A total synthesis of the unique tris-oxazole macrolide ulapualide A produced by the marine nudibranch *Hexabranchus sanguineus*

Shital K. Chattopadhyay and Gerald Pattenden*

School of Chemistry, The University of Nottingham, University Park, Nottingham, UK NG7 2RD

Received (in Cambridge, UK) 27th January 2000, Accepted 3rd February 2000 Published on the Web 19th June 2000

A total synthesis of ulapualide A (1), whose relative stereochemistry was assigned on the basis of an earlier molecular mechanics study of its hypothetical metal chelated complex 9, is described. The synthesis is based on: i, elaboration of the double functionalised tris-oxazole 11; ii, synthesis and installation of the top side chain 16 (C-26–C-41) *via* a stereoselective Wittig reaction, leading to 17; iii, conversion of 17 into 73a and attachment of the C-1–C-9 portion 18; iv, macrocyclisation of 19 by an intramolecular Wadsworth–Emmons olefination leading to the macrolide 20; v, incorporation of the C-9 methyl group (to 80) and, finally vi, manipulation of the side chain functionality in 80 and introduction of the terminal formyl enamine residue. The synthetic ulapualide A showed NMR spectroscopic data which were almost identical to those described for the natural product, and did not separate from the natural material in HPLC analysis. Small differences in the ¹³C NMR spectroscopic data however lead us to conclude that the stereochemistry of the synthetic ulapualide differs from that in the natural product at one or more of the stereogenic centres along the C-28–C-33 portion of the side chain.

Ulapualide A $(1)^1$ together with kabiramide C $(2)^2$, were the first members of an extraordinarily unique family of trisoxazole based macrolides to be isolated from nature. The "ulapualides" derive their name from the Hawaiian words "ula", meaning red and "pua", meaning flower, since the founder member 1 was 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, closely followed by the isolation and characterisation of the structurally similar "halichondramides", e.g. 3, from the sponge Halichondria,³ and the mycalolides, e.g. 4, from a sponge of the genus Mycale.⁴ The molecules 1-4, all show structures based on a 25-membered macrolide core which incorporates a novel tris-oxazole unit and to which is attached a lipid-like side chain that terminates in an unusual formyl enamine residue. The molecules 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. Interestingly however, the halichondramide imide **5** and the ester **6**, containing incomplete tris-oxazole chromophores, were isolated as co-metabolites of halichondramides from *Halichondria*.³ More recently the structurally related halishigamides **7** and **8** from the Okinawan marine sponge *Halichondria*⁵ have been added to this strikingly unusual family of secondary metabolites.

Members of the ulapualide family of natural products show a profound range of interesting and unusual biological activities. For example, all of the metabolites show pronounced antifungal activity, and they also inhibit cell divisions in the fertilised sea urchin egg assay. In addition, some members show ichthyotoxic properties whilst others inhibit leukemia cell proliferation. In earlier publications we have suggested that some of the unique biological properties of these molecules could be associated with their capacity to sequester and transport



J. Chem. Soc., *Perkin Trans.* 1, 2000, 2429–2454 2429

This journal is © The Royal Society of Chemistry 2000





metal ions, *i.e.* behave as ionophores, using the several oxazole nitrogen and side chain oxygen ligand binding sites present in their structures.⁶ The combination of a unique chemical structure with novel biological properties encouraged us to examine a total synthesis of the founder member, ulapualide A (1), of this family of marine metabolites and to examine their ionophore properties. In the immediately preceding paper⁷ we described concise synthetic routes to the tris-oxazole ring system found in the natural product, and in this paper we describe the extension of this work culminating in a total synthesis of ulapualide A, with the relative stereochemistry shown in structure 1.⁸

In spite of considerable effort over a substantial period of time, it was not until after we had published our completed synthetic studies in this area, that anything was known about the stereochemistries of members of the family of ulapualides isolated from nudibranchs and sponges.⁹ The relative stereochemistry shown in structure **1** for ulapualide **A** is that predicted by ourselves based on a molecular mechanics study on a "dummy" metal chelated ulapualide **A**, *e.g.* **9**, using varying combinations of its oxygen and nitrogen atom ligating sites.⁶ Interestingly, this study showed that the stereochemistry of a major part of the polyol side chain in **1** correlated with corresponding chiral centres in scytophycin **B** (**10**), a related metabolite whose structure had been established by X-ray crystallography measurements.^{10,11}

A successful total synthesis of ulapualide A required attention to a number of details including: i, a synthetic method for the synthesis of the unusual tris-oxazole unit making up the macrolide core; ii, a concise synthesis of the (C-28–C-39) side chain in 1 containing several oxy and methyl substituted chiral centres; iii, a method for elaborating the terminal formyl enamine unit associated with the side chain, and iv, the development of methods for producing the macrolide core in the natural product.¹²

In the preceding publication⁷ we described the full details of a convenient synthesis of gram quantities of the functionalised Wittig salt **11**. In the same publication we also highlighted the scope for producing the entire tris-oxazole macrolide **13** by utilising a macrolactamisation from the ester **12**, followed by oxazoline and oxazole ring formation. In other model studies we found that the formyl enamine unit in the ulapualides, *i.e.* **14**, could be produced smoothly from a corresponding aldehyde by reaction with *N*-methylformamide in the presence of pyridine– toluene-*p*-sulfonic acid (Scheme 1).¹³ This procedure led to a mixture of rotamers of the *E*-isomer of **14**, as found in all the naturally occurring ulapualides.

At the outset of our studies we considered a range of strategies for elaborating the tris-oxazole based macrolide core in ulapualide A and some of these are summarised on structure **15**. Thus, we considered an obvious macrolactonisation from an





appropriate ω -hydroxy carboxylic acid precursor, an intramolecular olefination reaction producing the C-25–C-26 alkene bond, and the utilisation of intramolecular sp²–sp² coupling (*e.g.* Stille, Suzuki) reactions involving substituted oxazole ring precursors.¹⁴ As mentioned earlier, we also considered making one or other of the oxazole rings in the natural product as the last step utilising a macrolactamisation protocol, *viz.* **12–>13**. An alternative, less obvious, macrolide ring forming strategy was to effect an intramolecular olefination reaction producing the C-8–C-9 bond in the molecule, as a conjugated enone, and then to later introduce the C-9 α -methyl group stereoselectively using the conformational bias of the macrolide core.

With model work completed and adequate precedent established,⁸ the synthetic strategy we actually decided on to prepare ulapualide A was based on: (i) elaboration of the tris-oxazole phosphonium salt 11 and the protected polyol aldehyde 16, followed by (ii) their coupling to the alkene 17, (iii) attachment of the ω -carboxy substituted keto-phosphonate residue 18 producing 19, (iv) macrocyclisation *via* an intramolecular Wadsworth–Emmons olefination leading to 20, and (v) sequential functional group manipulation, introduction of the C-9 methyl group, and finally the terminal *N*-methyl *N*-alkenyl-formamide residue (Scheme 2).

The aforementioned design required the synthesis of the three principal building blocks **11**, **16** and **18**. The synthesis of the tris-oxazole substituted phosphonium salt **11** has already been presented.⁷ We will now describe syntheses of the protected polyol aldehyde **16** and the ω -carboxy phosphonate **18**, followed by their coupling which leads to **17**, and the addition of **18**, producing **19**. Macrocyclisation of **19** to **20**, followed by incorporation of the C-9 methyl group and manipulation of the terminal formyl enamine residue then completes the synthesis of ulapualide A.

Synthesis of the C-26–C-41 fragment 16 (R = MOM; R' = TBDMS)

An armoury of modern asymmetric synthesis methods is now available for elaborating the chiral 1,3-diol and chiral 1-oxy, 2methyl substitution patterns in the C-26–C-41 side chain unit in ulapualide A. The most important decision that needed to be made before embarking on a synthesis of **16** was simply the choice of appropriate hydroxy protecting groups at C-30, C-38 and C-41, such that they could be removed in a selective manner as and when required. We therefore made the dimethyl acetal, MOM, TBDMS, TBDPS derivative **21** our target since these protecting groups could be removed selectively in the order CH(OMe)₂>OMOM>OTBDMS using dimethylboryl bromide.¹⁵ We designed a convergent synthesis of the C-26–C-



Scheme 2



Thus, Sharpless epoxidation ¹⁸ of (E)-5-benzyloxypent-2-enol 24, followed by chelation controlled addition of methylmagnesium bromide to the resulting epoxy alcohol 25¹⁹ in the presence of CuI first led to the corresponding 1,3-diol 26 in 66% yield; a small amount (20%) of the unwanted corresponding 1,2-diol resulting from non-selective ring opening in 25 was produced in this reaction but it was easily removed following treatment of the crude product with sodium periodate and chromatography. The primary alcohol group in 26 was next protected as its *tert*-butyldiphenylsilyl ether 27 and this was followed by protection of the secondary alcohol group as the corresponding methyl ether, producing 28.

Hydrogenolysis of **28**, and oxidation of the resulting primary alcohol **29** then led to the differentially protected aldehyde **30** (Scheme 4). Our plan now was to elaborate the extended aldehyde **40** from **30**, involving an *anti*-aldol reaction between **30** and the boron enolate derived from the unsaturated imide **34** (Scheme 5).²⁰ The imide **34** was smoothly produced from the mono-benzyl ether of propane-1,3-diol, following: i, oxidation and a Wittig reaction between the resulting aldehyde and ethoxycarbonylmethylenetriphenylphosphorane, leading to **31**; ii, saponification and conversion into the acid chloride **33**, and finally iii, treatment of **33** with the anion derived from 4phenylmethyl-2-oxazolidone. When the aldehyde **30** was added to a solution of the boron enolate derived from the imide **34** at -78 °C, work up and chromatography led to the *anti*-aldol product 35 as a 1:1 mixture of Z- and E-isomers in 70% yield and >95% de.

In readiness for oxidative cleavage of the double bond in 35, the imide residue was next converted into the C-29 α -methyl group (cf. 38) following reduction to the methanol 36 using lithium methoxyborohydride,²¹ mesylation (to 37) and further reduction of 37 using lithium methoxyborohydride. Protection of the secondary alcohol group in 38 as its tertbutyldimethylsilyl ether 39, followed by ozonolysis of the alkene bond in 39 at -78 °C then produced the aldehyde 40 in 80% yield. The addition of Brown's (+)-allyldiisopinocamphenylborane 22 ((+)-IPCBOMe) to the aldehyde 40 proceeded in a highly diastereoselective manner (de 89%) and, after chromatography, gave rise to the α -OH orientated homoallylic alcohol 41 in 65-70% yield. The stereochemistry of the newly formed C-28-OH centre in 41 was determined through extensive NMR experiments, i.e. ¹H COSY, C-H correlation,²³ homonuclear decoupling and NOE data, matching of computer predicted coupling constants together with correlation of ¹³C chemical shift data for the acetonide 44 (derived from 41 and its diastereoisomer 42) with those data reported in the literature for authentic syn- and anti-1,3-diol acetonides.²⁴ These data have been collected on structures 43 (predicted shift data), 44 (data from 41) and 45, (data from the diastereoisomer 42 produced after reaction between the aldehyde 40 and (-)-allyldiisopinocamphenylborane).

With the stereochemical integrity of the secondary alcohol **41** containing five of the eight chiral centres in the C-26–C-41 unit in ulapualide A established, its conversion into the key aldehyde precursor **22** (for elaboration to **63**) was then accomplished following: i, methylation to **46**; ii, deprotection of the *tert*-butyldimethylsilyl ether (to **47**) and reprotection as the MOM ether **48**; iii, ozonolysis to **49**; iv, dimethylacetal **50** formation; v, deprotection of **50** leading to **51**; and finally oxidation of **51** to **22** using TPAP–NMO (Scheme 5).

The synthesis of the phosphonate 23 containing the remaining three chiral centres in the ulapualide A side chain was achieved in twelve steps starting from the E-allylic alcohol 24 and featured the controlled ring opening of the chiral α -epoxy alcohols 52 and 57 by methyl nucleophiles as key reactions (Scheme 6).²⁵ Thus, treatment of the chiral epoxide **52** derived from 24 with trimethylaluminium at 0 °C produced a 9:1 mixture of regioisomeric diols in favour of 53 which on cleavage with sodium periodate gave the aldehyde 54 in 84% yield. A Wittig reaction between 54 and ethoxycarbonylmethylenetriphenylphosphorane next led to the E-unsaturated ester 55 which on reduction with DIBAL-H accessed the (E)-hex-2-en-1-ol 56. Epoxidation of 56 to 57 via the Sharpless protocol using (-)-diethyl tartrate, followed by chelation controlled epoxide ring opening with methylmagnesium bromide next led to the 1,3-diol 58 in 85% yield. Protection of the primary and secondary hydroxy groups in 58 as the tert-butyldimethylsilyl ether 59, followed by selective deprotection of the primary



Scheme 4 Reagents and conditions: i, (-)-DET, Ti(OⁱPr)₄, t-BuOOH (61%); ii, MeMgBr, CuI, (66%); iii, t-BuPh₂SiCl, (94%); iv, NaH, MeI, (66%); v, H₂, Pd(OH)₂-C, (92%); vi, (COCl)₂, DMSO, Et₃N, (87%).



Scheme 5 *Reagents and conditions*: i, DMSO, (COCl)₂, Et₃N, then EtO₂CCH=PPh₃ (68%); ii, LiOH, H₂O (95%); iii, (COCl)₂, DMF; iv, BuLi, 4-phenylmethyl-2-oxazolidone, -78 °C (80%); v, Bu₂BOTf, Et₃N, -78 °C, then **30** (70%); vi, LiBH₄–MeOH (90%); vii, MeSO₂Cl–iPr₂NEt (90%); viii, LiBH₄–MeOH (82%); ix, t-BuMeSiSO₂CF₃–CH₂Cl₂ (95%); x, O₃, CH₂Cl₂, -78 °C (80%); xi CH₂=CHCH₂MgBr, (+)-IPCBOMe, -78 °C (70%); xii, MeOTf, 2,6-di-*tert*-butylpyridine (98%); xiii, PPTS, ethanol (90%); xiv, MOM-Cl, iPr₂NEt (95%); xv, O₃, PPh₃ (89%); xvi, TMOF, MeOH, *p*TSA (98%); xviii, TBAF (100%); xviii, TPAP, NMO (89%).

alcohol then gave **60** which was smoothly oxidised to the corresponding aldehyde **61** using TPAP–NMO. Finally, treatment of the aldehyde **61** with methyl dimethylphosphonate in the presence of n-BuLi, followed by oxidation of the resulting alcohol **62** using pyridinium dichromate (PDC) in DMF then produced the phosphonate **23**.

A Wadsworth–Emmons olefination reaction between 22 and 23 using barium hydroxide in wet THF as base²⁶ next gave the *E*-alkene 63 in an excellent 95% yield (Scheme 7). Hydrogen-

ation of **63** in the presence of Pearlmans catalyst²⁷ then resulted in simultaneous reduction of the alkene bond and hydrogenolysis of the benzyl protecting group in **63** producing the alcohol **64** in quantitative yield. Protection of the alcohol **64** as the corresponding *tert*-butyldiphenylsilyl ether **21**, followed by treatment of the dimethyl acetal with boron dimethyl bromide¹⁵ then led to the C-26–C-41 side chain fragment **16** in ulapualide A in readiness for coupling to the tris-oxazole phosphonium salt **11** *en route* to **17** and then to **19** and the macrolide **20**.

J. Chem. Soc., Perkin Trans. 1, 2000, 2429–2454 2433



Scheme 6 *Reagents and conditions*: i, (+)-DET, Ti(OiPr)₄, t-BuOOH (76%); ii, Me₃Al; iii, NaIO₄ (84%); iv, Ph₃PCHCO₂Et (94%); v, DIBAL-H (96%); vi, (-)-DET, Ti(iPr)₄, t-BuOOH (85%); vii, MeMgBr, CuI, THF; NaIO₄, MeOH–H₂O (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 7 Reagents and conditions: i, Ba(OH)₂, wet THF (95%); ii, Pd(OH)₂-C, H₂ (94%); iii, imidazole, TBDPS-Cl (94%); iv, Me₂BBr, CH₂Cl₂ (95%).

Synthesis of the C-1–C-8 fragment 18

Our strategy for the synthesis of the homochiral β -hydroxy carboxylic acid phosphonate derivative 18 relied on access to the TBDPS intermediate 67 followed by elaboration of the alkene residue in 67 to the corresponding β -keto phosphonate unit. A range of chemical²⁸ and biological²⁹ methods are now available for the preparation of homochiral β-hydroxy esters from reductions of the corresponding β -keto esters. We were attracted to the use of baker's yeast for the reduction of 65 to the (3R)-hydroxy ester 66 since this conversion had already been described by Hirama et al.29 during their studies of the total synthesis of compactin. Thus, saponification of the known β-keto ester 65,30 using 1 M potassium hydroxide, followed by reduction of the resulting potassium carboxylate using actively fermenting baker's yeast and work-up of the (3R)hydroxy carboxylic acid with benzyl bromide first produced the benzyl ester 66 in 35% overall yield from 65 and with >99% ee, as measured by ¹H NMR analysis (Scheme 8). Protection of the hydroxy group in 66 next gave the TBDPS derivative 67, which, after hydroboration (to 68) and further oxidation, gave rise to the aldehyde 69. When the aldehyde 69 was treated with the anion derived from dimethyl methylphosphonate,31 a mixture

of diastereoisomers of the corresponding β -hydroxy phosphonate **70** was produced which was easily oxidised using PDC in DMF leading to the β -keto phosphonate derivative **71**. Hydrogenolysis of the benzyl ester group in **71** finally produced the ω -carboxy phosphonate **18**.

Elaboration of the macrolide precursor 73 from the tris-oxazole 11 and the polyol side chain 16

We examined two obvious approaches to the macrolide **20** core in ulapualide A **1**. The first involved an intramolecular olefination reaction from the aldehyde phosphonate **19** (Scheme 9), and the second used macrolactonisation from the ω -hydroxy carboxylic acid derivative **79** (Scheme 10). In both of these strategies we first required a synthesis of the unit **17** derived from the ter-oxazole phosphonium salt **11** and the C-26–C-41 fragment **16**, followed by connection of the β -keto phosphonate residue **18**. The unit **17** was readily prepared following an *E*selective Wittig reaction between the aldehyde **16** and the teroxazole phosphonium salt **11** using *n*-butyllithium as base at -78 °C. The *E*-geometry assigned to the newly introduced disubstituted double bond in **17** followed conclusively from the magnitude (*J* 15.5 Hz) of the vicinal couplings associated with



Scheme 8 Reagents and conditions: i, NaH in THF, then BuLi, $CH_2=CHCH_2Br$; ii, KOH, EtOH, 0 °C; iii, D-glucose, baker's yeast, KH_2PO_4 , H_2O ; iv, PhCH₂Br, aliquot 336, NaHCO₃ (~15–30% overall); v, TBDPS-Cl, imidazole, DMF, rt (81%); vi, BH₃·DMS, H₂O₂, NaOH (78%); vii, PDC, DCM (78%); vii, MePO(OMe)₂, BuLi (55%); ix, PDC, DMF, (84%); x, Pd-C, H₂, EtOAc (98%).



Scheme 9 Reagents and conditions: i, n-BuLi, THF, -78 °C, 70%; ii, DIBAL-H, 0 °C, 75%; iii, Dess–Martin periodinane, DCM, 98%; iv, Me₂BBr, DCM, -78 °C, 95%; v, 2,4,6-trichlorobenzoyl chloride, Et₃N, rt, 3 h, 42%; vi, K₂CO₃, 18-crown-6, toluene, 10–33%.

the olefinic hydrogens in the ¹H NMR spectrum of the alkene. Treatment of **17** with DIBAL-H next resulted in simultaneous reduction of the oxazole ester group and the ketone function at C-36 leading to the diol **72**, which was then cleanly oxidised with Dess–Martin periodinane³² to the keto-aldehyde **73a** in quantitative yield. Inspection and comparison of the NMR data for **17** and **73a** established that the conversion into **73a** had proceeded with preservation of the stereochemical integrity at the C-37 (α -keto methyl) centre. Deprotection of the MOM

ether group in **73a** proceeded selectively using boron dimethyl bromide in CH₂Cl₂ at -78 °C and finally led to the secondary alcohol-aldehyde intermediate **73b** in readiness for its coupling to the β -keto phosphonate **18**.

Formation of the tris-oxazole macrolide core 20, and elaboration to ulapualide

The two aforementioned strategies towards the macrolide core

J. Chem. Soc., Perkin Trans. 1, 2000, 2429–2454 2435



Scheme 10 Reagents and conditions: i, Ba(OH)₂·8H₂O, wet THF, rt, 3 h, 85%; ii, Me₂CuLi, 0 °C, 3 h, 50%; iii, Me₂BBr, -78 °C, 1 h, 50%; iv, Ba(OH)₂·8H₂O, wet THF, rt, 3.5 h, 88%; v, Pd(PPh₃)₄, morpholine, rt, 2 h, 76%.

20 in ulapualide were now evaluated.³³ The most useful method involved esterification of the phosphonate carboxylic acid 18 with the secondary alcohol 73b, leading to 19, followed by an intramolecular Wadsworth-Emmons olefination, using K_2CO_3 in the presence of 18-crown-6,³⁴ which produced the E-macrolide enone 20 in an unoptimised 30% yield (Scheme 9). In a second approach to the macrolide 20, shown in Scheme 10, the tris-oxazole aldehyde 73a was first reacted with the keto phosphonate 74 leading to 75 which was then treated with Me₂CuLi producing 76 as a mixture of C-9 Me epimers with concomitant deprotection of the allyl ester. Deprotection of the MOM ether in 76, using Me₂BBr then gave rise to the ω -hydroxy acid 77. Similarly, the aldehyde 73b reacted with the phosphonate 74 producing enone 78 which was then deprotected with Pd(0) catalysis giving rise to the hydroxy acid 79. The macrolactonisations of 77 and 79, under Yamaguchi conditions³³ gave disappointing low yields (5-10%) of the corresponding macrolide, cf. 20, under a range of conditions (Scheme 10). This outcome was possibly due to the steric incumberance around the reacting centres in the substrates, and the overall synthetic approach to 20 was less convenient than that proceeding via the aldehyde phosphonate 19.

Treatment of the tris-oxazole macrolide enone 20 with lithium dimethylcuprate in ether at 0 °C led to a 3:2 mixture of C-9 methyl epimers of 80, which could be separated cleanly by column chromatography. Comparison of the NMR spectroscopic data between the epimers of 80 and those of natural ulapualide A, together with consideration of our molecular mechanics modelling data⁶ allowed us to assign the α -(equatorial) methyl epimer, *i.e.* 80a, as the major product of the methyl cuprate addition to the enone 20; this outcome is consistent with the delivery of the cuprate to the least hindered face of the enone unit in 20, relative to the bulky β-orientated TBDPS ether at C-3. Deprotection of the C-38 TBDMS ether group in either of the epimers 80 was smoothly accomplished using trimethylsilyl triflate³⁵ at -78 °C, and acetylation of the resulting secondary alcohol 81 then produced the corresponding acetate 82 (Scheme 11). Selective deprotection of the primary alcohol TBDPS group in 82a using pyridine HF,³⁶ and oxidation of the resulting alcohol 83a using Dess-Martin periodinane³² then gave the corresponding aldehyde 84a. The same synthetic methods were also used to convert 81b into 84b. When a solution of either 84a or 84b in benzene was heated with N-methylformamide in the presence of pyridine-toluene-p-sulfonic acid¹³ for 10-12 h, chromatography gave the E-isomers of the corresponding N-methyl-N-alkenylformamides 85a and 85b respectively in 40% yield. The syntheses of the ulapualide A structure 1 and its C-9 methyl epimer were then completed following deprotection of the tert-butyldiphenylsilyl ether group in 85a and 85b using pyridine•HF.

Stereochemistry of natural and synthetic ulapualide A

Several years ago we carried out a molecular mechanics study of ulapualide A and some of its hypothetical metal conjugates,⁶ in order to provide a working stereochemical model on which to



Scheme 11 Reagents and conditions: i, Me₂CuLi, Et₂O, 0 °C, 55%; ii, TMSOTf, -78 °C, 85%; iii, Ac₂O, DMAP, pyridine, 90%; iv, HF•pyridine, 85%; v, Dess-Martin periodinane, 90%; vi, NHMeCHO, PPTS, benzene, 40%; vii, HF•Py, pyridine, THF, 80%.

base the synthetic work described in this paper. Thus, briefly, we first showed that in a ulapualide-metal conjugate only two of the three oxazole nitrogen centres could complex with the metal at any time, and the best fit energy minimised arrangement was that shown in the complex **86**. We next added the various side



chain substituents in ulapualide to this complex, in sequence, one at a time, and energy minimised each epimer. Each of the epimers of higher energy was discarded, and when all the substituents had been added, each stereocentre was again inverted and the structure re-minimised as a double check. Interestingly, deletion of the metal (we used octahedral Co(III) as a typical "dummy" metal) from the complex and re-minimisation showed that the metal–ligand conjugate was only 12 kJ mol⁻¹ higher in energy than the ligand alone. Using this procedure we arrived at the relative stereochemistry shown in 1 (*cf.* 9) as the most favourable stereostructure for ulapualide A. In the cases of the centres C-9, C-33 and C-37, the "energetic penalty" upon stereocentre inversions was found to be very marginal, *i.e.* 2.3–4.2 kJ mol⁻¹.

With the stereomodel **1** for ulapualide, and no other information to hand, in 1990 we embarked on the ambitious total synthesis presented here, leading to both the C-9 α - and C-9 β -methyl epimers of the stereostructure. Much to our interest, and almost disbelief, *both* the α - and β -methyl epimers of our synthetic ulapualide showed ¹H NMR spectroscopic data which were almost superimposable on those of a sample of natural ulapualide A, and the samples had retention times in HPLC analysis that were similarly close. Very small differences between the compounds were found however on inspection of their ¹³C NMR spectroscopic data, which are shown in Table 1. Even within these data the only discernable differences were associated with the chemical shifts of C-32 (δ 81.0 ppm observed and δ 81.8 ppm natural; $\Delta\delta$ 0.8 ppm), the C-33 methyl group (δ 14.2 ppm observed against δ 15.5 ppm natural; $\Delta\delta$ 1.3 ppm) and C-34 (δ 26.6 ppm observed and δ 27.6 ppm natural; $\Delta\delta$ 1.0 ppm), with other chemical shifts mostly lying within 0.4 ppm of each other. These differences are shown below on structures **87** (synthetic) and **88** (natural). The similarities in the ¹³C NMR spectra were really quite eerie and disconcerting.



Furthermore, under normal circumstances and in the absence of spectroscopic data recorded for the natural product, at the same time, under similar dilution, in the same solvent, on the same instrument, one might have been forgiven for saying that either of the C-9 a- and C-9 β-methyl epimers of the synthetic ulapualide were identical to the natural product. We do not believe this to be the case however. In the first instance our spectroscopic data do not allow us to distinguish the C-9 α -methyl epimer of synthetic ulapualide from its corresponding β-methyl epimer. Secondly, the differences in chemical shift associated with the C-32 to C-34 carbon centres in the ¹³C NMR spectra of synthetic and natural ulapualide clearly indicate that one or other of the C-32 and C-33 centres is incorrect, *i.e.* most likely *syn(cis)*-orientated in the natural product. Apart from these differences however the remainder of the stereochemistry of the synthetic and natural ulapualide are, for all intents and purposes, identical. Based on these data and analyses, and before the important paper presented by Panek

J. Chem. Soc., Perkin Trans. 1, 2000, 2429–2454 2437



Fig. 1 The numbering system used to interpret NMR data is shown in the structure above, and is based on the system by Scheuer *et al.* in their structure determination of the natural product.

Table 1 13 C NMR data of ulapualide A and synthetic compounds 85a and 85b

C atom	Natural ulapualide	α-Methyl epimer 85a	β-Methyl epimer 85b
1	172.6 (s)	172.6	172.7
2	42.95 (t)	42.9	42.9
3	68.4 (d)	68.7	68.8
4	37.2 (t)	37.3	37.1
5	20.8 (t)	20.6	20.7
6	43.9 (t)	44.0	44.0
7	210.5 (s)	210.4	210.4
8	48.1 (t)	47.9	47.9
9	28.2 (d)	27.7	27.7
10	146.5 (s)	146.6	146.5
12	154.2 (s)	154.3	154.2
14	133.5 (d)	133.4	133.5
15	131.7 (s)	131.9	131.6
17	156.2 (s)	156.2	156.2
19	137.4 (d)	137.4	137.4
20	130.2 (s)	130.1	130.5
22	162.7 (s)	162.8	162.6
24	137.8 (s)	137.8	137.8
25	117.2 (d)	117.5	117.6
26	139.9 (d)	139.6	139.1
27	33.7 (t)	33.1	33.1
28	80.0 (d)	79.9	79.9
29	34.6 (d)	34.1	34.0
30	73.0 (d)	72.8	72.8
31	32.1 (t)	32.0	32.0
32	81.8 (d)	81.0	81.0
33	40.4 (d)	40.4	40.6
34	27.6 (t)	26.6	26.6
35	39.8 (t)	39.9	39.8
36	211.8 (s)	211.6	211.5
37	48.6 (d)	48.6	48.7
38	77.3 (d)	77.6	77.3
39	37.0 (d)	36.9	36.9
40	112.2 (d)	112.2	112.1
	110.5 (d)	110.5	110.5
41	129.6 (d)	129.6	129.6
	125.5 (d)	125.2	125.1
43	162.2 (d)	162.2	162.2
	161.0 (d)	161.0	161.0
44	33.1 (a)	33.1	33.1
45	195(a)	19.2	19.8
380Ac	170.1(s)	170.1	170.2
	20.9 (g)	20.9	20.9
46	134(a)	13.4	13.4
47	15.5(q)	14.2	14.2
320Me	58 1 (a)	57.8	57.9
48	91 (a)	91	91
.5 280Me	57.8 (q)	57.6	57.6
49	189(a)	18.9	18.9

and Fusetani and their co-workers⁹ analysing the stereochemistry of the related mycalolides (*cf.* **4**) was published during 1999, we would have revised the relative stereochemistry of natural ulapualide to the C-32-(β)-methoxy epimer *i.e.* **89**, or the C-33-(α)-methyl epimer of structure **1**.



After the preliminary publication of our total synthesis of ulapualide A (with the relative stereochemistry shown in 1), Panek and Fusetani and their collaborators, unambiguously established the stereochemistry of the related mycalolide



metabolites as shown in structure 90.[†] At the same time these authors found that ulapualide B had the same stereochemistry along its C-28–C-39 backbone as the mycalolides, *viz.* 91.

It is uncanny therefore that the differences between our synthetic ulapualide and natural ulapualide A are simply: i, the differing stereochemistry at C-32, *i.e.* β -OMe instead of α -OMe, which is reflected in the different shift data in their ¹³C NMR spectra, and ii, the mirror image (enantiomeric) relationship between the C-28–C-30 centres in the two compounds, which is **not** reflected in their ¹³C NMR shift data, *viz.* C-28, δ 79.9 ppm (natural δ 80.0 ppm), C-29, δ 34.1 ppm (natural δ 34.6 ppm), C-30, δ 72.8 ppm (natural δ 73.0 ppm), C-29–Me, δ 9.1 ppm (natural δ 9.1 ppm).

Metal binding studies with natural ulapualides

The dearth of natural and synthetic ulapualide A 1 prevented us from carrying out an evaluation of the metal binding properties of this particular secondary metabolite. However in contemporaneous studies, and prompted by our earlier protestations of the metal binding properties of several marine metabolies (particularly ulapualides and cyclopeptides), Siegel and co-workers³⁷ examined and compared the metal binding of dihydrohalichondramide **92** isolated from the sponge *Halichondria* sp., the tris-oxazole **93** and the diphenyloxazole **94**. Using fluorescence quenching and NMR techniques, these authors demonstrated that the molecules **92–94** showed similar, but small, binding constants, *i.e.* 10² and 10⁴ for the metals Ag⁺, and Cu²⁺, Fe²⁺, Hg²⁺, and Pb²⁺, providing little evidence of any significant chelate effect. Siegel and co-workers³⁷ were led to

 $[\]dagger$ Note added at proof-stage: After the completion and acceptance of this paper Liu and Panek published a total synthesis of (–)-mycalolide **90**.³⁸



conclude, therefore, that any antifungal properties of dihydrohalichondramide **92** and its relatives are probably not associated with their properties to bind metals *in vivo*.

Experimental

For general experimental details see ref. 7. Also petrol refers to the fraction of light petroleum with the distillation range 40–60 °C. $[a]_{\rm D}$ has units of 10^{-1} deg cm² g⁻¹.

(E)-Ethyl 5-benzyloxypent-2-enoate 31

Dimethyl sulfoxide (22 ml, 0.312 mol) was added dropwise over 20 min to a stirred solution of oxalyl chloride (20 ml, 0.226 mol) in dry dichloromethane (120 ml) at -78 °C under nitrogen. After 15 min, a solution of the mono-benzyl ether of propane-1,3-diol (26 g, 0.175 mm) in dry dichloromethane (40 ml) was added dropwise over 30 min and the mixture was stirred at -78 °C for a further 1 h. Triethylamine (68 ml, 0.485 mol) was added dropwise over 30 min to the stirred mixture which was then stirred for a further 2 min. A solution of ethoxycarbonylmethylenetriphenylphosphorane (64 g, 0.184 mol) in dry dichloromethane (120 ml) was added in one portion and the mixture was then allowed to warm to room temperature and stirred overnight. The mixture was diluted with dichloromethane (200 ml) and the solution was washed successively with water (2 × 200 ml), saturated NaHCO₃ (200 ml) and brine (100 ml) and then dried (MgSO₄). The dried extracts were concentrated in vacuo and the residue was triturated with a mixture of ether (100 ml) and petroleum ether (200 ml) in an ice-bath for 1 h. The precipitated phosphine oxide was filtered off and the filtrate was concentrated in vacuo to leave a pale yellow oil. Distillation gave the (E)-ester (28 g, 68%) as a colourless liquid, bp 140 °C at 1 mmHg; v_{max} (film)/cm⁻¹ 1718, 1656; δ_{H} (400 MHz) 7.32 (5H, m, Ar), 6.97 (1H, dt, J 15.7 and 6.9 Hz, =CHCH₂), 5.89 (1H, dt, J 15.7 and 1.6 Hz, =CHCO₂Et), 4.50 (2H, s, PhCH2O), 4.18 (2H, q, J 7.1 Hz, CH2CH3), 3.57 (2H, t, J 6.5 Hz, CH2O), 2.49 (2H, apparent qd, J ca. 6.6 and 1.6 Hz, CH₂CH=), 1.2 (3H, t, J 7.1 Hz, CH₂CH₃); δ_{C} (100 MHz) 166.3 (s), 145.5 (d), 138.0 (s), 128.3 (d), 128.2 (d), 127.6 (d), 127.5 (d), 122.9 (d), 72.9 (t), 68.2 (t), 60.1 (t), 32.7 (t), 14.2 (q); m/z (EI) (Found: 234.1260. C₁₄H₁₈O₃ requires 234.1256).

(E)-5-Benzyloxypent-2-en-1-ol 24

A solution of DIBAL-H (1 M in hexane, 250 ml) was added dropwise over 1 h to a stirred solution of the ester **31** (28 g, 119.5 mmol) in dry THF (250 ml) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 2 h and then quenched with 2 M HCl (10 ml slowly, then 250 ml after the mixture had set to a gel). The aqueous phase was extracted with ethyl acetate (2 × 200 ml) and the combined organic extracts were dried (MgSO₄), and then concentrated *in vacuo* to leave a yellow oil. Distillation gave the *alcohol* (19.3 g, 84%) as a colourless oil, bp 130 °C at 1 mmHg (Found: C, 74.8; H, 8.75. C₁₂H₁₆O₂ requires C, 75.0; H, 8.4%); v_{max} (film)/cm⁻¹ 3393 (br), 3031, 2860, 1497, 1099; $\delta_{H}(400 \text{ MHz})$ 7.36–7.29 (5H, m, Ph), 5.75–5.7 (2H, m, CH=CH), 4.53 (2H, s, PhCH₂O), 4.05–4.0 (2H, br, CH₂OH), 3.53 (2H, t, *J* 6.6 Hz, =CH₂OCH₂Ph), 2.40–2.3 (2H, m), 2.22 (1H, br s, OH); $\delta_{C}(100 \text{ MHz})$ 138.2 (s), 131.0 (d), 128.8 (d), 128.3 (d), 127.6 (d), 127.5 (d), 72.8 (t), 69.5 (t), 63.3 (t), 32.5 (t); *m/z* (EI) 192 (M⁺).

[3-(2-Benzyloxyethyl)oxiran-2-yl]methanol 25

Titanium(IV) isopropoxide (2.6 ml), (-)-diethyl tartrate (1.72 ml) and the allylic alcohol 24 (16.1 g) were added sequentially over 30 min to a suspension of powdered 4 Å sieves (2.5 g) in dry dichloromethane (170 ml) at -20 °C under nitrogen. The mixture was stirred at -20 °C for 30 min, and then *tert*-butyl hydroperoxide (3 M in isooctane, 55.7 ml) was added dropwise over 30 min. The mixture was stirred at -20 °C for 10 h and then kept in a freezer overnight. The mixture was quenched with water (100 ml) at 20 °C and then allowed to warm to room temperature. A solution of NaOH (30%) in brine (20 ml) was added and the mixture was stirred vigorously for 45 min at room temperature and then diluted with dichloromethane (100 ml). The layers were allowed to separate and the inhomogenous aqueous layer was extracted with dichloromethane (3×150) ml). The combined organic extracts were dried (Na₂SO₄), and then concentrated in vacuo to leave a pale yellow liquid which was purified by flash chromatography on silica, using ether as eluent to give the *epoxide* (10.64 g, 61%) as a colourless oil; $[a]_{D}^{21}$ +32 (*c*, 1.0 in CHCl₃) (Found: C, 68.4; H, 7.9. $C_{12}H_{16}O_3$ requires C, 69.2, H, 7.7%). $v_{max}(film)/cm^{-1}$ 3436 (br), 3063, 1496, 1455, 1208, 1100; $\delta_{\rm H}$ (400 MHz) 7.36–7.20 (5H, m, Ph), 4.47 (2H, s, CH₂Ph), 3.81–3.74 (1H, m), 3.65 (2H, t, J 6.0 Hz, CH₂O), 3.53– 3.43 (1H, m), 3.03 (1H, m), 2.91 (1H, dt, J 4.6 and 6.0 Hz, CHCH₂O), 1.95–1.71 (2H, m); δ_c(100 MHz) 137.8 (s), 128.0 (d), 127.7 (d), 72.6 (t), 66.5 (t), 61.5 (t), 58.6 (t), 53.4 (d), 31.7 (t); m/z (EI) (Found: 207.1041, (M⁺ - 1). C₁₂H₁₅O₃ requires 207.1021).

5-Benzyloxy-2-methylpentane-1,3-diol 26

A solution of methylmagnesium bromide (2 M in THF, 87 ml, 0.26 mol) was added dropwise over 30 min to a stirred suspension of cuprous iodide (4.95 g, 26 mmol) in dry THF (180 ml) at -20 °C under nitrogen. The mixture was stirred at -20 °C for a further 30 min and then a solution of the epoxy alcohol 25 (18 g, 86.4 mmol) in dry THF (90 ml) was added dropwise over 15 min. The mixture was stirred at -20 °C for 2.5 h, then quenched with saturated aqueous NH₄Cl (180 ml) and allowed to warm to room temperature. It was then stirred vigorously for 30 min before extracting with ether (4 \times 200 ml). The combined organic extracts were washed with saturated aqueous NH₄Cl $(2 \times 100 \text{ ml})$, and brine (100 ml), then dried (MgSO₄) and concentrated in vacuo to leave a pale yellow oil. Analysis of the ¹H NMR spectrum of the residue indicated that a 4:1 mixture of 1,2- and 1,3-regioisomeric diol products had been formed in favour of the required 1,3-diol. A solution of the residue in methanol (360 ml) and water (90 ml), was stirred with NaIO₄ (4.5 g, 21 mmol) for 6 h and then the methanol was removed in vacuo. The residue was diluted with water (400 ml) and then extracted with dichloromethane $(3 \times 200 \text{ ml})$. The combined organic extracts were dried (MgSO₄) and then concentrated in vacuo to leave a pale yellow oil. Flash chromatography on silica using diethyl ether as eluent first gave 4-benzyloxy-2methylbutanal (2.65 g, 16%) and then the diol (12.8 g, 66%) as a colourless oil; $[a]_{D}^{21}$ -2.1 (c, 2.5 in CHCl₃) (Found: C, 69.3; H, 9.3. C₁₃H₂₀O₃ requires C, 69.6; H, 9.0%); v_{max}(film)/cm⁻¹ 3392, 3088, 1496; $\delta_{\rm H}$ (400 MHz) 7.32 (5H, m, Ph), 4.53 (2H, s, CH₂Ph), 3.95 (1H, br s, OH), 3.8–3.6 (5H, m), 3.42 (1H, br s, OH), 1.73–1.63 (3H, m), 0.86 (3H, d, J 6.9 Hz, Me); $\delta_c(100$ MHz) 137.8 (s, Ar), 128.6 (d), 127.9 (d), 127.7 (d), 77.5 (d), 73.6 (t), 69.5 (t), 67.7 (t), 40.3 (d), 34.5 (t), 13.9 (q); m/z (EI) 206 $(M - H_2O)^+$.

5-Benzyloxy-1-(*tert*-butyldiphenylsilanyloxy)-2-methylpentan-3-ol 27

Imidazole (6.65 g, 95.5 mmol) and tert-butyldiphenylsilyl chloride (15 ml, 57.7 mmol) were added sequentially to a solution of the 1,3-diol 26 (11 g, 49 mmol) in dry DMF (55 ml) at room temperature under nitrogen. The solution was stirred at room temperature overnight and then diluted with water (300 ml). The combined organic extracts were washed with water $(2 \times 100 \text{ ml})$ and brine (100 ml), then dried (Na₂SO₄) and concentrated in vacuo to leave a pale yellow oil. Purification by flash chromatography on silica using 7:1 petrol-ethyl acetate as eluent gave the *silyl ether* (21.3 g, 94%) as a colourless oil; $[a]_{D}^{21} - 5.4 (c,$ 1.8 in CHCl₃) (Found: C, 75.3; H, 8.7. C₂₉H₃₈O₃Si requires C, 75.3; H, 8.3%); $v_{max}(film)/cm^{-1}$ 3502 (br), 3070, 2959, 1472; δ_H(400 MHz) 7.66–7.60 (4H, m, Ph), 7.41–7.30 (11H, m, ArH), 4.53 (2H, s, PhCH₂O), 3.81 (1H, ddd, J 9.3, 7.0 and 2.7 Hz, CHOH), 3.6-3.70 (4H, m), 2.0-1.80 (3H, m), 1.05 (9H, s), 0.87 (3H, d, J 6.9 Hz, Me); $\delta_{\rm C}$ (67.8 MHz) 138.7 (s), 136 (d), 133.6 (s), 130.1 (d), 128.8 (d), 128.1 (d), 128.0 (d), 128 (d), 74.0 (d), 73.98 (t), 69.0 (t), 68.8 (t), 40.9 (d), 34.7 (t), 27.3 (q, t-Bu), 19.6 (s, t-Bu), 13.7 (q, Me); m/z (EI) 327 (M⁺ – t-Bu-Ph) (3%).

(5-Benzyloxy-3-methoxy-2-(methyl)pentyloxy)-*tert*butyldiphenylsilane 28

Sodium hydride (60% in oil, 1.6 g, 40 mmol) was added in one portion to a stirred solution of the alcohol 27 (9.1 g, 19.66 mmol) in dry DMF (25 ml) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 5 min and then methyl iodide (6 ml, 96.4 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 2 h and then quenched with saturated aqueous NH₄Cl (200 ml), diluted with water (200 ml) and extracted with ether $(3 \times 100 \text{ ml})$. The combined ether extracts were washed with water $(2 \times 100 \text{ ml})$ and brine (50 ml), then dried (MgSO₄) and concentrated *in vacuo* to leave a pale yellow oil. Purification by flash chromatography on silica using petrol-ethyl acetate 10:1 as eluent gave the methyl ether (7.7 g, 66%) as a colourless oil; $[a]_{D}^{21}$ +4.5 (c, 4.4 in CHCl₃) (Found: C 75.8; H, 8.7. C₃₀H₄₀O₃Si requires C, 75.6; H, 8.5%); v_{max}(film)/ cm⁻¹ 3070, 2931, 1473; $\delta_{\rm H}$ (400 MHz) 7.70–7.65 (4H, m, Ph), 7.37-7.27 (11H, m, Ph), 4.48 (1H, d, J 7 Hz, CHHPh), 4.52 (1H, d, J7 Hz, CHHPh), 3.66 (4H, m), 3.58 (1H, ddd, J 8.9, 5.9 and 3.0 Hz, CHOMe), 3.28 (s, 3H, OCH₃), 1.9-2.0 (1H, m), 1.80-1.60 (2H, m), 1.05 (9H, s, t-Bu), 0.88 (3H, d, J 7 Hz, Me); $\delta_{\rm C}(100 \text{ MHz}) 136.0 \text{ (s)}, 135.6 \text{ (d)}, 133.9 \text{ (d)}, 133.8 \text{ (s)}, 129.65 \text{ (d)},$ 128.3 (d), 127.65 (d), 127.5 (d), 79.0 (d), 73.0 (t), 63.75 (t), 65.7 (t), 38.1 (d), 30.4 (t), 26.9 (q, t-Bu), 19.3 (s, t-Bu), 12.1 (q, Me); m/z (EI) 419 (M - t-Bu)⁺.

5-(*tert*-Butyldiphenylsilanyloxy)-3-methoxy-4-methylpentan-1-ol 29

Pearlman's catalyst [Pd(OH)₂-C, 400 mg] was added to a flask containing a solution of the benzyl ether 28 (4.0 g, 8.4 mmol) in methanol (40 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 $(2 \times 25 \text{ ml})$ and the combined filtrate was concentrated in vacuo to leave a colourless oil. Purification by flash chromatography on silica using 3:1 petrol-ethyl acetate as eluent gave the *alcohol* (2.98 g, 92%) as a colourless oil; $[a]_{\rm D}^{21}$ +11.3 (c, 5.6 in CHCl₃) (Found: C, 71.3; H, 9.1. C₂₃H₃₄O₃Si requires C, 71.5; H, 8.9%); $v_{max}(film)/cm^{-1}$ 3431 (br), 3071, 2960, 1473; δ_H(400 MHz) 7.7–7.6 (4H, m, Ph), 7.4–7.3 (6H, m, Ph), 3.7 (2H, t, J 5.8 Hz, CH₂O), 3.64 (1H, dd, J 10.2 and 5.9 Hz, CHHOSi), 3.4-3.6 (1H, m), 3.52 (1H, dd, J 10.2, 6.6 Hz, CHHOSi), 3.33 (3H, s, OMe), 2.61 (1H, br s, OH), 2.2-2.1 (1H, m), 1.67-1.62 (2H, m), 1.10 (9H, s), 0.84 (3H, d, J 6.9 Hz, Me); δ_{c} (67.80 MHz) 136.0 (d), 134.1 (s), 133.65 (s), 130.1 (d), 128.1 (d), 82.5 (d), 66.2 (t), 61.9 (t), 57.3 (q, OMe), 37.4

(d), 31.6 (t), 27.3 (q, t-Bu), 19.7 (s, t-Bu), 11.8 (q, Me); *m/z* (EI) 297 (M⁺ - t-Bu - MeOH).

5-(*tert*-Butyldiphenylsilanyloxy)-3-methoxy-4-methylpentanal 30

A solution of DMSO (1.44 ml) in dry dichloromethane (5 ml) was added dropwise over 5 min to a solution of oxalyl chloride (1.07 ml) in dry dichloromethane (20 ml) at -78 °C under nitrogen. After 5 min, a solution of the alcohol 29 (3.9 g) in dry dichloromethane (10 ml) was added dropwise over 15 min and the mixture was stirred at -78 °C for 1.5 h. Triethylamine (6.42) ml) 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 $(2 \times 50 \text{ ml})$. The combined dichloromethane extracts were washed with water (50 ml) and brine (50 ml) then dried (Na₂SO₄) and evaporated in vacuo to leave a pale yellow oil. Purification by flash chromatography on silica, using dichloromethane as eluent gave the aldehyde (3.3 g, 87%) as an unstable colourless viscous oil; $[a]_{D}^{21}$ +1.4 (c, 1.9 in CHCl₃); $v_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3030, 2930, 2857, 1725, 1471; $\delta_{\text{H}}(400 \text{ MHz})$ 9.80 (1H, apparent t, J 2 Hz, CHO), 7.7-7.6 (4H, m, ArH), 7.5-7.4 (6H, m, ArH), 3.9 (1H, ddd, J7.9, 5.3 and 4.6 Hz, CHOMe), 3.60 (1H, dd, J 10.3 and 5.2 Hz, CHHOSi), 3.44 (1H, dd, J 10.3 and 6.7 Hz, CHHOSi), 3.26 (3H, s, OMe), 2.4-2.6 (2H, m, CH₂CHO), 2.0–2.1 (1H, m, CHMe), 1.05 (9H, s), 0.85 (3H, d, J 6.9 Hz, Me); $\delta_{\rm C}(100$ MHz) 201.8 (d, CHO), 135.7 (d, Ar), 135.6 (d, Ar), 133.6 (s, Ar), 133.5 (s, Ar), 129.8 (d, Ar), 129.8 (d, Ar), 127.8 (d, Ar), 77.2 (d, C-3), 65.5 (t, C-5), 57.2 (q, OCH₃), 44.6 (t), 37.8 (d), 27.0 (q, t-Bu), 19.3 (s, t-Bu), 11.8 (q, Me); m/z (EI) (Found: M⁺ + Na, 407.1975. C₂₃H₃₂O₃ SiNa requires 407.2018).

5-Benzyloxypent-2-enoic acid 32

A solution of lithium hydroxide monohydrate (2.7 g, 64.9 mmol) in water (100 ml) was added in one portion to a solution of the ester 31 (7.6 g, 32.4 mmol) in 1,4-dioxane (150 ml) and the mixture was then stirred at room temperature for 3 h. The mixture was concentrated in vacuo and the residue was then diluted with water (100 ml). The aqueous solution was extracted with ether $(2 \times 100 \text{ ml})$ and was then acidified to pH 1.0 with 2 M HCl (50 ml) before extracting with 2×150 ml portions of ethyl acetate. The combined extracts were washed successively with water (50 ml) and brine (50 ml), and then dried (MgSO₄). The organic extracts were evaporated under reduced pressure to leave the acid (6.3 g, 95%) as a liquid; $v_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3300–2500, 1698, 1650, 1454; $\delta_{\text{H}}(400 \text{ MHz})$ 7.3– 7.2 (5H, m, Ph), 7.03 (1H, dt, J 15.8 and 6.6 Hz, CH₂CH=), 5.83 (1H, dt, J 15.8, 1.6 Hz, =CHCO₂Et), 4.45 (2H, s, CH₂Ph), 3.53 (2H, t, J 6.6 Hz, CH₂O), 2.47 (2H, apparent qd, J 6.6 and 1.6 Hz, $CH_2CH=$) which was used without further purification.

4-Benzyl-3-(5-benzyloxypent-2-enoyl)-1,3-oxazolidin-2-one 34

Dimethylformamide (80 µl, 1 mmol) and freshly distilled oxalyl chloride (2.0 ml, 23 mmol) were added dropwise over 5 min to a solution of the acid **32** (4.1 g, 20 mmol) in dry dichloromethane (20 ml) at room temperature under argon. The solution was stirred at room temperature for 30 min, and then the solvent was removed *in vacuo* to leave the corresponding acid chloride **33** as a liquid. In a separate flask, *n*-BuLi (1.6 M, 9.4 ml, 15 mmol) was added dropwise over 15 min to a solution of the 4-phenylmethyl-1,3-oxazolid-2-one (2.65 g, 15 mmol) in dry THF (30 ml) at -78 °C under nitrogen until a pale yellow colour remained. A solution of the acid chloride (20 mmol maximum) in dry THF (10 ml) was added dropwise over 10 min to the stirred anion solution at -78 °C. The mixture was stirred at -78 °C for 0.5 h and then allowed to warm to room temperature where it was stirred for 0.5 h. Aqueous 1 M potassium

carbonate (10 ml) was added and the mixture was then stirred at room temperature for 1 h. The mixture was diluted with water (70 ml) and extracted with ethyl acetate (3×75 ml). The combined extracts were washed with water (50 ml), dried over MgSO₄, and then concentrated in vacuo to leave a yellow oil. Flash chromatography on silica using dichloromethane-diethyl ether (25:1) as eluent gave the imide (4.3 g, 80%) as a colourless oil; $[a]_{D}^{20}$ +50.5 (c, 2.6 in CHCl₃) (Found: C 71.5; H, 6.3. C22H24NO4 requires C, 72.1; H, 6.5%); vmax(film)/cm⁻¹ 3028, 2859, 1778, 1682; $\delta_{\rm H}$ (270 MHz) 7.3–7.1 (12H, m, ArH plus HC=CH), 4.67-4.61 (4H, m), 4.45 (2H, s, PhCH₂O), 4.13-4.07 (2H, apparent ABq, 5-H), 3.55 (2H, t, J 6.3 Hz, CH₂OBz), 3.23 (1H, dd, J 13.5 and 3.1 Hz, PhCHH), 2.70 (1H, dd, J 13.5 and 9.6 Hz, PhCHH), 2.53 (2H, apparent q, J 6.3 Hz, CH₂CH=); $\delta_{\rm C}(100 \text{ MHz})$ 164.7 (s), 153.3 (s), 148.0 (d), 138.0 (s, Ph), 135.3 (s, Ph), 129.4 (d), 128.8 (d), 128.5 (d), 128.3 (d), 127.6 (d), 127.5 (d), 127.3 (d, Ph), 121.7 (d), 72.9 (t, PhCH₂O), 68.2 (t), 66.1 (t), 55.2 (d), 37.8 (t, PhCH₂C), 33.0 (t, C-4); m/z (CI) (Found $M^{+} + 1,\, 366.1687. \, C_{22}H_{23}NO_4 \, requires \, 366.1705).$

4-Benzyl-3-{5-benzyloxy-2-[5-(*tert*-butyldiphenylsilanyloxy)-1hydroxy-3-methoxy-4-methylpentyl]pent-3-enoyl}oxazolidin-2one 35

Bu₂BOTf (1.7 ml, 8 mmol) and Et₃N (1.4 ml, 10 mmol) were added to a solution of the imide 34 (2.6 g, 7.11 mmol) in dry dichloromethane (50 ml) at -78 °C under nitrogen 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 30 (3 g, 7.8 mmol) in dry dichloromethane (15 ml) was added dropwise over 0.5 h to the mixture which was then further stirred at -78 °C for 1.5 h. The mixture was allowed to warm to 0 °C and held at that temperature for 2 h. It was then quenched by adding a solution of NaOAc (0.5 g) in methanol and water (10 ml, 10:1). After 20 min, aqueous H2O2 (3 ml, 27%) 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 was extracted with dichloromethane $(3 \times 100 \text{ ml})$. The combined organic extracts were washed with water (50 ml) and dried (Na₂SO₄), then filtered, and the filtrate was concentrated in vacuo to leave a yellow oil. Flash chromatography on silica using 50:1 dichloromethane-ether as eluent gave recovered aldehyde (1 g) (eluted first) and then the secondary alcohol (2.90 g, 70% based on recovered aldehyde) as a colourless oil; $[a]_{D}^{20}$ +4.4 (c, 5.1 in CHCl₃) (Found: C, 71.6; H, 7.5; N, 1.5. C₄₅H₅₅NO₇Si requires C, 72.0; H, 7.3; N, 1.8%); ν_{max} (film)/cm⁻¹ 3500 (br), 2930, 1781, 1694; δ_H(400 MHz) 7.7–7.65 (4H, m, Ph), 7.4–7.3 (16H, m, Ph), 6.0-5.95 (2H, m, HC=CH), 4.9 (4.57) (1H, dd, J 8.0 and 4.1 Hz), 4.7-4.65 (1H, m, 4'-H), 4.48 and 4.52 (2H, J 7 Hz, PhCH₂O), 4.30–4.2 (1H, m, 5-H), 4.16–4.09 (2H, m, 1-H), 4.07 (2H, d, J 4.7 Hz, 9-H), 4.22-4.16 (2H, m, 9-H), 3.67-3.55 (1H, m, 3H/3'-H), 3.53 (3.32) (3H, s, OMe), 3.23 (1H, t, J 13.5 Hz, 5'-H), 2.70 (1H, dd, J 13.5 and 9.7 Hz), 2.0 (1H, sextet, J 6.5 Hz, 2-H), 1.75–1.69 (m, 1H, 4-H), 1.55–1.48 (1H, m, 4-H), 1.06 (9H, s, t-Bu), 0.90 (0.88) (3H, d, J 6.9 Hz); δ_C(100 MHz) 173.7 (173.34) (s, C-1'), 153.0 (152.91) (s, C-2'), 138.2, 135.6, 133.8 (s, Ph), 136.2 (d), 135.6 (d), 135.0 (d), 133.7 (d), 132.8 (132.4) (d, C-8), 129.6 (d), 129.4 (d), 128.9 (d), 128.3 (d), 127.65 (d), 127.3 (d, Ph), 126.7 (126.4), (d, C-7), 79.3 (d, C-3), 72.7 (71.9) (t, PhCH₂O), 70.2 (66.6) (t, C-9), 69.4 (67.1) (d, C-5), 65.8 (65.7) (t, C-3'), 57.5 (57.4) (q, OMe), 55.0 (d, C-4'), 51.6 (48.0) (d, C-6), 37.9 (d, C-2), 37.4 (t, C-5'), 34.0 (33.8) (t, C-4), 26.9 (q, t-Bu), 19.2 (s, t-Bu), 12.4 (q, Me); m/z (FAB) (Found M⁺ + 1, 750.3710. C₄₅H₅₆NO₇Si requires 750.3826).

2-(3-Benzyloxyprop-1-enyl)-7-(*tert*-butyldiphenylsilanyloxy)-5methoxy-6-methylheptane-1,3-diol 36

Dry methanol (0.39 ml, 9.5 mmol) and $LiBH_4$ (4.8 ml, 2.5 M in THF, 9.6 mmol) were added to a solution of the imide **35** (2.85

g, 3.80 mmol) in dry THF (35 ml) at 0 °C under nitrogen and the resulting mixture was stirred at 0 °C for 0.5 h. The mixture was quenched by slow addition of aqueous NaOH (1 M, 22 ml) and then allowed to warm to room temperature. Ethyl acetate (100 ml) was added and the separated aqueous phase was then extracted with more ethyl acetate $(3 \times 50 \text{ ml})$. The combined organic extracts were washed with water (50 ml) and brine (50 ml), then dried over Na2SO4 and concentrated in vacuo to leave a colourless viscous oil. Purification by flash chromatography on silica using ethyl acetate-petrol (2:1) as eluent gave the 1,3*diol* (1.96 g, 90%) as a colourless viscous oil; $[a]_{D}^{20}$ +13.8 (c, 4.0 in CHCl₃) (Found: C, 72.5; H, 8.7. C₃₅H₄₈O₅Si requires C, 72.9; H, 8.4%); $v_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3416 (br), 2930, 1428, 1086; $\delta_{\text{H}}(400$ MHz) 7.7-7.65 (4H, m, Ph), 7.4-7.28 (11H, m, Ph), 5.93-5.70 (2H, m, HC=CH), 4.5 and 4.52 (2H, both d, J 7 Hz, PhCH₂O), 4.15-4.09 (1H, m, H-3), 4.06 (2H, apparent t, J 6.4 Hz), 4.03 (2H, d, J 5 Hz, H-3'), 3.78-3.73 (3.64-3.59) (2H, m, H-7), 3.71 (3.67) (2H, apparent dd, J 9.9 and 5.1 Hz, H-1), 3.58-3.52 (1H, m, H-5), 3.32 (3.31) (3H, s, OMe), 2.68–2.55 (2H, br s, 2 × OH), 2.62-2.57 (2.33-2.30) (1H, m, H-2), 2.04-2.00 (1H, m, H-6), 1.80-1.73 (1.49-1.41) (2H, m, H-4), 1.06 (9H, s, t-Bu), 0.88 (0.87) (3H, d, J 6.5 Hz, C-7–Me); $\delta_{\rm C}$ (67.8 MHz) 138.2, 138.0 (q), 133.7, 133.6 (q), 135.6, 135.5, 128.9, 128.3, 127.74, 127.7, 127.6, 127.55, 127.1 (all ArCH), 130.5 (130.3), 129.65 (129.5) (CH, C7/8), 80.0 (79.9) (CH, C-3), 72.4 (71.9) (PhCH₂O), 70.6 (CH₂, C-5), 69.8 (69.5) (CH₂, C-1), 57.5 (57.4) (OMe), 50.0 (45.6) (CH₂, C-6), 37.6 (37.5) (CH, C-2), 33.1 (CH, C-4), 26.8 (s, t-Bu), 19.2 (q, t-Bu), 12.7 (12.6) (C-2-Me); *m*/*z* (FAB) (Found: $M^+ + 1$, 577.3349. $C_{35}H_{48}O_5Si$ requires 577.3336).

Methanesulfonic acid 5-benzyloxy-2-[5-(*tert*-butyldiphenylsilanyloxy)-1-hydroxy-3-methoxy-4-methylpentyl]pent-3-enyl ester 37

N,N-Diisopropylethylamine (1.28 ml, 7.37 mmol) and methanesulfonyl chloride (0.255 ml, 3.3 mmol) were added sequentially to a stirred solution of the diol 36 (1.9 g, 3.30 mmol) in dry dichloromethane (38 ml) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C for 1 h and then at room temperature for 1 h. Aqueous potassium carbonate (1 M, 38 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 $(3 \times 50 \text{ ml})$ and the combined organic extracts were then dried (Na2SO4) and concentrated in vacuo to leave a pale yellow oil. Flash chromatography on silica using dichloromethane-ether (20:1) as eluent gave the pure methanesulfonate (1.94 g, 90%), as an oil; $[a]_{D}^{20} + 2.0$ (c, 3.4 in CHCl₃) (Found: C, 65.9; H, 7.9. C₃₆H₅₀O₇SSi requires C, 66.0; H, 7.7%); $v_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3468, 2959, 2932; $\delta_{\text{H}}(400 \text{ MHz})$ 7.68– 7.64 (4H, m, Ph), 7.43-7.28 (11H, m, Ph), 5.94-5.60 (2H, m, HC=CH), 4.52 and 4.50 (2H, both d, J 7 Hz, PhCH₂O), 4.35 (1H, dd, J 15.8 and 7.8 Hz, H-10), 4.20 (1H, dd, J 9.8 and 6.7 Hz), 4.15-4.10 (1H, m, CHOH), 4.07 (4.02) (2H, d, J 6.5 Hz, CH₂OCH₂Ph), 3.71 (3.60) (2H, dd, J 9.9 and 5.0 Hz, CH₂O-SiR₃), 3.57-3.52 (1H, m, CHOMe), 3.31 (3.30) (3H, s, OMe), 3.00 (2.97) (3H, s, SMe), 2.80-2.76 (2.55-2.48) (1H, m, CH-CH=CH-), 2.05-2.00 (1H, m, CHMe), 1.78-1.71 (1.42-1.33) (2H, m), 1.06 (9H, s, t-Bu), 0.38 (0.36) (3H, d, J 7.3 Hz, C2-Me); δ_c(67.8 MHz) 138.1, 138.0, 133.9, 133.5 (all s, Ph), 135.5, 135.5, 129.5, 128.3, 127.8, 127.6 (all CH, Ph), 132.1 (131.5) and 127.5 (127.2) (CH, C7/8), 79.9 (79.9) (CH, C-3), 72.4 (71.9) (PhCH₂O), 70.2 (65.4) (CH₂, C-4), 67.9 (69.9) (CH₂, C-10), 66.7 (66.6) (CH, C-5), 65.4 (CH₂, C-1), 57.4 (57.3) (OMe), 48.1 (43.5) (CH, C-6), 37.4 (37.4) (CH, C-2), 37.1 (37.0) (SMe), 33.3 (33.1) (CH₂, C-4), 26.8 (t-Bu), 19.2 (s, t-Bu), 12.7 (12.6) (CH₃, C2-Me); m/z (FAB) (Found: $M^+ + 1$, 655.3085. $C_{36}H_{50}O_7SSi$ requires 655.3125).

1-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxy)-7-methoxy-4,8dimethylnon-2-en-5-ol 38

Dry methanol (0.38 ml, 9.32 mmol) and lithium borohydride

(2 M in THF, 4.66 ml, 9.32 mmol) were added sequentially to a stirred solution of the methanesulfonate 37 (1.74 g, 2.66 mmol) in dry diglyme (44 ml) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C for 90 min and then quenched by adding aqueous sodium hydroxide (1 M, 45 ml) dropwise. The mixture was extracted with dichloromethane $(3 \times 50 \text{ ml})$ and the combined extracts were dried (Na₂SO₄) and concentrated in vacuo to leave a pale yellow oil. The oil was purified by flash chromatography on silica using dichloromethane-ether (50:1) as eluent to give the reduced product (1.2 g, 82%) as a colourless viscous oil; $[a]_{D}^{20}$ +14.3 (c, 6.0 in CHCl₃); v_{max} (film)/cm⁻¹ 3473, 2960, 2930 (Found: C, 74.7; H, 8.8. C₃₅H₄₈O₄Si requires C, 74.9; H, 8.6%); δ_H(400 MHz) 7.69–7.66 (4H, m, Ph), 7.42–7.30 (11H, m, Ph), 5.76-5.55 (2H, m, HC=CH), 4.52 and 4.5 (2H, d, J 7 Hz, PhCH₂O), 4.09 (1H, apparent td, J 5.4 and 1.4 Hz, H-5), 4.02 (1H, apparent d, J 5.6 Hz, H-3), 3.75-3.69 (1H, m, CHOH), 3.72-3.68 (3.66-3.59) (2H, m, H-9), 3.62-3.57 (1H, m, H-7), 3.34 (3.32) (3H, s, OMe), 2.56 (1H, br s, OH), 2.43 (2.26) (1H, sextet, J 6.5 Hz, H-4), 2.07-2.00 (1H, m, H-8), 1.62-1.50 (2H, m, H-6), 1.07 (9H, s, t-Bu), 1.05 (1.00) (3H, d, J 6.7 Hz, CHMe), 0.89 (0.88) (3H, d, J 6.9 Hz, C8–Me); $\delta_{c}(100 \text{ MHz})$ 138.3, 138.2, 133.7, 133.6 (all q, Ar), 135.5, 135.5, 129.5, 128.2, 128.0, 127.9, 127.6, 127.5, 127.4 (all CH, Ph), 136.2 (135.9), 127.2 (127.0) (CH, C-7/8), 79.7 (79.6) (CH, C-3), 72.1 (71.8) (PhCH₂O), 71.8 (71.7) (CH, C-5), 70.7 (65.82) (CH₂, C-9), 65.7 (65.59) (CH₂, C-1), 57.4 (OCH₃), 42.9 (38.7) (CH, C-6), 37.6 (CH, C-2), 33.3 (32.9) (CH₂, C-4), 26.8 (26.6) (t-Bu), 19.2 (q, t-Bu), 17.05 (16.1) (CH₃, C-6), 12.5 (12.4) (Me, C-2); m/z (FAB) $561 (M + H)^+$.

1-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxy)-7-methoxy-4,8dimethylnon-2-en-5-yl *tert*-butyldimethylsilyl ether 39

A solution of tert-butyldimethylsilyl trifluoromethanesulfonate (2.5 ml, 10.54 mmol) in dry dichloromethane (10 ml) was added dropwise over 10 min to a stirred solution of the alcohol 38 (4.93 g, 8.78 mmol) and 2,6-lutidine (2.5 ml, 21.07 mmol) in dry dichloromethane (45 ml) at 0 °C under nitrogen. 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 (3 ml) was added followed by dichloromethane (50 ml) and the solution was then washed with water $(2 \times 50 \text{ ml})$ and brine (25 ml) and finally dried (Na₂SO₄). The dried filtrate was concentrated in vacuo to leave a pale yellow oil. Purification by flash chromatography on silica using ether-dichloromethane (50:1) as eluent gave the bis-silyl ether (5.6 g, 95%) as a colourless oil; $[a]_{D}^{25}$ +17.6 (*c*, 9 in CHCl₃) (Found: C, 73.3; H, 9.6; C₄₁H₆₂O₄Si₂ requires C, 73.0; H, 9.2%); δ_{H} (400 MHz) 7.60–7.14 (15H, m), 5.57-5.17 (2H, m), 4.43 (2H, s), 4.40 (2H, s), 3.91-3.60 (2H, m), 3.45-3.36 (2H, m), 3.18 (3H, s), 3.15 (3H, s), 2.65-2.35 (1H, m), 2.10–1.95 (1H, m), 1.30–1.27 (2H, m), 1.1 (9H, s), 1.04 and 0.99 (3H, both d, J 7 Hz), 0.91 and 0.85 (two singlets, 9H), 0.86 (3H, d, J 7 Hz), 0.04 (6H, 4 singlets); δ_c(100 MHz) 138.4, 138.3, 136.6, 135.6, 135.4, 133.8, 129.5, 128.3, 128.3, 127.8, 127.7, 127.6, 127.5, 126.6, 126.39, 78.3, 76.5, 76.3, 76.3, 72.45, 72.2, 72.17, 71.6, 70.1, 66.1, 56.2, 56.1, 42.55, 38.4, 37.2, 37.1, 33.98, 34.0, 26.9, 26.0, 19.2, 18.1, 15.5, 13.4, 11.4, 4.4, 4.3, 4.2; m/z (FAB) (Found: M⁺ + 1, 675.4265. C₄₁H₆₂O₄Si₂ requires 675.4289).

3-(*tert*-Butyldimethylsilanyloxy)-7-(*tert*-butyldiphenylsilanyloxy)-5-methoxy-2,6-dimethylheptanal 40

A solution of the alkene **39** (1.4 g, 2.1 mmol) in dry dichloromethane (30 ml) was ozonised at -78 °C in the presence of a small amount of Sudan-Red indicator until the solution turned blue. Oxygen was then bubbled through the solution for 10 min to remove any excess of ozone. Triphenylphosphine (0.69 g, 2.59 mmol) was added in one portion under nitrogen and the solution was then stirred at -78 °C for 15 min before being allowed to warm to room temperature. The solution was concentrated *in vacuo* to leave a residue which was purified by chromatography over silica using petrol–ethyl acetate (6:1) as eluent to give the *aldehyde* (0.93 g, 80%) as a colourless oil; $[a]_{D}^{20}$ – 3.7 (*c*, 5.8 in CHCl₃); $\delta_{H}(270 \text{ MHz})$ 9.64 (1H, d, *J* 1.3 Hz, CHO), 7.6–7.55 (4H, m), 7.36–7.31 (6H, m), 4.15 (1H, dt, *J* 8 and 3.6 Hz), 3.46–3.38 (3H, m), 3.2 (3H, s), 2.51 (1H, dq, *J* 6.3 and 1.3 Hz), 2.06–1.95 (m, 1H), 1.42 (1H, ddd, *J* 14.4, 8.6 and 2.3 Hz), 1.30 (1H, ddd, *J* 3.6, 10.1 and 14.2 Hz), 1.02 (3H, d, *J* 7 Hz), 0.98 (9H, s), 0.79 (9H, s), 0.73 (3H, d, *J* 6.9 Hz), 0.00 (6H, s); $\delta_{C}(67.8 \text{ MHz})$ 203.9 (CHO), 135.6 (CH), 133.7 (C), 129.6 (CH), 127.6 (CH), 78.0 (CH), 69.9 (CH), 66.0 (CH₂), 56.0 (OCH₃), 52.8 (CH), 36.7 (CH), 35.0 (CH₂), 26.9 (C–CH₃), 25.9 (C–CH₃), 19.2 (C), 18.0 (q), 10.9 (CH₃), 9.0 (CH₃), -4.3 (CH₃), -4.4 (CH₃); *m/z* (FAB) 567 (M⁺ + H₂O).

6-(*tert*-Butyldimethylsilanyloxy)-10-(*tert*-butyldiphenylsilanyloxy)-8-methoxy-5,9-dimethyldec-1-en-4-ol 41

A solution of allylmagnesium bromide (1.0 M in ether, 1.58 ml) was added dropwise over 2 min to a stirred solution of (+)-IPC₂BOMe (0.46 g, 1.55 mmol) in dry ether (1.5 ml) at -78 °C under argon. 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 40 (0.86 g, 1.54 mmol) in dry ether (3 ml) was slowly added via cannula. The mixture was stirred at -78 °C for 5 h and then quenched by the slow addition of aqueous sodium hydroxide (3 M, 1.12 ml). The mixture was warmed to room temperature and aqueous H2O2 (30%, 0.44 ml) 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 organic extracts were washed with water $(2 \times 20 \text{ ml})$ and brine (25 ml), then dried (Na₂SO₄) and concentrated in vacuo to leave an oil. Purification by flash chromatography on silica using petrolethyl acetate (9:1) as eluent gave the alcohol (0.65 g, 70%) as a colourless oil; $[a]_{D}^{20}$ +10.9 (c, 4.2 in CHCl₃) (Found: C, 70.4; H, 10.2. C₃₅H₅₈O₄Si₂ requires C, 70.2; H, 9.8%); δ_H(400 MHz) 7.68-7.65 (4H, m, ArH), 7.46-7.37 (6H, m, ArH), 5.8 (1H, ddt, J 17, 14 and 7 Hz, H₂C=CHCH₂), 5.15-5.05 (2H, m, =CH₂), 4.10 (1H, apparent dt, J 2 and 7 Hz, 4-H), 3.90 (1H, dt, J 2 and 6 Hz), 3.55 (2H, apparent d, J 7 Hz, 10-H) 3.40 (1H, br s, OH), 3.35 (1H, ddd, J 2, 4 and 9 Hz), 3.28 (3H, s, OMe), 2.32 (1H, quintet, J7 Hz), 2.15 (1H, quintet, J7 Hz), 2.08-2.04 (1H, m, 9-H), 1.76-1.69 (1H, m, 7-H), 1.65 (1H, tq, J 2 and 7 Hz, 5-H), 1.55 (1H, ddd, J 2.6, 6 and 14.5 Hz, 7-H), 1.07 (9H, s), 1.03 (3H, d, J 7.1 Hz), 0.88 (9H, s), 0.86 (3H, d, J 7 Hz), 0.084 (3H, s), $0.076 (3H, s); \delta_{C}(100 \text{ MHz}) 135.7 (d), 134.6 (s), 129.8 (d), 127.8$ (d), 116.6 (t), 79.2 (d), 70.5 (d), 66.1 (t), 56.45 (OCH₃), 40.1 (d), 39.6 (d), 37.3 (t), 35.6 (t), 27.0 (q, t-Bu), 26.0 (q, t-Bu), 19.4 (s, t-Bu), 18.0 (s, t-Bu), 11.3 (q, Me), 11.0 (q, Me), -4.1 (q, Me), $-4.4(q, Me); m/z (FAB) (Found: M^{+} + 1, 599.3962. C_{35}H_{58}O_4Si_2)$ requires 599.3951).

6-(*tert*-Butyldimethylsilanyloxy)-10-(*tert*-butyldiphenylsilanyloxy)-4,8-dimethoxy-5,9-dimethyldec-1-ene 46

2,6-Di-*tert*-butylpyridine (2.13 g, 10.8 mmol) and methyl trifluoromethanesulfonate (0.612 ml, 5.41 mmol) were added sequentially to a solution of the alcohol **41** (0.22 g, 0.36 mmol) in chloroform (7.5 ml) under nitrogen. The mixture was heated to reflux for 70 min and then cooled to room temperature. Concentrated NH₄OH (0.78 ml, 10.82 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 × 25 ml), water (20 ml) and brine (25 ml), then dried (Na₂SO₄) and concentrated *in vacuo* to leave a pale yellow oil. Purification by flash chromatography on silica using dichloromethane–petrol (3:2) as eluent gave the *methyl ether* (0.21 g, 95%) as a colourless oil; $[a]_{D}^{20}$ +16.2 (c, 3.2 in CHCl₃) (Found: C, 70.8; H, 10.1. $\begin{array}{l} C_{36}H_{60}O_4{\rm Si}_2 \mbox{ requires C. 70.5; H, 9.9\%}; \delta_{\rm H}(360\mbox{ MHz})\ 7.40-7.50 \\ (6{\rm H, m}),\ 7.65-7.70\ (4{\rm H, m}),\ 5.85\ (1{\rm H, ddt},\ J\ 17,\ 14\mbox{ and }7\ {\rm Hz}, \\ {\rm H}_2{\rm C}{=}{\rm C}H{\rm C}{\rm H}_2),\ 5.16-5.06\ (2{\rm H, m}),\ 4.01\ (1{\rm H, m}),\ 3.60\ (2{\rm H, m}), \\ 3.48\ (1{\rm H, m}),\ 3.33\ (3{\rm H, s}),\ 3.31\ (3{\rm H, s}),\ 2.95\ (1{\rm H, m}),\ 2.35\ (2{\rm H, m}), \\ 3.48\ (1{\rm H, m}),\ 3.33\ (3{\rm H, s}),\ 3.31\ (3{\rm H, s}),\ 2.95\ (1{\rm H, m}),\ 2.35\ (2{\rm H, m}), \\ 3.48\ (1{\rm H, m}),\ 1.36\ (1{\rm H, m}),\ 1.35\ (3{\rm H, m}),\ 1.15\ (9{\rm H, s}),\ 0.92\ (3{\rm H, d},\ J\ 7\ {\rm Hz}),\ 0.85\ (12{\rm H, s},\ 9{\rm H}\ +\ obscured\ doublet,\ 3{\rm H}); \\ \delta_{\rm C}(100\ {\rm MHz})\ 135.6\ ({\rm CH}),\ 134.6\ ({\rm CH}),\ 133.8\ ({\rm C}),\ 129.5\ ({\rm CH}), \\ 127.6\ ({\rm CH}),\ 117.2\ ({\rm CH}_2),\ 82.75\ ({\rm CH}),\ 78.7\ ({\rm CH}),\ 69.9\ ({\rm CH}), \\ 66.2\ ({\rm CH}_2),\ 57.3\ ({\rm OCH}_3),\ 56.8\ ({\rm OCH}_3),\ 42.5\ ({\rm CH}),\ 37.4\ ({\rm CH}), \\ 34.8\ ({\rm CH}_2),\ 33.0\ ({\rm CH}_2),\ 29.9\ (t{\rm -Bu}),\ 26.0\ (t{\rm -Bu}),\ 19.25\ (q),\ 18.0\ (q),\ 11.45\ ({\rm CH}_3),\ 8.6\ ({\rm CH}_3),\ -4.0\ ({\rm Me}),\ -4.6\ ({\rm Me});\ m/z\ ({\rm FAB}) \\ 614\ ({\rm M}\ +\ {\rm H})^+. \end{array}$

1-(*tert*-Butyldiphenylsilanyloxy)-3,7-dimethoxy-2,6-dimethyldec-9-en-5-ol 47

Pyridinium toluene-p-sulfonate (160 mg) was added to a solution of the bis-silyl ether 46 (1.30 g, 2.1 mmol) in ethanol (17 ml) and the mixture was heated to reflux for 9 h, then concentrated in vacuo. The residue was purified by chromatography over silica using dichloromethane-ether (7:1) as eluent to give the *alcohol* (948 mg, 90%) as a colourless oil; $[a]_{D}^{20}$ +7.6 (c, 2.5 in CHCl₃) (Found: C, 73.0; H, 9.7. C₃₀H₄₆O₄Si requires C, 72.3; H, 9.2%); $\delta_{\rm H}(270~{\rm MHz})$ 7.76 (4H, br m), 7.45–7.35 (6H, m), 5.87 (1H, ddt, J 15, 12 and 7 Hz, CH=CH₂), 5.12-5.0 (2H, m), 3.75 (1H, m), 3.56 (4H, m), 3.35 (3H, s), 3.32 (3H, s), 2.56 (1H, m), 2.21 (1H, m), 2.05 (1H, m), 1.65 (1H, m), 1.54 (3H, m), 1.12 (9H, s), 0.98 (3H, d, J 7 Hz), 0.96 (3H, d, J 7 Hz); δ_c(100 MHz) 136.4 (d), 136.4 (d), 136.1 (q), 130.3 (d), 128.4 (d), 117.6 (t), 82.7 (d), 80.3 (CH), 71.8 (CH, C-OH), 66.6 (t), 58.3 (OCH₃), 41.2 (s), 38.8 (s), 35.93 (CH₂), 35.8 (t), 27.7 (s), 20.1 (q), 12.9 (s), 11.7 (s, CH₃) (Found: $M^+ + 1$, 499.3232. $C_{30}H_{46}O_4Si$ requires 499.3243).

tert-Butyl(3,7-dimethoxy-5-methoxymethoxy-2,6-dimethyldec-9-enyloxy)diphenylsilane 48

Methoxymethyl chloride (0.56 ml, 8.3 mmol) was added dropwise to a solution of the alcohol 47 (0.83 g, 1.66 mmol) and diisopropylethylamine (2.8 ml, 16.6 mmol) in dry dichloromethane (50 ml) under nitrogen, and the mixture was then heated under reflux for 1 h. The mixture was cooled to room temperature, and another portion of methoxymethyl chloride was added and the mixture was 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 several times with water (until the yellow colour faded), followed by brine (50 ml) and then dried (Na₂SO₄). The mixture was concentrated in vacuo to leave a pale yellow residue which was purified by flash chromatography on silica using dichloromethane-ether (25:1) as eluent to give the MOM-ether (0.85 g, 95%) as a colourless viscous oil; $[a]_{D}^{20}$ +16.6 (c, 2.2 in CHCl₃); (Found: C, 71.3; H, 9.6. C₃₂H₅₀SiO₂ requires C, 70.9; H, 9.2%) δ_H(400 MHz) 7.72–7.69 (4H, m), 7.45–7.38 (6H, m), 5.82 (1H, ddt, J 15 11 and 7Hz, CH=CH₂) 5.20-5.08 (2H, m, =CH₂), 4.6 and 4.7 (2H, d, J 6.7 Hz, CH2O), 3.82-3.75 (1H, m), 3.60-3.50 (3H, m), 3.35 (6H, s, 2 × OMe), 3.33 (3H, s, OMe), 3.20–3.10 (1H, m), 2.40-2.31 (2H, m), 2.19-2.10 (1H, m), 2.00-1.90 (1H, m), 1.45-1.41 (2H, m), 1.12 (9H, m), 0.90 (3H, d, J 7.2 Hz, Me), 0.85 (3H, d, J 7.0 Hz, Me); $\delta_{\rm C}$ (67.8 MHz) 136.0 (d), 135.7 (d), 134.9 (s), 134.1 (d), 129.9 (d), 127.9 (d), 117.4 (t), 96.7 (t), 82.0 (d), 78.65 (d), 76.9 (d), 66.3 (t), 57.5 (q, OMe), 57.3 (q, OMe), 56.0 (q, OMe), 40.0 (s), 37.8 (s), 35.3 (t), 32.3 (t), 27.1 (q, t-Bu), 19.55 (s, t-Bu), 11.7 (q, Me), 9.4 (q, Me) (Found: $M^+ + 1$, 543.3505. C₃₂H₅₀SiO₅ requires 543.3453).

9-(tert-Butyldiphenylsilanyloxy)-3,7-dimethoxy-5-methoxymethoxy-4,8-dimethylnonanal 49

A solution of the alkene **48** (0.82 g, 1.51 mmol) in dry dichloromethane (40 ml) was ozonised at -78 °C in the presence of a small amount of Sudan-Red indicator until a blue colour persisted and then oxygen was bubbled through the solution for 10 min. Triphenylphosphine (0.49 g, 1.85 mmol) was added, and the mixture was stirred at -78 °C for 15 min under nitrogen, and then allowed to warm to room temperature. The mixture was concentrated in vacuo to leave a pale yellow residue which was purified by chromatography on silica using dichloromethane-ether (12:1) as eluent to give the aldehyde (0.73 g, 89%) as a labile colourless viscous liquid; $[a]_{D}^{20} + 20.0 (c, c)$ 1.75 in CHCl₃); δ_H(400 MHz) 9.85 (1H, t, J 1.3 Hz, CHO), 7.80-7.71 (4H, m), 7.5-7.4 (6H, m), 4.6 (1H, d, J 6 Hz, CHHO), 3.52 (1H, d, J 6 Hz, CHHO), 3.80 (1H, ddd, J 9.3, 4.7 and 2.2 Hz), 3.68 (1H, apparent q, J 5.2 Hz), 3.55 (3H, m), 3.3 (3H, s, OMe), 3.20 (3H, s, OCH₃), 3.11 (3H, s), 2.65 (2H, m), 2.14 (1H, m), 1.88 (1H, m), 1.45 (2H, m), 1.31 (2H, m), 1.00 (9H, s), 0.91 (3H, d, J 6.7 Hz), 0.82 (3H, d, J 6.8 Hz); $\delta_{\rm C}(100$ MHz) 200.8 (CHO), 135.1 (d), 133.1 (s), 129.0 (d), 127.0 (d), 96.2 (t), 77.6 (d), 77.2 (d), 76.8 (d), 65.4 (t), 57.0 (OCH₃), 56.3 (OCH₃), 55.2 (OCH₃), 45.66 (t), 41.0 (d), 36.6 (d), 31.6 (t), 26.3 (t-Bu), 18.6 (Me), 10.6 (q, Me), 9.1 (q, Me) (Found: M + Na 579.3243. $C_{31}H_{48}O_6SiNa$ requires 579.3302); which was used immediately in the next step.

tert-Butyl(3,7,9,9-tetramethoxy-5-methoxymethoxy-2,6-dimethyl-nonyloxy)diphenylsilane 50

Toluene-p-sulfonic acid (12 mg, catalytic) was added in one portion to a solution of the aldehyde 49 (780 mg, 1.4 mmol) in a mixture of trimethyl orthoformate (32 ml) and dry methanol (22 ml) at room temperature under nitrogen. The homogeneous mixture was stirred for 1 h and then quenched with saturated sodium bicarbonate (5 ml). It was then concentrated in vacuo and the residue was extracted with dichloromethane (3×50) ml). The combined organic extract was washed successively with water (50 ml) and brine (50 ml), then dried (Na₂SO₄), and concentrated in vacuo to leave a pale yellow oil. Purification by chromatography on silica using dichloromethane-ether (7:1) as eluent gave the dimethyl acetal (830 mg, 98%) as a colourless oil; $[a]_{D}^{20}$ +17.8 (c, 1.65 in CHCl₃); δ_{H} (400 MHz) 7.72–7.69 (4H, m), 7.45-7.38 (6H, m), 4.72 (1H, d, J 6.7 Hz, CHHO), 4.64 (1H, d, J 6.7 Hz, CHHO), 4.56 (1H, t, J 5.6 Hz), 3.86 (1H, m), 3.54 (br d, 1H, J 6.3 Hz), 3.38 (3H, s, OCH₃), 3.37 (3H, s, OCH₃), 3.36 (3H, s, OCH₃), 3.35 (3H, s, OCH₃), 3.34 (3H, s, OCH₃), 3.33-3.27 (2H, m), 2.19-2.12 (1H, m), 1.95-1.91 (1H, m), 1.83 (2H, t, J 5.4 Hz), 1.43 (2H, t, J 5.5 Hz), 1.18 (9H, s, t-Bu), 0.95 (3H, d, J 7.0 Hz), 0.86 (3H, d, J 7.0 Hz); δ_c(100 MHz) 135.8 (d), 135.7 (s), 133.9 (d), 129.6 (d), 127.7 (d), 102.3 (d), 96.7 (t), 79.4 (d), 78.2 (d), 77.5 (d), 66.1 (t), 58.1 (OCH₃), 57.0 (OCH₃), 55.8 (OCH₃), 53.2 (OCH₃), 52.0 (OCH₃), 41.4 (d), 37.4 (d), 35.2 (t), 32.1 (t), 26.9 (q, t-Bu), 19.3 (s), 11.3 (q, CH₃), 9.45 (q, CH₃); *m*/*z* (FAB) (Found: M + Na, 613.3492. $C_{33}H_{54}O_7SiNa$ requires 613.3537).

3,7,9,9-Tetramethoxy-5-methoxymethoxy-2,6-dimethylnonan-1ol 51

Tetrabutylammonium fluoride (442 mg, 1.69 mmol) was added in one portion to a stirred solution of the silyl ether **50** (0.825 g, 1.39 mmol) in dry THF (12.5 ml) at room temperature under nitrogen 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 concentrated *in vacuo* to leave a residue which was extracted with dichloromethane (3 × 50 ml). The combined organic extracts were washed with water (50 ml) and brine (50 ml) then dried (Na₂SO₄) and concentrated *in vacuo* to leave a pale yellow oil. Purification by chromatography on silica using ether– dichloromethane (3:1) as eluent gave the *alcohol* (484 mg, 98%) as a colourless, viscous liquid; $[a]_{D}^{20}$ +43.6 (*c*, 1.6 in CHCl₃); $\delta_{\rm H}(400 \text{ MHz}) 4.67 (1\text{H}, d, J7 \text{ Hz}, CHHO), 4.59 (1\text{H}, d, J7 \text{ Hz},$ CH*H*O), 4.45 (1H, t, *J* 5.6 Hz, C*H*(OMe)₂), 3.69–3.43 (3H, m), 3.38 (6H, s, 2 × OCH₃), 3.33 (3H, s, OCH₃), 3.29 (3H, s, OCH₃), 3.27 (3H, s, OCH₃), 3.28–3.15 (1H, m), 1.92–1.82 (2H, m), 1.74 (2H, t, *J* 6 Hz), 1.52–1.35 (2H, m), 0.85 (3H, d, *J* 7 Hz, CH*M*e), 0.84 (3H, d, *J* 6.9 Hz, CH*M*e); δ_{C} (100 MHz) 102.2 (d), 96.5 (t), 80.8 (d), 79.3 (d), 77.9 (d), 65.6 (t), 58.0 (q, OCH₃), 57.9 (q, OCH₃), 55.6 (q, OCH₃), 53.2 (q, OCH₃), 52.3 (q, OCH₃), 41.0 (d), 38.0 (d), 35.1 (t), 33.4 (t), 12.5 (q, Me), 9.3 (q, Me); *m/z* (FAB) (Found: M⁺ + Na 375.2325. C₁₇H₃₆O₇Na requires 375.2579).

3,7,9,9-Tetramethoxy-5-methoxymethoxy-2,6-dimethylnonanal 22

A mixture of the alcohol 51 (127 mg, 0.36 mmol), Nmethylmorpholine N-oxide (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 tetrapropylammonium perruthenate (12 mg, 0.036 mmol) 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 $(2 \times 25 \text{ ml})$ 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; $[a]_{D}^{20}$ +13.1 (c, 1.3 in CHCl₃); δ_{H} (400 MHz) 9.79 (1H, d, J 1.5 Hz, CHO), 4.64 (1H, d, J 7 Hz, OCHH), 4.59 (1H, d, J 7 Hz, OCHH), 4.55 (1H, t, J 5.7 Hz), 3.84 (1H, m), 3.38 (3H, s, OMe), 3.37 (3H, s, OMe), 3.36 (3H, s, OMe), 3.35 (3H, s, OMe), 3.34 (3H, s, OMe), 3.32 (1H, br m), 2.82 (1H, br m), 1.80 (1H, m), 1.75 (2H, br m), 1.65 (2H, br m), 1.10 (3H, d, J 6.9 Hz, CHMe), 0.85 (3H, d, J 6.9 Hz, CHMe); δ_c(100 MHz) 204.1 (d), 102.4 (d), 96.7 (t), 79.3 (d), 77.5 (d), 77.1 (d), 58.0 (q), 57.5 (q), 56.0 (q), 53.3 (q), 52.4 (q), 49.3 (d), 41.0 (d), 35.1 (t), 34.1 (t), 9.3 (q), 8.7 (q).

[3-(2-Benzyloxyethyl)oxiran-2-yl]methanol 52

Titanium(IV) isopropoxide (2.64 ml, 8.9 mmol), (+)-diethyl tartrate (1.84 ml, 10.7 mmol) and 5-benzyloxypent-2-en-1-ol 24 (16.0 g) were added sequentially over 30 min to a suspension of powdered 4 Å molecular sieves (2.8 g) in dry dichloromethane (200 ml) at -20 ° C under nitrogen. The mixture was stirred at -20 °C for 30 min, and then *tert*-butyl hydroperoxide (3 M in isooctane, 55.5 ml, 1656 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 more dichloromethane $(3 \times 200 \text{ ml})$ and the combined organic extracts then washed with brine and dried over sodium sulfate. The solution was concentrated in vacuo to leave a pale yellow oil which was purified by flash chromatography on silica using diethyl ether as eluent to give the *epoxide* (13.1 g, 76%) as a colourless oil; $[a]_{D}^{25}$ -30.0 (c, 3.9 in CHCl₃) (Found: C, 69.4; H, 7.9. C₁₂H₁₆O₃ requires C, 69.2; H, 7.7%.); $v_{max}(film)/cm^{-1}$ 3427 (br), 2921, 2863, 1454, 1363, 1101, 1029; $\delta_{\rm H}(270 \text{ MHz})$ 7.36–7.20 (5H, m, Ph), 4.47 (2H, s, PhCH₂O), 3.81-3.74 (1H, m), 3.56 (2H, t, J 6.0 Hz, CH₂O), 3.53-3.43 (1H, m), 3.03 (1H, m), 2.91 (1H, dt, J 4.6 and 2.3 Hz), 1.95–1.71 (2H, m, CH₂CH=); δ_C(67.8 MHz) 137.8 (s, Ph), 128.03 (d), 127.69 (d), 72.6 (t, PhCH₂O), 66.5 (t, C-5), 61.5 (t, C-1), 58.6 (d, C-2), 53.4 (d, C-3), 31.7 (t, C-4).

4-Benzyloxy-2-methylbutyraldehyde 54

Trimethylaluminium (2 M in hexane, 75 ml, 150 mmol) was added dropwise over 30 min to a stirred solution of the epoxy alcohol **52** (10.0 g, 48 mmol) in dry dichloromethane (300 ml) at 0 $^{\circ}$ C under argon. The mixture was allowed to warm slowly to

room temperature and then stirred for 15 h. After cooling back to 0 °C, dilute HCl (2 M, 150 ml) was added cautiously and the two layers were allowed to separate. The separated aqueous layer was further extracted with dichloromethane $(2 \times 200 \text{ ml})$ and the combined organic extracts were concentrated in vacuo to leave a colourless oil. Analysis of the ¹H NMR spectrum of the residue showed the presence of a ca. 9:1 mixture of regioisomeric products in favour of the required 5-benzyloxy-3-methylpentane-1,2-diol 53. A solution of the residue in methanol (450 ml) and water (100 ml), was stirred with sodium periodate (9.6 g) for 6 h and then the methanol was removed under vacuum. The residue was diluted with water (200 ml) and the mixture was then extracted with dichloromethane $(3 \times$ 200 ml). The combined dichloromethane extracts were dried (MgSO₄) and then concentrated *in vacuo* to leave a pale yellow oil. Flash chromatography on silica using ether as eluent gave the aldehyde (7.8 g, 84%) as an unstable colourless oil; v_{max} (film)/ cm^{-1} 2932, 2869, 1723, 1453, 1364, 1100, 739, 698; δ_{H} (270 MHz) 9.63 (1H, d, J 1.7 Hz, CHO), 7.34-7.25 (5H, m, Ph), 4.47 (2H, s, PhCH₂O), 3.55–3.48 (2H, m, CH₂O), 2.52 (1H, apparent sextet d, J 6.9 and 1.7 Hz, CHMe), 2.10-1.97 (1H, m, H-3), 1.74-1.62 (1H, m, H-3), 1.09 (3H, d, J 6.9 Hz, Me); δ_c(67.8 MHz) 204.5 (d, C-1), 138.0 (s, Ph), 128.2 (d), 128.1 (d), 127.55 (d), 72.8 (t, PhCH₂O), 67.2 (t, C-4), 43.5 (d, C-2), 30.6 (t, C-3), 13.0 (q, Me).

Ethyl 6-benzyloxy-4-methylhex-2-enoate 55

Ethoxycarbonylmethylenetriphenylphosphorane (14.6 g, 42 mmol) was added in one portion to a solution of the aldehyde 54 (7.50 g, 39 mmol) in dry dichloromethane (200 ml) at room temperature under nitrogen and the resulting yellow solution was stirred overnight. The mixture was concentrated in vacuo to leave a pale yellow viscous liquid which was purified by flash chromatography on silica using petrol-ethyl acetate (4:1) as eluent to give the ester (9.60 g, 94%) as a colourless oil; $v_{max}(film)/cm^{-1}$ 2979, 2858, 1723, 1655; δ_{H} 7.28–7.14 (5H, m, ArH), 6.77 (1H, dd, J 7.9 and 15.8 Hz, EtO₂C-CH=CH), 5.72 (1H, dd, J 1.3 and 15.8 Hz, =CHCO₂Et), 4.38 (2H, s, OCH₂Ar), 4.08 (2H, q, J 6.9 Hz, OCH₂CH₃), 3.41–3.33 (2H, m), 2.45 (1H, apparent septet, J 7 Hz, CHMe), 1.59 (2H, q, J 7 Hz, OCH₂CH₂), 1.19 (2H, t, J 6.9 Hz, OCH₂CH₃), 0.97 (3H, d, J 7 Hz, CH₃); $\delta_{\rm C}$ 166.6 (s), 153.6 (d, C-3), 138.3 (s, Ar), 128.2 (d, Ar), 127.5 (d, Ar), 127.5 (d, Ar), 119.9 (d, C2), 72.9 (t, OCH₂), 67.8 (t, OCH₂), 60.0 (t, OCH₂), 35.7 (t, C-5), 33.3 (d, C-4), 19.3 (q, Me), 14.2 (q, Me).

6-Benzyloxy-4-methylhex-2-en-1-ol 56

A solution of DIBAL-H in hexane (1 M, 70 ml, 70 mmol) was added over 30 min to a stirred solution of the ester 55 (9.0 g, 34 mmol) in dry tetrahydrofuran (100 ml) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 2 h, and then guenched with 2 M aqueous HCl (5 ml initially, followed by 50 ml after the reaction had set to a gel). The aqueous phase was separated and then extracted with ethyl acetate $(3 \times 50 \text{ ml})$. The combined extracts were dried over MgSO4 and then concentrated in vacuo to leave a yellow oil. Flash chromatography on silica using dichloromethane-ether (7:1) as eluent gave the alcohol (7.28 g, 96%) as an oil; $[a]_{D}^{21} - 31.2 (c, 14.1 in CHCl_3)$ (Found: C, 76.1; H, 9.5. C₁₄H₂O requires C, 76.3; H, 9.2%); v_{max}(film)/cm⁻¹ 3385, 2924, 2863; $\delta_{\rm H}$ (270 MHz) 7.44–7.36 (5H, m, ArH), 5.73–5.35 (2H, m, HC=CH), 4.46 (2H, ABq, J 7 Hz, PhCH₂O), 4.05 (2H, br s, CH₂OH), 3.57 (2H, t, J 6.6 Hz, CH₂OBz), 2.40 (1H, septet, J 6.6 Hz, CHMe), 2.10 (1H, br s, OH), 1.60 (2H, ddd, J 13.2, 6.8 and 3.3 Hz, CH₂CHMe), 1.00 (3H, d, J 6.6 Hz); δ_c(90.6 MHz) 138.2 (s, Ph), 137.8 (d, C-3), 128.7 (d), 127.8 (d), 127.7 (d), 127.4 (d, C-2), 72.6 (t, PhCH₂O), 68.3 (t, C-6), 63.5 (t, C-1), 36.7 (t, C-5), 33.9 (d, C-4), 20.5 (q, C-4-Me).

[3-(3-Benzyloxy-1-methylpropyl)oxiran-2-yl]methanol 57

Titanium(IV) isopropoxide (1.0 ml, 3.4 mmol), (-)-diethyl tar-

trate (0.7 ml, 4.0 mmol) and the allylic alcohol 56 (7.0 g, 32 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 nitrogen. The mixture was stirred at -20 °C for 30 min, then tert-butyl hydroperoxide (3 M, in isooctane, 21.3 ml, 64 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 40 ml of water. The mixture was warmed to room temperature over 30 min, and then sodium hydroxide in brine (30%, 8 ml) was added, and the mixture was stirred at room temperature for 30 min. The separated aqueous phase was extracted with more dichloromethane (50 ml \times 3) and the combined organic extracts were then washed with brine (50 ml) and dried (Na₂SO₄). The solution was concentrated in vacuo to leave a pale yellow oil, which was purified by flash chromatography on silica using petrol-ethyl acetate (3:2) as eluent to give the epoxide (6.4 g, 85%) as a colourless oil; $[a]_D$ + 14.9 (c, 10.7 in CHCl₃) (Found: C, 71.3; H, 8.8. C14H20O3 requires C, 71.2; H, 8.5%); vmax(film)/ cm^{-1} 3415, 2963, 2876; δ_{H} (250 MHz) 7.35–7.24 (5H, m, Ar), 4.50 (2H, apparent ABq, J ca. 7 Hz, PhCH₂O), 3.86-3.79 (1H, m, CHO), 3.58-3.49 (3H, m, CHO and CH2O), 2.96-2.89 (2H, m, CHO and OH), 2.77 (1H, dd, J 6.6 and 2.5 Hz, CHO), 1.90-1.82 (1H, m, CH), 1.66–1.54 (2H, m, CH₂), 0.94 (3H, d, J 6.6 Hz, Me); δ_c(67.8 MHz) 138.4, (s, Ph), 128.2 (d), 127.7 (d), 127.5 (d), 72.8 (t, PhCH₂O), 68.0 (t, C-3), 61.8 (t, C-1), 60.3 (d, C-2), 57.0 (d, C-1), 34.2 (t, C-2), 32.4 (C-1), 15.8 (q, Me).

6-Benzyloxy-2,4-dimethylhexane-1,3-diol 58

Methylmagnesium bromide (3 M in THF, 28.5 ml) was added over 1 h to a stirred suspension of CuI (1.67 g, 8.8 mmol) in dry tetrahydrofuran (75 ml) at 0 °C under nitrogen. The mixture was stirred for 30 min at 0 °C and then a solution of the epoxy alcohol 57 (6.5 g) in dry THF (50 ml) was added over 30 min. The reaction was stirred at <5 °C for 15 h and then quenched by the addition of saturated aqueous ammonium chloride (150 ml). The mixture was stirred vigorously at room temperature for 30 min and then extracted with ether (150 ml \times 3). The combined organic extracts were washed with brine (150 ml), and then concentrated in vacuo to leave a pale yellow oil. Analysis of the ¹H NMR 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 under vacuum. The residue was diluted with water (100 ml) and then extracted with dichloromethane $(3 \times 100 \text{ ml})$. The combined dichloromethane extracts were dried over MgSO4 and then concentrated in vacuo to leave a pale yellow oil. Flash chromatography on silica using petrol-ethyl acetate (1:1) as eluent gave the 1,3-diol (5.85 g, 84%) as a liquid; $[a]_{D}^{24}$ +10.8 (c, 10.3 in CHCl₃) (Found: C, 71.1; H, 9.9. C₁₅H₂₄O₃ requires C, 71.4; H, 9.5%); v_{max}(film)/cm⁻¹ 3408, 2957, 2857; $\delta_{\rm H}$ (270 MHz) 7.36–7.29 (5H, m, Ph), 4.53 (2H, s, PhCH₂O), 3.76 (2H, br d, J 5.6 Hz, H-1), 3.64–3.47 (3H, m, H-6, plus OH), 3.34 (1H, br q, J 5.3 Hz, H-3), 3.24 (1H, br t, J 5.3 Hz, OH), 1.95 (1H, heptet J 6.9 Hz, H-4), 1.85 (1H, d sextet, J 7.3 and 3.5 Hz, H-2), 1.72 (2H, q, J 5.6 Hz, H-5), 0.96 (3H, d, J 6.9 Hz, Me), 0.89 (3H, d, J 7.3 Hz, Me); $\delta_{\rm C}$ (67.8 MHz) 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, Me), 14.0 (q, Me).

[4,6-Bis(*tert*-butyldimethylsilanyloxy)-3,5-dimethylhexyloxymethyl]benzene 59

A solution of *tert*-butyldimethylsilylmethanesulfonate (1.98 ml, 8.61 mmol) in dry dichloromethane (5 ml) was added dropwise over 5 min to a stirred solution of the diol **58** (1.05 g, 4.1 mmol) and 2,6-lutidine (1.98 ml, 17.20 mmol) in dry dichloromethane (10 ml) at 0 $^{\circ}$ C under nitrogen and the resulting solution was stirred at 0 $^{\circ}$ C for 1 h. The mixture was allowed to warm to

room temperature and then stirred for one more hour before being quenched with methanol (100 µl). The mixture was diluted with dichloromethane (50 ml), and then washed with water (25 ml) and brine (25 ml) and dried (Na₂SO₄). It was then filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica using petroldichloromethane (1:1) as eluent to give the pure *bis-silyl ether* (1.92 g, 97.5%) as a colourless oil; $[a]_{D}^{21} - 1.4 (c, 2.2 \text{ in CHCl}_{3})$ (Found: C, 67.45; H, 11.6. C₂₇H₅₂O₃Si₂ requires C, 67.5; H 10.8%); $\delta_{\rm H}$ (400 MHz) 7.36–7.34 (5H, m, Ar), 4.53 (1H, d, J 10 Hz, PhCHHO), 4.51 (1H, d, J 10 Hz, PhCHHO), 3.75 (1H, m, CHOH), 3.58–3.40 (4H, m, OCH₂ and OCH₂), 1.90–1.82 (2H, m, CH₂), 0.96–0.83 (m, $2 \times CH$, $2 \times Me$, $2 \times t$ -Bu), 0.08–0.04 $(4 \times \text{SiMe}); \delta_{c}(100 \text{ MHz}) 138.8 \text{ (s, Ar)}, 128.7 \text{ (d)}, 127.7 \text{ (d)},$ 127.55 (d), 78.5 (d, C-3), 73.0 (t, CH₂), 69.3 (t, OCH₂), 65.7 (t, OCH₂), 40.0 (d, C-2/C-4), 33.7 (d, C-4/C-2), 31.6 (t, C-5), 26.3 (q, t-Bu), 26.1 (q, t-Bu), 19.5 (s, t-Bu), 16.4 (s, t-Bu), 17.6 (q, C-2/C-4 Me), 14.9 (q, C-4/C-2-Me), -3.7 (q, SiMe), -3.9 (s, SiMe), -5.1 (s, SiMe), -5.2 (s, SiMe); m/z 481 (M + H⁺) $(22\%), 503 (M + Na^{+}) (30\%).$

6-Benzyloxy-3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethylhexan-1-ol 60

Pyridinium toluene-p-sulfonate (55 mg) was added in one portion to a solution of the bis-silvl ether 59 (0.53 g, 1.1 mmol) in dichloromethane and methanol (14 ml, 1:1) and the resulting solution was stirred at room temperature under nitrogen for 8 h. It was then quenched with a solution of saturated NaHCO₃ (5 ml), concentrated in vacuo and then diluted with dichloromethane (50 ml) and water (50 ml). The aqueous layer was extracted with dichloromethane $(2 \times 25 \text{ ml})$ and the combined organic extracts were dried (Na₂SO₄) and then concentrated in vacuo. The residue was purified by chromatography on silica using dichloromethane as eluent to give the primary alcohol (0.38 g, 96%) as a colourless oil; $[a]_{D}^{20} - 1.6 (c, 9.0 \text{ in CHCl}_3)$ (Found: C, 68.6; H, 10.8. C₂₁H₃₈O₃Si requires C, 68.8; H, 10.4%); v_{max}(film)/ cm^{-1} 3423, 2956, 1461; δ_{H} (400 MHz) 7.45–7.29 (5H, m, Ar), 4.54 (1H, d, J 11 Hz, PhCHHO), 4.51 (1H, d, J 11 Hz, PhCHHO), 3.78-3.47 (5H, m, 1-H, 6-H and 3-H), 2.71 (1H, t, J 6 Hz), 1.96–1.82 (3H, m, 5-H and 4/2-H), 1.49–1.38 (1H, m, 2/4-H), 1.07 (6H, d, J 7 Hz, 2 × Me), 0.98 (9H, s, t-Bu), 0.11 (3H, s, SiMe), 0.10 (3H, s, SiMe); $\delta_{\rm C}$ (67.8 MHz) 138.5 (s, Ar), 128.3 (d), 127.5 (d), 127.5 (d), 81.4 (d, C-3), 72.9 (t, OCH₂), 68.8 (t, OCH₂), 66.2 (t, OCH₂), 36.9 (d, C-2/C-4), 35.5 (d, C-4/ C-2), 32.38 (t, C-5), 26.0 (q, t-Bu), 18.2 (q, t-Bu), 16.5 (q, Me), 16.0 (q, Me), -4.15 (q, SiMe), -4.35 (q, SiMe) (Found: M^+ + H, 367.2668. $C_{21}H_{38}O_3Si$ requires 367.2675).

6-Benzyloxy-3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethylhexanal 61

N-Methylmorpholine N-oxide (0.30 g, 2.5 mmol) was added in one portion to a suspension of the alcohol 60 (0.46 g, 1.24 mmol) and powdered 4 Å molecular sieves (0.7 g) in dry dichloromethane and the resulting mixture was stirred at room temperature under nitrogen for 0.5 h. Tetrapropylammonium perruthenate (0.02 g, 0.06 mmol) was added 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; $[a]_{D}^{24} - 23.3$ (c, 8.8) in CHCl₃); $v_{max}(film)/cm^{-1}$ 2851, 2795, 1754, 1697; $\delta_{H}(400$ MHz) 9.81 (1H, d, J 2.8 Hz, CHO), 7.39-7.29 (5H, m, Ar), 4.55 (1H, d, J 12 Hz, PhCHHO), 4.49 (1H, d, J 12 Hz, PhCHHO), 3.81 (1H, apparent, 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, J7 Hz, C-2-Me), 0.94 (3H, d, J7 Hz, C-4-Me), 0.06 (3H, s, SiMe), 0.04 (3H, s, SiMe); $\delta_{c}(67.8 \text{ MHz}) 205.2 \text{ (d, C-1)}, 138.4 \text{ (s, Ar)}, 128.3 \text{ (d)},$

127.5 (d), 127.5 (d), 78.6 (d, C-3), 72.9 (t, OCH₂), 68.45 (t, OCH₂), 49.2 (d, C-2), 35.4 (d, C-4), 32.4 (t, C-5), 25.9 (q, t-Bu), 18.15 (s, t-Bu), 15.6 (q, C-2Me), 12.5 (q, C-4Me), -4.15 (q, SiMe), -4.53 (q, SiMe).

[7-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-2-hydroxy-3,5dimethylheptyl]phosphonic acid dimethyl ester 62

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 dimethyl methylphosphonate (0.29 ml, 2.55 mmol) in dry THF (22 ml) at -78 °C under nitrogen and the resulting solution was stirred for 0.5 h at -78 °C. A solution of the aldehyde 61 (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 aqueous saturated NaHCO₃ solution (5.6 ml) and allowed to come to room temperature. The mixture was extracted with ethyl acetate $(3 \times 50 \text{ ml})$ and the combined organic extracts were dried (Na2SO4) and then concentrated in *vacuo* to leave a pale yellow oil. Flash chromatography on silica using ethyl acetate as eluent gave a mixture of diastereomers of the hydroxy phosphonate (0.53 g, 90%) as a colourless oil; $[a]_{D}^{23}$ -1.7 (c, 4 in CHCl₃) (Found: C, 58.8; H, 9.7. C₂₄H₄₅O₆ SiP requires C, 59.0; H, 9.2%); δ_H(400 MHz) 7.31–7.21 (5H, m, ArH), 4.49-4.43 (2H, m), 3.72 (3.72) (3H, s), 3.71 (3.69) (3H, s, OMe), 3.7-3.6 (1H, m), 3.59 (1H, br s, OH), 3.58-3.40 (1H, m), 2.01-1.98 (1H, m), 1.96-1.70 (2H, m), 1.37-1.35 (1H, m), 0.95 (3H, d, J 6.7 Hz), 0.92 (3H, d, J 7.1 Hz), 0.88 (9H, s), 0.06 (3H, s), 0.045 (3H, s); $\delta_{\rm C}(100 \text{ MHz})$ 138.5 (s), 128.2 (d), 127.5 (d), 127.39 (d), 80.7 (79.6) (d, C-4), 72.8 (t, OCH₂), 68.75 (68.1) (t, OCH₂), 65.6, 52.4 (52.3) (q, OCH₃), 52.1 (52.1) (q, OCH₃), 42.7 (42.5), 39.7 (39.6), 34.7 (34.5).

[7-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-3,5-dimethyl-2oxoheptyl]phosphonic acid dimethyl ester 23

Pyridinium dichromate (2.86 g, 7.60 mmol) was added in one portion to a solution of the alcohol 62 (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 (3×50 ml). The combined ether extracts were washed with water (3×25) ml) and brine (25 ml), then dried (Na₂SO₄) and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica using ethyl acetate as eluent to give the keto*phosphonate* (0.49 g, 92%) as a colourless oil; $[a]_{D}^{21}$ -79.9 (c, 2.5 in CHCl₃) (Found: C, 59.6; H, 9.2. C₂₄H₄₃SiPO₆ requires C, 59.3; H, 8.9%); v_{max} (film)/cm⁻¹ 1715; δ_{H} (400 MHz) 7.46–7.28 (5H, m, ArH), 4.44 (1H, d, J 12 Hz, PhCHHO), 4.39 (1H, d, J 12 Hz, PhCHHO), 3.71 (3H, d, J 1 Hz, OCH₃), 3.68 (3H, d, J1Hz, OCH₃), 3.46-3.37 (2H, m, OCH₂), 3.37 (1H, d, J18Hz, CH), 3.34 (1H, d, J 18 Hz, CH), 3.01-2.89 (1H, m), 1.76-1.75 (1H, m), 1.35-1.33 (1H, m), 0.97 (3H, d, J 6.8 Hz, CHMe), 0.87 (3H, d, J 6.8 Hz, CHMe), 0.78 (9H, s, t-Bu), -0.04 (3H, s, SiMe), -0.12 (3H, s, SiMe); δ_{c} (67.8 MHz) 205.7 (s), 138.4 (s), 128.2 (d), 127.4 (d), 79.4 (d, C-4), 72.8 (t, OCH₂), 68.4 (t, OCH₂), 52.9 (q, OMe), 52.8 (OMe), 49.9 (d, C-3), 43.9 (t, C-1), 42.0 (t, C-1), 34.6 (t, C-5), 31.6 (t, C-6), 25.9 (q, t-Bu), 18.1 (s, t-Bu), 15.6 (C-3-Me), 13.91 (C-4-Me), -4.51 (q, SiMe), -4.62 (q, SiMe).

1-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-10,14,16,16-tetramethoxy-12-methoxymethoxy-3,5,9,13-tetramethylhexadec-7en-6-one 63

A solution of the ketophosphonate **23** (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 **22** (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 extract was washed with saturated NaHCO₃ (10 ml) and brine (10 ml) and then dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography on silica using petrol-ethyl acetate (2:1) as eluent to give the *E-alkene* (73 mg, 95%) as a colourless oil; $[a]_D^{20}$ $-9.4 (c, 1.78 \text{ in CHCl}_3); \delta_{\text{H}}(400 \text{ MHz}) 7.26-7.35 (5\text{H, m}), 6.83$ (1H, dd, J 15.8 and 6.8 Hz), 6.23 (1H, dd, J 15.8 and 1.5 Hz), 4.61 (1H, d, J 6.8 Hz, OCHHO), 4.53 (1H, d, J 6.8 Hz, OCHHO), 4.4-4.5 (3H, m), 3.96 (1H, dd, J 8 and 3 Hz), 3.80 (1H, m), 3.60 (1H, m), 3.48 (1H, m), 3.39 (3H, s, OCH₃), 3.38 (3H, s, OCH₃), 3.36 (3H, s, OCH₃), 3.34 (3H, s, OCH₃), 3.32 (3H, s, OCH₃), 3.25 (1H, m), 3.06 (1H, m), 2.76 (1H, m), 1.91-1.81 (5H, m), 1.68-1.65 (2H, m), 1.55-1.44 (2H, m), 1.40-1.30 (2H, m), 1.06 (3H, d, J 7 Hz), 1.01 (3H, d, J 7 Hz), 0.95 (3H, d, J 7 Hz), 0.91 (3H, d, J 7 Hz), 0.85 (9H, s); δ_c(67.8 MHz) 203.1 (s), 148.6 (d), 138.6 (d), 130.2 (d), 128.3 (d), 127.6 (d), 127.5 (d), 102.2 (d), 96.6 (t), 80.4 (d), 79.2 (d), 78.3 (d), 77.5 (d), 76.5 (d), 72.9 (t), 68.9 (q, OMe), 57.9 (q, OMe), 57.5 (q, OMe), 55.7 (q, OMe), 53.2 (q, OMe), 52.1 (q, OMe), 48.4 (d), 41.1 (d), 38.9 (d), 35.1 (t), 33.3 (d), 33.1 (t), 30.8 (t), 26.2 (q), 18.4 (s), 16.8 (q), 14.2 (q), 13.2 (q), 9.2 (q), -4.1 (q), -4.3 (q); *m/z* (FAB) (Found: M + Na, 733.4652. $C_{39}H_{70}O_9SiNa$ requires 733.4687).

4-(*tert*-Butyldimethylsilanyloxy)-1-hydroxy-10,14,16,16-tetramethoxy-12-methoxymethoxy-3,5,9,13-tetramethylhexadecan-6one 64

A solution of the enone 63 (64 mg, 0.1 mmol) in dry methanol (5 ml) was hydrogenated overnight in the presence of Pearlman's catalyst (25 mg). The mixture was filtered through Celite and the filtrate was concentrated in vacuo to leave the product (52.6 mg, 94%) as a liquid; $[a]_{\rm D}^{20}$ +5.6 (c, 1.0 in CH₂Cl₂); $\delta_{\rm H}$ (500 MHz) 4.67 (1H, d, J 6.7 Hz, OCHHOMe), 4.61 (1H, d, J 6.7 Hz, OCHHOMe), 4.51 (1H, t, J 5.75 Hz), 3.85 (1H, dd, J 2.6 and 8.3 Hz), 3.73 (2H, m, CH2OH), 3.68 (1H, m), 3.54 (1H, m), 3.36 (3H, s, OMe), 3.31 (3H, s, OMe), 3.29 (3H, s, OMe), 3.28 (3H, s, OMe), 3.27 (3H, s, OMe), 3.20 (2H, m), 2.82 (1H apparent quintet J 7.3 Hz), 2.48-2.42 (3H, m), 1.86-1.75 (5H, m), 1.67-1.61 (1H, m), 1.57-1.53 (1H, m), 1.52-1.43 (1H, m) 1.38-1.25 (3H, m), 0.96 (6H, d, J 7 Hz, 2 × Me), 0.90 (3H, d, J 7 Hz, Me), 0.85 (9H, s, t-Bu), 0.75 (3H, d, J 7 Hz, Me), -0.1 (6H, s, $2 \times \text{Me}$; $\delta_{\text{C}}(67.8 \text{ MHz}) 213.0, 102.1 (d), 96.5 (t), 80.8 (d), 79.2$ (d), 78.1 (d), 76.5 (d), 60.2 (t), 58.0 (q), 56.7 (q), 55.7 (q), 53.1 (q), 52.0 (q), 50.0 (d), 42.2 (t), 41.3 (d), 35.1 (t), 33.7 (t), 33.4 (d), 33.1 (d), 31.5 (t), 26.4 (t), 26.1 (q), 18.4 (s), 16.7 (q), 14.0 (q), 13.3 (q), 9.3 (q), -4.3 (q), -4.4 (q); m/z (FAB) 645 (M + Na)⁺.

4-(*tert*-Butyldimethylsilanyloxy)-1-(*tert*-butyldiphenylsilanyloxy)-10,14,16,16-tetramethoxy-12-methoxymethoxy-3,5,9,13tetramethylhexadecan-6-one 21

Imidazole (51 mg) and TBDPS-Cl (162 µml) were added to a solution of the alcohol 64 (310 mg, 0.5 mmol) in dry DMF (3 ml) under nitrogen at 0 °C, and the mixture was then allowed to warm to room temperature and stirred for 14 h. The mixture was diluted with water (15 ml) and extracted with ether (3×20 ml). The combined organic extracts were washed with water $(3 \times 10 \text{ ml})$ and brine (10 ml), then dried (Na₂SO₄) and concentrated in vacuo to leave a pale yellow oil. Purification by chromatography on silica using ether-dichloromethane (3:1) as eluent gave the corresponding TBDPS ether (405 mg, 94%) as a colourless oil; $[a]_{D}^{20}$ +1.8 (c, 1.6 in CHCl₃); δ_{H} (360 MHz) 7.74– 7.68 (4H, m, ArH), 7.48-7.29 (6H, m, ArH), 4.72 (1H, d, J 6.7 Hz, OCHH-OMe), 4.64 (1H, d, J 6.7 Hz, OCHH-OMe), 4.57 (1H, t, J 5.8 Hz, 16-H), 3.86 (1H, dd, J 8.1 and 2.5 Hz), 3.81 (1H, m), 3.75 (1H, dd, J 6.7 and 4.4 Hz), 3.65 (1H, dt, J 9.5 and 5.6 Hz), 3.64 (3H, s, OMe), 3.63 (3H, s, OMe), 3.54 (3H, s, OMe), 3.52 (3H, s, OMe), 3.50 (3H, s, OMe), 3.30-3.20 (2H, m), 2.80 (1H, quintet, J 7 Hz), 2.56 (2H, m), 1.93–1.82 (5H, m), 1.60 (1H, m), 1.41-1.28 (4H, m), 1.08 (9H, s), 0.95 (3H, d, J 7.1

Hz), 0.93 (3H, d, *J* 7 Hz), 0.87 (3H, d, *J* 6.9 Hz), 0.85 (9H, s, t-Bu), 0.81 (3H, d, *J* 7 Hz), 0.07 (3H, s), -0.04 (3H, s); $\delta_{\rm C}(100$ MHz) 213.8 (s) 135.6 (d), 134.0 (s), 129.7 (s), 127.7 (d), 102.3 (d), 96.8 (t), 81.0 (d), 79.33 (d), 78.8 (d), 77.5 (d), 62.2 (t), 58.1 (OMe), 58.9 (OMe), 55.8 (OMe), 53.3 (OMe), 52.1 (OMe), 50.0 (d), 42.3 (t), 41.4 (d), 35.2 (t), 33.8 (t), 33.6 (d), 33.1 (d), 31.6 (t), 27.0 (q, t-Bu), 26.6 (t), 26.2 (q, t-Bu), 19.3 (s), 18.4 (s), 16.3 (q, Me), 14.3 (q, Me), 13.4 (q, Me), 9.5 (q, Me), -4.13 (q, SiMe), -4.3 (q, SiMe); *m*/*z* (FAB) (Found: M – 1, 859.5535. C₄₈H₈₃O₉Si₂ requires 859.5576).

13-(*tert*-Butyldimethylsilanyloxy)-16-(*tert*-butyldiphenylsilanyloxy)-3,7-dimethoxy-5-methoxymethoxy-4,8,12,14-tetramethyl-11-oxohexadecanal 16

A solution of dimethylboryl bromide (260 µl, 0.58 mmol) in dichloromethane (2.25 M) was added to a solution of the dimethyl acetal 21 (100 mg, 0.12 mmol) in dry ether (3 ml) at -78 °C under nitrogen. The mixture was stirred for an hour and then quenched by pouring into a stirred mixture of THF (3 ml) and saturated NaHCO₃ (3 ml). The separated aqueous phase was extracted with ether $(3 \times 20 \text{ ml})$ and the combined ether extracts were washed with saturated NaHCO₃ (10 ml) and brine (10 ml) and then dried (Na₂SO₄). The ether extracts were concentrated in vacuo to leave the pure aldehyde (90 mg, 95%) as a viscous oil; $[a]_{D}^{21}$ +1.9 (c, 1.05 in CHCl₃); δ_{H} (500 MHz) 9.87 (1H, t, J 2 Hz, CHO), 7.71-7.68 (4H, m, ArH), 7.48-7.29 (6H, m, ArH), 4.72 (1H, d, J 6.5 Hz, OCHH-OMe), 4.66 (1H, d, J 6.5 Hz, OCHH–OMe), 3.86 (1H, dd, J 2.5 and 8.2 Hz), 3.80–3.63 (4H, m), 3.44 (3H, s, OMe), 3.39 (3H, s, OMe), 3.39 (3H, s, OMe), 3.37-3.35 (1H, m), 2.82-2.80 (1H, m), 2.75 (1H, dd, J 2.5 and 6.5 Hz), 2.72–2.53 (2H, m), 1.97–1.81 (4H, m), 1.43– 1.29 (5H, m), 1.08 (9H, s, t-Bu), 1.06 (3H, d, J 8.1 Hz), 1.00 (3H, d, J 7.9 Hz), 0.94 (3H, d, J 7.1 Hz), 0.90 (3H, d, J 6.9 Hz), 0.87 (9H, s), 0.08 (3H, s), -0.04 (3H, s); $\delta_{\rm C}(69.89~{\rm MHz})$ 213.6 (s, C=O), 201.4 (d, CHO), 135.5 (d), 133.6 (s), 129.5 (d), 127.6 (d), 96.7 (t), 80.7 (d), 78.5 (d), 77.6 (d), 76.5 (d), 61.99 (t), 57.5 (OMe), 56.7 (OMe), 55.8 (OMe), 49.7 (d), 46.2 (t), 42.1 (t), 41.7 (d), 33.6 (t), 33.0 (d), 33.3 (d), 31.6 (t), 26.8 (q, t-Bu), 26.4 (t), 26.1 (q, t-Bu), 19.1 (s), 18.3 (s, t-Bu), 16.1 (q, Me), 14.0, (q, Me), 13.2 (q, Me), 9.6 (q, Me), -4.3 (q, Me), -4.5 (q, Me).

3-Oxohept-6-enoic acid methyl ester 65

A solution of methyl acetoacetate (23.2 g, 0.2 mol) in dry THF (30 ml) was added dropwise over 45 min to a stirred suspension of NaH (60% in oil, 9.6 g, 0.24 mol) in dry THF (200 ml) at 0 °C under nitrogen. The turbid mixture was stirred at 0 °C for 10 min and then a solution of *n*-butyllithium (1.6 M) in hexane (130 ml, 0.21 mol) was added dropwise over 30 min. The brown solution was stirred at 0 °C for a further 10 min and then a solution of allyl bromide (26.6 ml, 0.22 mol) in dry THF (50 ml) was added dropwise over 20 min. The mixture was warmed to room temperature over 30 min and then quenched with dilute hydrochloric acid (2 M, 200 ml). The separated aqueous layer was extracted with diethyl ether $(2 \times 200 \text{ ml})$ and the combined organic extracts were washed with brine (200 ml) then dried (MgSO₄) and concentrated in vacuo. The residue was purified by distillation to give the β -ketoester (18.5 g, 59%) as a pale yellow oil, bp 110 °C at 40 mmHg (Found: C 61.6; H, 8.0. C₈H₁₂O₃ requires C, 61.5; H, 7.7%); v_{max}(film)/cm⁻¹ 2955, 1751; $\delta_{\rm H}(250~{\rm MHz},~{\rm CDCl_3})$ 5.79 (1H, ddt, J 16.7, 10.2 and 6.5 Hz, CH=CH₂), 5.08–4.97 (2H, m, =CH₂), 3.73 (3H, s, CO₂Me), 3.46 (2H, s, COCH₂CO), 2.65 (2H, t, J 7.4 Hz, CH₂CO), 2.33 (2H, dt, J 7.4 and 6.5 Hz, CH₂CH=CH₂); $\delta_{\rm C}$ (67.8 MHz, CDCl₃) 201.6 (s, 3-C), 167.3 (s, 1-C), 136.3 (d, 6-C), 115.2 (t, 7-C), 52.0 (q, CO₂ Me), 48.7 (t, 2-C), 41.7 (t, 4-C), 27.1 (t, 5-C).

3-Hydroxyhept-6-enoic acid benzyl ester 66

A solution of KOH (9.8 g, 0.18 mol) in water (175 ml) was

added in one portion to a stirred solution of the β -ketoester 65 (12.4 g, 0.008 mol) in ethanol (200 ml) at 0 °C. The mixture was stirred at room temperature for 20 h and then evaporated in vacuo. The yellow residue was diluted with water (300 ml) and added in one portion to an actively fermenting mixture of Dglucose (500 g, 2.77 mol), baker's yeast (435 g), KH₂PO₄ (1.05 g, 7.6 mmol), MgSO₄ (0.52 g, 4.35 mmol) and water (1.37 l) at 25 °C. The broth was stirred at room temperature for 2 days, then silica (1 kg) and acetone (2.5 l) were added and the mixture was filtered in vacuo. The filter cake was washed with acetone $(3 \times 500 \text{ ml})$, and the combined organic extracts were then concentrated to ~100 ml in vacuo. Water (400 ml) was added and the mixture was acidified to pH 1.0 with concentrated hydrochloric acid and then saturated with NaCl. The mixture was placed under continuous extraction with dichloromethane for 2 days. The dried (MgSO₄) organic liquor was evaporated in vacuo to leave the corresponding β -hydroxyacid as a viscous brown oil. A solution of benzyl bromide (6 ml, 50 mmol) and aliquat 336 (5.8 g, 14.2 mmol) in dichloromethane (45 ml) was added to a solution of the crude β-hydroxyacid (4.1 g) and NaHCO₃ (2.5 g) in water (30 ml), and the two phase mixture was stirred at room temperature for 3 days. The separated aqueous layer was extracted with dichloromethane $(2 \times 50 \text{ ml})$ and the combined organic extracts were then dried (MgSO₄) and concentrated in vacuo. The residue was purified by chromatography on silica using petrol-diethyl ether (3:2) as eluent to give the benzyl ester (3.93 g) as a colourless oil; $[a]_D - 15.8 (c, 1.5 \text{ in CHCl}_3); \delta_H(250 \text{ MHz},$ CDCl₃) 7.45-7.35 (5H, m, ArH), 5.85 (1H, ddt, J 16.5, 10.3 and 6.5 Hz, CH=CH₂), 5.11-4.90 (2H, m, =CH₂), 4.10-4.01 (1H, m, CHOH), 3.15 (1H, br s, OH), 2.60–2.45 (2H, m, CH₂CO), 2.25– 2.05 (2H, s, CH₂CH=CH₂), 1.70-1.50 (2H, m, CH₂); δ_C(100 MHz, CDCl₃) 172.5 (s, 1-C), 138.0 (d, 6-C), 128.7 (d, Ar), 128.4 (s, Ar), 126.7 (d, Ar), 114.9 (t, 6-C), 67.4 (t, OCH₂Ph), 66.4 (d, 3-C), 41.5 (t, 2-C), 35.6 (t, C-5) and 29.7 (t, 4-C); m/z (EI) (Found: M – H₂O, 215.9893. C₁₄H₁₆O₂ requires 216.1150).

3-(tert-Butyldiphenylsilanyloxy)hept-6-enoic acid benzyl ester 67

A solution of the alcohol 66 (3.3 g, 14 mmol), imidazole (2.1 g, 30.9 mmol) and tert-butylchlorodiphenylsilane (4 ml, 15.4 mmol) in dry DMF (35 ml) was stirred at room temperature for 16 h under a nitrogen atmosphere and then quenched with water (180 ml), and extracted with ether (3×100 ml). The combined organic extracts were washed with water $(2 \times 50 \text{ ml})$ and brine (50 ml), then dried (MgSO₄) and concentrated in vacuo. The residue was purified by chromatography over silica using petrol-diethyl ether (10:1) as eluent to give the silyl ether (5.4 g, 81%) as a colourless oil; $[a]_{D} - 11.0 (c, 1.5 \text{ in CHCl}_{3})$ (Found: C, 76.2; H, 7.9. C₃₀H₃₆O₃Si requires C, 76.2; H, 7.7%); $v_{\rm max}$ (film)/cm⁻¹ 3069, 2930, 2892, 1736, 1640; $\delta_{\rm H}$ (360 MHz, CDCl₃) 7.72–7.67 (4H, m, ArH), 7.48–7.28 (11H, m, ArH), 5.60 (1H, ddt, J 16.5, 10.3 and 6.5 Hz, CH=CH₂), 5.06 (1H, d, J 12.3 Hz, OCHHPh), 4.98 (1H, d, J 12.3Hz, OCHHPh), 4.91-4.85 (2H, m, =CH₂), 4.25 (1H, quintet, J 6 Hz, CH-OH), 2.60 (1H, dd, J 6.6 and 14.8 Hz, CHH-CO), 2.53 (1H, dd, J 6.0 and 14.8 Hz, CHH-CO), 2.05-2.00 (2H, m, CH₂C=CH₂), 1.62-1.56 (2H, m, CH₂), 1.06 (9H, s, t-Bu); δ_C(90 MHz, CDCl₃) 171.1 (s, 1-C), 138.0 (d, 6-C), 135.9 (d), 135.9 (d), 133.9 (s), 133.8 (s), 129.6 (d), 128.4 (d), 128.2 (d), 128.1 (d), 127.5 (d), 114.5 (t, 6-C), 69.9 (d, 3-C), 66.2 (t, OCH₂Ph), 41.9 (t, C-2), 36.1 (t, 5-C), 29.0 (t, 4-C), 26.9 (q, t-Bu), 19.3 (s, t-Bu); m/z (FAB), 473 (M + H)⁺, 495 $(M + Na)^+$, 415 $(M^+ - t-Bu)$.

3-(*tert*-Butyldiphenylsilanyloxy)-7-hydroxyheptanoic acid benzyl ester 68

A solution of the olefin **67** (4.5 g, 9.52 mmol) in dry THF (30 ml) was added to a stirred solution of borane–dimethyl sulfide complex (2 M, 5.5 ml, 11 mmol) in dry THF (40 ml) at 0 $^{\circ}$ C under nitrogen. The mixture was allowed to warm to room temperature over 3 h and then evaporated *in vacuo*. Sodium

hydroxide solution (3 M, 3.5 ml) and 30% aqueous H₂O₂ (1.2 ml) were added successively to a solution of the residue in THF (30 ml) at 0 °C. The turbid solution was warmed to room temperature over 2 h and then quenched with water (100 ml) and extracted with ether (3 \times 100 ml). The ether extracts were dried (MgSO₄), and then concentrated in vacuo. The residue was purified by flash chromatography on silica using diethyl etherpetrol (1:1) as eluent to give the alcohol (3.57 g, 78%) as an oil; $[a]_{D}^{21}$ -11.5 (c, 1.6 in CHCl₃) (Found: C, 73.2; H, 8.1. C₃₀H₃₈O₄Si requires C, 73.4; H, 7.8%); $v_{max}(\text{film})/\text{cm}^{-1}$ 3396, 3068, 1735; $\delta_{\text{H}}(360 \text{ MHz}, \text{CDCl}_3)$ 7.72–7.67 (4H, m, ArH), 7.47–7.29 (11H, m, ArH), 5.1 (1H, d, J 11.6 Hz, OCHHPh), 5.03 (1H, d, J 11.6 Hz, OCHHPh), 4.27-4.22 (1H, m, CHO), 3.47 (2H, t, J 6 Hz, CH₂OH), 2.62 (1H, dd, J 6.1 and 12 Hz, CHHCO₂CH₂Ph), 2.55 (1H, dd, J 6.1 and 12 Hz, CHHCO₂Ph), 1.52-1.42 (6H, m, $3 \times CH_2$), 1.06 (9H, s, t-Bu); δ_c (100 MHz, CDCl₃) 171.3 (s, 1-C), 135.9 (d, Ar), 134.0 (s, Ar), 128.8 (d), 128.5 (d), 128.3 (d), 128.2 (d), 127.5 (d), 70.3 (d, 3-C), 66.2 (t, OCH₂Ph), 62.4 (t, 7-C), 42.0 (t, 2-C), 36.6 (t, 6-C), 32.3 (t, 5-C), 27.0 (q, t-Bu), 20.8 (t, 4-C), 19.3 (s, t-Bu); m/z (FAB) 513 (M + Na)⁺, 491 $(M + H)^+$ (Found: M⁺ + 1, 491.2706. C₃₀H₃₈O₄Si requires 491.2617).

3-(*tert*-Butyldiphenylsilanyloxy)-7-oxoheptanoic acid benzyl ester 69

Pyridinium dichromate (3.2 g, 9.2 mmol) was added in one portion to a stirred solution of the alcohol 68 (2.66 g, 5.42 mmol) in dry dichloromethane (50 ml) under a nitrogen atmosphere at room temperature. The solution was stirred for 23 h at room temperature, filtered through Celite and the filtrate was then evaporated in vacuo. The residue was purified by flash chromatography over silica using petrol-diethyl ether (3:1) as eluent to give the *aldehyde* (2.06 g, 78%) as a colourless oil; $[a]_{D}^{21}$ -10.3 (c, 2.7 in CHCl₃); $v_{max}(film)/cm^{-1}$ 3069, 2931, 1734; $\delta_{\rm H}(250~{\rm MHz},{\rm CDCl_3})$ 9.71 (1H, br s, CHO), 7.68–7.63 (4H, m, ArH), 7.46-7.25 (11H, m, ArH), 5.05 (1H, d, J 12.5 Hz, OCHHPh), 4.97 (1H, d, J, 12.5 Hz, OCHHPh), 4.20 (1H, apparent quintet, J 6 Hz, CHODBDPS), 2.60 (1H, dd, J 6.5 and 14.8 Hz, CHHCO₂CH₂Ph), 2.52 (1H, dd, J 6 and 14.8 Hz, CHHCO₂CH₂Ph), 2.05-2.00 (2H, m, CH₂CHO), 1.62-1.56 (4H, m, 2 × CH₂), 1.06 (9H, s, t-Bu); $\delta_{\rm C}$ (67.8 MHz, CDCl₃) 202.1 (d, 7-C), 171.0 (s, 1-C), 135.8 (d), 135.7 (d), 133.7 (s), 133.6 (s), 129.6 (d), 128.4 (d), 128.2 (d), 128.1 (d), 127.5 (d), 69.7 (d, 3-C), 66.2 (t, OCH₂Ph), 43.3 (t, 2-C), 41.8 (t, 6-C), 36.1 (t, 5-C), 26.9 (q, t-Bu), 19.2 (t, 4-C), 17.1 (s, t-Bu); *m/z* (EI) $431 (M - t-Bu)^+ 5.2\%$.

3-(*tert*-Butyldiphenylsilanyloxy)-8-(dimethoxyphosphoryl)-7hydroxyoctanoic acid benzyl ester 70

A solution of n-butyllithium (1.6 M in hexane, 2.8 ml, 4.5 mmol) was added dropwise over 15 min to a stirred solution of the dimethyl methylphosphonate (0.49 ml, 4.5 mmol) in dry THF (65 ml) at -78 °C under a nitrogen atmosphere. The colourless solution was stirred at -78 °C for 30 min and then added via cannula over 20 min to a stirred solution of the aldehyde 69 (1.7 g, 3.48 mmol) in dry THF (60 ml) at -78 °C under an atmosphere of nitrogen. The mixture was stirred at -78 °C for 2 h, then quenched with saturated NaHCO₃ solution (8 ml) and allowed to cool to room temperature. The mixture was extracted with EtOAc (100 ml) and the separated aqueous layer was re-extracted with EtOAc (2×220 ml). The combined organic phases were then washed with saturated brine (20 ml) and dried (MgSO₄). The filtrate was concentrated in vacuo to leave a pale yellow oil which was purified by flash chromatography on silica using ethyl acetate as eluent to give a mixture of diastereoisomers of the β -hydroxyphosphonate (1.2 g, 55%) as a colourless oil; $[a]_{D}^{21} - 13.4$ (c, 5.0 in CHCl₃); v_{max} (film)/cm⁻¹ 3388, 2953, 1732; $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.68–7.64 (4H, m, ArH), 7.41-7.25 (11H, m, ArH), 5.02 (1H, d, J 12.5 Hz,

OCHHPh), 4.96 (1H, d, J 12.5 Hz, OCHHPh), 4.20 (1H, m, CHOTBDPS), 3.77 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 3.75 (3H, s, OCH₃), 3.74 (3H, s, OCH₃), 3.39 (1H, br s, OH), 2.55 (1H, dd, J 6.7 and 14.5 Hz), 2.46 (1H, dd, J 6.5 and 14.5 Hz), 1.81–1.77 (2H, m, CH₂PO), 1.51–1.48 (2H, m, CH₂), 1.45–1.24 (4H, m, 2 × CH₂), 1.02 (9H, s, t-Bu); $\delta_{\rm C}$ (100 MHz, CDCl₃) 171.2 (s, 1-C), 135.9 (d, Ar), 134.0 (s), 133.9 (s), 132.1 (s), 132.0 (s), 129.6 (d), 128.5 (d), 128.2 (d), 126.2 (d), 127.5 (d), 70.3 (70.2) (d, 3-C or 7-C), 66.2 (66.1) (t, OCH₂ Ph), 52.4 (q, OCH₃), 42.0 (38.0) (t, 2-C), 37.6 (36.8) (t, 6-C), 33.1 (CH₂, d, J_{P-C} 137 Hz), 26.9 (q, t-Bu), 20.6 (t, C-4), 19.3 (s, t-Bu), 20.6 (t, C-4), 19.3 (s), t-Bu); (Found: M⁺ + 613.2611. C₃₃H₄₅O₇PSi requires 613.2750).

3-(*tert*-Butyldiphenylsilanyloxy)-8-(dimethoxyphosphoryl)-7oxooctanoic acid benzyl ester 71

Pyridinium dichromate (4 g, 11.5 mmol) was added in one portion to a stirred solution of the β -hydroxyphosphonate 70 (1.3 g, 2.1 mmol) in dry DMF (10 ml) under nitrogen at room temperature. The dark orange solution was stirred at room temperature for 36 h and then diluted with water (100 ml). The mixture was extracted with ether $(3 \times 50 \text{ ml})$ and the combined organic extracts were washed with water $(2 \times 50 \text{ ml})$ and brine (25 ml), and then dried (MgSO₄). The filtrate was concentrated *in vacuo* to leave a brown oil which was purified by flash chromatography on silica using ethyl acetate as eluent to give the β -keto phosphonate (1.09 g, 84%) as a colourless oil; $[a]_{D}^{21}$ -14.2 (c, 2.0 in CHCl₃); v_{max}(film)/cm⁻¹ 3070, 2999, 1732, 1599; δ_H(360 MHz, CDCl₃) 7.71–7.66 (4H, m, ArH), 7.48–7.31 (9H, m, ArH), 7.29-7.27 (2H, m, ArH), 5.0 (1H, d, J 12.4 Hz, OCHHPh), 4.92 (1H, d, J 12.4 Hz, OCHHPh), 4.21 (1H, quintet, J 6 Hz, CHOTBDPS), 3.79 (3H, d, J_{P-C} 0.88 Hz, OCH₃), 3.77 (3H, d, J_{P-C} 0.9 Hz, OCH₃), 2.97 (2H, d, J_{P-C} 22.67 Hz, CH₂O), 2.62 (1H, dd, J 6.65 and 14.9 Hz, CHH-CO₂CH₂Ph), 2.56 (1H, dd, J 5.9 and 14.9 Hz, CHHCO₂-CH₂Ph), 2.35 (2H, dt, J 1.4 and 6.4 Hz), 1.57-1.43 (4H, m, $2 \times CH_2$), 1.05 (9H, s, t-Bu); δ_C (67.8 MHz, CDCl₃) 201.0 (C=O, d, J_{P-CO} 6 Hz), 170.9 (s, 1-C), 135.8 (d), 135.7 (d), 133.7 (s), 133.6 (s), 132.0 (d), 131.8 (d), 131.7 (d, Ar), 129.5 (d, Ar), 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.4, (all d, Ar), 69.7 (d, 3-C), 66.1 (t, CH₂Ph), 52.8 (q, OCH₃), 52.8 (q, OCH₃), 43.5 (t, 2-C), 41.9 (t, C-6), 41.7 (CH₂, 8-C, J_{P-C} 128 Hz), 36.3 (t, 5-C), 26.8 (q, t-Bu), 19.1 (t, 4-C), 18.3 (s, t-Bu); *m*/*z* (FAB) 553 (M – t-Bu)⁺ (13%) (Found: $M^+ - 57$, 553.1791. $C_{33}H_{44}O_7PSi$ requires 553.1780).

3-(*tert*-Butyldiphenylsilanyloxy)-8-(dimethoxyphosphoryl)-7oxooctanoic acid 18

A solution of the benzyl ester 71 (1.0 g, 1.70 mmol) in ethyl acetate (50 ml) was hydrogenated in the presence of palladium on charcoal (10%, 500 mg) for 24 h. The solution was filtered through Celite and the filter cake was then washed with ethyl acetate (3 \times 25 ml). The filtrate was concentrated *in vacuo* to leave the *acid* (0.86 g, 98%) as a colourless foam; $[a]_{\rm D}^{21}$ -13.7 (c, 2.9 in CHCl₃); v_{max} (film)/cm⁻¹ 1714, 1588; δ_{H} (360 MHz, CDCl₃) 7.72-7.67 (4H, m ArH), 7.49-7.29 (6H, m, ArH), 4.16-4.14 (1H, m, CHOTBDPS), 3.8 (3H, s, OMe), 3.0 (2H, d, J 22.7 Hz, CH₂PO), 2.5 (2H, apparent d, J 6 Hz, CH₂CO₂Ph), 2.4 (2H, m, CH₂), 1.53–1.50 (4H, m, 2 × CH₂), 1.07 (9H, s); $\delta_{\rm C}$ (100 MHz, CDCl₃) 201.2 (s, 7-C), 174.5 (s, 1-C), 135.9 (s, Ar), 133.9 (d), 133.8 (d), 129.8 (d), 127.6 (d), 69.8 (d, 3-C), 53.2 (q, OCH₃), 43.7 (t, 2-C), 41.6 (t, 6-C), 40.4 (d, J_{P-C} 112 Hz, CH₂PO), 35.9 (5-C), 27.0 (q, t-Bu), 19.3 (s, t-Bu), 18.6 (t, 4-C); m/z (FAB) (Found: $(M + H)^+$, 521.2132. $C_{26}H_{38}O_7SiP$ requires 521.2124).

The ter-oxazole alkene ester 17

A solution of *n*-butyllithium (1.6 M) in hexane (112 µl, 0.2

mmol) was added dropwise over 5 min to a stirred suspension of the phosphonium salt 11 (114 mg, 0.19 mmol) in dry THF (6 ml) under a nitrogen atmosphere at -30 °C. The deep red solution was stirred at room temperature for 1.5 h and then re-cooled to -78 °C. A solution of the aldehyde 55 (150 mg, 0.19 mmol) in dry THF (8 ml) was added dropwise over 15 min and the yellow solution was then warmed to room temperature over 2 h. The mixture was quenched with saturated ammonium chloride solution (5 ml) and then diluted with dichloromethane (20 ml). The separated aqueous layer was extracted with dichloromethane $(2 \times 10 \text{ ml})$ and the combined organic phases were washed with saturated brine (20 ml), then dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by chromatography on silica using petrol-ethyl acetate (1:1) as eluent to give unreacted aldehyde (29 mg) and then the olefin (109 mg, 70% based on recovered aldehyde) as a colourless foam; $[a]_{D}^{25}$ +2.71 (c, 0.7 in CHCl₃); δ_{H} (500 MHz) 8.46 (1H, s), 8.36 (1H, s), 8.29 (1H, s), 7.71-7.68 (4H, m), 7.48-7.36 (6H, m), 6.95 (1H, dt, J 7.5 and 15.5 Hz), 6.48 (1H, d, J 16.1 Hz), 4.7 (d, J 6.7 Hz, OCHH-OMe), 4.62 (d, J 6.7 Hz, OCHHOMe), 3.99 (3H, s, CO₂Me), 3.86 (1H, dd, J 2.4 and 7.8 Hz), 3.8–3.7 (2H, m), 3.7-3.6 (1H, m), 3.45 (3H, s, OMe), 3.4 (3H, s, OMe), 3.35 (3H, s, OMe), 2.8 (1H, quintet, J7 Hz), 2.6-2.5 (4H, m), 1.9-1.4 (6H, m), 1.4-1.3 (4H, m), 1.1 (9H, s, t-Bu), 1.0 (3H, d, J 8.6 Hz), 0.98 (3H, d, J 6 Hz), 0.9 (3H, d, J 6 Hz), 0.88 (9H, s, SiBu), -0.04 (3H, s, SiMe), -0.06 (3H, s, SiMe); $\delta_{\rm C}(100$ MHz) 213.8 (s), 162.2 (s), 161.4 (s), 156.5 (s), 155.6 (s), 144.0 (s), 139.4 (s), 138.9 (s), 135.7 (d), 134.1 (s), 131.0 (s), 129.7 (d), 127.7 (d), 117.9 (d), 96.8 (t), 81.5 (d), 81.1 (d), 78.7 (d), 77.4 (d), 62.2 (t), 57.7 (q, OMe), 57.1 (q, OMe), 55.9 (q, OMe), 52.5 (q, OMe), 50.1 (d), 42.3 (t), 40.7 (d), 34.6 (t), 33.9 (t), 33.6 (d), 33.2 (d), 31.6 (t), 29.8 (t), 27.0 (q, t-Bu), 26.6 (t), 26.2 (q, t-Bu), 19.3 (s, t-Bu), 18.5 (s, t-Bu), 16.3 (q, Me), 14.2 (q, Me), 13.4 (q, Me), 9.4 (q, Me), -4.1 (q, SiMe), -4.3 (q, SiMe); m/z (FAB) 1095 $(M + Na)^{+}$.

The ter-oxazole alcohol 72

A solution of DIBAL-H (1.5 M) in toluene (233 µl, 3.5 mmol) was added dropwise over 5 min to a stirred solution of the ketoester 18 in dry THF (4 ml) under a nitrogen atmosphere at 0 °C. The mixture was stirred at 0 °C for 45 min and then warmed to room temperature over 2 h. It was then cooled back to 0 °C where it was quenched with aqueous sodium hydroxide (1 M, 1 ml). The mixture was diluted with ethyl acetate (25 ml) and water (10 ml) and the separated aqueous phase was then extracted with ethyl acetate (2×25 ml). The combined organic phases were washed with 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 a mixture of diastereomers of the diol (77 mg, 75%) as a colourless foam; $[a]_{D}^{25}$ +6.8 (c, 3.1 in CHCl₃); $v_{max}(film)/cm^{-1}$ 3583, 3016, 2991, 2858; $\delta_{\rm H}$ (500 MHz) 8.39 (8.33) (1H, s), 8.32 (8.31) (1H, s), 7.70-7.68 (4H, m), 7.47-7.29 (6H, m), 6.95 (1H, dt, J 7.5 and 15.8 Hz), 6.48 (1H, d, J 16 Hz), 4.71 (2H, s, CH₂OH), 4.67 (d, J 6.7 Hz, OCHHOME), 4.60 (d, J 6.7 Hz, OCH-HOMe), 3.86 (1H, dd, J 8 and 2.5 Hz), 3.79-3.43 (4H, m), 3.41 (3.40) (3H, s, OMe), 3.39 (3.38) (3H, s, OMe), 3.37 (3.36) (3H, s, OMe), 3.35-3.27 (1H, m), 2.80 (1H, quintet, J 7.7 Hz), 2.61-2.53 (3H, m), 2.07-1.87 (4H, m), 1.42-1.31 (6H, m), 1.08 (1.07) (9H, s, t-Bu), 0.98 (3H, d, J 7 Hz), 0.97 (3H, d, J 7 Hz), 0.90 (3H, d, J 7 Hz), 0.85 (3H, d, J 7 Hz), 0.87 (9H, s), 0.07 (0.14) $(3H, s), -0.04 (0.12) (3H, s); \delta_{C}(67.8 \text{ MHz}) 162.0 (s), 156.2 (s),$ 155.2 (s), 141.6 (s), 138.1 (d), 138.7 (d), 135.5 (d), 135.1 (d), 133.9 (s), 133.8 (s), 131.4 (s), 130.4 (s), 129.5 (d), 127.6 (d), 117.8 (d), 96.6 (d), 82.7 (84.3) (d), 81.3 (80.9) (d), 77.5 (d), 73.3 (d), 71.4 (d), 61.9 (t), 57.5 (q, OMe), 56.8 (OMe), 56.7 (55.7) (OMe), 49.9 (d), 41.1 (t), 40.6 (d), 40.5 (d), 35.9 (d), 35.3 (d), 34.7 (t), 34.6 (t), 33.9 (d), 33.7 (t), 33.6 (t), 33.4 (t), 33.0 (t), 26.8 (q, t-Bu), 19.1 (18.3) (s, t-Bu), 18.2 (18.1) (s, t-Bu), 16.5 (16.1)

(q, Me), 15.6 (15.5) (q, Me), 14.0 (13.2) (q, Me), 13.2 (13.1) (q, Me), 9.4 (9.3) (q, Me), -4.1 (-4.0) (q, SiMe), -4.3 (-4.2) (q, SiMe); m/z (FAB) 1067 (M + Na)⁺.

The ter-oxazole aldehyde 73a

A solution of Dess-Martin periodinane (535 mg, 1.25 mmol) and pyridine (0.6 ml) in dichloromethane (12 ml) was added to a stirred solution of the diol 72 (0.25 g, 0.24 mmol) in dichloromethane (12 ml) under nitrogen at room temperature and the mixture was stirred for 1 h. It was then diluted with diethyl ether (100 ml) and stirred at room temperature with a mixture of saturated aqueous sodium bicarbonate (20 ml) and saturated sodium thiosulfate (20 ml) for twenty minutes. The organic phase was separated, and then dried (Na₂SO₄) and evaporated in vacuo. The residue was purified by chromatography on silica using ethyl acetate-petrol (2:1) as eluent to give the keto aldehyde (246 mg, 98%) as colourless foam; $[a]_{D}^{25}$ +2.3 (c, 3.0 in CHCl₃); δ_H(500 MHz) 10.1 (1H, s, CHO), 8.4 (1H, s, =CH), 8.45 (1H, s, =CH), 8.3 (1H, s, =CH), 7.7 (4H, br s, Ar-H), 7.5–7.3 (6H, m, Ar-H), 6.9 (1H, dt, J7.5 and 16 Hz, CH=CH-CH₂), 6.5 (1H, d, J 16 Hz, CH-CH=CH₂), 4.72 (1H, d, J 6.7 Hz, OCH-HOMe), 4.64 (1H, d, J 6.7 Hz, OCHHOMe), 3.9 (1H, dd, J 2.4 and 8 Hz), 3.8-3.42 (3H, m), 3.42 (3H, s, OMe), 3.41 (3H, s, OMe), 3.40 (3H, s, OMe), 3.4-3.3 (1H, m), 2.8 (1H, m), 2.6-2.5 (4H, m), 1.9–1.4 (6H, m), 1.4–1.31 (4H, m), 1.1 (9H, s, t-Bu), 1.0 (3H, d, J 7 Hz), 0.9 (3H, d, J 7 Hz), 0.91 (3H, d, J 7 Hz), 0.88 (3H, d, J 7 Hz), 0.88 (9H, s, t-Bu), 0.07 (3H, s, SiMe), -0.04 (3H, s, SiMe); $\delta_{\rm C}(90$ MHz) 213.8 (s, 36-C), 184.2 (d, CHO), 162.2 (s, Ox-C), 156.7 (s, Ox-C), 156.1 (s, Ox-C), 143.7 (d, Ox-C), 141.7 (s, Ox-C), 139.4 (d, 26-C), 138.9 (d, Ox-C), 135.6 (d, Ar), 134.0 (s, Ar), 130.7 (s, Ox-C), 130.4 (s, Ox-C), 129.6 (d, Ar), 127.7 (d, Ar), 117.8 (d, 25-C), 96.7 (t, OCH₂OCH₃), 81.4 (d, OCH), 81.05 (d, OCH), 78.6 (d, OCH), 62.2 (t, C-41), 57.6 (q, OMe), 56.9 (q, OMe), 55.8 (q, OMe), 50.0 (d, 37-C), 42.3 (t, 35-C), 40.7 (d, 38-C), 34.5 (t, 27-C), 33.8 (t, 31-C), 33.5 (d), 33.1 (d), 31.5 (t), 30.4 (d, CH-Me), 29.8 (t), 26.9 (q, t-Bu), 26.5 (t, 40-C), 26.2 (q, t-Bu), 19.3 (s, t-Bu), 18.4 (s, t-Bu), 16.2 (q, Me), 14.1 (q, Me), 13.3 (q, Me), 9.5 (q, Me); $m/z \ 1065 \ (M + Na)^+$.

The ter-oxazole (C-30) hydroxy aldehyde 73b

A solution of dimethylboryl bromide (2.67 M) in dichloromethane (111 µl, 0.3 mmol) was added to a stirred solution of the MOM-ether 73a (62 mg, 0.06 mmol) in dichloromethane (5 ml) at -78 °C under nitrogen and the mixture was then stirred at -78 °C for 45 min. It was then quenched by addition into a stirred solution of saturated sodium bicarbonate (2 ml) and THF (2 ml) at room temperature. The mixture was diluted with dichloromethane (25 ml) and the organic layer was washed with brine (10 ml), then dried (Na₂SO₄) and evaporated in vacuo. The residue was purified by chromatography over silica using ethyl acetate as eluent to give the *alcohol* (61 mg, 99%) as a colourless foam; $[a]_{D}^{25}$ -7.7 (c, 1.1 in CHCl₃); $\delta_{H}(500 \text{ MHz})$ 10.0 (1H, s, CHO), 8.4 (1H, s, Ox-H), 8.4 (1H, s, Ox-H), 8.3 (1H, s, Ox-H), 7.7-7.4 (4H, m, Ar-H), 7.4-7.3 (6H, m, Ar-H), 6.9 (1H, dt, J 7.4 and 15.7 Hz, 26-H), 6.5 (1H, d, J 16 Hz, 25-H), 3.8 (1H, t, J 8 Hz, -CHOMe), 3.8-3.6 (5H, m), 3.45 (3H, s, OMe), 3.4 (3H, s, OMe), 2.8-2.75 (1H, quintet, J 7.4 Hz), 2.7 (1H, m), 2.6-2.4 (3H, m), 1.9–1.6 (7H, m), 1.5–1.1 (3H, m), 1.1 (9H, s, t-Bu), 1.0 (3H, d, J 7 Hz), 0.95 (3H, d, J 7 Hz), 0.9 (3H, d, J 7 Hz), 0.85 (9H, s, t-Bu), 0.1 (3H, s, SiMe), 0.05 (3H, s, SiMe); $\delta_{\rm C}$ (90 MHz) 213.7 (s, C-6), 184.0 (d, CHO), 162.0 (s, Ox-C), 156.4 (s, Ox-C), 155.8 (s, Ox-C), 143.6 (d, Ox- C), 141.5 (s, Ox-C), 139.3 (d, Ox-C), 139.2 (d, Ox-C), 138.7 (d, 16-C), 135.5 (d, Ar), 133.8 (s, Ar), 130.6 (s, Ox-C), 130.3 (s, Ox-C), 129.5 (d, Ar), 127.5 (d, Ar), 117.4 (d), 81.9 (d), 81.8 (d), 78.5 (d), 70.7 (d), 62.0 (t, 41-C), 57.8 (q, OMe), 57.3 (q, OMe), 49.9 (d, 37-C), 42.2 (t, 34-C), 40.7 (d), 34.3 (t), 34.2 (t), 33.9 (d), 33.6 (t), 32.9 (d), 30.2 (d), 29.6 (t), 26.8 (s, t-Bu), 26.2 (t), 26.1 (s, t-Bu), 19.1 (s, t-Bu), 18.2 (s, t-Bu), 16.1

(q, Me), 14.0 (q, Me), 13.9 (q, Me), 11.2 (q, Me), -4.3 (q, SiMe), -4.5 (q, SiMe).

The ter-oxazole phosphonate aldehyde 19

Triethylamine (38 µl, 0.27 mmol) and 2,4,6-trichlorobenzoyl chloride (38 µl, 0.24 mmol) were added sequentially to a stirred solution of the acid 18 (128 mg, 0. 245 mmol) in toluene (0.5 ml) at room temperature under nitrogen and the resulting solution was stirred at room temperature for 3 h. A solution of the alcohol 73b (99 mg, 0.1 mmol) and DMAP (31 mg, 0.254 mmol) in toluene (1 ml) was added and the mixture was stirred at room temperature under nitrogen for 90 min, and then quenched with saturated ammonium chloride solution (2 ml). The mixture was diluted with ethyl acetate (25 ml), washed with brine (10 ml), and then dried (Na2SO4) and concentrated in vacuo. The residue was purified by chromatography on silica using ethyl acetate as eluent to give the ester (90 mg, 60%) as a colourless foam; $[a]_{D}^{25}$ +6.2 (c, 0.6 in CHCl₃); $\delta_{H}(500 \text{ MHz})$ 10.1 (1H, s, CHO), 8.4 (1H, s, Ox-H), 8.4 (1H, s, Ox-H), 8.3 (1H, s, Ox-H), 7.7-7.5 (4H, m, Ar), 7.4-7.3 (6H, m, Ar), 6.9 (1H, dt, J 7.4 and 15.4 Hz), 6.5 (1H, d, J 15.9 Hz), 5.2-5.15 (1H, m), 4.25-4.21 (1H, m), 3.9-3.8 (1H, m), 3.8 (3H, s, OMe), 3.75 (3H, s, OMe), 3.7-3.6 (3H, m), 3.3 (3H, s, OMe), 3.25 (3H, s, OMe), 3.2–3.15 (1H, m), 3.0 (2H, d, *J*_{P-CH2} 22.6 Hz), 2.95–2.9 (1H, m), 2.8-2.75 (1H, m), 1.9-1.7 (5H, m), 1.6-1.4 (10H, m), 1.4-1.3 (3H, m), 1.05 (18H, s, 2 × t-Bu), 1.0 (3H, d, J 7.1 Hz), 0.9 (3H, d, J 7.2 Hz), 0.85 (9H, s, t-Bu), 0.80 (3H, d, J 6.7 Hz), 0.07 (3H, s, SiMe), -0.04 (3H, s, SiMe); $\delta_{c}(90 \text{ MHz})$ 213.9 (s), 201.3 (d, J_{P-CO} 6 Hz, 7-C), 170.85 (d), 170.8 (s), 162.2 (s), 156.7 (s), 156.1 (s), 143.8 (d), 141.7 (s), 139.5 (d), 139.0 (d), 138.9 (d), 136.0 (d), 135.9 (d), 135.7 (d), 134.0 (s), 133.9 (s), 132.5 (s), 130.7 (d), 130.3 (d), 129.8 (d), 129.7 (d), 128.1 (d), 127.7 (d), 117.9 (d), 81.5 (d), 81.0 (d), 78.6 (d), 76.8 (d), 69.6 (d), 62.2 (t), 57.9 (q, OMe), 57.8 (q, OMe), 53.3 (q, OMe), 53.2 (q, OMe), 50.1 (d), 43.9 (t), 42.5 (t), 41.8 (t), 40.4 (d), 35.8 (t), 35.1 (t), 34.0 (d), 33.8 (t), 33.0 (d), 31.0 (t), 29.7 (t), 27.0 (q, t-Bu), 26.9 (q, t-Bu), 26.2 (q, t-Bu), 19.4 (s, t-Bu), 19.2 (s, t-Bu), 18.6 (t), 18.4 (s, t-Bu), 16.2 (q, Me), 14.2 (q, Me), 13.4 (q, Me), 9.4 (q, Me); No M⁺ could be observed.

The ter-oxazole macrolide 20

A solution of the aldehyde phosphonate **19** (21 mg, 0.14 mmol) in dry toluene (8 ml) was added dropwise over 8 h to a stirred solution of powdered potassium carbonate (3.9 mg, 0.03 mmol) and 18-crown-6 (14.8 mg, 0.06 mmol) in dry toluene (16 ml) at room temperature under argon. The solution was stirred at room temperature for 12 h and then quenched with saturated ammonium chloride solution (3 ml). The aqueous phase was separated and extracted with ether $(2 \times 25 \text{ ml})$. The combined organic extract was washed with saturated potassium chloride $(3 \times 50 \text{ ml})$, then dried (Na₂SO₄) and evaporated *in vacuo*. The residue was purified by chromatography on silica using diethyl ether-petrol (3:1) as eluent to give the macrolactone (6 mg, 31%) as a colourless foam; $[a]_{\rm D}^{25}$ +10.8 (c, 0.5 in CHCl₃); $\delta_{\rm H}$ (500 MHz) 8.2 (1H, s, Ox-H), 8.15 (1H, s, Ox-H), 7.90 (1H, s, Ox-H), 7.85-7.8 (4H, m, Ar-H), 7.75-7.7 (6H, m, Ar-H), 7.7 (1H, d, J 15 Hz, 9-H), 7.5–7.4 (11H, m, Ar-H and 8-H), 7.25–7.2 (1H, m, 26-H), 6.4 (1H, d, J 15.8 Hz, 25-H), 5.2 (1H, dt, J 1 and 7.6 Hz, 30-H), 4.55–4.50 (1H, m, 3-H), 3.89 (1H, dd, J 2.5 and 8.2 Hz), 3.8–3.75 (1H, m), 3.7–3.65 (1H, m), 3.45–3.4 (1H, m), 3.35 (3H, s, OMe), 3.3 (3H, s, OMe), 3.1 (1H, dd, J 4.3 and 9.1 Hz), 2.8–2.75 (3H, m), 2.6 (1H, dd, J 16.5 and 5.4 Hz), 2.55–2.5 (3H, m), 2.45–2.4 (1H, m), 2.3 (1H, dt, J 4.8 and 14.2 Hz), 2.2 (1H, dt, J 4.2 and 12.0 Hz), 2.0-1.7 (7H, m), 1.6-1.55 (2H, m), 1.2 (9H, s, t-Bu), 1.1 (9H, s, t-Bu), 1.0 (3H, d, J 7.1 Hz), 0.95 (3H, d, J7 Hz), 0.9 (3H, d, J6.9 Hz), 0.85 (9H, s, t-Bu), 0.8 (3H, d, J6.8 Hz), 0.04 (3H, s, SiMe), -0.05 (3H, s, SiMe); δ_{c} (125 MHz) 213.5 (s, 36-C), 200.3 (s, 7-C), 170.7 (s, 1-C), 162.6 (s, 22-C), 156.9 (17-C), 155.2 (s, 12-C), 140.0 (d, 9-C), 139.2 (d, 26-C), 138.3 (d,

24-C), 137.3 (d, 19-C), 137.0 (s, Ar), 136.0 (d, Ar), 135.9 (d, Ar), 135.6 (d, Ar), 134.3 (s, Ar), 134.1 (s, Ar), 130.9 (s, 20-C), 130.2 (s, 15-C), 129.6 (d, Ar), 128.3 (d, Ar), 127.6 (d, Ar), 126.8 (d, 8-C), 81.4 (d, 32-C), 79.7 (d, 32-C), 78.5 (d, 38-C), 73.1 (d, 30-C), 69.5 (d, 3-C), 62.1 (t, 41-C), 57.8 (q, OMe), 50.0 (d, 37-C), 44.8 (t, 6-C), 42.4 (t, 2-C), 40.9 (t, 35-C), 39.5 (d, 33-C), 36.8 (t, 4-C), 34.4 (d, 29-C), 33.7 (t, 27-C), 33.3 (d, 39-C), 32.4 (t, 31-C), 30.4 (t, 40-C), 29.7 (t, 34-C), 27.3 (q, t-Bu), 26.9 (q, t-Bu), 26.2 (q, t-Bu), 20.1 (t, 5-C), 19.4 (s, t-Bu), 19.2 (s, t-Bu), 18.4 (s, t-Bu), 16.2 (q, Me), 14.2 (q, Me), 13.7 (q, Me), 8.2 (q, Me), -4.1 (s, SiMe), -4.4 (s, SiMe); *m/z* (FAB) 1398 (M +Na)⁺.

C-9 α - and β - Methyl epimeric macrolide 80

A solution of methyllithium (1.4 M) in ether (61 µl, 0.22 mmol) was added dropwise to a stirred suspension of CuI (22 mg, 0.11 mmol) in dry ether (2.4 ml) at -5 °C under argon and the resulting solution was stirred at -5 °C for 30 min. A solution of the enone 20 (22 mg, 0.016 mmol) in dry ether (3 ml) was added dropwise over 15 min and the resulting yellow solution was then stirred at 0 °C for 3.5 h before being quenched with a 1:1 mixture of saturated ammonium chloride (3 ml) and concentrated ammonia (3 ml). The mixture was extracted with ether (2×20) ml) and the combined organic phases were washed with brine (10 ml), then dried (Na₂SO₄) and evaporated in vacuo. The residue was purified by chromatography over silica using petrol-ethyl acetate (6:4) as eluent to give the 3-methyl ketone (12 mg) as a 3:2 mixture of two diastereomers. Further chromatography gave: (i) the "9 β -methyl" diastereoisomer **80b**, as an oil; $[a]_D$ -13.0 (c, 1.0 in CHCl₃); $\delta_{\rm H}(500$ MHz) 8.15 (1H, s), 8.1 (1H, s), 7.8-7.7 (8H, m, Ar), 7.5-7.4 (12H, m), 7.15-7.1 (1H, m, 26-H), 6.5 (1H, d, J 16.1 Hz), 5.2 (1H, ddd, J 1, 6 and 8 Hz, 30-H), 4.35-4.3 (1H, m, 3-H), 3.9 (1H, dd, J 2.4 and 8.1 Hz), 3.85-3.8 (1H, m, 41-H), 3.7-3.65 (1H, m, 41-H), 3.5-3.45 (1H, m), 3.4 (3H, s, OMe), 3.35 (3H, s, OMe), 3.2 (1H, dd, J 8.8 and 16 Hz, 8-H), 3.0 (1H, dd, J 3.5 and 9.6 Hz), 2.85-2.80 (1H, quintet, J 7.7 Hz), 2.7 (1H, dd, J 16 and 5 Hz, 8-H), 2.65–2.5 (6H, m), 2.45-2.4 (1H, m), 2.3-2.25 (1H, m), 1.9-1.85 (2H, m), 1.85-1.8 (2H, m), 1.7-1.6 (2H, m), 1.6-1.5 (2H, m), 1.4-1.35 (1H, m), 1.1 (9H, s, t-Bu), 1.05 (9H, s, t-Bu), 1.0 (3H, d, J 7 Hz), 0.9 (3H, d, J 7 Hz), 0.85 (3H, d, J 7 Hz), 0.8 (3H, d, J 6.8 Hz), 0.04 (3H, s, SiMe), -0.2 (3H, s, SiMe); $\delta_{\rm C}(125$ MHz) 213.7 (s, 36-C), 210.5 (s, 7-C), 170.6 (s, 1-C), 162.4 (s, 22-C), 156.5 (s, 17-C), 154.1 (s, 12-C), 146.6 (s, 10-C), 138.4 (d, 26-C), 137.4 (d, 24-C), 137.1 (d, 19-C), 136.0 (d, Ar), 135.9 (d, Ar), 135.6 (d, Ar), 134.4 (d, 14-C), 134.2 (s, Ar), 134.0 (d, Ar), 133.4 (s, Ar), 131.9 (s, 15-C), 130.7 (s, 20-C), 129.6 (d, Ar), 129.5 (d, Ar), 127.7 (d, Ar), 127.6 (d, Ar), 127.5 (d, Ar), 117.6 (d, 25-C), 81.3 (d, 33-C), 80.6 (d, 28-C), 78.5 (d, 38-C), 72.7 (d, 30-C), 70.2 (d, 3-C), 62.2 (t, 41-C), 58.0 (q, OMe), 57.6 (q, OMe), 50.1 (d, 37-C), 47.7 (t, 8-C), 44.3 (t, 6-C), 42.5 (t, 2-C), 41.0 (t, 35-C), 39.5 (d, 33-C), 36.2 (t, 4-C), 34.5 (d, 29-C), 33.8 (d, 39-C), 33.1 (t, 27-C), 31.3 (t, 31-C), 29.8 (t, 40-C), 27.2 (d, 9-C), 27.2 (q, t-Bu), 26.9 (q, t-Bu), 26.2 (q, t-Bu), 26.1 (t, 34-C), 20.0 (q, 49-C), 19.8 (t, 5-C), 19.5 (s, t-Bu), 19.3 (s, t-Bu), 18.4 (s, t-Bu), 16.2 (q, 47-C), 14.2 (q, 45-C), 13.8 (q, 46-C), 8.8 (q, 48-C), -4.3 (q, SiMe), -4.2 (q, SiMe); m/z 1413 (M + Na)⁺. (ii) The "9 α -methyl" diastereoisomer 80a, as an oil; $\delta_{\rm H}$ (500 MHz) 8.12 (2H, s, 2 × Ox-H), 7.80–7.73 (8H, m, ArH), 7.50-7.34 (13H, m, ArH and Ox-H), 7.20-7.14 (1H, m, 26-H), 6.42 (1H, d, J 15.8 Hz), 5.19-5.16 (1H, m, 30-H), 4.36-4.30 (1H, m, 3-H), 3.91–3.89 (1H, dd, J 2.5 and 8.2 Hz, 41-H), 3.81-3.75 (1H, m, 41-H), 3.72-3.67 (1H, m, 38-H), 3.47-3.43 (1H, m), 3.38 (3H, s, OMe), 3.34 (3H, s, OMe), 3.29-3.27 (1H, m), 3.22 (1H, dd, J 7.8 and 16.7 Hz), 3.00-2.99 (1H, m), 2.83-2.80 (1H, m), 2.72–2.71 (1H, m), 2.65 (1H, dd, J 5 and 15.6 Hz), 2.61-2.51 (5H, m), 2.45-2.41 (2H, m), 2.33-2.26 (1H, m), 1.96-1.93 (2H, m), 1.80–1.68 (6H, m), 1.63–1.47 (5H, m), 1.12 (9H, s, t-Bu), 1.10 (9H, s, t-Bu), 0.99 (3H, d, J 6.9 Hz); δ_c(125 MHz) 213.6 (s, 36-C), 210.6 (s, 7-C), 170.5 (s, 1-C), 162.5 (s, 22-C), 156.5 (s, 17-C), 154.2 (s, 12-C), 146.6 (s, 10-C), 138.9 (d, 26-C),

138.4 (d, 24-C), 137.3 (d, 19-C), 136.0 (d, Ar), 135.9 (d, Ar), 135.6 (d, Ar), 134.3 (d, 14-C), 134.2 (s, Ar), 134.0 (d, Ar), 133.5 (s, Ar), 131.9 (s, 15-C), 130.9 (s, 20-C), 129.6 (d, Ar), 130.1 (d, Ar), 127.7 (d, Ar), 127.6 (d, Ar), 127.5 (d, Ar), 117.3 (d, 25-C), 81.4 (d, 32-C), 80.6 (d, 28-C), 78.5 (d, 38-C), 72.7 (d, 30-C), 69.7 (d, 3-C), 62.2 (t, 41-C), 57.9 (q, OMe), 57.5 (q, OMe), 50.1 (d, 37-C), 47.6 (t, 8-C), 44.1 (t, 6-C), 42.5 (t, 2-C), 41.5 (t, 35-C), 39.2 (d, 33-C), 36.3 (t, 4-C), 34.4 (d, 29-C), 33.8 (d, 39-C), 33.1 (t, 27-C), 32.0 (t, 31-C), 29.5 (t, 40-C), 27.1 (d, 9-C), 27.2 (q, t-Bu), 26.9 (q, t-Bu), 26.2 (q, t-Bu), 19.8 (s, t-Bu), 19.6 (t, 5-C), 19.4 (s, t-Bu), 19.3 (q, 49-C), 18.4 (s, t-Bu), 16.2 (q, 47-C), 14.2 (q, 45-C), 13.7 (q, 46-C), 8.7 (q, 48-C), -4.3 (q, SiMe), -4.2 (q, SiMe); m/z 1413 (M + Na)⁺.

C-9 α -and β - methyl epimers of the macrolide C-38 alcohol 81

Trimethylsilyl trifluoromethanesulfonate (2.3 µl, 0.015 mmol) was added in one portion to a solution of the TBDMS-ether 80b (7 mg, 0.005 mmol) in dry dichloromethane (1.5 ml) at -78 °C under nitrogen and the resulting solution was stirred at -78 °C for 1 h. The mixture was quenched by addition into a stirred solution of THF (1 ml) and saturated sodium bicarbonate (1 ml) and then diluted with dichloromethane (20 ml). The separated organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by chromatography on silica gel using a mixture of petrol and ethyl acetate as eluent to give the alcohol (5.8 mg, 85%) as a colourless foam; $\delta_{\rm H}$ (500 MHz) 8.13 (1H, s, Ox-H), 8.12 (1H, s, Ox-H), 7.8-7.7 (8H, m, ArH), 7.5-7.4 (13H, m, ArH and Ox-H), 7.1-7.0 (1H, m, 26-H), 6.5 (1H, d, J 16 Hz, 25-H), 5.3-5.2 (1H, m, 30-H), 4.35-4.3 (1H, m, 3-H), 3.85-3.8 (1H, m, 41-H), 3.75-3.7 (1H, m, 41-H), 3.6-3.5 (1H, m, 39-H), 3.41 (3H, s, OMe), 3.5-3.4 (1H, m), 3.41 (1H, m), 3.35 (3H, s, OMe), 3.2 (1H, dd, J 8.6 and 16.3 Hz, 8-H), 3.0 (1H, dd, J 4 and 14 Hz), 2.9–2.8 (1H, m), 2.7–2.65 (2H, m), 2.65–2.6 (4H, m), 2.5 (1H, dd, J 7.6 and 15.5 Hz), 2.4 (1H, dd, J 5.1 and 11.2 Hz), 2.3–2.2 (1H, m), 1.9–1.7 (7H, m), 1.6–1.55 (4H, m), 1.4 (3H, d, J 7.1 Hz), 1.1 (9H, s, t-Bu), 1.0 (9H, s, t-Bu), 0.95 (3H, d, J 6.8 Hz), 0.9 (3H, d, J 6.8 Hz), 0.85 (3H, d, J 6.8 Hz); δ_c(125 MHz) 215.8 (s, 36-C), 210.7 (s, 7-C), 170.4 (s, 1-C), 162.4 (s, 22-C), 156.50 (s, 17-C), 154.2 (s, 12-C), 146.6 (s, 10-C), 138.5 (d, 26-C), 137.4 (d, 24-C), 137.1 (d, 19-C), 136.0 (d, Ar), 135.9 (d, Ar), 135.6 (d, Ar), 134.4 (d, 14-C), 134.1 (s, Ar), 134.0 (d, Ar), 133.4 (s, Ar), 131.9 (s, 15-C), 130.7 (s, 20-C), 129.7 (d, Ar), 129.6 (d, Ar), 129.5 (d, Ar), 127.7 (d, Ar), 127.6 (d, Ar), 127.5 (d, Ar), 117.4 (d, 25-C), 81.1 (d, 32-C), 80.2 (d, 28-C), 78.0 (d, 38-C), 72.8 (d, 30-C), 70.2 (d, 3-C), 61.9 (t, 41-C), 57.8 (q, OMe), 57.6 (q, OMe), 48.8 (d, 37-C), 47.8 (t, 8-C), 44.4 (t, 6-C), 41.2 (t, 2-C), 41.0 (t, 35-C), 39.7 (d, 33-C), 36.1 (t, 4-C), 34.2 (d, 29-C), 33.0 (t, 40-C), 32.7 (d, 39-C), 32.0 (t, 34-C), 31.7 (t, 31-C), 27.4 (d, 9-C), 27.2 (q, t-Bu), 26.9 (q, t-Bu), 26.4 (t, 34-C), 19.7 (q, 49-C), 19.6 (t, 5-C), 19.4 (s, t-Bu), 19.2 (s, t-Bu), 16.9 (47-C), 14.2 (q, 46-C), 13.7 (q, 45-C), 8.8 (q, 48-C). The corresponding 9a-methyl diastereoisomer 80a was prepared using an identical procedure and showed $\delta_{\rm H}(500$ MHz) 8.11 (2H, s, 2 × Ox-H), 7.79–7.73 (8H, m, ArH), 7.50–7.38 (13H, 12 × ArH and 1 × Ox-H), 7.18–7.12 (1H, m, 26-H), 6.42 (1H, d, J 16 Hz), 5.19-5.16 (1H, m, 30-H), 4.36-4.34 (1H, m, 3-H), 3.83-3.81 (1H, m, 41-H), 3.74-3.69 (1H, m, 41-H), 3.63-3.61 (1H, m, 38-H), 3.47-3.44 (1H, m), 3.38 (3H, s, OMe), 3.33 (3H, s, OMe), 3.29-3.26 (1H, m), 3.20 (1H, dd, J 7.8 and 16.6 Hz, 8-H), 3.00 (1H, dd, J 2.5 and 10 Hz), 2.85-2.79 (1H, m), 2.73-2.67 (2H, m), 2.65-2.62 (2H, m), 2.60-2.57 (3H, m), 2.47-2.36 (2H, m), 2.12–2.07 (1H, m), 1.97–1.91 (3H, m), 1.87–1.77 (4H, m), 1.71–1.66 (2H, m), 1.63–1.58 (2H, m), 1.54–1.45 (2H, m), 1.12 (9H, s, t-Bu), 1.09 (9H, s, t-Bu), 0.98 (3H, d, J 6.7 Hz), 0.95 (3H, d, J 6.9 Hz), 0.89 (3H, d, J 7 Hz), 0.87 (3H, d, J 6.8 Hz); $\delta_{\rm C}(125 \text{ MHz}) 215.7 \text{ (s, 36-C)}, 210.6 \text{ (s, 7-C)}, 170.6 \text{ (s, 1-C)}, 162.5$ (s, 22-C), 156.5 (s, 17-C), 154.2 (s, 12-C), 146.5 (s, 10-C), 138.9 (d, 26-C), 137.3 (d, 24-C), 137.0 (d, 19-C), 136.1 (d, Ar), 135.9 (d, Ar), 135.7 (d, Ar), 134.3 (s, Ar), 134.2 (s, Ar), 134.0 (s, Ar),

133.5 (d, 14-C), 131.9 (s, 15-C), 130.6 (s, 20-C), 129.7 (d, Ar), 129.6 (d, Ar), 127.7 (d, Ar), 127.6 (d, Ar), 117.3 (d, 25-C), 81.2 (d, 33-C), 80.0 (d, 28-C), 78.1 (d, 38-C), 72.91 (d, 30-C), 69.7 (d, 3-C), 61.8 (t, 41-C), 57.9 (q, OMe), 57.6 (q, OMe), 48.8 (d, 37-C), 47.6 (t, 8-C), 44.1 (t, 6-C), 41.5 (t, 2-C), 41.0 (t, 35-C), 39.3 (d, 32-C), 36.3 (t, 4-C), 34.4 (d, 29-C), 33.6 (t, 40-C), 32.8 (d, 39-C), 32.1 (t, 34-C), 32.0 (t, 31-C), 27.1 (d, 9-C), 27.0 (q, t-Bu), 26.9 (q, t-Bu), 26.3 (t, 34-C), 19.7 (s, t-Bu), 19.6 (t, 5-C), 19.4 (s, t-Bu), 19.2 (q, 49-C), 16.7 (q, 47-C), 14.3 (q, 46-C), 13.7 (q, 45-C), 8.7 (q, 48-C).

C-9 α- and β-Methyl epimers of the macrolide C-38 acetate 82

Acetic anhydride (0.2 ml) was added to a solution of the secondary alcohol 81 (16.5 mg, 0.013 mmol) and DMAP (1 mg) in a mixture of dichloromethane (0.5 ml) and dry pyridine (0.5 ml) at room temperature under nitrogen and the resulting solution was stirred at room temperature for 12 h. The mixture was diluted with dichloromethane (20 ml) and water (5 ml) and the organic extract was washed successively with water $(2 \times 10 \text{ ml})$, copper sulfate $(2 \times 5 \text{ ml})$ and brine (5 ml), then dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography over silica using ethyl acetate-petrol (2:1) as eluent to give the *acetate* (15.5 mg, 91%) as a colourless foam; $\delta_{\rm H}(500$ MHz) 8.15 (1H, s), 8.1 (1H, s), 7.8-7.7 (8H, m, Ar-H), 7.5-7.4 (12H, m, ArH), 7.15–7.1 (1H, m, 26-H), 6.47 (1H, d, J 16 Hz, 25-H), 5.25–5.2 (1H, m, 30-H), 5.15 (1H, dd, J 3.4 and 9.1 Hz, 38-H), 4.35-4.3 (1H, m, 3-H), 3.85-3.8 (1H, m, 41-H), 3.7-3.65 (1H, m, 41-H), 3.45–3.4 (1H, m), 3.4 (3H, s, OMe), 3.35 (3H, s, OMe), 3.2 (1H, dd, J 8.7 and 16.4 Hz, 8-H), 3.0 (1H, dd, J 4.1 and 9.8 Hz), 2.95-2.9 (1H, m), 2.7-2.5 (6H, m), 2.4-2.35 (2H, m), 2.3-2.2 (2H, m), 2.0 (3H, COMe), 1.9-1.85 (2H, m), 1.85-1.8 (2H, m), 1.8–1.75 (2H, m), 1.7–1.6 (2H, m), 1.6–1.5 (2H, m), 1.1 (9H, s, t-Bu), 1.05 (9H, s, t-Bu), 1.05 (3H, d, J 7 Hz), 0.9 (3H, d, J 7 Hz), 0.86 (3H, d, J 6.9 Hz), 0.85 (3H, d, J 7 Hz), 0.84 (3H, d, J 6.8 Hz); $\delta_{\rm C}(125$ MHz) 211.7 (s, 36-C), 210.5 (s, 7-C), 170.6 (s, 1-C), 170.2 (s, COMe), 162.4 (s, 22-C), 156.5 (s, 17-C), 154.2 (s, 12-C), 146.6 (s, 10-C), 138.4 (d, 26-C), 137.4 (d, 24-C), 137.1 (d, 19-C), 136.0 (d, Ar), 135.9 (d, Ar), 135.5 (d, Ar), 134.4 (d, 14-C), 134.2 (s, Ar), 133.8 (d, Ar), 133.4 (s, Ar), 131.9 (s, 15-C), 130.7 (s, 20-C), 129.7 (d, Ar), 129.6 (d, Ar), 129.5 (d, Ar), 127.7 (d, Ar), 127.6 (d, Ar), 127.5 (d, Ar), 117.5 (d, 25-C), 81.2 (d, 32-C), 80.5 (d, 28-C), 78.5 (d, 38-C), 72.7 (d, 30-C), 70.2 (d, 3-C), 61.5 (t, 41-C), 58.0 (t, OMe), 57.6 (OMe), 48.2 (d, 37-C), 47.8 (t, 8-C), 44.3 (t, 6-C), 41.1 (t, 2-C), 40.0 (t, 35-C), 39.5 (d, 33-C), 36.2 (t, 4-C), 34.5 (d, 29-C), 32.8 (t, 27-C), 32.0 (t, 40-C), 31.6 (t, 31-C), 30.5 (d, 39-C), 27.2 (d, 9-C), 27.1 (q, t-Bu), 26.9 (q, t-Bu), 26.4 (t, 34-C), 20.9 (q, COMe), 19.9 (q, 49-C), 19.7 (t, 5-C), 19.4 (s, t-Bu), 19.2 (s, t-Bu), 16.6 (q, C-47), 13.8 (q, C-46), 13.4 (q, 45-C), 8.8 (q, 48-C). The corresponding 9α -methyl diastereoisomer **82b** was prepared using an identical procedure and showed $\delta_{\rm H}(500 \text{ MHz})$ 8.12 (1H, s, Ox-H), 8.11 (1H, s, Ox-H), 7.74-7.72 (8H, m, Ar-H), 7.50-7.39 (13H, m, 12-ArH and 1-Ox-H), 6.42 (1H, d, J 15.8 Hz), 7.19 (1H, ddd, J 6.2, 9.3 and 15.7 Hz, 26-H), 5.19–5.15 (1H, m, 38-H), 4.36– 4.32 (1H, m, 3-H), 3.83–3.79 (1H, m, 41-H), 3.72–3.67 (1H, m, 41-H1) 3.48-3.42 (1H, m), 3.38 (3H, s, OMe), 3.33 (3H, s, OMe), 3.30–3.26 (1H, m), 3.21 (1H, dd, J 8.9 and 13.6 Hz), 3.00-2.97 (1H, m), 2.94-2.88 (1H, m), 2.73-2.65 (2H, m), 2.64 (1H, dd, J 5.1 and 10.9 Hz), 2.59 (1H, dd, J 6.7 and 15.9 Hz), 2.54-2.50 (3H, m), 2.48-2.40 (3H, m), 2.33-2.28 (1H, m), 2.08-2.06 (1H, m), 2.02 (3H, s, COMe), 1.96-1.92 (1H, m), 1.88-1.70 (6H, m), 1.63–1.54 (3H, m), 1.48–1.45 (2H, m), 1.34 (3H, d, J7 Hz), 1.12 (9H, s, t-Bu), 1.10 (9H, s, t-Bu), 0.89 (3H, d, J 6.9 Hz), 0.88 (3H, d, J 6.8), 0.86 (3H, d, J 6.9 Hz); δ_C(125 MHz) 211.7 (s, 36-C), 210.6 (s, 7-C), 170.6 (s, 1-C), 170.1 (s, COMe), 162.4 (s, 22-C), 156.5 (s, 17-C), 146.6 (s, 10-C), 138.9 (d, 26-C), 137.3 (d, 24-C), 137.0 (d, 19-C), 136.1 (d, Ar), 135.9 (d, Ar), 135.6 (d, Ar), 134.3 (s, Ar), 134.2 (s, Ar), 133.8 (s, Ar), 133.5 (d, 14-C), 131.9 (s, 15-C), 130.7 (s, 20-C), 129.7 (d, Ar), 129.6 (d, Ar),

127.7 (d, Ar), 127.6 (d, Ar), 117.3 (d, 25-C), 81.3 (d, 32-C), 80.6 (d, 28-C), 78.5 (d, 38-C), 72.7 (d, 30-C), 69.7 (d, 3-C), 61.5 (t, 41-C), 58.0 (q, OMe), 57.5 (q, OMe), 48.2 (d, 37-C), 47.6 (t, 8-C), 44.1 (t, 6-C), 41.5 (t, 2-C), 40.0 (t, 35-C), 39.2 (d, 33-C), 36.3 (t, 4-C), 34.5 (d, 29-C), 33.2 (t, 27-C), 32.8 (t, 31-C), 31.5 (t, 40-C), 30.5 (d, 39-C), 27.1 (d, 9-C), 27.1 (q, t-Bu), 26.9 (q, t-Bu), 26.4 (t, 34-C), 20.9 (q, *COMe*), 19.7 (s, t-Bu), 19.6 (s, t-Bu), 19.4 (t, 5-C), 19.3 (q, 49-C), 16.6 (q, 47-C), 13.7 (q, 46-C), 13.4 (q, 45-C), 8.7 (q, 48-C).

C-9 α- and β-Methyl epimers of the macrolide C-41 alcohol 83

Pyridine-HF (0.1 ml) was added to a solution of the silvl ether 82 (11 mg, 0.008 mmol) in dry THF (0.5 ml) and pyridine (0.5 ml) at room temperature under nitrogen and the resulting solution was stirred at room temperature for 1.5 h then diluted with ethyl acetate (5 ml) and quenched with saturated aqueous sodium bicarbonate (2 ml). The organic extract was washed successively with water (2 × 10 ml), copper sulfate (2 × 5 ml) and brine (5 ml), then dried (Na₂SO₄) and evaporated in vacuo. The residue was purified by chromatography over silica gel using ethyl acetate as eluent to give the alcohol (7.4 mg, 84%) as a colourless foam; $\delta_{\rm H}$ (500 MHz) 8.14 (1H, s, Ox-H), 8.13 (1H, s, Ox-H), 7.81–7.74 (4H, m, Ar-H), 7.48–7.40 (7H, m, ArH and Ox-H), 7.13-7.06 (1H, m, 26-H), 6.49 (1H, d, J 15.9 Hz, 25-H), 5.27-5.24 (1H, m, 30-H), 5.17 (1H, dd, J 3.9 and 8.6 Hz, 39-H), 4.37-4.33 (1H, m, 3-H), 3.83-3.81 (1H, m, 41-H), 3.69-3.67 (1H, m, 41-H), 3.46-3.43 (1H, m), 3.41 (3H, s, OMe), 3.36 (3H, s, OMe), 3.16 (1H, dd, J 8.7 and 15.8 Hz, 8-H), 3.03-2.96 (2H, m), 2.78–2.67 (4H, m), 2.62 (1H, dd, J 5 and 16 Hz), 2.54–2.47 (4H, m), 2.37 (1H, dd, J 5.1 and 16.4 Hz), 2.30-2.24 (1H, m), 2.05 (3H, s, COMe), 1.89-1.85 (3H, m), 2.03-2.00 (2H, m), 1.81-1.77 (4H, m), 1.13 (3H, d, J 7.2 Hz), 1.08 (9H, s, t-Bu), 0.99 (3H, d, J 6.1Hz), 0.91–0.87 (9H, 2 × d, J 7 Hz); $\delta_{\rm C}(125$ MHz) 211.7 (s, 36-C), 210.9 (s, 7-C), 170.7 (s, 1-C), 170.2 (s, COMe), 162.4 (s, 22-C), 156.5 (s, 17-C), 154.2 (s, 12-C), 146.6 (s, 10-C), 138.4 (d, 26-C), 137.5 (d, 24-C), 137.1 (d, 19-C), 136.0 (d, Ar), 135.9 (d, Ar), 134.5 (s, Ar), 133.4 (d, 14-C), 131.8 (s, 15-C), 130.0 (s, 20-C), 129.6 (d, Ar), 129.5 (d, Ar), 127.6 (d, Ar), 127.5 (d, Ar), 117.5 (d, 25-C), 80.8 (d, 32-C), 80.1 (d, 28-C), 78.3 (d, 38-C), 72.8 (d, 30-C), 70.2 (d, 3-C), 60.4 (t, 41-C), 57.8 (q, OMe), 57.7 (q, OMe), 48.0 (d, 37-C), 47.9 (t, 8-C), 44.4 (t, 6-C), 41.1 (t, 2-C), 40.1 (t, 35-C), 39.4 (d, 33-C), 36.2 (t, 4-C), 34.2 (d, 29-C), 33.5 (t, 27-C), 33.0 (t, 40-C), 30.9 (d, 39-C), 29.8 (t, 31-C), 27.5 (d, 9-C), 27.1 (q, t-Bu), 26.5 (t, 34-C), 20.9 (q, COMe), 19.8 (q, 49-C), 19.6 (s, t-Bu), 19.4 (t, 5-C), 16.5 (q, 47-C), 13.8 (q, 46-C), 13.5 (q, 45-C), 8.8 (q, 48-C). The corresponding 9a-methyl diastereoisomer 83a was prepared using an identical procedure and showed $\delta_{\rm H}(500 \text{ MHz}) 8.12$ (2H, s, Ox-H), 7.80-7.75 (4H, m, Ar-H), 7.55-7.39 (7H, m, 6 Ar-H and 1 Ox-H), 7.15 (1H, ddd, J 2.9, 7 and 15.6 Hz), 6.42 (1H, d, J 15.8 Hz, 25-H), 5.20-5.16 (1H, m, 30-H), 4.38-4.34 (1H, m, 3-H), 3.86-3.81 (1H, m. 41-H), 3.71-3.67 (1H, m, 41-H), 3.48-3.42 (1H, m), 3.38 (3H, s, OMe), 3.33 (3H, s, OMe), 3.31-3.28 (1H, m), 3.18 (1H, dd, J 7.7 and 16.4 Hz), 3.01-2.94 (2H, m), 2.73–2.70 (1H, m), 2.67 (1H, dd, J 5.4 and 16 Hz), 2.60 (1H, dd, J 6.6 and 16.1 Hz), 2.55-2.52 (3H, m), 2.46 (1H, dd, J 6 and 16.5 Hz), 2.40–2.33 (2H, m), 2.06 (3H, s, OCOMe), 1.94-1.92 (1H, m), 1.83-1.74 (5H, m), 1.69-1.68 (1H, m), 1.64-1.54 (4H, m), 1.48-1.42 (2H, m), 1.35 (3H, d, J 6.9 Hz, 49-Me), 1.13 (3H, d, J 7.1 Hz, Me), 1.10 (9H, s, t-Bu), 0.99 (3H, d, J 7.0 Hz, Me), 0.89 (3H, d, J 7 Hz, Me), 0.87 (3H, d, J 6.8 Hz, Me); δ_C(125 MHz) 211.5 (s, 36-C), 210.6 (s, 7-C), 170.6 (s, 1-C), 170.2 (s, COMe), 162.4 (s, 22-C), 156.5 (s, 17-C), 154.3 (s, 12-C), 146.6 (s, 10-C), 138.9 (d, 26-C), 137.3 (d, 24-C), 137.0 (d, 19-C), 136.1 (d, Ar), 135.9 (d, Ar), 134.3 (s, Ar), 134.1 (s, Ar), 133.5 (d, 14-C), 131.9 (s, 15-C), 130.6 (s, 20-C), 129.6 (d, Ar), 127.6 (d, Ar), 117.3 (d, 25-C), 81.1 (d, 32-C), 80.5 (d, 28-C), 78.2 (d, 38-C), 72.8 (d, 30-C), 69.7 (d, 3-C), 60.5 (t, 41-C), 57.9 (q, OMe), 57.5 (q, OMe), 48.0 (d, 37-C), 47.7 (t, 8-C), 44.1 (t, 6-C),

41.5 (t, 4-C), 40.1 (t, 35-C), 39.4 (d, 33-C), 36.3 (t, 4-C), 34.3 (d, 29-C), 33.5 (t, 27-C), 33.3 (t, 32-C), 31.6 (t, 40-C), 31.0 (d, 39-C), 27.2 (d, 9-C), 27.1 (q, t-Bu), 26.5 (t, 34-C), 21.0 (q, CO*Me*), 19.6 (s, t-Bu), 19.5 (q, 49-C), 19.4 (t, 5-C), 16.5 (q, 47-C), 14.2 (q, 46-C), 13.5 (q, 45-C), 8.7 (q, 48-C).

The macrolide C-41 aldehyde 84

Dess-Martin periodinane (3 mg, 0.0069 mmol) was added in one portion to a solution of the alcohol 83 (5 mg, 0.005 mmol) in dry dichloromethane (1 ml) at room temperature under nitrogen and the resulting solution was stirred at room temperature for 1 h. The mixture was diluted with ether (5 ml) and then stirred with a mixture of saturated aqueous sodium bicarbonate (2 ml) and saturated aqueous sodium thiosulfate (2 ml) for 20 min. The separated organic phase was washed with brine (2 ml), then dried (Na₂SO₄) and evaporated in *vacuo*. The residue was purified by chromatography over silica using ethyl acetate as eluent to give the aldehyde (4.5 mg, 90%) as a colourless foam; $\delta_{\rm H}$ (500 MHz) 9.85 (1H, t, J 1.2 Hz, 42-H), 8.15 (1H, s, Ox-H), 8.14 (1H, s, Ox-H), 7.82–7.74 (4H, m, Ar-H), 7.49–7.41 (7H, m, ArH and Ox-H), 7.13–7.06 (1H, m, 26-H), 6.50 (1H, d, J 16.1 Hz), 5.26-5.23 (1H, m, 30-H), 5.16 (1H, dd, J 4.7 and 7.8 Hz, 38-H) 4.36–4.32 (1H, m, 3-H), 3.48– 3.43 (1H, m), 3.41 (3H, s, OMe), 3.37 (3H, s, OMe), 3.15 (1H, dd, J 8.7 and 16.2 Hz, 8-H), 3.04-3.00 (1H, m), 2.89-2.85 (1H, m), 2.75-2.67 (2H, m), 2.62-2.48 (8H, m), 2.41-2.33 (2H, m), 2.27-2.20 (1H, m), 2.06 (3H, s, OCOMe), 1.95-1.73 (4H, m), 1.63–1.48 (3H, m), 1.35 (3H, d, J 7 Hz), 1.16 (3H, d, J 7 Hz), 1.08 (9H, s, t-Bu), 1.05 (3H, d, J 6.9 Hz), 0.90 (3H, d, J 7 Hz), 0.87 (3H, d, J 6.8 Hz); δ_c(125 MHz) 210.9 (s, 36-C), 210.5 (s, 7-C), 201.3 (d, 42-C), 170.6 (s, 1-C), 170.0 (s, COMe), 162.9 (s, 22-C), 156.5 (s, 17-C), 154.2 (s, 12-C), 146.7 (s, 10-C), 138.4 (d, 26-C), 137.5 (d, 24-C), 137.1 (d, 19-C), 136.0 (d, Ar), 135.9 (d, Ar), 134.5 (s, Ar), 134.1 (s, Ar), 133.3 (d, 14-C), 131.9 (s, 15-C), 130.8 (s, 20-C), 129.6 (d, Ar), 129.5 (d, Ar), 127.6 (d, Ar), 127.5 (d, Ar), 117.5 (d, 25-C), 81.1 (d, 32-C), 80.2 (d, 28-C), 77.6 (d, 38-C), 72.8 (d, 30-C), 70.2 (d, 3-C), 57.9 (q, OMe), 57.6 (q, OMe), 48.4 (d, 37-C), 47.9 (t, 8-C), 46.0 (t, 40-C), 44.4 (t, 6-C), 41.1 (t, 2-C), 39.9 (t, 35-C), 39.7 (d, 33-C), 36.2 (t, 4-C), 34.4 (d, 29-C), 33.1 (t, 27-C), 31.8 (t, 31-C), 29.5 (d, 39-C), 27.4 (d, 9-C), 27.1 (q, t-Bu), 26.5 (t, 34-C), 20.9 (q, COMe), 19.8 (s, t-Bu), 19.7 (q, 49-C), 19.5 (t, 5-C), 16.5 (q, 47-C), 13.9 (q, 46-C), 13.3 (q, 45-C), 8.8 (q, 48-C); m/z (FAB) 1101 $(M + Na)^+$. The corresponding 9 α -methyl diastereoisomer 84a was prepared using an identical procedure and showed $\delta_{\rm H}(500$ MHz) 9.85 (1H, t, J 1.5 Hz), 8.12 (2H, s, Ox-H), 7.80-7.72 (4H, m, Ar-H), 7.49-7.39 (7H, m, Ar-H and Ox-H), 7.18-7.12 (1H, ddd, J 2.8, 6.8 and 16 Hz), 6.42 (1H, d, J 15.9 Hz), 5.21-5.15 (2H, m, 30-H and 39-H), 4.37-4.33 (1H, m, 3-H), 3.48-3.42 (1H, m), 3.38 (3H, s, OMe), 3.33 (3H, s, OMe), 3.31-3.28 (1H, m), 3.20 (1H, dd, J 7.7 and 16.4 Hz, 8-H), 3.01–2.98 (1H, m), 2.89-2.84 (1H, m), 2.73-2.71 (1H, m), 2.66 (1H, dd, J 4.4 and 16 Hz), 2.61 (1H, dd, J 5.3 and 16 Hz), 2.57–2.55 (1H, m), 2.54– 2.51 (5H, m), 2.45 (1H, dd, J 5.8 and 16.6 Hz), 2.41 (1H, dd, J 7.4 and 15.5 Hz), 2.38–2.36 (2H, m), 2.06 (3H, s, OCOCH₃), 1.94-1.93 (2H, m), 1.82-1.77 (4H, m), 1.73-1.68 (2H, m), 1.66-1.58 (3H, m), 1.30 (3H, d, J 6.9 Hz), 1.15 (3H, d, J 7.2), 1.05 (3H, d, J 7 Hz), 0.89 (3H, d, J 7 Hz), 0.87 (3H, d, J 6.8 Hz), 1.10 (9H, s, t-Bu); δ_c(125 MHz) 210.9 (s, 36-C), 210.5 (s, 7-C), 201.2 (d, 41-C), 170.6 (s, 1-C), 170.0 (s, COMe), 162.4 (s, 22-C), 156.5 (s, 17-C), 154.3 (s, 12-C), 146.6 (s, 10-C), 138.9 (d, 26-C), 137.3 (d, 24-C), 137.0 (d, 19-C), 136.1 (d, Ar), 135.9 (d, Ar), 134.3 (s, Ar), 134.2 (s, Ar), 133.5 (d, 14-C), 131.9 (s, 15-C), 130.9 (s, 20-C), 129.6 (d, Ar), 127.6 (d, Ar), 125.6 (d, Ar), 117.3 (d, 25-C), 81.2 (d, 32-C), 80.5 (d, 28-C), 77.6 (d, 38-C), 72.8 (d, 30-C), 69.7 (d, 3-C), 57.9 (q, OMe), 57.5 (q, OMe), 48.5 (d, 37-C), 47.6 (t, 8-C), 45.9 (t, 40-C), 44.1 (t, 6-C), 41.5 (t, 2-C), 39.9 (t, 35-C), 39.3 (d, 32-C), 36.3 (t, 4-C), 34.5 (d, 29-C), 33.2 (t, 27-C), 32.1 (t, 31-C), 29.5 (d, 39-C), 27.2 (d, 9-C), 27.1 (q,

t-Bu), 26.5 (t, 34-C), 20.9 (q, CO*Me*), 19.7 (s, t-Bu), 19.5 (q, 49-C), 19.3 (t, 5-C), 17.8 (q, Me, 47-C), 14.2 (q, Me, 46-C), 13.8 (q, 45-C), 8.7 (q, 48-C); *m/z* (FAB) 1101 (M + Na)⁺.

The macrolide N-methyl-N-alkenylformamide 85

N-Methylformamide (0.4 µl, 0.007 mmol) was added to a solution of the aldehyde 84b (5 mg, 0.005 mmol) and pyridinium toluene-p-sulfonate (0.29 mg, 0.001 mmol) in dry benzene (1.5 ml) and the mixture was heated under reflux for 3 h. An additional portion of N-methylformamide (1 drop) was added and the refluxing was continued for 6 h. The mixture was purified by chromatography over silica using ethyl acetate-petrol (3:1) as eluent to give a mixture of rotamers of the *E*-alkenylformamide (2.25 mg, 40%) as a colourless foam; $\delta_{\rm H}$ (500 MHz) 8.4 (1H, s, CHO), 8.15 (8.14) (1H, s, Ox-H), 8.13 (8.12) (1H, s, Ox-H), 7.80-7.74 (m, 4H, ArH), 7.48-7.40 (m, 7H, 6 × ArH and Ox-H), 7.13–7.06 (m, 1H, 26-H), 6.56 (7.22) (d, 1H, J 14 Hz, 41-H), 6.49 (6.48) (1H, d, J 16 Hz, 25-H), 5.26-5.22 (1H, m, 30-H), 5.20 (1H, dd, J4 and 9 Hz, 38-H), 5.1 (5.0) (1H, dd, J9.4 and 14 Hz, 40-H), 4.35-4.32 (1H, m, 3-H), 3.47-3.45 (1H, m), 3.42 (3H, s, OMe), 3.36 (3H, s, OMe), 3.10 (3.13) (3H, s, NMe), 3.04-3.00 (1H, m), 2.86-2.80 (1H, m), 2.76-2.72 (3H, m), 2.65-2.59 (2H, m), 2.57-2.49 (2H, m), 2.41-2.36 (2H, m), 2.07 (2.06) (3H, s, COMe), 1.90-1.76 (3H, m), 1.52-1.48 (4H, m), 1.35 (3H, d, J 7 Hz, 49-C), 1.13 (1.12) (3H, d, J 7.1 Hz), 1.10 (3H, d, J 7.2 Hz), 1.08 (s, 9H, t-Bu), 0.90 (0.89) (3H, d, J 7 Hz), 0.87 (0.86) (3H, d, J 7 Hz); δ_c(125 MHz) 211.3 (s, 36-C), 210.5 (s, 7-C), 170.1 (s, 1-C), 170.0 (s, COMe), 162.4 (162.2) (d, CHO), 161.0 (s, 22-C), 156.5 (s, 17-C), 154.2 (s, 12-C), 146.7 (s, 10-C), 138.5 (d, 26-C), 137.5 (d, 24-C), 137.1 (d, 19-C), 136.0 (d, Ar), 135.9 (d, Ar), 134.4 (s, Ar), 134.1 (s, Ar), 133.4 (d, 14-C), 130.0 (s, 15-C), 130.8 (s, 20-C), 129.6 (d, Ar), 129.5 (d, Ar), 127.6 (d, Ar), 127.5 (d, Ar), 117.5 (d, 25-C), 110.6 (112.2) (d, 40-C), 72.8 (d, 30-C), 70.2 (d, 3-C), 57.9 (q, OMe), 57.6 (q, OMe), 48.6 (48.4) (d, 37-C), 47.8 (t, 8-C), 44.4 (t, 6-C), 41.1 (t, 2-C), 39.9 (t, 35-C), 39.7 (d, 32-C), 36.9 (d, 39-C), 36.2 (t, 4-C), 34.5 (d, 29-C), 33.1 (t, 27-C), 31.9 (t, 31-C), 27.6 (d, 9-C), 27.1 (q, t-Bu), 26.3 (t, 34-C), 20.9 (q, COMe), 20.7 (t, 5-C), 19.8 (s, t-Bu), 19.6 (19.7) (q, 45-C), 19.5 (q, 49-C), 13.9 (q, 47-C), 13.5 (13.4) (q, 46-C), 8.8 (q, 48-C). The corresponding 9α-methyl diastereoisomer 85a was prepared using an identical procedure and showed $\delta_{\rm H}(500$ MHz) 8.35 (1H, s, CHO), 8.14 (2H, s, Ox-H), 7.79-7.71 (4H, m, ArH), 7.51-7.36 (7H, m, 6 × ArH and Ox-H), 7.14-7.12 (1H, m, 26-H), 6.55 (7.23) (1H, d, J 13.9 Hz, 41-H), 6.42 (1H, d, J 15.5 Hz, 25-H), 5.41-5.29 (1H, m), 5.24-5.19 (1H, m, 38-H), 5.06-5.00 (1H, m, 40-H), 4.38-4.26 (1H, m, 3-H), 3.48-3.46 (1H, m), 3.38 (3H, m, OMe), 3.33 (3H, s, OMe), 3.10 (3.14) (3H, s, NMe), 3.00-2.99 (1H, m), 2.86-2.83 (1H, m), 2.73-2.70 (2H, m), 2.65-2.60 (2H, m), 2.57-2.48 (2H, m), 2.46-2.39 (2H, m), 2.07 (2.06) (3H, s, COCH₃), 1.89–1.76 (3H, m), 1.53–1.47 (4H, m), 1.36 (3H, d, J 7Hz, 49-C), 1.12 (3H, d, J 7Hz), 1.09 (9H, s, t-Bu), 0.97–0.87 (9H, m, $3 \times Me$); $\delta_{C}(125 \text{ MHz}) 211.5$ (s, 36-C), 210.4 (s, 7-C), 172.7 (s, 1-C), 170.5 (s, COMe), 162.6 (s, 22-C), 162.2 (161.0) (d, CHO), 156.4 (s, 17-C), 154.3 (s, 12-C), 146.5 (s, 10-C), 138.9 (d, 26-C), 137.4 (d, 24-C), 137.0 (d, 19-C), 136.0 (d, Ar), 135.9 (d, Ar), 134.1 (s, Ar), 133.5 (d, 14-C), 130.7 (s, 20-C), 130.02 (124.4) (d, 41-C), 129.6 (d, Ar), 127.6 (d, Ar), 117.3 (d, 25-C), 110.6 (d, 40-C), 81.3 (d, 32-C), 80.5 (d, 28-C), 77.3 (d, 38-C), 72.8 (d, 30-C), 69.7 (d, 3-C), 58.0 (q, OMe), 57.5 (q, OMe), 48.6 (d, 37-C), 47.6 (t, 8-C), 44.1 (t, 6-C), 41.5 (t, 2-C), 39.9 (t, 35-C), 39.8 (d, 33-C), 36.9 (37.0) (d, 39-C), 34.02 (d, 29-C), 33.1 (t, 27-C), 32.2 (t, 31-C), 27.6 (q, NMe), 27.5 (d, 9-C), 27.1 (q, t-Bu), 20.9 (q, COMe), 20.7 (t, 5-C), 19.8 (18.9) (q, 45-C), 14.2 (q, 47-C), 13.7 (13.4) (46-C), 9.1 (q, 48-C); m/z (FAB) 1142 $(M + Na)^+$.

Ulapualide A with relative stereochemistry shown in structure 1

Pyridine HF (0.1 ml) was added to a solution of the silyl ether **85b** (1 mg, 0.0009 mmol) in a mixture of dry THF (0.1 ml) and

dry pyridine (0.1 ml) at room temperature under nitrogen and the resulting solution was stirred at room temperature for 24 h. A further amount of pyridine HF (0.1 ml) was added and the mixture was stirred for an additional 12 hours. The mixture was diluted with dichloromethane (5 ml) and then quenched with saturated aqueous sodium bicarbonate (1 ml). The separated organic extract was dried and then concentrated in vacuo to leave a residue which was purified by chromatography over silica using ethyl acetate as eluent to give ulapualide A (0.6 mg, 80%) as a colourless oil; $[a]^{21}$ -43.3 (c, 0.3 in MeOH); $\delta_{\rm H}(500 \text{ MHz})$ 8.36 (1H, s, CHO), 8.13 (2H, s, Ox-H), 7.47 (1H, Ox-H), 7.06-7.05 (1H, m, 26-H), 6.56 (7.22) (1H, d, J 13.4 Hz, 41-H), 6.48 (1H, d, J 16 Hz), 5.45-5.35 (1H, m, 30-H), 5.21-5.19 (1H, m, 38-H), 5.05 (1H, dd, J 9.6 and 13.6 Hz, 40-H), 4.35-4.30 (1H, m, 3-H), 3.51-3.48 (1H, m), 3.45 (3H, s, OMe), 3.36 (3H, s, OMe), 3.10 (3.15) (3H, s, NMe), 3.03-3.00 (1H, m), 2.86-2.82 (1H, m), 2.75-2.70 (2H, m), 2.60-2.59 (1H, m), 2.58-2.47 (6H, m), 2.07 (3H, s, COMe), 1.94-1.87 (3H, m), 1.86-1.84 (4H, m), 1.58-1.55 (4H, m), 1.39 (3H, d, J7 Hz, C-9Me), 1.13 (3H, d, J7 Hz), 1.11 (3H, d, J 7 Hz), 0.97 (3H, d, J 7 Hz), 0.89 (3H, d, J 2 Hz); $\delta_{\rm C}(125 \text{ MHz}) 211.5 \text{ (s, 36-C)}, 210.4 \text{ (s, 7-C)}, 172.6 \text{ (s, 1-C)},$ 170.1 (s, COMe), 162.7 (s, 22-C), 162.2 (161.0) (d, 43-C), 156.4 (s, 17-C), 154.3 (s, 12-C), 146.6 (s, 10-C), 139.6 (d, 26-C), 137.8 (d, 24-C), 137.4 (d, 19-C), 133.4 (d, 14-C), 131.9 (s, 15-C), 130.1 (125.2) (d, 41-C), 117.5 (d, 25-C), 110.5 (112.2) (d, 40-C), 81.0 (d, 32-C), 79.9 (d, 28-C), 77.6 (d, 38-C), 72.8 (d, 30-C), 68.7 (d, 3-C), 57.8 (q, OMe), 57.6 (q, OMe), 48.6 (d, 37-C), 44.0 (t, 6-C), 42.9 (t, 2-C), 40.3 (d, 33-C), 39.9 (t, 35-C), 37.3 (t, 39-C), 36.9 (37.0) (d, 39-C), 34.1 (d, 29-C), 33.1 (t, 27-C), 32.8 (27.3) (44-C), 32.0 (t, 31-C), 27.7 (d, 9-C), 26.6 (t, 34-C), 20.9 (q, COMe), 20.6 (t, 5-C), 19.2 (q, 45-C), 18.9 (q, 49-C), 14.2 (q, 47-C), 13.4 (13.6) (q, 46-C), 9.1 (q, 48-C). The corresponding C-9 β-methyldiastereoisomer was prepared using an identical procedure and showed $\delta_{\rm H}(500$ MHz) 8.36 (1H, s, CHO), 8.13 $(2H, s, 2 \times Ox-H)$, 7.48 (1H, s, Ox-H), 7.05–7.02 (1H, m, 26-H), 6.57 (7.23) (1H, d, J 14.1 Hz, 41-H), 6.52 (1H, d, J 16.2 Hz, 25-H), 5.43-5.38 (1H, m, 30-H), 5.21-4.19 (1H, m, 38-H), 5.05 (1H, dd, J 9 and 14.1 Hz, 40-H), 4.34–4.29 (1H, m, 3-H), 3.54– 3.48 (1H, m), 3.46 (3H, s, OMe), 3.38 (3H, s, OMe), 3.23-3.17 (1H, m), 3.11 (3.15) (3H, s, NMe), 2.87-2.84 (1H, m), 2.73-2.69 (1H, m), 2.63–2.46 (6H, m), 2.08 (3H, s, COMe), 1.95–1.86 (3H, m), 1.85-1.81 (4H, m), 1.59-1.56 (4H, m), 1.37 (3H, d, J 7 Hz, C-9-Me), 1.14 (3H, d, J 7 Hz), 1.11 (3H, d, J 6.9 Hz), 0.96 (3H, d, J 6.8 Hz), 0.90 (0.92) (3H, d, J 6.9 Hz); $\delta_{\rm C}$ (125 MHz) 211.5 (s, 36-C), 210.4 (s, 7-C), 172.7 (s, 1-C), 170.2 (s, COMe), 162.6 (s, 22-C), 162.2 (161.0) (d, 43-C), 156.4 (s, 17-C), 154.6 (s, 12-C), 146.5 (s, 10-C), 139.1 (d, 26-C), 137.8 (d, 24-C), 137.3 (d, 19-C), 133.5 (d, 14-C), 130.5 (s, 20-C), 129.6 (125.1) (d, 41-C), 117.6 (d, 25-C), 110.5 (112.1) (d, 40-C), 81.0 (d, 32-C), 79.9 (d, 28-C), 78.9 (d, 38-C), 72.7 (d, 30-C), 68.8 (d, 3-C), 57.8 (q, OMe), 57.6 (q, OMe), 48.7 (d, 37-C), 47.9 (t, 8-C), 44.0 (t, 6-C), 42.8 (t, 2-C), 40.6 (d, 33-C), 39.8 (t, 35-C), 37.0 (t, 4-C), 36.9 (d, 39-C), 34.0 (d, 29-C), 33.1 (t, 27-C), 32.0 (t, 31-C), 27.7 (d, 9-C), 26.3 (t, 34-C), 20.9 (q, COMe), 20.7 (t, 5C), 19.8 (q, 45-C), 18.9 (q, 49-C), 14.2 (q, 47-C), 13.4 (13.6) (q, 46-C), 9.1 (q, 48-C); m/z 903.4358. $(M + Na)^+$ requires 903.4368.

Acknowledgements

We thank the EPSRC for a Research Fellowship (to S. K. C.), and Milton Kiefel, John Maddock, Michael Reader and David Waite for their contributions to the early part of these synthetic studies. We also thank Professor P. J. Sheuer for a sample of naturally derived ulapualide A.

References

- 1 J. A. Roesener and P. J. Scheuer, J. Am. Chem. Soc., 1986, 108, 846. 2 S. Matsunaga, N. Fusetani, K. Hashimoto, K. Koseke and M.
- Norma, J. Am. Chem. Soc., 1986, 108, 847.

- 3 (a) S. Matsunaga, N. Fusetani, K. Hashimoto, M. Norma, H. Naoguchi and U. Sankawa, J. Org. Chem., 1989, 54, 1360; (b) M. R. Kernan, T. F. Molinski and D. J. Faulkner, J. Org. Chem., 1988, 53, 5014.
- 4 N. Fusetani, K. Yasumuro, S. Matsunaga and K. Hashimoto, *Tetrahedron Lett.*, 1989, **30**, 2809.
- 5 J. Kobayashi, M. Tsuda, H. Fuse, T. Sasaki, Y. Mikami, J. Nat. Prod., 1997, **60**, 150.
- 6 J. Maddock, G. Pattenden and P. G. Wight, J. Comput. Aided Mol. Des., 1993, 7, 573.
- 7 S. K. Chattopadhyay, J. Kempson, A. McNeil, G. Pattenden, M. Reader, D. E. Rippon and D. Waite, *J. Chem. Soc.*, *Perkin Trans. 1*, 2000, preceding paper (DOI: 10.1039/b000750l).
- 8 Preliminary communication: S. K. Chattopadhyay and G. Pattenden, *Tetrahedron Lett.*, 1998, **39**, 6095 and references cited therein.
- 9 S. Matsunaga, P. Liu, C. A. Celatka, J. S. Panek and N. Fusetani, J. Am. Chem. Soc., 1999, **121**, 5605.
- 10 M. Ishibashi, R. E. Moore, G. M. L. Patterson, C. Xu and J. Clardy, J. Org. Chem., 1986, **51**, 5300. For a synthesis of scytophycin, see I. Paterson, C. Watson, K.-S. Yeung, P. A. Wallace and R. A. Ward, J. Org. Chem., 1997, **62**, 452.
- 11 For a synthesis of the related metabolite aplyronin, see K. Yamada, M. Ojika, T. Ishigaki, Y. Yoshida, H. Ekimoto and M. Arakawa, J. Am. Chem. Soc., 1993, 115, 11020; H. Kigoshi, M. Ojika, T. Ishigaki and K. Suenaga, J. Am. Chem. Soc., 1994, 116, 7443.
- 12 For other synthetic work towards ulapualide see, (a) J. S. Panek, R. T. Beresis and C. A. Celatka, J. Org. Chem., 1996, 61, 6494; (b) J. S. Panek and R. T. Beresis, J. Org. Chem., 1996, 61, 6496; (c) C. A. Celatka, P. Liu and J. S. Panek, *Tetrahedron Lett.*, 1997, 38, 5445; (d) C. A. Celatka, P. Liu and J. S. Panek, *Tetrahedron Lett.*, 1997, 38, 5445; (e) P. Liu and J. S. Panek, *Tetrahedron Lett.*, 1998, 39, 6143; (f) P. Liu and J. S. Panek, *Tetrahedron Lett.*, 1998, 39, 6147.
- 13 For earlier work, see M. J. Kiefel, J. Maddock and G. Pattenden, *Tetrahedron Lett.*, 1992, 33, 3227; for alternative methods for the synthesis of terminal *N*-methyl-*N*-alkenylformamides, see I. Paterson, C. Cowden and C. Watson, *Synlett*, 1996, 209 and references therein.
- 14 M. Duncton and G. Pattenden, J. Chem. Soc., Perkin Trans. 1, 1999, 1235.

- 15 Y. Guindon, C. Yoakim and H. E. Morton, J. Org. Chem., 1984, 49, 3912.
- S. K. Chattopadhyay and G. Pattenden, *Tetrahedron Lett.*, 1995, 36, 5251.
 M. J. Kiefel, J. Maddock and G. Pattenden, *Tetrahedron Lett.*, 1992,
- 33, 3227. 18 T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 1980, 102,
- 5974. 19 A. P. Kozikowski and P. D. Stein, J. Org. Chem., 1984, **49**, 2301.
- 20 D. A. Evans, J. Bartroli and T. L. Shih, J. Am. Chem. Soc., 1981, 103, 2127.
- 21 T. D. Penning, S. W. Djuric, R. A. Haack, V. J. Kalish, J. M. Miyashiro, B. W. Rowell and S. S. Yu, *Synth. Commun.*, 1990, 20, 307.
- 22 H. C. Brown and P. V. Ramachandran, J. Org. Chem., 1995, 500, 1.
- 23 Molecular modelling software MACROMODEL (version 4.5) was used for these calculations.
- 24 S. D. Rychnovosky, B. Rogers and G. Yang, J. Org. Chem., 1993, 58, 3511.
- 25 H. Nagaoka and Y. Kishi, Tetrahedron, 1981, 37, 3873.
- 26 See (a) C. Alvarez-Ibra, S. Arias, G. Bannon, M. J. Fernandez, M. Rodrignez and V. Sinisterra, J. Chem. Soc., Chem. Commun., 1987, 1509; (b) I. Paterson, K.-S. Yeung and J. B. Smaill, Synlett, 1993, 774.
- 27 W. M. Pearlman, Tetrahedron Lett., 1967, 8, 1663.
- 28 R. Noyori and H. Takaya, Acc. Chem. Res., 1990, 23, 345.
- 29 M. Hirama, M. Shimizu and M. Iwashita, J. Chem. Soc., Chem. Commun., 1983, 599.
- 30 D. E. Rippon, PhD Thesis, University of Nottingham, 1990.
- 31 M. Mikolajczyk and P. Balczewski, Synthesis, 1984, 691.
- 32 D. B. Dess and J. C. Martin, J. Org. Chem., 1983, 48, 4155.
- 33 S. K. Chattopadhyay and G. Pattenden, *Synlett*, 1997, 1345.
- S. K. C. Nicolaou, S. P. Sietz and M. R. Pavia, J. Am. Chem. Soc., 1982, 104, 2030; P. A. Aristoff, J. Org. Chem., 1981, 46, 1954.
- 35 V. Bou and J. Vilarrasa, *Tetrahedron Lett.*, 1990, **31**, 567.
 36 K. C. Nicolaou, S. P. Seitz, M. R. Pavia and N. A. Petasis, *J. Org. Chem.*, 1979, **44**, 4011.
- 37 D. M. James, E. Winter, D. J. Faulkner and J. S. Siegel, *Heterocycles*, 1993, **35**, 675.
- 38 P. Liu and J. S. Panek, J. Am. Chem. Soc., 2000, 122, 1235.