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

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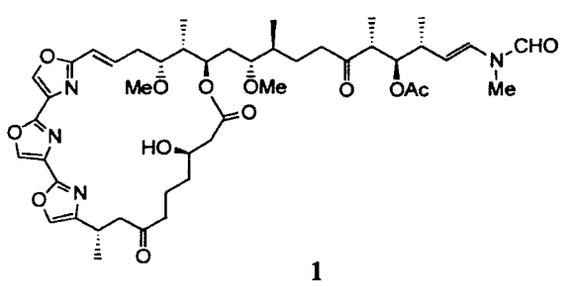
A total synthesis of ulapualide A (**1**), whose relative stereochemistry was assigned on the basis of an earlier molecular mechanics study of its hypothetical metal chelated complex **9**, is described. The synthesis is based on: i, elaboration of the double functionalised tris-oxazole **11**; ii, synthesis 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 ^{13}C 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 tris-oxazole based macrolides to be isolated from nature. The "ulapualides" derive their name from the Hawaiian words "ula", meaning red and "pua", meaning flower, since 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



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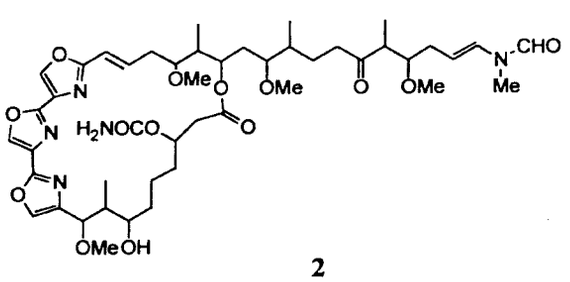

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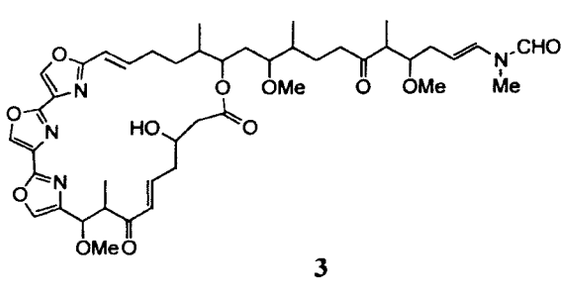

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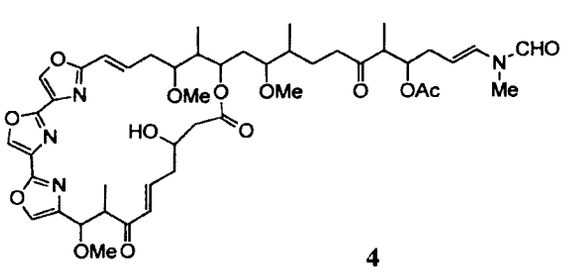

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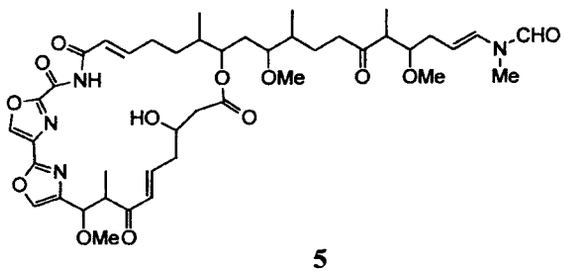

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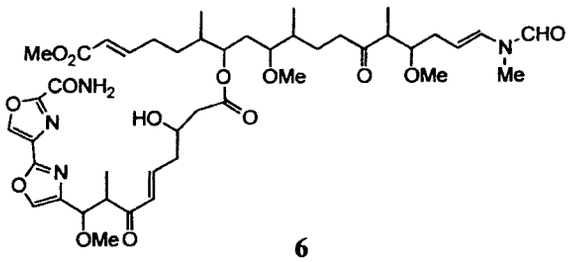

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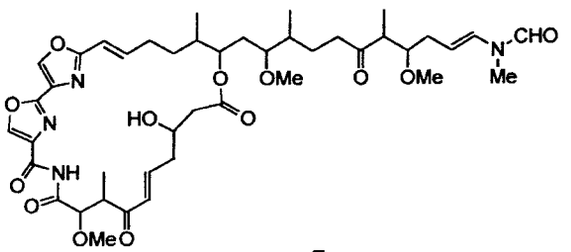

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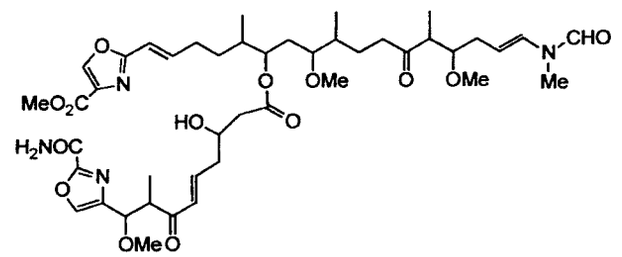

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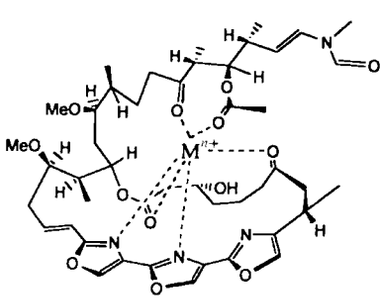
metal ions, *i.e.* behave as ionophores, using the several oxazole nitrogen and side chain oxygen ligand binding sites present in their structures.[6] The combination of a unique chemical structure with novel biological properties encouraged us to examine a total synthesis of the founder member, ulapualide A (**1**), of this family of marine metabolites and to examine their ionophore properties. In the immediately preceding paper[7] 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 publication[7] 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



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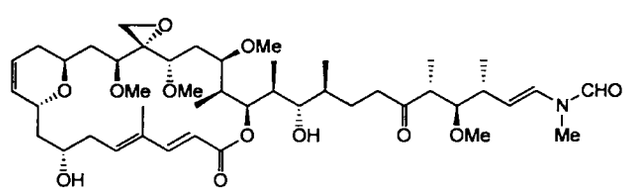

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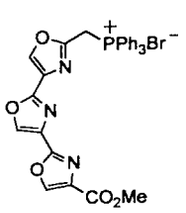

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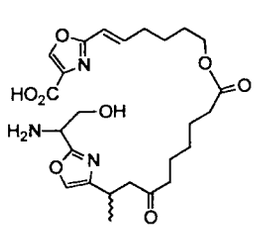

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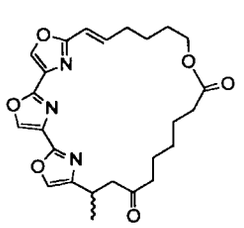

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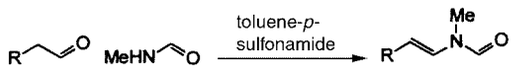


Scheme 1

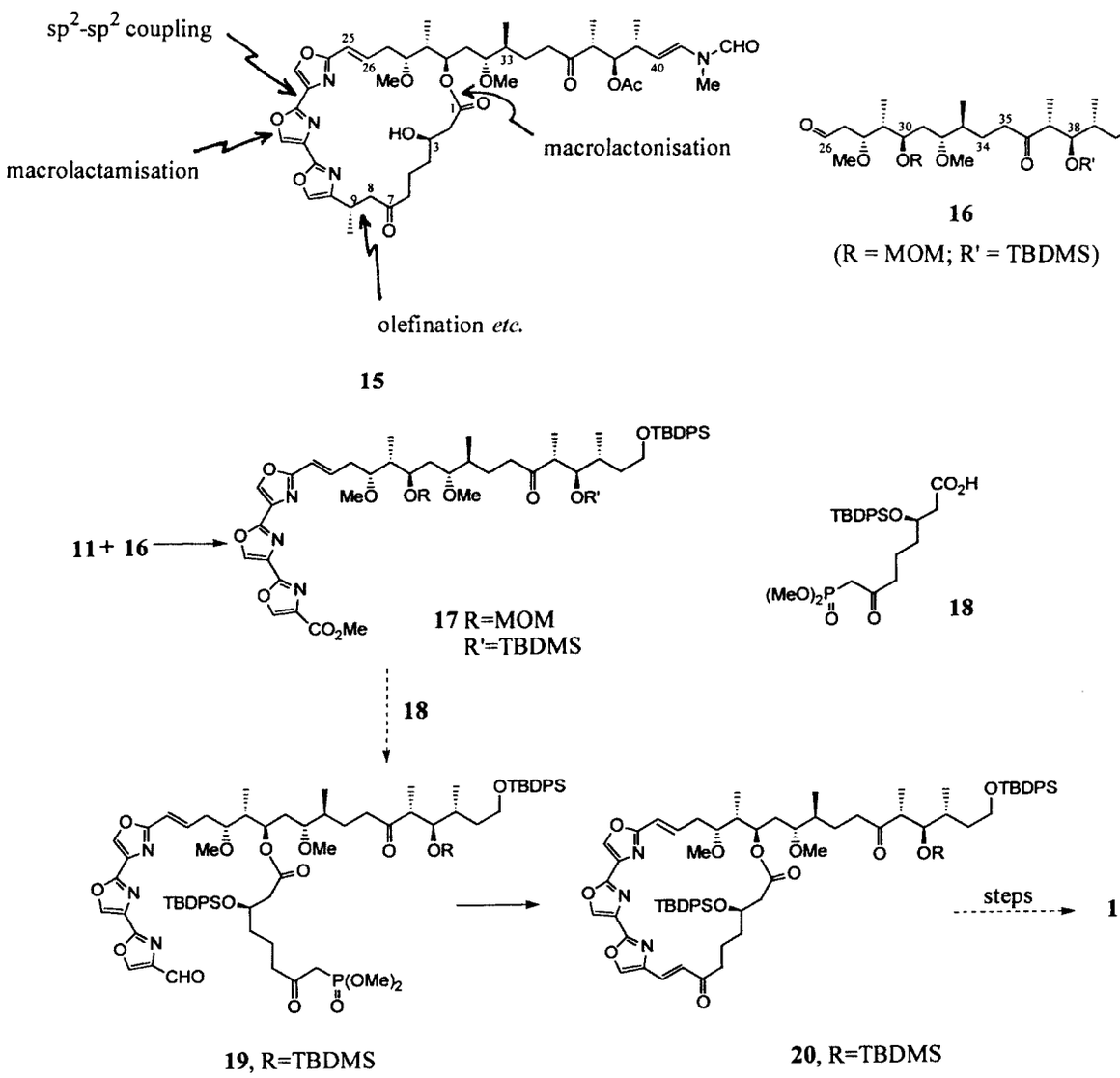
appropriate ω-hydroxy carboxylic acid precursor, an intramolecular olefination reaction producing the C-25–C-26 alkene bond, and the utilisation of intramolecular sp^2–sp^2 coupling (*e.g.* Stille, Suzuki) reactions involving substituted oxazole ring precursors.[14] As mentioned earlier, we also considered 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*-alkenylformamide 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.

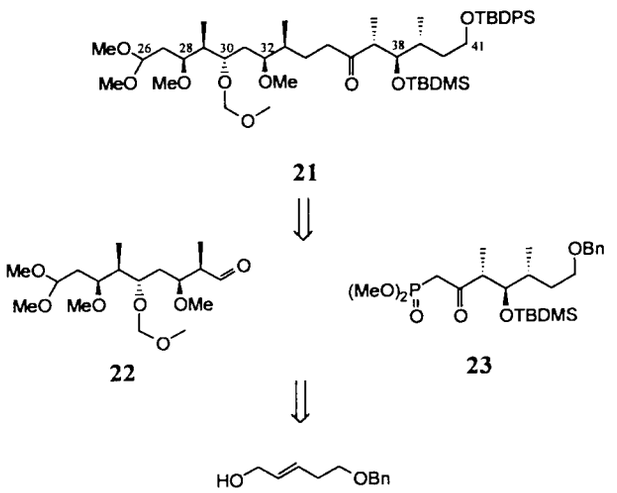
Synthesis of the C-26–C-41 fragment 16 (R = MOM; R′ = TBDMS)

An armoury of modern asymmetric synthesis methods is now available for elaborating the chiral 1,3-diol and chiral 1-oxy, 2-methyl 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

41 unit **21**[16] based on a Wadsworth–Emmons olefination reaction between the aldehyde **22** and the phosphonate **23**, which were both synthesised from the same precursor, *i.e.* (*E*)-5-benzyloxypent-2-enol **24** (Scheme 3).[17]



Scheme 3

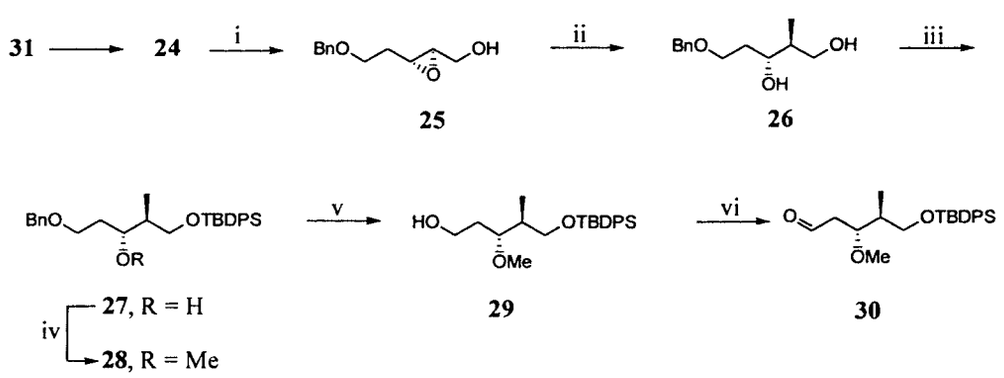
Thus, Sharpless epoxidation[18] of (*E*)-5-benzyloxypent-2-enol **24**, followed by chelation controlled addition of methylmagnesium bromide to the resulting epoxy alcohol **25**[19] in the presence of CuI first led to the corresponding 1,3-diol **26** in 66% yield; a small amount (20%) of the unwanted 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 4-phenylmethyl-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.

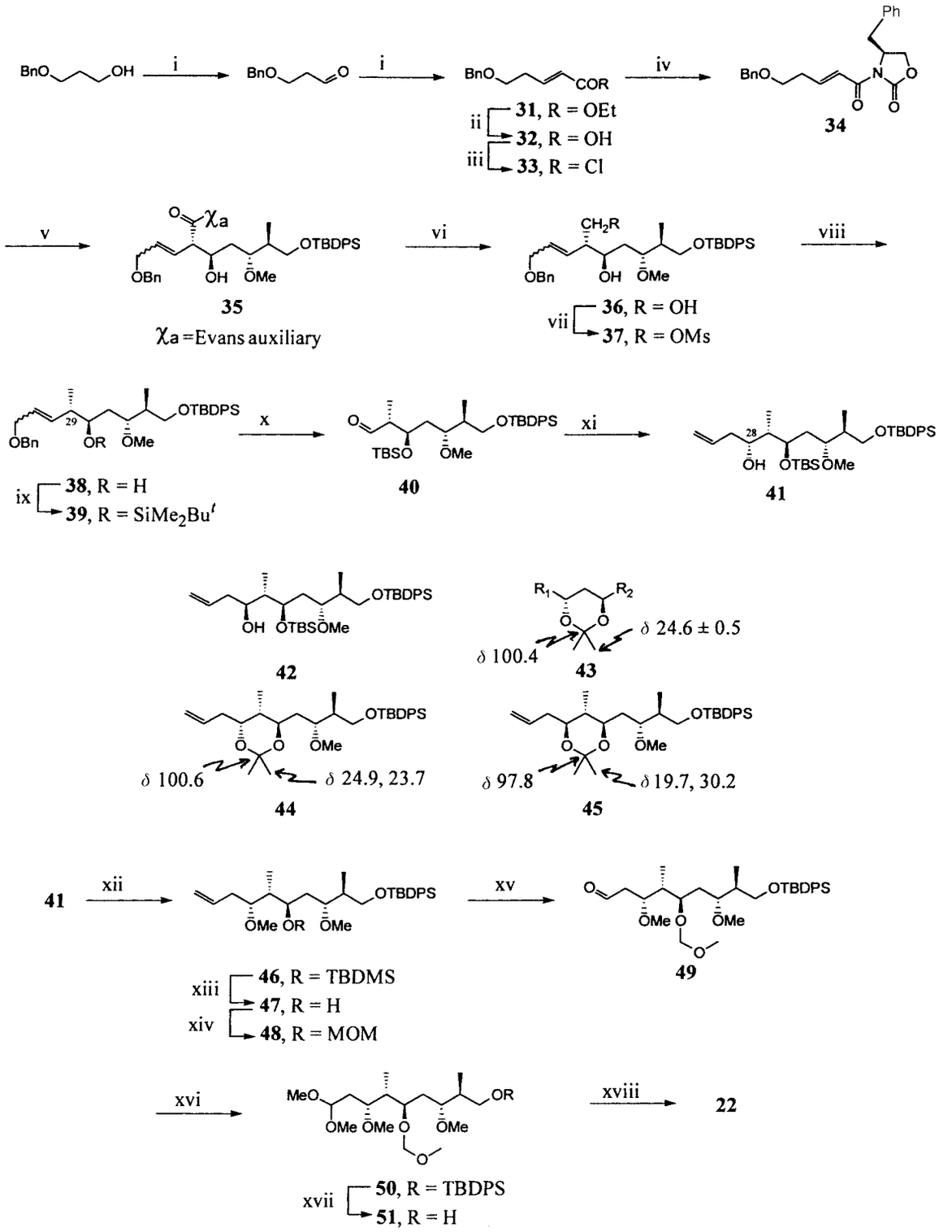
In readiness for oxidative cleavage of the double bond in **35**, the imide residue was next converted into the C-29 α-methyl group (*cf.* **38**) following reduction to the methanol **36** using lithium methoxyborohydride,[21] mesylation (to **37**) and further reduction of **37** using lithium methoxyborohydride. Protection of the secondary alcohol group in **38** as its *tert*-butyldimethylsilyl 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.* ^{1}H COSY, C–H correlation,[23] homonuclear decoupling and NOE data, matching of computer predicted coupling constants together with correlation of ^{13}C 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



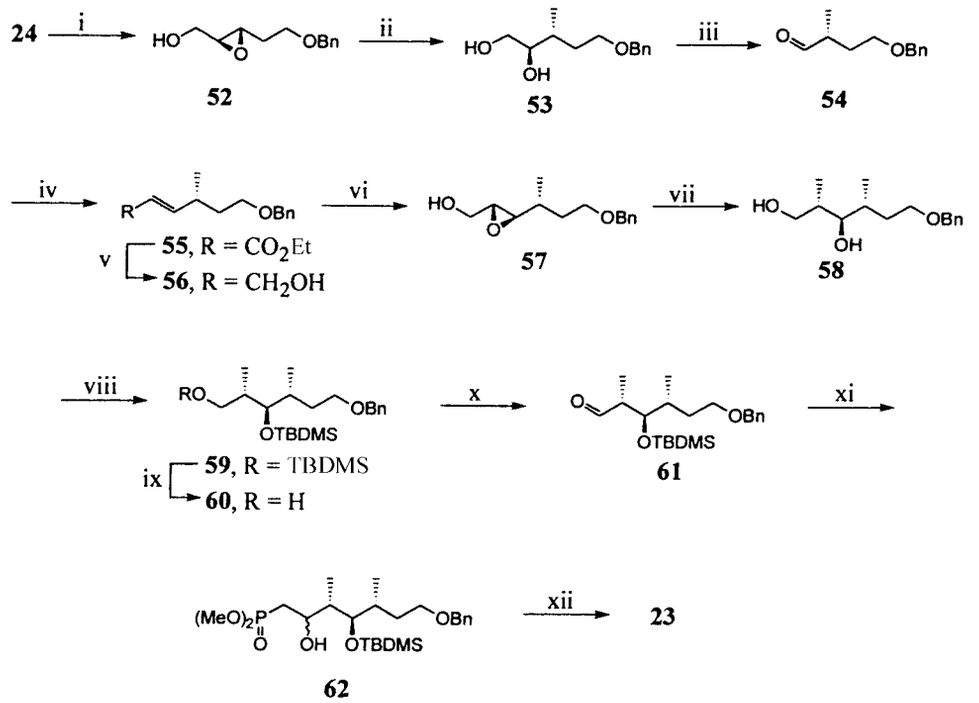
Scheme 4 *Reagents and conditions*: i, (−)-DET, $Ti(O^{i}Pr)_4$, t-BuOOH (61%); ii, MeMgBr, CuI, (66%); iii, t-$BuPh_2SiCl$, (94%); iv, NaH, MeI, (66%); v, H_2, $Pd(OH)_2$-C, (92%); vi, $(COCl)_2$, DMSO, Et_3N, (87%).



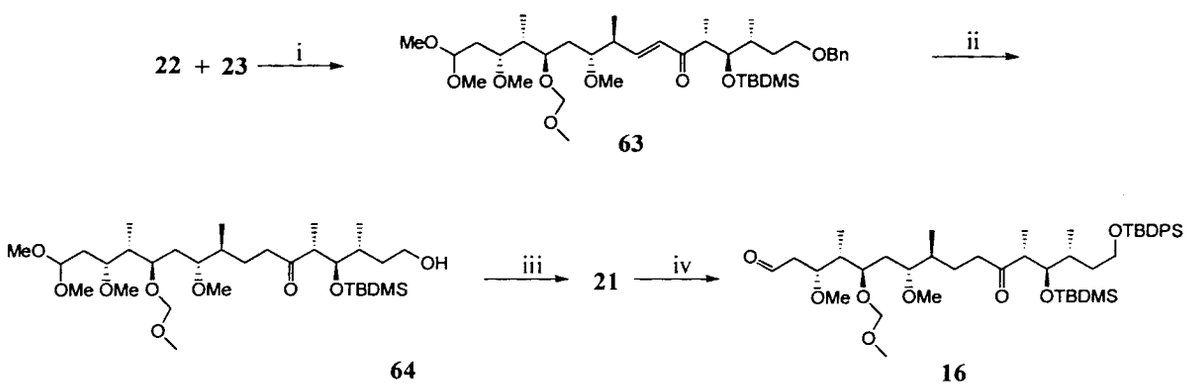
Scheme 5 *Reagents and conditions*: i, DMSO, $(COCl)_2$, Et_3N, then $EtO_2CCH{=}PPh_3$ (68%); ii, LiOH, H_2O (95%); iii, $(COCl)_2$, DMF; iv, BuLi, 4-phenylmethyl-2-oxazolidone, −78 °C (80%); v, Bu_2BOTf, Et_3N, −78 °C, then **30** (70%); vi, $LiBH_4$–MeOH (90%); vii, $MeSO_2Cl$–iPr_2NEt (90%); viii, $LiBH_4$–MeOH (82%); ix, t-BuMeSiSO_2CF_3–CH_2Cl_2 (95%); x, O_3, CH_2Cl_2, −78 °C (80%); xi $CH_2{=}CHCH_2MgBr$, (+)-IPCBOMe, −78 °C (70%); xii, MeOTf, 2,6-di-*tert*-butylpyridine (98%); xiii, PPTS, ethanol (90%); xiv, MOM-Cl, iPr_2NEt (95%); xv, O_3, PPh_3 (89%); xvi, TMOF, MeOH, *p*TSA (98%); xvii, 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 base[26] next gave the *E*-alkene **63** in an excellent 95% yield (Scheme 7). Hydrogenation of **63** in the presence of Pearlmans catalyst[27] 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 bromide[15] 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**.



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



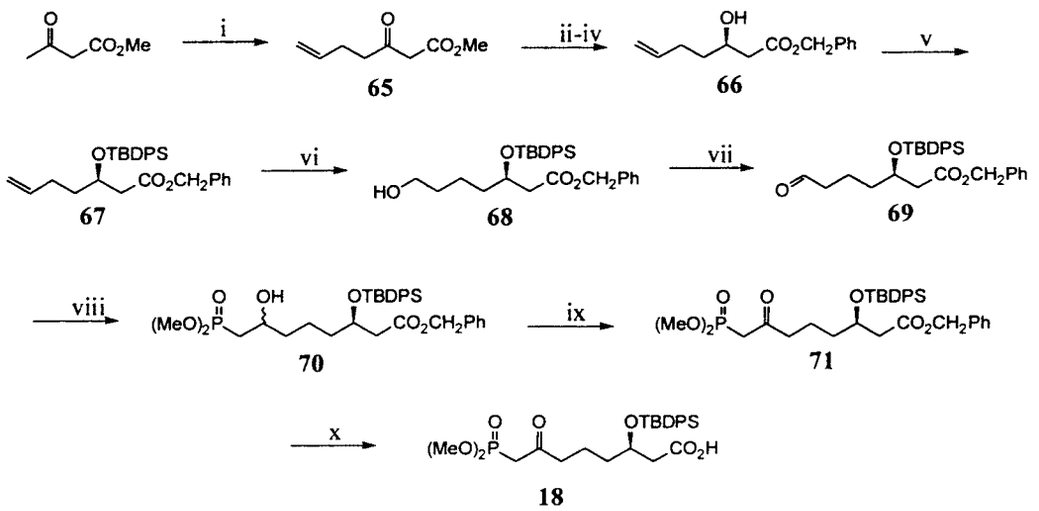
Scheme 7 *Reagents and conditions*: i, $Ba(OH)_2$, wet THF (95%); ii, $Pd(OH)_2$-C, H_2 (94%); iii, imidazole, TBDPS-Cl (94%); iv, Me_2BBr, CH_2Cl_2 (95%).

Synthesis of the C-1–C-8 fragment 18

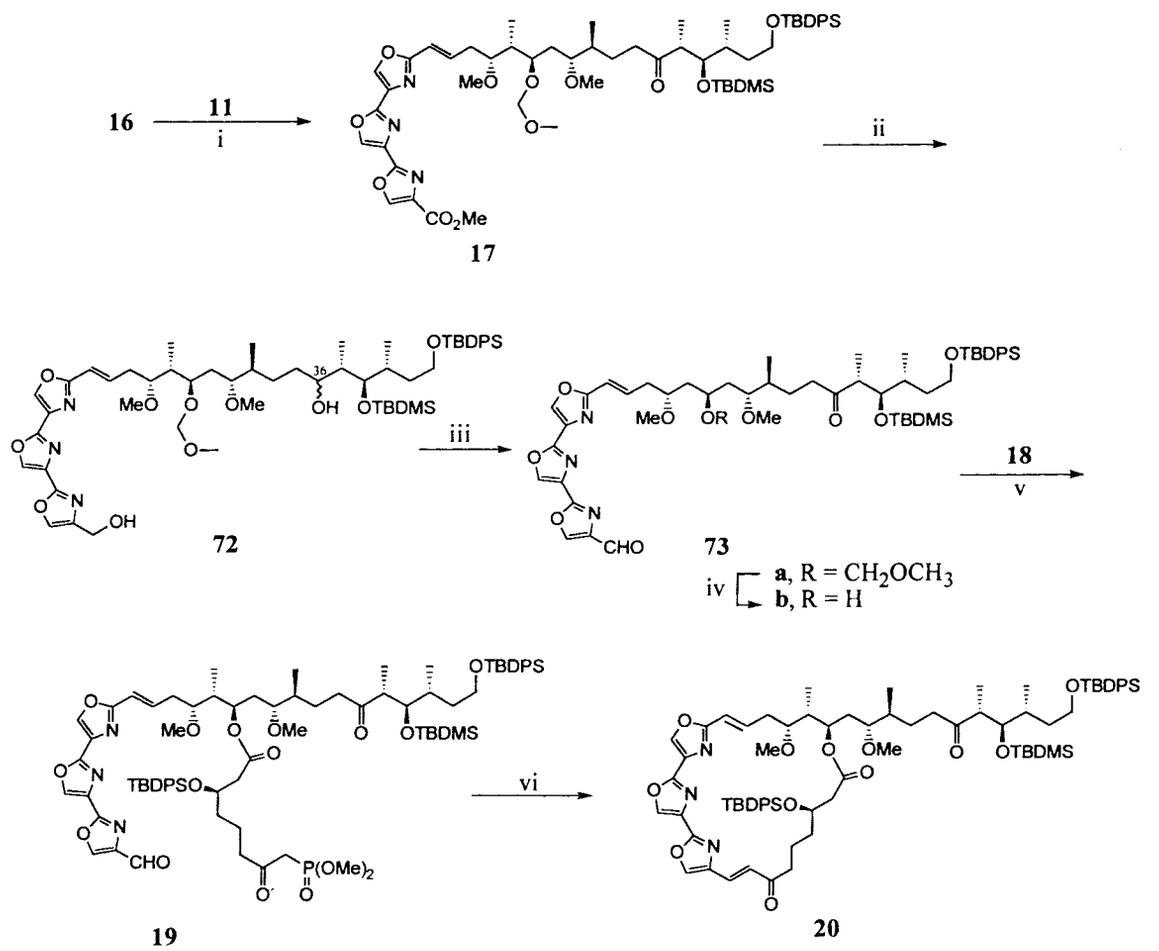
Our strategy for the synthesis of the homochiral β-hydroxy carboxylic acid phosphonate derivative **18** relied on access to the TBDPS intermediate **67** followed by elaboration of the alkene residue in **67** to the corresponding β-keto phosphonate unit. A range of chemical[28] and biological[29] methods 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 (3*R*)-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 (3*R*)-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 ^{1}H 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 ter-oxazole 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, $PhCH_2Br$, aliquot 336, $NaHCO_3$ (~15–30% overall); v, TBDPS-Cl, imidazole, DMF, rt (81%); vi, BH_3·DMS, H_2O_2, NaOH (78%); vii, PDC, DCM (78%); vii, $MePO(OMe)_2$, BuLi (55%); ix, PDC, DMF, (84%); x, Pd-C, H_2, EtOAc (98%).

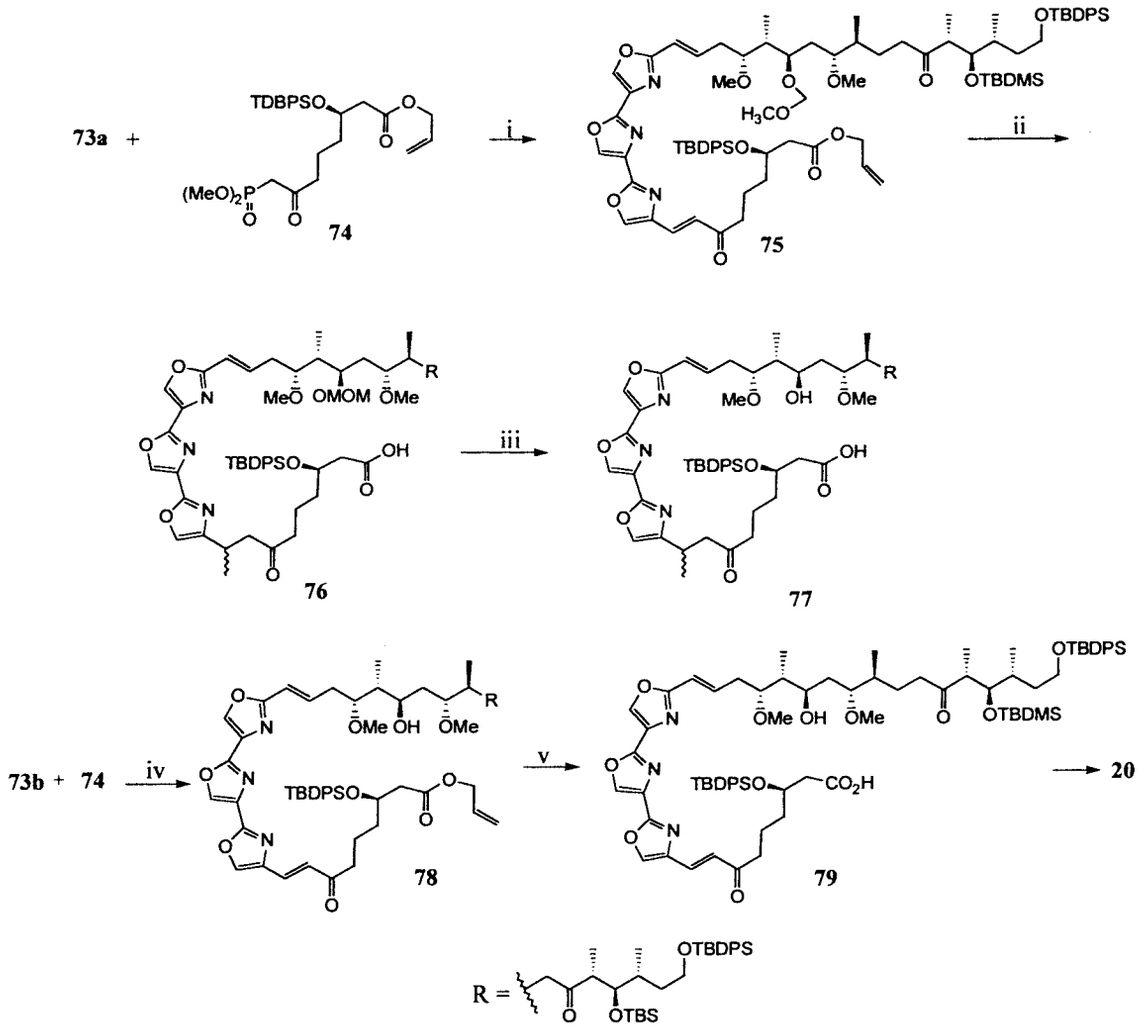


Scheme 9 *Reagents and conditions*: i, *n*-BuLi, THF, −78 °C, 70%; ii, DIBAL-H, 0 °C, 75%; iii, Dess–Martin periodinane, DCM, 98%; iv, Me_2BBr, DCM, −78 °C, 95%; v, 2,4,6-trichlorobenzoyl chloride, Et_3N, rt, 3 h, 42%; vi, K_2CO_3, 18-crown-6, toluene, 10–33%.

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 periodinane[32] 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 CH_2Cl_2 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



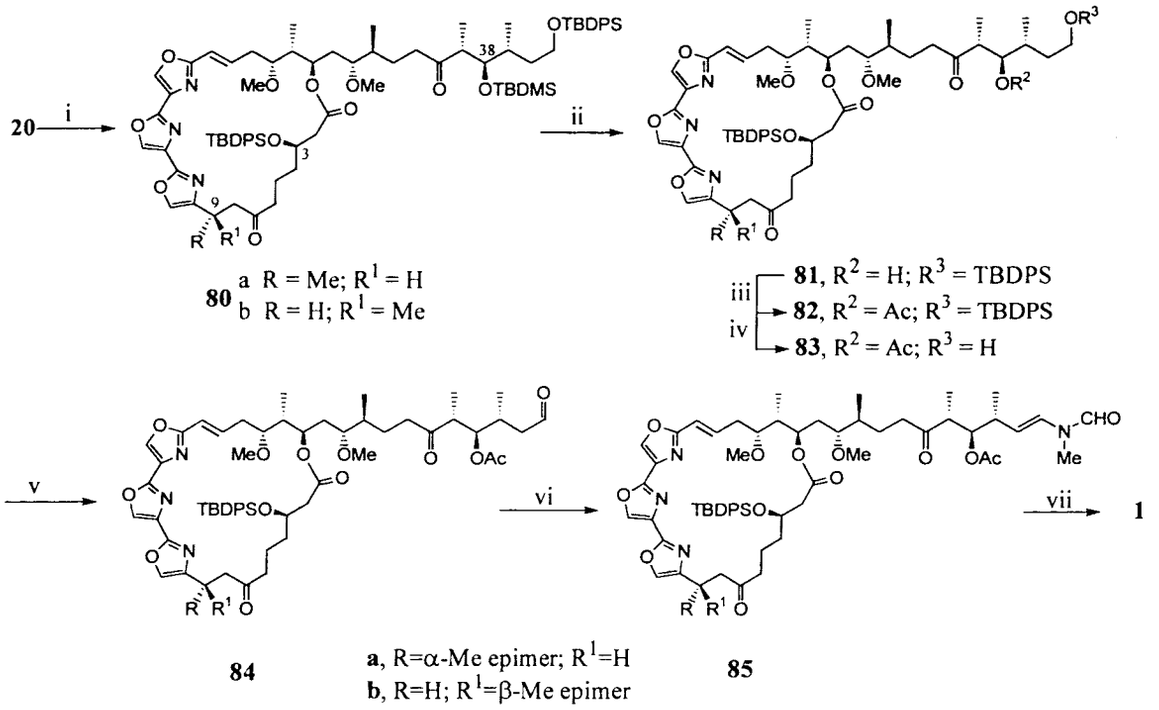
Scheme 10 *Reagents and conditions*: i, $Ba(OH)_2 \cdot 8H_2O$, wet THF, rt, 3 h, 85%; ii, Me_2CuLi, 0 °C, 3 h, 50%; iii, Me_2BBr, −78 °C, 1 h, 50%; iv, $Ba(OH)_2 \cdot 8H_2O$, wet THF, rt, 3.5 h, 88%; v, $Pd(PPh_3)_4$, morpholine, rt, 2 h, 76%.

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 Me_2CuLi 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 Me_2BBr 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 conditions[33] 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 data[6] 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 triflate[35] 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 periodinane[32] 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 acid[13] 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.

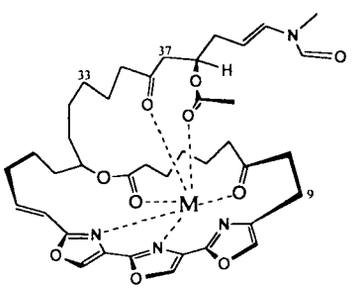
Stereochemistry of natural and synthetic ulapualide A

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, Me_2CuLi, Et_2O, 0 °C, 55%; ii, TMSOTf, −78 °C, 85%; iii, Ac_2O, 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



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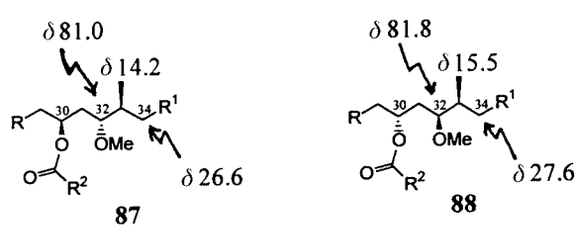
chain substituents in ulapualide to this complex, in sequence, one at a time, and energy minimised each epimer. Each of the epimers of higher energy was discarded, and when all the substituents had been added, each stereocentre was again inverted and the structure re-minimised as a double check. Interestingly, 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 ^{13}C 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 ^{13}C 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 α- 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 ^{13}C 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

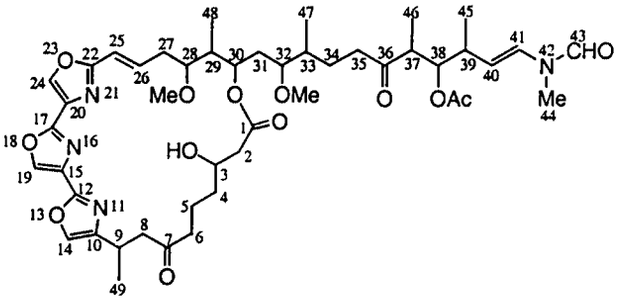
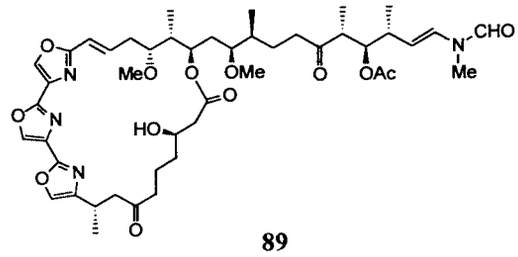


Fig. 1 The numbering system used to interpret NMR data is shown in the structure above, and is based on the system by Scheuer *et al.* in their structure determination of the natural product.

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 (q)	33.1	33.1
45	19.5 (q)	19.2	19.8
38OAc	170.1 (s)	170.1	170.2
	20.9 (q)	20.9	20.9
46	13.4 (q)	13.4	13.4
47	15.5 (q)	14.2	14.2
32OMe	58.1 (q)	57.8	57.9
48	9.1 (q)	9.1	9.1
28OMe	57.8 (q)	57.6	57.6
49	18.9 (q)	18.9	18.9

and Fusetani and their co-workers[9] 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**.



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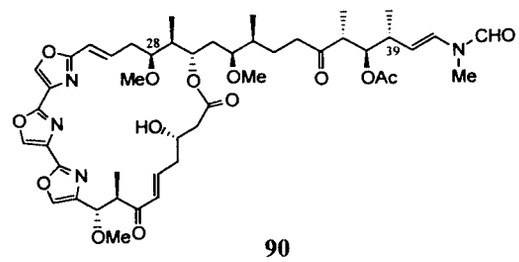
After the preliminary publication of our total synthesis of ulapualide A (with the relative stereochemistry shown in **1**), Panek and Fusetani and their collaborators, unambiguously established the stereochemistry of the related mycalolide



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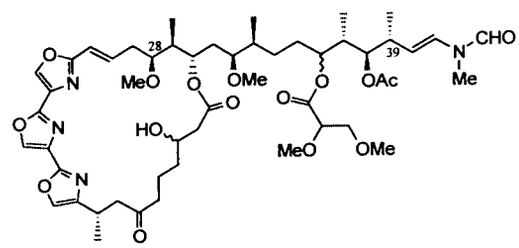

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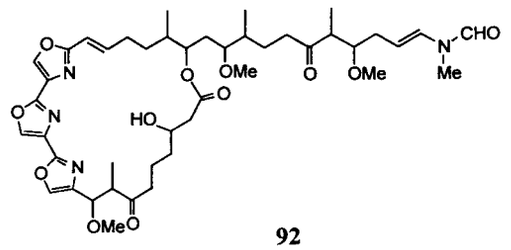
metabolites as shown in structure **90**.† At the same time these authors found that ulapualide B had the same stereochemistry along its C-28–C-39 backbone as the mycalolides, *viz.* **91**.

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 ^{13}C 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 ^{13}C 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-workers[37] 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.* 10^2 and 10^4 for the metals Ag^+, and Cu^{2+}, Fe^{2+}, Hg^{2+}, and Pb^{2+}, providing little evidence of any significant chelate effect. Siegel and co-workers[37] were led to

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



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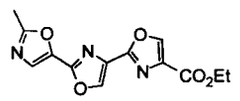

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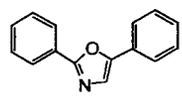

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conclude, therefore, that any antifungal properties of dihydrohalichondramide **92** and its relatives are probably not associated with their properties to bind metals *in vivo*.

Experimental

For general experimental details see ref. 7. Also petrol refers to the fraction of light petroleum with the distillation range 40–60 °C. $[\alpha]_D$ has units of 10^{-1} deg cm^2 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 $NaHCO_3$ (200 ml) and brine (100 ml) and then dried ($MgSO_4$). 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; ν_{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, =C*H*CH$_2$), 5.89 (1H, dt, *J* 15.7 and 1.6 Hz, =C*H*CO$_2$Et), 4.50 (2H, s, PhC*H*$_2$O), 4.18 (2H, q, *J* 7.1 Hz, C*H*$_2$CH$_3$), 3.57 (2H, t, *J* 6.5 Hz, C*H*$_2$O), 2.49 (2H, apparent qd, *J ca.* 6.6 and 1.6 Hz, C*H*$_2$CH=), 1.2 (3H, t, *J* 7.1 Hz, CH$_2$C*H*$_3$); 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. $C_{14}H_{18}O_3$ 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 ($MgSO_4$), 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. $C_{12}H_{16}O_2$ requires C, 75.0; H, 8.4%); ν_{max}(film)/cm^{-1} 3393 (br), 3031, 2860, 1497, 1099; δ_H(400 MHz) 7.36–7.29 (5H, m, Ph), 5.75–5.7 (2H, m, C*H*=C*H*), 4.53 (2H, s, PhC*H*$_2$O), 4.05–4.0 (2H, br, C*H*$_2$OH), 3.53 (2H, t, *J* 6.6 Hz, =C*H*$_2$OCH$_2$Ph), 2.40–2.3 (2H, m), 2.22 (1H, br s, OH); δ_C(100 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 (Na_2SO_4), 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; $[\alpha]_D^{21}$ +32 (*c*, 1.0 in $CHCl_3$) (Found: C, 68.4; H, 7.9. $C_{12}H_{16}O_3$ requires C, 69.2, H, 7.7%). ν_{max}(film)/cm^{-1} 3436 (br), 3063, 1496, 1455, 1208, 1100; δ_H(400 MHz) 7.36–7.20 (5H, m, Ph), 4.47 (2H, s, C*H*$_2$Ph), 3.81–3.74 (1H, m), 3.65 (2H, t, *J* 6.0 Hz, C*H*$_2$O), 3.53–3.43 (1H, m), 3.03 (1H, m), 2.91 (1H, dt, *J* 4.6 and 6.0 Hz, C*H*CH$_2$O), 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). $C_{12}H_{15}O_3$ 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 NH_4Cl (180 ml) and allowed to warm to room temperature. It was then stirred vigorously for 30 min before extracting with ether (4 × 200 ml). The combined organic extracts were washed with saturated aqueous NH_4Cl (2 × 100 ml), and brine (100 ml), then dried ($MgSO_4$) and concentrated *in vacuo* to leave a pale yellow oil. Analysis of the ^{1}H 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 $NaIO_4$ (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 × 200 ml). The combined organic extracts were dried ($MgSO_4$) and then concentrated *in vacuo* to leave a pale yellow oil. Flash chromatography on silica using diethyl ether as eluent first gave 4-benzyloxy-2-methylbutanal (2.65 g, 16%) and then the *diol* (12.8 g, 66%) as a colourless oil; $[\alpha]_D^{21}$ −2.1 (*c*, 2.5 in $CHCl_3$) (Found: C, 69.3; H, 9.3. $C_{13}H_{20}O_3$ requires C, 69.6; H, 9.0%); ν_{max}(film)/cm^{-1} 3392, 3088, 1496; δ_H(400 MHz) 7.32 (5H, m, Ph), 4.53 (2H, s, C*H*$_2$Ph), 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); δ_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$_2$O)$^+$.

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 × 100 ml) and brine (100 ml), then dried (Na_2SO_4) 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; $[\alpha]_D^{21}$ −5.4 (*c*, 1.8 in $CHCl_3$) (Found: C, 75.3; H, 8.7. $C_{29}H_{38}O_3Si$ requires C, 75.3; H, 8.3%); ν_{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, PhCH_2O), 3.81 (1H, ddd, *J* 9.3, 7.0 and 2.7 Hz, C*H*OH), 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); δ_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 NH_4Cl (200 ml), diluted with water (200 ml) and extracted with ether (3 × 100 ml). The combined ether extracts were washed with water (2 × 100 ml) and brine (50 ml), then dried ($MgSO_4$) 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; $[\alpha]_D^{21}$ +4.5 (*c*, 4.4 in $CHCl_3$) (Found: C, 75.8; H, 8.7. $C_{30}H_{40}O_3Si$ requires C, 75.6; H, 8.5%); ν_{max}(film)/cm^{-1} 3070, 2931, 1473; δ_H(400 MHz) 7.70–7.65 (4H, m, Ph), 7.37–7.27 (11H, m, Ph), 4.48 (1H, d, *J* 7 Hz, C*H*HPh), 4.52 (1H, d, *J* 7 Hz, CH*H*Ph), 3.66 (4H, m), 3.58 (1H, ddd, *J* 8.9, 5.9 and 3.0 Hz, C*H*OMe), 3.28 (s, 3H, OCH_3), 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); δ_C(100 MHz) 136.0 (s), 135.6 (d), 133.9 (d), 133.8 (s), 129.65 (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 × 25 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; $[\alpha]_D^{21}$ +11.3 (*c*, 5.6 in $CHCl_3$) (Found: C, 71.3; H, 9.1. $C_{23}H_{34}O_3Si$ requires C, 71.5; H, 8.9%); ν_{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, CH_2O), 3.64 (1H, dd, *J* 10.2 and 5.9 Hz, C*H*HOSi), 3.4–3.6 (1H, m), 3.52 (1H, dd, *J* 10.2, 6.6 Hz, CH*H*OSi), 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 × 50 ml). The combined dichloromethane extracts were washed with water (50 ml) and brine (50 ml) then dried (Na_2SO_4) 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; $[\alpha]_D^{21}$ +1.4 (*c*, 1.9 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3030, 2930, 2857, 1725, 1471; δ_H(400 MHz) 9.80 (1H, apparent t, *J* 2 Hz, C*H*O), 7.7–7.6 (4H, m, ArH), 7.5–7.4 (6H, m, ArH), 3.9 (1H, ddd, *J* 7.9, 5.3 and 4.6 Hz, C*H*OMe), 3.60 (1H, dd, *J* 10.3 and 5.2 Hz, C*H*HOSi), 3.44 (1H, dd, *J* 10.3 and 6.7 Hz, CH*H*OSi), 3.26 (3H, s, OMe), 2.4–2.6 (2H, m, CH_2CHO), 2.0–2.1 (1H, m, C*H*Me), 1.05 (9H, s), 0.85 (3H, d, *J* 6.9 Hz, Me); δ_C(100 MHz) 201.8 (d, *C*HO), 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, OCH_3), 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. $C_{23}H_{32}O_3$ 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 × 100 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 ($MgSO_4$). The organic extracts were evaporated under reduced pressure to leave the *acid* (6.3 g, 95%) as a liquid; ν_{max}(film)/cm^{-1} 3300–2500, 1698, 1650, 1454; δ_H(400 MHz) 7.3–7.2 (5H, m, Ph), 7.03 (1H, dt, *J* 15.8 and 6.6 Hz, CH_2CH=), 5.83 (1H, dt, *J* 15.8, 1.6 Hz, =C*H*CO_2Et), 4.45 (2H, s, CH_2Ph), 3.53 (2H, t, *J* 6.6 Hz, CH_2O), 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 $MgSO_4$, 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; $[\alpha]_D^{20}$ +50.5 (*c*, 2.6 in $CHCl_3$) (Found: C 71.5; H, 6.3. $C_{22}H_{24}NO_4$ requires C, 72.1; H, 6.5%); ν_{max}(film)/cm^{-1} 3028, 2859, 1778, 1682; δ_H(270 MHz) 7.3–7.1 (12H, m, ArH plus *H*C=C*H*), 4.67–4.61 (4H, m), 4.45 (2H, s, PhCH_2O), 4.13–4.07 (2H, apparent ABq, 5-H), 3.55 (2H, t, *J* 6.3 Hz, CH_2OBz), 3.23 (1H, dd, *J* 13.5 and 3.1 Hz, PhC*H*H), 2.70 (1H, dd, *J* 13.5 and 9.6 Hz, PhCH*H*), 2.53 (2H, apparent q, *J* 6.3 Hz, CH_2CH=); δ_C(100 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, Ph*C*H_2O), 68.2 (t), 66.1 (t), 55.2 (d), 37.8 (t, PhCH_2C), 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)-1-hydroxy-3-methoxy-4-methylpentyl]pent-3-enoyl}oxazolidin-2-one 35

Bu_2BOTf (1.7 ml, 8 mmol) and Et_3N (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 H_2O_2 (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 × 100 ml). The combined organic extracts were washed with water (50 ml) and dried (Na_2SO_4), 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; $[\alpha]_D^{20}$ +4.4 (*c*, 5.1 in $CHCl_3$) (Found: C, 71.6; H, 7.5; N, 1.5. $C_{45}H_{55}NO_7Si$ 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, *H*C=C*H*), 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, PhCH_2O), 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, PhCH_2O), 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. $C_{45}H_{56}NO_7Si$ requires 750.3826).

2-(3-Benzyloxyprop-1-enyl)-7-(*tert*-butyldiphenylsilanyloxy)-5-methoxy-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 × 50 ml). The combined organic extracts were washed with water (50 ml) and brine (50 ml), then dried over Na_2SO_4 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; $[\alpha]_D^{20}$ +13.8 (*c*, 4.0 in $CHCl_3$) (Found: C, 72.5; H, 8.7. $C_{35}H_{48}O_5Si$ requires C, 72.9; H, 8.4%); ν_{max}(film)/cm^{-1} 3416 (br), 2930, 1428, 1086; δ_H(400 MHz) 7.7–7.65 (4H, m, Ph), 7.4–7.28 (11H, m, Ph), 5.93–5.70 (2H, m, *H*C=C*H*), 4.5 and 4.52 (2H, both d, *J* 7 Hz, PhCH_2O), 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); δ_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) (C*H*, C-3), 72.4 (71.9) (Ph*C*H_2O), 70.6 (CH_2, C-5), 69.8 (69.5) (CH_2, C-1), 57.5 (57.4) (OMe), 50.0 (45.6) (CH_2, 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 × 50 ml) and the combined organic extracts were then dried (Na_2SO_4) 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; $[\alpha]_D^{20}$ +2.0 (*c*, 3.4 in $CHCl_3$) (Found: C, 65.9; H, 7.9. $C_{36}H_{50}O_7SSi$ requires C, 66.0; H, 7.7%); ν_{max}(film)/cm^{-1} 3468, 2959, 2932; δ_H(400 MHz) 7.68–7.64 (4H, m, Ph), 7.43–7.28 (11H, m, Ph), 5.94–5.60 (2H, m, *H*C=C*H*), 4.52 and 4.50 (2H, both d, *J* 7 Hz, PhCH_2O), 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, C*H*OH), 4.07 (4.02) (2H, d, *J* 6.5 Hz, CH_2OCH$_2$Ph), 3.71 (3.60) (2H, dd, *J* 9.9 and 5.0 Hz, CH_2O-SiR_3), 3.57–3.52 (1H, m, C*H*OMe), 3.31 (3.30) (3H, s, OMe), 3.00 (2.97) (3H, s, SMe), 2.80–2.76 (2.55–2.48) (1H, m, C*H*–CH=CH–), 2.05–2.00 (1H, m, C*H*Me), 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 *C*H, Ph), 132.1 (131.5) and 127.5 (127.2) (CH, C7/8), 79.9 (79.9) (CH, C-3), 72.4 (71.9) (Ph*C*H_2O), 70.2 (65.4) (CH_2, C-4), 67.9 (69.9) (CH_2, C-10), 66.7 (66.6) (CH, C-5), 65.4 (CH_2, 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) (CH_2, C-4), 26.8 (t-Bu), 19.2 (s, t-Bu), 12.7 (12.6) (CH_3, 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-4,8-dimethylnon-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 × 50 ml) and the combined extracts were dried (Na_2SO_4) 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; $[\alpha]_D^{20}$ +14.3 (*c*, 6.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3473, 2960, 2930 (Found: C, 74.7; H, 8.8. $C_{35}H_{48}O_4Si$ 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, *H*C=C*H*), 4.52 and 4.5 (2H, d, *J* 7 Hz, PhCH_2O), 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, C*H*OH), 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, CH*Me*), 0.89 (0.88) (3H, d, *J* 6.9 Hz, C8–Me); δ_C(100 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) (PhCH_2O), 71.8 (71.7) (CH, C-5), 70.7 (65.82) (CH_2, C-9), 65.7 (65.59) (CH_2, C-1), 57.4 (OCH_3), 42.9 (38.7) (CH, C-6), 37.6 (CH, C-2), 33.3 (32.9) (CH_2, C-4), 26.8 (26.6) (t-Bu), 19.2 (q, t-Bu), 17.05 (16.1) (CH_3, C-6), 12.5 (12.4) (Me, C-2); *m*/*z* (FAB) 561 $(M + H)^+$.

1-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxy)-7-methoxy-4,8-dimethylnon-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 × 50 ml) and brine (25 ml) and finally dried (Na_2SO_4). 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; $[\alpha]_D^{25}$ +17.6 (*c*, 9 in $CHCl_3$) (Found: C, 73.3; H, 9.6; $C_{41}H_{62}O_4Si_2$ 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. $C_{41}H_{62}O_4Si_2$ 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; $[\alpha]_D^{20}$ −3.7 (*c*, 5.8 in $CHCl_3$); δ_H(270 MHz) 9.64 (1H, d, *J* 1.3 Hz, C*H*O), 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); δ_C(67.8 MHz) 203.9 (CHO), 135.6 (CH), 133.7 (C), 129.6 (CH), 127.6 (CH), 78.0 (CH), 69.9 (CH), 66.0 (CH_2), 56.0 (OCH_3), 52.8 (CH), 36.7 (CH), 35.0 (CH_2), 26.9 (C–CH_3), 25.9 (C–CH_3), 19.2 (C), 18.0 (q), 10.9 (CH_3), 9.0 (CH_3), −4.3 (CH_3), −4.4 (CH_3); *m*/*z* (FAB) 567 $(M^+ + H_2O)$.

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 (+)-IPC_2BOMe (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 H_2O_2 (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 × 20 ml) and brine (25 ml), then dried (Na_2SO_4) and concentrated *in vacuo* to leave an oil. Purification by flash chromatography on silica using petrol–ethyl acetate (9:1) as eluent gave the *alcohol* (0.65 g, 70%) as a colourless oil; $[\alpha]_D^{20}$ +10.9 (*c*, 4.2 in $CHCl_3$) (Found: C, 70.4; H, 10.2. $C_{35}H_{58}O_4Si_2$ 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, H_2C=C*H*CH_2), 5.15–5.05 (2H, m, =CH_2), 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, *J* 7 Hz), 2.15 (1H, quintet, *J* 7 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); δ_C(100 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 (OCH_3), 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 NH_4OH (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 (Na_2SO_4) 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; $[\alpha]_D^{20}$ +16.2 (*c*, 3.2 in $CHCl_3$) (Found: C, 70.8; H, 10.1.

$C_{36}H_{60}O_4Si_2$ requires C. 70.5; H, 9.9%); δ_H(360 MHz) 7.40–7.50 (6H, m), 7.65–7.70 (4H, m), 5.85 (1H, ddt, *J* 17, 14 and 7 Hz, H_2C=C*H*CH_2), 5.16–5.06 (2H, m), 4.01 (1H, m), 3.60 (2H, m), 3.48 (1H, m), 3.33 (3H, s), 3.31 (3H, s), 2.95 (1H, m), 2.35 (2H, m), 2.10 (1H, m), 1.86 (1H, m), 1.35 (3H, m), 1.15 (9H, s), 0.92 (3H, d, *J* 7 Hz), 0.85 (12H, s, 9H + obscured doublet, 3H); δ_C(100 MHz) 135.6 (CH), 134.6 (CH), 133.8 (C), 129.5 (CH), 127.6 (CH), 117.2 (CH_2), 82.75 (CH), 78.7 (CH), 69.9 (CH), 66.2 (CH_2), 57.3 (OCH_3), 56.8 (OCH_3), 42.5 (CH), 37.4 (CH), 34.8 (CH_2), 33.0 (CH_2), 29.9 (t-Bu), 26.0 (t-Bu), 19.25 (q), 18.0 (q), 11.45 (CH_3), 8.6 (CH_3), −4.0 (Me), −4.6 (Me); *m*/*z* (FAB) 614 $(M + H)^+$.

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; $[\alpha]_D^{20}$ +7.6 (*c*, 2.5 in $CHCl_3$) (Found: C, 73.0; H, 9.7. $C_{30}H_{46}O_4Si$ requires C, 72.3; H, 9.2%); δ_H(270 MHz) 7.76 (4H, br m), 7.45–7.35 (6H, m), 5.87 (1H, ddt, *J* 15, 12 and 7 Hz, C*H*=CH_2), 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 (OCH_3), 41.2 (s), 38.8 (s), 35.93 (CH_2), 35.8 (t), 27.7 (s), 20.1 (q), 12.9 (s), 11.7 (s, CH_3) (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 (Na_2SO_4). 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; $[\alpha]_D^{20}$ +16.6 (*c*, 2.2 in $CHCl_3$); (Found: C, 71.3; H, 9.6. $C_{32}H_{50}SiO_2$ 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, C*H*=CH_2) 5.20–5.08 (2H, m, =CH_2), 4.6 and 4.7 (2H, d, *J* 6.7 Hz, CH_2O), 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); δ_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. $C_{32}H_{50}SiO_5$ 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; $[\alpha]_D^{20}$ +20.0 (*c*, 1.75 in $CHCl_3$); δ_H(400 MHz) 9.85 (1H, t, *J* 1.3 Hz, C*H*O), 7.80–7.71 (4H, m), 7.5–7.4 (6H, m), 4.6 (1H, d, *J* 6 Hz, C*H*HO), 3.52 (1H, d, *J* 6 Hz, CH*H*O), 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, OCH_3), 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); δ_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 (OCH_3), 56.3 (OCH_3), 55.2 (OCH_3), 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-dimethylnonyloxy)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 (Na_2SO_4), 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; $[\alpha]_D^{20}$ +17.8 (*c*, 1.65 in $CHCl_3$); δ_H(400 MHz) 7.72–7.69 (4H, m), 7.45–7.38 (6H, m), 4.72 (1H, d, *J* 6.7 Hz, C*H*HO), 4.64 (1H, d, *J* 6.7 Hz, CH*H*O), 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, OCH_3), 3.37 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 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 (OCH_3), 57.0 (OCH_3), 55.8 (OCH_3), 53.2 (OCH_3), 52.0 (OCH_3), 41.4 (d), 37.4 (d), 35.2 (t), 32.1 (t), 26.9 (q, t-Bu), 19.3 (s), 11.3 (q, CH_3), 9.45 (q, CH_3); *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-1-ol 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 (Na_2SO_4) 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; $[\alpha]_D^{20}$ +43.6 (*c*, 1.6 in $CHCl_3$); δ_H(400 MHz) 4.67 (1H, d, *J* 7 Hz, C*H*HO), 4.59 (1H, d, *J* 7 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 × OCH$_3$), 3.33 (3H, s, OCH$_3$), 3.29 (3H, s, OCH$_3$), 3.27 (3H, s, OCH$_3$), 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*Me*), 0.84 (3H, d, *J* 6.9 Hz, CH*Me*); 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, OCH$_3$), 57.9 (q, OCH$_3$), 55.6 (q, OCH$_3$), 53.2 (q, OCH$_3$), 52.3 (q, OCH$_3$), 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. $C_{17}H_{36}O_7Na$ 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), *N*-methylmorpholine *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 × 25 ml) and the combined ether extracts were concentrated *in vacuo* to leave a brown residue. Chromatography on silica using dichloromethane–ether (3 : 1) as eluent gave the *aldehyde* (112 mg, 89%) as a colourless oil; $[a]_D^{20}$ +13.1 (*c*, 1.3 in CHCl$_3$); δ_H(400 MHz) 9.79 (1H, d, *J* 1.5 Hz, C*H*O), 4.64 (1H, d, *J* 7 Hz, OC*H*H), 4.59 (1H, d, *J* 7 Hz, OCH*H*), 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, CH*Me*), 0.85 (3H, d, *J* 6.9 Hz, CH*Me*); 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 × 200 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 CHCl$_3$) (Found: C, 69.4; H, 7.9. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%.); ν_{max}(film)/cm^{-1} 3427 (br), 2921, 2863, 1454, 1363, 1101, 1029; δ_H(270 MHz) 7.36–7.20 (5H, m, Ph), 4.47 (2H, s, PhCH_2O), 3.81–3.74 (1H, m), 3.56 (2H, t, *J* 6.0 Hz, CH_2O), 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, CH_2CH=); δ_C(67.8 MHz) 137.8 (s, Ph), 128.03 (d), 127.69 (d), 72.6 (t, Ph*C*H$_2$O), 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 °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 × 200 ml) and the combined organic extracts were concentrated *in vacuo* to leave a colourless oil. Analysis of the ^{1}H 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 × 200 ml). The combined dichloromethane extracts were dried ($MgSO_4$) 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; ν_{max}(film)/cm^{-1} 2932, 2869, 1723, 1453, 1364, 1100, 739, 698; δ_H(270 MHz) 9.63 (1H, d, *J* 1.7 Hz, C*H*O), 7.34–7.25 (5H, m, Ph), 4.47 (2H, s, PhCH$_2$O), 3.55–3.48 (2H, m, CH_2O), 2.52 (1H, apparent sextet d, *J* 6.9 and 1.7 Hz, C*H*Me), 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, Ph*C*H$_2$O), 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; ν_{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, EtO$_2$C–CH=C*H*), 5.72 (1H, dd, *J* 1.3 and 15.8 Hz, =C*H*CO$_2$Et), 4.38 (2H, s, OCH$_2$Ar), 4.08 (2H, q, *J* 6.9 Hz, OCH_2CH$_3$), 3.41–3.33 (2H, m), 2.45 (1H, apparent septet, *J* 7 Hz, C*H*Me), 1.59 (2H, q, *J* 7 Hz, OCH$_2$CH_2), 1.19 (2H, t, *J* 6.9 Hz, OCH$_2$CH_3), 0.97 (3H, d, *J* 7 Hz, CH_3); δ_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, OCH$_2$), 67.8 (t, OCH$_2$), 60.0 (t, OCH$_2$), 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 quenched 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 × 50 ml). The combined extracts were dried over $MgSO_4$ 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. $C_{14}H_2O$ requires C, 76.3; H, 9.2%); ν_{max}(film)/cm^{-1} 3385, 2924, 2863; δ_H(270 MHz) 7.44–7.36 (5H, m, ArH), 5.73–5.35 (2H, m, *H*C=C*H*), 4.46 (2H, ABq, *J* 7 Hz, PhCH$_2$O), 4.05 (2H, br s, CH_2OH), 3.57 (2H, t, *J* 6.6 Hz, CH_2OBz), 2.40 (1H, septet, *J* 6.6 Hz, C*H*Me), 2.10 (1H, br s, OH), 1.60 (2H, ddd, *J* 13.2, 6.8 and 3.3 Hz, CH_2CHMe), 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, Ph*C*H$_2$O), 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 × 3) and the combined organic extracts were then washed with brine (50 ml) and dried (Na_2SO_4). 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; $[\alpha]_D$ +14.9 (*c*, 10.7 in $CHCl_3$) (Found: C, 71.3; H, 8.8. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%); ν_{max}(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, PhCH_2O), 3.86–3.79 (1H, m, C*H*O), 3.58–3.49 (3H, m, C*H*O and CH_2O), 2.96–2.89 (2H, m, C*H*O and OH), 2.77 (1H, dd, *J* 6.6 and 2.5 Hz, C*H*O), 1.90–1.82 (1H, m, C*H*), 1.66–1.54 (2H, m, CH_2), 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, PhCH_2O), 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 × 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 ^{1}H 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 × 100 ml). The combined dichloromethane extracts were dried over $MgSO_4$ 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; $[\alpha]_D^{24}$ +10.8 (*c*, 10.3 in $CHCl_3$) (Found: C, 71.1; H, 9.9. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.5%); ν_{max}(film)/cm^{-1} 3408, 2957, 2857; δ_H(270 MHz) 7.36–7.29 (5H, m, Ph), 4.53 (2H, s, PhCH_2O), 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); δ_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 °C under nitrogen and the resulting solution was stirred at 0 °C for 1 h. The mixture was allowed to warm to room temperature and then stirred for 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 (Na_2SO_4). It was then filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica using petrol–dichloromethane (1:1) as eluent to give the pure *bis-silyl ether* (1.92 g, 97.5%) as a colourless oil; $[\alpha]_D^{21}$ −1.4 (*c*, 2.2 in $CHCl_3$) (Found: C, 67.45; H, 11.6. $C_{27}H_{52}O_3Si_2$ requires C, 67.5; H 10.8%); δ_H(400 MHz) 7.36–7.34 (5H, m, Ar), 4.53 (1H, d, *J* 10 Hz, PhC*H*HO), 4.51 (1H, d, *J* 10 Hz, PhCH*H*O), 3.75 (1H, m, C*H*OH), 3.58–3.40 (4H, m, OCH_2 and OCH_2), 1.90–1.82 (2H, m, CH_2), 0.96–0.83 (m, 2 × C*H*, 2 × Me, 2 × t-Bu), 0.08–0.04 (4 × SiMe); δ_C(100 MHz) 138.8 (s, Ar), 128.7 (d), 127.7 (d), 127.55 (d), 78.5 (d, C-3), 73.0 (t, CH_2), 69.3 (t, OCH_2), 65.7 (t, OCH_2), 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*-silyl 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 $NaHCO_3$ (5 ml), concentrated *in vacuo* and then diluted with dichloromethane (50 ml) and water (50 ml). The aqueous layer was extracted with dichloromethane (2 × 25 ml) and the combined organic extracts were dried (Na_2SO_4) and then concentrated *in vacuo*. The residue was purified by chromatography on silica using dichloromethane as eluent to give the *primary alcohol* (0.38 g, 96%) as a colourless oil; $[\alpha]_D^{20}$ −1.6 (*c*, 9.0 in $CHCl_3$) (Found: C, 68.6; H, 10.8. $C_{21}H_{38}O_3Si$ requires C, 68.8; H, 10.4%); ν_{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, PhC*H*HO), 4.51 (1H, d, *J* 11 Hz, PhCH*H*O), 3.78–3.47 (5H, m, 1-H, 6-H and 3-H), 2.71 (1H, t, *J* 6 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); δ_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, OCH_2), 68.8 (t, OCH_2), 66.2 (t, OCH_2), 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; $[\alpha]_D^{24}$ −23.3 (*c*, 8.8 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2851, 2795, 1754, 1697; δ_H(400 MHz) 9.81 (1H, d, *J* 2.8 Hz, C*H*O), 7.39–7.29 (5H, m, Ar), 4.55 (1H, d, *J* 12 Hz, PhC*H*HO), 4.49 (1H, d, *J* 12 Hz, PhCH*H*O), 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, *J* 7 Hz, C-2-Me), 0.94 (3H, d, *J* 7 Hz, C-4-Me), 0.06 (3H, s, SiMe), 0.04 (3H, s, SiMe); δ_C(67.8 MHz) 205.2 (d, C-1), 138.4 (s, Ar), 128.3 (d),

127.5 (d), 127.5 (d), 78.6 (d, C-3), 72.9 (t, OCH_2), 68.45 (t, OCH_2), 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-3,5-dimethylheptyl]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 $NaHCO_3$ solution (5.6 ml) and allowed to come to room temperature. The mixture was extracted with ethyl acetate (3 × 50 ml) and the combined organic extracts were dried (Na_2SO_4) 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; $[\alpha]_D^{23}$ −1.7 (*c*, 4 in $CHCl_3$) (Found: C, 58.8; H, 9.7. $C_{24}H_{45}O_6$ 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); δ_C(100 MHz) 138.5 (s), 128.2 (d), 127.5 (d), 127.39 (d), 80.7 (79.6) (d, C-4), 72.8 (t, OCH_2), 68.75 (68.1) (t, OCH_2), 65.6, 52.4 (52.3) (q, OCH_3), 52.1 (52.1) (q, OCH_3), 42.7 (42.5), 39.7 (39.6), 34.7 (34.5).

[7-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-3,5-dimethyl-2-oxoheptyl]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 (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was purified by flash chromatography on silica using ethyl acetate as eluent to give the *ketophosphonate* (0.49 g, 92%) as a colourless oil; $[\alpha]_D^{21}$ −79.9 (*c*, 2.5 in $CHCl_3$) (Found: C, 59.6; H, 9.2. $C_{24}H_{43}SiPO_6$ requires C, 59.3; H, 8.9%); ν_{max}(film)/cm^{-1} 1715; δ_H(400 MHz) 7.46–7.28 (5H, m, ArH), 4.44 (1H, d, *J* 12 Hz, PhC*H*HO), 4.39 (1H, d, *J* 12 Hz, PhCH*H*O), 3.71 (3H, d, *J* 1 Hz, OCH_3), 3.68 (3H, d, *J* 1 Hz, OCH_3), 3.46 –3.37 (2H, m, OCH_2), 3.37 (1H, d, *J* 18 Hz, C*H*), 3.34 (1H, d, *J* 18 Hz, C*H*), 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, CH*Me*), 0.87 (3H, d, *J* 6.8 Hz, CH*Me*), 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, OCH_2), 68.4 (t, OCH_2), 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-7-en-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 $NaHCO_3$ (10 ml) and brine (10 ml) and then dried (Na_2SO_4) 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; $[\alpha]_D^{20}$ −9.4 (*c*, 1.78 in $CHCl_3$); δ_H(400 MHz) 7.26–7.35 (5H, 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, OC*H*HO), 4.53 (1H, d, *J* 6.8 Hz, OCH*H*O), 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, OCH_3), 3.38 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.34 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 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-6-one 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; $[\alpha]_D^{20}$ +5.6 (*c*, 1.0 in CH_2Cl_2); δ_H(500 MHz) 4.67 (1H, d, *J* 6.7 Hz, OC*H*HOMe), 4.61 (1H, d, *J* 6.7 Hz, OCH*H*OMe), 4.51 (1H, t, *J* 5.75 Hz), 3.85 (1H, dd, *J* 2.6 and 8.3 Hz), 3.73 (2H, m, C*H*$_2$OH), 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 × Me); δ_C(67.8 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-3,5,9,13-tetramethylhexadecan-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 × 10 ml) and brine (10 ml), then dried (Na_2SO_4) 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; $[\alpha]_D^{20}$ +1.8 (*c*, 1.6 in $CHCl_3$); 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, OC*H*H–OMe), 4.64 (1H, d, *J* 6.7 Hz, OCH*H*–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); δ_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. $C_{48}H_{83}O_9Si_2$ 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 $NaHCO_3$ (3 ml). The separated aqueous phase was extracted with ether (3 × 20 ml) and the combined ether extracts were washed with saturated $NaHCO_3$ (10 ml) and brine (10 ml) and then dried (Na_2SO_4). The ether extracts were concentrated *in vacuo* to leave the pure *aldehyde* (90 mg, 95%) as a viscous oil; $[\alpha]_D^{21}$ +1.9 (*c*, 1.05 in $CHCl_3$); δ_H(500 MHz) 9.87 (1H, t, *J* 2 Hz, C*H*O), 7.71–7.68 (4H, m, ArH), 7.48–7.29 (6H, m, ArH), 4.72 (1H, d, *J* 6.5 Hz, OC*H*H–OMe), 4.66 (1H, d, *J* 6.5 Hz, OCH*H*–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); δ_C(69.89 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 × 200 ml) and the combined organic extracts were washed with brine (200 ml) then dried ($MgSO_4$) 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. $C_8H_{12}O_3$ requires C, 61.5; H, 7.7%); ν_{max}(film)/cm^{-1} 2955, 1751; δ_H(250 MHz, $CDCl_3$) 5.79 (1H, ddt, *J* 16.7, 10.2 and 6.5 Hz, C*H*=CH_2), 5.08–4.97 (2H, m, =CH_2), 3.73 (3H, s, CO_2Me), 3.46 (2H, s, COCH_2CO), 2.65 (2H, t, *J* 7.4 Hz, CH_2CO), 2.33 (2H, dt, *J* 7.4 and 6.5 Hz, CH_2CH=CH_2); δ_C(67.8 MHz, $CDCl_3$) 201.6 (s, 3-C), 167.3 (s, 1-C), 136.3 (d, 6-C), 115.2 (t, 7-C), 52.0 (q, CO_2 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 D-glucose (500 g, 2.77 mol), baker's yeast (435 g), KH_2PO_4 (1.05 g, 7.6 mmol), $MgSO_4$ (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 × 500 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 ($MgSO_4$) 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 $NaHCO_3$ (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 × 50 ml) and the combined organic extracts were then dried ($MgSO_4$) 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; $[\alpha]_D$ −15.8 (*c*, 1.5 in $CHCl_3$); δ_H(250 MHz, $CDCl_3$) 7.45–7.35 (5H, m, ArH), 5.85 (1H, ddt, *J* 16.5, 10.3 and 6.5 Hz, C*H*=CH_2), 5.11–4.90 (2H, m, =CH_2), 4.10–4.01 (1H, m, C*H*OH), 3.15 (1H, br s, OH), 2.60–2.45 (2H, m, CH_2CO), 2.25–2.05 (2H, s, CH_2CH=CH_2), 1.70–1.50 (2H, m, CH_2); δ_C(100 MHz, $CDCl_3$) 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, OCH_2Ph), 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 − H_2O, 215.9893. $C_{14}H_{16}O_2$ 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 × 50 ml) and brine (50 ml), then dried ($MgSO_4$) 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; $[\alpha]_D$ −11.0 (*c*, 1.5 in $CHCl_3$) (Found: C, 76.2; H, 7.9. $C_{30}H_{36}O_3Si$ requires C, 76.2; H, 7.7%); ν_{max}(film)/cm^{-1} 3069, 2930, 2892, 1736, 1640; δ_H(360 MHz, $CDCl_3$) 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, C*H*=CH_2), 5.06 (1H, d, *J* 12.3 Hz, OC*H*HPh), 4.98 (1H, d, *J* 12.3Hz, OCH*H*Ph), 4.91–4.85 (2H, m, =CH_2), 4.25 (1H, quintet, *J* 6 Hz, C*H*–OH), 2.60 (1H, dd, *J* 6.6 and 14.8 Hz, C*H*H–CO), 2.53 (1H, dd, *J* 6.0 and 14.8 Hz, CH*H*–CO), 2.05–2.00 (2H, m, CH_2C=CH_2), 1.62–1.56 (2H, m, CH_2), 1.06 (9H, s, t-Bu); δ_C(90 MHz, $CDCl_3$) 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, OCH_2Ph), 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 °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 H_2O_2 (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 × 100 ml). The ether extracts were dried ($MgSO_4$), and then concentrated *in vacuo*. The residue was purified by flash chromatography on silica using diethyl ether–petrol (1 : 1) as eluent to give the *alcohol* (3.57 g, 78%) as an oil; $[\alpha]_D^{21}$ −11.5 (*c*, 1.6 in $CHCl_3$) (Found: C, 73.2; H, 8.1. $C_{30}H_{38}O_4Si$ requires C, 73.4; H, 7.8%); ν_{max}(film)/cm^{-1} 3396, 3068, 1735; δ_H(360 MHz, $CDCl_3$) 7.72–7.67 (4H, m, ArH), 7.47–7.29 (11H, m, ArH), 5.1 (1H, d, *J* 11.6 Hz, OC*H*HPh), 5.03 (1H, d, *J* 11.6 Hz, OCH*H*Ph), 4.27–4.22 (1H, m, C*H*O), 3.47 (2H, t, *J* 6 Hz, CH_2OH), 2.62 (1H, dd, *J* 6.1 and 12 Hz, C*H*HCO$_2$CH$_2$Ph), 2.55 (1H, dd, *J* 6.1 and 12 Hz, CH*H*CO$_2$Ph), 1.52–1.42 (6H, m, 3 × CH$_2$), 1.06 (9H, s, t-Bu); δ_C(100 MHz, $CDCl_3$) 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, OCH$_2$Ph), 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. $C_{30}H_{38}O_4Si$ 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; $[\alpha]_D^{21}$ −10.3 (*c*, 2.7 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3069, 2931, 1734; δ_H(250 MHz, $CDCl_3$) 9.71 (1H, br s, C*H*O), 7.68–7.63 (4H, m, ArH), 7.46–7.25 (11H, m, ArH), 5.05 (1H, d, *J* 12.5 Hz, OCH*H*Ph), 4.97 (1H, d, *J*, 12.5 Hz, OC*H*HPh), 4.20 (1H, apparent quintet, *J* 6 Hz, C*H*ODBDPS), 2.60 (1H, dd, *J* 6.5 and 14.8 Hz, C*H*HCO$_2$CH$_2$Ph), 2.52 (1H, dd, *J* 6 and 14.8 Hz, CH*H*CO$_2$CH$_2$Ph), 2.05–2.00 (2H, m, CH_2CHO), 1.62–1.56 (4H, m, 2 × CH$_2$), 1.06 (9H, s, t-Bu); δ_C(67.8 MHz, $CDCl_3$) 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, OCH$_2$Ph), 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)-7-hydroxyoctanoic 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 $NaHCO_3$ 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 ($MgSO_4$). 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; $[\alpha]_D^{21}$ −13.4 (*c*, 5.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3388, 2953, 1732; δ_H(400 MHz, $CDCl_3$) 7.68–7.64 (4H, m, ArH), 7.41–7.25 (11H, m, ArH), 5.02 (1H, d, *J* 12.5 Hz, OC*H*HPh), 4.96 (1H, d, *J* 12.5 Hz, OCH*H*Ph), 4.20 (1H, m, CHOTBDPS), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 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, CH_2PO), 1.51–1.48 (2H, m, CH_2), 1.45–1.24 (4H, m, 2 × CH_2), 1.02 (9H, s, t-Bu); δ_C(100 MHz, $CDCl_3$) 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, OCH$_2$ Ph), 52.4 (q, OCH_3), 42.0 (38.0) (t, 2-C), 37.6 (36.8) (t, 6-C), 33.1 (CH_2, d, $J_{P\text{-}C}$ 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. $C_{33}H_{45}O_7PSi$ requires 613.2750).

3-(*tert*-Butyldiphenylsilanyloxy)-8-(dimethoxyphosphoryl)-7-oxooctanoic 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 × 50 ml) and the combined organic extracts were washed with water (2 × 50 ml) and brine (25 ml), and then dried ($MgSO_4$). 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; $[\alpha]_D^{21}$ −14.2 (*c*, 2.0 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3070, 2999, 1732, 1599; δ_H(360 MHz, $CDCl_3$) 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, OC*H*HPh), 4.92 (1H, d, *J* 12.4 Hz, OCH*H*Ph), 4.21 (1H, quintet, *J* 6 Hz, C*H*OTBDPS), 3.79 (3H, d, $J_{P\text{-}C}$ 0.88 Hz, OCH_3), 3.77 (3H, d, $J_{P\text{-}C}$ 0.9 Hz, OCH_3), 2.97 (2H, d, $J_{P\text{-}C}$ 22.67 Hz, CH_2O), 2.62 (1H, dd, *J* 6.65 and 14.9 Hz, C*H*HCO$_2$CH$_2$Ph), 2.56 (1H, dd, *J* 5.9 and 14.9 Hz, CH*H*CO$_2$CH$_2$Ph), 2.35 (2H, dt, *J* 1.4 and 6.4 Hz), 1.57–1.43 (4H, m, 2 × CH$_2$), 1.05 (9H, s, t-Bu); δ_C(67.8 MHz, $CDCl_3$) 201.0 (C=O, d, $J_{P\text{-}CO}$ 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, *C*H$_2$Ph), 52.8 (q, OCH_3), 52.8 (q, OCH_3), 43.5 (t, 2-C), 41.9 (t, C-6), 41.7 (CH_2, 8-C, $J_{P\text{-}C}$ 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)-7-oxooctanoic 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 × 25 ml). The filtrate was concentrated *in vacuo* to leave the *acid* (0.86 g, 98%) as a colourless foam; $[\alpha]_D^{21}$ −13.7 (*c*, 2.9 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1714, 1588; δ_H(360 MHz, $CDCl_3$) 7.72–7.67 (4H, m ArH), 7.49–7.29 (6H, m, ArH), 4.16–4.14 (1H, m, C*H*OTBDPS), 3.8 (3H, s, OMe), 3.0 (2H, d, *J* 22.7 Hz, CH_2PO), 2.5 (2H, apparent d, *J* 6 Hz, CH_2CO$_2$Ph), 2.4 (2H, m, CH_2), 1.53–1.50 (4H, m, 2 × CH_2), 1.07 (9H, s); δ_C(100 MHz, $CDCl_3$) 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, OCH_3), 43.7 (t, 2-C), 41.6 (t, 6-C), 40.4 (d, $J_{P\text{-}C}$ 112 Hz, CH_2PO), 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 × 10 ml) and the combined organic phases were washed with saturated brine (20 ml), then dried (Na_2SO_4) 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 $CHCl_3$); 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, *OCH*H–OMe), 4.62 (d, *J* 6.7 Hz, OCH*H*OMe), 3.99 (3H, s, CO_2Me), 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, *J* 7 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); δ_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 keto-ester **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 $CHCl_3$); ν_{max}(film)/cm^{-1} 3583, 3016, 2991, 2858; δ_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, CH_2OH), 4.67 (d, *J* 6.7 Hz, OC*H*HOME), 4.60 (d, *J* 6.7 Hz, OCH-*H*OMe), 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); δ_C(67.8 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 (Na_2SO_4) 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 $CHCl_3$); δ_H(500 MHz) 10.1 (1H, s, CHO), 8.4 (1H, s, =C*H*), 8.45 (1H, s, =C*H*), 8.3 (1H, s, =C*H*), 7.7 (4H, br s, Ar-H), 7.5–7.3 (6H, m, Ar-H), 6.9 (1H, dt, *J* 7.5 and 16 Hz, CH=C*H*–CH_2), 6.5 (1H, d, *J* 16 Hz, C*H*–CH=CH_2), 4.72 (1H, d, *J* 6.7 Hz, OC*H*-HOMe), 4.64 (1H, d, *J* 6.7 Hz, OCH*H*OMe), 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); δ_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, OCH_2OCH_3), 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 (Na_2SO_4) 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 $CHCl_3$); δ_H(500 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); δ_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 (Na_2SO_4) 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; $[\alpha]_D^{25}$ +6.2 (*c*, 0.6 in $CHCl_3$); δ_H(500 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, $J_{P\text{-}CH_2}$ 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); δ_C(90 MHz) 213.9 (s), 201.3 (d, $J_{P\text{-}CO}$ 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 × 25 ml). The combined organic extract was washed with saturated potassium chloride (3 × 50 ml), then dried (Na_2SO_4) 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; $[\alpha]_D^{25}$ +10.8 (*c*, 0.5 in $CHCl_3$); δ_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, *J* 7 Hz), 0.9 (3H, d, *J* 6.9 Hz), 0.85 (9H, s, t-Bu), 0.8 (3H, d, *J* 6.8 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 (Na_2SO_4) 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 "9β-methyl" diastereoisomer **80b**, as an oil; $[\alpha]_D$ −13.0 (*c*, 1.0 in $CHCl_3$); δ_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); δ_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 "9α-methyl" diastereoisomer **80a**, as an oil; δ_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 (Na_2SO_4) 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; δ_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 9α-methyl diastereoisomer **80a** was prepared using an identical procedure and showed δ_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); δ_C(125 MHz) 215.7 (s, 36-C), 210.6 (s, 7-C), 170.6 (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 × 10 ml), copper sulfate (2 × 5 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; δ_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, CO*Me*), 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); δ_C(125 MHz) 211.7 (s, 36-C), 210.5 (s, 7-C), 170.6 (s, 1-C), 170.2 (s, CO*Me*), 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, CO*Me*), 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 δ_H(500 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-H[1]) 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, CO*Me*), 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, *J* 7 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, CO*Me*), 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 silyl 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 (Na_2SO_4) 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; δ_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, CO*Me*), 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); δ_C(125 MHz) 211.7 (s, 36-C), 210.9 (s, 7-C), 170.7 (s, 1-C), 170.2 (s, CO*Me*), 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, CO*Me*), 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 9α-methyl diastereoisomer **83a** was prepared using an identical procedure and showed δ_H(500 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, OCO*Me*), 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, CO*Me*), 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 (Na_2SO_4) 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; δ_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, OCO*Me*), 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, CO*Me*), 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, CO*Me*), 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 9α-methyl diastereoisomer **84a** was prepared using an identical procedure and showed δ_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, OCOCH_3), 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, CO*Me*), 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; δ_H(500 MHz) 8.4 (1H, s, C*H*O), 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, *J* 4 and 9 Hz, 38-H), 5.1 (5.0) (1H, dd, *J* 9.4 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, CO*Me*), 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, CO*Me*), 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, CO*Me*), 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 δ_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, $CO\mathit{CH}_3$), 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 × Me); δ_C(125 MHz) 211.5 (s, 36-C), 210.4 (s, 7-C), 172.7 (s, 1-C), 170.5 (s, CO*Me*), 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, CO*Me*), 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; $[\alpha]^{21}$ −43.3 (*c*, 0.3 in MeOH); δ_H(500 MHz) 8.36 (1H, s, C*H*O), 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, CO*Me*), 1.94–1.87 (3H, m), 1.86–1.84 (4H, m), 1.58–1.55 (4H, m), 1.39 (3H, d, *J* 7 Hz, C-9*Me*), 1.13 (3H, d, *J* 7 Hz), 1.11 (3H, d, *J* 7 Hz), 0.97 (3H, d, *J* 7 Hz), 0.89 (3H, d, *J* 2 Hz); δ_C(125 MHz) 211.5 (s, 36-C), 210.4 (s, 7-C), 172.6 (s, 1-C), 170.1 (s, CO*Me*), 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, CO*Me*), 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 δ_H(500 MHz) 8.36 (1H, s, C*H*O), 8.13 (2H, s, 2 × 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, CO*Me*), 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); δ_C(125 MHz) 211.5 (s, 36-C), 210.4 (s, 7-C), 172.7 (s, 1-C), 170.2 (s, CO*Me*), 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, CO*Me*), 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.

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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**, 5449; (*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.
16 S. K. Chattopadhyay and G. Pattenden, *Tetrahedron Lett.*, 1995, **36**, 5251.
17 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.
34 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.