Diastereoselective synthesis of the tetrahydropyranoid core of the polyketide herbicide herboxidiene and model studies pertaining to attachment of the side-chain

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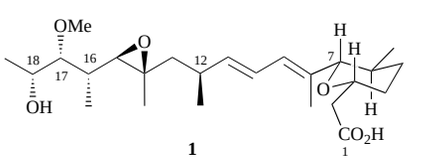
A diastereoselective synthesis of compound 2, which embodies the tetrahydropyranyl core of the polyketide herbicide herboxidiene (1), has been developed using asymmetric epoxidation of nerol as the initial step. Ketone 2 has been elaborated to phosphine oxide 24 which engages in a Horner–Wittig reaction with nonanal to give the *E*,*E*-diene 27, an analogue of herboxidiene. However, unlike compound 1, congeners 2 and 27 are not phytotoxic.

In 1992 workers at Monsanto described the isolation of herboxidiene, a secondary metabolite produced by *Streptomyces* sp. A7847.[1] The compound was so named because it displays powerful phytotoxic properties and, at application rates of 35 g acre^{-1}, selectively controls a range of crop pests including broadleaf annual weeds such as oilseed rape, wild buckwheat and morning glory while remaining harmless to wheat. Through a combination of spectroscopic and degradation studies, the Monsanto group assigned the polyketide structure **1** to herboxidiene although uncertainty remained regarding the relative stereochemistries at C-7, C-12, C-16, C-17 and C-18 as well as the absolute configuration of the compound. Very recently (1997), workers at Novartis AG (Basel) and Geneva[2] re-isolated herboxidiene and, by means of X-ray crystallographic, degradation and partial synthesis studies, have unambiguously established its structure, which is represented by **1**. Structurally



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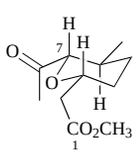

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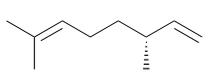

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speaking, herboxidiene is unlike any previously known phytotoxic compound and, as such, must be considered an important lead for the development of herbicides with new modes of action.

Like others,[3] we have embarked (in 1994) on a program aimed at developing a total synthesis of herboxidiene. Our original intentions had been, *inter alia*, to (i) resolve the stereochemical ambiguities that remained, at that time, regarding the structure of herboxidiene and (ii) establish which structural features of the molecule might be responsible for its intriguing phytotoxic properties. Herein, we detail[4] a diastereoselective synthesis of tetrahydropyran **2**, a compound which embodies the cyclic core of herboxidiene. In addition, we disclose a useful method for attachment of a 'dummy' side-chain to this core molecule.

Results and discussion

Preliminary synthetic considerations and confirmation of C-7 stereochemistry

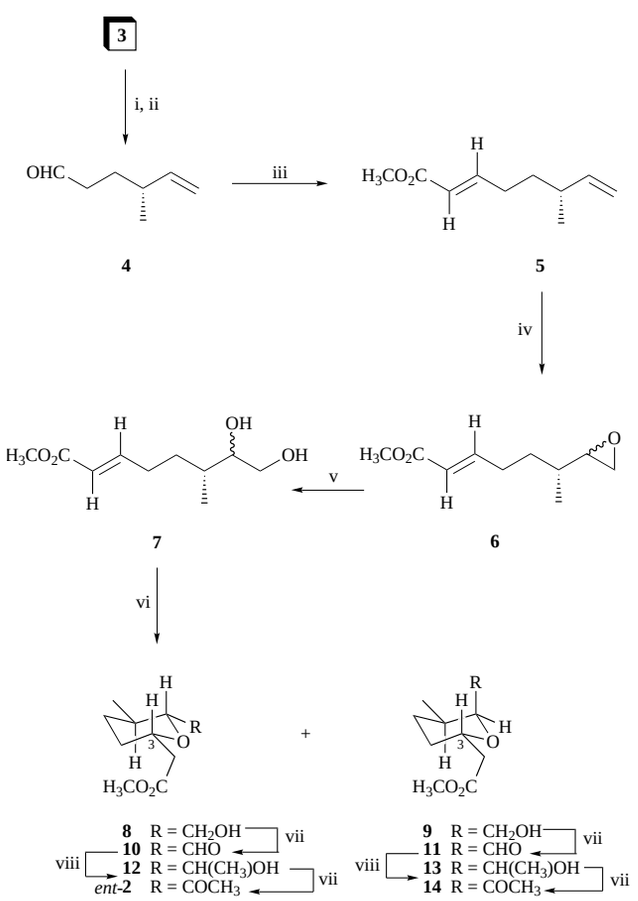
The tetrahydropyran **2** was chosen as our initial synthetic target because this material had been obtained during the degradation work[1,2] carried out on herboxidiene. Consequently, any pathway to herboxidiene which passed through this intermediate could provide reassurance, at a relatively early stage, that the synthesis was 'on track'. An obvious further attractive feature of compound **2** was that the C-7 acyl group should serve as a useful 'handle' for attachment of the side-chain (C-8 to C-19) of herboxidiene (**1**). (Tetrahydropyran-2′-yl)acetic acids and their derivatives have been obtained[5] in an efficient manner *via* intramolecular nucleophilic addition of an oxyanion to a tethered acrylate moiety. Such an approach to compound **2** was considered attractive not least because heteroatoms (*e.g.* nitrogen, sulfur, phosphorus) other than oxygen could be introduced into the six-membered ring associated with herboxidiene thereby providing a flexible route to a significant range of analogues.

With such general considerations in mind, our initial (1994) efforts were focussed on addressing the issue of the (relative) stereochemistry at C-7 in compounds **1** and **2**. To these ends a synthetic sequence was sought which would provide samples of both compound **2** and its C-7 epimer. This was achieved (Scheme 1) using cheap and commercially available (Fluka) (−)-β-citronellene (**3**) as starting material. Compound **3** was subjected to selective oxidative cleavage of the tetra-substituted double-bond using a modification of literature procedures[6,7] and the known aldehyde **4**[6,7] was thereby obtained in 50% yield. Subjection of compound **4** to a Wadsworth–Emmons reaction[8] with the anion derived from methyl diethylphosphonoacetate afforded a *ca.* 20:1 mixture (as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture) of the double unsaturated ester **5** and its (2*Z*)-isomer (85% combined yield). The former product (**5**) could be purified by MPLC but attempts to effect *cis*-dihydroxylation of the non-conjugated double-bond within this compound by using the Sharpless procedure (cat. OsO_4, Bu^{t}OOH)[9] failed because the conjugated double-bond reacted preferentially. In contrast, reaction of diene **5** with *m*-chloroperoxybenzoic acid (MCPBA) resulted in regioselective epoxidation of the terminal double bond and a 3:2 mixture of the diastereoisomeric epoxides **6** (96%) was obtained. Treatment of this mixture with aqueous perchloric acid[10] then gave the corresponding mixture of *vicinal*-diols **7**

Table 1 Comparison of the ^1H and ^{13}C NMR spectral data obtained from synthetically derived *ent*-**2** with those reported[2] for compound **2** [obtained by degradation of herboxidiene (**1**)][a]

δ_H	δ_C
Compound *ent*-**2**	
3.79 (m, 1H, H-3), 3.68 (s, 3H, OCH_3), 3.41 (d, *J* 10.2 Hz, 1H, H-7), 2.58 (dd, *J* 15.0 and 7.5 Hz, 1H, H-2), 2.45 (dd, *J* 15.0 and 5.6 Hz, 1H, H-2), 2.14 (s, 3H, $COCH_3$), 1.88 (ddd, *J* 13.2, 7.2 and 3.6 Hz, 1H), 1.70 (ddd, *J* 13.2, 6.0 and 3.6 Hz, 1H), 1.53 (m, 1H), 1.38 (m, 1H), 1.27 (m, 1H), 0.85 (d, *J* 7.0 Hz, 3H, CH_3)[c]	207.8 (s), 171.5 (s), 89.0 (d), 73.7 (d), 51.7 (q), 41.2 (t), 32.2 (t), 31.8 (q), 31.1 (t), 25.8 (d), 16.9 (q)[d]
Compound **2**[b]	
3.84–3.76 (m, 1H), 3.69 (s, 3H), 3.42 (d, *J* 10.5 Hz, 1H), 2.59 (dd, *J* 15 and 7.5 Hz, 1H), 2.46 (dd, *J* 15 and 5 Hz, 1H), 2.15 (s, 3H), 1.89 (ddd, *J* 13, 7 and 3.5 Hz, 1H), 1.71 (ddd, *J* 12.5, 5.5 and 2 Hz, 1H), 1.61–1.49 (m, 1H), 1.47–1.35 (m, 1H), 1.34–1.22 (m, 1H), 0.83 (d, *J* 6.5 Hz, 3H)	207.55 (s), 171.40 (s), 89.02 (d), 73.81 (d), 51.55 (q), 41.17 (t), 32.26 (t), 31.80 (q), 31.12 (t), 25.69 (d), 16.86 (q)

[a] All data obtained using $CDCl_3$ as solvent. [b] Data obtained from reference 2. [c] Data recorded at 300 MHz in $CDCl_3$. [d] Data recorded at 75 MHz in $CDCl_3$.



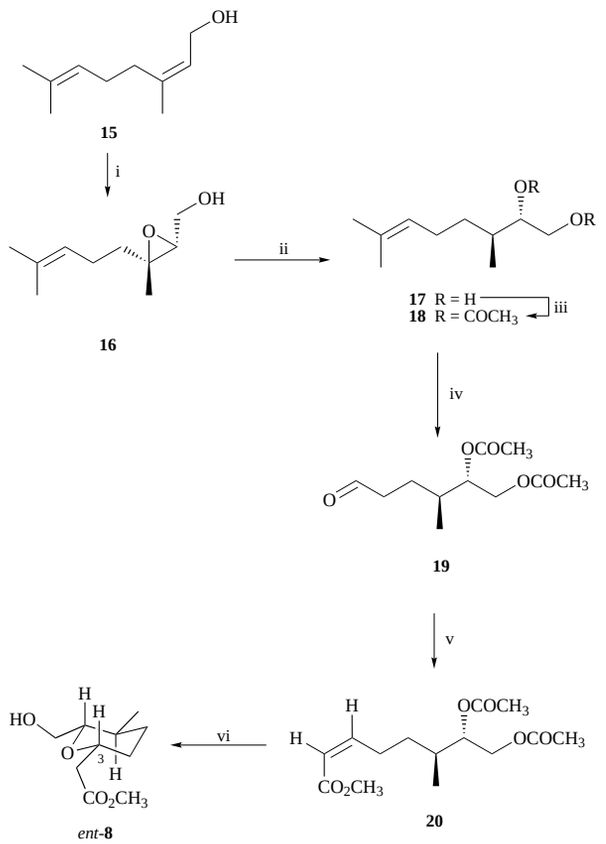
Scheme 1 *Reagents and conditions*: i, MCPBA (1.2 mol equiv.), $NaHCO_3$ (2 mol equiv.), CH_2Cl_2, 0–5 °C, 0.5 h; ii, $HClO_4$, H_2O–THF, 18 °C, 4 h then $Pb(OAc)_4$ (1.1 mol equiv.), Et_2O, 18 °C, 2 h; iii, $CH_3O_2CCH_2P(O)(OCH_2CH_3)_2$ (1 mol equiv.), NaH (1.3 mol equiv.), $CH_3OCH_2CH_2OCH_3$, 0 °C, *ca.* 2 h; iv, MCPBA (1.04 mol equiv.), CH_2Cl_2, 18 °C, 2 h; v, $HClO_4$, H_2O–THF, 18 °C, 16 h; vi, NaH (1.1 mol equiv.), THF, −78 to 18 °C, 1 h; vii, PCC (1.84 mol equiv.), NaOAc (0.7 mol equiv.), CH_2Cl_2, 18 °C, 3 h; viii, CH_3MgCl (1 mol equiv.), THF, −60 to 0 °C, 1.5 h

(65% combined yield). Reaction of these latter compounds with sodium hydride, under conditions established by Martin and co-workers,[11] resulted in an intramolecular Michael-addition reaction and the formation of a mixture of the hydroxymethyl-substituted tetrahydropyrans **8** and **9** (48% combined yield). These cyclisation products were accompanied by modest amounts (*ca.* 6%) of their respective C-3 epimers which could be removed by MPLC. However, compounds **8** and **9** could only be separated from one another by HPLC so, for preparative purposes, it was more convenient to subject the mixture to reaction with pyridinium chlorochromate (PCC)–sodium acetate.[12] Under such conditions the corresponding mixture of aldehydes **10** and **11** was obtained in 51% combined yield. Attempts to improve upon this yield by using other oxidants, including Swern-type reagents, were unsuccessful. Treatment of the mixture of aldehydes **10** and **11** with methylmagnesium chloride resulted in formation of the diastereoisomeric secondary alcohols **12** and **13** (79% combined yield) and these were subjected to reaction with PCC–sodium acetate. In this way the corresponding mixture of ketones *ent*-**2** and **14** was obtained (66% combined yield). These compounds were separated from one another by HPLC and each was characterised spectroscopically. The NMR, IR and mass spectral data obtained for *ent*-**2** were in excellent agreement with those reported[1,2] for compound **2** which had been obtained by degradation of herboxidiene (Table 1). In the 300 MHz ^1H NMR spectrum of *ent*-**2**, (herboxidiene numbering system) H-7 (δ 3.41) resonates as a doublet and the value of the vicinal coupling constant ($J_{7,6}$ = 10.2 Hz) implies a *trans*-diaxial relationship between H7 and H6.[13] In the analogous spectrum of compound **14** H-7 (δ 3.90) also appears as a doublet but now the magnitude of the vicinal coupling ($J_{7,6}$ = 3.0 Hz) suggests that this proton is equatorially orientated. For herboxidiene itself, H-7 appears as a doublet (at δ 3.34) and $J_{7,6}$ = 9.9 Hz. These data left little doubt that the C-7 substituents in both **1** and **2** are in the equatorial orientation—a conclusion confirmed by the recent report[2] from the Novartis and Geneva groups.

Development of a diastereoselective route to tetrahydropyran 2

A completely diastereoselective synthesis of tetrahydropyran **2** is shown in Scheme 2. This began with the Sharpless asymmetric epoxidation[14] of nerol (**15**) using diethyl (−)-tartrate as chiral ligand. However, like others,[15] we were only able to obtain modest enantiomeric excesses (ees) in this reaction.[15] On the basis of $[\alpha]_D$ determinations, the epoxy alcohol **16** (76%) used for the present work is calculated to be in *ca.* 50% ee. It is assumed, therefore, that all the products derived from this compound, including target **2**, are of comparable ee. While highly enriched (>95% ee) samples of **16** can be obtained by repeated recrystallisation of the derived 3,5-dinitrobenzoate[15b] this was not done for the reaction sequence described here.

Epoxide **16** was subjected to reductive cleavage with $NaCNBH_3$–BF_3·diethyl ether and the resulting diol **17**[16] (73%) then converted into the corresponding diacetate **18** (96%) under standard conditions. Ozonolytic cleavage of this last compound furnished the aldehyde **19** (97%) which was immediately subjected to Still's modification[17] of the Wadsworth–Emmons olefination reaction thereby ensuring almost exclusive formation of the (*Z*)-unsaturated ester **20** (78%). Confirmation that the *Z*-acrylate had been obtained followed from the observation that the spin-spin coupling between the two olefinic protons in compound **20** was of the order of 11.6 Hz. Treatment of acrylate **20** with potassium carbonate in methanol resulted in sequential acetate hydrolysis and intramolecular Michael reaction to give tetrahydropyran *ent*-**8** (88%). The C-3 epimer of *ent*-**8** was not detected in the reaction mixture and it is believed, on the basis of model studies,[18] that the (*Z*)-geometry about the double bond in **20** exerts a controlling influence in ensuring a *cis*-relationship between the anomeric substituents in the cyclisation product. Thus, the conversion **20**→*ent*-**8** is believed



Scheme 2 *Reagents and conditions*: i, reference 16; ii, reference 16; iii, $(CH_3CO)_2O$ (3.3 mol equiv.), DMAP (trace), pyridine, 18 °C, 3 h; iv, O_3, CH_2Cl_2, −60 °C, 0.25 h then PPh_3 (1 mol equiv.), −30 to 18 °C, 0.5 h; v, $CH_3O_2CCH_2P(O)(OCH_2CF_3)_2$ (1 mol equiv.), 18-C-6–MeCN complex (5 mol equiv.), $KN(TMS)_2$ (1 mol equiv.), THF, −78 °C, 1 h; vi, K_2CO_3 (5 mol equiv.), CH_3OH, 18 °C, 24 h then CH_3OH, H_2SO_4 (trace), 18 °C, 16 h

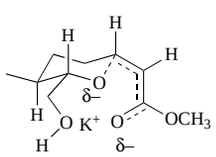
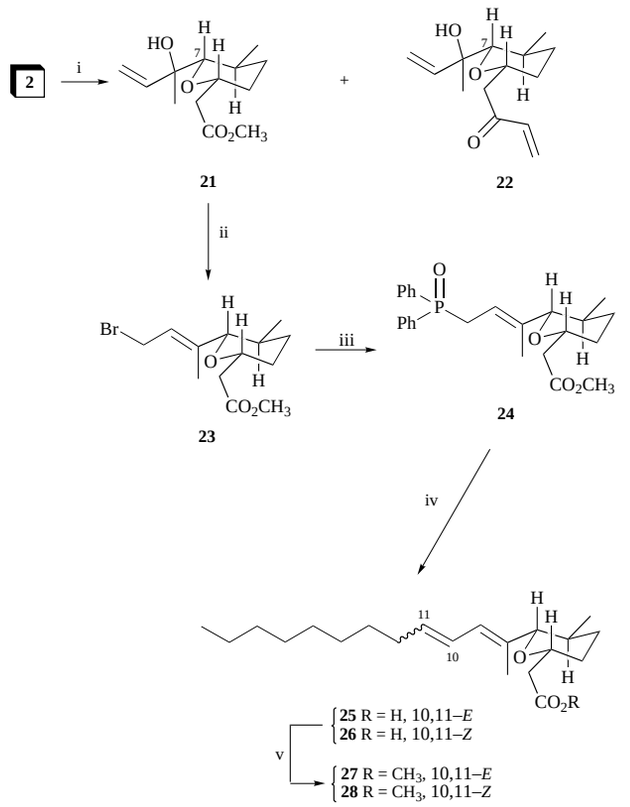


Fig. 1 Possible transition state structure associated with the cyclisation reaction leading to *ent*-**8**

to involve a stabilised transition state structure such as that depicted in Fig. 1 wherein chelation of the participating metal ion (K^+) by two partially negatively charged oxygens can only take place because of the *Z*-geometry about the double bond. The transformation of *ent*-**8** into compound **2** was readily achieved by the pathway established earlier for the enantiomeric series (Scheme 1). Thus, oxidation of alcohol *ent*-**8** gave *ent*-**10** (51%) which was immediately reacted with methylmagnesium chloride. Oxidation of the resulting mixture of diastereoisomeric diols *ent*-**12** (77%) then gave the target compound **2** {51%, $[a]_D$ −47.6 (*c* 0.9 in $CHCl_3$)}, the NMR, IR and mass spectra of which were identical with *ent*-**2**. The optical rotation of the sample of compound **2** obtained by degradation of herboxidiene has been reported[2] as $[a]_D$ −92.5 ($CHCl_3$) so the synthesis described here (Scheme 2) affords that enantiomer of keto ester **2** (albeit in *ca*. 50% ee at this stage) required for any projected synthesis of the naturally occurring antipode of herboxidiene.

Model studies pertaining to attachment of the side-chain

The manner in which the side-chain (C-8 to C-19) of herboxidiene is connected to the tetrahydropyranyl core is reminiscent of that seen in the ionophore antibiotic indanomycin (X-14547A). Consequently, we have applied certain aspects of the work of both the Nicolaou[19] and Ley[20] groups in their total syntheses of the latter compound for the purposes of attaching a model side-chain to the tetrahydropyranoid core of herboxidiene. To these ends, synthetically derived ketone **2** was



Scheme 3 *Reagents and conditions*: i, $H_2C{=}C(H)MgBr$ (1.1 mol equiv.), THF, −78 to 0 °C, 1 h; ii, PBr_3 (1.2 mol equiv.), Et_2O, 0 °C, 1 h; iii, Ph_2POEt (2 mol equiv.), THF, reflux, 2 h; iv, $H_3C(CH_2)_7CHO$ (1.2 mol equiv.), NaH (11 mol equiv.), THF, 45 °C, 2 h; v, CH_3OH, H_2SO_4 (trace), 18 °C, 3 h

reacted with vinylmagnesium bromide and in this way a diastereoisomerically pure allylic alcohol **21** (50% at 73% conversion) was obtained along with significant amounts (43% at 73% conversion) of the bis-vinylated material **22**. Compounds **21** and **22** could be readily separated from one another by flash chromatography on silica gel and the former compound was reacted with phosphorus tribromide in diethyl ether at 0 °C to give the rearranged allylic bromide **23** (91%). Reaction of primary bromide **23** with diphenylethoxyphosphine (Aldrich) in refluxing THF resulted in a Michaelis–Arbuzov reaction and formation of the phosphine oxide **24** (84%) which was obtained as a crystalline solid. Treatment of compound **24** with commercially available nonanal under standard Horner–Wittig conditions then gave a mixture of *E*,*E*-diene **25** and what is believed to be its 10,11-*Z*-isomer **26**. Interestingly, the Horner–Wittig reaction was accompanied by hydrolysis of the C-1 ester group, a feature which may prove useful in the final stages of the projected synthesis of herboxidiene itself. However, for the purposes of readily separating and then characterising the two coupling products the mixture was re-esterified under standard conditions (methanol–sulfuric acid) and the resulting esters (*ca*. 85 : 15 mixture of isomers, >94% combined yield from **24**) separated by semi-preparative HPLC on silica gel. The 300 MHz ^1H NMR spectrum of the major isomer, **27**, showed, *inter alia*, three distinct resonances due to alkenic protons, the lowest field of which (δ 6.24, doublet of doublets with $J_{10,11}$ = 14.9 Hz and $J_{10,9}$ = 10.6 Hz) is assigned to H-10. The resonance due to H-9 appears as a doublet ($J_{9,10}$ = 10.6 Hz) at δ 5.92 while that due to

H-11 appears as a multiplet centred at δ 5.66. These data are very similar to the analogous values derived from herboxidiene itself.[1] The magnitude (14.9 Hz) of the vicinal coupling between H-10 and H-11 is indicative of *E*-geometry about the 10,11-double bond within diene **27**. In the analogous spectrum of the minor diene, **28**, the resonances due to the alkenic protons were less definitive as far as assignment of double bond geometry was concerned. Thus, the signals due to H-9 and H-10 appeared as overlapping multiplets while the signal due to H-11 was an isolated but non-first order multiplet.

The results detailed above suggest that Wittig–Horner chemistry might be useful for connecting the side-chain[21] and core of herboxidiene to one another. Work aimed at achieving this outcome is currently underway in our laboratories. Kocienski and co-workers have demonstrated[3] that coupling of such fragments can also be effected using a modified Julia olefination reaction between a side-chain-based sulfone and a core-based aldehyde. However, like the approach described here, this method also leads to mixtures of isomeric dienes.

Biological evaluation of compounds 2, 21, 23–25 and 27

Compounds **2**, **21**, **23**–**25** and **27** were each subjected to a range of standard herbicidal assays but they did not show any useful phytotoxic properties. These results clearly suggest that the oxygenated side-chain of herboxidiene is critical for herbicidal activity.

Experimental

Melting points were recorded with a Kofler hot stage apparatus and are uncorrected. Proton (δ_H) and carbon (δ_C) NMR spectra were recorded with a Varian Unity 300, Varian Gemini 300 or JEOL GX-400 spectrometer operating at 300 or 400 MHz for proton and 75 or 100 MHz for carbon. All such spectra were recorded in deuteriochloroform ($CDCl_3$) solution at 22 °C. The protonicities (where cited) of the carbon atoms observed in ^{13}C NMR spectra were determined by distortionless enhancement polarisation transfer (DEPT) or attached proton test (APT) experiments. *J* Values are given in Hz. Infrared spectra (ν_{max}) were recorded with either a Perkin-Elmer 983G infrared spectrophotometer or a Perkin-Elmer 1800 Series FTIR spectrophotometer. Samples were analysed either as thin films on sodium chloride plates (for liquids) or as potassium bromide discs (for solids). Low resolution electron-impact mass spectra (*m*/*z*) were recorded at 70 eV on either a VG Micromass 7070F mass spectrometer or a JEOL AX-505H mass spectrometer. High resolution mass spectra were recorded using the VG Micromass 7070F instrument. Unless otherwise stated, optical rotations were measured in methanol at 22 °C using a Perkin-Elmer 241 Polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Medium pressure liquid chromatography (MPLC) was conducted using a Büchi 681 pump, Büchi 'plastiglass' columns packed with Kieselgel 60 (230–400 mesh ASTM) and a Büchi 684 fraction collector. Normal phase high performance liquid chromatography (HPLC) was conducted using an ISCO Model 2350 pump connected to an Exsil 100 semi-preparative column (1 × 25 cm). The components were detected using an ERMA ERC-7512 refractive index detector interfaced with a Spectra-Physics SP4270 integrator. Diethyl ether and tetrahydrofuran (THF) were distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc) and hexane were all distilled from calcium hydride. Unless otherwise specified, reactions were run at room temperature (18 °C).

(*R*)-4-Methylhex-5-enal 4

The conversion of (−)-β-citronellene (Fluka)† into compound **4** was achieved by the procedure of Paquette[6] and Kocienski.[7] Thus, a magnetically stirred mixture of citronellene **3** (20.0 g, 0.145 mol) and sodium hydrogen carbonate (24.3 g, 0.29 mol) in CH_2Cl_2 (500 ml) was cooled to 0 °C (ice–salt bath) then treated, portionwise, with MCPBA (80% peracid, 37.4 g, 0.17 mol). The reaction mixture was stirred at 0 °C for 0.5 h then quenched with $Na_2S_2O_5$ (250 ml of 1 M aqueous solution). The organic layer was separated, washed with $NaHCO_3$ (1 × 100 ml of saturated aqueous solution) and water (1 × 100 ml) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give (−)-β-citronellene monoepoxide (27.0 g, 0.16 mol, mixture of diastereoisomers) as a clear, colourless oil. This material was added dropwise to a magnetically stirred solution of $HClO_4$ (109 ml of a 0.07 M aqueous solution) in THF (400 ml). Stirring was continued overnight then the solvent was removed under reduced pressure and the residue extracted with diethyl ether (3 × 50 ml). The combined organic phases were washed with NaOH (1 × 20 ml of a 2 M aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. This material was subjected to Kugelrohr distillation (140 °C at 0.5 mmHg) thereby affording β-citronellene diol (18.6 g, 79%) as a colourless oil. A solution of this diol (11.0 g, 64 mmol) in diethyl ether (200 ml) was treated, portionwise, with lead tetraacetate (32.8 g, 70.2 mmol). The resulting mixture was stirred at room temperature for 2 h then the precipitated lead salts were removed by vacuum filtration through a pad of Celite. The filtrate was mixed with $NaHCO_3$ (100 ml of saturated aqueous solution) and extracted with diethyl ether (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and then concentrated under reduced pressure to give a light-yellow oil. This material was subjected to flash chromatography (silica gel, CH_2Cl_2 elution) to afford, after concentration of the appropriate fractions (R_F 0.8), the title compound **4**[6,7] (4.90 g, *ca*. 50% based on impurities present) as a clear colourless oil; ν_{max}(NaCl)/cm^{-1} 1728 and 1640; δ_H(300 MHz) 9.75 (1H, t, *J* 1.6), 5.61 (1H, m), 5.20–4.92 (2H, complex m), 2.42 (2H, m), 1.90 (1H, m), 1.73–1.50 (2H, complex m) and 1.01 (3H, d, *J* 6.7); δ_C(75 MHz) 202.6, 143.3, 113.8, 41.8, 37.4, 28.4 and 20.2; *m*/*z* 112 (M^+, 25%), 111 (16), 95 (100), 83 (20), 69 (29) and 55 (39).

(6*R*,2*E*)-Methyl 6-methylocta-2,7-dienoate 5

A nitrogen atmosphere was established above a magnetically stirred suspension of NaH (2.26 g of a 60% dispersion in mineral oil, 56 mmol) in 1,2-dimethoxyethane (DME) (60 ml) maintained at or below 10 °C with the aid of a water-bath. Methyl diethylphosphonoacetate (8.80 g, 42 mmol) was added dropwise to the reaction mixture which was stirred at room temperature for 1 h then cooled to −5 °C (ice–salt bath). (*R*)-4-Methylhex-5-enal **4** (4.80 g, *ca*. 42 mmol), obtained by the procedures defined above, was injected into the reaction mixture *via* syringe at such a rate that the (internal) temperature stayed below 0 °C. Stirring was continued at 0 °C for 0.5 h then at room temperature for 1 h. The reaction mixture was then poured onto ice (50 g) and extracted with diethyl ether (3 × 30 ml). The combined extracts were washed with water (3 × 20 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to MPLC (silica gel, 5:95 diethyl ether–hexane elution) and concentration of the appropriate fractions (R_F 0.5) afforded the title compound **5** (5.90 g, 81%) as a clear colourless oil; $[a]_D$ −9.2 (*c* 1.1); ν_{max}(NaCl)/cm^{-1} 2950, 1725, 1657, 1435, 1270, 1175, 1050, 990, 915 and 855; δ_H(300 MHz) 6.96 (1H, dt, *J* 15.8 and 6.8), 5.82 (1H, dt, *J* 15.8 and 1.7), 5.65 (1H, ddd, *J* 17.4, 10.3 and 7.6), 4.97 (2H, m), 3.72 (3H, s), 2.28–2.08 (3H, complex m), 1.44 (2H, q, *J* 7.6) and 1.01 (3H, d, *J* 6.6); δ_C(75 MHz) 167.1, 149.5, 143.7, 120.8, 113.3, 51.3, 37.3, 34.6, 29.9 and 20.1; *m*/*z* 169 ($M^+ + H$, 21%), 137 ($M^+ - OCH_3$, 69), 109 (33), 95 (100), 81 (84), 69 (46) (Found: $M^+ - OCH_3$, 137.0966. $C_{10}H_{16}O_2$ requires $M^+ - OCH_3$, 137.0966).

† This material is supplied in *ca*. 70% ee. On this basis, it is assumed that all of the derived compounds **4**–**14** and *ent*-**2** are of comparable ee.

(6*R*,7*R*,2*E*)-Methyl and (6*R*,7*S*,2*E*)-methyl 7,8-epoxy-6-methyloct-2-enoate 6

MCPBA (60% peracid, 6.84 g, 24 mmol) was added in portions to a magnetically stirred solution of ester **5** (3.90 g, 23 mmol) in CH_2Cl_2 (300 ml) maintained at 0 °C (ice–salt bath). The reaction mixture was allowed to warm to room temperature and after 2 h was filtered through a sintered-glass funnel. The filtrate was washed, successively, with $Na_2S_2O_5$ (1 × 30 ml of a 1 M aqueous solution) and $NaHCO_3$ (1 × 30 ml of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, CH_2Cl_2 elution) gave, after concentration of the appropriate fractions (R_F 0.6), the title compounds **6** (4.10 g, 96% of a 3:2 mixture of isomers) as a clear, colourless oil; ν_{max}(NaCl)/cm^{-1} 2960, 1725, 1655, 1445, 1275, 1210, 1180, 1045 and 985; δ_H(300 MHz) 6.97–6.89 (1H, complex m), 5.85–5.78 (1H, complex m), 3.70 (3H, s), 2.75–2.66 (2H, complex m), 2.52–2.43 (1H, complex m), 2.31–2.20 (2H, m), 1.57–1.26 (3H, complex m), 1.01 (3/5 × 3 H, d, *J* 6.5) and 0.94 (2/5 × 3H, d, *J* 6.8); δ_C(75 MHz) 167.0, 166.9, 149.1, 148.8, 121.1, 121.0, 56.7, 56.4, 51.4, 51.3, 46.6, 45.6, 35.8, 35.4, 32.9, 31.6, 29.6, 29.5, 16.7 and 15.7; *m*/*z* 185 (M^+ + H, 66%), 153 (M^+ − OCH_3, 100), 125 (29), 107 (51) and 95 (45).

(6*R*,7*R*,2*E*)-Methyl and (6*R*,7*S*,2*E*)-methyl 7,8-dihydroxy-6-methyloct-2-enoate 7

The 3:2 mixture of epoxides **6** (3.11 g, 16.9 mmol) obtained by the procedure outlined above was added dropwise to a magnetically stirred solution of $HClO_4$ (15 ml of 0.07 M aqueous solution) in THF (150 ml) maintained at room temperature. The resulting mixture was stirred at room temperature overnight then concentrated under reduced pressure and the residue extracted with diethyl ether (3 × 50 ml). The combined organic phases were washed with $NaHCO_3$ (1 × 20 ml of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil which was subjected to MPLC (silica gel, 5:95 CH_3OH–CH_2Cl_2 elution). Concentration of the appropriate fractions (R_F 0.5 in 1:9 CH_3OH–CH_2Cl_2) afforded a 3:2 mixture of the title compounds **7** (2.20 g, 65%) as a clear, colourless oil; ν_{max}(NaCl)/cm^{-1} 3400, 2950, 1720, 1652, 1434, 1280, 1208, 1171, 1122, 1034, 985 and 850; δ_H(300 MHz) 7.00–6.87 (1H, complex m), 5.74 (1H, d with further coupling, *J* 15.6), 3.69 (3H, s), 3.72–3.40 (3H, complex m), 2.95 (2H, s), 2.37–2.08 (2H, complex m), 1.78–1.50 (2H, complex m), 1.36–1.22 (1H, complex m) and 0.88 (3H, m); δ_C(75 MHz) 167.2(1), 167.1(7), 149.5, 149.3, 121.0, 120.9, 75.9, 75.6, 64.8, 64.6, 51.4, 35.4, 35.1, 31.2, 30.7, 29.7, 29.5, 15.1 and 14.2 (one resonance obscured or overlapping); *m*/*z* 185 (M^+ − OH, 11%), 171 (M^+ − OCH_3, 30), 139 (100), 109 (46), 81 (76) and 69 (62) (Found: M^+ − OH, 185.1177. $C_{10}H_{18}O_4$ requires M^+ − OH, 185.1178).

(2*S*,5*R*,6*R*)-Methyl 6-hydroxymethyl-5-methyltetrahydro-2*H*-pyran-2-acetate 8 and (2*S*,5*R*,6*S*)-methyl 6-hydroxymethyl-5-methyltetrahydro-2*H*-pyran-2-acetate 9

The 3:2 mixture of esters **7** (1.60 g, 7.9 mmol) was added to a magnetically stirred suspension of NaH (350 mg of a 60% dispersion in mineral oil, 8.75 mmol) in dry THF (50 ml) maintained at −78 °C (dry-ice–acetone bath). The reaction mixture was allowed to warm to 18 °C, stirred at this temperature for 1 h then poured onto ice (30 g). The resulting mixture was extracted with ethyl acetate (3 × 30 ml) and the combined organic phases washed with water (1 × 20 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil (900 mg). ^{1}H NMR spectroscopic analysis suggested this material was comprised of a *ca*. 12:6:1:1 mixture of tetrahydropyrans **8** and **9** as well as their C-3 (herboxidiene numbering) epimers. A portion (100 mg) of this mixture was subjected to semi-preparative HPLC (silica gel, 2:3 EtOAc–hexane elution, flow rate 2 ml min^{-1}). In this manner three fractions, A–C, were obtained.

Concentration of fraction A (t_R 11.4 min) afforded compound **8** (55 mg, ≡31%) as a clear, colourless oil; $[a]_D$ −4.9 (*c* 0.6); ν_{max}(NaCl)/cm^{-1} 3462, 2950, 2870, 1733, 1435, 1380, 1350, 1292, 1198, 1156, 1088 and 1019; δ_H(300 MHz) 3.81–3.75 (1H, complex m), 3.72 (1H, dd, *J* 11.7 and 2.8), 3.67 (3H, s), 3.49 (1H, dd, *J* 11.7 and 7.0), 3.10 (1H, m), 2.54 (1H, dd, *J* 15.1 and 7.5), 2.41 (1H, dd, *J* 15.1 and 5.4), 2.22 (1H, br s), 1.82–1.74 (1H, complex m), 1.71–1.63 (1H, complex m), 1.50–1.36 (1H, complex m), 1.36–1.16 (2H, complex m) and 0.82 (3H, d, *J* 6.6); δ_C(75 MHz) 171.6, 83.5, 74.0, 63.7, 51.6, 41.2, 32.1, 31.5, 31.2 and 17.1; *m*/*z* 184 (M^+ − H_2O, 13%), 171 (M^+ − OCH_3, 91), 139 (86), 129 (M^+ − $CH_2CO_2CH_3$, 57), 111 (50), 97 (67), 81 (40), 69 (47) and 59 (100) (Found: M^+ − H_2O, 184.1100. $C_{10}H_{18}O_4$ requires M^+ − H_2O, 184.1099).

Concentration of fraction B (t_R 11.9 min) afforded compound **9** (30 mg, ≡17%) as a clear colourless oil; $[a]_D$ +7.45 (*c* 0.5); ν_{max}(NaCl)/cm^{-1} 3467, 2934, 1741, 1437, 1173 and 1102; δ_H(300 MHz) 3.80 (1H, m), 3.69 (3H, s), 3.60 (2H, m), 3.43 (1H, m), 2.59 (1H, dd, *J* 15.1 and 7.8), 2.44 (1H, dd, *J* 15.1 and 5.6), 2.08 (1H, br s), 1.86–1.60 (3H, complex m), 1.54–1.44 (2H, complex m) and 0.91 (3H, d, *J* 6.9); δ_C(75 MHz) 171.8, 81.5, 75.0, 64.5, 51.8, 41.6, 31.0, 28.5, 26.1 and 12.1; *m*/*z* (70 eV) 203 (M^+ + H, 10%), 202 (M^+, 2), 184 (29), 171 (100), 139 (74), 129 (63) and 111 (48) (Found: M^+, 202.1203. $C_{10}H_{18}O_4$ requires M^+, 202.1205).

Concentration of fraction C (t_R 14.5 min) afforded a *ca*. 1:1 mixture of the *epi*-C-3 isomers of compounds **8** and **9** (10 mg, ≡6%) as a clear, colourless oil.

The crude reaction mixture could be subjected to MPLC in order to separate compounds **8** and **9** from their *epi*-C-3 isomers. The resulting mixture of **8** and **9** was then subjected to the next step of the reaction sequence.

(2*S*,5*R*,6*R*)-Methyl 6-formyl-5-methyltetrahydro-2*H*-pyran-2-acetate 10 and (2*S*,5*R*,6*S*)-methyl 6-formyl-5-methyltetrahydro-2*H*-pyran-2-acetate 11

The *ca*. 2:1 mixture of alcohols **8** and **9** (600 mg, 2.97 mmol) obtained by the procedure described above was added to a magnetically stirred mixture of PCC (1.18 g, 5.47 mmol) and sodium acetate (180 mg, 2.19 mmol) in CH_2Cl_2 (20 ml). After 3 h the reaction mixture was filtered through a pad of Celite and the filtrate concentrated under reduced pressure to give a yellow oil (450 mg) which contained an inseparable *ca*. 2:1 mixture of compounds **10** and **11**. This material was used for the next step of the reaction sequence.

Treatment of the purified alcohol **8** with PCC under the conditions just described afforded a yellow oil which was subjected to MPLC (silica gel, 2:3 EtOAc–hexane). Concentration of the appropriate fractions (R_F 0.3) then gave aldehyde **10** (51%) as a clear, colourless oil; ν_{max}(NaCl)/cm^{-1} 2925, 2860, 1740, 1445, 1380, 1200, 1085, 1020, 855 and 810; δ_H(300 MHz) 9.55 (1H, d, *J* 2.4), 3.88–3.78 (1H, complex m), 3.71 (3H, s), 3.44 (1H, dd, *J* 10.6 and 2.4), 2.64 (1H, dd, *J* 15.4 and 7.7), 2.47 (1H, dd, *J* 15.4 and 5.4), 1.97–1.89 (1H, complex m), 1.78–1.72 (1H, complex m), 1.68–1.53 (1H, complex m), 1.50–1.25 (2H, complex m) and 0.95 (3H, d, *J* 6.5); δ_C(75 MHz) 200.7, 171.5, 86.7, 73.6, 51.7, 41.0, 32.1, 30.8, 30.5 and 16.4; *m*/*z* 171 (M^+ − CHO, 100%), 139 (96), 127 (43), 111 (45), 97 (100), 81 (43) and 59 (69) (Found: M^+ − CHO, 171.1022. $C_{10}H_{16}O_4$ requires M^+ − CHO, 171.1021).

(2*S*,5*R*,6*R*)-Methyl 6-[(1*RS*)-1-hydroxyethyl]-5-methyltetrahydro-2*H*-pyran-2-acetate 12 and (2*S*,5*R*,6*S*)-methyl 6-[(1*RS*)-1-hydroxyethyl]-5-methyltetrahydro-2*H*-pyran-2-acetate 13

Methylmagnesium chloride (0.75 ml of a 3 M solution in THF,

2.25 mmol) was added dropwise to a magnetically stirred solution of a *ca*. 2:1 mixture of aldehydes **10** and **11** (450 mg, 2.25 mmol) in THF (10 ml) maintained at −60 °C under a nitrogen atmosphere. After addition was complete the reaction mixture was allowed to warm to 0 °C then stirred at this temperature for 1 h before being poured into a mixture of ice (10 g) and NH_4Cl (10 ml of a saturated aqueous solution). The resulting mixture was extracted with diethyl ether (3 × 20 ml) and the combined organic phases washed with water (1 × 30 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil (400 mg, *ca*. 79% yield) consisting of an inseparable mixture of compounds **12** and **13**. This material could be used for the next step of the reaction sequence.

Subjection of the purified aldehyde **10** to reaction with methylmagnesium chloride under the conditions just described afforded a yellow oil which was subjected to flash chromatography (silica gel, 2:3 EtOAc–hexane elution). Concentration of the appropriate fractions (R_F 0.2) then gave alcohol **12** (77%, *ca*. 4:1 mixture of diastereoisomers) as a clear, colourless oil; ν_{max}(NaCl)/cm^{-1} 3490, 2940, 2855, 1745, 1440, 1370, 1200, 1080, 900 and 820; δ_C(75 MHz) (major isomer) 177.0, 85.9, 74.4, 66.2, 51.6, 41.3, 32.4, 31.6, 30.6, 20.7 and 17.3; *m*/*z* 185 ($M^+ - OCH_3$, 9%) 171 (87), 139 (100), 111 (45), 97 (92), 71 (39) and 55 (53) (Found: $M^+ - OCH_3$, 185.1177. $C_{11}H_{20}O_4$ requires $M^+ - OCH_3$, 185.1178).

(2*S*,5*R*,6*R*)-Methyl 6-acetyl-5-methyltetrahydro-2*H*-pyran-2-acetate *ent*-2 and (2*S*,5*R*,6*S*)-methyl 6-acetyl-5-methyltetrahydro-2*H*-pyran-2-acetate 14

The *ca*. 1:1 mixture of alcohols **12** and **13** (400 mg, 1.85 mmol) obtained by the procedure outlined above was added to a magnetically stirred mixture of PCC (400 mg, 1.85 mmol) and sodium acetate (55 mg, 0.67 mmol) in CH_2Cl_2 (80 ml). The resulting mixture was stirred at 18 °C for 3 h then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a 1:1 mixture of keto esters *ent*-**2** and **14** (260 mg, 66%) as a pale-yellow oil. A portion (130 mg) of this material was subjected to semi-preparative HPLC (silica gel, 3:7 EtOAc–hexane elution, flow rate 2 ml min^{-1}) and in this manner two major fractions, A and B, were obtained.

Concentration of fraction A (t_R 11.2 min) afforded compound *ent*-**2** (68 mg, ≡34%) as a clear colourless oil; ν_{max}(NaCl)/cm^{-1} 2951, 2927, 1738, 1717, 1434, 1353, 1273, 1227, 1198, 1160, 1145, 1083 and 1021; δ_H and δ_C see Table 1; *m*/*z* (CI, methane) 215 ($M^+ + H$, 4%), 171 ($M^+ - COCH_3$, 88), 139 ($M^+ - CH_3OH - COCH_3$, 80) and 97 (100) (Found: $M^+ + H$, 215.1276. $C_{11}H_{18}O_4$ requires $M^+ + H$, 215.1283).

Concentration of fraction B (t_R 12.7 min) afforded compound **14**‡ (50 mg, ≡25%) as a clear, colourless oil; ν_{max}(NaCl)/cm^{-1} 2933, 1734, 1435, 1353, 1286, 1169 and 1068; δ_H(300 MHz)§ 3.90 (1H, d, *J* 3.0, H-7), 3.83 (1H, m, H-3), 3.70 (3H, s, OCH_3), 2.65 (1H, dd, *J* 15.0 and 7.8, H-2), 2.49 (1H, dd, *J* 15.0 and 5.4, H-2), 2.20 (1H, m), 2.12 (3H, s, $COCH_3$), 1.80 (1H, m), 1.69 (1H, m), 1.62–1.42 (2H, complex m), and 0.87 (3H, d, *J* 6.5, CH_3); δ_C(75 MHz) 210.2, 171.6, 85.5, 75.2, 51.7, 41.3, 30.1, 29.3, 27.3, 25.5, 12.2; *m*/*z* (CI, methane) 215 ($M^+ + H$, 4%), 187 (68), 171 ($M^+ - COCH_3$, 100).

(2*R*,3*S*)-3,7-Dimethyl-2,3-epoxyoct-6-en-1-ol 16

Titanium tetraisopropoxide (1.10 g, 3.84 mmol), diethyl D-(−)-tartrate (1.20 g, 5.76 mmol), and *tert*-butyl hydroperoxide (18.7 ml of a 2 M solution in *tert*-butyl alcohol, 0.150 mmol) were added, sequentially and *via* syringe, to a magnetically stirred suspension of powdered, commercially activated 4 Å molecular sieves (2.16 g) in CH_2Cl_2 (150 ml) maintained at −20 °C (dry-ice–CCl_4) under an atmosphere of nitrogen. The resulting mixture was stirred at this temperature for 0.25 h then a solution of nerol **15** (12.0 g, 77.9 mmol) in CH_2Cl_2 (20 ml) was added *via* syringe. The ensuing mixture was stirred at −20 °C for 2 h then allowed to warm to 0 °C and quenched with water (25 ml) then sodium hydroxide–sodium chloride (5.4 ml of 30% aqueous sodium hydroxide solution saturated with sodium chloride). The organic phase was separated then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colourless oil. This material was subjected to MPLC (silica gel, 2:3 EtOAc–hexane elution) and concentration of the appropriate fractions (R_F 0.6) afforded the title compound **16**[14,15] (10.1 g, 76%) as a clear, colourless oil; $[\alpha]_D$ +6.6 (*c* 4.08); δ_C(75 MHz) 132.3, 123.2, 64.4, 61.5, 61.1, 33.1, 25.5, 24.1, 22.1 and 17.5.

(2*S*,3*S*)-3,7-Dimethyloct-6-ene-1,2-diol 17

Sodium cyanoborohydride (95%, 7.80 g, 118 mmol) was added in one portion to a magnetically stirred solution of epoxide **16** (7.00 g, 41.2 mmol) in THF (200 ml) containing bromocresol green (10 mg). BF_3·diethyl ether (*ca*. 12 ml) was added dropwise until a yellow colour persisted. The course of reaction was then followed by analytical TLC and when all of the starting epoxide had been consumed (~5 h) the reaction mixture was quenched with HCl (9 ml of 6 M aqueous solution). The resulting mixture was filtered through a 2 cm deep pad of TLC grade silica gel and the filtrate was neutralised with NaOH (10% w/v aqueous solution) then extracted with diethyl ether (3 × 50 ml). The combined organic phases were washed with $NaHCO_3$ (1 × 50 ml of a saturated aqueous solution) and water (1 × 50 ml) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to MPLC (silica gel, 3:2 EtOAc–hexane elution) and concentration of the appropriate fractions (R_F 0.3) afforded the title diol **17**[16] (5.20 g, 73%) as a clear, colourless oil; $[\alpha]_D$ −4.2 (*c* 2.9); ν_{max}(NaCl)/cm^{-1} 3359 (br), 2962, 2919, 1452, 1374 and 1056; δ_H(300 MHz) 5.07 (1H, tm, *J* 7.0), 3.64 (1H, m), 3.47 (2H, d, *J* 6.6), 3.42 (2H, br s), 2.12–1.97 (1H, complex m), 1.97–1.84 (1H, m), 1.66 (3H, s), 1.58 (3H, s), 1.62–1.48 (2H, m), 1.23–1.07 (1H, m) and 0.87 (3H, d, *J* 6.9); δ_C(75 MHz) 131.5, 124.4, 76.2, 64.4, 35.7, 32.5, 25.6, 25.3, 17.6 and 15.0; *m*/*z* 172 (M^+, 26%), 141 ($M^+ - CH_2OH$, 10), 123 (37), 95 (34), 82 (100), 69 (72) and 55 (64) (Found: M^+, 172.1464. $C_{10}H_{20}O_2$ requires M^+, 172.1463).

(6*S*,7*S*)-7,8-Diacetoxy-2,6-dimethyloct-2-ene 18

Diol **17** (5.20 g, 30.3 mmol) was dissolved in pyridine (20 ml) containing acetic anhydride (9.8 ml, 100 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (10 mg). The reaction mixture was stirred at room temperature for 3 h then poured onto ice (50 g) and extracted with diethyl ether (1 × 100 ml). The separated organic phase was washed with HCl (2 × 20 ml of a 1 M aqueous solution), $NaHCO_3$ (2 × 20 ml of a saturated aqueous solution) and brine (1 × 20 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give diacetate **18** (7.40 g, 96%) as a clear colourless oil; R_F 0.85 (silica gel, 1:1 EtOAc–hexane elution); $[\alpha]_D$ +8.3 (*c* 4.9); ν_{max}(NaCl)/cm^{-1} 2967, 2925, 1734, 1453, 1370, 1231 and 1048; δ_H(300 MHz) 5.04 (1H, tm, *J* 7.7), 4.94 (1H, m), 4.26 (1H, dd, *J* 12.7 and 3.1), 4.03 (1H, dd, *J* 12.7 and 7.6), 2.04 (3H, s), 2.01 (3H, s), 2.00–1.70 (3H, complex m), 1.65 (3H, s), 1.57 (3H, s), 1.50–1.30 (1H, complex m), 1.21–1.09 (1H, complex m) and 0.91 (3H, d, *J* 6.8); δ_C(75 MHz) 170.7, 170.5, 131.8, 123.9, 74.9, 63.5, 33.8, 32.2, 25.6, 25.2, 21.0, 20.7, 17.6 and 15.0; *m*/*z* 256 (M^+, 1%), 196 ($M^+ - CH_3CO_2H$, 3), 154 (3), 121 (33), 82 (100) and 69 (33) (Found: M^+, 256.1675. $C_{14}H_{24}O_4$ requires M^+, 256.1675).

(4*S*,5*S*)-5,6-Diacetoxy-4-methylhexanal 19

A solution of diacetate **18** (5.50 g, 21.5 mmol) in CH_2Cl_2 (300

‡ The instability of this compound has precluded the acquisition of the usual range of spectroscopic and/or analytical data.
§ NMR assignments based on the herboxidiene numbering system.

ml) was cooled to −60 °C then treated with a stream of ozone gas until a blue colour persisted. The reaction mixture was then warmed to −30 °C and triphenylphosphine (5.50 g, 21.5 mmol) carefully added in portions. After the addition was complete, the reaction mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue was subjected to MPLC (silica gel, 1:3 EtOAc–hexane elution) and concentration of the appropriate fractions (R_F 0.6 in 1:1 EtOAc–hexane) gave the title compound **19**‡ (4.78 g, 97%) as a clear, colourless oil; $[a]_D$ +3.8 (*c* 2.0); ν_{max}(NaCl)/cm^{-1} 2964, 1739, 1370, 1227 and 1047; δ_H(300 MHz) 9.73 (1H, t, *J* 1.4), 4.91 (1H, td, *J* 6.4 and 3.2), 4.27 (1H, dd, *J* 12.5 and 2.9), 4.02 (1H, dd, *J* 12.5 and 6.5), 2.56–2.20 (2H, complex m), 2.03 (3H, s), 2.00 (3H, s), 1.88–1.62 (2H, complex m), 1.52–1.36 (1H, complex m), 0.90 (3H, d, *J* 2.9); δ_C(75 MHz) 201.7, 170.7, 170.5, 74.4, 63.3, 41.1, 33.5, 24.0, 20.9, 20.7 and 15.0; *m*/*z* 201 (M^+ − CHO, 1%), 187 (M^+ − CH_3CO, 4), 145 (29) and 97 (100).

(6*S*,7*S*,2*Z*)-Methyl 7,8-diacetoxy-6-methyloct-2-enoate 20

$KN(TMS)_2$ (26.1 ml of a 0.5 M solution in toluene, 13 mmol) was added dropwise to a magnetically stirred solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (4.15 g, 13 mmol) and 18-crown-6–CH_3CN complex (20.0 g, 65.2 mmol) in dry THF (50 ml) maintained at −78 °C under an atmosphere of nitrogen. The reaction mixture was stirred at −78 °C for 0.25 h then treated with aldehyde **19** (3.00 g, 13.0 mmol). After 1 h at this temperature, the reaction mixture was quenched with NH_4Cl (20 ml of a saturated aqueous solution) then allowed to warm to room temperature. The resulting mixture was extracted with diethyl ether (3 × 50 ml), the combined organic phases were washed with water (1 × 100 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to MPLC (silica gel, 35:65 EtOAc–hexane elution) and concentration of the appropriate fractions (R_F 0.6) gave the title compound **20** (2.92 g, 78%) as a clear, colourless oil; $[a]_D$ +9.4 (*c* 5.1); ν_{max}(NaCl)/cm^{-1} 2951, 1738, 1721, 1642, 1437, 1369, 1226, 1175, 1049 and 821; δ_H(300 MHz) 6.15 (1H, dt, *J* 11.6 and 7.7), 5.74 (1H, d, *J* 11.6), 4.91 (1H, td, *J* 6.9 and 3.0), 4.25 (1H, dd, *J* 12.0 and 3.0), 4.02 (1H, dd, *J* 12.0 and 7.4), 3.65 (3H, s), 2.64 (2H, m), 2.02 (3H, s), 2.00 (3H, s), 1.78 (1H, m), 1.53 (1H, m), 1.25 (1H, m) and 0.92 (3H, d, *J* 6.9); δ_C(75 MHz) 170.7, 170.4, 166.5, 149.7, 119.6, 74.8, 63.4, 50.9, 33.9, 31.3, 26.2, 20.9, 20.7 and 14.9; *m*/*z* 286 (M^+, 5%), 187 (61), 171 (42), 139 (56), 127 (78), 113 (70), 97 (85), 81 (90), 71 (55) and 53 (100) (Found: M^+ − OCH_3, 255.1225. $C_{14}H_{22}O_6$ requires M^+ − OCH_3, 255.1232).

(2*R*,5*S*,6*S*)-Methyl 6-hydroxymethyl-5-methyltetrahydro-2*H*-pyran-2-acetate *ent*-8

A mixture of ester **20** (2.00 g, 7.00 mmol), K_2CO_3 (4.83 g, 35 mmol) and methanol (10 ml) was stirred at room temperature for 24 h then filtered through a sintered-glass funnel. The filtrate was dissolved in water (50 ml) and acidified to pH 2–3 with HCl (concentrated aqueous solution). The resulting mixture was extracted with diethyl ether (3 × 50 ml) and the combined extracts dried ($MgSO_4$), filtered and then concentrated under reduced pressure. The oil obtained in this manner was suspended in methanol (20 ml) containing 98% H_2SO_4 (three drops) and the resulting mixture stirred at room temperature for 16 h then poured onto ice (50 g) and extracted with diethyl ether (3 × 50 ml). The combined organic extracts were washed with $NaHCO_3$ (1 × 50 ml of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the title compound *ent*-**8** (1.25 g, 88%) as a clear, colourless oil; $[a]_D$ +3.8 (*c* 4.3). This material was identical, by ^{1}H NMR, ^{13}C NMR and infra-red spectroscopy as well as mass spectrometry, with compound **8** obtained earlier.

(2*R*,5*S*,6*S*)-Methyl 6-formyl-5-methyltetrahydro-2*H*-pyran-2-acetate *ent*-10

The alcohol *ent*-**8** (800 mg, 4 mmol) was stirred with PCC (860 mg, 4 mmol) and sodium acetate (120 mg, 1.5 mmol) in CH_2Cl_2 (20 ml) at room temperature for 3 h. The by now black reaction mixture was filtered through a sintered-glass funnel and the filtrate concentrated under reduced pressure. The residue was subjected to MPLC (silica gel, 2:3 EtOAc–hexane elution) to give, after concentration of the appropriate fractions (R_F 0.3, silica gel, 15:85 EtOAc–hexane elution), the title aldehyde *ent*-**10** (400 mg, 51%) as a clear colourless oil. This material was identical, by ^{1}H NMR, ^{13}C NMR and infra-red spectroscopy as well as mass spectrometry, with compound **10** obtained earlier.

(2*R*,5*S*,6*S*)-Methyl 6-[(1*RS*)-1-hydroxyethyl]-5-methyltetrahydro-2*H*-pyran-2-acetate *ent*-12

Subjection of the aldehyde *ent*-**10** (600 mg, 3 mmol) to reaction with methylmagnesium chloride (1 mol equiv.) under the same conditions as described for enantiomer **10** afforded a light-yellow oil which was subjected to flash chromatography (silica gel, 2:3 EtOAc–hexane). Concentration of the appropriate fractions (R_F 0.2) then gave the title alcohol *ent*-**12** (500 mg, 77%, *ca*. 4:1 mixture of diastereoisomers) as a clear, colourless oil. This material was identical, by ^{1}H NMR, ^{13}C NMR and infra-red spectroscopy as well as mass spectrometry, with compound **12** obtained earlier.

(2*R*,5*S*,6*S*)-Methyl 6-acetyl-5-methyltetrahydro-2*H*-pyran-2-acetate 2

DMSO (0.37 ml, 4.8 mmol) was added dropwise to a magnetically stirred solution of oxalyl chloride (0.2 ml, 2.4 mmol) in CH_2Cl_2 (30 ml) maintained at −60 °C under a nitrogen atmosphere. The reaction mixture was stirred at this temperature for 0.16 h then the mixture of alcohols *ent*-**12** (400 mg, 2.0 mmol) was injected *via* syringe. The reaction mixture, which had become cloudy, was stirred at −60 °C for 1 h. After this time, triethylamine (2 ml) was added to the reaction mixture which was then allowed to warm to room temperature. Water (30 ml) was then added and the organic phase was separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the light-yellow oil thereby obtained to flash chromatography (silica gel, 2:3 EtOAc–hexane elution) afforded, after concentration of the appropriate fractions (R_F 0.6), the title compound **2**[1,2] (220 mg, 51%) as a clear, colourless oil; $[a]_D$ −47.6 (*c* 0.9; $CHCl_3$). Compound **2** produced in this manner was identical, by ^{1}H NMR, ^{13}C NMR and infra-red spectroscopy as well as mass spectrometry, with enantiomer *ent*-**2** obtained earlier.

(2*R*,5*S*,6*S*)-Methyl 6-[(1*R* or *S*)-1-hydroxy-1-methylprop-2-enyl]-5-methylpyran-2-acetate 21

Vinylmagnesium bromide (2.57 ml of a 1 M solution in THF, 2.57 mmol) was added dropwise to a magnetically stirred solution of ketone **2** (500 mg, 2.34 mmol) in THF (100 ml) maintained at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred at −78 °C for a further 1 h then warmed to 0 °C, poured into NH_4Cl (200 ml of a saturated aqueous solution) and extracted with diethyl ether (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and then concentrated under reduced pressure to give a light-yellow oil (520 mg) which was subjected to flash chromatography (silica gel; 1:4 EtOAc–hexane elution). In this way fractions containing three major components, A–C, were obtained.

Concentration of the fractions containing component A (R_F 0.5) afforded the starting ketone **2** (136 mg, 27% recovery) as a clear, colourless oil. This material was identical, in all respects, with an authentic sample.

Concentration of the fractions containing component B (R_F 0.4) afforded the title alcohol **21** (206 mg, 50% at 73% conver-

sion, single diastereoisomer) as a clear, colourless oil; ν_{max}(NaCl)/cm^{-1} 3511, 2931, 1741, 1437, 1380, 1282, 1202, 1081, 1021 and 920; δ_H(300 MHz) 5.92 (1H, dd, *J* 17.5 and 11.8), 5.35 (1H, d, *J* 17.5), 5.12 (1H, d, *J* 11.8), 3.82–3.70 (1H, complex m), 3.68 (3H, s), 2.91 (1H, d, *J* 9.2), 2.75 (1H, br s), 2.55–2.30 (2H, complex m), 1.85–1.80 (2H, complex m), 1.57–1.28 (3H, complex m), 1.25 (3H, s) and 0.84 (3H, d, *J* 5.9); δ_C(75 MHz) 171.7, 142.6, 114.0, 88.8, 74.6, 74.0, 51.7, 41.1, 33.6, 32.3, 31.7, 22.4 and 19.1; *m*/*z* 242 (M^+, 2%), 225 ($M^+ - OH$, 9), 211 (20), 171 (100), 139 (92), 111 (39), 97 (75) and 71 (47) (Found: M^+, 242.1528. $C_{13}H_{22}O_4$ requires M^+, 242.1518).

Concentration of the fractions containing component C (R_F 0.3) afforded compound **22** (177 mg, 43% at 73% conversion) as a clear, colourless oil; ν_{max}(NaCl)/cm^{-1} 3502, 2931, 1679, 1615, 1410, 1080, 1020 and 921; δ_H(300 MHz) 6.45–6.15 (2H, complex m), 5.98–5.82 (2H, complex m), 5.34 (1H, dd, *J* 17.4 and 1.4), 5.12 (1H, dd, *J* 10.6 and 1.4), 3.89–3.73 (1H, complex m), 2.96–2.82 (2H, complex m), 2.58 (1H, dd, *J* 16.0 and 4.8), 1.80–1.52 (2H, complex m), 1.51–1.20 (4H, complex m), 1.21 (3H, s) and 0.81 (3H, d, *J* 6.4); δ_C(75 MHz) 198.9, 142.5, 137.0, 128.8, 114.0, 88.9, 74.8, 74.0, 45.8, 33.7, 32.3, 32.1, 22.4 and 19.2; *m*/*z* 221 ($M^+ - OH$, 5%), 171 (18), 167 (19), 139 (22), 121 (44), 97 (64), 71 (29) and 55 (100) (Found: $M^+ - OH$, 221.1542. $C_{14}H_{22}O_3$ requires $M^+ - OH$, 221.1542).

(2*R*,5*S*,6*S*)-Methyl 6-(3-bromo-1-methylprop-1-enyl)-5-methylpyran-2-acetate 23

PBr_3 (270 mg, 1 mmol) was injected, *via* syringe, into a magnetically stirred solution of alcohol **21** (200 mg, 0.83 mmol) in diethyl ether (20 ml) maintained at 0 °C under a nitrogen atmosphere. After the addition was complete, the reaction mixture was stirred at 0 °C for a further 1 h and then poured onto ice (*ca*. 20 g). The resulting mixture was extracted with diethyl ether (1 × 30 ml) and the separated organic phase then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 1:9 EtOAc–hexane elution) afforded, after concentration of the appropriate fractions (R_F 0.4), the title bromide **23**‡ (230 mg, 91%) as a clear, colourless oil; $[\alpha]_D$ −5.2 (*c* 1.5); ν_{max}(NaCl)/cm^{-1} 2926, 1740, 1291, 1200, 1070, 1020 and 865; δ_H(300 MHz) 5.69 (1H, t, *J* 6.6), 4.00 (2H, m), 3.75 (1H, m), 3.65 (3H, s), 3.34 (1H, d, *J* 9.5), 2.58 (1H, dd, *J* 15.4 and 6.6), 2.39 (1H, dd, *J* 15.4 and 6.6), 1.89–1.75 (1H, complex m), 1.68 (3H, s), 1.61–1.41 (2H, complex m), 1.39–1.11 (2H, complex m) and 0.71 (d, *J* 6.7, 3H); δ_C(75 MHz) 171.7, 141.4, 123.9, 89.5, 73.8, 51.5, 41.2, 32.3, 32.2, 31.5, 28.1, 17.4 and 11.5.

(2*R*,5*S*,6*S*)-Methyl 6-(3-diphenylphosphinoyl-1-methylprop-1-enyl)-5-methylpyran-2-acetate 24

A magnetically stirred solution of bromide **23** (200 mg, 0.66 mmol) and diphenylethoxyphosphine (304 mg, 1.32 mmol) in THF (10 ml) was heated at reflux until the starting materials had been consumed (*ca*. 2 h) as determined by TLC analysis. The solvent was then removed under reduced pressure and the resulting solid was recrystallised (diethyl ether) to give the phosphine oxide **24** (235 mg, 84%) as a fine white powder, mp 125–126 °C; R_F 0.3 (silica gel, 3:2 EtOAc–hexane elution); $[\alpha]_D$ −32.8 (*c* 0.5); ν_{max}(NaCl)/cm^{-1} 2952, 2929, 2851, 1733, 1437, 1181, 1121, 1103, 1070, 1019, 751, 721, 697, 557 and 513; δ_H(300 MHz) 7.78 (4H, m), 7.50 (6H, m), 5.50 (1H, m), 3.70 (1H, m), 3.68 (3H, s), 3.38–2.93 (3H, complex m), 2.58 (1H, dd, *J* 15.1 and 6.3), 2.39 (1H, dd, *J* 15.1 and 6.6), 2.02–1.58 (2H, complex m), 1.52 (3H, br s), 1.50–1.02 (3H, complex m), 0.43 (3H, d, *J* 6.0); *m*/*z* 427 (M^+, 21%), 426 (M^+, 61), 395 ($M^+ - OCH_3$, 12), 324 (25), 285 (21), 217 (27), 203 (40), 202 (100), 201 (85), 149 (25), 125 (11), 77 (41) (Found: M^+, 426.1965; C, 70.6; H, 7.8; P, 7.6. $C_{25}H_{31}O_4P$ requires M^+, 426.1960; C, 70.4; H, 7.3; P, 7.3%).

(2*R*,5*S*,6*S*)-Methyl 5-methyl-6-[(2*E*,4*E*)-trideca-2,4-dien-2-yl]-pyran-2-acetate 27 and (2*R*,5*S*,6*S*)-methyl 5-methyl-6-[(2*E*,4*Z*)-trideca-2,4-dien-2-yl]pyran-2-acetate 28

Phosphine oxide **24** (100 mg, 0.23 mmol) and nonanal (40 mg, 0.28 mmol) were added to a magnetically stirred suspension of NaH (100 mg of a 60% dispersion in mineral oil, 2.5 mmol) in dry THF (10 ml) maintained under a nitrogen atmosphere. The resulting mixture was warmed to 45 °C and stirred at this temperature for 2 h then cooled to room temperature and poured onto ice (20 g). The solution so obtained was acidified to pH 2–3 with HCl (concentrated aqueous solution) and extracted with diethyl ether (3 × 20 ml). The combined organic extracts were washed with water (1 × 50 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil, consisting of a mixture of free-acids **25** and **26**, was suspended in methanol (10 ml) containing 98% H_2SO_4 (three drops). The resulting mixture was stirred magnetically at room temperature for 3 h then poured onto ice (20 g) and extracted with diethyl ether (3 × 50 ml). The combined organic phases were washed with $NaHCO_3$ (1 × 20 ml of a saturated aqueous solution) and brine (1 × 20 ml) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a colourless oil (*ca*. 80 mg). This material was subjected to semi-preparative HPLC (silica gel, 5:95 EtOAc–hexane elution, flow rate 2 ml min^{-1}) and in this manner two major fractions, A and B, were obtained.

Concentration of fraction A (t_R 20.6 min) afforded compound **27** (70 mg, 82%) as a clear, colourless oil; $[\alpha]_D$ +15.7 (*c* 0.35); λ_{max}($CHCl_3$)/nm 247; ν_{max}(NaCl)/cm^{-1} 2953, 2924, 2852, 1743, 1457, 1437, 1197, 1161, 1068, 1020 and 965; δ_H(300 MHz) 6.24 (1H, dd, *J* 14.9 and 10.6), 5.92 (1H, d, *J* 10.6), 5.66 (1H, m), 3.84–3.69 (1H, complex m), 3.65 (3H, s), 3.32 (1H, d, *J* 10.0), 2.61 (1H, dd, *J* 15.2 and 6.2), 2.39 (1H, dd, *J* 15.2 and 6.8), 2.08 (2H, m), 1.89–1.50 (3H, complex m), 1.69 (3H, s), 1.45–1.21 (14H, complex m), 0.88 (3H, br t, *J* 6.3) and 0.70 (3H, d, *J* 6.5); δ_C(75 MHz) 171.9, 135.1, 134.0, 128.3, 125.9, 90.5, 73.8, 51.5, 41.3, 33.0, 32.3, 32.2, 31.9, 31.6, 29.7, 29.4, 29.2, 22.7, 17.7, 14.1 and 12.1 (one resonance obscured or overlapping); *m*/*z* 350 (M^+, 100%), 335 ($M^+ - CH_3$, 77), 319 ($M^+ - OCH_3$, 32), 237 (65), 198 (86), 149 (39), 109 (47), 95 (86), 81 (73) and 69 (57) (Found: M^+, 350.2818. $C_{22}H_{38}O_3$ requires M^+, 350.2821).

Concentration of fraction B (t_R 19.5 min) afforded compound **28**‡ (10 mg, 12%) as a clear, colourless but unstable oil; ν_{max}/cm^{-1} 2926, 2856, 1743, 1437, 1377, 1310, 1197, 1160, 1068, 1020 and 965; δ_H(300 MHz) 6.20 (2H, m), 5.45 (1H, m), 3.86–3.70 (1H, complex m), 3.66 (3H, s), 3.39 (1H, d, *J* 9.8), 2.62 (1H, dd, *J* 15.2 and 6.1), 2.40 (1H, dd, *J* 15.2 and 7.3), 2.16 (2H, m), 1.90–1.50 (3H, complex m), 1.70 (3H, s), 1.45–1.21 (14H, complex m), 0.88 (3H, br t, *J* 6.9) and 0.70 (d, *J* 6.9, 3H); δ_C(75 MHz) 136.1, 132.5, 124.0, 123.3, 90.8, 73.8, 41.3, 32.3, 32.2, 31.9, 31.7, 29.7, 29.5, 29.3, 22.7, 17.7, 14.1 and 12.0 (four resonances obscured or overlapping).

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