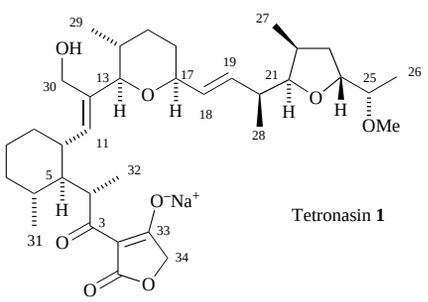
Synthesis of the acyltetronic acid ionophore tetronasin (ICI M139603)

Steven V. Ley,*[a] Dearg S. Brown,[b] J. Andrew Clase,[a] Antony J. Fairbanks,[a] Ian C. Lennon,[b] Helen M. I. Osborn,[a] Elaine S. E. Stokes (née Owen)[b] and David J. Wadsworth[b]

[a] *Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW*
[b] *Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY*

A synthetic strategy for the preparation of tetronasin 1, an acyltetronic acid ionophore demonstrating antibiotic, antiparasitic and growth promotion in ruminants is described. The key step involves a metal mediated cyclization reaction which creates two rings and four new stereocentres in a highly efficient manner. The configurations of three of these stereocentres are as required for the synthesis of tetronasin. The remaining stereocentre is readily epimerised to the natural configuration at a later stage of the synthesis.

Tetronasin (ICI M139603) **1**, an acyltetronic acid ionophore



Tetronasin **1**

produced by *Streptomyces longisporoflavus*,[1] is of commercial interest owing to its biological activity as an antibiotic, antiparasitic and growth promotion agent in ruminants.[2] It has also attracted attention owing to its unusual structure[1] and properties[3] and has been the subject of extensive biosynthetic[4] and synthetic studies.[5]

In terms of total synthesis, tetronasin **1** presents a significant challenge in that it contains twelve stereogenic centres, three different heterocyclic ring systems, two stereodefined alkenes and a triequatorially substituted cyclohexane unit. Furthermore, the acyltetronic acid group occurs in only a limited number of natural products, consequently there are relatively few methods available for its construction.

In the initial synthesis plan towards tetronasin **1** we propose to adopt a conceptually interesting approach involving a metal templated polyene cyclization reaction of an open chain precursor **2**. It was hoped that metal chelation might encourage a favourable reacting conformation leading directly to an advanced polycyclic species **3** which could be further processed to **1** (Scheme 1). The required open chain precursor **2** in turn, could be assembled from readily prepared building blocks **4**–**8** in a convergent fashion.

Results and discussion

In previous studies we had shown that the stannyl tetronic acid fragment **4** was indeed an excellent precursor for acyltetronic acids and had completed the synthesis of three natural products, carlosic acid, carolinic acid and agglomerin A.[6] In this published work the tri-*n*-butyl stannyl group served as a suitable coupling component with acid chlorides under palladium catalysed conditions.

The stabilised Wittig reagent **5** is a known three carbon building block.[7] The synthesis of the remaining fragments **6**, **7** and **8** are reported below, together with further coupling studies leading to the synthesis of tetronasin **1** itself.

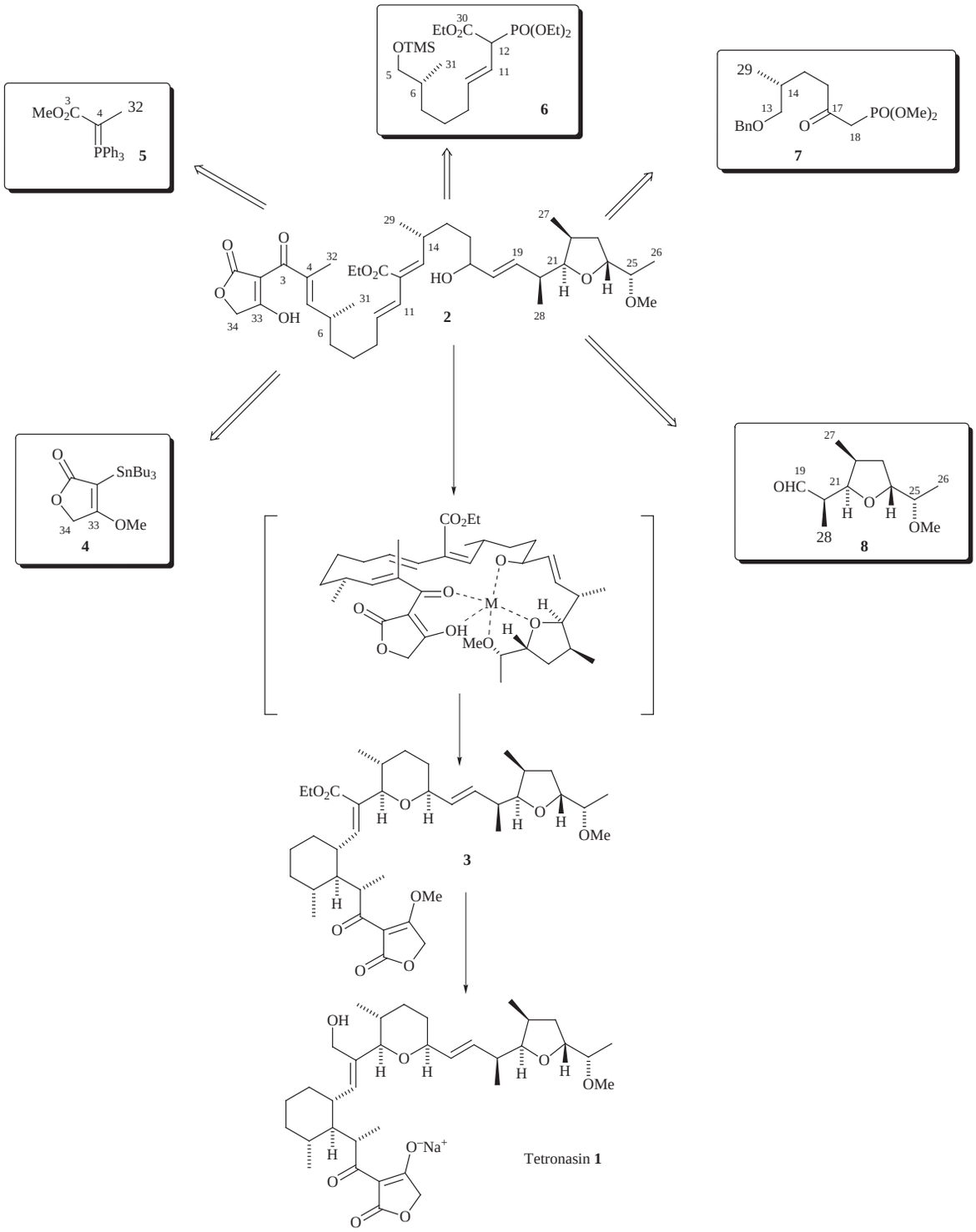
The preparation of the phosphonate **6** could be readily achieved from the alcohol **9**[5f] in a series of straightforward steps (Scheme 2).

Firstly **9** was converted to the corresponding tosylate **10** which was then coupled with the Grignard reagent derived from 5-bromopent-1-ene in the presence of Li_2CuCl_4 to afford the olefin **11**.[8] This in turn was subjected to ozonolysis followed by Lehnert modified Knoevenagel condensation[9] of the resulting aldehyde **12** with triethylphosphonoacetate to give **13** as a mixture of the desired allyl and undesired vinyl isomers in a ratio of 4:1 in favour of the former isomer. Removal of the benzyl protecting group improved this ratio to 200:1 in favour of the allyl isomer, and subsequent treatment with TMSCl in the presence of triethylamine afforded the silyl protected phosphonate **6**.

The keto phosphonate fragment **7** was also readily obtained from the same initial chiral alcohol **9**. Firstly, conversion[10] to the corresponding bromide **15** was necessary and this was followed by reaction of **15** with the dianion generated from dimethyl 2-oxopropylphosphonate to give the required coupling component **7** in 56% overall yield (Scheme 3).

For the synthesis of the remaining tetrahydrofuran aldehyde fragment **8** we report two routes, both of which are efficient and allow access to multigramme quantities of material. We have previously published[5f] an earlier route to this material, but it is less amenable to scale up and is therefore not reported here.

Consistent with our synthesis plan to use common building blocks wherever possible, one route to **8** employs the chiral alcohol **9**, the use of which was reported earlier. Oxidation of **9** under Swern conditions[11] followed by addition of (*Z*)-crotyl-(+)-diisopinocampheylborane[12] and oxidative work-up gave **16** in which three of the required stereogenic centres are set up in place (Scheme 4). After standard protection as the *tert*-butyldimethylsilyl ether and hydroboration with 9-BBN, oxidative work-up followed by a Swern oxidation gave the aldehyde **19**. This was homologated to the allylic ester **20** by reaction with



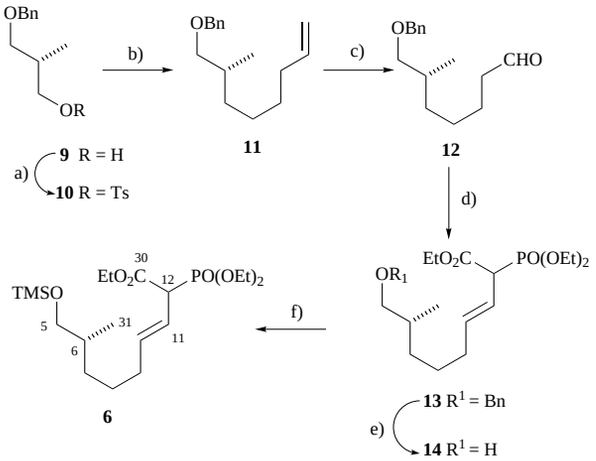
Scheme 1

triethylphosphonoacetate under the Masamune–Roush conditions[13] and subsequently reduced with diisobutylaluminium hydride in tetrahydrofuran in excellent overall yield.

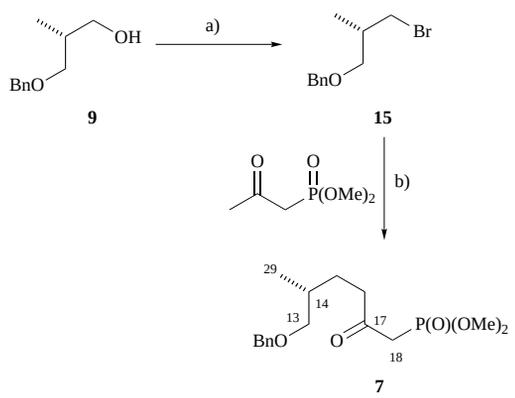
The stage was now set to introduce the remaining two stereogenic centres *via* a Sharpless asymmetric oxidation procedure.[14] Thus, reaction of **21** with titanium(IV) isopropoxide, *tert*-butylhydroperoxide and (+)-diethyl tartrate gave the desired epoxide **22** (Scheme 4).

Deprotection of **22** with tetra-*n*-butylammonium fluoride in THF at 60 °C resulted in concomitant intramolecular epoxide ring opening to provide the tetrahydrofuran **23** in 85% yield. The remaining steps in the synthesis were relatively straightforward and proceeded in equally high yields. Selective tosylation of the primary hydroxy group in **23** to give **24** was achieved by reaction with dibutyltin oxide[15] followed by toluene-*p*-sulfonyl chloride and triethylamine. This was then transformed to **26** by reduction with Super Hydride ($LiEt_3BH$) and subsequent alkylation of the hydroxy group with methyl iodide and potassium hydride. Finally, deprotection with hydrogen using palladium on charcoal as catalyst, followed by oxidation with tetra-*n*-propylammonium perruthenate (TPAP)[16] gave the required tetrahydrofuran aldehyde **8** (Scheme 4). This material was identical in all respects to that which we had prepared by the earlier route[5f] and to that obtained by natural product degradation.[5f]

In the second route to aldehyde **8** (Scheme 5) we sought to exploit additional synthetic methodology developed in our laboratories[17] for the formation of carbon–carbon bonds



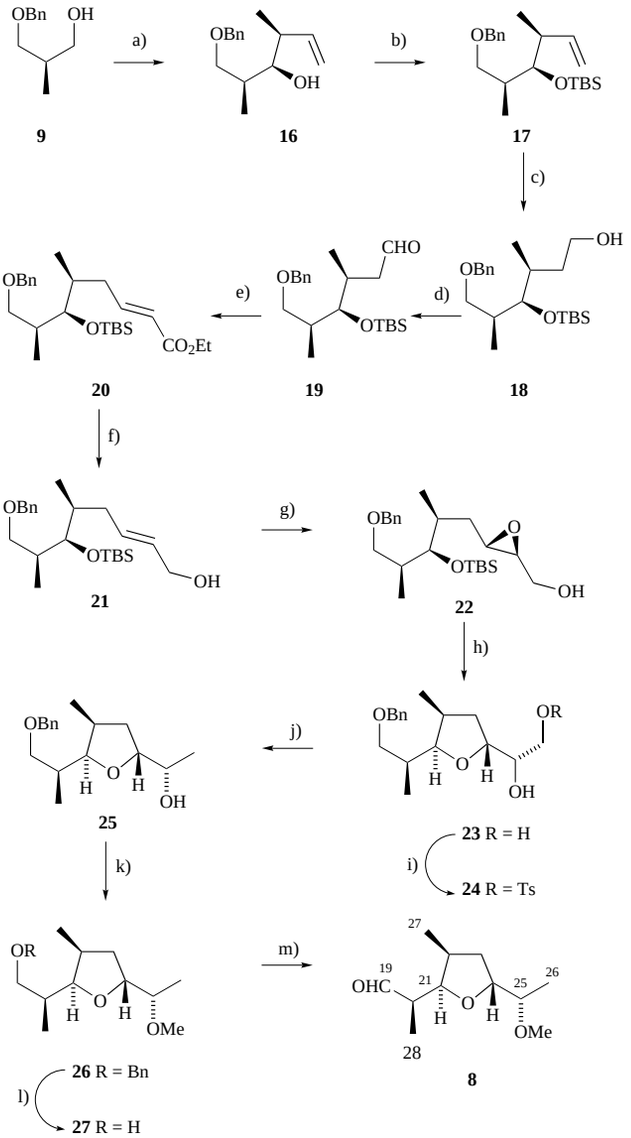
Scheme 2 *Reagents*: a) TsCl, pyridine, 88%; b) $BrMg(CH_2)_3CH{=}CH_2$, Li_2CuCl_4, 93%; c) O_3, −78 °C, PPh_3, 71%; d) $TiCl_4$, NMM, $EtO_2CCH_2P(O)(OEt)_2$, 90%; e) Na, NH_3, 77%; f) TMSCl, Et_3N, 98%



Scheme 3 *Reagents*: a) NBS, PPh_3, CH_2Cl_2, 89%; b) NaH, Bu^{n}Li, THF, 71%

adjacent to oxygen in cyclic ethers using 2-phenylsulfonyl derivatives.

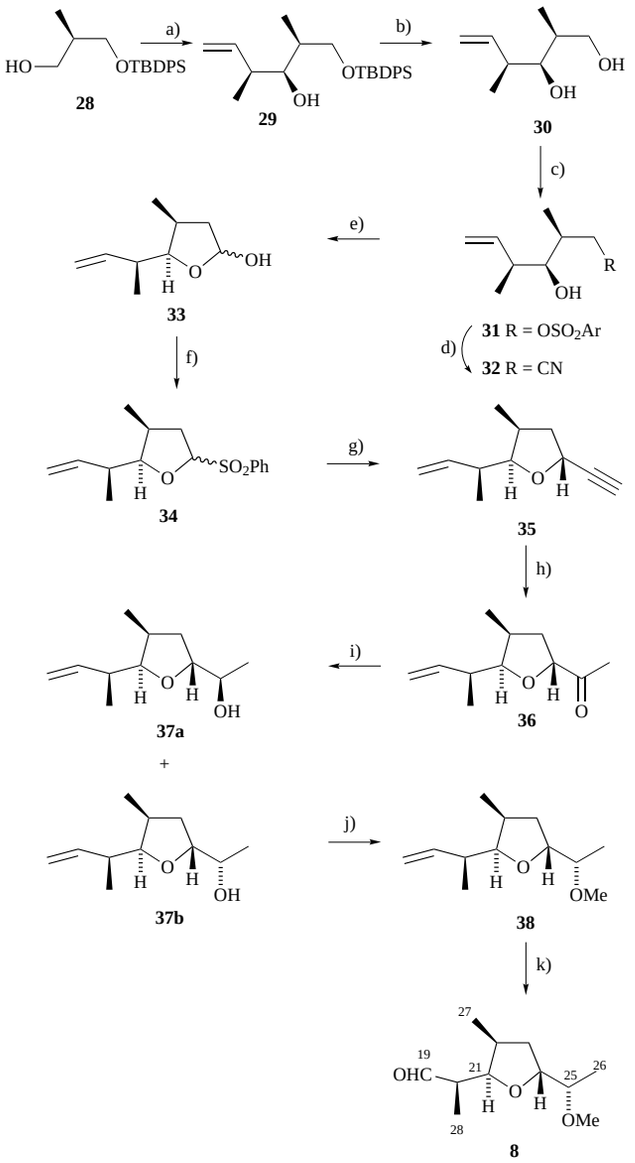
Accordingly, the alcohol **28**[5f] was oxidised under Swern conditions[11] and the aldehyde thus formed treated with (*E*)-crotyl-(−)-diisopinocampheylborane[12] to afford the alkene **29** after work-up with diethanolamine.[18] Deprotection of the silyl ether with TBAF afforded diol **30** with three of the required five stereogenic centres efficiently established. The diol **30** was next converted to the nitrile **32** by selective 2-mesitylenesulfonylation of the primary hydroxy group and displacement with sodium cyanide in 67% overall yield for these first four steps. The nitrile group in **32** was reduced with diisobutylaluminium hydride and the intermediate lactol treated with phenylsulfinic acid, using our previously established protocol,[17] to afford the crystalline sulfone **34** in good yield. Sulfone **34** was then reacted with ethynylmagnesium bromide in the presence of zinc chloride at room temperature to afford stereoselectively the *trans*-substituted tetrahydrofuran **35**. This was then hydrolysed with mercuric oxide and sulfuric acid[19] to yield the corresponding acetyl derivative **36** in 71% yield from the sulfone **34**. Finally, the carbonyl group in **36** was reduced with sodium borohydride in methanol at room temperature to afford a mixture of diastereomeric alcohols **37a** and **37b** (3 : 2 **37a** : **37b**). Alternatively, reduction with L-Selectride[20] in THF at −78 °C afforded exclusively alcohol **37a** which could be readily inverted to the required isomer **37b** using standard Mitsunobu[21] reaction conditions. Methylation of alcohol **37b** followed by ozonolysis of ether **38** afforded the furan fragment **8**. This second route to **8** is complementary to the first sequence, it provides efficient access to good quantities of **8**, and, moreover, it employs methods developed by our group.



Scheme 4 *Reagents*: a) i) DMSO, $(COCl)_2$, CH_2Cl_2 then Et_3N; ii) (+)-(*Z*)-crotyldiisopinocampheylborane, THF then NaOH, H_2O_2, 70%; b) TBDMSOTf, Et_3N, CH_2Cl_2, 100%; c) 9-BBN, THF then NaOH, H_2O_2, 95%; d) DMSO, $(COCl)_2$, CH_2Cl_2 then Et_3N, 85%; e) $EtO_2CCH_2PO(OEt)_2$, LiCl, Pr^i_2EtN, MeCN, 93%; f) DIBAL-H, THF, 97%; g) L-(+)-diethyl tartrate, Bu^{t}OOH, $Ti(OPr^i)_4$, CH_2Cl_2, 80%; h) TBAF, THF, 85%; i) Bu_2SnO, MeOH, TsCl, Et_3N, 94%; j) $LiEt_3BH$, THF, 92%; k) KH, THF then MeI, 90%; l) Pd/C, H_2, MeOH, 95%; m) TPAP, NMO, 4 Å sieves, CH_2Cl_2, 93%

Now that all the key fragments as outlined in the initial plan for the synthesis of tetronasin **1** were available, their coupling and further processing could be investigated (Scheme 6).

Firstly we assembled the C-13 to C-26 unit by coupling the central keto phosphonate **7** with the terminal aldehyde group of the tetrahydrofuran fragment **8** using the previously described Masamune–Roush conditions[13] to give the enone product **39** in a completely (*E*)-selective fashion with no detectable epimerization of the sensitive stereogenic centre adjacent to the aldehyde functionality. Reduction of the enone **39** with Noyori's (*S*)-BINAL-H reagent[22] proceeded well to give the alcohol **40** with excellent control of the newly formed stereogenic centre. The minor amount of the unwanted diasteroisomer was readily inverted to give more **40** using the Mitsunobu procedure[21] followed by hydrolysis in the normal way. The stereochemical outcome of this reduction reaction is in agreement with the model predicted by Noyori[22] and also confirmed by the fact that it was later converted to the natural product itself. Following protection of **40** as its *tert*-butyldimethylsilyl ether **41** and



Scheme 5 *Reagents*: a) i) $(COCl)_2$, DMSO, Et_3N; ii) (*E*)-crotyl-(−)-diisopinocampheylborane, THF, −85 °C; iii) NaOH (aq), H_2O_2; iv) $HN(CH_2CH_2OH)_2$, Et_2O, 74%; b) TBAF, THF, 100%; c) Et_3N, DMAP, 2,4,6-triisopropylbenzenesulfonyl chloride, 90%; d) NaCN, DMSO, 100%; e) DIBAL-H, PhMe, 94%; f) $PhSO_2H$, $CaCl_2$, CH_2Cl_2, 93%; g) HC≡CMgBr, $ZnBr_2$, THF, 88%; h) yellow HgO, H_2SO_4 (aq), acetone, 81%; i) $NaBH_4$, MeOH, 89% (**37a**:**37b** 3:2); j) i) NaH, THF; ii) MeI, 87%; k) i) O_3; ii) Ph_3P, 84%

removal of the benzyl group with sodium in ammonia at −33 °C, the intermediate alcohol **42** was oxidised to the aldehyde **43** in 95% yield using catalytic TPAP[16] and *N*-methylmorpholine-*N*-oxide as cooxidant. Coupling of **43** to the next key fragment **6** in the proposed synthesis of **1** was best achieved using lithium hexamethyldisilazide in THF at −78 °C to deprotonate the ester phosphonate **6** which was then reacted with **43** and worked-up by treatment with a pH 3 buffer to give **45** in its deprotected form in excellent yield and with excellent stereochemical control. Many alternative conditions were investigated for this coupling but were much less successful, giving either mixtures of double bond isomers or causing racemisation of the stereogenic centre next to the aldehyde group in **43**. Once again we found it most convenient to oxidise the hydroxy group in **45** to the aldehyde **46** using the TPAP reagent system which proceeded in 95% yield and with no detectable scrambling of the sensitive stereogenic centres.

Further homologation of **46** was achieved *via* a Wittig reaction followed by silyl deprotection with Dowex-50W in methanol to give **48** as a pure product in excellent overall yield (Scheme 6).

Whilst compound **48** is a suitable material on the pathway to natural product tetronasin **1** based on our original synthesis plan, it also contains all the elements necessary to undergo a metal mediated polyene cyclization in its own right. Namely, the secondary hydroxy group is ideally placed to undergo a conjugate addition to the acceptor dienic ester unit which, *via* reequilibration of the resulting enolate, could undergo the second cyclization by Michael addition to the terminal methacrylate unit to assemble the cyclohexyl ring of the natural product in one operation. This attractive option was thus worthy of investigation in spite of the realization that we would be setting a tough challenge in forming two new rings and creating four new stereogenic centres simultaneously. Nevertheless, we felt confident that the natural conformation might lead to favourable transition states and hence to the double cascade cyclization reaction under appropriate conditions. Moreover, for various reasons, the product of this process might be more readily converted to tetronasin **1**.

Although we investigated many conditions for this ambitious concept we were pleased to find that treatment of **48** with potassium hexamethyldisilazide in toluene at 0 °C gave a *single product* **49** in 67% yield!

What should be noticed in this reaction is that we do form the tetrahydropyran and cyclohexane rings with complete control, but the configuration of the C-4 (tetronasin numbering) methyl substituent is opposite to that found in tetronasin **1**. The proof of configuration of this C-4 centre follows from extensive NMR investigation and later experiments. Other metal bases, solvents and temperature conditions used in this reaction were much less satisfactory, leading to either monocyclization or decomposition. We also investigated methods to install the correctly configured methyl substituent by later introduction *via* alkylation or by epimerisation of the C-4 stereogenic centre in **49** but without success.

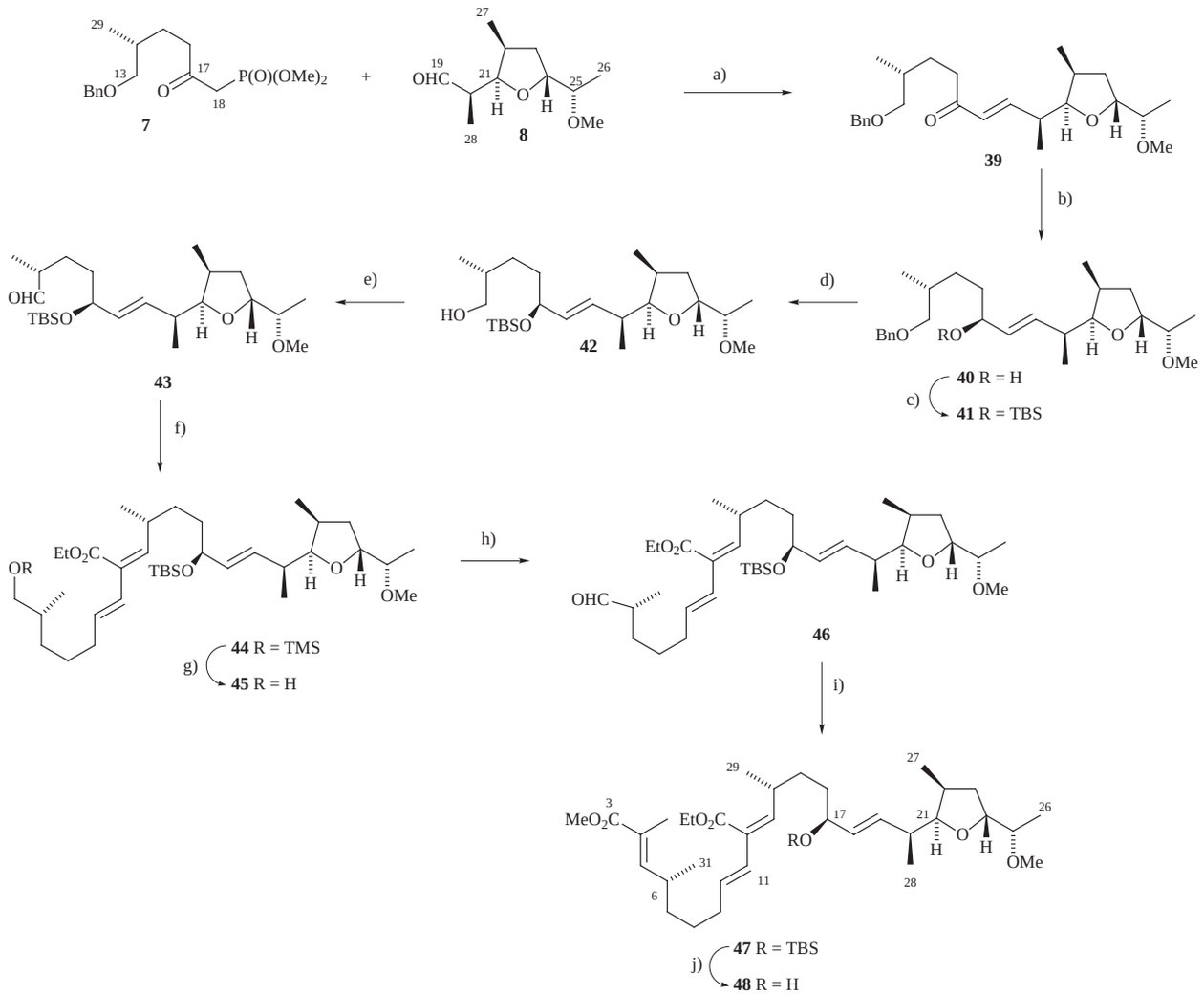
In order to correct this stereochemical problem we devised an alternative sequence which proved to be very satisfactory. Firstly we found that the diester **49** could be selectively reduced to the alcohol **51** using lithium borohydride in THF to give **51** in 58% yield together with some of the diol **50** (19%) and a little (4%) recovered starting material (Scheme 7). Reaction of **51** with *tert*-butyldimethylsilyl triflate gave the protected derivative **52** which upon treatment with diisobutylaluminium hydride in CH_2Cl_2 gave the differentiated diol **53** (79%). This could then be oxidised to the aldehyde **54** using the Dess–Martin periodinane reagent.[23] Although aldehyde **54** could not be epimerised under any base mediated conditions which we investigated, we found that epimerisation to the required aldehyde **55** could be achieved in 85% yield by simply refluxing the aldehyde **54** with morpholine and catalytic toluene-*p*-sulfonic acid (Scheme 7). This aldehyde **55** was identical in all respects to that prepared by Yoshii[5g] as a late stage precursor in their synthesis of tetronasin which involved reaction of **55** with $N_2CHCO_2CH_2COOCH_3$ in the presence of $ZrCl_4$ to give the β-keto ester derivative **56**.[5g] This, upon Dieckmann cyclization and deprotection using conditions first developed by our group involving tetra-*n*-butylammonium fluoride in THF,[24] following work-up as the sodium salt gave the acyltetronic acid natural product tetronasin **1**.

In summary we report above the concise formal synthesis of tetronasin **1**, an important ionophore antibiotic using some of the methods and reagents developed in our laboratory.

Experimental

General experimental

Ether refers to diethyl ether and petrol refers to light petroleum (bp 40–60 °C). Petrol was distilled and other solvents were dried and distilled before use; ether and tetrahydrofuran from



Scheme 6 *Reagents*: a) LiCl, DIPEA, MeCN, 67%; b) (*S*)-BINAL-H, 63%; c) TBSCl, imidazole, CH_2Cl_2, 98%; d) Na, NH_3, 99%; e) TPAP, NMO, 4 Å sieves, 95%; f) LHMDS, **6**, THF, 82%; g) acetate buffer (aq), 100%; h) TPAP, NMO, 4 Å sieves, CH_2Cl_2, 95%; i) $MeO_2C(Me)=PPh_3$, $CHCl_3$, 100%; j) Dowex 50W, MeOH, 100%

sodium–benzophenone ketyl, dichloromethane from phosphorous pentoxide, toluene from sodium, acetonitrile from calcium hydride, dimethylformamide from calcium hydride below 50 °C and dimethyl sulfoxide from calcium hydride. Other solvents were purified by standard procedures as necessary.

Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F254) and visualised by ultra-violet light (254 nm), acidic ammonium molybdate, basic potassium permanganate, acidic palladium chloride or iodine as appropriate. The products were purified by column chromatography on Merck silica gel 60 (Art. 9385 230–400 mesh) under pressure unless otherwise stated. Florisil 200–300 mesh (supplied by BDH) was used for florisil chromatography.

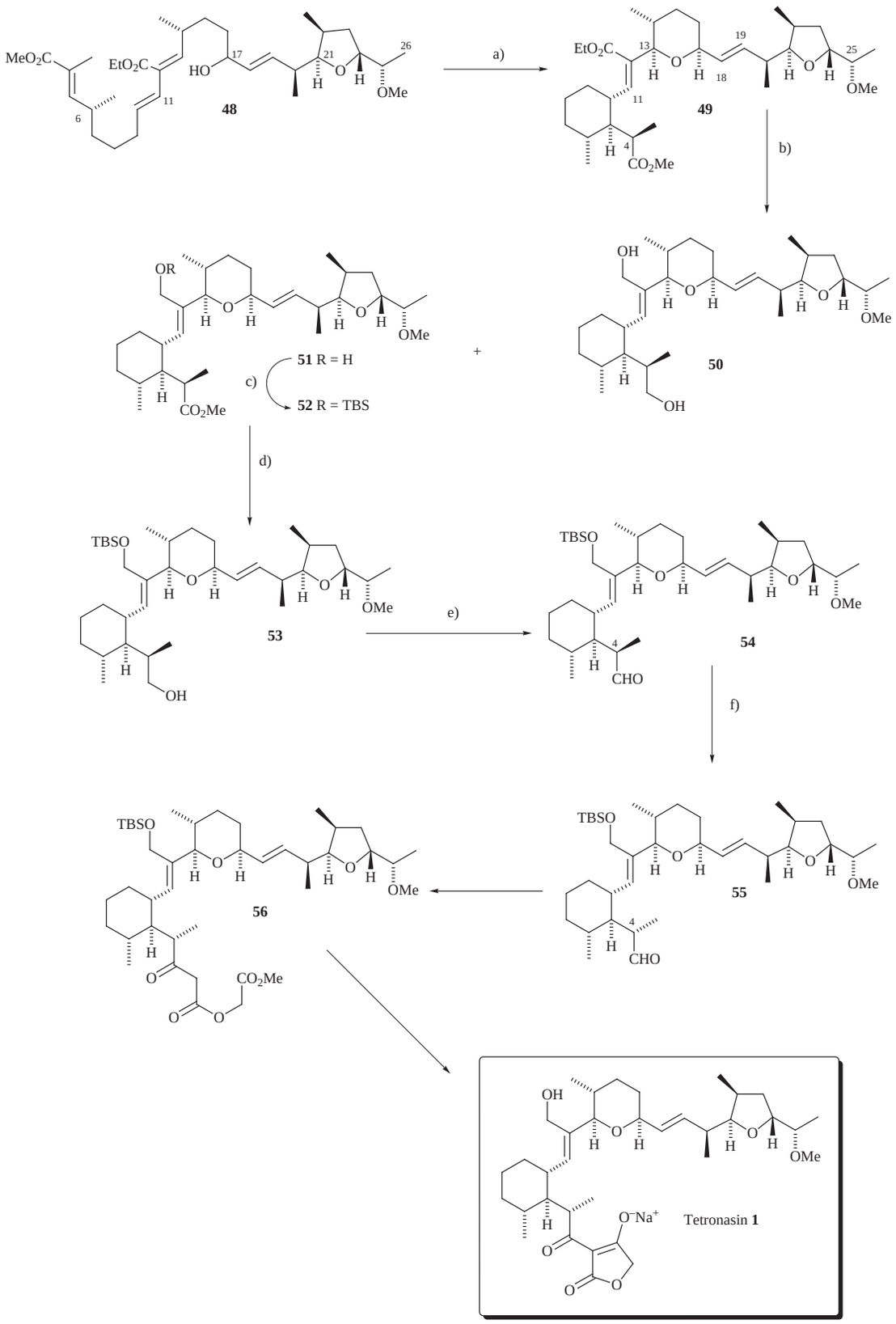
^{1}H NMR spectra were recorded on Bruker AM-200, Bruker WM-250, JEOL GSX-270, Bruker AM-400 or Bruker DRX-500 spectrometers using $CDCl_3$ as solvent and residual $CHCl_3$ as reference unless otherwise stated. Mass spectra were obtained on VG 7070B, VG 12-253, VG ZAB-E (SERC mass spectrometry service, Swansea), Kratos MS 890, Kratos MALDI-2 or Bruker Apex2 FT-ICR (4.7 T magnet) spectrometers. MALDI spectra were recorded using 2,5-dihydroxybenzoic acid as matrix. IR spectra were recorded on a Perkin-Elmer 983G spectrophotometer as liquid films or Nujol mulls. Optical rotations were measured using an Optical Activity AA-1000 polarimeter. Elemental microanalyses were performed in the microanalytical laboratories of Imperial College Chemistry Department or of Cambridge University Chemistry Department or by MEDAC Services, Brunel University. Melting points were performed on a Reichert hot stage apparatus and are uncorrected.

(2*R*)-(−)-3-(Benzyloxy)-2-methylpropan-1-ol 9

A solution of (2*R*)-methyl 3-hydroxy-2-methylpropanoate (100 g, 0.848 mol), dihydropyran (108 ml, 1.18 mol) and pyridinium *p*-toluenesulfonate (12 g, 0.06 mol) in dichloromethane (500 cm^3) was stirred at room temperature for 16 hours. The solution was poured into saturated aqueous $NaHCO_3$ (100 cm^3) and dichloromethane (300 cm^3). The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness. The product was used without any further purification.

Lithium aluminium hydride (26.8 g, 0.71 mol) was suspended in ether (300 cm^3) and cooled to 0 °C. The crude ester in ether (200 cm^3) was added dropwise over 1 hour at 0 °C. The mixture was allowed to warm to room temperature and stirred for a further 4 hours. The reaction was cooled to 0 °C and quenched by the careful addition of water (25 cm^3), 2 M aqueous sodium hydroxide (25 cm^3) and water (75 cm^3). The resulting mixture was stirred at room temperature for 30 minutes and filtered. The solids were repeatedly washed with ether and the combined filtrates evaporated to dryness, to yield the crude *THP alcohol* (145 g, 0.83 mmol).

Potassium *tert*-butoxide (112 g, 1 mol) was dissolved in THF (200 cm^3) and cooled to 0 °C. A solution of the crude THP alcohol (~145 g, 0.83 mmol) in THF (300 cm^3) was added and



Scheme 7 *Reagents*: a) KHMDS, toluene, 67%; b) $LiBH_4$, THF, 19% of **50** and 58% of **51**; c) TBSOTf, pyridine, THF, 91%; d) DIBAL-H, CH_2Cl_2, 79%; e) periodinane, CH_2Cl_2, 88%; f) morpholine, *p*-TSA, CH_2Cl_2, 85%

stirred for 40 minutes at 0 °C. Benzyl bromide (106 cm^3, 0.89 mol) was added slowly over 45 minutes, the mixture was allowed to warm to room temperature and stirred for 16 hours. The reaction was quenched by the addition of water (500 cm^3), then extracted with ether (4 × 150 cm^3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness. The crude residue was dissolved in methanol (400 cm^3) and Amberlite-120 acidic ion-exchange resin (200 g) added. The mixture was stirred vigorously at room temperature for 16 hours, filtered and the resin washed several times with methanol and ethyl acetate. The combined filtrates were evaporated to dryness. Chromatography of the residue on silica gel (50% ether–petrol) yielded the *alcohol* **9** (140 g, 90%) as a pale yellow oil (Found: C, 73.05; H, 9.07. $C_{11}H_{16}O_2C$

requires C,73.30; H, 8.95%); $[\alpha]_D^{23}$ +15 (*c* 3.8 in $CHCl_3$), {lit.[25] $[\alpha]_D^{23}$ −12.9 (*c* 3.44 in $CHCl_3$, enantiomer)}; ν_{max}(thin film)/cm^{-1} 3404, 2957, 1494, 1362, 1309, 1096, 1040, 737 and 698; δ_H(270 MHz; $CDCl_3$) 7.39–7.27 (5H, m, Ar*H*), 4.52 (2H, s, CH_2Ph), 3.64–3.59 (3H, m, 1-H_2, 3-H), 3.46 (1H, dd, *J* 9.0 and 8.0, 3-H), 2.50 (br s, OH), 2.14–2.04 (1H, m, 2-H), 0.88 (3H, d, *J* 7.1, 2-Me); *m*/*z* (EI) 180 (M^+), 162 ($M^+ - H_2O$), 91 ($C_7H_7^+$) and 89 ($M^+ - C_7H_7$).

(2*S*)-3-(Benzyloxy)-2-methyl-1-(toluene-*p*-sulfonyl)propane 10

The alcohol **9** (22.54 g, 125 mmol) was dissolved in pyridine (200 cm^3) and cooled to 0 °C, toluene-*p*-sulfonyl chloride (47.68 g, 250 mmol) was added portionwise and the reaction mixture was then stirred for 48 hours. The mixture was concentrated *in vacuo* and dissolved in ether (1000 cm^3). The organics were washed with aqueous sodium hydrogen carbonate, 1 M hydrochloric acid, water and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 20% ether–petrol) to give *tosylate* **10** (38.34 g, 88%) (Found: C, 65.04; H, 6.83. $C_{18}H_{22}O_4S$ requires C, 64.65; H, 6.63%); $[\alpha]_D^{20}$ +34.8 (*c* 1.80 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3062, 3030, 2963, 2861, 1922, 1810, 1598, 1494, 1451, 1361, 1307, 1292, 1258, 1210, 1177, 1098, 1019, 978, 815, 792, 738, 699 and 666; δ_H(270 MHz; $CDCl_3$) 7.78 (2H, d, *J* 8.5, OTsH), 7.29 (7H, m, Ph, OTs), 4.40 (2H, s, PhCH_2O), 4.04 (1H, dd, *J* 9.3 and 5.9, 1-H_1), 3.99 (1H, dd, *J* 9.4 and 5.9, 1-H_1), 3.34 (2H, m, 3-H_2), 2.41 (3H, s, Ph*Me*), 2.10 (1H, m, 2-H), 0.94 (3H, d, *J* 6.8, 2-Me); *m*/*z* (EI) 334 (M^+), 243 ($M^+ - C_7H_7$) and 91 ($C_7H_7^+$).

(7*R*)-8-(Benzyloxy)-7-methyloct-1-ene 11

5-Bromopent-1-ene (23.47 g, 156 mmol) in THF (50 cm^3) was added *via* cannula to a mixture of magnesium turnings (4.6 g, 189 mmol) and 1,2-dibromoethane (1 drop). After the reaction had commenced the mixture was heated under reflux for 1 hour. After cooling, the Grignard reagent was added *via* cannula to the tosylate **10** (36.81 g, 105 mmol) at −78 °C, followed by lithium tetrachlorocuprate (8.02 cm^3, 0.82 mmol), then allowed to warm to room temperature and stirred overnight. The mixture was poured into dilute sulfuric acid (125 cm^3 of a 1 M aqueous solution) and ether (1500 cm^3). The organic layer was separated and washed with water and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 1.5% ether–petrol) to give *alkene* **11** (22.63 g, 93%) (Found: C, 82.59; H, 10.63. $C_{16}H_{24}O$ requires C, 82.70; H, 10.41%); $[\alpha]_D^{20}$ −2.9 (neat); ν_{max}(thin film)/cm^{-1} 3067, 3030, 2927, 2854, 1639, 1494, 1451, 1362, 1307, 1204, 1100, 1029, 993, 910, 734 and 697; δ_H(270 MHz; $CDCl_3$) 7.31 (5H, m, PhH), 5.79 (1H, m, 2-H), 4.98 (2H, m, 1-H_2), 4.49 (2H, s, PhCH_2O), 3.32 (1H, dd, *J* 9.0 and 6.1, 8-H_1), 3.26 (1H, dd, *J* 9.0 and 6.6, 8-H_1), 1.74 (1H, m, 7-H), 2.05 (2H, m, 3-H_2), 1.28 (6H, m, 4-H_2, 5-H_2 and 6-H_2), 0.92 (3H, d, *J* 6.6, 7-Me); *m*/*z* (EI) 232 (M^+), 214 ($M^+ - H_2O$), 199 ($M^+ - H_2O$ − Me), 141 ($M^+ - C_7H_7$) and 91 ($C_7H_7^+$).

(6*R*)-7-(Benzyloxy)-6-methylheptanal 12

Alkene **11** (21.14 g, 91 mmol) in dichloromethane (500 cm^3) was cooled to −78 °C, and ozone (50 l h^{-1}, 115 V) passed through until the reaction was complete by TLC. Triphenylphosphine (23.86 g, 91 mmol) was added and the mixture then allowed to warm to room temperature and stirred for 16 hours. The mixture was concentrated *in vacuo* then triturated with petrol (100 cm^3), filtered and the filtrate concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 20% ether–petrol) to give *aldehyde* **12** (15.1 g, 71%) (Found: C, 82.59; H, 10.63. $C_{16}H_{24}O$ requires C, 82.70; H, 10.41%); $[\alpha]_D^{20}$ +35.0 (neat); ν_{max}(thin film)/cm^{-1} 3067, 3030, 2926, 2858, 2717, 1726, 1497, 1453, 1410, 1389, 1364, 1206, 1099, 1029, 737, 698 and 644; δ_H(270 MHz; $CDCl_3$) 9.75 (1H, t, *J* 2.0, 1-H), 7.35 (5H, m, PhH), 4.49 (2H, s, PhCH_2O), 3.28 (2H, m, 7-H_2), 2.41 (2H, dt, *J* 7.3 and 2.0, 2-H_2), 1.46 (7H, m, 3-H_2, 4-H_2, 5-H_2 and 6-H), 0.92 (3H, d, *J* 6.8, 6-Me); *m*/*z* (EI) 234 (M^+), 191 ($M^+ - C_3H_7$) and 91 ($C_7H_7^+$).

(2*E*,7*R*)-Diethyl 1-ethoxycarbonyl-8-benzyloxy-7-methylnon-2-enylphosphonate 13a and (1*E*,7*R*)-diethyl 1-ethoxycarbonyl-8-benzyloxy-7-methylnon-1-enylphosphonate 13b

Aldehyde **12** (13.85 g, 59 mmol) was dissolved in THF (50 cm^3) and added to titanium tetrachloride (22.43 g, 118 mmol) in THF (400 cm^3) at 5 °C, followed by triethylphosphonoacetate (11.7 cm^3, 50 mmol), and *N*-methylmorpholine (26 cm^3, 236 mmol). The mixture was stirred for 4.5 hours, water was then added (100 cm^3), stirred vigorously for 15 minutes, and the mixture poured into ether (300 cm^3). The organics were washed with water, aqueous sodium hydrogen carbonate and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a 4 : 1 mixture of allylic to vinylic phosphonates. The residue was purified by chromatography (SiO_2, 20% acetone–petrol) to give *allylic* and *vinylic benzylphosphonates* **13a** and **13b** (23.27 g, 90%) (Found: C, 62.88; H, 8.49. $C_{23}H_{37}O_6$ requires C, 62.70; H, 8.47%); ν_{max}(thin film)/cm^{-1} 2978, 2930, 2857, 1733, 1617, 1451, 1389, 1368, 1257, 1147, 1097, 1027, 969, 740 and 699; δ_H(270 MHz; $CDCl_3$) *Allylic* **13a**: 7.35 (5H, m, PhH), 5.64 (2H, m, 2-H and 3-H), 4.48 (2H, s, PhCH_2O), 4.17 [6H, m, (OCH_2Me) × 3], 3.30 (1H, m, 8-H_1), 3.23 (1H, m, 8-H_1), 2.06 (2H, m, 4-H_2), 1.50 [14H, m, 5-H_2, 6-H_2, 7-H and (OCH_2CH_3) × 3], 0.91 (3H, d, *J* 6.7, 7-Me); *Vinylic* **13b**: 7.35 (5H, m, PhH), 7.10 (1H, dt, *J* 23.0 and 7.5, 2-H), 4.48 (2H, s, PhCH_2O), 4.17 [6H, m, (OCH_2Me) × 3], 3.30 (1H, m, 8-H_1), 3.23 (1H, m, 8-H_1) 2.50 (2H, ddd, *J* 14.9, 7.5 and 3.1, 3-H_2), 1.50 [16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H and (OCH_2CH_3) × 3], 0.90 (3H, d, *J* 6.7, 7-Me); *m*/*z* (EI) 440 (M^+), 395 (M^+ − OEt), 367 (M^+ − OEt − C_2H_4), 349 (M^+ − OEt − C_2H_4 − H_2O) and 91 ($C_7H_7^+$).

(2*E*,7*R*)-Diethyl 1-ethoxycarbonyl-8-hydroxy-7-methylnon-2-enylphosphonate 14a and (1*E*,7*R*)-diethyl 1-ethoxycarbonyl-8-hydroxy-7-methylnon-1-enylphosphonate 14b

Ammonia (200 cm^3) was redistilled from sodium under an argon atmosphere, a small amount of sodium added (200 mg) and then the benzylphosphonate **13** (10.82 g, 24.6 mmol) was added in ether (10 cm^3). Sodium was added until the solution remained slightly blue and the mixture was then stirred for 45 minutes. Solid ammonium chloride was added until the blue colour dissipated. The ammonia was evaporated and ether (200 cm^3) added. The organics were washed with water, and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 40% acetone–petrol) to give *hydroxyphosphonates* **14** (6.57 g, 77%) (Found: C, 54.55; H, 8.88. $C_{16}H_{30}O_6P$ requires C, 54.85; H, 8.92%); ν_{max}(thin film)/cm^{-1} 3427, 2929, 1734, 1443, 1368, 1149, 1025 and 973; δ_H(270 MHz; $CDCl_3$) *Allylic* **14a**: 5.64 (2H, m, 2-H and 3-H), 4.18 [6H, m, (OCH_2Me) × 3], 3.65 (1H, dd, *J* 23.9 and 8.8, 1-H), 3.43 (2H, m, 8-H_2), 2.10 (2H, m, 4-H_2), 1.67 (1H, br s, OH), 1.27 [14H, m, 5-H_2, 6-H_2, 7-H and (OCH_2CH_3) × 3], 0.89 (3H, d, *J* 6.8, 7-Me); *Vinylic* **14b**: δ_H(270 MHz; $CDCl_3$) 7.10 (1H, dt, *J* 23.4 and 8.1, 2-H), 4.18 [6H, m, (OCH_2Me) × 3], 3.43 (2H, m, 8-H_2), 2.48 (2H, ddd, *J* 10.1, 8.1 and 3.2, 3-H_2), 1.67 (1H, br s, OH), 1.27 [16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H and (OCH_2CH_3) × 3], 0.89 (3H, d, *J* 6.8, 7-Me); *m*/*z* (EI) 350 (M^+), 320 ($M^+ - CH_2O$), 305 (M^+ − OEt) and 277 (M^+ − OEt − C_2H_4).

(2*E*,7*R*)-Diethyl 1-ethoxycarbonyl-8-trimethylsilyloxy-7-methylnon-2-enylphosphonate 6 and (1*E*,7*R*)-diethyl 1-ethoxycarbonyl-8-trimethylsilyloxy-7-methylnon-1-enylphosphonate

Triethylamine (4.5 cm^3) and chlorotrimethylsilane (1.5 cm^3) were mixed in a dry centrifuge tube and centrifuged for 10 minutes. The solution (3 cm^3) was added to the alcohol **14** (1.86 g, 5.3 mmol) in dichloromethane (20 cm^3) at 0 °C. The mixture was poured onto water (20 cm^3) and extracted into dichloro-

methane (3 × 75 cm^3). The organics were washed with water, aqueous sodium hydrogen carbonate, and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, ether) to give *silyloxyphosphonate* **6** (2 g, 98%) (Found: C, 53.86; H, 9.41. $C_{19}H_{39}O_6PSi$ requires C, 54.00; H, 9.30%); ν_{max}(thin film)/cm^{-1} 3433, 2926, 2855, 1723, 1461, 1388, 1369, 1251, 1028, 970, 876, 841, 797 and 748; δ_H(270 Hz; $CDCl_3$) *Allylic*: 5.64 (2H, m, 2-H and 3-H), 4.18 [6H, m, (OCH_2Me) × 3], 3.67 (1H, dd, *J* 23.6 and 9.2, 1-H), 3.35 (2H, m, 8-H_2), 2.06 (2H, m, 4-H_2), 1.30 (5H, m, 5-H_2, 6-H_2 and 7-H), 1.36 [9H, m, (OCH$_2$CH_3) × 3], 0.85 (3H, d, *J* 6.7, 7-Me); *Vinylic*: 7.10 (1H, dt, *J* 23.0 and 7.5, 2-H), 4.18 [6H, m, (OCH_2Me) × 3], 3.35 (2H, m, 8-H_2), 2.46 (2H, ddd, *J* 15.0, 7.5 and 3.0, 3-H_2), 1.30 (7H, m, 4-H_2, 5-H_2, 6-H_2 and 7-H), 1.36 [9H, m, (OCH$_2$CH_3) × 3], 0.84 (3H, d, *J* 6.7, 7-Me); *m*/*z* (EI) 422 (M$^+$), 407, 392, 377, 349, 335, 250, 224, 149, 103, 75 and 73.

(*S*)-3-(Benzyloxy)-1-bromo-2-methylpropane 15

A solution of *N*-bromosuccinimide (19.75 g, 0.111 mol) in dichloromethane (100 cm^3) was added to the alcohol **9** (20 g, 0.110 mol) and triphenylphosphine (29.1 g, 0.110 mol) in dichloromethane (200 cm^3) at a rate sufficient to maintain the internal temperature at 20 °C. The mixture was stirred for 1.5 hours then concentrated *in vacuo*. The residue was dissolved in ether (450 cm^3), washed with water, and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was titurated with petrol, the solid filtered and the filtrate concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 5% ether–petrol) to give *bromide* **15** (24 g, 89%) as a colourless oil (Found: C, 54.30; H, 6.22. $C_{11}H_{15}OBr$ requires C, 54.43; H, 6.22%); $[\alpha]_D^{20}$ +12.3 (*c* 1.00 in EtOH); ν_{max}(thin film)/cm^{-1} 2962, 2858, 1493, 1450, 1361, 1333, 1254, 1231, 1098, 1027, 736 and 697; δ_H(500 MHz; $CDCl_3$) 7.34 (5H, m, PhH), 4.53 (2H, s, PhCH_2O), 3.53 (2H, m, 1-H_1, 3-H_1), 3.43 (2H, m, 1-H_1, 3-H_1), 2.13 (1H, m, 2-H), 1.04 (3H, d, *J* 6.8, 2-Me).

(5*R*)-Dimethyl 6-(benzyloxy)-5-methyl-2-oxohexyl phosphonate 7

A solution of dimethyl (2-oxopropyl)phosphonate (18.02 g, 109 mmol) in THF (10 cm^3) was added *via* cannula to sodium hydride (4.55 g, 109 mmol, 60% dispersion in oil) and stirred for 1.5 hours. *n*-Butyllithium (43.4 cm^3, 109 mmol) was added *via* cannula and the mixture stirred for 20 minutes. Bromide **15** (24 g, 99 mmol) in THF (20 cm^3) was added *via* cannula then stirred for 45 minutes. The mixture was poured into 5% hydrochloric acid solution (105 cm^3) and ether (1050 cm^3). The organic layer was removed and washed with water, brine, and dried ($MgSO_4$), then concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, ether then 40% acetone–petrol) to give starting material (6.65 g) and *keto phosphonate* **7** (14.62 g, 71%) (Found: C, 57.34; H, 7.81. $C_{16}H_{25}OP\cdot 1/2\ H_2O$ requires C, 56.97; H, 7.77%); $[\alpha]_D^{20}$ −1.5 (*c* 2.67 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3027, 2925, 2853, 2239, 1710, 1494, 1403, 1366, 1262, 1184, 1033, 813, 739 and 700; δ_H(500 MHz; $CDCl_3$) 7.30 (5H, m, PhH), 4.47 (2H, s, PhCH_2O), 3.75 [6H, d, *J* 11.2, P(OMe)$_2$], 3.28 (2H, d, *J* 5.5, 6-H_2), 3.05 (2H, d, *J* 22.7, 1-H_2), 2.63 (2H, m, 3-H_2), 1.59 (3H, m, 4-H_2, 5-H), *m*/*z* (EI) 324 (M$^+$), 219 [M$^+$ − P(O)(OMe)$_2$].

(2*S*,3*R*,4*S*)-(−)-1-(Benzyloxy)-2,4-dimethylhex-5-en-3-ol 16

Dichloromethane (300 cm^3) was cooled to −78 °C under an argon atmosphere. DMSO (20 cm^3, 0.28 mol) was added, followed by the dropwise addition of oxalyl chloride (15 cm^3, 0.17 mol). Stirring was continued for 10 minutes at −78 °C, then a solution of the alcohol **9** (20 g, 0.11 mol) in dichloromethane (100 cm^3) was added by cannula. The mixture was stirred at −78 °C for 1 hour, then triethylamine (40 cm^3, 0.32 mol) was added. After stirring at −78 °C for 15 minutes, the mixture was allowed to warm to room temperature and diluted with ether (600 cm^3), washed with 2% aqueous $KHSO_4$ (200 cm^3), water (200 cm^3) and brine (200 cm^3). The mixture was dried ($MgSO_4$), filtered and evaporated to dryness. The resulting yellow oil was passed down a pad of florisil, eluting with ether. The crude aldehyde was used without any further purification.

cis-Butene (40 cm^3) was condensed into a measuring cylinder at −78 °C and transferred by cannula into a stirred solution of potassium *tert*-butoxide (15.6 g, 0.14 mol) in THF (250 cm^3) at −78 °C. *n*-Butyllithium (2.5 M in hexanes, 60 cm^3, 0.14 mol) was added dropwise and the mixture was warmed to −45 °C for 10 minutes. The solution was recooled to −78 °C, before adding (+)-*B*-methoxydiisopinocampheylborane (53 g, 0.16 mol) in ether (100 cm^3) by cannula. Stirring was continued for 45 minutes, then the mixture was cooled to −90 °C. Boron trifluoride–diethyl ether (25 cm^3, 0.2 mol) was added, followed immediately by a pre-cooled (−78 °C) solution of the crude aldehyde in ether (100 cm^3). Stirring was continued at −90 °C for 16 hours. The reaction mixture was allowed to warm to room temperature, 3 M aqueous sodium hydroxide (250 cm^3) added, then the mixture heated to a gentle reflux before adding 30% aqueous hydrogen peroxide (80 cm^3) dropwise. The resulting mixture was heated under reflux for 5 hours, cooled to room temperature and the organic phase separated and washed with saturated aqueous Na_2SO_3. The combined aqueous phases were extracted with ethyl acetate (4 × 150 cm^3) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. Repeated chromatography of the residue on silica gel (10–20% ether–petrol) yielded the *alkene* **16** (18 g, 70%) as a colourless oil (Found: C, 77.15; H, 9.53. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%); $[\alpha]_D^{20}$ −21.4 (*c* 4.7 in MeOH) {lit.,[26] $[\alpha]_D^{20}$ −17.5 *c* 4.7 in MeOH, (95:5 mixture)}; ν_{max}(thin film)/cm^{-1} 3478, 3029, 2960, 1636, 1498, 1206, 1028 and 698; δ_H(500 MHz; $CDCl_3$) 7.39–7.27 (5H, m, Ar*H*), 5.83 (1H, ddd, *J* 17.1, 10.6 and 7.3, 5-H), 5.05 (1H, dd, *J* 16.9 and 4.2, 6-H *trans*), 5.02 (1H, dd, *J* 9.0 and 4.2, 6-H *cis*), 4.51 (2H, s, CH_2Ph), 3.64 (1H, dd, *J* 9.1 and 4.2, 1-H), 3.48 (1H, dd, *J* 9.1 and 6.2, 1-H), 3.40 (1H, m, 3-H), 3.17 (1H, d, *J* 4.3, OH), 2.33 (1H, m, 4-H), 1.92–1.97 (1H, m, 2-H), 1.04 (3H, d, *J* 6.8, 4-Me), 0.96 (3H, d, *J* 7.0, 2-Me); *m*/*z* (EI) 235 (MH$^+$), 234 (M$^+$), 179, 107 and 91 ($C_7H_7^+$) [Found (CI, NH_3) MH$^+$ 235.1698. $C_{15}H_{23}O_2$ requires 235.1698].

(3*S*,4*R*,5*S*)-(−)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3,5-dimethylhex-1-ene 17

tert-Butyldimethylsilyl triflate (16 cm^3, 68.6 mmol) was added over 30 minutes to a solution of the alcohol **16** (14.6 g, 62.4 mmol) and triethylamine (26 cm^3, 187 mmol) in dichloromethane (100 cm^3), cooled to −30 °C. The mixture was then stirred at −30 °C for a further 30 minutes, before being allowed to warm to room temperature. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (200 cm^3), extracted with ether (3 × 150 cm^3) and the combined organic solvents were dried ($MgSO_4$), filtered, and evaporated to dryness. Chromatography of the residue on silica gel (2% ether–petrol) yielded the *silyl ether* **17** (22.9 g, 100%) as a colourless oil (Found: C, 72.45; H, 10.50. $C_{21}H_{36}O_2Si$ requires C, 72.36; H, 10.41%); $[\alpha]_D^{20}$ −18.2 (*c* 2 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3066, 3023, 2956, 2853, 1948, 1600, 1470, 1305, 1096, 911 and 774 cm^1; δ_H(500 MHz; $CDCl_3$) 7.33–7.27 (5H, m, Ar*H*), 5.83–5.76 (1H, m, 2-H), 5.00–4.93 (2H, m, 1-H_2), 4.46 (1H, d, *J* 16, CH_2Ph), 4.44 (1H, d, *J* 16, CH_2Ph), 3.57 (1H, dd, *J* 9.2 and 4.8, 6-H), 3.50 (1H, t, *J* 5.1, 4-H), 3.26 (1H, dd, *J* 9.2 and 8.1, 6-H), 2.39–2.35 (1H, m, 3-H), 2.06–1.98 (1H, m, 5-H), 0.99 (3H, d, *J* 4.9, 3-Me), 0.97 (3H, d, *J* 4.8, 5-Me), 0.88 (9H, s, Bu^t), 0.03 (6H, s, $SiMe_2$); *m*/*z* (CI, NH_3) 349 (MH$^+$), 348 (M$^+$), 293 (M$^+$ − C_4H_7), 291 (M$^+$ − C_4H_9), 221, 199, 187 and 91 ($C_7H_7^+$) [Found (CI, NH_3) MH$^+$ 349.2563. $C_{21}H_{37}O_2Si$ requires 349.2563].

(3*S*,4*R*,5*S*)-(−)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3,5-dimethylhexan-1-ol 18

9-BBN (0.5 M in THF, 344 cm^3, 172 mmol) was added *via* cannula to a solution of the alkene **17** (20 g, 57 mmol) in THF (100 cm^3), and the solution heated at reflux for 2 hours. The mixture was cooled to 0 °C, water (20 cm^3) added carefully, followed by 2 M NaOH (200 cm^3) and 30% aqueous H_2O_2 (80 cm^3). The reaction mixture was warmed to room temperature and stirred for 1 hour, then the organic phase was separated, and washed with saturated aqueous Na_2SO_3. The aqueous layers were combined, saturated with K_2CO_3 and extracted with ether (3 × 200 cm^3). The combined organic solvents were dried ($MgSO_4$), filtered, and evaporated to dryness. Chromatography of the residue on silica gel (40% ether–petrol) yielded the *alcohol* **18** (19.94 g, 95%) as a colourless oil (Found: C, 69.00; H, 10.53. $C_{21}H_{38}O_3Si$ requires C, 68.80; H, 10.45%); $[\alpha]_D^{20}$ −11.4 (*c* 1.76 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3379, 3063, 3030, 2954, 2244, 1493, 1379, 1203, 1095, 909 and 773; δ_H(500 MHz; $CDCl_3$) 7.33–7.27 (5H, m, Ar*H*), 4.47 (1H, d, *J* 12.1, CH_2Ph), 4.44 (1H, d, *J* 12.0, CH_2Ph), 3.72–3.67 (1H, m, 1-H), 3.66–3.60 (1H, m, 1-H), 3.53–3.59 (2H, m, 4-H, 6-H), 3.29 (1H, dd, *J* 9.2 and 7.2, 6-H), 2.04–1.99 (1H, m, 5-H), 1.83–1.76 (1H, m, 2-H), 1.66 (1H, sept, *J* 6.5, 3-H), 1.59 (1H, t, *J* 5.5, OH), 1.46–1.39 (1H, m, 2-H), 0.97 (3H, d, *J* 7.0, 5-Me), 0.89 (3H, d, *J* 7.0, 3-Me), 0.88 (9H, s, Bu^t), 0.04 (3H, s, SiMe), 0.03 (3H, s, SiMe); *m*/*z* (EI) 309 ($M^+ - C_4H_9$), 293, 217, 201, 187 and 91 ($C_7H_7^+$) [Found (EI) $M^+ - C_4H_9$ 309.1866. $C_{17}H_{29}O_3Si$ requires 309.1886].

(3*S*,4*R*,5*S*)-(−)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-3,5-dimethylhexanal 19

Oxalyl chloride (6.84 cm^3, 76.6 mmol) was added slowly to a solution of dimethyl sulfoxide (11 cm^3, 153 mmol) in dichloromethane (500 cm^3) at −78 °C. The mixture was stirred at −78 °C for 10 minutes, then the alcohol **18** (14 g, 38.3 mmol) in dichloromethane (50 cm^3) was added. After stirring at −78 °C for 1 hour, triethylamine (27 cm^3, 192 mmol) was added and the temperature was maintained at −78 °C for 15 minutes before allowing the mixture to warm to room temperature. The reaction mixture was diluted with ether (600 cm^3), the organic phase separated, and washed with 2% aqueous $KHSO_4$, dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography of the residue on silica gel (10% ether–petrol) yielded the *aldehyde* **19** (11.7 g, 85%) as a colourless oil; $[\alpha]_D^{20}$ −2.9 (*c* 1.87 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3029, 2954, 2882, 1723, 1459, 1380, 1252, 1095, 836 and 774; δ_H(500 MHz; $CDCl_3$) 9.72 (1H, t, *J* 1.8, 1-H), 7.33–7.27 (5H, m, Ar*H*), 4.49 (1H, d, *J* 12.0, CH_2Ph), 4.44 (1H, d, *J* 12.0, CH_2Ph), 3.56–3.52 (2H, m, 4-H, 6-H), 3.27 (1H, dd, *J* 9.1 and 7.1, 6-H), 2.55–2.50 (1H, m, 2-H), 2.33–2.27 (2H, m, 2-H, 5-H), 1.97–1.91 (1H, m, 3-H), 0.99 (3H, d, *J* 7.0, 5-Me), 0.92 (3H, d, *J* 6.6, 3-Me), 0.88 (9H, s, Bu^t), 0.04 (3H, s, SiMe), 0.03 (3H, s, SiMe); *m*/*z* (EI) 365 (MH^+), 307 ($M^+ - C_4H_9$), 293 ($M^+ - C_4H_7O$), 263, 215, 199, 149 and 91 ($C_7H_7^+$) [Found (CI, NH_3) MH^+ 365.2512. $C_{21}H_{37}O_3Si$ requires 365.2512].

(2*E*,5*S*,6*R*,7*S*)-(−)-Ethyl 8-(benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-5,7-dimethyloct-2-enoate 20

Triethylphosphonoacetate (9 cm^3, 45 mmol) was added to a suspension of lithium chloride (1.9 g, 45 mmol) in acetonitrile (250 cm^3), followed by diisopropylethylamine (8 cm^3, 45 mmol). The suspension was stirred for 15 minutes, then the aldehyde **19** (11.7 g, 32 mmol) in acetonitrile (50 cm^3) was added. The reaction mixture was stirred for 20 hours, then poured into saturated aqueous $NaHCO_3$ and ether. The organic phase was separated and the aqueous phase extracted with ether (3 × 200 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography of the residue on silica gel (7% ether–petrol) yielded the *ester* **20** (12.95 g, 93%) as a colourless oil (Found: C, 69.03; H, 9.88. $C_{25}H_{42}O_4Si$ requires C, 69.08; H, 9.74%); $[\alpha]_D^{20}$ −6.0 (*c* 2.0 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3029, 2930, 1718, 1649, 1459, 1256, 1096, 982 and 774; δ_H(500 MHz; $CDCl_3$) 7.33–7.27 (5H, m, Ar*H*), 6.95–6.87 (1H, m, 3-H), 5.78 (1H, dt, *J* 15.6 and 1.4, 2-H), 4.49 (1H, d, *J* 12.1, CH_2Ph), 4.44 (1H, d, *J* 12.1, CH_2Ph), 4.16 (2H, q, *J* 7.2, 1′-H_2), 3.53 (1H, dd, *J* 6.0 and 3.0, 6-H), 3.50 (1H, dd, *J* 9.1 and 4.8, 8-H), 3.27 (1H, dd, *J* 9.1 and 7.3, 8-H), 2.31–2.26 (1H, m, 7-H), 2.11–2.06 (1H, m, 4-H), 2.02–1.93 (1H, m, 4-H), 1.85–1.77 (1H, m, 5-H), 1.28 (3H, t, *J* 7.1, 2′-Me), 0.97 (3H, d, *J* 6.9, 7-Me), 0.89 (9H, s, Bu^t), 0.85 (3H, d, *J* 6.8, 5-Me), 0.04 (3H, s, SiMe), 0.03 (3H, s, SiMe); *m*/*z* (EI) 389 ($M^+ - C_2H_5O$), 377 ($M^+ - C_4H_9$), 293, 285, 187, 145 and 91 ($C_7H_7^+$) [Found (EI) $M^+ - C_4H_9$ 377.2148. $C_{21}H_{33}O_4Si$ requires 377.2148].

(2*E*,5*S*,6*R*,7*S*)-(−)-8-(Benzyloxy)-6-(*tert*-butyldimethylsilyloxy)-5,7-dimethyloct-2-en-1-ol 21

DIBAL-H (1.5 M in toluene, 40 cm^3, 58 mmol) was added to the ester **20** (10.5 g, 24 mmol) in THF (100 cm^3) at −78 °C. The reaction mixture was stirred at −78 °C for 2 hours, then quenched by the addition of water (2 cm^3), maintained at −78 °C for 15 minutes and saturated aqueous Na_2SO_4 was added. The mixture was allowed to warm to room temperature (CARE: exothermic at 20 °C, required recooling and stirred at −40 °C for an additional 30 minutes), the resulting gel broken up and solid Na_2SO_4 added. The mixture was filtered and the solids rinsed several times with ethyl acetate. The combined solvents were evaporated to dryness. Chromatography of the residue on silica gel (30% ether–petrol) yielded the *allylic alcohol* **21** (9.2 g, 97%) as a colourless oil (Found: C, 70.34; H, 10.37. $C_{23}H_{40}O_3Si$ requires C, 70.36; H, 10.27%); $[\alpha]_D^{20}$ −6.2 (*c* 1.9 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3343, 3086, 3062, 3026, 2929, 2854, 1803, 1604, 1405, 1379, 1204, 1096, 1027 and 836; δ_H(500 MHz; $CDCl_3$) 7.33–7.27 (5H, m, Ar*H*), 5.64–5.62 (2H, m, 2-H, 3-H), 4.49 (1H, d, *J* 12.0, CH_2Ph), 4.45 (1H, d, *J* 12.0, CH_2Ph), 4.08–4.06 (2H, m, 1-H_2), 3.56–3.52 (2H, m, 6-H, 8-H), 3.27 (1H, dd, *J* 9.2 and 7.4, 8-H), 2.18–2.11 (1H, m, 4-H), 2.01–1.96 (1H, m, 7-H), 1.95–1.88 (1H, m, 4-H), 1.73–1.65 (1H, m, 5-H), 1.23 (1H, t, *J* 5.9, OH), 0.96 (3H, d, *J* 7.0, 7-Me), 0.89 (9H, s, Bu^t), 0.85 (3H, d, *J* 6.8, 5-Me), 0.04 (3H, s, SiMe), 0.03 (3H, s, SiMe); *m*/*z* (EI) 392 (M^+), 335 ($M^+ - C_4H_9$), 317 ($M^+ - C_4H_9$-H_2O), 293, 243, 187, 145, 115 and 91 ($C_7H_7^+$) [Found (EI) M^+ 392.2747. $C_{23}H_{40}O_3Si$ requires 392.2747].

(2*S*,2′*S*,3′*R*,3*S*,4′*S*)-(−)-2-[5′-(Benzyloxy)-3′-(*tert*-butyldimethylsilyloxy)-2′,4′-dimethylpentyl]-3-(hydroxymethyl)-oxirane 22

L-(+)-Diethyl tartrate (880 mg, 4.2 mmol) in dichloromethane (10 cm^3) was added to a slurry of activated powdered 4 Å molecular sieves (1 g) in dichloromethane (50 cm^3) at −20 °C, followed by a solution of titanium(IV) isopropoxide (1.1 cm^3 in 2.0 cm^3 of dichloromethane, 3.5 mmol). *tert*-Butylhydroperoxide (3.0 M in isooctane, 19.8 cm^3, 57.2 mmol) was added dropwise and the reaction mixture was stirred at −20 °C for 30 minutes before the allylic alcohol **21** (11 g, 27.94 mmol, dried over 4 Å molecular sieves) in dichloromethane (20 cm^3) was added. The reaction was stirred at −20 °C for 3.5 hours, then quenched by the addition of citric acid monohydrate (300 mg) dissolved in 10% acetone–ether (100 cm^3). The mixture was allowed to warm to room temperature, stirred for 20 minutes, and then filtered through Celite, washed with dichloromethane (3 × 100 cm^3), and the combined organic solvents were evaporated to dryness. Chromatography of the residue on silica gel (40% ether–petrol) yielded the *epoxide* **22** (9.1 g, 80%) as a colourless oil (Found: C, 67.39; H, 9.88. $C_{23}H_{40}O_4Si$ requires C, 67.60; H, 9.87%); $[\alpha]_D^{20}$ −22.3 (*c* 1.4 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3434, 2928, 1459, 1360, 1253, 1094, 903, 837 and 698; δ_H(500 MHz; $CDCl_3$) 7.33–7.27 (5H, m, Ar*H*), 4.51 (1H, d, *J* 12.0, CH_2Ph), 4.46 (1H, d, *J* 12.0, CH_2Ph), 3.86 (1H, ddd, *J* 12.6, 5.7 and 2.7, 1″-H), 3.64 (1H, ddd, *J* 12.3, 8.1 and 4.9, 1″-H), 3.56–3.51 (2H, m, 5′-H_2), 3.29 (1H, dd, *J* 9.1 and 7.4, 3′-H), 2.96–2.93 (1H, m, 2-H), 2.89–2.84 (1H, m, 3-H), 1.99–

1.95 (1H, m, 4′-H), 1.90–1.86 (1H, m, 2′-H), 1.70–1.63 (2H, m, OH, 1′-H), 1.40 (1H, ddd, *J* 15.6, 9.9 and 5.7, 1′-H), 0.97 (3H, d, *J* 7.0, 4′-Me), 0.93 (3H, d, *J* 6.8, 2′-Me), 0.88 (9H, s, Bu^t), 0.03 (6H, s, $SiMe_2$); *m*/*z* (EI) 351 ($M^+ - C_4H_9$), 293 ($M^+ - C_6H_{15}Si$), 259, 215, 199 and 91 ($C_7H_7^+$) [Found (EI) $M^+ - C_4H_9$ 351.1992. $C_{19}H_{31}O_4Si$ requires 351.1992].

(1*S*,1″*S*,2′*R*,4′*S*,5′*R*)-(−)-1-[Tetrahydro-5′-(2″-benzyloxy-1″-methylethyl)-4′-methylfuran-2′-yl]ethane-1,2-diol 23

TBAF (40 cm^3, 1 M in THF) was added to a solution of the epoxide **22** (9.0 g, 22 mmol) in THF (40 cm^3). The mixture was heated at 60 °C for 4 hours, cooled to room temperature, diluted with dichloromethane (200 cm^3) and washed with brine (50 cm^3). The organic phase was dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography of the residue on silica gel (75% ethyl acetate–petrol) yielded the *diol* **23** (5.5 g, 85%) as a colourless oil (Found: C, 69.27; H, 8.92. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90%); $[\alpha]_D^{20}$ −5.0 (*c* 1.2 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3290, 2919, 2833, 1449, 1361, 1282 and 1102; δ_H(270 MHz; $CDCl_3$) 7.34–7.26 (5H, m, Ar*H*), 4.53 (1H, d, *J* 12.0, CH_2Ph), 4.49 (1H, d, *J* 12.2, CH_2Ph), 4.11–4.04 (1H, m, 2′-H), 3.68–3.63 (4H, m, 1-H, 2-H_2, 5′-H), 3.61 (1H, dd, *J* 8.5 and 3.6, 2″-H), 3.43 (1H, dd, *J* 8.8 and 6.6, 2″-H), 2.32–2.17 (3H, m, 2 × OH, 4′-H), 1.99–1.95 (1H, m, 3′-H_b), 1.85–1.82 (1H, m, 1″-H), 1.73 (1H, dd, *J* 12.5 and 6.6, 3′-H_a), 0.95 (3H, d, *J* 7.1, 1″-Me), 0.91 (3H, d, *J* 7.1, 4′-Me); *m*/*z* (EI) 295 (MH^+), 294 (M^+), 263, 257, 245, 233 and 91 ($C_7H_7^+$) [Found (EI) MH^+ 295.1910. $C_{17}H_{27}O_4$ requires 295.1909].

(1*S*,1″*S*,2′*R*,4′*S*,5′*R*)-(−)-1-[Tetrahydro-5′-(2″-benzyloxy-1″-methylethyl)-4′-methylfuran-2′-yl]-2-(toluene-*p*-sulfonyloxy)-ethanol 24

Dibutyltin oxide (2.4 g, 10 mmol) was added to a solution of the diol **23** (2.7 g, 9.2 mmol) in methanol (50 cm^3) and the resulting mixture was heated at reflux for 45 minutes. After cooling to room temperature, triethylamine (10 cm^3, 32 mmol) and toluene-*p*-sulfonyl chloride (11.8 g, 61 mmol) were added sequentially. The mixture was stirred at room temperature for 15 minutes, poured into saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3 × 100 cm^3). The combined organic solvents were dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography of the residue on silica gel (35–60% ether–petrol) yielded the *tosylate* **24** (3.9 g, 94%) as a colourless oil; $[\alpha]_D^{20}$ −19.3 (*c* 0.94 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3383, 2961, 1596, 1450, 1357, 1188 and 1176; δ_H(500 MHz; $CDCl_3$) 7.78 (2H, d, *J* 8.3, ArH), 7.35–7.26 (7H, m, Ar*H*), 4.54 (1H, d, *J* 12.1, CH_2Ph), 4.44 (1H, d, *J* 12.1, CH_2Ph), 4.19 (1H, dd, *J* 10.4 and 3.3, 2-H), 3.99 (1H, dd, *J* 10.4 and 6.8, 2-H), 3.93 (1H, ddd, *J* 15.9, 9.3 and 6.7, 2′-H), 3.77–3.72 (1H, m, 1-H), 3.57 (1H, dd, *J* 8.9 and 3.3, 2″-H), 3.53 (1H, dd, *J* 10.4 and 4.0, 5′-H), 3.34 (1H, dd, *J* 8.9 and 7.1, 2″-H), 2.44 (3H, s, *Me*Ar), 2.29–2.23 (1H, m, 4′-H), 2.16 (1H, br s, OH), 1.97 (1H, ddd, *J* 15.8, 9.4 and 6.5, 3′-H_b), 1.77–1.81 (1H, m, 1″-H), 1.73 (1H, dd, *J* 12.5 and 6.5, 3′-H_a), 0.94 (3H, d, *J* 6.7, 1″-Me), 0.87 (3H, d, *J* 7.1, 4′-Me); *m*/*z* (EI) 449 (MH^+), 448 (M^+), 357 ($M^+ - C_7H_7$), 342, 299, 245 and 91 ($C_7H_7^+$) [Found (EI) MH^+ 449.2000. $C_{24}H_{33}O_6S$ requires 449.2000].

(1*S*,1″*S*,2′*R*,4′*S*,5′*R*)-(−)-1-[Tetrahydro-5′-(2″-benzyloxy-1″-methylethyl)-4′-methylfuran-2′-yl]ethanol 25

A solution of the tosylate **24** (3.9 g, 8.71 mmol) in THF (20 cm^3) was added dropwise to Super Hydride (40 cm^3, 1 M in THF) at 0 °C. The mixture was stirred at room temperature for 6 hours and then quenched by careful addition of brine (50 cm^3). The solution was concentrated to half the original volume and diluted with dichloromethane (250 cm^3). The organic phase was washed with brine (2 × 50 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography of the residue on silica gel (50–60% ether–petrol) yielded the *alcohol* **25** (2.23 g, 92%) as a colourless oil (Found: C, 73.28; H, 9.40. $C_{17}H_{26}O_3$ requires C, 73.34; H, 9.41%); $[\alpha]_D^{20}$ −7.5 (*c* 1.4 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3389, 2962, 2929, 2872, 1450 and 1072; δ_H(500 MHz; $CDCl_3$) 7.31–7.17 (5H, m, Ar*H*), 4.52 (1H, d, *J* 12.2, CH_2Ph), 4.42 (1H, d, *J* 11.7, CH_2Ph), 3.93–3.80 (2H, m, 1-H, 2′-H), 3.63–3.52 (2H, m, 2″-H, 5′-H), 3.36 (1H, dd, *J* 8.8 and 6.8, 2″-H), 2.25–2.20 (1H, m, 4′-H), 1.98 (1H, ddd, *J* 16.1, 9.8 and 6.4, 3′-H_b), 1.84 (1H, d, *J* 2.9, OH), 1.80–1.74 (1H, m, 1″-H), 1.50 (1H, dd, *J* 11.7 and 5.9, 3′-H_a), 1.01 (3H, d, *J* 6.4, 1-Me), 0.88 (3H, d, *J* 6.4, 1″-Me), 0.85 (3H, d, *J* 6.8, 4′-Me); *m*/*z* (EI) 279 (MH^+), 278 (M^+), 235, 233 ($M^+ - C_2H_5O$), 191, 187 ($M^+ - C_7H_7$), 129 and 91 ($C_7H_7^+$) [Found (EI) MH^+ 279.1960. $C_{17}H_{27}O_3$ requires 279.1960].

(1′*S*,1″*S*,2*R*,3*S*,5*R*)-(−)-Tetrahydro-5-(1′-methoxyethyl)-3-methyl-2-(2″-benzyloxy-1″-methylethyl)furan 26

The secondary alcohol **25** (3.5 g, 12.5 mmol), in THF (30 cm^3), was added to a suspension of KH (30 g of a 35% dispersion in oil, 26 mmol), in THF (20 cm^3) at 0 °C. After 15 minutes, methyl iodide (4 cm^3, 64 mmol) was added and the mixture was allowed to warm to room temperature. Stirring was continued for 3 hours, before quenching with methanol (20 cm^3). The mixture was diluted with dichloromethane (300 cm^3), washed with brine (2 × 25 cm^3), the organic solvents were dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography of the residue on silica gel (10% ether–petrol) yielded the *methyl ether* **26** (3.3 g, 90%) as a colourless oil (Found: C, 73.80; H, 9.67. $C_{18}H_{28}O_3$ requires C, 73.93; H, 9.65%); $[\alpha]_D^{20}$ −7.5 (*c* 1.3 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3027, 2964, 2928, 2874, 2014, 1493, 1450, 1370 and 1240; δ_H(270 MHz; $CDCl_3$) 7.39–7.24 (5H, m, Ar*H*), 4.58 (1H, d, *J* 12.0, CH_2Ph), 4.49 (1H, d, *J* 11.9, CH_2Ph), 3.98 (1H, ddd, *J* 11.7, 6.6 and 5.1, 5-H), 3.7 (1H, dd, *J* 9.0 and 3.2, 2″-H), 3.58 (1H, dd, *J* 10.3 and 3.7, 2-H), 3.37 (3H, s, OMe), 3.40–3.27 (2H, m, 1′-H, 2″-H), 2.24–2.20 (1H, m, 3-H), 1.97–1.95 (1H, m, 4-H_b), 1.87–1.82 (1H, m, 1″-H), 1.66 (1H, dd, *J* 12.5 and 6.8, 4-H_a), 1.10 (3H, d, *J* 6.4, 1′-Me), 0.96 (3H, d, *J* 6.6, 1″-Me), 0.90 (3H, d, *J* 6.8, 3-Me); *m*/*z* (EI) 293 (MH^+), 292 (M^+), 260 (M^+ − MeOH), 242, 233 ($M^+ - C_3H_7O$), 201 ($M^+ - C_7H_7$) and 91 ($C_7H_7^+$) [Found (EI) MH^+ 293.2117. $C_{18}H_{29}O_3$ requires 293.2117].

(1″*S*,2*S*,2′*R*,3′*S*,5′*R*)-(+)-2-[Tetrahydro-5′-(1″-methoxyethyl)-3′-methylfuran-2′-yl]-2-methylethanol 27

10% Palladium on carbon (300 mg) was added to the benzyl ether **26** (1.6 g, 5.5 mmol) in methanol (20 cm^3), under an argon atmosphere, the mixture degassed and then stirred under a hydrogen atmosphere for 16 hours. The flask was flushed with argon, the catalyst removed by filtration, and the solvent evaporated to dryness. Chromatography of the residue on silica gel (60% ether–petrol) yielded the *alcohol* **27** (1.06 g, 95%) as a low melting solid (Found: C, 65.02; H, 10.75. $C_{11}H_{23}O_3$ requires C, 65.31; H, 10.96%); $[\alpha]_D^{20}$ +39.0 (*c* 0.9 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3452, 2965, 2877, 1459, 1374, 1150, 1090, 1009, 965, 894 and 800; δ_H(500 MHz; $CDCl_3$) 3.99 (1H, ddd, *J* 9.6, 6.6 and 4.9, 5′-H), 3.64 (1H, dd, *J* 10.1 and 4.0, 1-H), 3.61–3.53 (3H, m, 1-H, 2′-H, OH), 3.38 (3H, s, OMe), 3.37–3.32 (1H, m, 1″-H), 2.32–2.27 (1H, m, 3′-H), 1.97 (1H, ddd, *J* 12.5, 9.5 and 6.5, 4′-H_b), 1.88–1.82 (1H, m, 2-H), 1.65 (1H, dd, *J* 12.5 and 6.6, 4′-H_a), 1.09 (3H, d, *J* 6.4, 1″-Me), 0.92 (3H, d, *J* 7.1, 2-Me), 0.77 (3H, d, *J* 6.8, 3′-Me); *m*/*z* (EI) 203 (MH^+), 202 (M^+), 170 (M^+ − MeOH), 143 [M^+ − CH(Me)-OMe] and 59 ($C_3H_7O^+$) [Found (EI) MH^+ 203.1647. $C_{11}H_{23}O_3$ requires 203.1647; Found (EI) M^+ 202.1569. $C_{11}H_{22}O_3$ requires 202.1569].

(2*S*,3*S*,4*S*)-2,4-Dimethyl-1-[(1,1-dimethylethyl)diphenylsilyloxy]hex-5-en-3-ol 29

DMSO (3.4 cm^3, 3.75 g, 48 mmol) in dry dichloromethane (10 cm^3) was added dropwise to a stirred solution of oxalyl chloride (12 cm^3, 24 mmol, 2.0 M in dichloromethane) in dry dichloro-

methane (40 cm^3) at −60 °C under argon. The solution was stirred at −60 °C for 10 minutes then a solution of alcohol **28**[5f] (6.57 g, 20 mmol) in dry dichloromethane (40 cm^3) was added dropwise *via* a cannula. After stirring at −60 °C for a further 20 minutes, triethylamine (6.7 cm^3, 4.86 g, 48 mmol) was added and the mixture was allowed to warm to room temperature. The reaction mixture was quenched with excess 1% w/v aqueous $KHSO_4$ and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give crude (*S*)-3-[(1,1-dimethylethyl)diphenylsilyloxy]-2-methylpropanal.

Condensed *trans*-but-2-ene (7 cm^3) was added to a solution of freshly sublimed potassium *tert*-butoxide (2.8 g, 25 mmol) in dry THF (25 cm^3) at −78 °C. *n*-Butyllithium (10 cm^3, 2.5 M in hexanes, 25 mmol) was added dropwise at −78 °C, the solution stirred at −45 °C for 10 minutes, recooled to −78 °C and a solution of (−)-*B*-methoxydiisopinocamphenylborane (9.49 g, 30 mmol) in dry ether (30 cm^3) added. After stirring at −78 °C for 45 minutes boron trifluoride–diethyl ether (4.43 cm^3, 5.11 g, 36 mmol) was added, the mixture cooled to −85 °C and a solution of the crude (*S*)-3-[(1,1-dimethylethyl)-diphenylsilyloxy]-2-methylpropanal in ether (40 cm^3) was added. The mixture was stirred at −85 °C for a further 20 hours, allowed to warm to room temperature and then 3 M aqueous NaOH (18 cm^3) and 30% aqueous hydrogen peroxide (7.5 cm^3) were added. The reaction mixture was heated at reflux for 1 hour, cooled and carefully quenched with saturated aqueous Na_2SO_3. Saturated aqueous NaCl was added and the solution extracted with ether. The combined extracts were dried ($MgSO_4$), concentrated *in vacuo* and dissolved in dry ether (100 cm^3). Diethanolamine (3.2 cm^3, 3.47 g, 33 mmol) was added to this solution and the mixture stirred for 16 hours under argon. The mixture was filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography on silica gel (10–25% ether–petrol) afforded *alcohol* **29** (5.69 g, 74%) as a colourless oil (Found: C, 75.61; H, 9.16. $C_{24}H_{34}O_2Si$ requires C, 75.34; H, 8.96%); $[\alpha]_D^{20}$ +8.2 (*c* 1.02 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3506, 3070, 2960, 2930, 2858, 1638, 1589, 1461, 1427, 1388, 1112, 998, 823, 740 and 703; δ_H(270 MHz; $CDCl_3$) 7.48–7.35 (6H, m, *m*-H, *p*-H), 7.07–7.63 (4H, m, *o*-H), 5.82 (1H, ddd, *J* 17.8, 9.5 and 8.3, 5-H), 5.13–5.05 (2H, m, 6-H), 3.73–3.71 (2H, m, 1-H), 3.58 (1H, dt, *J* 8.3 and 2.6, 3-H), 2.40 (1H, d, *J* 2.6, OH), 2.33–2.23 (1H, m, 4-H), 1.88–1.75 (1H, m, 2-H), 1.06 (9H, s, Bu′), 0.95 (3H, d, *J* 6.8, CH_3), 0.94 (3H, d, *J* 6.8, CH_3); *m*/*z* (EI) 325 (M^+ − Bu′, 14%), 269, 229, 199 and 109.

(2*S*,3*S*,4*S*)-2,4-Dimethylhex-5-ene-1,3-diol 30

Tetrabutylammonium fluoride (3.3 cm^3, 1 M in THF, 3.3 mmol) was added in one portion to a stirred solution of silyl ether **29** (1.15 g, 3 mmol) in dry THF (1.5 cm^3) at room temperature under argon. The mixture was stirred at room temperature for 3 hours, transferred to a silica gel chromatography column and purified by flash column chromatography (1% methanol in 5–60% ether–petrol) to afford *diol* **30** (0.43 g, 100%) as a white solid (Found: C, 66.61; H, 11.35. $C_8H_{16}O_2$ requires C, 66.63; H, 11.18%); mp 43–44 °C; $[\alpha]_D^{20}$ +8.0 (*c* 1.00 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3437, 2970, 1636, 1459, 1380, 1240, 1099, 1025, 1002, 971, 925 and 681; δ_H(270 MHz; $CDCl_3$) 5.70 (1H, ddd, *J* 16.5, 10.9 and 8.8, 5-H), 5.20–5.10 (2H, m, 6-H), 3.74 (1H, dd, *J* 10.7 and 4.3, 1-H), 3.68 (1H, dd, *J* 10.7 and 5.5, 1-H), 3.49 (1H, dd, *J* 8.8 and 1.6, 3-H), 2.59 (1H, br s, OH), 2.25 (1H, tq, *J* 8.8 and 6.8, 4-H), 2.17 (1H, br s, OH), 1.90–1.80 (1H, m, 2-H), 0.96 (3H, d, *J* 6.8, CH_3), 0.95 (3H, d, *J* 7.1, CH_3); *m*/*z* (EI) (M^+ − $HOCH_2$, 2%), 109, 89, 71 and 56.

(2*S*,3*S*,4*S*)-(3-Hydroxy-2,4-dimethylhex-5-enyl) 2′,4′,6′-tris-(1-methylethyl)benzenesulfonate 31

A mixture of diol **30** (6.92 g, 48 mmol), 2,4,6-triisopropylbenzenesulfonyl chloride (16.1 g, 53 mmol), triethylamine (8.1 cm^3, 5.87 g, 58 mmol) and 4-(dimethylamino)pyridine (122 mg, 1 mmol) in dry dichloromethane (240 cm^3) was stirred at room temperature under argon for 5 days. The reaction was quenched with 1 M HCl and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (10–50% ether–petrol) afforded *sulfonate* **31** (17.8 g, 90%) as a colourless oil (Found: C, 67.12; H, 9.60. $C_{23}H_{38}O_4S$ requires C, 67.28; H, 9.33%); $[\alpha]_D^{20}$ +12.7 (*c* 1.08 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3556, 2962, 1636, 1599, 1559, 1459, 1424, 1374, 1345, 1178, 967, 810 and 665; δ_H(270 MHz; $CDCl_3$) 7.18 (2H, s, *m*-H), 5.67 (1H, ddd, *J* 17.7, 9.7 and 8.7, 5-H), 5.17–5.07 (2H, m, 6-H), 4.16 (2H, sept, *J* 6.7, *o*-CH), 4.14 (1H, dd, *J* 9.5 and 7.7, 1-H), 3.96 (1H, dd, *J* 9.5 and 6.5, 1-H), 3.39 (1H, dt, *J* 8.9 and 3.0, 3-H), 2.91 (1H, sept, *J* 6.7, *p*-CH), 2.33–2.07 (2H, m, 2-H, 4-H), 1.67 (1H, dd, *J* 3.0 and 1.0, OH), 1.26 (18H, d, *J* 6.7, CMe_2), 0.94 (3H, d, *J* 6.8, CH_3), 0.91 (3H, d, *J* 6.8, CH_3); *m*/*z* (EI) 410 (M^+, 5%), 355, 284, 267, 251, 218, 202 and 187.

(3*S*,4*R*,5*S*)-4-Hydroxy-3,5-dimethylhept-6-enenitrile 32

A mixture of sulfonate **31** (14.4 g, 35 mmol) and sodium cyanide (2.06 g, 42 mmol) in dry DMSO (35 cm^3) was heated at 65 °C under argon for 2 hours.[27] The mixture was cooled, transferred to a silica gel chromatography column and purified by flash column chromatography (1% methanol in 50% ether–petrol) to afford *nitrile* **32** (5.36 g, 100%) as a colourless oil (Found: C, 70.59; H, 9.96; N, 8.98. $C_9H_{15}NO$ requires C, 70.55; H, 9.87; N, 9.14%); $[\alpha]_D^{20}$ +24.8 (*c* 1.05 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3474, 3075, 2970, 2247, 1630, 1459, 1419, 1381, 1101, 984 and 919; δ_H(270 MHz; $CDCl_3$) 5.68 (1H, ddd, *J* 17.6, 9.7 and 8.7, 6-H), 5.16 (1H, dd, *J* 17.6 and 1.7, 7-H), 5.15 (1H, dd, *J* 9.7 and 1.7, 7-H), 3.32 (1H, dt, *J* 8.5 and 2.9, 4-H), 2.48 (1H, dd, *J* 16.7 and 7.0, 2-H), 2.38 (1H, dd, *J* 16.7 and 7.0, 2-H), 2.21 (1H, tq, *J* 8.7 and 7.0, 5-H), 2.09 (1H, sext d, *J* 7.0 and 2.9, 3-H), 1.81 (1H, dd, *J* 2.9 and 1.0, OH), 1.02 (3H, d, *J* 7.0, CH_3), 0.98 (3H, d, *J* 7.0, CH_3); *m*/*z* (EI) 98 (M^+ − C_4H_9, 62%) and 56.

(1′*S*,2*RS*,4*S*,5*R*)-Tetrahydro-4-methyl-5-(1′-methylprop-2′-enyl)furan-2-ol 33

Diisobutylaluminium hydride (4.0 cm^3, 1.5 M in toluene, 6 mmol) was added dropwise to a stirred solution of nitrile **32** (306 mg, 2 mmol) in dry toluene (6 cm^3) at −78 °C under argon. The reaction was stirred at −78 °C for 2 hours, quenched with ethyl acetate (2 cm^3) and allowed to warm to room temperature. The reaction was acidified with 2 M HCl (6 cm^3) and stirred for a further 1 hour. The two phase mixture was saturated with solid NaCl, the layers separated, and the aqueous layer extracted with dichloromethane. The organic fractions were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography using Florisil (40% ether–petrol) afforded *lactol* **33** (294 mg, 94%) (20 : 80 mixture of anomers) as a colourless oil (Found: C, 69.36; H, 10.56. $C_9H_{16}O_2$ requires C, 69.19; H, 10.32%); ν_{max}(thin film)/cm^{-1} 3413, 2966, 1628, 1453, 1293, 1073, 998 and 911; δ_H(500 MHz; $CDCl_3$) 5.89 (0.2H, ddd, *J* 17.3, 10.2 and 7.5, *minor* 19-H), 5.85 (0.8H, ddd, *J* 17.3, 10.0 and 7.7, *major* 19-H), 5.57 (0.8H, dt, *J* 5.7 and 3.5, *major* 24-H), 5.43–5.40 (0.2H, m, *minor* 24-H), 5.09 (0.2H, dt, *J* 17.3 and 1.3, *minor* 18-H), 5.08 (0.8H, ddd, *J* 17.3, 1.6 and 1.0, *major* 18-H), 5.04 (0.2H, dd, *J* 10.2 and 1.5, *minor* 18-H), 5.02 (0.8H, dd, *J* 10.0 and 1.3, *major* 18-H), 3.86 (0.8H, dd, *J* 9.3 and 4.6, *major* 21-H), 3.58 (0.2H, dd, *J* 9.5 and 4.6, *minor* 21-H), 3.23–3.15 (0.2H, br s, *minor* OH), 3.07–2.97 (0.8H, br s, *major* OH), 2.45–2.37 (0.2H, m, *minor* 22-H), 2.35 (0.2H, ddd, *J* 7.1, 4.6 and 2.5, *minor* 23-H), 2.34 (0.2H, ddd, *J* 7.1, 4.6 and 2.5, *minor* 23-H), 2.33–2.25 (1H, m, *minor*/*major* 20-H), 2.25–2.15 (0.8H, m, *major* 22-H), 1.98 (0.8H, ddd, *J* 13.5, 7.1 and 4.0, *major* 23-H), 1.90 (0.8H, ddd, *J* 13.5, 5.7 and 2.6, *major* 23-H), 1.12 (0.6H, d, *J* 7.1, *minor* 22-CH_3), 0.98 (3H, d, *J* 6.8, *minor*/*major* 20-CH_3), 0.91 (2.4H, d, *J* 7.1, *major* 22-CH_3); *m*/*z* (EI) 139 (M^+ − OH, 100%), 95, 85 and 55.

(1′*S*,2*R*,3*S*,5*RS*)-Tetrahydro-3-methyl-2-(1′-methylprop-2′-enyl)-5-(phenylsulfonyl)furan 34 †

A mixture of lactol **33** (0.52 g, 3.3 mmol), benzenesulfonic acid (1.41 g, 9.9 mmol) and anhydrous calcium chloride (1.10 g, 9.9 mmol) in dry dichloromethane (8 cm^3) was stirred at room temperature under argon for 14 hours. The reaction was quenched with excess water and extracted with dichloromethane. The combined extracts were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography on silica gel (25% ether–petrol) afforded *sulfone* **34** (0.86 g, 93%) (5*R*:5*S* 7:93) as a white solid (Found: C, 64.12; H, 7.03. $C_{15}H_{20}O_3S$ requires C, 64.62; H, 7.19%); mp 84–87 °C; ν_{max}($CHCl_3$)/cm^{-1} 2970, 1638, 1447, 1308, 1287, 1148, 1073 and 687; δ_H(270 MHz; $CDCl_3$) 7.95–7.90 (2H, m, 5*R*/5*S* *o*-H), 7.67–7.63 (1H, m, 5*R*/5*S* *p*-H), 7.67–7.53 (2H, m, 5*R*/5*S* *m*-H), 5.84 (0.93H, ddd, *J* 17.3, 10.3 and 7.1, 5*S* 19-H), 5.83 (0.07H, ddd, *J* 17.3, 10.3 and 7.1, 19-H), 5.05 (1H, dt, *J* 17.3 and 1.3, 5*R*/5*S* 18-H), 5.02 (0.93H, dt, *J* 10.3 and 1.3, 5*S* 18-H), 4.97 (0.07H, dt, *J* 10.3 and 0.8, 5*R* 18-H), 4.91 (0.93H, t, *J* 7.5, 5*S* 24-H), 4.74 (0.07H, d, *J* 9.2, 5.0, 5*R* 24-H), 3.97 (0.93H, dd, *J* 9.9 and 4.1, 5*S* 21-H), 3.60 (0.07H, dd, *J* 9.2 and 5.4, 5*R* 21-H), 2.80 (0.93H, dt, *J* 13.9 and 7.0, 5*S* 23-H), 2.52 (0.07H, ddd, *J* 14.1, 9.1 and 7.8, 5*R* 23-H), 2.50–2.37 (1H, m, 5*R*/5*S* 22-H), 2.29 (0.07H, ddd, *J* 14.1, 5.0 and 2.9, 5*R* 23-H), 2.30–2.20 (1H, m, 5*R*/5*S* 20-H), 2.07 (0.93H, ddd, *J* 13.7, 7.8 and 1.2, 5*S* 23-H), 1.06 (0.21H, d, *J* 7.1, 5*R*, 22-CH_3), 0.96 (3H, d, *J* 6.8, 5*R*/5*S* 20-CH_3), 0.92 (2.79H, d, *J* 7.0, 5*S* 22-CH_3); *m*/*z* (EI) 139 (M^+ − $PhSO_2$, 14%), 125, 110, 83 and 55.

(1′*S*,2*R*,3*S*,5*R*)-Tetrahydro-5-ethynyl-3-methyl-2-(1′-methylprop-2′-enyl)furan 35

Anhydrous zinc bromide (1.2 cm^3, 1.2 mmol, 1 M solution in THF) was added to a stirred solution of ethynylmagnesium bromide (10 cm^3, 2.0 mmol, 0.2 M solution in THF) and the mixture was stirred at room temperature under argon for 30 minutes. Solid sulfone **34** (0.14 g, 0.5 mmol) was added and the solution stirred for 19 hours. The reaction was quenched with saturated aqueous 1 M HCl and extracted with ether. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (4–5% ether–petrol) afforded *acetylene* **35** (72 mg, 88%) (5*R*:5*S* > 20:1) as a colourless oil $[\alpha]_D^{20}$ +30.9 (*c* 1.00 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3928, 2967, 2878, 1636, 1455, 1381, 1335, 1072, 1008, 962, 912; δ_H(270 MHz; $CDCl_3$) 5.91 (1H, ddd, *J* 17.3, 10.2 and 7.3, 19-H), 5.08 (1H, ddd, *J* 17.3, 1.8 and 1.2, 18-H), 5.02 (1H, ddd, *J* 10.2, 1.8 and 0.8, 18-H), 4.73 (1H, td, *J* 7.3 and 2.2, 24-H), 3.73 (1H, dd, *J* 9.3 and 4.6, 21-H), 2.41 (1H, d, *J* 2.2, 26-H), 2.40–2.23 (2H, m, 20-H, 22-H), 2.20 (1H, dt, *J* 12.5 and 7.1, 23-H), 2.00 (1H, ddd, *J* 12.5, 7.6 and 2.4, 23-H), 0.98 (3H, d, *J* 6.6, CH_3), 0.93 (3H, d, *J* 7.1, CH_3); *m*/*z* (EI) 164 (M^+, 0.3%) and 109 {Found (EI) M^+ 164.1150. $C_{11}H_{16}O$ requires 164.1201; Found (EI) $[M - C_4H_7]^+$ 109.0653. C_7H_9O requires 109.0653}.

(1″*S*,2′*R*,4′*S*,5′*R*)-1-[Tetrahydro-4′-methyl-5′-(1″-methylprop-2″-enyl)furan-2′yl]ethan-1-one 36

A solution of acetylene **35** (66 mg, 0.4 mmol) in acetone (4 cm^3) was added to a solution of yellow mercuric(II) oxide (50 mg) in 0.75 M sulfuric acid (2.0 cm^3) at 60 °C.[19] The reaction was stirred at 60 °C for 12 minutes, cooled to 0 °C and quenched with 1 M HCl (10 cm^3). The mixture was extracted with dichloromethane, the combined extracts dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (10% ether–petrol) afforded *ketone* **36** (59 mg, 81%) as a light yellow oil. $[\alpha]_D^{20}$ +41 (*c* 1.00 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2967, 1713, 1636, 1453, 1353, 1087, 1006 and 909; δ_H(270 MHz; $CDCl_3$) 5.94 (1H, ddd, *J* 17.3, 10.3 and 7.2, 19-H), 5.12 (1H, ddd, *J* 17.3, 1.7 and 1.2, 18-H), 5.05 (1H, ddd, *J* 10.3, 1.7 and 0.8, 18-H), 4.42 (1H, t, *J* 8.5, 24-H), 3.62 (1H, dd, *J* 9.5 and 4.2, 21-H), 2.40–1.90 (4H, m, 20-H, 22-H, 23-H), 2.19 (3H, s, 26-H), 0.98 (3H, d, *J* 6.6, CH_3), 0.96 (3H, d, *J* 6.8, CH_3); *m*/*z* (EI) 182 (M^+, 23%), 149, 139, 95 and 55 [Found (EI) M^+ 182.1307. $C_{11}H_{18}O_2$ requires 182.1307].

(1*R*,1″*S*,2′*R*,4′*S*,5′*R*)-1-[Tetrahydro-4′-methyl-5′-(1″-methylprop-2-enyl)furan-2-yl]ethanol 37a and (1*S*,1″*S*,2′*R*,4′*S*,5′*R*)-1-[tetrahydro-4′-methyl-5′-(1″-methylprop-2″-enyl)furan-2-yl]-ethanol 37b

Sodium borohydride (11.3 mg, 0.3 mmol) was added to a stirred solution of ketone **36** (5.5 mg, 0.03 mmol) in methanol (0.6 cm^3) at room temperature. The mixture was stirred for 30 minutes, quenched with 1 M HCl and concentrated *in vacuo*. The aqueous layer was extracted with dichloromethane and then the combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (1% methanol in 15% ether–petrol) afforded the (1*R*,1″*S*,2′*R*,4′*S*,5′*R*)-*alcohol* **37a** (3.1 mg, 56%) as a colourless gum $[\alpha]_D^{20}$ −13.3 (*c* 1.00 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3448, 2986, 1635, 1453, 1379, 1261, 1085, 1010, 965 and 909; δ_H(500 MHz; $CDCl_3$) 5.92 (1H, ddd, *J* 17.3, 10.4 and 6.9, 19-H), 5.07 (1H, dt, *J* 17.3 and 1.4, 18-H), 5.00 (1H, dt, *J* 10.4 and 1.3, 18-H), 3.81 (1H, q, *J* 7.7, 24-H), 3.53–3.50 (1H, m, 25-H), 3.49 (1H, dd, *J* 9.7 and 4.0, 21-H), 2.58 (1H, d, *J* 2.0, OH), 2.33–2.25 (2H, m, 20-H, 22-H), 1.70 (2H, dd, *J* 7.7 and 3.9, 23-H), 1.08 (3H, d, *J* 6.3, CH_3), 0.95 (6H, d, *J* 6.8, CH_3); *m*/*z* (EI) 129 (M^+ − C_4H_7, 100%), 121, 111 and 95 [Found (CI) MNH_4^+ 202.1807. $C_{11}H_{24}NO_2$ requires 202.1807].

Further elution (1% methanol in 20% ether–petrol) afforded the (1*S*,1″*S*,2′*R*,4′*S*,5′*R*)-*alcohol* **37b** (2.0 mg, 36%) as a colourless gum $[\alpha]_D^{20}$ +5.0 (*c* 1.00 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3429, 2965, 1635, 1459, 1379, 1076, 1033, 1010 and 907; δ_H(500 MHz; $CDCl_3$) 5.92 (1H, ddd, *J* 17.3, 10.3 and 7.2, 19-H), 5.08 (1H, dt, *J* 17.3 and 1.4, 18-H), 5.01 (1H, ddd, *J* 10.3, 1.7 and 0.9, 18-H), 4.03–3.97 (2H, m, 24-H, 25-H), 3.58 (1H, dd, *J* 9.7 and 4.0, 21-H), 2.33–2.25 (2H, m, 20-H, 22-H), 2.07 (1H, ddd, *J* 12.2, 9.5 and 6.5, 23-H), 1.94 (1H, s, OH), 1.57 (1H, ddd, *J* 12.2, 6.2 and 1.2, 23-H), 1.07 (3H, d, *J* 6.4, CH_3), 0.96 (3H, d, *J* 6.9, CH_3), 0.95 (3H, d, *J* 6.7, CH_3); *m*/*z* (EI) 129 (M^+ − C_4H_7, 100%), 121, 111 and 95 [Found (CI) MNH_4^+ 202.1807. $C_{11}H_{24}NO_2$ requires 202.1807].

(1*R*,1″*S*,2′*R*,4′*S*,5′*R*)-1-[Tetrahydro-4′-methyl-5′-(1″-methylprop-2″-enyl)furan-2′-yl]ethanol 37a

L-Selectride (1.2 cm^3, 1.0 M solution in THF, 2.1 mmol) was added to a solution of ketone **36** (191 mg, 1.05 mmol) in THF (3.2 cm^3) under argon at −78 °C and the mixture stirred at this temperature for 3 hours. The reaction was allowed to warm to room temperature, quenched with 1 M HCl and extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (1% methanol in 15% ether–petrol) afforded the (1*R*,1″*S*,2′*R*,4′*S*,5′*R*)-*alcohol* **37a** (141 mg, 73%) as a colourless gum with analytical data identical to that reported previously.

Tetrahydro-5-(1′-methoxyethyl)-3-methyl-2-(1″-methylprop-2″-enyl)furan 38

Sodium hydride (60% dispersion in oil, 38.4 mg, 1.6 mmol) was added to a stirred solution of alcohol **37b** (29.5 mg, 0.16 mmol) in dry THF (4.8 cm^3) at room temperature under argon. After 15 minutes iodomethane (0.15 cm^3, 341 mg, 2.4 mmol) was added and the mixture was stirred at room temperature for a further 4 hours. The reaction was quenched with saturated aqueous NH_4Cl and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (15% ether–petrol) afforded *methyl ether* **38** (27.3 mg,

† For compounds **8**, **34**–**55** the NMR assignments follow the atom numbering of Tetronasin **1**.

87%) as a colourless gum (Found: C, 72.80; H, 11.50. $C_{12}H_{22}O_2$ requires C, 72.68; H, 11.18%); $[\alpha]_D^{25}$ +4.1 (*c* 1.02 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2967, 1638, 1456, 1371, 1094, 1013, 909; δ_H(270 MHz; $CDCl_3$) 5.93 (1H, ddd, *J* 17.3, 10.4 and 7.0, 19-H), 5.07 (1H, ddd, *J* 17.3, 1.7 and 1.2, 18-H), 4.99 (1H, ddd, *J* 10.4, 1.7 and 1.0, 18-H), 3.97 (1H, ddd, *J* 8.6, 7.1 and 4.5, 24-H), 3.54 (1H, dd, *J* 9.6 and 4.0, 21-H), 3.45–3.33 (1H, m, 25-H), 3.39 (3H, s, OMe), 2.33–2.17 (2H, m, 20-H, 22-H), 2.01 (1H, ddd, *J* 12.4, 8.7 and 6.6, 23-H), 1.66 (1H, ddd, *J* 12.4, 7.0 and 1.3, 23-H), 1.08 (3H, d, *J* 6.4, 25-CH_3), 0.95 (3H, d, *J* 6.8, CH_3), 0.93 (3H, d, *J* 7.1, CH_3); *m*/*z* (EI) 198 (M^+, 1%), 143, 95, 59 and 55.

(1″*S*,2*R*,2′*R*,3′*S*,5′*R*)-2-[Tetrahydro-5′-(1″-methoxyethyl)-3′-methylfuran-2′-yl]propanal 8

Ozone was passed through a solution of alkene **38** (23.8 mg, 0.12 mmol) in dry dichloromethane (18 cm^3) for 30 minutes at −78 °C. The reaction mixture was then degassed for 15 minutes and concentrated *in vacuo* to approximately 2–3 cm^3. Triphenylphosphine (47 mg, 0.18 mmol) was then added and the solution stirred at room temperature under argon for 4 hours. The reaction mixture was concentrated *in vacuo* and purified by column chromatography on silica gel (10–25% ether–petrol) to afford *aldehyde* **8** (20.1 mg, 84%) as a colourless gum (Found: C, 65.75; H, 10.16. $C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07%); $[\alpha]_D^{20}$ −58.5 (*c* 1.00 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2968, 1724, 1459, 1371, 1092 and 1011; δ_H(270 MHz; $CDCl_3$) 9.80 (1H, d, *J* 2.7, 19-H), 4.02 (1H, ddd, *J* 8.9, 6.7 and 4.5, 24-H), 3.88 (1H, dd, *J* 10.2 and 4.1, 21-H), 3.40–3.30 (1H, m, 25-H), 3.36 (3H, s, OMe), 2.53–2.40 (1H, m, 20-H), 2.40–2.27 (1H, m, 22-H), 2.02 (1H, ddd, *J* 12.4, 9.0 and 6.6, 23-H), 1.69 (1H, dd, *J* 12.4 and 6.8, 23-H), 1.08 (3H, d, *J* 6.4, 25-CH_3), 1.00 (3H, d, *J* 7.1, 20-CH_3), 0.94 (3H, d, *J* 7.1, 22-CH_3); *m*/*z* (EI) 200 (M^+, 100%), 157, 111, 85, 83 and 59.

(3*E*,1″*S*,2*S*,2′*R*,3′*S*,5′*R*,8*R*)-9-Benzyloxy-8-methyl-2-[tetrahydro-5′-(1″-methoxyethyl)-3′-methylfuran-2′-yl]non-3-en-5-one 39

Keto phosphonate **7** (1.97 g, 5.99 mmol) in acetonitrile (3 cm^3) was added to lithium chloride (254 mg, 5.99 mmol) in acetonitrile (30 cm^3) and stirred for 10 minutes. Diisopropylethylamine (870 μl, 4.99 mmol) was added, followed by aldehyde **8** (1.0 g, 4.99 mmol) *via* cannula, and the mixture stirred for 16 hours. The mixture was poured into a mixture of 5% aqueous ammonium chloride (60 cm^3) and ether (350 cm^3). The organic layer was separated, washed with water, and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 20% acetone–petrol) to give *enone* **39** (0.95 g, 67%) (Found: C, 74.30; H, 9.73. $C_{25}H_{38}O_4$ requires C, 74.59; H, 9.51%); $[\alpha]_D^{23}$ −9.4 (*c* 1.12 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3029, 2965, 2930, 2875, 1675, 1671, 1628, 1494, 1451, 1370, 1190, 1095, 1009, 930, 864, 802, 737 and 698; δ_H(270 MHz; $CDCl_3$) 7.33 (5H, m, Ph), 6.92 (1H, dd, *J* 16.4 and 7.2, 19-H), 6.12 (1H, dd, *J* 16.4 and 0.9, 18-H), 4.48 (2H, s, PhCH_2O), 3.96 (1H, m, 24-H), 3.60 (1H, dd, *J* 9.6 and 4.1, 21-H), 3.34 (3H, m, 13-H_2 and 25-H), 3.31 (3H, s, 25-OMe), 2.57 (2H, m, 20-H, 22-H), 2.50 (2H, m, 16-H_2), 2.42 (1H, m, 23-H_1), 1.78 (2H, m, 14-H, 15-H_1), 1.68 (1H, ddd, *J* 12.5, 7.0 and 1.1, 23-H_1), 1.48 (1H, m, 15-H_1), 1.07 (3H, d, *J* 6.3, 26-Me), 1.00 (3H, d, *J* 6.8, 28-Me), 0.94 (6H, d, *J* 6.8, 27-Me, 29-Me); *m*/*z* 402 (M^+), 387 (M^+ − Me), 343 (M^+ − OC_3H_7), 143 and 91 ($C_7H_7^+$).

(3*E*,1″*S*,2*S*,2′*R*,3′*S*,5*S*,5′*R*,8*R*)-9-Benzyloxy-8-methyl-2-[tetrahydro-5′-(1″-methoxyethyl)-3′-methylfuran-2′yl]non-3-en-5-ol 40

Methanol (6.9 cm^3 of a 2.0 M solution in THF, 13.8 mmol) was added to lithium aluminium hydride (13.8 cm^3 of a 1.0 M solution in THF, 13.8 mmol) at room temperature. After 5 minutes (*S*)-1,1′-binaphth-2-ol (*S*-BINAL) (3.94 g, 10 mmol) was added dropwise and then stirred for 30 minutes, and cooled to −100 °C. Enone **39** (2.78 g, 6.9 mmol) in THF (13 cm^3) was added slowly over 10 minutes and the mixture stirred at this temperature for 16 hours. The reaction was quenched by the sequential addition of methanol (6.6 cm^3) followed by water (6.6 cm^3). The mixture was warmed to room temperature, then solid sodium hydrogen carbonate added and the mixture stirred for 1 hour and then filtered. The filtrate was poured into ether (300 cm^3) and the organic layer separated. The organics were washed with water and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The oil was triturated with petrol to remove *S*-BINAL, filtered and the filtrate concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 50% ether–petrol) to give *S-alcohol* **40** (1.75 g, 63%) (Found: C, 74.32; H, 10.12. $C_{25}H_{40}O_4$ requires C, 74.22; H, 9.97%); $[\alpha]_D^{20}$ +2.6 (*c* 1.0 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3413, 3028, 2922, 1594, 1494, 1450, 1375, 1203, 1093, 862, 802, 735 and 697; δ_H(500 MHz; $CDCl_3$) 7.28 (5H, m, Ph), 5.84 (1H, dd, *J* 15.5 and 7.1, 19-H), 5.50 (1H, ddd, *J* 15.5, 7.3 and 1.0, 18-H), 4.48 (2H, s, PhCH_2O), 4.0 (2H, m, 24-H, 17H), 3.50 (1H, dd, *J* 9.6 and 4.1, 21-H), 3.31 (3H, s, 25-OMe), 3.38 (2H, m, 13-H_1, 25-H), 3.22 (1H, m, 13-H_1), 2.26 (2H, m, 20-H, 22-H), 1.90 (1H, m, 23-H_1), 1.80 (1H, m, 14-H), 1.62 (1H, ddd, *J* 12.4, 7.0 and 1.3, 23-H_1), 1.50 (3H, m, 15-H_1, 16-H_2), 1.08 (1H, m, 15-H_1), 1.08 (3H, d, *J* 6.6, 26-Me), 0.92 (9H, m, 27-Me, 28-Me, 29-Me); *m*/*z* 404 (M^+), 386 (M^+ − H_2O), 345 (M^+ − OC_3H_7) and 143.

(3*E*,1″*S*,2*S*,2′*R*,3′*S*,5*S*,5′*R*,8*R*)-9-Benzyloxy-5-*tert*-butyldimethylsilyloxy-8-methyl-2-[tetrahydro-5′-(1″methoxyethyl)-3′-methylfuran-2′-yl]non-3-ene 41

(*S*)-Alcohol **40** (2.03 g, 5 mmol) was dissolved in DMF (40 cm^3) and added *via* cannula to a mixture of imidazole (444 mg, 7.5 mmol) and *tert*-butylchlorodimethylsilane. The reaction was stirred for 16 hours, then poured into water (40 cm^3) and ether (250 cm^3). The organic layer was separated, washed with water and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 15% acetone–petrol) to give the *silyl ether* **41** (2.54 g, 98%) (Found: C, 71.86; H, 10.34. $C_{31}H_{54}O_4Si$ requires C, 71.76; H, 10.49%); $[\alpha]_D^{20}$ −10.8 (*c* 1.94 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2958, 2929, 2855, 1460, 1370, 1250, 1201, 1096, 968, 863, 836, 813, 776, 734, 697 and 663; δ_H(500 MHz; $CDCl_3$) 7.29 (5H, m, Ph), 5.66 (1H, ddd, *J* 15.6, 6.7 and 1.1, 19-H), 5.41 (1H, ddd, *J* 15.6, 6.9 and 1.1, 18-H), 4.48 (2H, s, PhCH_2O), 4.02 (1H, m, 17-H), 3.94 (1H, m, 24-H), 3.50 (1H, dd, *J* 9.4 and 4.1, 21-H), 3.36 (3H, s, 25-OMe), 3.32 (2H, m, 13-H_2), 3.21 (1H, qd, *J* 9.0 and 7.0, 25-H), 2.22 (2H, m, 20-H, 22-H), 1.97 (1H, m, 23-H_1), 1.74 (1H, m, 14-H), 1.66 (1H, m, 23-H_1), 1.47 (3H, m, 15-H_1, 16-H_2), 1.07 (3H, d, *J* 6.3, 26-Me), 1.06 (1H, m, 15-H_1), 0.92 (9H, m, 27-Me, 28-Me, 29-Me), 0.82 (9H, s, Si-Bu^t), 0.06 (3H, s, SiMe), 0.04 (3H, s, SiMe); *m*/*z* 519 (M^+), 461 (M^+ − OC_3H_7) and 143.

(6*E*,1″*S*,2*R*,2′*R*,3′*S*,5*S*,5′*R*,8*S*)-5-*tert*-Butyldimethylsilyloxy-2-methyl-8-[tetrahydro-5′-(1″-methoxyethyl)-3′-methylfuran-2′-yl]non-6-en-1-ol 42

Sodium (1 g) was added to ammonia (125 cm^3) at −78 °C. Silyl ether **41** (1.6 g, 3.09 mmol) in ether (10 cm^3) was then added, and the reaction stirred for 48 hours by which time the blue colouration had dissipated. The reaction was gradually warmed to room temperature, the ammonia evaporated, and ether (500 cm^3) added. The ether was washed with water and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 50% ether–petrol) to give *alcohol* **42** (1.31 g, 99%) (Found: C, 67.24; H, 11.29. $C_{24}H_{48}O_4Si$ requires C, 67.24; H, 11.28%); $[\alpha]_D^{20}$ −8.2 (*c* 1.16 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3399, 2930, 1462, 1375, 1250, 1093, 835, 775 and 663; δ_H(500 MHz; $CDCl_3$) 5.67 (1H, dd, *J* 15.7 and 6.6, 19-H), 5.43 (1H, ddd, *J* 15.6, 6.8 and 1.1, 18-H), 4.05 (1H, m, 17-H), 3.96 (1H, m, 24-H), 3.51 (1H, dd, *J* 9.5 and 4.1, 21-H), 3.42 (2H, m, 13-H_2), 3.37 (3H, s, 25-OMe), 3.33 (1H,

m, 25-H), 2.23 (2H, m, 20-H, 22-H), 1.96 (1H, m, 23-H_1), 1.68–1.44 (7H, m, OH, 14-H, 15-H_2, 16-H_2, 23-H_1), 1.08 (3H, d, *J* 6.3, 26-Me), 0.93 (3H, d, *J* 6.8, 29-Me), 0.92 (3H, d, *J* 7.0, 28-Me), 0.89 (3H, d, *J* 6.7, 27-Me), 0.88 (9H, s, Si-Bu^t), 0.03 (6H, s, $SiMe_2$); *m*/*z* 371 ($M^+ - Bu^t$), 353, 341 ($M^+ - Bu^t -$ 2Me), 296, 281, 257 and 143.

(6*E*,1″*S*,2*R*,2′*R*,3′*S*,5*S*,5′*R*,8*S*)-5-*tert*-Butyldimethylsilyloxy-2-methyl-8-[tetrahydro-5′-(1″-methoxyethyl)-3′-methylfuran-2′-yl]non-6-enal 43

(*a*) The alcohol **42** (25 mg, 0.087 mmol) was dissolved in dichloromethane (2 cm^3). *N*-methylmorpholine-*N*-oxide (12 mg, 0.087 mmol) and powdered 4 Å molecular sieves (100 mg) were added followed by tetra-*n*-propylammonium perruthenate (5 mg). The reaction was stirred for 25 minutes then filtered through a silica pad, washing with ether (30 cm^3). The combined washings and filtrate were then concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 20% ether–petrol) to give *aldehyde* **43** (24 mg, 95%).

(*b*) Oxalyl chloride (1.4 cm^3, 2.0 M solution in dichloromethane, 2.8 mmol) was cooled to −78 °C, then dimethyl sulfoxide (398 μl, 5.6 mmol) added. The solution was stirred for ten minutes then alcohol **42** (1 g, 2.33 mmol) was added *via* cannula and stirred for a further 30 minutes. Triethylamine (1.56 cm^3, 11.2 mmol) was added and the reaction kept at this temperature for 10 minutes then allowed to warm to room temperature over 30 minutes. The mixture was poured into water (40 cm^3) and extracted with dichloromethane (3 × 40 cm^3). The combined organic extracts were washed with water (2 × 20 cm^3) and brine (100 cm^3), then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 20% ether–petrol) to give *aldehyde* **43** (0.94 g, 95%).

Aldehyde **43**: (Found: C, 67.31; H, 10.55. $C_{24}H_{46}O_4Si$ requires C, 67.55; H, 10.87%); $[a]_D^{20}$ −8.2 (*c* 1.16 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2960, 2930, 2855, 2706, 1725, 1458, 1371, 1251, 1190, 1094, 1069, 1007, 968, 836, 776 and 663; δ_H(500 MHz; $CDCl_3$) 9.59 (1H, d, *J* 2.0, 13-H), 5.69 (1H, dd, *J* 15.7 and 6.6, 19-H), 5.41 (1H, ddd, *J* 15.6, 6.8 and 1.2, 18-H), 4.09 (1H, m, 17-H), 3.95 (1H, m, 24-H), 3.49 (1H, dd, *J* 9.6 and 4.1, 21-H), 3.38 (3H, s, 25-OMe), 3.30 (1H, m, 25-H), 2.30 (1H, m, 14-H), 2.25 (2H, m, 20-H, 22-H), 1.99 (1H, ddd, *J* 12.4, 8.9 and 6.7, 23-H_1), 1.75 (1H, m, 15-H_1), 1.62 (1H, ddd, *J* 12.4, 6.7 and 1.2, 23-H_1), 1.49 (2H, m, 16-H_2), 1.35 (1H, m, 15-H_1), 1.08 (6H, m, 26-Me, 29-Me), 0.90 (6H, m, 27-Me, 28-Me), 0.85 (9H, s, Si-Bu^t), 0.01 (6H, s, $SiMe_2$); *m*/*z* 426 (M^+) and 143.

(1′*E*,2*Z*,8*E*,1‴*S*,2″*R*,3″*S*,4*R*,5″*R*,6′*R*,7*S*,10*S*)-Ethyl 7-*tert*-butyldimethylsilyloxy-2-(7′-trimethylsilyloxy-6′-methylhept-1′-enyl)-4-methyl-10-[tetrahydro-5″-(1‴-methoxyethyl)-3″-methylfuran-2″-yl]undeca-2,8-dienoate 44a and (1′*E*,2*Z*,8*E*,1‴*S*,2″*R*,3″*S*,4*R*,5″*R*,6′*R*,7*S*,10*S*)-ethyl 7-*tert*-butyldimethylsilyloxy-2-(7′-trimethylsilyloxy-6′-methylhept-1′-enyl)-4-methyl-10-[tetrahydro-5″-(1‴-methoxyethyl)-3″-methylfuran-2″-yl]undeca-2,8-dienoate 44b

Phosphonate **6** (0.98 g, 2.33 mmol, 1.5 equiv.) in THF (2 cm^3) was cooled to −78 °C under argon. Lithium bis(trimethylsilyl)-amide (2.28 cm^3, 1.0 M in THF, 2.28 mmol, 1.47 equiv.) was added dropwise and the solution allowed to warm to room temperature over 30 minutes. The solution was cooled to −78 °C for 10 minutes then aldehyde **43** (0.66 g, 1.55 mmol) in dry THF (2 cm^3) was added dropwise *via* syringe. After 10 minutes the reaction mixture was allowed to warm to room temperature over 1.5 hours and was then stirred for a further 15 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride (5 cm^3), and extracted with ether (3 × 75 cm^3). The organic layer was separated, washed with water and brine, then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 60% petrol–ethyl acetate) to give *triene* **44** (0.73 g, 68%, 82% based on recovered starting material, mixture of *Z*:*E* of 4.6:1) as a colourless oil, together with unreacted *aldehyde* **43** (0.11 g, 17%). For *triene* **44** (Found: C, 67.53; H, 10.72. $C_{39}H_{74}O_6Si_2$ requires C, 67.38; H, 10.73%); ν_{max}(thin film)/cm^{-1} 2959, 2931, 2857, 1725, 1460, 1372, 1333, 1251, 1190, 1151, 1094, 963, 877, 839 and 776; δ_H(500 MHz; $CDCl_3$) 6.35 [1H, d, *J* 10.6, 13-H(*E*)], 5.98 (1H, d, *J* 15.9, 11-H), 5.65 (2H, m, 10-H, 19-H), 5.64 [1H, 11-H(*E*)], 5.46 [1H, d, *J* 10.3, 13-H(*Z*)], 5.38 (1H, dd, *J* 15.6 and 8.9, 18-H), 4.26 [2H, q, *J* 7.1, $OCH_2Me(Z)$], 4.20 [2H, q, *J* 7.1, $OCH_2Me(E)$], 4.01 (1H, m, 17-H), 3.94 (1H, m, 24-H), 3.49 (2H, m, 5-H_1 and 21-H), 3.43 (1H, m, 5-H_1), 3.37 (3H, s, 25-OMe), 3.33 (1H, m, 25-H), 2.60 [1H, m, 14-H(*E*)], 2.45 [1H, m, 14-H(*Z*)], 2.23 (3H, m, 20-H, 9-H_2), 2.04 (2H, m, 22-H), 1.97 (1H, m, 23-H_1), 1.64 (2H, m, 23-H_1, 6-H), 1.39 (2H, m, 16-H_2), 1.3–0.75 (15H, m, 7-H_2, 8-H_2, 15-H_2, 27-Me, 28-Me and OCH_2CH_3), 1.08 (3H, d, *J* 6.3, 26-Me), 0.98 (3H, d, *J* 6.6, 29-Me), 0.87 (9H, s, Si-Bu^t), 0.02 (3H, s, SiMe); *m*/*z* 622 (M^+), 577 (M^+ − OEt) and 143.

(1′*E*,2*Z*,8*E*,1‴*S*,2″*R*,3″*S*,4*R*,5″*R*,6′*R*,7*S*,10*S*)-Ethyl 7-*tert*-butyldimethylsilyloxy-2-(7′-hydroxy-6′-methylhept-1′-enyl)-4-methyl-10-[tetrahydro-5″-(1‴-methoxyethyl)-3″-methylfuran-2″yl]undeca-2,8-dienoate 45a and (1′*E*,2*E*,8*E*,1‴*S*,2″*R*,3″*S*,4*R*,5″*R*,6′*R*,7*S*,10*S*)-ethyl 7-*tert*-butyldimethylsilyloxy-2-(7′-hydroxy-6′-methylhept-1′-enyl)-4-methyl-10-[tetrahydro-5″-(1‴-methoxyethyl)-3″-methylfuran-2″-yl]undeca-2,8-dienoate 45b

Triene **44** (1.25 g, 1.81 mmol) was stirred in dry THF (100 cm^3) at room temperature under argon. Aqueous acetate buffer (50 cm^3, pH 3, ~0.003 M in acetate) and methanol (25 cm^3) were then added. After 1 h, ether (200 cm^3) was added and the mixture shaken. The organic extracts were separated and then washed with water (150 cm^3), and brine (150 cm^3), dried ($MgSO_4$), filtered, the solvent removed *in vacuo* and the residue purified by flash column chromatography (75% petrol–ethyl acetate) to afford the *alcohol* **45** (1.12 g, quant.) as a colourless oil (Found: C, 69.30; H, 10.70. $C_{36}H_{66}O_6Si$ requires C, 69.41; H, 10.68%); ν_{max}(thin film)/cm^{-1} 3463, 2928, 1721, 1461, 1370, 1250, 1191, 1146, 1094, 964, 836 and 776; δ_H(500 MHz; $CDCl_3$) 6.33 [1H, d, *J* 10.3, 13-H(*E*)], 5.98 [1H, d, *J* 16.0, 11-H(*Z*)], 5.65 (2H, m, 10-H, 19-H), 5.47 [1H, d, *J* 10.3, 13-H(*Z*)], 5.38 (1H, ddd, *J* 14.5, 6.7 and 1.1, 18-H), 4.25 [2H, q, *J* 7.1, $OCH_2Me(Z)$], 4.23 [2H, q, *J* 7.1, $OCH_2Me(E)$], 4.04 (1H, m, 17-H), 3.95 (1H, m, 24-H), 3.49 (1H, dd, *J* 9.5 and 4.1, 21-H), 3.42 (1H, dd, *J* 9.5 and 4.1, 5-H_1), 3.38 (3H, s, 25-OMe), 3.34 (1H, dd, *J* 10.0 and 6.0, 5-H_1), 3.33 (1H, m, 25-H), 2.60 [1H, m, 14-H(*E*)], 2.45 [1H, m, 14-H(*Z*)], 2.22 (3H, m, 20-H, 9-H_2), 2.17 (2H, m, 22-H, 23-H_1), 1.65 (1H, ddd, *J* 12.5, 6.9 and 1.3, 23-H_1), 1.60 (1H, m, 6-H), 1.5–1.25 (11H, m, 7-H_2, 8-H_2, 16-H_2, 15-H_2, OCH_2CH_3), 1.08 (3H, d, *J* 6.3, 26-Me), 0.98 (3H, d, *J* 6.6, 27-Me), 0.92 (6H, d, *J* 6.9, 28-Me, 29-Me), 0.88 (3H, d, *J* 6.7, 6-Me), 0.87 (9H, s, Si-Bu^t), 0.02 (6H, s, $SiMe_2$).

(1′*E*,2*Z*,8*E*,1‴*S*,2″*R*,3″*S*,4*R*,5″*R*,6′*R*,7*S*,10*S*)-Ethyl 7-*tert*-butyldimethylsilyloxy-2-(7′-oxo-6′-methylhept-1′-enyl)-4-methyl-10-[tetrahydro-5″-(1‴-methoxyethyl)-3″-methylfuran-2″-yl]undeca-2,8-dienoate 46

(*a*) The alcohol **45** (72.3 mg, 0.03 mmol) was dissolved in dichloromethane (15 cm^3). *N*-Methylmorpholine-*N*-oxide (25 mg, 0.174 mmol) and powdered 4 Å molecular sieves (100 mg) were added followed by tetra-*n*-propylammonium perruthenate (10 mg). The reaction was stirred for 30 minutes then filtered through a silica pad, washing exhaustively with ether (30 cm^3). The combined filtrate and washings were then concentrated *in vacuo*. The residue was purified by chromatography (florisil, 25% ether–petrol) to give *aldehyde* **46** (68 mg, 95%).

(*b*) Oxalyl chloride (203 μl, 2.0 M solution in dichloromethane, 0.406 mmol) was cooled to −78 °C, then dimethyl sulfoxide (58 μl, 0.817 mmol) was added. The solution was stirred for 10 minutes then alcohol **45** (211 mg, 0.34 mmol) was added *via* cannula and the resultant mixture stirred for a further 30 minutes. Triethylamine (226 μl, 1.63 mmol) was added, the mixture

kept at this temperature for 10 minutes and then allowed to warm to room temperature over 30 minutes. The mixture was poured into water (5 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The organics were washed with water (2 × 10 cm^3) and brine (10 cm^3), then dried (Na_2SO_4) filtered and concentrated *in vacuo*. The residue was purified by chromatography (florisil, 20% ether–petrol) to give *aldehyde* **46** (183 mg, 98%) ν_{max}(thin film)/cm^{-1} 2961, 2931, 1857, 1719, 1649, 1460, 1368, 1257, 1176, 1147, 1095, 1006, 984, 836 and 776; δ_H(500 MHz; $CDCl_3$) 9.61 (1H, d, *J* 1.9, 5-H), 6.35 [1H, d, *J* 10.6, 13-H(*E*)], 5.98 (1H, d, *J* 15.6, 11-H), 5.65 (2H, m, 10-H, 19-H), 5.48 [1H, d, *J* 10.3, 13-H(*Z*)], 5.38 (1H, ddd, *J* 16.6, 7.2 and 1.0, 18-H), 4.25 [2H, q, *J* 7.1, OCH_2Me(*Z*)], 4.20 [2H, q, *J* 7.1, OCH_2-Me(*E*)], 4.02 (1H, m, 17-H), 3.92 (1H, m, 24-H), 3.48 (1H, dd, *J* 10.0 and 4.0, 21-H), 3.36 (3H, s, 25-OMe), 3.31 (1H, m, 25-H), 2.48 (1H, m, 14-H), 2.34 (4H, m, 20-H, 22-H and 9-H_2), 1.96 (1H, m, 23-H_1), 1.70 (1H, m, 6-H), 1.65 (1H, m, 23-H_1), 1.4–0.75 (11H, m, 7-H_2, 8-H_2, 15-H_2, 16-H_2, OCH_2CH_3), 1.08 (6H, 2 × d, *J* 7.1 and 7.2, 6-Me, 26-Me), 0.99 (3H, d, *J* 6.6, 29-Me), 0.92 (6H, m, 27-Me, 28-Me), 0.87 (9H, s, Si-Bu^t), 0.02 (3H, s, SiMe), 0.01 (3H, s, SiMe).

(2*E*,8*E*,10*Z*,16*E*,1″*S*,2′*R*,3′*S*,4*R*,5′*R*,12*R*,15*S*,18*S*)-Methyl 15-*tert*-butyldimethylsilyloxy-10-ethoxycarbonyl-18-[tetrahydro-5′-(1″-methoxyethyl)-3′-methylfuran-2′-yl]-2,4,12-trimethylnonadeca-2,8,10,16-tetraenoate 47a and (2*E*,8*E*,10*E*,16*E*,1″*S*,2′*R*,3′*S*,4*R*, 5′*R*,12*R*,15*S*,18*S*)-methyl *tert*-butyldimethylsilyloxy-10-ethoxycarbonyl-18-[tetrahydro-5′-(1″-methoxyethyl)-3-methylfuran-2′-yl]-2,4,12-trimethylnonadeca-2,8,10,16-tetraenoate 47b

The aldehyde **46** (63 mg, 0.101 mmol) was dissolved in chloroform (10 cm^3) and then 2-(methoxycarbonyl)ethylenetriphenylphosphorane (200 mg, 0.555 mmol) was added. The reaction was heated under reflux in the dark for 16 hours, concentrated *in vacuo* and then dissolved in ether. The solution was filtered through a small pad of silica washing with 50% ether–petrol and the combined filtrates and washings concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 25% ether–petrol) to give the *tetraene*-**47** (70 mg, 100%) (Found: C, 69.43; H, 10.10. $C_{40}H_{70}O_7Si$ requires C, 69.52; H, 10.22%); ν_{max}(thin film)/cm^{-1} 2956, 2928, 2854, 1714, 1645, 1459, 1371, 1248, 1190, 1152, 1095, 964, 835, 776 and 750; δ_H(500 MHz; $CDCl_3$) 6.65 (1H, dd, *J* 10.1 and 1.4, 5-H), 6.35 [1H, d, *J* 10.4, 13-H(*E*)], 5.95 (1H, d, *J* 15.7, 11-H), 5.64 (2H, m, 10-H, 19-H), 5.47 [1H, d, *J* 10.3, 13-H(*Z*)], 5.38 (1H, dd, *J* 15.6 and 6.7, 18-H), 4.25 [2H, q, *J* 7.1, OCH_2Me(*Z*)], 4.20 [2H, q, *J* 7.1, OCH_2Me(*E*)], 4.03 (1H, m, 17-H), 3.94 (1H, m, 24-H), 3.73 (3H, s, CO_2Me), 3.49 (1H, dd, *J* 9.4 and 4.1, 21-H), 3.36 (3H, s, 25-OMe), 3.32 (1H, m, 25-H), 2.47 (2H, m, 6-H, 14-H), 2.22 (2H, m, 20-H, 22-H), 2.06 (2H, m, 9-H_2), 1.96 (1H, m, 23-H_1), 1.83 (3H, d, *J* 1.5, 32-Me), 1.65 (1H, m, 23-H_1), 1.5–1.2 (8H, m, 7-H_2, 8-H_2, 15-H_2, 16-H_2), 1.31 (3H, t, *J* 7.1, OCH_2CH_3), 1.08 (3H, d, *J* 6.3, 26-Me), 0.99 (3H, d, *J* 6.6, 31-Me), 0.98 (3H, d, *J* 6.6, 27-Me), 0.92 (6H, d, *J* 6.9, 28-Me, 29-Me), 0.87 (9H, s, OSi-Bu^t), 0.02 (3H, s, SiMe), 0.01 (3H, s, SiMe); *m*/*z* (CI) 708 ($M^+ + NH_4$), 559 (M^+ − TBDMS − Me), 513 (M^+ − TBDMSO − OEt), 417, 388, 315, 143 [Found (CI) MNH_4^+ 708.5235. $C_{40}H_{74}O_7NSi$ requires 708.5234].

(2*E*,8*E*,10*Z*,16*E*,1″*S*,2′*R*,3′*S*,4*R*,5′*R*,12*R*,15*S*,18*S*)-Methyl 10-ethoxycarbonyl-15-hydroxy-18-[tetrahydro-5′-(1″-methoxyethyl)-3′-methylfuran-2-yl]-2,4,12-trimethylnonadeca-2,8,10,16-tetraenoate 48a and (2*E*,8*E*,10*E*,16*E*,1″*S*,2′*R*,3′*S*,4*R*,5′*R*,12*R*,15*S*,18*S*)-methyl 10-ethoxycarbonyl-15-hydroxy-18-[tetrahydro-5′-(1″-methoxyethyl)-3′-methylfuran-2′-yl]-2,4,12-trimethylnonadeca-2,8,10,16-tetraenoate 48b

The tetraene **47** (366 mg, 0.53 mmol) was dissolved in methanol (12 cm^3) and Dowex-50W 400 mesh (4 mg) was added. The reaction was stirred for 48 hours then the resin filtered off and washed exhaustively with ether. The combined organic extracts were concentrated *in vacuo* and the residue was purified by chromatography (SiO_2, 70% ether–petrol), to give *alcohol* **48** (134 mg, 100%) (Found: C, 70.09; H, 9.78. $C_{34}H_{56}O_7$ requires C, 70.80; H, 9.79%); ν_{max}(thin film)/cm^{-1} 3436, 2963, 2930, 1713, 1646, 1452, 1378, 1248, 1189, 1093, 1015, 966 and 751; δ_H(500 MHz; $CDCl_3$) 6.52 (1H, dd, *J* 10.0 and 1.4, 5-H), 6.35 [1H, d, *J* 9.6, 13-H(*E*)], 5.95 (1H, d, *J* 15.7, 11-H), 5.70 (1H, dd, *J* 15.6 and 7.2, 19-H), 5.62 (1H, dt, *J* 15.7 and 6.7, 10-H), 5.50 (1H, ddd, *J* 15.6, 7.1 and 0.9, 18-H), 5.48 [1H, d, *J* 9.7, 13-H(*Z*)], 4.26 [2H, q, *J* 7.1, OCH_2Me(*Z*)], 4.20 [2H, q, *J* 7.2, OCH_2-MeH(*E*)], 4.01 (2H, m, 17-H, 24-H), 3.73 (3H, s, CO_2Me), 3.52 (1H, dd, *J* 9.7 and 4.0, 21-H), 3.37 (3H, s, 25-OMe), 3.33 (1H, m, 25-H), 2.57 (2H, m, 6-H, 14-H), 2.25 (2H, m, 20-H, 22-H), 2.05 (2H, m, 9-H_2), 1.97 (1H, m, 23-H_1), 1.83 (3H, d, *J* 1.4, 32-Me), 1.32 (9H, m, 7-H_2, 8-H_2, 15-H_2, 16-H_2, 23-H_1), 1.31 (3H, t, *J* 7.1, OCH_2CH_3), 1.08 (3H, d, *J* 6.3, 26-Me), 1.00 (3H, d, *J* 6.4, 31-Me), 0.99 (3H, d, *J* 6.6, 27-Me), 0.93 (3H, d, *J* 6.8, 28-Me or 29-Me), 0.92 (3H, d, *J* 6.9, 28-Me or 29-Me); *m*/*z* (CI) 594 (MNH_4^+), 576 (M^+), 559 (M^+ − OH), 530, 513, 143 [Found (CI) MNH_4^+ 594.4370. $C_{34}H_{60}O_7N$ requires 594.4369].

(2*Z*)-Ethyl 2-[(2*R*,3*R*,6*S*)-tetrahydro-3-methyl-6-{3-(1*E*)-[(1′*S*,2*R*,3*S*,5*R*)-tetrahydro-5-(1′-methoxyethyl)-3-methylfuran-2-yl]but-1-enyl}-2*H*-pyran-2-yl)-3-(1*S*,1′*R*,2*S*,3*R*)-[3-methyl-2-(1′-methoxycarbonylethyl)cyclohexyl]prop-2-enoate 49

(*a*) The alcohol **48** (34.4 mg, 0.0596 mmol) was dissolved in toluene (4 cm^3) and cooled to 0 °C for 15 minutes in an ice bath. Potassium bis(trimethylsilyl)amide (131 µl, 0.5 M solution in toluene, 0.065 mmol) was added quickly and the yellow solution stirred for 30 minutes. The reaction was quenched with a dilute solution of acetic acid in toluene and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 35% ether–petrol), to give *diester* **49** (27 mg, 67%).

(*b*) The alcohol **48** (10.5 mg, 0.0182 mmol) was dissolved in toluene (1 cm^3), HMPA (3 µl, 0.0182 mmol) was added and the solution was cooled to 0 °C for 15 minutes in an ice bath. Potassium bis(trimethylsilyl)amide (40 µl, 0.5 M solution in toluene, 0.02 mmol) was added quickly and the yellow solution stirred for 30 minutes. The reaction was quenched with a dilute solution of acetic acid in toluene and extracted with ether (3 × 20 cm^3). The organics were washed with water and brine, then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 35% ether–petrol) to give *diester* **49** (6.5 mg, 62%) (Found: C, 69.93; H, 9.46. $C_{34}H_{56}O_7$ requires C, 70.80; H, 9.79%); $[a]_D^{20}$ −22.5 (*c* 0.92 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2923, 1725, 1451, 1371, 1205, 1095 and 1013; δ_H(500 MHz; $CDCl_3$) 5.89 (1H, d, *J* 10.5, 11-H), 5.76 (1H, dd, *J* 15.9 and 6.3, 19-H), 5.50 (1H, dd, *J* 15.1 and 5.7, 18-H), 4.20 (2H, q, *J* 7.1, OCH_2Me), 3.95 (1H, ddd, *J* 8.6, 7.0 and 5.0, 24-H), 3.82 (1H, m, 17-H), 3.77 (1H, d, *J* 9.8, 13-H), 3.66 (3H, s, CO_2Me), 3.50 (1H, dd, *J* 9.5 and 4.1, 21-H), 3.38 (3H, s, 25-OMe), 3.34 (1H, qd, *J* 6.3 and 5.0, 25-H), 2.83 (1H, dtd, *J* 11.0, 11.0 and 3.1, 10-H), 2.51 (1H, m, 4-H), 2.23 (2H, m, 20-H, 22-H), 1.96 (1H, ddd, *J* 12.4, 8.6 and 6.8, 23-H_1), 1.83–1.50 (8H, m, 15-H_1, 5-H, 9-H_1, 23-H_1, 8-H_1, 7-H_1, 16-H_1, 14-H), 1.38–1.00 (6H, m, 6-H, 7H_1, 15-H_1, 8-H_1, 9-H_1, 16-H_1), 1.29 (3H, t, *J* 7.1, OCH_2CH_3), 1.08 (3H, d, *J* 6.9, 26-Me), 1.07 (3H, d, *J* 6.9, 32-Me), 0.93 (3H, d, *J* 6.8, 27-Me or 28-Me), 0.92 (3H, d, *J* 6.9, 27-Me or 28-Me), 0.75 (3H, d, *J* 7.5, 31-Me), 0.74 (3H, d, *J* 6.6, 29-Me); δ_C(125.6 MHz; $CDCl_3$) 177.59 (CO_2Et), 167.59 (CO_2CH_3), 145.41 (11-C), 138.62 (12-C), 134.07 (19-C), 130.13 (18-C), 85.91 (21-C), 83.72 (13-C), 80.23 (24-C), 79.54 (25-C), 78.40 (17-C), 60.13 (OCH_2CH_3), 57.42 (25-OMe), 51.49 (CO_2Me), 49.85 (5-C), 40.79 (10-C), 40.36 (4-C), 36.60 (20-C or 22-C), 36.09 (14-C), 35.82 (16-C), 35.29 (23-C), 35.23 (20-C or 22-C), 33.22 (9-C), 32.94 (15-C), 32.74 (6-C), 32.44 (7-C), 25.49 (8-C), 19.78 (31-C), 17.65 (29-C), 16.44 (27-C or 28-C), 15.94 (26-C), 14.27 (OCH_2CH_3), 13.51 (27-C or 28-C), 8.97 (32-C); *m*/*z* (EI) 594 (MNH_4^+), 143 and 85 [Found (EI) M^+ 576.4030. $C_{34}H_{56}O_7$ requires 576.4025].

(2*R*)-2-((1*S*,2*S*,6*R*)-6-Methyl-2-{3-hydroxy-2-[(2*R*,3*R*,6*S*)-tetrahydro-3-methyl-6-(1*E*)-((2*R*,3*S*,5*R*)-3-{tetrahydro-5-[(*R*)-1-methoxyethyl]-3-methylfuran-2-yl}but-1-enyl)-2*H*-pyran-2-yl]prop-1-enyl}cyclohexyl)propanol 50 and (2*R*)-methyl 2-((1*S*,2*S*,6*R*)-6-methyl-2-{3-hydroxy-2-[(2*R*,3*R*,6*S*)-tetrahydro-3-methyl-6-(1*E*)-((2*R*,3*S*,5*R*)-3-{tetrahydro-5-[(1*R*)-1-methoxyethyl]-3-methylfuran-2-yl}but-1-enyl)-2*H*-pyran-2-yl]prop-1-enyl}cyclohexyl)propanoate 51

Diester **49** (24 mg, 0.042 mmol) was stirred in dry THF (1 cm^3) at room temperature under argon. Lithium borohydride (0.2 cm^3, 2.0 M solution in THF, 0.4 mmol) was then added. After 60 hours methanol (5 cm^3) was added, the reaction mixture stirred for a further 10 minutes and solvent then removed *in vacuo*. The crude residue was then co-evaporated with methanol (3 × 5 cm^3) and purified by flash chromatography (85% petrol–ethyl acetate) to give *monomethyl ester* **51** (13 mg, 58%) as a colourless oil together with some recovered starting material (1 mg, 4%) and more polar material identified as the di-reduced compound **50** (4 mg, 19%). *Monomethyl ester* **51** $[\alpha]_D^{20}$ −18.3 (*c* 0.3 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3528, 2926, 1733, 1456, 1379, 1297, 1260, 1205, 1094, 1055, 1014, 911, 862 and 801; δ_H(500 MHz; $CDCl_3$) 5.76 (1H, dd, *J* 15.8 and 6.5, 19-H), 5.51 (1H, dd, *J* 15.8 and 5.9, 18-H), 5.26 (1H, d, *J* 10.0, 11-H), 4.18 (1H, dd, *J* 11.7 and 8.9, 30-H_1), 4.11 (1H, dd, *J* 11.9 and 2.2, 30-H_2), 3.95 (1H, ddd, *J* 8.6, 6.9 and 4.8, 24-H), 3.79 (1H, m, 17-H), 3.66 (3H, s, CO_2Me), 3.53 (1H, d, *J* 10.0, 13-H), 3.50 (1H, dd, *J* 9.6 and 4.2, 21-H), 3.37 (3H, s, 25-OMe), 3.33 (1H, qd, *J* 6.3 and 5.0, 25-H), 3.09 (1H, dd, *J* 8.8 and 2.1, OH), 2.73 (1H, m, 4-H), 2.23 (3H, m, 10-H, 20-H, 22-H), 1.97 (1H, ddd, *J* 12.4, 8.7 and 6.7, 23-H_1), 1.86 (1H, m, 15-H_1), 1.73 (1H, m, 5-H), 1.67–1.12 (12H, m, 6-H, 7-H_2, 8-H_2, 9-H_2, 14-H, 15-H_1, 16-H_2, 23-H_1), 1.08 (3H, d, *J* 6.7, 32-Me), 1.07 (3H, d, *J* 6.1, 26-Me), 0.92 (3H, d, *J* 6.9, 28-Me), 0.91 (3H, d, *J* 7.1, 27-Me), 0.75 (3H, d, *J* 6.5, 31-Me), 0.69 (3H, d, *J* 6.6, 29-Me); *m*/*z* (CI) 552 (MNH_4^+), 535 (M^+ + H), 517 (M^+ + H − H_2O), 143, 111, 85 and 59 [Found (CI) MNH_4^+ 552.426. $C_{32}H_{58}NO_6$ requires 552.426].

Diol **50** $[\alpha]_D^{20}$ −4.94 (*c* 0.85 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3446, 2965, 2925, 2848, 1646, 1519, 1452, 1376, 1297, 1225, 1192, 1152, 1055, 1012, 908, 863 and 802; δ_H(500 MHz; $CDCl_3$) 5.69 (1H, dd, *J* 15.7 and 7.4, 19-H), 5.48 (1H, dd, *J* 15.7 and 6.8, 18-H), 5.27 (1H, d, *J* 10.0, 11-H), 4.23 (1H, dd, *J* 11.8 and 8.1, 30-H_1), 4.12 (1H, dd, *J* 11.4, 30-H_1), 3.98 (1H, ddd, *J* 9.0, 6.9 and 4.2, 24-H), 3.80 (1H, m, 17-H), 3.54 (3H, m, 3-H_2, 21-H), 3.53 (1H, d, *J* 10.0, 13-H), 3.40 (1H, m, 25-H), 3.38 (3H, s, 25-OMe), 2.94 (1H, d, *J* 8.1, 20-OH), 2.37 (1H, s, 3-OH), 2.27 (3H, m, 10-H, 6-H and 20-H), 2.02 (2H, m, 23-H_1, 22-H), 1.87 (1H, m, 15-H_1), 1.77 (4H, m, 14-H, 23-H_1, 8-H_1, 7-H_1), 1.43 (3H, m, 16-H_1, 4-H, 9-H_1), 1.21 (2H, m, 8-H_1, 15-H_1, 16-H_1), 1.05 (3H, d, *J* 6.4, 26-Me), 1.00 (2H, m, 9-H_1, 7-H_1), 0.92 (12H, m, 27-Me, 28-Me, 31-Me and 32-Me), 0.69 (3H, d, *J* 6.6, 29-Me); δ_C(125.6 MHz; $CDCl_3$) 139.62 (11-C), 135.49 (19-C), 134.27 (12-C), 129.86 (18-C), 91.19 (13-C), 85.83 (21-C), 80.27 (24-C), 79.26 (25-C), 78.64 (17-C), 68.23 (3-C), 58.39 (30-C), 57.36 (25-OMe), 49.17 (5-C), 39.84 (10-C), 38.45 (22-C), 36.93 (20-C), 36.61 (7-C), 35.10 (6-C), 34.96 (23-C), 34.58 (9-C), 33.26 (4-C), 32.43 (14- or 15- or 16-C), 32.39 (14- or 15- or 16-C), 32.30 (14- or 15- or 16-C), 25.63 (8-C), 22.23 (31-C), 18.00 (29-C), 16.73 (27- or 28-C), 15.79 (26-C), 13.52 (27- or 28-C), 12.44 (32-C); *m*/*z* (CI) 507 (MH^+), 489, 471 (M^+ − $2H_2O$), 329, 234, 223, 183, 167, 143, 111, 85 and 41 [Found (CI) M^+ 507.405. $C_{31}H_{55}O_5$ requires 507.405].

(2*R*)-Methyl 2-((1*S*,2*S*,6*R*)-6-methyl-2-(3-*tert*-butyldimethylsilyloxy-2-[(2*R*,3*R*,6*S*)-tetrahydro-3-methyl-6-(1*E*)-[(2*R*,3*S*,5*R*)-3-{tetrahydro-5-[(*R*)-1-methoxyethyl]-3-methylfuran-2-yl}but-1-enyl)-2*H*-pyran-2-yl]prop-1-enyl}cyclohexyl)propanoate 52

Alcohol **51** (10 mg, 0.019 mmol) and dry pyridine (6.2 cm^3, 0.076 mmol) were stirred in dry THF (3 cm^3) at −30 °C under argon. *tert*-Butyldimethylsilyl triflate (9 cm^3, 0.038 mmol) was added and stirring was continued at this temperature. After 30 minutes methanol (0.5 cm^3) was added and the reaction mixture allowed to warm to room temperature. The solvent was removed *in vacuo* and the residue purified by flash chromatography (90% petrol–ethyl acetate) to give *silyl ether* **52** (11 mg, 91%) as a colourless oil; $[\alpha]_D^{20}$ −38.1 (*c* 0.75 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 2927, 2855, 1735, 1462, 1378, 1254, 1205, 1064, 839 and 775; δ_H(500 MHz; $CDCl_3$) 5.75 (1H, dd, *J* 15.9 and 6.9, 19-H), 5.52 (1H, dd, *J* 15.5 and 6.3, 18-H), 5.28 (1H, d, *J* 9.9, 11-H), 4.13 (1H, d, *J* 10.8, 30-H_1), 4.06 (1H, d, *J* 10.7, 30-H_1), 3.95 (1H, m, 24-H), 3.77 (1H, m, 17-H), 3.65 (3H, s, CO_2Me), 3.51 (1H, dd, *J* 9.5 and 4.0, 21-H), 3.37 (3H, s, 25-OMe), 3.36 (1H, d, *J* 9.8, 13-H), 3.35 (1H, qd, *J* 6.7 and 5.1, 25-H), 2.65 (1H, m, 4-H), 2.31 (1H, m, 10-H), 2.2 (2H, m, 20-H, 22-H), 1.98 (1H, m, 23-H_1), 1.80 (1H, m, 15-H_1), 1.69 (1H, m, 5-H), 1.67–1.12 (12H, m, 6-H, 7-H_2, 8-H_2, 9-H_2, 14-H, 15-H_1, 16-H_2, 23-H_1), 1.07 (3H, d, *J* 6.3, 26-Me), 1.02 (3H, d, *J* 7.1, 32-Me), 0.94 (3H, d, *J* 6.8, 28-Me), 0.91 (3H, d, *J* 7.0, 27-Me), 0.87 (9H, s, Si-Bu^t), 0.74 (3H, d, *J* 6.6, 31-Me), 0.73 (3H, d, *J* 6.5, 29-Me), 0.07 (3H, s, SiMe), 0.06 (3H, s, SiMe); *m*/*z* (CI) 666 (MNH_4^+), 517 (M^+ − TBDMSO), 143, 111, 85 and 59 [Found (CI) MNH_4^+ 666.513. $C_{38}H_{72}NO_6Si$ requires 666.513].

(2*R*)-2-((1*S*,2*S*,6*R*)-6-Methyl-2-(3-*tert*-butyldimethylsilyloxy-2-[(2*R*,3*R*,6*S*)-tetrahydro-3-methyl-6-(1*E*)-((2*R*,3*S*,5*R*)-3-{tetrahydro-5-[(*R*)-1-methoxyethyl]-3-methylfuran-2-yl}but-1-enyl)-2*H*-pyran-2-yl]prop-1-enyl}cyclohexyl)propanol 53

Ester **52** (11.0 mg, 0.017 mmol) was stirred in dry dichloromethane (3 cm^3) at −78 °C under argon. DIBAL-H (26 cm^3 of a 1.0 M solution in dichloromethane, 0.026 mmol) was then added and the reaction mixture stirred at this temperature. After 30 minutes saturated aqueous sodium potassium tartrate (0.5 cm^3) and methanol (0.5 cm^3) were then added and the reaction mixture allowed to warm to room temperature overnight. Further dichloromethane (5 cm^3) and water (5 cm^3) were added and the aqueous layer separated. The organic extracts were dried ($MgSO_4$), filtered, the solvent removed *in vacuo* and the residue purified by flash chromatography (80% petrol–ethyl acetate) to give *alcohol* **53** (8.3 mg, 79%) as a colourless oil; $[\alpha]_D^{20}$ −27 (*c* 0.2 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3470 br (OH); δ_H(500 MHz; $CDCl_3$) 5.62 (1H, dd, *J* 15.4 and 8.3, 19-H), 5.47 (1H, dd, *J* 15.4 and 7.7, 18-H), 5.28 (1H, d, *J* 10.2, 11-H), 4.07 (2H, m, 30-H_2), 3.99 (1H, ddd, *J* 9.9, 6.9 and 3.6, 24-H), 3.79 (1H, m, 17-H), 3.58 (1H, dd, *J* 10.0 and 4.0, 21-H), 3.52–3.45 (3H, m, 3-H_2, 25-H), 3.40–3.38 (1H, m, 13-H), 3.38 (3H, s, 25-OMe), 2.29–2.18 (3H, m, 10-H, 20-H, 22-H), 2.12–2.06 (1H, m, 23-H_1), 1.84 (1H, m, 4-H), 1.70–0.90 (14H, m), 1.02 (3H, d, *J* 6.4, 26-Me), 0.91–0.88 (12H, 4 × d, 27-Me, 28-Me, 31-Me, 32-Me), 0.88 (9H, s, Bu^t), 0.76 (3H, d, *J* 6.5, 29-Me), 0.07, 0.06 (6H, 2 × s, Me_2Si); *m*/*z* (FAB) 622 (MH^+, 40%), 488 (50), 154 (75), 143 (100) [Found (FAB) MH^+ 621.492 50. $C_{37}H_{69}O_5Si$ requires 621.49143].

(2*R*)-2-((1*S*,2*S*,6*R*)-6-Methyl-2-(3-*tert*-butyldimethylsilyloxy-2-[(2*R*,3*R*,6*S*)-tetrahydro-3-methyl-6-(1*E*)-((2*R*,3*S*,5*R*)-3-{tetrahydro-5-[(*R*)-1-methoxyethyl]-3-methylfuran-2-yl)but-1-enyl)-2*H*-pyran-2-yl]prop-1-enyl}cyclohexyl)propanal 54

Alcohol **53** (8.3 mg, 0.013 mmol) was stirred in dry dichloromethane (2 cm^3) under argon at room temperature. Dess–Martin periodinane (11.4 mg, 0.027 mmol) was then added. After 20 minutes the solvent was then removed *in vacuo* and the residue purified by flash chromatography (80% petrol–ethyl acetate, 5:1) to give *aldehyde* **54** (7.3 mg, 88%) as a colourless oil; $[\alpha]_D^{20}$ −60 (*c* 0.14 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1721 (C=O); δ_H(500 MHz; $CDCl_3$) 9.71 (1H, s, 3-H), 5.74 (1H, dd, *J* 15.8 and 6.6, 19-H), 5.51 (1H, dd, *J* 15.8 and 6.0, 18-H), 5.24 (1H, d, *J* 10.1, 11-H), 4.14 (1H, d, *J* 10.8, 30-H_1), 4.06 (1H, d, *J* 10.8, 30-H_1), 3.95 (1H, ddd, *J* 12.0, 7.0 and 4.9, 24-H), 3.77 (1H, br dd, *J* 10.0 and 6.3, 17-H), 3.51 (1H, dd, *J* 9.5 and 4.0, 21-H), 3.36 (3H, s, 25-OMe), 3.36 (2H, m, 13-H, 25-H), 2.52 (1H, br q,

J 6.6, 4-H), 2.43 (1H, dq, *J* 10.8 and 3.7, 10-H), 2.26–2.10 (2H, m, 20-H, 22-H), 1.97 (1H, ddd, *J* 15.3, 8.5 and 7.0, 23-H_1), 1.84–1.81 (2H, m), 1.70–1.10 (12H, m), 1.07 (3H, d, *J* 6.3, 26-Me), 1.02 (3H, d, *J* 6.9, 32-Me), 0.93, 0.91 (6H, 2 × d, *J* 7.0, 6.8, 27-Me, 28-Me), 0.88 (9H, s, Bu^t), 0.74 (3H, d, *J* 6.5, 29-Me), 0.67 (3H, d, *J* 6.5, 31-Me), 0.07, 0.06 (6H, 2 × s, Me_2Si); *m*/*z* (electrospray): Found MNa^+ 641.460. $C_{37}H_{66}NaO_5Si$ requires: 641.458.

(2*S*)-2-((1*S*,2*S*,6*R*)-6-Methyl-2-(3-*tert*-butyldimethylsilyloxy-2-[(2*R*,3*R*,6*S*)-tetrahydro-3-methyl-6-(1*E*)-((2*R*,3*S*,5*R*)-3-{tetrahydro-5-[(*R*)-1-methoxyethyl]-3-methylfuran-2-yl)but-1-enyl)-2*H*-pyran-2-yl]prop-1-enyl}cyclohexyl)propanal 55

Aldehyde **54** (4.0 mg, 6.5 mmol) together with morpholine (0.5 equiv.) and toluene-*p*-sulfonic acid (0.1 equiv.) were stirred together in dry dichloromethane (2 cm^3) at reflux under argon. After a period of 6 h the reaction mixture had boiled dry and the heat source was removed. Further dichloromethane (3 cm^3) was added and at this point TLC analysis indicated complete consumption of starting material and the formation of a single product. The crude reaction mixture was washed with dilute aqueous hydrochloric acid (1.0 M, 3 cm^3), water (2 cm^3), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was then purified by flash chromatography (90% petrol–ethyl acetate) to give *aldehyde* **55** (3.4 mg, 85%) as a colourless oil; $[\alpha]_D^{20}$ −34 (*c* 0.14 in $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1721 (C=O); δ_H(500 MHz; $CDCl_3$) 9.68 (1H, s, 3-H), 5.71 (1H, dd, *J* 1.58 and 6.3, 19-H), 5.52 (1H, dd, *J* 15.8 and 5.4, 18-H), 5.04 (1H, d, *J* 10.4, 11-H), 4.15 (1H, d, *J* 11.2, 30-H_1), 4.11 (1H, d, *J* 11.2, 30-H_2), 3.95 (1H, m, 24-H), 3.76 (1H, m, 17-H), 3.52 (1H, dd, *J* 9.3 and 4.1, 21-H), 3.38 (3H, s, 25-OMe), 3.35 (1H, m, 25-H), 3.28 (1H, d, *J* 9.9, 13-H), 2.50 (1H, br q, *J* 6.3, 4-H), 2.43 (1H, dq, *J* 10.4 and 3.0, 10-H), 2.27–2.20 (2H, m, 20-H, 22-H), 2.00–1.94 (1H, m, 23-H), 1.83–1.11 (14H, m), 1.09 (3H, d, *J* 7.1, 32-Me), 1.08 (3H, d, *J* 6.1, 26-Me), 0.94 (3H, d, *J* 6.8), 0.92 (6H, d, *J* 6.7), 0.88 (9H, s, Bu^t), 0.71 (3H, d, *J* 6.5, 29-Me), 0.07, 0.06 (6H, 2 × s, Me_2Si); *m*/*z* (MALDITOF) 527 (MNa^+ − TBDMS, 100%), 288 (90) [Found (electrospray) MNa^+ 641.459 68. $C_{37}H_{66}NaO_5Si$ requires 641.457 72].

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