

Tetrahedron Vol. 51, No. 34, pp. 9413-9436, 1995 Copyright © 1995 Elsevier Science Ltd Printed in Great Britain. All rights reserved 0040-4020/95 \$9.50+0.00

0040-4020(95)00547-1

The Total Synthesis of Swinholide A. Part 2: A Stereocontrolled Synthesis of a C₁-C₁₅ Segment.

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Abstract: The C₁-C₁₅ 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, $13 \rightarrow 35$, followed by cyclisation to give the dihydropyrone 36, (*ii*) the Ferrier-type rearrangement, $38 \rightarrow 39$, and (*iii*) the vinylogous Mukaiyama aldol reaction, $39 \rightarrow 40$.

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 synthesis³ of the C_1 - C_{15} segment **3**, which incorporates the *trans*-substituted dihydropyran ring.



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 C₉ 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.



Racemic Synthesis of C₁-C₁₅ 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 ⁿBu₂BOTf/ⁱPr₂NEt, 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 Me₃SiOTf/ⁱPr₂NEt in CCl₄, 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, CH₂Cl₂; TfOH, CH₂Cl₂; K₂CO₃, MeOH; (MeCN)₂PdCl₂, CH₂Cl₂; TBAF, THF) gave only traces of 15 (<20%). Reduction of the carbonyl group in 15 using the Luche conditions⁵ 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, ^{*n*}Bu₄NI, 20 °C, 16 h; (b) (COCl)₂, DMSO, CH₂Cl₂, -78 °C, 1 h; Et₃N, -78 \rightarrow 20 °C, (c) ^{*n*}Bu₂BOTf, ^{*i*}Pr₂NEt, CH₂Cl₂, -78 \rightarrow 0 °C, 1 h; 12, -78 \rightarrow 0 °C, 1.5 h; (d) TMSOTf, ^{*i*}Pr₂NEt, CCl₄, -78 \rightarrow 20 °C, 3 h; (e) NaBH₄, CeCl₃.7H₂O, MeOH/EtOH, -78 \rightarrow 0 °C, 3 h; (f) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 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 (TiCl₄, BF₃•OEt₂, TMSOTf), ZnBr₂ in CH₂Cl₂ gave a 72% yield of a 65 : 35 mixture of C₉ 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} (TiCl₄, CH₂Cl₂, -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, $TiCl_2(O'Pr)_2$, 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 C₇. Initially, we carried out this reaction using TiCl₄ in CH₂Cl₂ 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 TiCl₂(OⁱPr)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 C₇ aldehyde into the swinholide side-chain. This required controlled formation of the C₇ stereocentre. We elected to explore a novel vinylogous Mukaiyama aldol reaction¹⁰ between the aldehyde **21** and the silyl dienol ether **25**¹¹ (Scheme **5** and **Table 1**). Initial studies¹² 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 TiCl₄. However, use of TiCl₄ gave only decomposition, while the milder Lewis acid TiCl₂(OⁱPr)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 BF₃•OEt₂ 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 (Et₂O/CH₂Cl₂), 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 C₇ 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 ₂ Ti(O ⁱ Pr) ₂	CH ₂ Cl ₂	$-78 \rightarrow -40$	72 : 28	24	49
2	$Cl_2Ti(O^jPr)_2$	CH ₂ Cl ₂	$-40 \rightarrow -20$	78:22	40	44
3	BF3•OEt2	Et ₂ O	$-78 \rightarrow -20$	83:17	61	19
4	BF3•OEt2	THF	$-78 \rightarrow 20$	58 : 42	50	20
5	BF3•OEt2	CH ₂ Cl ₂	-78	86:14	62	0
6	BF3•OEt2	CH ₂ Cl ₂	-95	87:13	57	16
7	BF3•OEt2	10% Et ₂ O/CH ₂ Cl ₂	-78	90:10	70	11

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Since β -chelation of the aldehyde and the dihydropyran oxygen with BF₃•OEt₂ 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 C9 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 C₉ 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 preswinhholide 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 C₁₃ sidechain.



Figure 1

Completion of the Racemic C1-C15 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 H₂ and H₃. A similar reaction on the C₇ epimeric aldehyde **27** gave **29** in 80% yield. At this stage, circumstantial evidence for the desired stereochemistry at C₇ was provided by comparison of the ¹H and ¹³C 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 C₇ and C₉.

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(OCOCF₃)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 CD₃CN for **30** showed

that H₇, H₉ and H₁₀ were all on the same face of the molecule, thereby proving that the major alcohol diastereomer **28** had the *desired* relative stereochemistry at C₇. The epimeric mercurial **31** showed ¹H NMR NOE enhancements in C₆D₆ that were fully consistent with minor alcohol diastereomer **29** having the undesired C₇ stereochemistry.



Scheme 6: (a) $(MeO)_2P(O)CH_2CO_2Me$, *n*-BuLi, THF, $0 \rightarrow 20$ °C, 3 h; (b) $CaCO_3$, $Hg(OCOCF_3)_2$, THF, 2.5 h then aq. KBr; (c) TBSOTf, 2.6-lutidine, CH_2CI_2 , -78 °C, 20 min; (d) DDQ, CH_2CI_2 , H_2O , 20 °C, 18 h.

Protection of the C₇ 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 nickel¹⁶ or Li/4,4'-di-*tert*-butylbiphenyl¹⁷ led to rapid reduction of the diene system, while use of TMSI¹⁸ removed both the benzyl and silyl ethers in moderate yield (40%). Use of DDQ in wet dichloromethane¹⁹ 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 reprotection 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) (+)-Ipc₂BCl, ^{*i*}Pr₂NEt, PhMe, 0 °C, 1 h; 34, -78 \rightarrow -20 °C, 18 h; H₂O₂, MeOH, pH7 buffer; (b) 1.05 equiv. Me₃SiOTf, 0.8 equiv. ^{*i*}Pr₂NEt, CH₂Cl₂, -78 \rightarrow 20 °C, 2.5 h.

Enolisation of 13 with (+)-Ipc₂BCl/ⁱPr₂NEt 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**, [α]²⁰ = +66.2° (*c* 2.6, CHCl₃), as colourless needles (m.p. 62–63 °C).

Completion of the Asymmetric Synthesis of the C₁-C₁₅ 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 reduction⁵ 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 BF₃•OEt₂ again gave γ -addition, providing an 81 : 19 mixture of the two C₇ 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 C₁₅ 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 derivatives²² of this alcohol, followed by ¹H NMR analysis, allowed assignment of the configuration at C₇ as *S* based upon chemical shift differences in the two diastereomers (*i.e.* C₃<u>H</u> Δ_{δ} (*S*-*R*) = -0.09; C₉<u>H</u> Δ_{δ} (*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) NaBH₄. CeCl_{3.7H₂O, EtOH, -78 °C, 2 h; (b) Ac₂O, ${}^{4}Pr_{2}NEt$, CH₂Cl₂, 20 °C, 18 h; (c) 24, 2.2 equiv. TiCl₂(O^{*i*}Pr)₂, PhMe, -42 °C, 0.5 h; (d) 25, 2.2 equiv. BF₃•OEt₂, 9:1 CH₂Cl₂/Et₂O, -78 °C, 1 h; (e) (MeO)₂P(O)CH₂CO₂Me, ^{*n*}BuLi, THF, 0 \rightarrow 20 °C, 3 h; (f) TBSOTf, 2,6-lutidine, CH₂Cl₂, -78 °C, 20 min; (g) K₂CO₃, MeOH, 20 °C, 5.5 h; (h) Dess-Martin periodinane, CH₂Cl₂, 20 °C, 1 h.}

Protection of the C₇ 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

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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, $13 \rightarrow 35$, and a series of substrate-controlled reactions, (*i*) Luche reduction, $36 \rightarrow 37$, (*ii*) the Ferrier-type rearrangement, $38 \rightarrow 39$, and the vinylogous Mukaiyama aldol reaction, $39 \rightarrow 40$. 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), ⁿBu₄NI (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 NH₄Cl solution (20 ml, sat. aq.). After diluting with CH₂Cl₂ (250 ml), the mixture was washed with NH₄Cl solution (250 ml, sat. aq.) and the aqueous phase was then extracted with CH₂Cl₂ (3 x 150 ml). The combined extracts were washed successively with water (250 ml) and brine (1 x 150 ml, sat. aqueous), then dried (Na₂SO₄) and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (gradient elution with 20 \rightarrow 50% EtOAc/hexane) to give 3-benzyloxypropanol as a colourless liquid (18.3g, 93%): bp 96-97 °C (0.1 mm Hg), lit²³ bp 114 °C (0.9 mm Hg); R_f = 0.27 (50% EtOAc/hexane); ¹H NMR δ (250 MHz, CDCl₃) 7.27-7.35 (5H, m, C₆H₅), 4.52 (2H, s, CH₂Ph), 3.78 (2H, t, *J* = 5.8 Hz, OCH₂CH₂CH₂OH), 3.66 (2H, t, *J* = 5.8 Hz, OCH₂CH₂OH), 2.27 (1H, br, O<u>H</u>), 1.86 (2H, tt, *J* = 5.8, 5.8 Hz, CH₂CH₂CH₂CH₂D.

To a cooled $(-78 \,^{\circ}\text{C})$ solution of oxalyl chloride (3.4 ml, freshly distilled, 39 mmol) in CH₂Cl₂ (100 ml) was added dry DMSO (5.6 ml, freshly distilled from CaH₂, 79 mmol) dropwise and the resulting mixture was stirred at -78 $^{\circ}$ C for 5 min. A solution of 3-benzyloxypropan-1-ol (5.00 g, 30.1 mmol) in CH₂Cl₂ (20 ml) was then added *via* cannula and the mixture was stirred at -78 $^{\circ}$ 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 NH₄Cl (50 ml, sat. aqueous). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 30 ml). The combined organic extracts were then washed successively with HCl (70 ml, 1*M*), NaHCO₃ solution (70 ml, sat. aq.), and brine (70 ml, sat. aq.) then dried (Na₂SO₄) 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; ¹H NMR δ (250 MHz, CDCl₃) 9.79 (1H, t, J = 1.8 Hz, C<u>H</u>O), 7.26-7.38 (5H, m, C₆<u>H</u>₅), 4.53 (2H, s, PhC<u>H</u>₂), 3.81 (2H, t, J = 6.1 Hz, C<u>H</u>₂CH₂CHO), 2.69 (2H, td, J = 6.1, 1.8 Hz, C<u>H</u>₂CHO).

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

To a cooled (-78 °C) solution of n-Bu₂BOTf (8.8 g, 32.1 mmol) in CH₂Cl₂ (100 ml) was added *i*-Pr₂NEt (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 CH₂Cl₂ (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 CH₂Cl₂ (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 CH₂Cl₂ (2 x 30 ml). The combined organic layers were dried (Na₂SO₄) 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; Rf = 0.27 (30%) EtOAc/hexane); IR (liquid film) 3480 (s br, OH), 1680 (vs, C=O) cm⁻¹ (s); ¹H NMR δ (250 MHz, CDCl₃) 7.40–7.23 (6H, m, C_{6H5} 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</u>₂Ph), 4.37–4.24 (1H, m, 13-CH), 3.76–3.60 (2H, m, 15-CH₂), 2.78–2.63 (2H, m, 12-CH₂), 1.92–1.70 (2H, m, 14-CH₂); ¹³C NMR δ (100.6 MHz, CDCl₃) 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 (Cl⁺(NH₃)) 286 (90, [M+NH₄]⁺), 269 (100, [M+H]⁺), 251 (30), 233 (80), 182 (30), 108 (25); HRMS (CI+(NH₃)) Calcd for C₁₄H₁₈O₃Cl ([M+H]+): 269.0944, found 269.0944; Anal. calcd for C14H17ClO3: C, 62.57; H, 6.38; Cl, 13.19; found: C, 62.40; H, 6.41; Cl, 13.46.

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

To a cooled (-78 °C) solution of the aldol product 14 (1.06 g, 3.95 mmol) in CH₂Cl₂ (25 ml) was added Pr2NEt (0.55 ml, 3.2 mmol), followed by Me3SiOTf (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 NaHCO3 solution (40 ml, sat. aq.). The aqueous phase was extracted further with CH₂Cl₂ (2 x 20 ml), and the combined organic layers were dried (MgSO₄) and concentrated in vacuo to give a dark brown oil. The crude material was purified by flash chromatography (10% Et₂O/CH₂Cl₂) 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 CH₂Cl₂ (10 ml) was added Ac₂O (0.189 ml, 2.0 mmol), ⁱPr₂NEt (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, 1M aq.). The aqueous phase was further extracted with CH_2Cl_2 (3 x 10 ml) and each extract was subsequently washed with NaHCO3 solution (30ml, sat. aq.) then combined, dried (MgSO₄) and concentrated in vacuo. Purification of the resultant oil by flash chromatography (5% Et₂O/ CH_2Cl_2 gave 15 as a viscous yellow oil (0.547 g, 60%). Repeating the reaction under similar conditions, but using CCl₄ in place of CH₂Cl₂ and adding the reagents at -20 °C, gave a 61% yield of 15: $R_f = 0.26$ (10% Et₂O/CHCl₃); IR (liquid film) 1680 (vs, C=O) cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 7.36–7.27 (6H, m, C₆H₅) 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</u>₂Ph), 3.68–3.56 (2H, m, 15-CH₂), 2.57-2.43 (2H, m, 12-CH), 2.13-2.05 (1H, m, 14-CH_a), 2.00-1.92 (1H, m, 14-CH_b); ¹³C NMR 8 (100.6 MHz, CDCl₃) 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 (Cl⁺(NH₃)) 233 (100, [M+H]⁺), 108 (30), 91 (40); HRMS (Cl⁺(NH₃)) Calcd for C₁₄H₁₇O₃ ([M+H]⁺): 233.1178, found: 233.1177; Anal calcd for C₁₄H₁₆O₃: C, 72.39; H, 6.94; found: C, 72.27; H, 7.06.

(2RS,4SR)-4-Acetoxy-2-benzyloxyethyl-3,4-dihydro-2H-pyran (17).

To a solution of CeCl₃,7H₂O (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 NaBH₄ in EtOH (24 ml of a 0.3M 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 Et₂O (4 x 30 ml). The combined extracts were then washed with brine (40 ml, sat. aq.), dried (Na₂SO₄) and concentrated in vacuo to give the crude allylic alcohol **16** as an oil (1.5 g). To a solution of this material in CH₂Cl₂ (30 ml) was added Et₃N (1.5 ml, 10.8 mmol) followed by Ac₂O (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 NaHCO₃ 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 (Na₂SO₄) 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, CDCl₃) 7.38–7.25 (5H, m, C₆H₅), 6.42 (1H, d, J = 6.2 Hz, 9-CH), 5.36 (1H, m, 11-CH), 4.73 (1H, ddd, J= 6.2, 3.9, 2.4 Hz, 10-CH), 4.50 (2H, s, CH₂Ph), 4.24-4.14 (1H, m, 13-CH), 3.66-3.51 (2H, m, 15-CH₂), 2.24 (1H, dddd, J = 13.3, 6.6, 1.9, 1.9 Hz, 12-CH_AH_B), 2.05–1.65 (6H, m, 12-CH_ACH_B, 14-CH₂, and CH₃CO₂); ¹³C NMR δ (100.6 MHz, CDCl₃) 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+(NH₃)) 294 (5, [M+NH₄]+), 234 (30), 217 (100); HRMS (CI+(NH₃)) Calcd for C₁₆H₂₄O₄N ([M+NH₄]⁺): 294.1705, found: 294.1705; Anal calcd for C₁₆H₂₀O₄: C, 69.55; H, 7.30; found C, 69.52; H, 7.46.

(2RS, 6SR)-6-Benzyloxyethyl-5,6-dihydro-2-methoxycarbonyl-methyl-2*H*-pyran (19) and (2RS, 6RS)-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 ZnBr₂ (*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 Et₂O 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% Et₂O/hexane); IR (liquid film) 1740 (s) cm⁻¹; ¹H NMR δ (250 MHz, CDCl₃) 7.35-7.26 (5H, m, C₆<u>H</u>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<u>H_AH_BPh</u>), 4.47 (1H, d, J = 11.8 Hz, CH_A<u>H</u>_BPh), 3.88-3.78 (1H, m, 13-C<u>H</u>), 3.67 (3H, s, CO₂<u>Me</u>), 3.60-3.54 (2H, m, 15-C<u>H</u>₂), 2.66 (1H, dd, J = 14.9, 9.2 Hz, 8-C<u>H_AH_B</u>), 2.46 (1H, dd, J = 14.9, 5.1 Hz, 8-CH_A<u>H_B</u>), 2.05-1.89 (2H, m, 12-C<u>H</u>₂), 1.80 (2H, br q, J = 6.2 Hz, 14-C<u>H</u>₂); ¹³C NMR δ (100.6 MHz, CDCl₃) 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⁺(NH₃)) 308 (15, [M+NH₄]⁺), 291 (100, [MH]⁺), 199 (15), 91 (25); HRMS (CI⁺(NH₃)) Calcd for C₁₇H₂₃O₄ ([MH]⁺): 291.1596, found: 291.1596.

20: $R_f = 0.37$ (40% Et₂O/hexane); IR (liquid film) 1740 (s) cm⁻¹; ¹H NMR δ (250 MHz, CDCl₃) 7.37-7.27 (5H, m, C₆<u>H</u>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<u>H</u>₂Ph + 9-C<u>H</u>), 3.80-3.51 (6H, m, CO₂<u>Me</u> + 13-C<u>H</u> + 15-C<u>H</u>₂), 2.54 (1H, dd, J = 15.0, 6.2 Hz, 8-C<u>H</u>_AH_B), 2.44 (1H, dd, J = 15.0, 7.9 Hz, 8-CH_A<u>H</u>_B), 1.98-1.93 (2H, m, 12-C<u>H</u>₂), 1.84-1.75 (2H, m, 14-C<u>H</u>₂); ¹³C NMR δ (100.6 MHz, CDCl₃) 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⁺(NH₃)) 308 (10, [M+NH₄]⁺), 291 (100, [M+H]⁺), 199 (10), 157 (5), 108 (5), 91 (10, [PhCH₂]⁺); HRMS (CI⁺(NH₃)) calc for C₁₇H₂₃O₄ ([M+H]⁺) 291.1596, found 291.1596.

(2RS,6SR)-2-Allyl-6-benzyloxyethyl-5,6-dihydro-2H-pyran (23).

To a cooled (-78 °C) solution of 17 (40.5 mg, 0.147 mmol) in CH₂Cl₂ (1 ml) under an atmosphere of argon was added allyltrimethylsilane (0.0327 ml, 0.206 mmol), followed by a solution of TiCl₄ in CH₂Cl₂ (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 NaHCO₃ solution (2 ml, sat. aq.), then allowed to warm to room temperature and partitioned between NaHCO3 solution (30 ml, sat. aq.) and Et2O (30 ml). The aqueous phase was extracted further with Et₂O (2 x 30 ml) and the combined extracts were washed with brine (30 ml, sat, aq.), dried (Na₂SO₄) 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 ¹³C NMR spectra of this compound showed it to be a single isomer – the reaction selectivity was therefore $\geq 97\%$: Rf = 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, CDCl₃) 7.38-7.23 (5H, m, C₆H₅), 5.93-5.70 (3H, m, 7-CH, 10-CH & 11-CH), 5.09 (1H, br d, J $= 8.6 \text{ Hz}, 6-C\underline{H}_AH_B$), 5.04 (1H, br s, 6-CH_A<u>H</u>_B), 4.45 (2H, s, C<u>H</u>₂Ph), 4.20 (1H, br s, 9-C<u>H</u>), 3.93-3.83 (1H, m, 13-CH), 3.69-3.53 (2H, m, 15-CH2), 2.46-2.34 (1H, m, 8-CHAHB), 2.29-2.18 (1H, m, 8-CHAHB), 1.96-1.90 (2H, m, 12-CH₂), 1.80 (2H, q, J = 6.5 Hz, 14-CH₂); ¹³C NMR δ (100.6 MHz, CDCl₃) 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+(NH₃)) 276 (5, [M+NH₄]⁺), 259 (100, [M+H]⁺), 241 (5), 217 (10), 182 (5), 169 (5), 127 (7), 108 (25), 91 (45); HRMS (CI+(NH₃)) Calcd for C₁₇H₂₃O₂ ([M+H]+): 259.1698, found: 259.1698.

(2RS,6SR)-6-Benzyloxyethyl-5,6-dihydro-2-formylmethyl-2H-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 Cl₂Ti(Oi-Pr)₂ in CH₂Cl₂ (0.094 ml of a 1.5M solution, 0.14 mmol). The resulting mixture was stirred at -42 °C for 1.7 h. The reaction mixture was quenched with NaHCO3 solution (2 ml, sat. aq.) then warmed to room temperature and partitioned between NaHCO₃ solution (15 ml, sat. aq.) and CH₂Cl₂ (15 ml). The aqueous phase was extracted with CH₂Cl₂ (3 x 15 ml) and the combined extracts were dried (Na₂SO₄) 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, CDCl₃) 9.76 $(1H, dd, J = 3.0, 1.6 Hz, 7-CHO), 7.34-7.26 (5H, m, C_{6H_5}), 5.90-5.85 (1H, m, 11-CH), 5.68 (1H, br d, J)$ = 10.2 Hz, 10-C<u>H</u>), 4.77–4.75 (1H, m, 9-C<u>H</u>), 4.53 (1H, d, J = 11.9 Hz, C<u>H</u>_AH_BPh), 4.43 (1H, d, J = 11.9 Hz, $CH_{AHB}Ph$), 3.89–3.82 (1H, m, 13-CH), 3.60–3.50 (2H, m, 15-CH₂), 2.73 (1H, ddd, J = 16.2, 9.1, 3.0Hz, 8-CH_AH_B), 2.49 (1H, ddd, J = 16.2, 4.5, 1.6 Hz, 8-CH_AH_B), 2.07–1.92 (2H, m, 12-CH₂), 1.79 (2H, dt, J = 6, 6 Hz, 14-CH₂). Irradiation of 9-CH ($\delta_{\rm H}$ 4.75-4.77) gave nuclear Overhauser enhancements to 7-CHO $(\delta_{\rm H} 9.76)$, 8-CH_A ($\delta_{\rm H} 2.73$), 8-CH_B ($\delta_{\rm H} 2.49$) and 10-CH ($\delta_{\rm H} 5.68$). Irradiation of 13-CH ($\delta_{\rm H} 3.82-3.89$) gave nuclear Overhauser enhancements to 8-CH_A ($\delta_{\rm H}$ 2.73), 12-CH₂ ($\delta_{\rm H}$ 1.92-2.07) and 14-CH₂ ($\delta_{\rm H}$ 1.79). Irradiation of 8-CH_A ($\delta_{\rm H}$ 2.73) gave nuclear Overhauser enhancements to 7-CHO ($\delta_{\rm H}$ 9.76), 9-CH ($\delta_{\rm H}$ 4.75-4.77), 13-CH ($\delta_{\rm H}$ 3.82-3.89) and 8-CH_B ($\delta_{\rm H}$ 2.49). Irradiation of 8-CH_B ($\delta_{\rm H}$ 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); ¹³C NMR δ (100.6 MHz, CDCl₃) 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+(NH₃)) 278 (100, [M+NH₄]+), 261 (75, [MH]+), 234 (25), 217 (95), 127 (60), 108 (30); HRMS (CI⁺(NH₃)) Calcd for C₁₆H₂₄O₃N ([M+NH₄]⁺): 278.1756, found 278.1756; Anal calcd for C₁₆H₂₀O₃: C, 73.82; H, 7.74, found: C, 73.64; H, 7.77.

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(2RS,6RS)-6-Benzyloxyethyl-5,6-dihydro-2-formylmethyl-2H-pyran (22).

To a cooled (-78 °C) solution of 20 (15.5 mg, 0.053 mmol) in CH₂Cl₂ (1.0 ml) was added a solution of DIBAL-H in hexanes (0.058 ml of a 1.0M solution, 0.058 mmol). The resulting mixture was stirred at this temperature for 1 h. More DIBAL-H (0.016 ml of a 1.0M 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 NaHCO3 solution (10 ml, sat. aq.) then combined, dried (Na2SO4), 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, CDCl₃) 9.74 (1H, t, J = 2.3 Hz, C<u>H</u>O), 7.40-7.27 (5H, m, C₆H₅), 5.89-5.85 (1H, m, 11-CH), 5.62 (1H, dm, J = 10 Hz, 10-CH), 4.62-4.54 (1H, m, 9-CH), 4.53 (1H, d, J = 12.0 Hz, CH_AH_BPh), 4.49 (1H, d, J = 12.0 Hz, CH_AH_BPh), 3.82-3.76 (1H, m, 13-C<u>H</u>), 3.66-3.54 (2H, m, 15-C<u>H</u>₂), 2.53 (2H, dd, J = 6.2, 2.3 Hz, 8-C<u>H</u>₂), 2.02-1.97 (2H, m, 12-C<u>H</u>₂), 1.81 (2H, dt, J = 6.2, 6.2 Hz, $14-CH_2$). Irradiation of 9-CH (δ 4.62-4.54) gave nuclear Overhauser enhancements to 8-CH₂ (δ 2.53), 13-CH (δ 3.82-3.76), 10-CH (δ 5.62), and CHO (δ 9.74). Irradiation of 13-CH (δ 3.82-3.76) gave nuclear Overhauser enhancements to $14-CH_2$ (δ 1.81), 12-CH₂ (δ 2.02-1.97), 9-CH (δ 4.54-4.62), and CHO (δ 9.74); ¹³C NMR δ (100.6 MHz, CDCl₃) 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,7S)-6-[(2R,6S)-6-{2-benzyloxyethyl}-5,6-dihydro-2*H*-pyran-2-yl]-5-(*tert*-butyldimethyl-silyloxy)-2-methylhexa-2-dienal (26) and (E,7R)-6-[(2R,6S)-6-{2-benzyloxyethyl}-5,6-dihydro-2*H*-pyran-2-yl]-5-(*tert*-butyldimethyl-silyloxy)-2-methylhexa-2-dienal (27).

To a cooled $(-78 \,^{\circ}\text{C})$ solution of the aldehyde **21** (0.232 g, 0.892 mmol) in a mixture of CH₂Cl₂ (8.5 ml) and Et₂O (1 ml) was added a solution of 2-methyl-1-trimethylsilyloxy-1,3-butadiene (**25**) (0.153 g, 0.98 mmol) in CH₂Cl₂ (1 ml) followed by dropwise addition of BF₃·OEt₂ (0.120 ml, 0.98 mmol). After 2.3 h, the reaction was quenched by the addition of a mixture of THF (5 ml), H₂O (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 NaHCO₃ solution (40 ml, sat. aq.) and extracted with CH₂Cl₂ (3 x 30 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated *in vacuo* to give an oil which was purified using flash chromatography (eluting with a gradient system of 15–70% Et₂O in CH₂Cl₂) 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, CDCl₃) 9.38 (1H, s, 3-CHO), 7.36–7.26 (5H, m, C_{6H5}), 6.54 (1H, br t, J = 7.2 Hz, 5-CH), 5.86–5.80 (1H, m, 11-CH), 5.61 (1H, dddd, J = 10.3, 2, 2, 2 Hz, 10-CH), 4.50–4.45 (3H, m, 9-CH and CH₂Ph), 4.10–4.02 (1H, br m, 7-CH), 4.00–3.92 (1H, m, 13-CH), 3.65–3.52 (2H, m, 15-CH₂), 2.94 (1H, brd, J = 3.8 Hz, OH), 2.56–2.41 (2H, m, 6-CH₂), 2.14 (1H, dm, J = 17.4 Hz, 12-CH_AH_B), 1.97–1.70 (7H, m, 4-CMe, 8-CH_AH_B, 12-CH_ACH_B, 14-CH₂), 1.57 (1H, ddd, J = 14.5, 9.2, 3.2 Hz, 8-CH_AH_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); ¹³C NMR δ (100.6 MHz, CDCl₃) 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⁺(NH₃)) 345 (25, [M+H]⁺), 327 (40), 231 (100), 141 (45), 127 (45), 108 (40), 91 (70); HRMS (CI⁺(NH₃)) Calcd for C₂₁H₂₉O₄ (M+H⁺): 345.2066, found: 345.2066; Anal Calcd for C₂₁H₂₈O₄: C, 73.23; H, 8.19, found: C, 73.03; H, 8.27.

27: $R_f = 0.30$ (20% Et₂O/CH₂Cl₂); IR (liquid film) 3460 (br), 1685 (s) 700 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 9.42 (1H, s, 3-C<u>H</u>O), 7.36–7.26 (5H, m, C₆H₅), 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>_AH_BPh), 4.49 (1H, d, J = 11.8 Hz, CH_AH_BPh), 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); ¹³C NMR δ (100.6 MHz, CDCl₃) 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 (Cl⁺(NH₃)) 345 (40, [M+H]⁺), 327 (100), 231 (60), 217 (95), 141 (35), 127 (45), 108 (40), 91 (50, [PhCH₂]⁺); HRMS (Cl⁺(NH₃)) Calcd for C₂₁H₂₉O₄ ([M+H]⁺): 345.2066, found 345.2066.

(*E*,*E*,7S)-Methyl-8-[(2*R*,6S)-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 ⁿBuLi 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 Et₂O (3 x 20 ml). Each extract was washed with brine (10 ml, sat. aq.), then combined, dried (Na₂SO₄) 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 ¹H and ¹³C 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; ¹H NMR δ (400 MHz, CDCl₃) 7.35–7.25 (6H, m, 3-CH and C₆H₅), 5.90 (1H, br t, J = 7.3 Hz, 5-CH), 5.83–5.77 (2H, m, 2-CH and 11-CH), 5.61 (1H, m, $10-C\underline{H}$), 4.49 (2H, s, C \underline{H}_2 Ph), 4.45 (1H, br d, J = 7.2 Hz, 9-C \underline{H}), 3.97–3.89 (2H, m, 7-C \underline{H} and 13-C \underline{H}), 3.73 (3H, s, CO_2Me), 3.63–3.52 (2H, m, 15-CH₂), 2.69 (1H, d, J = 4.4 Hz, OH), 2.44–2.28 (2H, m, 6- CH_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); ¹³C NMR δ (100.6 MHz, CDCl₃) 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⁺(NH₃)) 418 (20, [M+ NH₄]⁺), 401 (100, [M+H]⁺), 383 (20), 217 (30), 127 (65), 108 (70), 91 (60), 81 (20); HRMS (CI⁺(NH₃)) Calcd for C₂₄H₃₃O₅ ([M+H]⁺): 401.2328, found: 401.2327; Anal calcd for C₂₄H₃₂O₅ C, 71.97; H, 8.05; found C, 71.93; H, 8.16%.

(E, E, 7R)-Methyl-8-[(2R, 6S)-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% Et₂O/CH₂Cl₂); IR (liquid film) 3460 (br), 1715 (s) cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 7.36–7.25 (6H, m, C₆H₅ 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, CH_AH_BPh), 4.48 (1H, d, J = 11.8 Hz, CH_AH_BPh), 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, CO₂<u>Me</u>), 3.62–3.53 (2H, m, 15-C<u>H₂), 2.46–2.30 (2H, m, 6-C<u>H₂), 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); ¹³C NMR δ (100.6 MHz, CDCl₃) 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+(NH₃)) 401 (80, [M+H]⁺), 383 (20), 305 (40), 231 (60), 217 (100), 127 (70), 108 (50), 91 (50); HRMS (CI⁺(NH₃)) Calcd for C₂₄H₃₃O₅ ([M+H]⁺): 401.2328, found: 401.2328.</u></u>

(2"E,4"E,1R,3R,5S,6S,8S)-5-Bromomercurio-3-(2'-benzyloxyethyl)-8-(5"-methoxy-carbonyl-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 CaCO₃ (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 (Na₂SO₄) and concentrated in vacuo to give an oil that was purified by flash chromatography (10% Et₂O/CH₂Cl₂) 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, CD₃CN) 7.37–7.26 (6H, m, 3-C<u>H</u> and C₆<u>H</u>₅), 6.01 (1H, br t, J = 7.6 Hz, 5-C<u>H</u>), 5.85 (1H, d, J = 15.8 Hz, 2-CH), 4.47 (1H, d, J = 12.1 Hz, CHAHBPh), 4.45 (1H, d, J = 12.1 Hz, CHAHBPh), 4.31 (1H, br ddd, J = 6, 6, 6 Hz, 9-CH), 4.02 (1H, dd, J = 7.6, 5.5 Hz, 10-CH), 3.93–3.86 (1H, m, 7-CH), 3.85–3.77 (1H, m, 13-CH), 3.68 (3H, s, CO₂Me), 3.52-3.45 (2H, m, 15-CH₂), 2.70 (1H, ddd, J = 9.4, 7.7, 4.4 Hz, 11-CH), 2.59-2.44 (2H, m, 6-CH2), 2.18-2.05 (2H, m, 8-CHAHB and 12-CHAHB), 1.85-1.63 (7H, m, 4-CMe, 8-CHAHB, 12-CHAHB, 14-CH2). Irradiation of 7-CH (δ_H 3.86-3.93) gave nuclear Overhauser enhancements to 5-CH (δ_H 6.01), 6-CH₂ (δ_H 2.59-2.44), 8-CH_AH_B (δ_H 2.1), 9-CH (δ_H 4.31) and 10-CH (δ_H 4.02). Irradiation of 9-CH ($\delta_{\rm H}$ 4.31) gave nuclear Overhauser enhancements to 7-CH ($\delta_{\rm H}$ 3.86-3.93), 8-CH_AH_B (δ_H 2.1) and 10-CH (δ_H 4.02); ¹³C NMR δ (100.6 MHz, CDCl₃) 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+(NH₃)) 681 (5, [M+H]+), 401 (100), 383 (20), 217 (35), 127 (40), 108 (45), 91 (30); HRMS (Cl+(NH₃)) Calcd for C₂₄H₃₂O₅⁷⁹BrO₅²⁰²Hg ([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''-methoxy-carbonyl-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, C₆D₆) 7.59 (1H, d, J = 15.7 Hz, 3-C<u>H</u>), 7.33–7.09 (5H, m, C₆<u>H</u>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<u>H</u>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, CO₂<u>Me</u>), 3.47–3.43 (1H, m, 10-C<u>H</u>), 3.36–3.26 (2H, m, 15-C<u>H</u>₂), 2.20–2.03 (3H, m, 6-C<u>H</u>₂ and 11-C<u>H</u>), 1.81 (1H, ddd, J = 13.0, 6.6, 3.3 Hz, 8-C<u>H</u>_AH_B), 1.77–1.63 (3H, m, 12-C<u>H</u>_AH_B and 14-C<u>H</u>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<u>H</u>_B), 1.00–0.90 (1H, m, 12-CH_A<u>H</u>_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<u>H</u>₂ (δ_{H} 2.20-2.03), and 8-C<u>H</u>_A<u>H</u>_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<u>H</u>_B & 14-C<u>H</u>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,7S)-Methyl-8-[(2R,6S)-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 CH₂Cl₂ (2 ml) was added 2,6lutidine (0.047 ml, 0.4 mmol) followed by *t*-BuMe₂SiOTf (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 NaHCO₃ solution (20 ml, sat. aq.) and extracted with CH₂Cl₂ (3 x 15 ml). The combined organic layers were dried (Na₂SO₄) 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, CDCl₃) 7.37–7.26 (6H, m, 3-C<u>H</u> and C₆<u>H</u>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<u>H</u>_AH_BPh), 4.48 (1H, d, *J* = 12.0 Hz, CH_A<u>H</u>_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 CO₂<u>Me</u>), 3.63–3.55 (2H, m, 15-C<u>H</u>₂), 2.42–2.25 (2H, m, 6-C<u>H</u>₂), 2.00–1.90 (2H, m, 12-C<u>H</u>₂), 1.85–1.76 (2H, m, 14-C<u>H</u>₂), 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</u>_AH_B), 1.40 (1H, ddd, J = 14.2, 9.7, 2.7 Hz, 8-CH_A<u>H</u>_B), 0.89 (9H, s, C<u>Me</u>₃), 0.09 (3H, s, Si<u>Me</u>_AMe_B), 0.07 (3H, s, SiMe_A<u>Me</u>_B); ¹³C NMR δ (100.6 MHz, CDCl₃) 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⁺(NH₃)) 532 (15, [M+NH₄]⁺), 515 (90, [M+H]⁺), 383 (40), 217 (75), 108 (70), 91 (100); HRMS (CI⁺(NH₃)) Calcd for C₃₀H₄₇O₅Si ([M+H]⁺): 515.3193, found: 515.3195.

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

To a solution of the benzyl ether **32** (16 mg, 0.031 mmol) in CH₂Cl₂ (2 ml) was added DDQ (36 mg, 0.16 mmol) and H₂O (0.2 ml). The resulting mixture was stirred at room temperature for 18 h and was then partitioned between CH₂Cl₂ (10 ml) and NaHCO₃ solution (10 ml, sat. aq.). The aqueous phase was back extracted with CH₂Cl₂ (2 x 10 ml) and the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (elution with 10% EtOAc/hexane then 10% Et₂O/CH₂Cl₂) 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 CH₂Cl₂ (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 CH₂Cl₂ (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*-dimethylethyl-enediamine (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 NaHCO₃ solution (300 ml, sat. aq.), then dried (MgSO₄) 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; ¹H NMR δ (250 MHz, CDCl₃) 8.04 (2H, d m, $J = \sim 8$ Hz, Ar<u>H</u>), 7.55 (1H, tt, J = 7.3, 1.3 Hz, Ar<u>H</u>), 7.43 (2H, br dd, $J = \sim 8$, 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 Hz,4-C<u>H</u>_AH_B), 5.11 (1H, dm, J = 10.2 Hz, 4-CH_AH_B), 4.37 (2H, t, J = 6.7 Hz, 1-C<u>H</u>₂), 2.52 (2H, tddd, J = 6.7, 6.7, 1.5, 1.5 Hz, 2-C<u>H</u>₂); ¹³C NMR δ (62.5 MHz, CDCl₃) 166.8, 134.2, 133.0, 130.5, 129.7, 128.5, 117.5, 64.1, 33.3; Anal. calcd for C₁₁H₁₂O₂: 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 Me₂CO (35 ml) and H₂O (80 ml) was added *N*-methylmorpholine *N*-oxide (22.3 g, 0.190 moles), followed by a solution of OsO₄ 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 Et₂O (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 NaHCO₃ solution (50 ml, sat. aqueous). The acid and NaHCO₃ phases were further back-extracted with Et₂O (2 x 75 ml). The combined Et₂O layers were then dried (Na₂SO₄) and concentrated *in vacuo* to give a solid. Recrystallisation from EtOAc/hexane afforded two crops of (*2RS*)-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; ¹H NMR δ (250 MHz, CDCl₃) 8.01 (2H, d m, $J = \sim 8$ Hz, Ar<u>H</u>), 7.54 (1H, tt, J = 7.3, 1.3 Hz, Ar<u>H</u>),

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7.41 (2H, br dd, J = -8, 8 Hz, Ar<u>H</u>), 4.56 (1H, ddd, J = 11.2, 8.4, 5.6 Hz, 15-C<u>H</u>_AH_B), 4.40 (1H, ddd, J = 11.2, 5.5, 5.5 Hz, 15-CH_A<u>H</u>_B), 3.92–3.81 (1H, m, 13-C<u>H</u>), 3.67 (1H, ddd, J = 11.2, 6.0, 3.1 Hz, C<u>H</u>_AH_BOH), 3.55–3.40 (2H, m, CH_A<u>H</u>_BOH & 13-CHO<u>H</u>), 2.96 (1H, br t, J = 6.0 Hz, CH₂O<u>H</u>), 2.03–1.74 (2H, m, 14-C<u>H</u>₂); ¹³C NMR δ (62.5 MHz, CDCl₃) 167.2, 133.3, 130.1, 129.8, 128.6, 69.1, 66.8, 61.8, 32.6; Anal. calcd for C₁₁H₁₄O₄: 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 Me₂CO (30 ml) and H₂O (100 ml) was added NaIO₄ (27.8 g, 130 mmol) in one portion. The resulting mixture soon became a thick shurry 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 H₂O (50 ml) and the suspension was extracted with Et₂O (3 x 75 ml). The organic phases were washed with NaHCO₃ solution (50 ml, sat. aq.) and brine (50 ml, sat. aq.), then combined, dried (Na₂SO₄) and concentrated *in vacuo* to give an oil that was passed down a 12 cm column of silica eluting with 5% Et₂O/CH₂Cl₂. 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); ¹H NMR δ (250 MHz, CDCl₃) 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-CH₂), 2.90 (2H, td, *J* = 6.1, 1.5 Hz, 2-CH₂).

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

To a solution of (+)-Ipc₂BCl (14.18 g, 44.2 mmol) in Et₂O (100 ml) was added *i*-Pr₂NEt (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 Et₂O (5 ml + 5 ml rinse) was then added via cannula and the resulting pale yellow suspension was stirred at 0 $^{\circ}$ C for 2 h, then cooled to -78 $^{\circ}$ C. A solution of 3-benzoyloxypropanal (34) (7.48 g, 42 mmol) in Et₂O (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 NaHCO₃ solution (50 ml, sat. aq.) and the aqueous phases were back-extracted with Et₂O (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 H₂O₂ 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 Et₂O (2 x 75 ml) and the combined extracts were dried (Na₂SO₄) and concentrated in vacuo to give the crude product which was purified by flash chromatography (gradient elution with $40 \rightarrow 60\%$ Et₂O/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: Rf = 0.17 (50% Et₂O/petroleum ether bp 40-60); $[\alpha]_D^{20} = -16.0^\circ$ (c 2.51, CHCl₃) (80% ee); IR (thin film) 3494 (m, br), 1715 (s) cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 8.01 (2H, dm, J = -8 Hz, Ar<u>H</u>), 7.55 (1H, tm, J = -7.5 Hz, Ar<u>H</u>), 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, 12-12) CH₂), 2.02–1.83 (2H, m, 14-CH₂); ¹³C NMR δ (62.5 MHz, CDCl₃) 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 C14H16ClO4 ([M+H]⁺): 283.0737, found: 283.0752; Anal calcd for C14H15ClO4: C, 59.48; H, 5.35; found: C, 59.66; H, 5.27%.

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

To a cooled (-78 °C) solution of (5*R*)-7-benzoyloxy-1-chloro-5-hydroxy-hept-1-en-3-one (**35**) (4.06 g, 14.4 mmol) in CH₂Cl₂ (10 ml) was added ${}^{i}Pr_{2}NEt$ (2.0 ml, 11.5 mmol) followed by Me₃SiOTf (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 NaHCO₃ solution (30 ml, sat. aq.), which resulted in a colour change from dark green to dark brown, and were then combined, dried (Na₂SO₄) and concentrated in vacuo to give a black oil. Flash chromatography (gradient elution with $30 \rightarrow 40\%$ 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 Et₂O 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 \geq 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, CHCl₃), ca 70% ee) was dissolved in hot Et₂O (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% Et₂O/petroleum ether to give enantiomerically enriched 36 (2.07 g, $[\alpha]_D^{20} = +61.5^\circ$ (c 3.0 CHCl₃)). The process was repeated twice more to give enantiomerically-pure **36** (1.71 g, 60%, $[α]_D^{20}$ = +66.2° (*c* 2.7, CHCl₃): 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, CDCl₃) 8.01 (2H, br d, J = -8 Hz, Ar<u>H</u>), 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-C<u>H</u>), 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); ¹³C NMR δ (100.6 MHz, CDCl₃) 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+, NH₃) 264 (25, [M+NH₄]+), 247 (100, [M+H]⁺), 124 (20), 105 (30); Anal. calcd for C₁₄H₁₄O₄: C, 68.28; H, 5.73, found: C, 68.42; H, 5.69.

(2R,4S)-4-Hydroxy-2-benzoyloxyethyl-3,4-dihydro-2H-pyran (37).

To a solution of CeCl₃·7H₂O (13.8 g, 10.3 mmol) in absolute EtOH (100 ml) was added a solution of (2R)-2benzoyloxyethyl-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 NaBH₄ (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 (Na₂SO₄) 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% Et₂O/petroleum ether bp 40–60): R_f = 0.26 (60% Et₂O/petroleum ether bp 40-60); $[\alpha]_D^{20} = -11.7^\circ$ (c 3.4, CHCl₃); 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, 8 Hz, 4 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-CH₂), 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-CH₂), 1.68 (1H, ddd, J = 13.1, 11.2, 9.1 Hz, $12-CH_AH_B$); $1^{3}C$ NMR δ (100.6 MHz, CDCl₃) 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+, NH₃) 266 (5, [M+NH₄]+), 248 (20), 231 (100), 109 (15); HRMS (CI+, NH₃) Calcd for $C_{14}H_{20}NO_4$ ([M+NH4]⁺): 266.1392, found: 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392, found: 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50, found (M-NH4)⁺): 266.1392; Anal. calcd for $C_{14}H_{16}O_4$: 266.1392; Anal. calcd for $C_{14}H$ C, 67.57; H, 6.42%.

(2R,4S)-4-Acetoxy-2-benzoyloxyethyl-3,4-dihydro-2H-pyran (38).

To a solution of (2R). (4S)-4-hydroxy-2-benzoyloxyethyl-3,4-dihydro-2H-pyran (37) (2.32 g, 9.35 mmol, crude from the previous step) in CH₂Cl₂ (40 ml) was added ⁱPr₂NEt (3.0 ml, 17.2 mmol) and DMAP (0.060 g, 0.5 mmol), followed by Ac₂O (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 NaHCO₃ solution (30 ml, sat. aq.). The aqueous phases were back-extracted with CH2Cl2 (2 x 20 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give a pale vellow oil, which was purified by flash chromatography through a short column of silica (40% Et₂O/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); $[\alpha]_D^{20} = -36.5^\circ$ (c 3.1, CHCl₃); IR (thin film) 1721 (s) cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 8.02 (2H, br d, J = -8 Hz, Ar<u>H</u>), 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, $13-CH_2), 2.29$ (1H, dddd, J = 13.4, 6.6, 2.5, 10.5) 1.5 Hz, 12-CHAHB), 2.20-2.08 (1H, m, 14-CHAHB), 2.06-1.97 (4H, m, 14-CHAHB & OCOMe), 1.79 (1H, ddd, J = 13.4, 10.3, 8.1 Hz, 12-CH_AH_B); ¹³C NMR δ (100.6 MHz, CDCl₃) 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+, NH₃) 308 (5, [M+NH₄]+), 248 (20), 231 (100), 108 (15); HRMS ((CI+, NH₃) Calcd for C₁₆H₂₂NO₅ ([M+NH₄]+): 308.1498, found: 308.1498; Anal calcd for C₁₆H₁₈O₅: C, 66.20; H, 6.25, found: C, 66.25; H, 6.35%.

(2R,6S)-6-Benzoyloxyethyl-5,6-dihydro-2-formylmethyl-2H-pyran (39).

To a cooled (-42 °C) solution of (2R,4S)-4-acetoxy-2-benzoyloxyethyl-3,4-dihydro-2H-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 Cl₂Ti(OⁱPr)₂ in CH₂Cl₂ (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 NaHCO₃ solution (5 ml, sat. aq.). After warming to room temperature, the mixture was partitioned between NaHCO₃ solution (30 ml, sat. aq.) and CH₂Cl₂ (50 ml). The aqueous phase was extracted with CH₂Cl₂ (3 x 20 ml) and the combined organic extracts were dried (Na₂SO₄) 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 ¹³C NMR showed it to be single isomer indicating $\geq 97\%$ diastereoselectivity: $R_f = 0.25$ (30% EtOAc/hexane); $[\alpha]_D^{20} = -17.5^\circ$ (c 2.9, CHCl₃); IR 1725 (s) cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 9.79 (1H, dd, J = 2.8, 1.2 Hz, 7-CHO), 8.02 (2H, br d, J = 2.8, 1.2 Hz, 8.02 (2H, br d, J = 2.8, 1.2 Hz, 8.02 (2H, br d, J = 2.8, 1.2 Hz, J = 2.8 ~ 8 Hz, Ar<u>H</u>), 7.54 (1H, br t, $J = \sim 8$ Hz, Ar<u>H</u>), 7.43 (2H, br dd, $J = \sim 8$, 8 Hz, Ar<u>H</u>), 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-CH₂), 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-CH₂), 1.99-1.92 (2H, m, 14-CH₂); ¹³C NMR δ (100.6 MHz, CDCl₃) 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 C₁₆H₁₈O₄: C, 70.06; H, 6.61, found: C, 69.97; H, 6.65%.

(E,7S)-6-[(2R,6S)-6-(2-benzoyloxyethyl)-5,6-dihydro-2*H*-pyran-2-yl]-5-(*tert*-butyldimethylsilyloxy)-2-methylhexa-2-dienal (40) and (E,7R)-6-[(2R,6S)-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

BF₃•OEt₂ (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), H₂O (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 NaHCO₃ solution (30 ml, sat. aq.) and extracted with CH₂Cl₂ (3 x 20 ml). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product. Flash chromatography (gradient elution with $20 \rightarrow 70\%$ Et₂O/CH₂Cl₂) 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% Et₂O/CH₂Cl₂); $[\alpha]_D^{20} = +1.6^{\circ}$ (*c* 5.3, CHCl₃); IR (thin film) 3470 (br), 1720 (s), 1685 (s) cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 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-CH₂), 2.18 (1H, dm, J = 17.4 Hz, 12-CH_AH_B), 2.06–1.92 (3H, m, 12-CH_AH_B & 14-CH₂), 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); ¹³C NMR δ (100.6 MHz, CDCl₃) 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 (Cl⁺, NH₃) 376 (5, [M+NH₄]⁺), 359 (5, [M+H]⁺), 341 (30), 245 (85), 231 (100), 105 (60); HRMS (+FAB, NOBA) Calcd for C₂₁H₂₇O₅ ([M+H]⁺): 359.18583, found: 359.18750; Anal Calcd for C₂₁H₂₆O₅: C, 70.37; H, 7.31, found: C, 70.22; H, 7.35%.

41: $R_f = 0.26$ (20% Et_2O/CH_2Cl_2); $[\alpha]_D^{20} = -23.7^\circ$ (*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-C<u>H</u>), 8.01 (2H, dm, J = -8 Hz, Ar<u>H</u>), 7.53 (1H, tt, J = 7.4, 1.3 Hz, Ar<u>H</u>), 7.40 (2H, br dd, J = -8, 8 Hz, Ar<u>H</u>), 6.59 (1H, ddd, J = 7.2, 7.2, 1.2 Hz, 5-C<u>H</u>), 5.84–5.79 (1H, m, 11-C<u>H</u>), 5.60 (1H, ddd, J = 10.3, 4.1, 2.5 Hz, 10-C<u>H</u>), 4.49–4.36 (3H, m, 9-C<u>H</u> & 15 C<u>H</u>₂), 4.10–4.04 (1H, m, 7-C<u>H</u>), 3.96 (1H, ddd, J = 8.3, 8.3, 4.6, 4.6 Hz, 13-C<u>H</u>), 3.77 (1H, br s, O<u>H</u>), 2.48 (2H, br dd, J = 6.6, 6.6 Hz, 6-C<u>H</u>₂), 2.13 (1H, dm, J = 17.3 Hz, 12-C<u>H</u>_AH_B), 2.06–1.91 (3H, m, 12-CH_AH_B & 14-C<u>H</u>₂), 1.79 (1H, ddd, J = 14.6, 10.5, 9.4 Hz, 8-C<u>H</u>_AH_B), 1.70 (3H, d, J = 1.2 Hz, 4-C<u>Me</u>), 1.54 (1H, ddd, J = 14.6, 2.8, 2.8 Hz, 8-CH_AH_B); ¹³C NMR δ (100.6 MHz, CDCl₃) 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⁺, NH₃) 376 (60, [M+NH₄]⁺), 359 (10, [M+H]⁺), 341 (70), 245 (70), 231 (100), 105 (25); HRMS (CI⁺(NH₃)) Calcd for C₂₁H₂₇O₅ ([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 Et₂O (4 x 30 ml). The combined organic layers were then dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product. Flash chromatography (gradient elution with 40 \rightarrow 50% EtOAc/hexane) gave the dienoate **42** as a colourless oil (0.560 g, 88%): R_f = 0.16 (40% EtOAc/hexane); $[\alpha]_D^{20} = +0.8^{\circ}$ (*c* 2.9, CHCl₃); IR (liquid film) 3480 (br), 1725 (s), 1715 (s) cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 8.01 (2H, dm, *J* = ~8 Hz, Ar<u>H</u>), 7.54 (1H, br t, *J* = ~8 Hz, Ar<u>H</u>), 7.42 (2H, br dd, *J* = ~8, 8 Hz, Ar<u>H</u>), 7.28 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 5.88 (1H, br dd, *J* = 7.4, 7.4 Hz, 4-C<u>H</u>), 5.80–5.85 (1H, m, 11-C<u>H</u>), 5.77 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.63 (1H, ddd, *J* = 10.3, 4.0, 2.1 Hz, 10-C<u>H</u>), 4.51–4.38 (3H, m, 9-C<u>H</u> and 15-C<u>H</u>₂), 3.97–3.89 (2H, m, 7-C<u>H</u> and 13-C<u>H</u>), 3.72 (3H, s, CO₂<u>Me</u>), 2.58 (1H, br d, *J* = 3.7 Hz, O<u>H</u>), 2.35 (1H, ddd, *J* = 15.0, 7.5, 7.5 Hz, 6-C<u>H</u>_AH_B), 2.26 (1H, br ddd, J = 15.0, 6.4, 6.4 Hz, 6-CH_AH_B), 2.15 (1H, dm, J = 17.4 Hz, 12-CH_AH_B), 2.06–1.91 (3H, m, 12-CH_AH_B & 14-CH₂), 1.72 (1H, ddd, J = 14.5, 9.7, 2.5 Hz, 8-CH_AH_B), 1.71 (3H, s, 4-CM_c), 1.52 (1H, ddd, J = 14.5, 9.7, 3.0 Hz, 8-CH_AH_B); ¹³C NMR δ (100.6 MHz, CDCl₃) 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⁺, NH₃) 432 (5, [M+NH₄]⁺), 415 (40, [M+H]⁺), 400 (15), 245 (30), 231 (100), 105 (50); HRMS (+FAB, NOBA) Calcd for C₂₄H₃₁O₆ ([M+H]⁺): 415.2122, found 415.2133; Anal calcd for C₂₄H₃₀O₆: 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 CH₂Cl₂ (15 ml) was added 2,6lutidine (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 CH₂Cl₂ (20 ml). The aqueous phase was back-extracted with CH₂Cl₂ (2 x 30 ml) and the combined organic layers were washed with NaHCO₃ solution (30 ml, sat. aq.), then combined, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography (gradient elution with $5\rightarrow 8\%$ 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); $[\alpha]_D^{20} = -45.0^\circ$ (c 2.9, CHCl₃); IR (liquid film) 1725 (s) cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 8.02 (2H, dm, J = ~8 Hz, ArH), 7.54 (1H, tt, J = ~8, 1 Hz, ArH), 7.43 (2H, br dd, J = ~8, 8 Hz, ArH), 7.24 (1H, d, J = 15.7 Hz, 3-CH), 5.87 (1H, br dd, J = 7.4, 7.3 Hz, 5-CH), 5.77 (1H, dddd, J = 7.4, 7.3 Hz, 5-CH), 5.77 (1H, dddd, J = 7.4, 7.3 Hz, 5-CH), 5.77 (1H, dddd, J = 7.4, 7.3 Hz, 5-CH), 5.77 (1H, dddd, J = 7.4, 7.3 Hz, 5-CH), 5.77 (1H, dddd, J = 7.4, 7.3 Hz, 5-CH), 5.77 (1H, dddd, J = 7.4, 7.3 Hz, 5-CH), 5.77 (1H, dddd, J = 7.4, 7.3 Hz, 5-CH), 5.77 (1H, dddd, J = 7.4, 7.3 Hz, 5-CH), 5.77 (1H, dddd, J = 7.4, 7.3 Hz, 5-CH), 5.77 (1H, dddd, J = 7.4, 7.4 Hz, 7.4 10.0, 5.0, 2.5, 2.5 Hz, 11-C<u>H</u>), 5.73 (1H, d, J = 15.7, 2-C<u>H</u>), 5.64 (1H, br d, J = 10.0 Hz, 10-C<u>H</u>), 4.55– 4.48 (1H, m, 15-C \underline{H}_AH_B), 4.41-4.34 (1H, m, 15-C $\underline{H}_A\underline{H}_B$), 4.33 (1H, br d, J = 10.6 Hz, 9-C \underline{H}), 4.03-3.97 $(1H, m, 7-CH), 3.77 (1H, dddd, J = 8.9, 8.9, 3.9, 3.9 Hz, 13-CH), 3.71 (3H, s, CO_2Me), 2.26 (1H, ddd, J = 8.9, 8.9, 3.9, 3.9 Hz, 13-CH), 3.71 (3H, s, CO_2Me), 3.72 (1H, ddd, J = 8.9, 8.9, 3.9, 3.9 Hz, 13-CH), 3.71 (3H, s, CO_2Me), 3.72 (1H, ddd, J = 8.9, 8.9, 3.9, 3.9 Hz), 3.9 Hz, 13-CH), 3.71 (3H, s, CO_2Me), 3.72 (1H, ddd, J = 8.9, 8.9, 3.9, 3.9 Hz), 3.9 Hz), 3.71 (3H, s, CO_2Me), 3.72 (1H, ddd, J = 8.9, 8.9, 3.9, 3.9, 3.9 Hz), 3.9 Hz), 3.71 (3H, s, CO_2Me), 3.72 (3H, s, CO_2Me), 3.71 (3H, s, CO_$ = 15.2, 6.4, 6.4 Hz, 6-CHAHB), 2.16 (1H, ddd, J = 15.2, 8.2, 4.3 Hz, 6-CHAHB), 2.06-1.95 (3H, m, 12- $CH_2 \& 14-CH_AH_B$, 1.94–1.84 (1H, m, 14- CH_AH_B), 1.71 (3H, s, 4- CM_e), 1.58 (1H, ddd, J = 14.4, 10.7, 1.542.4 Hz, $8-CH_AH_B$), 1.37 (1H, ddd, J = 14.4, 10.1, 2.5 Hz, $8-CH_AH_B$), 0.86 (9H, s, SiCMe₃), 0.10 (3H, s, s) Si<u>Me</u>_AMe_B), 0.06 (3H, s, SiMe_A<u>Me</u>_B); ¹³C NMR δ (100.6 MHz, CDCl₃) 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 C₃₀H₄₅O₆Si ([M+H]⁺): 529.2985, found 529.2956; Anal calcd for C₃₀H₄₄O₆Si: C, 68.15; H, 8.39, found: C, 68.12; H, 8.44%.

(*E*,*E*,*7S*)-Methyl-8-[(*2R*,*6S*)-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 K₂CO₃ (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 Et₂O (30 ml) and the aqueous phase was extracted with Et₂O (3 x 20 ml). The combined organic layers were combined, dried (Na₂SO₄) 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); $[\alpha]_D^{20} = -81.6^{\circ}$ (*c* 1.5, CHCl₃); IR (thin film) 3466 (br, m), 1720 (s) cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 7.31 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 5.92 (1H, br dd, *J* = 7.4, 7.4 Hz, 5-C<u>H</u>), 5.79 (1H, d, *J* = 15.7 Hz, 2-C<u>H</u>), 5.78–5.73 (1H, m, 11-C<u>H</u>), 5.60 (1H, dm, *J* = 10.2 Hz, 10-C<u>H</u>), 4.34 (1H, br d, *J* = 10.7 Hz, 9-C<u>H</u>), 4.02–3.95 (1H, m, 7-C<u>H</u>), 3.79–3.66 (6H, m, 13-C<u>H</u>, 14-C<u>H</u>₂ & CO₂<u>Me</u>), 2.67 (1H, br s, O<u>H</u>), 2.44–2.32 (2H, m, 6-C<u>H</u>₂), 2.04 (1H, dddd, *J* = 17.3, 2.4, 2.4, 2.4 Hz, 12-C<u>H</u>_AH_B), 1.88 (1H, dm, *J* = 17.3 Hz, 12-CH_A<u>H</u>_B), 1.76 (3H, s, 4-C<u>Me</u>), 1.75–1.71

(2H, m, 14-C<u>H</u>₂), 1.70 (1H, ddd, J = 14.4, 10.7, 2.1 Hz, 8-C<u>H</u>_AH_B), 1.37 (1H, ddd, J = 14.4, 10.0, 2.4 Hz, 8-CH_A<u>H</u>_B), 0.86 (9H, s, SiC<u>Me</u>₃), 0.063 (3H, s, Si<u>Me</u>_AMe_B), 0.056 (3H, s, SiMe_A<u>Me</u>_B); ¹³C NMR δ (100.6 MHz, CDCl₃) 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⁺, NH₃) 425 (10, [M+H]⁺), 293 (10), 197 (20), 127 (100); HRMS Calcd for C₂₃H₄₁O₅Si ([M+H]⁺): 425.2725, found: 425.2724; Anal calcd for C₂₃H₄₀O₅Si: C, 65.05; H, 9.49, found: C, 65.22; H, 9.61%.

(E,E,7S)-Methyl-8-[(2R,6S)-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 CH₂Cl₂ (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), NaHCO₃ solution (15 ml, sat. aq.) and Et₂O (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 Et₂O (2 x 20 ml). The combined organic layers were washed with successively with NaHCO3 solution (20 ml, sat. aq.) and brine (20 ml, sat. aq.), dried (Na₂SO₄) and concentrated *in vacuo* to give a pale yellow oil. Filtration through a short plug of silica, eluting with 5% Et₂O/CH₂Cl₂ 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); $[\alpha]_D^{20} = -83.3^\circ$ (c 1.74, CHCl₃); IR (thin film) 1722 (s) cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 9.78 (1H, dd, J = 2.4, 1.4 Hz, CHO), 7.33 (1H, d, J = 15.7 Hz, 3-C<u>H</u>), 5.96 (1H, br dd, J = 7.4, 7.4 Hz, 5-C<u>H</u>), 5.82–5.73 (2H, m, 2-C<u>H</u> and 11-CH), 5.64 (1H, dm, J = 10.3 Hz, 10-CH), 4.30 (1H, br d, J = 10.8 Hz, 9-CH), 4.14–4.07 (1H, m, 13-CH), 4.01-3.92 (1H, m, 7-C<u>H</u>), 3.73 (3H, s, CO₂<u>Me</u>), 2.63 (1H, ddd, J = 16.5, 8.6, 2.4 Hz, 14-C<u>H</u>_A), 2.49 (1H, ddd, J = 16.5, 3.9, 1.4 Hz, 14-CHB), 2.43-2.33 (2H, m, 6-CH2), 2.04-1.95 (2H, m, 12-CH2), 1.77 (3H, s, 4-CMe), 1.69 (1H, ddd, J = 14.4, 10.8, 2.2 Hz, $8-CH_AH_B$), 1.39 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd, J = 14.4, 10.0, 2.6 Hz, 8-CMe), 1.69 (1H, ddd), CH_A<u>H</u>_B), 0.86 (9H, s, C<u>M</u>e₃), 0.03 (6H, s, Si<u>M</u>e₂); ¹³C NMR δ (100.6 MHz, CDCl₃) 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+, NH₃) 440 (5, [M+NH₄]+), 423 (30, [M+H]+), 405 (25), 291 (60), 273 (30), 125 (100), 91 (20), 81 (65); HRMS (CI+, NH₃) Calcd for C₂₃H₃₉O₅Si ([M+H]+): 423.2567, found: 423.2567.

Acknowledgements: We thank the SERC/EPSRC (GR/H01922), Rhône Poulenc Rorer, and Merck Sharp & Dohme (Terlings Park) for their support, and Dr P. Pitchen and Dr C. G. Newton (RPR Dagenham) for helpful discussions.

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(Received in UK 10 May 1995; revised 4 July 1995; accepted 7 July 1995)