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The Total Synthesis of Swinholide A. Part 2: A Stereocontrolled Synthesis of a C_1-C_{15} Segment.

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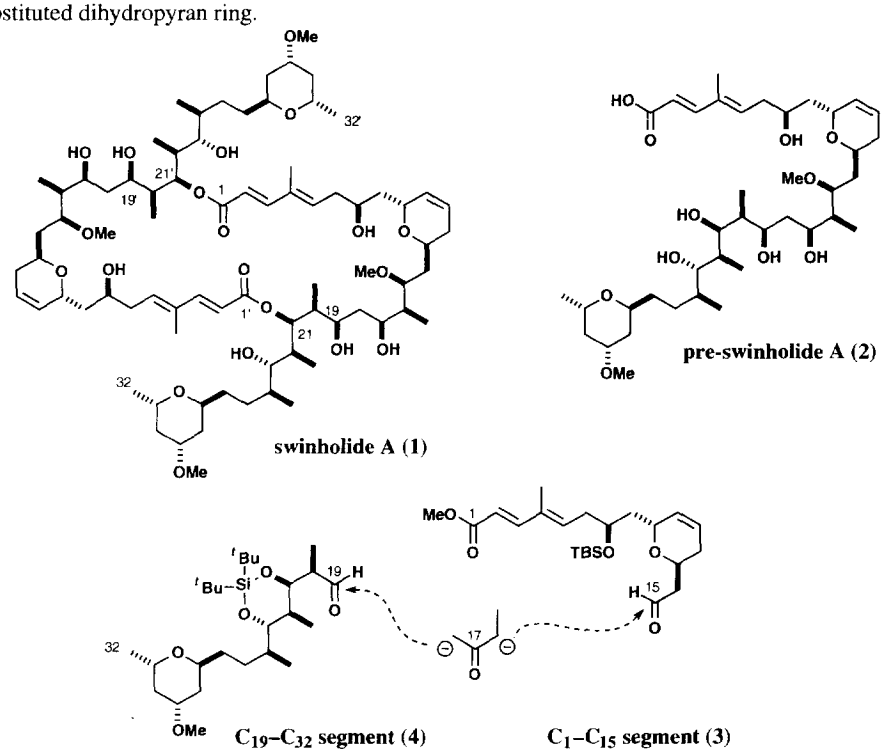
Abstract: The C_1–C_{15} segment **3** of swinholide A was prepared in 10 steps (14% yield) from the methyl ketone **13**. Key steps include *(i)* the asymmetric aldol reaction, **13** → **35**, followed by cyclisation to give the dihydropyrone **36**, *(ii)* the Ferrier-type rearrangement, **38** → **39**, and *(iii)* the vinylogous Mukaiyama aldol reaction, **39** → **40**.

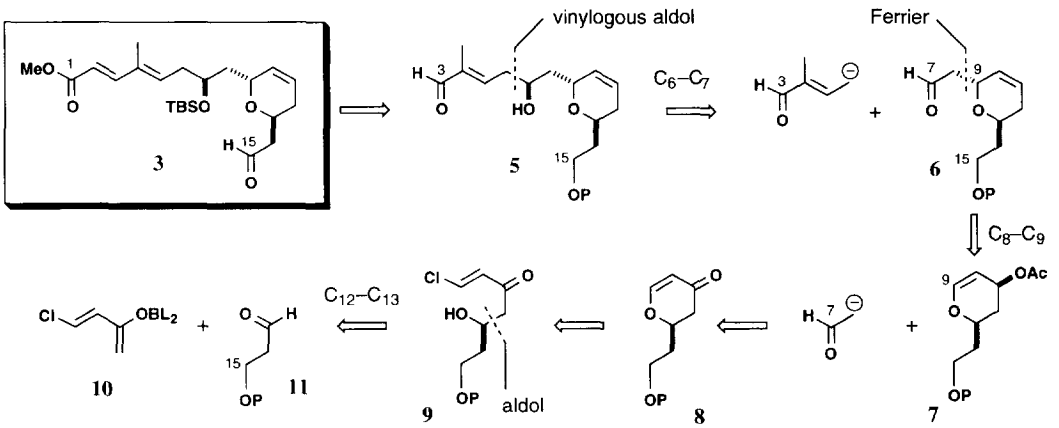
In the preceding paper,[1a] we outlined our strategy for the total synthesis of the cytotoxic marine macrodiolide swinholide A (**1**).[2] As indicated in **Scheme 1**, this involves the stereoselective tandem aldol coupling of the two aldehyde segments **3** and **4** with a C_{16}–C_{18} butanone linking unit, leading first to pre-swinholide A (**2**). In this second paper of the series,[1] we describe the synthesis[3] of the C_1–C_{15} segment **3**, which incorporates the *trans*-substituted dihydropyran ring.



Scheme 1

Our strategy for the synthesis of the C_1–C_{15} segment **3** is summarised in **Scheme 2**. We proposed that the enal **5** could be prepared from the aldehyde **6** through use of a vinylogous aldol reaction. Furthermore, we envisaged that the C_9 sidechain in **6** could be introduced by a variation of the Ferrier rearrangement using the

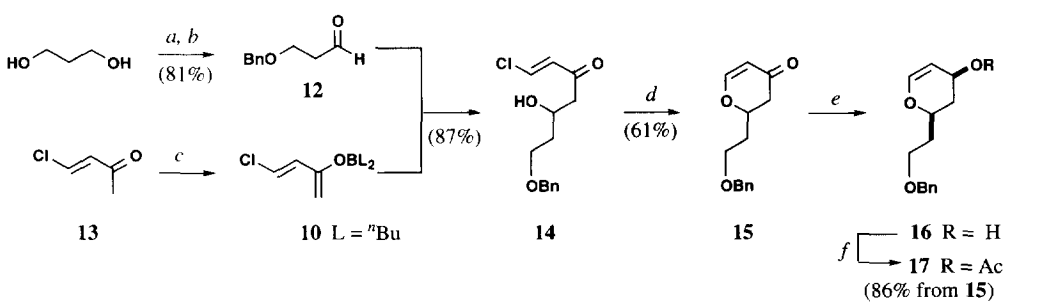
glycal **7** with an appropriate enolate nucleophile. Glycal **7** should be available, in turn, from the dihydropyrone **8**. Preparation of **8** using our previously described[4a] tandem aldol/cyclisation protocol seemed to be the most direct approach. In this case, the open-chain aldol adduct **9** was first required from addition of the boron enolate **10** to aldehyde **11**. The asymmetric variant would employ chiral ligands on boron in **10**.



Scheme 2

Racemic Synthesis of C_1–C_{15} Segment

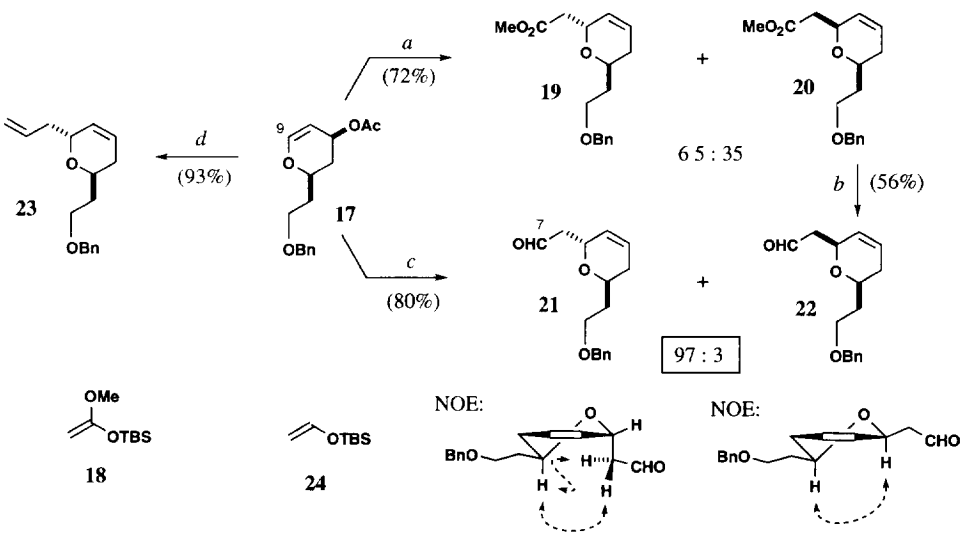
We initially explored a racemic route to the C_1–C_{15} segment **3** by starting with 3-benzyloxypropanal (**12**) and the β-chloroenone **13** (**Scheme 3**).[4b] Aldehyde **12** was prepared in two steps by mono-protection of propane-1,3-diol, followed by Swern oxidation (81%). Using $^nBu_2BOTf/^iPr_2NEt$, the aldol reaction between the methyl ketone **13** and the aldehyde **12** gave **14** in 87% yield. Cyclisation of **14**, using our standard conditions[4a] of $Me_3SiOTf/^iPr_2NEt$ in CCl_4, then provided the racemic dihydropyrone **15** in 61% yield. Attempts to optimise this reaction by changing solvent had little effect, whilst alternative cyclisation conditions (TBSOTf, CH_2Cl_2; TfOH, CH_2Cl_2; K_2CO_3, MeOH; $(MeCN)_2PdCl_2$, CH_2Cl_2; TBAF, THF) gave only traces of **15** (<20%). Reduction of the carbonyl group in **15** using the Luche conditions[5] gave the allylic alcohol **16** as a single diastereomer, which was then acetylated to give the acid-sensitive dihydropyran **17** in 86% overall yield.



Scheme 3: (a) KH, BnBr, THF, DMPU, $^nBu_4NI$, 20 °C, 16 h; (b) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h; Et_3N, –78 → 20 °C, (c) $^nBu_2BOTf$, $^iPr_2NEt$, CH_2Cl_2, –78 → 0 °C, 1 h; **12**, –78 → 0 °C, 1.5 h; (d) TMSOTf, $^iPr_2NEt$, CCl_4, –78 → 20 °C, 3 h; (e) $NaBH_4$, $CeCl_3.7H_2O$, MeOH/EtOH, –78 → 0 °C, 3 h; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 20 °C, 3 h.

Modified Ferrier-Type Rearrangements

Our initial work focussed on the Ferrier-type rearrangement[6,7] of dihydropyran **17** with the silyl ketene acetal **18**[8] (**Scheme 4**). While low yields were obtained with strong Lewis acids ($TiCl_4$, $BF_3{\bullet}OEt_2$, TMSOTf), $ZnBr_2$ in CH_2Cl_2 gave a 72% yield of a 65 : 35 mixture of C_9 alkylation products. The stereochemical outcome of the reaction was determined by reducing the ester products with DIBAL to the corresponding aldehydes (**21** and **22**), followed by ^1H NMR NOE studies. This showed that the desired 2,6-*trans* isomer **21** was indeed the major dihydropyran product. The poor diastereoselectivity in this reaction was disappointing, as related Ferrier-type rearrangements on other glycals with a variety of carbon-centred nucleophiles are reported to give high levels of *trans* diastereoselectivity.[7] In contrast, use of allyltrimethylsilane as the nucleophile, under the conditions reported by Danishefsky[7b] ($TiCl_4$, CH_2Cl_2, –78 °C), gave exclusively the *trans* isomer **23** in 93% yield. This result indicated that the reaction diastereoselectivity was highly dependent on the reactivity of the nucleophile, with less reactive reagents apparently giving a higher degree of *trans* selectivity.



Scheme 4: (a) **18**, $ZnBr_2$, CH_2Cl_2, 20 °C, 2.5 h; (b) DIBAL, CH_2Cl_2, –78 °C, 1 h; (c) **24**, $TiCl_2(O^iPr)_2$, PhMe, –40 °C, 2 h; (d) $CH_2{=}CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, –78 °C, 15 min.

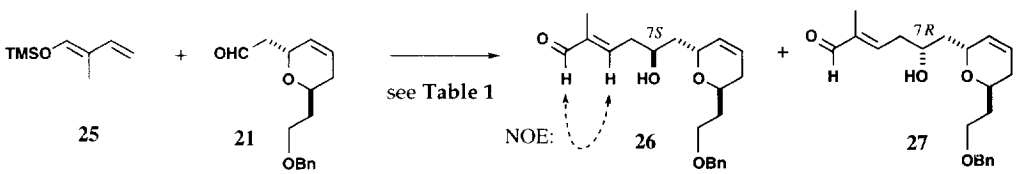
In the light of these results, we elected to use the silyl enol ether **24**[9] as the nucleophile, since this would be intermediate in reactivity between the silyl ketene acetal and allylsilane, and would also deliver directly the desired aldehyde oxidation level at C_7. Initially, we carried out this reaction using $TiCl_4$ in CH_2Cl_2 at –78 °C to give the desired aldehyde **21** in 25% isolated yield. Analysis of the crude product by GC showed only traces of the undesired *cis* diastereomer (**21** : **22**, 97 : 3). Finally, changing to the milder Lewis acid $TiCl_2(O^iPr)_2$ in PhMe at –40 °C improved the yield to 80%, whilst maintaining the excellent diastereoselectivity.

The level of diastereoselectivity obtained in the Ferrier rearrangement reaction of **17** depends upon subtle differences in the nature of the carbon-centred nucleophile. While we did not attempt to fully investigate these effects, it appears that the intrinsic preference for the oxonium ion derived from **17** to undergo

stereoelectronically-controlled, axial addition of nucleophiles is counterbalanced by other steric and electronic factors. Moreover, reaction through a competing S_N2' pathway may become important for certain nucleophiles.

Vinylogous Mukaiyama Aldol Reaction

With the desired aldehyde **21** in hand, we next turned our attention to elaborating the C_7 aldehyde into the swinholide side-chain. This required controlled formation of the C_7 stereocentre. We elected to explore a novel vinylogous Mukaiyama aldol reaction[10] between the aldehyde **21** and the silyl dienol ether **25**[11] (**Scheme 5** and **Table 1**). Initial studies[12] with simple aldehydes showed that γ-alkylation predominated with **25** and that the desired *E*-double bond geometry was formed exclusively. Substrate-controlled addition of the dienol ether **25** to a β-chelated Lewis acid complex with **21** was expected to favour the desired 1,3-*anti* product.[13] This would necessitate use of a di-coordinating Lewis acid like $TiCl_4$. However, use of $TiCl_4$ gave only decomposition, while the milder Lewis acid $TiCl_2(O^iPr)_2$ suffered from poor conversion (**Table 1**, entries 1-2) and only moderate selectivity (**26** : **27**, 78 : 22). We then considered other catalysts, including mono-coordinating Lewis acids *which would now preclude chelate organisation*. Gratifyingly, use of $BF_3{\bullet}OEt_2$ now led to good yields and selectivities for the desired product **26** (**Table 1**, entries 3-7). A series of reactions under different conditions eventually identified a mixed solvent system (Et_2O/CH_2Cl_2), which gave both the best diastereoselectivity (90% ds) and yield (70%). ^1H NMR NOE studies on the major isomer **26** showed that the newly created double bond had the desired *E* geometry. Determination of the relative stereochemistry at the newly formed C_7 stereocentre was accomplished at a later stage (*vide infra*).



Scheme 5

Table 1: Lewis acid promoted additions of silyl dienol ether **25** to aldehyde **21**.

entry	Lewis acid	solvent	temp (°C)	**26** : **27**	% yield	% SM (**21**)
1	$Cl_2Ti(O^iPr)_2$	CH_2Cl_2	−78 → −40	72 : 28	24	49
2	$Cl_2Ti(O^iPr)_2$	CH_2Cl_2	−40 → −20	78 : 22	40	44
3	$BF_3{\bullet}OEt_2$	Et_2O	−78 → −20	83 : 17	61	19
4	$BF_3{\bullet}OEt_2$	THF	−78 → 20	58 : 42	50	20
5	$BF_3{\bullet}OEt_2$	CH_2Cl_2	−78	86 : 14	62	0
6	$BF_3{\bullet}OEt_2$	CH_2Cl_2	−95	87 : 13	57	16
7	$BF_3{\bullet}OEt_2$	10% Et_2O/CH_2Cl_2	−78	90 : 10	70	11

Since β-chelation of the aldehyde and the dihydropyran oxygen with BF_3•OEt_2 is not possible, it was interesting to observe good levels of diastereoselectivity in this reaction. Reetz *et al.*[14a] and, more recently, Evans *et al.*[14b,c] have examined simpler chiral β-alkoxyaldehydes and explained the observed 1,3-anti selectivity for attack of certain carbon nucleophiles in terms of a dipole-dipole repulsion model. While such an effect from the C_9 stereocentre is also applicable to addition reactions with aldehyde **21**, as indicated in **Figure 1**, the remote C_{13} sidechain which terminates in a benzyl ether also appears to have a role in determining the stereochemical course of the reaction. As will be seen later, changing this hydroxyl protecting group has a small but significant effect on the level of diastereoselection obtained. Note that the preferred axial orientation of the C_9 sidechain in the dihydropyran **21**, in combination with the equatorial C_{13} sidechain, allows the benzyl ether to approach the aldehyde. Molecular modelling (MM2) indicated low energy conformations where the aldehyde carbonyl and benzyl ether are in close proximity to each other. In addition, as the synthesis progressed towards pre-swinhholide A, it became clear from inspection of the ^1H NMR spectra that substituents on the dihydropyran sidechains appear to be relatively close in space. In this way, the *trans*-substituted dihydropyran acts as a conformational anchor for the two sidechains. When functional groups in either of the sidechains undergo an asymmetric reaction, the level and sense of diastereocontrol may be affected by such a conformational preference. Thus, while the stereochemical course of this vinylogous Mukaiyama aldol reaction can be explained in terms of the polar model proposed by Evans *et al.*,[14b,c] we believe that there is also a significant influence from the C_{13} sidechain.

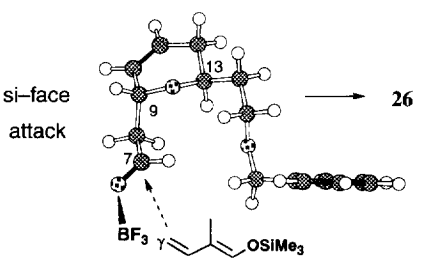


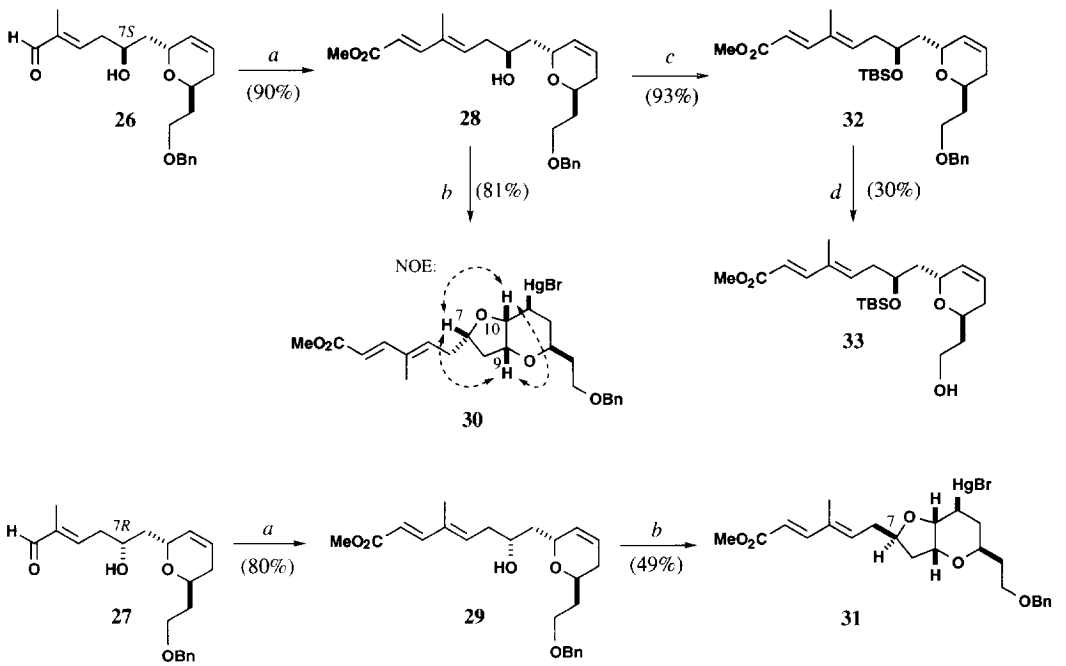
Figure 1

Completion of the Racemic C_1–C_{15} Segment

The next step in the synthesis required chain extension to give the C_2-C_3 *E*-alkene. This was best achieved by a Horner-Emmons reaction to give the dienoate **28** in 90% yield (**Scheme 6**). The *E* geometry was assigned on the basis of the large (15.7 Hz) coupling constant between H_2 and H_3. A similar reaction on the C_7 epimeric aldehyde **27** gave **29** in 80% yield. At this stage, circumstantial evidence for the desired stereochemistry at C_7 was provided by comparison of the ^1H and ^{13}C NMR data acquired for **28** and **29** with that reported[1c] for the methyl ester of pre-swinholide A by Kitagawa *et al.* For the major isomer **28**, there was good agreement with the literature data, whereas for **29** there were significant chemical shift differences particularly for C_7 and C_9.

We were also able to unambiguously assign the relative C_7 stereochemistry by separately cyclising the C_7 alcohol group onto the dihydropyran double bond in **28** and **29** using an intramolecular oxymercuration reaction mediated by $Hg(OCOCF_3)_2$.[15] Following treatment with aqueous KBr, the resulting bicyclic mercurials **30** and **31** were isolated in 81 and 49% yields, respectively. Detailed ^1H NMR NOE studies in CD_3CN for **30** showed

that H_7, H_9 and H_{10} were all on the same face of the molecule, thereby proving that the major alcohol diastereomer **28** had the *desired* relative stereochemistry at C_7. The epimeric mercurial **31** showed ^1H NMR NOE enhancements in C_6D_6 that were fully consistent with minor alcohol diastereomer **29** having the undesired C_7 stereochemistry.



Scheme 6: (a) $(MeO)_2P(O)CH_2CO_2Me$, *n*-BuLi, THF, 0 → 20 °C, 3 h; (b) $CaCO_3$, $Hg(OCOCF_3)_2$, THF, 2.5 h then aq. KBr; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 20 min; (d) DDQ, CH_2Cl_2, H_2O, 20 °C, 18 h.

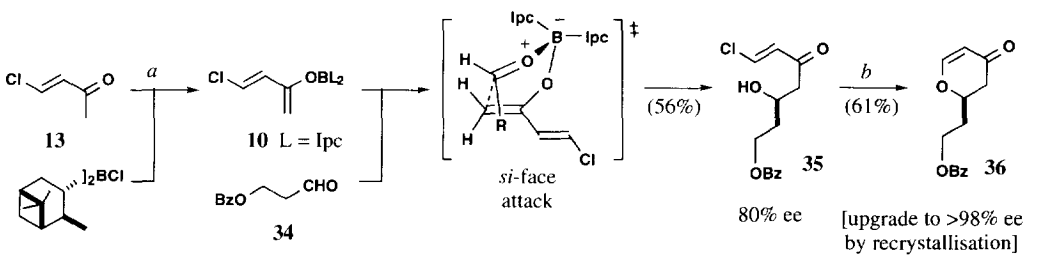
Protection of the C_7 hydroxyl in the desired isomer **28** as its *tert*-butyldimethylsilyl ether proceeded uneventfully using the silyl triflate to give **32** in 93% yield. At this stage, we had completed a *racemic* synthesis of a fully protected C_1–C_{15} segment **32** for swinholide A, and now required deprotection of the C_{15} benzyl ether to expose the corresponding alcohol **33** ready for subsequent oxidation. Unfortunately, we were unable to cleanly remove this protecting group, despite trying a variety of conditions. Attempted reduction with Raney nickel[16] or Li/4,4'-di-*tert*-butylbiphenyl[17] led to rapid reduction of the diene system, while use of TMSI[18] removed both the benzyl and silyl ethers in moderate yield (40%). Use of DDQ in wet dichloromethane[19] led to slow (18 h) removal of the benzyl ether, but this reaction also gave large amounts of polar byproducts along with the desired product **33** (30%).

Asymmetric Synthesis of Dihydropyrone 36

At this stage of the project, it was clear that although we had developed an expedient route to **33** in racemic form, we would require a different C_{15} hydroxyl protecting group to facilitate deprotection at the end of the sequence. At the same time, we wished to modify the route in order to prepare enantiomerically pure material.

After surveying various alternatives, we elected to protect the C_{15} primary alcohol as a benzoate ester as this seemed to offer a good compromise between stability to protic/Lewis acidic conditions and lability under basic conditions. In the first instance, we examined the feasibility of removing the benzyl ether in **15** followed by re-protection as a benzoate ester. While this provided material to examine the subsequent chemistry, it needlessly lengthened the synthesis. Therefore, we decided to re-examine the first steps in the synthesis to include the benzoate protection from the outset (**Scheme 7**).

We initially prepared the benzoate-containing aldehyde **34** in 62% yield using a two-step sequence involving mono-acylation of propane-1,3-diol, followed by oxidation with the Dess-Martin periodinane.[20] In order to avoid the use of the periodinane on a larger scale, we developed an alternative sequence starting from 3-buten-1-ol. This consisted of benzoylation, osmium tetroxide-catalysed dihydroxylation, and diol cleavage with sodium periodate to give the aldehyde **34** in 65% overall yield. An asymmetric aldol reaction between methyl ketone **13** and aldehyde **34** using isopinocampheyl (Ipc) ligands on the intermediate enol borinate **10** was then required.



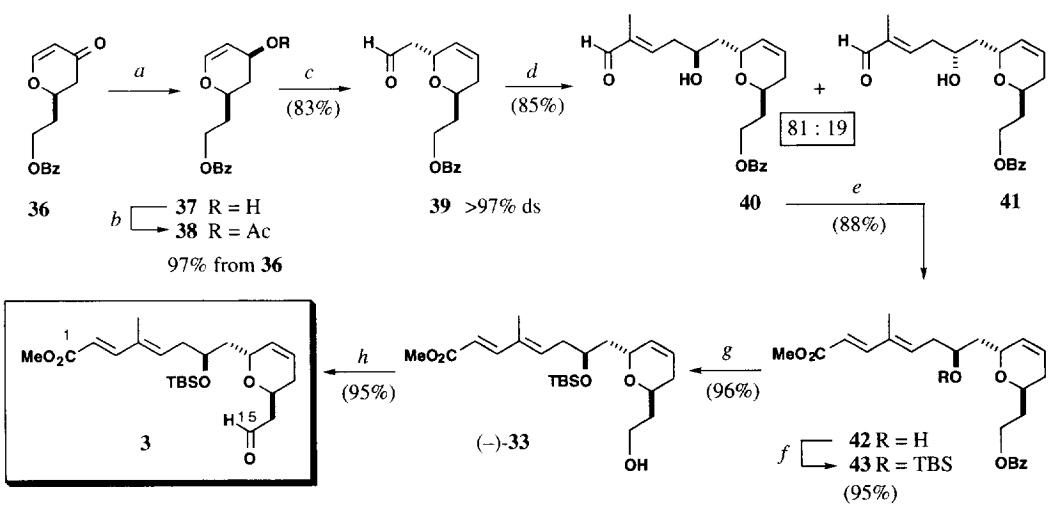
Scheme 7: (a) (+)-Ipc_2BCl, $^iPr_2NEt$, PhMe, 0 °C, 1 h; **34**, −78 → −20 °C, 18 h; H_2O_2, MeOH, pH7 buffer; (b) 1.05 equiv. Me_3SiOTf, 0.8 equiv. $^iPr_2NEt$, CH_2Cl_2, −78 → 20 °C, 2.5 h.

Enolisation of **13** with (+)-Ipc_2BCl/$^iPr_2NEt$ in toluene at 0 °C was followed by addition at −78 °C of aldehyde **34** to the derived boron enolate.[4a] Stirring was continued at this temperature for 3.5 h, before placing the reaction mixture in the freezer overnight (−20 °C, 18 h). The desired product **35** was obtained in 56% yield after mild oxidative workup, with approximately 80% ee. Higher yields of the aldol product (up to 77%) could be obtained by using shorter reaction times or by carrying out the aldol reaction in ether, but this also led to a reduction in enantioselectivity (50–60% ee). This unexpected result may be due to preferential decomposition of the minor boron aldolate when the reaction is maintained at −20 °C, thus leading to higher enantiomeric purity *via* a kinetic resolution process. Note that the enantioselectivity obtained in this reaction is somewhat lower than the corresponding ethyl ketone aldol reactions with the same Ipc ligands and is in the opposite stereochemical sense. We have previously proposed that the methyl ketone reaction proceeds through a twist-boat transition structure, while the ethyl ketone syn aldol addition prefers a chair transition structure.[21] Cyclisation of **35** under our standard conditions then gave the crystalline dihydropyrone **36** in 61% yield. Gratifyingly, this material could be recrystallised from ether/petroleum ether to give the *enantiomerically pure* dihydropyrone **36**, $[\alpha]_D^{20} = +66.2°$ (*c* 2.6, $CHCl_3$), as colourless needles (m.p. 62–63 °C).

Completion of the Asymmetric Synthesis of the C_1-C_{15} Segment 3

Elaboration of the enantiomerically pure pyrone **36** to the desired C_1–C_{15} segment **3** proceeded in a similar fashion to that developed earlier in the racemic benzyl ether series (**Scheme 8**). Hence, Luche reduction[5] gave the allylic alcohol **37** which was acetylated to give the acid-sensitive dihydropyran **38** in 97% overall yield. Ferrier rearrangement proceeded under similar conditions to those used for **17**, except that 2.2 equivalents of $Cl_2Ti(O^iPr)_2$ were required to drive the reaction to completion. This may be due to competing complexation of the Lewis acid with the benzoate ester moiety. The desired *trans* aldehyde **39** was isolated in 83% yield as a single diastereoisomer. Vinylogous Mukaiyama aldol reaction of this substrate with silyl dienol ether **25** using 2.2 equivalents of $BF_3{\bullet}OEt_2$ again gave γ-addition, providing an 81 : 19 mixture of the two C_7 epimers **40** and **41** in 85% combined yield. The desired isomer **40** was again the major product, but with somewhat reduced diastereoselectivity compared to the benzyl ether case (*cf* **26** : **27**, 90 : 10) indicating a role for the C_{15} protecting group in influencing the π-face selectivity of the aldehyde.

As before, a Horner-Emmons reaction on **40** gave the *E*-alkene **42** as a single double bond isomer in 88% yield. Formation of the *(R)* and *(S)*-MTPA ester derivatives[22] of this alcohol, followed by ^1H NMR analysis, allowed assignment of the configuration at C_7 as *S* based upon chemical shift differences in the two diastereomers (*i.e.* $C_3\underline{H}$ $\Delta\delta$ (*S*–*R*) = –0.09; $C_9\underline{H}$ $\Delta\delta$ (*S*–*R*) = +0.17). Formation of the MTPA esters also confirmed that the pyrone **36** had indeed been recrystallised to enantiomeric purity.



Scheme 8: (a) $NaBH_4$, $CeCl_3.7H_2O$, EtOH, –78 °C, 2 h; (b) Ac_2O, $^iPr_2NEt$, CH_2Cl_2, 20 °C, 18 h; (c) **24**, 2.2 equiv. $TiCl_2(O^iPr)_2$, PhMe, –42 °C, 0.5 h; (d) **25**, 2.2 equiv. $BF_3{\bullet}OEt_2$, 9:1 CH_2Cl_2/Et_2O, –78 °C, 1 h; (e) $(MeO)_2P(O)CH_2CO_2Me$, ^{n}BuLi, THF, 0 → 20 °C, 3 h; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 20 min; (g) K_2CO_3, MeOH, 20 °C, 5.5 h; (h) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 1 h.

Protection of the C_7 hydroxyl group as its TBS ether again proceeded without incident to give **43** in 95% yield. Fortunately, the benzoate ester could now be cleanly removed using K_2CO_3/MeOH, giving the alcohol (–)-**33** in excellent yield (96%). Spectral data for this compound were found to match those recorded earlier for the

racemic material obtained by debenzylation of **32**. Finally, oxidation to the aldehyde **3** using Dess-Martin periodinane proceeded in 95% yield, thus completing the asymmetric synthesis of the C_1–C_{15} segment.

Conclusions

In summary, the synthesis of the enantiomerically pure C_1–C_{15} segment **3** of swinholide A has been achieved. This synthetic route is highly efficient (10 steps, 14% overall yield from **13**), with the three stereocentres and two double bonds being introduced in a highly selective manner. The synthetic route relies upon a single reagent-controlled reaction, the aldol reaction, **13** → **35**, and a series of substrate-controlled reactions, (*i*) Luche reduction, **36** → **37**, (*ii*) the Ferrier-type rearrangement, **38** → **39**, and the vinylogous Mukaiyama aldol reaction, **39** → **40**. This route has proven amenable to scale up, allowing multi-gram quantities of the aldehyde **3** to be prepared, thus enabling the completion of the total synthesis of swinholide A.[1b,c]

Experimental Section

For general experimental details, see the preceding paper.[1a]

3-Benzyloxypropanal (12)

A 35% slurry of KH in mineral oil (13.7 g, 120 mmol) was washed free of oil with THF (3 x 20 ml), then suspended in THF (20 ml) and cooled to 0 °C. To this was added, dropwise with stirring, neat propane-1,3-diol (10 ml) over 1 h. Once the addition was complete, more propane-1,3-diol (70 ml) was gradually introduced, and to the resulting mixture was added 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU, 1.5 ml, 12.4 mmol), $^nBu_4NI$ (4.0 g, 10.8 mmol), and benzyl bromide (14.0 ml, 118 mmol). An exotherm was noted which was moderated by cooling in ice, and the resulting cloudy mixture was stirred at room temperature for 16 h, after which time the reaction was quenched with NH_4Cl solution (20 ml, sat. aq.). After diluting with CH_2Cl_2 (250 ml), the mixture was washed with NH_4Cl solution (250 ml, sat. aq.) and the aqueous phase was then extracted with CH_2Cl_2 (3 x 150 ml). The combined extracts were washed successively with water (250 ml) and brine (1 x 150 ml, sat. aqueous), then dried (Na_2SO_4) and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (gradient elution with 20 → 50% EtOAc/hexane) to give 3-benzyloxypropanol as a colourless liquid (18.3g, 93%): bp 96-97 °C (0.1 mm Hg), lit[23] bp 114 °C (0.9 mm Hg); R_f = 0.27 (50% EtOAc/hexane); ^{1}H NMR δ (250 MHz, $CDCl_3$) 7.27-7.35 (5H, m, $C_6\underline{H}_5$), 4.52 (2H, s, $C\underline{H}_2Ph$), 3.78 (2H, t, *J* = 5.8 Hz, $OCH_2CH_2C\underline{H}_2OH$), 3.66 (2H, t, *J* = 5.8 Hz, $OC\underline{H}_2CH_2CH_2OH$), 2.27 (1H, br, O<u>H</u>), 1.86 (2H, tt, *J* = 5.8, 5.8 Hz, $CH_2C\underline{H}_2CH_2$).

To a cooled (–78 °C) solution of oxalyl chloride (3.4 ml, freshly distilled, 39 mmol) in CH_2Cl_2 (100 ml) was added dry DMSO (5.6 ml, freshly distilled from CaH_2, 79 mmol) dropwise and the resulting mixture was stirred at –78 °C for 5 min. A solution of 3-benzyloxypropan-1-ol (5.00 g, 30.1 mmol) in CH_2Cl_2 (20 ml) was then added *via* cannula and the mixture was stirred at –78 °C for 0.25 h. Triethylamine (25 ml, 180 mmol) was then introduced rapidly and the resulting thick white slurry was allowed to warm to room temperature and quenched with NH_4Cl (50 ml, sat. aqueous). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were then washed successively with HCl (70 ml, 1*M*), $NaHCO_3$ solution (70 ml, sat. aq.), and brine (70 ml, sat. aq.) then dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil. The crude product was purified by flash chromatography (20% EtOAc/hexane) to give **12** as a colourless oil (4.30 g, 87%): R_f = 0.20 (20% EtOAc/hexane); IR (liquid film) 1725 (vs, CHO) cm^{-1}; ^{1}H NMR

δ (250 MHz, $CDCl_3$) 9.79 (1H, t, J = 1.8 Hz, C<u>H</u>O), 7.26-7.38 (5H, m, C_6<u>H_5</u>), 4.53 (2H, s, PhC<u>H_2</u>), 3.81 (2H, t, J = 6.1 Hz, C<u>H_2</u>CH_2CHO), 2.69 (2H, td, J = 6.1, 1.8 Hz, CH_2C<u>H</u>O).

(*E*,5*RS*)-7-Benzyloxy-1-chloro-5-hydroxyhepten-3-one (14).

To a cooled (–78 °C) solution of *n*-Bu_2BOTf (8.8 g, 32.1 mmol) in CH_2Cl_2 (100 ml) was added *i*-Pr_2NEt (7.0 ml, 40.2 mmol) and the resulting mixture was stirred at this temperature for 15 min so that most of the crystallised boron triflate dissolved. A solution of freshly distilled *E*-4-chlorobut-3-en-2-one[4b] (2.8 g, 27 mmol) in CH_2Cl_2 (10 ml) was then added causing a solid to be formed and the reaction was stirred at –78 °C for 1.25 h then warmed to 0 °C for 15 min to allow the remaining solid to dissolve, then recooled to -78 °C for 0.5 h. To this mixture was added a solution of **12** (5.3 g, 32 mmol) in CH_2Cl_2 (20 ml) and stirring at –78 °C was continued for a further 1.5 h. The reaction mixture was warmed to 0 °C and then quenched with pH 7 buffer solution (10 ml). The mixture was then washed with pH 7 buffer solution (30 ml) and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a dark orange oil. The crude product was columned twice through flash silica (30% EtOAc/hexane) to give **14** as a slightly yellow oil, which crystallised upon storage at –20 °C (6.26 g, 87%). An analytical sample was obtained by recrystallisation from hexane: mp 37–38 °C; R_f = 0.27 (30% EtOAc/hexane); IR (liquid film) 3480 (s br, OH), 1680 (vs, C=O) cm^{-1} (s); ^{1}H NMR δ (250 MHz, $CDCl_3$) 7.40–7.23 (6H, m, C_6<u>H_5</u> and 9-C<u>H</u>), 6.52 (1H, d, J = 13.6 Hz, 10-C<u>H</u>), 4.52 (2H, s, C<u>H_2</u>Ph), 4.37–4.24 (1H, m, 13-C<u>H</u>), 3.76–3.60 (2H, m, 15-C<u>H_2</u>), 2.78–2.63 (2H, m, 12-C<u>H_2</u>), 1.92–1.70 (2H, m, 14-C<u>H_2</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 197.0, 137.9, 137.6, 132.7, 128.4, 127.8, 127.7, 73.3, 68.0, 66.8, 47.8, 36.0; m/z ($CI^+(NH_3)$) 286 (90, $[M+NH_4]^+$), 269 (100, $[M+H]^+$), 251 (30), 233 (80), 182 (30), 108 (25); HRMS ($CI^+(NH_3)$) Calcd for $C_{14}H_{18}O_3Cl$ ($[M+H]^+$): 269.0944, found 269.0944; Anal. calcd for $C_{14}H_{17}ClO_3$: C, 62.57; H, 6.38; Cl, 13.19; found: C, 62.40; H, 6.41; Cl, 13.46.

(2*RS*)-2-(Benzyloxyethyl)-2,3-dihydro-4*H*-pyran-4-one (15).

To a cooled (–78 °C) solution of the aldol product **14** (1.06 g, 3.95 mmol) in CH_2Cl_2 (25 ml) was added ^{i}Pr_2NEt (0.55 ml, 3.2 mmol), followed by Me_3SiOTf (0.802 ml, 4.15 mmol) dropwise. After stirring at –78 °C for 15 min, the mixture was warmed to 0 °C for 2.5 h, and then to room temperature for 0.5 h. The reaction mixture was then washed with $NaHCO_3$ solution (40 ml, sat. aq.). The aqueous phase was extracted further with CH_2Cl_2 (2 x 20 ml), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a dark brown oil. The crude material was purified by flash chromatography (10% Et_2O/CH_2Cl_2) to give the product (*ca.* 0.66g) contaminated with a few percent of starting material, which was removed by the following procedure. To a solution of this material in CH_2Cl_2 (10 ml) was added Ac_2O (0.189 ml, 2.0 mmol), ^{i}Pr_2NEt (0.383 ml, 2.2 mmol) and DMAP (22 mg, 0.18 mmol). The resulting mixture was stirred at room temperature for 2 h, and then washed with HCl (30 ml, 1*M* aq.). The aqueous phase was further extracted with CH_2Cl_2 (3 x 10 ml) and each extract was subsequently washed with $NaHCO_3$ solution (30ml, sat. aq.) then combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the resultant oil by flash chromatography (5% Et_2O/ CH_2Cl_2) gave **15** as a viscous yellow oil (0.547 g, 60%). Repeating the reaction under similar conditions, but using CCl_4 in place of CH_2Cl_2 and adding the reagents at –20 °C, gave a 61% yield of **15**: R_f = 0.26 (10% $Et_2O/CHCl_3$); IR (liquid film) 1680 (vs, C=O) cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.36–7.27 (6H, m, C_6<u>H_5</u> and 9-C<u>H</u>), 5.40 (1H, d, J = 6.0 Hz, 10-C<u>H</u>), 4.66–4.59 (1H, m, 13-C<u>H</u>), 4.50 (2H, s, C<u>H_2</u>Ph), 3.68–3.56 (2H, m, 15-C<u>H_2</u>), 2.57–2.43 (2H, m, 12-C<u>H</u>), 2.13–2.05 (1H, m, 14-C<u>H_a</u>), 2.00–1.92 (1H, m, 14-C<u>H_b</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 192.5, 163.1, 138.0, 128.4, 127.7, 127.6, 107.1, 76.7, 73.2, 65.3, 41.9, 34.6; m/z ($CI^+(NH_3)$) 233 (100, $[M+H]^+$), 108 (30), 91 (40); HRMS ($CI^+(NH_3)$) Calcd for $C_{14}H_{17}O_3$ ($[M+H]^+$): 233.1178, found: 233.1177; Anal calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; found: C, 72.27; H, 7.06.

(2*RS*,4*SR*)-4-Acetoxy-2-benzyloxyethyl-3,4-dihydro-2*H*-pyran (17).
To a solution of $CeCl_3.7H_2O$ (2.7 g, 7.2 mmol) in MeOH (50 ml) was added a solution of glycal **15** (1.52 g, 6.55 mmol) in MeOH (50 ml) and the mixture was diluted with more MeOH (100 ml). After cooling to –78 °C, a solution of $NaBH_4$ in EtOH (24 ml of a 0.3*M* solution, 7.2 mmol) was added over a period of 3 h using a syringe pump. The reaction mixture was then allowed to warm to room temperature and quenched with pH7 buffer solution (30 ml). The volatiles were removed *in vacuo* and the residue was poured into pH7 buffer solution (50 ml) and extracted with Et_2O (4 x 30 ml). The combined extracts were then washed with brine (40 ml, sat. aq.), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude allylic alcohol **16** as an oil (1.5 g). To a solution of this material in CH_2Cl_2 (30 ml) was added Et_3N (1.5 ml, 10.8 mmol) followed by Ac_2O (0.93 ml, 9.8 mmol) and DMAP (40 mg, 0.33 mmol). After stirring at room temperature for 3 h, the mixture was washed with $NaHCO_3$ solution (20 ml, sat. aq.) and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil which was purified using flash chromatography (20% EtOAc/hexane) through a short column of silica to give **17** as a colourless oil (1.55 g, 86%). *NB*: The product is very acid-sensitive and the chromatographic step should be performed as quickly as possible: R_f = 0.41 (30% EtOAc/hexane); IR (liquid film) 1730 (vs) cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 7.38–7.25 (5H, m, $C_6\underline{H}_5$), 6.42 (1H, d, *J* = 6.2 Hz, 9-C<u>H</u>), 5.36 (1H, m, 11-C<u>H</u>), 4.73 (1H, ddd, *J* = 6.2, 3.9, 2.4 Hz, 10-C<u>H</u>), 4.50 (2H, s, $C\underline{H}_2Ph$), 4.24–4.14 (1H, m, 13-C<u>H</u>), 3.66-3.51 (2H, m, 15-$C\underline{H}_2$), 2.24 (1H, dddd, *J* = 13.3, 6.6, 1.9, 1.9 Hz, 12-$C\underline{H}_AH_B$), 2.05–1.65 (6H, m, 12-$CH_AC\underline{H}_B$, 14-$C\underline{H}_2$, and $C\underline{H}_3CO_2$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 170.8, 146.5, 138.3, 128.3, 127.59, 127.56, 100.8, 73.0, 71.5, 66.1, 65.4, 34.8, 33.4, 21.2; m/z ($CI^+(NH_3)$) 294 (5, $[M+NH_4]^+$), 234 (30), 217 (100); HRMS ($CI^+(NH_3)$) Calcd for $C_{16}H_{24}O_4N$ ($[M+NH_4]^+$): 294.1705, found: 294.1705; Anal calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30; found C, 69.52; H, 7.46.

(2*RS*, 6*SR*)-6-Benzyloxyethyl-5,6-dihydro-2-methoxycarbonyl-methyl-2*H*-pyran (19) and (2*RS*, 6*RS*)-6-Benzyloxyethyl-5,6-dihydro-2-methoxycarbonyl-methyl-2*H*-pyran (20).
To a solution of **17** (45 mg, 0.163 mmol) in CH_2Cl_2 (1 ml) at room temperature was added a solution of 1-*tert*-butyldimethylsilyloxy-1-methoxyethene (**18**) (50 mg, 0.27 mmol) in CH_2Cl_2 (2 ml) and a catalytic amount of dry $ZnBr_2$ (*ca* 10 mg). The resulting suspension was stirred at room temperature for 2.5 h and then filtered through a small plug of flash silica held in a pasteur pipette using Et_2O as the eluent. Removal of the solvent *in vacuo* gave a brown oil which was purified by flash chromatography (10% EtOAc/hexane) to give the less polar 2,6-*cis*-isomer **20** (12.1 mg, 26%) and the more polar 2,6-*trans*-isomer **19** (22.2 mg, 47%). The reaction selectivity was therefore 65 : 35 favouring the *trans* isomer **19**.
19: R_f = 0.29 (40% Et_2O/hexane); IR (liquid film) 1740 (s) cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 7.35-7.26 (5H, m, $C_6\underline{H}_5$), 5.90-5.82 (1H, m, 11-C<u>H</u>), 5.72-5.65 (1H, m, 10-C<u>H</u>), 4.69-4.62 (1H, m, 9-C<u>H</u>), 4.51 (1H, d, *J* = 11.8 Hz, $C\underline{H}_AH_BPh$), 4.47 (1H, d, *J* = 11.8 Hz, $CH_A\underline{H}_BPh$), 3.88-3.78 (1H, m, 13-C<u>H</u>), 3.67 (3H, s, $CO_2\underline{Me}$), 3.60-3.54 (2H, m, 15-$C\underline{H}_2$), 2.66 (1H, dd, *J* = 14.9, 9.2 Hz, 8-$C\underline{H}_AH_B$), 2.46 (1H, dd, *J* = 14.9, 5.1 Hz, 8-$CH_A\underline{H}_B$), 2.05-1.89 (2H, m, 12-$C\underline{H}_2$), 1.80 (2H, br q, *J* = 6.2 Hz, 14-$C\underline{H}_2$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 171.5, 138.5, 128.3, 128.0, 127.7, 127.5, 125.4, 73.1, 69.6, 66.8, 65.1, 51.6, 39.1, 35.4, 30.5; m/z ($CI^+(NH_3)$) 308 (15, $[M+NH_4]^+$), 291 (100, $[MH]^+$), 199 (15), 91 (25); HRMS ($CI^+(NH_3)$) Calcd for $C_{17}H_{23}O_4$ ($[MH]^+$): 291.1596, found: 291.1596.
20: R_f = 0.37 (40% Et_2O/hexane); IR (liquid film) 1740 (s) cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 7.37-7.27 (5H, m, $C_6\underline{H}_5$); 5.85-5.79 (1H, m, 11-C<u>H</u>), 5.63 (1H, br d, *J* = 10.2 Hz, 10-C<u>H</u>), 4.62-4.49 (3H, m, $C\underline{H}_2Ph$ + 9-C<u>H</u>), 3.80-3.51 (6H, m, $CO_2\underline{Me}$ + 13-C<u>H</u> + 15-$C\underline{H}_2$), 2.54 (1H, dd, *J* = 15.0, 6.2 Hz, 8-$C\underline{H}_AH_B$), 2.44 (1H, dd, *J* = 15.0, 7.9 Hz, 8-$CH_A\underline{H}_B$), 1.98-1.93 (2H, m, 12-$C\underline{H}_2$), 1.84-1.75 (2H, m, 14-$C\underline{H}_2$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 171.5; 138.6, 128.8, 128.3, 127.6, 127.5, 125.7, 73.0, 71.6, 71.1, 66.7, 51.6, 40.5, 36.1, 31.0; m/z ($CI^+(NH_3)$) 308 (10, $[M+NH_4]^+$), 291 (100, $[M+H]^+$), 199 (10), 157 (5), 108 (5), 91 (10, $[PhCH_2]^+$); HRMS ($CI^+(NH_3)$) calc for $C_{17}H_{23}O_4$ ($[M+H]^+$) 291.1596, found 291.1596.

(2*RS*,6*SR*)-2-Allyl-6-benzyloxyethyl-5,6-dihydro-2*H*-pyran (23).
To a cooled (–78 °C) solution of **17** (40.5 mg, 0.147 mmol) in CH_2Cl_2 (1 ml) under an atmosphere of argon was added allyltrimethylsilane (0.0327 ml, 0.206 mmol), followed by a solution of $TiCl_4$ in CH_2Cl_2 (0.15 ml of a 1.0 *M* solution, 0.15 mmol). The resulting orange solution was stirred at –78 °C for 15 min. The reaction was quenched by the addition of $NaHCO_3$ solution (2 ml, sat. aq.), then allowed to warm to room temperature and partitioned between $NaHCO_3$ solution (30 ml, sat. aq.) and Et_2O (30 ml). The aqueous phase was extracted further with Et_2O (2 x 30 ml) and the combined extracts were washed with brine (30 ml, sat. aq.), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/hexane) to give **23** as a colourless oil (35.1 mg, 93%). Examination of the ^1H and ^{13}C NMR spectra of this compound showed it to be a single isomer – the reaction selectivity was therefore ≥97%: R_f = 0.29 (20% EtOAc/ hexane); IR (liquid film) 2920 (m), 2860 (m), 1365 (m), 1090 (s), 1030 (m), 915 (s), 740 (s), 700 cm^{-1}; ^1H NMR δ (250 MHz, $CDCl_3$) 7.38-7.23 (5H, m, $C_6\underline{H}_5$), 5.93-5.70 (3H, m, 7-C$\underline{H}$, 10-C$\underline{H}$ & 11-C$\underline{H}$), 5.09 (1H, br d, *J* = 8.6 Hz, 6-C$\underline{H}_A$H$_B$), 5.04 (1H, br s, 6-CH$_A\underline{H}_B$), 4.45 (2H, s, C$\underline{H}_2$Ph), 4.20 (1H, br s, 9-C$\underline{H}$), 3.93-3.83 (1H, m, 13-C$\underline{H}$), 3.69-3.53 (2H, m, 15-C$\underline{H}_2$), 2.46-2.34 (1H, m, 8-C$\underline{H}_A$H$_B$), 2.29-2.18 (1H, m, 8-CH$_A\underline{H}_B$), 1.96-1.90 (2H, m, 12-C$\underline{H}_2$), 1.80 (2H, q, *J* = 6.5 Hz, 14-C$\underline{H}_2$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 138.5, 135.2, 129.2, 128.4, 127.7, 127.5, 124.4, 116.7, 73.1, 72.3, 66.9, 64.8, 38.8, 35.6, 30.7; m/z ($CI^+(NH_3)$) 276 (5, $[M+NH_4]^+$), 259 (100, $[M+H]^+$), 241 (5), 217 (10), 182 (5), 169 (5), 127 (7), 108 (25), 91 (45); HRMS ($CI^+(NH_3)$) Calcd for $C_{17}H_{23}O_2$ ($[M+H]^+$): 259.1698, found: 259.1698.

(2*RS*,6*SR*)-6-Benzyloxyethyl-5,6-dihydro-2-formylmethyl-2*H*-pyran (21).
To a cooled (–42 °C) solution of the glycal **17** (36.4 mg, 0.132 mmol) in PhMe (0.5 ml) was added a solution of *tert*-butyldimethylsilyloxyethene (**24**) (27 mg, 0.17 mmol) in PhMe (1 ml), followed by a solution of $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ in CH_2Cl_2 (0.094 ml of a 1.5*M* solution, 0.14 mmol). The resulting mixture was stirred at –42 °C for 1.7 h. The reaction mixture was quenched with $NaHCO_3$ solution (2 ml, sat. aq.) then warmed to room temperature and partitioned between $NaHCO_3$ solution (15 ml, sat. aq.) and CH_2Cl_2 (15 ml). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 ml) and the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a pale brown oil which was purified by flash chromatography (20% EtOAc/hexane) to give **21** as a colourless oil (27.6 mg, 80%). Examination of the product by capillary gas-liquid chromatography (run isothermally at 220 °C) showed it to contain 3% of the *cis* isomer **20** – the diastereoselectivity was therefore 97%: R_f = 0.14 (20% EtOAc/hexane); IR (liquid film) 1725 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.76 (1H, dd, *J* = 3.0, 1.6 Hz, 7-C$\underline{H}$O), 7.34–7.26 (5H, m, $C_6\underline{H}_5$), 5.90–5.85 (1H, m, 11-C$\underline{H}$), 5.68 (1H, br d, *J* = 10.2 Hz, 10-C$\underline{H}$), 4.77–4.75 (1H, m, 9-C$\underline{H}$), 4.53 (1H, d, *J* = 11.9 Hz, C$\underline{H}_A$H$_B$Ph), 4.43 (1H, d, *J* = 11.9 Hz, CH$_A\underline{H}_B$Ph), 3.89–3.82 (1H, m, 13-C$\underline{H}$), 3.60–3.50 (2H, m, 15-C$\underline{H}_2$), 2.73 (1H, ddd, *J* = 16.2, 9.1, 3.0 Hz, 8-C$\underline{H}_A$H$_B$), 2.49 (1H, ddd, *J* = 16.2, 4.5, 1.6 Hz, 8-CH$_A\underline{H}_B$), 2.07–1.92 (2H, m, 12-C$\underline{H}_2$), 1.79 (2H, dt, *J* = 6, 6 Hz, 14-C$\underline{H}_2$). Irradiation of 9-CH (δ_H 4.75-4.77) gave nuclear Overhauser enhancements to 7-CHO (δ_H 9.76), 8-CH$_A$ (δ_H 2.73), 8-CH$_B$ (δ_H 2.49) and 10-CH (δ_H 5.68). Irradiation of 13-CH (δ_H 3.82-3.89) gave nuclear Overhauser enhancements to 8-CH$_A$ (δ_H 2.73), 12-CH$_2$ (δ_H 1.92-2.07) and 14-CH$_2$ (δ_H 1.79). Irradiation of 8-CH$_A$ (δ_H 2.73) gave nuclear Overhauser enhancements to 7-CHO (δ_H 9.76), 9-CH (δ_H 4.75-4.77), 13-CH (δ_H 3.82-3.89) and 8-CH$_B$ (δ_H 2.49). Irradiation of 8-CH$_B$ (δ_H 2.49) gave nuclear Overhauser enhancements to 7-CHO (δ_H 9.76), 8-CH$_A$ (δ_H 2.73), 9-CH (δ_H 4.75-4.77) and 10-CH (δ_H 5.68); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 200.9, 138.4, 128.3, 127.8, 127.7, 127.5, 125.5, 73.0, 67.9, 66.4, 64.9, 47.7, 35.2, 30.3; m/z ($CI^+(NH_3)$) 278 (100, $[M+NH_4]^+$), 261 (75, $[MH]^+$), 234 (25), 217 (95), 127 (60), 108 (30); HRMS ($CI^+(NH_3)$) Calcd for $C_{16}H_{24}O_3N$ ($[M+NH_4]^+$): 278.1756, found 278.1756; Anal calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74, found: C, 73.64; H, 7.77.

(2*RS*,6*RS*)-6-Benzyloxyethyl-5,6-dihydro-2-formylmethyl-2*H*-pyran (22).
To a cooled (–78 °C) solution of **20** (15.5 mg, 0.053 mmol) in CH_2Cl_2 (1.0 ml) was added a solution of DIBAL-H in hexanes (0.058 ml of a 1.0*M* solution, 0.058 mmol). The resulting mixture was stirred at this temperature for 1 h. More DIBAL-H (0.016 ml of a 1.0*M* solution, 0.016 mmol) was then added and, after stirring at –78 °C for a further 20 min, the reaction was quenched by the addition of methanol (0.10 ml). After allowing to warm to room temperature, the mixture was partitioned between potassium sodium tartrate solution (15 ml, sat. aq.) and CH_2Cl_2 (15 ml), then the aqueous phase was extracted further with CH_2Cl_2 (15 ml). Each organic extract was washed with $NaHCO_3$ solution (10 ml, sat. aq.) then combined, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by flash chromatography (20% EtOAc/hexane) to give recovered **20** (3.1 mg, 20%) and product **22** as a colourless oil (7.7 mg, 56%): R_f = 0.16 (15% EtOAc/hexane); IR (liquid film) 1725 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.74 (1H, t, *J* = 2.3 Hz, C<u>H</u>O), 7.40-7.27 (5H, m, $C_6\underline{H}_5$), 5.89-5.85 (1H, m, 11-C<u>H</u>), 5.62 (1H, dm, *J* = 10 Hz, 10-C<u>H</u>), 4.62-4.54 (1H, m, 9-C<u>H</u>), 4.53 (1H, d, *J* = 12.0 Hz, $CH_A\underline{H}_BPh$), 4.49 (1H, d, *J* = 12.0 Hz, $C\underline{H}_AH_BPh$), 3.82-3.76 (1H, m, 13-C<u>H</u>), 3.66-3.54 (2H, m, 15-C$\underline{H}_2$), 2.53 (2H, dd, *J* = 6.2, 2.3 Hz, 8-C$\underline{H}_2$), 2.02-1.97 (2H, m, 12-C$\underline{H}_2$), 1.81 (2H, dt, *J* = 6.2, 6.2 Hz, 14-C$\underline{H}_2$). Irradiation of 9-C<u>H</u> (δ 4.62-4.54) gave nuclear Overhauser enhancements to 8-CH_2 (δ 2.53), 13-C<u>H</u> (δ 3.82-3.76), 10-C<u>H</u> (δ 5.62), and C<u>H</u>O (δ 9.74). Irradiation of 13-C<u>H</u> (δ 3.82-3.76) gave nuclear Overhauser enhancements to 14-C$\underline{H}_2$ (δ 1.81), 12-C$\underline{H}_2$ (δ 2.02-1.97), 9-C<u>H</u> (δ 4.54-4.62), and C<u>H</u>O (δ 9.74); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 201.7, 138.5, 128.4, 128.3, 127.7, 127.6, 126.2, 73.0, 71.0, 70.5, 66.3, 48.5, 36.0, 30.9.

(*E*,7*S*)-6-[(2*R*,6*S*)-6-{2-benzyloxyethyl}-5,6-dihydro-2*H*-pyran-2-yl]-5-(*tert*-butyldimethylsilyloxy)-2-methylhexa-2-dienal (26) and (*E*,7*R*)-6-[(2*R*,6*S*)-6-{2-benzyloxyethyl}-5,6-dihydro-2*H*-pyran-2-yl]-5-(*tert*-butyldimethyl-silyloxy)-2-methylhexa-2-dienal (27).
To a cooled (–78 °C) solution of the aldehyde **21** (0.232 g, 0.892 mmol) in a mixture of CH_2Cl_2 (8.5 ml) and Et_2O (1 ml) was added a solution of 2-methyl-1-trimethylsilyloxy-1,3-butadiene (**25**) (0.153 g, 0.98 mmol) in CH_2Cl_2 (1 ml) followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.120 ml, 0.98 mmol). After 2.3 h, the reaction was quenched by the addition of a mixture of THF (5 ml), H_2O (1 ml) and hydrochloric acid (0.4 ml of a 1*M* solution) and then warmed to room temperature for 10 min. The mixture was then poured into $NaHCO_3$ solution (40 ml, sat. aq.) and extracted with CH_2Cl_2 (3 x 30 ml). The combined organic layers were then dried (Na_2SO_4) and concentrated *in vacuo* to give an oil which was purified using flash chromatography (eluting with a gradient system of 15–70% Et_2O in CH_2Cl_2) to give the more polar, major epimer **26** (0.194 g, 63%) and the less polar, minor epimer **27** (20 mg, 7%), both as colourless oils, together with some recovered **21** (2.6 mg, 11%). The aldehyde *si : re* face selectivity was therefore 90 : 10.
26: R_f = 0.22 (30% Et_2O/CH_2Cl_2); IR (liquid film) 3440 (br), 1685 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.38 (1H, s, 3-C<u>H</u>O), 7.36–7.26 (5H, m, $C_6\underline{H}_5$), 6.54 (1H, br t, *J* = 7.2 Hz, 5-C<u>H</u>), 5.86–5.80 (1H, m, 11-C<u>H</u>), 5.61 (1H, dddd, *J* = 10.3, 2, 2, 2 Hz, 10-C<u>H</u>), 4.50–4.45 (3H, m, 9-C<u>H</u> and C$\underline{H}_2$Ph), 4.10–4.02 (1H, br m, 7-C<u>H</u>), 4.00–3.92 (1H, m, 13-C<u>H</u>), 3.65–3.52 (2H, m, 15-C$\underline{H}_2$), 2.94 (1H, brd, *J* = 3.8 Hz, O<u>H</u>), 2.56–2.41 (2H, m, 6-C$\underline{H}_2$), 2.14 (1H, dm, *J* = 17.4 Hz, 12-C$\underline{H}_AH_B$), 1.97–1.70 (7H, m, 4-C<u>Me</u>, 8-C$\underline{H}_AH_B$, 12-$CH_AC\underline{H}_B$, 14-C$\underline{H}_2$), 1.57 (1H, ddd, *J* = 14.5, 9.2, 3.2 Hz, 8-$CH_A\underline{H}_B$). Irradiation of 3-CHO (δ_H 9.38) gave nuclear Overhauser enhancement to 5-CH (δ_H 6.54). Irradiation of 5-CH (δ_H 6.54) gave nuclear Overhauser enhancement to 3-CHO (δ_H 9.38); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 195.2, 150.6, 140.7, 138.3, 128.9, 128.4, 127.6, 127.5, 124.4, 72.9, 68.6, 67.5, 66.8, 65.7, 39.7, 36.8, 34.4, 30.1, 9.4; m/z ($CI^+(NH_3)$) 345 (25, $[M+H]^+$), 327 (40), 231 (100), 141 (45), 127 (45), 108 (40), 91 (70); HRMS ($CI^+(NH_3)$) Calcd for $C_{21}H_{29}O_4$ ($M+H^+$): 345.2066, found: 345.2066; Anal Calcd for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19, found: C, 73.03; H, 8.27.
27: R_f = 0.30 (20% Et_2O/CH_2Cl_2); IR (liquid film) 3460 (br), 1685 (s) 700 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.42 (1H, s, 3-C<u>H</u>O), 7.36–7.26 (5H, m, $C_6\underline{H}_5$), 6.61 (1H, br dt, *J* = 7.2, 1.3 Hz, 5-C<u>H</u>), 5.85–5.79

(1H, m, 11-C<u>H</u>), 5.59 (1H, dm, J = 10.3 Hz, 10-C<u>H</u>), 4.51 (1H, d, J = 11.8 Hz, C<u>H</u>$_A$H$_B$Ph), 4.49 (1H, d, J = 11.8 Hz, CH$_A$<u>H</u>$_B$Ph), 4.42 (1H, dm, J = 10.0 Hz, 9-C<u>H</u>), 4.10–4.02 (2H, m, O<u>H</u> and 7-C<u>H</u> or 13-C<u>H</u>), 4.01–3.94 (1H, m, 7-C<u>H</u> or 13-C<u>H</u>), 3.63–3.53 (2H, m, 15-C<u>H</u>$_2$), 2.57–2.44 (2H, m, 6-C<u>H</u>$_2$), 2.08 (1H, dm, J = 17.4 Hz,), 2.00–1.71 (7H, m), 1.52 (1H, ddd, J = 14.6, 2.1, 2.1 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 195.3, 150.6, 140.6, 138.3, 128.4, 128.3, 127.7, 127.6, 124.3, 73.5, 73.0, 71.3, 66.7, 65.7, 39.5, 36.9, 35.0, 30.1, 9.5; m/z (CI$^+$(NH_3)) 345 (40, [M+H]$^+$), 327 (100), 231 (60), 217 (95), 141 (35), 127 (45), 108 (40), 91 (50, [PhCH$_2$]$^+$); HRMS (CI$^+$(NH_3)) Calcd for $C_{21}H_{29}O_4$ ([M+H]$^+$): 345.2066, found 345.2066.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{2-benzyloxyethyl}-5,6-dihydro-2*H*-pyran-2-yl]-7-hydroxy-4-methylocta-2,4-dienoate (28).

To a cooled (0 °C) solution of trimethylphosphonoacetate (0.26 ml, 1.6 mmol) in THF (5 ml) was added a solution of ^{n}BuLi in hexanes (1.0 ml of a 1.6 *M* solution, 1.6 mmol). The resulting mixture was stirred at room temperature for 15 min then recooled to 0 °C. A solution of the unsaturated aldehyde **26** (0.184 g, 0.535 mmol) in THF (5 ml) was added, and stirring at 0 °C was continued for 15 min, followed by warming to room temperature for 45 min. The reaction was quenched by the addition of pH7 buffer solution (5 ml), then poured into more pH 7 buffer solution (20 ml) and extracted with Et_2O (3 x 20 ml). Each extract was washed with brine (10 ml, sat. aq.), then combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography (40% EtOAc/hexane) to give **28** as a colourless oil (0.192 g, 90%). Examination of the ^{1}H and ^{13}C NMR spectra for this compound showed it to be a single geometric isomer: R_f = 0.20 (40% EtOAc/hexane); IR (liquid film) 3440 (br), 1715 (s) cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.35–7.25 (6H, m, 3-C<u>H</u> and C$_6$<u>H</u>$_5$), 5.90 (1H, br t, J = 7.3 Hz, 5-C<u>H</u>), 5.83–5.77 (2H, m, 2-C<u>H</u> and 11-C<u>H</u>), 5.61 (1H, m, 10-C<u>H</u>), 4.49 (2H, s, C<u>H</u>$_2$Ph), 4.45 (1H, br d, J = 7.2 Hz, 9-C<u>H</u>), 3.97–3.89 (2H, m, 7-C<u>H</u> and 13-C<u>H</u>), 3.73 (3H, s, CO$_2$<u>Me</u>), 3.63–3.52 (2H, m, 15-C<u>H</u>$_2$), 2.69 (1H, d, J = 4.4 Hz, O<u>H</u>), 2.44–2.28 (2H, m, 6-C<u>H</u>$_2$), 2.11 (1H, br ddd, J = 17.4, 4.4, 4.4 Hz), 1.96-1.72 (7H, m), 1.52 (1H, ddd, J = 14.4, 9.2, 3.1 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 167.8, 149.4, 138.3, 137.7, 134.6, 129.2, 128.3, 127.52, 127.49, 124.1, 115.6, 72.9, 68.8, 67.9, 66.8, 65.4, 51.4, 39.7, 36.8, 34.6, 30.2, 12.4; m/z (CI$^+$(NH_3)) 418 (20, [M+NH_4]$^+$), 401 (100, [M+H]$^+$), 383 (20), 217 (30), 127 (65), 108 (70), 91 (60), 81 (20); HRMS (CI$^+$(NH_3)) Calcd for $C_{24}H_{33}O_5$ ([M+H]$^+$): 401.2328, found: 401.2327; Anal calcd for $C_{24}H_{32}O_5$ C, 71.97; H, 8.05; found C, 71.93; H, 8.16%.

(*E*,*E*,7*R*)-Methyl-8-[(2*R*,6*S*)-6-{2-benzyloxyethyl}-5,6-dihydro-2*H*-pyran-2-yl]-7-hydroxy-4-methylocta-2,4-dienoate (29).

This compound was prepared from **27**, in a similar manner to **28**, to give the 7-*epi* diastereomer **29** as a colourless oil: R_f = 0.20 (10% Et_2O/CH_2Cl_2); IR (liquid film) 3460 (br), 1715 (s) cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.36–7.25 (6H, m, C$_6$<u>H</u>$_5$ and 3-C<u>H</u>), 5.96 (1H, br t, J = 7.3 Hz, 5-C<u>H</u>), 5.83–5.77 (2H, m, 2-C<u>H</u> and 11-C<u>H</u>), 5.59 (1H, dm, J = 10.2 Hz, 10-C<u>H</u>), 4.52 (1H, d, J = 11.8 Hz, C<u>H</u>$_A$H$_B$Ph), 4.48 (1H, d, J = 11.8 Hz, CH$_A$<u>H</u>$_B$Ph), 4.39 (1H, br d, J = 10.1 Hz, 9-C<u>H</u>), 3.99–3.92 (2H, m, 7-C<u>H</u> and 13-C<u>H</u>), 3.88 (1H, br s, O<u>H</u>), 3.74 (3H, s, CO$_2$<u>Me</u>), 3.62–3.53 (2H, m, 15-C<u>H</u>$_2$), 2.46–2.30 (2H, m, 6-C<u>H</u>$_2$), 2.07 (1H, br ddd, J = 17.3, 5.1, 3.8 Hz), 1.99–1.70 (7H, m), 1.51 (1H, ddd, J = 14.7, 2.2, 2.2 Hz); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 167.9, 149.5, 138.3, 137.7, 134.5, 128.6, 128.3, 127.7, 127.5, 124.2, 115.5, 73.5, 73.0, 71.8, 66.7, 65.6, 51.5, 39.4, 36.8, 35.1, 30.2, 12.4; m/z (CI$^+$(NH_3)) 401 (80, [M+H]$^+$), 383 (20), 305 (40), 231 (60), 217 (100), 127 (70), 108 (50), 91 (50); HRMS (CI$^+$(NH_3)) Calcd for $C_{24}H_{33}O_5$ ([M+H]$^+$): 401.2328, found: 401.2328.

(2''*E*,4''*E*,1*R*,3*R*,5*S*,6*S*,8*S*)-5-Bromomercurio-3-(2'-benzyloxyethyl)-8-(5''-methoxycarbonyl-3''-methyl-penta-2'',4''-dienyl)-2,7-dioxabicyclo[4,3,0]nonane (30).

To a solution of the alcohol **28** (17.7 mg, 0.044 mmol) in THF (1 ml) at room temperature was added $CaCO_3$ (9 mg, 0.09 mmol) followed by $Hg(OCOCF_3)_2$ (28 mg, 0.066 mmol). The resulting suspension was stirred at room temperature for 2.5 h. The reaction mixture was then diluted with THF (1 ml) and treated with KBr solution (2 ml, sat. aq.). After being vigorously stirred for 15 min, the mixture was poured into KBr (20 ml, sat. aq.) and extracted with Et_2O (3 x 10 ml). The combined extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to give an oil that was purified by flash chromatography (10% Et_2O/CH_2Cl_2) to give **30** as a colourless oil (24.1 mg, 81%): R_f = 0.27 (10% Et_2O/CH_2Cl_2); IR (liquid film) 1710 cm^{-1}; ^1H NMR δ (400 MHz, CD_3CN) 7.37–7.26 (6H, m, 3-C<u>H</u> and $C_6\underline{H}_5$), 6.01 (1H, br t, *J* = 7.6 Hz, 5-C<u>H</u>), 5.85 (1H, d, *J* = 15.8 Hz, 2-C<u>H</u>), 4.47 (1H, d, *J* = 12.1 Hz, $C\underline{H}_AH_BPh$), 4.45 (1H, d, *J* = 12.1 Hz, $CH_A\underline{H}_BPh$), 4.31 (1H, br ddd, *J* = 6, 6, 6 Hz, 9-C<u>H</u>), 4.02 (1H, dd, *J* = 7.6, 5.5 Hz, 10-C<u>H</u>), 3.93–3.86 (1H, m, 7-C<u>H</u>), 3.85–3.77 (1H, m, 13-C<u>H</u>), 3.68 (3H, s, $CO_2\underline{Me}$), 3.52–3.45 (2H, m, 15-$C\underline{H}_2$), 2.70 (1H, ddd, *J* = 9.4, 7.7, 4.4 Hz, 11-C<u>H</u>), 2.59–2.44 (2H, m, 6-$C\underline{H}_2$), 2.18–2.05 (2H, m, 8-$C\underline{H}_AH_B$ and 12-$C\underline{H}_AH_B$), 1.85–1.63 (7H, m, 4-C<u>Me</u>, 8-$CH_A\underline{H}_B$, 12-$CH_A\underline{H}_B$, 14-$C\underline{H}_2$). Irradiation of 7-C<u>H</u> (δ_H 3.86-3.93) gave nuclear Overhauser enhancements to 5-C<u>H</u> (δ_H 6.01), 6-$C\underline{H}_2$ (δ_H 2.59-2.44), 8-$C\underline{H}_AH_B$ (δ_H 2.1), 9-C<u>H</u> (δ_H 4.31) and 10-C<u>H</u> (δ_H 4.02). Irradiation of 9-C<u>H</u> (δ_H 4.31) gave nuclear Overhauser enhancements to 7-C<u>H</u> (δ_H 3.86-3.93), 8-$C\underline{H}_AH_B$ (δ_H 2.1) and 10-C<u>H</u> (δ_H 4.02); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 167.8, 149.3, 138.2, 136.7, 134.7, 128.4, 127.8, 127.7, 116.0, 78.9, 76.5, 74.6, 73.1, 69.0, 66.7, 51.5, 50.3, 35.7, 35.1, 34.2, 31.9, 12.5; m/z ($CI^+(NH_3)$) 681 (5, $[M+H]^+$), 401 (100), 383 (20), 217 (35), 127 (40), 108 (45), 91 (30); HRMS ($CI^+(NH_3)$) Calcd for $C_{24}H_{32}O_5{}^{79}BrO_5{}^{202}Hg$ ($[M+H]^+$): 681.1139, found: 681.1139.

(2''*E*,4''*E*,1*R*,3*R*,5*S*,6*S*,8*R*)-5-Bromomercurio-3-(2'-benzyloxyethyl)-8-(5''-methoxycarbonyl-3''-methyl-penta-2'',4''-dienyl)-2,7-dioxabicyclo[4,3,0]nonane (31).

This compound was prepared from **29**, in a similar way to mercurial **30**, to give **31** as a colourless oil: ^1H NMR δ (400 MHz, C_6D_6) 7.59 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 7.33–7.09 (5H, m, $C_6\underline{H}_5$), 5.94 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.67 (1H, br t, *J* = 7.3 Hz, 5-C<u>H</u>), 4.33 (2H, s, $C\underline{H}_2Ph$), 4.15–4.07 (1H, m, 7-C<u>H</u>), 3.73–3.69 (1H, m, 9-C<u>H</u>), 3.68–3.63 (1H, m, 13-C<u>H</u>), 3.48 (3H, s, $CO_2\underline{Me}$), 3.47–3.43 (1H, m, 10-C<u>H</u>), 3.36–3.26 (2H, m, 15-$C\underline{H}_2$), 2.20–2.03 (3H, m, 6-$C\underline{H}_2$ and 11-C<u>H</u>), 1.81 (1H, ddd, *J* = 13.0, 6.6, 3.3 Hz, 8-$C\underline{H}_AH_B$), 1.77–1.63 (3H, m, 12-$C\underline{H}_AH_B$ and 14-$C\underline{H}_2$), 1.46 (3H, s, 4-C<u>Me</u>), 1.23 (1H, ddd, *J* = 13.0, 7.8, 6.2 Hz, 8-$CH_A\underline{H}_B$), 1.00–0.90 (1H, m, 12-$CH_A\underline{H}_B$). Irradiation of 7-C<u>H</u> (δ_H 4.07-4.15) gave nuclear Overhauser enhancements to 5-C<u>H</u> (δ_H 5.67), 6-$C\underline{H}_2$ (δ_H 2.20-2.03), and 8-$C\underline{H}_AH_B$ (δ_H 1.81). Irradiation of 9-C<u>H</u> & 13-C<u>H</u> (δ_H 3.73-3.63) gave nuclear Overhauser enhancements to 8-$CH_A\underline{H}_B$ (δ_H 1.23), 10-C<u>H</u> (δ_H 3.47-3.43) and 12-$C\underline{H}_AH_B$ & 14-$C\underline{H}_2$ (δ_H 1.77-1.63). Irradiation of 10-C<u>H</u> (δ_H 3.47-3.43) gave nuclear Overhauser enhancements to 9-C<u>H</u> (δ_H 3.73) and 11-C<u>H</u> (δ_H 2.1).

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{2-benzyloxyethyl}-5,6-dihydro-2*H*-pyran-2-yl]-7-(*tert*-butyldimethylsilyl-oxy)-4-methylocta-2,4-dienoate (32).

To a cooled (–78 °C) solution of the alcohol **28** (53.7 mg, 0.134 mmol) in CH_2Cl_2 (2 ml) was added 2,6-lutidine (0.047 ml, 0.4 mmol) followed by *t*-$BuMe_2SiOTf$ (0.039 ml, 0.17 mmol). The resulting mixture was stirred at –78 °C for 0.5 h, then allowed to warm to room temperature. The reaction mixture was poured into $NaHCO_3$ solution (20 ml, sat. aq.) and extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product, which was purified using flash chromatography (10% EtOAc/hexane) to give **32** as a colourless oil (64.2 mg, 93%): R_f = 0.19 (10% EtOAc/hexane); IR (liquid film) 1720 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.37–7.26 (6H, m, 3-C<u>H</u> and $C_6\underline{H}_5$), 5.90 (1H, br t, *J* = 7.4 Hz, 5-C<u>H</u>), 5.81–5.73 (2H, m, 2-C<u>H</u> and 11-C<u>H</u>), 5.63 (1H, dm, *J* = 10.4 Hz, 10-C<u>H</u>), 4.51 (1H, d, *J* = 12.0 Hz, $C\underline{H}_AH_BPh$), 4.48 (1H, d, *J* = 12.0 Hz, $CH_A\underline{H}_BPh$), 4.29 (1H, br d, *J* = 10.6

Hz, 9-C<u>H</u>), 4.03–3.95 (1H, m, 7-C<u>H</u>), 3.78–3.68 (4H, m, 13-C<u>H</u> and CO_2<u>Me</u>), 3.63–3.55 (2H, m, 15-C<u>H_2</u>), 2.42–2.25 (2H, m, 6-C<u>H_2</u>), 2.00–1.90 (2H, m, 12-C<u>H_2</u>), 1.85–1.76 (2H, m, 14-C<u>H_2</u>), 1.73 (3H, s, 4-C<u>Me</u>), 1.65 (1H, ddd, J = 13.7, 10.7, 2.5 Hz, 8-C<u>$H_A$$H_B$</u>), 1.40 (1H, ddd, J = 14.2, 9.7, 2.7 Hz, 8-CH_A<u>H_B</u>), 0.89 (9H, s, C<u>Me</u>$_3$), 0.09 (3H, s, Si<u>Me$_A$</u>Me$_B$), 0.07 (3H, s, SiMe$_A$<u>Me$_B$</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 167.9, 149.6, 138.4, 137.9, 134.1, 130.3, 128.3, 127.5, 127.4, 123.9, 115.3, 73.0, 69.0, 68.0, 66.9, 63.8, 51.4, 40.5, 37.5, 35.7, 30.9, 25.9, 18.0, 12.4, -4.3, -4.7; m/z (CI$^+$(NH_3)) 532 (15, $[M+NH_4]^+$), 515 (90, $[M+H]^+$), 383 (40), 217 (75), 108 (70), 91 (100); HRMS (CI$^+$(NH_3)) Calcd for $C_{30}H_{47}O_5Si$ ($[M+H]^+$): 515.3193, found: 515.3195.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{2-hydroxyethyl}-5,6-dihydro-2*H*-pyran-2-yl]-7-(*tert*-butyldimethylsilyloxy)-4-methylocta-2,4-dienoate (33).

To a solution of the benzyl ether **32** (16 mg, 0.031 mmol) in CH_2Cl_2 (2 ml) was added DDQ (36 mg, 0.16 mmol) and H_2O (0.2 ml). The resulting mixture was stirred at room temperature for 18 h and was then partitioned between CH_2Cl_2 (10 ml) and $NaHCO_3$ solution (10 ml, sat. aq.). The aqueous phase was back extracted with CH_2Cl_2 (2 x 10 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (elution with 10% EtOAc/hexane then 10% Et_2O/CH_2Cl_2) to give **33** as a colourless oil (3.8 mg, 30%) together with some recovered starting material (0.8 mg, 5%). The spectral data for this compound is given later, where it was prepared by benzoate ester cleavage of **43**.

3-Benzoyloxypropanal (34).

To a stirred solution of 3-butene-1-ol (16.2 g, 0.225 moles) in CH_2Cl_2 (500 ml) was added dry pyridine (23.5 ml, 0.29 moles) and the resulting mixture was cooled in ice. Neat benzoyl chloride (36.5 ml, 0.26 moles) was then added dropwise from a pressure equalising dropping funnel, which was subsequently rinsed through with CH_2Cl_2 (5 ml), and the resulting suspension was stirred at room temperature for 18 h. The reaction mixture was then cooled in ice, and the excess benzoyl chloride was quenched by the addition of *N,N*-dimethylethylenediamine (11 ml, 0.10 moles). After stirring at room temperature for 1 h, the mixture was washed with hydrochloric acid (2 x 300 ml, 3M) and $NaHCO_3$ solution (300 ml, sat. aq.), then dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Distillation under reduced pressure afforded 1-benzoyloxybut-3-ene as a colourless liquid (34.3 g, 87%): bp 122–124 °C (18 mm Hg); IR (liquid film) 1719 (s) cm^{-1}; ^{1}H NMR δ (250 MHz, $CDCl_3$) 8.04 (2H, d m, J = ~ 8 Hz, Ar<u>H</u>), 7.55 (1H, tt, J = 7.3, 1.3 Hz, Ar<u>H</u>), 7.43 (2H, br dd, J = ~ 8, 8 Hz, Ar<u>H</u>), 5.88 (1H, dddd, J = 17.1, 13.4, 10.2, 6.7 Hz, 3-C<u>H</u>), 5.17 (1H, dddd, J = 17.1, 1.5, 1.5, 1.5 Hz,4-C<u>$H_A$$H_B$</u>), 5.11 (1H, dm, J = 10.2 Hz, 4-CH_A<u>H_B</u>), 4.37 (2H, t, J = 6.7 Hz, 1-C<u>H_2</u>), 2.52 (2H, tddd, J = 6.7, 6.7, 1.5, 1.5 Hz, 2-C<u>H_2</u>); ^{13}C NMR δ (62.5 MHz, $CDCl_3$) 166.8, 134.2, 133.0, 130.5, 129.7, 128.5, 117.5, 64.1, 33.3; Anal. calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86, found: C, 75.17; H, 6.93%.

To a solution of 4-benzoyloxy-but-1-ene (23.7 g, 0.135 moles) in a mixture of Me_2CO (35 ml) and H_2O (80 ml) was added *N*-methylmorpholine *N*-oxide (22.3 g, 0.190 moles), followed by a solution of OsO_4 in *t*-BuOH (7 ml of a 0.02 M solution, 0.14 mmol). The resulting brown two-phase mixture was stirred vigorously at room temperature and became homogeneous within 2 h. After 18 h, solid sodium sulfite (2 g) was added and stirring was continued for a further 15 min. The reaction mixture was then extracted with Et_2O (6 x 75 ml) and the organic layers were washed successively with sodium sulfite solution (50 ml, sat. aqueous), hydrochloric acid (50 ml, 3 M), and $NaHCO_3$ solution (50 ml, sat. aqueous). The acid and $NaHCO_3$ phases were further back-extracted with Et_2O (2 x 75 ml). The combined Et_2O layers were then dried (Na_2SO_4) and concentrated *in vacuo* to give a solid. Recrystallisation from EtOAc/hexane afforded two crops of (2*RS*)-2-hydroxy-3-(benzoyloxy)butan-1-ol as colourless needles (23.3 g, 82%): mp 50-51 °C; IR (thin film) 3347 (s, br), 1715 (s) cm^{-1}; ^{1}H NMR δ (250 MHz, $CDCl_3$) 8.01 (2H, d m, J = ~ 8 Hz, Ar<u>H</u>), 7.54 (1H, tt, J = 7.3, 1.3 Hz, Ar<u>H</u>),

7.41 (2H, br dd, J = ~ 8, 8 Hz, ArH), 4.56 (1H, ddd, J = 11.2, 8.4, 5.6 Hz, 15-CH_AH_B), 4.40 (1H, ddd, J = 11.2, 5.5, 5.5 Hz,15-CH_AH_B), 3.92–3.81 (1H, m, 13-CH), 3.67 (1H, ddd, J = 11.2, 6.0, 3.1 Hz, CH_AH_BOH), 3.55–3.40 (2H, m, CH_AH_BOH & 13-CHOH), 2.96 (1H, br t, J = 6.0 Hz, CH_2OH), 2.03–1.74 (2H, m, 14-CH_2); ^{13}C NMR δ (62.5 MHz, $CDCl_3$) 167.2, 133.3, 130.1, 129.8, 128.6, 69.1, 66.8, 61.8, 32.6; Anal. calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71, found: C, 62.94; H, 6.75%.

To a solution of (*2RS*)-2-hydroxy-3-(benzoyloxy)butan-1-ol (13.5 g, 64.3 mmol) in a mixture of Me_2CO (30 ml) and H_2O (100 ml) was added $NaIO_4$ (27.8 g, 130 mmol) in one portion. The resulting mixture soon became a thick slurry and an exotherm occurred, which was moderated by cooling in ice, and stirring was continued at 0 °C for 15 min. The reaction mixture was then poured into H_2O (50 ml) and the suspension was extracted with Et_2O (3 x 75 ml). The organic phases were washed with $NaHCO_3$ solution (50 ml, sat. aq.) and brine (50 ml, sat. aq.), then combined, dried (Na_2SO_4) and concentrated *in vacuo* to give an oil that was passed down a 12 cm column of silica eluting with 5% Et_2O/CH_2Cl_2. Removal of the solvent under vacuum gave **34** as a colourless oil (9.37 g, 83%). *NB*: This compound is best used immediately for any subsequent reactions as it undergoes facile elimination of benzoic acid: R_f = 0.21 (30% EtOAc/hexane); ^{1}H NMR δ (250 MHz, $CDCl_3$) 9.85 (1H, t, J = 1.5 Hz, 1-CHO), 7.99 (2H, dm, J = ~ 8 Hz, ArH), 7.55 (1H, tt, J = 7.3, 1.3 Hz, ArH), 7.42 (2H, br dd, J = ~ 8, 8 Hz, ArH), 4.65 (2H, t, J = 6.1 Hz, 3-CH_2), 2.90 (2H, td, J = 6.1, 1.5 Hz, 2-CH_2).

(*E*,5*R*)-7-Benzoyloxy-1-chloro-5-hydroxyhept-1-en-3-one (35).

To a solution of (+)-Ipc_2BCl (14.18 g, 44.2 mmol) in Et_2O (100 ml) was added *i*-Pr_2NEt (8.0 ml, 46 mmol) and the resulting solution was cooled to 0 °C. A solution of (*E*)-4-chlorobut-3-en-2-one (**13**) (4.81 g, 46 mmol) in Et_2O (5 ml + 5 ml rinse) was then added *via* cannula and the resulting pale yellow suspension was stirred at 0 °C for 2 h, then cooled to –78 °C. A solution of 3-benzoyloxypropanal (**34**) (7.48 g, 42 mmol) in Et_2O (5 ml + 5 ml rinse) was then added *via* cannula and the reaction was stirred at –78 °C for 2 h, after which time the reaction was sealed and placed in a freezer at –20 °C for 20 h, then stirred at 0 °C for 0.5 h. A bright orange colour developed during this time. The reaction mixture was then washed successively with hydrochloric acid (50 ml, 3 M) and $NaHCO_3$ solution (50 ml, sat. aq.) and the aqueous phases were back-extracted with Et_2O (50 ml). The organic layers were poured directly into a vigorously stirred mixture containing pH 7 buffer solution (100 ml) and MeOH (60 ml) at 0 °C and then H_2O_2 solution (45 ml, 30% aq.) was added. After stirring at 0 °C for 0.5 h, the layers were separated and the organic layer was washed successively with H_2O (75 ml), sodium metabisulphite (75 ml, 10% aq.) and brine (75 ml, sat. aq.). The aqueous phases were back-extracted with Et_2O (2 x 75 ml) and the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (gradient elution with 40→60% Et_2O/hexane) to give **35** as a colourless oil (6.2 g, 52%, *ca* 70% ee). Performing the reaction on a smaller scale (0.59 g of benzoyloxypropanal, 3.3 mmol) in PhMe afforded **35** (0.52 g, 56%) with *ca* 80% ee: R_f = 0.17 (50% Et_2O/petroleum ether bp 40-60); $[\alpha]_D^{20}$ = –16.0° (*c* 2.51, $CHCl_3$) (80% ee); IR (thin film) 3494 (m, br), 1715 (s) cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.01 (2H, dm, J = ~8 Hz, ArH), 7.55 (1H, tm, J = ~7.5 Hz, ArH), 7.42 (2H, br dd, J = ~8, 8 Hz, ArH), 7.33 (1H, d, J = 13.7 Hz, 9-CH), 6.52 (1H, d, J = 13.7 Hz, 10-CH), 4.58–4.39 (2H, m, 15-CH_2), 4.36–4.22 (1H, br m, 13-CH), 3.25 (1H, br d, J = 3.4 Hz, OH), 2.73 (2H, d, J = 5.9 Hz, 12-CH_2), 2.02–1.83 (2H, m, 14-CH_2); ^{13}C NMR δ (62.5 MHz, $CDCl_3$) 197.2, 166.8, 138.1, 133.1, 132.5, 130.1, 129.6, 128.4, 64.4, 61.5, 47.5, 35.5; m/z (+FAB, NOBA) 305 (10, $[M + Na]^+$), 283 (90, $[M+H]^+$), 265 (30), 161 (100), 137 (90); HRMS (+FAB, NOBA) Calcd for $C_{14}H_{16}ClO_4$ ($[M+H]^+$): 283.0737, found: 283.0752; Anal calcd for $C_{14}H_{15}ClO_4$: C, 59.48; H, 5.35; found: C, 59.66; H, 5.27%.

(*2R*)-2-(Benzoyloxyethyl)-2,3-dihydro-4*H*-pyran-4-one (36).

To a cooled (–78 °C) solution of (*5R*)-7-benzoyloxy-1-chloro-5-hydroxy-hept-1-en-3-one (**35**) (4.06 g, 14.4 mmol) in CH_2Cl_2 (10 ml) was added ^{i}Pr_2NEt (2.0 ml, 11.5 mmol) followed by Me_3SiOTf (2.92 ml, 15.1

mmol). The resulting mixture was stirred at –78 °C for 5 min, then allowed to warm to room temperature and stirred for 1.25 h. A dark green colour developed during this time. The reaction mixture was poured into hydrochloric acid (50 ml, 1 M) and extracted with CH_2Cl_2 (2 x 30 ml). The organic layers were washed with $NaHCO_3$ solution (30 ml, sat. aq.), which resulted in a colour change from dark green to dark brown, and were then combined, dried (Na_2SO_4) and concentrated *in vacuo* to give a black oil. Flash chromatography (gradient elution with 30→40% EtOAc/petroleum ether bp 40-60) gave semi-pure **36** as a yellow oil (2.35 g, 66%). Most of the coloured impurity could be removed by treatment of an Et_2O solution of the product with decolourising charcoal to give, after filtration and removal of the solvent under vacuum, the dihydropyrone **36** as a pale yellow solid (2.10 g, 59%). On a smaller scale, it was not necessary to treat the chromatographed product with decolourising charcoal, and **36** was isolated in 61% yield. Dihydropyrone of ≥50% ee could be recrystallised to enantiomeric purity according to the following procedure. Dihydropyrone **36** (2.85 g, $[\alpha]_D^{20}$ = +46° (*c* 3.0, $CHCl_3$), *ca* 70% ee) was dissolved in hot Et_2O (*ca* 20 ml) and petroleum ether (bp 40–60) was added with warming until the solution became slightly cloudy. The cystallisation was then seeded with a crystal of enantiomerically-pure product and the mixture was left at room temperature until no more crystals were being formed, and was then cooled to 0 °C for 0.5 h. The solid was collected by decantation of the mother liquors and the resulting needles were washed with 50% Et_2O/petroleum ether to give enantiomerically enriched **36** (2.07 g, $[\alpha]_D^{20}$ = +61.5° (*c* 3.0 $CHCl_3$)). The process was repeated twice more to give enantiomerically-pure **36** (1.71 g, 60%, $[\alpha]_D^{20}$ = +66.2° (*c* 2.7, $CHCl_3$): mp (racemate) 45–46 °C; (single enantiomer) 62–63 °C; R_f = 0.23 (40% EtOAc/hexane); IR (thin film) 1719 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 8.01 (2H, br d, *J* = ~8 Hz, ArH), 7.56 (1H, br t, *J* = ~8 Hz, ArH), 7.44 (2H, br dd, *J* = ~8, 8 Hz), 7.35, (1H, d, *J* = 6.0 Hz, 9-CH), 5.43 (1H, dd, *J* = 6.0, 0.8 Hz, 10-CH), 4.64 (1H, dddd, *J* = 12.6, 8.4, 4.2, 4.2 Hz, 13-CH), 4.50 (2H, m, 15-CH_2), 2.62 (1H, dd, *J* = 16.7, 13.4 Hz, 12-CH_AH_B), 2.52 (1H, ddd, *J* = 16.7, 3.1, 0.8 Hz, 12-CH_AH_B), 2.31-2.22 (1H, m, 14-CH_AH_B), 2.19-2.11 (1H, m, 14-CH_AH_B); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 191.9, 166.3, 162.9, 133.1, 129.8, 129.5, 128.4, 107.3, 76.3, 60.3, 41.8, 33.6; m/z (CI^+, NH_3) 264 (25, $[M+NH_4]^+$), 247 (100, $[M+H]^+$), 124 (20), 105 (30); Anal. calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73, found: C, 68.42; H, 5.69.

(2*R*,4*S*)-4-Hydroxy-2-benzoyloxyethyl-3,4-dihydro-2*H*-pyran (37).
To a solution of $CeCl_3 \cdot 7H_2O$ (13.8 g, 10.3 mmol) in absolute EtOH (100 ml) was added a solution of (2*R*)-2-benzoyloxyethyl-2,3-dihydro-4H-pyran-4-one (**36**) (2.30 g, 9.35 mmol) in EtOH (100 ml) and the resulting mixture was cooled to –78 °C. A solution of $NaBH_4$ (0.48 g, 12.7 mmol) in EtOH (50 ml) was then added over 1 h from a pressure equalising dropping funnel. The reaction mixture was then warmed to room temperature and quenched with pH 7 buffer solution (50 ml). Most of the EtOH was removed *in vacuo* and the residue was poured into H_2O (100 ml) and extracted with Et_2O (4 x 75 ml). The extracts were then washed with brine (50 ml, sat. aq.) and combined, dried (Na_2SO_4) and concentrated *in vacuo* to give **37** as a pale yellow oil (2.32 g, 100%). This material was usually sufficiently pure to take on to the next step, but an analytical sample was obtained by flash chromatography (60% Et_2O/petroleum ether bp 40–60): R_f = 0.26 (60% Et_2O/petroleum ether bp 40-60); $[\alpha]_D^{20}$ = –11.7° (*c* 3.4, $CHCl_3$); IR (thin film) 3419 (s, br), 1718 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 8.01 (2H, dm, *J* = ~8 Hz, ArH), 7.53 (1H, br t, *J* = ~8 Hz, ArH), 7.41 (2H, br dd, *J* = ~8, 8 Hz, ArH), 6.34 (1H, d, *J* = 6.2 Hz, 9-CH), 4.75 (1H, ddd, *J* = 6.2, 1.9, 1.9 Hz, 10-CH), 4.48–4.38 (3H, m, 11-CH and 15-CH_2), 4.12 (1H, dddd, *J* = 11.1, 7.6, 4.3, 2.0 Hz, 13-CH)), 2.18 (1H, dddd, *J* = 13.1, 6.5, 1.9. 1.9 Hz, 12-CH_AH_B), 2.13–1.96 (2H, m, 14-CH_2), 1.68 (1H, ddd, *J* = 13.1, 11.2, 9.1 Hz, 12-CH_AH_B); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 166.5, 144.7, 132.9, 130.1, 129.5, 128.3, 105.5, 71.5, 62.6, 61.2, 37.8, 34.1; m/z (CI^+, NH_3) 266 (5, $[M+NH_4]^+$), 248 (20), 231 (100), 109 (15); HRMS (CI^+, NH_3) Calcd for $C_{14}H_{20}NO_4$ ($[M+NH_4]^+$): 266.1392, found: 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found C, 67.57; H, 6.42%.

(2*R*,4*S*)-4-Acetoxy-2-benzoyloxyethyl-3,4-dihydro-2*H*-pyran (38).
To a solution of *(2R),(4S)*-4-hydroxy-2-benzoyloxyethyl-3,4-dihydro-2*H*-pyran (**37**) (2.32 g, 9.35 mmol, crude from the previous step) in CH_2Cl_2 (40 ml) was added $^iPr_2NEt$ (3.0 ml, 17.2 mmol) and DMAP (0.060 g, 0.5mmol), followed by Ac_2O (1.32 ml, 14.0 mmol). The resulting mixture was stirred at room temperature for 18 h and was then washed with hydrochloric acid (30 ml, 1 M) and $NaHCO_3$ solution (30 ml, sat. aq.). The aqueous phases were back-extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil, which was purified by flash chromatography through a short column of silica (40% Et_2O/petroleum ether bp 40-60) to give the glycal **38** as a colourless oil (2.63 g, 97%). This material is very acid-sensitive, and the chromatographic step should be performed as quickly as possible to minimise the exposure time to silica: $R_f = 0.26$ (20% EtOAc/hexane); $[\alpha]_D^{20} = -36.5°$ (*c* 3.1, $CHCl_3$); IR (thin film) 1721 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 8.02 (2H, br d, *J* = ~8 Hz, ArH), 7.56 (1H, br t, *J* = ~8 Hz, ArH), 7.44 (2H, br dd, *J* = ~8, 8 Hz, ArH), 6.44 (1H, dd, *J* = 6.3. 1.4 Hz, 9-CH), 5.38 (1H, dddd, *J* = 8.1, 6.6, 2.6, 1.4 Hz, 11-CH), 4.77 (1H, ddd, *J* = 6.3, 2.6, 1.5 Hz, 10-CH), 4.49–4.40 (2H, m, 15-CH_2), 4.22 (1H, dddd, *J* = 10.3, 8.9, 4.1, 2.5 Hz, 13-CH), 2.29 (1H, dddd, *J* = 13.4, 6.6, 2.5, 1.5 Hz, 12-CH_AH_B), 2.20–2.08 (1H, m, 14-CH_AH_B), 2.06–1.97 (4H, m, 14-CH_AH_B & OCOMe), 1.79 (1H, ddd, *J* = 13.4, 10.3, 8.1 Hz, 12-CH_AH_B); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 170.8, 166.4, 146.3, 133.0, 130.1, 129.5, 128.3, 100.9, 71.0, 65.1, 61.1, 33.7, 33.3, 21.2; m/z (CI^+, NH_3) 308 (5, $[M+NH_4]^+$), 248 (20), 231 (100), 108 (15); HRMS ((CI^+, NH_3) Calcd for $C_{16}H_{22}NO_5$ ($[M+NH_4]^+$): 308.1498, found: 308.1498; Anal calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25, found: C, 66.25; H, 6.35%.

(2*R*,6*S*)-6-Benzoyloxyethyl-5,6-dihydro-2-formylmethyl-2*H*-pyran (39).
To a cooled (–42 °C) solution of *(2R,4S)*-4-acetoxy-2-benzoyloxyethyl-3,4-dihydro-2*H*-pyran (**38**) (0.510 g, 1.76 mmol) in PhMe (15 ml) was added *tert*-butyldimethylsilyloxyethene (**24**) (0.36 g, 2.3 mmol), followed by slow addition of $Cl_2Ti(O^iPr)_2$ in CH_2Cl_2 (1.95 ml of a 2 M solution, 3.9 mmol). The resulting pale yellow solution was stirred at –42 °C for 0.5 h and the reaction was then quenched with $NaHCO_3$ solution (5 ml, sat. aq.). After warming to room temperature, the mixture was partitioned between $NaHCO_3$ solution (30 ml, sat. aq.) and CH_2Cl_2 (50 ml). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil which was purified by flash chromatography (gradient elution with 20→30% EtOAc/hexane) to give the aldehyde **39** as a colourless oil (0.392 g, 81%). Performing the reaction on a smaller scale (53.0 mg, 0.183 mmol of starting material) afforded the same product in 83% yield. Examination of the product by ^1H and ^{13}C NMR showed it to be single isomer indicating ≥97% diastereoselectivity: $R_f = 0.25$ (30% EtOAc/hexane); $[\alpha]_D^{20} = -17.5°$ (*c* 2.9, $CHCl_3$); IR 1725 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.79 (1H, dd, *J* = 2.8, 1.2 Hz, 7-CHO), 8.02 (2H, br d, *J* = ~8 Hz, ArH), 7.54 (1H, br t, *J* = ~8 Hz, ArH), 7.43 (2H, br dd, *J* = ~8, 8 Hz, ArH), 5.90–5.85 (1H, m, 11-CH), 5.70 (1H, dm, *J* = 10.9 Hz, 10-CH), 4.83–4.75 (1H, m, 9-CH), 4.46–4.36 (2H, m, 15-CH_2), 3.89–3.82 (1H, m, 13-CH), 2.76 (1H, ddd, *J* = 16.3, 9.0, 2.8 Hz, 8-CH_AH_B), 2.53 (1H, ddd, *J* = 16.3, 4.6, 1.2 Hz, 8-CH_AH_B), 2.12–1.99 (2H, m, 12-CH_2), 1.99-1.92 (2H, m, 14-CH_2); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 200.7, 166.4, 132.9, 130.2, 129.5, 128.3, 127.9, 125.1, 67.8, 64.9, 61.4, 47.7, 34.1, 30.2; m/z (EI) 274 (5, $[M]^+$), 231 (60), 179 (40), 169 (30), 140 (50), 113 (30), 105 (100), 77 (50); HRMS (EI) Calcd for $C_{16}H_{18}O_4$ ($[M]^+$): 274.1205; Found: 274.1189. Anal Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61, found: C, 69.97; H, 6.65%.

(*E*,7*S*)-6-[(2*R*,6*S*)-6-(2-benzoyloxyethyl)-5,6-dihydro-2*H*-pyran-2-yl]-5-(*tert*-butyldimethylsilyloxy)-2-methylhexa-2-dienal (40) and (*E*,7*R*)-6-[(2*R*,6*S*)-6-(2-benzoyloxyethyl)-5,6-dihydro-2*H*-pyran-2-yl]-5-(*tert*-butyldimethylsilyloxy)-2-methylhexa-2-dienal (41).
To a cooled (–78 °C) solution of the aldehyde **39** (0.392 g, 1.43 mmol) in a mixture of CH_2Cl_2 (9 ml) and Et_2O (1 ml) was added 2-methyl-1-trimethylsilyloxy-1,3-butadiene (**25**) (0.295 ml, 1.57 mmol). Freshly distilled

BF_3•OEt_2 (0.387 ml, 3.15 mmol) was then added dropwise and the resulting pale yellow solution was stirred at –78 °C for 1 h, followed by the addition of a mixture comprising of THF (5 ml), H_2O (1 ml) and hydrochloric acid (0.5 ml, 1*M*). The resulting solution was warmed to room temperature, stirred for 10 min and was then poured into $NaHCO_3$ solution (30 ml, sat. aq.) and extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Flash chromatography (gradient elution with 20 → 70% Et_2O/CH_2Cl_2) afforded the less polar, minor epimer **41** (76 mg, 15%) and the more polar, major epimer **40** (0.357 g, 70%), together with some recovered **39** (34 mg, 9%). The aldehyde *si:re* face selectivity was therefore 81 : 19.

40: R_f = 0.20 (30% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = +1.6° (*c* 5.3, $CHCl_3$); IR (thin film) 3470 (br), 1720 (s), 1685 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.33 (1H, s, 3-CHO), 8.01 (2H, dm, *J* = ~8.0 Hz, ArH), 7.55 (1H, tt, *J* = 7.4, 1.4 Hz, ArH), 7.42 (2H, br dd, *J* = ~8, 8 Hz, ArH), 6.53 (1H, td, *J* = 7.2, 1.2 Hz, 5-CH), 5.87–5.82 (1H, m, 11-CH), 5.64 (1H, ddd, *J* = 10.3, 4.1, 2.1 Hz, 10-CH), 4.55–4.48 (2H, m, 9-CH and 15-CH_AH_B), 4.42–4.36 (1H, m, 15-CH_AH_B), 4.13–4.02 (1H, m, 7-CH), 3.98–3.91 (1H, m, 13-CH), 2.81 (1H, d, *J* = 9.4 Hz, OH), 2.50–2.35 (2H, m, 6-CH_2), 2.18 (1H, dm, *J* = 17.4 Hz, 12-CH_AH_B), 2.06–1.92 (3H, m, 12-CH_AH_B & 14-CH_2), 1.75 (1H, ddd, *J* = 14.5, 9.8, 2.5 Hz, 8-CH_AH_B), 1.67 (3H, br d, *J* = 1.2 Hz, 4-CMe), 1.56 (1H, ddd, *J* = 14.5, 9.8, 3.0 Hz, 8-CH_AH_B); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 195.1, 166.5, 150.4, 140.8, 133.1, 130.1, 129.5, 129.1, 128.4, 124.1, 68.5, 67.2, 65.0, 61.5, 40.0, 37.0, 33.5, 30.1, 9.4; m/z (CI^+, NH_3) 376 (5, $[M+NH_4]^+$), 359 (5, $[M+H]^+$), 341 (30), 245 (85), 231 (100), 105 (60); HRMS (+FAB, NOBA) Calcd for $C_{21}H_{27}O_5$ ($[M+H]^+$): 359.18583, found: 359.18750; Anal Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31, found: C, 70.22; H, 7.35%.

41: R_f = 0.26 (20% Et_2O/CH_2Cl_2); $[\alpha]_D^{20}$ = –23.7° (*c* 3.1, $CHCl_3$); IR (thin film) 3486 (br, s), 1715 (s), 1682 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 9.36 (1H, s, 3-CH), 8.01 (2H, dm, *J* = ~8 Hz, ArH), 7.53 (1H, tt, *J* = 7.4, 1.3 Hz, ArH), 7.40 (2H, br dd, *J* = ~8, 8 Hz, ArH), 6.59 (1H, ddd, *J* = 7.2, 7.2, 1.2 Hz, 5-CH), 5.84–5.79 (1H, m, 11-CH), 5.60 (1H, ddd, *J* = 10.3, 4.1, 2.5 Hz, 10-CH), 4.49–4.36 (3H, m, 9-CH & 15 CH_2), 4.10–4.04 (1H, m, 7-CH), 3.96 (1H, dddd, *J* = 8.3, 8.3, 4.6, 4.6 Hz, 13-CH), 3.77 (1H, br s, OH), 2.48 (2H, br dd, *J* = 6.6, 6.6 Hz, 6-CH_2), 2.13 (1H, dm, *J* = 17.3 Hz, 12-CH_AH_B), 2.06–1.91 (3H, m, 12-CH_AH_B & 14-CH_2), 1.79 (1H, ddd, *J* = 14.6, 10.5, 9.4 Hz, 8-CH_AH_B), 1.70 (3H, d, *J* = 1.2 Hz, 4-CMe), 1.54 (1H, ddd, *J* = 14.6, 2.8, 2.8 Hz, 8-CH_AH_B); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 195.1, 166.4, 150.4, 140.6, 133.0, 130.0, 129.5, 128.5, 128.3, 124.0, 72.7, 70.7, 65.3, 61.2, 39.8, 36.6, 33.9, 29.8, 9.3; m/z (CI^+, NH_3) 376 (60, $[M+NH_4]^+$), 359 (10, $[M+H]^+$), 341 (70), 245 (70), 231 (100), 105 (25); HRMS ($CI^+(NH_3)$) Calcd for $C_{21}H_{27}O_5$ ($[M+H]^+$) 359.1858, found: 359.1858.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-(2-benzoyloxyethyl)-5,6-dihydro-2*H*-pyran-2-yl]-7-hydroxy-4-methylocta-2,4-dienoate (42).

To a cooled (0 °C) solution of trimethylphosphonoacetate (0.75 ml, 4.6 mmol) in THF (15 ml) was added *n*-BuLi in hexanes (2.6 ml of a 1.6 M solution, 4.2 mmol) and the resulting solution was stirred at 0 °C for 15 min. A solution of the α,β-unsaturated aldehyde **40** (0.548 g, 1.53 mmol) in THF (3 ml + 2 x 2 ml rinses) was added *via* cannula and the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with pH 7 buffer solution (10 ml), then poured into brine (50 ml, sat. aq.), and extracted with Et_2O (4 x 30 ml). The combined organic layers were then dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. Flash chromatography (gradient elution with 40→50% EtOAc/hexane) gave the dienoate **42** as a colourless oil (0.560 g, 88%): R_f = 0.16 (40% EtOAc/hexane); $[\alpha]_D^{20}$ = +0.8° (*c* 2.9, $CHCl_3$); IR (liquid film) 3480 (br), 1725 (s), 1715 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 8.01 (2H, dm, *J* = ~8 Hz, ArH), 7.54 (1H, br t, *J* = ~8 Hz, ArH), 7.42 (2H, br dd, *J* = ~8, 8 Hz, ArH), 7.28 (1H, d, *J* = 15.7 Hz, 3-CH), 5.88 (1H, br dd, *J* = 7.4, 7.4 Hz, 4-CH), 5.80–5.85 (1H, m, 11-CH), 5.77 (1H, d, *J* = 15.7 Hz, 2-CH), 5.63 (1H, ddd, *J* = 10.3, 4.0, 2.1 Hz, 10-CH), 4.51–4.38 (3H, m, 9-CH and 15-CH_2), 3.97–3.89 (2H, m, 7-CH and 13-CH), 3.72 (3H, s, CO_2Me), 2.58 (1H, br d, *J* = 3.7 Hz, OH), 2.35 (1H, ddd, *J* = 15.0, 7.5, 7.5 Hz, 6-CH_AH_B), 2.26

(1H, br ddd, J = 15.0, 6.4, 6.4 Hz, 6-$CH_A\underline{H}_B$), 2.15 (1H, dm, J = 17.4 Hz, 12-C$\underline{H}_A$H$_B$), 2.06–1.91 (3H, m, 12-$CH_A\underline{H}_B$ &14-C$\underline{H}_2$), 1.72 (1H, ddd, J = 14.5, 9.7, 2.5 Hz, 8-C$\underline{H}_A$H$_B$), 1.71 (3H, s, 4-C$\underline{Me}$), 1.52 (1H, ddd, J = 14.5, 9.7, 3.0 Hz, 8-$CH_A\underline{H}_B$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 167.8, 166.5, 149.4, 137.4, 134.7, 133.0, 130.1, 129.5, 129.4, 128.4, 123.9, 115.7, 68.7, 67.7, 64.9, 61.5, 51.4, 39.9, 37.0, 33.6, 30.2, 12.3; m/z (+FAB, NOBA) 437 (50, $[M+Na]^+$), 415 (60, $[M+H]^+$), 383 (15), 275 (10), 245 (40), 231 (100); (CI^+, NH_3) 432 (5, $[M+NH_4]^+$), 415 (40, $[M+H]^+$), 400 (15), 245 (30), 231 (100), 105 (50); HRMS (+FAB, NOBA) Calcd for $C_{24}H_{31}O_6$ ($[M+H]^+$): 415.2122, found 415.2133; Anal calcd for $C_{24}H_{30}O_6$: C, 69.55; H, 7.30, found: C, 69.44; H, 7.43%.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-(2-benzyloxyethyl)-5,6-dihydro-2*H*-pyran-2-yl]-7-(*tert*-butyldimethylsilyloxy)-4-methylocta-2,4-dienoate (43).

To a cooled (–78 °C) solution of the alcohol **42** (0.503 g, 1.21 mmol) in CH_2Cl_2 (15 ml) was added 2,6-lutidine (0.28 ml, 2.4 mmol) and the mixture was stirred for 5 min. TBSOTf (0.33 ml, 1.4 mmol) was then added and stirring at –78 °C was continued for 15 min, followed by the addition of pH7 buffer solution (3 ml). The mixture was then warmed to room temperature and partitioned between hydrochloric acid (20 ml, 1 M) and CH_2Cl_2 (20 ml). The aqueous phase was back-extracted with CH_2Cl_2 (2 x 30 ml) and the combined organic layers were washed with $NaHCO_3$ solution (30 ml, sat. aq.), then combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient elution with 5→8% EtOAc/petroleum ether bp 40-60) to give the *tert*-butyldimethylsilyl ether **43** as a viscous, colourless oil (0.608 g, 95%): R_f = 0.24 (10% EtOAc/hexane); $[\alpha]_D^{20}$ = –45.0° (*c* 2.9, $CHCl_3$); IR (liquid film) 1725 (s) cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.02 (2H, dm, J = ~8 Hz, Ar$\underline{H}$), 7.54 (1H, tt, J = ~8, 1 Hz, Ar$\underline{H}$), 7.43 (2H, br dd, J = ~8, 8 Hz, Ar$\underline{H}$), 7.24 (1H, d, J = 15.7 Hz, 3-C$\underline{H}$), 5.87 (1H, br dd, J = 7.4, 7.3 Hz, 5-C$\underline{H}$), 5.77 (1H, dddd, J = 10.0, 5.0, 2.5, 2.5 Hz, 11-C$\underline{H}$), 5.73 (1H, d, J = 15.7, 2-C$\underline{H}$), 5.64 (1H, br d, J = 10.0 Hz, 10-C$\underline{H}$), 4.55–4.48 (1H, m, 15-C$\underline{H}_A$H$_B$), 4.41–4.34 (1H, m, 15-$CH_A\underline{H}_B$), 4.33 (1H, br d, J = 10.6 Hz, 9-C$\underline{H}$), 4.03–3.97 (1H, m, 7-C$\underline{H}$), 3.77 (1H, dddd, J = 8.9, 8.9, 3.9, 3.9 Hz, 13-C$\underline{H}$), 3.71 (3H, s, $CO_2\underline{Me}$), 2.26 (1H, ddd, J = 15.2, 6.4, 6.4 Hz, 6-C$\underline{H}_A$H$_B$), 2.16 (1H, ddd, J = 15.2, 8.2, 4.3 Hz, 6-$CH_A\underline{H}_B$), 2.06–1.95 (3H, m, 12-C$\underline{H}_2$ & 14-C$\underline{H}_A$H$_B$), 1.94–1.84 (1H, m, 14-$CH_A\underline{H}_B$), 1.71 (3H, s, 4-C$\underline{Me}$), 1.58 (1H, ddd, J = 14.4, 10.7, 2.4 Hz, 8-C$\underline{H}_A$H$_B$), 1.37 (1H, ddd, J = 14.4, 10.1, 2.5 Hz, 8-$CH_A\underline{H}_B$), 0.86 (9H, s, SiC$\underline{Me}_3$), 0.10 (3H, s, Si$\underline{Me}_A$Me$_B$), 0.06 (3H, s, Si$Me_A\underline{Me}_B$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 167.9, 166.4, 149.5, 137.7, 134.0, 132.9, 130.4, 130.2, 129.4, 128.4, 123.6, 115.2, 69.1, 67.6, 63.3, 61.5, 51.4, 40.3, 37.3, 34.6, 30.9, 25.8, 18.0, 12.3, –4.4, –4.8; m/z (+FAB NOBA) 529 (50, $[M+H]^+$), 497 (20), 471 (30), 397 (20), 389 (30), 365 (35), 303 (95), 283 (85), 231 (100); HRMS (+FAB, NOBA) Calcd for $C_{30}H_{45}O_6Si$ ($[M+H]^+$): 529.2985, found 529.2956; Anal calcd for $C_{30}H_{44}O_6Si$: C, 68.15; H, 8.39, found: C, 68.12; H, 8.44%.

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{2-hydroxyethyl}-5,6-dihydro-2*H*-pyran-2-yl]-7-(*tert*-butyldimethylsilyloxy)-4-methylocta-2,4-dienoate (33).

To a solution of the benzoate ester **43** (0.546 g, 1.03 mmol) in dry MeOH (15 ml) was added anhydrous K_2CO_3 (0.55 g, 4.0 mmol) and the resulting suspension was stirred at room temperature for 3 h. The mixture was then partitioned between brine (30 ml, sat. aq.) and Et_2O (30 ml) and the aqueous phase was extracted with Et_2O (3 x 20 ml). The combined organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (30% EtOAc/hexane) to give the primary alcohol (-)-**33** as a viscous, colourless oil (0.421g, 96%): R_f = 0.23 (30% EtOAc/hexane); $[\alpha]_D^{20}$ = –81.6° (*c* 1.5, $CHCl_3$); IR (thin film) 3466 (br, m), 1720 (s) cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 7.31 (1H, d, J = 15.7 Hz, 3-C$\underline{H}$), 5.92 (1H, br dd, J = 7.4, 7.4 Hz, 5-C$\underline{H}$), 5.79 (1H, d, J = 15.7 Hz, 2-C$\underline{H}$), 5.78–5.73 (1H, m, 11-C$\underline{H}$), 5.60 (1H, dm, J = 10.2 Hz, 10-C$\underline{H}$), 4.34 (1H, br d, J = 10.7 Hz, 9-C$\underline{H}$), 4.02–3.95 (1H, m, 7-C$\underline{H}$), 3.79–3.66 (6H, m, 13-C$\underline{H}$, 14-C$\underline{H}_2$ & $CO_2\underline{Me}$), 2.67 (1H, br s, O$\underline{H}$), 2.44–2.32 (2H, m, 6-C$\underline{H}_2$), 2.04 (1H, dddd, J = 17.3, 2.4, 2.4, 2.4 Hz, 12-C$\underline{H}_A$H$_B$), 1.88 (1H, dm, J = 17.3 Hz, 12-$CH_A\underline{H}_B$), 1.76 (3H, s, 4-C$\underline{Me}$), 1.75–1.71

(2H, m, 14-C$\underline{H}_2$), 1.70 (1H, ddd, J = 14.4, 10.7, 2.1 Hz, 8-C$\underline{H}_A$H$_B$), 1.37 (1H, ddd, J = 14.4, 10.0, 2.4 Hz, 8-CH$_A\underline{H}_B$), 0.86 (9H, s, SiC$\underline{Me}_3$), 0.063 (3H, s, Si$\underline{Me}_A$Me$_B$), 0.056 (3H, s, SiMe$_A\underline{Me}_B$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 168.0, 149.5, 137.5, 134.3, 129.8, 123.7, 115.5, 69.5, 68.1, 67.1, 61.1, 51.4, 40.4, 37.6, 37.4, 30.7, 25.8, 18.0, 12.4, –4.3, –4.9; m/z (CI$^+$, NH_3) 425 (10, [M+H]$^+$), 293 (10), 197 (20), 127 (100); HRMS Calcd for $C_{23}H_{41}O_5Si$ ([M+H]$^+$): 425.2725, found: 425.2724; Anal calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49, found: C, 65.22; H, 9.61%.

***(E,E,7S)*-Methyl-8-[(2*R*,6*S*)-6-formylmethyl-5,6-dihydro-2*H*-pyran-2-yl]-7-(*tert*-butyldimethylsilyloxy)-4-methylocta-2,4-dienoate (3).**

To a solution of the alcohol (-)-**33** (99 mg, 0.233 mmol) in CH_2Cl_2 (5 ml) was added solid Dess-Martin periodinane (0.211 g, 0.50 mmol) and the resulting mixture was stirred at room temperature for 2.5 h. The reaction mixture was then poured into a vigorously stirred mixture of sodium thiosulphate (1.4 g), $NaHCO_3$ solution (15 ml, sat. aq.) and Et_2O (25 ml) and stirring was continued until all the solid had dissolved and the organic layer was clear (*ca* 10 min). The layers were separated and the aqueous phase was extracted with Et_2O (2 x 20 ml). The combined organic layers were washed with successively with $NaHCO_3$ solution (20 ml, sat. aq.) and brine (20 ml, sat. aq.), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil. Filtration through a short plug of silica, eluting with 5% Et_2O/CH_2Cl_2 gave, after removal of the solvent under vacuum, the aldehyde **3** as a colourless oil (94.9 mg, 96%): R_f = 0.16 (10% EtOAc/hexane); $[\alpha]_D^{20}$ = –83.3° (*c* 1.74, $CHCl_3$); IR (thin film) 1722 (s) cm^{-1}; ^{1}H NMR δ (400 MHz, $CDCl_3$) 9.78 (1H, dd, J = 2.4, 1.4 Hz, C$\underline{H}$O), 7.33 (1H, d, J = 15.7 Hz, 3-C$\underline{H}$), 5.96 (1H, br dd, J = 7.4, 7.4 Hz, 5-C$\underline{H}$), 5.82–5.73 (2H, m, 2-C$\underline{H}$ and 11-C$\underline{H}$), 5.64 (1H, dm, J = 10.3 Hz, 10-C$\underline{H}$), 4.30 (1H, br d, J = 10.8 Hz, 9-C$\underline{H}$), 4.14–4.07 (1H, m, 13-C$\underline{H}$), 4.01–3.92 (1H, m, 7-C$\underline{H}$), 3.73 (3H, s, $CO_2\underline{Me}$), 2.63 (1H, ddd, J = 16.5, 8.6, 2.4 Hz, 14-C$\underline{H}_A$), 2.49 (1H, ddd, J = 16.5, 3.9, 1.4 Hz, 14-C$\underline{H}_B$), 2.43–2.33 (2H, m, 6-C$\underline{H}_2$), 2.04–1.95 (2H, m, 12-C$\underline{H}_2$), 1.77 (3H, s, 4-C$\underline{Me}$), 1.69 (1H, ddd, J = 14.4, 10.8, 2.2 Hz, 8-C$\underline{H}_A$H$_B$), 1.39 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CH$_A\underline{H}_B$), 0.86 (9H, s, C$\underline{Me}_3$), 0.03 (6H, s, Si$\underline{Me}_2$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 200.9, 168.0, 149.6, 137.7, 134.3, 130.3, 123.2, 115.4, 69.2, 67.8, 62.5, 51.5, 49.0, 40.3, 37.6, 30.2, 25.8, 18.0, 12.4,–4.4, –4.8; m/z (CI$^+$, NH_3) 440 (5, [M+NH_4]$^+$), 423 (30, [M+H]$^+$), 405 (25), 291 (60), 273 (30), 125 (100), 91 (20), 81 (65); HRMS (CI$^+$, NH_3) Calcd for $C_{23}H_{39}O_5Si$ ([M+H]$^+$): 423.2567, found: 423.2567.

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