Approaches to a synthesis of galbonolide B

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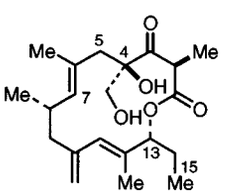
An approach to the C(7)–C(15) fragment of galbonolide B **2** has been completed in which the diene fragment **51** was assembled from (*R*)-3-*tert*-butyldimethylsilyloxypentan-2-one **29** by conversion into the unsaturated ester **30**, acylation of the sulfone **47** using this ester, reductive desulfurisation, methylenation using a Wittig reaction and deprotection. Following model studies, the aldehyde **62**, prepared by oxidation of the alcohol **51**, was converted into a mixture of the epimeric alcohols **63** and these were converted into the di(methylene)tridecadienoic acid **65** using a phosphine catalysed Ireland–Claisen rearrangement. Sharpless epoxidations of the alcohol **67** using either L-(+)- or D-(−)-diethyl tartrate were highly stereoselective and gave the epoxides **68** and **69** which were clearly distinguishable. Model studies using the heptadiene monoepoxide **70** led to a synthesis of the monoprotected dihydroxy aldehyde **76** so establishing a protocol for the introduction into the vicinal diol of the galbonolides. Finally, aldol addition of *tert*-butyl acetate to the aldehyde **78** followed by selective protection, deprotection and cyclisation completed a synthesis of the macrolide **85**.

The galbonolides are 14-membered macrolides which exhibit a broad range of antifungal activity.[1] The structure **1** originally



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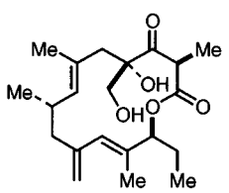

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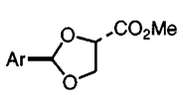

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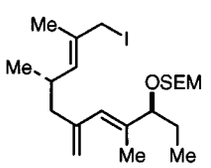

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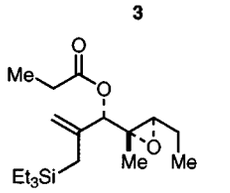

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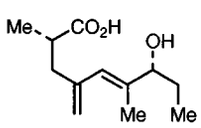

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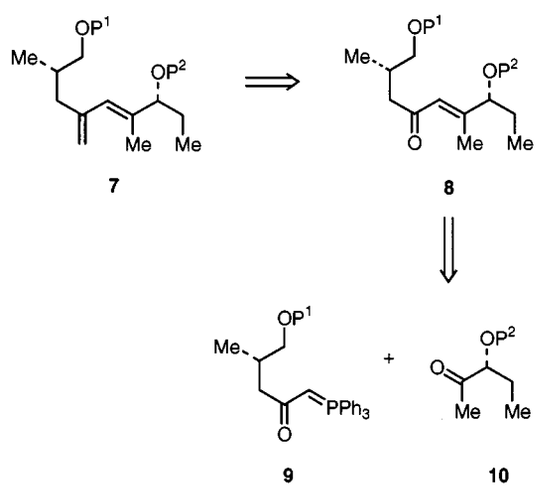
assigned to galbonolide B by reference to the Celmer model[1] was subsequently revised to the (4*S*,13*S*)-diastereoisomer **2** on the basis of an X-ray structure determination and a total synthesis in which a key step was the stereoselective alkylation of an enolate anion derived from dioxolane **3** using the iodide **4**.[2] In addition an ingenious stereoselective synthesis of the C(7)–C(15) fragment **6** has been described based on the Ireland–Claisen rearrangement of the propanoate **5** followed by 1,4-elimination to introduce the conjugated diene.[3] We here report an approach to the C(7)–C(15) fragment and studies into strategies for completion of a synthesis of galbonolide B **2**. This work was carried out before the structure of the natural product was revised and was directed towards the synthesis of the (4*R*,13*R*)-diastereoisomer **1**. Nevertheless, the chemistry should be applicable for a synthesis of the natural product.

At the onset of our work, it was intended to prepare the α,β-unsaturated ketone **8** by means of a Wittig condensation between the keto ylid **9** and the 3-alkoxypentan-2-one **10**, and to convert the ketone into the diene **7**, corresponding to the C(7)–C(15) fragment of galbonolide B, by methylenation (Scheme 1).

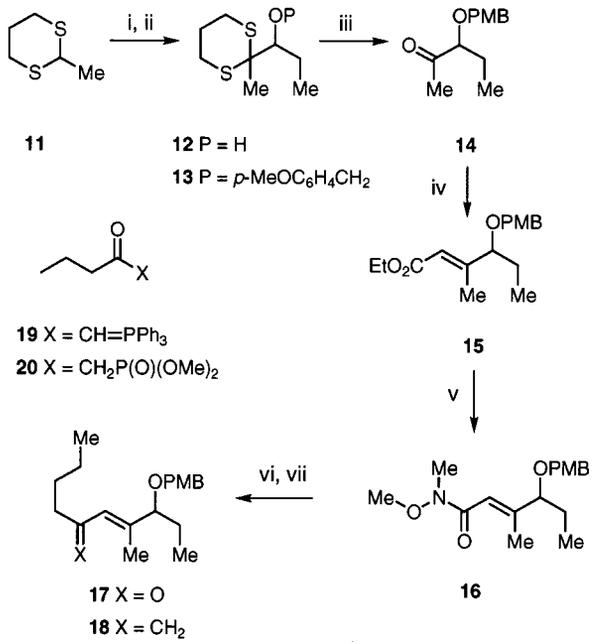


7 **8** **9** **10**

Scheme 1

Results and discussion

The diene **18** was synthesized to gain familiarity with the proposed chemistry, see Scheme 2. The racemic 3-alkoxypentan-2-one **14** was prepared in three steps from 2-methyl-1,3-dithiane **11**, with better results for the lithiation of the dithiane being obtained using *sec*-butyllithium. Although condensations of the ketone **14** with either the keto phosphorane **19** or the keto phosphonate **20** were unsuccessful (the reactants were generally recovered unchanged), the ketone **14** reacted cleanly with triethyl phosphonoacetate to give the unsaturated ester **15** as a 10:1 mixture of (*E*)- and (*Z*)-isomers (NOE). Ester **15** was converted into the Weinreb amide **16** which gave the ketone **17** on treatment with butyllithium, and a Wittig reaction of this enone with methylene(triphenyl)phosphorane gave the



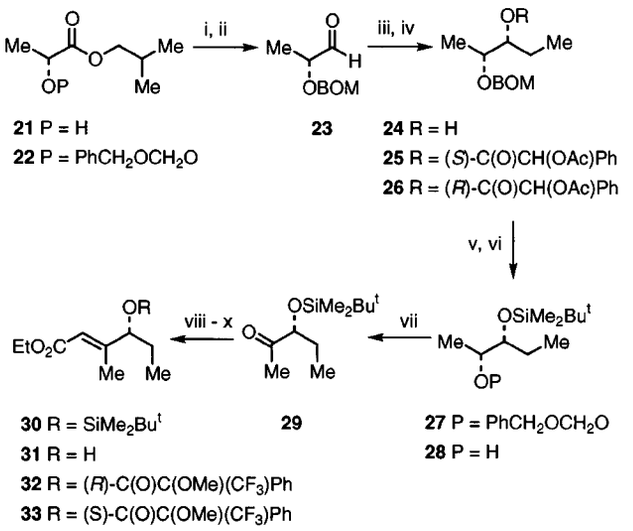
Scheme 2 *Reagents and conditions*: i, *sec*-Butyllithium, −20 °C then propanal, −78 °C (66%); ii, sodium hydride, 0 °C, then *p*-methoxybenzyl chloride, NBu_4I, DMF (77%); iii, mercuric chloride, calcium carbonate (85%); iv, triethyl phosphonoacetate, sodium hydride (79%); v, trimethylaluminium, *N*,*O*-dimethylhydroxylamine hydrochloride (62%); vi, *n*-butyllithium (46%); vii, Ph_3PMeBr, *n*-butyllithium (74%).

conjugated diene **18**. The difficulties in reacting the keto phosphorane **19** or keto phosphonate **20** with the ketone **14** have precedent[4] and may be due, at least in part, to the steric hindrance to attack on the 2-substituted ketone. However, the preparation of the ester **15** using triethyl phosphonoacetate, followed by conversion of the ester functionality into the ketone by addition of the organometallic reagent, provided a useful alternative synthesis of the α,β-unsaturated ketone. It was now necessary to prepare the enantiomerically enriched ester **15** for reaction with a chiral organometallic reagent to achieve a synthesis of the target fragment **7**.

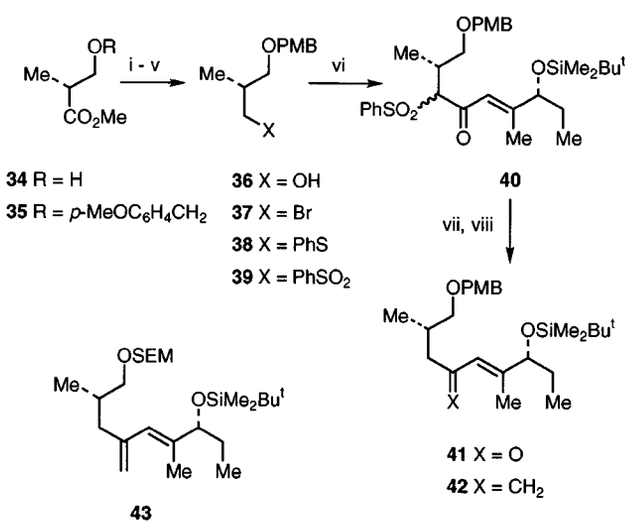
Commercially available isobutyl (*R*)-lactate **21** was converted into its benzyloxymethyl ester **22**[5] which was reduced to (2*R*)-2-(benzyloxymethoxy)propanal **23** (Scheme 3). Chelation controlled addition[6] of ethylmagnesium bromide to **23** was enhanced by the presence of zinc bromide[7] and gave predominantly the *syn*-alcohol **24** with *syn*:*anti*-stereoselectivities within the range *syn*:*anti* = 97:3 to 94:6, better stereoselectivity being obtained for smaller scale reactions. The configuration of the *syn*-alcohol **24** at C(3) was checked by comparison of the ^1H NMR chemical shifts of its *O*-acetylmandelates **25** and **26**.[8]

Protection–deprotection and oxidation then gave the 3-silyloxyketone **29** which was condensed with triethyl phosphonoacetate to give the (*R*)-ester **30**. The optical purity of this ester was checked by desilylation and conversion of the hydroxy ester **31** into its (*R*)- and (*S*)-Mosher's derivatives **32** and **33**. Comparison of the ^{19}F NMR spectra of these indicated that the optical purity of the hydroxy ester **31** was in the region of 84–96%, with better enantiomeric excesses being obtained for smaller scale preparations.

The bromide **37** was prepared from methyl (*R*)-3-hydroxy-2-methylpropanoate **34**, see Scheme 4, but preliminary attempts to convert this into either an organolithium or Grignard reagent for reaction with the Weinreb amide derived from the ester **30** resulted only in decomposition. The bromide was therefore converted, *via* sulfide **38**, into the sulfone **39** and conditions developed for the acylation of the lithiated sulfone by the ester **30** to yield ketone **40**. Significant improvements in the yield of this acylation were obtained when a solution of magnesium bromide–diethyl ether was added to the lithiated sulfone prior



Scheme 3 *Reagents and conditions*: i, $BnOCH_2Cl$, Hunig's base (72%); ii, diisobutylaluminium hydride, −78 °C (75%); iii, ethylmagnesium bromide, zinc bromide, 0 °C (65%); iv, (*R*)- or (*S*)-*O*-acetylmandelic acid, 4-*N*,*N*-dimethylaminopyridine, dicyclohexylcarbodiimide (56%); v, *tert*-butyldimethylsilyl chloride, imidazole (94%); vi, hydrogen, Pd/C, 60 psi (94%); vii, dimethyl sulfoxide, oxalyl chloride, −50 °C, triethylamine (98%); viii, triethyl phosphonoacetate, sodium hydride (89%); ix, Bu_4NF (92%); x, (*R*)- or (*S*)-Mosher's acid chloride, triethylamine, 4-*N*,*N*-dimethylaminopyridine (90%).

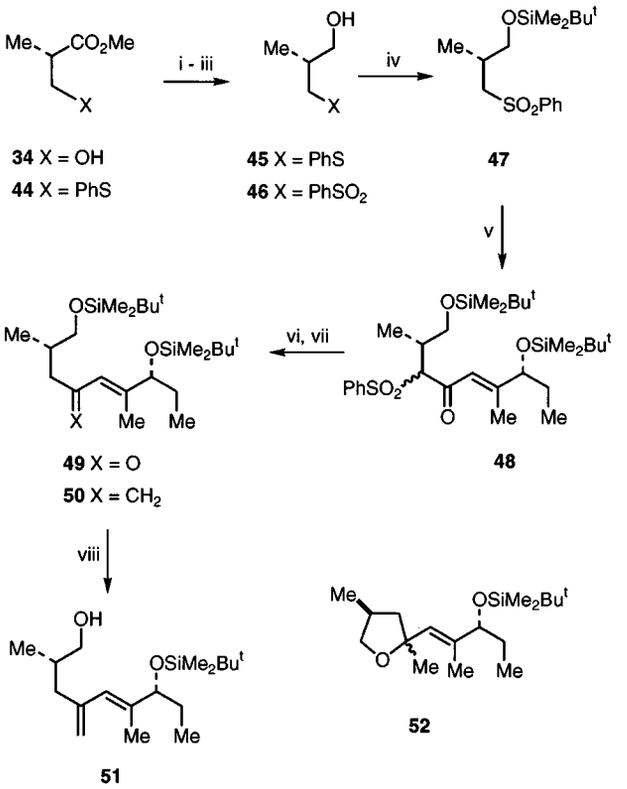


Scheme 4 *Reagents and conditions*: i, *p*-methoxybenzyl trichloroacetimidate, chlorosulfonic acid (78%); ii, lithium aluminium hydride (98%); iii, *N*-bromosuccinimide, triphenylphosphine (93%); iv, thiophenol, DBU (96%); v, oxone (86%); vi, *n*-butyllithium, $MgBr_2{\cdot}Et_2O$, then **30** (96%); vii, lithium naphthalenide, −78 °C (82%); viii, Ph_3PMeBr, *n*-butyllithium (76%).

to the addition of the ester.[9] Reductive desulfurisation[10] then gave the ketone **41** which was converted into the diene **42** using a Wittig reaction. It remained to deprotect the primary alcohol of **42** to complete a synthesis of the C(7)–C(15) fragment of the galbonolides. However, attempts to remove the *p*-methoxybenzyl group oxidatively using dichlorodicyanoquinone[11] or ceric ammonium nitrate[12] resulted in decomposition, and the use of other procedures[13] for removal of the *p*-methoxybenzyl group resulted in either decomposition, perhaps because of instability of the alcohol (*vide infra*) or recovery of starting material.

It was necessary to investigate the use of other protecting groups for the primary alcohol. Attempted deprotection of the SEM-ether **43**,[14] prepared following the route used to prepare the *p*-methoxybenzyl ether **42**, gave rise to a complex mixture of products even when buffered conditions were used. However,

monodesilylation[15] of the bis-*tert*-butyldimethylsilyl ether **50**, prepared as outlined in Scheme 5, gave the required primary



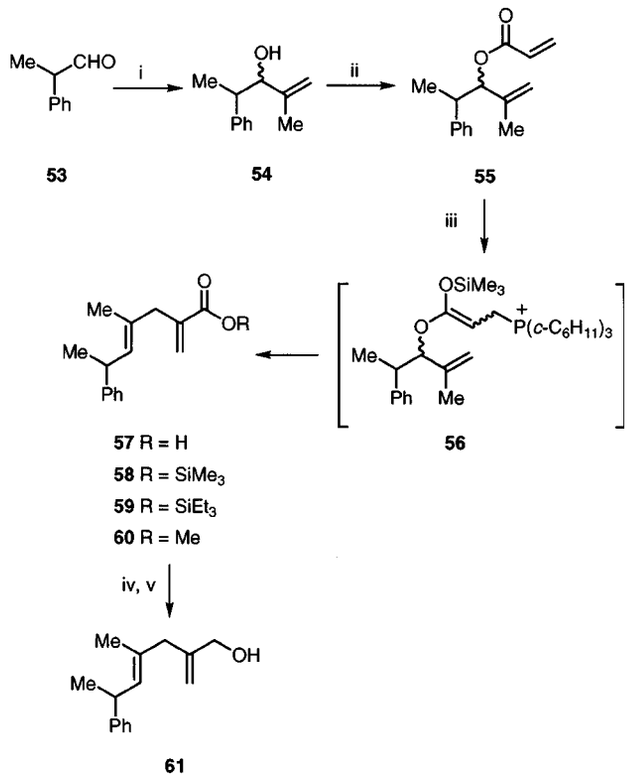
Scheme 5 *Reagents and conditions*: i, diphenyl disulfide, Bu_3P (96%); ii, lithium aluminium hydride (91%); iii, *m*-chloroperoxybenzoic acid (97%); iv, *tert*-butyldimethylsilyl chloride, imidazole (93%); v, butyllithium, magnesium bromide diethyl etherate, then **30** (90%); vi, lithium naphthalenide, −78 °C (70%); vii, methyl(triphenyl)phosphonium bromide, *n*-butyllithium (78%); viii, Bu_4NF (87%).

alcohol **51** in excellent yield (87%). This alcohol was found to be very sensitive to acid with cyclisation to the epimeric tetrahydrofurans **52** being observed on standing in chloroform.

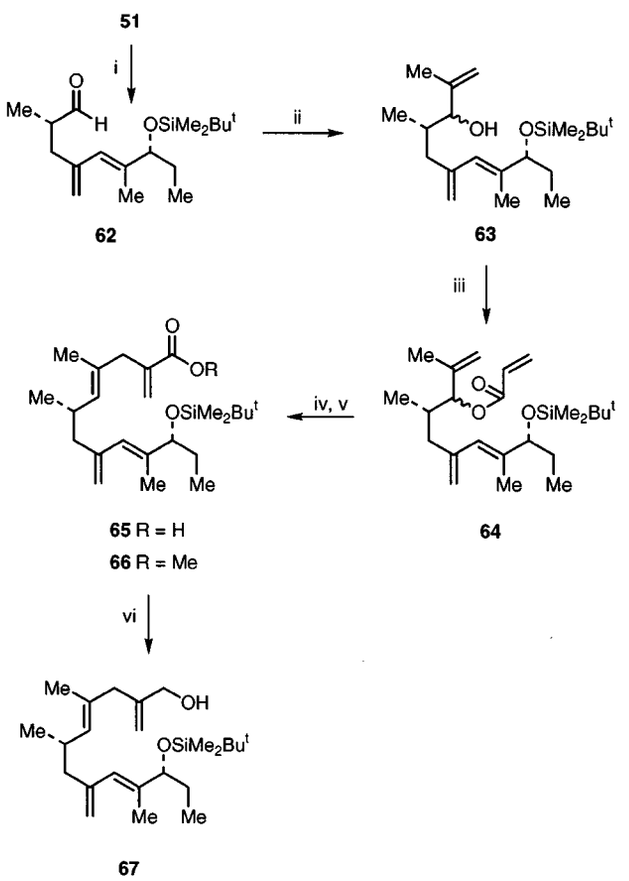
This phase of the work completed a convergent synthesis of the alcohol **51** which corresponds to the C(7)–C(15) fragment **7** of the galbonolides. At this point, the recently reported phosphine catalysed Ireland–Claisen rearrangement of α,β-unsaturated esters[16] was identified as a useful procedure for the preparation of advanced intermediates for a synthesis of galbonolide B **2**. To gain familiarity with this chemistry, model studies were carried out starting with (racemic) 2-phenylpropanal **53**.

Addition of prop-2-enyllithium to 2-phenylpropanal **53** gave a mixture of the secondary alcohols **54**[17] which were acylated with acryloyl chloride to give the esters **55** (Scheme 6). Rearrangement of these was achieved by heating a solution with tricyclohexylphosphine, trimethylsilyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile at 75 °C for 17 h, and gave a good yield of the dienyl acid **57** *via* the *in situ* generation and rearrangement of the silylated conjugate addition product **56**.[16] The use of trimethylsilyl chloride rather than triethylsilyl chloride was preferred because of the faster hydrolysis of the trimethylsilyl ester **58** compared with its triethylsilyl analogue **59**. Esterification of the acid **57** using diazomethane gave the methyl ester **60** which was reduced using diisobutylaluminium hydride to give the alcohol **61**.

The same procedures were used to convert the aldehyde **62**, prepared by oxidation of alcohol **51**, into the chain extended allylic alcohol **67**, see Scheme 7. Thus treatment of the aldehyde with 2-lithiopropene, generated in this case from 2-bromopropene by halogen–metal exchange using *tert*-butyllithium, gave the epimeric alcohols **63**. Alternatively, on a small



Scheme 6 *Reagents and conditions*: i, 2-bromopropene, *sec*-butyllithium (80%); ii, acryloyl chloride (57%); iii, tricyclohexylphosphine (cat.), trimethylsilyl chloride, DBU, acetonitrile, 75 °C, 17 h (75%); iv, diazomethane (82%); v, diisobutylaluminium hydride (72%).

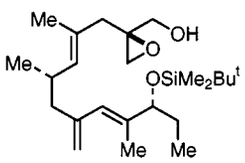


Scheme 7 *Reagents and conditions*: i, dimethyl sulfoxide, oxalyl chloride, −50 °C, then triethylamine; ii, 2-bromopropene, *tert*-butyllithium (75% from **51**); iii, acryloyl chloride, triethylamine (83%); iv, tricyclohexylphosphine (cat.), trimethylsilyl chloride, DBU, acetonitrile, 75 °C (96%); v, diazomethane (85%); vi, diisobutylaluminium hydride (90%).

scale, the aldehyde was reacted with 2-bromopropene and chromium(II) chloride.[18] Esterification of the alcohols **63** with acryloyl chloride gave the esters **64** which on treatment with tricyclohexylphosphine, trimethylsilyl chloride, and DBU in acetonitrile at 75 °C, gave the rearranged acid **65** in excellent yield (96%). Reduction of the corresponding methyl ester **66** gave the allylic alcohol **67**. The ester **66** and alcohol **67** have the same carbon skeleton as the C(3)–C(15) fragment of galbonolide B **2** and are promising advanced intermediates for incorporation into a synthesis of the natural product.

Two problems have to be addressed for a conversion of either the ester **66** or alcohol **67** into galbonolide B; the stereoselective introduction of the vicinal diol unit, and the chain extension to compete the assembly of the carbon framework. Moreover the sensitivity of the natural product to both acid and base[1] will determine the conditions allowable for any final deprotection.

It was considered that stereoselective epoxidation–epoxide-opening could be used for the introduction of the vicinal diol moiety and this approach was shown to be feasible by Sharpless epoxidation of the allylic alcohol **67**.[19] The use of L-(+)- and D-(−)-diethyl tartrate gave rise to the (*S*)- and (*R*)-epoxides **68** and **69** which were distinguishable by ^{1}H NMR spectroscopy.



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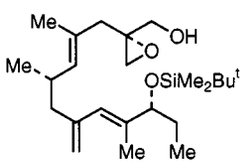

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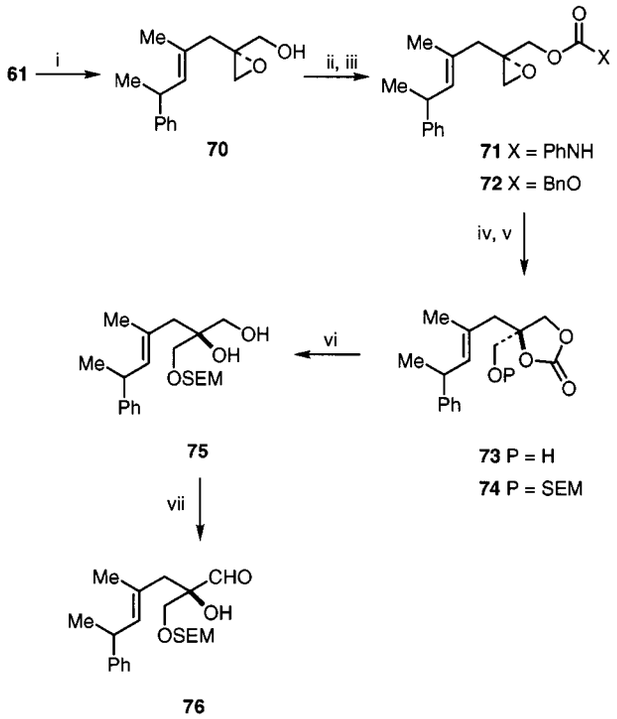
Excellent stereoselectivities were observed in these epoxidations with only traces of the minor diastereoisomer being obtained in each case. As preliminary studies into the ring-opening of these epoxides using oxygen nucleophiles were not successful, model studies were carried out at this juncture using the epoxides **70** prepared from the allylic alcohol **61**, see Scheme 8. As the starting alcohol was racemic, these epoxides were obtained as a 1 : 1 mixture of epimers at C(6), which could not be separated, but this mixture was used since it was felt that the remote chiral centre would have little effect on the chemistry of the epoxide.

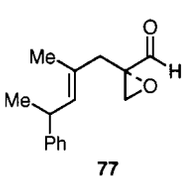
The epoxides **70** were converted into the carbamate **71**[20] and the carbonate **72**.[21] The Lewis acid induced ring-opening reactions of these were then studied as a route to the dioxolanone **73**. The choice of solvent was found to be important in these reactions. Aluminium trichloride, boron trifluoride–diethyl ether and diethylaluminum chloride all gave the dioxolanone **73** in yields of 40–45% from the benzyl carbonate **72** if ether was used as the solvent, a similar yield being obtained from the carbamate **71** using perchloric acid in acetonitrile. However better yields were obtained in dichloromethane, for example a 76% yield of the dioxolanone **73** was obtained from the benzyl carbonate **72** using aluminium chloride in this solvent and 69% was obtained using boron trifluoride–diethyl ether. The structure of the dioxolanone **73** was assigned on the basis of its spectroscopic data with the configuration at the tertiary centre being assigned by analogy with literature reactions.[20,21] Protection of the hydroxymethyldioxolanone gave the (2-trimethylsilylethoxy)methyl ether **74** which was hydrolysed to the diol **75**. This in turn was oxidized to the aldehyde **76** which structurally corresponds to the vicinal diol containing the C(3)–C(8) fragment of galbonolide B.

At this stage, it was decided to investigate procedures for the addition of the three remaining carbons to complete the synthesis of the carbon skeleton of galbonolide B. Preliminary attempts to effect stereoselective aldol reactions of the aldehydes **76** or **77**, prepared by oxidation of the hydroxy epoxide **70**, using enol borinates gave rise to complex mixtures of products. However, oxidation of the alcohol **67** using tetrapropylammonium perruthenate (TPAP)[22] gave the aldehyde **78** and addition of the lithium enolate generated from *tert*-butyl acetate using lithium hexamethyldisilazide gave the aldol adducts **79** as a mixture of epimers at C(3) (Scheme 9). These were protected as their *tert*-butyldiphenylsilyl ethers **80** as it was expected that removal of the *tert*-butyldimethylsilyl ether from C(13) would be faster than removal of the *tert*-butyldiphenylsilyl ether from C(3) so providing access to cyclisation precursors. However, this was not found to be the case. After cleavage of the *tert*-butyl ester, deprotection of the hydroxy group at C(3) by cleavage of the *tert*-butyldiphenylsilyl ether was faster than deprotection at C(13). Indeed deprotection of the *tert*-butyldimethylsilyl ether from C(13) required prolonged treatment with an excess of tetrabutylammonium fluoride.

Other protecting groups were screened for protection of the C(3)-hydroxy group. The alcohol **79** was converted into its (2-trimethylsilylethoxy)methyl ether **81**, but subsequent cleavage of the *tert*-butyl ester using trimethylsilyl triflate and triethylamine to obtain the free acid, was accompanied by elimination of the 3-substituent and gave the α,β-unsaturated acid **86** (68%) as the major product. However, after protection of the 3-hydroxy group as its *p*-methoxyphenoxymethyl ether **82**,[23] cleavage of the *tert*-butyl ester gave some of the required bis-protected dihydroxy acid **83** (35%), although the elimination product **86** was still obtained as a significant by-product (30%). Selective mono-deprotection of the *tert*-butyldimethylsilyl ether **83** by treatment with tetrabutylammonium fluoride then gave the hydroxy acid **84** which was cyclised to the macrolide **85** using the modified Yamaguchi method[24] in a yield of 43%.



Scheme 8 *Reagents and conditions*: i, titanium tetraisopropoxide, 3 Å sieves, *tert*-butyl hydroperoxide, D-(−)-diethyl tartrate (62%); ii, PhNCO (**71**, 73%); iii, benzyl chloroformate (**72**, 90%); iv, 5% aq. $HClO_4$ (45% from **71**) or aluminium trichloride, dichloromethane (76% from **72**); v, (2-trimethylsilylethoxy)methyl chloride, Hunig's base (52%); vi, lithium hydroxide, dimethoxyethane, water (81%); vii, dimethyl sulfoxide, oxalyl chloride then triethylamine (46%).



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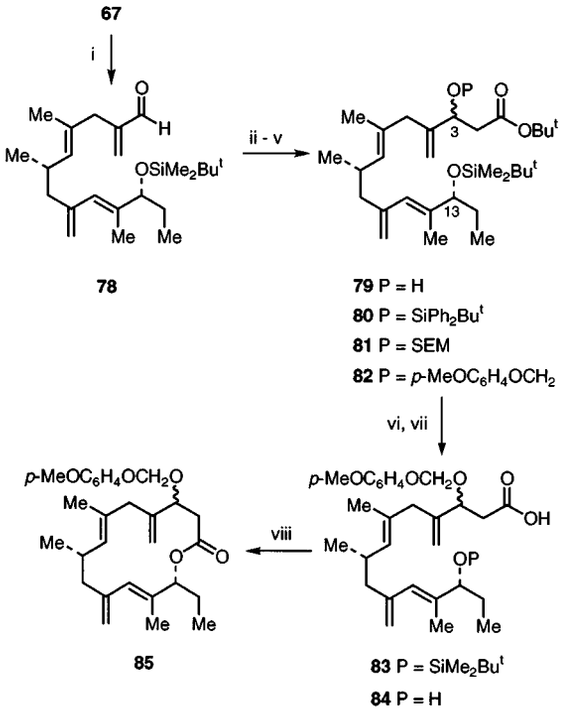
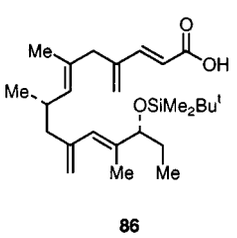


Scheme 9 *Reagents and conditions*: i, TPAP, *N*-morpholine *N*-oxide, 3 Å sieves (81%); ii, lithium hexamethyldisilazide–*tert*-butyl acetate, −78 °C (88%); iii, *tert*-butyldiphenylsilyl chloride, imidazole (93%); iv, (2-trimethylsilylethoxy)methyl chloride, Hunig's base (87%); v, *p*-$MeOC_6H_4OCH_2Cl$, Hunig's base (66%), vi, trimethylsilyl triflate, triethylamine (**83**, 35%; **86**, 30%); vii, Bu_4NF (69%); viii, 2,6-dichlorobenzoyl chloride, triethylamine, then 4-*N*,*N*-dimethylaminopyridine, toluene, 95 °C (43%).



Conclusions

The work outlined in this paper provides a basis for a proposed synthesis of galbonolide B. Aspects of general interest include the development of the highly stereoselective chelation controlled addition of ethylmagnesium bromide to the aldehyde **23**, the completion of the convergent synthesis of the diene **51**, the use of the phosphine promoted Ireland–Claisen rearrangement for the efficient synthesis of the tetraene **67**, the development of the ring-opening of the hydroxy epoxide **70** leading to the mono-protected dihydroxy aldehyde **76**, and the completion of the synthesis of the macrocyclic analogue **85** of galbonolide B. The convergent synthesis of the C(7)–C(15) fragment **51** makes this intermediate available in significant quantities. The phosphine induced Ireland–Claisen rearrangement provides a swift access to the tetraene **67** and modification of the epoxide **68** following the chemistry used in the synthesis should give access to the fully functionalised C(3)–C(15) part of galbonolide B including the vicinal diol containing component. Conditions have been found for the final stages of a synthesis including assembly of the macrocyclic ring. Further work in this area would concentrate on improvements to the protecting group strategy and completion of the synthesis.

Experimental

Proton nuclear magnetic resonance spectra were recorded on Bruker AC300 (300 MHz), Varian XL300 (300 MHz) and Varian Gemini 200 (200 MHz) spectrometers, carbon nuclear magnetic resonance spectra were recorded on Bruker AC300 (75 MHz) and Varian Gemini 200 (50 MHz) spectrometers, and fluorine nuclear magnetic resonance spectra were recorded on a Varian Unity 500 (470 MHz) spectrometer, respectively, in chloroform-d_1, unless otherwise stated. Mass spectra were recorded on Kratos MS25, Kratos Concept and Fisons VG Trio 2000 mass spectrometers using electron impact (E.I.), chemical ionisation (C.I.), fast atom bombardment (FAB) and electrospray (ESP) techniques. Infrared spectra were recorded on a Perkin-Elmer 1710 FTIR spectrometer as either an evaporated film or liquid film on sodium chloride plates unless otherwise stated.

Flash column chromatography was carried out using Merck silica gel 60H (40–60 μm, 230–300 mesh) or May and Baker sorbsil C60 silica gel as the stationary phase. Analytical high pressure liquid chromatography (HPLC) was performed using a C18 Novapak cartridge (8 mm × 10 cm) with a Perkin-Elmer diode array system for detection. Melting points were recorded on a Köfler heated stage microscope and are uncorrected. Optical rotations were measured on an Optical Activity AA-100 polarimeter operating at 589 nm.

Light petroleum refers to the fraction with bp 40–60 °C and was redistilled before use. Ether refers to diethyl ether. All solvents were distilled and purified by standard procedures.

2-Methyl-2-(1-hydroxypropyl)-1,3-dithiane **12**[25] (2.4 g, 66%) was prepared from 2-methyl-1,3-dithiane (2.5 g, 18.6 mmol) using *s*-butyllithium (1.3 M in cyclohexane; 17 cm^3, 22.3 mmol) as base (−20 °C; 2 h). Methyl (*R*)-3-(4-methoxybenzyloxy)-2-methylpropanoate **35**[26] (5.5 g, 78%) was prepared from 4-methoxybenzyl 2,2,2-trichloroacetimidate (16 g, 59.1 mmol) and methyl (*R*)-3-hydroxy-2-methylpropanoate (3.5 g, 29.6 mmol) in hexane–dichloromethane (6:1) at 0 °C and had $[a]_D^{20}$ −9.8 (*c* 1.0, $CHCl_3$). Methyl (2*R*)-2-methyl-3-phenylthiopropanoate **44** (22.3 g, 96%) prepared according to the published procedure[27] had $[a]_D^{22}$ 66.6 (*c* 1, $CHCl_3$) {lit.,[27] $[a]_D^{22}$ 64.3 (*c* 1.59, $CHCl_3$)} and was reduced using lithium aluminium hydride to (2*R*)-2-methyl-3-phenylthiopropan-1-ol **45**[28] (17.6 g, 91%) with $[a]_D^{23}$ −13 (*c* 2.2, $CHCl_3$) {lit.,[28] $[a]_D$ −18.9 (*c* 3.9, CH_2Cl_2)}. 2-Methyl-4-phenylpent-1-en-3-ol **54**[17] (9.76 g, 80%) was prepared as a 4.9:1 mixture of diastereoisomers by the addition of prop-2-enyllithium, from *s*-butyllithium (1.3 M in cyclohexane; 63.6 cm^3, 82.7 mmol) and 2-bromopropene (10 g, 82.7 mmol) in tetrahydrofuran (500 cm^3) at −78 °C, to 2-phenylpropanal **53** (9.1 cm^3, 68.9 mmol).

2-Methyl-2-[1-(4-methoxybenzoyloxy)propyl]-1,3-dithiane 13

Sodium hydride (60% w/w in mineral oil; 624 mg, 15.6 mmol) was washed twice with dry hexane under an inert atmosphere and the remainder of the hexane removed with a stream of argon. Tetrahydrofuran (40 cm^3) and alcohol **12** (2.0 g, 10.4 mmol) in tetrahydrofuran (2 cm^3) were added. After stirring for 2 h the reaction mixture was cooled to 0 °C and 4-methoxybenzyl chloride (1.7 cm^3, 12.5 mmol), tetrabutylammonium iodide (770 mg, 2.08 mmol) and *N*,*N*-dimethylformamide (1 cm^3) were added and the mixture stirred for 24 h. Water and ether were added, the two phases separated and the organic phase washed with brine. The aqueous phases were extracted with ether and the organic phases dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue [light petroleum:ether (10:1)] gave the *title compound* **13** (2.5 g, 77%) as a colourless oil (Found: $M^+ + H$, 313.1309. $C_{16}H_{25}O_2S_2$ requires *M*, 313.1296); ν_{max}/cm^{-1} 1613, 1587, 1515, 1250, 1077 and 1036; δ_H 1.06 (3 H, t, *J* 8, CH_2CH_3), 1.61 (4 H, m, 2-CH_3, $CHHCH_3$), 1.99 (3 H, m, 5-H_2, $CHHCH_3$), 2.86 (4 H, m, 4-H_2, 6-H_2), 3.63 (1 H, dd, *J* 9.5, 2.5, CHO), 3.81 (3 H, s, OCH_3), 4.59 and 4.89 (each 1 H, d, *J* 10,

ArC*H*H) and 6.88 and 7.36 (each 2 H, d, *J* 8.5, ArH); *m*/*z* (C.I.) 313 ($M^+ + 1$, 40%), 133 (100) and 121 (99).

3-(4-Methoxybenzyloxy)pentan-2-one 14

Calcium carbonate (60 mg, 0.64 mmol) and mercury(II) chloride (350 mg, 1.28 mmol) were added to the dithiane **13** (200 mg, 0.64 mmol) in 80% aqueous methanol (10 cm^3) and the reaction mixture heated under reflux for 4 h. After cooling to room temperature, the white solids were filtered off and the solvent removed under reduced pressure. The residue was dissolved in ether and washed with brine, saturated aqueous ammonium chloride and water, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the *title compound* **14** (121 mg, 85%) as a colourless oil (Found: M^+, 222.1255. $C_{13}H_{18}O_3$ requires *M*, 222.1256); ν_{max}/cm^{-1} 1714, 1613, 1514, 1249 and 1034; δ_H 0.94 (3 H, t, *J* 7.5, 5-H_3), 1.70 (2 H, m, 4-H_2), 2.16 (3 H, s, 1-H_3), 3.68 (1 H, t, *J* 6.5, 3-H), 3.81 (3 H, s, OCH_3), 4.38 and 4.51 (each 1 H, d, *J* 11.5, ArC*H*H) and 6.89 and 7.27 (each 2 H, d, *J* 8.5, ArH); *m*/*z* (E.I.) 222 (M^+, 9%), 221 (10), 137 (32) and 121 (100).

Ethyl (2*E*)-4-(4-methoxybenzyloxy)-3-methylhex-2-enoate 15

Sodium hydride (60% w/w in mineral oil; 72 mg, 1.8 mmol) was washed with dry hexane under an inert atmosphere and the remainder of the solvent removed with a stream of argon. Benzene (7.5 cm^3) was added and then triethyl phosphonoacetate (0.36 cm^3, 1.80 mmol) and the reaction mixture stirred for 1 h. Ketone **14** (400 mg, 1.80 mmol) in benzene (2 cm^3) was added and the reaction mixture heated to 60 °C for 2 h. The mixture was cooled to room temperature, saturated aqueous ammonium chloride was added and the mixture was extracted twice with dichloromethane. The extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum: ether (8:1)] gave the *title compound* **15** (413 mg, 79%) as a colourless oil containing *ca*. 10% of its (*Z*)-isomer (Found: $M^+ + NH_4$, 310.2031. $C_{17}H_{28}NO_4$ requires *M*, 310.2018); ν_{max}/cm^{-1} 1718, 1650, 1613, 1515, 1250, 1218, 1173 and 1037; δ_H 0.88 (3 H, t, *J* 8, 6-H_3), 1.31 (3 H, t, *J* 7.5, C$H_3$$CH_2O$), 1.62 (2 H, m, 5-$H_2$), 2.11 (3 H, d, *J* 1, 3-CH_3), 3.63 (1 H, t, *J* 7, 4-H), 3.81 (3 H, s, OCH_3), 4.19 (3 H, m, $CH_3C$$H_2O$, ArC*H*H), 4.43 (1 H, d, *J* 11.5, ArCH*H*), 5.85 (1 H, s, 2-H) and 6.87 and 7.24 (each 2 H, d, *J* 7.5, ArH); δ_C 10.1, 14.0, 14.3, 26.8, 55.3, 59.8, 70.4, 85.3, 113.8, 117.4, 129.4, 130.4, 158.2, 159.2, 166.5; *m*/*z* (C.I.) 310 ($M^+ + 18$, 76%), 293 ($M^+ + 1$, 10) and 121 (100). Selected peaks for the minor (*Z*)-isomer; δ_H 0.94 (3 H, t, *J* 8, 6-H_3), 12.6 (3 H, t, *J* 7.5, C$H_3$$CH_2O$), 1.88 (3 H, s, 3-$CH_3$), 3.79 (3 H, s, OCH_3). Unchanged starting material **14** (84 mg, 21%) was also recovered.

(2*E*)-*N*-Methoxy-*N*-methyl-4-(4-methoxybenzyloxy)-3-methylhex-2-enamide 16

Trimethylaluminium (2 M in toluene; 1.5 cm^3, 3 mmol) was added slowly to *N*,*O*-dimethylhydroxylamine hydrochloride (300 mg, 3 mmol) suspended in benzene (3 cm^3) at *ca*. 5 °C. The reaction was stirred for 1 h until no further gas was evolved. This solution (3.0 cm^3, 2.01 mmol) was added to the ester **15** (300 mg, 1.02 mmol) in benzene (10 cm^3) and the mixture heated under reflux for 1 h then cooled to 0 °C and aqueous hydrogen chloride (5%) was added carefully. The mixture was extracted with ether and the extracts dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue [light petroleum: ether (8:1)] gave the *title compound* **16** (190 mg, 62%) as a colourless oil (Found: $M^+ + H$, 308.1857. $C_{17}H_{26}NO_4$ requires *M*, 308.1862); ν_{max}/cm^{-1} 1658, 1638, 1613, 1514, 1249 and 1035; δ_H 0.90 (3 H, t, *J* 8, 6-H_3), 1.63 (2 H, m, 5-H_2), 2.10 (3 H, d, *J* 1, 3-CH_3), 3.24 (3 H, s, N-CH_3), 3.68 (4 H, m, N-OCH_3, 4-H), 3.80 (3 H, s, ArOCH_3), 4.22 and 4.48 (each 1 H, d, *J* 11.5, ArC*H*H), 6.32 (1 H, s, 2-H) and 6.88 and 7.27 (each 2 H, d, *J* 8.5, ArH); *m*/*z* (C.I.) 308 ($M^+ + 1$, 23%), 280 (56), 263 (40) and 121 (100).

(6*E*)-8-(4-Methoxybenzyloxy)-7-methyldec-6-en-5-one 17

n-Butyllithium (1.6 M in hexanes; 0.56 cm^3, 0.9 mmol) was added slowly to the amide **16** (230 mg, 0.748 mmol) in tetrahydrofuran (10 cm^3) at 0 °C. The reaction mixture was stirred for 0.5 h and then poured into ethanolic hydrogen chloride (5%; 10 cm^3). The mixture was partitioned between brine and dichloromethane–ether (1:1). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum: ether (8:1)] gave the *title compound* **17** (114 mg, 50%) as a colourless oil (Found: $M^+ + H$, 305.2129. $C_{19}H_{29}O_3$ requires *M*, 305.2117); ν_{max}/cm^{-1} 1690, 1616, 1514, 1249, 1070 and 1036; δ_H 0.91 (6 H, m, 1-H_3, 10-H_3), 1.33 (2 H, m, 9-H_2), 1.56 (4 H, m, 2-H_2, 3-H_2), 2.07 (3 H, d, *J* 1, 7-CH_3), 2.47 (2 H, t, *J* 7.5, 4-H_2), 3.60 (1 H, t, *J* 6.5, 8-H), 3.81 (3 H, s, OCH_3), 4.20 and 4.44 (each 1 H, d, *J* 11.5, ArC*H*H), 6.23 (1 H, s, 6-H) and 6.88 and 7.24 (each 2 H, d, *J* 8.5, ArH); *m*/*z* (C.I.) 305 ($M^+ + 1$, 18%), 227 (6), 185 (10), 167 (28), 137 (38) and 121 (100).

(4*E*)-3-(4-Methoxybenzyloxy)-4-methyl-6-methylenedec-4-ene 18

n-Butyllithium (1.6 M in hexanes; 0.308 cm^3, 0.493 mmol) was added to methyl(triphenyl)phosphonium bromide (176 mg, 0.492 mmol) suspended in ether (1 cm^3) at 0 °C. The reaction mixture was stirred for 1 h and then the ketone **17** (30 mg, 98.7 μmol) in ether (0.2 cm^3) was added. The reaction mixture was stirred for 2 h then water was added and the mixture extracted with pentane. The extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum: ether (20:1)] gave the *title compound* **18** (22 mg, 74%) as a colourless oil (Found: $M^+ + H$, 303.2336. $C_{20}H_{31}O_2$ requires *M*, 303.2324); ν_{max}/cm^{-1} 1613, 1514, 1248, 1069 and 1038; δ_H 0.91 (6 H, m, 1-H_3, 10-H_3), 1.20–1.70 (6 H, m, 2-H_2, 8-H_2, 9-H_2), 1.74 (3 H, d, *J* 1, 4-CH_3), 2.13 (2 H, t, *J* 6.5, 7-H_2), 3.57 (1 H, t, *J* 7, 3-H), 3.81 (3 H, s, OCH_3), 4.19 and 4.43 (each 1 H, d, *J* 11.5, ArC*H*H), 4.87 and 5.04 (each 1 H, m, 1′-H), 5.77 (1 H, s, 5-H) and 6.88 and 7.26 (each 2 H, d, *J* 8.5, ArH); *m*/*z* (E.I) 303 ($M^+ + 1$, 6%), 302 (M^+, 7) and 244 (7).

2-Methylpropyl (*R*)-2-(benzyloxymethoxy)propanoate 22

Benzyl chloromethyl ether (120 g, 0.769 mol), distilled before use, was slowly added to 2-methylpropyl (*R*)-(+)-lactate (75 g, 0.513 mol) and diisopropylethylamine (274 cm^3, 1.54 mol) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 18 h, then diluted with dichloromethane and washed with aqueous hydrogen chloride (3 M) and dried ($MgSO_4$). Concentration under reduced pressure gave the *title compound* **22** (143 g) as a colourless oil. For large scale synthesis this material was used without further purification. Flash chromatography for characterisation [light petroleum: ether (10:1)] gave the *title compound* **22** (typically 72%) as a colourless oil, $[a]_D^{20}$ 69 (*c* 1.4, $CHCl_3$) (Found: M^+, 266.1519. $C_{15}H_{22}O_4$ requires *M*, 266.1518); ν_{max}/cm^{-1} 1750, 1498, 1176, 1122, 1083, 1050 and 1026; δ_H 0.93 [6 H, d, *J* 6.5, $HC(CH_3)_2$], 1.45 (3 H, d, *J* 6.5, 3-H_3), 1.94 (1 H, m, 2′-H), 3.91 (2 H, m, 1′-H_2), 4.33 (1 H, q, *J* 6.5, 2-H), 4.65 (2 H, s, ArCH_2), 4.84 (2 H, s, OCH_2O) and 7.34 (5 H, m, ArH); δ_C 19.1, 19.5, 28.2, 70.4, 71.4, 72.0, 94.4, 128.2, 128.4, 128.9, 138.2 and 173.6; *m*/*z* (C.I.) 284 ($M^+ + 18$, 88%), 267 ($M^+ + 1$, 22), 254 (23), 159 (73) and 91 (100).

Diisobutylaluminium hydride (1 M in hexane; 29.3 cm^3, 29.3 mmol) was added dropwise over 45 min to the ester **22** (6.5 g, 24.4 mmol) in hexane (210 cm^3) at −78 °C. The reaction

mixture was stirred for 1.5 h then water (10 cm^3) was added. The reaction mixture was warmed to room temperature and the two layers separated. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography of the residue [light petroleum : ether (8 : 1–4 : 1)] gave (*R*)-2-benzyloxymethoxy)propanal **23**[26] (3.55 g, 75%) as a colourless oil, $[\alpha]_D^{20}$ 15.0 (*c* 0.86, $CHCl_3$) {lit.,[29] for the (*S*)-enantiomer, $[\alpha]_D^{20}$ −22.7 (*c* 2.3 in tetrahydrofuran)} (Found: $M^+ + NH_4$, 212.1277. $C_{11}H_{18}NO_3$ requires *M*, 212.1287); ν_{max}/cm^{-1} 1736, 1381, 1179 and 1041; δ_H 1.34 (3 H, d, *J* 7, 3-H_3), 4.12 (1 H, qd, *J* 7, 1, 2-H), 4.65 and 4.75 (each 1 H, d, *J* 11.5, ArC*H*H), 4.88 (2 H, s, OCH_2O), 7.32 (5 H, m, ArH) and 9.65 (1 H, d, *J* 1, 1-H); *m*/*z* (C.I.) 212 ($M^+ + 18$, 100%), 184 (32), 108 (77) and 91 (91).

(2*R*,3*R*)-2-(Benzyloxymethoxy)pentan-3-ol 24

Zinc bromide (44 g, 0.196 mol) was suspended in ether (350 cm^3) and the mixture cooled to 0 °C. Ethylmagnesium bromide (3 M in ether; 65.3 cm^3, 0.196 mol) was added and the reaction mixture stirred for 0.5 h before being added *via* cannula to the aldehyde **23** (19 g, 97.9 mmol) in ether (350 cm^3) cooled to 0 °C. A white precipitate formed on addition. After 25 min, an excess of ethylmagnesium bromide (3 M in ether, 130.7 cm^3, 0.392 mol) was added and the reaction mixture stirred for 4 h. After cooling to −40 °C, water (70 cm^3) was added and the reaction mixture was allowed to warm slowly to room temperature over a period of several hours. The white solids were filtered off and the filtrate concentrated under reduced pressure. HPLC indicated that the ratio of *syn* : *anti*-products was 94 : 6. Distillation of the residue through a Vigreux column (10 cm) gave the *title compound* **24** (14.3 g, 65%) as a colourless oil, bp 92–96 °C (0.1 mmHg) $[\alpha]_D^{20}$ −34.2 (*c* 1.12, $CHCl_3$) (Found: $M^+ + H$, 225.1502. $C_{13}H_{21}O_3$ requires *M*, 225.1491); ν_{max}/cm^{-1} 3459, 1454, 1151, 1106 and 1043; δ_H 1.01 (3 H, t, *J* 7.5, 5-H_3), 1.21 (3 H, d, *J* 6.5, 1-H_3), 1.52 (2 H, m, 4-H_2), 2.61 (1 H, d, *J* 4, OH), 3.37 (1 H, m, 3-H), 3.64 (1 H, m, 2-H), 4.62 and 4.69 (each 1 H, d, *J* 11.5, ArC*H*H), 4.82 and 4.88 (each 1 H, d, *J* 7, OC*H*HO) and 7.34 (5 H, m, ArH); δ_C 10.4, 17.3, 26.4, 70.3, 76.7, 78.0, 94.3, 128.3, 128.4, 129.0 and 138.0; *m*/*z* (C.I.) 242 ($M^+ + 18$, 9%).

(*S*)-(+)-Acetylmandelic acid (21 mg, 0.107 mmol), 4-(dimethylamino)pyridine (1 mg) and 1,3-dicyclohexylcarbodiimide (20 mg, 96.9 μmol) were added to the alcohol **24** (20 mg, 89.3 μmol) in dichloromethane (1 cm^3) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 17 h, then filtered and washed with aqueous hydrochloric acid (3 M), saturated aqueous sodium hydrogen carbonate and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue [light petroleum : ether (3 : 1)] gave (2*R*,3*R*)-2-(benzyloxymethoxy)-pentan-3-yl (*S*)-2-acetylmandelate **25** (15 mg, 42%) as a colourless oil (Found: $M^+ + NH_4$, 418.2237. $C_{23}H_{32}NO_6$ requires *M*, 418.2230); ν_{max}/cm^{-1} 1746, 1628, 1234, 1180 and 1045; δ_H 0.59 (3 H, t, *J* 7.5, 5′-H_3), 1.23 (3 H, d, *J* 6.5, 1′-H_3), 1.57 (2 H, m, 4′-H_2), 2.24 (3 H, s, CH_3CO), 3.91 (1 H, m, 2′-H), 4.68 (2 H, s, $ArCH_2$), 4.82 and 4.86 (each 1 H, d, *J* 7, OC*H*HO), 4.93 (1 H, m, 3′-H), 5.95 (1 H, s, 2-H) and 7.42 (10 H, m, ArH); δ_C 9.2, 16.2, 20.7, 22.9, 69.6, 73.4, 74.7, 79.0, 93.7, 127.7, 127.8, 128.4, 128.7, 129.2, 133.9, 138.0, 168.9 and 170.3; *m*/*z* (C.I.) 418 ($M^+ + 18$, 100%), 326 (18) and 298 (29).

Following this procedure, the alcohol **24** (20 mg, 89.3 μmol) and (*R*)-(−)-acetylmandelic acid (21 mg, 0.107 mmol), 4-(dimethylamino)pyridine (1 mg) and 1,3-dicyclohexycarbodiimide (20 mg, 96.9 μmol) gave (2*R*,3*R*)-2-(benzyloxymethoxy)pentan-3-yl (*R*)-2-acetylmandelate **26** (20 mg, 56%) as a colourless oil (Found: $M^+ + NH_4$, 418.2225. $C_{23}H_{32}NO_6$ requires *M*, 418.2230); ν_{max}/cm^{-1} 1744, 1232, 1211, 1178 and 1042; δ_H 0.99 (6 H, m, 1′-H_3, 5′-H_3), 1.70 (2 H, m, 4′-H_2), 2.24 (3 H, s, CH_3CO), 3.69 (1 H, m, 2′-H), 4.44 (2 H, s, $ArCH_2$), 4.45 and 4.53 (each 1 H, d, *J* 11.5, OC*H*HO), 4.91 (1 H, m, 3′-H), 5.96 (1 H, s, 2-H) and 7.42 (10 H, m, ArH); δ_C 9.7, 16.2, 20.7, 23.1, 69.4, 73.8, 74.7, 79.0, 93.8, 127.7, 127.8, 127.9, 128.4, 128.8, 129.3, 133.9, 137.8, 168.7 and 170.4; *m*/*z* (C.I.) 418 ($M^+ + 18$, 63%), 360 (19), 326 (30), 298 (45) and 106 (100).

(2*R*,3*R*)-2-(Benzyloxymethoxy)-3-*tert*-butyldimethylsilyloxypentane 27

tert-Butyldimethylsilyl chloride (42 g, 0.278 mol) was added to a solution of imidazole (39.5 g, 0.58 mol) and the alcohol **24** (52 g, 0.232 mol) in *N*,*N*-dimethylformamide (180 cm^3) at 0 °C. The reaction mixture was stirred for 36 h then diluted with hexane, washed with brine and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue [light petroleum : ether (50 : 1)] gave the *title compound* **27** (73.5 g, 94%) as a colourless oil, $[\alpha]_D^{20}$ 18.9 (*c* 1.88, $CHCl_3$) (Found: $M^+ + H$, 339.2358. $C_{19}H_{35}O_3Si$ requires *M*, 339.2355); ν_{max}/cm^{-1} 1463, 1256, 1154, 1115, 1044, 836 and 775; δ_H 0.05 [6 H, s, $Si(CH_3)_2$], 0.89 [12 H, m, $SiC(CH_3)_3$, 5-H_3], 1.35 (3 H, d, *J* 6.5, 1-H_3), 1.50 (2 H, m, 4-H_2), 3.59 (1 H, m, 3-H), 3.73 (1 H, m, 2-H), 4.62 (2 H, s, $ArCH_2$), 4.81 (2 H, s, OCH_2O) and 7.35 (5 H, m, ArH); δ_C −4.6, −4.4, 10.6, 15.4, 18.6, 24.7, 26.2, 26.4, 69.9, 76.3, 76.7, 94.6, 128.1, 128.3, 128.9, 138.5; *m*/*z* (C.I.) 339 ($M^+ + 1$, 10%) and 231 (52).

(2*R*,3*R*)-3-*tert*-Butyldimethylsilyloxypentan-2-ol 28

A mixture of the benzyloxymethyl ether **27** (14 g, 41.4 mmol) and palladium on carbon (10%; 2.1 g) in acetic acid–ethanol (95%) (200 cm^3; 15 : 85) was shaken under an atmosphere of hydrogen at 60 psi for 24 h. The reaction mixture was then filtered through a small pad of charcoal on top of a pad of Celite,® washing the reaction vessel three times with ethanol (95%). The filtrate was concentrated under reduced pressure and the residue dissolved in ether, washed with saturated aqueous sodium hydrogen carbonate and dried ($MgSO_4$). The solvent was removed under reduced pressure and flash chromatography of the residue [light petroleum : ether (10 : 1)] gave the *title compound* **28** (8.45 g, 94%) as a colourless oil, $[\alpha]_D^{20}$ −21.2 (*c* 1.28, $CHCl_3$) (Found: $M^+ + H$, 219.1774. $C_{11}H_{27}O_2Si$ requires *M*, 219.1780); ν_{max}/cm^{-1} 3425, 1464, 1362, 1256, 1094, 1065, 1013, 940, 895, 863, 838 and 775; δ_H 0.09 [6 H, s, $Si(CH_3)_2$], 0.88 (3 H, t, *J* 7.5, 5-H_3), 0.91 [9 H, s, $SiC(CH_3)_3$], 1.13 (3 H, d, *J* 6.5, 1-H_3), 1.58 (2 H, m, 4-H_2), 2.11 (1 H, br s, OH), 3.38 (1 H, dt, *J* 6, 5, 3-H) and 3.67 (1 H, dq, *J* 6.5, 5, 2-H); δ_C −4.6, −4.2, 9.5, 15.8, 18.6, 20.1, 26.4, 26.8, 69.0 and 78.2; *m*/*z* (C.I.) 236 ($M^+ + 18$, 8%) and 219 (9).

(3*R*)-3-*tert*-Butyldimethylsilyloxypentan-2-one 29

Dimethyl sulfoxide (3.4 cm^3, 48 mmol) in dichloromethane (10 cm^3) was added dropwise to oxalyl chloride (2.1 cm^3, 24 mmol) in dichloromethane (45 cm^3) cooled to below −50 °C. The reaction mixture was stirred for 2 min and then the alcohol **28** (3.5 g, 16 mmol) in dichloromethane (20 cm^3) was added slowly. The reaction mixture was stirred for 15 min, triethylamine (8.1 cm^3, 100 mmol) was added and the reaction mixture was allowed to warm to room temperature before water (25 cm^3) was added. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* **29** (3.38 g, 98%) as a pale yellow liquid, $[\alpha]_D^{20}$ 39.8 (*c* 0.72, $CHCl_3$) (Found: $M^+ + H$, 217.1626. $C_{11}H_{25}O_2Si$ requires *M*, 217.1624); ν_{max}/cm^{-1} 1719, 1464, 1390, 1255, 1131, 1019, 839 and 778; δ_H 0.06 and 0.07 (each 3 H, s, $SiCH_3$), 0.91 (3 H, t, *J* 7.5, 5-H_3), 0.93 [9 H, s, $SiC(CH_3)_3$], 1.63 (2 H, m, 4-H_2), 2.16 (3 H, s, 1-H_3) and 3.93 (1 H, t, *J* 6.5, 3-H); *m*/*z* (C.I.) 234 ($M^+ + 18$, 82%) and 217 ($M^+ + 1$, 100).

Ethyl (2*E*,4*R*)-4-*tert*-butyldimethylsilyloxy-3-methylhex-2-enoate 30

Sodium hydride (60% w/w in mineral oil; 277 mg, 6.93 mmol)

was washed with hexane under an inert atmosphere and the remainder of the solvent removed with a stream of argon. Benzene (30 cm^3) and triethyl phosphonoacetate (1.4 cm^3, 6.93 mmol) were added. The reaction mixture was stirred for 1 h and then the ketone **29** (1.0 g, 4.62 mmol) in benzene (10 cm^3) was added. After stirring at 60 °C for 3 h, the reaction was cooled and quenched with saturated aqueous ammonium chloride. The product was extracted with dichloromethane, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (50 : 1)] gave the *title compound* **30** (1.18 g, 89%) as a colourless oil, $[\alpha]_D^{20}$ 13.6 (*c* 0.91, $CHCl_3$) (Found: $M^+ + NH_4$, 304.2302. $C_{15}H_{34}NO_3Si$ requires *M*, 304.2308); ν_{max}/cm^{-1} 1720, 1656, 1464, 1257, 1217, 1156, 1104, 1045, 1018, 837 and 777; δ_H 0.04 and 0.08 (each 3 H, s, $SiCH_3$), 0.88 (3 H, t, *J* 7.5, 6-H_3), 0.94 [9 H, s, $SiC(CH_3)_3$], 1.32 (3 H, t, *J* 7, CH_3CH_2O), 1.58 (2 H, m, 5-H_2), 2.10 (3 H, d, *J* 1, 3-CH_3), 4.00 (1 H, t, *J* 5.5, 4-H), 4.19 (2 H, q, *J* 7, CH_3CH_2O) and 5.88 (1 H, s, 2-H); δ_C −5.0, −4.7, 9.5, 14.3, 14.7, 18.2, 25.8, 28.9, 59.6, 78.4, 115.1, 160.8 and 197.0; *m*/*z* (C.I.) 304 ($M^+ + 18$, 100%) and 287 ($M^+ + 1$, 24).

Ethyl (2*E*,4*R*)-4-hydroxy-3-methylhex-2-enoate 31 and conversion to Mosher's esters 32 and 33

Tetrabutylammonium fluoride (1 M in tetrahydrofuran; 3.5 cm^3, 3.49 mmol) was added to the ester **30** (500 mg, 1.75 mmol) and the reaction mixture stirred for 1.5 h. Water was added and the two layers separated. The aqueous layer was extracted with ether and the combined organic phases dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (5 : 1)] gave the *title compound* **31** (577 mg, 92%) as a colourless oil, $[\alpha]_D^{20}$ −2.9 (*c* 1.27, $CHCl_3$) (Found: $M^+ + H$, 173.1182. $C_9H_{17}O_3$ requires *M*, 173.1178); ν_{max}/cm^{-1} 3436, 1718, 1654, 1219 and 1157; δ_H 0.87 (3 H, t, *J* 7.5, 6-H_3), 1.24 (3 H, t, *J* 7, CH_3CH_2O), 1.59 (2 H, m, 5-H_2), 2.05 (3 H, d, *J* 1, 3-CH_3), 2.58 (1 H, br s, OH), 3.97 (1 H, t, *J* 6, 4-H), 4.11 (2 H, q, *J* 7, CH_3CH_2O) and 5.86 (1 H, s, 2-H); δ_C 10.1, 14.7, 15.2, 28.2, 60.2, 78.2, 115.6, 160.7 and 167.4; *m*/*z* (C.I.) 173 ($M^+ + 1$, 100%).

Oxalyl chloride (0.053 cm^3, 0.61 mmol) was added to (*R*)-(+)-Mosher's acid (30 mg, 0.128 mmol) and *N*,*N*-dimethylformamide (0.015 cm^3, 0.19 mmol) in hexane (2.5 cm^3) and the mixture stirred for 1 h. The precipitate was filtered off and the filtrate concentrated under reduced pressure to give the (+)-Mosher's acid chloride (29 mg, 90%) as a colourless oil; ν_{max}/cm^{-1} 1791, 1452, 1263 and 1133. The alcohol **31** (10 mg, 58.1 μmol), triethylamine (0.04 cm^3, 0.172 mmol) and 4-dimethylaminopyridine (<1 mg) in dichloromethane (0.5 cm^3) were added to the (+)-Mosher's acid chloride (29 mg, 0.125 mmol) and the mixture was stirred for 3 h. The reaction mixture was diluted with ether and washed with aqueous hydrogen chloride (1 M), saturated aqueous sodium hydrogen carbonate, brine, and dried ($MgSO_4$). Concentration under reduced pressure gave the (*R*)-(+)-Mosher's ester **32** (29 mg, 90%) as a pale yellow oil (Found: $M^+ + NH_4$, 406.1831. $C_{19}H_{27}F_3NO_5$ requires *M*, 406.1841); ν_{max}/cm^{-1} 1751, 1719, 1657, 1225, 1163 and 1018; δ_H 0.85 (3 H, t, *J* 7.5, 6-H_3), 1.32 (3 H, t, *J* 7, CH_3CH_2O), 1.77 (2 H, m, 5-H_2), 2.16 (3 H, s, 3-CH_3), 3.56 (3 H, s, OCH_3), 4.20 (2 H, q, *J* 7, CH_3CH_2O), 5.34 (1 H, t, *J* 6.5, 4-H), 5.89 (1 H, s, 2-H) and 7.42–7.55 (5 H, m, ArH); δ_F −72.7 (major), −73.0 (minor); *m*/*z* (C.I.) 406 ($M^+ + 18$, 100%). Alternatively, pyridine (0.009 cm^3, 0.116 mmol) was added to the alcohol **31** (10 mg, 58.1 μmol) and (+)-Mosher's acid chloride (29 mg, 0.116 mmol) in dichloromethane (0.5 cm^3) and the mixture stirred for 1 h. Work-up as above gave the (*R*)-(+)-Mosher's ester **32** (20 mg, 90%).

The alcohol **31** (22 mg, 0.128 mmol) was similarly reacted with the (−)-Mosher's acid chloride (65 mg, 2.57 mmol) to give the (*S*)-(−)-Mosher's ester **33** (46 mg, 93%) as a colourless oil (Found: $M^+ + NH_4$, 406.1831. $C_{19}H_{27}F_3NO_5$ requires *M*, 406.1841); ν_{max}/cm^{-1} 1752, 1719, 1655, 1224 and 1123; δ_H 0.96 (3 H, t, *J* 7.5, 6-H_3), 1.32 (3 H, t, *J* 7, CH_3CH_2O), 1.67 (2 H, m, 5-H_2), 2.07 (3 H, d, *J* 1, 3-CH_3), 3.61 (3 H, s, OCH_3), 4.19 (2 H, q, *J* 7, CH_3CH_2O), 5.28 (1 H, t, *J* 6.5, 4-H), 5.77 (1 H, s, 2-H) and 7.37–7.55 (5 H, m, ArH); δ_F −72.7 (minor), −73.0 (major); *m*/*z* (C.I.) 406 ($M^+ + 18$, 100%).

(*S*)-3-(4-Methoxybenzyloxy)-2-methylpropan-1-ol 36

Lithium aluminium hydride (2.3 g, 60.6 mmol) was suspended in ether (120 cm^3) and the mixture cooled to 0 °C. The methyl ester **35** (6.9 g, 29.7 mmol) in ether (100 cm^3) was added slowly then the reaction mixture was stirred for 1 h at room temperature. After cooling to 0 °C, water (6.3 cm^3) and aqueous sodium hydroxide (10%; 4.8 cm^3) were added and the mixture stirred for 20 min. The white solid was filtered off and the filtrate concentrated under reduced pressure to give the *title compound* **36** (6.1 g, 98%) as a colourless oil, $[\alpha]_D^{22}$ −18.7 (*c* 1.14, $CHCl_3$) (Found: $M^+ + NH_4$, 228.1599. $C_{12}H_{12}NO_3$ requires *M*, 228.1600); ν_{max}/cm^{-1} 3413, 1613, 1587, 1514, 1248, 1090 and 1036; δ_H 0.91 (3 H, d, *J* 7, 2-CH_3), 2.06 (1 H, m, 2-H), 2.78 (1 H, br s, OH), 3.43 (1 H, m, 3-H), 3.53 (1 H, dd, *J* 9, 5, 3-H′), 3.61 (2 H, m, 1-H_2), 3.83 (3 H, s, OCH_3), 4.48 (2 H, s, $ArCH_2$) and 6.91 and 7.27 (each 2 H, d, *J* 8.5, ArH); δ_C 14.0, 36.1, 55.7, 68.2, 73.5, 75.5, 114.3, 129.7, 130.6 and 159.7; *m*/*z* (C.I.) 228 ($M^+ + 18$, 11%), 210 (M^+, 5) and 121 (100).

(*R*)-1-Bromo-3-(4-methoxybenzyloxy)-2-methylpropane 37

The alcohol **36** (1.4 g, 6.67 mmol) and triphenylphosphine (1.9 g, 7.24 mmol) in dichloromethane (5 cm^3) were cooled to 0 °C. *N*-Bromosuccinimide (1.3 g, 7.24 mmol) was added portionwise, keeping the reaction temperature below 5 °C. The reaction mixture was then warmed to room temperature and stirred for 1 h before being filtered through a column of silica and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (30 : 1)] on base washed silica gave the *title compound* **37** (1.7 g, 93%) as a colourless oil, $[\alpha]_D^{22}$ −10.6 (*c* 1.33, $CHCl_3$) (Found: M^+, 272.0417. $C_{12}H_{17}O_2{}^{79}Br$ requires *M*, 272.0412); ν_{max}/cm^{-1} 1613, 1586, 1514, 1249, 1174, 1094, 1037 and 820; δ_H 1.07 (3 H, d, *J* 7, 2-CH_3), 2.13 (1 H, m, 2-H), 3.37 and 3.52 (each 2 H, m), 3.85 (3 H, s, OCH_3), 4.49 (2 H, s, $ArCH_2$) and 6.93 and 7.31 (each 2 H, d, *J* 8.5, ArH); δ_C 16.4, 36.1, 38.8, 55.8, 73.0, 73.4, 114.3, 129.7, 130.9 and 159.9; *m*/*z* (E.I.) 274 [$M(^{81}Br)^+$, 10%], 272 [$M(^{79}Br)^+$, 10] and 121 (100).

(*R*)-1-(4-Methoxybenzyloxy)-2-methyl-3-phenylthiopropane 38

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.72 cm^3, 4.83 mmol) and thiophenol (0.5 cm^3, 4.83 mmol) were added to benzene (10 cm^3) cooled in an ice–water bath. The bromide **37** (1.1 g, 4.03 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature. After stirring for 2 h the mixture was filtered and the filtrate diluted with ether, washed with aqueous sodium hydroxide (10%), aqueous hydrogen chloride (3 M), brine and dried ($MgSO_4$). Flash chromatography of the residue [light petroleum : ether (25 : 1)] gave the *title compound* **38** (1.2 g, 96%) as a colourless oil, $[\alpha]_D^{23}$ 12.5 (*c* 1.62, $CHCl_3$) (Found: M^+, 302.1343. $C_{18}H_{22}O_2S$ requires *M*, 302.1341); ν_{max}/cm^{-1} 1612, 1584, 1512, 1246, 1088 and 1033; δ_H 1.06 (3 H, d, *J* 7, 2-CH_3), 2.07 (1 H, m, 2-H), 2.78 (1 H, dd, *J* 13, 7.5, 3-H), 3.15 (1 H, dd, *J* 13, 5.5, 3-H′), 3.41 (2 H, d, *J* 6, 1-H_2), 3.81 (3 H, s, OCH_3), 4.42 (2 H, s, $ArCH_2$), 6.88 (2 H, d, *J* 8.7, ArH) and 7.33 (7 H, m, ArH); *m*/*z* (E.I.) 302 (M^+, 30%), 181 (29) and 121 (100).

(*R*)-1-(4-Methoxybenzyloxy)-2-methyl-3-phenylsulfonylpropane 39

The sulfide **38** (3.9 g, 12.9 mmol) in methanol (50 cm^3) was cooled to 0 °C and oxone® (12 g, 38.7 mmol of active oxidant)

in water (50 cm^3) was added slowly. The mixture was allowed to warm to room temperature and stirred for 16 h then concentrated under reduced pressure and the resulting slurry diluted with water and extracted with dichloromethane (×3). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (3 : 1)] gave the *title compound* **39** (3.7 g, 85%) as a colourless oil, $[\alpha]_D^{17}$ −3.4 (*c* 1.2, $CHCl_3$) (Found: M^+, 334.1235. $C_{18}H_{22}O_4S$ requires *M*, 334.1239); ν_{max}/cm^{-1} 1612, 1586, 1514, 1304, 1247, 1148 and 1085; δ_H 1.11 (3 H, d, *J* 7, 2-CH_3), 2.38 (1 H, m, 2-H), 2.91 (1 H, dd, *J* 14, 8, 3-H), 3.27 (1 H, dd, *J* 9.5, 6.5, 1-H), 3.40 (2 H, m, 1-H′, 3-H′), 3.81 (3 H, s, OCH_3), 4.35 (2 H, s, $ArCH_2$), 6.86 and 7.18 (each 2 H, d, *J* 8.5, ArH), 7.57 (3 H, m, ArH) and 7.90 (2 H, m, ArH); *m*/*z* (E.I.). 334 (M^+, 3%).

(2*R*,5*E*,7*R*)-7-*tert*-Butyldimethylsilyloxy-1-(4-methoxybenzyloxy)-2,6-dimethyl-3-phenylsulfonylnon-5-en-4-one 40

1,2-Dibromoethane (1.1 cm^3, 12.5 mmol) in benzene (1.5 cm^3) was added to magnesium turnings (365 mg, 15 mmol) in ether (11 cm^3) at a rate to maintain reflux, then the reaction mixture was heated under reflux for 1 h to give a solution of magnesium bromide–diethyl ether (*ca*. 1 M).

n-Butyllithium (1.2 M in hexanes; 2.5 cm^3, 3 mmol) was added to sulfone **39** (1.0 g, 2.99 mmol) in tetrahydrofuran (21 cm^3) at −78 °C. After 10 min, freshly prepared magnesium bromide–diethyl ether (3.0 cm^3, 1 M in ether, 3 mmol) was added resulting in the formation of a white precipitate. The reaction mixture was stirred at −78 °C for 45 min and 15 min at 0 °C then cooled to −78 °C before addition of the ester **30** (390 mg, 1.36 mmol) in tetrahydrofuran (4 cm^3). The reaction mixture was allowed to warm slowly to room temperature and stirred for 1 h. Saturated aqueous ammonium chloride was added and the reaction mixture extracted with ether (×2). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (3 : 1)] gave the *title compound* **40** (749 mg, 96%) as a pale yellow oil, a 1 : 1 mixture of epimers at C(3) (Found: $M^+ + H$, 575.2857. $C_{31}H_{47}O_6SSi$ requires *M*, 575.2863); ν_{max}/cm^{-1} 1684, 1614, 1514, 1308, 1250, 1150 and 1084; δ_H 0.00, 0.02, 0.08 and 0.1 (each 1.5 H, s, $SiCH_3$), 0.80 and 0.87 (each 1.5 H, t, *J* 8, 9-H_3), 0.92 and 0.94 [each 4.5 H, s, $SiC(CH_3)_3$], 1.06 (1.5 H, d, *J* 7, 2-CH_3), 1.43 (3.5 H, m, 2-CH_3, 8-H_2), 1.88 and 1.96 (each 1.5 H, s, 6-CH_3), 2.75 (1 H, m, 2-H), 3.30 (0.5 H, dd, *J* 9.5, 5, 1-H), 3.39 (0.5 H, dd, *J* 9.5, 4, 1-H), 3.50 (0.5 H, dd, *J* 9.5, 5.5, 1-H′), 3.66 (0.5 H, dd, *J* 9.5, 5, 1-H′), 3.83 and 3.85 (each 1.5 H, s, OCH_3), 3.93 (1 H, m, 7-H), 4.20–4.46 (3 H, m, $ArCH_2$, 3-H), 6.26 and 6.43 (each 0.5 H, s, 5-H), 6.89, 7.23 and 7.52 (each 2 H, m, ArH), 7.64 (1 H, m, ArH) and 7.86 (2 H, m, ArH); *m*/*z* (C.I.) 593 ($M^+ + 18$, 0.4%), 575 ($M^+ + 1$, 2) and 121 (100).

(2*R*,5*E*,7*R*)-7-*tert*-Butyldimethylsilyloxy-1-(4-methoxybenzyloxy)-2,6-dimethylnon-5-en-4-one 41

Lithium wire (135 mg, 19.2 mmol) was added in small pieces to naphthalene (1.2 g, 9.4 mmol) in tetrahydrofuran (11.6 cm^3) and the mixture sonicated in an ultrasound bath under an inert atmosphere for 1 h, to produce a dark green solution of lithium naphthalenide (*ca*. 0.8 M).

Lithium naphthalenide in tetrahydrofuran was added dropwise to the keto sulfone **40** (2.5 g, 4.35 mmol) in tetrahydrofuran (70 cm^3) at −78 °C until the starting material had just been consumed (TLC). The reaction mixture became a brown–orange colour during the addition. Saturated aqueous ammonium chloride was added and the reaction mixture warmed to room temperature and diluted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (10 : 1)] gave the *title compound* **41** (1.6 g, 82%) as a colourless oil, $[\alpha]_D^{22}$ 10.5 (*c* 2.18, $CHCl_3$) (Found: $M^+ + H$, 435.2926. $C_{25}H_{43}O_4Si$ requires *M*, 435.2931); ν_{max}/cm^{-1} 1688, 1617, 1514, 1362, 1249, 1097, 837 and 777; δ_H 0.04 and 0.09 (each 3 H, s, $SiCH_3$), 0.89 (3 H, t, *J* 7, 9-H_3), 0.95 [12 H, m, $SiC(CH_3)_3$, 2-CH_3], 1.40 (2 H, m, 8-H_2), 2.07 (3 H, s, 6-CH_3), 2.34 (2 H, m, 3-H, 2-H), 2.66 (1 H, dd, *J* 15, 5, 3-H′), 3.34 (2 H, m, 1-H_2), 3.84 (3 H, s, OCH_3), 3.97 (1 H, t, *J* 5.5, 7-H), 4.46 (2 H, s, $ArCH_2$), 6.30 (1 H, s, 5-H) and 6.91 and 7.28 (each 2 H, d, *J* 8.5, ArH); *m*/*z* (C.I.) 435 ($M^+ + 1$, 1%), 303 (4) and 121 (100).

(2*R*,5*E*,7*R*)-7-*tert*-Butyldimethylsilyloxy-2,6-dimethyl-1-(4-methoxybenzyloxy)-4-methylenenon-5-ene 42

n-Butyllithium (1.5 M in hexanes; 4.6 cm^3, 6.90 mmol) was added to methyl(triphenyl)phosphonium bromide (2.5 g, 6.90 mmol) in tetrahydrofuran (56 cm^3) at 0 °C. The solution was stirred for 20 min then the enone **41** (1.5 g, 3.45 mmol) in tetrahydrofuran (10 cm^3) was added. The mixture was allowed to warm to room temperature and stirred for 3 h then quenched with water, extracted with pentane, and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (50 : 1)] gave the *title compound* **42** (1.14 g, 76%) as a colourless oil, $[\alpha]_D^{23}$ 37.4 (*c* 1.09, $CHCl_3$) (Found: $M^+ + H$, 433.3106. $C_{26}H_{45}O_3Si$ requires *M*, 433.3138); ν_{max}/cm^{-1} 1613, 1514, 1249, 1040 and 835; δ_H 0.04 and 0.08 (each 3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7, 9-H_3), 0.92 [12 H, m, $SiC(CH_3)_3$, 2-CH_3], 1.56 (2 H, m, 8-H_2), 1.74 (3 H, d, *J* 1, 6-CH_3), 1.91 (2 H, m, 2-H, 3-H), 2.30 (1 H, m, 3-H′), 3.25 (1 H, dd, *J* 9, 6, 1-H), 3.33 (1 H, dd, *J* 9, 5, 1-H′), 3.85 (3 H, s, OCH_3), 3.93 (1 H, t, *J* 6.5, 7-H), 4.46 (2 H, s, $ArCH_2$), 4.88 and 5.01 (each 1 H, s, 1′-H), 5.74 (1 H, s, 5-H) and 6.91 and 7.30 (each 2 H, d, *J* 8.5, ArH); δ_C −5.0, −4.6, 10.2, 13.2, 17.0, 18.3, 25.9, 29.2, 32.3, 42.2, 55.3, 72.6, 75.2, 80.1, 113.7, 114.6, 126.0, 129.1, 131.0, 140.4, 144.1 and 159.1; *m*/*z* (C.I.) 433 ($M^+ + 1$, 2%), 301 (17) and 121 (100).

(2*R*)-2-Methyl-3-phenylsulfonylpropan-1-ol 46[30]

m-Chloroperoxybenzoic acid (*ca*. 50% by mass; 44.6 g, 121 mmol) was suspended in dichloromethane (250 cm^3) and cooled to 0 °C. The sulfide **45** (11 g, 60.4 mmol) in dichloromethane (50 cm^3) was added slowly, keeping the reaction temperature below 25 °C. When the addition was complete, the reaction mixture was stirred for 1 h then aqueous sodium sulfite (5%; 60 cm^3) was added and the mixture stirred for 0.5 h. The white solids were filtered off and washed with dichloromethane. The organic filtrate was washed with aqueous sodium hydroxide (2 M), brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the title compound **46**[30] (12.5 g, 97%) as a viscous colourless oil, $[\alpha]_D^{20}$ −8.8 (*c* 1.17, $CHCl_3$) (Found: $M^+ + NH_4$, 232.1007. $C_{10}H_{18}NO_3S$ requires *M*, 232.1007); ν_{max}/cm^{-1} 3529, 1585, 1302, 1147 and 1085; δ_H 1.10 (3 H, d, *J* 7, 2-CH_3), 1.74 (1 H, br s, OH), 2.34 (1 H, m, 2-H), 2.97 (1 H, dd, *J* 14, 6.5, 3-H), 3.36 (1 H, dd, *J* 14, 6, 3-H′), 3.51 (1 H, dd, *J* 11, 6.5, 1-H), 3.75 (1 H, dd, *J* 11, 5, 1-H′), 7.61 (3 H, m, Ar-H) and 7.90 (2 H, m, Ar-H); δ_C 17.5, 31.9, 59.7, 66.6, 128.3, 129.9, 134.2 and 140.3; *m*/*z* (C.I.) 232 ($M^+ + 18$, 100%).

(*R*)-1-*tert*-Butyldimethylsilyloxy-2-methyl-3-phenylsulfonylpropane 47[31]

tert-Butyldimethylsilyl chloride (13.9 g, 92.4 mmol) and then imidazole (13.1 g, 193 mmol) were added to the hydroxy sulfone **46** (16.5 g, 77.1 mmol) in *N*,*N*-dimethylformamide (40 cm^3) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 17 h then diluted with hexane, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue (dichloromethane) gave the title compound **47**[31] (23.4 g, 93%) as a viscous colourless oil, $[\alpha]_D^{18}$ −6.8 (*c* 1.14, $CHCl_3$) {lit.,[31] for

(*S*)-enantiomer $[\alpha]_D$ 8.2 (*c* 5, $CHCl_3$)} (Found: $M^+ + H$, 329.1609. $C_{16}H_{29}O_3SSi$ requires *M*, 329.1607); ν_{max}/cm^{-1} 1473, 1307, 1252, 1151, 1086, 839 and 779; δ_H −0.03 and 0.01 (each 3 H, s, $SiCH_3$), 0.83 [9 H, s, $SiC(CH_3)_3$], 1.07 (3 H, d, *J* 7, 2-CH_3), 2.18 (1 H, m, 2-H), 2.86 (1 H, dd, *J* 14, 8, 3-H), 3.35 (1 H, dd, *J* 10, 6.5, 1-H), 3.41 (1 H, dd, *J* 14, 4.5, 3-H′), 3.55 (1 H, dd, *J* 10, 5, 1-H′), 7.59 (3 H, m, ArH) and 7.90 (2 H, m, ArH); δ_C −5.5, −5.4, 17.2, 26.3, 59.4, 66.9, 128.3, 129.7, 133.9 and 140.5; *m*/*z* (C.I.) 330 ($M^+ + 1$, 100%) and 272 (49).

(2*R*,5*E*,7*R*)-1,7-Bis(*tert*-butyldimethylsilyloxy)-2,6-dimethyl-3-phenylsulfonylnon-5-en-4-one 48

Following the procedure outlined for the synthesis of the keto sulfone **40**, the sulfone **47** (54 g, 0.165 mol) was treated with *n*-butyllithium (1.6 M in hexanes; 108 cm^3, 0.173 mol) and magnesium bromide etherate (1 M in ether; 173 cm^3, 0.173 mol), and acylated using the ester **30** (23.5 g, 82.3 mmol) to give, after flash chromatography [light petroleum : ethyl acetate (30 : 1)], the *title compound* **48** (42.1 g, 90%) as a viscous pale yellow oil, a 1 : 1 mixture of epimers at C(3) (Found: $M^+ + H$, 569.3144. $C_{29}H_{53}O_5SSi_2$ requires *M*, 569.3152); ν_{max}/cm^{-1} 1685, 1615, 1472, 1322, 1257, 1151, 1085, 837 and 778; δ_H 0.03 (12 H, m, 4 × $SiCH_3$), 0.91 [21 H, m, 2 × $SiC(CH_3)_3$, 9-H_3], 1.03 and 1.39 (each 1.5 H, d, *J* 7, 2-CH_3), 1.52 (2 H, m, 8-H_2) 1.91 and 1.97 (each 1.5 H, d, *J* 1, 6-CH_3), 2.58 (1 H, m, 2-H), 3.38 (0.5 H, dd, *J* 10, 5, 1-H), 3.52 (1 H, m, 1-H), 3.73 (0.5 H, dd, *J* 10, 5, 1-H′), 3.96 (1 H, m, 7-H), 4.18 (0.5 H, d, *J* 9, 3-H), 4.38 (0.5 H, d, *J* 7, 3-H), 6.31 and 6.45 (each 0.5 H, s, 5-H), 7.52 (2 H, m, ArH), 7.64 (1 H, m, ArH) and 7.86 (2 H, m, ArH); δ_C 9.82, 14.7, 16.1, 16.5, 16.6, 18.6, 18.7, 18.8, 26.3, 26.4, 29.4, 36.1, 36.5, 65.5, 66.0, 76.6, 78.4, 78.5, 79.3, 122.6, 129.3, 129.4, 129.5, 129.6, 134.2, 134.3, 139.4, 139.7, 164.0, 164.3, 192.3 and 192.5; *m*/*z* (FAB) 569 (M^+, 20%), 511 (100) and 437 (99).

(2*R*,5*E*,7*R*)-1,7-Bis(*tert*-butyldimethylsilyloxy)-2,6-dimethylnon-5-en-4-one 49

Following the procedure outlined for the synthesis of the ketone **41**, the keto sulfone **48** (42 g, 71.7 mmol) gave, after flash chromatography [light petroleum : ether (50 : 1)], the *title compound* **49** (21.5 g, 70%) as a colourless oil, $[\alpha]_D^{17}$ 30.8 (*c* 1.45, $CHCl_3$) (Found: $M^+ + H$, 429.3219. $C_{23}H_{49}O_3Si_2$ requires *M*, 429.3220); ν_{max}/cm^{-1} 1690, 1626, 1473, 1258, 1099, 838 and 776; δ_H 0.05 (3 H, s, $SiCH_3$), 0.07 (6 H, s, 2 × $SiCH_3$), 0.1 (3 H, s, $SiCH_3$), 0.89 (3 H, t, *J* 7, 9-H_3), 0.91 [9 H, s, $SiC(CH_3)_3$], 0.93 (3 H, d, *J* 8, 2-CH_3), and 0.95 [9 H, s, $SiC(CH_3)_3$], 1.58 (2 H, m, 8-H_2), 2.08 (3 H, d, *J* 1, 6-CH_3), 2.22 (2 H, m, 2-H, 3-H), 2.67 (1 H, dd, *J* 19, 8.5, 3-H′), 3.43 (1 H, dd, *J* 10, 6, 1-H), 3.51 (1 H, dd, *J* 10, 5, 1-H′), 3.98 (1 H, t, *J* 5.5, 7-H) and 6.31 (1 H, s, 5-H); δ_C −5.4, −5.0, 9.5, 15.6, 16.7, 18.2, 18.3, 25.8, 25.9, 29.0, 32.5, 48.4, 67.6, 77.2, 78.2, 122.2, 158.5 and 201.5; *m*/*z* (FAB) 429 ($M^+ + 1$, 70%), 371 (65) and 239 (100).

(2*R*,5*E*,7*R*)-1,7-Bis(*tert*-butyldimethylsilyloxy)-2,6-dimethyl-4-methylenenon-5-ene 50

Following the procedure outlined for the synthesis of the diene **42**, the enone **49** (4.59 g, 10.7 mmol) was reacted with the ylid generated from methyl(triphenyl)phosphonium bromide (11.5 g, 32.1 mmol) and *n*-butyllithium (1.6 M in hexanes; 20 cm^3, 32.1 mmol) to give, after flash chromatography [light petroleum : ether (40 : 1)], the *title compound* **50** (3.57 g, 78%) as a colourless oil, $[\alpha]_D^{17}$ 30.8 (*c* 1.45, $CHCl_3$) (Found: $M^+ + H$, 427.3454. $C_{24}H_{51}O_2Si_2$ requires *M*, 427.3428); ν_{max}/cm^{-1} 1627, 1428, 1254, 1093, 837 and 775; δ_H 0.04 (3 H, s, $SiCH_3$), 0.08 (6 H, s, 2 × $SiCH_3$), 0.09 (3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7, 9-H_3), 0.93 [21 H, m, 2 × $SiC(CH_3)_3$, 2-CH_3], 1.55 (2 H, m, 8-H_2), 1.79 (5 H, m, 6-CH_3, 2-H, 3-H), 2.31 (1 H, dd, *J* 12, 5, 3-H′), 3.43 (2 H, m, 1-H_2), 3.93 (1 H, t, *J* 6.5, 7-H), 4.89 and 5.02 (each 1 H, s, 1′-H) and 5.75 (1 H, s, 5-H); δ_C −5.4, −5.0, −4.6, 10.2, 13.2, 16.5, 18.2, 18.3, 25.9, 26.0, 29.2, 34.5, 41.8, 67.9, 80.1, 114.5, 126.1, 140.2 and 144.4; *m*/*z* (C.I.) 427 ($M^+ + 1$, 15%), 369 (15), 295 (46) and 163 (100).

(2*R*,5*E*,7*R*)-7-*tert*-Butyldimethylsilyloxy-2,6-dimethyl-4-methylenenon-5-en-1-ol 51

Tetrabutylammonium fluoride (TBAF; 1 M in tetrahydrofuran; 11.0 cm^3, 11.0 mmol) was added slowly to the diene **50** (4.25 g, 9.96 mmol) in tetrahydrofuran (50 cm^3) at 0 °C. After 1 h, additional TBAF (5.5 cm^3, 5.5 mmol) was added and the mixture stirred a further 1 h. Saturated aqueous ammonium chloride was added, the aqueous phase was extracted with ether and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (5 : 1)] gave the *title compound* **51** (2.72 g, 87%) as a colourless oil, $[\alpha]_D^{20}$ 20.4 (*c* 1.03, $CHCl_3$) (Found: $M^+ + H$, 313.2565. $C_{18}H_{37}O_2Si$ requires *M*, 313.2563); ν_{max}/cm^{-1} 3342, 1627, 1467, 1253, 1067, 1038, 837 and 775; δ_H (C_6D_6) 0.15 and 0.17 (each 3 H, s, $SiCH_3$), 0.77 (1 H, br s, OH), 0.95 (6 H, m, 2-CH_3, 9-H_3), 1.08 [9 H, s, $SiC(CH_3)_3$], 1.62 (2 H, m, 8-H_2), 1.84 (5 H, m, 2-H, 3-H, 6-CH_3), 2.33 (1 H, dd, *J* 13, 6, 3-H′), 3.32 (2 H, m, 1-H_2), 3.98 (1 H, t, *J* 6.5, 7-H), 5.03 and 5.11 (each 1 H, s, 4-C*H*H) and 5.89 (1 H, s, 5-H); δ_C (C_6D_6) −4.8, −4.5, 10.3, 13.4, 16.6, 18.4, 26.1, 29.5, 34.8, 42.2, 67.7, 80.4, 115.0, 126.6, 140.6 and 144.5; *m*/*z* (C.I.) 313 ($M^+ + 1$, 8%), 198 (15) and 181 (100).

It was found that under acidic conditions, for example on standing in solution in chloroform, that the alcohol **51** gave the (4*S*)-2-[(1*E*,3*R*)-3-*tert*-butyldimethylsilyloxy-2-methylpent-1-enyl]-2,4-dimethyltetrahydrofuran **52** as a mixture of epimers at C(2) (Found: $M^+ + H$, 313.2569. $C_{18}H_{37}O_2Si$ requires *M*, 313.2563); ν_{max}/cm^{-1} 1455, 1217, 1107 and 1046; δ_H 0.03, 0.04, 0.06 and 0.07 (each 1.5 H, s, $SiCH_3$), 0.83 and 0.84 (each 1.5 H, t, *J* 7.5, 5′-H_3), 0.92 [9 H, s, $SiC(CH_3)_3$], 1.03 and 1.07 (each 1.5 H, d, *J* 6.5, 4-CH_3), 1.34 and 1.41 (each 1.5 H, s, 2-CH_3), 1.54 (3 H, m, 4′-H_2, 3-H), 1.68 and 1.71 (each 1.5 H, d, *J* 1, 2′-CH_3), 2.15 (1 H, m, 3-H′), 2.37 (1 H, m, 4-H), 3.31 (0.5 H, t, *J* 8.5, 5-H), 3.39 (0.5 H, t, *J* 8, 5-H), 3.83 (1 H, m, 3′-H), 3.96 (1 H, m, 5-H′) and 5.43 and 5.59 (each 0.5 H, s, 1′-H); δ_C −5.0, −4.9, −4.6, −4.5, 10.2, 10.3, 11.5, 11.7, 17.4, 18.1, 18.3, 25.7, 25.8, 25.9, 27.2, 27.5, 29.1, 33.9, 34.1, 47.6, 48.2, 73.5, 73.7, 80.3, 80.5, 83.0, 83.3, 132.6, 134.1, 136.7 and 137.7; *m*/*z* (C.I.) 313 ($M^+ + 1$, 25%), 198 (31) and 181 (100).

3-Propenoyloxy-2-methyl-4-phenylpent-1-ene 55

Propenoyl chloride (10 cm^3, 0.123 mol) was added to the alcohol **54** (18 g, 0.102 mol) and diisopropylethylamine (21.9 cm^3, 0.123 mol) in dichloromethane (500 cm^3) at −10 °C. The reaction was stirred for 1 h, water was added, and the organic phase washed with saturated aqueous sodium hydrogen carbonate, aqueous hydrogen chloride (1 M) and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue [light petroleum : ether (20 : 1)] gave the *title compound* **55** (13.45 g, 57%), a colourless oil, as a mixture of diastereoisomers (Found: $M^+ + NH_4$, 248.1647. $C_{15}H_{22}NO_2$ requires *M*, 248.1651); ν_{max}/cm^{-1} 3030, 1724, 1635, 1406, 1266, 1190, 1045, 984, 962, 903, 809, 764 and 701; δ_H (major isomer) 1.32 (3 H, d, *J* 7, 5-H_3), 1.63 (3 H, s, 2-CH_3), 3.10 (1 H, m, 4-H), 4.81–6.49 (6 H, m) and 7.23 (5 H, m, ArH); (minor isomer) 1.23 (3 H, d, *J* 7, 5-H_3) and 1.74 (3 H, s, 2-CH_3); *m*/*z* (C.I.) 248 ($M^+ + 18$, 100%), 176 (35) and 159 (11).

4-Methyl-2-methylene-6-phenylhept-4-enoic acid 57

Tricyclohexylphosphine (195 mg, 0.695 mmol) in toluene (0.9 cm^3) was added to the ester **55** (1.6 g, 6.95 mmol), trimethylsilyl chloride (4.8 cm^3, 38.2 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.6 cm^3, 17.4 mmol) in acetonitrile (80 cm^3). The mixture was heated at 75 °C for 17 h then cooled and concentrated

under reduced pressure. The residue was dissolved in ether and washed with aqueous hydrogen chloride (3 M), brine and dried ($MgSO_4$). Concentration under reduced pressure and chromatography of the residue [light petroleum : ether (4 : 1)] gave the *title compound* **57** (1.2 g, 75%) as a colourless oil (Found: $M^+ + NH_4$, 248.1642. $C_{15}H_{22}NO_2$ requires *M*, 248.1651); ν_{max}/cm^{-1} 3200, 1694, 1627, 1494, 1294, 1228, 1156 and 1025; δ_H 1.35 (3 H, d, *J* 7, 7-H_3), 1.68 (3 H, d, *J* 1.5, 4-CH_3), 3.02 (2 H, s, 3-H_2), 3.72 (1 H, dq, *J* 9, 7, 6-H), 5.44 (1 H, d, *J* 9, 5-H), 5.64 and 6.37 (each 1 H, d, *J* 1.5, 2-CH), 7.26 (5 H, m, ArH) and 10.45 (1 H, br s, OH); *m*/*z* (C.I.) 248 ($M^+ + 18$, 100%).

Methyl 4-methyl-2-methylene-6-phenylhept-4-enoate 60

Ethereal diazomethane was added dropwise to the acid **57** (3.95 g, 17.2 mmol) in ether (39 cm^3) at 0 °C until the reaction mixture remained a pale yellow colour. A few drops of glacial acetic acid were added to destroy the excess of diazomethane and the reaction mixture was washed with saturated sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (30 : 1)] gave the *title compound* **60** (3.16 g, 82%) as a colourless oil (Found: $M^+ + NH_4$, 262.1801. $C_{16}H_{24}NO_2$ requires *M*, 262.1807); ν_{max}/cm^{-1} 1724, 1631, 1439 and 1142; δ_H 1.33 (3 H, d, *J* 7, 7-H_3), 1.66 (3 H, s, 4-CH_3), 3.00 (2 H, br s, 3-H_2), 3.72 (4 H, m, OCH_3, 6-H), 5.39 (1 H, d, *J* 9.5, 5-H), 5.50 and 6.19 (each 1 H, s, 2-CH) and 7.26 (5 H, m, ArH); *m*/*z* (C.I.) 262 ($M^+ + 18$, 100%) and 245 ($M^+ + 1$, 18).

4-Methyl-2-methylene-6-phenylhept-4-en-1-ol 61

Diisobutylaluminium hydride (1 M in hexane; 56.8 cm^3, 56.8 mmol) was added slowly to the ester **60** (6.3 g, 25.8 mmol) in tetrahydrofuran (150 cm^3) at −78 °C. The reaction was stirred for 1 h then saturated aqueous ammonium chloride (25 cm^3) was added. After warming to room temperature, Celite® was added and the mixture stirred for 20 min before being filtered and washed with ether. The filtrate was concentrated under reduced pressure and flash chromatography of the residue [light petroleum : ether (4 : 1)] gave the *title compound* **61** (4 g, 72%) as a colourless oil (Found: $M^+ + NH_4$, 234.1855. $C_{15}H_{24}NO$ requires *M*, 234.1858); ν_{max}/cm^{-1} 3323, 3026, 1651, 1602, 1494, 1451, 1060, 1024 and 899; δ_H 1.37 (3 H, d, *J* 7, 7-H_3), 1.54 (1 H, s, OH), 1.68 (3 H, d, *J* 1.5, 4-CH_3), 2.81 (2 H, s, 3-H_2), 3.23 (1 H, m, 6-H), 4.05 (2 H, s, 1-H_2), 4.93 and 5.11 (each 1 H, d, *J* 1, 2-CH), 5.44 (1 H, dq, *J* 9.5, 1.5, 5-H) and 7.26 (5 H, m, ArH); *m*/*z* (C.I.) 234 ($M^+ + 18$, 100%), 217 ($M^+ + 1$, 24), 199 (30) and 145 (29).

(2*S*,5*E*,7*R*)-7-*tert*-Butyldimethylsilyloxy-2,6-dimethyl-4-methylenenon-5-enal 62

Dimethyl sulfoxide (0.384 cm^3, 5.42 mmol) in dichloromethane (1.1 cm^3) was added dropwise to oxalyl chloride (0.237 cm^3, 2.71 mmol) in dichloromethane (4.4 cm^3) cooled to −50 °C. The reaction was stirred for 5 min then the alcohol **51** (0.7 g, 2.26 mmol) in dichloromethane (2.1 cm^3) was added. After stirring for 15 min, triethylamine (0.919 cm^3, 11.3 mmol) was added and the mixture warmed to room temperature. Water was added and the two layers were separated. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* **62** (0.655 g, 94%) as a pale yellow oil, $[\alpha]_D^{20}$ 55.1 (*c*, 1.06, $CHCl_3$) (Found: $M^+ + H$, 311.2403. $C_{18}H_{35}O_2Si$ requires *M*, 311.2406); ν_{max}/cm^{-1} 1733, 1629, 1473, 1257, 1066, 1017, 838 and 775; δ_H 0.04 and 0.08 (each 3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7.5, 9-H_3), 0.93 [9 H, s, $SiC(CH_3)_3$], 1.09 (3 H, d, *J* 7, 2-CH_3), 1.57 (2 H, m, 8-H_2), 1.74 (3 H, d, *J* 1.5, 6-CH_3), 2.10 (1 H, dd, *J* 13.5, 8, 3-H), 2.48 (1 H, m, 2-H), 2.59 (1 H, dd, *J* 13.5, 6, 3-H′), 3.94 (1 H, t, *J* 6, 7-H), 4.94 and 5.09 (each 1 H, s, 4-CH), 5.75 (1 H, s, 5-H) and 9.67 (1 H, d, *J* 1.5, 1-H); δ_C 10.0, 13.1, 13.4, 18.3, 25.8, 29.1, 38.9, 45.0, 79.6, 115.7, 124.8, 141.8, 142.3 and 204.6; *m*/*z* (C.I.) 328 ($M^+ + 18$, 14%), 311 ($M^+ + 1$, 7), 196 (24) and 179 (100).

(4*S*,7*E*,9*R*)-9-*tert*-Butyldimethylsilyloxy-2,4,8-trimethyl-6-methyleneundeca-1,7-dien-3-ol 63

tert-Butyllithium (1.7 M in pentane; 20 cm^3, 1.29 mmol) was added to 2-bromopropene (0.057 cm^3, 0.644 mmol) in tetrahydrofuran (4 cm^3) at −78 °C. The reaction mixture was stirred for 0.5 h then the aldehyde **62** (100 mg, 0.322 mmol) in tetrahydrofuran (0.5 cm^3) was added. The reaction was stirred at −78 °C for 1 h and then at 0 °C for 2 h. Water was added, the mixture extracted with ether, and the ether extracts dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue gave the *title compounds* **63** (85 mg, 75%) as a colourless oil (Found: M^+, 352.2796. $C_{21}H_{40}O_2Si$ requires *M*, 352.2798); ν_{max}/cm^{-1} 3425, 3076, 1651, 1463, 1257, 1066, 1016, 898, 838 and 775; δ_H (C_6D_6) 0.17 [6 H, m, $Si(CH_3)_2$], 0.51 (1 H, br s, OH), 0.91–1.10 [15 H, m, $SiC(CH_3)_3$, 11-H_3, 4-CH_3], 1.66 (5 H, m, 10-H_2, 2-CH_3), 1.90 (4.3 H, m, 8-CH_3, 4-H, 5-H_2), 2.06 (0.7 H, dd, *J* 13, 8.5, 5-H), 2.41 (0.7 H, dd, *J* 13, 6, 5-H′), 2.84 (0.3 H, m, 4-H), 3.63 (0.3 H, d, *J* 6.5, 3-H), 3.82 (0.7 H, d, *J* 4, 3-H), 3.99 (1 H, t, *J* 6.5, 9-H), 4.87–5.18 (4 H, m, 1-H_2, 6-CH_2) and 5.91 (1 H, m, 7-H); *m*/*z* (C.I.) 353 (M^+ 5%), 238 (52), 221 (100) and 203 (51).

Alternatively, 2-bromopropene (0.086 cm^3, 0.966 mmol) was added to the aldehyde **62** (100 mg, 0.322 mmol) in *N*,*N*-dimethylformamide (2 cm^3) which had been degassed by passing nitrogen through it for 40 min. Chromium(II) chloride (237 mg, 1.93 mmol) and nickel(II) bromide (<1 mg) were added and the mixture stirred for 48 h. Saturated aqueous ammonium chloride and chloroform were added and stirred for 20 min. The mixture was extracted with ethyl acetate (×3) and the extracts washed with brine and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue gave the alcohols **63** (107 mg, 95%).

(4*S*,7*E*,9*R*)-3-Propenoyloxy-9-*tert*-butyldimethylsilyloxy-2,4,8-trimethyl-6-methyleneundeca-1,7-diene 64

Acryloyl chloride (0.537 cm^3, 6.61 mmol) was added slowly to the alcohol **63** (1.55 g, 4.4 mmol) and triethylamine (0.92 cm^3, 6.61 mmol) in dichloromethane (45 cm^3) at 0 °C. The reaction was stirred for 1 h then saturated aqueous sodium hydrogen carbonate was added. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (15 : 1)] gave the *title compound* **64** (1.48 g, 83%) as a colourless oil, a 1 : 1 mixture of epimers at C(3) (Found: M^+, 406.2906. $C_{24}H_{42}O_3Si$ requires *M*, 406.2903); ν_{max}/cm^{-1} 3081, 1730, 1635, 1463, 1405, 1261, 1189, 1066, 900, 837 and 776; δ_H 0.06 [6 H, m, $Si(CH_3)_2$], 0.92 [15 H, m, $SiC(CH_3)_3$, 11-H_3, 4-CH_3], 1.57 (2 H, m, 10-H_2), 1.76 (6 H, m, 2-CH_3, 8-CH_3), 1.95 (2 H, m, 5-H_2), 2.21 and 2.44 (each 0.5 H, m, 4-H), 3.96 (1 H, m, 9-H), 4.90–5.22 (5 H, m, 3-H, 1-H_2, 6-CH_2), 5.74 (1 H, s, 7-H), 5.85 (1 H, m, 3′-H), 6.18 (1 H, m, 2′-H), 6.46 (1 H, m, 3′-H′); *m*/*z* (C.I.) 424 ($M^+ + 18$, 8%), 407 ($M^+ + 1$, 4), 292 (20), 275 (100) and 203 (27).

(4*E*,6*S*,9*E*,11*R*)-11-*tert*-Butyldimethylsilyloxy-4,6,10-trimethyl-2,8-dimethylenetrideca-4,9-dienoic acid 65

Tricyclohexylphosphine (64 mg, 0.228 mmol) in toluene (0.5 cm^3) was added to the ester **64** (930 mg, 2.29 mmol), trimethylsilyl chloride (1.6 cm^3, 12.6 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.856 cm^3, 5.72 mmol) in acetonitrile (23 cm^3). The mixture was heated to 70 °C and stirred for 16 h, cooled, then concentrated under reduced pressure. The residue was dissolved in ether, washed with aqueous hydrogen chloride (2 M), brine and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue [light

petroleum : ether (5 : 1)] gave the *title compound* **65** (0.89 g, 96%) as a colourless oil, $[\alpha]_D^{22}$ 30 (*c* 1.12, $CHCl_3$) (Found: $M^+ + H$, 407.2981. $C_{24}H_{43}O_3Si$ requires *M*, 407.2981); ν_{max}/cm^{-1} 3400, 1697, 1629, 1439, 1254, 1066, 1019, 837 and 776; δ_H 0.04 and 0.08 (each 3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7.5, 13-H_3), 0.96 [12 H, m, $SiC(CH_3)_3$, 6-CH_3], 1.58 (5 H, m, 4-CH_3, 12-H_2), 1.73 (3 H, d, *J* 1, 10-CH_3), 2.06 (2 H, m, 7-H_2), 2.52 (1 H, m, 6-H), 2.98 (2 H, s, 3-H_2), 3.94 (1 H, t, *J* 6.5, 11-H), 4.84 and 4.98 (each 1 H, s, 8-CH), 5.04 (1 H, d, *J* 9, 5-H), 5.67 (1 H, d, *J* 1, 2-CH), 5.75 (1 H, s, 9-H) and 6.36 (1 H, s, 2-CH′); δ_C −4.9, −4.6, 10.1, 13.2, 16.1, 18.3, 20.6, 25.9, 29.2, 31.4, 40.7, 45.8, 80.0, 114.6, 126.1, 127.7, 130.0, 134.3, 138.4, 140.2, 144.1 and 172.4; *m*/*z* (C.I.) 407 ($M^+ + 1$, 4%), 292 (34) and 275 (100).

Methyl (4*E*,6*S*,9*E*,11*R*)-11-*tert*-butyldimethylsilyloxy-4,6,10-trimethyl-2,8-dimethylenetrideca-4,9-dienoate 66

Ethereal diazomethane was added to the unsaturated acid **65** (434 mg, 1.07 mmol) in ether (10 cm^3) at 0 °C until no further gas was evolved and the reaction mixture remained a pale yellow colour. A few drops of glacial acetic acid were added and the reaction mixture was washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (10 : 1)] gave the *title compound* **66** (381 mg, 85%) as a colourless oil, $[\alpha]_D^{17}$ 28 (*c* 0.96, $CHCl_3$) (Found: M^+, 420.3052. $C_{25}H_{44}O_3Si$ requires *M*, 420.3060); ν_{max}/cm^{-1} 1727, 1630, 1440, 1255, 1142, 1067, 1019 and 838; δ_H 0.04 and 0.08 (each 3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7.5, 13-H_3), 0.93 [12 H, m, $SiC(CH_3)_3$, 6-CH_3], 1.56 (5 H, m, 12-H_2, 4-CH_3), 1.73 (3 H, d, *J* 1, 10-CH_3), 2.05 (2 H, m, 7-H_2), 2.51 (1 H, m, 6-H), 2.98 (2 H, s, 3-H_2), 3.77 (3 H, s, OCH_3), 3.93 (1 H, t, *J* 6.5, 11-H), 4.84 and 4.97 (each 1 H, s, 8-CH), 5.03 (1 H, d, *J* 9, 5-H), 5.54 (1 H, d, *J* 1.5, 2-CH), 5.75 (1 H, s, 9-H) and 6.21 (1 H, d, *J* 1, 2-CH′); δ_C −5.0, −4.6, 10.1, 13.1, 16.1, 18.3, 20.6, 25.9, 29.2, 31.3, 41.2, 45.8, 51.8, 77.2, 80.0, 114.6, 125.4, 126.1, 127.2, 130.2, 134.4, 139.0, 140.2, 144.2 and 167.9; *m*/*z* (C.I.) 438 ($M^+ + 18$, 11%), 421 ($M^+ + 1$, 9) and 289 (100).

(4*E*,6*S*,9*E*,11*R*)-11-*tert*-Butyldimethylsilyloxy-4,6,10-trimethyl-2,8-dimethylenetrideca-4,9-dien-1-ol 67

Diisobutylaluminium hydride (1 M in hexane; 5 cm^3, 4.97 mmol) was added slowly to the ester **66** (0.949 g, 2.26 mmol) in tetrahydrofuran (13.5 cm^3) at −78 °C. The mixture was stirred for 1 h then saturated aqueous ammonium chloride (2.5 cm^3) was added. After warming to 0 °C, Celite® was added and the reaction mixture was allowed to warm to room temperature and stirred for 0.5 h then filtered, and the filtrate concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (10 : 1)] gave the *title compound* **67** (0.796 g, 90%) as a colourless oil, $[\alpha]_D^{22}$ (*c* 0.75, $CHCl_3$) (Found: $M^+ + H$, 393.3195. $C_{24}H_{45}O_2Si$ requires *M*, 393.3189); ν_{max}/cm^{-1} 3343, 1630, 1463, 1256, 1066, 1018, 898, 836 and 775; δ_H 0.03 and 0.08 (each 3 H, s, $SiCH_3$), 0.85 (3 H, t, *J* 7.5, 13-H_3), 0.94 [12 H, m, $SiC(CH_3)_3$, 6-CH_3], 1.45 (1 H, t, *J* 6.5, OH), 1.58 (5 H, m, 4-CH_3, 12-H_2), 1.72 (3 H, d, *J* 1, 10-CH_3), 2.06 (2 H, m, 7-H_2), 2.52 (1 H, m, 6-H), 2.89 (2 H, br s, 3-H_2), 3.94 (1 H, t, *J* 6.5, 11-H), 4.06 (2 H, d, *J* 6.5, 1-H_2), 4.85 (1 H, s, 8-CH), 4.93 (1 H, s, 2-CH), 4.98 (1 H, s, 8-CH′), 5.06 (1 H, d, *J* 9.5, 5-H), 5.10 (1 H, s, 2-CH′) and 5.75 (1 H, s, 9-H); δ_C −5.0, −4.6, 10.6, 13.7, 16.2, 18.7, 21.1, 26.3, 29.6, 31.8, 44.7, 46.3, 65.9, 75.4, 80.5, 111.5, 114.9, 126.5, 131.4, 134.1, 140.7, 144.8 and 147.4; *m*/*z* (C.I.) 410 ($M^+ + 18$, 10%), 393 ($M^+ + 1$, 35), 278 (58) and 261 (100).

(2*S*,4*E*,6*S*,9*E*,11*R*)-11-*tert*-Butyldimethylsilyloxy-2,2-epoxymethano-4,6,10-trimethyl-8-methylenetrideca-4,9-dien-1-ol 68

Titanium(IV) isopropoxide (0.35 M in dichloromethane; 0.02 cm^3, 7 μmol) and L-(+)-diethyl tartrate (0.48 M in dichloromethane; 0.018 cm^3, 8.7 μmol) were added to the alcohol **67** (58 mg, 0.148 mmol) and powdered 3 Å molecular sieves in dichloromethane (0.3 cm^3) at −20 °C. After stirring for 0.5 h, *tert*-butyl hydroperoxide (3 M in isooctane; 0.1 cm^3, 0.3 mmol) was added and the reaction mixture stirred for 3.75 h then warmed to 0 °C. Water (0.1 cm^3) was added and, after stirring for 0.5 h, the mixture was warmed to room temperature. Aqueous sodium hydroxide (30%; saturated with sodium chloride) was added and the mixture stirred for 0.5 h before being diluted with water and dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (6 : 1)] gave the *title compound* **68** (37 mg, 61%) as a colourless oil, $[\alpha]_D^{20}$ 14 (*c* 1.4, $CHCl_3$) (Found: M^+, 408.3058. $C_{24}H_{44}O_3Si$ requires *M*, 408.3060); ν_{max}/cm^{-1} 3444, 1627, 1463, 1255, 1066, 1017, 836 and 775; δ_H 0.04 and 0.08 (each 3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7.5, 13-H_3), 0.93 [12 H, m, $SiC(CH_3)_3$, 6-CH_3], 1.56 (2 H, m, 12-H_2), 1.64 (3 H, d, *J* 1, 4-CH_3), 1.7 (1 H, br s, OH), 1.72 (3 H, d, *J* 1, 10-CH_3), 2.05 (2 H, d, *J* 7, 7-H_2), 2.16 (1 H, d, *J* 14, 3-H), 2.51 (2 H, m, 3-H′, 6-H), 2.71 and 2.93 (each 1 H, d, *J* 5, 2-CH), 3.63 (1 H, dd, *J* 12, 8.5, 1-H), 3.75 (1 H, dd, *J* 12, 3, 1-H′), 3.93 (1 H, t, *J* 6.5, 11-H), 4.85 and 4.98 (each 1 H, s, 8-CH), 5.08 (1 H, d, *J* 9.5, 5-H) and 5.75 (1 H, s, 9-H); δ_C 10.6, 13.7, 17.4, 18.7, 21.1, 26.3, 29.6, 31.7, 43.2, 46.3, 50.3, 59.2, 63.0, 80.4, 115.1, 126.3, 129.3, 135.6, 140.9 and 144.6; *m*/*z* (C.I.) 426 ($M^+ + 18$, 2%), 409 ($M^+ + 1$, 2), 294 (6), 277 (70) and 113 (100).

(2*R*,4*E*,6*S*,9*E*,11*R*)-11-*tert*-Butyldimethylsilyloxy-2,2-epoxymethano-4,6,10-trimethyl-8-methylenetrideca-4,9-dien-1-ol 69

Following the procedure outlined for the synthesis of the epoxide **68**, the alcohol **67** (100 mg, 0.255 mmol), D-(−)-diethyl tartrate (3.2 mg, 15 μmol), titanium(IV) isopropoxide (3.6 mg, 12.8 μmol) and *tert*-butyl hydroperoxide (3 M in isooctane; 0.17 cm^3, 0.51 mmol) gave, after flash chromatography [light petroleum : ether (5 : 1)] the *title compound* **69** (97 mg, 93%) as a colourless oil, $[\alpha]_D^{20}$ 50 (*c* 1, $CHCl_3$) (Found: M^+, 408.3054. $C_{24}H_{44}O_3Si$ requires *M*, 408.3060); ν_{max}/cm^{-1} 3426, 1628, 1463, 1256, 1067, 836 and 775; δ_H 0.04 and 0.08 (each 3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7.5, 13-H_3), 0.93 [12 H, m, $SiC(CH_3)_3$, 6-CH_3], 1.55 (3 H, m, 12-H_2, OH), 1.69 and 1.75 (each 3 H, d, *J* 1, 4-CH_3, 10-CH_3), 2.03 (1 H, dd, *J* 9, 3, 7-H), 2.08 (1 H, dd, *J* 9, 2.5, 7-H′), 2.21 and 2.44 (each 1 H, d, *J* 14, 3-H), 2.53 (1 H, m, 6-H), 2.70 and 2.93 (each 1 H, d, *J* 5, 2-CH), 3.65 (1 H, dd, *J* 12.5, 9, 1-H), 3.73 (1 H, dd, *J* 12.4, 4.5, 1-H′), 3.94 (1 H, t, *J* 6.5, 11-H), 4.87 and 4.98 (each 1 H, s, 8-CH), 5.07 (1 H, d, *J* 9, 5-H) and 5.75 (1 H, s, 9-H); δ_C 10.6, 13.7, 17.4, 18.7, 21.0, 26.3, 29.6, 31.7, 43.1, 46.2, 50.3, 59.3, 62.9, 80.4, 115.1, 126.4, 129.3, 135.6, 140.8 and 144.6; *m*/*z* (C.I.) 426 ($M^+ + 18$, 3%), 409 ($M^+ + 1$, 2), 277 (50) and 123 (100).

(2*R*,4*E*)-2,2-Epoxymethano-4-methyl-6-phenylhept-4-en-1-ol 70

Following the procedure outlined for the synthesis of the hydroxy epoxide **68**, the allylic alcohol **61** (3.9 g, 18.1 mmol) was treated with D-(−)-diethyl tartrate (0.185 cm^3, 1.08 mmol), titanium(IV) isopropoxide (0.269 cm^3, 0.903 mmol) and *tert*-butyl hydroperoxide (3 M in isooctane; 12.0 cm^3, 36.1 mmol) to give, after flash chromatography [light petroleum : ether (4 : 1–3 : 1–1 : 1)] the *title compound* **70** (2.6 g, 62%) as a colourless oil, a 1 : 1 mixture of epimers at C(6) (Found: $M^+ + NH_4$, 250.1808. $C_{15}H_{24}NO_2$ requires *M*, 250.1807); ν_{max}/cm^{-1} 3423, 3027, 1601, 1492, 1450 and 1045; δ_H 1.34 (3 H, d, *J* 7, 7-H_3), 1.73 (3 H, d, *J* 1.5, 4-CH_3), 2.21 and 2.48 (each 1 H, d, *J* 14, 3-H), 2.67 and 2.91 (each 1 H, m, 2-CH), 3.66 (3 H, m, 1-H_2, 6-H), 5.43 (1 H, d, *J* 9.5, 5-H) and 7.26 (5 H, m, ArH); *m*/*z* (C.I.) 250 ($M^+ + 18$, 98%), 234 (46), 232 (M^+, 40) and 220 (100).

(2*S*,4*E*)-2,2-Epoxymethano-4-methyl-6-phenylhept-4-enyl phenylcarbamate 71

Phenyl isocyanate (0.056 cm^3, 0.474 mmol) was added to the alcohol **70** (100 mg, 0.431 mmol) and triethylamine (0.066 cm^3, 0.474 mmol) in dichloromethane (1.0 cm^3) at 0 °C. The reaction mixture was stirred for 1 h and then washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (5 : 1)] gave the *title compound* **71** (110 mg, 73%) as a colourless oil, ν_{max}/cm^{-1} 3329, 1737, 1714, 1540, 1498, 1445, 1217 and 1068; δ_H 1.33 (3 H, d, *J* 7, 7-H_3), 1.76 (3 H, d, *J* 1.5, 4-CH_3), 2.25, 2.31, 2.49 and 2.55 (each 0.5 H, d, *J* 14, 3-H_2), 2.71 and 2.82 (each 1 H, m, 2-CH), 3.71 (1 H, m, 6-H), 4.10, 4.13, 4.27 and 4.33 (each 0.5 H, d, *J* 12, 1-H), 5.46 (1 H, d, *J* 9, 5-H), 6.70 (1H, m, NH) and 7.26 (10 H, m, ArH); *m*/*z* (C.I.) 369 (M^+ + 18, 75%), 352 (M^+ + 1, 100), 288 (61) and 250 (37).

Benzyl (2*S*,4*E*)-2,2-epoxymethano-4-methyl-6-phenylhept-4-enyl carbonate 72

Benzyl chloroformate (0.195 cm^3, 1.38 mmol) was added to the epoxy alcohol **70** (160 mg, 0.69 mmol) and pyridine (0.122 cm^3, 1.52 mmol) in tetrahydrofuran (2 cm^3) at −20 °C. The mixture was allowed to warm to room temperature and stirred for 16 h then diluted with ether, washed with aqueous hydrogen chloride (1.5 M), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (10 : 1)] gave the *title compound* **72** (228 mg, 90%) as a colourless oil, (Found: $M^+ + NH_4$, 384.2164. $C_{23}H_{30}NO_4$ requires *M*, 384.2175); ν_{max}/cm^{-1} 3029, 1752, 1601, 1494, 1261, 958 and 699; δ_H 1.30 (3 H, m, 7-H_3), 1.72 (3 H, s, 4-CH_3), 2.25, 2.30, 2.44 and 2.49 (each 0.5 H, d, *J* 14, 3-H), 2.65 and 2.68 (each 0.5 H, d, *J* 5, 2-CH), 2.79 (1 H, m, 2-CH′), 3.69 (1 H, m, 6-H), 4.09, 4.10, 4.20 and 4.24 (each 0.5 H, d, *J* 11.5, 1-H), 5.16 (2 H, s, $ArCH_2$), 5.43 (1 H, d, *J* 9.5, 5-H) and 7.26 (10 H, m, ArH); *m*/*z* (C.I.) 384 (M^+ + 18, 100%) and 250 (16).

(4*R*)-4-[(2*E*)-2-Methyl-4-phenylpent-2-enyl]-4-hydroxymethyl-1,3-dioxolan-2-one 73

The phenyl carbamate **71** (60 mg, 0.171 mmol) was stirred in aqueous perchloric acid (5%)–acetonitrile (1 : 3, 1 cm^3) for 17 h then the mixture was diluted with hexane and washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (1 : 1)] gave the *title compound* **73** (21 mg, 45%) as a colourless oil, a 1 : 1 mixture of epimers at C(4′) (Found: $M^+ + NH_4$, 294.1682. $C_{16}H_{24}NO_4$ requires *M*, 294.1705); ν_{max}/cm^{-1} 3444, 1799, 1450, 1201 and 1070; δ_H 1.36 (3 H, d, *J* 7.5, 5′-H_3), 1.80 (3 H, m, 2′-CH_3), 2.35 (3 H, m, 1′-H_2, OH), 3.50 (1 H, m, 1″-H), 3.72 (2 H, m, 1″-H′, 4′-H), 4.18, 4.23, 4.42 and 4.48 (each 0.5 H, d, *J* 9, 5-H), 5.43 (1 H, d, *J* 9.5, 3′-H) and 7.24 (5 H, m, ArH); *m*/*z* (E.I.) 276 (M^+, 5%), 261 (4), 144 (81) and 105 (100).

Aluminium trichloride (1 M in nitrobenzene; 1.1 cm^3, 1.15 mmol) was added to the benzyl carbonate **72** (350 mg, 0.956 mmol) in dichloromethane (3.5 cm^3) at −20 °C and the mixture allowed to warm slowly to room temperature for 2 h. Water was added and the organic phase washed with aqueous hydrogen chloride (3 M), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography, as above gave the dioxolanone **73** (200 mg, 76%).

(4*R*)-4-[(2*E*)-2-Methyl-4-phenylpent-2-enyl]-4-[(2-trimethylsilylethoxy)methoxymethyl]-1,3-dioxolan-2-one 74

(2-Trimethylsilylethoxy)methyl chloride (0.27 cm^3, 1.45 mmol) was added to the dioxolanone **73** (200 mg, 0.725 mmol) and diisopropylethylamine (0.5 cm^3, 2.89 mmol) in dichloromethane (0.5 cm^3) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 16 h, then diluted with dichloromethane, washed with aqueous hydrogen chloride (3 M) and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue [light petroleum : ether (5 : 1)] gave the *title compound* **74** (152 mg, 52%), a colourless oil, as a 1 : 1 mixture of epimers at C(4′) (Found: $M^+ + NH_4$, 424.2518. $C_{22}H_{38}NO_5Si$ requires *M*, 424.2519); ν_{max}/cm^{-1} 1806, 1451, 1250, 1115, 1071, 861 and 837; δ_H 0.03 [9 H, s, $Si(CH_3)_3$], 0.09 (2 H, m, $SiCH_2$), 1.34 (3 H, d, *J* 7, 5′-H_3), 1.80 (3 H, m, 2′-CH_3), 2.37 and 2.49 (each 1 H, d, *J* 14, 1′-H), 3.60 (5 H, m, 4′-H, 1″-CH_2, CH_2CH_2O), 4.14, 4.20, 4.37 and 4.39 (each 0.5 H, d, *J* 8, 5-H), 4.60 and 4.63 (each 0.5 H, d, *J* 6, OHC*H*O), 4.69 (1 H, s, OCH_2O), 5.43 (1 H, d, *J* 9.5, 3′-H) and 7.24 (5 H, m, ArH); *m*/*z* (C.I.) 424 (M^+ + 18, 100%), 369 (14) and 320 (25).

(2*S*,4*E*)-4-Methyl-6-phenyl-2-[(2-trimethylsilylethoxy)methoxymethyl]hept-4-ene-1,2-diol 75

Lithium hydroxide monohydrate (78 mg, 1.85 mmol) was added to the cyclic carbonate **74** (150 mg, 0.369 mmol) in dimethoxyethane–water (5 : 1) and the mixture stirred for 3 h at room temperature then diluted with water and extracted with ether. The extract was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (1 : 1)] gave the *title compound* **75** (114 mg, 81%) as a colourless oil, ν_{max}/cm^{-1} 3424, 1452, 1249, 1110, 1057, 860 and 836; δ_H 0.00 [9 H, s, $SiC(CH_3)_3$], 0.93 (2 H, m, $SiCH_2$), 1.27 (3 H, m, 7-H_3), 1.85 (3 H, d, *J* 1.5, 4-CH_3), 2.00 (1 H, m, 1-OH), 2.26 (2 H, m, 3-H_2), 2.76 and 2.77 (each 0.5 H, s, 2-OH), 3.54 (7 H, m, 1-H_2, 6-H, CH_2CH_2O, 1′-H_2), 4.39 and 4.44 (each 0.5 H, d, *J* 6.5, O*H*CHO), 4.47 (1 H, s, OCH_2O), 5.43 (1 H, d, *J* 9, 5-H) and 7.12 (5 H, m, ArH); *m*/*z* (C.I.) 398 (M^+ + 18, 15%) and 280 (16).

(2*R*,4*E*)-2-Hydroxy-4-methyl-6-phenyl-2-[(2-trimethylsilylethoxy)methoxymethyl]hept-4-enal 76

Dimethyl sulfoxide (0.056 cm^3, 0.79 mmol) in dichloromethane (0.125 cm^3) was added to oxalyl chloride (0.035 cm^3, 0.395 mmol) in dichloromethane (0.5 cm^3) at −50 °C. The reaction mixture was stirred for 2 min and the alcohol **75** (100 mg, 0.263 mmol) in dichloromethane (0.24 cm^3) was added. The mixture was stirred for 15 min, triethylamine (0.134 cm^3, 1.64 mmol) was added, and the mixture allowed to warm to room temperature. After partitioning between water and dichloromethane, the organic phase was washed with aqueous hydrogen chloride (3 M) and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography of the residue [light petroleum : ether (3 : 1)] gave the *title compound* **76** (47 mg, 46%) as a colourless oil (Found: $M^+ + NH_4$, 396.2580. $C_{21}H_{38}NO_4Si$ requires *M*, 396.2570); ν_{max}/cm^{-1} 3454, 1736, 1451, 1250, 1111, 1058, 860 and 836; δ_H 0.01 [9 H, s, $Si(CH_3)_3$], 0.93 (2 H, m, $SiCH_2$), 1.23 (3 H, m, 7-H_3), 1.68 and 1.72 (each 1.5 H, d, *J* 1.5, 4-CH_3), 2.12 and 2.21 (each 1 H, d, *J* 14, 3-H), 3.51 (6 H, m, 2-OH, 6-H, 1′-H_2, CH_2CH_2O), 4.36 and 4.40 (each 0.5 H, d, *J* 7, O*H*CHO), 4.42 (1 H, s, OCH_2O), 5.31 (1 H, m, 5-H), 7.18 (5 H, m, ArH) and 9.48 and 9.53 (each 0.5 H, s, 1-H); *m*/*z* (C.I.) 396 (M^+ + 18, 80%), 248 (64) and 90 (100).

(2*S*,4*E*)-2,2-Epoxymethano-4-methyl-6-phenylhept-4-enal 77

The epoxy alcohol **70** (100 mg, 0.431 mmol), 4-methylmorpholine-*N*-oxide (87 mg, 0.645 mmol) and powdered 3 Å molecular sieves were stirred in dichloromethane (5 cm^3) for 10 min then tetrapropylammonium perruthenate (8 mg, 21.6 μmol) was added and the suspension stirred for 3.5 h. The mixture was filtered through a short column of silica and concentrated under reduced pressure to give the *title compound* **77** (62 mg, 63%) as a colourless oil (Found: $M^+ + NH_4$, 248.1656. $C_{15}H_{22}NO_2$ requires *M*, 248.1650); ν_{max}/cm^{-1} 1728, 1601, 1494, 1451, 1026, 869, 760 and 701; δ_H 1.32 (3 H, d, *J* 7, 7-H_3), 1.68 and 1.71 (each 1.5 H, d, *J* 1.5, 4-CH_3), 2.60 (2 H, m, 3-H_2), 2.97 (2 H, m, 2-CH_2), 3.68 (1 H, m, 6-H), 5.40 (1 H, m, 5-H), 7.23

(5 H, m, ArH) and 8.95 (1 H, s, 1-H); δ_C 18.1, 22.7, 23.0, 36.8, 36.9, 38.5, 38.6, 49.5, 61.1, 61.2, 126.4, 127.4, 128.7, 128.8, 128.9, 135.0, 135.1, 147.0, 147.1 and 199.2; *m*/*z* (C.I.) 248 (M^+ + 18, 100%).

(4*E*,6*S*,9*E*,11*R*)-11-*tert*-Butyldimethylsilyloxy-4,6,10-trimethyl-2,8-dimethylenetrideca-4,9-dienal 78

4-Methylmorpholine-*N*-oxide (130 mg, 0.963 mmol), the alcohol **67** (360 mg, 0.918 mmol) and powdered 3 Å molecular sieves were stirred in dichloromethane (9 cm^3) for 5 min then tetrapropylammonium perruthenate (6.4 mg, 18.4 μmol) was added. The suspension was stirred for 2 h, filtered through a short column of silica and concentrated under reduced pressure to give the *title compound* **78** (289 mg, 81%) as a colourless oil, $[\alpha]_D^{23}$ 24.6 (*c* 1.27, $CHCl_3$) (Found: M^+ + H, 391.3024. $C_{24}H_{43}OSi$ requires *M*, 391.3032); ν_{max}/cm^{-1} 1698, 1463, 1361, 1256, 1066, 1017, 837 and 776; δ_H 0.04 and 0.08 (each 3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7.5, 13-H_3), 0.94 [12 H, m, $SiC(CH_3)_3$, 6-CH_3], 1.58 (5 H, m, 4-CH_3, 12-H_2), 1.73 (3 H, s, 10-CH_3), 2.06 (2 H, m, 7-H_2), 2.53 (1 H, m, 6-H), 2.95 (2 H, br s, 3-H_2), 3.94 (1 H, t, *J* 6.5, 11-H), 4.82 and 4.97 (each 1 H, s, 8-CH), 5.04 (1 H, d, *J* 9, 5-H), 5.75 (1 H, s, 9-H), 6.09 and 6.28 (each 1 H, s, 2-CH) and 9.65 (1 H, s, 1-H); δ_C −5.0, −4.6, 10.1, 13.2, 16.1, 18.2, 20.6, 25.9, 29.2, 31.3, 37.1, 45.8, 79.9, 114.6, 126.1, 129.7, 134.5, 134.6, 140.2, 144.2, 148.5 and 194.3; *m*/*z* (C.I.) 408 (M^+ + 18, 3%), 391 (M^+ + 1, 6), 276 (9) and 259 (100).

tert-Butyl (6*E*,8*S*,11*E*,13*R*)-13-*tert*-butyldimethylsilyloxy-3-hydroxy-6,8,12-trimethyl-4,10-dimethylenepentadeca-6,11-dienoate 79

n-Butyllithium (1.6 M in hexane; 1.1 cm^3, 0.18 mmol) was added slowly to 1,1,1,3,3,3-hexamethyldisilazane (0.38 cm^3, 0.181 mmol) at 0 °C and the mixture stirred for 0.5 h. The solvent was removed under a stream of argon and tetrahydrofuran (2.5 cm^3) and *tert*-butyl acetate (0.244 cm^3, 0.186 mmol) were added. After 45 min, the aldehyde **78** (235 mg, 0.603 mmol) in tetrahydrofuran (2.5 cm^3) was added and the stirring continued for 1 h. Water was added and the mixture allowed to warm to room temperature. The organic phase was washed with aqueous hydrogen chloride (1 M), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (10 : 1)] gave the *title compound* **79** (267 mg, 88%) as a colourless oil, a 1 : 1 mixture of epimers at C(3); ν_{max}/cm^{-1} 3459, 1732, 1717, 1462, 1369, 1256, 1152, 1066, 836 and 775; δ_H 0.04 and 0.08 (each 3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7.5, 15-H_3), 0.93 [12 H, m, $SiC(CH_3)_3$, 8-CH_3], 1.55 [14 H, m, $OC(CH_3)_3$, 6-CH_3, 14-H_2], 1.74 (3 H, s, 12-CH_3), 2.08 (2 H, m, 9-H_2), 2.52 (3 H, m, 2-H_2, 8-H), 2.71 and 2.81 (each 1 H, d, *J* 15, 5-H), 3.13 and 3.16 (each 0.5 H, d, *J* 4.5, 3-OH), 3.94 (1 H, t, *J* 6.5, 13-H), 4.43 (1 H, m, 3-H), 4.84 (1 H, s, 10-CH), 4.94 (1 H, s, 4-CH), 4.97 (1 H, s, 10-CH′), 5.06 (1 H, d, *J* 9, 7-H), 5.18 (1 H, s, 4-CH′) and 5.75 (1 H, s, 11-H); δ_C −5.0, −4.6, 10.1, 13.2, 15.8, 18.3, 20.6, 25.9, 28.1, 29.2, 31.4, 41.2, 43.4, 43.5, 45.6, 45.9, 70.2, 70.3, 80.0, 81.3, 111.8, 114.6, 126.1, 130.8, 134.1, 134.2, 140.2, 140.2, 144.2, 147.6 and 172.1; *m*/*z* (ESP) 1035 (10%), 1030 (2), 524 (M^+ + 18, 100), 319 (16), 153 (20).

tert-Butyl (6*E*,8*S*,11*E*,13*R*)-13-*tert*-butyldimethylsilyloxy-3-*tert*-butyldiphenylsilyloxy-6,8,12-trimethyl-4,10-dimethylenepentadeca-6,11-dienoate 80

tert-Butyldiphenylsilyl chloride (0.173 cm^3, 0.664 mmol) and imidazole (94 mg, 1.38 mmol) were added to the alcohols **79** (280 mg, 0.553 mmol) in *N*,*N*-dimethylformamide (0.5 cm^3) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h before being diluted with hexane and washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (12 : 1)] gave the *title compound* **80** (381 mg, 93%), a colourless oil, as a 1 : 1 mixture of epimers at C(3) (Found: M^+ + Na, 767.4857. $C_{46}H_{72}NaO_4Si_2$ requires *M*, 767.4867); ν_{max}/cm^{-1} 3073, 1734, 1428, 1367, 1256, 1151, 1112, 1068 and 837; δ_H 0.06 and 0.10 (each 3 H, s, $SiCH_3$), 0.92 [15 H, m, $OSiC(CH_3)_3$, 15-H_3, 8-CH_3], 1.12 [9 H, s, $OSiC(CH_3)_3$], 1.34 [9 H, s, $OC(CH_3)_3$], 1.54 (5 H, m, 6-CH_3, 14-H_2), 1.73 and 1.74 (each 1.5 H, d, *J* 1, 12-CH_3), 2.04 (2 H, m, 9-H_2), 2.49 (3 H, m, 2-H_2, 8-H), 2.73 (2 H, s, 5-H_2), 3.95 (1 H, t, *J* 6.5, 13-H), 4.60 (1 H, m, 3-H), 4.78 (1 H, s, 10-CH), 4.82 and 4.85 (each 0.5 H, s, 4-CH), 4.97 (3 H, m, 7-H, 10-CH′, 4-CH′), 5.76 (1 H, s, 11-H), 7.42 (6 H, m, ArH) and 7.72 (4 H, m, ArH); δ_C −4.9, −4.6, 10.1, 13.2, 15.9, 18.3, 19.4, 20.5, 26.0, 27.0, 28.1, 29.2, 29.7, 31.3, 31.4, 41.2, 43.0, 45.76, 45.81, 74.1, 80.07, 80.16, 112.4, 114.6, 126.2, 127.4, 127.5, 129.59, 129.64, 130.7, 133.7, 134.1, 134.4, 134.5, 136.0, 140.1, 144.2, 147.3 and 169.8; *m*/*z* (ESP) 762 (M^+ + 18, 81%), 654 (44), 598 (36) and 466 (53).

tert-Butyl (6*E*,8*S*,11*E*,13*R*)-13-*tert*-butyldimethylsilyloxy-6,8,12-trimethyl-4,10-dimethylene-3-(2-trimethylsilylethoxy)-methoxypentadeca-6,11-dienoate 81

(2-Trimethylsilylethoxy)methyl chloride (0.04 cm^3, 0.225 mmol) was added to diisopropylethylamine (0.078 cm^3, 0.415 mmol) and the alcohol **79** (57 mg, 0.113 mmol) in dichloromethane (0.3 cm^3). The mixture was stirred for 16 h, diluted with ether, washed with aqueous hydrogen chloride (3 M), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (25 : 1)] gave the *title compound* **81** (87 mg), a colourless oil, as a 1 : 1 mixture of epimers at C(3) (Found: M^+ + NH_4, 654.4952. $C_{36}H_{72}NO_5Si_2$ requires *M*, 654.4949); ν_{max}/cm^{-1} 1736, 1368, 1250, 1029 and 836; δ_H 0.04 (3 H, s, $SiCH_3$), 0.05 [9 H, s, $SiC(CH_3)_3$], 0.08 (3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7.5, 15-H_3), 0.97 [14 H, m, $SiC(CH_3)_3$, $SiCH_2$, 8-CH_3], 1.48 [9 H, s, $OC(CH_3)_3$], 1.55 (5 H, m, 6-CH_3, 14-H_2), 1.73 (3 H, s, 12-CH_3), 2.02 (1 H, dd, *J* 13.5, 7.5, 9-H), 2.10 (1 H, m, 9-H′), 2.51 (3 H, m, 2-H_2, 8-H), 2.69 (2 H, s, 5-H_2), 3.55 (0.5 H, m, CH_2CHHO), 3.67 (1 H, m, CH_2CHHO), 3.77 (0.5 H, m, CH_2CHHO), 3.94 (1 H, t, *J* 6.5, 13-H), 4.50 (1 H, dd, *J* 8.5, 5, 3-H), 4.65 (2 H, s, OCH_2O), 4.85 (1 H, s, 10-CH), 4.97 (1 H, s, 4-CH), 4.99 (1 H, s, 10-CH′), 5.05 (1 H, d, *J* 9, 7-H), 5.16 (1 H, s, 4-CH′) and 5.76 (1 H, s, 11-H); *m*/*z* (C.I.) 654 (M^+ + 18, 2%), 464 (4), 422 (6) and 391 (7).

(2*E*,6*E*,8*S*,11*E*,13*R*)-13-*tert*-Butyldimethylsilyloxy-6,8,12-trimethyl-4,10-dimethylenepentadeca-2,6,11-trienoic acid 86

Triethylamine (0.066 cm^3, 50 mmol) and trimethylsilyl trifluoromethanesulfonate (0.078 cm^3, 0.426 mmol) were added to the *tert*-butyl ester **80** (65 mg, 0.102 mmol) in ether (1.5 cm^3) at 0 °C. After 6 h, the reaction was diluted with ether, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (5 : 1–2 : 1)] gave the *title compound* **86** (40 mg, 68%) as a colourless oil (Found: M^+, 432.3064. $C_{26}H_{44}O_3Si$ requires *M*, 432.3060); ν_{max}/cm^{-1} 3400–2300, 1693, 1627, 1284, 1253, 1066, 1020, 837 and 775; δ_H 0.04 and 0.08 (each 3 H, s, $SiCH_3$), 0.87 (3 H, t, *J* 7, 15-H_3), 0.98 [12 H, m, $SiC(CH_3)_3$, 8-CH_3], 1.56 (5 H, m, 6-CH_3, 14-H_2), 1.71 (3 H, s, 12-CH_3), 2.05 (2 H, m, 9-H_2), 2.53 (1 H, m, 8-H), 2.97 (2 H, s, 5-H_2), 3.94 (1 H, t, *J* 6.5, 13-H), 4.83 and 4.98 (each 1 H, d, *J* 1.0, 10-CH), 5.05 (1 H, d, *J* 9, 7-H), 5.43 and 5.55 (each 1 H, s, 4-CH), 5.75 (1 H, s, 11-H), 6.01 (1 H, d, *J* 15, 2-H) and 7.45 (1 H, d, *J* 15, 3-H); *m*/*z* (C.I.) 433 (M^+ + 1, 2%), 403 (3) and 301 (100).

tert-Butyl (6*E*,8*S*,11*E*,13*R*)-13-*tert*-butyldimethylsilyloxy-3-(4-methoxyphenoxy)methoxy-6,8,12-trimethyl-4,10-dimethylene-pentadeca-6,11-dienoate 82

The alcohol **79** (224 mg, 0.443 mmol), diisopropylethylamine (0.153 cm^3, 0.885 mmol) and (4-methoxyphenoxy)methyl chlor-

ide (153 mg, 0.885 mmol) in dichloromethane (1.1 cm^3) were heated under reflux for 1.6 h. The reaction mixture was cooled, diluted with dichloromethane, washed with aqueous hydrogen chloride (1 M), brine and dried ($MgSO_4$). After concentration under reduced pressure, flash chromatography of the residue [light petroleum : ether (25 : 1)] gave the *title compound* **82** (188 mg, 66%), a colourless oil, as a 1 : 1 mixture of epimers at C(3) (Found: $M^+ + NH_4$, 660.4654. $C_{38}H_{66}NO_6Si$ requires *M*, 660.4659); ν_{max}/cm^{-1} 1733, 1509, 1214, 1005 and 835; δ_H 0.05 and 0.08 (each 3 H, s, $SiCH_3$), 0.86 (3 H, t, *J* 7.5, 15-H_3), 0.93 [12 H, m, $SiC(CH_3)_3$, 8-CH_3], 1.40 [9 H, s, $OC(CH_3)_3$], 1.56 (5 H, m, 6-CH_3, 14-H_2), 1.74 (3 H, s, 12-CH_3), 2.02 (1 H, dd, *J* 13.5, 7.5, 9-H), 2.10 (1 H, m, 9-H′), 2.53 (3 H, m, 2-H_2, 8-H), 2.68 (2 H, s, 5-H_2), 3.80 (3 H, s, OCH_3), 3.94 (1 H, t, *J* 6.5, 13-H), 4.64 (1 H, m, 3-H), 4.86 (1 H, s, 10-CH), 4.99 (2 H, s, 4-CH, 10-CH′), 5.04 (1 H, d, *J* 9.5, 7-H), 5.12 (1 H, d, *J* 7, OC*H*HO), 5.17 (2 H, m, 4-CH′, OCH*H*O), 5.76 (1 H, s, 11-H) and 6.84 and 7.01 (each 2 H, m, ArH); δ_C −5.0, −4.6, 10.1, 13.2, 15.8, 18.3, 20.5, 25.9, 28.0, 29.1, 31.4, 41.3, 41.7, 45.8, 55.7, 80.0, 80.6, 91.9, 114.5, 117.4, 126.1, 130.3, 134.7, 140.2, 144.2, 151.9, 154.5 and 169.9; *m*/*z* (C.I.) 660 (M^+ + 18, 21%).

(6*E*,8*S*,11*E*,13*R*)-13-*tert*-Butyldimethylsilyloxy-3-(4-methoxyphenoxy)methoxy-6,8,12-trimethyl-4,10-dimethylenepentadeca-6,11-dienoic acid 83

Following the procedure outlined above for the synthesis of the acid **86**, the ester **82** (41 mg, 63.9 μmol) gave, after flash chromatography [light petroleum : ether (3 : 1–1 : 1)], the α,β-unsaturated carboxylic acid **86** (8 mg, 30%) followed by the *title compound* **83** (13 mg, 35%) as a colourless oil, a 1 : 1 mixture of epimers at C(3) (Found: $M^+ + NH_4$, 604.4032. $C_{34}H_{58}NO_6Si$ requires *M*, 604.4033); ν_{max}/cm^{-1} 3400–2300, 1714, 1509, 1216, 1006 and 835; δ_H 0.05 and 0.09 (each 3 H, s, $SiCH_3$), 0.87 (3 H, t, *J* 7.5, 15-H_3), 0.94 [12 H, m, $SiC(CH_3)_3$, 8-CH_3], 1.56 (5 H, m, 6-CH_3, 14-H_2), 1.74 (3 H, s, 12-CH_3), 2.03 (1 H, dd, *J* 13.5, 7.5, 9-H), 2.10 (1 H, m, 9-H′), 2.58 (3 H, m, 2-H_2, 8-H), 2.70 (2 H, s, 5-H_2), 3.78 (3 H, s, OCH_3), 3.94 (1 H, t, *J* 6.5, 13-H), 4.66 (1 H, m, 3-H), 4.86 (1 H, s, 10-CH), 5.03 (3 H, m, 4-CH, 7-H, 10-CH′), 5.10 and 5.18 (each 1 H, d, *J* 7, OC*H*HO), 5.22 (1 H, s, 4-CH′), 5.77 (1 H, s, 11-H) and 6.82 and 6.97 (each 2 H, d, *J* 9, ArH); δ_C −5.0, −4.6, 10.1, 13.2, 15.8, 18.3, 20.5, 25.9, 29.1, 31.4, 39.9, 41.8, 45.7, 55.6, 80.0, 91.5, 114.4, 114.7, 117.2, 126.1, 130.1, 134.8, 140.2, 144.2, 151.5, 154.5 and 175.8; *m*/*z* (C.I.) 604 (M^+ + 18, 2%), 455 (19), 331 (50) and 123 (100).

(6*E*,8*S*,11*E*,13*R*)-13-Hydroxy-3-(4-methoxyphenoxy)methoxy-6,8,12-trimethyl-4,10-dimethylenepentadeca-6,11-dienoic acid 84

Tetrabutylammonium fluoride (1 M in tetrahydrofuran; 0.4 cm^3, 0.401 mmol) was added to the silyl ether **83** (47 mg, 80.2 μmol) and the mixture stirred for 16 h then diluted with ether, washed with saturated aqueous ammonium chloride, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue [light petroleum : ether (1 : 3)] gave the *title compound* **84** (26 mg, 69%) a colourless oil, as a 1 : 1 mixture of epimers at C(3) (Found: $M^+ + NH_4$, 490.3174. $C_{28}H_{44}NO_6$ requires *M*, 490.3169); ν_{max}/cm^{-1} 3406, 1714, 1508, 1215, 1085 and 1004; δ_H 0.94 (6 H, m, 8-CH_3, 15-H_3), 1.56 (3 H, s, 6-CH_3), 1.64 (2 H, m, 14-H_2), 1.78 (3 H, s, 12-CH_3), 2.10 (2 H, d, *J* 7, 9-H_2), 2.59 (3 H, m, 2-H_2, 8-H), 2.71 (2 H, s, 5-H_2), 3.79 (3 H, s, OCH_3), 4.00 (1 H, t, *J* 6.5, 13-H), 4.65 (1 H, m, 3-H), 4.90 (1 H, s, 10-CH), 5.04 (3 H, m, 4-CH, 7-H, 10-CH′), 5.11 and 5.19 (each 1 H, d, *J* 7, OC*H*HO), 5.22 (1 H, s, 4-CH′), 5.83 (1 H, s, 11-H) and 6.83 and 6.98 (each 2 H, d, *J* 9, ArH); δ_C 10.1, 13.1, 15.8, 20.6, 27.8, 31.5, 39.7, 42.2, 55.6, 77.2, 79.5, 91.6, 114.5, 115.1, 115.2, 117.2, 127.2, 130.2, 134.6, 139.3, 143.9, 151.5 and 154.6; *m*/*z* (C.I.) 490 (M^+ + 18, 0.2%), 472 (M^+, 0.2), 455 (3), 349 (2) and 124 (100).

(6*E*,8*S*,11*E*,13*R*)-13-Ethyl-3-(4-methoxyphenoxy)methoxy-6,8,12-trimethyl-4,10-dimethylenetrideca-6,11-dien-13-olide 85

2,6-Dichlorobenzoyl chloride (0.016 cm^3, 0.111 mmol) was added to triethylamine (0.017 cm^3, 0.122 mmol) and the hydroxy acid **84** (25 mg, 53 μmol) in tetrahydrofuran (0.5 cm^3). The mixture was stirred for 2 h, filtered, diluted with toluene (25 cm^3) and added slowly, over 2 h, to 4-(dimethylamino)pyridine (65 mg, 0.53 mmol) in toluene (10.6 cm^3) at 95 °C. When the addition was complete, the mixture was stirred for 0.5 h, cooled and concentrated under reduced pressure. The residue was dissolved in ether, washed with aqueous hydrogen chloride (1 M), saturated aqueous sodium hydrogen carbonate, brine and dried ($MgSO_4$). Concentration under reduced pressure and flash chromatography of the residue [light petroleum : ether (10 : 1)] gave the *title compound* **85** (10.5 mg, 43%), as mixtures of epimers at C(3) (Found: M^+ + H, 455.2803. $C_{28}H_{39}O_5$ requires *M*, 455.2797); ν_{max}/cm^{-1} 1734, 1647, 1622, 1508, 1442, 1243, 1214, 1079, 1015, 903 and 828; δ_H 0.84 and 0.85 (1.2 H and 1.8 H, t, *J* 7.5, 2′-H_3), 0.96 and 1.01 (1.2 H and 1.8 H, d, *J* 7, 8-CH_3), 1.40 (1.2 H, s, 6-CH_3), 1.63–1.76 (5.6 H, m, 6-CH_3, 12-CH_3, 1′-H_2), 1.81 (1.2 H, s, 12-CH_3), 2.03–2.30 (2 H, m, 9-H_2), 2.38 (0.4 H, m, 8-H), 2.53–2.92 (4.6 H, m, 2-H_2, 5-H_2, 8-H), 3.80 and 3.81 (1.8 H and 1.2 H, s, OCH_3), 4.63 (1 H, t, *J* 7, 13-H), 4.77 (1 H, m, 3-H), 4.84–5.32 (7 H, m, OCH_2O, 4-CH_2, 7-H, 10-CH_2), 5.86 and 5.88 (0.4 H and 0.6 H, s, 11-H) and 6.81–7.07 (4 H, m, ArH); δ_C 8.6, 9.1, 14.7, 15.8, 16.0, 16.5, 20.3, 22.9, 25.2, 25.9, 33.1, 34.6, 39.9, 40.8, 42.0, 45.1, 45.2, 46.2, 55.7, 73.3, 76.8, 77.2, 78.1, 79.9, 91.57, 91.64, 113.8, 114.3, 114.4, 114.6, 115.1, 116.5, 117.1, 117.2, 126.4, 129.7, 130.5, 130.8, 133.2, 133.7, 134.1, 134.4, 143.0, 144.2, 145.1, 151.4, 151.5, 154.5, 154.6, 169.5 and 170.1; *m*/*z* (C.I.) 472 (M^+ + 18, 18%), 455 (M^+ +1, 10), 331 (63), 155 (45) and 124 (100).

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