Total synthesis of the cholesterol biosynthesis inhibitor 1233A *via* a (π-allyl)tricarbonyliron lactone complex

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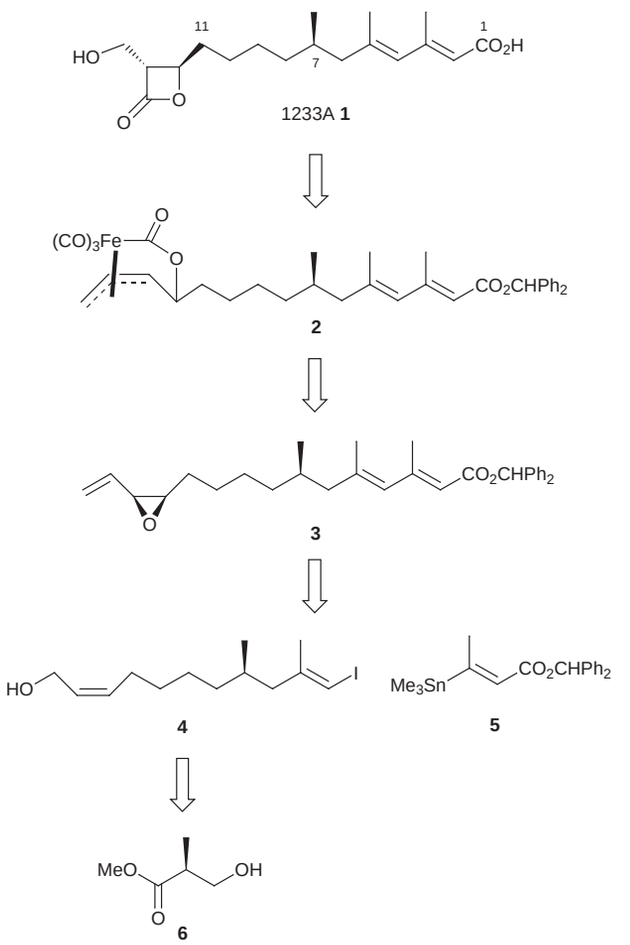
The total synthesis of the β-lactone cholesterol synthase inhibitor 1233A (**1**) is described employing the oxidative decomplexation of a (π-allyl)tricarbonyliron lactone (**2**) as the key synthetic step.

Introduction

Naturally occurring β-lactones have attracted considerable attention during the last few years owing to their interesting structures and biological activities.[1] One of the early members of this class of natural products to be identified was the antibiotic 1233A (**1**), isolated from the fungus *Cephalosporium* sp.[2] More recently, **1** was also independently isolated from *Scopulariopsis* sp. and *Fusarium* sp.[3] and named respectively as F-244[4] and L-659,699.[5] Following this work, 1233A (**1**) was shown to be a potent specific inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase;[3–5] this is a key regulatory enzyme in the formation of mevalonate during the early stages of cholesterol biosynthesis. Antibiotic 1233A (**1**) showed inhibitory activity *in vitro*, in cultured cells and proved to be orally active in mice.[3–6] Both the β-lactone and the hydroxymethyl functionalities were found to be essential for the inhibitory activity which is believed to occur by nucleophilic attack of a cysteine thiol residue of the enzyme active site onto the carbonyl group of the β-lactone unit.[1] The absolute configuration of **1** was determined[7] and five total syntheses[8,9] and two formal syntheses[10] have been described in the literature to date.

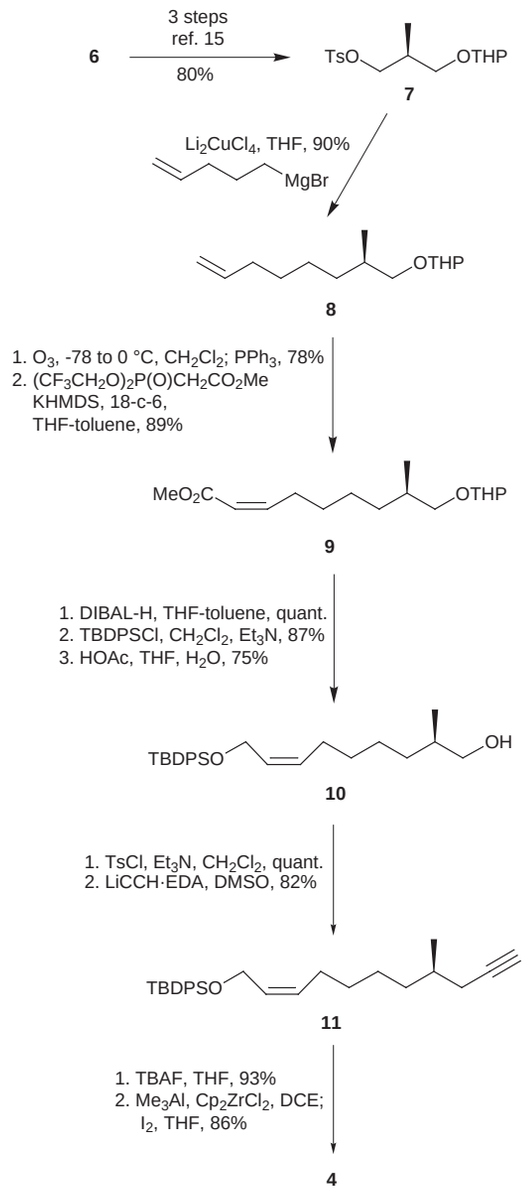
With the exception of the Kocienski synthesis,[9] which makes use of a Lewis acid catalysed [2+2] cycloaddition, all the other approaches involve β-lactone formation *via* a ring closure of a β-hydroxyacid, employing $PhSO_2Cl$ in pyridine.[11] We envisioned that the β-lactone motif in **1** could be readily synthesised from a (π-allyl)tricarbonyliron lactone complex precursor (**2**), making use of the oxidative decomplexation procedure with ceric ammonium nitrate (CAN) discovered in our laboratory (Scheme 1).[12,13] Iron lactone **2** was known to be available from the alkenyl epoxide **3** by treatment with $Fe_2(CO)_9$.[12,14] This two step sequence has already been applied successfully by our group during the synthesis of valilactone, a potent esterase inhibitor.[15] Coupling of vinyl iodide **4** and vinyl stannane **5** under Stille conditions[16] should provide access, after some manipulation, to the desired alkenyl epoxide **3** (Scheme 1).



Scheme 1

Results and discussion

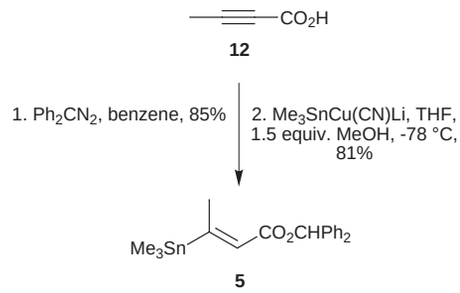
As outlined in Scheme 1 the synthesis begins from commercially available methyl (2*S*)-3-hydroxy-2-methylpropanoate (**6**) as a source of the chirality at C-7, and follows straightforward steps to the vinyl iodide coupling partner **4** (Scheme 2). Thus, β-hydroxyester **6** was easily transformed to the tosylate **7** in 80% yield following slight modifications of literature procedures[17] which comprise of protection of the hydroxy functionality in **6** as the tetrahydropyran (THP) acetal, reduction of the methyl ester and tosylation of the resulting hydroxy group. Displacement of the tosylate in **7** with pent-4-en-1-ylmagnesium bromide under copper catalysed conditions (Li_2CuCl_4)[18] gave alkene **8** in 90% yield. The (*Z*)-alkene present in **4** was easily introduced at this stage by ozonolysis of the terminal olefin in **8** (78% yield) and Horner–Wadsworth–Emmons olefination of the resulting aldehyde with bis(2,2,2-



Scheme 2

trifluoroethyl) (methoxycarbonylmethyl)phosphonate[19] to give the desired (*Z*)-α,β-unsaturated methyl ester **9** (89% yield).† Quantitative reduction of methyl ester **9** with diisobutylaluminium hydride (DIBAL-H) and protection of the resulting primary alcohol as the corresponding *tert*-butyldiphenylsilyl ether (87% yield), followed by removal of the THP acetal with HOAc–THF–H_2O furnished alcohol **10** (75% yield). Tosylation of **10** occurred quantitatively however displacement of the tosylate with lithium acetylide–ethylenediamine complex in DMSO proved problematic; prolonged reaction times resulted in migration of the silyl protecting group from the oxygen atom to the terminus of the alkyne group. When an excess of lithium acetylide–ethylenediamine complex (240 mol%) was used, shorter reaction times were required and the desired alkyne **11** could be obtained in 82% yield. Attempts to transform the terminal alkyne **11** to the desired vinyl iodide under Negishi conditions[20] were unsuccessful. However, deprotection of the silyl ether (TBAF, 93%) followed by zirconium catalysed carboalumination–iodination on the free hydroxy alkyne furnished vinyl iodide **4** (86% yield) very cleanly.

The other coupling partner required for the Stille coupling, namely the vinyl stannane **5**, was readily available from but-2-ynoic acid **12** (Scheme 3). Protection of the carboxylic acid in



Scheme 3

12 as the corresponding diphenylmethyl ester (85% yield), followed by treatment with stannyl cuprate $Me_3SnCu(CN)Li$[21] in the presence of CH_3OH led to the required *E*-vinyl stannane **5** (81% yield). The corresponding *Z*-vinyl stannane was not detected in this reaction. The reaction when using $Me_3SnCu(SPh)Li$[22] was less reproducible, leading to **5** in a variable 56–82% yield.

Having prepared the vinyl iodide **4** and vinyl stannane **5**, the Stille coupling was attempted using $PdCl_2(CH_3CN)_2$ in DMF as the conditions of choice,[16] which led to the dienoate **13** in 62% yield (Scheme 4).‡ Alcohol **13** was transformed in three steps to the alkenyl epoxide **3** required for the (π-allyl)tricarbonyliron lactone formation. Thus, Sharpless epoxidation[23,24] of **13** using (*R*,*R*)-(+)-diisopropyl tartrate (DIPT) under stoichiometric conditions gave the epoxy alcohol **14** with the required (12*R*,13*S*) configuration in 80% yield and excellent 90% de.§ When catalytic oxidation conditions[24,25] were investigated, the same yield was obtained but a poorer 66% de§ was observed. Oxidation of the primary hydroxy group in **14** with catalytic tetra-*n*-propylammonium perruthenate (TPAP)[26] and NMO as co-oxidant, followed by Wittig methylenation of the resulting crude aldehyde provided alkenyl epoxide **3** in an excellent 78% combined yield. It is noteworthy that the mild TPAP oxidation leaves the labile epoxide functionality in the α position intact.

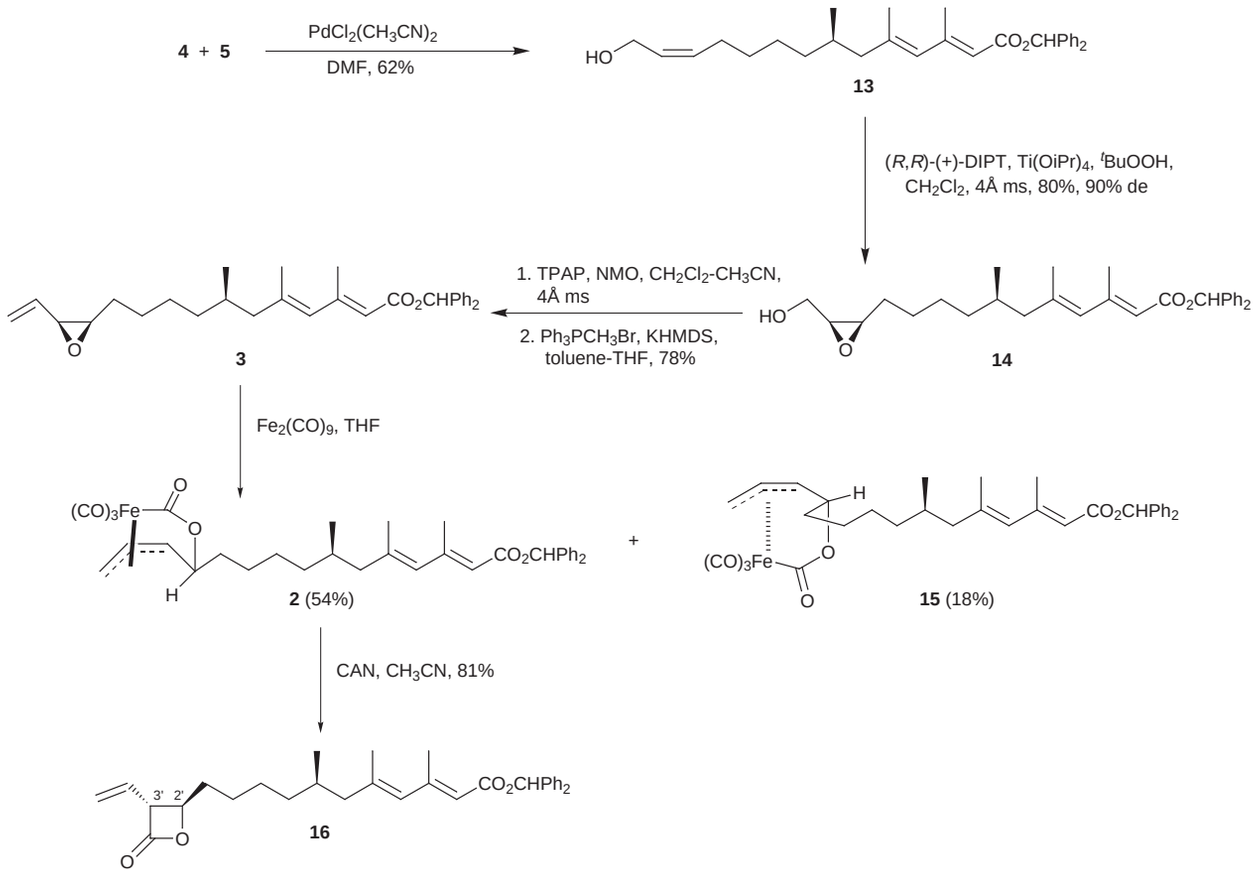
With alkenyl epoxide **3** in hand, the next crucial steps in the synthesis of 1233A (**1**) were investigated. Thus, **3** was first subjected to (π-allyl)tricarbonyliron lactone complex formation by treatment with diiron nonacarbonyl [$Fe_2(CO)_9$] in THF under standard conditions.[12,14] The *exo*- and *endo*-iron lactones **2** and **15** were obtained as a readily separable mixture in 54% and 18% yields respectively (Scheme 4). A poorer reaction yield and selectivity, **2** (35%) and **15** (24%), was obtained when alternative conditions [$Fe_2(CO)_9$ in C_6H_6 under sonication] were used.[12,14] Subsequent oxidative decomplexation of **2** with CAN in CH_3CN[12,13] afforded **16** in an excellent 81% yield. Compound **16** was identified as a β-lactone on the basis of its IR spectrum which showed a distinctive band at 1828 cm^{-1}. The coupling constant $J_{2',3'} = 4.2$ Hz in the ^1H NMR ($CDCl_3$) of **16** denotes the *anti* disposition of the substituents in the ring.[13]

The last key transformation necessary to accomplish the total synthesis of 1233A (**1**) was the conversion of the terminal double bond in β-lactone **16** to the required hydroxymethyl group present in **1** (Scheme 5). When β-lactone **16** was sub-

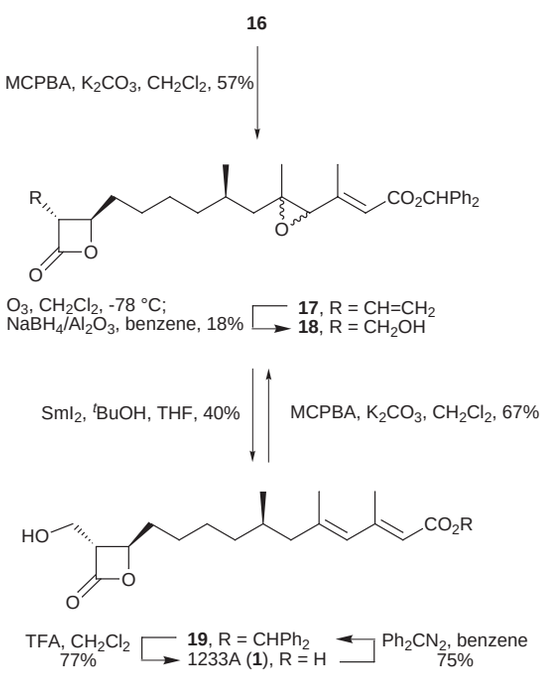
† A small amount (7%) of an inseparable mixture of the *Z*- and *E*-alkenes was also obtained after column chromatography.

‡ For optimum yields, 12–25 mol% of the catalyst [$PdCl_2(CH_3CN)_2$] and excess of the vinyl stannane **5** were required. Pd_2dba_3–$AsPh_3$ (as reported by V. Farina and B. Krishnan, *J. Am. Chem. Soc.*, 1991, **113**, 9585) or $Pd(PPh_3)_4$ failed to bring about the catalytic cycle.

§ The de values were determined by ^1H NMR (C_6D_6) on the epoxy acetates (AcCl, DMAP, Et_3N, DCM) derived from the products of the Sharpless epoxidation with (+)- and (−)-DIPT, in the presence of Eu(hfbc)$_3$, as reported in ref. 25.



Scheme 4



Scheme 5

jected to ozonolysis (DCM, −78 °C), it was clearly evident that the C4–C5 double bond of the dienoate system had an unexpected higher reactivity to ozonolysis than the terminal olefin, leading to C4–C5 bond cleavage. Several competitive ozonolysis experiments and attempts to selectively dihydroxylate the terminal olefin were unsuccessful. Consequently we were forced to protect the C4–C5 double bond prior to ozonolysis. We therefore took advantage of the high reactivity of this bond and carried out a protection by selective epoxidation in the presence of the terminal olefin. Indeed, when **16** was treated with *m*-chloroperbenzoic acid (MCPBA) in DCM, the epoxy-β-lactone **17** was obtained in 57% yield as a 2:1 mixture of diastereoisomers (Scheme 5). Ozonolysis of **17** (DCM, −78 °C) and *in situ* reductive work up of the ozonide with $NaBH_4$ on Al_2O_3 was now successful and the hydroxymethyl β-lactone **18** was obtained, albeit in only 18% yield. β-Lactone **18** proved to be identical (^1H and ^{13}C NMR, IR and high resolution mass spectrometry) to a sample obtained from natural 1233A (**1**)[27] by benzhydryl protection of the carboxylic acid and epoxidation with MCPBA.

Removal of the epoxide and deprotection of the diphenylmethyl ester from **18** were then studied to complete the synthesis of 1233A (**1**). The removal of the epoxide was difficult and using KSeCN[28] or P_2I_4[29] did not lead to the desired product. However using SmI_2 (THF–^{t}BuOH) a 40% yield of **19** could be realised.[30] The diphenylmethyl ester was then cleaved by treatment with TFA to afford 1233A (**1**) in 77% yield. This synthetic sample of **1** was identical by ^1H and ^{13}C NMR, IR and optical rotation to an authentic sample of natural 1233A.[27]

In conclusion, we have developed a synthesis of 1233A (**1**) where the formation of a (π-allyl)tricarbonyliron lactone complex (**2**) from an alkenyl epoxide (**3**) and its subsequent oxidative decomplexation, leading to a β-lactone (**16**), were used as key steps.

Experimental

General

Petrol refers to petroleum ether (bp 40–60 °C). Petrol was distilled and other solvents were dried and distilled before use; Et_2O and THF from sodium–benzophenone; DCM, CH_3CN, toluene, DMF and DMSO from CaH_2. Other solvents were purified by standard procedures as necessary. All reactions were performed under Ar atmosphere, unless otherwise stated.

Organic phases were dried ($MgSO_4$) before concentration in a rotary evaporator. Analytical thin layer chromatography (TLC) was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised by ultra-violet light (254 nm), acidic ammonium molybdate, basic potassium permanganate, acidic palladium chloride or iodine as appropriate. The products were purified by column chromatography on Merck silica gel 60 (Art. 9385 230–400 mesh) under pressure unless otherwise stated. Silica gel 60 PF_{254} from Merck (Art. 1.07747) was used for preparative TLC. Florisil 200–300 mesh (supplied by BDH) was used for florisil chromatography. ^{1}H NMR spectra were recorded on Bruker WM-250, JEOL GSX-270, Bruker AM-500 or Bruker DRX-600 spectrometers using $CDCl_3$ as solvent and residual $CHCl_3$ as reference at δ 7.26 ppm unless otherwise stated. ^{13}C NMR spectra were recorded on Bruker AM-400 or Bruker DRX-600 spectrometers, operating at 100 and 150 MHz respectively, using $CDCl_3$ as solvent and reference at δ 77.0 ppm unless otherwise stated. When inseparable mixtures of diastereoisomers are obtained, NMR data are quoted as a mixture. Proton–tin couplings are given as averages of the ^{117}Sn–H and ^{119}Sn–H couplings. Low resolution mass spectra were recorded under EI conditions on a VG 7070B. CI low resolution and CI accurate mass measurements were recorded using a VG 12-253 or a VG ZAB-E (SERC mass spectrometry service, Swansea) spectrometers or under FAB conditions on a Kratos MS890 spectrometer. IR spectra were recorded on a Perkin-Elmer 983G spectrophotometer or Perkin-Elmer 1620 FT spectrophotometer as liquid films or Nujol mulls. Optical rotations were measured using an Optical Activity AA-1000 polarimeter. $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Elemental microanalyses were performed either in the Imperial College Chemistry Department Microanalytical laboratory or MEDAC Services, Brunel University. Melting points were performed on a Reichert hot stage apparatus and are uncorrected. HCl refers to aqueous 1 M hydrochloric acid, $NaHCO_3$ refers to saturated aqueous sodium hydrogencarbonate solution, brine refers to saturated aqueous sodium chloride solution.

(7*R*)-7-Methyl-8-(tetrahydro-2*H*-pyran-2-yloxy)oct-1-ene (8)

To a suspension of Mg (6.75 g, 280 mmol) in THF (120 cm^3) was added a crystal of iodine, followed by 5-bromopent-1-ene (30.5 cm^3, 237 mmol) in THF (120 cm^3). Once the reaction had commenced the mixture was heated under reflux for 1 h and then allowed to cool to rt. Half this solution was then transfered *via* a cannula (30 min) into a flask containing a solution of the tosylate **7** (50.2 g, 153 mmol) in THF (250 cm^3) at −78 °C. Before the Grignard addition was complete, Li_2CuCl_4 (8.4 cm^3, 0.1 M in THF, 0.84 mmol) was added. The reaction mixture was stirred at −78 °C for 90 min and then allowed to warm to rt and stir overnight. The resulting yellow–grey mixture was poured into Et_2O (1000 cm^3) containing HCl (200 cm^3, 1.5 M) and saturated aqueous NH_4Cl (100 cm^3), and the mixture was vigorously stirred. The organic layer was separated and the aqueous layer was extracted with Et_2O (200 cm^3). The combined organic layer was washed with HCl (200 cm^3, 1.5 M), H_2O (200 cm^3), $NaHCO_3$ (200 cm^3) and brine (200 cm^3), then dried and concentrated to give a yellow oil. Chromatography (8% Et_2O in petrol) gave **8** (31.0 g, 90%, 1:1 mixture of diastereoisomers) as a colourless oil (Found: C, 74.19; H, 11.58. $C_{14}H_{26}O_2$ requires C, 74.29; H, 11.58%); ν_{max}/cm^{-1} (thin film) 3073, 2928, 2857, 1639, 1458, 1410, 1377, 1351, 1321, 1260, 1200, 1183, 1122, 1077, 1062, 1033, 976, 907, 869, 814, 731; δ_H (250 MHz; $CDCl_3$) 0.90 and 0.92 (3H, 2 × d, *J* 6.8, Me), 1.05–1.95 (13H, m, 6 × CH_2 and H7), 2.01–2.08 (2H, m, 2 × H3), 3.08–3.91 (4H, m, 2 × CH_2O), 4.52–4.59 (1H, m, O_2CH), 4.88–5.03 (2H, m, 2 × H1) and 5.71–5.89 (1H, m, H2); EI *m*/*z* 226 (M^+, 0.2%), 125 ($M^+ - C_5H_9O_2$, 1.0), 101 ($C_5H_9O_2^+$, 16) and 85 ($C_5H_9O^+$, 100).

(6*R*)-6-Methyl-7-(tetrahydro-2*H*-pyran-2-yloxy)heptanal

Alkene **8** (31.0 g, 137.0 mmol) was dissolved in DCM (700 cm^3) and cooled to −78 °C. Ozone in oxygen (40 L h^{-1}, 140 V) was bubbled overnight through the solution, allowing the reaction to slowly warm up to 0 °C. TLC monitoring showed complete turnover to the ozonide (RF-value: 0.61, petrol–EtOAc 8:1) and the solution was purged with Ar. PPh_3 (35.6 g, 135.7 mmol) was added and the mixture stirred while being allowed to warm to rt. After complete turnover (TLC) the mixture was concentrated and petrol was added until no further triphenylphosphine oxide precipitated. The mixture was filtered through a pad of Celite® and the residues were washed with Et_2O–petrol (1:1) and the filtrate concentrated. Chromatography (10% Et_2O–petrol) gave *(6R)-6-methyl-7-(tetrahydro-2H-pyran-2-yloxy)heptanal* (24.5 g, 78%, 1:1 mixture of diastereoisomers) as a colourless oil (Found: C, 68.18; H, 10.78. $C_{13}H_{24}O_3$ requires C, 68.38; H, 10.60%); ν_{max}/cm^{-1} (thin film) 2936, 2867, 2716, 1723, 1452, 1440, 1409, 1380, 1352, 1322, 1261, 1200, 1184, 1122, 1077, 1063, 1032, 976, 904, 869, 813, 739; δ_H (500 MHz; $CDCl_3$) 0.91 and 0.93 (3H, 2 × d, *J* 6.7, Me), 1.10–1.90 (13H, m, 6 × CH_2 and H6), 2.44 (2H, dt, *J* 1.7 and 7.4, 2 × H2), 3.12–3.89 (4H, m, 2 × CH_2O), 4.54–4.58 (1H, m, O_2CH) and 9.68 (1H, t, *J* 1.7, H1); EI *m*/*z* 228 (M^+, 0.7%), 127 ($M^+ - C_5H_9O_2$, 6.4), 101 ($C_5H_9O_2^+$, 16) and 85 ($C_5H_9O^+$, 100).

Methyl (2*Z*,8*R*)-8-methyl-9-(tetrahydro-2*H*-pyran-2-yloxy)-non-2-enoate (9)

18-Crown-6 (70.0 g, 262.5 mmol) and bis(2,2,2-trifluoroethyl) methoxycarbonylmethylphosphonate (21 cm^3, 31.5 g, 99.0 mmol) were dissolved in THF (1800 cm^3) and cooled to −78 °C. KHMDS (198 cm^3, 0.5 M in toluene, 99.0 mmol) was added dropwise. *(6R)-6-Methyl-7-(tetrahydro-2H-pyran-2-yloxy)-heptanal* (22.5 g, 98.7 mmol) was dissolved in THF (200 cm^3) and slowly added to the above solution such that the temperature did not rise above −70 °C. The resulting mixture was then allowed to warm up to rt and stirred overnight. The reaction was quenched by the addition of saturated NH_4Cl (750 cm^3). The mixture was partitioned between H_2O (250 cm^3) and Et_2O (1000 cm^3). The aqueous phase was washed with Et_2O (2 × 1000 cm^3) and the combined organic phase was washed with brine, dried and concentrated to give a white oil. This residue was suspended in Et_2O–petrol (2:1) and filtered through a plug of silica. Concentration of the filtrate gave a yellow oil (44.0 g), still containing toluene. Chromatography of this solution (gradient: petrol to 7.5% Et_2O–petrol) gave **9** (24.9 g, 89%, 1:1 mixture of diastereoisomers) (Found: C, 67.62; H, 10.11. $C_{16}H_{28}O_4$ requires C, 67.57; H, 9.92%); ν_{max}/cm^{-1} (thin film) 2930, 2857, 1723, 1642, 1436, 1406, 1377, 1351, 1322, 1284, 1199, 1172, 1136, 1121, 1077, 1062, 1033, 976, 904, 883, 869, 817, 724; δ_H (500 MHz; $CDCl_3$) 0.90 and 0.92 (3H, 2 × d, *J* 6.7 8-Me), 1.10–1.85 (13H, m), 2.65 (2H, m, 2 × H4), 3.11–3.88 (4H, m, 2 × CH_2O), 3.70 (3H, s, OMe), 4.54–4.57 (1H, m, O_2CH), 5.76 (1H, dt, *J* 1.7 and 11.5, H2) and 6.22 (1H, dt, *J* 7.1 and 11.5, H3); δ_C ($CDCl_3$) 166.8 (CO), 150.9 (C8), 119.1 (C7), 99.0 and 99.8* (C2′), 73.1 and 72.9* (C1), 62.2 and 62.1* (C6′), 50.9 (OMe), 33.5 (C2), 33.4, 30.7, 29.3, 29.0, 26.6, 25.5, 19.6 and 19.5* (CH_2), 17.2 and 17.1* (8-Me), [* diastereomers]; EI *m*/*z* 284 (M^+, 0.05%), 269 (M^+ − Me, 1.5), 183 ($M^+ - C_5H_9O_2$, 5.5), 101 ($C_5H_9O_2^+$, 8) and 85 ($C_5H_9O^+$, 100). In addition an inseparable mixture of (*Z*)- and (*E*)-esters (2.1 g, 7%) was recovered.

(2*Z*,8*R*)-8-Methyl-9-(tetrahydro-2*H*-pyran-2-yloxy)non-2-en-1-ol

The ester **9** (14.55 g, 51.2 mmol) was dissolved in THF (300 cm^3) and cooled to −78 °C. DIBAL-H (77 cm^3, 1.5 M in toluene, 115.5 mmol) was added dropwise (45 min) and the resulting mixture was stirred overnight. The reaction was quenched

by the careful addition of HCl and then was diluted with EtOAc (1000 cm^3). The organic phase was washed with HCl, H_2O, $NaHCO_3$ and brine, then was dried and concentrated to give *(2Z,8R)-8-methyl-9-(tetrahydro-2H-pyran-2-yloxy)non-2-en-1-ol* (13.12 g, 100%, 1:1 mixture of diastereoisomers) as a pale yellow oil (Found: C, 70.50; H, 11.05. $C_{15}H_{28}O_3$ requires C, 70.27; H, 11.01%); ν_{max}/cm^{-1} (thin film) 3388, 2926, 2845, 1465, 1353, 1200, 1120, 1061, 1032, 977; δ_H (270 MHz; $CDCl_3$) 0.89 and 0.93 (3H, 2 × d, *J* 6.6, Me), 1.05–1.85 (13H, m), 2.03–2.19 (2H, m, 2 × H4), 3.11–3.89 (4H, m, 2 × CH_2O), 4.19 (2H, t, *J* 5.6, 2 × H1), 4.54–4.57 (1H, m, O_2CH) and 5.47–5.64 (2H, m, H2, H3); EI *m/z* 256 (M^+, 0.05%), 101 ($C_5H_9O_2^+$, 7) and 85 ($C_5H_9O^+$, 100).

(2*Z*,8*R*)-1-(*tert*-Butyldiphenylsilyloxy)-8-methyl-9-(tetrahydro-2*H*-pyran-2-yloxy)non-2-ene

(2Z,8R)-8-Methyl-9-(tetrahydro-2H-pyran-2-yloxy)non-2-en-1-ol (13.12 g, 51.2 mmol) was dissolved in DCM (300 cm^3) and then Et_3N (30 cm^3) and *tert*-butylchlorodiphenylsilane (13.8 cm^3, 53.0 mmol) were added. The resulting mixture was stirred for 3 days and then was concentrated and partitioned between EtOAc and HCl. The organic phase was washed with H_2O, $NaHCO_3$ and brine, then was dried and concentrated to give a pale yellow oil (28.95 g). Chromatography (8% Et_2O–petrol) gave *(2Z,8R)-1-(tert-butyldiphenylsilyloxy)-8-methyl-9-(tetrahydro-2H-pyran-2-yloxy)non-2-ene* (22.18 g, 87%, 1:1 mixture of diastereoisomers) (Found: C, 75.26; H, 9.67. $C_{31}H_{46}O_3Si$ requires C, 75.25; H, 9.37%); ν_{max}/cm^{-1} (thin film) 3068, 3014, 2930, 2855, 1588, 1460, 1427, 1359, 1261, 1200, 1185, 1112, 1075, 1033, 976, 904, 869, 818, 746, 703; δ_H (500 MHz; $CDCl_3$) 0.88 and 0.90 (3H, 2 × d, *J* 6.7, Me), 1.04 (9H, s, ^{t}Bu), 1.17–1.82 (15H, m), 3.10–3.87 (4H, m, 2 × CH_2O), 4.24 (2H, dd, *J* 0.9 and 6.2, 2 × H1), 4.53–4.56 (1H, m, O_2CH), 5.39–5.61 (2H, m, H2, H3) and 7.36–7.70 (10H, m, ArH); EI *m/z* 494 (M^+, 0.1%), 437 ($M^+ - {}^t$Bu, 5), 353 ($M^+ - {}^t$Bu − C_5H_9O, 6), 199 (Ph_2SiOH^+, 78) and 85 ($C_5H_9O^+$, 100).

(2*R*,7*Z*)-9-(*tert*-Butyldiphenylsilyloxy)-2-methylnon-7-en-1-ol (10)

(2Z,8R)-1-(tert-Butyldiphenylsilyloxy)-8-methyl-9-(tetrahydro-2H-pyran-2-yloxy)non-2-ene (34.2 g, 69 mmol) was dissolved in HOAc–THF–H_2O (600 cm^3:750 cm^3:150 cm^3) and warmed at 45 °C for 36 h. When TLC monitoring showed only a small amount of starting material left, the reaction mixture was diluted with Et_2O (2.5 L) and washed with H_2O (6 × 500 cm^3), $NaHCO_3$ (3 × 400 cm^3) and brine (400 cm^3), then the organic phase was dried and concentrated. Chromatography (gradient: 6 to 100% Et_2O–petrol) gave **10** (21.3 g, 75%) (Found: C, 76.05; H, 9.26. $C_{26}H_{38}O_2Si$ requires C, 76.04; H, 9.33%); $[a]_D^{20}$ +3.2 (*c* 0.80 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3347, 3068, 3047, 3014, 2929, 2855, 1653, 1460, 1426, 1388, 1359, 1262, 1188, 1111, 1085, 1008, 939, 823, 740, 703, 613; δ_H (270 MHz; $CDCl_3$) 0.88 (3H, d, *J* 6.8, Me), 1.05 (9H, s, ^{t}Bu), 1.05–1.35 (7H, m, 3 × CH_2, OH), 1.48–1.67 (1H, m, H2), 1.83–1.89 (2H, m, 2 × H6), 3.38–3.47 (2H, m, 2 × H1), 4.25 (2H, dd, *J* 0.7 and 6.1, 2 × H9), 5.35–5.64 (2H, m, H7, H8) and 7.34–7.72 (10H, m, ArH); EI *m/z* 353 ($M^+ - {}^t$Bu, 3%) and 199 (Ph_2SiOH^+, 100).

(2*R*,7*Z*)-9-(*tert*-Butyldiphenylsilyloxy)-2-methyl-1-(*p*-tolylsulfonyloxy)non-7-ene

The alcohol **10** (18.5 g, 45 mmol) was dissolved in DCM (360 cm^3), Et_3N (72 cm^3) and toluene-*p*-sulfonyl chloride (12.1 g, 64 mmol) were added and the reaction stirred at rt (TLC monitoring). The mixture was diluted with Et_2O (500 cm^3) and washed with HCl (3 M, 2 × 250 cm^3), H_2O (250 cm^3), $NaHCO_3$ (2 × 250 cm^3) and brine (250 cm^3). The combined aqueous layer was extracted with DCM (2 × 150 cm^3) and the combined organic layer was dried and concentrated. Chromatography (6% Et_2O–petrol) gave *(2R,7Z)-9-(tert-butyldiphenylsilyloxy)-2-methyl-1-(p-tolylsulfonyloxy)non-7-ene* (25.8 g, 100%) (Found: C, 70.39; H, 7.95. $C_{33}H_{44}O_4SiS$ requires C, 70.17; H, 7.85%); $[a]_D^{20}$ −1.4 (*c* 1.81 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2929, 2855, 1597, 1461, 1427, 1360, 1177, 1111, 967, 815, 742, 704, 665; δ_H (270 MHz; $CDCl_3$) 0.84 (3H, d, *J* 6.8, 2-Me), 1.04 (9H, s, ^{t}Bu), 0.90–1.85 (9H, m), 2.42 (3H, s, ArMe), 3.77 (1H, dd, *J* 6.4 and 9.3, H1), 3.83 (1H, dd, *J* 5.8 and 9.3, H1), 4.22 (2H, dd, *J* 0.9 and 6.4, 2 × H9), 5.30–5.63 (2H, m, H7, H8) and 7.30–7.79 (14H, m, ArH); δ_C ($CDCl_3$) 144.8, 134.0, 133.3 (C-*ipso*, C-quart.), 135.7, 130.9, 129.8, 129.4, 128.0, 127.8 (C-Ar, C7, C8), 75.2 (C1), 60.4 (C9), 32.9 (C2), 32.6, 29.7, 27.5, 26.3, 19.2 (CH_2, CMe_3), 26.9, 26.7 (CMe_3), 21.8 (Ar-Me), 16.5 (Me); EI *m/z* 507 ($M^+ - {}^t$Bu, 0.1%), 353 ($M^+ - {}^t$Bu − $C_7H_6SO_2$, 8), 292 ($M^+ - {}^t$BuPh$_2$SiOCH$_2$, 28) and 199 (Ph_2SiOH^+, 100).

(2*Z*,8*R*)-1-(*tert*-Butyldiphenylsilyloxy)-8-methylundec-2-en-10-yne (11)

(2R,7Z)-9-(tert-Butyldiphenylsilyloxy)-2-methyl-1-(p-tolylsulfonyloxy)non-7-ene (2.82 g, 5.0 mmol) was dissolved in DMSO (12.5 cm^3). Lithium acetylide–ethylenediamine complex (0.60 g, 6.0 mmol) was added and the resulting mixture stirred. After 15 min, more lithium acetylide ethylenediamine complex (0.60 g, 6.0 mmol) was added and stirring continued for a further 15 min until TLC showed the reaction to be essentially complete. The reaction mixture was poured into a vigorously stirred mixture of petrol (100 cm^3) and brine (25 cm^3) (**CAUTION!**). After 5 min the petrol layer was separated and the aqueous layer extracted with petrol (2 × 50 cm^3). The combined organic extract was washed with brine (25 cm^3), then dried and concentrated to give a yellow oil. Chromatography (gradient: 5% to 50% Et_2O–petrol) gave **11** (1.70 g, 82%) (Found: C, 80.34; H, 9.09. $C_{28}H_{38}OSi$ requires C, 80.32; H, 9.15%); $[a]_D^{20}$ −0.6 (*c* 1.39 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3305, 3066, 3047, 3014, 2955, 2927, 2855, 2173, 2117, 1956, 1886, 1821, 1653, 1588, 1459, 1428, 1388, 1376, 1359, 1262, 1188, 1111, 1083, 1029, 1007, 998, 989, 923, 740, 703, 614; δ_H (270 MHz; $CDCl_3$) 0.95 (3H, d, *J* 6.8, Me), 1.04 (9H, s, ^{t}Bu), 0.80–1.40 (6H, m, 3 × CH_2), 1.45–1.65 (1H, m, H8), 1.84–1.87 (2H, m, 2 × H4), 1.92 (1H, t, *J* 2.7, H11), 2.05–2.12 (2H, m, 2 × H9), 4.24 (2H, dd, *J* 0.6 and 6.1, 2 × H1), 5.38–5.62 (2H, m, H2, H3) and 7.30–7.71 (10H, m, ArH); EI *m/z* 264 (9%), 213 (33), 207 (100) and 199 (Ph_2SiOH^+, 17).

(2*Z*,8*R*)-8-Methylundec-2-en-10-yn-1-ol

The silyl ether **11** (965 mg, 2.3 mmol) was dissolved in THF (3 cm^3), then tetra-*n*-butylammonium fluoride (2.6 cm^3, 1.0 M in THF, 2.6 mmol) was added and the reaction stirred overnight. The resulting mixture was diluted with Et_2O (70 cm^3) and washed with H_2O (3 × 50 cm^3) and brine. The organic phase was dried and concentrated to give a yellow oil that was purified by chromatography (gradient: 20% to 30% Et_2O–petrol) to give *(2Z,8R)-8-methylundec-2-en-10-yn-1-ol* (389 mg, 93%); $[a]_D^{20}$ −1.0 (*c* 0.50 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3324, 3011, 2926, 2864, 2116, 1459, 1379, 1002; δ_H (500 MHz; $CDCl_3$) 0.97 (3H, d, *J* 6.8, Me), 1.14–1.46 (6H, m, 3 × CH_2), 1.58 (1H, br s, OH), 1.61–1.68 (1H, m, H8), 1.95 (1H, t, *J* 2.7, H11), 2.04–2.08 (3H, m, 2 × H4, H9), 2.10 (1H, ddd, *J* 2.7, 6.3 and 12.4, H9), 4.19 (2H, d, *J* 5.4, 2 × H1) and 5.51–5.63 (2H, m, H2, H3); δ_C ($CDCl_3$) 133.0 (C2), 128.5 (C3), 83.5 (C10), 69.2 (C11), 58.5 (C1), 35.8 (CH_2), 32.4 (C8), 29.8, 27.4, 26.7, 25.8 (CH_2), 19.5 (Me); EI *m/z* 149 ($M^+ - HOCH_2$, 5%) and 41 ($C_3H_5^+$, 100); HRMS: Found: $(M + NH_4)^+$, 198.1858. $C_{12}H_{24}ON$ requires *M*, 198.1858.

(2*Z*,8*R*,10*E*)-8,10-Dimethyl-11-iodoundeca-2,10-dien-1-ol (4)

Zirconocene dichloride (2.04 g, 7.0 mmol) was suspended in 1,2-dichloroethane (40 cm^3) and cooled to −10 °C. Trimethylaluminium (50 cm^3, 2 M in hexanes, 100 mmol) was added.

After stirring for 1 h, *(2Z,8R)-8-methylundec-2-en-10-yn-1-ol* (2.48 g, 14.0 mmol) in 1,2-dichloroethane (25 cm^3) was added dropwise for 30 min. The resulting mixture was stirred overnight at 40 °C and then cooled at −30 °C. Iodine (7.10 g, 28.0 mmol) in THF (50 cm^3) was added dropwise. The reaction was allowed to warm up to 0 °C for 30 min and then aqueous diluted HCl and Et_2O were added until a two phase system was obtained (**CAUTION!**). The organic layer was separated and the aqueous layer extracted with Et_2O. The combined organic phase was washed twice with $NaHCO_3$, dried and concentrated to give a green oil. Chromatography (gradient: 20% to 30% Et_2O–petrol) gave **4** (3.80 g, 86%) (Found: C, 48.49; H, 7.23. $C_{13}H_{23}IO$ requires C, 48.46; H, 7.19%); $[a]_D^{20}$ −2.0 (*c* 1.70 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3322, 3054, 3010, 2922, 2852, 1611, 1459, 1376, 1271, 1143, 1023, 759, 665; δ_H (500 MHz; $CDCl_3$) 0.80 (3H, d, *J* 6.6, 8-Me), 1.04–1.36 (6H, m, 3 × CH_2), 1.55–1.63 (1H, m, H8), 1.79 (3H, d, *J* 0.8, 10-Me), 1.99 (1H, dd, *J* 8.0 and 13.1, H9), 2.07 (2H, dt, *J* ~ 6.6 and 6.6, 2 × H4), 2.18 (1H, dd, *J* 6.1 and 13.1, H9), 4.18–4.20 (2H, m, 2 × H1), 5.51–5.63 (2H, m, H2, H3) and 5.82 (1H, q, *J* 0.8, H11); δ_C ($CDCl_3$) 147.2 (C10), 133.0 (C2), 128.4 (C3), 75.2 (C11), 58.6 (C1), 47.6 (C9), 36.4 (C7), 30.8 (C8), 29.7, 27.4, 26.5 (C4, C5, C6), 23.7 (10-Me), 19.3 (8-Me); EI *m/z* 322 (M^+, 0.1%), 195 ($M^+ - I$, 2.4), 177 ($M^+ - I - H_2O$, 15) and 81 (100); HRMS: Found: M^+, 322.0794. $C_{13}H_{23}IO$ requires *M*, 322.0795.

Diphenylmethyl but-2-ynoate

Benzophenone hydrazone (24.0 g, 130 mmol) was dissolved in DCM–Et_3N (1:1, 750 cm^3) and cooled to −20 °C. Lead(IV) acetate (72.7 g, 156 mmol, 95% purity) in DCM (375 cm^3) was added dropwise. After the addition was complete the mixture was allowed to warm up to rt and then was diluted with DCM (500 cm^3) and washed with H_2O (6 × 750 cm^3). The organic layer was dried and concentrated to give *diphenyldiazomethane* (24.0 g) as a purple oil that was directly dissolved in benzene (1000 cm^3). *But-2-ynoic acid* (**12**) (10.0 g, 119 mmol) was added in small portions. Once the addition was complete (1 h) the mixture was allowed to stir overnight. The reaction mixture was then heated (70 °C, 1 h) and the bulk of the benzene removed by distillation. Residual benzene was removed on a rotary evaporator. The resulting residue crystallised on standing to give a brown solid. Recrystallisation gave *diphenylmethyl but-2-ynoate* as a white solid (26.4 g, 85%); mp 76–77 °C (from EtOH) (Found: C, 81.56; H, 5.51. $C_{17}H_{14}O_2$ requires C, 81.58; H, 5.64%); ν_{max}/cm^{-1} (thin film) 2918, 2241, 1701, 1599, 1490, 1447, 1354, 1262, 1188, 1068, 984, 874, 741, 695; δ_H (270 MHz; $CDCl_3$) 2.00 (3H, s, Me), 6.92 (1H, s, C*H*Ph_2) and 7.27–7.36 (10H, m, ArH); EI *m/z* 250 (M^+, 11.5%), 183 ($M^+ - Ph$, 12.5) and 166 ($M^+ - C_4H_4O_2$, 100).

Diphenylmethyl (*E*)-3-(trimethylstannyl)but-2-enoate (5)

A degassed solution of hexamethylditin (10.00 g, 30.6 mmol) in THF (300 cm^3) was cooled to −20 °C and MeLi (22 cm^3, 1.4 M in Et_2O, 30.8 mmol) was added. After stirring for 20 min the mixture was cooled to −48 °C and neat CuCN (2.85 g, 31.8 mmol) was added. The slightly yellow–green solution turned immediately yellow–orange and stirring was continued for 30 min. The mixture was then cooled to −78 °C and methanol (1.3 cm^3) was added. After 5 min *diphenylmethyl but-2-ynoate* (5.10 g, 20.2 mmol) dissolved in THF (200 cm^3) was added dropwise *via* a cannula (20 min). Stirring was continued for 4 h 30 min at −78 °C and then the reaction was quenched by the addition of NH_4OH–NH_4Cl buffer [180 cm^3 of a solution prepared from sat. aqueous NH_4Cl (500 cm^3) and NH_4OH (50 cm^3)]. Stirring was continued at rt until a deeply blue coloured solution was obtained. This solution was extracted with DCM (2 × 500 cm^3), and the organic phase was dried and concentrated. Chromatography (1% Et_2O–petrol) followed by recrystallisation from methanol gave **5** (5.37 g, 81%); mp 60–61 °C (from MeOH) (Found: C, 57.91; H, 5.70. $C_{20}H_{24}O_2Sn$ requires C, 57.87; H, 5.83%); ν_{max}/cm^{-1} (thin film) 3061, 3029, 2979, 2913, 1947, 1713, 1597, 1491, 1448, 1344, 1244, 1157, 1102, 1079, 1030, 1000, 913, 864, 769, 744, 698, 630; δ_H (270 MHz; $CDCl_3$) 0.21 (9H, t, $J_{Sn,H}$ 54.0, $SnMe_3$), 2.43 (3H, dd, *J* 2.0, $J_{Sn,H}$ 52.0, Me), 6.14 (1H, dt, *J* 2.0, $J_{Sn,H}$ 73.0, H2), 6.93 (1H, s, C*H*Ph_2) and 7.22–7.37 (10H, m, ArH); δ_C ($CDCl_3$) 170.1 (CO), 163.1 (C2), 140.5, 128.4, 127.8, 127.2 (C-Ar), 127.4 (C3), 76.1 (*C*HPh_2), 21.7 (Me), −9.9 ($SnMe_3$); EI *m/z* 401 (M^+ − Me, 3.2%) and 167 (100).

Diphenylmethyl (2*E*,4*E*,7*R*,12*Z*)-14-hydroxy-3,5,7-trimethyltetradeca-2,4,12-trienoate (13)

A degassed solution of the vinyl iodide **4** (174 mg, 0.54 mmol) in DMF (4 cm^3) was added *via* a cannula to palladium(II) chloride bisacetonitrile complex (36 mg, 0.14 mmol, 25 mol%) suspended in DMF (1 cm^3). Then, a degassed solution of the vinyl stannane **5** (739 mg, 1.78 mmol) in DMF (6 cm^3) was added and the resulting mixture was stirred at rt in the dark until TLC monitoring showed no vinyl iodide left (72 h). The reaction was then filtered over Celite® and the residues were washed with Et_2O (180 cm^3). The filtrate was washed with $NaHCO_3$ (2 × 100 cm^3) and the combined aqueous layer was washed with Et_2O (2 × 100 cm^3). The combined organic phase was washed with H_2O (100 cm^3) and brine (100 cm^3), then was dried and concentrated. The residue obtained was triturated with petrol (100 cm^3) and the yellow precipitates were filtered off over Celite® and washed with petrol–Et_2O 1:1 (150 cm^3). The filtrate was concentrated and this procedure repeated. The yellow oil obtained after concentration of the filtrates was purified by chromatography (gradient: 12% to 20% Et_2O–petrol) to give **13** (148 mg, 62%) as an oil (Found: C, 80.32; H, 8.62. $C_{30}H_{38}O_3$ requires C, 80.68; H, 8.58%); $[a]_D^{20}$ −9.0 (*c* 2.61 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3387, 3027, 2923, 2853, 1710, 1601, 1493, 1376, 1333, 1228, 1139, 1079, 1024, 885, 742, 699, 663; δ_H (500 MHz; $CDCl_3$) 0.82 (3H, d, *J* 6.6, 7-Me), 1.08–1.39 (6H, m, 3 × CH_2), 1.60–1.67 (1H, m, H7), 1.81 (3H, d, *J* 1.2, 5-Me), 1.81–1.86 (1H, m, H6), 2.06–2.11 (3H, m, H6, 2 × H11), 2.24 (3H, d, *J* 1.2, 3-Me), 4.19 (2H, dd, *J* ~ 6.6 and 6.6, 2 × H14), 5.53–5.61 (2H, m, H12, H13), 5.71 (1H, q, *J* 1.2, H4), 5.81 (1H, q, *J* 1.2, H2), 6.93 (1H, s, C*H*Ph_2) and 7.23–7.30 (10H, m, ArH); δ_C ($CDCl_3$) 166.0 (C1), 155.5 (C3), 141.8, 140.7 (C5), 133.1 (C13), 129.5, 128.5, 128.4, 127.7, 127.2 (C-Ar, C4, C12), 117.1 (C2), 76.1 (*C*HPh_2), 58.6 (C14), 49.1 (C6), 36.7, 29.8, 27.4, 26.6 (C8, C9, C10, C11), 31.0 (C7), 19.9, 19.4, 18.5 (3 × Me); EI *m/z* 371 (0.1%), 235 ($M^+ - Ph_2CH - CO_2$, 0.1) and 167 (Ph_2CH^+, 100).

Diphenylmethyl (2*E*,4*E*,7*R*,12*R*,13*S*)-12,13-epoxy-14-hydroxy-3,5,7-trimethyltetradeca-2,4-dienoate (14)

A solution of L-(+)-diisopropyl tartrate (361 mg, 1.54 mmol) in DCM (4 cm^3) was added to a slurry of activated powdered 4 Å molecular sieves (2 g) in DCM (8 cm^3) and stirred for 30 min. Then, the mixture was cooled to −28 °C and titanium(IV) isopropoxide (0.460 cm^3, 438 mg, 1.54 mmol) was added. After 25 min of stirring, *tert*-butyl hydroperoxide (1.10 cm^3, 3 M in isooctane, 3.20 mmol) was added and 30 min later the allylic alcohol **13** (687 mg, 1.54 mmol) dissolved in DCM (20 cm^3) was added *via* a cannula. The mixture was stirred for 36 h at −24 °C and then quenched by the addition of D/L-tartaric acid (9 cm^3 of a solution of 110 mg in 21 cm^3 of acetone–H_2O, 5:2) and allowed to warm to rt. The resulting slurry was then filtered through a plug of Celite® and the residues were washed with Et_2O–DCM (300 cm^3, 1:1). The filtrate was concentrated and the residue chromatographed (gradient: 30% to 50% Et_2O–petrol) to give **14** (569 mg, 80%) as an oil (Found: C, 77.53; H, 8.54. $C_{30}H_{38}O_4$ requires C, 77.89; H, 8.28%); $[a]_D^{20}$ −5.7 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3428, 2922, 2854, 1708, 1602, 1492, 1448, 1377, 1228, 1138, 1028, 884, 744, 699, 664; δ_H (500

MHz; $CDCl_3$) 0.84 (3H, d, *J* 6.6, 7-Me), 1.10–1.65 (9H, m, H7, 4 × CH_2), 1.81 (3H, d, *J* 0.9, 5-Me), 1.84 (1H, dd, *J* 8.3 and 13.1, H6), 2.08 (1H, dd, *J* 6.1, 13.1, H6), 2.24 (3H, d, *J* 1.0, 3-Me), 3.03 (1H, dt, *J* 4.4 and 6.1, H12), 3.15 (1H, dt, *J* 4.4 and 6.9, H13), 3.64–3.70 (1H, m, H14), 3.85 (1H, ddd, *J* 4.2, 6.8 and 11.3, H14), 5.71 (1H, s, H4), 5.81 (1H, s, H2), 6.93 (1H, s, C*H*Ph_2) and 7.26–7.37 (10H, m, ArH); δ_C ($CDCl_3$) 165.9 (C1), 155.4 (C3), 141.6, 140.6 (C-*ipso*, C5), 129.4 (C4), 128.4, 127.6, 127.0 (C-Ar), 117.1 (C2), 76.1 (*C*HPh_2), 60.8 (C13), 57.1, 56.8 (C12, C14), 49.0 (C6), 36.6 (C8), 30.9 (C7), 27.9, 26.8, 26.7 (C9, C10, C11), 19.8, 19.4, 18.5 (3 × Me); EI *m*/*z* 279 (0.1%), 184 (0.1) and 167 (Ph_2CH^+, 100).

Similarly, the epoxy alcohols from the reaction with L-(+)- and D-(−)-diisopropyl tartrate under catalytic conditions were obtained, and the diastereomeric excesses, both under catalytic (66% de) and stoichiometric (90% de) conditions, determined by ^{1}H NMR (C_6D_6) on the derived epoxy acetates in the presence of Eu(hfbc)$_3$.[25]

O-acetate derived from 14

Acetyl chloride (0.01 cm^3, 0.117 mmol) was added to a solution of **14** (36 mg, 0.078 mmol), Et_3N (0.06 cm^3) and DMAP (11 mg, 0.09 mmol) in DCM (1 cm^3) and the mixture was stirred for 1 h. The reaction was quenched by the addition of 3-(dimethylamino)propylamine (0.05 cm^3) and the resulting mixture concentrated. The residue was dissolved in DCM (2 cm^3) and filtered over a plug of silica (petrol–EtOAc, 4:1) to give the corresponding acetate (37 mg, 94%). The *O*-acetate derived from the product of the reaction with D-(−)-diisopropyl tartrate was obtained in a similar way.

Diphenylmethyl (2*E*,4*E*,7*R*,12*R*,13*S*)-12,13-epoxy-3,5,7-trimethylpentadeca-2,4,14-trienoate (3)

The epoxy alcohol **14** (235 mg, 0.51 mmol) was dissolved in DCM–MeCN (12:1, 6.5 cm^3). Powdered 4 Å molecular sieves (500 mg) were added and the resulting slurry stirred for 10 min. Then, NMO (90 mg, 0.75 mmol) was added followed by TPAP (10 mg, 0.03 mmol) and stirring continued in the dark for 40 min until TLC showed no starting material left. The mixture was filtered through a plug of Celite®, washing with DCM. Concentration of the filtrate gave crude *diphenylmethyl (2E,4E,7R,12R,13R)-12,13-epoxy-14-oxo-3,5,7-trimethyltetradeca-2,4-dienoate* as an oil, which was used in the next step without further purification.

Methyltriphenylphosphonium bromide (399 mg, 1.12 mmol) was suspended in toluene (5 cm^3) and cooled to −20 °C. KHMDS (2.1 cm^3, 0.5 M in toluene, 1.05 mmol) was added and the mixture allowed to warm up to −5 °C (20 min). The crude aldehyde dissolved in THF (9 cm^3) was added and the reaction stirred for 2 h. The mixture was diluted with petrol (40 cm^3) and filtered through a plug of Celite®, washing with petrol–Et_2O (1:1, 100 cm^3). The filtrate was concentrated and purified by chromatography (5% Et_2O–petrol) to give **3** (182 mg, 78%) as a colourless oil.

Diphenylmethyl (2E,4E,7R,12R,13R)-12,13-epoxy-14-oxo-3,5,7-trimethyltetradeca-2,4-dienoate (Found: C, 77.88; H, 7.69. $C_{30}H_{36}O_4$ requires C, 78.23; H, 7.88%); $[\alpha]_D^{20}$ +17.4 (*c* 2.00 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2926, 1717, 1602, 1449, 1379, 1228, 1138, 1023, 743, 699; δ_H (500 MHz; $CDCl_3$) 0.83 (3H, d, *J* 6.6, 7-Me), 1.11–1.79 (9H, m, H7, 4 × CH_2), 1.81 (3H, d, *J* 1.2, 5-Me), 1.80–1.86 (1H, m, H6), 2.04–2.09 (1H, m, H6), 2.24 (3H, d, *J* 1.1, 3-Me), 3.24–3.28 (1H, m, H12), 3.34 (1H, dd, *J* ~ 5.5 and 5.5, H13), 5.71 (1H, s, H4), 5.81 (1H, s, H2), 6.92 (1H, s, C*H*Ph_2), 7.21–7.37 (10H, m, ArH) and 9.47 (1H, d, *J* 5.2, H14); EI *m*/*z* 460 (M$^+$, 0.1%) and 167 (Ph_2CH^+, 100).

Compound **3** (Found: C, 81.11; H, 8.39. $C_{31}H_{38}O_3$ requires C, 81.18; H, 8.35%); $[\alpha]_D^{20}$ +2.7 (*c* 0.26 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2922, 1708, 1617, 1448, 1226, 1136, 1021; δ_H (500 MHz; $CDCl_3$) 0.83 (3H, d, *J* 6.6, 7-Me), 1.03–1.73 (9H, m, H7, 4 × CH_2), 1.81 (3H, d, *J* 1.2, 5-Me), 1.83–1.86 (1H, m, H6), 2.04–2.09 (1H, m, H6), 2.24 (3H, d, *J* 1.2, 3-Me), 3.06–3.09 (1H, m, H12), 3.40 (1H, dd, *J* 4.4 and 7.4, H13), 5.34 (1H, dd, *J* 0.7 and 10.7, H15), 5.46 (1H, dd, *J* 0.7 and 16.4, H15), 5.71 (1H, ddd, *J* 7.4, 10.5 and 16.3, H14), 5.71 (1H, s, H4), 5.81 (1H, s, H2), 6.92 (1H, s, C*H*Ph_2) and 7.21–7.37 (10H, m, ArH); δ_C ($CDCl_3$) 166.0 (C1), 155.5 (C3), 141.8, 140.7 (C-*ipso*, C5), 132.6 (C14), 129.5 (C4), 128.5, 127.7, 127.2 (C-Ar), 120.4 (C6), 76.1 (*C*HPh_2), 36.8 (C8), 31.0 (C7), 27.8, 26.9, 26.6 (C9, C10, C11), 19.9, 19.4, 18.5 (3 × Me); EI *m*/*z* 458 (M$^+$, 0.1%), 352 (0.1), 291 (3) and 167 (Ph_2CH^+, 100).

[(12-*exo*-13,14,15-η^3)-(2*E*,4*E*,7*R*,12*R*)-1-Diphenylmethoxy-3,5,7-trimethyl-1-oxo-12-formyloxypentadec-2,4,14-trien-13-ylato] tricarbonyliron (2) and [(12-*endo*-13,14,15-η^3)-(2*E*,4*E*,7*R*,12*R*)-1-diphenylmethoxy-3,5,7-trimethyl-1-oxo-12-formyloxypentadec-2,4,14-trien-13-ylato] tricarbonyliron (15)

The vinyl epoxide **3** (154 mg, 0.34 mmol) was dissolved in THF (10 cm^3) and diiron nonacarbonyl (620 mg, 1.70 mmol) was added. After 45 min of stirring, TLC showed no presence of starting material **3** and the mixture was diluted with Et_2O (50 cm^3) and toluene (7 cm^3) and was then filtered through a pad of Celite®. The filtrate was concentrated until approximately 3–5 cm^3 and this residue was purified by chromatography (gradient: 5% to 30% Et_2O–petrol) to give firstly **15** (37 mg, 18%) and then **2** (114 mg, 54%) as an oil.

Compound **15**; ν_{max}/cm^{-1} (thin film) 3404, 3029, 2926, 2858, 2079, 2014, 1707, 1662, 1491, 1448, 1377, 1339, 1228, 1138, 1024, 990, 885, 744, 700, 659; δ_H (500 MHz; C_6D_6) 0.84 (3H, d, *J* 6.5, 7-Me), 0.90–1.60 (9H, m, H7, 4 × CH_2), 1.64 (3H, s, 5-Me), 1.74 (1H, dd, *J* 8.5 and 13.8, H6), 1.97 (1H, dd, *J* 6.1 and 13.8, H6), 2.40 (3H, s, 3-Me), 2.81 (1H, d, *J* 13.1, H15$_{exo}$), 2.86 (1H, d, *J* 7.9, H15$_{endo}$), 3.70–3.76 (1H, m, H12), 3.80–3.83 (2H, m, H13, H14), 5.69 (1H, s, H4), 6.12 (1H, s, H2) and 7.08–7.44 (11H, m, C*H*Ph_2, ArH); δ_C (C_6D_6) 210.0, 208.0, 203.8 [Fe(CO)], 199.0 [Fe(CO)O], 165.8 (C1), 155.4 (C3), 141.5, 135.6 (C-*ipso*, C5), 130.0 (C4), 128.7, 128.3, 128.0, 127.8, 125.5 (C-Ar, C_6D_6), 117.9 (C2), 90.6 (C14), 81.9 (C13), 76.4 (*C*HPh_2), 72.8 (C12), 58.4 (C15), 49.2 (C6), 37.3, 36.9 (C8, C11), 31.1 (C7), 27.4, 26.1 (C9, C10), 19.9, 19.5, 18.3 (3 × Me); EI *m*/*z* 352 (20%) and 167 (Ph_2CH^+, 100).

Compound **2** (Found: C, 67.24; H, 6.33. $C_{35}H_{38}FeO_4$ requires C, 67.10; H, 6.11%); $[\alpha]_D^{20}$ +18.3 (*c* 0.40 in C_6H_6); ν_{max}/cm^{-1} (thin film) 3404, 3029, 2926, 2858, 2079, 2014, 1707, 1662, 1491, 1448, 1377, 1339, 1228, 1138, 1024, 990, 885, 744, 700, 659; δ_H (500 MHz; C_6D_6) 0.76 (3H, d, *J* 6.6, 7-Me), 0.96–1.54 (9H, m, H7, 4 × CH_2), 1.58 (3H, d, *J* 1.2, 5-Me), 1.65 (1H, dd, *J* 8.7 and 13.5, H6), 1.91 (1H, dd, *J* 6.4 and 13.5, H6), 2.34 (3H, d, *J* 1.2, 3-Me), 2.58 (1H, dd, *J* 1.5 and 13.0, H15$_{endo}$), 2.70 (1H, dd, *J* 1.7 and 8.1, H15$_{exo}$), 3.54–3.57 (1H, m, H12), 3.72 (1H, br d, *J* 7.7, H13), 3.85 (1H, ddd, *J* ~ 7.6, 7.6 and 13.1, H14), 5.62 (1H, s, H4), 6.05 (1H, s, H2) and 6.99–7.40 (11H, m, C*H*Ph_2, ArH); δ_C (C_6D_6) 210.3, 207.0, 204.0 [Fe(CO)], 199.8 [Fe(CO)O], 165.8 (C1), 155.5 (C3), 141.5, 141.4 (C-*ipso*, C5), 129.9 (C4), 130.3, 129.9, 128.7, 128.2, 128.0, 127.8, 127.7, 127.6, 125.8 (C-Ar, C_6D_6), 117.9 (C2), 92.0 (C14), 81.3 (C13), 76.4 (*C*HPh_2), 74.0 (C12), 57.1 (C15), 49.2 (C6), 38.5, 37.0 (C8, C11), 31.1 (C7), 26.9, 26.0 (C9, C10), 19.9, 19.5, 18.3 (3 × Me); EI *m*/*z* 352 (20%) and 167 (Ph_2CH^+, 100).

Diphenylmethyl [2*E*,4*E*,7*R*,(2′*R*,3′*R*)]-11-(4′-oxo-3′-vinyloxetan-2′-yl)-3,5,7-trimethylundeca-2,4-dienoate (16)

The *exo*-π-allyltricarbonyliron lactone **2** (27 mg, 0.043 mmol) in degassed MeCN (1.5 cm^3) was cooled to 0 °C and added to a 0 °C degassed suspension of CAN¶ (155 mg, 0.280 mmol) in

¶ CAN was dried before use in a desiccator over P_2O_5 under 0.01 mm Hg for 48–72 h.

MeCN (0.5 cm^3). The mixture was stirred for 2 h at 0 °C and then was allowed to warm to rt and stirred for a further 3 h; it was then partitioned between cold Et_2O (20 cm^3) and H_2O (15 cm^3). The aqueous layer was extracted with Et_2O and the combined organic layer was washed with H_2O (3 × 20 cm^3), dried and concentrated. Chromatography (gradient: 5 to 50% Et_2O–petrol) gave **16** (18 mg, 81%) as an oil; $[\alpha]_D^{20}$ +6.9 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2923, 2852, 1828, 1714, 1628, 1452, 1141, 859, 697, 663; δ_H (500 MHz; $CDCl_3$) 0.83 (3H, d, *J* 6.7, 7-Me), 1.25–1.45 (8H, m, 4 × CH_2), 1.72–1.93 (2H, m, H6, H7), 1.81 (3H, d, *J* 1.0, 5-Me), 2.08 (1H, dd, *J* 5.7 and 13.0, H6), 2.24 (3H, d, *J* 1.0, 3-Me), 3.85 (1H, dd, *J* 4.2 and 7.3, H3′), 4.37 (1H, dt, *J* 4.2 and 7.3, H2′), 5.31 (1H, d, *J* 10.1, H2″), 5.34 (1H, d, *J* 17.2, H2″), 5.71 (1H, s, H4), 5.81 (1H, s, H2), 5.90 (1H, ddd, *J* 7.3, 10.2, 17.3, H1″), 6.92 (1H, s, C*H*Ph_2) and 7.21–7.37 (10H, m, ArH); δ_C ($CDCl_3$) 169.1 (CO, lactone), 166.0 (C1), 155.4 (C3), 141.5, 140.7 (C-*ipso*, C5), 129.6 (C4), 128.7 (C1″), 128.6, 127.8, 127.2 (C-Ar), 120.1 (C2″), 117.2 (C2), 77.8 (C2′), 76.1 (*C*HPh_2), 59.8 (C3′), 49.0 (C6), 36.7, 34.2 (C11, C8), 30.9 (C7), 26.7, 25.2 (C9, C10), 19.9, 19.4, 18.5 (3 × Me); EI *m*/*z* 486 (M^+, 12%) and 442 ($M^+ - CO_2$, 12).

Diphenylmethyl [2*E*,4*R*/*S*,5*S*/*R*,7*R*,(2′*R*,3′*R*)]-4,5-epoxy-11-(4′-oxo-3′-vinyloxetan-2′-yl)-3,5,7-trimethylundec-2-enoate (17)

The β-lactone **16** (9.7 mg, 20 μmol) and anhydrous K_2CO_3 (80 mg) in dry DCM (3 cm^3) were treated with MCPBA (20 mg, 100 μmol, 80%) in three portions. After 30 min TLC showed no starting **16** present and solid $Na_2S_2O_5$ was added and stirring continued for 30 min. The reaction mixture was filtered through a pad of Celite® washing with DCM and the filtrate was concentrated to give a colourless oil that was purified by preparative TLC (50% EtOAc–petrol) to give **17** (5.7 mg, 57%) as an oil; ν_{max}/cm^{-1} (thin film) 3030, 2930, 2858, 1825, 1720, 1651; δ_H (600 MHz; $CDCl_3$) 0.94 and 0.97 (3H, 2 × d, *J* 6.6, 7-Me), 1.13 and 1.14 (3H, 2 × s, 5-Me), 1.15–1.94 (11H, m, H7, 5 × CH_2), 2.18 and 2.19 (3H, 2 × br s, 3-Me), 3.20 and 3.22 (1H, 2 × s, H4), 3.84–3.87 (1H, m, H3′), 4.35–4.39 (1H, m, H2′), 5.30–5.36 (2H, m, 2 × H2″), 5.87–5.94 (1H, m, H1″), 5.98–6.00 (1H, m, H2), 6.91 (1H, s, C*H*Ph_2) and 7.31–7.38 (10H, m, ArH); δ_C (100 MHz; $CDCl_3$) 168.8 (CO lactone), 165.3 (C1), 153.5 (C3), 140.5 (*ipso* ArC), 128.4, 128.0, 127.8, 127.1, 127.0 (C4, ArC), 120.2 (C2″), 116.1 (C2), 77.7 (C2′), 76.4 (*C*HPh_2), 66.2, 65.9 (C4), 63.4 (C5), 59.7 (C3′), 45.9, 45.7 (C6), 30.1, 29.7 (C7), 37.1, 36.8, 34.1, 26.5, 26.4, 25.2, 25.1 (C8, C9, C10, C11), 19.9, 19.6 (7-Me), 16.5 (3-Me), 15.4, 15.1 (5-Me); HRMS: Found: $(M + H)^+$, 503.2818. $C_{32}H_{39}O_5$ requires 503.2797.

Diphenylmethyl [2*E*,4*R*/*S*,5*S*/*R*,7*R*,(2′*R*,3′*R*)]-4,5-epoxy-11-(3′-hydroxymethyl-4′-oxooxetan-2′-yl)-3,5,7-trimethylundec-2-enoate (18)

The β-lactone **17** (1.30 mg, 2.6 μmol) was dissolved in DCM (3 cm^3) and cooled to −78 °C. Ozone in oxygen (30 L h^{-1}, 140 V) was bubbled through the solution and after 1.5 min TLC showed no presence of starting material. The solution was purged with Ar, and benzene (1.5 cm^3) and $NaBH_4$ on Al_2O_3 (50 mg, 137 μmol) were added. The mixture was allowed to warm to rt and stirred for 14 h. It was then filtered over Celite® and concentrated to give a colourless oil that was purified by chromatography (gradient: 50% to 70% Et_2O–petrol) to give **18** as an oil (0.23 mg, 18%); ν_{max}/cm^{-1} (thin film) 3452, 2931, 1817, 1715, 1652; δ_H (600 MHz; $CDCl_3$) 0.94 and 0.97 (3H, 2 × d, *J* 6.5, 7-Me), 1.13 and 1.14 (3H, 2 × s, 5-Me), 1.19–1.95 (11H, m, H7, 5 × CH_2), 2.18 and 2.19 (3H, 2 × br s, 3-Me), 3.20 and 3.24 (1H, 2 × s, H4), 3.35–3.42 (1H, m, H3′), 3.88–3.91 (1H, m, C*H*$_2$OH), 4.02–4.07 (1H, m, C*H*$_2$OH), 4.57–4.61 (1H, m, H2′), 5.98–6.00 (1H, m, H2), 6.90 (1H, s, C*H*Ph_2) and 7.28–7.37 (10H, m, ArH); δ_C (150 MHz; $CDCl_3$) 169.4 (lactone CO), 165.3 (C1), 153.4 (C3), 140.5 (*ipso* ArC), 128.5, 127.81, 127.78, 127.1, 127.0 (ArC), 116.2 (C2), 76.4 (*C*HPh_2), 74.9 (C2′), 66.2, 65.4 (C4), 63.4, 63.3 (C5), 58.6 (C3′), 58.2 (CH_2OH), 45.9, 45.7 (C6), 30.10, 30.07 (C7), 37.1, 36.8, 34.1, 34.0, 26.5, 26.4, 25.2, 25.1 (C8, C9, C10, C11), 20.0, 19.6 (7-Me), 16.52, 16.51 (3-Me), 15.5, 15.2 (5-Me); HRMS: Found: M^+, 506.2654. $C_{31}H_{38}O_6$ requires 506.26681.

β-Lactone **19** (81 mg, 0.165 mmol) and anhydrous K_2CO_3 (360 mg) in dry DCM (5 cm^3) were treated with MCPBA (350 mg, 1 mmol, 50%) and the resulting mixture stirred for 5 min. Solid $Na_2S_2O_5$ was added and stirring continued for 10 min. The reaction mixture was filtered through Celite® washing with DCM. The filtrate was concentrated to give a colourless oil that was purified by chromatography (gradient: 50% to 70% Et_2O–petrol) to give **18** (56 mg, 67%) as an oil. This material was found to be identical by ^1H and ^{13}C NMR, IR and high resolution mass spectrometry to the material prepared from **17**.

Diphenylmethyl [2*E*,4*E*,7*R*,(2′*R*,3′*R*)]-11-(3′-hydroxymethyl-4′-oxooxetan-2′-yl)-3,5,7-trimethylundeca-2,4-dienoate (19)

The epoxy β-lactone **18** (7.0 mg, 13.8 μmol) dissolved in ^{t}BuOH (0.053 cm^3, 0.53 M in THF, 28.0 μmol) and THF (4 cm^3) was treated with SmI_2 (0.28 cm^3, 0.01 M in THF, 28.0 μmol). After 5 min of stirring the solution colour changed from blue to yellow and the reaction was quenched by the addition of HCl (1 cm^3, 0.1 M) and partitioned between EtOAc and HCl (0.1 M). The organic phase was washed with $NaHCO_3$ and brine, then was dried and concentrated to give a colourless oil that was purified by chromatography (20% Et_2O–petrol) to give **19** (2.8 mg, 40%) (Found: C, 75.69; H, 7.91. $C_{31}H_{38}O_5$ requires C, 75.89; H, 7.81%); $[\alpha]_D^{20}$ +32 (*c* 0.08 in DCM); ν_{max}/cm^{-1} (thin film) 3942, 2926, 1818, 1707, 1601; δ_H (600 MHz; $CDCl_3$) 0.84 (3H, d, *J* 6.6, 7-Me), 1.10–1.96 (10H, m, H6, H7, 2 × H8, 2 × H9, 2 × H10, 2 × H11), 1.82 (3H, br s, 5-Me), 2.08 (1H, dd, *J* 6.2 and 13.2, H6), 2.25 (3H, br s, 3-Me), 3.40 (1H, dt, *J* 4.2 and 4.8, H3′), 3.88 (1H, dd, *J* 3.8 and 11.6, C*H*$_2$OH), 4.03 (1H, dd, *J* 4.9 and 11.6, C*H*$_2$OH), 4.56–4.59 (1H, m, H2′), 5.72 (1H, br s, H4), 5.82 (1H, br s, H2), 6.93 (1H, s, C*H*Ph_2) and 7.27–7.37 (10H, m, ArH); δ_C (150 MHz; $CDCl_3$) 169.6 (lactone CO), 166.0 (C1), 155.4 (C3), 141.5 (C5), 140.6 (*ipso* ArC), 129.6 (C4), 128.4, 127.7, 127.2 (ArC), 117.2 (C2), 76.1 (*C*HPh_2), 74.9 (C2′), 58.6 (C3′), 58.1 (CH_2OH), 49.0 (C6), 30.9 (C7), 36.6, 34.0, 26.6, 25.2 (C8, C9, C10, C11), 19.8 (3-Me), 19.4 (7-Me), 18.5 (5-Me); EI *m*/*z* 261 ($M^+ - CO_2 - Ph_2CH$, 0.1%), 167 ($CHPh_2^+$, 100).

Benzophenone hydrazone (400 mg, 2.00 mmol) was dissolved in DCM–Et_3N (12 cm^3, 1:1) and cooled to −20 °C. Lead(IV) acetate (1.11 g, 2.5 mmol, 95% purity) in DCM (6 cm^3) was added dropwise and the resulting mixture was allowed to warm to rt and partitioned between DCM (50 cm^3) and H_2O (6 × 50 cm^3). The organic layer was dried and concentrated to give *diphenyldiazomethane* (340 mg, 86%) as a purple oil that was dissolved in benzene (14 cm^3). Natural 1233A (**1**) (500 mg, 1.54 mmol) was added in portions and once the addition was complete (15 min) the mixture was heated for 1 h at 70 °C. The mixture was filtered over Celite® and concentrated to give a brown oil that was purified by chromatography (gradient: 10% to 50% Et_2O–petrol) to give **19** (560 mg, 75%) as an oil.

[2*E*,4*E*,7*R*,(2′*R*,3′*R*)]-11-(3′-Hydroxymethyl-4′-oxooxetan-2′-yl)-3,5,7-trimethylundeca-2,4-dienoic acid [1233A, (1)]

A solution of the protected ester **19** (8.0 mg, 16 μmol) and anisole (0.014 cm^3, 0.13 mmol) in DCM (0.2 cm^3) was cooled to −20 °C and TFA (0.043 cm^3, 0.25 mmol) was added. The mixture was allowed to slowly warm to −10 °C for 25 min and was then concentrated and purified by chromatography (80% Et_2O–petrol) to give 1233A (**1**) (4.1 mg, 77%) as a white solid; $[\alpha]_D^{20}$ +29.0 (*c* 0.21 in $CHCl_3$) [lit.,[8a] +28.6 (*c* 0.62 in $CHCl_3$)]; ν_{max}/cm^{-1} (thin film) 3498, 2934, 1820 (β-lactone), 1791, 1676, 1625;

δ_H (600 MHz; $CDCl_3$) 0.84 (3H, d, *J* 6.6, 7-Me), 1.10–1.16 (1H, m, H8), 1.30–1.46 (5H, m, H8, 2 × H9, 2 × H10), 1.66 (1H, dq, *J* 6.7 and 13.2, H7), 1.75–1.81 (4H, m, 5-Me, H11), 1.86 (1H, dd, *J* 8.3 and 13.3, H6), 1.89–1.94 (1H, m, H11), 2.09 (1H, dd, *J* 6.2 and 13.2, H6), 2.25 (3H, s, 3-Me), 3.41 (1H, q, *J* 4.4, H3′), 3.89 (1H, dd, *J* 4.1 and 11.6, CH_2OH), 4.05 (1H, dd, *J* 5.0 and 11.6, CH_2OH), 4.58 (1H, ddd, *J* 4.2, 6.0 and 7.3, H2′), 5.69 (1H, s, H2) and 5.73 (1H, s, H4); δ_C (100 MHz; $CDCl_3$) 171.5, 169.7, 157.0 (C3), 142.0 (C5), 129.5 (C4), 116.6 (C2), 74.9 (C2′), 58.6 (C3′), 58.1 (CH_2OH), 49.0 (C6), 36.6 (C8), 34.0 (C11), 30.9 (C7), 26.6 (C9), 25.2 (C10), 19.9 (3-Me), 19.4 (7-Me), 18.5 (5-Me); ES *m*/*z* 325.29 [$(M + H)^+$, 100%].

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Paper 9/03641E