-D **26-29**. [32] The structures of the halishigamides suggests that oxazole formation could occur late, possibly as a final step, in the biosynthesis of such metabolites. Indeed, research within our group is also being carried out into the total synthesis of halichondramide ester, **22**, yet another natural product possessing an 'incomplete' *tris*-oxazole backbone. Starting from the *tris*-serine precursor, **44**, biomimetic synthesis is easy to envisage for this molecule. Cyclisation of two serine residues affords the *bis*-oxazole unit, **50**, which after

sequential dehydration and oxidation gives the imide, **52**. Addition of methanol then reveals the methyl ester, **53**, and the primary amide, **54**.

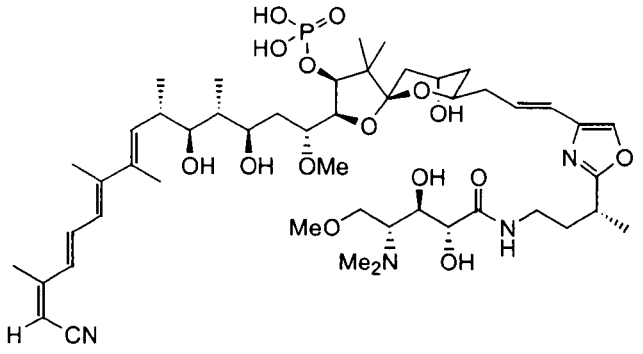



Repeating these simple transformations separately on each of the three oxazole rings soon reveals the biomimetic origin of all the related metabolites, including the recently discovered halishigamides A-D.

## *1.6 Oxazole Containing Natural Products*

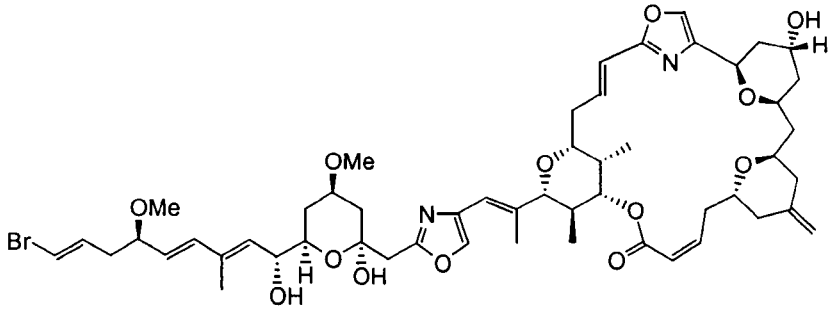
The occurrence of natural products containing the oxazole heterocycle has become more widespread in recent years. The vast majority of these secondary metabolites contain an isolated heterocycle, but much of the recent interest in the 5-membered heteroaromatic motif has been sparked by natural products that contain contiguously linked oxazole heterocycles which form *bis*- and *tris*-oxazole arrays. This section of the thesis is not intended to be a thorough review of oxazole containing compounds, but rather just to highlight some of the many oxazoles in nature that have been of interest within our research group and that of others.

Probably one of the most popular oxazole containing natural products to attract the synthetic chemist is calyculin A **55** which was isolated from the marine sponge *Discodermia calyx* in 1986. [48] The presence of a 2,4-disubstituted oxazole amongst a wide variety of other functionality together with its striking biological activity has led to three successful total syntheses of calyculin A reported by the research groups of Evans, [49a] Masamune [49b] and Smith. [49c]



**55**

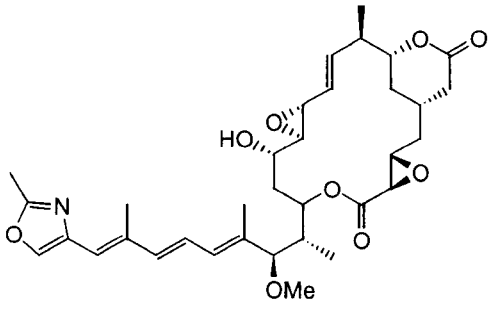
Phorboxazoles A and B also pose a significant challenge to the organic chemist, and were isolated from the Indian Ocean marine sponge *Phorbas sp.* in 1995. [50] Their gross structures were shown to encompass an unprecedented molecular architecture of four oxane rings, two 2,4-disubstituted oxazole rings and a 21-membered macrolactone, incorporating fifteen asymmetric centres. They exhibit a broad range of biological activity, showing exciting cytotoxic, cytostatic and antifungal properties. A total synthesis of phorboxazole A **56** was completed by Forsyth *et al* [51] and more recently, the research group of Evans [52] has completed the synthesis of phorboxazole B.



**56**

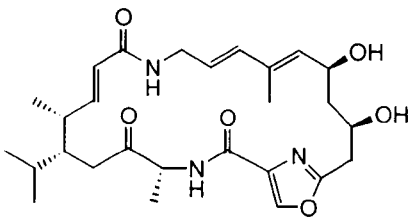
Rhizoxin A **57** is a highly functionalised macrolactone from the pathogenic fungus *Rhizopus chinensis*. [53] It differs from many of the natural products discussed in this

section, by the presence of the oxazole at the terminus of the side chain. Rhizoxin A has stimulated much interest within the chemical community, not only by its intriguing structure, but also by exhibiting diverse and significant biological activity. A total synthesis of rhizoxin A was reported by Ohno *et al.* [54]

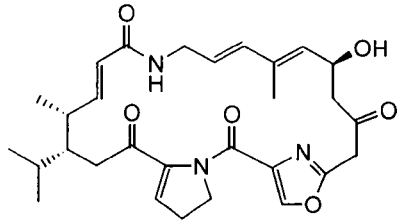



**57**

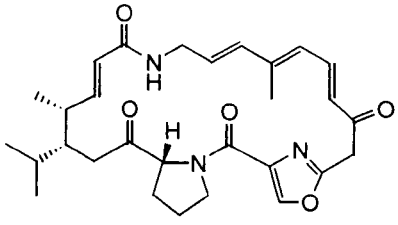
One of the largest groups of natural compounds that contain oxazoles are found within the macrolide antibiotics known as the virginiamycins. [55] The virginiamycins are produced by various species of Streptomyces bacteria and are separated into two groups. [56] The group A virginiamycins are characterised by a common 23-membered macrolide lactone-lactam accommodating a variety of functionality including an oxazole ring, a 1,3-diene, an acrylamide unit and an amino acid residue. The group B virginiamycins are cyclic hexadepsipeptides. The biological activity of the virginiamycin antibiotics has been utilised in food additives to improve the growth of cattle and they have recently been recognised as cholecystokinin antagonists for treating panic, anxiety and cancer withdrawal. [57] However, despite the biological significance and the knowledge of the existence of these compounds for many years a total synthesis, despite considerable effort, had proved elusive. It was not until 1996 that the total synthesis of virginiamycin M2 **58** was achieved by Schlessinger *et al.* [58] The total synthesis of madumycin II **59**, by Meyers *et al*, [59] and of the related antibiotic anhydropristinamycin IIB **60**, by Pattenden *et al*, [60] were reported contemporaneously.



**58**

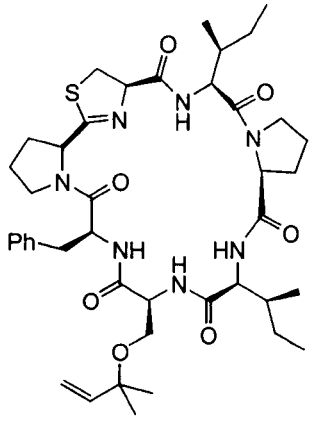


**59**



**60**

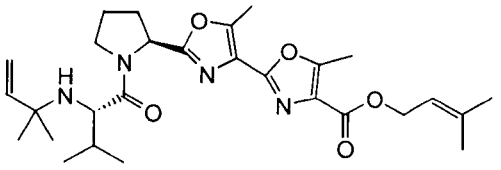
Another well documented class of natural products containing heterocyclic rings are the cyclic peptides. The high density of hetero-atoms in possible chelating arrangements has aroused considerable interest over recent years with regard to their biosynthesis and their use as metal transport agents *in vivo*. This interest has culminated in a total synthesis of mollamide A **61** within our research group, [61] a novel reverse prenyl substituted cyclic peptide isolated from the ascidian (sea squirt) *Didemnum molle*. [62]



**61**

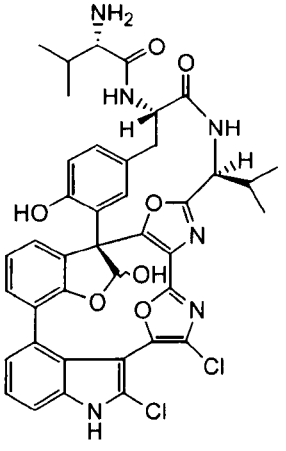
Natural products containing oxazole units linked contiguously are significantly less common. Muscoride A **48**, is a novel *bis*-oxazole based peptidic alkaloid isolated from the terrestrial cyano-bacterium *Nostac muscorum*, [46b] which displays weak antibacterial activity. The molecule is unique because the *bis*-oxazole unit is derived presumably from two threonine residues making it the only natural product bearing two contiguous 5-methyl oxazoles. The total synthesis of muscoride A has been

accomplished recently by two groups, Wipf *et al* in 1996, [63] and Pattenden *et al* in 1997. [64]



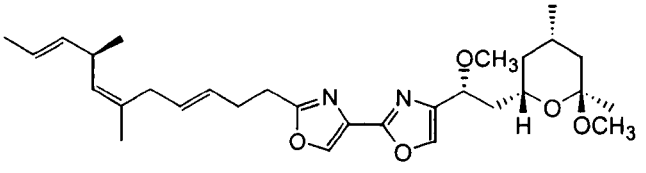
**48**

The *bis*-oxazole containing compound diazonamide A **62**, isolated from the colonial ascidian *Diazona chinesis* is composed of a highly complex bicyclic framework encompassing a chlorinated indole, a benzofuran and a chlorinated *bis*-oxazole moiety. [65] Diazonamide A displays potent *in vitro* cytotoxicity, but its structural complexity has so far eluded the organic chemist and a total synthesis has yet to be reported.



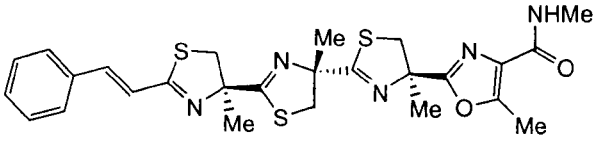
**62**

A further *bis*-oxazole containing compound, hennoxazole A **47**, was isolated from the marine sponge *Polyfibrospongia* sp. and was shown to be highly active against the herpes simplex virus. [46a] Its structure is characterised by the presence of a 2,4-disubstituted *bis*-oxazole moiety, a pyranoid glycoside and a rather unusual skipped triene unit. Wipf *et al* reported the total synthesis of the enantiomer of hennoxazole A in 1995, [66] thus confirming the previous structure elucidation. This achievement has been followed by the synthesis of hennoxazole A itself by Williams *et al* in 1998. [67]



**47**

Thiangazole **63**,[68] together with the related tantazoles,[69] *eg* tantazole B **64**, and mirabazoles,[70] *eg* mirabazole C **65**, constitute a unique and novel family of cytotoxic alkaloids, which show structures based on the linear fusion of four or five successive 2,4-disubstituted thiazole/oxazole rings terminating in a 2-cinnamyl or 2-isopropyl thiazoline. The alkaloid thiangazole was isolated in 1992 from the gliding bacterium *Polyangium sp.*, and it has been shown to be one hundred percent effective against HIV-1. A total synthesis of thiangazole was completed in 1994 by Pattenden *et al*[71a,b] together with the groups of Wipf, [71c] Ehrler[71d] and Heathcock.[71e]

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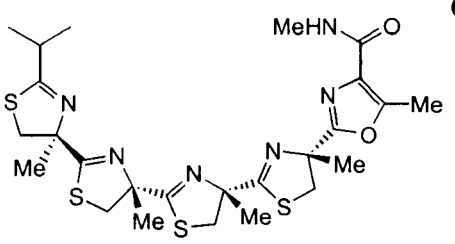
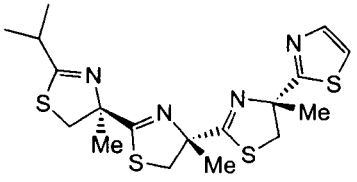


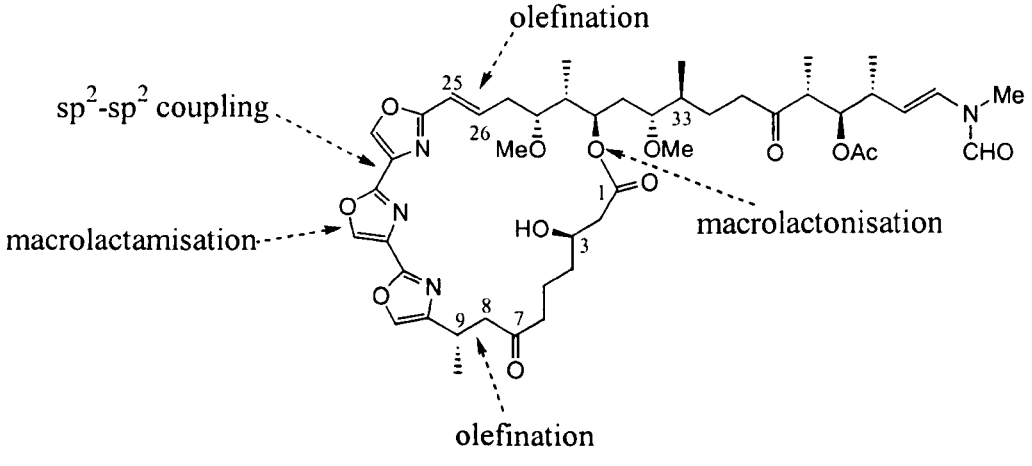

**64**



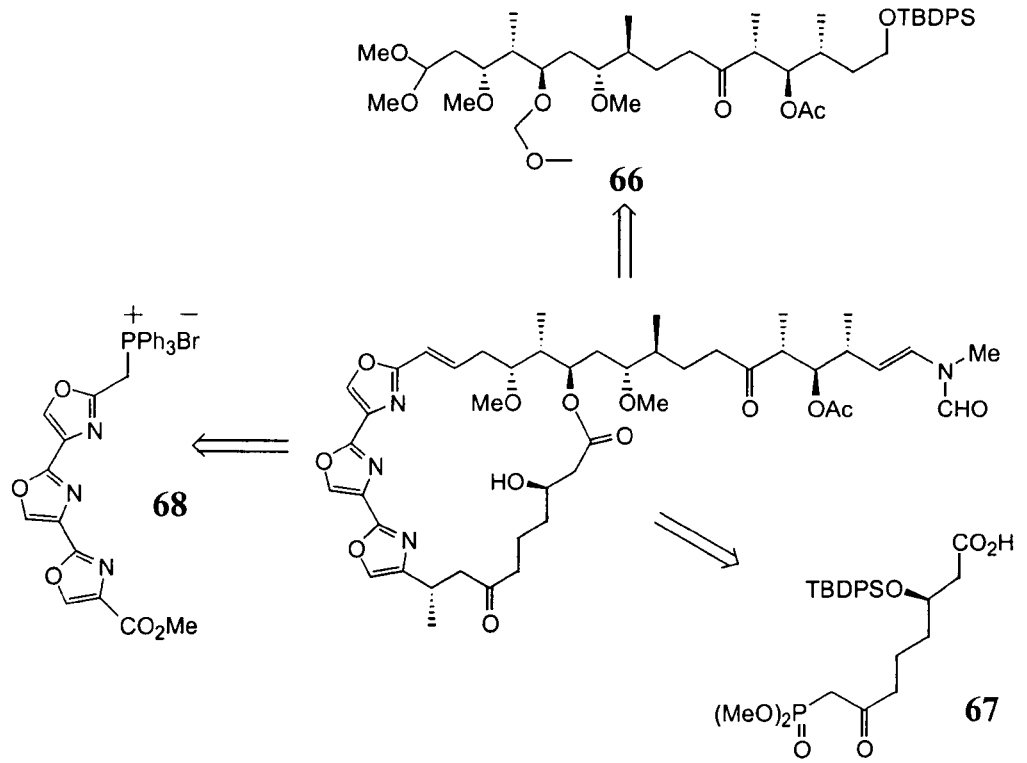

**65**

### *1.7 A Total Synthesis of Ulapualide A*

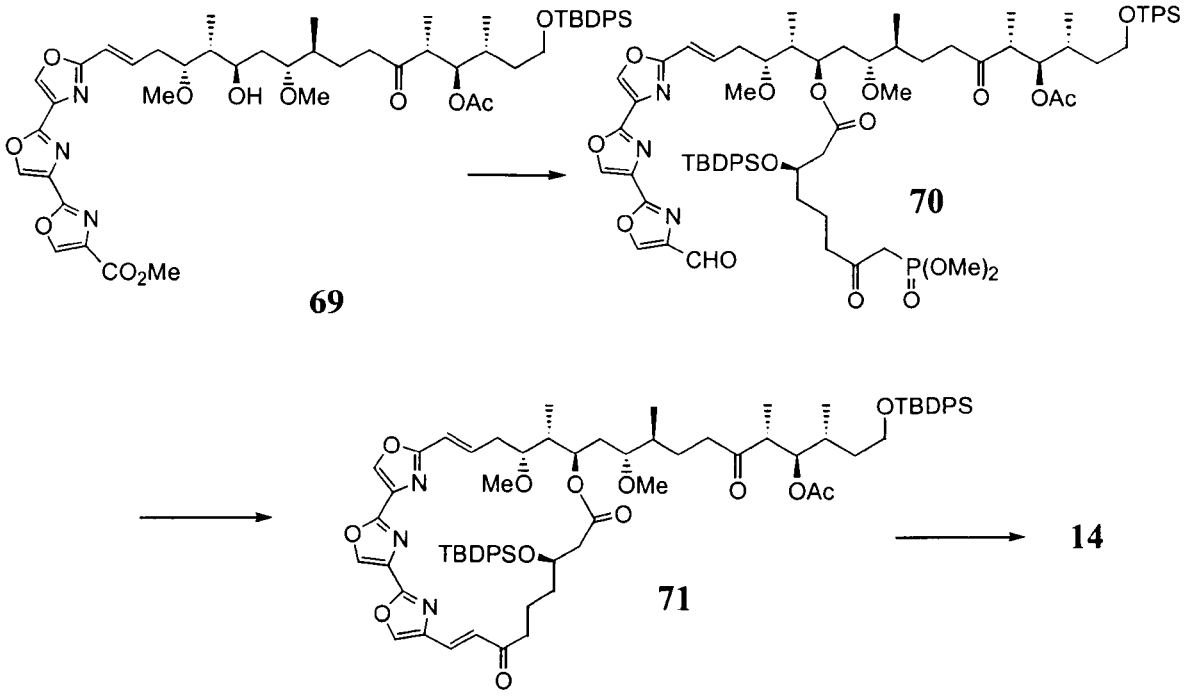
The first total synthesis of ulapualide A was recently completed by Chattopadhyah and Pattenden. [72] At the outset of these studies, a wide range of strategies and disconnections were entertained, with the most notable involving elaboration of the *tris*-oxazole based macrolide core. Some of these ideas are summarised below.



Thus, our research group considered an obvious macrolactonisation from an appropriate ω-hydroxy carboxylic acid precursor, an intramolecular olefination reaction producing the C25-C26 alkene bond, and the utilisation of intramolecular $sp^2$-$sp^2$ coupling (*eg* Stille, Suzuki) reactions involving substituted oxazole ring precursors. An alternative, less obvious, macrolide ring forming strategy was to effect an intramolecular olefination reaction producing the C8-C9 bond in the molecule, as a conjugated enone, and then to later introduce the C9 α-methyl group stereoselectively using the conformational bias of the macrolide core. Indeed, with model work completed and adequate precedent established, the synthetic strategy followed to ulapualide A was based upon the design of the three principal building blocks **66**, **67** and **68**.




With all of these building blocks to hand, elaboration of the *tris*-oxazole phosphonium salt **68** and the protected polyol aldehyde **66**, led to the alkene **69**. Attachment of a ω-carboxy substituted keto-phosphonate residue **67** then produced **70**, which after macrocyclisation *via* an intramolecular Wadsworth-Emmons olefination led to **71**. The synthesis of ulapualide A was then completed by manipulation of the functionality in **71**, and simultaneous introduction of the *N*-methyl *N*-alkenylformamide residue.




The total synthesis of ulapualide A addressed a number of important issues. Aside from the obvious synthetic endeavours towards this natural product, ulapualide A has also posed a number of additional questions. Most significantly, it provided an opportunity to pursue the idea of metal chelation in nature. Indeed, the first working stereochemical model of ulapualide A came from molecular modelling of some of its hypothetical metal conjugates[42] and prompted by this early work, Siegel and co-workers took the metal chelation idea one step further. [73] Using the related *tris*-oxazole containing natural product, dihydrohalichondramide **18**, and employing fluorescence quenching and nmr techniques, these authors demonstrated that metal binding constants in the range $10^2$-$10^4$ for the metals $Ag^+$, $Cu^{2+}$, $Fe^{2+}$, $Hg^{2+}$ and $Pb^{2+}$ provided little evidence of any significant chelate effect.

It was hoped that the total synthesis of ulapualide A would confirm the predicted stereochemistry, for which there had been much debate. However, the synthesis did not succeed in giving conclusive answers, although very small differences between synthetic and natural ulapualide A (in the $^{13}C$ nmr spectroscopic data) did lead us to conclude that the stereochemistry of synthetic ulapualide A differed from that in the natural at one or more of the stereogenic centres along the side-chain. There was also uncertainty regarding the stereochemistry of the C9-methyl group of ulapualide A. This centre had been generated *via* a cuprate addition onto the enone system in **71** and

gave a 3:2 mixture of methyl epimers, both of which closely resembled the natural product.

### *1.8 Aims and Objectives*

When I joined the research group in October 1997, the initial theme of my research was to investigate an alternative synthetic route towards the *tris*-oxazole backbone in the ulapualides, and to base this route on the recently isolated halishigamides **26-29**. If successful, the application of this design to ulapualide A would then enable us to:

- address the problems of stereochemistry in the side-chain in ulapualide arising from the discrepencies between natural and synthetic material.

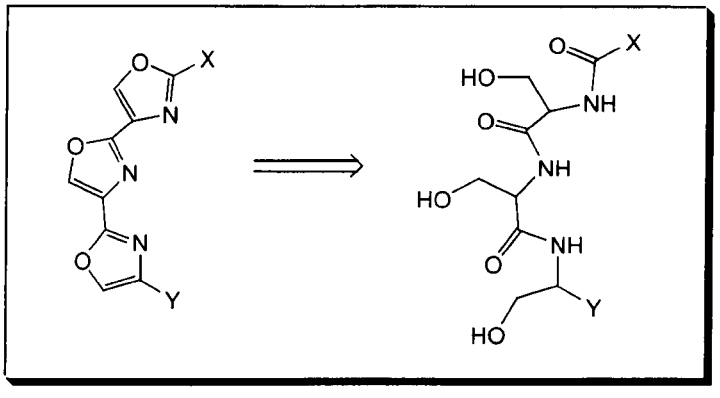
- develop an alternative route for the stereoselective introduction of the C9-methyl group in ulapualide A.

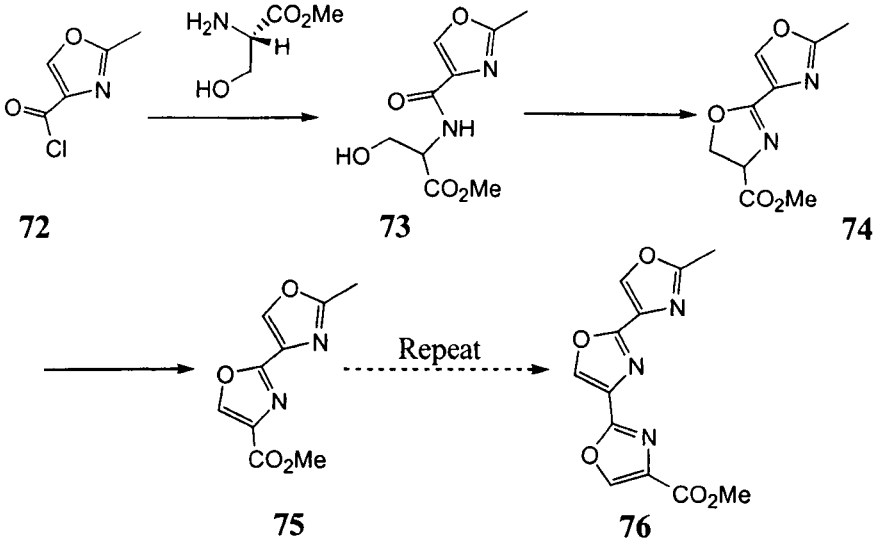
# RESULTS AND DISCUSSION

## 2.1 *The tris-Oxazole System 76*

### 2.1.1 *New Synthetic Studies towards tris-Oxazole Systems*

Despite the achievement of the first total synthesis of ulapualide A, the molecule still held areas of interest and considerable synthetic challenge. This challenge was largely concerned with the *tris*-oxazole fragment which, up until now, had been synthesised *via* the biogenetic patterned synthesis based on the sequential oxazole amide-serine cyclisations followed by oxidations of intermediate oxazolines *viz* **72→76**.





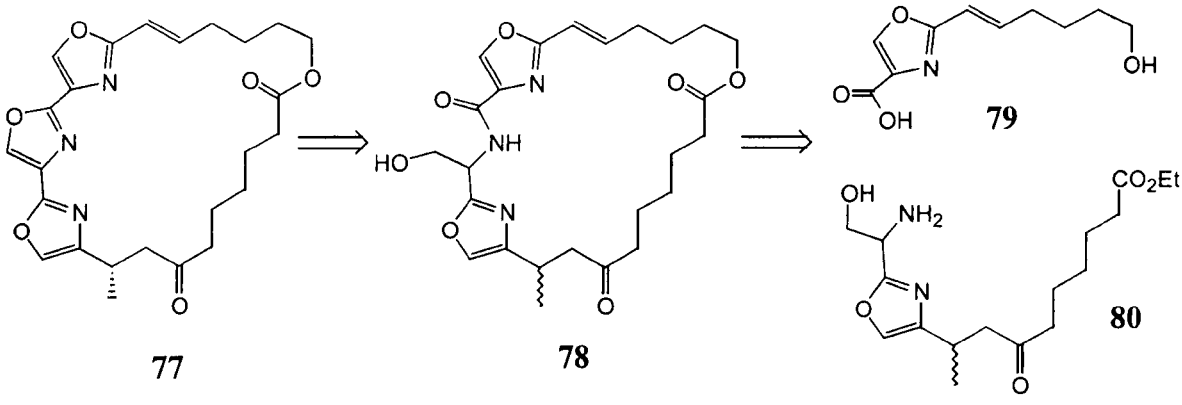

**72** **73** **74** **75** **76**

**Scheme 1**

However, in light of the structures isolated by Kobayashi *et al* **(26-29)**, and their possible implications in the biosynthesis of such compounds, a convergent approach

to the *tris*-oxazole unit was highly desirable. It was anticipated that elaboration of the central oxazole ring could act as the final step in the synthesis of the *tris*-oxazole moiety.

This route provided the impetus for my PhD work and was based on the model system **77** utilising a macrolactamisation strategy, leading to **78**, followed by oxazoline and oxazole ring formation using the substituted mono-oxazoles **79** and **80** as key precursors (**Scheme 2**).

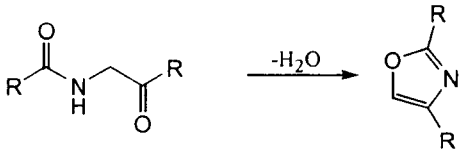



**Scheme 2**

### *2.1.2 Oxazole Formation*

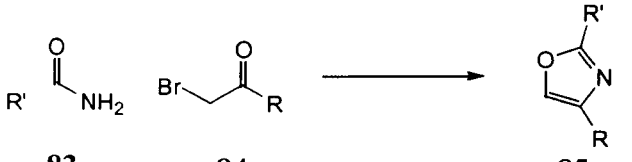
Pivotal to the success of this model study was a knowledge of oxazole chemistry, in particular oxazole formation. Indeed, the widespread occurrence, uses and syntheses of oxazole derivatives has continued to stimulate the organic chemist ever since the first synthesis of 2-methyloxazole in 1876. As such, oxazoles have been the subject of several reviews[74] and with such a plethora of syntheses now available, only the most pertinent examples will be mentioned here.

The Robinson-Gabriel reaction is one of the oldest methods available for oxazole synthesis and involves the cyclodehydration of α-acylamino carbonyl compounds **81**. A variety of dehydrating agents, including $PCl_5$, $P_2O_5$,[75] $POCl_3$,[76] $SOCl_2$[77] and polyphosphoric acid, have been used to effect the transformation.



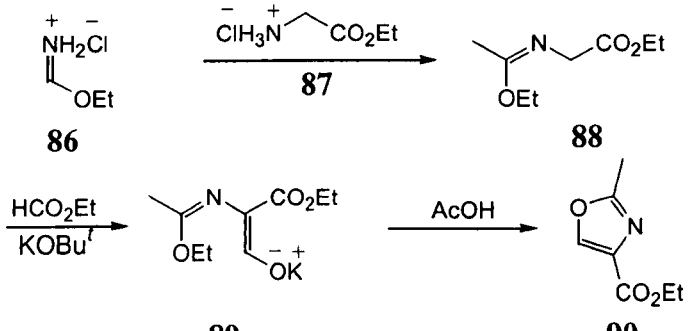
81 82

Variations upon this theme are common, most notably in the reaction of a primary amide **83** with an α-halocarbonyl compound **84** to produce an intermediate 2-acylaminoketone which can undergo dehydration in the usual way to produce a 2,4-disubstituted oxazole **85**. The utility of this method has recently been demonstrated by Panek *et al* in a synthesis of the *tris*-oxazole backbone of ulapualide A.[78]



83 84 85

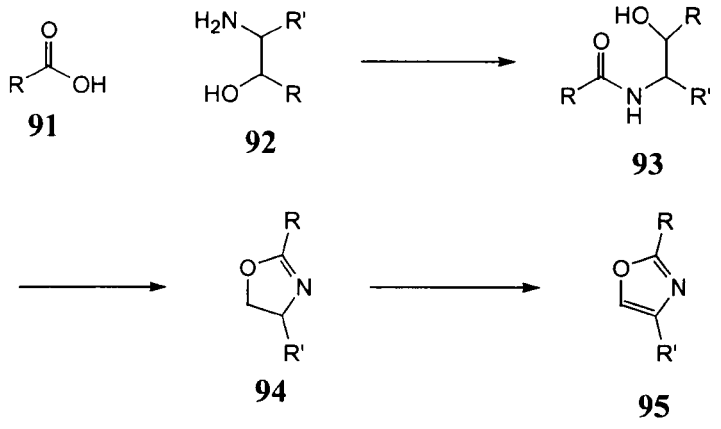
Early work by Cornforth[79] is also reminiscent of the Robinson synthesis, with the condensation between ethyl acetimidate hydrochloride **86** and glycine ethyl ester hydrochloride **87** producing an imino ether **88**. Formylation of this intermediate to give **89** was followed by an immediate cyclisation in boiling acetic acid to produce the desired 2,4-disubstituted oxazole **90** in good yield (**Scheme 3**).



86 87 88 89 90

**Scheme 3**

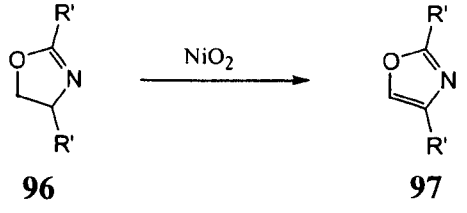
In contrast to these methods, probably the most widely used route to oxazole formation in recent years involves amide formation followed by cyclisation to an oxazoline and subsequent oxidation to give the oxazole (**Scheme 4**).



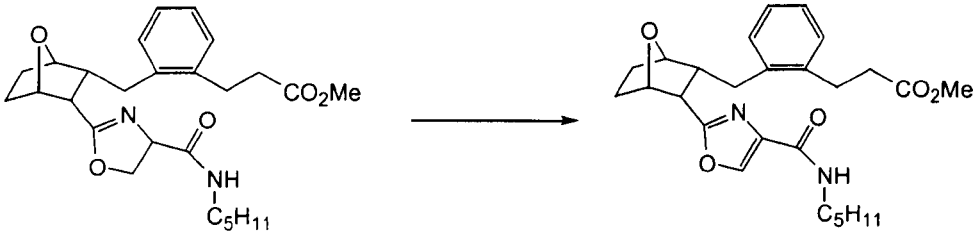

**Scheme 4**

Initial formation of the oxazoline can be achieved in many ways, with activation of the hydroxy amide **93** being required for cyclisation to occur. Activation can be promoted by thionyl chloride, followed by treatment with silver triflate;[80] methanesulfonyl chloride and triethylamine;[81] triphenylphosphine, carbon tetrachloride and DIPEA;[81] under Mitsunobu conditions;[82] phosphorus oxychloride;[83] or the commonly encountered Burgess reagent[84] or DAST.[85] Careful considerations must be taken when choosing a suitable reagent for this transformation, since elimination, aziridine formation or epimerisation may also occur.[86]

The oxazoline-oxazole oxidation has been developed extensively and, in general, proceeds by either a radical pathway or an addition elimination sequence; in either case the need for an enolisable group at the 4-position seems necessary to effect this transformation in good yield. Meyers performed the requisite oxidation of an oxazoline to an oxazole using nickel peroxide in a range of hydrocarbon solvents,[87] after finding that other oxidants such as manganese dioxide, DDQ and phenanthrenquinone produced disappointing results.



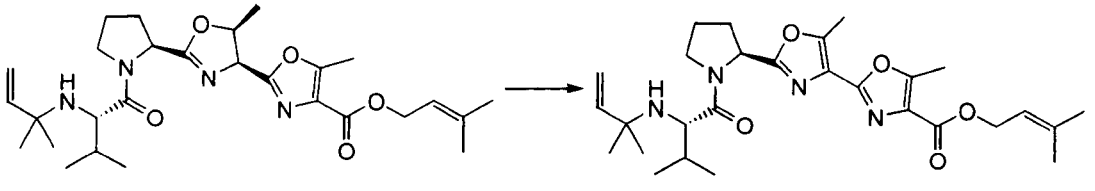
As an alternative to the somewhat capricious $NiO_2$ oxidation, Bristol-Myers Squibb discovered a novel oxidation procedure using a mixture of $CuBr_2$ and DBU for the oxidation of **98** to **99**.[88]



**98** **99**

In a similar fashion, the Kharasch-Sosnovsky reaction,[89] later to be modified by the Meyers group,[90] found application in numerous natural product syntheses. A cocktail of copper(II) acetate, copper(I) bromide and *tert*-butyl hydroperoxide were eventually found to be the optimum conditions for oxidation to take place.

More recently, the addition-elimination oxidation of $BrCCl_3$/DBU has found increasing popularity.[91] So too, a similar oxidation developed by Jung which uses DBU and $CCl_4$ in pyridine and MeCN.[92] Indeed, this oxidation found application in the total synthesis of Muscoride A **48** by Pattenden *et al.*[64]

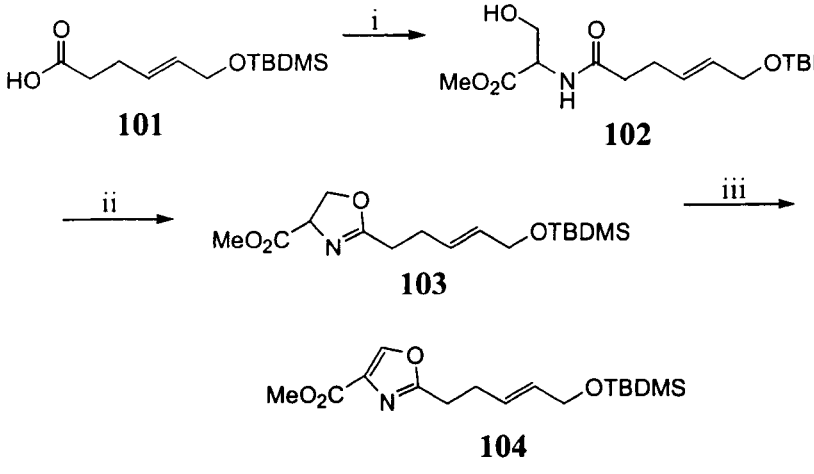


**100** **48**

Finally, an alternative pathway developed by Wipf *et al* has also proven to be extremely useful in oxazole formation *en route* to natural products. Wipf, having encountered problems with the oxidation of oxazolines, returned to the Robinson-Gabriel type cyclisation of a β-keto amide to produce an oxazole.[93] Thus oxidation of a β-hydroxy amide with the Dess-Martin reagent,[94] followed by mild cyclodehydration of the intermediate β-keto amide with triphenylphosphine, iodine and triethylamine allowed the rapid synthesis of highly substituted and

functionalised oxazoles in good overall yield. Amido-aldehydes derived from serine residues were found to cyclise to the oxazole in a much less facile manner. Wipf overcame this problem by changing the reaction conditions and so used the bulky base 2,6-di-*tert*-butyl-4-methylpyridine, with dibromotetrachloroethane and triphenylphosphine. Under these conditions elimination did not occur spontaneously and required subsequent treatment with DBU to produce the oxazole.[66]

The use of both these approaches is shown by Wipf's total synthesis of the enantiomer of hennoxazole A.[66] Thus, condensation of the acid **101** with serine methyl ester hydrochloride, *via* the mixed anhydride, gave the β-amido alcohol **102** which was cyclised to the oxazoline **103** with the Burgess' reagent.[84] Oxidation of **103** with copper(II) bromide and DBU then gave the desired oxazole **104** in 73% overall yield (**Scheme 5**).



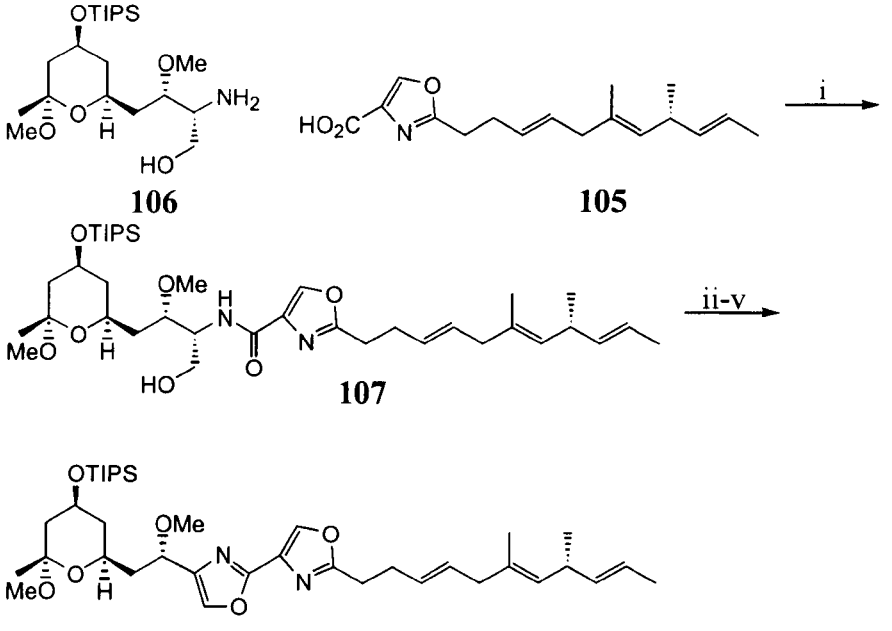

**101** **102** **103** **104**

*Reagents:* i, Serine.OMe.HCl, i-BuOCOCl, $Et_3N$, $CH_2Cl_2$; ii, Burgess' reagent, THF; iii, $CuBr_2$, DBU, HMTA, $CH_2Cl_2$, (73% over 3 steps).

**Scheme 5**

Elaboration of the side chain in **104** and saponification of the ester gave the acid precursor **105** to the second oxazole. The acid **105** was next coupled to the tetrahydropyran-amine unit **106** under standard peptide coupling conditions to give the β-amido alcohol **107** in 63% yield. Oxidation of **107** with Dess-Martin periodinane then gave the intermediate amido aldehyde, which was smoothly

cyclodehydrated using the conditions described previously to give the enantiomer of hennoxazole A **108** after desilylation with TBAF in 42% overall yield (**Scheme 6**).[66]




**106** **105** **107**

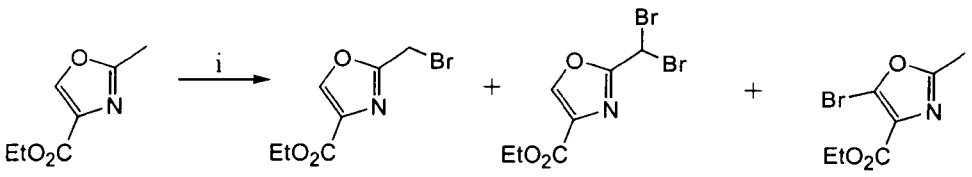
**108**

*Reagents:* i, PyBOP, DIPEA, $CH_2Cl_2$, (63%); ii, Dess-Martin periodinane, $CH_2Cl_2$; iii, $BrCl_2CCCl_2Br$, $PPh_3$, 2,6-di-*tert*-butyl-4-methylpyridine, $CH_2Cl_2$; iv, DBU, MeCN; TBAF, THF, (42% over 4 steps)

**Scheme 6**

### *2.1.3 The Model Study*

As highlighted in the previous section, the methodology of Cornforth[79] was utilised to generate the 'top' 2,4-disubstituted oxazole, **90**, of the model system. Exposure of this oxazole to *N*-bromosuccinimide under reflux conditions in carbon tetrachloride[95] provided a crude mixture of mono- and di-brominated esters, **109** and **110** respectively, together with a small amount of the 5-substituted product **111** and unreacted starting material. After extensive and somewhat troublesome purification, the desired mono-brominated oxazole **109** was isolated albeit in only 41% yield (**Scheme 7**).

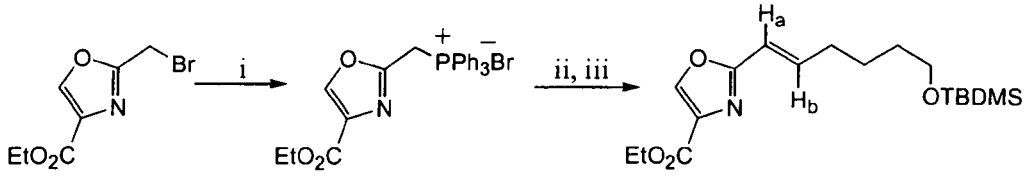



**90** **109** **110** **111**

*Reagents:* i, NBS/AIBN, (41%).

**Scheme 7**

Additon of an ethereal solution of triphenylphosphine to **109** next gave the Wittig salt **112** as a hygroscopic pale yellow solid. Deprotonation of this mono-oxazole phosphonium salt with *n*-butyllithium at –78°C in THF produced a solution of the corresponding ylide which slowly decolourised upon addition of the model C5-aldehyde , leading to the expected olefin **113** in an acceptable 45% yield (**Scheme 8**). $^1$H nmr data confirmed the formation of the (*E*)-geometric isomer of **113** after examination of the coupling constants for the respective olefinic protons ($H_a/H_b$ $J$ = 16.0 Hz).



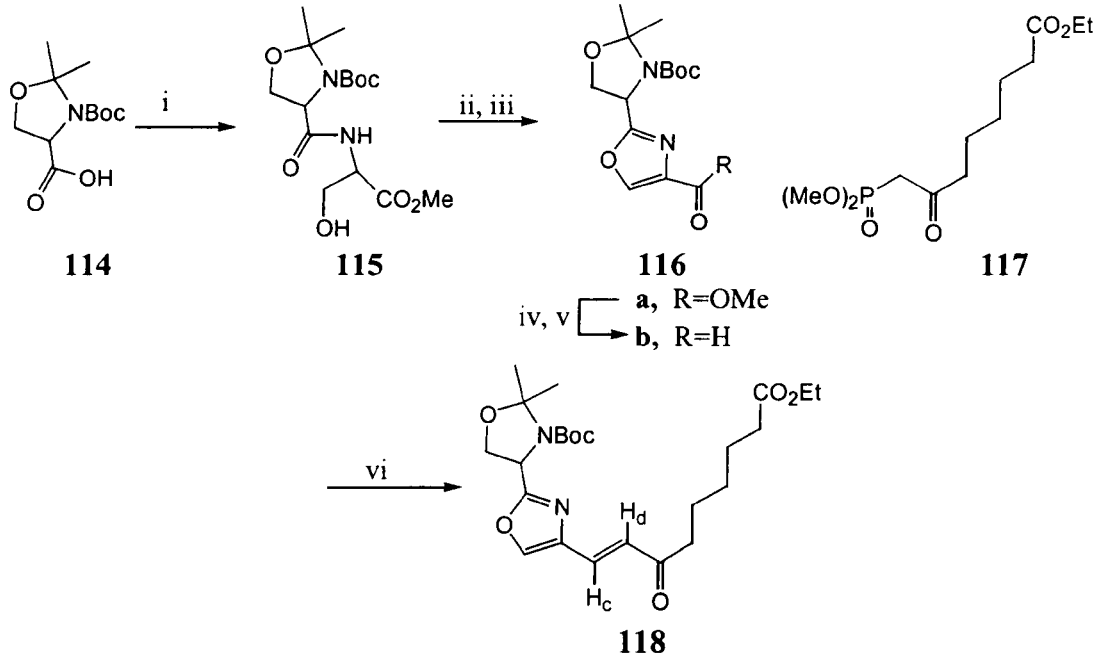

**109** **112** **113**

*Reagents:* i, $PPh_3$, (82%); ii, *n*-BuLi, THF, -78 °C; iii, 5-*tert*-butyldimethylsilylpentanal, (45%).

**Scheme 8**

The lower chain **118** was synthesised in eight steps starting from the Garner acid **114**,[96] a common chiral building block which features in many heterocyclic natural product syntheses. A peptide coupling reaction between **114** and serine methyl ester first gave the corresponding amide **115** in readiness for the cyclodehydration-oxidation sequence to install the 'bottom' oxazole ring of the model system. This sequence utilised Burgess' reagent[84] to give the corresponding oxazoline in a 61% yield and as a mixture of diastereoisomers. Oxidation of this mixture with $BrCCl_3$/DBU[91] finally led to the oxazole, **116a**, in a good yield of 75%.

Following reduction of the methyl ester group in **116a** to the corresponding aldehyde, **116b**, a Wadsworth-Emmons olefination using **117** as the coupling partner and employing finely ground barium hydroxide octahydrate as base,[97] successfully gave the enone, **118**, in a 71% yield (**Scheme 9**). Again, examination of the coupling constants ($H_c/H_d$ $J$ = 15.6 Hz) confirmed the (*E*)-geometry.

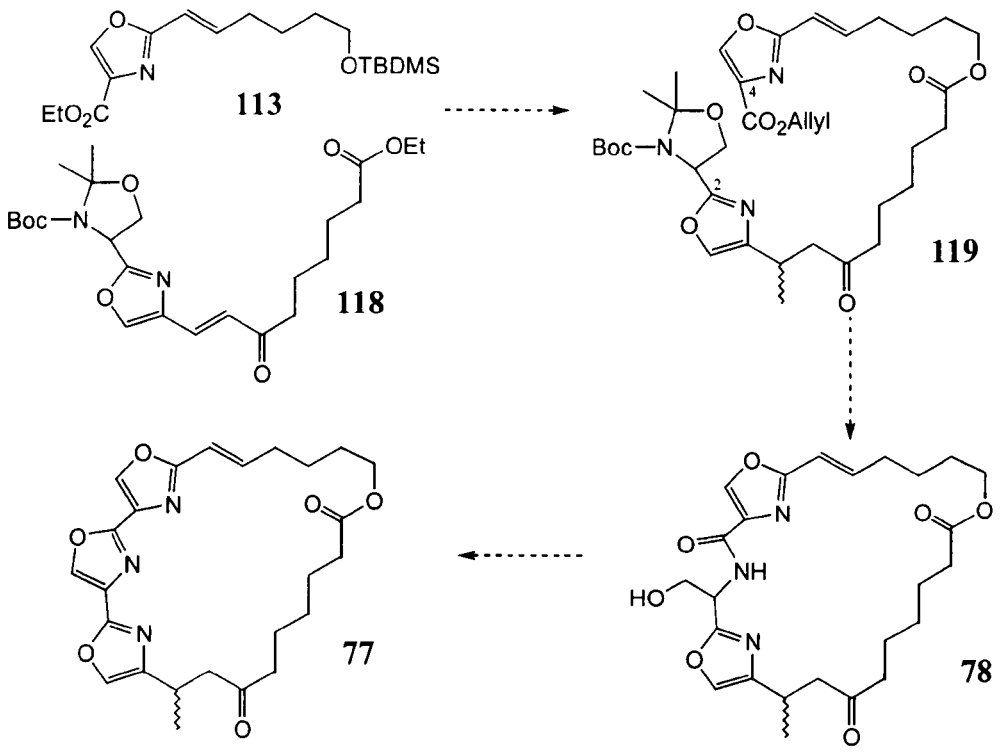



*Reagents:* i, Serine OMe.HCl, $Et_3N$, 0 °C then DCC, (74%); ii, Burgess reagent, THF, (75%); iii, $BrCCl_3$, DBU, 0-25 °C, (75%); iv, DIBAL-H; v, $PySO_3$ in DMSO, $Et_3N$, (60%); vi, $Ba(OH)_2.8H_2O$, **117**, THF, (71%).

**Scheme 9**

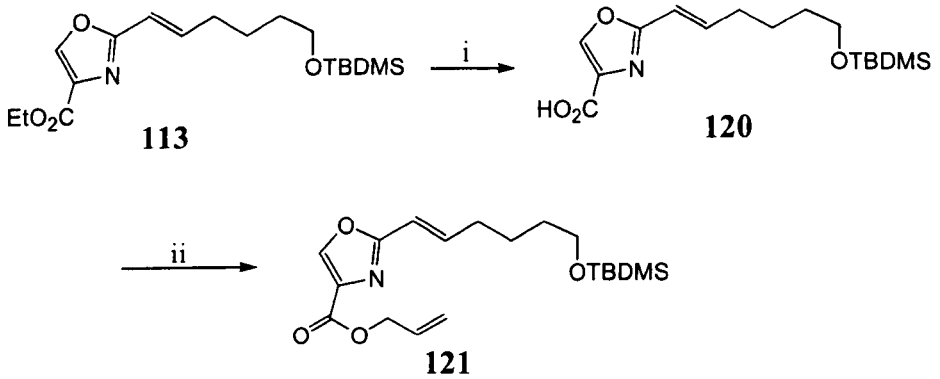
With the top and bottom fragments, **113** and **118**, now in hand, protecting group manipulation and coupling of these fragments was now envisaged to give the pre-cyclisation fragment, **119**. The realisation of a macrolactamisation protocol requires that the ester function at the C4 position of the 'top' oxazole in **119** must be removed to reveal a free carboxylic acid, such that a ring forming lactamisation reaction may be performed with the fully deprotected serine residue at the C2 position of the 'bottom' oxazole heterocycle. Protecting group chemistry was therefore of utmost importance, especially when applied to ulapualide A itself, so not as to affect any of the sensitive functionality present in the side-chain. For

this reason, allyl ester protection of the carboxyl group was chosen, with the mild deprotection conditions of palladium (0) unlikely to affect any other part of the molecule (**Scheme 10**).




**Scheme 10**

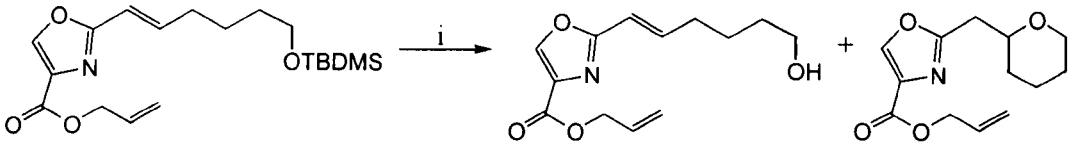
Thus, hydrolysis of the top-chain ester, **113**, using lithium hydroxide in a 3:1 THF:water mixture afforded the carboxylic acid, **120**, in quantitative yield. Protection of the acid as the allyl ester was then effected by reacting **120** with allyl bromide under phase transfer conditions, to give the fully protected oxazole, **121** in a 59% yield (**Scheme 11**).




*Reagents:* i, LiOH, 3:1 THF:$H_2O$ (100%); ii, Allyl bromide, aliquat 336, 5d (59%).

**Scheme 11**

To reveal the free hydroxyl of the TBDMS ether, **121** was reacted with a slight excess of TBAF in THF only to provide the deprotected alcohol, **122**, in a disappointing 32% yield. Transformation of the substrate to a less polar product had also occurred. Analysis of this material indicated loss of the olefinic peaks which suggested that a conjugate addition of the naked anion into the alkene could have occurred, thus producing the tetrahydropyran product **123**. Acid deprotection however, using a 3:1:1 mixture of AcOH:THF:$H_2O$, gave the alcohol **122** in a 95% yield (**Scheme 12**).[98]




**121** **122** **123**

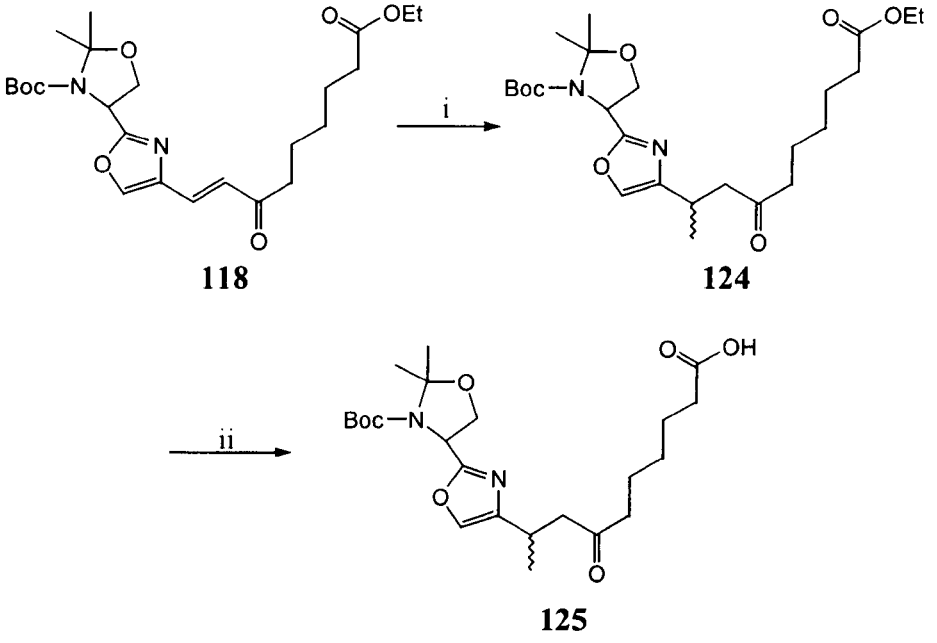
*Reagents:* i, TBAF, THF, 12h

**Scheme 12**

With the C5 top-chain now complete, our attention turned to the bottom fragment **125**. The double bond of the conjugated enone system in **118** needed to be reduced in order to give the correct conformation for the macrocyclisation step, and also to avoid any complications with the palladium(0) deprotection of the allyl ester.

Hydrogenation of **118** with both homogeneous and heterogeneous catalysts proved fruitless, even under the forcing conditions of 70atms $H_2$. Attention therefore turned to the selective 1,4-reduction of the enone using calcium metal in liquid ammonia.[99] A variety of conditions were tried ranging from 5 equivalents through to 30 equivalents of calcium. 'Selective' reduction of the enone only occurred under the extreme conditions of 30 equivalents, although disappearance of the oxazole proton resonance at $\delta$ 7.77 ppm also occurred under these conditions. As a consequence of these disappointing results, it was decided that conjugate addition of a methyl carbanion to the enone in **118** was now the most

favoured route. Thus, addition of methyl lithium to a cooled solution of copper iodide first produced a yellow solution of the methyl cuprate, $Me_2CuLi$. Dropwise addition of the enone system **118** then led to a clear solution and formation of the C9 β-methyl ketone, **124**, in an adequate 55% yield (**Scheme 13**).



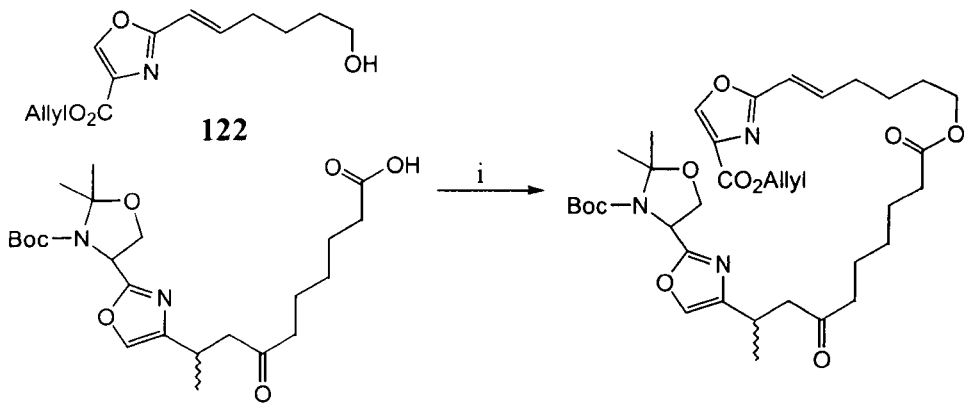

**118** **124** **125**

*Reagents:* i, $Me_2CuLi$, 2h (55%); ii, LiOH, 3:1 THF:$H_2O$ (100%).

**Scheme 13**

Exposure of the oxazole ester, **124**, to aqueous lithium hydroxide next presented the requisite acid, **125**, in a quantitative yield.

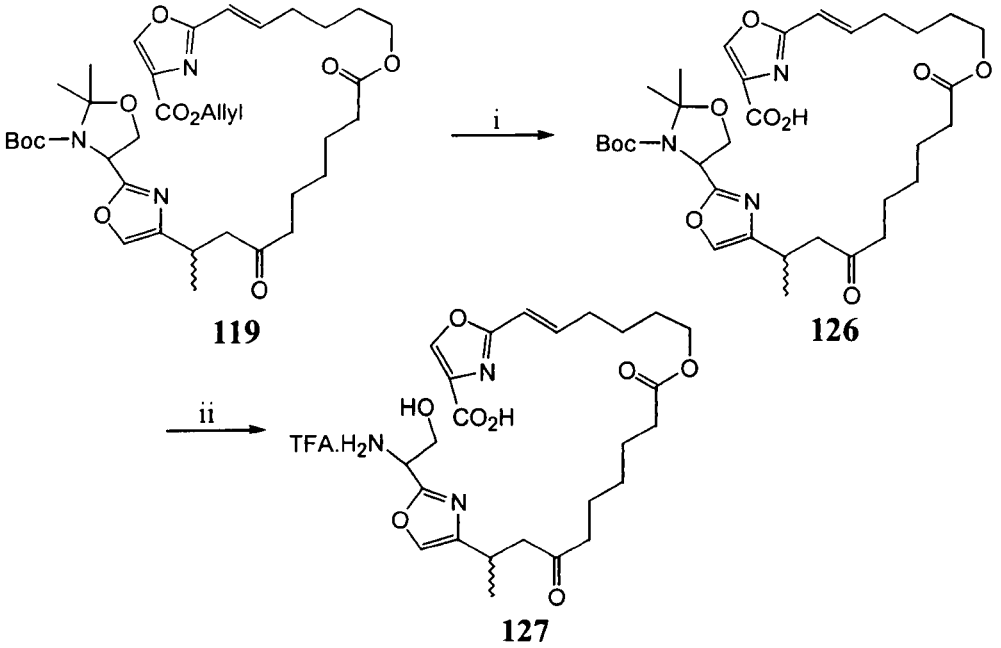
To complete the synthesis of the model system, we required to couple the top and bottom chains, **122** and **125**. Deprotection and macrolactamisation, followed by cyclodehydration and oxidation would then furnish the target. A review of the literature revealed a plethora of available methods for ester formation. [100] One of the most common methods found, a carbodiimide condensation, involved treatment of the carboxylic acid with the alcohol and EDC in dichloromethane containing a catalytic amount of DMAP. This method served us well, giving an excellent 73% yield of **119** from the two respective fragments **122** and **125** (**Scheme 14**).




*Reagents:* i, EDC, DMAP, $CH_2Cl_2$, (73%).

**Scheme 14**

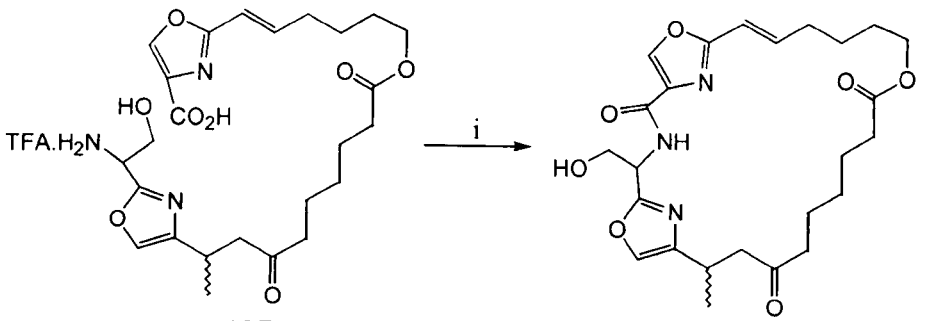
With both the top and bottom chains now successfully coupled, all that remained was to unmask the carboxylic acid and deprotect the BOC-protected oxazolidine in **119**, in order to attempt macrolide formation. Cleavage of the allyl ester was the first deprotection performed (**Scheme 15**), using pyrrolidine in the presence of a catalytic amount of palladium(0) to give the desired acid, **126**, in a crude 70% yield.[101] A 50% TFA solution next gave the deprotected oxazolidine **127** and we were now ready to try the crucial macrolactamisation reaction.




*Reagents:* i, $Pd(PPh_3)_4$, pyrrolidine; ii, 50% TFA in $CH_2Cl_2$

**Scheme 15**

Like esterification, these types of transformation were just as prevalent within the literature.[102] Diphenylphosphorylazide (DPPA) seemed to be a fairly common phosphorus based acyl activating reagent, and so this was used in the initial macrolactamisation studies. Indeed, exposure of the substrate, **127**, to DPPA in the presence of DIPEA under high dilution conditions afforded the macrolactam **78** in 20% yield (**Scheme 16**).



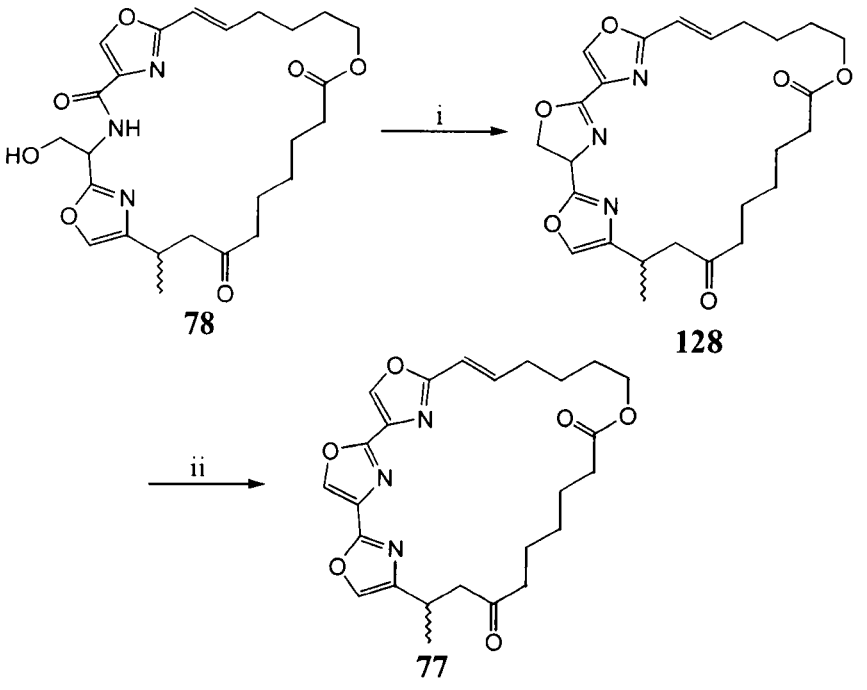

**127** **78**

*Reagents:* i, DPPA, DIPEA, DMF, 5d, (20%).

**Scheme 16**

Enthused by this positive result, a cyclodehydration procedure towards the desired ring system now became feasible. This was effected using Burgess' reagent[84] to give the oxazoline, **128**, in a 67% yield. 'Oxidation' using $BrCCl_3$/DBU, [91] however, did not give the desired *tris*-oxazole, possibly due to enolisation of the ketone on the bottom chain.

In retrospect, the failure of this reaction was not too surprising. All previous examples of this oxidation have required an enolisable group at the 4-position of the oxazole ring and in our system, this was not the case. A similar oxidation using $CCl_4$/DBU/pyridine/MeCN had also been used in our research group to furnish the *bis*-oxazole core of muscoride A. Even here, the presence of an ester functionality attached to the terminal oxazole made enolisation possible through the oxazole ring (see page 31).




*Reagents:* i, Burgess' reagent (67%); ii, $NiO_2$ (46%).

**Scheme 17**

A metal oxide oxidation, although renowned for being low yielding, was now the next option. Thus, portionwise addition of nickel peroxide[87] to a refluxing solution of **128** gave the *tris*-oxazole macrolide, **77**, in a surprisingly good yield of 46%, probably due to the high degree of conjugation acting as the driving force (**Scheme 17**).

The structure of **77** followed conclusively from inspection of its $^1H$ nmr spectrum which showed three singlets at δ 8.07, 8.06 and 7.19 ppm, indicative of the three oxazole protons of ulapualide A which occur at δ 8.15, 8.13 and 7.48 ppm respectively. Another characteristic feature of the *tris*-oxazole moiety is its UV absorption spectrum which displays absorption maxima in the range $\lambda_{max}$ 240-260 nm. Indeed, this diagnostic fingerprint occurred at λ 263 nm for the model system and reinforced our evidence for its structure.

### *2.1.4 Conclusions*

We have demonstrated a new approach to the *tris*-oxazole macrocyclic portion of ulapualide A. The design for this synthesis was inspired by the isolation of the halishigamides and the possible implications that these molecules have regarding the biosynthesis of the *tris*-oxazole backbone in the ulapualides. This model study has been achieved using a number of oxazole ring-forming reactions with the key macrolactamisation reaction allowing the central oxazole ring to be formed at the final stage of the synthesis.

## 2.2 *The Side-Chain in Ulapualide A*

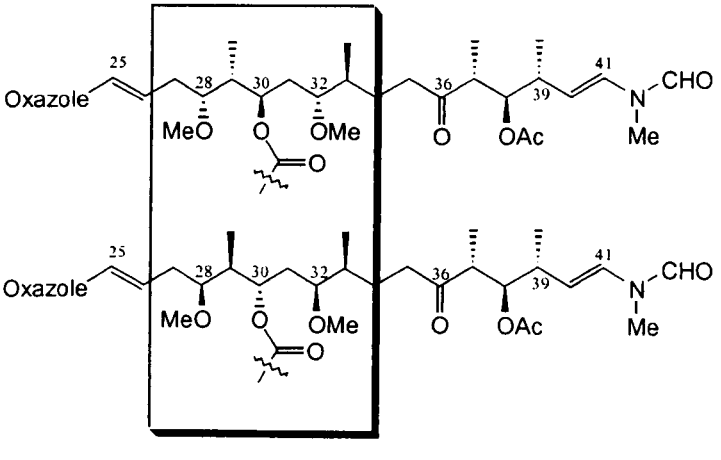
### *2.2.1 The Stereochemical Dilemma*

The completion of the aforementioned model study paved the way for its application to the natural product, ulapualide A. For this to be realised, the synthetic problem of the side-chain had to be addressed. The side-chain of ulapualide A, contains eight out of the ten chiral centres found within this natural product and has proved a somewhat daunting challenge, made all the more difficult by the differences found between the cmr data of Chattopadhyay's synthetic and natural ulapualide A. Upon completion of ulapualide A, in January 1998, these differences led us to conclude that the stereochemistry of the synthetic ulapualide differed from that in the natural product at one or more of the stereogenic centres along the C28-C33 portion of the top-chain. This suspicion was later confirmed by Panek and Fusetani who through extensive nmr techniques together with degradation studies, established the stereochemistry of the related mycalolide metabolites **22-24**, stating that this prediction applied to the ulapualides.[103]

As illustrated below, it is interesting to see where the differences in stereochemistry lie. For the C28-C32 portion of the top-chain, Panek's prediction appears to be enantiomeric as compared to ours. The C33 centre together with the remaining three chiral centres at C37-C39 are of the same stereochemistry to that predicted by the metal chelation model.

***Molecular Modelling Prediction***

***Synthetic Modelling Prediction***



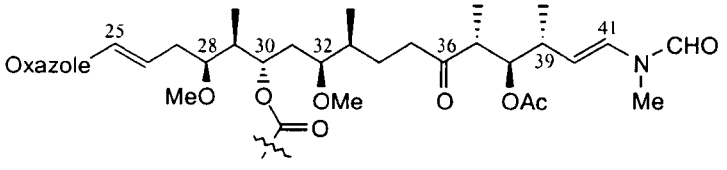
It is uncanny therefore that the differences between our synthetic ulapualide and natural ulapualide A are simply:

- The differing stereochemistry at C32, *ie* β-OMe instead of α-OMe, which is reflected in the different data in their cmr spectra, *viz* C-32, δ 81.0ppm (natural δ 81.8ppm).

- The mirror image (enantiomeric) relationship between the C28-C30 centres in the two compounds, which is *not* reflected in their cmr shift data, *viz* C-28, δ 79.9ppm (natural δ 80.0ppm), C-29, δ 34.1ppm (natural δ 34.6), C-30, δ 72.8ppm (natural δ 73.0ppm), C-29-Me, δ 9.1ppm (natural δ 9.1ppm).

### *2.2.2 Strategy and Design*

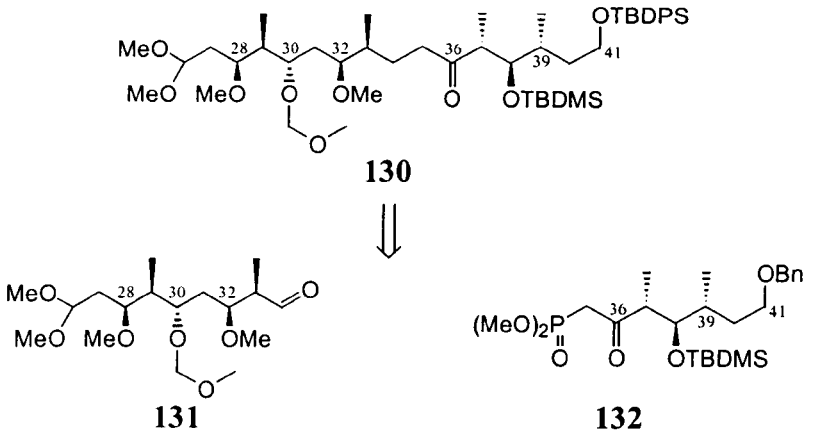
With the remarkable correlations made between synthetic and natural ulapualide A, together with the findings of Panek, it was decided to embark on a newly designed synthesis to the revised stereochemistry of the top-chain, with **129** now as our target.




**129**

For this revised target, we still intended to use many of the key disconnections made previously in our recent total synthesis. Hence, prudent disconnection across the olefinic double bond C25-C26 and the ester at C30 together with the formyl enamine disconnetion revealed the C16 structure **130** now as our target. Notice the choice of hydroxy protecting groups at C30, C38 and C41, together with the dimethyl acetal masking the aldehyde at C26. With this dimethyl acetal, MOM, TBDMS, TBDPS derivative **130**, we were confident of selective removal

in the order $CH(OMe)_2$>OMOM>OTBDMS using the reagent dimethyl boron bromide.[104]

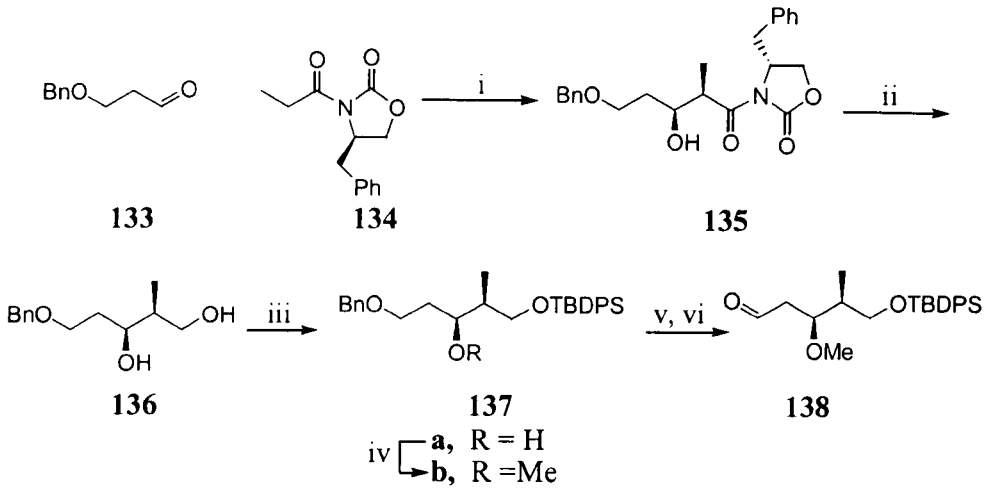



**Scheme 18**

This C26-C41 fragment **130** was to be derived from the elaboration of the two sub-units **131** and **132** using a Wadsworth-Emmons coupling procedure. The stereochemical detail associated with each of these sub-units would be generated by applying the Evans' chiral aldol protocol in combination with the controlled ring opening of chiral epoxy alcohols by methyl nucleophiles.

### *2.2.3 The C26-C34 Aldehyde Fragment 131*

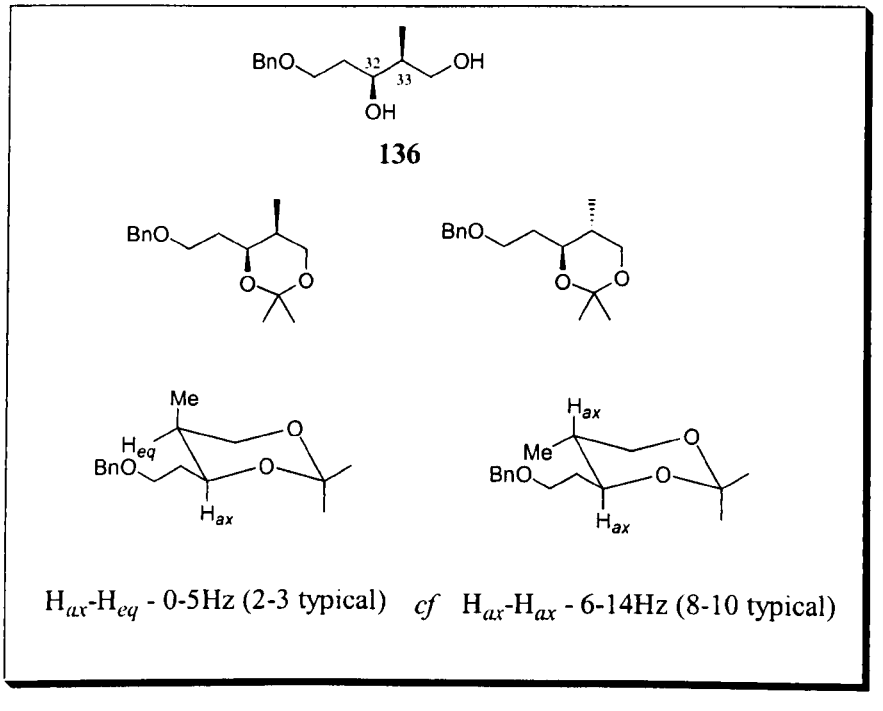
Rapid generation of the first two chiral centres in this fragment **131** came from the Evans aldol reaction between the C3-aldehyde **133** and the commercially available (*R*)-4-benzyl-3-propionyl-2-oxazolidinone **134**.[105] Addition of this aldehyde to a solution of the boron enolate derived from the imide **134** at –78 °C led to the *syn*-aldol product **135** in 80% yield and with excellent diastereoselectivity (de>95% from $^1H$ nmr). Reduction of the auxilliary in **135** with lithium methoxyborohydride[106] then gave the diol **136** which, following protection, gave the mixed methyl ether-silyl ether **137b** in 56% yield over three steps (**Scheme 19**).



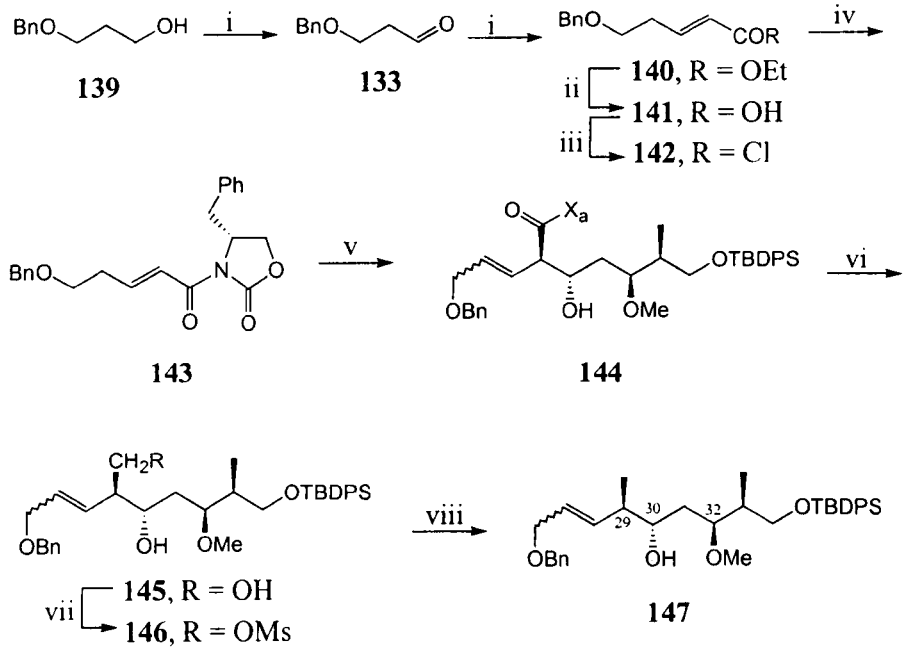

*Reagents:* i, $Bu_2BOTf$, $Et_3N$, -78 °C (80%); ii, $LiBH_4$-MeOH (90%); iii, *tert*-$BuPh_2SiCl$, imidazole, (94%); iv, NaH, MeI, (66%); v, $H_2$, $Pd(OH)_2$-C, (92%); vi, $(COCl)_2$, DMSO, $Et_3N$, (87%).

**Scheme 19**

The stereochemical assignment of the *syn*-aldol product **135** was secured by conversion of the diol **136** into the corresponding acetonide from which the $^1H$ nmr vicinal coupling constants for the protons on carbons C32-C33 could be readily extracted. Indeed, $J_{32,\ 33}$ = 2.6 Hz confirmed the desired *syn*-stereochemistry.[107]



Hydrogenolysis of **137b** and oxidation of the resulting primary alcohol next led to the protected aldehyde **138**. This aldehyde was now ready to undergo a second Evans aldol reaction,[105] this time with the boron enolate derived from the unsaturated imide **143** (**Scheme 20**). The imide **143** was produced smoothly from the mono benzyl ether of propane-1,3-diol **139**, following: i, oxidation and a Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane, leading to **140**; ii, saponifiaction of **140** and conversion into the acid chloride **142**, and finally iii, treatment of **142** with the anion derived from (*R*)-4-phenylmethyl-2-oxazolidinone to produce **143**. When the aldehyde **138** was added to a solution of the boron enolate derived from the imide **143** at –78 °C, work-up and chromatography led to the *anti*-aldol product **144** as a 1:1 mixture of *Z*- and *E*-isomers in 70% yield and >95% de.



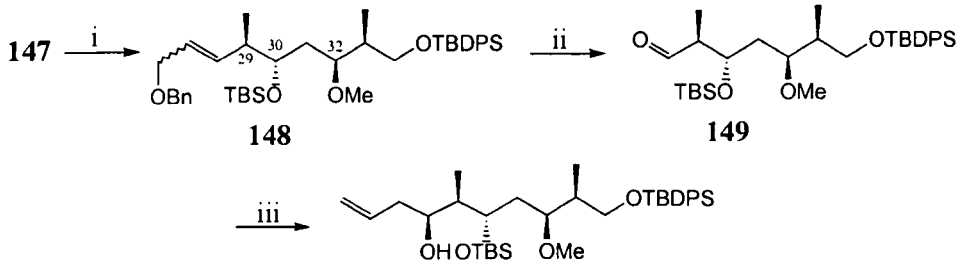

*Reagents:* i, DMSO, $(COCl)_2$, $Et_3N$, then $EtO_2CCH{=}PPh_3$ (68%); ii, LiOH, $H_2O$ (95%); iii, $(COCl)_2$, DMF; iv, *n*-BuLi, 4-phenylmethyl-2-oxazolidone, -78 °C (80%); v, $Bu_2BOTf$, $Et_3N$, -78 °C, then **138** (70%); vi, $LiBH_4$-MeOH (90%); vii, $MeSO_2Cl$-$^iPr_2NEt$ (90%); viii, $LiBH_4$-MeOH (82%).

**Scheme 20**

In readiness for oxidative cleavage of the double bond in **144**, the imide residue was next reduced to the alcohol **145** in a 90% yield using lithium methoxyborohydride.[106] Mesylation of **145** using mesyl chloride in the presence

of triethylamine then gave the mesylate **146** in 85% yield which was further reduced, again using lithium borohydride. This gave the corresponding C29-β-methyl compound **147** in a 95% yield. Notice how the reductive removal of the auxilliary followed by the deoxygenation step has allowed the *syn*-aldol reaction to function as an apparent *anti*-aldol reaction, generating the 1,2-*anti* relationship across the C29-C30 bond. This protocol has been utilised by others in several polypropionate natural product syntheses,[108] including rapamycin.[21d]

The C30-hydroxy group in **147** was next protected as its silyl ether to give **148** in 98% yield (**Scheme 21**). Ozonolysis of **148** at –78 °C, followed by a reductive work-up procedure using $PPh_3$, then led to the aldehyde **149** in 80% yield. Brown's chemistry was next utilised to generate the C27-C28 bond of the top chain and also install the final chiral centre of this fragment.[109] Hence, addition of Brown's (-)-allyldiisopinocampheylborane to the aldehyde **149** proceeded in a highly diastereoselective manner and after chromatography, gave rise to the required hydroxy olefin **150 (Scheme 21)**.

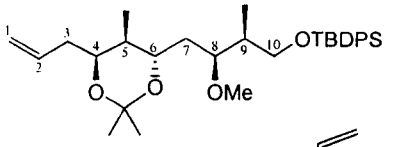



*Reagents:* i, TBDMS-OTf, 2,6-lutidine, $CH_2Cl_2$ (95%); ii, $O_3$, $CH_2Cl_2$, -78 °C (80%); iii, $CH_2$=$CHCH_2MgBr$, (-)IPCBOMe, -78 °C (70%).

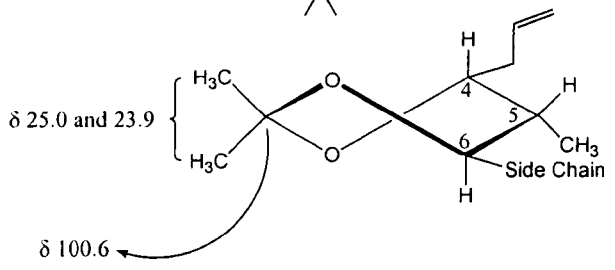
**Scheme 21**

With all of the chiral centres now in place for this fragment, it was a good time to prove the stereochemical assignment of the C28-C30 *anti*-diol. Indeed, much work in analysing the stereochemistry of 1,3-diols has been done by the research groups of Rychnovsky and Evans which relies on the conformational properties of the corresponding 1,3-diol acetonides (4,6-dialkyl-2,2-dimethyl-1,3-dioxanes).[107] Chemical shift correlation of the $^{13}C$ nmr resonances of the three acetonide

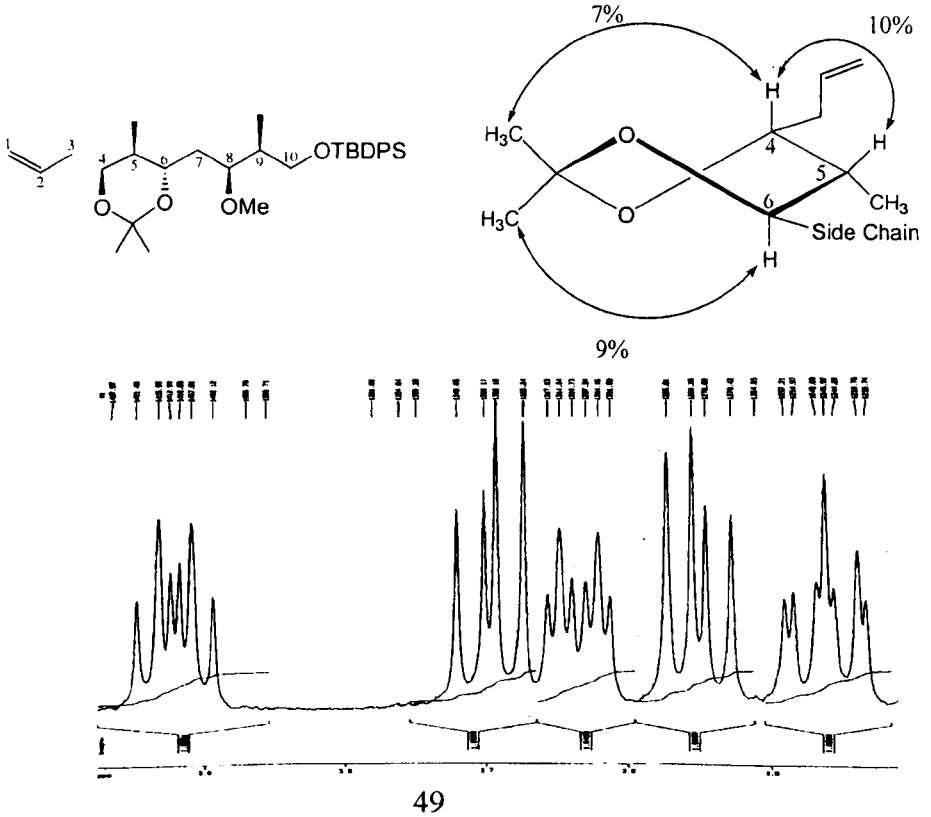
carbons has been shown to be a reliable method for determination of the relative stereochemistry in such systems. Application of this method to our own system produced the acetonide **151**. The ketal carbon resonance at δ 100.6ppm in **151** together with the two methyl carbons resonating at δ 23.9ppm and δ 25.0ppm was indicative of an *anti*-acetonide existing in a twist-boat conformation in order to avoid the 1,3-diaxial interactions that would be present in either chair conformation.



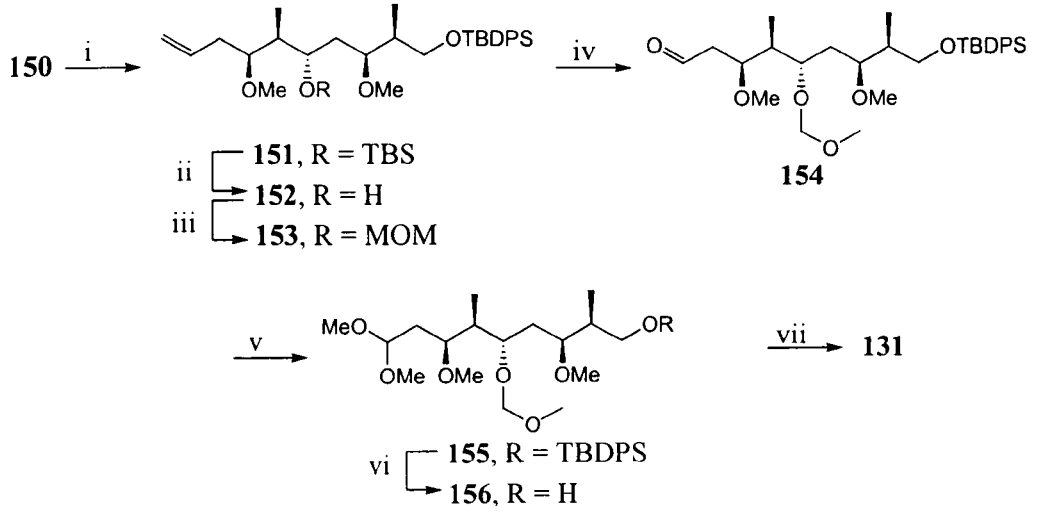

**151**




This stereochemical assignment was further reinforced by examination of the nOe enhancements obtained after irradiating the C4 and C5 protons. This was possible due to the clear splitting in this region of the $^{1}H$ nmr.



With the stereochemistry of fragment **150** now secure, the final stages of our synthesis were nothing more than protecting group manipulations. Hence, conversion of the C28 secondary alcohol in **150** into the corresponding methyl ether **151** was achieved under mild methylating conditions using methyl triflate and 2,6-DTBP. Selective deprotection of the secondary TBS ether in **151** using PPTS in ethanol next gave the desired alcohol **152** which was immediately re-protected as its methoxymethyl ether **153** in a 95% yield. Ozonolysis of the terminal double bond in **153** then led to the aldehyde **154** which was protected as its dimethyl ketal **155** in 95% yield. Finally, deprotection of the primary silyl ether in **155** using TBAF provided the alcohol **156** in quantitative yield, which after oxidation using TPAP-NMO[110] produced the aldehyde **131** (**Scheme 22**). We were now in a position to couple this aldehyde with the β-keto phosphonate fragment, **132**.



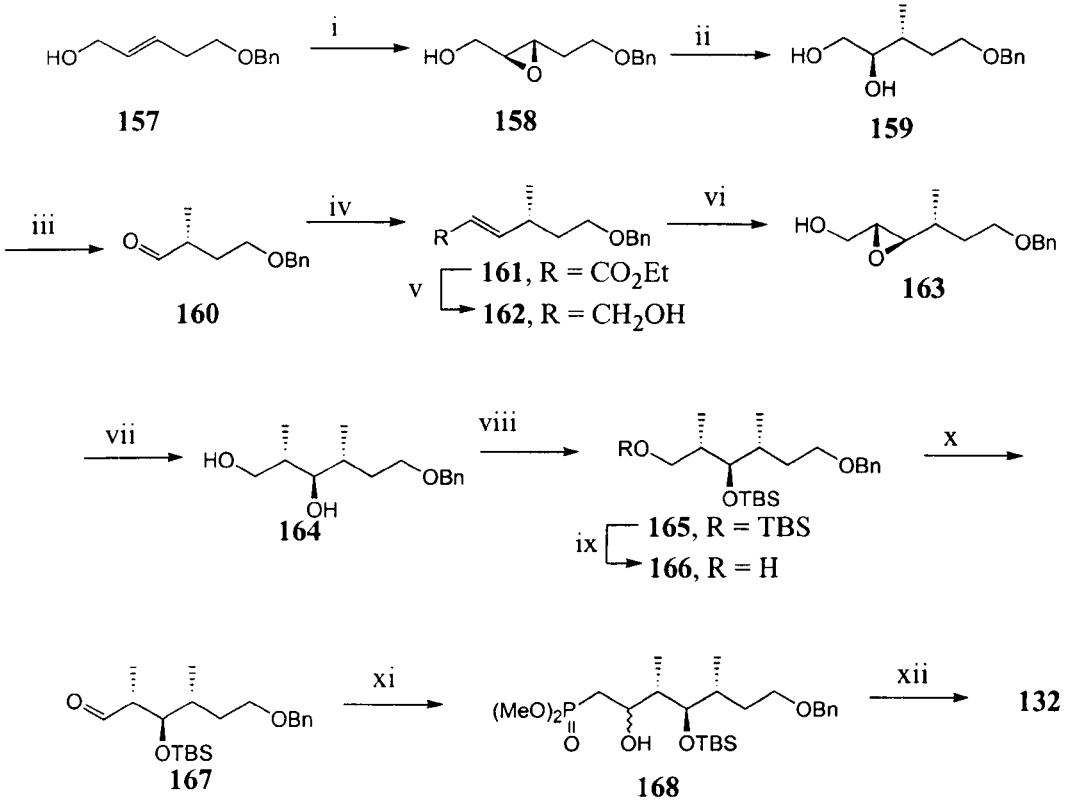

*Reagents:* i, MeOTf, 2,6-di-*tert*-butylpyridine (98%); ii, PPTS, ethanol, (90%); iii, MOM-Cl, $^{i}Pr_2NEt$ (95%); iv, $O_3$, $PPh_3$, (89%); v, TMOF, MeOH, pTSA (98%); vi, TBAF, (100%); vii, TPAP, NMO (89%)

**Scheme 22**

### *2.2.4 The C35-C41 β-Keto Phosphonate Fragment 132*

The synthesis of the phosphonate **132**, required for the projected coupling reaction with **131**, was achieved in twelve steps starting from the *E*-allylic alcohol **157** and

featured the regiospecific chiral epoxide ring opening reactions **158→159** and **163→164** as key reactions.[111]



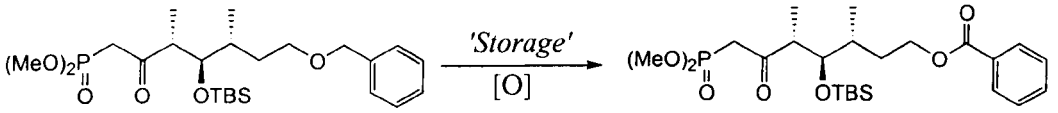

*Reagents and conditions:* i, (+)-DET, $Ti(O^iPr)_4$, t-BuOOH (76%); ii, $Me_3Al$; iii, $NaIO_4$ (84%); iv, $Ph_3PCHCO_2Et$ (94%); v, DIBAL (96%); vi, (-)-DET, $Ti(O^iPr)_4$, t-BuOOH (85%); vii, MeMgBr, CuI, THF; $NaIO_4$, MeOH-$H_2O$ (89%); viii, TBDMS-OTf, 2,6-Lutidine (100%); ix, PPTS, MeOH, DCM (96%); x, TPAP, NMO (94%); xi, $MePO(OMe)_2$, *n*-BuLi (90%); xii, PDC, DMF (92%).

**Scheme 23**

Hence, the phosphonate was synthesised from the chiral 1,2-diol intermediate **159** which was itself produced from the *E*-allylic alcohol **157** using a similar strategy to that used in the synthesis of **143**. After periodate cleavage of this diol to the aldehyde **160**, a Wittig reaction between **160** and carbomethoxytriphenylyphosphorane next led to the *E*-unsaturated ester **161** which on reduction with DIBAL-H accessed the *E*-hex-2-en-1-ol **162**. Epoxidation of **162** to **163** using the Sharpless protocol[112] with (-)-diethyl tartrate, followed by chelation controlled epoxide ring opening with methylmagnesium

bromide next led to the 1,3-diol **164** in 85% yield. Protection of the primary and secondary hydroxy groups in **164** as their *tert*-butyldimethylsilyl ether **165**, followed by selective deprotection of the primary alcohol, then gave **166** which was smoothly oxidised to the corresponding aldehyde **167** using TPAP-NMO.[110] Finally, treatment of the aldehyde **167** with dimethyl methyl phosphonate in the presence of *n*-BuLi followed by oxidation of the resulting carbinol **168** using PDC in DMF then produced the phosphonate **132 (Scheme 23)**.

After storage of the phosphonate **132** for ~1 year, $^{1}H$ nmr revealed to our surprise that the benzyl ether contained within this fragment had been oxidised to the corresponding benzoate ester **169 (Scheme 24)**. This was confirmed *via* $^{13}C$ nmr which showed a singlet at δ 166.6 ppm, indicative of an ester carbonyl carbon, and also by mass measurement data. We were confident however, that this fragment was still a suitable precursor to the key Wadsworth-Emmons olefination and that selective deprotection of the benzoate ester could be achieved later in the synthesis.

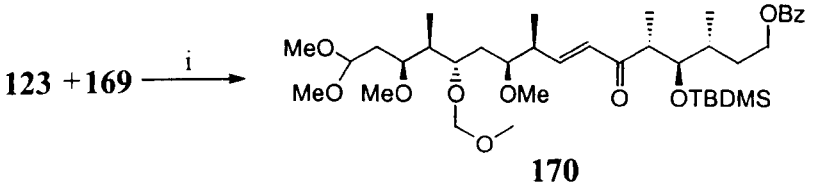



**132** **169**

**Scheme 24**

### *2.2.5 The Wadsworth-Emmons Olefination*

The crucial Wadsworth-Emmons olefination between the phosphonate **132** and the aldehyde **123** was accomplished to give the *E*-alkene **169** in an excellent 90% yield using barium hydroxide in wet THF as medium (**Scheme 25**).[97]




**170**

*Reagents and conditions:* i, $Ba(OH)_2.8H_2O$, wet THF (90%).

**Scheme 25**

### *2.2.6 Conclusions*

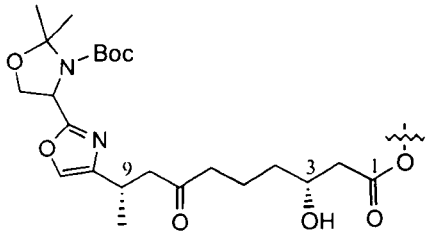
The major hurdle in the synthesis of the side-chain **170** was deciphering the information presented to us with the completion of Chattopadhyay's total synthesis of ulapualide A and comparison with the natural product. We were greatly aided in this process by the timely publication of Panek *et al* and it was this that prompted us to revise our target to **130**.

The synthesis was based largely upon the previous synthesis by Chattopadhyay which used the Wadsworth-Emmons olefination as the key coupling reaction. The stereochemical detail associated with each of the two sub-units **123** and **169** necessary to perform this key reaction was generated using a combination of Evans aldol, Brown's allylboration and Sharpless epoxidation techniques. All of this chemistry was put in place to give 800 mg of **170** with the stereochemical integrity of the newly generated centres along the C28-C33 portion of the side-chain confirmed *via* a range of nmr techniques.

## *2.3 The Bottom-Chain 171 of Ulapualide A*

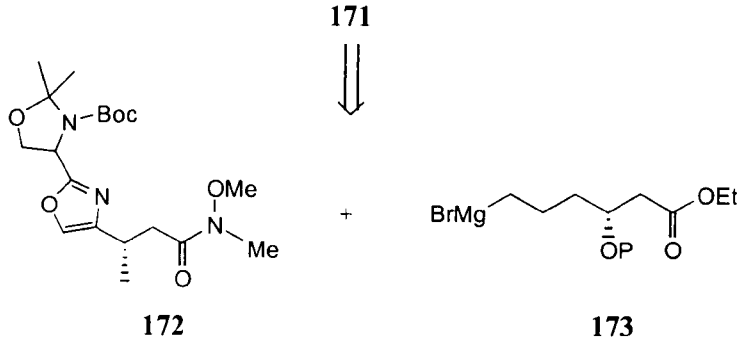
### *2.3.1 Strategy and Design*

With eight out of the ten chiral centres found within ulapualide A now in place, we needed to address the remaining two chiral centres at C3 and C9 contained along the bottom chain of the natural product. Hence, disconnecting across the central oxazole ring and the lactone functionality in the natural product reveals **171**, the fragment of interest.




**171**

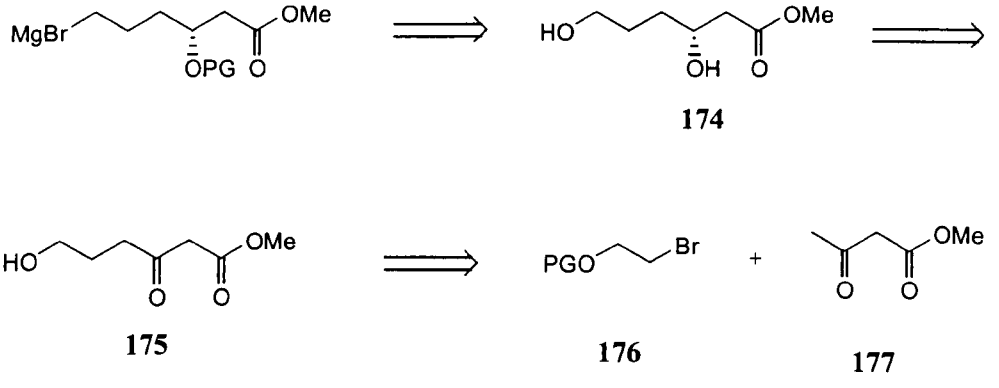
Essentially, this fragment consists of a β-methyl ketone moiety attached both to an oxazole ring system and to a β-hydroxy ester which closes the lactone ring. The major problem encountered with the corresponding fragment in our previous total synthesis of ulapualide A was knowing which methyl orientation (α or β) had been generated at the C9 position. A 1,4 conjugate addition of methyl carbanion onto an α,β-unsaturated ketone gave a 3:2 mixture of C9 methyl epimers, with the major product assigned as the α-orientation. This assignment followed from comparison of nmr spectroscopic data between both epimers and natural ulapualide A, together with consideration of molecular mechanics modelling data. Alternative chemistry therefore needed to be employed to give each of the C9 methyl epimers separately. One possible disconnection, across the C6-C7 bond, revealed the Weinreb amide **172** and a functionalised Grignard coupling partner, **173** (**Scheme 26**).




**Scheme 26**

Results from the work of Mann *et al* have suggested that formation of the Weinreb amide **172** containing the chiral methyl group would be feasible.[113] This goal can be reached using the technique of cupration of chiral bromoallenes derived from propargylic mesylates. With this strategy, the control of stereochemistry turns out to be a problem of controlling the ethynylation of a chiral (enantiomerically pure) aldehyde.

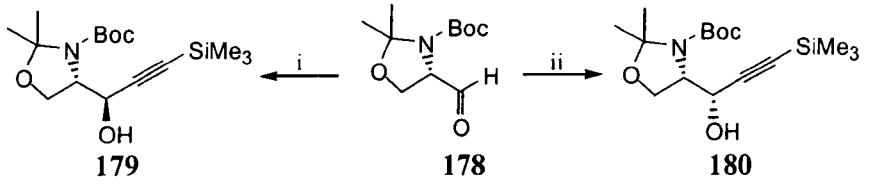
Disconnection of the Grignard partner **173** led us to the chiral β-hydroxy ester **174**, formed from the stereoselective reduction of the β-keto ester **175**. To complete the retrosynthetic strategy, the β-keto ester **175** would be accessible from the alkylation of the dianion of methyl acetoacetate **177** with **176** (**Scheme 27**).




**Scheme 27**

### *2.3.2 The Weinreb Amide Fragment 172*

Work towards the Weinreb amide fragment **172** began with the protected, configurationally stable Garner aldehyde **178** which has been widely used in nucleophilic addition reactions.[114] The addition of nucleophiles to **178** under chelation control has been shown to produce good *syn-* or *threo*-selectivity, whereas good Felkin-Ahn control in which chelation is precluded has been shown to give high levels of *anti-* or *erythro*-selectivity.[114b] Indeed, the additon of ethynyltrimethylsilane to Garner's aldehyde **178** under either Felkin-Ahn or chelation controlled conditions has earlier been shown to proceed with high *erythro-* and *threo*-levels of selectivity respectively (**Scheme 28**). These observations provided us with an ideal route to access both of the C9-methyl epimers found in ulapualide after converting each of the alcohol groups in **179** and **180** into their corresponding methyl groups.



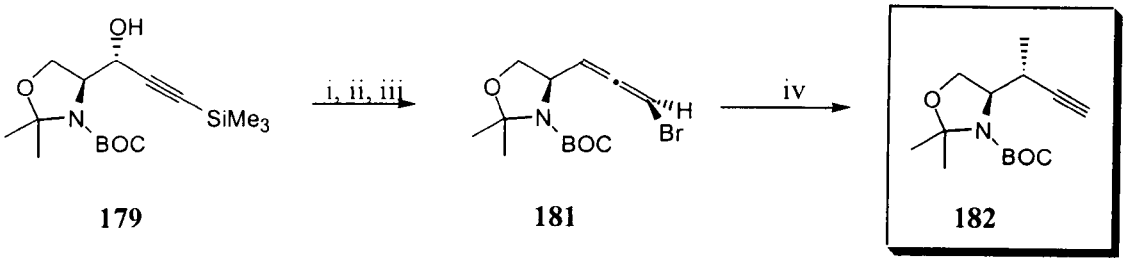

**179** **178** **180**

*Reagents:* i, $^{n}$BuLi, (1-ethynyl)trimethylsilane, HMPT, THF; ii, EtMgBr, (1-ethynyl)trimethylsilane, CuI, THF/$Me_2S$

***Felkin-Ahn*** ***Chelated***


**Scheme 28**

Hence reaction of **178** with lithiated ethynyltrimethylsilane in THF at –78 °C in the presence of the cation-complexing agent HMPT produced the *erythro*-alkynol **179** with 95% diastereoselectivity.[114a] After desilylation, the alcohol was transformed into the mesylate using triethylamine and mesyl chloride. $S_N2$

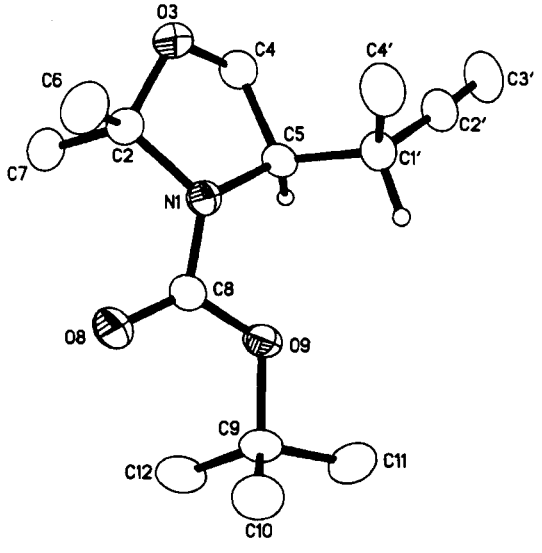



**179** **181** **182**

*Reagents and conditions:* i, TBAF; ii, $MeSO_2Cl$, $Et_3N$; iii, LiBr, $CuBr.Me_2S$, THF (38% over 3 steps); iv, MeMgBr, LiBr, $CuBr.Me_2S$ (80%).

**Scheme 29**

reaction of $CuLiBr_2$ on this mesylate then gave the bromo-allene **181** which was then alkylated using the cuprate derived from methyl magnesium bromide, copper bromide-dimethyl sulfide complex and lithium bromide (**Scheme 29**). This gave the propargylic derivative **182** as a crystalline solid in 80% yield where the expected *anti*-stereochemistry was confirmed by an X-ray crystal structure analysis (**Figure 2.3.2.1** and **Appendix 4.3**).

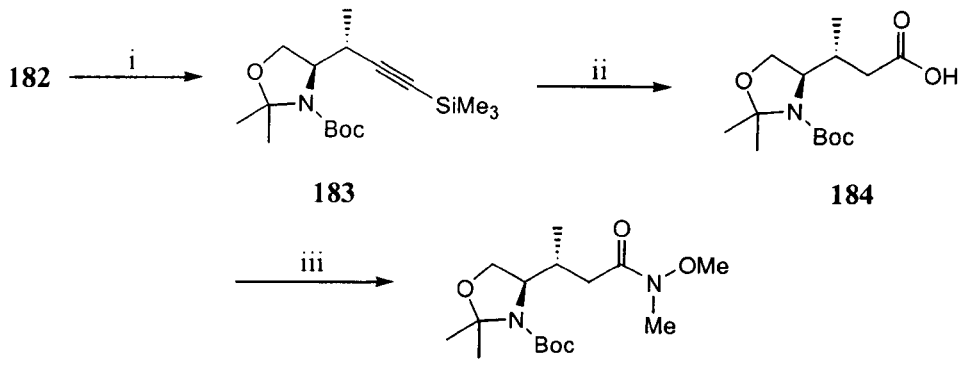



*X-ray structure showing the anti-stereochemistry for compound **182***

**Figure 2.3.2.1**

With this compound in hand, and the stereochemistry secure, we next needed to manipulate the terminal acetylene in **182** into a Weinreb amide. This was

successfully accomplished after silylation of **182** and subsequent oxidation with dicyclohexylborane and $H_2O_2$ to give the carboxylic acid **184** which was further transformed into the Weinreb amide **185** *via* a peptide coupling reaction with *N,O*-dimethylhydroxylamine hydrochloride, employing pyBOP as the coupling reagent (**Scheme 30**).



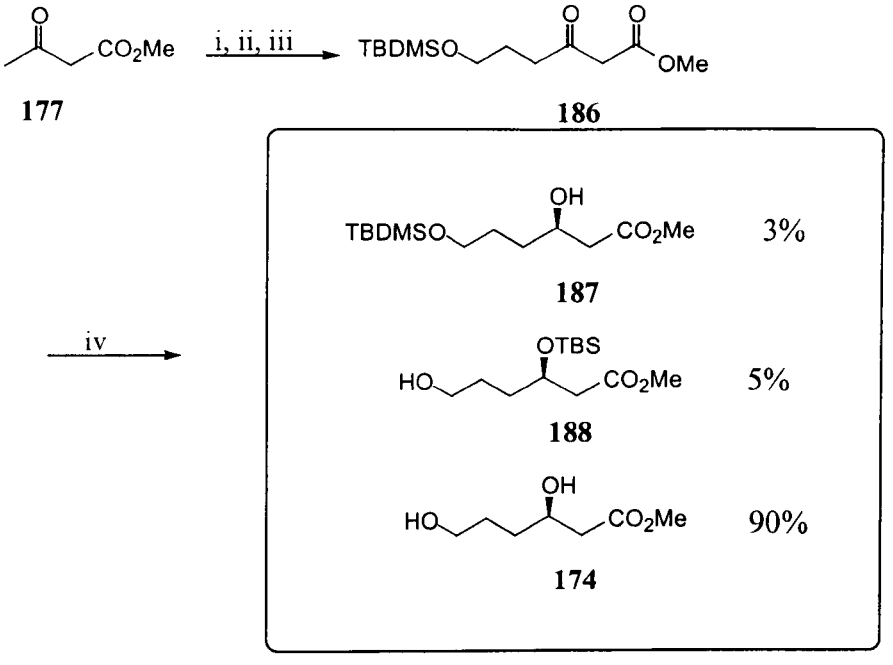

*Reagents:* i, *n*-BuLi, $Me_3SiCl$ (61%); ii, Dicyclohexylborane, NaOH, $H_2O_2$; iii, (MeO)MeNH.HCl, py-BOP, $Et_3N$ (54% over two steps).

**Scheme 30**

### *2.3.3 The β-Hydroxyester Fragment 173*

With the Weinreb amide fragment **185** now in hand, our attention was directed towards the synthesis of its coupling partner **173**. Thus, methyl acetoacetate **177** was first converted into its dianion, which was then alkylated with the TBDMS protected iodide **176** to give the β-ketoester **186** in a 73% yield.[115] Noyori's well known BINAP ligand was next used to effect the chiral reduction of the β-keto ester **186**.[116] However, (*R*)-Ru-BINAP reduction under 100 atmospheres of hydrogen for 6 days gave only a 3% yield of the desired alcohol **187**. By far the major product of this reaction was the diol **174**, obtained from the chiral reduction of the β-keto ester moiety followed by deprotection of the primary TBS-ether (**Scheme 31**). (presumably due to the slightly acidic conditions associated with using methanol as solvent.) However, re-protection of this compound using TBS-Cl/imidazole in DMF gave **187** in multigram quantities. The enantiomeric excess

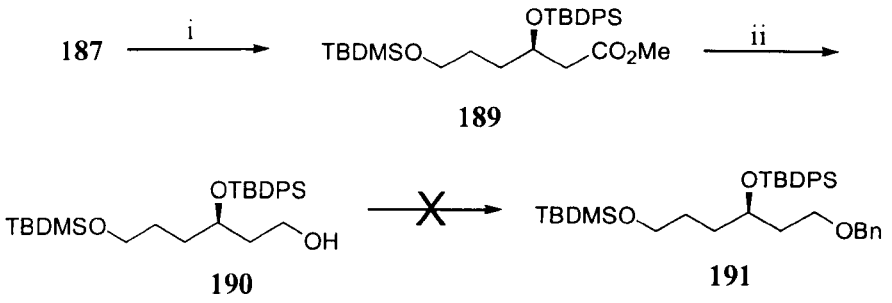
of this alcohol was >95% as determined by $^{19}F$ nmr analysis of its Mosher's ester derivative.[117]




*Reagents:* i, NaH; ii, *n*-BuLi; iii, TBDMS-protected **176**, (80%); iv, (*R*)-Ru-BINAP, MeOH, 100 atms $H_2$, 6 days.

**Scheme 31**

Protection of the secondary alcohol in **187** using TPS-Cl and imidazole in DMF then gave the desired TPS-ether **189** in 86% yield. Reduction of the ester in **189** using DIBAL-H in THF at –78 °C then gave the primary alcohol **190** in 84% yield. Attempted benzyl protection of this primary alcohol using sodium hydride as base however gave only a mixture of silyl migration products, presumably as a result of the alkoxide anion attack at the silicon centres of both the TBS and TPS protecting groups. Milder conditions of $Ag_2O$ failed to give any benzylated product (**Scheme 32**).

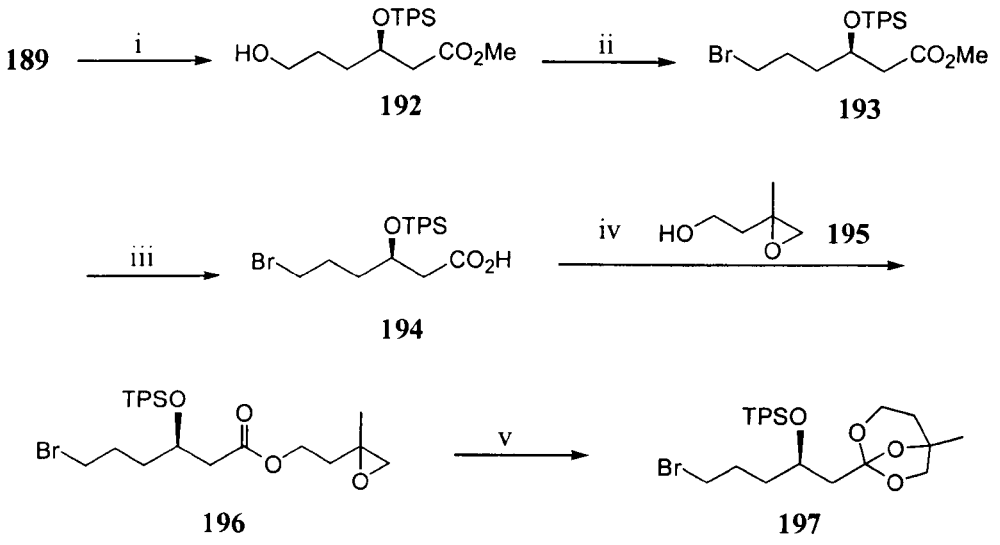



*Reagents:* i, TPS-Cl, imidazole, DMF (86%); ii, DIBAL-H, THF, -78°C (84%).

**Scheme 32**

With the failure of this approach, re-examination of our protecting group strategy uncovered the ABO-ortho ester method for the protection of polyfunctionalised carboxylic acids. Ortho esters are ideal carboxyl protective groups against nucleophilic attack by hydroxide or organometallic reagents. Studies carried out by Wipf *et al* on the mushroom components (S)-γ-hydroxyleucine lactone and (S)-α-vinylglycine have demonstrated the versatility of this protocol[118] which is complementary to the OBO-ester technology of Corey.[119]

Thus, returning to our multigram stock of compound **189**, selective deprotection of the primary TBS ether using CSA in a 1:1 MeOH:$CH_2Cl_2$ mixture provided the alcohol **192** which was brominated under the mild conditions of $CBr_4/PPh_3$ to give the bromide **193** in 87% yield over two steps (**Scheme 33**). Hydrolysis of the methyl ester using LiOH in 3:1 THF:water next gave the carboxylic acid, **194**, albeit in only 80% yield. Also evident in the crude $^1H$ nmr of this reaction were olefinic signals due to $E_2$ elimination of hydrogen bromide leading to a terminal olefin. Condensation of carboxylic acid **194** with the epoxy alcohol **195** in the presence of EDC and DMAP next led to the epoxy ester **196** in a 64% yield. Zirconocene-catalysed ortho ester formation was next achieved using 10 mol% of $Cp_2ZrCl_2$ and 2 mol% of $AgClO_4$ which finally led to the ortho ester **197** in 87% yield (**Scheme 33**).

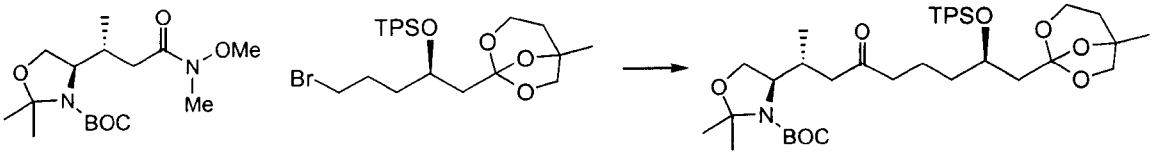



*Reagents:* i, CSA, 1:1 MeOH:$CH_2Cl_2$ (98%); ii, $CBr_4$, $PPh_3$ (92%); iii, LiOH, THF-$H_2O$ (80%); iv, EDC, DMAP, $CH_2Cl_2$ (64%); v, $Cp_2ZrCl_2$, $AgClO_4$, $CH_2Cl_2$(87%).

**Scheme 33**

### *2.3.4 The Coupling Reaction*

With both of the fragments **185** and **197** now at our disposal, thoughts were directed towards the key coupling reaction. Initial attempts at Grignard reagent formation proved fruitless with starting bromide **197** being recovered. However, work carried out by Negishi *et al* has highlighted a clean and convenient procedure for converting primary alkyl iodides into the corresponding alkyllithium derivative by treatment with *tert*-butyllithium.[120] Although we had a primary bromide, lithium-halogen exchange was still attempted in dry diethyl ether at –78 °C using two equivalents of *tert*-butyllithium. After addition of the Weinreb amide, **185**, and warming to room temperature, tlc showed the appearance of two new products. To our pleasure, $^1H$ nmr together with nominal mass measurement data indeed provided evidence that the reaction had been successful, albeit in a meagre yield of 15% (**Scheme 34**).

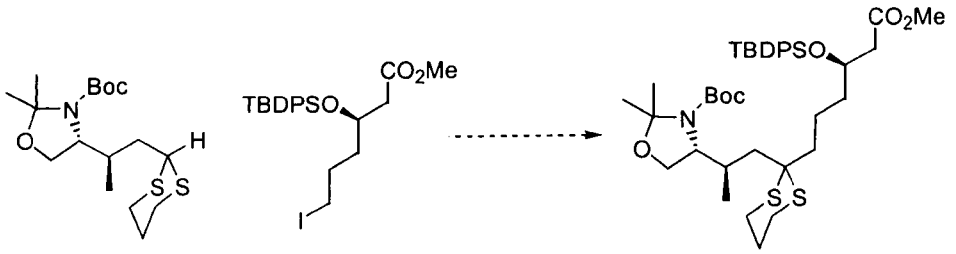


**185** **197** **198**

*Reagents:* i, *tert*-BuLi, $Et_2O$ (15%).

**Scheme 34**

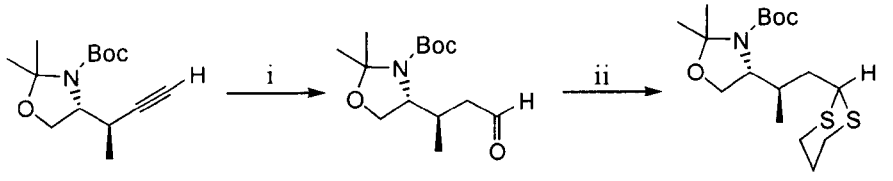
Although disappointed by the repeatedly poor yields of this reaction, we were still confident that the methods used to generate chirality in each of the two fragments **185** and **197** was *not* the problem but that the stumbling block lay in the fragment coupling. The use of dithiane coupling reactions for the generation of protected aldol linkages and, more importantly in our case, as a tactic for the union of major synthetic building blocks has received much attention in the literature.[121] Indeed, coupling of 1,3-dithianes with electrophiles has been exploited in the total syntheses of many natural products and the generality of the *tert*-BuLi-10% HMPA/THF protocol developed by Smith *et al* in their total synthesis of rapamycin seemed an attractive route for our own system. Hence, the plan was still to construct the C6-C7 bond, but now to effect this transformation *via* a dithiane alkylation approach.



**199** **200** **201**

This route was made all the more attractive due to the fact that we had multigram quantities of the electrophile **193** at our disposal. Furthermore, the chemistry involved in forming the dithiane fragment deviated only slightly from the chemistry that had been used to generate the Weinreb amide. Starting from the acetylene **182**, hydroboration using thexylchloroborane-methyl sulfide followed by pH7 buffered oxidative work-up with hydrogen peroxide, first gave a 58%

yield of the aldehyde **202**.[122] Careful considerations were taken when deciding the appropriate set of conditions for dithiane formation bearing in mind we had present the acid sensitive Garner motif. A range of conditions were tried, all of which gave the desired product **199** but in pitiful yield, with the majority of material falling to baseline on tlc (**Scheme 35**).

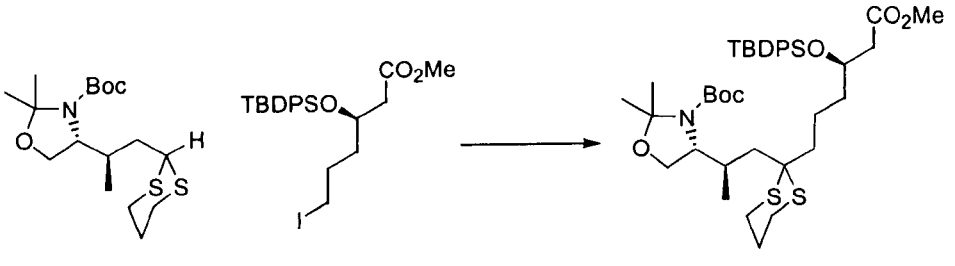



**182** **202** **199**

*Reagents:* i, ThxBHCl.$Me_2S$, $CH_2Cl_2$ then $H_2O_2$, NaOH (58%); ii, $TMSSCH_2CH_2CH_2STMS$, $ZnI_2$, $Et_2O$, (12%).

**Scheme 35**

Not deterred by this unforeseen problem and confident that the dithiane coupling was the correct strategy, we decided to test the feasibility of this coupling with what little material we had to hand. Hence, using 'standard' dithiane metallating conditions, we were pleased to see a 20% yield of the desired coupled product, **201** (**Scheme 36**). Prolonged reaction times and slight variations in the reaction conditions failed to increase the yield, but with returned starting material, it was a slight improvement on the Weinreb amide coupling strategy.



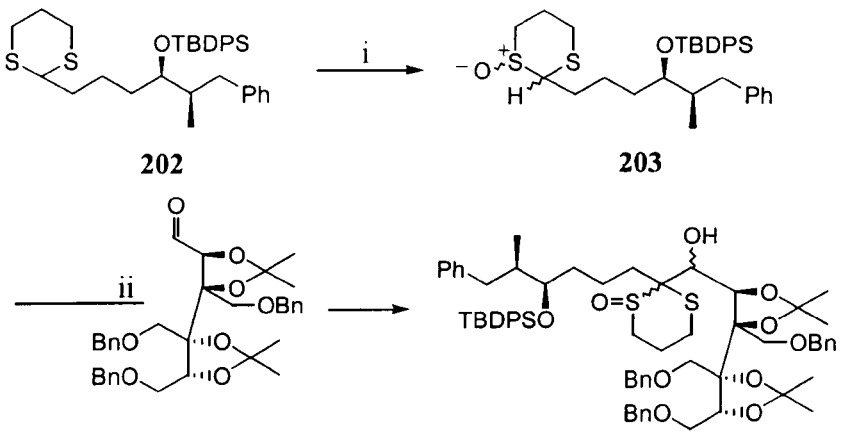

**199** **200** **201**

*Reagents:* i, *tert*-BuLi, 10% HMPA/THF, -78 °C, (20%).

**Scheme 36**

We speculated that the lack of success in the crucial dithiane alkylation reaction, *viz* **199** + **200** → **201**, was possibly due to the inherent difficulty in effecting clean metalation of the dithiane **199**. Aware that many 1,3-dithiane systems prove

stubborn to lithiation, we were drawn to the work of Armstrong and Jones who, similar to ourselves, had reported difficulties with dithiane metallation utilising a variety of bases, solvent systems and chelating additives.[123] This problem was eventually solved by increasing the acidity of the dithiane **202** by conversion to the monosulfoxide **203** using *m*CPBA, which was then readily metallated using *n*-butyllithium at –78 °C. Addition of the aldehyde **204** provided the sulfoxide **205** in good overall yield (**Scheme 37**).



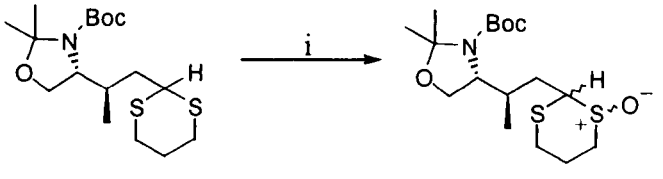

**202** **203**

**204** **205**

*Reagents:* i, *m*CPBA; ii, *n*-BuLi, THF, -78 °C, (67% over 2 steps).

**Scheme 37**

Hence, for our own system, we decided to oxidise the dithiane **199** to the corresponding monosulfoxide **206** in order to make the C2 proton (dithiane numbering) more acidic. Treatment of dithiane **199** with *m*CPBA at 0 °C provided the monosulfoxide **206** as a mixture of four possible diastereoisomers that appeared as two major spots by tlc.

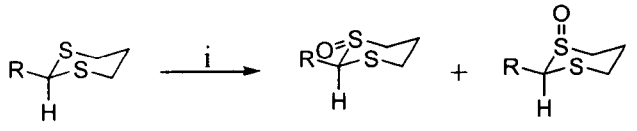



**199** **206**

*Reagents:* i, *m*CPBA, 0 °C, (73%).

**Scheme 38**

One pair of diastereoisomers arose from oxidation of the equatorial or axial lone pairs on a sulfur atom, creating the *trans* and *cis* monosulfoxides. Another pair of diastereoisomers would then be generated depending on which sulfur atom had been oxidised. After column chromatography, the major product corresponded to the *trans* pair of sulfoxides. The assignment of *trans* stereochemistry to the major isomer (**Scheme 39**) follows by analogy to the oxidation of other mono-substituted dithianes previously reported by Carey and co-workers which also gave predominantly the *trans* isomer.[124]

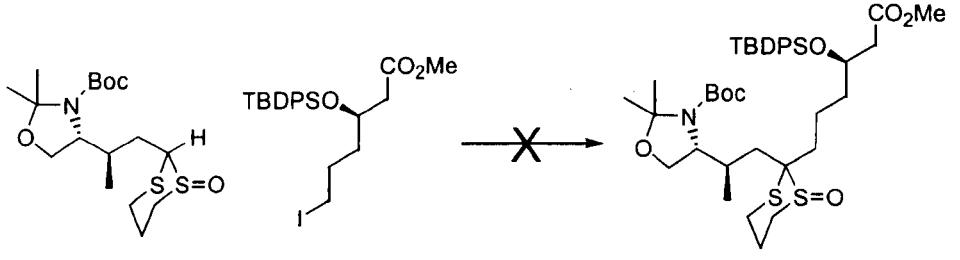



**199** *trans* *cis*

*Reagents:* i, *m*CPBA, 0°C.

**Scheme 39**

With both coupling fragments **206** and **200** in hand, we were ready to continue with the synthesis of the side chain (**Scheme 40**). However, following treatment of the *trans*-monosulfoxide **206** with *n*-butyllithium at –78 °C for 15min and addition of the alkyl iodide **200**, we were again disappointed to find only a 14% yield of desired product **207**. Repeating the reaction with *tert*-butyllithium as base failed to give any improvement in yield and with these consistently poor results, we were eventually forced into considering alternative coupling strategies.



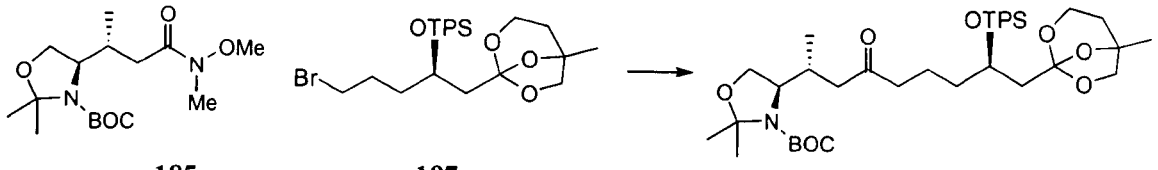

**206** **200** **207**

*Reagents:* i, *n*-BuLi, THF, -78 °C.

**Scheme 40**

### *2.3.5 A Modified Approach to the Bottom-Chain 171*

To date, the various efforts made towards synthesising the bottom-chain of ulapualide A **171** have not been successful. However, the initial results that we had achieved whilst employing a lithio-addition to the Weinreb amide had been encouraging (**Scheme 41**).



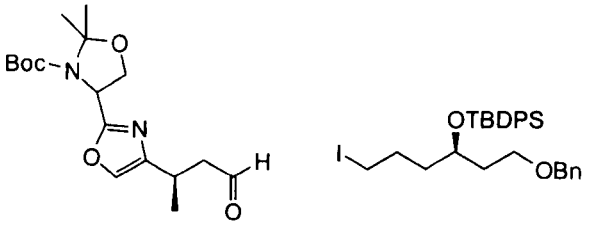

**185** **197** **198**

*Reagents:* i, *tert*-BuLi, $Et_2O$ (15%).

**Scheme 41**

Although the yield of the reaction (**Scheme 41**) was very low (15%), we reasoned that a possible cause was the chelating ability of the ortho-ester protecting group which would preclude any addition into the Weinreb amide **185**. We felt that the Grignard strategy provided us with the greatest opportunity for synthesising the bottom chain of ulapualide A **171** and therefore we sought to explore the reaction further by changing the nature of both the organometallic precursor and the electrophilic partner.

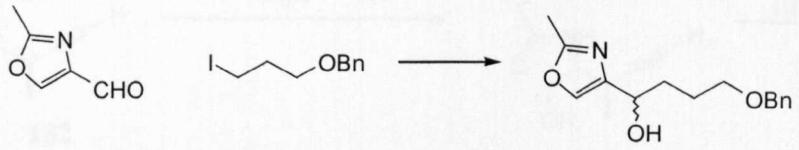
The initial focus of the approach was to synthesise the oxazole-aldehyde **208** together with its projected coupling partner **209**. Notice how on this occasion we wanted to increase the convergency of the route by introducing the oxazole ring at an earlier stage in the synthesis, *ie* before performing the fragment coupling. This would obviously have implications regarding the nature of the nucleophile **209**.




**208** **209**

We felt a lithio-derivative would prove too basic with the possibility of deprotonation at the C5 position of the oxazole ring in fragment **208**. A Grignard derivative was therefore the initial target, but this time containing a benzyl protected alcohol as opposed to an ortho-ester group which we had previously synthesised.

To test the feasibility of this approach, we decided to carry out a model study with the aldehyde derived from Cornforth oxazole **210**, and the simple C3 iodide **211**. The results of this model study are shown in **Scheme 42**.




**210** **211** **212**

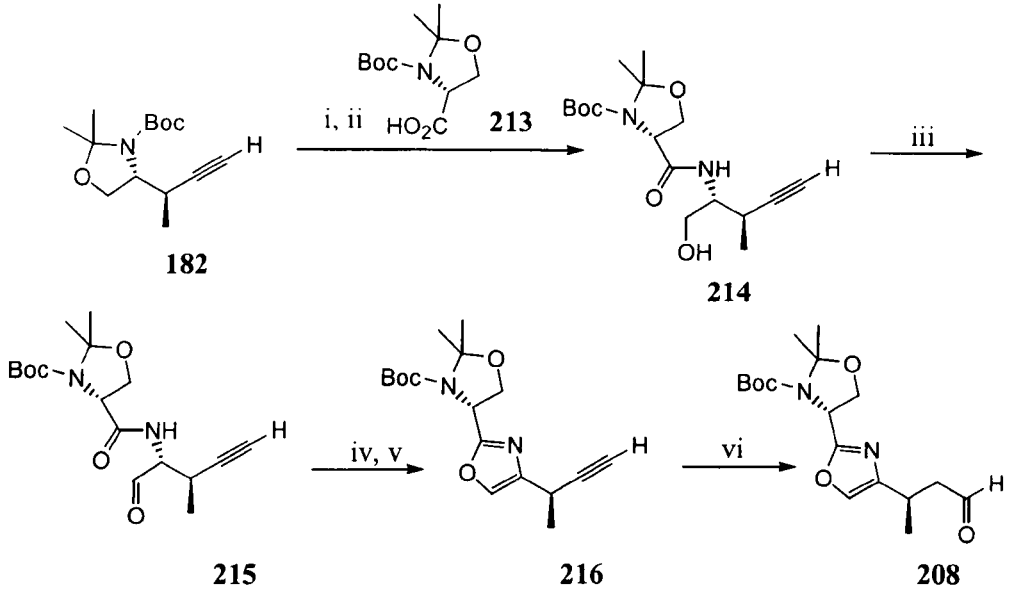
| Entry | Additive | Yield **212**(%) |
|---|---|---|
| 1 | - | - |
| 2 | $Me_2Zn$ | 15 |
| 3 | $MgBr_2$ | 55 |

**Scheme 42**

Due to the basic nature of the alkyllithium, it was necessary to transmetallate for another metal. Ultimately, the Grignard reagent derived from freshly prepared $MgBr_2$, proved to give the higher yielding reaction. In the zinc case, the major product was attributed to methyl-zinc addition into the aldehyde. This platform allowed us to continue with some degree of confidence in the synthesis of the oxazole-aldehyde **208**, and its coupling partner **209**.

Hence, treatment of the oxazolidine **182** with 4 M hydrochloric acid in dioxane cleaved both the acetonide and the *tert*-butyloxycarbonyl protecting groups to give the hydrochloride salt of the amino-alcohol. The crude amino-alcohol was then coupled to Garner acid **213**, under carbodiimide-mediated coupling

conditions to provide the amide **214**. Oxidation of the alcohol in **214** was accomplished upon exposure to Dess-Martin periodinane to give the aldehyde **215**, which underwent finally a cyclodehydration reaction, using the modified procedure developed by Wipf *et al*,[66] to produce the oxazole-acetylene product **216** in moderate yield. Hydroboration utilising the previously employed thexylborane then gave the oxazole-aldehyde **208** in a rather disappointing yield of 37%.

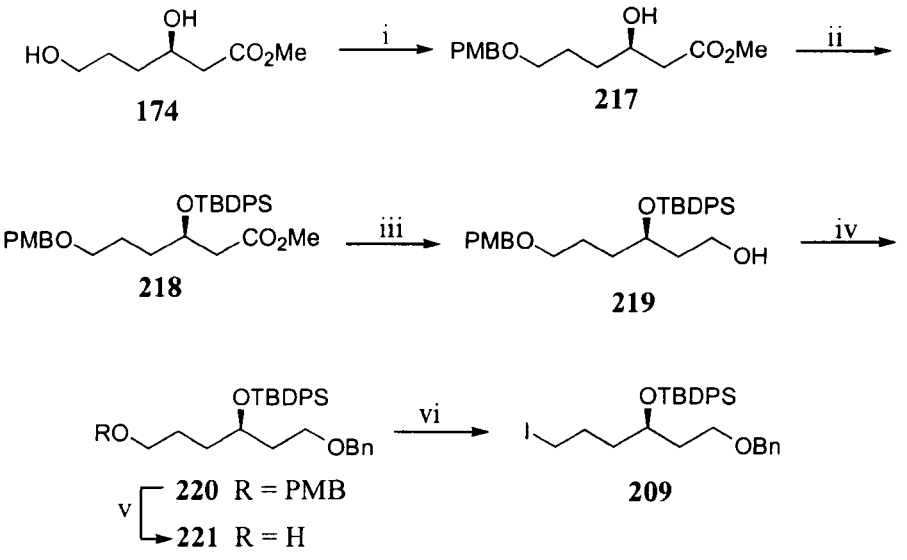



*Reagents:* i, 4 M HCl in dioxane; ii, EDC, $Et_3N$, $CH_2Cl_2$, (63% over 2 steps); iii, Dess-Martin periodinane, $CH_2Cl_2$, (82%); iv, $BrCl_2CCCl_2Br$, $PPh_3$, 2,6-di-*tert*-butyl-4-methylpyridine, $CH_2Cl_2$; v, DBU, MeCN, (42% over 2 steps); vi, ThxBHCl.$Me_2S$, $CH_2Cl_2$ then $H_2O_2$, NaOH (37%).

**Scheme 43**

Due to problems encountered with the scrambling of silicon protecting groups in the previous synthesis of the bottom chain (**Scheme 32**, page 60), we needed to explore a different protecting group strategy. Accordingly, exposure of the diol **174** to PMB-trichloroacetimidate in the presence of triflic acid gave the PMB-ether **217** in 74% yield. Protection of the secondary alcohol **217** as its TBDPS-ether followed by reduction of the methyl ester with DIBAL-H then provided the alcohol **219** in 67% yield over 2 steps. Benzyl protection of this alcohol using benzyl trichloroacetimidate, again with triflic acid as the catalyst, provided **220** in

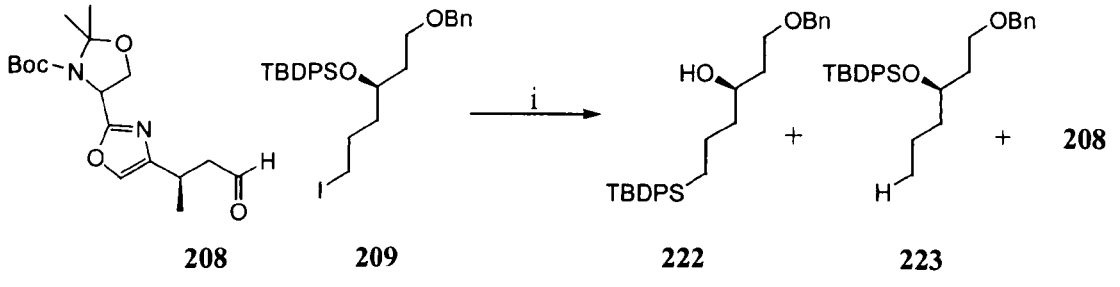
84% yield. Removal of the PMB-ether was next accomplished using DDQ to give the alcohol **221** in 59% yield which after conversion to the corresponding iodide **209** using $PPh_3$/iodine/imidazole now put us in a position to try our crucial Grignard coupling reaction.




*Reagents:* i, $PMBOC(=NH)CCl_3$, TfOH, $Et_2O$ (74%); ii, TPS-Cl, imidazole, DMF; iii, DIBAL-H, THF, -78°C (67% over 2 steps); iv, $BnOC(=NH)CCl_3$, TfOH, $Et_2O$ (84%); v, DDQ, 19:1 $CH_2Cl_2$:$H_2O$, (59%); vi, $PPh_3$, $I_2$, imidazole, $CH_3CN$, $Et_2O$, (96%).

**Scheme 44**

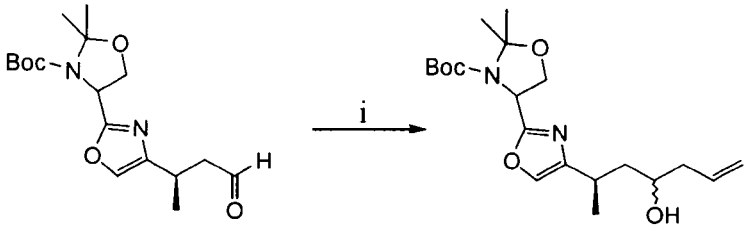
The Grignard coupling was carried out using identical conditions to the model study, but much to our disappointment gave none of the desired product. Instead, all that was recovered was starting aldehyde **208**, proton-quenched iodide **223** and 5-10% of a product that was tentatively assigned as compound **222**, presumably arising from a Brook-type rearrangement of compound **209**.[125]




*Reagents:* i, *tert*-BuLi, $MgBr_2$, $Et_2O$

**Scheme 45**

In an effort to understand the failings of this Grignard reaction, we needed to identify, as far as possible, which component of the coupling was flawed. To this end, we decided to react the oxazole-aldehyde **208** with the commercially available Grignard allylmagnesium bromide and indeed, we were pleased to observe almost complete consumption of the starting material within 10 minutes of the reaction being started. $^1$H-nmr spectroscopic analysis of the crude reaction mixture together with mass measurement data confirmed the formation of **224** as an unresolved mixture of diastereoisomers.

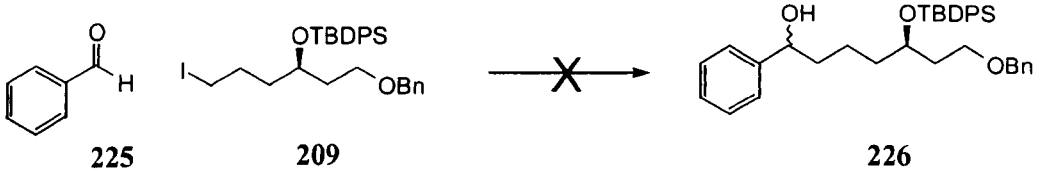



**208** **224**

*Reagents:* i, Allylmagnesium bromide, $Et_2O$.

**Scheme 46**

Knowing the aldehyde **208** was capable of accepting a Grignard reagent, we wanted to investigate the reactivity of the Grignard reagent derived from the alkyl iodide **209**. For this investigation, we decided benzaldehyde would be an ideal electrophile, but unfortunately following formation of the Grignard and addition to an ethereal solution of benzaldehyde cooled to –78 °C, we failed to observe any reaction, with reduced product **223** being recovered after quenching with saturated ammonium chloride.




**225** **209** **226**

**Scheme 47**

As a result of these two simple 'test' reactions, we can tentatively draw conclusions on the failure of this Grignard reaction. We have identified that the

aldehyde fragment **208** does indeed react with allylmagnesium bromide and that the stumbling block lay with the alkyl iodide/Grignard component. Possible explanations for its lack of reactivity are numerous, and may involve chelation of magnesium about the two ether oxygens contained within this fragment. As such, a continued investigation into this coupling is underway with 'fine tuning' of fragment **209** necessary to result in a total synthesis of the bottom chain **217** and ultimately in ulapualide A itself.

## *2.4 Conclusions*

The main emphasis throughout this period of research has been the alternative construction of the 25-membered *tris*-oxazole core of ulapualide A. Our disconnection strategy, centred around the halishigamides, simplified the problem to the synthesis of the two subunits **79** and **80**. Cornforth methodology allowed for the incorporation of the 'top' oxazole ring in **79**, while some more recent chemistry generated the 'bottom' oxazole in **80**. The success of the key macrolactamisation reaction saw the completion of the *tris*-oxazole backbone **77**, albeit on a model system.

Ever since this success, we have sought to apply the model study to the real target of ulapualide A. In this application, we have 'reviewed' the stereochemistry of the side-chain and, taking the important publication of Panek and Fusetani *et al* into consideration, the stereochemistry of four chiral centres was revised. This revised side-chain target **130** was generated in a similar manner to the previous synthesis by Chattopadhyay. Hence, the main disconnection relied upon a Wadsworth-Emmons olefination reaction leading to the advanced precursors **131** and **132**. A combination of Evans aldol, Brown allylboration and Sharpless epoxidation reactions allowed for the rapid generation of all eight chiral centres. The target **170** was finally completed following a Wadsworth-Emmons olefination employing barium hydroxide octahydrate as base.

The bottom chain **171** provided the next challenge *en route* to ulapualide A. In this fragment we had to generate *both* C9-methyl epimers separately and our initial strategy was based upon a Grignard additon of bromide **197** to the Weinreb amide **185**. Noyori's BINAP chemistry generated the chiral hydroxyl group in fragment **197**, while either chelation or Felkin-Ahn controlled additions to an aldehyde provided the basis for the stereochemistry of the C9-methyl group. However, all attempts to effect fragment coupling *via* the Grignard reaction met with little success and our synthetic efforts were then concentrated upon a

dithiane alkylation strategy. The repeated failings of this strategy led us to re-evaluate the initial Grignard coupling reaction and early indications have shown that minor alterations to the existing fragments will result in their successful coupling.

# EXPERIMENTAL

## *3.1 General Details*

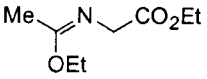
All melting points were determined on a Kofler hot-stafe apparatus and are uncorrected. Optical rotations were recorded in spectroscopic grade chloroform or methanol on a Jasco DIP-370 polarimeter at ambient temperature. $[\alpha]_D$ values are recorded in units of $10^{-1}$ deg $cm^2$ $g^{-1}$. Ultraviolet spectra were recorded on a Philips PU 8700 spectrophotometer as solutions in either deionised water, or spectroscopic grade methanol or ethanol. $\varepsilon$ values are recorded in units of $dm^3$ $mol^{-1}$ $cm^{-1}$. Infrared spectra were obtained using a Perkin-Elmer 1600 series FT-IR instrument or a Nicolet Magna 550 instrument either as liquid films or as dilute solutions in spectroscopic grade chloroform. Proton nmr spectra were recorded on either a Bruker WM 250 (250 MHz), a Bruker DPX 360 (360 MHz), a Bruker AM 400 (400 MHz), a Bruker DRX 500 (500 MHz), a Varian Unity 300 (300 MHz), a Varian Inova 400 (400 MHz) or a Jeol EX 270 (270 MHz) spectrometer as dilute solutions in deuterochloroform at ambient temperature, unless otherwise stated. The chemical shifts are quoted in parts per million (ppm) relative to residual chloroform as internal standard ($\delta$ 7.27) and the multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; sep., septet; br., broad; m, multiplet; app., apparent. All coupling constants are quoted in Hertz. Carbon-13 nmr spectra were recorded on either a Bruker DPX 360 (at 90.6 MHz), a Bruker DRX 500 (at 125.8 MHz), or a Jeol EX-270 (at 67.8 MHz) instrument as dilute solutions in deuterochloroform, unless otherwise stated. Chemical shifts are reported relative to internal chloroform standard ($\delta$ 77.0) on a broad band decoupled mode, and the multiplicities determined using a DEPT sequence. Where required, H-H COSY, H-C COSY and nOe spectra were recorded on a Bruker DPX 360 (360 MHz), or a Bruker DRX 500 (500 MHz) instrument using standard Bruker software with no modifications. Where a mixture of compounds has been produced, the data given is for that mixture unless otherwise stated. Mass spectra were recorded on a VG Autospec, a MM-701CF, a VG Micromass 7070E or a Micromass LCT spetrometer using electron ionisation (EI), electrospray (ES), or fast atom bombardment (FAB) techniques. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

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

Routinely, dry organic solvents were stored under nitrogen and/or over sodium wire. Other organic solvents were dried by distillation from the following: THF and benzene (potassium benzophenone ketyl), dichloromethane (calcium hydride) and methanol (magnesium methoxide). Other organic solvents and reagents were purified by the accepted literature procedures. Dess-Martin periodinane was prepared according to the modified procedure of Ireland and Liu.[94b] All organic extracts were dried with magnesium sulfate unless otherwise stated. Solvent was removed on a Büchi rotary evaporator. Where necessary, reactions requiring anhydrous conditions were performed in a flame or oven dried apparatus under a nitrogen or argon atmosphere as stated.

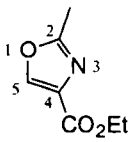
## *3.2 The Model Study*

**[(1-Ethoxyethylidene)amino]-acetic acid ethyl ester 88.**[79]



Using a modification of the Cornforth procedure,[79] a cooled (0 °C) suspension of ethyl acetimidate hydrochloride (25.0 g, 0.2 mol) in ether (100 ml) was shaken for 5 min in a separating funnel with a cooled (0 °C) solution of potassium carbonate (33.1 g, 0.24 mol) in water (70 ml). The separated aqueous phase was extracted with diethyl ether (30 ml) and a cooled (0 °C) solution of glycine ethyl ester hydrochloride (28.2 g, 0.2 mol) in water (30 ml) was then added to the combined organic phases with further shaking for 15 min. The separated aqueous layer was once again extracted with diethyl ether (30 ml) and the combined organic phases were washed with water (3 x 30 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow oil which was distilled to give the imino ether (20.7 g, 59%) as a colourless liquid, bp 90 °C at 10 mmHg (lit. bp[79] 85-86 °C at 7.5 mmHg); $\nu_{max}$(film)/cm$^{-1}$ 1745 and 1677; $\delta_H$(250 MHz, $CDCl_3$) 4.24-4.09 (4H, m, $CO_2CH_2CH_3$ and $OCH_2CH_3$), 4.04 (2H, s, $CH_2$), 1.88 (3H, s, Me) and 1.31-1.24 (6H, m); $\delta_C$(69.2 MHz, $CDCl_3$) 171.2 (s), 164.8 (s), 60.9 (t), 60.8 (t), 51.3 (t), 15.2 (q), 14.2 (q) and 14.1 (q); *m/z* (EI) (Found: $M^+$, 173.1072; $C_8H_{15}NO_3$ requires $M^+$ 173.1052).

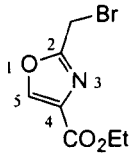
**2-Methyloxazole-4-carboxylic acid ethyl ester 90.**[79]



Using a modification of the Cornforth procedure,[79] a solution of the imino ether **88** (69.1 g, 0.40 mol) in dry THF (150 ml) was added dropwise over 40 min to a stirred suspension of potassium *tert*-butoxide (49.2 g, 0.44 mol) in dry THF (150 ml) under a nitrogen atmosphere at –10 °C. Ethyl formate (35.5 ml, 0.44 mol) was added sequentially and after stirring at –10 °C for 1 h, dry diethyl ether (100 ml) was added to the brown solution. The mixture was held at this temperature for 1 h and was then evaporated *in vacuo* to leave the potassium enolate salt **89** as a hygroscopic yellow

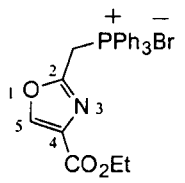
solid. Hot acetic acid (110 ml) was added to the vigorously stirred residue and reflux was maintained for 15 min before the mixture was cooled to room temperature. The resulting orange solid was dissolved in water (500 ml) and the solution was then basified cautiously with solid potassium carbonate before the aqueous mixture was extracted with diethyl ether (3 x 300 ml). The combined organic phases were washed with saturated brine (100 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow liquid. Distillation of the crude material gave the oxazole ester (50.4 g, 81%), as a straw coloured liquid, bp 106-110 °C at 20 mmHg (lit. bp[79] 106-110 °C at 12 mmHg); (Found: C, 54.2; H, 5.8; N, 8.8. $C_7H_9NO_3$ requires C, 54.2; H, 5.8; N, 9.0%); $\lambda_{max}$(EtOH)/nm 217 (4760); $\nu_{max}$(film)/$cm^{-1}$ 1738, 1592 and 1109; $\delta_H$(270 MHz, $CDCl_3$) 8.12 (1H, s, 5-H), 4.37 (2H, q, *J* 7.0 Hz, $OCH_2CH_3$), 2.50 (3H, s, $CH_3$) and 1.37 (3H, t, *J* 7.0 Hz, $OCH_2CH_3$); $\delta_C$(67.8 MHz, $CDCl_3$) 162.0 (s), 160.9 (s), 143.4 (d), 133.1 (s), 60.7 (t), 13.9 (q) and 13.4 (q); *m/z* (EI) (Found: $M^+$, 155.0619; $C_7H_9NO_3$ requires 155.0582).

**2-Bromomethyloxazole-4-carboxylic acid ethyl ester 109.**



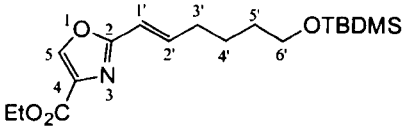

Solid NBS (6.9 g, 39.0 mmol) and AIBN (400 mg, 20% w/w) were added to a stirred solution of the oxazole ester **90** (2.0 g, 13.0 mmol) in carbon tetrachloride (40 ml) and the suspension was then heated under reflux in a nitrogen atmosphere for 17 h. The mixture was cooled to room temperature, then evaporated *in vacuo* to leave a residue which was purified by chromatography on silica using 1:1 toluene:ethyl acetate as eluent to give the *bromomethyloxazole* (1.23 g, 41%) as a yellow oil; $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 1726, 1317 and 1114; $\delta_H$(360 MHz, $CDCl_3$) 8.25 (1H, s, 5-H), 4.49 (2H, s, $CH_2Br$), 4.39 (2H, q, *J* 7.2 Hz, $OCH_2CH_3$), 1.40 (3H, t, *J* 7.2 Hz, $OCH_2CH_3$); $\delta_C$(67.5 MHz, $CDCl_3$) 160.5 (s), 159.9 (s), 144.7 (d), 134.1 (s), 61.3 (t), 19.3 (t) and 14.0 (q); *m/z* (EI) 235, 233 ($M^+$, 6, 6%), 190, 188 (15, 15), 154 (91), 110 (4) and 82 (7).

**4-Ethoxycarbonyloxazol-2-ylmethyltriphenylphosphonium bromide 112.**



A solution of triphenylphosphine (2.4 g, 9.2 mmol) in dry diethyl ether (17 ml) was added to a solution of the bromomethyloxazole **109** (1.1 g, 4.6 mmol) in dry diethyl ether (5 ml) under a nitrogen atmosphere and the solution was then stirred at room temperature for 24 h. The mixture was evaporated to dryness *in vacuo* to leave a yellow solid which was triturated in pentane (3 x 30ml). The residue was evaporated to dryness *in vacuo* to leave the *phosphonium salt* (1.9 g, 82%) as a pale yellow solid, mp >300 °C (decomp.); $\delta_H$(360 MHz, $CDCl_3$) 8.07 (1H, s, 5-H), 7.94-7.53 (15H, m, 3 x Ph), 6.10 (2H, d, $J_{P\text{-}H}$ 14.9 Hz, $CH_2P$), 4.28 (2H, q, $J$ 7.1 Hz, $OCH_2CH_3$) and 1.32 (3H, t, $J$ 7.1 Hz, $OCH_2CH_3$), which was used without further characterisation.

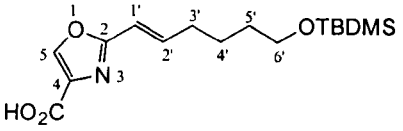
**2-[6'-(*tert*-Butyldimethylsilanyloxy)-hex-1'-enyl]-oxazole-4-carboxylic acid ethyl ester 113.**



A solution of *n*-butyllithium (2.35 M in hexane, 1.68 ml, 2.69 mmol) was added dropwise over 10 min to a stirred suspension of the phosphonium salt **112** (1.67 g, 2.69 mmol) in dry THF (40 ml) at –30 °C under a nitrogen atmosphere. The deep red solution was stirred at room temperature for 30 min, and was then cooled to –78 °C. A solution of 5-*tert*-butyldimethylsilylpentanal (0.87 g, 4.04 mmol) in dry THF (9 ml) was added dropwise over 5 min to the ylide solution at –78 °C and the mixture was allowed to warm to room temperature overnight. The mixture was quenched with saturated aqueous ammonium chloride solution (20 ml) and the separated aqueous layer was then extracted with diethyl ether (2 x 30 ml). The combined organic phases were washed with saturated brine (20 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 5:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the *olefin* (0.4 g, 41%) as a viscous oil; (Found:

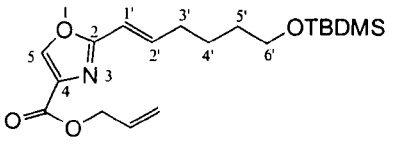
C, 60.9; H, 9.3; N, 3.9. $C_{18}H_{31}O_4NSi$ requires C, 61.1; H, 8.9; N, 4.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1664, 1318 and 1114; $\delta_H$(360 MHz, $CDCl_3$) 8.12 (1H, s, 5-H), 6.85 (1H, dt, *J* 16.0 and 7.0 Hz, 2'-H), 6.32 (1H, d, *J* 16.0 Hz, 1'-H), 4.39 (2H, q, *J* 7.1 Hz, $OCH_2CH_3$), 3.65-3.61 (2H, m, 6'-H), 2.30-2.28 (2H, m, 3'-H), 1.58-1.54 (4H, m, 4'-H and 5'-H), 1.39 (3H, t, *J* 7.1 Hz, $OCH_2CH_3$), 0.90 (9H, s, Bu$^t$) and 0.05 (6H, s, 2 x $CH_3$); $\delta_C$(67.5 MHz, $CDCl_3$) 161.6 (s), 160.4 (s), 142.9 (d), 142.5 (d), 133.3 (s), 115.8 (d), 62.7 (t), 61.2 (t), 32.5 (t), 32.1 (t), 25.9 (q), 24.7 (t), 18.3 (s), 14.3 (q) and -5.3 (q); *m/z* (FAB) (Found: $M^+$+H, 354.2119; $C_{18}H_{32}O_4NSi$ requires 354.2101).

**2-[6'-(*tert*-Butyldimethylsilanyloxy)-hex-1'-enyl]-oxazole-4-carboxylic acid 120.**



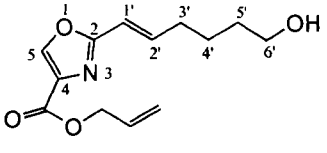

Lithium hydroxide (22 mg, 0.51 mmol) was added in one portion to a solution of the ester **113** (60 mg, 0.17 mmol) in a 3:1 mixture of THF:$H_2O$ (4 ml), and the mixture was then stirred at room temperature for 2 h. Water (2 ml) was added, followed by ethyl acetate (10 ml) and the mixture was cooled to 0 °C and then acidified to pH 1 with 2 M HCl (0.5 ml added dropwise). The separated aqueous layer was extracted with ethyl acetate (3 x 10ml) and the combined organic extracts were then washed with saturated brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to leave the *carboxylic acid* (20 mg, 99%) as a white solid, mp 210-212 °C (from ethanol); $\nu_{max}(CHCl_3)/cm^{-1}$ 3460, 1651 and 1110; $\delta_H$(360 MHz, $CDCl_3$) 8.21 (1H, s, 5-H), 6.89 (1H, dt, *J* 16.0 and 7.0 Hz, 2'-H), 6.33 (1H, dt, *J* 16.0 and 1.4 Hz, 1'-H), 3.66-3.63 (2H, m, 6'-H), 2.32-2.30 (2H, m, 3'-H), 1.59-1.56 (4H, m, 4'-H and 5'-H), 0.90 (9H, s, Bu$^t$) and 0.06 (6H, s, 2 x $CH_3$); $\delta_C$(67.5 MHz, $CDCl_3$) 165.3 (s), 162.5 (s), 144.3 (d) 143.6 (d), 133.9 (s), 116.0 (d), 63.2 (t), 32.9 (t), 32.6 (t), 26.4 (q), 25.1 (t), 18.8 (s) and -4.9 (q) *m/z* (ES) (Found: $M^+$+H, 326.2583; $C_{16}H_{28}O_4NSi$ requires 326.1787).

**2-[6'-(*tert*-Butyldimethylsilanyloxy)-hex-1'-enyl]-oxazole-4-carboxylic acid allyl ester 121.**




A solution of tricarpylmethylammonium chloride (77 mg, 0.2 mmol) and allyl bromide (23 mg, 0.2 mmol) in dichloromethane (0.3 ml) was added in one portion to a stirred suspension of the carboxylic acid **120** (62 mg, 0.2 mmol) and sodium hydrogen carbonate (16 mg, 0.2 mmol) in water (0.3 ml) at room temperature. The mixture was stirred vigorously at room temperature for 24 h, and then extracted with dichloromethane (3 x 10 ml). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 5:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the *olefin* (35 mg, 51%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1731, 1664, 1369, 1317, 1092 and 989; $\delta_H$(360 MHz, $CDCl_3$) 8.14 (1H, s, 5-H), 6.85 (1H, dt, *J* 16.0 and 7.0 Hz, 2'-H), 6.32 (1H, d, *J* 16.0 Hz, 1'-H), 6.01 (1H, ddt, *J* 17.1, 10.4 and 5.9 Hz, $CH_2CH{=}CH_2$), 5.39 (1H, dd, *J* 17.1 and 1.3 Hz =C*H*H), 5.29 (1H, dd, *J* 10.4 and 1.3 Hz, =CH*H*), 4.82 (2H, d, *J* 5.9 Hz, $CH_2$-CH=$CH_2$), 3.66-3.61 (2H, m, 6'-H), 2.31-2.28 (2H, m, 3'-H), 1.57-1.42 (4H, m, 4'-H and 5'-H), 0.89 (9H, s, Bu$^t$) and 0.05 (6H, s, 2 x $CH_3$); $\delta_C$ (67.5 MHz, $CDCl_3$) 161.7 (s), 161.0 (s), 143.0 (d), 142.6 (d), 133.7 (s), 131.7 (d), 119.0 (t), 115.8 (d), 65.7 (t), 62.7 (t), 32.5 (t), 32.1 (t), 25.9 (q), 24.7 (t), 18.3(s) and -5.4 (q); *m/z* (FAB) (Found: $M^+$+H, 366.2094; $C_{19}H_{32}O_4NSi$ requires 366.2101).

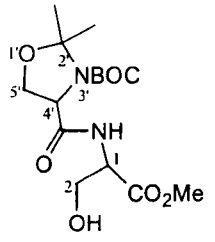
**2-(6'-Hydroxyhex-1'-enyl)-oxazole-4-carboxylic acid allyl ester 122.**




A solution of the silyl ether **121** (115 mg, 0.3 mmol) in a 3:1:1 mixture of AcOH:THF:$H_2O$ (3.0 ml) was stirred at room temperature for 2 h. The mixture was basified with saturated sodium hydrogen carbonate solution and the separated aqueous phase was then extracted with dichloromethane (3 x 10 ml). The combined organic

phases were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 5:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the *alcohol* (70 mg, 91%) as a straw coloured oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1732, 1664, 1316 and 990; $\delta_H$(360 MHz, $CDCl_3$) 8.14 (1H, s, 5-H) 6.85 (1H, dt, *J* 16.0 and 7.0 Hz, 2'-H), 6.32 (1H, d, *J* 16.0 Hz, 1'-H), 6.01 (1H, ddt, *J* 17.1, 10.4 and 5.9 Hz, $CH_2CH{=}CH_2$), 5.39 (1H, dd, *J* 17.1 and 1.3 Hz, =C*H*H), 5.29 (1H, dd, *J* 10.4 and 1.3 Hz, =CH*H*), 4.82 (2H, d, *J* 5.9 Hz, $CH_2CH{=}CH_2$), 3.66-3.61 (2H, m, 6'-H), 2.31-2.28 (2H, m, 3'-H) and 1.57-1.42 (4H, m, 4'-H and 5'-H); $\delta_C$(90 MHz, $CDCl_3$) 161.8 (s), 161.0 (s), 143.1 (d), 142.2 (d), 133.9 (s), 131.7 (d), 119.1 (t), 116.0 (d), 65.8 (t), 62.5 (t), 32.5 (t), 32.0 (t) and 24.6 (t).

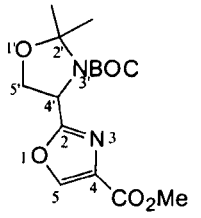
**4'-(2-Hydroxy-1-methoxycarbonylethylcarbamoyl)-2',2'-dimethyloxazolidine-3'-carboxylic acid *tert*-butyl ester 115.**[127]




Triethylamine (1.81 ml, 13.0 mmol) was added dropwise, over 2 min, to a stirred solution of serine methyl ester hydrochloride (0.58 g, 3.7 mmol) in dry dichloromethane (15 ml) at 0 °C under a nitrogen atmosphere. A solution of Garner acid **114**[96] (0.91 g, 3.7 mmol) in dry dichloromethane (5 ml) was added in one portion followed by HOBt (0.54 g, 4.0 mmol) and the resulting suspension was then stirred at room temperature for 15 min. A solution of DCC (0.83 g, 4.0 mmol) in dry dichloromethane (5 ml) was added to the suspension over 10 min and the mixture was then stirred at room temperature for 17 h. The mixture was evaporated *in vacuo* to leave a solid which was taken up in ethyl acetate (20 ml), washed with saturated aqueous sodium bicarbonate soution (3 x 15 ml), 10% aqueous citric acid solution (3 x 15 ml) and saturated brine (2 x 10 ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to leave a residue which was purified by chromatography on silica using a 3:1 ethyl acetate:petrol (bp 40-60 °C) as eluent to give the amide (0.9 g, 74%) as a straw coloured oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1743, 1681, 1368 and 1053; $\delta_H$(360

MHz, $d_6$-DMSO at 353 K) 7.81 (1H, dd, *J* 24.4 and 7.6 Hz, N*H*), 4.87 (1H, br s, OH), 4.46-4.39 (2H, m, 1-H and 4'-H), 4.15-4.08 (1H, m, 2-H), 3.93-3.87 (1H, m, 5'-H), 3.81-3.72 (1H, m, 5'-H), 3.68-3.63 (1H, br m, 2-H), 3.68 (3H, s, OC$H_3$), 1.58 (3H, s, C$H_3$), 1.48 (3H, s, C$H_3$), and 1.41 (9H, s, Bu$^t$); $\delta_C$(90 MHz, $d_6$-DMSO at 353 K) 171.1 (s), 170.5 (s), 151.2 (s), 94.1 (s), 79.3 (s), 66.7 (t), 61.5 (t), 59.4 (d), 54.7 (d), 52.0 (q), 28.1 (q), 25.0 (q) and 24.3 (q); *m/z* (FAB) (Found: $M^+$+H, 347.1813; $C_{15}H_{27}O_7N_2$ requires 347.1818).

**2',2'-Dimethyloxazolidine-[2,4']-bioxazolyl-4,3'-dicarboxylic acid 3'-*tert*-butyl ester 4-methyl ester 116a.** [127]

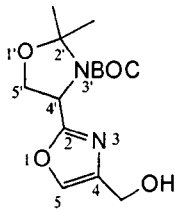



A solution of Burgess' reagent (0.77 g, 3.2 mmol)[84] in dry THF (10 ml) was added to a solution of the amide **115** (0.96 g, 2.8 mmol) in dry THF (20 ml) and the mixture was heated under reflux for 2 h in a nitrogen atmosphere. The mixture was evaporated to dryness *in vacuo* and the residue was purified by chromatography on silica using 1:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the oxazoline (6.1 g, 61%) as an oil; $\delta_H$ (360 MHz, $CDCl_3$ at 348 K, single diastereoisomer) 4.83-4.79 (1H, m, 4'-H), 4.61-4.56 (2H, m, 4-H and 5'-H), 4.43 (1H, dd, *J* 10.4 and 8.8 Hz, 5'-H), 4.16 (1H, dd, *J* 9.0 and 6.9 Hz, 5-H), 4.04 (1H, dd, *J* 9.0 and 3.2 Hz, 5-H), 3.78 (3H, s, $CO_2CH_3$) and 1.67-1.44 (15H, m, 2 x C$H_3$ and Bu$^t$); $\delta_C$(125 MHz, $CDCl_3$, single diastereoisomer) 171.4, 169.1, 151.3, 106.4, 95.2, 80.4, 70.2, 68.3, 66.7, 55.0, 52.8, 52.4, 28.4, 25.2 and 24.3; *m/z* (EI) (Found: $M^+$-$CH_3$, 313.1395; $C_{14}H_{21}N_2O_6$ requires 313.1400).

DBU (0.53 ml, 3.5 mmol) was added dropwise, over 2 min, to a stirred solution of the oxazoline (1.04 g, 3.2 mmol) in dry dichloromethane (30 ml) at 0 °C under a nitrogen atmosphere. Bromotrichloromethane (0.34 ml, 3.5 mmol) was added dropwise over 10 min and the mixture was allowed to warm to room temperature over 24 h.[91] The mixture was quenched with aqueous saturated ammonium chloride solution (2 x 20

ml), and the separated aqueous phase was then extracted with ethyl acetate (2 x 20 ml). The combined organic phases were dried ($MgSO_4$), and then evaporated *in vacuo* to leave a residue which was purified by chromatography on silica using 1:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the oxazole (0.8 g, 75%) as a mixture of rotamers; $\nu_{max}(CHCl_3)/cm^{-1}$ 2980, 1703, 1368, and 1110; $\delta_H$(360 MHz, $CDCl_3$, major rotamer) 8.21 (1H, s, 5-H), 5.20 -5.07 (1H, m, 4'-H), 4.29-4.09 (2H, m, 5'-H), 3.93 (3H, s, $CO_2CH_3$), 1.75 (3H, s, $CH_3$), 1.60 (3H, s, $CH_3$) and 1.30 (9H, s, $Bu^t$); $\delta_C$(125 MHz, $CDCl_3$, major rotamer) 164.0 (s), 161.3 (s), 150.9 (s), 143.6 (d), 133.4 (s), 95.1 (s), 80.5 (s), 67.4 (t), 55.0 (d), 52.1 (q), 28.0 (q), 25.1 (q) and 23.9 (q); *m/z* (FAB) (Found: $M^+$+H, 327.1531; $C_{15}H_{23}N_2O_6$ requires 327.1556).

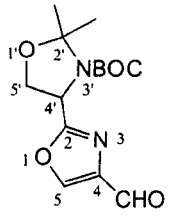
**4-Hydroxymethyl-2',2'-dimethyloxazolidine-[2,4']-bioxazolyl-3'-carboxylic acid *tert*-butyl ester.**




A solution of DIBAL-H (1.5 M in toluene, 5.1 ml, 7.7 mmol) was added dropwise, over 30 min, to a stirred solution of the oxazole ester **116a** (1.0 g, 3.06 mmol) in dry dichloromethane (10 ml) at 0 °C under a nitrogen atmosphere and the mixture was stirred at 0 °C for 4 h. The mixture was quenched with methanol (20 ml) followed by magnesium sulfate (20 g) and the filtered suspension was evaporated *in vacuo* to leave a viscous yellow residue. The residue was added to a saturated solution of potassium sodium tartrate and the mixture was stirred vigorously for 2 h. The mixture was extracted with ethyl acetate (2 x 200 ml), and the combined organic phases were then dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica using 1:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the *oxazole alcohol* (0.55 g, 61%) as a yellow oil; $\delta_H$ (360 MHz, $CDCl_3$, major rotamer) 7.55 (1H, s, 5-H), 5.13-4.98 (1H, m, 4'-H), 4.58 (2H, br s, $CH_2OH$), 4.26-4.04 (2H, m, 5'-H), 2.78 (1H, br s, OH), 1.73 (3H, s, $CH_3$), 1.59 (3H, s, $CH_3$) and 1.29 (9H, s, $Bu^t$); $\delta_C$ (125 MHz, $CDCl_3$) 163.7 (s), 151.2 (s), 140.6 (s), 134.9 (d), 95.0

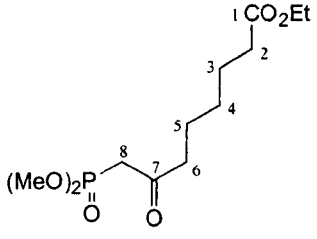
(s), 80.4 (s), 67.4 (t), 56.7 (t), 55.1 (d), 28.1 (q), 25.2 (q) and 24.2 (q); *m/z* (EI) (Found: $M^+$, 298.1535; $C_{14}H_{22}N_2O_5$ requires 298.1529).

**4-Formyl-2',2'-dimethyloxazolidine-[2,4']-bioxazolyl-3'-carboxylic acid *tert*-butyl ester 116b.**




A solution of pyridine-sulfur trioxide complex (0.87 g, 5.49 mmol) in DMSO (5 ml) was added dropwise, over 2 min, to a stirred solution of the alcohol (0.50g, 1.7mmol), DMSO (5 ml) and triethylamine (4.71 ml, 33.8 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 h and then quenched with a 10% aqueous solution of potassium hydrogen sulfate (10 ml). The separated aqueous layer was extracted with diethyl ether (3 x 25 ml) and the combined organic phases were then dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by chromatography on silica using ethyl acetate as eluent to give the *oxazole aldehyde* (0.4 g, 79%) as a colourless oil; $\delta_H$(360 MHz, $CDCl_3$, major rotamer) 9.95 (1H, s, C*H*O), 8.24 (1H, s, 5-H), 5.20-5.07 (1H, m, 4'-H), 4.31-4.12 (2H, m, 5'-H), 1.76 (3H, s, C$H_3$), 1.58 (3H, s, C$H_3$) and 1.31 (9H, s, Bu$^t$), which was used immediately without further characterisation.

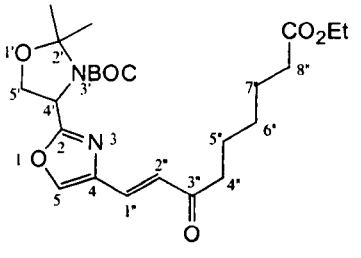
**8-(Dimethoxyphosphoryl)-7-oxo-octanoic acid ethyl ester 117.**[128]




A solution of *n*-butyllithium (2.35 M in hexane, 14.4 ml, 33.8 mmol) was added dropwise, over 10 min, to a stirred solution of dimethylmethyl phosphonate in dry

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

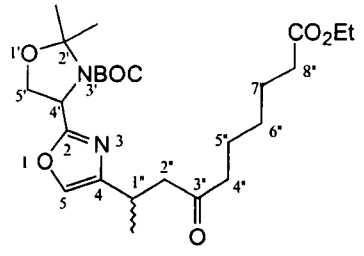
**4-(8''-Ethoxycarbonyl-3''-oxooct-1''-enyl)-2',2'-dimethyloxazolidine-[2,4']-bioxazolyl-3'-carboxylic acid *tert*-butyl ester 118.**




Barium hydroxide octahydrate (0.4 g, 1.4 mmol) was added in one portion to a stirred solution of the β-ketophosphonate **117** (0.4 g, 1.4 mmol) in dry THF (8 ml) under a nitrogen atmosphere at room temperature. The suspension was stirred for 30 min and a solution of the aldehyde **116b** (0.4 g, 1.4 mmol) in 40:1 THF:$H_2O$ (2 ml) was then added in one portion. The mixture was stirred at room temperature for 3 h then quenched with saturated aqueous sodium bicarbonate solution (20 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic phases were washed with saturated brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to leave a viscous oil.

Purification by chromatography on silica using 2:1 petrol (bp 40-60 °C):ethyl acetate as eluent gave the *alkene* (0.5 g, 71%) as a yellow oil; $\upsilon_{max}(CHCl_3)/cm^{-1}$ 2936, 1698, 1379 and 1097; $\delta_H$(360 MHz, $CDCl_3$, major rotamer) 7.77 (1H, s, 5-H), 7.36 (1H, d, *J* 15.6 Hz, 1''-H), 6.91 (1H, d, *J* 15.6 Hz, 2''-H), 5.15-5.00 (1H, m, 4'-H), 4.29-4.22 (1H, m, 5'-H), 4.15-4.09 (1H, br m, 5'-H), 4.12 (2H, q, *J* 7.2 Hz, $OCH_2CH_3$), 2.64-2.60 (2H, m, 4''-H), 2.30 (2H, t, *J* 7.4 Hz, 8''-H), 1.76-1.54 (9H, m, 5''-H, 6''-H, 7''-H and $OCH_2CH_3$) and 1.49-1.21 (15H, m, 2 x $CH_3$ and $Bu^t$); $\delta_C$ (125 MHz, $CDCl_3$) 200.0 (s), 173.8 (s), 160.2 (s), 151.3 (s), 139.4 (s), 137.7 (s), 129.3 (s), 127.3 (s), 95.3 (s), 81.3 (s), 67.3 (t), 60.2 (t), 55.1 (d), 41.5 (t), 34.1 (t), 28.7 (t), 28.1 (q), 25.2 (q), 24.7 (t), 24.2 (q), 23.7 (t) and 14.2 (q).

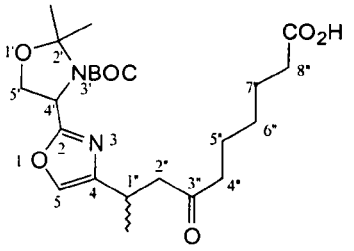
**4-(8''-Ethoxycarbonyl-1''-methyl-3''-oxooctyl)-2',2'-dimethyloxazolidine-[2,4']-bioxazolyl-3'-carboxylic acid *tert*-butyl ester 124.**




A solution of methyllithium (1.6 M in diethyl ether, 6.7 ml, 10.7 mmol) was added dropwise over 20 min to a stirred suspension of copper iodide (1.0 g, 5.4 mmol) in dry diethyl ether (20 ml) at –5 °C under an argon atmosphere and the resulting yellow solution was stirred at –5 °C for 30 min. A solution of the enone **118** (300 mg, 0.65 mmol) in dry diethyl ether (15 ml) was added dropwise over 10 min to the cuprate solution at –5 °C and the mixture was stirred at –5 °C for 3 h. The mixture was quenched with a 1:1 mixture of saturated aqueous ammonium chloride:ammonium hydroxide solution (20 ml) and the separated aqueous layer was then extracted with diethyl ether (2 x 30 ml). The combined organic phases were washed with saturated brine (30 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 1:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the *β-methyl ketone* (168 mg, 55%) as a viscous oil. $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1696; $\delta_H$(360 MHz, $CDCl_3$) 7.30 (1H, s, 5-H), 5.29-4.95 (1H, m, 4'-H), 4.22-4.16 (1H, m,

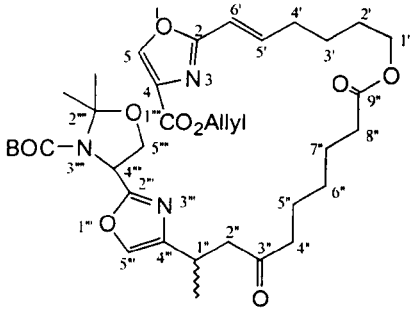
5'-H), 4.13-4.02 (1H, br m, 5'-H), 4.11 (2H, q, *J* 7.1 Hz, $OCH_2CH_3$), 3.30-3.24 (1H, m, 1''-H), 2.83 (1H, dd, *J* 6.0 and 16.9 Hz, 2''-H), 2.51 (1H, dd, *J* 8.1 and 17.2 Hz, 2''-H), 2.36 (2H, t, *J* 7.3 Hz, 4''-H), 2.27 (2H, t, *J* 7.4 Hz, 8''-H), 1.72-1.41 (9H, m, 5''-H, 6''-H, 7''-H and $OCH_2CH_3$) and 1.31-1.09 (18H, m, 2 x $CH_3$, Bu$^t$ and 1''-$CH_3$); $\delta_C$(90 MHz, $CDCl_3$) 209.2 (s), 173.6 (s), 162.8 (s), 151.2 (s), 133.1 (s), 94.9 (s), 80.1 (s), 67.5 (t), 60.2 (t), 55.2 (d), 48.3 (t), 42.9 (t), 34.1 (t), 28.6 (t), 28.1 (q), 26.8 (d), 25.1 (q), 24.6 (t), 24.5 (q), 23.1 (t), 19.4 (q) and 14.2 (q); *m/z* (FAB) (Found: $M^+$+H, 481.2944; $C_{25}H_{41}O_7N_2$ requires 481.2915).

**4-(8''-Carboxy-1''-methyl-3''-oxooctyl)-2',2'-dimethyloxazolidine-[2,4']-bioxazolyl-3'-carboxylic acid *tert*-butyl ester 125.**




Lithium hydroxide (22 mg, 0.5 mmol) was added in one portion to a solution of the ester **124** (60 mg, 0.17 mmol) in a 3:1 mixture of THF:$H_2O$ (4 ml), and the mixture was then stirred at room temperature for 2 h. Water (2 ml) was added, followed by ethyl acetate (10 ml) and the mixture was then acidified to pH 1 with 2 M HCl (0.5 ml added dropwise). The separated aqueous layer was extracted with ethyl acetate (3 x 10 ml), and the combined organic phases were then washed with saturated brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to leave the *carboxylic acid* (20 mg, 99%) as a viscous oil; $\delta_H$(360 MHz, $CDCl_3$) 7.32 (1H, s, 5-H), 5.12-4.98 (1H, m, 4'-H), 4.24-4.15 (1H, m, 5'-H), 4.13-4.03 (1H, m, 5'-H), 3.32-3.26 (1H, m, 1'-H), 2.88-2.82 (1H, m, 2''-H), 2.58-2.46 (1H, m, 2''-H), 2.40-2.27 (4H, m, 4''-H and 8''-H) and 1.73-1.12 (24H, m, 2 x $CH_3$, Bu$^t$, 5''-H, 6''-H, 7''-H and 1''-$CH_3$).

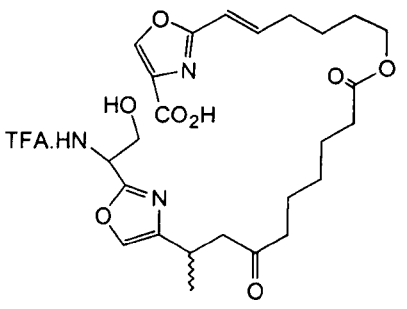
**4-{8-[6-4-Allyloxycarbonyloxazol-2-yl-hex-5'-enyloxycarbonyl]-1'''-methyl-3'''-oxooctyl}-2'''',2'''',-dimethyloxazolidine-[2''',4''']-bioxazolyl-3''''-carboxylic acid *tert*-butyl ester 119.**




1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (37 mg, 0.19 mmol) was added in one portion to a stirred solution of the acid **125** (77 mg, 0.18 mmol) and the alcohol **122** (50 mg, 0.20 mmol) in dichloromethane (6 ml) at 0 °C containing 4-(dimethylamino)pyridine (11 mg, 0.09 mmol). The mixture was stirred at 0 °C for 2 h and then at room temperature overnight before it was evaporated to dryness *in vacuo*. The residue was diluted with ethyl acetate (10 ml) and water (2 ml), and the organic layer was then separated, washed with saturated sodium bicarbonate (15 ml) and water (15 ml), dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 1:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the *ester* (89 mg, 73%) as an oil; $\upsilon_{max}(CHCl_3)/cm^{-1}$ 2934, 2253, 1793, 1730, 1720 and 1368; $\delta_H$ (360 MHz, $CDCl_3$) 8.14 (1H, s, 5-H), 7.31 (1H, s, 5'''-H), 6.83 (1H, dt, *J* 16.0 and 7.0 Hz, 5'-H), 6.33 (1H, d, *J* 16.0 Hz, 6'-H), 6.01 (1H, ddt, *J* 17.1, 10.4 and 5.8 Hz, $CH_2$ C*H*=$CH_2$), 5.37 (1H, dd, *J* 10.4 and 1.3 Hz, =C*H*H), 5.27 (1H, dd, *J* 10.4 and 1.3 Hz, =CH*H*), 5.08-4.96 (1H, m, 4''''-H), 4.82 (2H, dt, *J* 5.8 and 1.3 Hz, C$H_2$ CH=$CH_2$), 4.23-4.03 (4H, m, 1'-H and 5''''-H), 3.31-3.26 (1H, m, 1''-H), 2.83 (1H, dd, *J* 16.9 and 5.8 Hz, 2''-H), 2.51 (1H, dd, *J* 16.9 and 7.8 Hz, 2''-H), 2.40-2.27 (6H, m, 4''-H, 8''-H and 4'-H), 1.73-1.55 (10H, m, 2'-H, 3'-H and 2 x C$H_3$), 1.48-1.08 (15H, m, 5''-H, 6''-H, 7''-H and Bu$^t$), 0.90-0.80 (3H, m, 1''-C$H_3$); $\delta_C$(360 MHz, $CDCl_3$) 210.5 (s), 173.6 (s), 162.8 (s), 161.7 (s), 160.9 (s), 151.2 (s), 144.9 (s), 143.1, 141.8, 133.8 (s), 133.1, 131.7, 119.0 (t), 116.1, 94.9 (s), 80.1 (s), 67.4 (t), 65.7 (t), 63.8 (t), 55.1, 48.3 (t), 42.9 (t), 34.0 (t), 32.2 (t), 29.6 (t), 28.6 (t), 28.2, 28.1, 28.0 (t), 26.8, 25.0,

24.7 (t), 24.6, 24.2, 23.1 (t), 19.3 (q); *m/z* (FAB) (Found: $M^+$+H, 686.3677; $C_{36}H_{52}O_{10}N_3$ requires 686.3654).

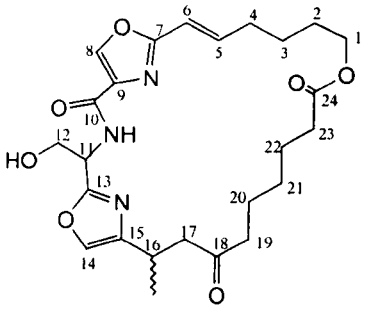
**Bis-oxazole amino acid ester 127.**




Pyrrolidine (33.1 μl, 0.4 mmol) was added in one portion to a stirred solution of the ester **119** (0.18 g, 0.3 mmol), tetrakis(triphenylphosphine)palladium (18 mg, 0.016 mmol) and triphenylphosphine (4.1 mg, 0.016 mmol) in dichloromethane (2 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 4 h, diluted with dichloromethane (10 ml) and then washed with 1 M HCl (3 ml). The separated organic layer was then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 9:1 dichloromethane:methanol as eluent to give the *carboxylic acid* (0.11 g, 70%) as an opaque oil, which was used immediately without characterisation.

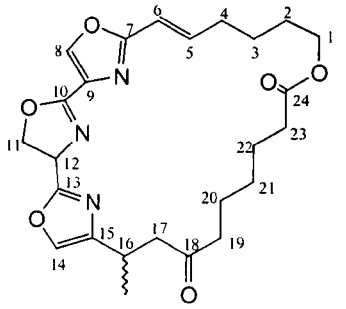
Trifluoroacetic acid (50% solution in dichloromethane, 1 ml) was added in one portion to the acid **126** at room temperature under a nitrogen atmosphere. After stirring for 1 h, toluene was added (1 ml) and the solution was concentrated *in vacuo*. Two subsequent additions of toluene (2 x 2 ml) followed by concentration *in vacuo* left the crude *trifluoroacetic acid salt of the amino alcohol* as a yellow residue, which was used immediately without characterisation.

**The oxazole-amide-oxazole macrolide 78.**



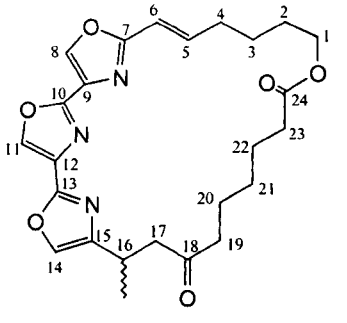
Diisopropylethylamine (37 mg, 0.29 mmol) was added in one portion to a stirred solution of the salt **127** (51 mg, 0.08 mmol) in dry DMF (16 ml) under a nitrogen atmosphere at 0 °C. The solution was stirred at 0 °C for 15 min and then diphenylphosphorylazide (0.034 g, 0.12 mmol) was added and the mixture was stirred for a further 3 min and then left at room temperature for 5 days under a nitrogen atmosphere. The mixture was diluted with ethyl acetate (20 ml) and poured into ice-cold water. The separated aqueous layer was extracted with ethyl acetate (3 x 20 ml) and the combined organic phases were washed with water (6 x 30 ml) and saturated brine (30 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using ethyl acetate as eluent to give the *amide* (14 mg, 36%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3399, 1715, 1688 and 1596; $\delta_H$(500 MHz, $CDCl_3$, major rotamer) 8.20 (1H, s, 8-H), 8.02 (1H, d, *J* 7.4 Hz, N*H*), 7.45 (1H, s, 14-H), 6.93 (1H, dt, *J* 16.2 and 6.8 Hz, 5-H), 6.37 (1H, d, *J* 16.2 Hz, 6-H), 5.46-5.42 (1H, m, 11-H), 4.27-4.10 (4H, m, 12-H and 1-H), 3.42-3.37 (1H, m, 16-H), 3.03 (1H, dd, *J* 16.7 and 11.0 Hz, 17-H), 2.62-2.56 (1H, m, 17-H), 2.54-2.35 (6H, m, 4-H, 19-H and 23-H), 1.84-1.61 (4H, m, 2-H and 3-H), 1.50-1.22 (6H, m, 20-H, 21-H and 22-H) and 0.97-0.91 (3H, m, 16-C*H*$_3$); $\delta_C$(360 MHz, $CDCl_3$) 209.5 (s), 173.6 (s), 161.0 (s), 160.8 (s), 145.3 (s), 144.4 (s), 141.7 (d), 140.5 (d), 136.1 (s), 134.2 (d), 132.1 (d), 128.6 (d), 116.0 (d), 64.6 (t), 63.8 (t), 48.3 (t), 43.0 (t), 34.4 (t), 31.9 (t), 29.7 (t), 28.6 (t), 27.8 (t), 24.7 (t), 23.4 (t), 19.4 (q); *m/z* (EI) (Found: $M^+$-$H_2O$, 469.2223; $C_{25}H_{31}O_6N_3$ requires 469.2167).

**The oxazole-oxazoline-oxazole macrolide 128.**



A solution of Burgess' reagent (4.5 mg, 0.02 mmol) in dry THF (0.2 ml) was added to a solution of the amide **78** (8 mg, 0.02 mmol) in dry THF (0.4 ml) and the mixture was heated under reflux for 2 h under a nitrogen atmosphere. The cooled mixture was evaporated to dryness *in vacuo* and the residue was purified by chromatography on silica using 1:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the *oxazoline* (5.5 mg, 72%); $\delta_H$(360 MHz, $CDCl_3$) 8.01 (1H, s, 8-H), 7.33 (1H, s, 14-H), 6.98-6.84 (1H, d, *J* 15.9 Hz, 5-H), 6.29 (1H, d, *J* 15.9 Hz, 6-H), 5.48-5.35 (1H, m, 12-H), 4.77-4.58 (2H, m, 11-H), 4.16-3.98 (2H, m, 1-H), 3.40 (1H, app. d, *J* 4.8 Hz, 16-H), 3.33-3.25 (1H, m, 17-H), 2.96-2.87 (1H, m, 17-H), 2.46-2.15 (6H, m, 19-H, 23-H and 4-H), 1.87-1.35 (4H, m, 2-H and 3-H), 1.29-1.03 (6H, m, 20-H, 21-H and 22-H) and 0.90-0.76 (3H, m, 16-C$H_3$).

**The *tris*-oxazole macrolide 77.**

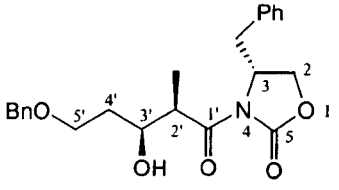


Freshly prepared nickel peroxide (150 mg) was added in three portions to a refluxing solution of the oxazoline **128** (50 mg) in dry benzene (3 ml) at one hour intervals. The mixture was heated under reflux for 2 h, and then filtered through celite. The filtrate was concentrated *in vacuo* to leave a viscous mass. Purification by chromatography on silica using ethyl acetate as eluent gave the *tris-oxazole macrolide* as a white solid; mp 140-142 °C (EtOAc); $\lambda_{max}$(EtOH)/nm 263 (1888); $\upsilon_{max}$($CHCl_3$)/$cm^{-1}$ 3019, 2929,

1715 and 1215; $\delta_H$(500 MHz, $CDCl_3$) 8.07 (1H, s, 8-H), 8.06 (1H, s, 11-H), 7.40 (1H, s, 14-H), 7.19 (1H, dt, *J* 15.9 and 7.1 Hz, 5-H), 6.31 (1H, dt, *J* 15.9 and 1.5 Hz, 6-H), 4.08 (2H, 2 x dt *J* 22.0 and 10.8 Hz, 1-H), 3.43-3.39 (1H, m, 16-H), 3.29 (1H, dd, *J* 17.2 and 6.0 Hz, 17-H), 2.63-2.57 (1H, m, 17-H), 2.49-2.35 (6H, m, 19-H, 23-H and 4-H), 1.80-1.60 (4H, m, 2-H and 3-H), 1.46-1.16 (6H, m, 20-H, 21-H and 22-H) and 0.93-0.78 (3H, m, 16-C*H*$_3$); $\delta_C$(125 MHz, $CDCl_3$) 210.25 (s), 173.86 (s), 162.77 (s), 156.57 (s), 154.26 (s), 146.65 (s), 143.23 (d), 137.27 (d), 137.02 (d), 133.40 (d), 131.76 (s), 130.39 (s), 115.21 (d), 65.86 (t), 48.08 (t), 43.64 (t), 34.58 (t), 31.13 (t), 29.70 (t), 29.15 (t), 27.44 (d), 26.88 (t), 25.06 (t), 24.45 (t) and 18.96 (q); *m/z* (FAB) (Found: $M^+$+H, 468.2154; $C_{25}H_{30}O_6N_3$ requires M 468.2134).

## *3.2 The Side-Chain Synthesis*

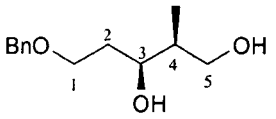
**(3'S,2'R)-3-Benzyl-4-(5'-benzyloxy-3'-hydroxy-2'-methylpentanoyl)-oxazolidin-5-one 135.**




A solution of dibutylborontriflate (1.0 M in dichloromethane, 27.5 ml, 37.5 mmol) and triethylamine (5.7 ml, 40.9 mmol) were added to a solution of the imide **134** (8.0 g, 34.0 mmol) in dry dichloromethane (65 ml) at –78 °C under a nitrogen atmosphere and the resulting pale yellow solution was stirred at –78 °C for 1 h and then at 0 °C for 30 min before being re-cooled to –78 °C. A solution of the aldehyde **133** (5.6 g, 34.0 mmol) in dry dichloromethane (20 ml) was added dropwise over 30 min to the mixture which was then stirred at –78 °C for 1.5 hr. The mixture was allowed to warm to 0 °C and held at that temperature for 2 h. It was then quenched by the addition of pH7 buffer solution (30.0 ml) followed by methanol (140 ml). After 30 min, $H_2O_2$ (30.0 ml of a 30% aqueous solution) was added dropwise and the mixture was stirred at 0 °C for 30 min. It was then diluted with water (100 ml) and the aqueous phase extracted with dichloromethane (3 x 100 ml). The combined organic phases were washed with water (50 ml) and dried ($Na_2SO_4$), then filtered, and the filtrate concentrated *in vacuo*. Chromatography on silica using 1:1 petrol (bp 40-60

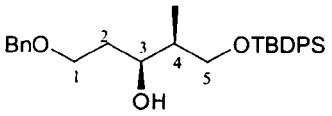
°C):diethyl ether as eluent gave the *secondary alcohol* (10.8 g, 80%) as a colourless oil; $[\alpha]_D$ –52.7 (*c*, 0.9 in $CHCl_3$); (Found: C, 69.7; H, 6.9; N, 3.5; $C_{23}H_{27}O_5N$ requires C, 69.5; H, 6.9; N, 3.5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2922, 2866, 1778, 1693, 1383, 1363, 1095 and 972; $\delta_H$(360 MHz, $CDCl_3$) 7.39-7.27 (8H, m, Ph), 7.26-7.20 (2H, m, Ph), 4.69 (1H, dddd, *J* 7.0, 7.0, 7.0 and 3.5 Hz, 4-H), 4.53 (2H, s, PhC$H_2$O), 4.23-4.17 (2H, m, 5-H), 3.83 (1H, ddd, *J* 13.7, 7.0 and 3.8 Hz, 3'-H), 3.75-3.64 (2H, m, 5'-H), 3.33 (1H, d, *J* 2.2 Hz, 2'-H), 3.27 (1H, dd, *J* 13.4 and 3.3 Hz, C$H_2$Ph), 2.79 (1H, dd, *J* 13.4 and 9.5 Hz, C$H_2$Ph), 1.95-1.85 (1H, m, 4'-H), 1.78-1.71 (1H, m, 4'-H) and 1.29 (3H, d, *J* 7.0 Hz, C$H_3$); $\delta_C$(90 MHz, $CDCl_3$) 176.49 (s), 152.93 (s), 137.95 (s), 135.02 (s), 129.30 (d), 128.81 (d), 128.28 (d), 127.55 (d), 127.25 (d), 73.08 (t), 70.23 (d), 68.18 (t), 66.56 (t), 55.07 (d), 42.45 (d), 37.62 (t), 33.64 (t) and 11.07 (q); *m/z* (EI): (Found $M^+$+Na, 420.1761; $C_{23}H_{27}O_5NNa$ requires 420.1787).

***(3S,4R)*-1-Benzyloxy-4-methylpentan-3,5-diol 136.**



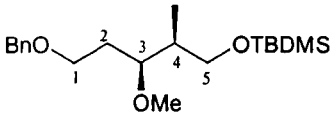

Dry methanol (1.5 ml, 37.5 mmol) and a solution of lithium borohydride (2.0 M in THF, 18.8 ml, 37.5 mmol) were each added dropwise to a solution of the imide **135** (5.9 g, 15.0 mmol) in dry THF (120 ml) at 0 °C under a nitrogen atmosphere and the resulting mixture was stirred at 0 °C for 30 min. The mixture was quenched by the addition of 1 M NaOH (87 ml) and then the mixture was allowed to warm to room temperature. Ethyl acetate (100 ml) was added and the separated aqueous phase was then extracted with ethyl acetate (3 x 50 ml). The combined organic phases were washed with water (50 ml) and saturated brine (50 ml), then dried ($Na_2SO_4$) and evaporated *in vacuo* to leave an inseparable mixture of the diol and the oxazolidine. This mixture was used immediately in the next step.

**(3S,4R)-1-Benzyloxy-5-(*tert*-butyldiphenylsilanyloxy)-4-methylpentan-3-ol 137a.**




Imidazole (3.5 g, 50.7 mmol) and *tert*-butyldiphenylsilyl chloride (8.5 g, 31.0 mmol) were added sequentially to a solution of the crude 1,3- diol **136** (10.3 g) in dry DMF (30 ml) at room temperature under a nitrogen atmosphere. The solution was stirred at room temperature for 12 h and then diluted with water (70 ml) and diethyl ether (70 ml) . The separated organic phase was washed with water (4 x 100 ml) and saturated brine (100 ml), then dried ($Na_2$ $SO_4$) and concentrated *in vacuo*. Purification by chromatography on silica using petrol (bp 40-60 °C):diethyl ether as eluent gave the *silyl ether* (5.7 g, 82% over 2 steps) as a colourless oil; $[\alpha]_D$ –0.9 (*c*, 0.9 in $CHCl_3$); (Found: C, 75.36; H, 8.34: $C_{29}H_{38}O_3Si$ requires C, 75.28; H, 8.28%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3497, 2931, 2859, 1362, 1111 and 998; $\delta_H$(360 MHz, $CDCl_3$) 7.71-7.65 (4H, m, Ph), 7.48-7.27 (11H, m, Ph), 4.55 (2H, s, PhC$H_2$O), 4.07-4.04 (1H, m, 3-H), 3.75-3.65 (4H, m, 1-H and 5-H), 1.91-1.68 (3H, m, 2-H and 4-H), 1.09 (9H, s, Bu$^t$) and 0.96 (3H, d, *J* 7.0 Hz, C$H_3$); $\delta_C$(90 MHz, $CDCl_3$) 138.22(s), 135.60 (d), 133.26 (s), 129.71 (d), 128.35 (d), 127.68 (d), 127.59 (d), 127.55 (d), 74.0 (d), 73.15 (t), 72.02 (d), 68.75 (t), 67.82 (t), 40.02 (d), 34.11 (t), 26.83 (q), 19.14 (s) and 10.76 (q); *m/z* (FAB) (Found $M^+$+H, 463.2656; $C_{29}H_{39}O_3Si$ requires 463.2668).

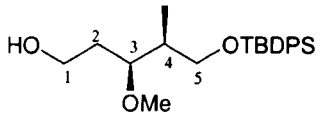
**(3S,4R)-1-Benzyloxy-5-(*tert*-butyldiphenylsilanyloxy)-4-methyl-3-methoxy pentane 137b.**




Sodium hydride (60% dispersion in oil, 1.3 g, 32.0 mmol) was added in one portion to a stirred solution of the alcohol **137a** (7.6 g, 16.0 mmol) in dry DMF (20 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 5 min and then methyl iodide (4.9 ml, 78.4 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 2 h and then quenched with saturated aqueous ammonium chloride solution (200 ml), diluted with water (200 ml) and extracted with

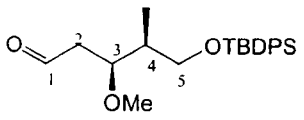
diethyl ether (3 x 100 ml). The combined organic phases were washed with water (2 x 100 ml) and saturated brine (50 ml), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by chromatography on silica using petrol (bp 40-60 °C):diethyl ether as eluent gave the *methyl ether* (5.0 g, 66 %) as a colourless oil; $[\alpha]_D$ +4.5 (*c*, 4.4 in $CHCl_3$); (Found: C, 75.8; H, 8.7; $C_{30}H_{40}O_3Si$ requires C, 75.6; H, 8.5%); $\nu_{max}$(film)/cm$^{-1}$ 2930, 2858, 1362 and 1104; $\delta_H$(360 MHz, $CDCl_3$) 7.70-7.65 (4H, m, Ph), 7.27-7.37 (11H, m, Ph), 4.48 (1H, d, *J* 7.0 Hz, PhC*H*HO), 4.52 (1H, d, *J* 7.0 Hz, PhCH*H*O), 3.77 (1H, dd, *J* 9.9 and 7.0 Hz, 3-H), 3.67-3.59 (4H, m, 1-H and 5-H), 3.39 (3H, s, OC$H_3$), 1.96-1.82 (3H, m, 2-H and 4-H), 1.05 (9H, s, Bu$^t$), 0.88 (3H, d, *J* 7.0 Hz, Me). $\delta_C$(90.0 MHz, $CDCl_3$) 138.50 (s), 135.56 (d), 133.87 (s), 129.51 (d), 128.29 (d), 127.57 (d), 127.54 (d), 127.43 (d), 78.31 (d), 72.93 (t), 67.41 (t), 65.69 (t), 58.31 (q), 39.15 (d), 31.96 (t), 26.86 (q), 19.24 (s) and 11.28 (q); *m/z* (EI) (Found $M^+$+$Na^+$, 499.2660; $C_{30}H_{40}O_3SiNa$ requires 499.2644).

***(3S,4R)*-5-(*tert*-Butyldiphenylsilanyloxy)-3-methoxy-4-methylpentan-1-ol.**



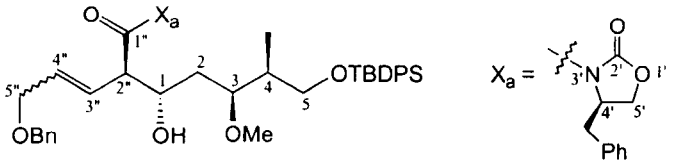

Pearlman's catalyst ($Pd(OH)_2$-C, 650 mg) was added in one portion to a solution of the benzyl ether **137b** (6.4 g, 13.4 mmol) in dry methanol (60 ml) at room temperature, and the flask was then evacuated prior to the introduction of hydrogen gas. The mixture was stirred under one atmosphere of hydrogen for 18 h and then filtered through celite. The filter cake was washed with ether (2 x 25 ml) and the combined filtrate was concentrated *in vacuo*. Purification by chromatography on silica using 2:1 (bp 40-60 °C):diethyl ether as eluent gave the *alcohol* (4.8 g, 92%) as a colourless oil; $[\alpha]_D$ -11.5 (*c*, 1.1 in $CHCl_3$); (Found: C, 71.10; H, 9.06; $C_{23}H_{34}O_3Si$ requires C, 71.46; H, 8.86%); $\nu_{max}$($CHCl_3$) /cm$^{-1}$ 3486, 2858, 1731, 1461, 1362 and 1083; $\delta_H$(360 MHz, $CDCl_3$) 7.72-7.66 (4H, m, Ph), 7.46-7.37 (6H, m, Ph), 3.77-3.66 (3H, m, 1-H and 5-H), 3.58-3.48 (2H, m, 3-H and 5-H), 3.35 (3H, s, OC$H_3$), 1.97-1.89 (1H, m, 4-H), 1.75-1.65 (2H, m, 2-H), 1.08 (9H, s, Bu$^t$) and 0.95 (3H, d, *J* 6.9 Hz, C$H_3$); $\delta_C$(90 MHz, $CDCl_3$) 135.91 (d), 133.75 (s), 129.58 (d), 127.61 (d), 81.83 (d), 65.30 (t), 61.31 (t), 57.88 (q), 38.49 (d), 33.22 (t), 26.87 (q), 19.24 (s) and 12.29 (q); *m/z* (EI) (Found $M^+$+Na, 409.2216; $C_{23}H_{34}O_3SiNa$ requires 409.2175).

***(3S,4R)*-5-(*tert*-Butyldiphenylsilanyloxy)-3-methoxy-4-methylpentanal 138.**




A solution of DMSO (0.4 ml) in dry dichloromethane (2 ml) was added dropwise over 5 min. to a solution of oxalyl chloride (0.3 ml) in dry dichloromethane (5 ml) at –78 °C under a nitrogen atmosphere. After 5 min., a solution of the alcohol (1.0 g, 2.6 mmol) in dry dichloromethane (3 ml) was added dropwise over 15 min. and the mixture was stirred at –78 °C for 1.5 h. Triethylamine (1.6 ml, 11.8 mmol) was added dropwise over 15 min. to the mixture which was then allowed to warm to room temperature. The mixture was diluted with water (50 ml) and dichloromethane (50 ml), and the aqueous layer was then separated and extracted with dichloromethane (2 x 50 ml). The combined organic phases were washed with water (50 ml) and saturated brine (50 ml) then dried ($Na_2SO_4$) and evaporated *in vacuo.* Purification by chromatography on silica using dichloromethane as eluent gave the *aldehyde* (0.8 g, 81%) as an unstable colourless viscous oil; $[\alpha]_D$ –13.8 (*c*, 1.0 in $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 2931, 2859, 1780, 1723, 1384, 1361 and 1111; $\delta_H$(360MHz, $CDCl_3$) 9.82 (1H, t, *J* 2.1 Hz, C*H*O), 7.74-7.62 (4H, m, Ph), 7.48-7.36 (6H, m, Ph), 3.94 (1H, dt, *J* 7.7 and 4.4 Hz, 3-H), 3.68 (1H, dd, *J* 10.2 and 6.9 Hz, 5-H), 3.56 (1H, dd, *J* 10.2 and 5.8 Hz, 5-H), 3.34 (3H, s, OC$H_3$), 2.65-2.56 (2H, m, 2-H), 1.91-1.85 (1H, m, 4-H), 1.07 (9H, s, Bu$^t$) and 0.91 (3H, d, *J* 6.9 Hz, C$H_3$); $\delta_C$(90 MHz, $CDCl_3$) 201.54 (d), 135.53 (d), 133.59 (s), 129.82 (d), 127.63 (d), 77.65 (d), 65.18 (t), 57.94 (q), 46.16 (t), 39.35 (d), 26.95 (q), 19.22 (s) and 11.62 (q); *m/z* (EI) (Found $M^+$+Na, 407.1975; $C_{23}H_{32}O_3SiNa$ requires 407.2018).

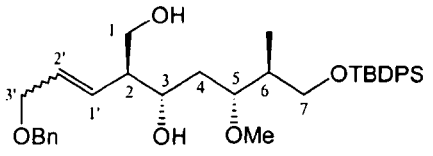
***(4'R,2''R,1S,3S,4R)*-4'-Benzyl-3'-{5''-benzyloxy-2''-[5-(*tert*-butyldiphenylsilanyloxy)-1-hydroxy-3-methoxy-4-methylpentyl]-pent-3''-enoyl}-oxazolidin-2'-one 144.**




A solution of dibutylborontriflate (1.0 M in dichloromethane, 2.2 ml, 2.2 mmol) and triethylamine (0.4 ml, 2.7 mmol) were added to a solution of the imide **143** (0.7 g, 1.9 mmol) in dry dichloromethane (15 ml) at –78 °C under a nitrogen atmosphere and the resulting pale yellow solution was stirred at –78 °C for 1 h and then at 0 °C for 30 min before being re-cooled to –78 °C. A solution of the aldehyde **138** (0.8 g, 2.1 mmol) in dry dichloromethane (5 ml) was added dropwise over 10 min to the mixture which was then stirred at –78 °C for 3 h. The mixture was allowed to warm to 0 °C and held at that temperature for a further 2 h. It was then quenched by adding a solution of NaOAc (0.2 g) in methanol and water (3 ml, 10:1). After 20 min., $H_2O_2$ (1 ml of a 30% aqueous solution) was added dropwise and the mixture stirred at 0 °C for 30 min. It was then diluted with water (20 ml) and the aqueous phase was extracted with dichloromethane (3 x 100 ml). The combined organic phases were washed with water (50 ml) and dried ($Na_2SO_4$), then concentrated *in vacuo*. Chromatography on silica using 50:1 dichloromethane:diethyl ether as eluent gave the *secondary alcohol* (0.6 g, 70% based on recovered aldehyde) as a colourless oil; $[\alpha]_D$ +4.4 (*c*, 0.7 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2931, 2859, 1781, 1695, 1384, 1361 and 1111; $\delta_H$(360 MHz, $CDCl_3$) 7.72-7.62 (4H, m, Ph), 7.45-7.25 (16H, m, Ph), 6.06-5.82 (2H, m, 3''-H and 4''-H), 4.94 (1H, dd, *J* 10.3 and 5.0 Hz, 2''-H), 4.73-4.64 (1H, m, 4'-H), 4.58-4.49 (1H, m, 1-H), 4.53 (2H, s, PhC$H_2$O), 4.28-4.18 (2H, m, 5'-H), 4.17-4.10 (2H, m, 5''-H), 4.08-4.03 (1H, m, 5-H), 3.72-3.68 (1H, m, 5-H), 3.67-3.52 (2H, m, 5-H and 3-H), 3.37 (3H, s, OC$H_3$), 3.28-3.16 (1H, m, C$H_2$Ph), 2.78-2.66 (1H, m, C$H_2$Ph), 2.06-1.89 (1H, m, 4-H), 1.69-1.57 (1H, m, 2-H), 1.55-1.48 (1H, m, 2-H), 1.07 (9H, s, Bu$^t$), and 0.94 (3H, app t, *J* 6.8 Hz, C$H_3$); $\delta_C$(90 MHz, $CDCl_3$) 174.01 (173.52) (s), 152.93 (152.75) (s), 138.13 (s), 135.55 (d), 135.53 (s), 134.90 (s), 133.86 (s), 133.22 (d), 129.48 (d), 129.37 (d), 129.34 (d), 128.87 (d), 128.31 (d), 128.30 (d), 127.82 (d),

127.70 (d), 127.55 (d), 127.30 (d), 126.01 (d), 79.03 (79.07) (d), 72.68 (t), 71.92 (t), 70.13 (t), 69.55 (d), 69.01 (d), 66.59 (t), 65.87 (t), 65.43 (65.38) (t), 58.42 (q), 55.03 (d), 51.29 (d), 48.10 (d), 38.96 (38.88) (d), 37.51 (37.43) (t), 35.99 (35.93) (t), 26.85 (q), 19.22 (s) and 12.34 (12.29) (q); *m/z* (FAB) (Found $M^+$+$Na^+$, 772.3620; $C_{45}H_{55}NO_7SiNa$ requires 772.3646).

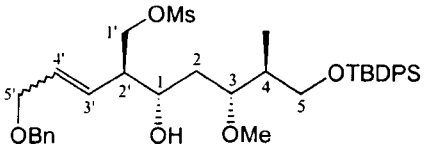
***(2R,3S,5S,6R)*-2-(3'-Benzyloxyprop-1'-enyl)-7-(*tert*-butyldiphenylsilanyloxy)-5-methoxy-6-methyl-heptane-1,3-diol 145.**




Dry methanol (0.7 ml, 16.0 mmol) and a solution of lithium borohydride (2.0 M in THF, 8.5 ml, 17.0 mmol) were each added dropwise to a solution of the imide **144** (4.9 g, 6.5 mmol) in dry THF (60 ml) at 0 °C under a nitrogen atmosphere and the resulting mixture was stirred at 0 °C for 1 h. The mixture was quenched by the addition of 1 M NaOH (10 ml) and then the mixture was allowed to warm to room temperature. Ethyl acetate (20 ml) was added and the separated aqueous phase was then extracted with ethyl acetate (3 x 50 ml). The combined organic phases were washed with water (50 ml) and saturated brine (50 ml), then dried ($Na_2SO_4$) and evaporated *in vacuo*. Purification by chromatography on silica using 2:1 (bp 40-60 °C):diethyl ether as eluent gave the *1,3-diol* (3.4 g, 90%) as a colourless viscous oil; $[\alpha]_D$ –2.7 (*c*, 0.75 in $CHCl_3$); (Found: C, 72.80; H.8.35; $C_{35}H_{48}O_5Si$ requires C, 73.10; H, 8.10%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3457, 2931, 2859, 1760, 1602, 1455, 1362, 1112 and 1077; $\delta_H$(360 MHz, $CDCl_3$) 7.71-7.63 (4H, m, Ph), 7.47-7.24 (11H, m, Ph), 5.94-5.63 (2H, m, 1'-H and 2'-H), 4.53 (2H, d, *J* 7.0 Hz, PhC$H_2$O), 4.11-3.95 (3H, m, 3'-H and 1-H), 3.80-3.73 (1H, m, 1-H), 3.72-3.60 (2H, m, 7-H), 3.59-3.53 (2H, m, 3-H and 5-H), 3.37 (3H, s, OC$H_3$), 2.58-2.49 (1H, m, 2-H), 1.95 (1H, quintet, *J* 4.3 Hz, 6-H), 1.72-1.63 (1H, m, 4-H), 1.53-1.41 (1H, m, 4-H), 1.10 (9H, s, Bu$^t$) and 1.01 (3H, dd, *J* 6.9 and 2.1 Hz, C$H_3$); $\delta_C$(90.0 MHz, $CDCl_3$) 138.10 (137.88) (s), 135.53 (135.51) (d), 133.65 (133.62) (s), 130.43 (130.30) (d), 130.22 (d), 129.76 (d), 129.56 (d), 128.33 (128.32) (d), 127.72 (d), 127.65 (d), 127.58 (d), 80.12 (79.86( (d), 72.42 (72.02) (t), 70.62 (t), 69.86 (69.71) (d), 65.77 (65.43) (t), 64.85 (64.40) (t), 58.32 (q), 49.78 (d),

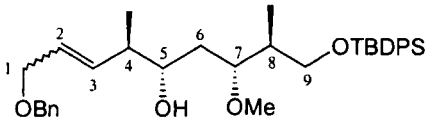
45.59 (d), 38.65 (38.63) (d), 35.37 (35.24) (t), 26.84 (q), 19.20 (s), 15.18, 12.77 (q) and 12.56 (q); *m/z* (FAB) (Found $M^+$+H, 577.3362; $C_{35}H_{49}O_5Si$ requires 577.3349).

***(2R',1S,3S,4R)*-Methanesulfonic acid-5'-benzyloxy-2'-[5-(*tert*-butyldiphenylsilanyloxy)-1-hydroxy-3-methoxy-4-methylpentyl]-pent-3'-enylester 146.**




*N,N*-Diisopropylethylamine (2.0 ml, 11.0 mmol) and methanesulphonyl chloride (0.4 ml, 5.1 mmol) were added sequentially to a stirred solution of the diol **145** (2.9 g, 5.1 mmol) in dry dichloromethane (58 ml) at 0 °C under a nitrogen atmosphere. The resulting solution was stirred at 0 °C for 1 h and then at room temperature for 1h. 1 M potassium carbonate solution (58 ml) was added and the resulting two phase mixture was stirred vigorously at room temperature for 10 min. The aqueous phase was extracted with dichloromethane (3 x 50 ml) and the combined organic phases were then dried ($Na_2SO_4$) and concentrated *in vacuo* to leave the crude *methanesulfonate* (3.0 g, 90%) as an oil which was used immediately in the next step.

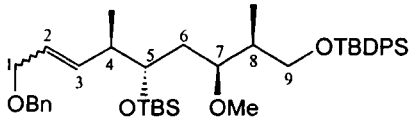
***(4R,5S,7S,8R)*-1-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxy)-7-methoxy-4,8-dimethylnon-2-en-5-ol 147.**




Dry methanol (1.0 ml, 24.0 mmol) and a solution of lithium borohydride (2.0 M in THF, 12.0 ml, 24.0 mmol) were each added dropwise to a solution of the mesylate **145** (4.5 g, 6.9 mmol) in dry THF (120 ml) at 0 °C under a nitrogen atmosphere and the resulting mixture was stirred at 0 °C for 1 h. The mixture was quenched by the addition of 1 M NaOH (120 ml) and then the mixture was allowed to warm to room temperature. Ethyl acetate (20 ml) was added and the separated aqueous phase was then extracted with ethyl acetate (3 x 50 ml). The combined organic phases were washed with water (50 ml) and saturated brine (50 ml), then dried ($Na_2SO_4$) and evaporated *in vacuo*. Purification by chromatography on silica using 2:1 (bp 40-60

°C):diethyl ether as eluent gave the *reduced product* (3.2 g, 82%) as a colourless viscous oil; $[\alpha]_D$ –6.54 (*c*, 1.3 in $CHCl_3$); $\nu_{max}$(film)/cm$^{-1}$ 2932, 2858, 1602, 1455, 1362, 1265, 1112, 1080 and 983; (Found C, 74.7; H, 8.8; $C_{35}H_{48}O_4Si$ requires 74.9, H; 8.6%); $\delta_H$(360 MHz, $CDCl_3$) 7.70-7.67 (4H, m, Ph), 7.47-7.27 (11H, m, Ph), 5.75-5.63 (2H, m, 2-H and 3-H), 4.52 (2H, s, PhC*H*$_2$O), 4.01 (2H, d, *J* 5.0 Hz, 1-H), 3.63-3.53 (4H, m, 9-H, 7-H and 5-H), 3.37 (3H, s, OC*H*$_3$), 2.37 (1H, br s, O*H*), 2.23-2.18 (1H, m, 4-H), 1.98-1.91 (1H, m, 8-H), 1.57 (2H, ddd, *J* 10.8 and 3.1 Hz, 6-H), 1.09 (9H, s, Bu$^t$), 1.01 (3H, d, *J* 6.9 Hz, 4-C*H*$_3$) and 0.99 (3H, d, *J* 6.9 Hz, 8-C*H*$_3$); $\delta_C$(90 MHz, $CDCl_3$) 135.80 (s), 135.62 (135.59) (d), 133.80 (133.77) (s), 129.59 (d), 128.36 (d), 127.78 (d), 127.62 (127.57) (d), 79.92 (d), 71.98 (d), 70.77 (t), 65.49 (t), 58.44 (q), 43.09 (d), 38.89 (d), 35.32 (t), 26.89 (q), 19.27 (s), 16.48 (q) and 12.64 (q); *m/z* (EI) (Found $M^+$+$Na^+$, 583.3245; $C_{35}H_{48}O_4SiNa$ requires 583.3220).

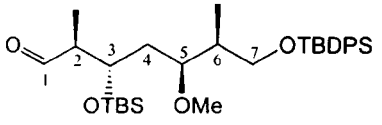
***(4R,5S,7S,8R)*-1-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxy)-7-methoxy-4,8-dimethylnon-2-en-5-ol, *tert*-butyldimethylsilyl ether 148.**




A solution of *tert*-butyldimethylsilyltrifluoromethane sulphonate (1.0 ml, 4.5 mmol) in dry dichloromethane (5 ml) was added dropwise over 5 min to a stirred solution of the alcohol **147** (2.1 g, 3.7 mmol) and 2,6-lutidine (1.1 ml, 9.0 mmol) in dry dichloromethane (20 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature where stirring was continued for an additional 1 h. Methanol (1.5 ml) was added followed by dichloromethane (10 ml) and the solution was then washed with water (2 x 50 ml) and saturated brine (25 ml) then dried ($Na_2SO_4$) and evaporated *in vacuo*. Purification by chromatography on silica using 50:1 diethyl ether:dichloromethane as eluent gave the *bis-silyl ether* (2.4 g, 95%) as a colourless oil; $[\alpha]_D$ –2.8 (*c*, 0.9 in $CHCl_3$); $\nu_{max}$($CHCl_3$)/cm$^{-1}$ 3438, 2955, 2929, 2856 and 1072; $\delta_H$(360 MHz, $CDCl_3$) 7.70-7.61 (4H, m, Ph), 7.46-7.28 (11H, m, Ph), 5.73-5.51 (2H, m, 2-H and 3-H), 4.49 (2H, s, PhC*H*$_2$O), 4.13-4.00 (1H, m, 1-H), 3.99-3.98 (1H, m, 1-H), 3.76-3.64 (2H, m, 9-H), 3.55-3.49 (1H, m, 7-H), 3.48-3.33 (1H, m, 5-H), 3.26 (3H, s, OC*H*$_3$), 2.59-2.37 (1H, m, 4-H), 1.94-1.86 (1H, m, 8-H), 1.59-1.41 (2H, m, 6-H), 1.08 (9H, s, Bu$^t$), 1.01 (3H,

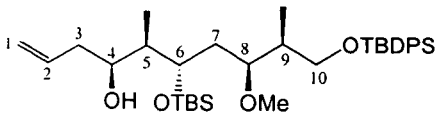
d, *J* 6.9 Hz, $CH_3$), 0.91-0.86 (12H, m, Bu$^t$ and $CH_3$) and 0.04 (6H, s, 2 x $CH_3$); $\delta_C$(90 MHz, $CDCl_3$) 138.44 (138.33) (s), 136.13 (d), 135.61 (d), 135.57 (d), 134.88 (s), 133.92 (d), 129.54 (d), 128.34 (d), 128.32 (d), 127.79 (d), 127.71 (d), 127.59 (d), 127.54 (d), 127.48 (d), 126.69 (d), 126.62 (d), 78.42 (d), 77.94 (d), 72.69 (d), 71.59 (t), 66.15 (t), 57.21 (q), 41.87 (d), 38.06 (d), 35.17 (t), 29.70 (t), 26.91 (q), 25.95 (d), 19.26 (s), 18.12 (s), 16.24 (q), 11.75 (q), 1.01 (q), -2.96 (q) and –4.24 (q); *m/z* (EI) (Found $M^+$+$Na^+$, 697.4087; $C_{41}H_{62}O_4Si_2Na$ requires 697.4084).

***(2R,3S,5S,6R)*-3-(*tert*-Butyldimethylsilanyloxy)-7-(*tert*-butyldiphenylsilanyloxy)-5-methoxy-2,6-dimethylheptanal 149.**



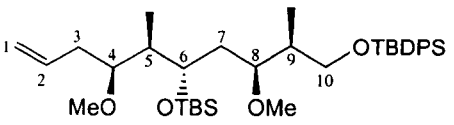

A solution of the alkene **148** (1.8 g, 2.6 mmol) in dry dichloromethane (40 ml) was ozonised at –78 °C until the solution turned blue. Oxygen was then bubbled through the solution for 10 min. to remove any excess of ozone. Triphenylphosphine (0.8 g, 2.9 mmol) was then added in one portion under a nitrogen atmosphere and the solution was stirred at –78 °C for 15 min. before warming to room temperature. The solution was concentrated *in vacuo* to leave a residue which was purified by chromatography on silica using 6:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the *aldehyde* (1.2 g, 80%) as a colourless oil; $[\alpha]_D$ +6.7 (*c*, 1.8 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3438, 2955, 2929, 2856 and 1072; $\delta_H$(360 MHz, $CDCl_3$) 9.75 (1H, d, *J* 1.6 Hz, C*H*O), 7.71-7.65 (4H, m, Ph), 7.48-7.27 (6H, m, Ph), 4.15 (1H, ddd, *J* 8.3, 5.1 and 3.4 Hz, 3-H), 3.70 (1H, dd, *J* 6.4 and 10.0 Hz, 7-H), 3.55 (1H, dd, , *J* 6.5 and 10.0 Hz, 7-H), 3.53-3.49 (1H, m, 5-H), 3.29 (3H, s, O$CH_3$), 2.60-2.50 (1H, m, 2-H), 1.95 (1H, dq, *J* 3.4 and 6.8 Hz, 6-H), 1.65 (1H, ddd, *J* 14.3, 7.5 and 4.3 Hz, 4-H), 1.55 (1H, ddd, *J* 19.4, 8.6 and 5.1 Hz, 4-H), 1.14 (3H, d, J 7.0 Hz, $CH_3$), 1.09 (9H, s, Bu$^t$), 0.92 (9H, s, Bu$^t$), 0.91 (3H, d, *J* 6.13 Hz, $CH_3$), 0.13 (3H, s, Si$CH_3$) and 0.12 (3H, s, Si$CH_3$); $\delta_C$(90.0 MHz, $CDCl_3$) 204.22 (d), 135.60 (d), 135.54 (d), 133.76 (s), 129.56 (d), 127.60 (d), 78.24 (d), 70.62 (d), 64.93 (t), 56.99 (q), 51.89 (d), 37.80 (d), 36.30 (t), 26.88 (q), 25.85 (q), 19.21 (s), 18.02 (s), 11.85 (q), 9.0 ($CH_3$), 9.73 (q), -4.34 (q) and –4.44 (q); *m/z* (EI) (Found $M^+$+$Na^+$, 579.3243; $C_{32}H_{52}O_4Si_2Na$ requires 579.3302).

***(4S,5R,6S,8S,9R)*-6-(*tert*-Butyldimethylsilanyloxy)-10-(*tert*-butyldiphenylsilanyloxy)-8-methoxy-5, 9-dimethyldec-1-en-4-ol 150.**



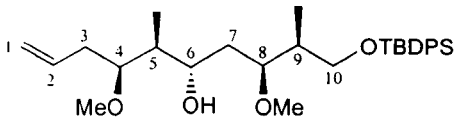

A solution of allylmagnesium bromide (1.0 M in ether, 2.65 ml, 2.65 mmol) was added dropwise over 2 min. to a stirred solution of (-)-$IPC_2BOMe$ (0.87 g, 2.76 mmol) in dry diethyl ether (3 ml) at –78 °C under an argon atmosphere. The resulting thick white slurry was stirred at –78 °C for 1 h and then allowed to warm to room temperature. The mixture was stirred for an additional hour at room temperature, then cooled to –90 °C and a solution of the aldehyde **149** (1.23 g, 2.21 mmol) in dry diethyl ether (6 ml) was cannulated slowly into it. The mixture was stirred at –78 °C for 5 h and then quenched by the slow addition of 3 M NaOH (2.0 ml). The mixture was warmed to room temperature and $H_2O_2$ (0.78 ml of a 30% aqueous solution) was then added slowly. The mixture was heated under reflux for an hour, then cooled to room temperature and diluted with ether (50 ml). The separated organic phase was washed with water (2 x 20 ml) and saturated brine (25 ml), then dried ($Na_2SO_4$) and evaporated *in vacuo*. Purification by chromatography on silica using 9:1 petrol (bp 40-60 °C):ethyl acetate as eluent gave the *alcohol* (0.93 g, 70%) as a colourless oil; $[\alpha]_D$ +5.3 (*c*, 2.0 in $CHCl_3$); (Found: C, 70.4; H, 10.2; $C_{35}H_{58}O_4Si_2$ requires C, 70.2; H, 9.8%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3438, 2955, 2929, 2856 and 1072; $\delta_H$(360 MHz, CDCl3) 7.71-7.65 (4H, m, Ph), 7.47-7.33 (6H, m, Ph), 5.81 (1H, ddt, *J* 17.2, 10.1 and 7.1 Hz, $H_2C$=C*H*$CH_2$), 5.10 (1H, dd, *J* 17.2 and 1.6 Hz, =C*H*H), 5.03 (1H, dd, *J* 10.1 and 1.6 Hz, =CH*H*), 4.15 (1H, dt, *J* 7.4 and 1.4 Hz, 6-H), 3.80 (1H, ddd, *J* 9.0, 5.1 and 1.6 Hz, 4-H), 3.74-3.65 (2H, m, 10-H), 3.52 (1H, dd, *J* 9.9 and 6.1 Hz, 8-H), 3.40 (1H, br s, OH), 3.29 (3H, s, O$CH_3$), 2.40-2.28 (1H, m, 3-H), 2.15-1.95 (2H, m, 3-H and 9-H), 1.85-1.75 (1H, m, 5-H), 1.73-1.57 (2H, m, 7-H), 1.07 (9H, s, Bu$^t$), 1.04 (3H, d, *J* 7.2 Hz, C$H_3$), 0.91 (9H, s, Bu$^t$), 0.85 (3H, d, *J* 7.0 Hz, C$H_3$), 0.12 (3H, s, Si$CH_3$) and 0.11 (3H, s, Si$CH_3$); $\delta_C$(90.6 MHz, $CDCl_3$) 135.57 (d), 135.52 (d), 135.38 (d), 133.74 (s), 133.70 (s), 129.61 (d), 127.64 (d), 127.61 (d), 116.89 (t), 77.63 (d), 76.61 (d), 70.13 (d), 65.13 (t), 57.23 (q), 39.34 (t), 38.32 (d), 37.79 (d), 35.43 (t), 26.88 (q), 25.83 (q), 19.23 (s), 17.88 (s), 11.23 (q), 10.65 (q), -4.35 (q) and -4.65 (q); *m/z* (EI) (Found: $M^+$+$Na^+$, 621.3770; $C_{35}H_{58}O_4Si_2Na$ requires 621.3771).

***(4S, 5R, 6S, 8S, 9R)*-6-(*tert*-Butyldimethylsilanyloxy)-10-*tert*-butyldiphenylsilanyloxy)-4, 8-dimethoxy-5, 9-dimethyldec-1-ene 151.**



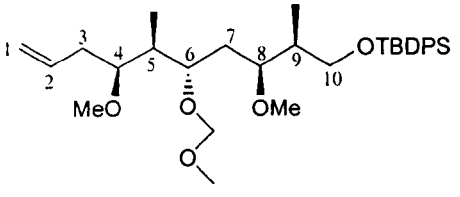

2,6-Di-*tert*-butylpyridine (11.5 ml, 51.0 mmol) and methyltrifluoromethane sulfonate (2.9 ml, 25.5 mmol) were added sequentially to a solution of the alcohol **150** (1.0 g, 1.7 mmol) in chloroform (35.0 ml) under a nitrogen atmosphere. The mixture was heated to reflux for 70 min. and then cooled to room temperature. Concentrated $NH_4OH$ (1.8 ml, 25.5 mmol) was added and the mixture was stirred at room temperature for 2 h and then diluted with dichloromethane (25 ml). The organic phase was washed successively with water (20 ml), 2 M HCl (3 x 25 ml), water (20 ml) and saturated brine (25 ml), then dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by chromatography on silica using 2:3 petrol (bp 40-60 °C):dichloromethane as eluent gave the *methyl ether* (1.0 g, 95%) as a colourless oil; $[\alpha]_D$ –15.2 (*c*, 1.1 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2930, 2857 and 1089; $\delta_H$(360 MHz, $CDCl_3$) 7.70-7.62 (4H, m, Ph), 7.45-7.35 (6H, m, Ph), 5.90-5.78 (1H, m, $H_2C$=C*H*$CH_2$), 5.14-5.06 (2H, m, *H*$_2$C=CH$CH_2$), 3.89 (1H, ddd, *J* 9.5, 3.8 and 1.7 Hz, 6-H), 3.69 (1H, dd, *J* 10.0 and 5.6 Hz, 10-H), 3.55 (1H, dd, *J* 10.0 and 6.8 Hz, 10-H), 3.40 (1H, dq, *J* 9.9 and 2.4 Hz, 8-H), 3.31 (3H, s, OC*H*$_3$), 3.29 (3H, s, OC*H*$_3$), 2.94 (1H, dt, *J* 6.8 and 1.8 Hz, 4-H), 2.41-2.30 (1H, m, 3-H), 2.29-2.23 (1H, m, 3-H), 2.07-1.96 (1H, m, 9-H), 1.79 (1H, m, 5-H), 1.47-1.35 (1H, m, 7-H), 1.32-1.27 (1H, m, 7-H), 1.06 (9H, s, Bu$^t$), 0.93 (3H, d, *J* 1.2 Hz, C*H*$_3$), 0.91 (3H, d, *J* 1.4 Hz, C*H*$_3$), 0.88 (9H, s, Bu$^t$), 0.05 (3H, s, SiC*H*$_3$) and 0.04 (3H, s, SiC*H*$_3$); $\delta_C$(90.6 MHz, $CDCl_3$) 135.64 (d), 135.59 (d), 134.58 (d), 133.99 (s), 133.94 (s), 129.51 (d), 129.48 (d), 127.58 (d), 117.18 (t), 82.62 (d), 79.53 (d), 70.20 (d), 65.02 (t), 57.53 (q), 57.30 (q), 42.37 (d), 37.92 (d), 34.77 (t), 33.98 (t), 26.91 (q), 25.96 (q), 19.26 (s), 18.06 (s), 12.62 (q), 8.84 (q), -3.89 (q) and -4.56 (q); *m/z* (EI) (Found: $M^+$+$Na^+$, 635.3893; $C_{36}H_{60}O_4Si_2Na$ requires 635.3928).

***(4S,5R,6S,8S,9R)*-10-(*tert*-Butyldiphenylsilanyloxy)-4,8-dimethoxy-5,9-dimethyldec-1-en-6-ol 152.**




Pyridinium *p*-toluene sulphonate (160 mg) was added to a solution of the *bis*-silyl ether **151** (1.3 g, 2.1 mmol) in ethanol (17 ml) and the mixture was heated to reflux for 9 h, then evaporated *in vacuo*. The residue was purified by chromatography on silica using 7:1 dichloromethane:diethyl ether as eluent to give the *alcohol* (948 mg, 90%) as a colourless oil; $[\alpha]_D$ –9.0 (*c*, 0.9 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3453, 1642, 1111 and 1081; (Found: C, 73.0; H, 9.7; $C_{30}H_{46}O_4Si$ requires C, 72.3; H, 9.2%); $\delta_H$(360 MHz, $CDCl_3$) 7.70-7.65 (4H, m, Ph), 7.46-7.36 (6H, m, Ph), 5.77 (1H, ddt, *J* 14.1, 7.6 and 6.5 Hz, C*H*=$CH_2$), 5.12 (1H, dq, *J* 17.1 and 1.5 Hz, H*H*C=$CHCH_2$), 5.05 (1H, dq, *J* 10.1 and 1.0 Hz, *H*HC=$CHCH_2$), 3.75-3.52 (6H, m, 10-H, 4-H, 8-H, 6-H and OH), 3.38 (3H, s, $OCH_3$), 3.36 (3H, s, $OCH_3$), 2.50-2.42 (1H, m, 3-H), 2.28-2.15 (1H, m, 3-H), 1.99-1.90 (1H, m, 5-H), 1.70 (1H, dt, *J* 7.1 and 2.5 Hz, 7-H), 1.63-1.44 (2H, m, 7-H and 9-H), 1.07 (9H, s, Bu$^t$), 0.97 (3H, d, *J* 6.9 Hz, $CH_3$) and 0.88 (3H, d, *J* 7.1 Hz, $CH_3$); $\delta_C$(90.6 MHz, $CDCl_3$) 135.62 (d), 135.59 (d), 135.17 (d), 133.87 (s), 133.83 (s), 129.54 (d), 129.52 (d), 127.59 (d), 116.91 (t), 82.49 (d), 79.49 (d), 71.36 (d), 65.42 (t), 58.43 (q), 57.35 (q), 39.84 (d), 38.93 (d), 37.00 (t), 34.76 (t), 26.88 (q), 19.26 (s), 12.50 (q) and 11.36 (q); *m/z* (FAB) (Found: $M^+$+H, 499.3240; $C_{30}H_{47}O_4Si$ requires 499.3244).

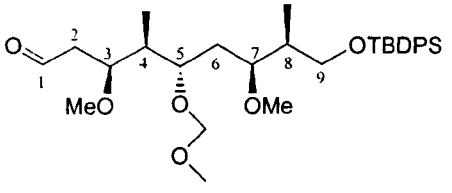
***(4S,5R,6S,8S,9R)*-10-(*tert*-Butyldiphenylsilanyloxy)-4,8-dimethoxy-6-methoxymethoxy-5,9-dimethyldec-1-ene 153.**




Methoxymethyl chloride (0.6 ml, 8.3 mmol) was added dropwise to a solution of the alcohol **152** (0.83 g, 1.7 mmol) and diisopropylethylamine (2.8 ml, 16.6 mmol) in dry dichloromethane (50 ml) under a nitrogen atmosphere, and the mixture was then heated to reflux for 1 h. The mixture was cooled to room temperature, and another

portion of methoxymethyl chloride was added and the mixture then heated to reflux for a further 1 h. The process was repeated once more by which time no starting alcohol was left by tlc analysis. The mixture was diluted with dichloromethane (100 ml) and washed with water (2 x 50 ml), followed by saturated brine (50 ml) and then dried ($Na_2SO_4$). The mixture was evaporated *in vacuo* and the residue purified by chromatography on silica using 25:1 dichloromethane:diethyl ether as eluent to give the *methoxymethyl ether* (0.85 g, 95%) as a colourless viscous oil; $[\alpha]_D$ –14.4 (*c*, 0.9 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2931 and 1090; $\delta_H$(360 MHz, $CDCl_3$) 7.70-7.66 (4H, m, Ph), 7.45-7.36 (6H, m, Ph), 5.83 (1H, ddt, *J* 17.2, 10.2 and 7.1 Hz, C*H*=$CH_2$) 5.14-5.05 (2H, m, $CH_2$=CH), 4.69 (1H, d, *J* 6.7 Hz, OCH*H*O), 4.60 (1H, d, *J* 6.7 Hz, OC*H*HO), 3.77-3.65 (2H, m, 10-H and 6-H), 3.60-3.48 (2H, m, 10-H and 8-H), 3.39 (3H, s, $OCH_3$), 3.38 (3H, s, $OCH_3$), 3.36 (3H, s, $OCH_3$), 3.10 (1H, q, *J* 5.5 Hz, 4-H), 2.33 (2H, t, *J* 6.6 Hz, 3-H), 2.00-1.86 (2H, m, 5-H and 9-H), 1.49-1.46 (2H, m, 7-H), 1.06 (9H, s, $Bu^t$) and 0.92 (6H, app t, *J* 6.8 Hz, 2 x $CH_3$); $\delta_C$(90.6 MHz, $CDCl_3$) 135.61 (d), 135.57 (d), 134.52 (d), 133.89 (s), 133.85 (s), 129.53 (d), 129.51 (d), 127.58 (d), 117.14 (t), 96.28 (t), 81.58 (d), 78.87 (d), 77.02 (d), 65.30 (t), 58.10 (q), 57.19 (q), 55.74 (q), 39.58 (d), 38.89 (d), 34.91 (t), 33.68 (t), 26.87 (q), 19.25 (s), 12.25 (q) and 9.11 (q); *m/z* (FAB) (Found: $M^+$+H, 543.3505; $C_{32}H_{51}O_5Si$ requires 543.3506).

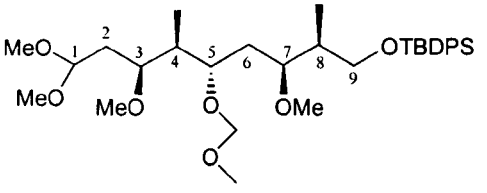
**(*3S,4R,5S,7S,8R*)-9-(*tert*-Butyldiphenylsilanyloxy)-3,7-dimethoxy-5-methoxymethoxy-4,8-dimethylnonanal 154.**




A solution of the alkene **153** (0.8 g, 1.5 mmol) in dry dichloromethane (40 ml) was ozonised at –78 °C until a blue colour persisted and then oxygen was bubbled through the solution for 10 min. Triphenylphosphine (0.5 g, 1.9 mmol) was added, and the mixture was stirred at –78 °C for 15 min. under a nitrogen atmosphere, and then allowed to warm to room temperature. The mixture was evaporated *in vacuo* and the residue was purified by chromatography on silica using 12:1 dichloromethane:diethyl ether as eluent to give the *aldehyde* (0.7 g, 89%) as a labile colourless liquid; $[\alpha]_D$ –

13.7 (*c*, 1.8 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 1722 and 1090; $\delta_H$(360 MHz, $CDCl_3$) 9.83 (1H, t, *J* 2.1 Hz, C*H*O), 7.72-7.68 (4H, m, Ph), 7.46-7.37 (6H, m, Ph), 4.71 (1H, d, *J* 6.8 Hz, OCH*H*O), 4.66 (1H, d, *J* 6.8 Hz, OC*H*HO), 3.76-6.35 (3H, m, 9-Hand 3-H), 3.41 (3H, s, OC$H_3$), 3.36 (3H, s, OC$H_3$), 3.33 (3H, s, OC$H_3$), 3.60 (1H, dd, *J* 10.0 and 6.4 Hz, 5-H), 3.56-3.50 (1H, m, 7-H), 2.65 (2H, m, 2-H), 2.03-1.90 (2H, m, 4-H and 8-H), 1.57-1.50 (2H, m, 6-H), 1.09 (9H, s, Bu$^t$), 0.97 (3H, d, *J* 4.8 Hz, C$H_3$) and 0.95 (3H, d, *J* 4.8 Hz, C$H_3$); $\delta_C$(90.6 MHz, $CDCl_3$) 201.29 (d), 135.54 (d), 135.49 (d), 133.80 (s), 133.74 (s), 129.51 (d), 129.49 (d), 127.54 (d), 96.58 (t), 78.75 (d), 77.64 (d), 77.24 (d), 65.13 (t), 57.94 (q), 57.54 (q), 55.75 (q), 46.09 (t), 41.32 (d), 38.59 (d), 33.89 (t), 26.82 (q), 19.20 (s), 12.19 (q) and 9.66 (q); *m/z* (FAB) (Found: $M^+$+$Na^+$, 567.3072; $C_{31}H_{48}O_6SiNa$ requires 567.3118).

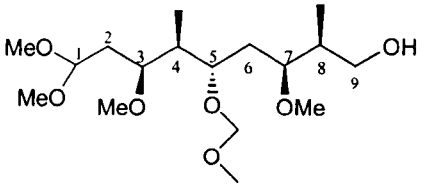
***(3S,4R,5S,7S,8R)*-9-(*tert*-Butyldiphenylsilanyloxy)-1,1,3,7-tetramethoxy-5-methoxymethoxy-4,8-dimethylnonane 155.**




*p*-Toluenesulphonic acid (12 mg, catalytic) was added in one portion to a solution of the aldehyde **154** (780 mg, 1.4 mmol) in a mixture of trimethyl orthoformate (32 ml) and dry methanol (22 ml) at room temperature under a nitrogen atmosphere. The homogeneous mixture was stirred for 1 h and then quenched with saturated aqueous sodium hydrogen carbonate solution (5 ml). The separated organic layer was dried ($Na_2SO_4$), evaporated *in vacuo* and the residue purified by chromatography on silica using 7:1 dichloromethane:diethyl ether as eluent to give the *dimethyl acetal* (830 mg, 98%) as a colourless oil; $[\alpha]_D$ –6.0 (*c*, 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3428, 2932 and 1088; $\delta_H$(360 MHz, $CDCl_3$) 7.71-7.68 (4H, m, Ph), 7.45-7.36 (6H, m, Ph), 4.71 (1H, d, *J* 6.8 Hz, OCH*H*O), 4.64 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.55 (1H, t, *J* 5.6 Hz, 1-H), 3.79-3.74 (1H, m, 5-H), 3.71 (1H, dd, *J* 10.0 and 5.9 Hz, 9-H), 3.57 (1H, dd, *J* 10.0 and 5.9 Hz, 9-H), 3.54-3.50 (1H, m, 7-H), 3.40 (3H, s, OC$H_3$), 3.36 (3H, s, OC$H_3$), 3.34 (3H, s, OC$H_3$), 3.33 (3H, s, OC$H_3$), 3.30 (3H, s, OC$H_3$), 3.26-3.19 (1H, m, 3-H), 2.03-1.87 (2H, m, 4-H and 8-H), 1.83 (2H, t, *J* 5.4 Hz, 2-H), 1.50 (2H, t, *J* 6.3 Hz, 6-H), 1.08 (9H, s, Bu$^t$), 0.95 (3H, d, *J* 1.0 Hz, C$H_3$) and 0.94 (3H, d, *J* 1.0 Hz,

$CH_3$); $\delta_C$(90.6 MHz, $CDCl_3$) 135.56 (d), 135.52 (d), 133.85 (s), 133.83 (s), 129.49 (d), 129.47 (d), 127.54 (d), 102.02 (d), 96.38 (t), 79.26 (d), 77.68 (d), 77.50 (d), 65.31 (t), 57.98 (q), 55.73 (q), 53.07 (q), 51.85 (q), 41.06 (d), 38.85 (d), 35.01 (t), 33.73 (t), 26.84 (q), 19.21 (s), 12.15 (q) and 9.37 (q); *m/z* (FAB) (Found: $M^+$+H, 590.3589; $C_{33}H_{54}O_7Si$ requires 590.3639).

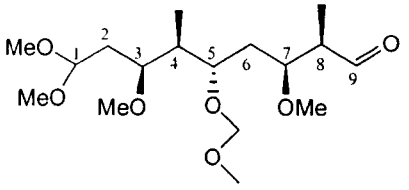
***(3S,4R,5S,7S,8R)*-1,1,3,7-Tetramethoxy-5-methoxymethoxy-4,8-dimethylnonan-9-ol 156.**




Tetrabutylammonium fluoride (442 mg, 1.7 mmol) was added in one portion to a stirred solution of the silyl ether **155** (825 mg, 1.4 mmol) in dry THF (12.5 ml) at room temperature under a nitrogen atmosphere and the mixture was stirred at room temperature for 5 h. An additional portion of TBAF (100 mg) was added and stirring was continued for a further 1 h by which time the starting material was completely consumed. The mixture was evaporated *in vacuo* to leave a residue which was extracted with dichloromethane (3 x 50 ml). The combined organic phases were washed with water (50 ml) and saturated brine (50 ml) then dried ($Na_2SO_4$) and evaporated *in vacuo.* Purification by chromatography on silica using 3:1 diethyl ether:dichloromethane as eluent gave the *alcohol* (484 mg, 98%) as a colourless, viscous liquid; $[\alpha]_D$ –44.2 (*c*, 1.3 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3464, 2934 and 1080; $\delta_H$(360 MHz, $CDCl_3$) 4.67 (1H, d, *J* 6.8 Hz, OCH*H*O), 4.59 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.51 (1H, t, *J* 5.8 Hz, 1-H), 3.76 (1H, ddd, *J* 9.8, 4.5 and 1.8 Hz, 5-H), 3.68 (1H, dd, *J* 10.8 and 8.9 Hz, 9-H), 3.50 (1H, dd, *J* 10.8 and 5.0 Hz, 9-H), 3.47-3.44 (1H, m, 7-H), 3.41 (3H, s, $OCH_3$), 3.38 (3H, s, $OCH_3$), 3.34 (3H, s, $OCH_3$), 3.32 (3H, s, $OCH_3$), 3.30 (3H, s, $OCH_3$), 3.22 (1H, sextet, *J* 5.1 Hz, 3-H), 2.98 (1H, br s, OH), 2.29-2.22 (1H, m, 8-H), 1.92-1.85 (1H, m, 4-H), 1.79 (2H, t, *J* 6.1 Hz, 2-H), 1.62-1.43 (2H, m, 6-H), 0.91(3H, d, *J* 7.0 Hz, $CH_3$) and 0.81 (3H, d, *J* 7.1 Hz, $CH_3$); $\delta_C$(90.6 MHz, $CDCl_3$) 102.07 (d), 96.45 (t), 82.05 (d), 79.21 (d), 77.53 (d), 65.63 (t), 57.94 (q), 57.51 (q), 55.71 (q), 53.03 (q), 52.11 (q), 40.98 (d), 35.41 (d), 34.97 (t), 31.36 (t),

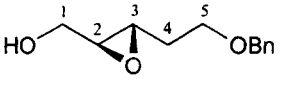
12.83 (q) and 9.12 (q); *m/z* (FAB) (Found: $M^+$+$Na^+$, 375.2328; $C_{17}H_{36}O_7Na$ requires 375.2359).

***(3S,4R,5S,7S,8R)*-1,1,3,7-Tetramethoxy-5-methoxymethoxy-4,8-dimethylnonanal 131.**




A mixture of the alcohol **156** (127 mg, 0.36 mmol), NMO (88 mg, 0.72 mmol) and powdered 4 Å-molecular sieves (0.5 g) in dry dichloromethane (10 ml) was stirred at room temperature for 10 min under nitrogen and then solid TPAP (12 mg, 0.036 mm) was added in one portion. The mixture was stirred for an additional 1 h then diluted with ether (100 ml) and filtered through celite. The filter cake was washed with ether (2 x 25 ml) and the combined ether extracts were concentrated *in vacuo* to leave a brown residue. Chromatography on silica using dichloromethane-ether (3:1) as eluent gave the *aldehyde* (112 mg, 89%) as a colourless oil, $[\alpha]_D$ –68.6 (*c*, 3.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1721; $\delta_H$(360 MHz, $CDCl_3$) 9.83 (1H, s, C*H*O), 4.68 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.60 (1H, d, *J* 6.8 Hz, OCH*H*O), 4.50 (1H, t, *J* 5.7 Hz, 1-H), 3.79-3.76 (2H, m, 5-H and 8-H), 3.39 (3H, s, $OCH_3$), 3.36 (3H, s, $OCH_3$), 3.33 (3H, s, $OCH_3$), 3.32 (3H, s, $OCH_3$), 3.30 (3H, s, $OCH_3$), 3.36-3.30 (1H, b. m, 7-H), 3.26-3.16 (1H, m, 3-H), 1.95-1.85 (1H, m, 4-H), 1.78 (2H, t, *J* 5.3 Hz, 2-H), 1.68-1.47 (2H, m, 6-H), 1.07 (3H, d, *J* 7.0 Hz, $CH_3$), 0.89 (3H, d, *J* 6.9 Hz, $CH_3$). $\delta_C$(90.6 MHz, $CDCl_3$) 204.8 (d), 102.0 (d), 96.5 (t), 79.1 (d), 78.0 (d), 77.4 (d), 57.9 (q), 57.7 (q), 55.8 (q), 53.1 (q), 52.2 (q), 49.3 (d), 40.8 (d), 34.9 (t), 34.4 (t), 9.1 (q) and 8.4 (q). *m/z* (EI) (Found: $M^+-CH_2$+$Na^+$, 359.2045; $C_{16}H_{32}O_7Na$ requires 359.2046).

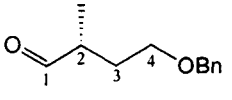
***(2S, 3R)*-[2-(5-Benzyloxyethyl)oxiranyl]methanol 158.**[72]




Titanium (IV) isopropoxide (2.64 ml, 8.9 mmol), (+)-diethyl tartarate (1.84 ml, 10.7 mmol) and 5-benzyloxypent-2-en-1-ol **157**[124] (16.0 g, 83.2 mmol) were added sequentially over 30 min to a suspension of powdered 4Å sieves (2.8 g) in dry

dichloromethane (200 ml) at –20 °C under a nitrogen atmosphere. The mixture was stirred at –20 °C for 30 min, and then *tert*-butylhydroperoxide (3 M in isooctane, 55.5 ml, 166.5 mmol) was added over 30 min. The resulting mixture was stirred at –20 °C for 8 h and then kept at –18 °C for 12 h. The reaction was quenched by the addition of water (100 ml) and then warmed to room temperature over 30 min. Sodium hydroxide in brine (30%, 20 ml) was added, and the mixture was then stirred at room temperature for 30 min before the two phases were separated. The aqueous phase was extracted with dichloromethane (3 x 200 ml) and the combined organic phases then washed with saturated brine and dried ($Na_2SO_4$). The solution was concentrated *in vacuo* to leave a pale yellow oil which was purified by chromatography on silica using diethyl ether as eluent to give the epoxide (13.1 g, 76%) as a colourless oil; $[\alpha]_D$ –30.0 (*c*, 3.9 in $CHCl_3$); (Found: C, 69.4; H, 7.9. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%); $\nu_{max}$(film)/cm$^{-1}$ 3427, 2921, 2863, 1454, 1363, 1101 and 1029; $\delta_H$(270 MHz, $CDCl_3$) 7.36-7.20 (5H, m, Ph), 4.47 (2H, s, PhC$H_2$O), 3.81-3.74 (1H, m, 2-H), 3.56 (2H, t, *J* 6.0 Hz, 5-H), 3.53-3.43 (1H, m, 1-H), 3.03-2.96 (1H, m, 1-H), 2.91 (1H, dt, *J* 4.6 and 2.3 Hz, 3-H) and 1.95-1.71 (2H, m, 4-H); $\delta_C$(67.8 MHz, $CDCl_3$) 137.8 (s), 128.03 (d), 127.69 (d), 72.6 (t), 66.5 (t), 61.5 (t), 58.6 (d), 53.4 (d) and 31.7 (t).

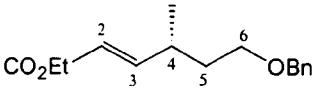
***(2R)*-4-Benzyloxy-2-methylbutyraldehyde 160.**[72]




A solution of trimethylaluminium (2 M in hexane, 75.0 ml, 150.0 mmol) was added dropwise over 30 min to a stirred solution of the epoxy alcohol **158** (10.0 g, 48.0 mmol) in dry dichloromethane (300 ml) at 0 °C under an argon atmosphere. The mixture was allowed to warm to room temperature and then stirred for 15 h. After cooling back to 0 °C, 2 M HCl (150 ml) was added cautiously and the two layers were allowed to separate. The separated aqueous layer was extracted with dichloromethane (2 x 200 ml) and the combined organic phases were concentrated *in vacuo*. Analysis of the p.m.r. spectrum of the residue showed the presence of an *ca* 9:1 mixture of regioisomeric products in favour of the required 5-benzyloxy-3-methylpentane-1, 2-diol **159**. A solution of the residue in methanol (450 ml) and water (100 ml), was stirred with sodium periodate (9.6 g) for 6 h before the solvent was removed *in vacuo*.

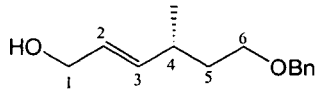
The residue was diluted with water (200 ml) and the mixture was then extracted with dichloromethane (3 x 200 ml). The combined organic phases were dried ($MgSO_4$) and then concentrated *in vacuo* to leave a pale yellow oil. Chromatography on silica using ether as eluent gave the aldehyde (7.8 g, 84%) as an unstable colourless oil; $\nu_{max}$(film)/cm$^{-1}$ 1723; $\delta_H$(270 MHz, $CDCl_3$) 9.63 (1H, d, *J* 1.7 Hz, C*H*O), 7.34-7.25 (5H, m, Ph), 4.47 (2H, s, PhC$H_2$O), 3.55-3.48 (2H, m, 4-H), 2.52 (1H, app sextet d, *J* 6.9 and 1.7 Hz, 2-H), 2.10-1.97 (1H, m, 3-H), 1.74-1.62 (1H, m, 3-H) and 1.09 (3H, d, *J* 6.9 Hz, $CH_3$); $\delta_C$(67.8 MHz, $CDCl_3$) 204.5 (d), 138.0 (s), 128.2 (d), 128.1 (d), 127.55 (d), 72.8 (t), 67.2 (t), 43.5 (d), 30.6 (t) and 13.0 (q).

***(4R)*-Ethyl-6-benzyloxy-4-methylhex-*(2E)*-enoate 161.**[72]



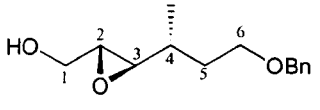

Carboethoxytriphenylphosphorane (14.6 g, 42 mmol) was added in one portion to a solution of the aldehyde **160** (7.50 g, 39.0 mmol) in dry dichloromethane (200 ml) at room temperature under a nitrogen atmosphere and the resulting yellow solution was stirred for 12 h. The mixture was concentrated *in vacuo* to leave a pale yellow viscous liquid which was purified by chromatography on silica using 4:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the ester (9.60 g, 94%) as a colourless oil; $\nu_{max}$(film)/cm$^{-1}$ 2979, 2858, 1723 and 1655; $\delta_H$(270 MHz, $CDCl_3$) 7.28-7.14 (5H, m, Ph), 6.77 (1H, dd, *J* 7.9 and 15.8 Hz, 3-H), 5.72 (1H, dd, *J* 1.3 and 15.8 Hz, 2-H), 4.38 (2H, s, OC$H_2$Ph), 4.08 (2H, q, *J* 6.9 Hz, OC$H_2$CH$_3$), 3.41-3.33 (2H, m), 2.45 (1H, app septet, *J* 7.0 Hz, 4-H), 1.59 (2H, q, *J* 7.0 Hz, 5-H), 1.19 (2H, t, *J* 6.9 Hz, OCH$_2$C$H_3$) and 0.97 (3H, d, *J* 7 Hz, C$H_3$); $\delta_C$(67.8 MHz, $CDCl_3$) 166.6 (s), 153.6 (d), 138.3 (s), 128.2 (d), 127.5 (d), 127.5 (d), 119.9 (d), 72.9 (t), 67.8 (t), 60.0 (t), 35.7 (t), 33.3 (d), 19.3 (q) and 14.2 (q).

***(4R)*-6-Benzyloxy-4-methylhex-*(2E)*-en-1-ol 162.**[72]




A solution of DIBAL-H (1 M in hexane, 70.0 ml, 70.0 mmol) was added over 30 min to a stirred solution of the ester **161** (9.0 g, 34.0 mmol) in dry THF (100 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 2 h, and then quenched with 2 M HCl (5 ml initially, followed by 50 ml after the reaction had set to a gel). The separated aqueous layer was then extracted with ethyl acetate (3 x 50 ml). The combined organic phases were dried ($MgSO_4$) and then concentrated *in vacuo* to leave a yellow oil. Chromatography on silica using 7:1 dichloromethane:diethyl ether as eluent gave the alcohol (7.28 g, 96%) as an oil; $[\alpha]_D$ - 31.2 (*c*, 14.1 in $CHCl_3$); (Found: C, 76.1; H, 9.5. $C_{14}H_{20}O_2$ requires C 76.3; H 9.2%); $\nu_{max}$(film)/$cm^{-1}$ 3385, 2924 and 2863; $\delta_H$(270 MHz, $CDCl_3$) 7.44-7.36 (5H, m, Ph), 5.73-5.35 (2H, m, 2-H and 3-H), 4.46 (2H, q, *J* 7.0 Hz, PhC$H_2$O), 4.05 (2H, br s, 1-H), 3.57 (2H, t, *J* 6.6 Hz, 6-H), 2.40 (1H, septet, *J* 6.6 Hz, 4-H), 2.10 (1H, br s, OH), 1.60 (2H, ddd, *J* 13.2, 6.8 and 3.3 Hz, 5-H) and 1.00 (3H, d, *J* 6.6 Hz, C$H_3$); $\delta_C$(90.6 MHz, $CDCl_3$) 138.2 (s), 137.8 (d), 128.7 (d), 127.8 (d), 127.7 (d), 127.4 (d), 72.6 (t), 68.3 (t), 63.5 (t), 36.7 (t), 33.9 (d) and 20.5 (q).

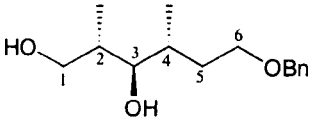
***(2S, 3R, 4R)*-[2-(6-Benzyloxy-4-methylpropyl)oxiranyl]methanol 163.**[72]




Titanium (IV) isopropoxide (1.0 ml, 3.4 mmol), (-)-diethyl tartarate (0.7 ml, 4.0 mmol) and the allylic alcohol **162** (7.0 g, 32.0 mmol) were added sequentially over 20 min to a stirred suspension of powdered 4 Å sieves (1.2 g) in dry dichloromethane (50 ml) at –20 °C under a nitrogen atmosphere. The mixture was stirred at –20 °C for 30 min, then *tert*-butylhydroperoxide (3 M in isooctane, 21.3 ml, 64.0 mmol) was added over 30 min and the resulting mixture was stirred at –20 °C for 8 h. It was then kept at –18 °C for 12 h before being quenched by the addition of water (40 ml). The mixture was warmed to room temperature over 30 min, and then sodium hydroxide in brine (30%, 8 ml) was added, and the mixture stirred at room temperature for 30 min. The

separated aqueous phase was extracted with dichloromethane (3 x 50 ml) and the combined organic phases were then washed with saturated brine (50 ml) and dried ($Na_2SO_4$). The solution was concentrated *in vacuo* to leave a pale yellow oil, which was purified by chromatography on silica using 3:2 petrol (bp 40-60 °C):ethyl acetate as eluent to give the epoxide (6.4 g, 85%) as a colourless oil; $[\alpha]_D$ +14.9 (*c*, 10.7 in $CHCl_3$); (Found: C, 71.3; H, 8.8. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%); $\nu_{max}$(film)/cm$^{-1}$ 3415, 2963 and 2876; $\delta_H$(250 MHz, $CDCl_3$) 7.35-7.24 (5H, m, Ph), 4.50 (2H, q, *J* 7.0 Hz, PhC$H_2$O), 3.86-3.79 (1H, m, 1-H), 3.58-3.49 (3H, m, 1-H and 6-H), 2.96-2.89 (2H, m, 2-H and OH), 2.77 (1H, dd, *J* 6.6 and 2.5 Hz, 3-H), 1.90-1.82 (1H, m, 4-H), 1.66-1.54 (2H, m, 5-H) and 0.94 (3H, d, *J* 6.6 Hz, C$H_3$); $\delta_C$(67.8 MHz, $CDCl_3$) 138.4 (s), 128.2 (d), 127.7 (d), 127.5 (d), 72.8 (t), 68.0 (t), 61.8 (t), 60.3 (d), 57.0 (d), 34.2 (t), 32.4 (C-1) and 15.8 (q).

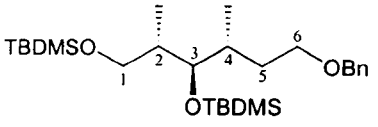
***(2R,3R,4R)*-6-Benzyloxy-2,4-dimethylhexane-1, 3-diol 164.**[72]




A solution of methylmagnesium bromide (3 M in THF, 28.5 ml, 85.5 mmol) was added over 1 h to a stirred suspension of CuI (1.67 g, 8.8 mmol) in dry THF (75 ml) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 30 min at 0 °C and then a solution of the epoxy alcohol **163** (6.5 g, 27.5 mmol) in dry THF (50 ml) was added over 30 min. The reaction was stirred at 0 °C for 15 h and then quenched by the addition of saturated aqueous ammonium chloride solution (150 ml). The mixture was stirred vigorously at room temperature for 30 min and then extracted with ether (3 x 150). The combined organic phases were washed with saturated brine (150 ml), and then concentrated *in vacuo*. Analysis of the p.m.r. spectrum of the residue showed that it was composed of a 9:1 mixture in favour of the required 1,3-diol. A solution of the residue in methanol (140 ml) and water (35 ml) was stirred with sodium periodate (1.5 g) for 7 h and then most of the methanol was removed *in vacuo*. The residue was diluted with water (100 ml) and then extracted with dichloromethane (3 x 100 ml). The combined organic phases were dried ($MgSO_4$) and then concentrated *in vacuo* to leave a pale yellow oil. Chromatography on silica using 1:1 petrol (bp 40-60 °C):ethyl acetate as eluent gave the 1,3-diol (5.85 g, 84%) as a liquid; $[\alpha]_D$ +10.8 (*c*, 10.3 in

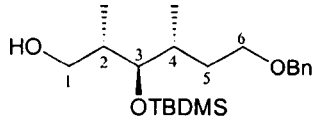
$CHCl_3$); (Found: C, 71.1; H, 9.9. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.5%); $\nu_{max}$(film)/$cm^{-1}$ 3408, 2957 and 2857; $\delta_H$(270 MHz, $CDCl_3$) 7.36-7.29 (5H, m, Ph), 4.53 (2H, s, PhC$H_2$O), 3.76 (2H, br d, *J* 5.6 Hz, 1-H), 3.64-3.47 (3H, m, 6-H and OH), 3.34 (1H, br q, *J* 5.3 Hz, 3-H), 3.24 (1H, br t, *J* 5.3 Hz, OH), 1.95 (1H, heptet, *J* 6.9 Hz, 4-H), 1.85 (1H, d sextet, *J* 7.3 and 3.5 Hz, 2-H), 1.72 (2H, q, *J* 5.6 Hz, 5-H), 0.96 (3H, d, *J* 6.9 Hz, C$H_3$) and 0.89 (3H, d, *J* 7.3 Hz, C$H_3$); $\delta_C$(67.8 MHz, $CDCl_3$) 137.8 (s), 128.3 (d), 128.8 (d), 127.6 (d), 81.3 (d), 72.9 (t), 67.8 (t), 67.4 (t), 36.8 (d), 33.1 (d), 30.0 (t), 16.7 (q) and 14.0 (q).

***(2R, 3R, 4R)*-6-Benzyloxy-1,3-(*tert*-butyldimethylsilanyloxy)-2, 4-dimethylhexane 165.**[72]



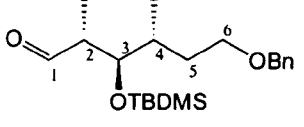

A solution of *tert*-butyldimethylsilylmethane sulphonate (1.98 ml, 8.61 mmol) in dry dichloromethane (5 ml) was added dropwise over 5 min. to a stirred solution of the diol **164** (1.05 g, 4.1 mmol) and 2,6-lutidine (1.98 ml, 17.20 mmol) in dry dichloromethane (10 ml) at 0 °C under a nitrogen atmosphere and the resulting solution was stirred at 0 °C for 1 h. The mixture was allowed to warm to room temperature and then stirred for 1 h before being quenched with methanol (100 μl). The mixture was diluted with dichloromethane (50 ml), and then washed with water (25 ml) and saturated brine (25 ml) and dried ($Na_2SO_4$). It was then filtered, and the filtrate concentrated *in vacuo*. The residue was purified by chromatography on silica using 1:1 petrol (bp 40-60 °C):dichloromethane as eluent to give the pure bis-silyl ether (1.92 g, 97.5%) as a colourless oil; $[\alpha]_D$ -1.4 (*c*, 2.2 in $CHCl_3$); (Found: C, 67.45; H, 11.6. $C_{27}H_{52}O_3Si_2$ requires C, 67.5; H 10.8%); $\delta_H$(400 MHz, $CDCl_3$) 7.36-7.34 (5H, m, Ph), 4.53 (1H, d, *J* 10 Hz, PhC*H*HO), 4.51 (1H, d, *J* 10 Hz, PhCH*H*O), 3.75 (1H, m, 3-H), 3.58-3.40 (4H, m, 1-H and 6-H), 1.90-1.82 (2H, m, 5-H), 0.96-0.83 (26H, m, 2-H, 4-H, 2 x C$H_3$ and 2 x Bu$^t$) and 0.08-0.04 (12H, m, 4 x SiC$H_3$); $\delta_C$(100 MHz, $CDCl_3$) 138.8 (s), 128.7 (d), 127.7 (d), 127.55 (d), 78.5 (d), 73.0 (t), 69.3 (t), 65.7 (t), 40.0 (d), 33.7 (d), 31.6 (t), 26.3 (q), 26.1 (q), 19.5 (s), 16.4 (s), 17.6 (q), 14.9 (q), -3.7 (q), -3.9 (s), -5.1 (s) and -5.2 (s); *m/z* 481 ($M^+$+$H^+$) (22%); 503 ($M^+$+$Na^+$) (30%)

***(2R, 3R, 4R)*-6-Benzyloxy-3-(*tert*-butyldimethylsilanyloxy)-2, 4-dimethylhexan-1-ol 166.**[72]




Pyridinium toluene-*p*-sulphonate (55 mg) was added in one portion to a solution of the *bis*-silyl ether **165** (0.53 g, 1.1 mmol) in dry dichloromethane and methanol (14 ml, 1:1) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 8 h. It was then quenched with a saturated aqueous sodium hydrogen carbonate solution (5 ml), concentrated *in vacuo* and then diluted with dichloromethane (50 ml) and water (50 ml). The aqueous layer was extracted with dichloromethane (2 x 25 ml) and the combined organic phases were dried ($Na_2SO_4$) and then concentrated *in vacuo*. The residue was purified by chromatography on silica using dichloromethane as eluent to give the primary alcohol (0.38, 96%) as a colourless oil; $[\alpha]_D$ -1.6 (*c*, 9.0 in $CHCl_3$); (Found: C, 68.6; H, 10.8; $C_{21}H_{38}O_3Si$ requires C, 68.8; H, 10.4%); $\nu_{max}$(film)/cm$^{-1}$ 3423, 2956 and 1461. $\delta_H$(400 MHz, $CDCl_3$) 7.45-7.29 (5H, m, Ph), 4.54 (1H, d, *J* 11 Hz, PhC*H*HO), 4.51 (1H, d, *J* 11 Hz, PhCH*H*O), 3.78-3.47 (5H, m, 1-H, 6-H and 3-H), 2.71 (1H, t, *J* 6.0 Hz, OH), 1.96-1.82 (3H, m, 5-H and 2-H), 1.49-1.38 (1H, m, 4-H), 1.07 (6H, d, *J* 7 Hz, 2 x C*H*$_3$), 0.98 (9H, s, Bu$^t$), 0.11 (3H, s, SiC*H*$_3$) and 0.10 (3H, s, SiC*H*$_3$); $\delta_C$(67.8 MHz, $CDCl_3$) 138.5 (s), 128.3 (d), 127.5 (d), 127.5 (d), 81.4 (d), 72.9 (t), 68.8 (t), 66.2 (t), 36.9 (d), 35.5 (d), 32.38 (t), 26.0 (q), 18.2 (q), 16.5 (q), 16.0 (q), -4.15 (q) and -4.35 (q); *m/z* (FAB) (Found: M$^+$+H 367.2668; $C_{21}H_{38}O_3Si$ requires 367.2675).

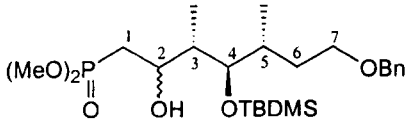
***(2R, 3R, 4R)*-6-Benzyloxy-3-(*tert*-butyldimethylsilanyloxy)-2, 4-dimethylhexanal 167.**[72]




*N*-Methylmorpholine *N*-oxide (0.30 g, 2.5 mmol) was added in one portion to a suspension of the alcohol **166** (0.46 g, 1.24 mmol) and powdered 4 Å molecular sieves (0.7 g) in dry dichloromethane (20 ml) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 0.5 h. Tetrapropylammonium

perruthenate (0.02 g, 0.06 mmol) was added in one portion and the mixture was stirred for 45 min. It was then diluted with ether (100 ml) and filtered through celite. The filtrate was concentrated *in vacuo* to leave a brown residue which was purified by chromatography on silica using dichloromethane as eluent to give the aldehyde (0.43 g, 96%) as a labile colourless oil; $[\alpha]_D$ -23.3 (*c*, 8.8 in $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 2851, 2795, 1754 and 1697; $\delta_H$(400 MHz, $CDCl_3$) 9.81 (1H, d, *J* 2.8 Hz, C*H*O), 7.39-7.29 (5H, m, Ph), 4.55 (1H, d, *J* 12 Hz, PhC*H*HO), 4.49 (1H, d, *J* 12 Hz, PhCH*H*O), 3.81 (1H, app t, *J* 4.2 Hz, 3-H), 3.59-3.47 (2H, m, 6-H), 2.57-2.53 (1H, m, 2-H), 1.9-1.94 (1H, m, 5-H), 1.84-1.79 (1H, m, 5-H), 1.48-1.43 (1H, m, 4-H), 1.10 (3H, d, *J* 7.0 Hz, C$H_3$), 0.94 (3H, d, *J* 7.0 Hz, C$H_3$), 0.06 (3H, s, SiC$H_3$) and 0.04 (3H, s, SiC$H_3$); $\delta_C$(67.8 MHz, $CDCl_3$) 205.2 (d), 138.4 (s), 128.3 (d), 127.5 (d), 127.5 (d), 78.6 (d), 72.9 (t), 68.45 (t), 49.2 (d), 35.4 (d), 32.4 (t), 25.9 (q), 18.15 (s), 15.6 (q) 12.5 (q), -4.15 (q) and -4.53 (q).

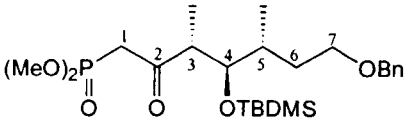
***(3R, 4R, 5R)*-[7-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-2-hydroxy-3,5-dimethylheptyl]-phosphonic acid, dimethyl ester 168.**[72]




A solution of *n*-butyllithium (1.6 M in hexane, 1.6 ml, 2.5 mmol) was added dropwise over 5 min. to a stirred solution of methyl dimethylphosphonate (0.29 ml, 2.55 mmol) in dry THF (22 ml) at –78 °C under a nitrogen atmosphere and the resulting solution was stirred for 0.5 h at –78 °C. A solution of the aldehyde **167** (0.44 g, 1.2 mmol) in dry THF (9 ml) was added dropwise over 20 min. and the mixture was stirred for an additional hour. It was then quenched with saturated aqueous sodium hydrogen carbonate solution (5.6 ml) and allowed to come to room temperature. The mixture was extracted with ethyl acetate (3 x 50 ml) and the combined organic phases were dried ($Na_2SO_4$) and then concentrated *in vacuo* to leave a pale yellow oil. Chromatography on silica using ethyl acetate as eluent gave the hydroxyphosphonate (0.53 g, 90%) as a colourless oil; $[\alpha]_D$ -1.7 (*c*, 4.0 in $CHCl_3$); (Found: C, 58.8; H, 9.7; $C_{24}H_{45}O_6$ SiP requires C, 59.0; H, 9.2%); $\delta_H$(400 MHz, $CDCl_3$) 7.31-7.21 (5H, m, Ph), 4.49-4.43 (2H, m, PhC$H_2$O), 3.72 (3.72) (3H, s, OC$H_3$), 3.71 (3.69) (3H, s, OC$H_3$), 3.70-3.60 (1H, m, 4-H) 3.59-3.40 (2H, m, 7-H), 2.01-1.98 (1H, m, 2-H), 1.96-1.70

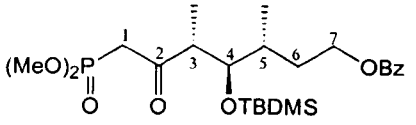
(5H, m, 6-H, 3-H and 1-H), 1.37-1.35 (1H, m, 5-H), 0.95 (3H, d, *J* 6.7 Hz, $CH_3$), 0.92 (3H, d, *J* 7.1 Hz, $CH_3$), 0.88 (9H, s, Bu$^t$), 0.06 (3H, s, $SiCH_3$), 0.045 (3H, s, $SiCH_3$). $\delta_C$ 138.5 (s), 128.2 (d), 127.5 (d), 127.39 (d), 80.7 (79.6) (d), 72.8 (t), 68.75 (68.1) (t), 65.6, 52.4 (52.3) (q), 52.1 (52.1) (q), 42.7 (42.5), 39.7 (39.6), 34.7 (34.5), 32.1, 31.5, 30.1, 26.1, 11.0, 16.2, 18.3, -4.0 and –4.3.

***(3R, 4R, 5R)*-[7-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-3, 5-dimethyl-2-oxoheptyl]-phosphonic acid, dimethyl ester 132.**[72]



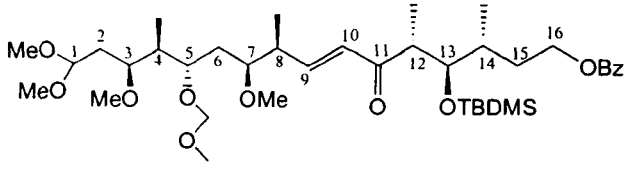

Pyridinium dichromate (2.86 g, 7.60 mmol) was added in one portion to a solution of the alcohol **168** (0.53 g, 1.1 mmol) in dry DMF (7 ml) and the resulting solution was then stirred at room temperature under nitrogen for 24 h. The mixture was diluted with water (35 ml) and then extracted with ether (3 x 50 ml). The combined organic phases were washed with water (3 x 25 ml) and saturated brine (25 ml), then dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using ethyl acetate as eluent to give the keto-phosphonate (0.49 g, 92%) as a colourless oil; $[\alpha]_D$ -79.9 (*c*, 2.5 in $CHCl_3$); (Found: C, 59.6; H, 9.2; $C_{24}H_{43}SiPO_6$ requires C, 59.3, H, 8.9%); $\nu_{max}$(film)/cm$^{-1}$ 1715. $\delta_H$(400 MHz, $CDCl_3$) 7.46-7.28 (5H, m, Ph), 4.44 (1H, d, *J* 12.0 Hz, PhC*H*HO), 4.39 (1H, d, *J* 12.0 Hz, PhCH*H*O), 3.71 (3H, d, *J* 1.0 Hz, OC$H_3$), 3.68 (3H, d, *J* 1.0 Hz, OC$H_3$), 3.46-3.37 (2H, m, 7-H), 3.37 (1H, d, *J* 18.0 Hz, 1-H), 3.34 (1H, d, *J* 18.0 Hz, 1-H), 3.01-2.89 (2H, m, 4-H and 3-H), 1.76-1.75 (2H, m, 6-H), 1.35-1.33 (1H, m, 5-H), 0.97 (3H, d, *J* 6.8 Hz, $CH_3$), 0.87 (3H, d, *J* 6.8 Hz, $CH_3$), 0.78 (9H, s, Bu$^t$), -0.04 (3H, s, SiC$H_3$) and -0.12 (3H, s, SiC$H_3$); $\delta_C$(67.8 MHz, $CDCl_3$) 205.7 (s), 138.4 (s), 128.2 (d), 127.4 (d), 127.4 (d), 79.4 (d), 72.8 (t), 68.4 (t), 52.9 (q), 52.8 (q), 49.9 (d), 43.9 (t), 42.0 (t), 34.6 (t), 31.6 (t), 25.9 (q), 18.1 (s), 15.6 (q), 13.91 (q), -4.51 (q) and -4.62 (q).

***(3R,4R,5R)*-Benzoic acid-4-(*tert*-butyldimethylsilanyloxy)-1-(dimethyloxyphosphoryl)-3,5-dimethyl-2-oxoheptyl ester 169.**




$[\alpha]_D$ –43.6 (*c*, 0.8 in $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1714, 1279 and 1042. $\delta_H$(360 MHz, $CDCl_3$) 8.05-8.02 (2H, m, Ph), 7.58-7.56 (1H, m, Ph), 7.54-7.50 (2H, m, Ph), 4.48-4.29 (2H, m, 7-H), 3.80-3.75 (7H, m, 4-H and 2 x $OCH_3$), 3.36 (1H, dd, *J* 22.4 and 13.9 Hz, 1-H), 3.13-2.96 (2H, m, 1-H and 3-H), 2.04-1.96 (1H, m, 6-H), 1.93-1.83 (1H, m, 6-H), 1.64-1.56 (1H, m, 5-H), 1.07 (3H, d, *J*, 6.9 Hz, $CH_3$), 1.04 (3H, d, *J* 6.9 Hz, $CH_3$), 0.87 (9H, s, $Bu^t$), 0.05 (3H, s, $SiCH_3$), and –0.03 (3H, s, $SiCH_3$); $\delta_C$(90 MHz, $CDCl_3$) 205.4 (s), 166.6 (s), 132.9 (s), 130.2 (s), 129.5 (d), 128.3 (d), 127.5 (d), 79.3 (d), 63.3 (t), 52.9 (q), 52.8 (q), 50.2 (d), 43.8 (t), 42.4 (t), 34.6 (d), 30.6 (t), 26.0 (q), 18.2 (s), 15.8 (q), 14.0 (q), -4.3 (q) and -4.5 (q). *m/z* (EI) (Found: $M^+$+$Na^+$ 523.1812; $C_{24}H_{41}O_7SiPNa$ requires 523.2257).

***(3S,4R,5S,7S,8R,12R,13R,14R)*-Benzoic acid-13-(*tert*-butyldimethylsilanyloxy)-1,1,3,7-tetramethoxy-5-methoxymethoxy-4,8,12,14-tetramethyl-11-oxo-hexadec-9-enyl ester 170.**

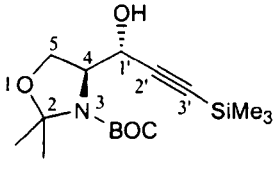



A solution of the ketophosphonate **169** (58.4 mg, 0.12 mmol) in dry THF (2.7 ml) was stirred in the presence of activated barium hydroxide octahydrate (30.2 mg, 0.095 mmol) at room temperature for 30 min, and then a solution of the aldehyde **123** (38.2 mg, 0.11 mmol) in 40:1 THF-water (2.6 ml) was added. The inhomogeneous mixture was stirred vigorously at room temperature for 3.5 h and then diluted with dichloromethane (50 ml). The organic phase was washed with saturated sodium hydrogen carbonate solution (10 ml) saturated brine (10 ml) and then dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 1:1 petrol (bp 40-60 °C):ethyl acetate as eluent to give the *E-alkene* (73 mg, 95%) as a colourless oil; $[\alpha]_D$ –26.4 (*c*, 0.6 in $CHCl_3$); $\nu_{max}$(film)/$cm^{-1}$ 1710. $\delta_H$(360 MHz,

$CDCl_3$) 8.04-7.94 (2H, m, Ph), 7.57-7.51 (1H, m, Ph), 7.45-7.36 (2H, m, Ph), 6.94 (1H, dd, *J* 6.6 and 16.0 Hz, 9-H), 6.18 (1H, dd, *J* 1.3 and 16.0 Hz, 10-H), 4.68 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.60 (1H, d, *J* 4.7 Hz, OCH*H*O), 4.50 (1H, t, *J* 5.6 Hz, 1-H), 4.48-4.38 (1H, m, 16-H), 4.37-4.27 (1H, m, 16-H), 3.98 (1H, dd, *J* 2.3 and 8.0 Hz, 13-H), 3.80-3.70 (1H, m, 5-H), 3.39 (3H, s, OC$H_3$), 3.38 (3H, s, OC$H_3$), 3.33 (3H, s, OC$H_3$), 3.32 (3H, s, OC$H_3$), 3.29 (3H, s, OC$H_3$), 3.19 (1H, q, *J* 6.0 Hz, 3-H), 3.09-3.02 (1H, m, 7-H), 2.76-2.67 (1H, m, 12-H), 2.06-1.93 (1H, m, 4-H), 1.92-1.82 (2H, m, 8-H and 2-H), 1.81-1.73 (3H, m, 2-H and 15-H), 1.69-1.54 (1H, m, 14-H), 1.43-1.35 (2H, m, 6-H), 1.07 (3H, d, *J*, 6.9 Hz, C$H_3$), 1.02 (6H, t, *J* 7.1 Hz, 2 x C$H_3$), 0.88 (3H, d, *J* 7.0 Hz, C$H_3$), 0.83 (9H, s, Bu$^t$), 0.06 (3H, s, SiC$H_3$), and –0.08 (3H, s, SiC$H_3$); $\delta_C$(90 MHz, $CDCl_3$) 202.9 (s), 166.6 (s), 148.7 (d), 132.8 (d), 130.3 (s), 130.0 (d), 129.4 (d), 128.3 (d), 102.0 (d), 96.5 (t), 81.0 (d), 78.8 (d), 77.9 (d), 77.3 (d), 63.5 (t), 57.9 (q), 57.5 (q), 55.7 (q), 53.1 (q), 51.9 (q), 48.2 (d), 41.1 (d), 38.3 (d), 34.9 (t), 33.4 (t), 33.0 (d), 29.5 (t), 26.1 (q), 18.3 (s), 16.8 (q), 14.4 (q), 14.1 (q), 9.2 (q), -4.1 (q) and -4.5 (q). *m/z* (EI) (Found: $M^+$+$Na^+$ 747.4494; $C_{39}H_{68}O_{10}SiNa$ requires 747.4479).

## *3.4 The Bottom-Chain Synthesis*

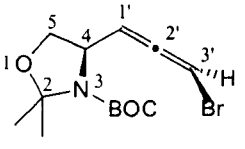
**(*4R,1'R*)-4-(1'-Hydroxytrimethylsilanylprop-2'-ynyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester 179.**[114a]




A solution of *n*-butyllithium (2.5 M in hexane, 10.0 ml, 25.0 mmol) was added dropwise to a stirred solution of (1-ethynyl)trimethylsilane (3.82 ml, 27.0 mmol) in dry THF (130 ml) at –78 °C under a nitrogen atmosphere. After stirring at –78 °C for 1 h, hexamethylphosphoroustriamide (6.18 ml, 34.0 mmol) was added, followed by a solution of **178** (3.92 g, 17.0 mmol) in dry THF (15 ml). After 2 h at –78 °C, saturated aqueous ammonium chloride solution (100 ml) was added and the mixture allowed to warm to room temperature. The mixture was diluted with water (100 ml) and the separated aqueous layer was then extracted with diethyl ether (3 x 100 ml).

The combined organic phases were washed with 0.5 M HCl (100 ml), saturated brine (100 ml), then dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 6:1 Petrol (bp 40-60 °C):ethyl acetate as eluent to give the alcohol (4.8 g, 85%) as a white solid; mp 62-64 °C (diethyl ether); $[\alpha]_D$ –72.7 (*c*, 1.1 in $CHCl_3$); (Found: C, 58.61; H, 8.84; N, 4.19. $C_{16}H_{29}O_4NSi$ requires C, 58.68; H, 8.93; N, 4.28%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3306, 2977, 2900, 1696, 1667, 1393, 1368 and 1092; $\delta_H$(360 MHz, $d_6$-DMSO at 353K) 5.43 (1H, d, *J* 6.4 Hz, OH), 4.54 (1H, dd, *J* 6.4 and 3.7 Hz, 1'-H), 4.04-3.92 (3H, m, 3-H and 4-H), 1.50 (3H, s, $CH_3$), 1.46 (12H, s, $Bu^t$ and $CH_3$), 0.17 (9H, s, $SiMe_3$); $\delta_C$(90 MHz, $d_6$-DMSO at 353K) 151.6 (s), 106.5 (s), 93.6 (s), 88.6 (s), 79.2 (s), 63.5 (t), 61.2 (d), 60.8 (d), 27.9 (q), 25.8 (q), 24.4 (q) and -0.4 (q); *m/z* (EI) (Found: $M^+$+H 328.1926; $C_{16}H_{30}O_4NSi$ requires 328.1944).

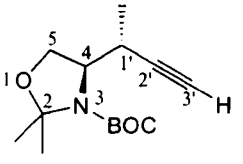
**(*4R,3'R*)-4-(3'-Bromopropa-1',2'-dienyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester 181.**




Solid tetrabutylammonium fluoride (42.3 g, 0.13 mol) was added in one portion to a stirred solution of the alcohol **179** (35.0 g, 0.11 mol) in dry THF (450 ml) under a nitrogen atmosphere at 0 °C and the solution was stirred at room temperature for 6 h. Diethyl ether (300 ml) was added followed by water (200 ml) and the separated organic layer was dried ($Na_2SO_4$) and evaporated *in vacuo*. The crude was dissolved into dry dichloromethane (200 ml) and cooled to –50 °C under a nitrogen atmosphere. Triethylamine (18.7 ml, 0.13 mol) was added dropwise, over 5 min, to this solution followed by methanesulfonyl chloride (10.4 ml, 0.13 ml) and the mixture was allowed to warm to room temperature over 1 h with vigorous stirring. The mixture was quenched with saturated aqueous ammonium chloride solution (200 ml) and the separated organic layer dried ($Na_2SO_4$) and evaporated *in vacuo*. The crude was dissolved into diethyl ether (50 ml) and filtered through silica gel. The diethyl ether was additionally dried ($Na_2SO_4$) and evaporated *in vacuo*. The crude was dissolved into dry THF (250 ml) and a solution of dry LiBr (17.4 g, 0.20 mol) and $CuBr.Me_2S$ (41.1 g, 0.20 mol) in dry THF (150 ml) was added and the mixture heated to 60 °C for

6 h under a nitrogen atmosphere. After cooling, diethyl ether (400 ml) was added followed by saturated aqueous ammonium chloride solution (200 ml). The separated organic layer was dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 1:1 Petrol (bp 40-60 °C):diethyl ether as eluent to give the *allene* (11.56 g, 36% over 3 steps) as brown crystals; mp 38-40 °C (diethyl ether); $[\alpha]_D$ –267.7 (*c*, 1.0 in $CHCl_3$); (Found: C, 49.18; H, 6.30; N, 4.36; Br 25.26. $C_{13}H_{20}O_3NBr$ requires C, 49.07; H, 6.34; N, 4.40; Br 25.11%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 2979, 2935, 2880, 1693, 1367, 1090, 1060 and 864; $\delta_H$(360 MHz, $d_6$-DMSO at 353 K) 6.52 (1H, d, *J* 5.6Hz, 3'-H), 5.66 (1H, app t, *J* 5.3 Hz, 1'-H), 4.52-4.51 (1H, m, 5-H), 4.07 (1H, ddd, *J* 9.1, 6.0 and 1.1 Hz, 4-H) 3.83 (1H, app dt, *J* 9.0, 1.2 and 1.0 Hz, 5-H), 1.47 (3H, s, $CH_3$) and 1.46 (12H, s, $CH_3$ and Bu$^t$); $\delta_C$(90 MHz, *d6*-DMSO at 353 K) 200.5 (s), 150.7 (s), 101.6 (d), 93.2 (s), 79.1 (s), 74.8 (d), 67.1 (t), 54.7 (d), 27.9 (q), 26.4 (q) and 23.7 (q); *m/z* (FAB) (Found: $M^+$+H, 318.068481; $C_{13}H_{21}O_3NBr$ requires 318.07048).

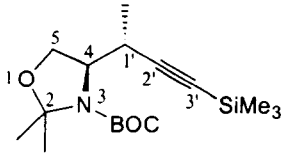
***(4R,1'R)*-4-(1'-Methylprop-2'-ynyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester 182.**




A solution of methylmagnesium bromide (3 M in diethyl ether, 11.7 ml, 35.0 mmol) was added dropwise to a stirred suspension of copper bromide-dimethyl sulfide complex (7.2 g, 35.0 mmol) and dry LiBr (3.0 g, 35.0 mmol) in dry THF (60 ml) at 0 °C under a nitrogen atmosphere. After stirring at 0 °C for 30 min, the solution was added dropwise *via* cannula to a solution of bromoallene **181** (2.2 g, 6.9 mmol) in dry THF (50 ml) at –78 °C under a nitrogen atmosphere. After 1 h at –78 °C saturated ammonium chloride solution (100 ml) was added and the mixture allowed to warm to room temperature. The mixture was diluted with water (100 ml) and the separated aqueous layer was then extracted with diethyl ether (2 x 100 ml). The combined organic phases were dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 1:1 petrol (bp 40-60 °C):diethyl ether as eluent to give the *acetylene* as a colourless oil; $[\alpha]_D$ –247.9 (*c*, 1.1 in $CHCl_3$); (Found:

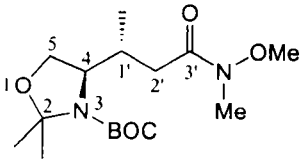
C, 66.60; H, 9.20; N, 5.20. $C_{14}H_{23}O_3N$ requires C, 66.37; H, 9.15; N, 5.53%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3306, 2938, 1681 and 1260; $\delta_H$(360 MHz, $d_6$-DMSO at 353 K) 4.05-3.93 (3H, m, 3-H and 4-H), 3.08-3.03 (1H, m, 3'-H), 2.80 (1H, d, *J* 2.53 Hz, 1'-H), 1.54 (3H, s, C*H*$_3$), 1.46 (9H, s, Bu$^t$), 1.44 (3H, s, C*H*$_3$) and 1.09 (3H, d, *J* 7.13 Hz, 1'-C*H*$_3$); $\delta_C$(90 MHz, $d_6$-DMSO at 353 K) 151.48 (s), 93.60 (s), 85.96 (s), 79.27 (s), 71.92 (d), 63.94 (t), 59.14 (d), 27.02 (d), 27.82 (q), 25.83 (q), 23.06 (q) and 14.30 (q); *m/z* (FAB) (Found: $M^+$+H, 254.1752; $C_{14}H_{24}O_3N$ requires 254.1756).

***(4R,1'R)*-4-(1'-Methyl-3'-trimethylsilanylprop-2'-ynyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester 183.**




A solution of *n*-butyllithium (1.7 M in hexane, 1.7 ml, 2.9 mmol) was added dropwise to a stirred solution of the acetylene **182** in dry THF (25 ml) at –78 °C under a nitrogen atmosphere. After stirring at –78 °C for 30 min and 1 h at room temperature, the mixture was cooled again to –78 °C and chlorotrimethylsilane (0.6 ml, 4.9 mmol) was added dropwise under a nitrogen atmosphere. After stirring for 12 h at room temperature, saturated aqueous ammonium chloride solution was added (10 ml). The separated aqueous layer was extracted with diethyl ether (2 x 30 ml) and the combined organic phases then dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 10:1 petrol (bp 40-60 °C):diethyl ether as eluent to give the *silyl protected acetylene* (0.4 g, 61%) as a colourless oil; $[\alpha]_D$ +0.4 (*c*, 1.1 in $CHCl_3$); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 2162, 1692, 1367 and 872; $\delta_H$(360 MHz, $d_6$-DMSO at 353 K) 4.04-3.92 (3H, m, 4-H and 5-H), 3.09-3.04 (1H, m, 1'-H), 1.54 (3H, s, C*H*$_3$), 1.46 (9H, s, Bu$^t$), 1.44 (3H, s, C*H*$_3$), 1.08 (3H, d, *J* 7.11 Hz, 1'-C*H*$_3$) and 0.15 (9H, s, $SiMe_3$); $\delta_C$(90 MHz, $d_6$-DMSO at 353 K) 151.54 (s), 109.19 (s), 93.66 (s), 90.39 (s), 79.30 (s), 64.08 (t), 59.14 (d), 25.70 (q), 25.78 (q), 27.86 (q), 14.51 (q) and –0.159 (q); *m/z* (EI) (Found: $M^+$+$Na^+$, 389.2233; $C_{19}H_{34}O_3N_2SiNa$ requires 389.2236).

***(4R,1'R)*-4-[2'-(Methoxymethylcarbamoyl)-1'-methylethyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester 185.**

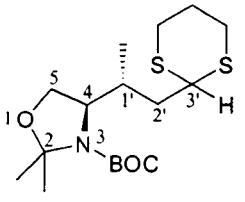



Borane-dimethylsulfide complex (0.47 ml, 4.91 mmol) was added dropwise to cyclohexene (1.0 ml, 9.84 mmol) at 0 °C under a nitrogen atmosphere. After stirring at 0 °C for 1 hr, the white solid was cooled to –35 °C and a solution of **183** (0.80 g, 2.46 mmol) in dry THF (60 ml) was added dropwise under a nitrogen atmosphere. After stirring at 40 °C for 12 h, methanol (6.25 ml), NaOH (6.25 ml of a 3 M solution) and $H_2O_2$ (6.25 ml of a 30% solution) were subsequently added and the mixture stirred for 3 h at 40 °C. The mixture was diluted with water and the aqueous layer washed with diethyl ether (2 x 50 ml). The separated aqueous layer was acidified using 2 M HCl (*ca* 20 ml) and then extracted with ethyl acetate (3 x 50 ml). The combined organic phases were dried ($Na_2SO_4$) and evaporated *in vacuo* to leave the crude *carboxylic acid* which was used without further purification.

Triethylamine (0.25 ml, 1.75 mmol) was added dropwise to a stirred solution of the crude carboxylic acid **184** in dry dichloromethane (15 ml) at –20 °C under a nitrogen atmosphere. The solution was stirred at –20 °C for 15 min and then N,O-dimethylhydroxylamine hydrochloride (0.34 g, 3.50 mmol), triethylamine (0.54 ml, 3.85 mmol) and benzo-1-yloxy tripyrrolidino phosphonium hexafluorophosphate (0.91 g, 1.75 mmol) were added separately, each in one portion. The mixture was stirred at –20 °C for 30 min and then at room temperature for 12 h. The mixture was diluted with dichloromethane (10 ml) and then washed with 2 M HCl (20 ml), saturated aqueous sodium hydrogen carbonate solution (20 ml) and saturated brine (20 ml). The combined organic phases were then dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on diethyl ether as eluent to give the *weinreb amide* as a white waxy solid; $[\alpha]_D$ –2.5 (*c*, 1.3 in $CHCl_3$); (Found: C, 58.42; H, 9.21; N, 8.05. $C_{16}H_{30}O_5N_2$ requires C, 58.16; H, 9.15; N, 8.48%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1682, 1650, 1366 and 1090; $\delta_H$(360 MHz, $CDCl_3$) 3.92-3.67 (3H,

m, 4-H and 5-H), 3.62 (3H, s, N(OC$H_3$)$CH_3$), 3.13 (3H, s, N(OCH$_3$)C$H_3$), 2.50-2.24 (3H, m, 1'-H and 2'-H), 1.60-1.49 (3H, m, C$H_3$) 1.43 (12H, br s, Bu$^t$ and C$H_3$) and 0.91 (3H, d, *J* 6.70 Hz, 1'-C$H_3$); $\delta_C$(90 MHz, $CDCl_3$) 173.3 (s), 152.7 (s), 93.9 (s), 79.8 (s), 64.7 (t), 61.4 (d), 61.0 (q), 36.2 (t), 32.5 (q), 32.2 (d), 28.6 (q), 26.5 (q), 23.0 (q), 15.7 (q); *m/z* (FAB) (Found: $M^+$+H, 331.2263; $C_{16}H_{31}O_5N_2$ requires 331.2233).

***(4R,1'R)*-4-[2'-[1'',3'']Dithan-2''-yl-1'-methylethyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester 199.**



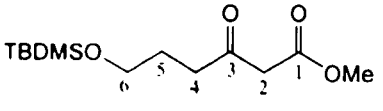

(a) Lithium aluminium hydride (30 mg, 0.76 mmol) was added in one portion to a stirred solution of the weinreb amide **185** (0.2 g, 0.61 mmol) in dry THF (7 ml) at 0 °C under a nitrogen atmosphere. After stirring at 0 °C for 20 min, the mixture was quenched with saturated aqueous sodium hydrogen sulfate solution (2 ml) and the separated aqueous layer was then extracted with diethyl ether (2 x 15 ml). The combined organic phases were washed with 2 M HCl (10 ml), saturated aqueous sodium hydrogen carbonate solution (10 ml), then dried ($Na_2SO_4$) and evaporated *in vacuo* to leave the crude *aldehyde* (0.13 g, 80%) which was used in step (c).

(b) Monochloroborane-dimethylsulfide complex (0.10 ml, 1.0 mmol) was added dropwise to 2,3-dimethyl-2-butene (0.12 ml, 1.0 mmol) at –10 °C under a nitrogen atmosphere. After stirring at –10 °C for 10 min, the mixture was allowed to warm to room temperature. After stirring at room temperature for 3 h, the mixture was cooled to 0 °C and a solution of the acetylene **182** (250 mg, 1.0 mmol) in dry dichloromethane (1 ml) was added dropwise under a nitrogen atmosphere. After stirring at room temperature for 12 h, NaOH (0.4 ml of a 2.5 M solution), pH 7 buffer solution (1 ml) and $H_2O_2$ (0.3 ml of a 30% solution) were subsequently added and the mixture stirred for 2 h at 0 °C. The mixture was diluted with diethyl ether (3 ml) and the aqueous layer saturated with solid potassium carbonate. The separated aqueous layer was then extracted with diethyl ether (2 x 10 ml), and the combined organic

phases were then washed with saturated brine (20 ml), dried ($Na_2SO_4$) and evaporated *in vacuo* to leave the crude aldehyde (157 mg, 58%) which was used immediately in step (c) without further purification.

(c) Zinc iodide (18 mg, 0.06 mmol) was added in one portion to a stirred solution of the crude aldehyde **202** (156 mg, 0.6 mmol) and 1,3-propanedithiobis(trimethylsilane) (0.16 g, 0.63 mmol) in dry diethyl ether (1.5 ml) at 0 °C under a nitrogen atmosphere. After stirring at room temperature for 8 h, the mixture was quenched with water (2 ml) and the separated aqueous phase extracted with diethyl ether (2 x 5 ml). The combined organic phases were washed with saturated brine (10 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 2:1 petrol (bp 40-60 °C):diethyl ether as eluent to give the *dithiane* (26 mg, 12%) as a white solid: mp 94-96 °C (diethyl ether); $[\alpha]_D$ +8.0 (*c*, 0.1 in $CHCl_3$); (Found: C, 56.22; H, 8.56; N, 3.64. $C_{17}H_{31}O_3NS$ requires C, 56.47; H, 8.64; N, 3.87%); $\upsilon_{max}$($CHCl_3$)/cm$^{-1}$ 2934, 1687, 1367 and 1083; $\delta_H$(360 MHz, $CDCl_3$) 4.05 (1H, dd, *J* 4.8 and 9.8 Hz, 3'-H), 3.92-3.70 (3H, m, 4-H and 5-H), 2.95-2.80 (4H, m, 2 x $SCH_2$), 2.76-2.60 (1H, m, 1'-H), 2.39-2.31 (1H, m, 2'-H), 2.13-2.05 (1H, m, 2'-H), 1.92-1.70 (2H, m, $SCH_2CH_2CH_2S$), 1.65-1.55 (3H, m, $CH_3$) 1.48 (12H, br s, Bu$^t$ and $CH_3$) and 0.92 (3H, d, *J* 6.80 Hz, 1'-$CH_3$); $\delta_C$(90 MHz, $CDCl_3$) 152.32 (s), 94.02 (s), 79.79 (s), 64.39 (t), 61.08 (d), 45.18 (d), 39.54 (t), 33.08 (d), 30.51 (t), 30.05 (t), 28.43 (q), 26.10 (t), 23.54 (q), 22.74 (q) and 13.96 (q); *m/z* (FAB) (Found: $M^+$, 361.1769; $C_{17}H_{31}O_3NS_2$ requires 361.1745).

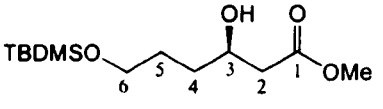
**6-(*tert*-Butyldimethylsilanyloxy)-3-oxohexanoic acid methyl ester 186.**[115]




Methylacetoacetate (2.0 g, 17.2 mmol) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil, 1.6 g, 38.7 mmol) in dry THF (40 ml) at 0 °C under a nitrogen atmosphere. After stirring at 0 °C for 15min, a solution of *n*-butyllithium (1.6 M in hexane, 23.0 ml, 36.8 mmol) was added dropwise, followed by a solution of 2-(*tert*-butyldimethylsilanyloxy)-1-iodoethane **176** (10.5 g, 36.8 mmol)

in dry THF (10 ml) under a nitrogen atmosphere. After stirring for 2 h at 0 °C, the dark orange suspension was poured cautiously onto water (100 ml). The mixture was acidified with 2 M HCl (*ca* 50 ml) and the separated aqueous layer was then extracted with diethyl ether (2 x 200 ml). The combined organic phases were washed with water (4 x 100 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The orange oil was purified by chromatography on silica using 6:1 petrol (bp 40-60 °C):diethyl ether as eluent to give the β-keto ester (3.8 g, 80%) as a pale yellow oil; $\upsilon_{max}(CHCl_3)/cm^{-1}$ 2954, 2930, 2857, 1745, 1716, 1322 and 1098; $\delta_H$(360 MHz, $CDCl_3$) 3.71 (3H, s, $CO_2CH_3$), 3.60 (2H, t, *J* 6.0 Hz, $CH_2O$), 3.46 (2H, s, $COCH_2CO$), 2.61 (2H, t, *J* 7.2 Hz, $CH_2CO_2Me$), 1.79 (2H, quint, *J* 6.2 Hz, $CH_2CH_2CH_2$), 0.86 (9H, s, Bu$^t$) 0.02 (6H, s, $(CH_3)_2Si$); $\delta_C$(90 MHz, $CDCl_3$) 202.57 (s), 167.59 (s), 61.77 (t), 52.21 (q), 48.99 (t), 39.41 (t), 26.49 (t), 25.82 (q), 18.20 (s) and -5.49(t); *m/z* (FAB) (Found: $M^+$-$CH_3$, 259.13645; $C_{12}H_{23}O_4Si$ requires 259.13657).

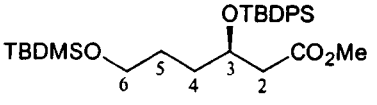
**(3*R*)-6-(*tert*-Butyldimethylsilanyloxy)-3-hydroxyhexanoic acid methyl ester 187.**




Benzeneruthenium (II) chloride dimer (46 mg, 0.1 mmol) was added to a stirred solution of (*R*)-BINAP (130 mg, 0.2 mmol) in dry dimethylformamide (1.5 ml) and the resulting solution was heated at 100 °C for 10 min under an argon atmosphere. The solvent was removed under a high vacuum (using a two-way tap to keep everything under argon). The black solid was heated between 50-60 °C under high vacuum (0.1 mbar) for 2 h (to further dry the catalyst) before cooling to room temperature. The freshly prepared catalyst and ester **186** (2.7 g, 10 mmol) were dissolved in dry methanol (10 ml) and the solution was degassed using freeze/pump/thaw cycles (x 4). The resulting mixture was transferred into a glass vessel of a high pressure hydrogenator under a stream of argon. The apparatus was then purged with hydrogen by pressurising to 10 atmospheres and depressurising to 1 atmosphere (x 5) followed by pressurising to 50 atmospheres and depressurising to 10 atmospheres (x 3). Finally, the hydrogenator was pressurised with hydrogen to 100 atmospheres and the mixture was stirred at this pressure for six days. The hydrogen was released carefully and the mixture was concentrated *in vacuo* to leave a black oil.

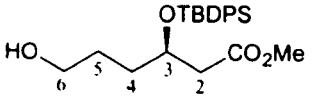
The oil was purified by chromatography on silica using 1:1 petrol (bp 40-60 °C):diethyl ether as eluent to give the *alcohol* (1.44 g, 52%) as a colourless oil; $[\alpha]_D$ –3.5 (*c*, 1.5 in $CHCl_3$); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3373 and 1726; $\delta_H$(360 MHz, $CDCl_3$) 4.09-4.00 (1H, m, 3-H), 3.69 (3H, s, $CO_2CH_3$), 3.82 (2H, t, *J* 5.7 Hz, 6-H), 2.48-2.41 (2H, m, 2-H), 1.65-1.58 (4H, m, 4-H and 5-H), 0.88 (9H, s, $Bu^t$) and 0.04 (6H, s, $Si(CH_3)_2$); $\delta_C$(90 MHz, $CDCl_3$) 173.12 (s), 67.86 (d), 63.12 (t), 51.64 (q), 41.32 (t), 33.60 (t), 28.81 (t), 25.84 (q), 18.23 (s) and –5.44 (q); *m/z* (EI) (Found: $M^+$+$Na^+$, 299.1653; $C_{13}H_{28}O_4SiNa$ requires 299.1655).

**(3*R*)-6-(*tert*-Butyldimethylsilanyloxy)-3-(*tert*-butyldiphenylsilanyloxy)-hexanoic acid methyl ester 189.**



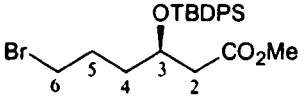

*tert*-Butyldimethylchlorosilane (9.4 g, 34.0 mmol) was added in one portion to a stirred solution of the alcohol **187** (1.9 g, 6.9 mmol) and imidazole (2.8 g, 41.0 mmol) in dry dimethylformamide (50 ml) at 0 °C under a nitrogen atmosphere. After stirring at room temperature for 12 h, the mixture was quenched with water (20 ml) and the separated aqueous phase extracted with diethyl ether (2 x 30 ml). The combined organic phases were washed with water (50 ml) and saturated brine (50 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 6:1 petrol (bp 40-60 °C):diethyl ether as eluent to give the *bis-silyl ether* (3.4 g, 86%) as a colourless oil; $[\alpha]_D$ –21.2 (*c*, 1.5 in $CHCl_3$); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 1732; $\delta_H$(360 MHz, $CDCl_3$) 7.71-7.65 (4H, m, Ph), 7.46-7.35 (6H, m, Ph), 4.23-4.18 (1H, m, 3-H), 3.54 (3H, s, $CO_2CH_3$), 3.46-3.36 (2H, m, 6-H), 2.48 (2H, m, 2-H), 1.53-1.40 (4H, m, 4-H and 5-H), 1.03 (9H, s, $Bu^t$), 0.85 (9H, s, $Bu^t$), -0.01 (6H, s, $Si(CH_3)$) and -0.02 (6H, s, $Si(CH_3)$); $\delta_C$(90 MHz, $CDCl_3$) 171.92 (s), 135.88 (d), 135.84 (d), 133.98 (s), 129.58 (d), 127.49 (d), 127.47 (d), 70.25 (d), 62.93 (t), 51.37 (q), 41.79 (t), 33.43 (t), 28.01 (t), 26.90 (q), 25.90 (q), 19.28 (s), 18.26 (s) and –5.36 (q); *m/z* (EI) (Found: $M^+$+$Na^+$, 537.2780; $C_{29}H_{46}O_4Si_2Na$ requires 537.2832).

***(3R)*-3-(*tert*-Butyldiphenylsilanyloxy)-6-hydroxyhexanoic acid methyl ester 192.**




10-Camphorsulfonic acid (140 mg, 0.58 mmol) was added in one portion to a stirred solution of the silyl protected alcohol **189** (1.7 g, 2.9 mmol) in a 1:1 mixture of dry dichloromethane and methanol (20 ml) at 0 °C under a nitrogen atmosphere. After stirring at room temperature for 2 h, the mixture was diluted with dichloromethane (10 ml) and quenched with saturated aqueous ammonium chloride solution (10 ml). The separated aqueous phase extracted with dichloromethane (2 x 20 ml). The combined organic phases were washed with water (20 ml) dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 3:1 petrol (bp 40-60 °C):diethyl ether as eluent to give the *alcohol* (1.32 g, 98%) as a colourless oil; $[\alpha]_D$ -19.3 (*c*, 1.3 in $CHCl_3$); (Found: C, 68.60; H, 7.93. $C_{23}H_{32}O_4Si$ requires C, 68.96; H, 8.05%); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3623 and 1732; $\delta_H$(360 MHz, $CDCl_3$) 7.73-7.65 (4H, m, Ph), 7.46-7.36 (6H, m, Ph), 4.28-4.22 (1H, m, 3-H), 3.55 (3H, s, $CO_2CH_3$), 3.43-3.40 (2H, m, 6-H), 2.48 (2H, m, 2-H), 1.56-1.44 (4H, m, 4-H and 5-H) and 1.05 (9H, s, Bu$^t$); $\delta_C$(90 MHz, $CDCl_3$) 171.81 (s), 135.84 (d), 135.80 (d), 133.76 (s), 129.67 (d), 129.63 (d), 127.49 (d), 69.89 (d), 62.47 (t), 51.39 (q), 41.58 (t), 33.06 (t), 27.70 (t), 26.85 (q) and 19.22 (s); *m/z* (EI) (Found: $M^+$+$Na^+$, 423.1887; $C_{23}H_{32}O_4SiNa$ requires 423.1968).

***(3R)*-6-Bromo-3-(*tert*-Butyldiphenylsilanyloxy)-hexanoic acid methyl ester 193.**



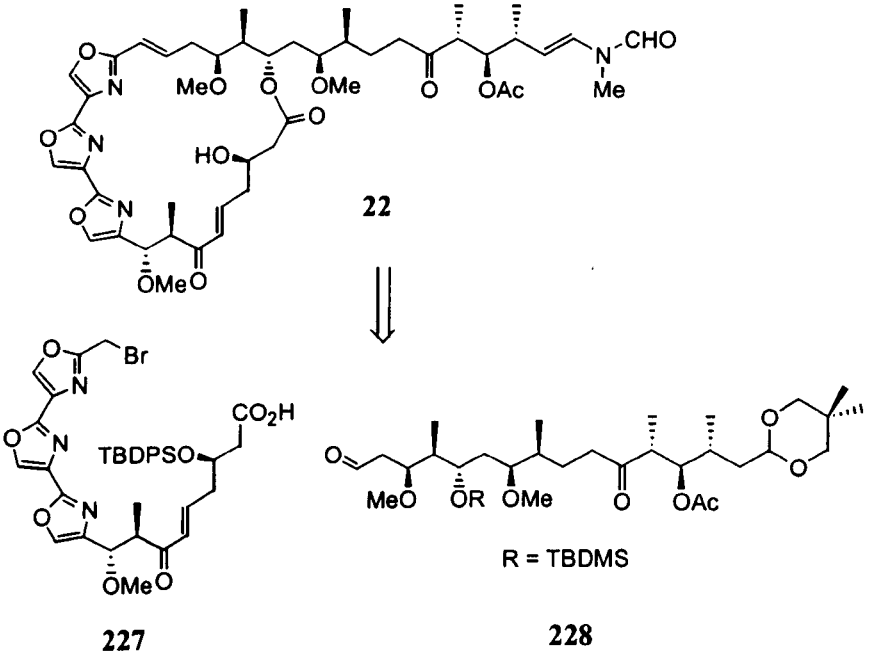

Carbon tetrabromide (0.8 g, 1.5 mmol) was added in several portions to a stirred solution of the alcohol **192** (0.61 g, 1.5 mmol) and triphenylphosphine (0.52 g, 2.0 mmol) in dry dichloromethane (10 ml) at room temperature under a nitrogen atmosphere. After stirring at room temperature for 2 h, the solvent was removed *in vacuo*. Petrol (*ca* 30 ml) was added to the residue with vigorous stirring and the resultant precipitate was filtered off. The filtrate was concentrated *in vacuo* to leave a

residue which was purified by chromatography on silica using 6:1 petrol (bp 40-60 °C):diethyl ether as eluent to give the *bromide* (0.64 g, 92%) as a cream oil; $[\alpha]_D$ – 23.0 (*c*, 2.0 in $CHCl_3$); $\upsilon_{max}(CHCl_3)$ $cm^{-1}$ 1733; $\delta_H$(360 MHz, $CDCl_3$) 7.72-7.65 (4H, m, Ph), 7.48-7.37 (6H, m, Ph), 4.23 (1H, m, 3-H), 3.56 (3H, s, $CO_2CH_3$), 3.19 (2H, m, 6-H), 2.48 (2H, m, 2-H), 1.86-1.78 (2H, m, 4-H), 1.63-1.57 (2H, m, 5-H) and 1.05 (9H, s, $Bu^t$); $\delta_C$ (90 MHz, $CDCl_3$) 171.53 (s), 135.86 (d), 135.83 (d), 133.71 (s), 129.76 (d), 129.69 (d), 127.62 (d), 127.55 (d), 69.38 (d), 51.46 (q), 41.75 (t), 35.47 (t), 33.46 (t), 27.96 (t), 26.91 (q) and 19.27 (s); *m/z* (EI) (Found: $M^+$+$Na^+$, 485.1099; $C_{23}H_{31}O_3SiBrNa$ requires 485.1124).

# APPENDIX

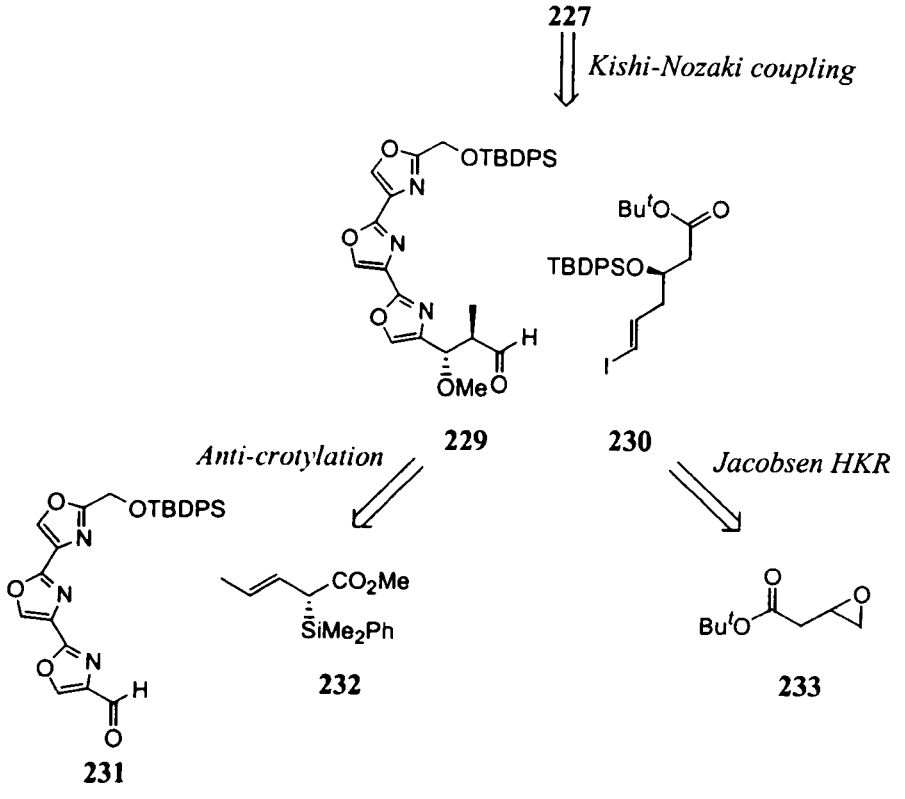
## *4.1 Contemporaneous Studies*

The unique structural features of the ulapualides has drawn the research group of Panek to also explore a synthesis of these natural products. Indeed, soon after their publication in 1999 regarding the stereochemistry of these secondary metabolites, Panek and Liu described a total synthesis of the natural product mycalolide A **22**.[126] A brief overview of the work of Panek's research group is therefore appropriate.




**Scheme 48**

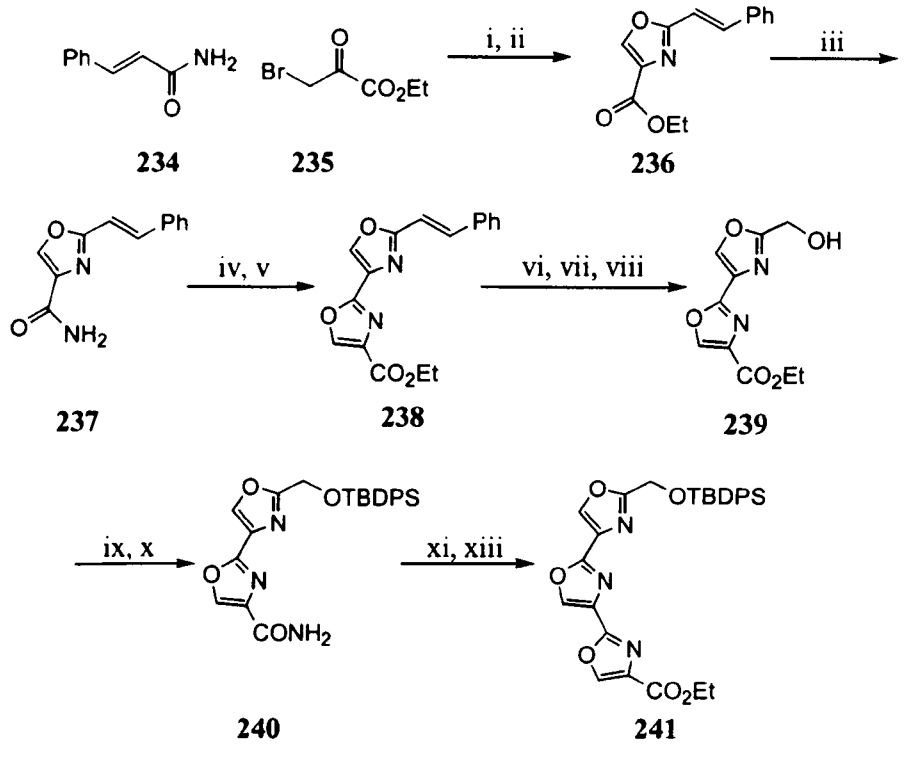
Retrosynthetic analysis of mycalolide A **22** led to fragments **227** and **228** through cleavage of the macrolide linkage and the C19-C20 olefin bond (**Scheme 48**). In the synthetic direction, union of **227** and **228** *via* a Schlosser-Wittig reaction would be followed by macrocyclisation. Further disconnection of **227** (**Scheme 49**) at the C6-C7 σ-bond produced subunits **229** and **230**, which served as the initial targets. It was anticipated that the stereogenic centre of **230** could be accessed by a hydrolytic kinetic resolution (HKR) of terminal epoxide **233**, and the *anti*-stereochemical relationship at C8 and C9 in **229** would be established utilising the research group's chiral silane methodology.




**Scheme 49**

The strategy towards the *tris*-oxazole backbone relied on Hantzsch-type methodology in which a linear sequence generated all three oxazole rings (**Scheme 50**). The synthetic sequence was initiated with the condensation between cinnamamide **234** and ethyl bromopyruvate **235** in a sodium bicarbonate buffered medium to give the corresponding hydroxy oxazoline. This condensation was immediately followed by dehydration affording the functionalised oxazole **236** in 83% yield. Conversion of the ethyl ester in **236** into the corresponding amide using aqueous ammonium hydroxide quantitatively gave the amido-oxazole **237** which underwent a second Hantzsch reaction resulting in the formation of the *bis*-oxazole **238**. The cinnamyl portion of the *bis*-oxazole, **238**, was next elaborated in a three-step process, employing a catalytic dihydroxylation with osmium tetroxide, oxidative cleavage using lead tetraacetate and reduction of the resulting aldehyde with sodium borohydride, to give the primary alcohol **239**. Amidation of the ester group in **239** followed by

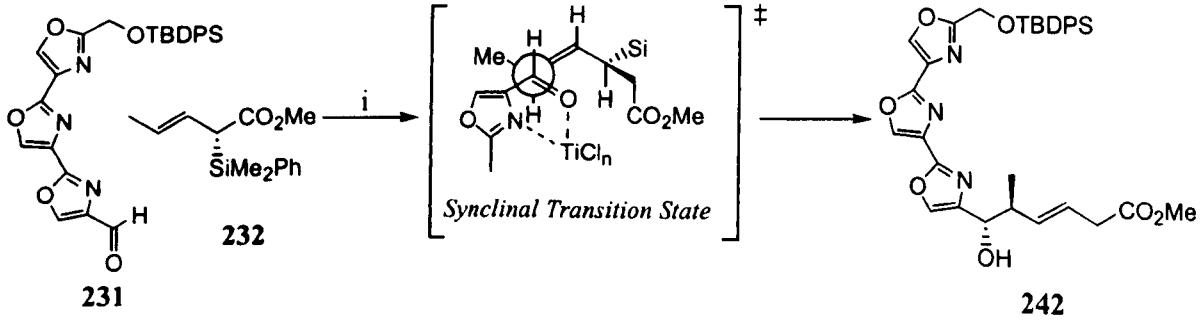
protection of the primary alcohol as its *tert*-butyldiphenylsilyl ether next provided the silylated *bis*-oxazole **240** in 90% yield. This material was subjected to a third, and final, Hantzsch reaction which finally gave the *tris*-oxazole **241**.




*Reagents:* i, $NaHCO_3$, THF; ii, TFAA (83% over 2 steps); iii, $NH_4OH$, (100%); iv, **235**, $NaHCO_3$, THF; v, TFAA (77% over 2 steps); vi, $OsO_4$, TMANO; vii, $Pb(OAc)_4$; viii, $NaBH_4$, (62% over 3 steps); ix, $NH_4OH$; x, TPS-Cl, imidazole, (90% over 2 steps); xi, **235**, $NaHCO_3$, THF; xii, TFAA, (86% over 2 steps).

**Scheme50**

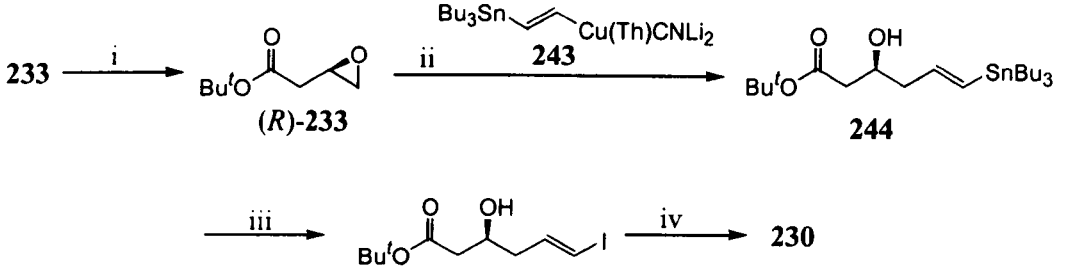
Construction of the subunit **229** and introduction of the C8-C9 stereocentres (**Scheme 51**) now required an *anti*-selective crotylation with the *tris*-oxazole aldehyde. In the presence of the lewis acid $TiCl_4$, the condensation between (*S*)-**232** and **231** provided homoallylic alcohol **242** in 65% yield with high diastereoselectivity (anti/syn > 30:1).




*Reagents:* i, $TiCl_4$, (65%).

**Scheme 51**

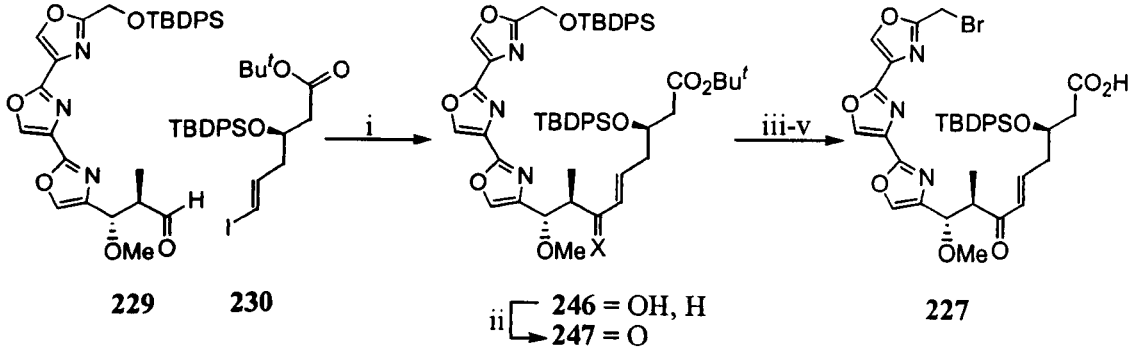
Synthesis of the subunit **230** (**Scheme 52**), was initiated by HKR of the racemic epoxide **233**. Thus, **233** was subjected to the resolution conditions as described by Jacobsen and co-workers, providing (*R*)-**233** of 99% ee in 94% yield. Nucleophilic epoxide ring opening using higher order cuprate **243**, followed by stannane-iodide exchange and protection of the hydroxyl as it TBDPS ether, furnished **230** in four steps (64% overall).




*Reagents:* i, (*R*, *R*)-Salen-Co, AcOH, $H_2O$, (94%); ii, **243**, THF, (76%); iii, TPS-Cl, imidazole, DMF, (92%); iv, $I_2$, THF, (100%).

**Scheme 52**

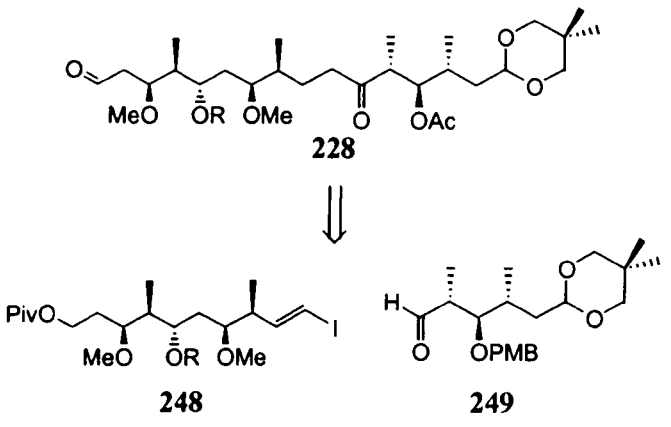
The assembly of **227** was accomplished by a Kishi-Nozaki coupling between **229** and **230** (**Scheme 53**). Treatment of **229** and **230** with $NiCl_2$-$CrCl_2$ in THF/DMF at RT afforded allylic alcohol **246** in 80% yield, as a 1:1 mixture of diastereoisomers. This material was subjected to a Dess-Martin periodinane oxidation to provide enone **247** quantitatively. Selective deprotection of the primary TBDPS ether with TBAF followed by conversion of the resulting alcohol to the benzylic bromide and hydrolysis of the *tert*-butyl ester with TFA, completed the synthesis of fragment **227**.




*Reagents:* i, $NiCl_2/CrCl_2$, THF/DMF, (80%); ii, Dess-Martin Periodinane, (99%); iii, TBAF, (99%); iv, $CBr_4/PPh_3$, (92%); v, TFA, (100%).

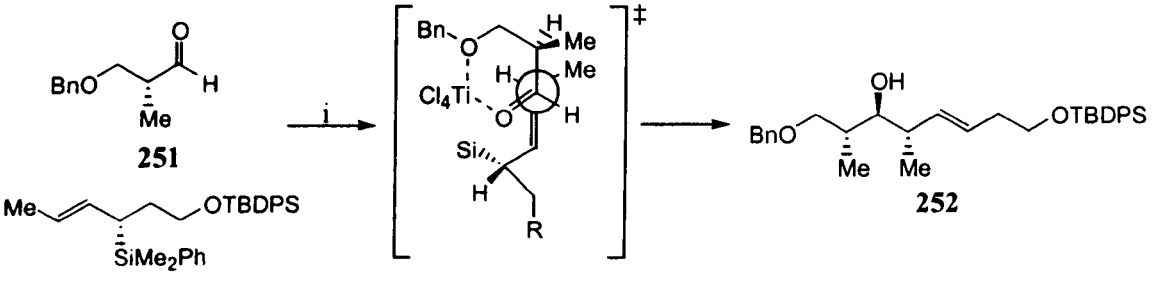
**Scheme 53**

The synthesis of the side-chain **228** relied upon another Nozaki-Kishi coupling between the vinyl iodide **248** and the aldehyde **249** (**Scheme 54**).




**Scheme 54**

Common with the synthesis of fragment **229**, chiral allylsilane methodology was applied in generating the stereogenic centres in both fragments **248** and **249**. A typical example of this chemistry is shown with the Lewis acid-promoted condensation of silane **250** with aldehyde **251** (**Scheme 55**). This installed the three contiguous chiral centres of fragment **249**.

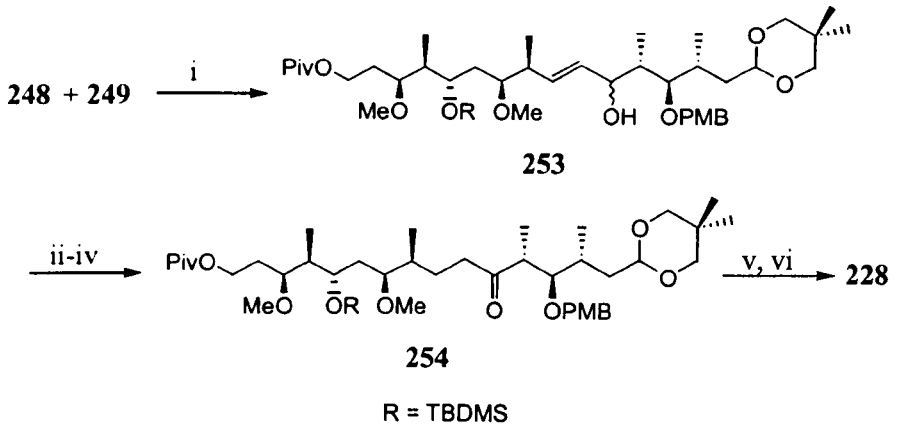



*Reagents;* i, $TiCl_4$, (79%).

**Scheme 55**

When the fragments **248** and **249** were treated with $NiCl_2/CrCl_2$ in THF-DMSO (3:1 v/v), the coupling product **253** was obtained in 88% yield as a 1:1 mixture of alcohol diastereoisomers (**Scheme 56**). This mixture was converted to keto-aldehyde **254** in 90% yield *via* a three step sequence and following PMB

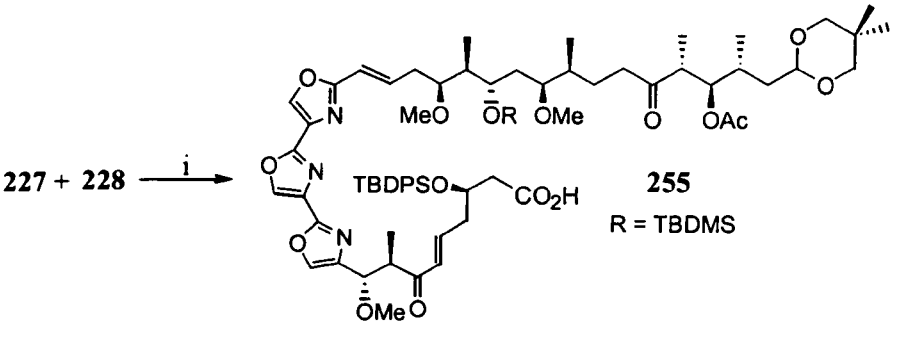
deprotection using DDQ and installation of an acetyl group at the C32 hydroxyl, the synthesis of the side-chain **228** was complete.




*Reagents:* i, $NiCl_2$-$CrCl_2$, THF/DMSO, (88%); ii, $PtO_2$; iii, DIBAL-H; iv, Dess-Martin Periodinane, (90% over 3 steps); v, DDQ, $CH_2Cl_2/H_2O$, (87%); vi, $Ac_2O$/DMAP (98%).

**Scheme 56**

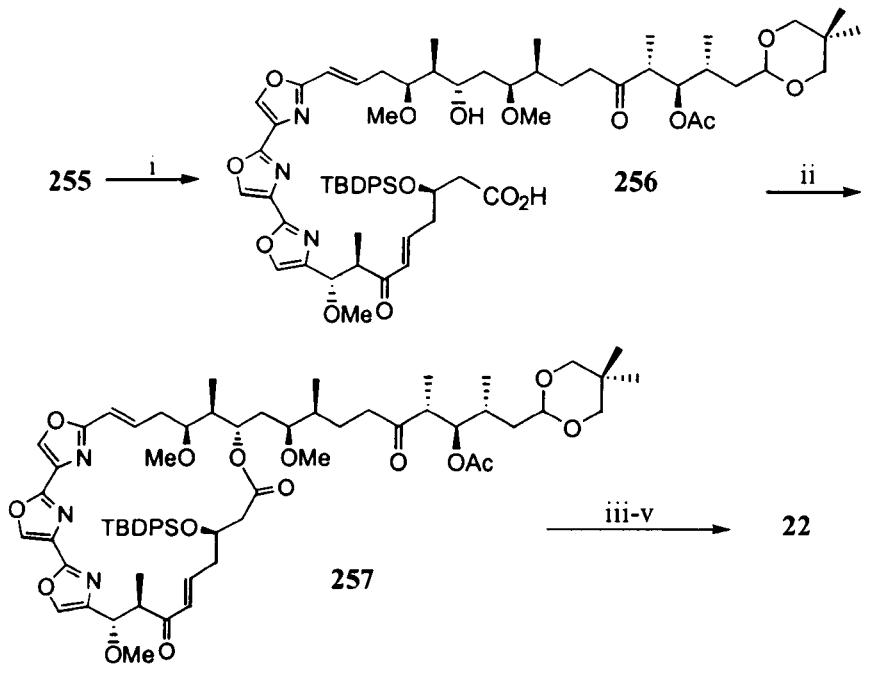
In all their studies, Panek *et al* have affected the key coupling of **227** and **228** *via* a Schlosser-Wittig olefination leading to good yields of the desired *tris*-oxazole (*E*)-olefin. Indeed, application of this to mycalolide A **22**, provided the desired product **255** as a single olefin isomer in 86% yield (**Scheme 57**).




*Reagents:* i, $Et_3P$/DMF, DBU, (86%).

**Scheme 57**

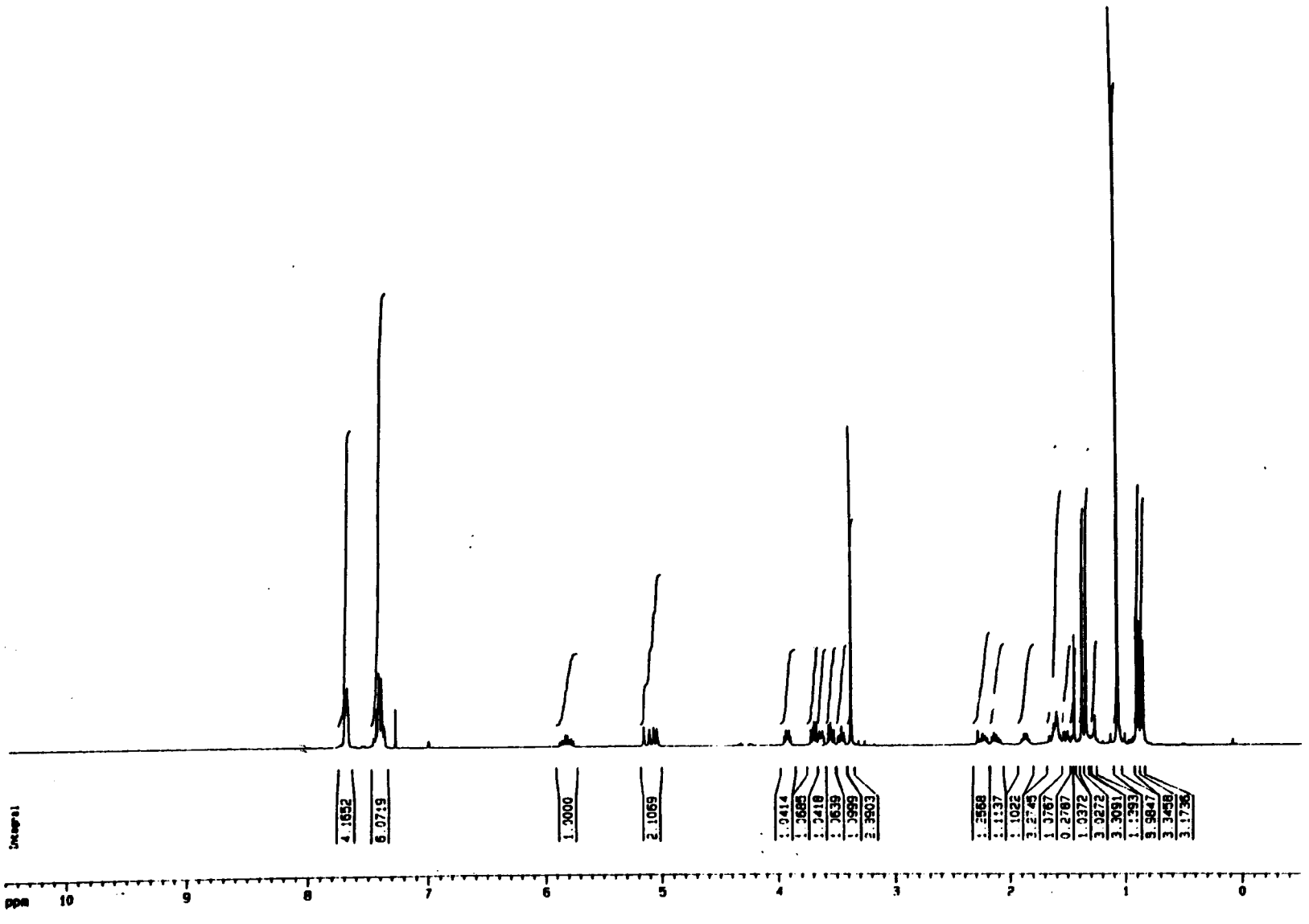
After removal of the TBS group in **255**, the resulting seco acid **256** was subjected to Yamaguchi esterification conditions, providing the macrocycle **257** in 66% yield. Hydrolysis of the acetal in **257**, followed by installation of the terminal *N*-methyl formamide group and deprotection using TBAF/AcOH, finally gave mycalolide A **22** (**Scheme 58**).




*Reagents:* i, PPTS/EtOH, (65%); ii, 2,4,6-$Cl_3$PhCOCl, $^iPr_2$NEt, DMAP, PhH, (66%); iii, PPTS, wet acetone; iv, PPTS,HCONHMe, PhH, (30% over 2steps); v, TBAF/AcOH, THF, (82%).

**Scheme 58**

In summary, the first total synthesis of (-)-mycalolide A was achieved via the application of two complimentary chemical processes, HKR, and chiral silane based methodology. The synthesis also confirmed the relative and absolute stereochemistry of mycalolide A.

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EXPNO                      7
PROCNO                     1

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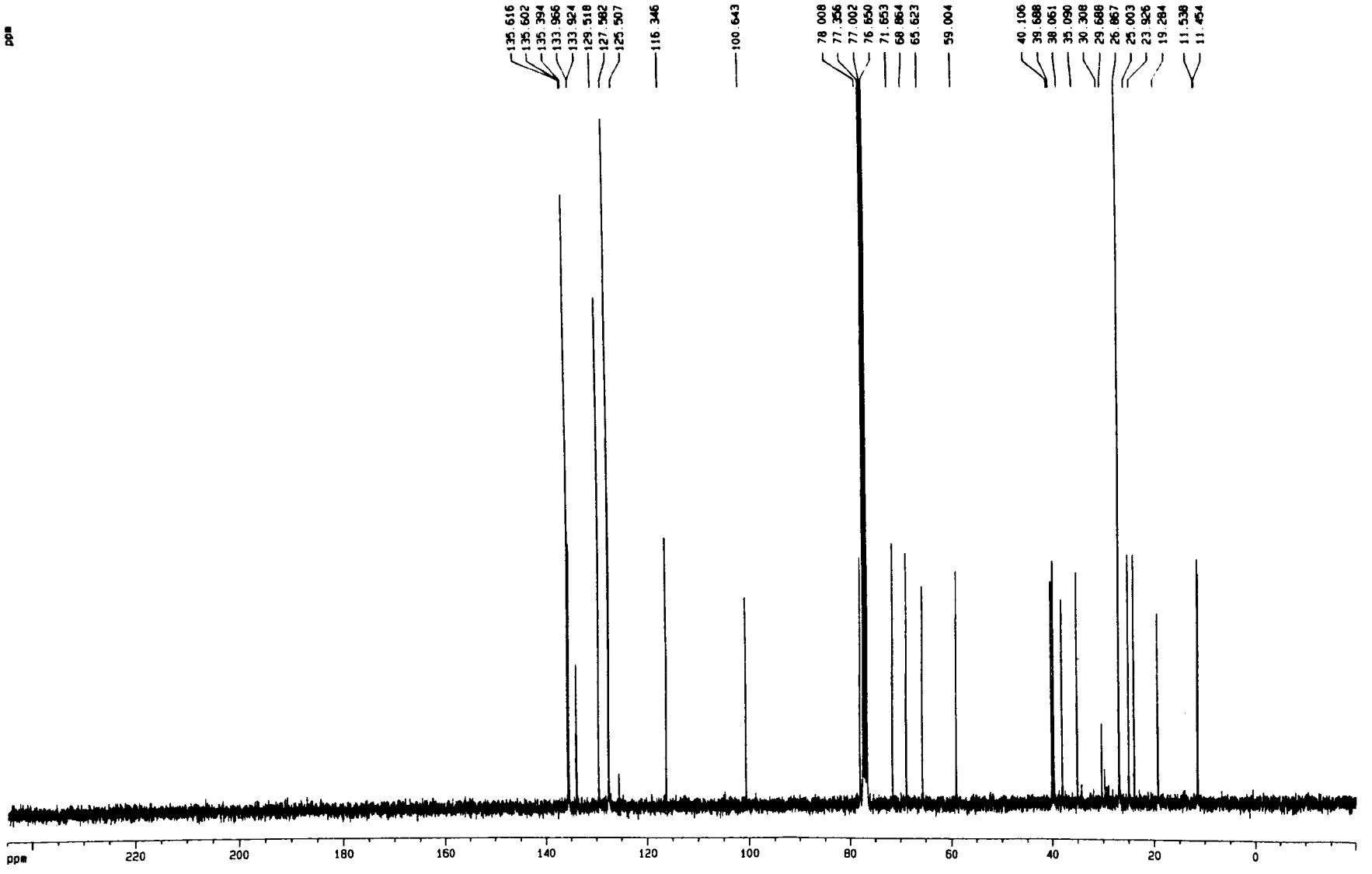
PULPROG               zg30
TD                    32768
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               4310 345 Hz
FIDRES          0 131541 Hz
AQ              3 8011379 sec
RG                   143 7
DW                116 000 usec
DE                  4 50 usec
TE                  300 0 K
D1              1 00000000 sec

------------ CHANNEL f1 -------------
NUC1                  1H
P1                 9 80 usec
PL1                -6 00 dB
SFO1          360 1319807 MHz

F2 - Processing parameters
SI                    16384
SF              360 1300100 MHz
WDW                      EM
SSB                       0
LB                 0 00 Hz
GB                        0
PC                 1 00

1D NMR plot parameters
CX                 30 00 cm
F1P                10 500 ppm
F1                 3781 36 Hz
F2P                -0 500 ppm
F2                 -180 07 Hz
PPMCM              0 36667 ppm/cm
HZCM               132 04767 Hz/cm
```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77.002
76.650
71.653
68.864
65.623
59.004
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35.090
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23.926
19.284
11.538
11.454
ppm
220
200
180
160
140
120
100
80
60
40
20
0

## 4.3 *X-Ray Crystallography Data for Compound* **182**

Table 1. Crystal data and structure refinement for YNTBES at 150(2)K.

| | |
|---|---|
| Empirical formula | C14 H23 N O3 |
| Formula weight | 253.33 |
| Crystal description | colourless block |
| Crystal size | 0.42 x 0.29 x 0.16 mm |
| Crystal system | Monoclinic |
| Space group | P2(1) |
| Unit cell dimensions | a = 5.9395(4) A alpha = 90 deg.<br>b = 13.1720(9) A beta = 101.330(1) deg.<br>c = 10.0751(7) A gamma = 90 deg. |
| Volume | 772.87(9) A^3 |
| Reflections for cell refinement | 4628 |
| Range in theta | 2.57 to 28.16 deg. |
| Z | 2 |
| Density (calculated) | 1.089 Mg/m^3 |
| Absorption coefficient | 0.076 mm^-1 |
| F(000) | 276 |
| Diffractometer type | Bruker SMART CCD area detector |
| Wavelength | 0.71073 A |
| Scan type | omega |
| Reflections collected | 6925 |
| Theta range for data collection | 2.06 to 28.68 deg. |
| Index ranges | -7<=h<=7, -17<=k<=17, -13<=l<=13 |
| Independent reflections | 1908 [R(int) = 0.030] |
| Observed reflections | 1797 [I>2sigma(I)] |
| Decay correction | none |
| Structure solution by | direct methods |
| Hydrogen atom location | difference Fourier |
| Hydrogen atom treatment | refined |
| Data / restraints / parameters | 1908/1/255 (least-squares on F^2) |
| Final R indices [I>2sigma(I)] | R1 = 0.0293, wR2 = 0.0786 |
| Final R indices (all data) | R1 = 0.0315, wR2 = 0.0801 |
| Goodness-of-fit on F^2 | 1.042 |

Final maximum delta/sigma 0.003

Weighting scheme
calc w=1/[\s^2^(Fo^2^)+(0.0626P)^2^+0.0042P] where P=(Fo^2^+2Fc^2^)/3

Largest diff. peak and hole 0.203 and -0.114 e.A^-3

Table 2. Atomic coordinates ( x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for YNTBES. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| N1 | 8992(2) | 3379(1) | 3313(1) | 28(1) |
| C2 | 10018(2) | 2387(1) | 3044(1) | 31(1) |
| O3 | 10679(2) | 1981(1) | 4374(1) | 36(1) |
| C4 | 9014(3) | 2314(1) | 5130(2) | 36(1) |
| C5 | 8449(2) | 3406(1) | 4673(1) | 27(1) |
| C6 | 12185(3) | 2489(2) | 2472(2) | 44(1) |
| C7 | 8262(3) | 1702(1) | 2168(2) | 40(1) |
| O8 | 8252(2) | 3890(1) | 1115(1) | 40(1) |
| C8 | 8048(2) | 4005(1) | 2285(1) | 30(1) |
| O9 | 6913(2) | 4770(1) | 2747(1) | 34(1) |
| C9 | 5653(3) | 5531(1) | 1807(2) | 34(1) |
| C10 | 7302(3) | 6127(2) | 1125(2) | 45(1) |
| C11 | 4635(3) | 6205(1) | 2764(2) | 47(1) |
| C12 | 3770(3) | 5018(2) | 787(2) | 46(1) |
| C1' | 9819(2) | 4223(1) | 5601(1) | 30(1) |
| C2' | 9227(3) | 4134(1) | 6953(1) | 36(1) |
| C3' | 8785(3) | 4027(2) | 8040(2) | 47(1) |
| C4' | 12430(3) | 4156(2) | 5698(2) | 42(1) |

Table 3. Bond lengths [A], angles [deg] for YNTBES.

| | |
|---|---|
| N1-C2 | 1.4887(18) |
| N1-C5 | 1.4683(15) |
| N1-C8 | 1.3564(17) |
| C2-O3 | 1.4240(18) |
| C2-C6 | 1.516(2) |
| C2-C7 | 1.522(2) |
| O3-C4 | 1.4303(18) |
| C4-C5 | 1.528(2) |
| C4-H4A | 0.98(2) |
| C4-H4B | 0.95(2) |
| C5-C1' | 1.5482(19) |
| C5-H5 | 0.956(19) |
| C6-H6A | 1.02(2) |
| C6-H6B | 0.98(3) |
| C6-H6C | 0.96(2) |
| C7-H7A | 0.93(3) |
| C7-H7B | 0.97(3) |
| C7-H7C | 0.93(3) |
| O8-C8 | 1.2177(16) |
| C8-O9 | 1.3453(17) |
| O9-C9 | 1.4782(17) |
| C9-C10 | 1.520(2) |
| C9-C11 | 1.520(2) |
| C9-C12 | 1.521(2) |
| C10-H10A | 0.95(3) |
| C10-H10B | 0.94(3) |
| C10-H10C | 0.95(3) |
| C11-H11A | 0.99(3) |
| C11-H11B | 0.99(3) |
| C11-H11C | 1.06(3) |
| C12-H12A | 0.91(3) |
| C12-H12B | 0.96(3) |
| C12-H12C | 0.97(3) |
| C1'-C2' | 1.4768(18) |
| C1'-C4' | 1.538(2) |
| C1'-H1'A | 0.99(2) |
| C2'-C3' | 1.184(2) |
| C3'-H3' | 0.962(19) |
| C4'-H4'A | 0.98(3) |
| C4'-H4'B | 0.97(3) |
| C4'-H4'C | 0.98(2) |
| | |
| C8-N1-C5 | 124.34(11) |
| C8-N1-C2 | 121.15(11) |
| C5-N1-C2 | 111.35(11) |
| O3-C2-N1 | 101.83(11) |
| O3-C2-C6 | 107.07(13) |
| N1-C2-C6 | 113.56(13) |
| O3-C2-C7 | 110.75(13) |
| N1-C2-C7 | 111.53(12) |
| C6-C2-C7 | 111.58(14) |
| C2-O3-C4 | 107.12(11) |

| | |
|---|---|
| C4-C5-C1' | 114.47(12) |
| N1-C5-H5 | 110.7(11) |
| C4-C5-H5 | 108.9(11) |
| C1'-C5-H5 | 108.7(11) |
| C2-C6-H6A | 111.8(12) |
| C2-C6-H6B | 106.5(15) |
| H6A-C6-H6B | 113(2) |
| C2-C6-H6C | 110.8(13) |
| H6A-C6-H6C | 107.8(18) |
| H6B-C6-H6C | 107(2) |
| C2-C7-H7A | 112.4(16) |
| C2-C7-H7B | 109.6(15) |
| H7A-C7-H7B | 112(2) |
| C2-C7-H7C | 109.9(17) |
| H7A-C7-H7C | 105(3) |
| H7B-C7-H7C | 107(2) |
| O8-C8-O9 | 125.44(12) |
| O8-C8-N1 | 123.99(13) |
| O9-C8-N1 | 110.56(10) |
| C8-O9-C9 | 120.77(10) |
| O9-C9-C10 | 110.49(13) |
| O9-C9-C11 | 101.75(12) |
| C10-C9-C11 | 110.94(15) |
| O9-C9-C12 | 110.06(13) |
| C10-C9-C12 | 112.22(14) |
| C11-C9-C12 | 110.90(15) |
| C9-C10-H10A | 111.9(15) |
| C9-C10-H10B | 113.1(18) |
| H10A-C10-H10B | 104(2) |
| C9-C10-H10C | 110.9(15) |
| H10A-C10-H10C | 106(2) |
| H10B-C10-H10C | 111(2) |
| C9-C11-H11A | 110.5(14) |
| C9-C11-H11B | 109.7(14) |
| H11A-C11-H11B | 111(2) |
| C9-C11-H11C | 108.5(13) |
| H11A-C11-H11C | 108.2(19) |
| H11B-C11-H11C | 108.5(19) |
| C9-C12-H12A | 109.8(15) |
| C9-C12-H12B | 112.4(14) |
| H12A-C12-H12B | 112(2) |
| C9-C12-H12C | 106.2(16) |
| H12A-C12-H12C | 107(2) |
| H12B-C12-H12C | 109(2) |
| C2'-C1'-C4' | 110.93(12) |
| C2'-C1'-C5 | 108.05(12) |
| C4'-C1'-C5 | 113.71(12) |
| C2'-C1'-H1'A | 107.4(10) |
| C4'-C1'-H1'A | 109.0(10) |
| C5-C1'-H1'A | 107.5(11) |
| C3'-C2'-C1' | 177.60(18) |
| C2'-C3'-H3' | 178.2(12) |
| C1'-C4'-H4'A | 111.2(13) |
| C1'-C4'-H4'B | 109.9(15) |
| H4'A-C4'-H4'B | 109(2) |
| C1'-C4'-H4'C | 110.3(12) |
| H4'A-C4'-H4'C | 104.8(18) |
| H4'B-C4'-H4'C | 111(2) |

Table 4. Anisotropic displacement parameters (Å^2 x 10^3) for YNTBES. The anisotropic displacement factor exponent takes the form: -2 pi^2 [ h^2 a*^2 U11 + ... + 2 h k a* b* U12 ]

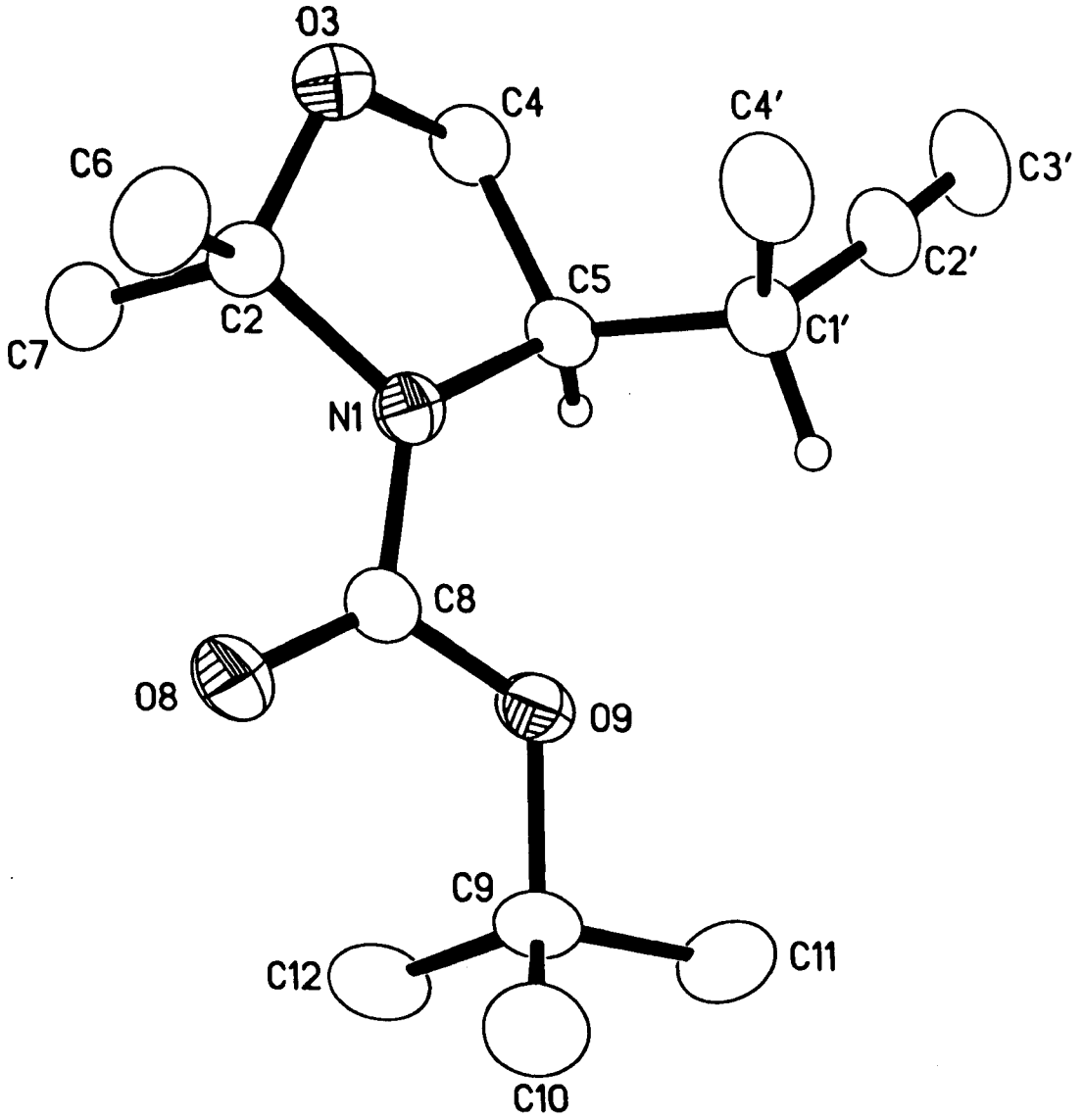
| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| N1 | 34(1) | 29(1) | 21(1) | 1(1) | 8(1) | 6(1) |
| C2 | 34(1) | 30(1) | 28(1) | 0(1) | 6(1) | 7(1) |
| O3 | 44(1) | 32(1) | 31(1) | 2(1) | 3(1) | 9(1) |
| C4 | 49(1) | 31(1) | 27(1) | 5(1) | 8(1) | 0(1) |
| C5 | 30(1) | 32(1) | 20(1) | 2(1) | 6(1) | 2(1) |
| C6 | 39(1) | 47(1) | 49(1) | -5(1) | 17(1) | 9(1) |
| C7 | 45(1) | 36(1) | 38(1) | -8(1) | 2(1) | 5(1) |
| O8 | 57(1) | 44(1) | 22(1) | 3(1) | 12(1) | 10(1) |
| C8 | 34(1) | 32(1) | 23(1) | 1(1) | 6(1) | 5(1) |
| O9 | 43(1) | 37(1) | 23(1) | 4(1) | 6(1) | 14(1) |
| C9 | 37(1) | 32(1) | 31(1) | 8(1) | 3(1) | 6(1) |
| C10 | 49(1) | 41(1) | 44(1) | 7(1) | 10(1) | -3(1) |
| C11 | 50(1) | 38(1) | 53(1) | 5(1) | 13(1) | 16(1) |
| C12 | 45(1) | 45(1) | 43(1) | 11(1) | -6(1) | 0(1) |
| C1' | 37(1) | 31(1) | 23(1) | 0(1) | 8(1) | -1(1) |
| C2' | 43(1) | 37(1) | 26(1) | -3(1) | 6(1) | -3(1) |
| C3' | 62(1) | 52(1) | 28(1) | -5(1) | 14(1) | -10(1) |
| C4' | 36(1) | 48(1) | 40(1) | -7(1) | 8(1) | -7(1) |

Table 5. Hydrogen coordinates ( x 10^4) and isotropic displacement parameters (A^2 x 10^3) for YNTBES.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H4A | 7630(40) | 1891(19) | 4910(20) | 46(5) |
| H4B | 9660(40) | 2280(20) | 6070(20) | 54(6) |
| H5 | 6850(30) | 3522(14) | 4622(18) | 28(4) |
| H6A | 13330(40) | 2981(18) | 3030(20) | 48(6) |
| H6B | 12810(40) | 1800(20) | 2440(30) | 60(7) |
| H6C | 11840(40) | 2734(18) | 1560(20) | 44(5) |
| H7A | 7020(50) | 1550(20) | 2570(30) | 63(7) |
| H7B | 7780(40) | 2000(20) | 1280(30) | 52(6) |
| H7C | 8920(50) | 1080(20) | 2040(30) | 70(7) |
| H10A | 8560(40) | 6380(20) | 1760(30) | 57(7) |
| H10B | 7980(50) | 5730(20) | 540(30) | 64(7) |
| H10C | 6570(40) | 6710(20) | 670(20) | 57(6) |
| H11A | 3800(40) | 6780(20) | 2270(30) | 59(6) |
| H11B | 5860(40) | 6440(20) | 3510(20) | 55(6) |
| H11C | 3440(40) | 5770(20) | 3180(20) | 50(6) |
| H12A | 2830(40) | 4660(20) | 1230(20) | 58(6) |
| H12B | 4370(40) | 4600(20) | 160(20) | 55(6) |
| H12C | 2860(40) | 5560(20) | 300(30) | 64(7) |
| H1'A | 9270(30) | 4896(15) | 5232(18) | 30(4) |
| H3' | 8470(30) | 3944(17) | 8936(19) | 40(5) |
| H4'A | 13010(40) | 3490(20) | 6010(20) | 50(6) |
| H4'B | 13200(40) | 4670(20) | 6320(30) | 61(7) |
| H4'C | 12810(30) | 4227(16) | 4800(20) | 40(5) |

Table 6. Torsion angles [deg] for YNTBES.

| | |
|---|---|
| C(8)-N(1)-C(2)-O(3) | -177.50(12) |
| C(5)-N(1)-C(2)-O(3) | -16.77(15) |
| C(8)-N(1)-C(2)-C(6) | 67.76(18) |
| C(5)-N(1)-C(2)-C(6) | -131.51(14) |
| C(8)-N(1)-C(2)-C(7) | -59.35(17) |
| C(5)-N(1)-C(2)-C(7) | 101.38(15) |
| N(1)-C(2)-O(3)-C(4) | 33.89(14) |
| C(6)-C(2)-O(3)-C(4) | 153.34(13) |
| C(7)-C(2)-O(3)-C(4) | -84.81(14) |
| C(2)-O(3)-C(4)-C(5) | -38.92(15) |
| C(8)-N(1)-C(5)-C(4) | 154.59(14) |
| C(2)-N(1)-C(5)-C(4) | -5.40(15) |
| C(8)-N(1)-C(5)-C(1') | -82.82(16) |
| C(2)-N(1)-C(5)-C(1') | 117.19(13) |
| O(3)-C(4)-C(5)-N(1) | 25.87(14) |
| O(3)-C(4)-C(5)-C(1') | -95.88(13) |
| C(5)-N(1)-C(8)-O(8) | -169.24(15) |
| C(2)-N(1)-C(8)-O(8) | -11.1(2) |
| C(5)-N(1)-C(8)-O(9) | 11.94(19) |
| C(2)-N(1)-C(8)-O(9) | 170.08(12) |
| O(8)-C(8)-O(9)-C(9) | 3.7(2) |
| N(1)-C(8)-O(9)-C(9) | -177.50(13) |
| C(8)-O(9)-C(9)-C(10) | -63.40(18) |
| C(8)-O(9)-C(9)-C(11) | 178.73(13) |
| C(8)-O(9)-C(9)-C(12) | 61.09(18) |
| N(1)-C(5)-C(1')-C(2') | -176.67(12) |
| C(4)-C(5)-C(1')-C(2') | -62.19(15) |
| N(1)-C(5)-C(1')-C(4') | -53.06(16) |
| C(4)-C(5)-C(1')-C(4') | 61.41(15) |
| C(4')-C(1')-C(2')-C(3') | -63(4) |
| C(5)-C(1')-C(2')-C(3') | 62(4) |


O3
C4
C4'
C3'
C6
C2'
C5
C2
C1'
C7
N1
C8
O8
O9
C9
C12
C11
C10

## 4.4 *Reprints of Synlett and Perkin I Publications*

**SYNLETT** Accounts and Rapid Communications in Synthetic Organic Chemistry **REPRINT**

*With Compliments of the Author*

Thieme

# A Macrolactamisation-Oxazoline Ring Forming Approach towards the *tris*-Oxazole Macrolide Core in the Ulapualides

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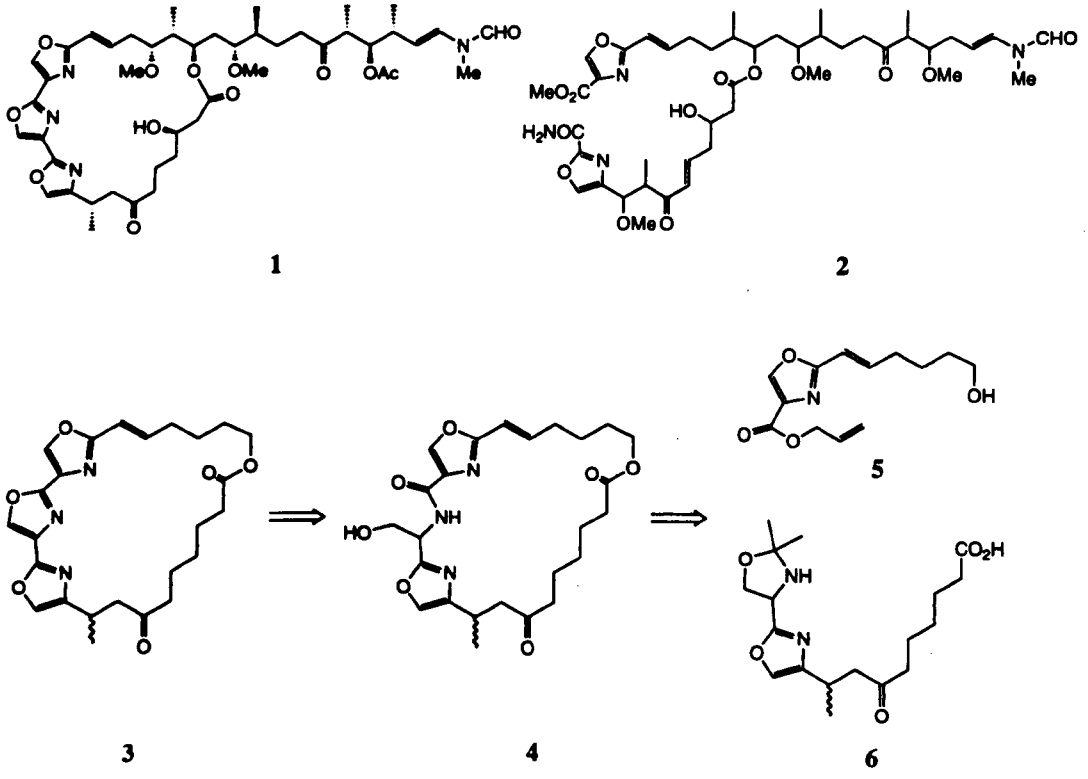
*Received 21 January 1999*

**Abstract:** A new design for the synthesis of the 25-membered *tris*-oxazole macrolide core, **3**, in the "ulapualide family" of marine natural products e.g. **1** isolated from nudibranchs and sponges, based on a macrolactamisation strategy, leading to **4**, followed by oxazoline and oxazole ring formation using the substituted monooxazoles **5** and **6** as key precursors, is described.

**Key words:** marine natural products, macrolactamisation, ring-formation, oxazolines

The "ulapualides" are a family of novel *tris*-oxazole containing bioactive macrolides found in nudibranchs and marine sponges; they include the halichondramides,[1] kabiramides,[2] mycalolides,[3] halishigamides[4] and the parent member ulapualide A **1**.[5] Interestingly, several members of the halishigamides isolated from the Okinawan marine sponge *Halichondria* have one or more incomplete oxazole rings in their structures, e.g. halishigamide D **2**, which could have implications regarding the biosynthetic origins of this intriguing family of marine metabolites.[6] During 1998 we described a total synthesis of the ulapualide A structure **1**,[7] with the relative stereochemistry shown, using a strategy based on elaboration of an appropriately functionalised linear *tris*-oxazole unit followed by addition of the lipid-like side chain, macrocyclisation, and functional group manipulation.[8] In a second generation synthetic approach to the ulapualides we now describe a synthesis of the 25-membered *tris*-oxazole macrolide core **3** in these structures based on a macrolactamisation strategy, leading to **4**, followed by oxazoline and oxazole ring formation, using the substituted monooxazoles **5** and **6** as key precursors (Scheme 1).[9]

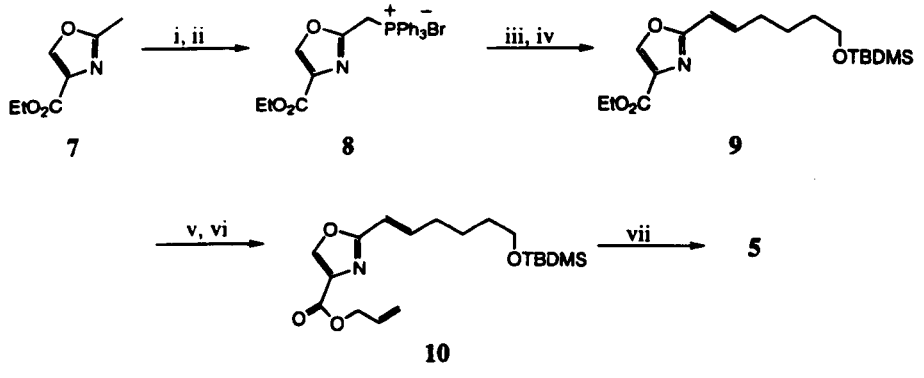
Thus, the known 2-methyloxazole **7**[10] was first elaborated to the corresponding phosphonium salt **8**, following bro-



**Scheme 1**

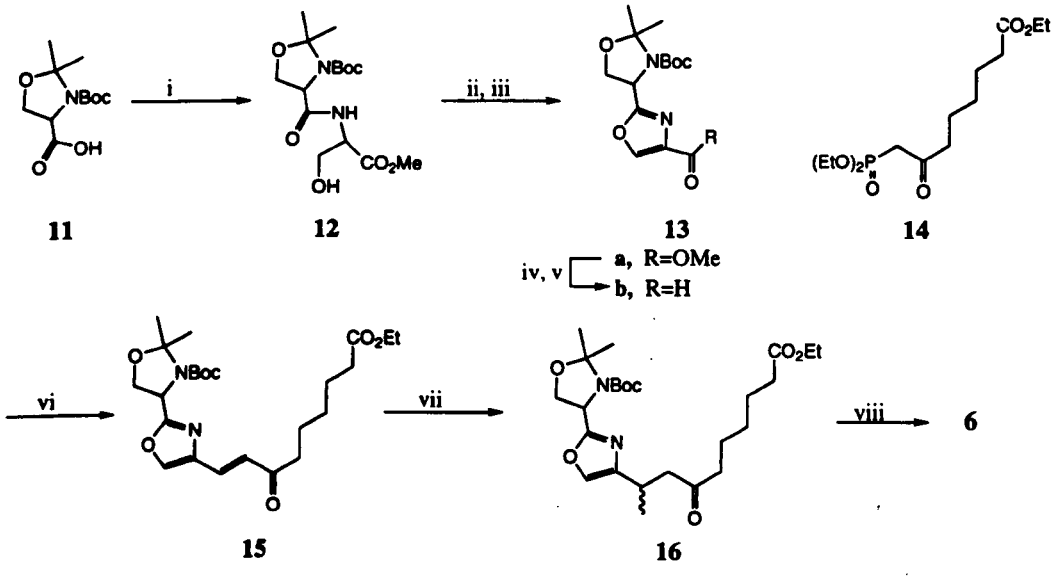
mination (NBS, AIBN, $CCl_4$, Δ; 41%) and treatment with triphenylphosphine ($Et_2O$, 25 °C, 24h; 82%). A Wittig reaction between **8** and 5-*tert*-butyldimethylsilylpentanal[11] (BuLi, $Et_2O$, -78 °C) next gave the *E*-alkene (**9**; ~45%),[12] which was then saponified (LiOH, THF-$H_2O$; 99%) and converted into the corresponding allyl ester **10** (allyl bromide, $NaHCO_3$, $H_2O$; 51%) (Scheme 2). Deprotection of the silyl ether group in **10** (AcOH, THF, $H_2O$, 25 °C; 91%) finally gave the primary alcohol **5** in readiness for coupling to the carboxylic acid **6**.

The carboxylic acid **6** was prepared starting from Garner's acid **11**[13] following conversion into the amide **12** using serine methyl ester HCl($Et_3N$, $CH_2Cl_2$, 0 °C then DCC; 74%), cyclodehydration to the corresponding oxazoline using Burgess' reagent[14] in THF (75%) and oxazole ring formation ($BrCCl_3$, DBU, 0-25°; 75%)[15] (Scheme 3). After conversion of the oxazole ester **13a** into the corresponding aldehyde **13b** (DIBAL-H, then $PySO_3$ in DMSO, $Et_3N$; 60% overall), a Wadsworth-Emmons olefination reaction with the keto-phosphonate **14**[16] [$Ba(OH)_2$.



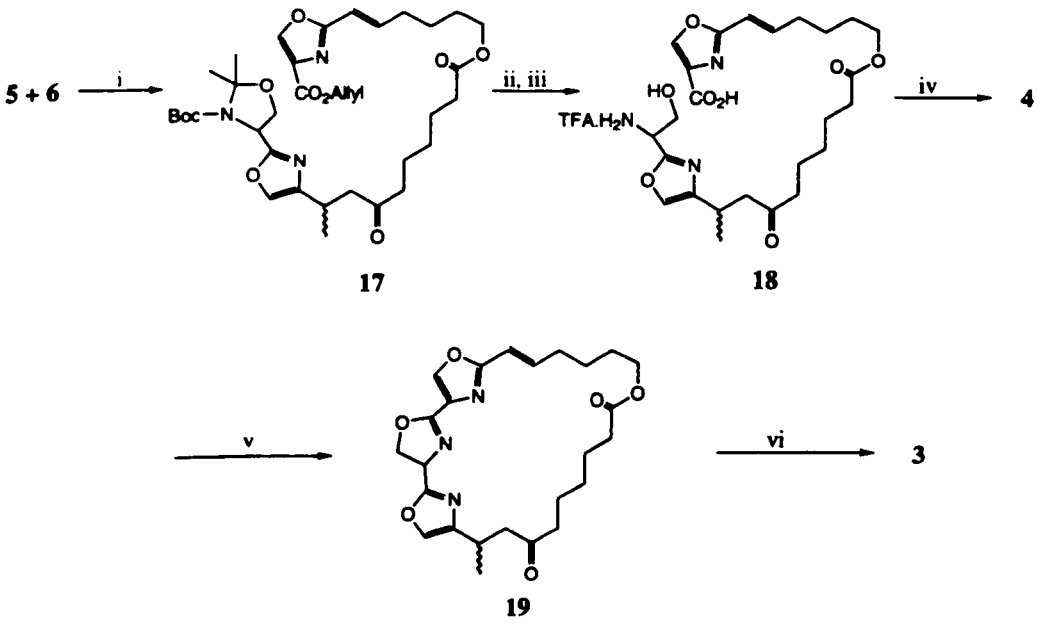

*Reagents and Conditions:* i, NBS/AIBN, $CCl_4$, Δ, 41%; ii, $PPh_3$, $Et_2O$, 25°C, 24h, 82%; iii, BuLi, $Et_2O$, -78°C; iv, 5-*tert*-butyldimethylsilylpentanal, 45%; v, LiOH, THF-$H_2O$, 99%; vi, Allyl bromide, $NaHCO_3$, $H_2O$, 51%; vii, AcOH, THF, $H_2O$, 25°C, 91%.

**Scheme 2**




*Reagents and Conditions:* i, Serine OMe.HCl, $CH_2Cl_2$, $Et_3N$, 0°C then DCC, 74%; ii, Burgess' reagent, THF, 75%; iii, $BrCCl_3$, DBU, 0-25°C, 75%; iv, DIBAL-H, $CH_2Cl_2$, 0°C; v, $PySO_3$ in DMSO, $Et_3N$, 60%; vi, $Ba(OH)_2.8H_2O$, **14**, THF, 71%; vii, $Me_2CuLi$, $Et_2O$, -5°C, 55%; viii, LiOH, THF, $H_2O$, 98%.

**Scheme 3**




*Reagents and Conditions:* i, EDC.HCl, DMAP, $CH_2Cl_2$, 0°C, 73%; ii, $(Ph_3P)_4Pd$-pyrrolidine, $CH_2Cl_2$, 70%; iii, 50% TFA solution in $CH_2Cl_2$; iv, DPPA, DIPEA, DMF, 20%; v, Burgess' reagent, THF, 69%; vi, $NiO_2$, $C_6H_6$, Δ, 46%.

**Scheme 4**

$8H_2O$, THF, 25 °C, 3h; 71%] next gave rise to the *E*-enone **15**. Conjugate addition of lithium dimethylcuprate ($Et_2O$, -5 °C, 55%) followed by saponification of the resulting keto-ester **16** (LiOH, THF, $H_2O$; 98%) then produced the carboxylic acid **6** as a viscous oil.

Esterification of the carboxylic acid **6** with the alcohol **5** in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide HCl containing 4-(dimethylamino)pyridine at 0 °C for 2h gave **17** in an excellent 73% yield, which was then deprotected sequentially using $(Ph_3P)_4Pd$-pyrrolidine (70%, carboxylic acid), followed by 50% TFA, leading to the TFA salt **18**.

Macrolactamisation of **18** was accomplished under high dilution using diphenylphosphoryl azide in the presence of diisopropylethylamine giving rise to the macrolactam-macrolide **4** as a mixture of diastereoisomers in an unoptimised 20% yield. The synthesis of the *tris*-oxazole macrolide **3** was then completed following cyclodehydration of **4** to the corresponding oxazole-oxazoline-oxazole **19** in the presence of Burgess' reagent, and oxidation of **19** using nickel peroxide[17] ($C_6H_6$, Δ; 46%). This convergent approach to the synthesis of the *tris*-oxazole macrolide core **3** in the ulapualides has many attractions over the linear approach described earlier in our total synthesis of the ulapualide A structure **1**. The development of this design towards a second generation synthesis of members of the ulapualides (halichondramides, kabiramides, mycalolides and halishigamides) is in progress in our laboratories.

## Acknowledgement

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(12) All new compounds showed satisfactory spectroscopic data together with mass spectrometry data. Typical procedures: i, *conversion of 18 into 4*; Diisopropylethylamine (37mg, 0.29mmol) was added in one portion to a stirred solution of **18** (51mg, 0.08mmol) in dry DMF (16ml) at 0 °C under a nitrogen atmosphere. The solution was stirred at 0 °C for 15min and then diphenylphosphoryl azide (34mg, 0.12mmol) was added and stirring was continued for 3min. The mixture was left at room temperature for 5 days, then diluted with ethyl acetate (20ml) and poured into ice-cold water. The separated aqueous layer was extracted with ethyl acetate (3 x 20ml) and the combined organic extracts were then washed with water (6 x 30ml) and brine (30ml), then dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by chromatography on silica using ethyl acetate as eluent to give **4** (14mg, 36%) as an oil. $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3399, 1715, 1688, 1596; $\delta_H$ (500MHz, $CDCl_3$, major rotamer) 8.20 (1H, s, 29-H), 8.02 (1H, d, *J* 7.4, N*H*), 7.45 (1H, s, 21-H), 6.93 (1H, dt, *J* 16.2 and 6.8, 2-H), 6.37 (1H, m, 1-H), 5.46-5.42 (1H, m, 22-H), 4.27-4.10 (4H, m, 23-H and 6-H), 3.42-3.37 (1H, m, 15-H), 3.03 (1H, dd, *J* 16.7 and 11.0, 14-H), 2.62-2.56 (1H, m, 14-H), 2.54-2.35 (6H, m, 12-H, 8-H and 3-H), 1.84-1.61 (4H, m, 4-H and 5-H), 1.50-1.22 (6H, m, 9-H, 10-H and 11-H) and 0.97-0.91 (3H, m, 16-H); $\delta_C$ (90MHz, $CDCl_3$) 209.5(s), 173.6(s), 161.0(s), 160.8(s), 145.3(s), 144.4(s), 141.7(d), 140.5(d), 136.1(s), 134.2(d), 132.1(d), 128.6(d), 116.0(d), 64.6(t), 63.8(t), 48.3(t), 43.0(t), 34.4(t), 31.9(t), 29.7(t), 28.6(t), 27.8(t), 24.7(t), 23.4(t), 19.4(q); m/z (EI) (Found $M^+$-$H_2O$, 469.2223, 100%. $C_{25}H_{31}O_6N_3$ requires M, 469.2167). ii, *conversion of 4 into 19*; Freshly prepared $NiO_2$ (150mg) was added in three portions to a solution of **4** (50mg, 0.11mmol) in refluxing dry benzene (3ml) at one hour intervals. The mixture was heated under reflux for two more hours, and then filtered through celite. The filtrate was concentrated in vacuo to leave a viscous mass. Purification by chromatography on silica using ethyl acetate as eluent gave **19** (14mg, 46%) as a white solid. m.p. 140-142 °C; $\lambda_{max}$(EtOH)/nm 263 (1888); $\upsilon_{max}(CHCl_3)/cm^{-1}$ 3019, 2929, 1715 and 1215; $\delta_H$ (500MHz, $CDCl_3$) 8.07 and 8.06 (2 x 1H, s, 31-H and 26-H), 7.40 (1H, s, 21-H), 7.19 (1H, dt, *J* 15.9 and 7.1, 2-H), 6.31 (1H, dt, *J* 15.9 and 1.5, 1-H), 4.08 (2H, 2 x dt, *J* 22.0 and 10.8, 6-H), 3.43-3.39 (1H, m, 15-H), 3.29 (1H, dd, *J* 17.2 and 6.0, 14-H), 2.63-2.57 (1H, m, 14-H), 2.49-2.35 (6H, m, 12-H, 8-H and 3-H), 1.80-1.60 (4H, m, 4-H and 5-H), 1.46-1.16 (6H, m, 9-H, 10-H and 11-H) and 0.93-0.78 (3H, m, 16-H); $\delta_C$ (125MHz, $CDCl_3$) 210.25(s), 173.86(s), 162.77(s), 156.57(s), 154.26(s), 146.65(s), 143.23(d), 137.27(d), 137.02(d), 133.40(d), 131.76(s), 130.39(s), 115.21(d), 65.86(t), 48.08(t), 43.64(t), 34.58(t), 31.13(t), 29.70(t), 29.15(t), 27.44(d), 26.88(t), 25.06(t), 24.45(t) and 18.96(q); m/z (FAB) (Found $M^+$+1, 468.2154, 7%. $C_{25}H_{30}O_6N_3$ requires M, 468.2134).
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# Towards a total synthesis of ulapualide A. Concise synthetic routes to the *tris*-oxazole ring system and *tris*-oxazole macrolide core in ulapualides, kabiramides, halichondramides, mycalolides and halishigamides

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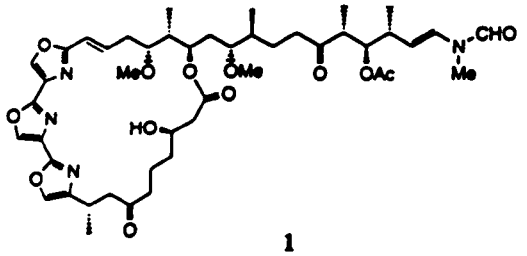
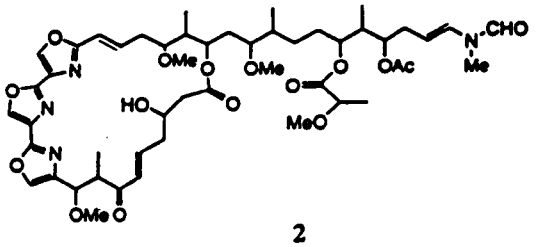
A range of methods for the synthesis of mono-, bis- and tris-2,4-disubstituted oxazoles were evaluated, which led ultimately to a concise synthesis of the three contiguous oxazole ring system **26** in the ulapualide family of 25-membered macrolides, *e.g.* **1**, found in marine organisms. The tris-oxazole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

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

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




**1**

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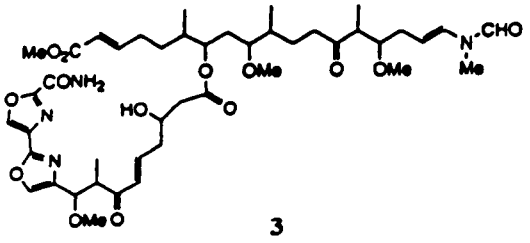
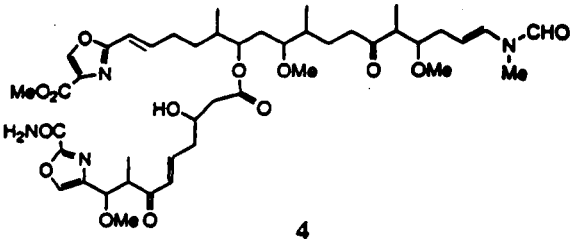



**3**




**4**

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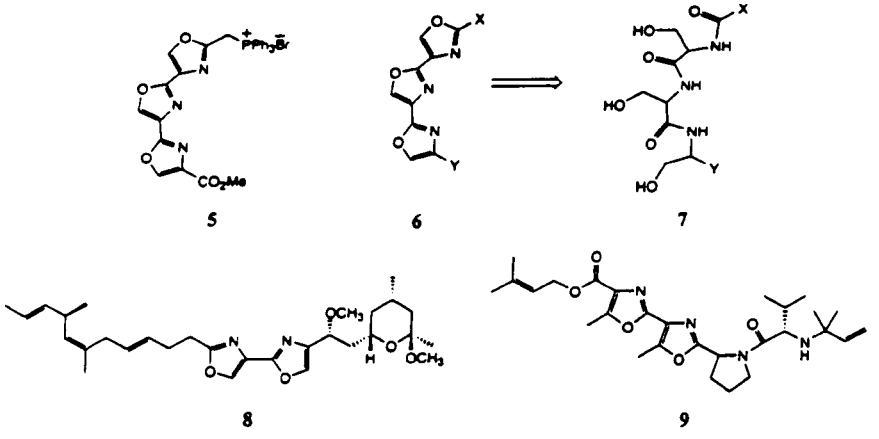
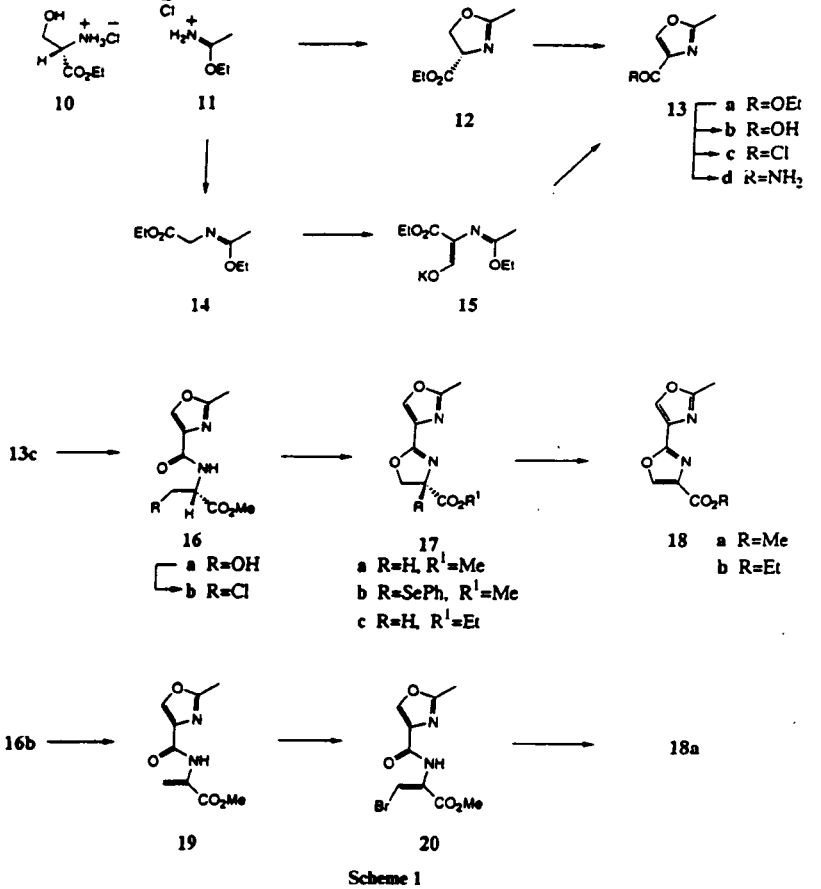


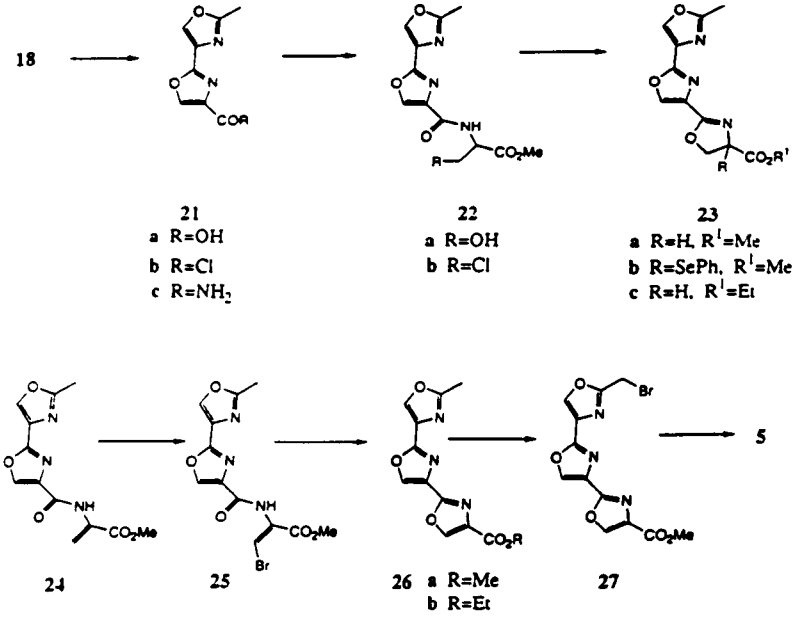
synthesis of ulapualide A, with the relative stereochemistry shown in structure **1**.[10]

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

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



**Scheme 1**



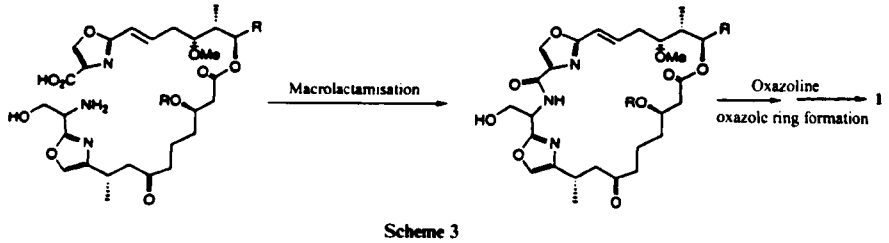

Scheme 2

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

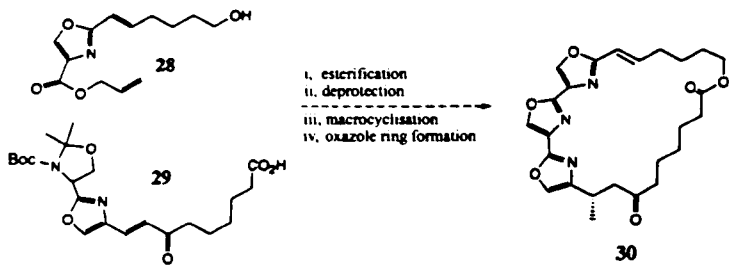
Repetition of the sequences detailed above *i.e.* acid chloride **21b** formation (from **18**), reaction with serine ester hydrochloride (to **22a**), chlorination (to **22b**), cyclisation to **23a** and oxidation (direct or *via* **23b**), or alternatively conversion of **22b** into **24** followed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

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

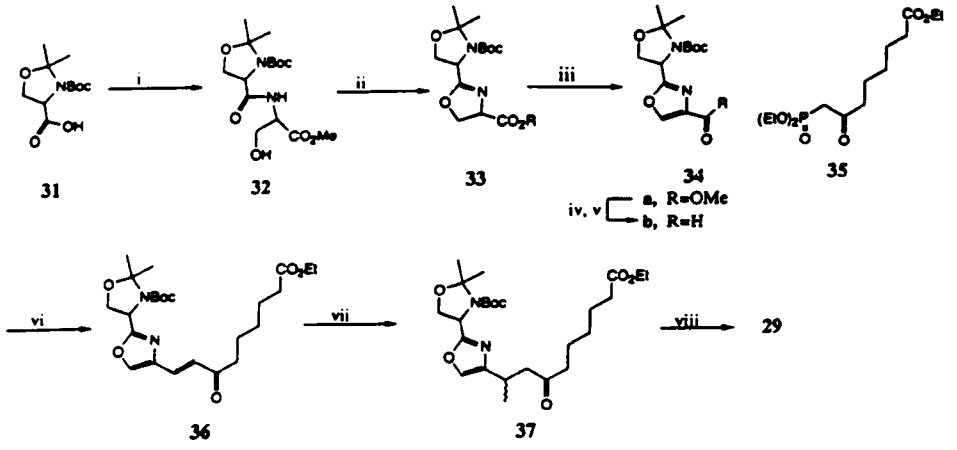
Preliminary details of the aforementioned synthesis of the tris-oxazole unit **26** in the ulapualides were described in 1990.[9] Other approaches to the same unit have been described more recently, which highlight the scope for the Hantzsch oxazole synthesis[19] and for [3 + 2] cycloaddition reactions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




Scheme 3




Scheme 4



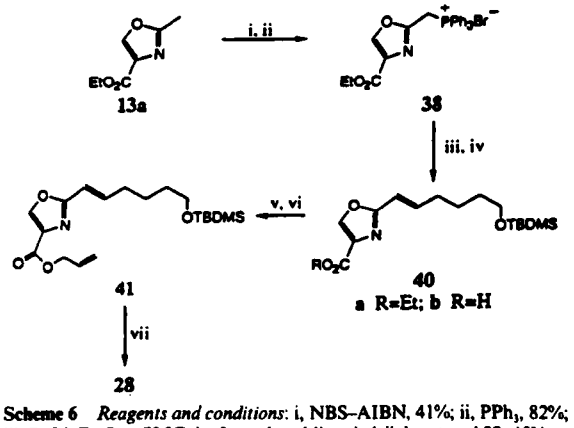

**Scheme 5** *Reagents and conditions*: i, SerineOMe·HCl, $Et_3N$, 0 °C then DCC, 74%; ii, Burgess' reagent, THF, 75%, iii, $BrCCl_3$, DBU, 0–25 °C, 75%; iv, DIBAL-H; v, $PySO_3$ in DMSO, $Et_3N$, 60%; vi, $Ba(OH)_2·8H_2O$, **14**, THF, 71%; vii, $Me_2CuLi$, $Et_2O$, −5 °C, 55%; viii, LiOH, THF, $H_2O$,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

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

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

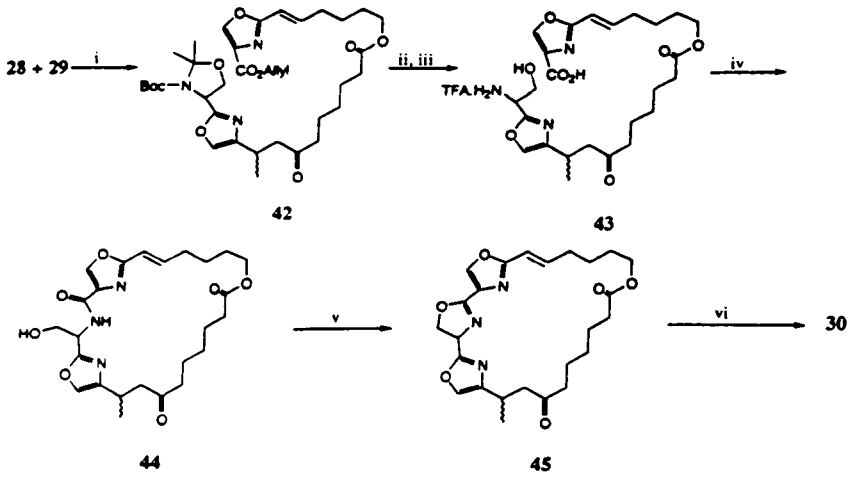
Esterification of the mono-oxazole carboxylic acid **29** with the mono-oxazole alcohol **28** in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride containing 4-(dimethylamino)pyridine next led to the ester **42** in a satisfactory 73% yield (Scheme 7), which was then deprotected sequentially using palladium(0) pyrrolidine (70% to the carboxylic acid) followed by 50% trifluoroacetic acid, leading to the trifluoroacetate salt of the amino acid **43**.

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




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

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




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

## Experimental

### General details

[All mps were determined on a Kofler hot stage apparatus and are uncorrected. Optical rotations were measured on a JASCO DIPA-370 polarimeter; $[\alpha]_D$ values are recorded in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. Ultraviolet spectra were recorded on a Philips PU 8720 spectrophotometer as dilute solutions in spectroscopic grade ethanol; $\varepsilon$ values are recorded in units of dm$^3$ mol$^{-1}$ cm$^{-1}$. Infrared spectra were obtained using a Perkin-Elmer 1600 series FT-IR instrument as either potassium bromide discs, liquid films or as dilute solutions in spectroscopic grade chloroform. Proton NMR spectra were recorded on either a Bruker WM250 (250 MHz), a Bruker AM400 (400 MHz), a Bruker DRX (500 MHz) or a JEOL EX-270 (270 MHz) spectrometer as dilute solutions in deuterochloroform or $d_6$-dimethyl sulfoxide. Chemical shifts are recorded relative to a solvent standard and the multiplicity of a signal is designated by one of the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet. All coupling constants, $J$, are reported in Hertz. Carbon-13 NMR spectra were recorded on either a Bruker AM400 (100.6 MHz) or JEOL EX-270 (67.8 MHz) instrument. The spectra were recorded as dilute solutions in deuterochloroform or $d_6$-dimethyl sulfoxide with chemical shifts reported relative to a solvent standard on a broad band decoupled mode and the multiplicities obtained using a DEPT sequence. The following symbolisms are used for the multiplicities in carbon-13 spectra: q = primary methyl; t = secondary methylene; d = tertiary methine; s = quarternary. Where required, assignment for $^1$H and $^{13}$C NMR spectra were confirmed by two-dimensional homonuclear ($^1$H) and/or heteronuclear ($^1$H/$^{13}$C) correlation spectroscopy. Matrix dimensions for two dimensional spectra were either 1024 points × 256 columns (homonuclear $^1$H) or 2048 points × 128 columns (heteronuclear $^1$H/$^{13}$C), and were recorded on a JEOL EX-270 instrument. Mass spectra were recorded on a AE1 MS-902, MM-70E or VG Autospec spectrometer using electron ionisation (EI) or fast atom bombardment (FAB) techniques. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser. Flash chromatography was performed on Merck silica gel 60 as the stationary phase and the solvents employed were either of analytical grade or were distilled before use. All reactions were monitored by TLC using Merck silica gel 60 $F_{254}$ precoated plastic backed plates, which were visualised with ultraviolet light and then with either vanillin solution, basic potassium permanganate solution, or phosphomolybdic acid solution.

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

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

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

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

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

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

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

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

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

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

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

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

Thionyl chloride (25 ml) was added to the oxazole acid **13b** (5.3 g, 42 mmol) with stirring, and the mixture was then heated under reflux for 4 h. The excess thionyl chloride was removed *in vacuo*, and the residue was then azeotroped with toluene to give the corresponding acid chloride **13c** as a cream solid, which was used immediately without further purification. A solution of the acid chloride in dry dichloromethane (25 ml) was added dropwise over 15 min to a stirred solution of DL-serine methyl ester hydrochloride (7.15 g, 46 mmol) and triethylamine (12.8 ml, 92 mmol) in dry dichloromethane (50 ml) under a nitrogen atmosphere at 0 °C. The mixture was stirred for 20 h at ambient temperature and then evaporated *in vacuo*. The residue was diluted with saturated sodium hydrogen carbonate solution (30 ml), then extracted with ethyl acetate (4 × 30 ml) and the combined organic phases were washed with saturated brine (30 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *oxazole serine derivative* (7.3 g, 77%) as a light brown solid. A small portion was purified by chromatography on silica to give the product as a white crystalline solid, mp 97–98 °C (ethyl acetate–petrol) (Found: C, 47.2; H, 5.4; N, 12.1. $C_9H_{12}N_2O_5$ requires C, 47.4; H, 5.3; N, 12.3%); $\lambda_{max}$(EtOH)/nm 222 (3330) and 233sh (3290); $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 3405 br, 1746, 1674, 1601, 1509 and 1106; $\delta_H$(250 MHz, $CDCl_3$) 8.09 (1H, s, 5'-H), 7.70 (1H, br d, *J* 7.4 Hz, N*H*), 4.81 (1H, ddd, *J* 7.4, 3.7 and 3.7 Hz, 4-H), 4.15–3.95 (2H, m, 5-H), 3.81 (3H, s, $CO_2Me$), 2.91 (1H, br t, *J* 5.6 Hz, O*H*) and 2.48 (3H, s, 2'-Me); $\delta_C$(67.8 MHz, $CDCl_3$) 170.5 (s, 2-C), 161.6 (s, $CO_2Me$), 160.8 (s, 2'-C), 141.3 (d, 5'-C), 135.3 (s, 4'-C), 62.7 (t, 5-C), 54.3 (d, 4-C), 52.6 (q, $CO_2Me$) and 13.6 (q, 2'-Me); *m/z* (EI) 210 ($M^+ - H_2O$, 4%), 198 (17), 197 (7), 169 (21), 110 (100) and 82 (11) (Found: *m/z* 198.0592 ($M^+ - H_2O$). $C_8H_{10}N_2O_4$ requires *M*, 198.0582).

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

Thionyl chloride (3 ml) was added cautiously to the oxazole serine derivative **16a** (1.0 g, 4.4 mmol) under a nitrogen atmosphere at 0 °C and the solution was then stirred at ambient temperature for 12 h. The excess thionyl chloride was evaporated *in vacuo* to leave a residue which was quenched with water (25 ml). The aqueous mixture was extracted with ethyl acetate (3 × 30 ml) and the combined organic extracts were washed with saturated brine (30 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *oxazole serine chloride* (1.04 g, 96%) as a cream solid. A small portion was recrystallised to give a white crystalline solid, mp 104–105 °C (from ethyl acetate–petrol) (Found: C, 43.9; H, 4.6; N, 11.5. $C_9H_{11}ClN_2O_4$ requires C, 43.8; H, 4.5; N, 11.4%); $\lambda_{max}$(EtOH)/nm 214 (10240); $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 3401, 1751, 1678, 1600, 1505 and 1107; $\delta_H$(250 MHz, $CDCl_3$) 8.07 (1H, s, 5'-H), 7.64 (1H, br d, *J* 7.8 Hz, N*H*), 5.09 (1H, ddd, *J* 7.8, 3.6 and 3.4 Hz, 4-H), 4.01 (1H, dd, *J* 11.3 and 3.4 Hz, 5-H), 3.90 (1H, dd, *J* 11.3 and 3.6 Hz, 5-H), 3.78 (3H, s, $CO_2Me$) and 2.44 (3H, s, 2'-Me); $\delta_C$(67.8 MHz, $CDCl_3$) 168.8 (s, 2-C), 161.5 (s, $CO_2Me$), 160.3 (s, 2'-C), 141.1 (d, 5'-C), 135.3 (s, 4'-C), 52.9 (d, 4-C), 52.6 (q, $CO_2Me$), 44.8 (t, 5-C) and 13.6 (q, 2'-Me); *m/z* (EI) 211 ($M^+$ − Cl, 9%), 210 (9), 189 (32), 187 (82), 151 (42), 123 (18) and 110 (100) (Found: *m/z* 194.0283. $C_8H_9N_2O_3$ requires *M*, 194.0275).

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

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

$\delta_H$(250 MHz, $CDCl_3$) 9.19 (1H, br s, NH), 8.12 (1H, s, 5'-H), 6.71 (1H, s, 5-H), 5.97 (1H, s, 5-H), 3.89 (3H, s, $CO_2Me$) and 2.50 (3H, s, 2'-Me); $\delta_C$(67.8 MHz, $CDCl_3$) 163.9 (s, 2-C), 161.3 (s, $CO_2Me$), 159.0 (s, 2'-C), 141.1 (d, 5'-C), 135.9 (s, 4'-C), 130.7 (s, 4-C), 108.9 (t, 5-C), 52.8 (q, $CO_2Me$) and 13.5 (q, 2'-Me); *m/z* (EI) 210 ($M^+$, 31%), 195 (5), 179 (3), 178 (10), 151 (4) and 110 (100).

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

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

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

Silver trifluoromethanesulfonate (13.7 g, 53 mmol) was added in one portion to a stirred solution of the oxazole serine chloride **16b** (11.15 g, 45 mmol) in dry benzene (225 ml) at room temperature under a nitrogen atmosphere. The suspension was heated under reflux for 6 h, then cooled to ambient temperature and evaporated *in vacuo*. The residue was partitioned between ethyl acetate (300 ml) and saturated sodium bicarbonate solution (300 ml), with vigorous stirring for 30 min. The separated aqueous layer was extracted with ethyl acetate (3 × 200 ml) and the combined organic phases were then washed with saturated sodium bicarbonate solution (3 × 150 ml). The second aqueous extract was washed further with ethyl acetate (3 × 100 ml) and the combined organic phases were then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *oxazole-oxazoline* (9.50 g, 99%) as a straw coloured oil; $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 2956, 1741, 1675, 1587, 1216 and 1108; $\delta_H$(250 MHz, $CDCl_3$) 8.07 (1H, s, 5'-H), 4.93 (1H, dd, *J* 10.5 and 7.9 Hz, 4-H), 4.68 (1H, dd, *J* 8.6 and 7.9 Hz, 5-H), 4.56 (1H, dd, *J* 10.5 and 8.6 Hz, 5-H), 3.80 (3H, s, $CO_2Me$) and 2.50 (3H, s, 2'-Me); $\delta_C$(67.8 MHz, $CDCl_3$) 170.1 (s, 2-C), 161.5 (s, $CO_2Me$), 158.9 (s, 2'-C), 140.3 (d, 5'-C), 128.7 (s, 4'-C), 68.6 (t, 5-C), 67.1 (d, 4-C), 51.4 (q, $CO_2Me$) and 12.4 (q, 2'-Me); *m/z* (EI) 210 ($M^+$, 5%), 151 (61), 126 (100), 110 (25) and 82 (14) (Found: *m/z* 210.0651. $C_9H_{10}N_2O_4$ requires *M*, 210.0648).

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

A solution of potassium hexamethyldisilazide in toluene (1.8 ml, 1.5 M, 2.7 mmol) was added dropwise to a stirred solution of the oxazoline ester **17a** (540 mg, 2.6 mmol) in dry THF (5 ml) at −78 °C under an atmosphere of nitrogen. The resulting orange solution was quenched with a solution of phenylselenyl bromide (728 mg, 3.1 mmol) in dry THF (2 ml), and then allowed to warm to ambient temperature. The solvent was evaporated *in vacuo* to leave a brown oil that was purified by column chromatography using hexane–diethyl ether (1:1) as eluent to give the *selenide* (433 mg, 45%) as a yellow oil; $\nu_{max}$(thin film)/$cm^{-1}$ 1729, 1644, 1597 and 1439; $\delta_H$(270 MHz, $CDCl_3$) 8.01 (1H, s), 7.75–7.53 (2H, m), 7.30–7.17 (3H, m), 4.78 (1H, d, *J* 10.6 Hz, CHH), 4.56 (1H, d, *J* 10.6 Hz, CHH), 3.7 (3H, s, OMe) and 2.42 (3H, 2'-Me); $\delta_C$(67.8 MHz, $CDCl_3$) 169.8 (s), 162.3 (s), 159.8 (s), 143.5 (s), 141.7 (d), 139.2 (s), 137.7 (d), 129.7 (d), 128.9 (d), 126.3 (s), 75.5 (t), 53.0 (q) and 13.7 (q); *m/z* (FAB) (Found: *m/z* 209 ($M^+$ − PhSe). $C_9H_9O_4N_2$ requires *M* 209, 20%), 103 (52), 81 (48) and 43 (100). The selenide was found to partially oxidise and eliminate to the bi-oxazole ester **18** upon standing overnight.

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

Triethyloxonium tetrafluoroborate (11 ml of a 1 M solution in $CH_2Cl_2$, 11 mmol) was added to a suspension of 2-methyloxazole-4-carboxamide[28] (1.26 g, 10 mmol) in dry dichloromethane (25 ml) and the resulting solution was stirred under nitrogen atmosphere for 6 h. L-Serine ethyl ester hydrochloride (1.70 g, 10 mmol) and triethylamine (2.80 ml, 22 mmol) were introduced and the mixture was then stirred overnight at ambient temperature. The mixture was evaporated to dryness *in vacuo* to leave an off-white solid which was preadsorbed onto silica and purified by flash chromatography using 2% methanol in chloroform as eluent to give the product (210 mg, 10%) as a pale yellow oil (starting material (720 mg, 43%) was also recovered); $\nu_{max}$(film)/$cm^{-1}$ 1735, 1670 and 1585; $\delta_H$(400 MHz, $CDCl_3$) 8.08 (1H, s, 5'-H), 4.90 (1H, dd, *J* 11 and 8 Hz, 4-H), 4.66 (1H, dd, *J* 9 and 11 Hz, 5-H), 4.58 (1H, dd, *J* 11 and 9 Hz, 5-H), 4.25 (2H, m, $CH_2CH_3$), 2.51 (3H, s, 2'-Me) and 1.31 (3H, t, *J* 7 Hz, $CH_2CH_3$); $\delta_C$(67.8 MHz, $CDCl_3$) 170.7 (s), 162.4 (s), 159.9 (s), 141.1 (d), 129.9 (s), 69.6 (t), 68.5 (d), 61.7 (t), 14.0 (q) and 13.6 (q) (Found: *m/z* 224.0788. $C_{10}H_{12}N_2O_4$ requires *M*, 224.0795).

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

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

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

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

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

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

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

Freshly prepared nickel peroxide (5 × 1g) was added portionwise every 0.5 h to a stirred solution of crude oxazoline **17c** (1.44 g, 6.42 mmol) in dry benzene (25 ml) heated under reflux. The mixture was heated under reflux for a further 2.5 h then cooled and filtered through a Celite pad. The Celite pad was washed with ethyl acetate (3 × 20 ml) and the solvents were then removed *in vacuo* to leave the crude product as an off-white solid. Purification by flash chromatography on silica using 2% methanol in chloroform as eluent afforded unreacted starting material (150 mg, 11%), (eluted second) and the bi-oxazole (0.67 g, 47%) as a white solid, mp 129–130 °C (ethyl acetate–petrol) (Found: C, 54.1; H, 4.5; N, 12.7. $C_{10}H_{10}N_2O_4$ requires C, 54.05; H, 4.5; N, 12.6%); $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 3000, 1730, 1640 and 1580; $\delta_H$(400 MHz, $CDCl_3$) 8.28 (1H, s, 5-H), 8.27 (1H, s, 5'-H), 4.42 (2H, q, *J* 7 Hz, $CH_2CH_3$), 2.56 (3H, s, 2'-Me) and 1.40 (3H, t, *J* 7 Hz, $CH_2CH_3$); $\delta_C$(67.8 MHz, $CDCl_3$) 162.8 (s), 161.0 (s), 155.7 (s), 143.5 (d), 139.3 (d), 134.7 (s), 129.8 (s), 61.3 (t), 14.4 (q) and 13.7 (q) (Found: *m/z* 222.0651. $C_{10}H_{10}N_2O_4$ requires *M*, 222.0641).

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

A solution of potassium hydroxide (3.4 g, 60 mmol) in water (50 ml) was added to the bi-oxazole **18a** (10.4 g, 50 mmol), and the mixture was heated under reflux for 1 h. The mixture was cooled to ambient temperature, evaporated *in vacuo*, then acidified with concentrated hydrochloric acid (pH 1) and cooled in ice for 30 min. The precipitate was filtered, then washed with water (20 ml) and freeze dried to leave the bi-oxazole acid (6.25 g, 64%) as a cream solid, mp > 210 °C (decomp.) (Found: C, 49.3; H, 3.0; N, 14.4. $C_9H_6N_2O_4$ requires C, 49.2; H, 2.9; N, 14.4%); $\lambda_{max}$(EtOH)/nm 208 (6430), 247 (7700) and 254 (7750); $\nu_{max}$(KBr disc)/$cm^{-1}$ 3143, 1681, 1644 and 1122; $\delta_H$(270 MHz, $d_6$-DMSO) 8.75 (1H, s, 5-H), 8.72 (1H, s, 5'-H) and 2.44 (3H, s, 2'-Me); $\delta_C$(67.8 MHz, $d_6$-DMSO) 162.6 (s, $CO_2H$), 161.8 (s, 2-C), 155.1 (s, 2'-C), 144.9 (d, 5-C), 140.4 (d, 5'-C), 134.2 (s, 4-C), 129.0 (s, 4'-C) and 13.4 (q, 2'-Me); *m/z* (EI) 194 ($M^+$, 13%), 150 (12), 110 (100) and 82 (10) (Found: *m/z* 194.0299. $C_9H_6N_2O_4$ requires *M*, 194.0328).

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

Thionyl chloride (50 ml) was added to the bi-oxazole acid **21a** (6.25 g, 32 mmol), and the stirred suspension was then heated under reflux for 6 h. The excess thionyl chloride was evaporated *in vacuo* and the residue was next azeotroped with toluene to leave the corresponding acid chloride **21b** as a cream solid which was used immediately without further purification. A solution of the acid chloride in dry dichloromethane (90 ml) was added dropwise over 20 min to a stirred solution of DL-serine methyl ester hydrochloride (5.5 g, 35 mmol) and triethylamine (10 ml, 71 mmol) in dry dichloromethane (62 ml) under a nitrogen atmosphere at 0 °C. The brown solution was stirred at ambient temperature for 14 h, evaporated *in vacuo*, and then diluted with saturated sodium bicarbonate solution (200 ml). The aqueous mixture was extracted with ethyl acetate (4 × 200 ml) and the combined organic extracts were washed with saturated brine (100 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *amide* (8.4 g, 88%) which crystallised as a cream solid, mp 141–142 °C (ethyl acetate) (Found: C, 48.5; H, 4.5; N, 14.2. $C_{12}H_{13}N_3O_6$ requires C, 48.8; H, 4.4; N, 14.2%); $\lambda_{max}$(EtOH)/nm 222 (13640), 235 (13380) and 254 (13970); $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 3402 br, 1746, 1676, 1596, 1508 and 1115; $\delta_H$(250 MHz, $CDCl_3$) 8.23 (1H, s, 5'-H), 8.14 (1H, s, 5"-H), 7.80 (1H, br d, *J* 7.9 Hz, N*H*), 4.87 (1H, ddd, *J* 7.9, 3.8 and 3.8 Hz, 4-H), 4.20–3.95 (2H, m, 5-H), 3.81 (3H, s, $CO_2Me$), 2.80 (1H, br m, O*H*) and 2.57 (3H, s, 2"-Me); $\delta_C$(67.8 MHz, $CDCl_3$) 170.4 (s, 2-C), 163.1 (s, $CO_2Me$), 160.3 (s, 2'-C), 154.9 (s, 2"-C), 141.2 (d, 5'-C), 139.0 (d, 5"-C), 136.5 (s, 4'-C), 129.4 (s, 4"-C), 62.7 (t, 5-C), 54.4 (d, 4-C), 52.5 (q, $CO_2Me$) and 13.7 (q, 2"-Me); *m/z* (EI) 295 ($M^+$, 7%), 277 (4), 265 (71), 264 (25), 236 (87), 177 (100), 149 (24) and 110 (32) (Found: *m/z* 236.0641. $C_{10}H_{10}N_3O_4$ requires *M*, 236.0639).

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

Thionyl chloride (45 ml) was added cautiously to the bi-oxazole serine derivative **22a** (8.4 g, 28 mmol) under a nitrogen atmosphere at 0 °C. The solution was stirred for 12 h at ambient temperature and the excess thionyl chloride was then evaporated *in vacuo*. The residue was quenched with water (200 ml) and the aqueous layer was then extracted with ethyl acetate (4 × 200 ml). The combined organic phases were washed with saturated brine (100 ml), then dried ($MgSO_4$) and evaporated *in vacuo* to leave the *bi-oxazole serine chloride* (8.7 g, 97%) which crystallised as a cream solid, mp 137–138 °C (diethyl ether) (Found: C, 46.0; H, 4.0; N, 13.1; Cl, 11.0. $C_{12}H_{12}ClN_3O_5$ requires C, 46.0; H, 3.9; N, 13.4; Cl, 11.3%); $\lambda_{max}$(EtOH)/nm 218 (10440) and 255 (10270); $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 3401, 1748, 1681, 1650 and 1588; $\delta_H$(270 MHz, $CDCl_3$) 8.24 (1H, s, 5'-H), 8.16 (1H, s, 5"-H), 7.75 (1H, br d, *J* 7.9 Hz, N*H*), 5.16 (1H, ddd, *J* 7.9, 4.0 and 3.6 Hz, 4-H), 4.04 (1H, dd, *J* 11.2 and 3.6 Hz, 5-H), 3.93 (1H, dd, *J* 11.2 and 4.0 Hz, 5-H), 3.82 (3H, s, $CO_2Me$) and 2.56 (3H, s, 2"-Me); $\delta_C$(67.8 MHz, $CDCl_3$) 168.5 (s, 2-C), 162.9 (s, $CO_2Me$), 159.8 (s, 2'-C), 154.9 (s, 2"-C), 141.2 (d, 5'-C), 139.0 (d, 5"-C), 136.1 (S, 4'-C), 129.4 (s, 4"-C), 52.7 (d, 4-C), 52.7 (q, $CO_2Me$), 44.4 (t, 5-C) and 13.5 (q, 2"-Me); *m/z* (EI) 315 ($M^+$, 1.5%), 3.3 (4), 278 (15), 256 (41), 254 (88), 177 (100), 149 (21) and 110 (28) (Found: *m/z* 313.4532. $C_{12}H_{12}ClN_3O_5$ requires *M*, 313.4528).

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

1,8-Diazabicyclo[5.4.0]undec-7-ene (900 µl, 6 mmol) was added dropwise to a stirred solution of the chloride **22b** (1.87 g, 6 mmol), in dry dichloromethane (20 ml), at room temperature under a nitrogen atmosphere. The mixture was stirred for 3 h and then washed with 2 M hydrochloric acid (2 × 10 ml) and the layers were separated. The organic phase was dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave the *olefin* (1.52 g, 92%) as an off-white solid. A small portion was recrystallised from diethyl ether–hexane (1:1) and had mp 148–149 °C (Found: C, 52.0; H, 4.06; N, 15.5. $C_{12}H_{13}N_3O_6$ requires C, 52.0; H, 4.0; N, 15.2%); $\nu_{max}$($CHCl_3$) $cm^{-1}$ 3383, 1715, 1694, 1582, 1515 and 1203; $\delta_H$(270 MHz, $CDCl_3$) 9.12 (1H, br s, N*H*), 8.20 (1H, s, 5-H), 8.12 (1H, s, 5'-H), 6.66 (1H, s, *E*=C*H*), 5.94 (1H, d, *J* 1 Hz, *Z*=C*H*), 3.82 (3H, s, $CO_2Me$) and 2.49 (3H, s,

2-*Me*); $\delta_C$(67.8 MHz, $CDCl_3$) 164.2 (s, CO), 163.2 (s, CO), 158.9 (s, 2-C), 154.7 (s, 2'-C), 141.6 (d, 5-C), 139.3 (d, 5'-C), 137.3 (s, 4-C), 130.9 (s, 4'-C), 129.9 (s, *C*$CO_2$Me), 110.1 (t, *C*$CH_2$), 53.1 (q, $CO_2$*Me*) and 13.9 (q, 2-*Me*); *m/z* (EI) 277 ($M^+$, 51%) and 177 (100).

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

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

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

Silver trifluoromethanesulfonate (12.5 g, 49 mmol) was added in one portion to a stirred solution of the bi-oxazole serine chloride **22b** (10.0 g, 41 mmol) in dry benzene (100 ml) under a nitrogen atmosphere, and the slurry was then heated under reflux for 6 h. The mixture was cooled to ambient temperature, evaporated *in vacuo*, and then the grey residue was slurried in ethyl acetate (300 ml) and saturated sodium bicarbonate (200 ml) with vigorous stirring for 30 min. The separated aqueous layer was extracted with ethyl acetate (3 × 100 ml) and the combined organic phases were washed with sodium hydrogen carbonate (3 × 100 ml). The second aqueous extract was washed with further ethyl acetate (3 × 100 ml) and the total combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo* to leave the *bi-oxazole-oxazoline* (5.3 g, 62%) which crystallised as a pale yellow solid, mp 181–182 °C (ethyl acetate); $\lambda_{max}$(EtOH)/nm 240 (13520) and 255 (13940); $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 1742, 1682, 1639, 1586 and 1113; $\delta_H$(250 MHz, $CDCl_3$) 8.26 (1H, s, 5'-H), 8.22 (1H, s, 5''-H), 4.95 (1H, dd, *J* 10.6 and 7.9 Hz, 4-H), 4.71 (1H, dd, *J* 8.7 and 7.9 Hz, 5-H), 4.60 (1H, dd, *J* 10.6 and 8.7 Hz, 5-H), 3.80 (3H, s, $CO_2$Me) and 2.54 (3H, s, 2''-Me); $\delta_C$(67.8 MHz, $CDCl_3$) 170.9 (s, 2-C), 162.6 (s, *C*$O_2$Me), 159.6 (s, 2'-C), 155.8 (s, 2''-C), 141.0 (d, 5'-C), 139.2 (d, 5''-C), 130.9 (s, 4'-C), 129.5 (s, 4''-C), 69.7 (t, 5-C), 68.3 (d, 4-C), 52.5 (q, $CO_2$Me) and 13.6 (q, 2''-Me); *m/z* (EI) 277 ($M^+$, 14%), 218 (100), 208 (24), 190 (78), 177 (37), 149 (11) and 110 (35) (Found: *m/z* 277.0653. $C_{12}H_{11}N_3O_5$ requires *M*, 277.0699).

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

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

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

(a) Solid *N*-bromosuccinimide (3.6 g, 20 mmol) was added to a stirred solution of the bi-oxazole-oxazoline **23a** (5.7 g, 20 mmol) in dry benzene (565 ml) under a nitrogen atmosphere at room temperature. The solution was irradiated for 23 h (sun lamp, 300 W) at 25 °C before the solvent was evaporated *in vacuo* to leave a brown residue. Purification by chromatography on silica using 1% methanol–chloroform as eluent gave the *ter-oxazole* (2.8 g, 50%) which crystallised as colourless needles, mp 217–218 °C (ethyl acetate–petrol) (Found: C, 51.9; H, 3.2; N, 15.2. $C_{12}H_9N_3O_5$ requires C, 52.3; H, 3.3; N, 15.3%); $\lambda_{max}$(EtOH)/nm 202 (10010), 249 (13130) and 255 (13600); $\nu_{max}$($CHCl_3$)/$cm^{-1}$ 1747 (CO), 1654, 1605, 1588 and 1115; $\delta_H$(250 MHz, $CDCl_3$) 8.41 (1H, s, 5-H), 8.31 (1H, s, 5'-H), 8.25 (1H, s, 5''-H), 3.94 (3H, s, $CO_2$Me) and 2.56 (3H, s, 2''-Me); $\delta_C$(67.8 MHz, $CDCl_3$) 163.0 (s, *C*$O_2$Me), 161.3 (s, 2-C), 156.3 (s, 2'-C), 155.5 (s, 2''-C), 143.8 (d, 5-C), 139.2 (s, 5'-C), 134.4 (s, 5''-C), 130.7 (s, 4-C), 129.6 (2 × s, 4' and 4''-C), 52.3 (q, $CO_2$Me) and 13.8 (q, 2''-Me); *m/z* (EI) (Found: $M^+$, 275.0491. $C_{12}H_9N_3O_5$ requires *M*, 275.0542, 100%), 244 (10), 216 (2), 149 (11), 124 (3) and 110 (63). This same ter-oxazole was produced from the same oxazoline **23a** using nickel peroxide in 40% yield according to the procedure described for the preparation of the bi-oxazole **18**.

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

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

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

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

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

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

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

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

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

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

A stirred solution of the ter-oxazole **26a** (0.89 g, 3.2 mmol), *N*-bromosuccinimide (633 mg, 3.6 mmol) and AIBN (45 mg) in distilled carbon tetrachloride (178 ml) was irradiated (sun lamp, 300 W) under reflux for 23 h in a nitrogen atmosphere. The mixture was cooled to ambient temperature, then evaporated *in vacuo*, and the residue was purified by chromatography on silica eluting with 7:1 dichloromethane–diethyl ether and then with 1% methanol–chloroform to give the *methyl bromide* (202 mg, 46% based on recovered starting material) as a white solid (methanol), mp > 230 °C (decomp.) (Found: C, 40.9; H, 2.3; N, 11.9. $C_{12}H_8BrN_3O_5$ requires C, 40.7; H, 2.3; N, 11.9%); $\lambda_{max}$(EtOH)/nm 245 (17345) and 255 (19310); $\nu_{max}$($CHCl_3$)/cm$^{-1}$ 1729, 1654, 1577, 1114 and 1100; $\delta_H$(400 MHz, $CDCl_3$) 8.43 (1H, s, 5-H), 8.37 (1H, s, 5′-H), 8.32 (1H, s, 5″-H), 4.52 (2H, s, $CH_2$Br) and 3.95 (3H, s, $CO_2$Me); $\delta_C$(67.8 MHz, $d_6$-DMSO) 161.1 (s, $CO_2$Me), 161.0, 155.4 and 155.0 (3 × s, 2, 2′ and 2″-C), 145.9, 142.3 and 141.3 (3 × d, 5, 5′ and 5″-C), 133.5, 130.2 and 129.8 (3 × s, 4, 4′ and 4″-C), 52.2 (q, $CO_2$Me) and 21.1 (t, $CH_2$Br); *m/z* (EI) (Found: *m/z* 354.9656, (16%). $C_{12}H_8BrN_3O_5$ requires *M*, 354.9627, 353 (17), 274 (100) and 242 (5).

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

A stirred solution of the oxazole bromide **27** (159 mg, 0.45 mmol) and triphenylphosphine (236 mg, 0.90 mmol) in distilled benzene (20 ml) was heated under reflux for 17 h in a nitrogen atmosphere. The mixture was cooled to ambient temperature and the precipitate was then filtered off and washed with dry diethyl ether (50 ml). The residue was dried *in vacuo* to give the *phosphonium salt* (210 mg, 76%) as a hygroscopic, cream powder; $\delta_H$(400 MHz, $CDCl_3$) 8.35 (1H, s, 5-H), 8.30 (1H, s, 5′-H), 8.21 (1H, s, 5″-H), 7.94 (6H, m, Ar), 7.80 (3H, m, Ar), 7.68 (6H, m, Ar), 6.20 (2H, d, *J* 14.9 Hz, $CH_2$P) and 3.94 (3H, s, $CO_2$Me); $\delta_C$(67.8 MHz, $CDCl_3$) 162.2 (s, $CO_2$Me), 155.3 and 155.2 (3 × s, 2, 2′ and 2″-C), 143.9, 142.1 and 139.4 (3 × d, 5, 5′ and 5″-C), 135.4 (d, Ar), 134.4 and 130.8 (3 × s, 4, 4′ and 4″-C), 134.2 (d, Ar), 134.1 (d, Ar), 130.5 (d, Ar), 130.3 (d, Ar), 117.7 (s, Ar), 116.9 (s, Ar), 52.3 (q, $CO_2$Me) and 26.6 ($CH_2$, d, $J_{P-C}$ 54 Hz, $CH_2$P) which was used directly without further purification.

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

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

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

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

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

DBU (0.53 ml, 3.5 mmol) was added dropwise, over 2 min, to a stirred solution of the oxazoline (1.04 g, 3.2 mmol) in dry dichloromethane (30 ml) at 0 °C under a nitrogen atmosphere. Bromotrichloromethane (0.34 ml, 3.5 mmol) was added dropwise over 10 min and the mixture allowed to warm to room temperature over 24 h.[23] The mixture was quenched with saturated ammonium chloride (2 × 20 ml), and the separated aqueous phase was then extracted with ethyl acetate (2 × 20 ml). The combined organic extracts were dried ($MgSO_4$), and then evaporated *in vacuo* to leave a residue which was purified by chromatography on silica using 1:1 petrol–ethyl acetate as eluent to give the *oxazole* (0.8 g, 75%) as a mixture of rotamers; $\nu_{max}(CHCl_3)/cm^{-1}$ 2980, 1703, 1368, and 1110; $\delta_H$(360 MHz, $CDCl_3$, major rotamer) 8.21 (1H, s), 5.20–5.07 (1H, m, 2-H), 4.29–4.09 (2H, m, 1-H), 3.93 (3H, s, $CO_2Me$), 1.75 (3H, s, $CH_3$), 1.60 (3H, s, $CH_3$) and 1.30 (9H, s, 'Bu); $\delta_C$(125 MHz, $CDCl_3$, major rotamer) 164.0 (s), 161.3 (s), 150.9 (s), 143.6 (d), 133.4 (s), 95.1 (s), 80.5 (s), 67.4 (t), 55.0 (d), 52.1 (q), 28.0 (q), 25.1 (q) and 23.9 (q); *m/z* (FAB) (Found: $M^+ + 1$, 327.1531 (11%). $C_{15}H_{23}N_2O_6$ requires *M*, 327.1556).

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

A solution of DIBAL-H (1.5 M in toluene, 5.1 ml) was added dropwise, over 30 min, to a stirred solution of the oxazole ester **34a** (1.0 g, 3.06 mmol) in dry dichloromethane (10 ml) at 0 °C under a nitrogen atmosphere and the mixture was stirred at 0 °C for 4 h. The mixture was quenched with methanol (20 ml) followed by magnesium sulfate (20 g) and the filtered suspension was evaporated *in vacuo* to leave a viscous yellow residue. The residue was added to a saturated solution of potassium sodium tartrate and the mixture was stirred vigorously for 2 h. The mixture was extracted with ethyl acetate (2 × 200 ml), and the combined organic extracts were then dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow residue. The residue was purified by chromatography on silica using 1:1 petrol–ethyl acetate as eluent to give the *oxazole alcohol* (0.55 g, 61%) as a yellow oil; $\delta_H$(360 MHz, $CDCl_3$, major rotamer) 7.55 (1H, s), 5.13–4.98 (1H, m, 2-H), 4.58 (2H, br s, $CH_2OH$), 4.26–4.04 (3H, m, 1-H), 2.78 (1H, br s, OH), 1.73 (3H, s, $CH_3$), 1.59 (3H, s, $CH_3$) and 1.29 (9H, s, 'Bu); $\delta_C$(125 MHz, $CDCl_3$) 163.7 (s), 151.2 (s), 140.6 (s), 134.9 (d), 95.0 (s), 80.4 (s), 67.4 (t), 56.7 (t), 55.1 (d), 28.1 (q), 25.2 (q) and 24.2 (q); *m/z* (EI) (Found: $M^+$, 298.1535 (1.26%) $C_{14}H_{22}N_2O_5$ requires *M*, 298.1529).

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

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

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

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

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

Barium hydroxide octahydrate (0.4 g, 1.4 mmol) was added in one portion to a stirred solution of the *β*-ketophosphonate **35** (0.4 g, 1.4 mmol) in dry THF (8 ml) under a nitrogen atmosphere at room temperature. The suspension was stirred for 30 min and a solution of the aldehyde **34b** (0.4 g, 1.4 mmol) in 40:1 THF–$H_2O$ (2 ml) was then added in one portion. The mixture was stirred at room temperature for 3 h then quenched with saturated sodium bicarbonate solution (20 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to leave a viscous oil. Purification by chromatography on silica using 2:1 petrol–ethyl acetate as eluent gave the *alkene* (0.5 g, 71%) as a yellow oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 2936, 1698, 1627, 1379, 1368 and 1097; $\delta_H$(360 MHz, $CDCl_3$, major rotamer) 7.77 (1H, s, 14-H), 7.36 (1H, d, *J* 15.6 Hz, 9-H), 6.91 (1H, d, *J* 15.6 Hz, 8-H), 5.15–5.00 (1H, m, 15-H), 4.29–4.22 (1H, m, 19-H), 4.15–4.09 (1H, br m, 19-H), 4.12 (2H, q, *J* 7.2 Hz, $OCH_2CH_3$), 2.64–2.60 (2H, m, 6-H), 2.30 (2H, t, *J* 7.4 Hz, 2-H), 1.76–1.54 (9H, m, 3-H, 4-H, 5-H and $OCH_2CH_3$) and 1.49–1.21 (15H, m, 2 × $CH_3$ and 'Bu); $\delta_C$(125 MHz, $CDCl_3$) 200.0 (s), 173.8 (s), 160.2 (s), 151.3 (s), 139.4 (s), 137.7 (s), 129.3 (s), 127.3 (s), 95.3 (s), 81.3 (s), 67.3 (t), 60.2 (t), 55.1 (d), 41.5 (t), 34.1 (t), 28.7 (t), 28.1 (q), 25.2 (q), 24.7 (t), 24.2 (q), 23.7 (t) and 14.2 (q).

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

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

added dropwise over 10 min to the cuprate solution at −5 °C and the mixture was stirred at −5 °C for 3 h. The mixture was quenched with a 1:1 mixture of saturated ammonium chloride–ammonium hydroxide solution (20 ml) and the separated aqueous layer was then extracted with diethyl ether (2 × 30 ml). The combined organic phases were washed with saturated brine (30 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 1:1 petrol–ethyl acetate as eluent to give the *3-methyl ketone* (168 mg, 55%) as a viscous oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1696; $\delta_H$(360 MHz, $CDCl_3$) 7.30 (1H, s, 14-H), 5.29–4.95 (1H, m, 15-H), 4.22–4.16 (1H, m, 19-H), 4.13–4.02 (1H, br m, 19-H), 4.11 (2H, q, *J* 7.1 Hz, $OCH_2CH_3$), 3.30–3.24 (1H, m, 9-H), 2.83 (1H, dd, *J* 6.0 and 16.9 Hz, 8-H), 2.51 (1H, dd, *J* 8.1 and 17.2 Hz, 8-H), 2.36 (2H, t, *J* 7.3 Hz, 6-H), 2.27 (2H, t, *J* 7.4 Hz, 2-H), 1.72–1.41 (9H, m, 3-H, 4-H, 5-H and $OCH_2CH_3$) and 1.31–1.09 (18H, m, 2 × $CH_3$, 'Bu and 9-$CH_3$); $\delta_C$(90 MHz, $CDCl_3$) 209.2 (s), 173.6 (s), 162.8 (s), 151.2 (s), 133.1 (s), 94.9 (s), 80.1 (s), 67.5 (t), 60.2 (t), 55.2 (d), 48.3 (t), 42.9 (t), 34.1 (t), 28.6 (t), 28.1 (q), 26.8 (d), 25.1 (q), 24.6 (t), 24.5 (q), 23.1 (t), 19.4 (q) and 14.2 (q); *m/z* (FAB) (Found: $M^+ + 1$, 481.2944 (10%). $C_{25}H_{41}O_7N_2$ requires *M*, 481.2915).

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

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

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

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

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

A solution of butyllithium (2.35 M) in hexane (1.68 ml, 2.69 mmol) was added dropwise over 10 min to a stirred suspension of the phosphonium salt **38** (1.67 g, 2.69 mmol) in dry THF (40 ml) at −30 °C under a nitrogen atmosphere. The deep red solution was stirred at room temperature for 30 min, and was then cooled to −78 °C. A solution of 5-*tert*-butyldimethylsilylpentanal **39** (0.87 g, 4.04 mmol) in dry THF (9 ml) was added dropwise over 5 min to the ylide solution at −78 °C and the mixture was allowed to warm to room temperature overnight. The mixture was quenched with saturated aqueous ammonium chloride solution (20 ml) and the separated aqueous layer was then extracted with diethyl ether (2 × 30 ml). The combined organic phases were washed with saturated brine (20 ml), then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 5:1 petrol–ethyl acetate as eluent to give the *olefin* (0.4 g, 41%) as a viscous oil (Found: C, 60.9; H, 9.3; N, 3.9. $C_{18}H_{31}O_4NSi$ requires C, 61.1; H, 8.9; N, 4.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730, 1664, 1318 and 1114; $\delta_H$(360 MHz, $CDCl_3$) 8.12 (1H, s, 5-H), 6.85 (1H, dt, *J* 16.0 and 7.0 Hz, 2′-H), 6.32 (1H, d, *J* 16.0 Hz, 1′-H), 4.39 (2H, q, *J* 7.1 Hz, $OCH_2CH_3$), 3.65–3.61 (2H, m, 6′-H), 2.30–2.28 (2H, m, 3′-H), 1.58–1.54 (4H, m, 4′ and 5′-H), 1.39 (3H, t, *J* 7.1 Hz, $OCH_2CH_3$), 0.90 (9H, s, 'Bu) and 0.05 (6H, s, 2, $CH_3$); $\delta_C$(67.5 MHz, $CDCl_3$) 161.6 (CO), 160.4 (2-C), 142.9 (5-C), 142.5 (2′-C), 133.3 (4-C), 115.8 (1′-C), 62.7 (6′-C), 61.2 ($OCH_2CH_3$), 32.5 (3′-C), 32.1 (5′-C), 25.9 ('Bu), 24.7 (4′-C), 18.3 (q-C), 14.3 ($OCH_2CH_3$) and −5.3 (Si-Me); *m/z* (FAB) (Found: $M^+ + 1$, 354.2119 (77%) $C_{18}H_{32}O_4NSi$ requires *M*, 354.2101).

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

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

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

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

The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 5:1 petrol–ethyl acetate as eluent to give the *olefin* (35 mg, 51%) as a colourless oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 1731, 1664, 1578, 1462, 1369, 1317, 1092 and 989; $\delta_H$(360 MHz, $CDCl_3$) 8.14 (1H, s, 5-H), 6.85 (1H, dt, *J* 16.0 and 7.0 Hz, HC=C*H*$CH_2$), 6.32 (1H, d, *J* 16.0 Hz, C*H*=$CHCH_2$), 6.01 (1H, ddt, *J* 17.1, 10.4 and 5.9 Hz, $CH_2CH$=$CH_2$), 5.39 (1H, dd, *J* 17.2 and 1.4 Hz, =C*H*H), 5.29 (1H, dd, *J* 10.4 and 1.1 Hz, =CH*H*), 4.82 (2H, d, *J* 5.9 Hz, $CH_2$=CH), 3.66–3.61 (2H, m, 6'-H), 2.31–2.28 (2H, m, 3'-H), 1.57–1.42 (4H, m, 4' and 5'-H), 0.89 (9H, s, 'Bu) and 0.05 (6H, s, 2 × $CH_3$); $\delta_C$(67.5 MHz, $CDCl_3$) 161.7 (CO), 161.0 (2-C), 143.0 (5-C), 142.6 (2'-C), 133.7 (4-C), 131.7, 119.0, 115.8 (1'-C), 65.7, 62.7 (6'-C), 32.5 (3'-C), 32.1 (5'-C), 25.9 ('Bu), 24.7 (4'-C), 18.3 and −5.4 (Si-Me); *m/z* (FAB) (Found: $M^+$ + 1, 366.2094 (66%). $C_{19}H_{32}O_4NSi$ requires *M*, 366.2101).

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

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

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

1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (37 mg, 0.19 mmol) was added in one portion to a stirred solution of the acid **29** (77 mg, 0.18 mmol) and the alcohol **28** (50 mg, 0.20 mmol) in dichloromethane (6 ml) at 0 °C containing 4-(dimethylamino)pyridine (11 mg, 0.09 mmol). The mixture was stirred at 0 °C for 2 h and then at room temperature overnight before it was evaporated to dryness *in vacuo*. The residue was diluted with ethyl acetate (10 ml) and water (2 ml), and the organic layer was then separated, washed with saturated sodium bicarbonate (15 ml) and water (15 ml), dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 1:1 petrol–ethyl acetate as eluent to give the *ester* (89 mg, 73%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3156, 2253, 1793, 1730, 1720, 1368, 1096 and 889; $\delta_H$(360 MHz, $CDCl_3$) 8.14 (1H, s, 9-H), 7.31 (1H, s, 30-H), 6.83 (1H, dt, *J* 16.0 and 7.0 Hz, 11-H), 6.33 (1H, d, *J* 16.0 Hz, 10-H), 6.01 (1H, ddt, *J* 17.1, 10.4 and 5.9 Hz, $CH_2CH$=$CH_2$), 5.37 (1H, dd, *J* 10.4 and 1.4 Hz, =C*H*H), 5.27 (1H, dd, *J* 10.4 and 1.1 Hz, =CH*H*), 5.08–4.96 (1H, m, 31-H), 4.82 (2H, dt, *J* 5.6 and 1.3 Hz, 3-H), 4.23–4.03 (4H, m, 32-H and 15-H), 3.31–3.26 (1H, m, 24-H), 2.83 (1H, dd, *J* 16.8 and 5.8 Hz, 23-H), 2.51 (1H, dd, *J* 16.9 and 7.8 Hz, 23-H), 2.40–2.27 (6H, m, 12-H, 17-H and 21-H), 1.73–1.55 (10H, m, 13-H, 14-H and 2 × $CH_3$), 1.48–1.08 (15H, m, 18-H, 19-H, 20-H and 'Bu) and 0.90–0.80 (3H, m, 25-H); $\delta_C$(360 MHz, $CDCl_3$) 210.5 (s), 173.6 (s), 162.8 (s), 161.7 (s), 160.9 (s), 151.2 (s), 144.9 (s), 143.1, 141.8, 133.8 (s), 133.1, 131.7, 119.0 (t), 116.1, 94.9 (s), 80.1 (s), 67.4 (t), 65.7 (t), 63.8 (t), 55.1, 48.3 (t), 42.9 (t), 34.0 (t), 32.2 (t), 29.6 (t), 28.6 (t), 28.2, 28.1, 28.0 (t), 26.8, 25.0, 24.7 (t), 24.6, 24.2, 23.1 (t), 19.3 (q); *m/z* (FAB) (Found: $M^+$ + 1, 686.3677 (100%). $C_{36}H_{52}O_{10}N_3$ requires *M*, 686.3654).

### Bis-oxazole amino acid ester 43

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

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

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

### The oxazole-oxazoline-oxazole macrolide 45

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

**The ter-oxazole macrolide 30**

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

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