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Asymmetric Epoxide Cyclisation Route to the F-pyran Fragment of the Altohyrtins and Key Aldol Studies

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Abstract—The evolution of an asymmetric synthesis of a differentially protected F-pyran ring of the altohyrtins is described, which relies on a key intramolecular cyclisation of a C_{43} hydroxyl group onto a C_{38}–C_{39} epoxide. The C_{38}–C_{39} epoxide stereochemistry was achieved through optimisation of substrate control. Key aldol studies towards coupling the F-pyran ring with an E-pyran ring precursor was investigated, but unsuccessful. © 2000 Elsevier Science Ltd. All rights reserved.

The structurally complex spongipyran macrolides exhibit extraordinarily potent cytotoxicity against human cancer cell lines.[1] At first there was some debate as to the relative and absolute stereochemistry of this family of macrolides, which were all isolated independently, guided by bioassays, from marine sponges by the Pettit,[2] Fusetani[3] and Kitagawa groups.[4] This, coupled with the molecule's potent biological activity, has prompted a number of synthetic studies of these molecules,[5] culminating in the total syntheses of altohyrtin C by Evans[6] and altohyrtin A by Kishi.[7] These total syntheses unambiguously verified the relative and absolute structural assignment as proposed by Kitagawa. We too have been involved with synthetic studies towards this class of molecules[8] and wish to report in full our synthesis of the differentially protected F pyran.[9] In this paper we disclose our successful route, as well as our initial route which failed, and studies concerning a key aldol reconnection towards the synthesis of the E,F-bis-pyran fragment.

Our retrosynthetic analysis of the altohyrtin macrolide used the proven late stage macrolactonisation and prior coupling of the northern and southern hemispheres by a Wittig reaction (Scheme 1).[5] The synthesis of the southern hemisphere **1**, the E,F-bis-pyran of the macrolide, can be simplified by *retro*-lactolisation and then aldol disconnection. Although the latter disconnection was published[9c] by another group during our studies, our synthesis offers the preparation of a differentially protected fragment for further coupling. Stereocontrolled synthesis of differentially protected **2** was achieved through cyclisation of the C_{43} hydroxyl onto an epoxide derived from **3**, which represents an alternative to the published strategies for the synthesis of this ring system.[6b,7b,9]

Our original retrosynthetic analysis relied on synthesising the protected penta-ol **4** from aldehyde **5** by Wittig type methodology or conversion to the alkyne followed by partial reduction (Scheme 2). Aldehyde **5** could be constructed by a Felkin Anh controlled nucleophilic addition onto the C_{43} aldehyde of **6** (X_c=chiral auxiliary) which in turn could be accessed by oxidation of the corresponding alcohol **7**. This alcohol could conceivably come from the directed epoxidation of **8** followed by ring opening with an oxygen nucleophile, or from asymmetric dihydroxylation of the alkene. Formation of **8** could be most easily achieved from an Evans boron aldol reaction.

Aldol adduct **8** was synthesised in greater than 95:5 diastereoselectivity, as judged by ^{1}H and ^{13}C NMR spectroscopy.[10] We anticipated that directed epoxidation of the alkene in **8**, with the *tert*-BuOOH/cat. $VO(acac)_2$ system, would deliver the undesired stereoisomer, in line with theory and literature precedent.[11] Epoxidation with *m*CPBA was expected to give little diastereoselection, due to the absence of any important unfavourable A-1,2 or A-1,3 interactions. Therefore we attempted to utilise Sharpless epoxidation conditions to access the desired isomer.[12] Attempted epoxidation with (+)-diethyl tartrate gave only a 20% yield of cleaved chiral auxiliary and what was tentatively assigned as the *tert*-butylhydroperoxyester. We assume that due to the Lewis acidic nature of the titanium species, this outcome is more favourable than the desired mis-matched epoxidation product. However, use of the alternate enantiomer of diethyl tartrate gave similar results.

Keywords: asymmetric synthesis; epoxidation; aldol reactions; pyran.
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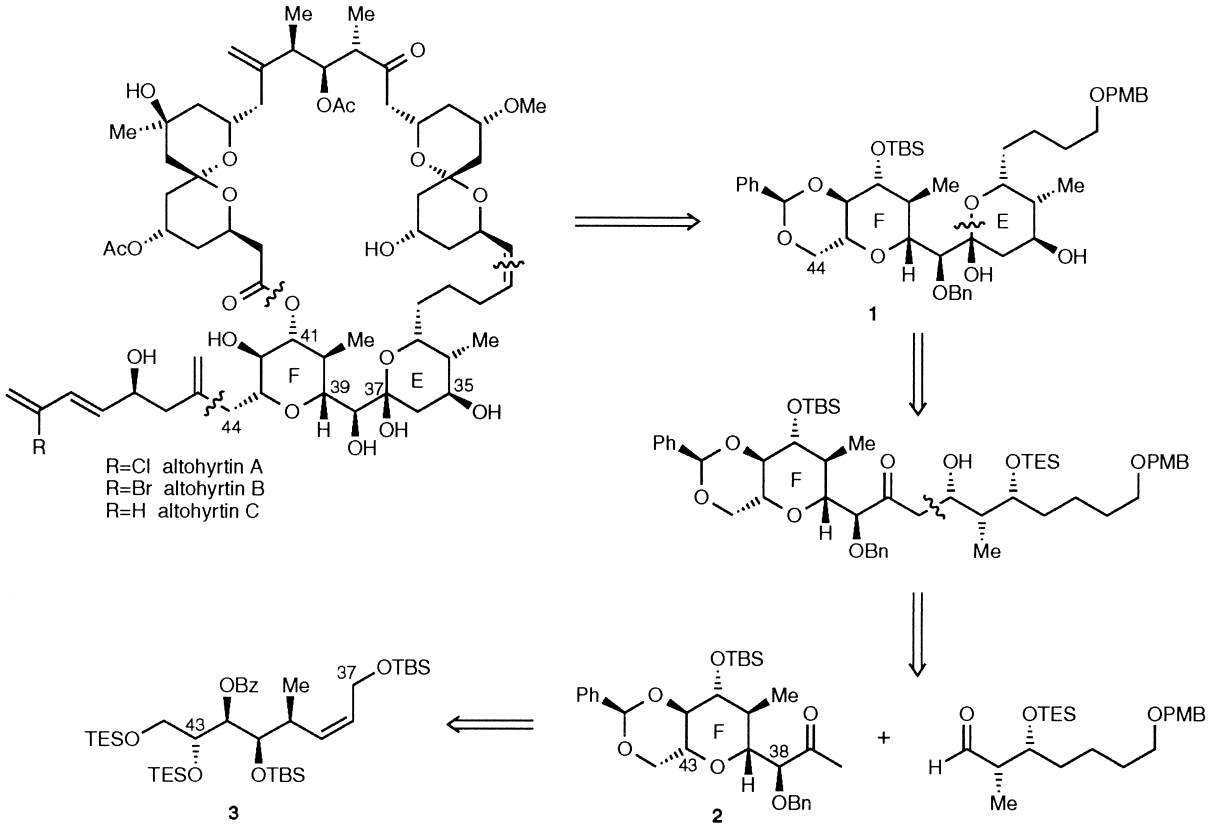
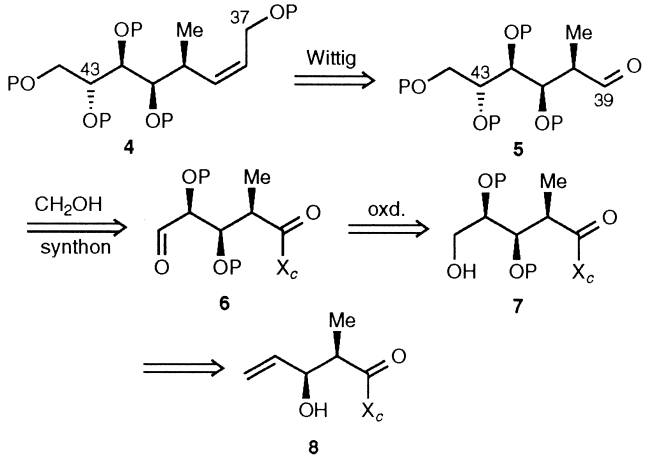


Scheme 1.

Use of *tert*-BuOOH/cat. $VO(acac)_2$ or *m*CPBA gave no reaction. Recourse to diastereoselective dihydroxylation was then sought.

The alcohol function of **8** was protected as its benzyl ether in order to simplify future protecting group manipulations. This could only be achieved by reductive removal of the chiral auxiliary, followed by protection of the resultant 1,3-diol as its benzylidene acetal **9** (Scheme 3). Subsequent treatment with DIBAL afforded a 16:1 mixture of regio-isomeric benzyl ethers in favour of **10**. The remaining primary hydroxyl function was then differentially protected as its *para*-methoxybenzyl (PMB) ether in 79% overall yield. Using the Sharpless mnemonic we predicted that AD-mix α would direct dihydroxylation to the desired face of **11**.[13] Reaction with AD-mix α, under standard conditions, gave a 5:1 mixture of diastereoisomers by ^1H NMR (Table 1 in Scheme 3). Control experiments with AD-mix β gave a 22:1 diastereoselection in favour of the same diastereoisomer. Theory suggested that AD-mix α should give the desired diol **12**-*syn*. However, the fact that AD-mix β gave an increased diastereoselection suggested that this ligand reinforced the natural substrate control toward the undesired matched diol **12**-*anti*. Substrate only controlled dihydroxylation using quinuclidine gave a 17:1 mixture, again favouring the same major diastereoisomer. This result was in line with models forwarded in the literature to account for the sense of dihydroxylation by OsO_4 with chiral allylic alcohols.[14] Unfortunately, although AD-mix α conflicted with substrate control, it could not override it. Subjecting **9** to each of the dihydroxylation experiments furnished the undesired *anti*-diastereoisomer.



Scheme 2.

In view of the strong substrate control of this system, we decided to use this to our advantage and manipulated **12**-*anti* to the desired **12**-*syn*. Selective protection of the primary hydroxyl with *tert*-butyldiphenylsilyl chloride (86%), mesylation of the secondary C_{42} hydroxyl group (97%) and treatment with TBAF with concomitant cyclisation (83%) gave the epoxide **13** (Scheme 4). Due to the preceding discussion concerning the stereochemical course of the dihydroxylation reaction and literature precedence for epoxide formation in this manner,[15] we were confident that we had prepared the *syn*-epoxide. Ring opening of the epoxide was then achieved under basic conditions with

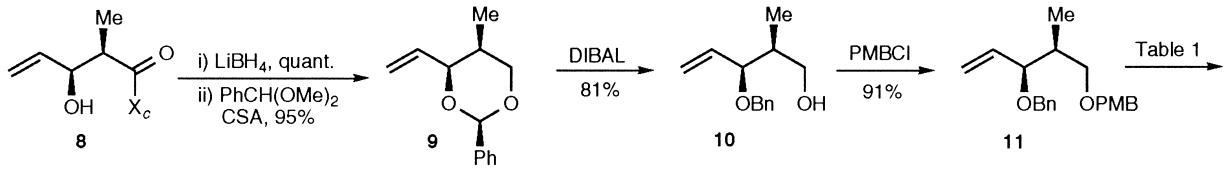
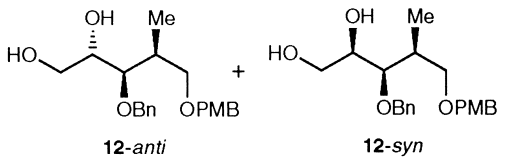


Table 1

conditions	Yield/%	diastereoselective ratio **12**-*anti* : **12**- *syn*
AD-mix α	90	5 : 1
AD-mix β	91	22 : 1
$K_2OsO_4•2H_2O$, $K_3Fe(CN)_6$ K_2CO_3, quinuclidine	91	17 : 1

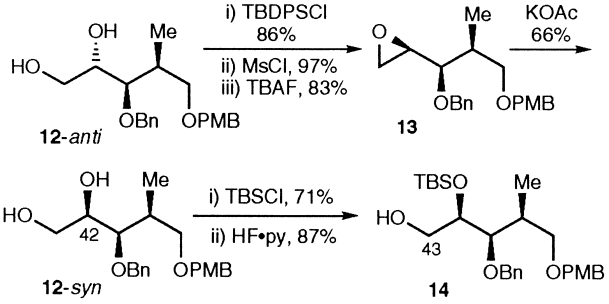


Scheme 3.

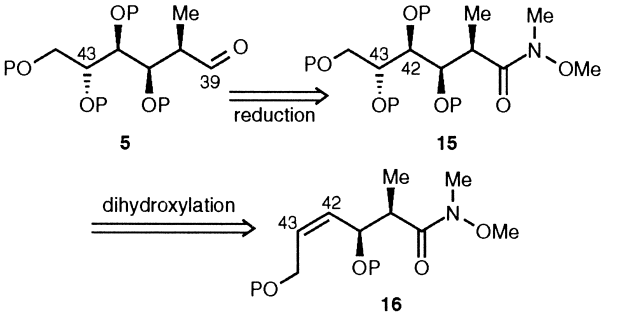
potassium acetate to give the desired diol **12**-*syn* (66%) whose spectroscopic data matched the minor diastereoisomer formed from the dihydroxylation of **11**. Bis-*tert*-butyldimethyl silyl protection (71% as well as 16% mono protection) followed by selective deprotection of the C_{43} primary hydroxyl group gave alcohol **14**. Although we had accessed material of the correct stereochemistry, the route was becoming cumbersome. In parallel we were investigating an alternative strategy which involved the dihydroxylation of an internal alkene to directly set up both the C_{42} and C_{43} hydroxyl stereocentres.

This alternate strategy required dihydroxylation of *Z*-alkene **16** to form **15** (Scheme 5) which could be easily reduced to the Wittig precursor **5** as shown in Scheme 2. A *syn* aldol reaction could furnish **16** stereoselectively. Evans boron aldol reaction[16] with *Z*-4-benzyloxy-but-2-en-1-al (**17**) gave **19** in 74% yield with a diastereoselection of 9:1 by ^{1}H NMR (Scheme 6). Aldehyde **17**, prepared by the monoprotection and Swern oxidation of *Z*-2-butene-1,4-diol (**18**), was sensitive towards in situ isomerisation to the *E*-aldehyde, but reliable material could be obtained if the aldehyde was used immediately. Transamination of **19** to form the Weinreb amide[17] followed by standard triethylsilyl protection of the hydroxyl group gave **20**. Unfortunately, attempted dihydroxylation of **20** under identical conditions to those used for **11** gave only recovered starting material. Protection of the hydroxyl group as the acetate gave the same result. This is curious given the wide range of alkenes for which the dihydroxylation reaction is successful, and may be due to deactivation of the alkene by two adjacent C–O bonds. At this point the use of the dihydroxylation reaction to furnish the desired stereocentres was abandoned.

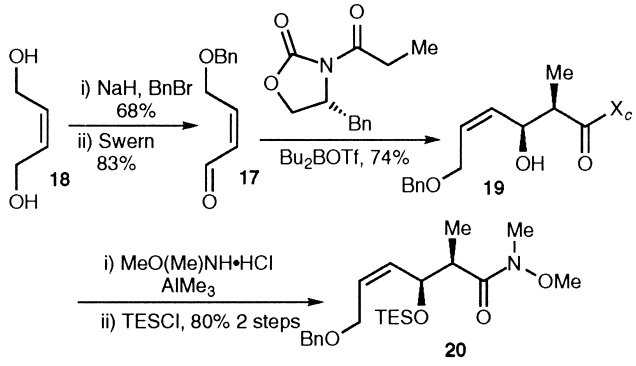
In the light of these results we proposed that **4** could be prepared via regioselective ring opening of epoxide **21** at C_{42} with an appropriate oxygen nucleophile.[18] The epoxide **21** could itself be derived from a substrate directed epoxidation or a Sharpless asymmetric epoxidation[12] of allylic alcohol **22**. During our studies Smith et al. reported the generation of these stereocentres (C_{42} and C_{43}) using this strategy.[9b] Our approach towards the F-ring system remained quite different so we continued with our proposed



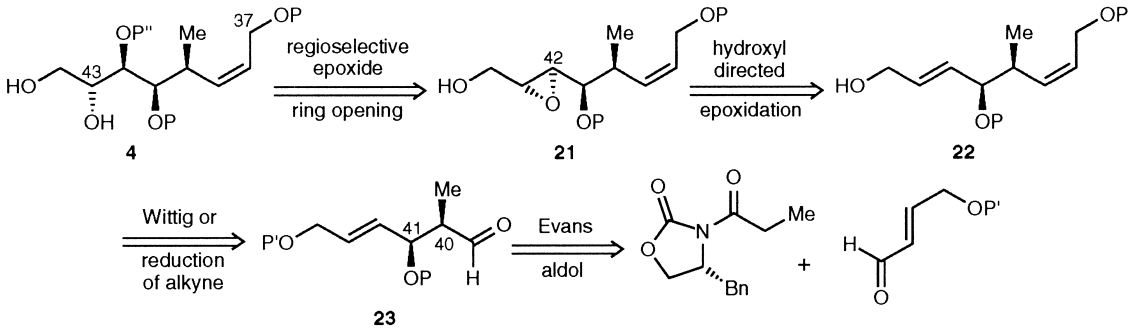
Scheme 4.



Scheme 5.



Scheme 6.



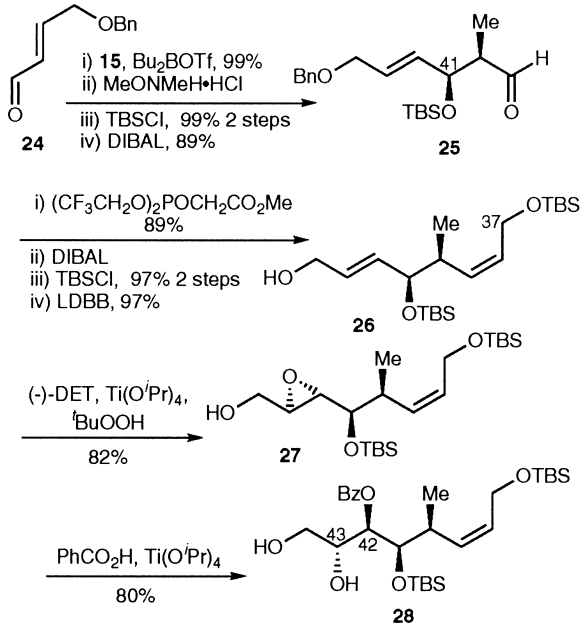
Scheme 7.

route. The *Z*-alkene of **22** could be accessed from the aldehyde **23** by a suitable Wittig reaction or via alkyne reduction. An Evans boron aldol reaction would set up the C_{40} and C_{41} absolute stereochemistry.

At this stage the choice of protecting groups had to be made. In **22** we decided to use P=*tert*-butyldimethylsilyl as literature precedent exists for the removal of primary over secondary hydroxyl groups.[19] This choice then required an orthogonal protecting group for the unmasking of the allylic alcohol. We decided to use a benzyl protecting group for P′ (**23**), which could be introduced in the initial aldol reaction. The oxygen nucleophile for the opening of the epoxide needed to be orthogonal to the C_{41} TBS ether, which would have to be unmasked for coupling reactions.

Compound **24** could be prepared from the in situ isomerisation of **17** (Scheme 6) in 55% overall yield from **18**. Although this sort of isomerisation has been noted for the slightly acidic oxidant pyridinium chlorochromate,[20] we speculate that in this reaction an addition/elimination of dimethyl sulfide accompanied by C_{42}–C_{43} bond rotation accounts for the preferential formation of **24**. Providing freshly prepared dibutylboron triflate[21] was used, the subsequent Evans aldol reaction proceeded in excellent yield and diastereoselection (Scheme 8). Weinreb amide formation followed by protection of the C_{41} secondary hydroxyl group as its TBS ether and controlled reduction with DIBAL gave aldehyde **25** which was subjected to a Still modified Horner–Wadsworth–Emmons reaction. Reduction of the methoxy ester with DIBAL and protection of the resultant C_{37} primary hydroxyl group as its TBS ether gave exclusively the differentially protected diene in good overall yield. Deprotection of the benzyl group could be achieved with lithium in liquid ammonia (96%), but on a larger scale (≥10 g) it was more convenient to use di-*tert*-butylbiphenyllithium (LDBB)[6a,22] under argon to give the allylic alcohol **26**. Attempts to perform the hydroxyl directed epoxidation under substrate control, using $VO(acac)_2$ with *tert*-BuOOH gave a 3:1 mixture of diastereoisomers in quantiative crude yield. Asymmetric epoxidation using (−)-diethyl tartrate[12] gave a single diastereoisomer **27** in 82% yield after chromatography. The epoxide stereochemistry was assigned using literature precedence confirming the reliability of the Sharpless model.[23] It was clear, from a comparison of ^{1}H NMR spectra, that the major compound from the substrate controlled reaction was identical to **27**. Regioselective ring opening of the epoxide was then performed with benzoic acid under Lewis acidic conditions[18] to give diol **28** as a single diastereoisomer with the required *anti* relationship between the C_{42} and C_{43} hydroxyl stereocentres. Fragment **28** was the differentially protected penta-ol **4** (Scheme 7) required for epoxidation–cyclisation studies.

We hoped that **28** would exert some inherent substrate control in an epoxidation reaction in order to avoid resorting to chiral epoxidising reagents. The proposed trajecory for epoxidation was rationalised from the conformer exhibiting the least A-1,3 strain (Fig. 1).[24] It was envisaged that



Scheme 8.

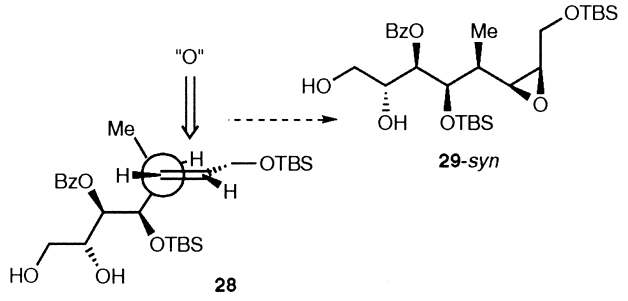


Figure 1.

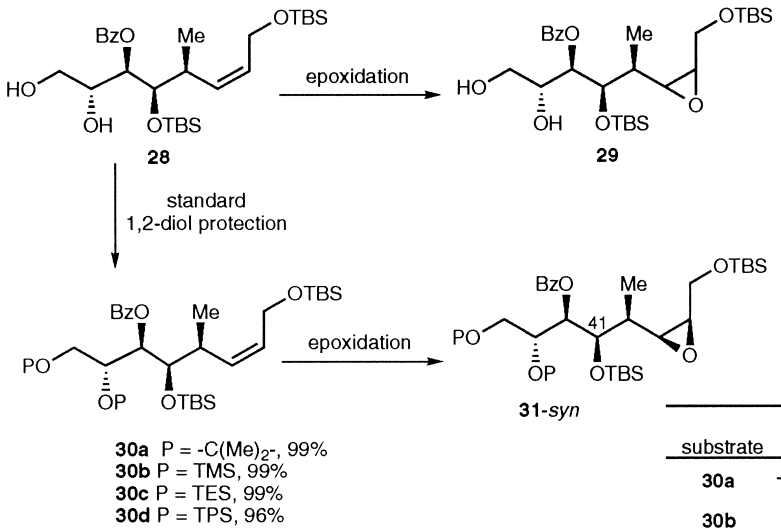


Table 2

reagents and conditions	yield	diastereomeric ratio
mCPBA, CH_2Cl_2, 0 °C	80	1:1
DMDO, CH_2Cl_2, -20 °C	>99	2:1

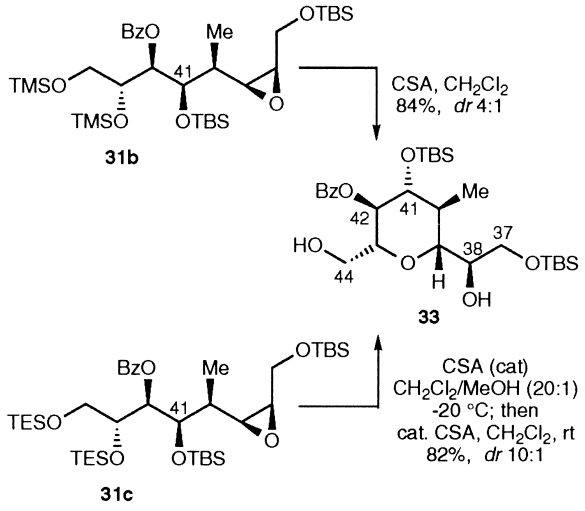
Table 3

substrate	P	reagents and conditions	yield	diastereomeric ratio
30a	-C(Me)$_2$-	DMDO, CH_2Cl_2, -20 °C	>99	4:1
30b	TMS	DMDO, CH_2Cl_2, -20 °C	>99	4:1
30c	TES	mCPBA, CH_2Cl_2, 0 °C	87	1:1
30c	TES	DMDO, CH_2Cl_2, -20 °C	97	7:1
30d	TPS	DMDO, CH_2Cl_2, -20 °C	86	8:1

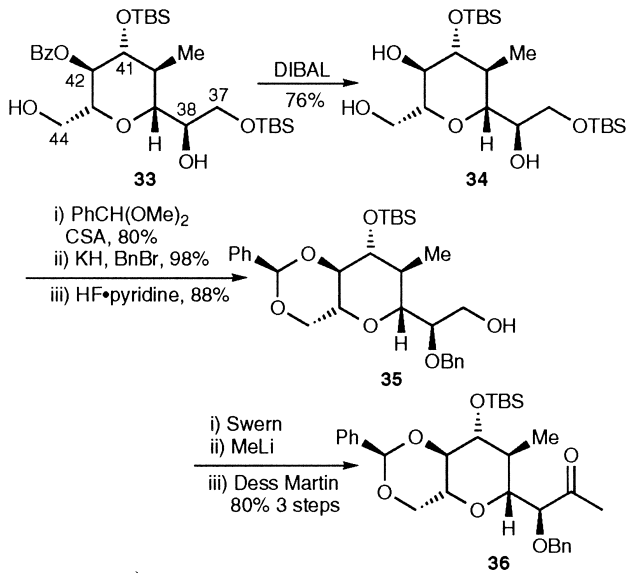
Scheme 9.

approach over the least sterically demanding face of the alkene would give the desired epoxide **29**. Treatment of **28** with *m*CPBA gave a 1:1 mixture of cyclised pyran diastereoisomers. Reaction with dimethyldioxirane[25] (DMDO) at −20°C gave **29** as a 2:1 mixture of diastereoisomers in quantitative yield (Table 2, Scheme 9). To prohibit any directing effect from the proximal hydroxyl groups, due to possible hydrogen bonding with reagents, the diol was protected as an acetonide **30a**. Epoxidation of the protected material with DMDO gave an improved diastereoselection of 4:1. As with the *m*CPBA epoxidation of **28**, acetonide **30a** also gave a 1:1 mixture of epoxides under these reaction conditions. The reaction was also successful at −78°C using the highly reactive trifluoro analogue of dimethyldioxirane prepared via reaction of Oxone® with 1,1,1-trifluoroacetone instead of acetone. Epoxidation using this reagent was complete within minutes, but unfortunately only gave a 1:1 mixture of diastereoisomers by ^{1}H NMR.

Continuation of the synthesis required selective deprotection of the acetonide protecting group of **31a** to leave the secondary C_{41} TBS ether intact. Under a variety of reaction conditions the only product obtained resulted from the removal of the primary TBS group to give the crystalline product **32** [Eq. (1)]. Single crystal X-ray crystallography of the major epoxide diastereoisomer **32** confirmed the desired *syn* stereochemistry. It was therefore necessary to investigate the use of alternative protecting groups which would allow selective removal. Bis-silyl protected compounds **30b** (TMS), **30c** (TES), and **30d** [triphenylsilyl (TPS)] were all synthesised by standard methods. Epoxidation of these compounds with DMDO gave good yields and the diastereoselection improved with increasing size of the protecting group (Table 3, Scheme 9). Again, treatment of **30c** with *m*CPBA gave a 1:1 mixture of diastereoisomers. The per-acid reagent appears to be insensitive to the subtle changes in sterics provided by protection of the diol functionality. Deprotection of the TPS ethers in the presence of TBS ethers proved unsuccessful, but selective deprotection of the two TMS ethers in **31b** was straightforward. Treatment of **31b** with CSA in CH_2Cl_2 under atmospheric conditions resulted in the selective removal of both TMS groups and the spontaneous cyclisation to the F-ring system **33** as a 4:1 mixture of diastereoisomers (Scheme 10). Selective removal of the TES ethers of **31c** was much more desirable, since the epoxidation proceeded with enhanced diastereomeric ratio (7:1). In order to minimise the removal of the primary TBS ether, optimised conditions required treatment of **31c** with catalytic CSA at −20°C in CH_2Cl_2/MeOH (20:1). Removal of volatiles as soon as the bis-TES ether had been deprotected (<4 h), gave a crude reaction mixture containing mainly epoxide diol with a small amount of cyclised material **33**. Subsequent treatment with catalytic

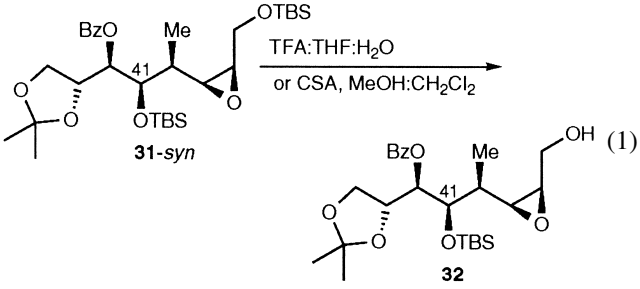


Scheme 10.



Scheme 11.

CSA in anhydrous CH_2Cl_2 induced complete cyclisation to give **33** in 82% yield with an upgraded 10:1 diastereomeric ratio after column chromatography. We were confident of having the correct stereochemistry due to the similarity of compounds **31a–d** which differed from each other just by diol protecting groups. Also the ^{1}H NMR spectrum of **33** showed large coupling constants (~8.5–11 Hz) between C_{42}–H and C_{43}–H; C_{42}–H and C_{41}–H; C_{39}–H and C_{40}–H indicating that all protons occupied axial positions.

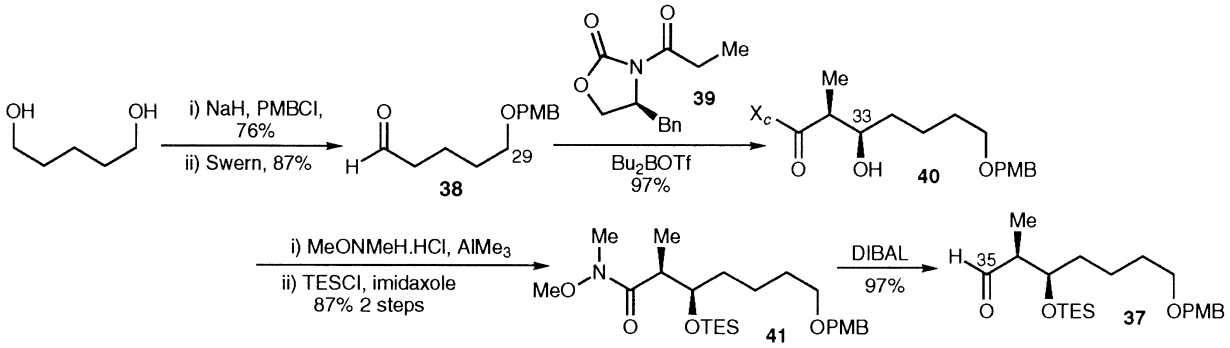


(1)

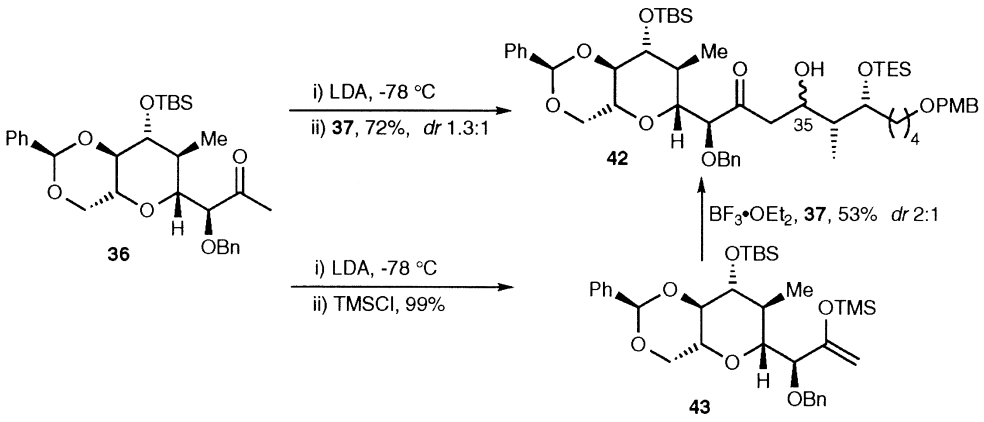
To access a differentially protected coupling fragment, the reactive benzoyl group was removed with DIBAL to give the crystalline triol **34** (Scheme 11) which was amenable to single crystal X-ray analysis and unequivocally confirmed the structure of this advanced intermediate. Protection of the 1,3-diol as its benzylidene acetal proceeded in good yield in the presence of 4 Å molecular sieves. This was necessary as liberation of methanol under the acidic conditions caused deprotection of the primary C_{37} TBS ether and additional benzylidene acetal protection of the resulting 1,2 (C_{37}–C_{38}) diol. Despite this precaution the desired benzylidene contained ~5% of inseparable bis-benzylidene impurity. This particular protecting group was chosen to allow selective deprotection of the C_{41} hydroxyl group for the late stage macrolactonisation. We envisaged selective unmasking of the C_{44} hydroxyl group would be possible by treatment with DIBAL. Coordination of the aluminium reagent to the comparatively less hindered C_{44} hydroxyl should occur in preference to chelation between C_{42}–O and the silyl protected C_{41}–O. The secondary C_{38} hydroxyl group was protected as its benzyl ether and selective removal of the primary TBS ether with HF·pyridine complex gave the protected pyran-alcohol **35**. Manipulation of the alcohol to give methyl ketone **36** required careful Swern oxidation using the more hindered di-*iso*-propylethylamine and quenching of the reaction at −40°C with pH7 buffer, to avoid epimerisation. Addition of methyl lithium followed by Dess Martin periodinane[26] oxidation gave **36** in good overall yield.

The key aldol reaction required the addition of aldehyde **37** to the kinetic enolate of **36** (Scheme 12). The former was prepared starting from the monoprotection of pentane-1,5-diol with *para*-methoxybenzyl chloride in 76% yield followed by Swern oxidation of the remaining hydroxyl group to the aldehyde **38** in 87% yield. Addition of aldehyde **38** to the *Z*-boron enolate of carboximide **39** afforded aldol product **40** in excellent yield as a single diastereoisomer by ^{1}H and ^{13}C NMR. Conversion to the Weinreb amide and protection of the secondary alcohol as its TES ether allowed separation of the chiral auxilliary and isolation of **41** in excellent yield. Controlled reduction with DIBAL afforded the desired aldehyde **37** in good yield. Aldehyde **37** was stable for ~2 weeks at −20°C under nitrogen.

We envisaged that control of the C_{35} stereocentre (Scheme 13) would arise from Felkin control in the addition of the kinetic enolate of **36** to aldehyde **37**. Any influence the chiral enolate derived from **36** would have on the stereocontrol of the key aldol reaction was unpredictable due to its complexity. Generation of the kinetic enolate of **36** with LDA at −78°C followed by quenching with aldehyde **37**



Scheme 12.



Scheme 13.

gave **42** as a separable 1.3:1 diastereomeric mixture in 72% yield (Scheme 13). This strategy was identical to that of Ley[9c] which proved unsuccessful in delivering the correct stereochemistry from the lithium enolate. Investigation by Heathcock and Flippin[27] into the addition of silyl enol ethers to 2-phenylpropanal, demonstrated that enhanced levels of Felkin selectivity could be obtained, relative to the lithium enolate, by the use of borontrifluoride etherate. Accordingly kinetic silyl enol ether **43** was prepared in quantitative crude yield by generating the lithium enolate as before and quenching with TMSCl. The subsequent borontrifluoride etherate promoted condensation gave 2:1 diastereoselection in favour of the same diastereoisomer in a reduced yield of 53% in addition to 28% recovered starting material. Larger silyl enol ethers were also investigated as we thought that steric bulk at this position might alter diastereoselectivity. The TBDPS enol ether was unstable and although the TIPS enol ether could be prepared it proved unreactive under the Lewis acid conditions employed for conversion of **43**. With the small amount of material prepared, cyclisation studies by selective removal of the TES protecting group using HF·pyridine complex gave a complicated mixture of products for each diastereoisomer. In view of the lack of precedent and difficulties associated with similar studies[9c] this particular coupling strategy was abandoned.

In conclusion, a differentially protected F-pyran fragment has been successfully synthesised via a route distinct from others in the literature. The key step in this synthesis was an intramolecular epoxide ring opening, the epoxide itself being formed via substrate controlled epoxidation of the corresponding alkene. Further studies will focus on a modified fragment and alternative coupling strategies to complete the E,F-bis-pyran of the altohyrtins for future total synthesis studies.

Experimental

General experimental details are as published[28] with the following amendments. Optical rotations were recorded on an Optical Activity AA-10 automatic polarimeter at room temperature and are given in 10^{-1} deg cm^2 g^{-1}. Concentrations (c) are quoted in g/100 mL.

In cases where there exists an unequal mixture of two diastereoisomers in the ^{13}C and ^{1}H NMR spectra, the minor diastereoisomer has been stated in parenthesis.

(4*R*,5*S*)-5-Methyl-2-phenyl-4-vinyl-[1,3]-dioxane (9). To a solution of aldol adduct **8** (4.50 g, 15.57 mmol) and MeOH (1.39 mL, 34.26 mmol) in THF (250 mL) at 0°C was added a 2 M solution of $LiBH_4$ in THF (17.13 mL, 34.26 mmol) dropwise. The mixture was stirred for 2 h then quenched with aqueous NaOH (2 M, 50 mL). After stirring for 18 h the volatile material was removed in vacuo and the resulting slurry was extracted with Et_2O (100 mL). The layers were separated and the aqueous layer extracted with more Et_2O (5×100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give the corresponding diol (1.81 g, 100% crude) as a light yellow oil $[\alpha]_D=-16.7$ (c 3.0, CH_2Cl_2); IR (thin film) ν_{max}/cm^{-1} 3356 (O–H), 3088–2882 (C–H); δ_H (250 MHz, $CDCl_3$) 0.80 (3H, d, J=7.0 Hz, CH*Me*), 1.82–1.98 (1H, m, C*H*Me), 2.15 (2H, s, 2×OH), 3.57 (1H, dd, J=10.7, 4.9 Hz, *H*CHOH), 3.63 (1H, dd, J=10.7, 7.0 Hz, HC*H*OH), 4.22–4.29 (1H, m, C*H*OH), 5.14 (1H, dt, J=10.6, 1.5 Hz, *H*CH=CH), 5.22 (1H, dt, J=17.4, 1.5 Hz, HC*H*=CH), 5.85 (1H, ddd, J=17.4, 10.6, 5.8 Hz, C*H*=CH$_2$); δ_C (62.9 MHz, $CDCl_3$) 11.1, 39.6, 65.5, 75.1, 115.4, 138.4; m/z (CI$^+$) 134 (100% MNH_4^+), 117.0914 (47% MH^+, $C_6H_{13}O_2$ requires 117.0916), 98 (32%).

To a solution of the above diol (317 mg, 2.73 mmol) in DMF (5 mL) was added benzaldehyde dimethylacetal (0.41 mL, 2.73 mmol) and CSA (31 mg, 0.14 mmol). The solution was stirred for 4 days before saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture extracted with Et_2O (2×70 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (20:1 pet. ether / EtOAc) afforded **9** (540 mg, 97%) as a mixture of diastereoisomers (15:1) which existed as a light yellow oil $[\alpha]_D=-20.0$ (c 3.0, CH_2Cl_2); IR (thin film) ν_{max}/cm^{-1} 3067–2850 (C–H); δ_H (250 MHz, $CDCl_3$) for major diastereoisomer:1.21 (3H, d, J=6.7 Hz, CH*Me*), 1.61–1.76 (1H, m, C*H*Me), 4.05 (1H, dd, J=11.3, 1.5 Hz, *H*CHCHMe), 4.16 (1H, dd, J=11.3, 2.5 Hz, HC*H*CHMe), 4.50–4.57 (1H, m, C*H*CH=CH$_2$), 5.22 (1H, dt, J=10.7, 1.7 Hz, *H*CH=CH), 5.35 (1H, dt, J=17.4, 1.7 Hz, HC*H*=CH), 5.59 (1H, s, C*H*Ph), 5.87 (1H, ddd, J=17.4, 10.7, 4.9 Hz, C*H*=CH$_2$), 7.30–7.60 (5H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 11.5, 32.8, 73.4,

80.1, 101.7, 115.3, 126.3, 128.3, 128.9, 136.8, 139.0; *m/z* (EI^+) 204.1146 (22% M^+, $C_{13}H_{16}O_2$ requires 204.1150), 148 (64%), 107 (100% $PhCHO^+$), 77 (41% Ph^+); (Found C, 76.30; H, 7.95. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.95).

(2*R*,3*R*)-2-Methyl-3-phenylmethoxy-4-penten-1-ol (10). To a solution of bezylidene acetal **9** (80 mg, 0.39 mmol) in CH_2Cl_2 (2 mL) at −78°C was added DIBAL (0.35 mL, 1.96 mmol). The white slurry was then warmed to 0°C over a 15 min period and was left at this temperature for 2 h. The clear colourless solution was then re-cooled to −78°C and excess DIBAL was quenched by addition of MeOH (0.2 mL) dropwise. On warming to 0°C the solution was diluted with CH_2Cl_2 (2 mL) and saturated aqueous sodium potassium tartrate (5 mL) was added and the mixture stirred vigorously for 6 h. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Purification by flash column chromatography (6:1 pet. ether/EtOAc) gave the desired alcohol **10** (65 mg, 81%) and the corresponding regioisomeric benzyl ether (4 mg, 5%) both as colourless oils. Data for **10** $[\alpha]_D$=+50.0 (*c* 3.0, CH_2Cl_2); IR (thin film) ν_{max}/cm^{-1} 3382 (O–H), 3065–2877 (C–H); δ_H (250 MHz, $CDCl_3$) 0.89 (3H, d, *J*=7.0 Hz, CH*Me*), 1.94–2.21 (2H, m, C*H*Me, O*H*), 3.52 (1H, dd, *J*=10.1, 4.3 Hz, *H*CHOH), 3.67 (1H, dd, *J*=10.1, 7.6 Hz, HC*H*OH), 3.90 (1H, dd, *J*=7.7, 4.4 Hz, C*H*OBn), 4.33 (1H, d, *J*=11.9 Hz, *H*CHPh), 4.61 (1H, d, *J*=11.9 Hz, HC*H*Ph), 5.28 (1H, ddd, *J*=17.1, 1.8, 0.9 Hz, *H*CH=CH), 5.34 (1H, ddd, *J*=10.4, 1.8, 0.9 Hz, HC*H*=CH), 5.84 (1H, ddd, *J*=17.1, 10.6, 7.7 Hz, *H*C=CH_2); 7.22–7.40 (5H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 12.1 39.5, 65.8, 70.4, 83.5, 118.8, 127.6, 127.7, 128.4, 135.8, 138.3; *m/z* (CI^+) 224 (39%, MNH_4^+) 207.1383 (100% MH^+, $C_{13}H_{19}O_2$ requires 207.1385), 189 (17%), 108 (23%, $BnOH^+$).

Data for regioisomeric benzyl ether δ_H (250 MHz, $CDCl_3$) 0.89 (3H, d, *J*=7.0 Hz, CH*Me*), 1.98–2.17 (1H, m, C*H*Me), 2.80 (<1H, bs, OH), 3.46–3.56 (2H, m, CH_2OBn), 4.20–4.30 (1H, m, C*H*OH), 4.50 (2H, s, CH_2Ph), 5.17 (1H, dt, *J*=10.4, 1.7 Hz, *H*CH=CH), 5.28 (1H, dt, *J*=17.1, 1.7 Hz, HC*H*=CH), 5.87 (1H, ddd, *J*=17.1, 10.4, 5.5 Hz, C*H*=CH_2), 7.24–7.40 (5H, m, ArH); *m/z* (EI^+) 206.1302 (100% M^+, $C_{13}H_{18}O_2$ requires 206.1307), 108 (23%, $BnOH^+$), 91 (100% Bn^+).

(3*R*,4*S*)-4-Methyl-5-[(4-methoxyphenyl)methoxy]-3-(phenylmethoxy)-1-pentene (11). To a suspension of KH (177 mg, 4.43 mmol) in THF (7 mL) at 0°C was added alcohol **10** (760 mg, 3.69 mmol) in THF (5 mL+5 mL wash) dropwise via cannula. After 30 mins PMBCl (0.55 mL, 4.06 mmol) was added followed by tetrabutylammonium iodide (68 mg, 0.18 mmol). After 5 min at 0°C the reaction was quenched with H_2O (30 mL) and diluted with Et_2O (20 mL). The layers were separated and the aqueous layer extracted with Et_2O (2×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a brown oil. Purification by flash column chromatography (9:1 pet./EtOAc) gave alkene **11** (1.21 g, 100%) as a colourless oil $[\alpha]_D$=+22.0 (*c* 5, CH_2Cl_2); IR (thin film) ν_{max}/cm^{-1} 3065–2857 (C–H), 1612 (Ar), 1586 (Ar), 1513 (Ar); δ_H (250 MHz, $CDCl_3$) 0.99 (3H, d, *J*=6.7 Hz, CH*Me*), 1.85–2.02 (1H, m, C*H*Me), 3.28 (1H, dd, *J*=9.0, 6.1 Hz, *H*CHOPMB), 3.49 (1H, dd, *J*=9.0, 6.6 Hz, HC*H*OPMB), 3.78 (3H, s, ArO*Me*), 3.82–3.90 (1H, m, C*H*OBn), 4.29 (1H, d, *J*=11.9 Hz, *H*CHPh), 4.37 (2H, s, OCH_2PMP), 4.58 (1H, d, *J*=11.9 Hz, HC*H*Ph), 5.17–5.31 (2H, m, CH_2=CH); 5.69–5.85 (1H, m, C*H*=CH_2), 6.80–7.38 (10H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 12.3, 38.7, 55.3, 70.5, 72.2, 72.7, 81.0, 113.7, 117.4, 127.3, 127.6, 128.2, 129.2, 130.8, 137.5, 139.0, 159.1; *m/z* (EI+) 326.1884 (15% M^+, $C_{21}H_{26}O_3$ requires 326.1882), 137 (33% $PMBO^+$), 121 (100%, PMB^+), 91 (68%, Bn^+); (Found C, 77.53; H, 8.06. $C_{21}H_{26}O_3$ requires C, 77.27; H, 8.03).

(2*S*,3*R*,4*S*)-4-Methyl-5-[(4-methoxyphenyl)methoxy]-3-(phenylmethoxy) pentan-1,2-diol (12). To a solution of AD-mix α (213 mg, 1.4 g $mmol^{-1}$) in 1:1 $^tBuOH/H_2O$ (2 mL) at 0°C was added alkene **11** (50 mg, 0.152 mmol) in 1:1 $^tBuOH/H_2O$ (1.5 mL) via pipette. After 3 h the solution was warmed to room temperature and stirred for 18 h. Anhydrous Na_2SO_3 (400 mg) was then added and the mixture was stirred for 1 h before CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (2:1 EtOAc/pet. ether) gave diol **12** (50 mg, 91%, dr 5:1) as a viscous colourless oil; IR (thin film) ν_{max}/cm^{-1} 3046 (O–H), 3031–2865 (C–H), 1612 (Ar), 1586 (Ar), 1513 (Ar); NMR data for major diastereoisomer **12**-*anti* δ_H (250 MHz, $CDCl_3$) 1.01 (3H, d, *J*=7.3 Hz, CH*Me*), 2.09–2.25 (1H, m, C*H*Me), 2.37 (1H, bs, OH), 3.41 (1H, dd, *J*=9.3, 7.3 Hz, *H*CHOPMB), 3.46 (1H, dd, *J*=9.3, 5.0 Hz, HC*H*OPMB), 3.55–3.82 (4H, m, CH_2OH, C*H*OBn, C*H*OH), 3.78 (3H, s, PhO*Me*), 4.38 (1H, d, *J*=11.5 Hz, *H*CHPMP), 4.45 (1H, d, *J*=11.5 Hz, HC*H*PMP), 4.53 (2H, s, CH_2Ph), 6.82–7.39 (10H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 12.2, 35.2, 55.3, 64.0, 72.2, 72.8, 74.1, 80.0, 113.8, 127.8 (two overlapping), 128.4, 129.6, 130.0, 138.4, 159.3; *m/z* (EI^+) 360.1939 (6% M^+, $C_{21}H_{28}O_5$ requires 360.1937), 137 (73%), 121 (100% PMB^+), 91 (83%, Bn^+); (Found C, 69.95; H, 7.96. $C_{21}H_{28}O_5$ requires C, 69.98; H, 7.83).

Treatment of **11** with AD-mix β in an identical fashion as above gave diol **12**, 91%, dr 22:1, $[\alpha]_D$=+9.3 (*c* 4.3, CH_2Cl_2). The major diastereoisomer observed possessed the same ^1H NMR characteristics as that above.

To a solution of potassium ferricyanide (150 mg, 0.456 mmol), potassium carbonate (61 mg, 0.444 mmol), quinuclidine (~0.8 mg, ~4 mol%) and potassium osmate-(vi)dihydrate (~0.6 mg, ~1 mol%) in 1:1 $^tBuOH/H_2O$ (2 mL) at 0°C was added alkene **11** (50 mg, 0.152 mmol) in 1:1 $^tBuOH/H_2O$ (2 mL) via syringe. After 3 h the solution was warmed to room temperature and stirred for 18 h. Anhydrous Na_2SO_3 (400 mg) was then added and the mixture was stirred for 1 h before CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts dried ($MgSO_4$) and concentrated in vacuo to give the crude diol product contaminated with ^tBuOH. Purification by flash column chromatography

gave diol **12** (50 mg, 91% dr 17:1). The major diastereoisomer observed possessed the same ^{1}H NMR characteristics as that above.

(2*R*,3*R*,4*S*)-4-Methyl-5-[(4-methoxyphenyl)methoxy]-3-(phenylmethoxy) pentan-1,2-oxirane (13). To a solution of diol **12**-*anti* (266 mg, 0.739 mmol, dr 17:1), DMAP (~4 mg, 4 mol%) and triethylamine (0.154 mL, 1.109 mmol) in CH_2Cl_2 (3 mL) was added *tert*-butylchlorodiphenylsilane (0.288 mL, 1.109 mmol) dropwise. After 18 h water (10 mL) was added followed by CH_2Cl_2 (10 mL). The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the crude alcohol contaminated with TBDPS-OH. Purification by flash column chromatography (9:1 pet./EtOAc) gave the primary TBS ether (379 mg, 86%, 17:1 mixture of diastereoisomers) as a colourless oil $[\alpha]_D$=+17.1 (*c* 4.1, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3480 (O–H), 3070–2856 (C–H), 1613 (Ar), 1588 (Ar), 1513 (Ar); δ_H (250 MHz, $CDCl_3$) 0.92 (3H, d, *J*=7.0 Hz, CH*Me*), 1.08 (9H, s, Si^{t}Bu), 2.21–2.37 (1H, m, C*H*Me), 2.52 (1H, d, *J*=4.3 Hz, OH), 3.34 (1H, dd, *J*=9.1, 5.5 Hz, *H*CHOPMB), 3.42 (1H, t, *J*=9.1 Hz, HC*H*OPMB), 3.65–3.82 (3H, m, CH_2OTBDPS, C*H*OBn), 3.78 (3H, s, PhO*Me*), 3.82–3.92 (1H, m, C*H*OH), 4.36 (1H, d, *J*=11.6 Hz, *H*CHPh), 4.39 (2H, s, CH_2PMP), 4.45 (1H, d, *J*=11.6 Hz, HC*H*Ph), 6.80–7.70 (19H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 11.1, 19.3, 27.0, 34.6, 55.3, 65.2, 71.8, 72.4, 72.5, 74.2, 78.5, 113.8, 127.5, 127.7, 127.8, 128.2, 129.4, 129.9, 130.6, 133.1, 135.7, 138.6, 159.1; *m/z* (CI$^+$) 616 (100% MNH_4^+) 599.3191 (27% MH^+, $C_{37}H_{47}O_5Si$ requires 599.3193), 121 (100% PMB^+); (Found C, 74.00; H, 7.91. $C_{37}H_{46}O_5Si$ requires C, 74.21; H, 7.74).

To a solution of the primary TBS ether from above (344 mg, 0.57 mmol, 17:1 mixture of diastereoisomers) in CH_2Cl_2 (2 mL) at 0°C was added triethylamine (0.16 mL, 1.14 mmol) followed by methanesulfonyl chloride (0.053 mL, 0.69 mmol) dropwise. The solution was warmed to room temperature and left for 18 h before it was quenched by the addition of ice cold water (10 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was then filtered through a short plug of silica (5:1 pet. ether/EtOAc) to give the secondary mesylate (372 mg, 97%, 17:1 mixture of diastereoisomers) as a pale yellow sticky gum $[\alpha]_D$=+24.1 (*c* 2.9 Hz, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3071–2858 (C–H), 3070–2856 (C–H), 1613 (Ar), 1588 (Ar), 1514 (Ar); δ_H (250 MHz, $CDCl_3$) 0.91 (3H, d, *J*=6.7 Hz, CH*Me*), 1.05 (9H, s, Si^{t}Bu), 1.92–2.10 (1H, m, C*H*Me), 2.92 (3H, s, SO_2Me), 3.29 (1H, dd, *J*=9.5, 5.2 Hz, *H*CHOPMB), 3.34 (1H, t, *J*=8.7 Hz, HC*H*OPMB), 3.77 (3H, s, PhO*Me*), 3.84–4.03 (3H, m, C*H*OBn, CH_2OTBDPS), 4.34 (1H, d, *J*=11.3 Hz, *H*CHPMP), 4.40 (1H, dd, *J*=11.3 Hz, HC*H*PMP), 4.41 (1H, dd, *J*=11.0 Hz, *H*CHPh), 4.64 (1H, d, *J*=11.0 Hz, HC*H*Ph), 4.98–5.06 (1H, m, C*H*OMs), 6.80–6.87 (20H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 12.1, 19.2, 26.9, 35.2, 38.6, 55.3, 62.9, 72.3, 72.7, 74.4, 78.9, 84.2, 113.8, 127.7, 127.9, 128.3, 129.5, 129.9, 130.0, 130.3, 132.7, 132.9, 135.6, 135.8, 138.1, 159.2; *m/z* (EI$^+$) 694.3221 (9% MNH_4^+, $C_{38}H_{52}NO_7SSi$ requires 694.3234) 403 (41%), 121 (100% PMB^+); (Found C, 67.50; H, 7.03. $C_{38}H_{48}O_7SSi$ requires C, 67.42; H, 7.15).

To a solution of the secondary mesylate (31 mg, 0.046 mmol) in THF (1 mL) was added TBAF (1 M solution in THF, 5% H_2O; 0.14 mL, 0.14 mmol) dropwise. The clear light yellow solution was stirred for 30 min then diluted with ether (10 mL) and water (10 mL). The layers were separated and the aqueous layer extracted with ether (2×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Purification by flash column chromatography (7:1 pet. ether/EtOAc) gave the desired epoxide **13** (13 mg, 83%) as a light yellow oil $[\alpha]_D$=+29.1 (*c* 5.5, CH_2Cl_2); IR (thin film) ν_{max}/cm^{-1} 3087–2858 (C–H), 1613 (Ar), 1586 (Ar), 1513 (Ar); δ_H (250 MHz, $CDCl_3$) 0.96 (3H, d, *J*=7.0 Hz, C*H*Me), 1.88–2.03 (1H, m, C*H*Me), 2.42 (1H, dd, *J*=4.9, 2.4 Hz, *H*CHOCH), 2.68 (1H, dd, *J*=4.9, 4.0 Hz, HC*H*OCH), 3.01–3.12 (2H, m, C*H*OCH_2, C*H*OBn), 3.28 (1H, dd, *J*=9.0, 5.3 Hz, *H*CHOPMB); 3.38 (1H, dd, *J*=9.0, 7.2 Hz, HC*H*OPMB); 3.71 (3H, s, ArO*Me*), 4.29 (2H, s, CH_2Ph), 4.45 (1H, d, *J*=11.8 Hz, *H*CHPMP); 4.78 (1H, d, *J*=11.8 Hz, HC*H*PMP), 6.70–7.30 (9H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 12.4, 37.3, 43.1, 54.2, 55.3, 71.9, 72.1, 72.8, 76.5, 77.0, 77.5, 81.0, 113.7, 127.4, 127.7, 128.2, 129.3, 130.5, 138.9, 159.1; *m/z* (CI$^+$) 360.2169 (79% MNH_4^+, $C_{21}H_{30}NO_5$ requires 360.2175), 343 (7% MH^+), 121 (100% PMB^+), 91 (19%, Bn^+); (Found C, 73.60; H, 7.77. $C_{21}H_{26}O_4$ requires C, 73.66; H, 7.65).

(2*R*,3*R*,4*S*)-4-Methyl-5-[(4-methoxyphenyl)methoxy]-3-(phenylmethoxy) pentan-1,2-diol (12-*syn*). To a solution of epoxide **13** (250 mg, 0.73 mmoL) in *N*,*N*-dimethylformamide (2 mL) was added potassium acetate (71 mg, 0.73 mmol) and the solution was set to reflux for 18 h. After cooling to ambient temperature HCl (1 M, 2 mL) was added and the mixture extracted with ether (4×5 mL). The organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude material was purified by flash column chromatography (2:1 pet. ether/EtOAc) to give diol **12**-*syn* (173 mg, 66%) as a colourless oil $[\alpha]_D$=+6.7 (*c* 3.0, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3405 (O–H), 1612 (Ar), 1586 (Ar), 1514 (Ar); δ_H (250 MHz, $CDCl_3$) 0.98 (3H, d, *J*=7.0 Hz, C*H*Me), 1.50–2.20 (3H, m, 2×OH, C*H*Me), 3.42 (1H, dd, *J*=9.3, 7.3 Hz, *H*CHOPMB), 3.48 (1H, dd, *J*=9.3, 4.7 Hz, HC*H*OPMB), 3.51 (1H, t, *J*=4.6 Hz, CHOBn), 3.58–3.62 (2H, m, CH_2OH), 3.74 (1H, q, *J*=5.1 Hz, C*H*OH), 3.78 (3H, s, ArO*Me*), 4.39 (1H, d, *J*=11.4 Hz, *H*CHPMP), 4.46 (1H, d, *J*=11.4 Hz, HC*H*PMP), 4.51 (1H, d, *J*=11.4 Hz, *H*CHPh), 4.60 (1H, d, *J*=11.4 Hz, HC*H*Ph), 6.80–7.40 (9H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 12.5, 35.5, 55.3, 64.4, 71.7, 71.8, 72.9, 80.2, 113.9, 127.9, 128.5, 129.5, 130.0, 138.2, 159.3; *m/z* (EI$^+$) 360.1937 (15% M^+, $C_{21}H_{28}O_5$ requires 360.1937), 137 (52%), 121 (100% PMB^+), 91 (88%, Bn^+).

(2*R*,3*R*,4*S*)-4-Methyl-2-(*tert*-butyldimethylsiloxy)-5-[(4-methoxyphenyl) methoxy]-3-(phenylmethoxy)pentan-1-ol (14). To a solution of diol **12**-*syn* (110 mg, 0.31 mmol) in *N*,*N*-dimethylformamide (2 mL) was added imidazole (146 mg, 2.16 mmol). Once all of the imidazole had dissolved *tert*-butyldimethylsilyl chloride (166 mg,

1.10 mmol) was added in one portion. The solution was stirred for 18 h then more imidazole (37 mg, 0.54 mmol) and *tert*-butyldimethylsilyl chloride (42 mg, 0.280 mmol) was added. After 2 h the reaction was quenched with water (5 mL) and extracted into ether (3×10 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a light yellow oil. Purification by flash column chromatography (9:1 pet. ether/EtOAc) gave the bis-TBS ether (130 mg, 71%) as a colourless oil $[\alpha]_D$=+14.3 (*c* 2.1, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 2855–2856 (C–H), 1613 (Ar), 1586 (Ar), 1514 (Ar); δ_H (250 MHz, $CDCl_3$) −0.05 (3H, s, SiMe), −0.01 (3H, s, SiMe), 0.00 (6H, s, 2×SiMe), 0.82 (9H, s, Si*t*Bu), 0.84 (9H, s, Si*t*Bu), 0.90 (3H, d, *J*=7.0 Hz, CH*Me*), 2.02–2.15 (1H, m, C*H*Me), 3.17 (1H, dd, *J*=9.0, 7.0 Hz, *H*CHOPMB), 3.35 (1H, dd, *J*=9.2, 7.0 Hz, HC*H*OPMB), 3.49 (1H, dd, *J*=5.8, 4.0 Hz, C*H*OBn), 3.52 (1H, dd, *J*=9.8, 5.5 Hz, *H*CHOTBS), 3.67 (1H, dd, *J*=10.2, 4.4 Hz, HC*H*OTBS), 3.70–3.84 (1H, m, C*H*OTBS), 3.74 (3H, s, ArO*Me*), 4.30 (2H, s, C*H*$_2$PMP), 4.43 (1H, d, *J*=11.6 Hz, *H*CHPh), 4.67 (1H, d, *J*=11.9 Hz, HC*H*Ph), 6.76–6.83 (2H, m, ArH), 7.13–7.30 (7H, m, Ar*H*); *m/z* (CI^+) 606 (45% MNH_4^+), 589.3720 (73% MH^+, $C_{33}H_{57}O_5Si_2$ requires 589.3745), 121 (100% PMB^+).

To a solution of bis-TBS ether prepared above (20 mg, 0.034 mmol) in THF (1 mL) was added freshly prepared, buffered pyridinium hydrofluoride (0.5 mL of a stock solution prepared from 10 mL of THF, 5.7 mL of pyridine and 2.1 g of Fluka pyridinium hydrofluoride). After 6.5 h the reaction mixture was poured over saturated aqueous $NaHCO_3$ (10 mL) and then extracted into ether (3×10 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (5:1 pet. ether/EtOAc) gave alcohol **14** (14 mg, 87%) as a colourless oil $[\alpha]_D$=+27.6 (*c* 1.5, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3452 (O–H), 2928–2855 (C–H), 1613 (Ar), 1586 (Ar), 1514 (Ar); δ_H (250 MHz, $CDCl_3$) 0.00 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.88 (9H, s, Si*t*Bu), 0.95 (3H, d, *J*=7.0 Hz, CH*Me*), 2.03–2.15 (2H, m, C*H*Me, O*H*), 3.22 (1H, dd, *J*=9.0, 6.3 Hz, *H*CHOPMB), 3.37 (1H, dd, *J*=8.9, 7.9 Hz, HC*H*OPMB), 3.57 (1H, dd, *J*=11.6, 4.3 Hz, *H*CHOH), 3.61–3.73 (2H, m, HC*H*OH, C*H*OBn), 3.77 (3H, s, ArO*Me*), 3.87 (1H, dt, *J*=6.7, 4.3 Hz, C*H*OTBS), 4.30 (1H, d, *J*=11.6 Hz, *H*CHPMP), 4.37 (1H, d, *J*=11.6 Hz, HC*H*PMP), 4.47 (1H, d, *J*=11.6 Hz, *H*CHPh), 4.70 (1H, d, *J*=11.6 Hz, HC*H*Ph), 6.80–6.87 (2H, m, ArH), 7.13–7.35 (7H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 11.6, 18.1, 25.9, 29.7, 34.4, 55.2, 64.1, 72.5, 72.8, 73.7, 74.1, 79.8, 113.6, 127.3 (two overlapping), 128.2, 129.3, 130.5, 139.0, 159.0; *m/z* (CI^+) 475.2872 (22% MH^+, $C_{27}H_{43}O_5Si$ requires 475.2880), 121 (100% PMB^+).

(*Z*)-4-Phenylmethoxy-but-2-en-1-al (17). To a stirred suspension of NaH (1.36 g, 56.75 mmol) in *N,N*-dimethylformamide (200 mL) at −20°C was added *Z*-butene-1,4-diol (4.70 mL, 56.75 mmol) over a 2 min period (*caution: vigorous evolution of gas*). After 20 min benzyl bromide (6.75 mL, 56.75 mmol) was added dropwise and the mixture was stirred at −20°C for 5 h. The mixture was then warmed to room temperature and water (300 mL) was added. The resulting solution was extracted with Et_2O (3×300 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (3:1 pet. ether/EtOAc) gave the mono protected alcohol[29] (6.91 g, 68%) as a light yellow oil bp 105–108°C at 0.1 mmHg δ_H (250 MHz, $CDCl_3$) 4.05–4.20 (4H, m, 2×CH_2O), 4.50 (2H, s, C*H*$_2$Ph), 5.65–5.90 (2H, m, C*H*=C*H*), 7.25–7.43 (5H, m, ArH).

To a solution of oxalyl chloride (0.81 mL, 9.27 mmol) in CH_2Cl_2 (20 mL) at −55°C was added dimethylsulfoxide (1.19 mL, 16.85 mmol) in CH_2Cl_2 (2 mL) dropwise via cannula. After 2 min the mono protected alcohol prepared above (1.5 g, 8.43 mmol) in CH_2Cl_2 (2 mL) was added dropwise via cannula to form a light yellow cloudy mixture which was stirred at −55°C for 15 min. Triethylamine (3.05 mL, 42.14 mmol) was then added and after 15 min the thick white slurry was warmed to room temperature. Water (40 mL) was added and the two layers were separated allowing the aqueous layer to be extracted with CH_2Cl_2 (2×70 mL). The combined organic layers were washed with 1 M HCl (20 mL) and saturated aqueous $NaHCO_3$ (20 mL) and then dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (8:1 pet. ether/EtOAc) gave *Z*-enal **17**[30] (1.20 g, 81%) as a light orange oil which was used immediately in the following step before isomerisation to the *E*-alkene took place δ_H (250 MHz, $CDCl_3$) 4.51 (2H, dd, *J*=5.5, 1.8 Hz, C*H*$_2$OBn), 4.59 (2H, s, C*H*$_2$Ph), 6.04 (1H, ddt, *J*=11.6, 6.7, 2.1 Hz, C*H*CHO), 6.62 (1H, dt, *J*=11.6, 5.8 Hz, C*H*=CHCHO), 7.24–7.44 (5H, m, ArH), 10.04 (1H, d, *J*=6.7 Hz, CHO). ^1H NMR is invariably contaminated with some of the *E*-alkene **24** due to in situ isomerism.

(*R*)-3-{(2*R*,3*R*,4*Z*)-3-Hydroxyl-2-methyl-6-phenylmethoxy-4-hexenoyl}-4-(phenylmethyl)-2-oxazolidinone (19). To a solution of substituted auxiliary **15** (2.61 g, 11.2 mmol) in CH_2Cl_2 (40 mL) at −10°C was added dibutylboron triflate (1 M in CH_2Cl_2; 13.22 mL, 13.22 mmol) followed by triethylamine (2.03 mL, 14.56 mmol) making sure the internal temperature did not rise above 0°C. The light yellow solution was stirred at 0°C for 30 mins before cooling in an acetone/dry ice bath. Once the internal temperature had dropped below −65°C, aldehyde **17** (2.17 g, 12.32 mmol) in CH_2Cl_2 (5 mL) was added over a 5 min period via syringe. The solution was kept at −78°C for 45 min then warmed to 0°C and stirred for 3 h. The light yellow/orange solution was re-cooled to −10°C and pH 7 phosphate buffer (2 M, 20 mL) was added, followed by methanol (40 mL) and 2:1 methanol / 30% hydrogen peroxide (40 mL) making sure the temperature did not rise above 0°C. All volatile material was removed in vacuo, and then water (100 mL) was added. The mixture was extracted into ether (3×150 mL) and the combined organic layers washed with 5% aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (2:1 pet. ether/EtOAc) gave a 9:1 mixture of *Z* and *E*-alkenes (3.39 g, 74%) in favour of the desired adduct **19**. The mixture was a colourless oil $[\alpha]_D$=−60.0 (*c* 5, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3446 (O–H), 1778 (C=O), 1695 (C=O), 1604 (Ar), 1584 (Ar); δ_H (250 MHz, $CDCl_3$) 1.28 (3H, d, *J*=7.0 Hz, CH*Me*), 2.56–3.04 (1H, bs, OH), 2.76 (1H, dd, *J*=13.3, 9.3 Hz, *H*CHPh of auxiliary), 3.21 (1H, dd, *J*=13.3, 9.3 Hz, HC*H*Ph of auxiliary), 3.88 (1H, qd, *J*=7.0, 4.6 Hz, C*H*Me), 4.52 (2H, s,

OCH_2Ph), 4.57–4.75 (1H m, CHBn), 4.70 (1H, dd, J=7.3, 4.9 Hz, CHOH), 5.60–5.81 (2H, m, CH=CH), 7.09–7.42 (10H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 11.9, 37.8, 43.1, 55.2, 66.2 (two overlapping), 68.8, 72.5, 127.4, 127.7, 127.8, 128.4, 129.0, 129.4 (two overlapping), 132.1, 135.1, 138.0, 153.2, 176.0; m/z (EI^+) 410.2007 (MH^+, $C_{24}H_{28}NO_5$ requires 410.1967), 284 (100%).

(2*R*,3*R*,4*Z*)-*N*-Methoxy-*N*,2-dimethyl-3-(triethylsiloxy)-6-phenylmethoxy-4-hexenamide (20). To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (36 mg, 0.366 mmol) in THF (1 mL) at 0°C was added 2 M trimethylaluminium in toluene (0.18 mL, 0.366 mmol) dropwise. After 30 min at 0°C and 20 min at room temperature the clear colourless solution was re-cooled to −15°C. Adduct **19** (50 mg, 0.122 mmol) in THF (0.5 mL+0.5 mL wash) was then added dropwise via cannula. The cloudy mixture was warmed to 0°C and stirred for 2.5 h in which time gas evolution slowly ceased and the cloudy mixture became a colourless solution. The solution was transferred via cannula to a mixture of CH_2Cl_2 (3 mL) and 0.5 M HCl (5 mL) at 0°C and stirred vigorously for 1.5 h. The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated in vacuo. To a solution of the unpurified alcohol/oxazolidinone mixture (~0.122 mmol) in *N*,*N*-dimethylformamide (1 mL) was added imidazole (17 mg, 0.244 mmol) followed by triethylsilylchloride (0.022 mL, 0.134 mmol). After 4.5 h water (4 mL) was added followed by Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2×5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (3:1 pet. ether/EtOAc) gave amide **20** (40 mg, 80%) as a colourless oil $[\alpha]_D$=22.2 (c 0.9, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3064–2734 (C–H), 1660 (C=O); δ_H (250 MHz, $CDCl_3$); 0.48–0.64 (6H, m, 3×SiCH_2Me), 0.93 (9H, t, J=7.9, 3×SiCH$_2$*Me*), 1.19 (3H, d, J=6.7 Hz, CH*Me*), 2.96–3.12 (1H, m, CHMe), 3.08 (3H, s, NMe), 3.62 (3H, s, OMe), 3.99 (1H, ddd, J=12.7, 4.5, 1.8 Hz, HCHOBn), 4.22 (1H, ddd, J=12.8, 7.3, 1.2 Hz, HCHOBn), 4.43 (1H, t, J=8.7 Hz, CHOTES), 4.50 (2H, s, CH_2Ph), 5.40–5.65 (2H, m, CH=CH), 7.17–7.44 (5H, m, ArH); m/z (EI^+) 407.2499 (M^+, $C_{22}H_{37}NO_4Si$ requires 407.2492), 378 {43% $(M-Et)^+$}, 91 (100% Bn^+).

(*E*)-4-Phenylmethoxy-but-2-en-1-al (24). To a solution of oxalyl chloride (4.61 mL, 52.84 mmol) in CH_2Cl_2 (140 mL) at −55°C was added dimethylsulfoxide (6.81 mL, 96.06 mmol) in CH_2Cl_2 (3 mL) dropwise via cannula. After 2 min alcohol (*Z*)-4-phenylmethoxy-but-2-en-1-ol (prepared for the synthesis of **17**) (8.55 g, 48.03 mmol) in CH_2Cl_2 (14 mL) was added dropwise via cannula to form a light yellow cloudy mixture which was stirred at −55°C for 15 min. Triethylamine (33.50 mL, 240.15 mmol) was then added and after 15 min the thick white slurry was warmed to 0°C. Water (200 mL) was then added and the two layers were separated allowing the aqueous layer to be extracted with CH_2Cl_2 (2×200 mL). The combined organic layers were washed with aqueous HCl (1 M; 100 mL) and then saturated aqueous $NaHCO_3$ (100 mL). Tlc (3:1 pet. ether/EtOAc) indicated a small amount of the desired *E*-alkene (R_f≅0.5) accompanied by the undesired *Z*-alkene (R_f≅0.6) as the major product. The solution in CH_2Cl_2 (≅500 mL) was stirred with aqueous HCl (1 M; 50 mL) for 24 h before the layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (8:1 pet. ether/EtOAc) gave enal **24**[29] (6.99 g, 83%) as a light orange oil IR (thin film) ν_{max}/cm^{-1} 3200–2730 (C–H), 1689 (C=O); δ_H (250 MHz, $CDCl_3$) 4.30 (2H, dd, J=4.0, 1.8 Hz, CH_2OBn), 4.60 (2H, s, CH_2Ph), 6.40 (1H, ddt, J=15.9, 7.9, 1.8 Hz, CHCHO), 6.85 (1H, dt, J=15.9, 4.0 Hz, CH=CHCHO), 7.24–7.44 (5H, m, ArH), 9.58 (1H, d, J=7.9 Hz, CHO); δ_C (62.9 MHz, $CDCl_3$) 68.5, 72.9, 127.6, 127.9, 128.5, 131.7, 137.3, 153.1, 193.3; m/z (CI^+) 177.0914 (MH^+, $C_{11}H_{13}O_2$ requires 177.0913), 146 (35% $CCCH_2OBnH^+$), 91 (100% Bn^+).

(2*R*,3*R*,4*E*)-2-Methyl-3-(*tert*-butyldimethylsiloxy)-6-(phenylmethoxy)hex-4-en-1-al (25). To a solution of substituted auxiliary **15** (8.74 g, 37.5 mmol) in CH_2Cl_2 (70 mL) at −10°C was added dibutylboron triflate (10.40 mL, 41.3 mmol) followed by triethylamine (6.80 mL, 48.8 mmol) making sure the internal temperature did not rise above 0°C. The light yellow solution was stirred at 0°C for 30 mins before cooling in an acetone/dry ice bath. Once the internal temperature had dropped below −65°C, aldehyde **24** (6.93 g, 39.4 mmol) in CH_2Cl_2 (15 mL) was added over a 5 min period via syringe. The solution was kept at −78°C for 45 min then warmed to 0°C and stirred for 45 min. The light yellow/orange solution was re-cooled to −10°C and pH 7 phosphate buffer (2 M, 70 mL) was added, followed by methanol (140 mL) and 2:1 methanol/30% hydrogen peroxide (140 mL) making sure the temperature did not rise above 0°C. The bulk of the volatile material was removed in vacuo, and then water (100 mL) was added. The mixture was extracted into ether (3×300 mL) and the combined organic layers washed with aqueous $NaHCO_3$ (5%, 200 mL) and brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (2:1 pet. ether/EtOAc) gave the aldol adduct (15.30 g, 100%, d.s.>95:5) as a colourless oil $[\alpha]_D$=−60.0 (c 5, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3450 (O–H), 1786 (C=O), 1696 (C=O), 1604 (Ar), 1586 (Ar); δ_H (250 MHz, $CDCl_3$) 1.25 (3H, d, J=7.0 Hz, CH*Me*), 2.78 (1H, dd, J=13.4, 9.5 Hz, CHCHHPh), 2.83 (1H, bs, OH), 3.24 (1H, dd, J=13.4, 3.4 Hz, CHCHHPh), 3.87 (1H, dq, J=7.0, 3.7 Hz, CHMe), 4.05 (2H, dt, J=5.5, 1.0 Hz, CH_2OBn), 4.09–4.24 (2H, m, CH_2CHBn), 4.45–4.61 (1H, m, CHOH), 4.52 (2H, s, OCH_2Ph), 4.63–4.74 (1H, m, CHCH$_2$Ph), 5.76 (1H, ddt, J=15.6, 5.5, 1.2 Hz, CH=CHCHOH), 5.92 (1H, dtd, J=15.6, 5.5, 1.2 Hz, CH=CHCH$_2$OBn), 7.16–7.40 (10H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 11.3, 37.8, 42.7, 55.2, 66.2, 70.0, 72.2, 127.5, 127.7, 127.8, 128.4, 128.7, 129.0, 129.4, 132.0, 135.0, 138.2, 153.0, 176.6; m/z (EI^+) 409.1937 (M^+, $C_{24}H_{27}NO_5$ requires 409.1889), 91 (100% Bn^+); (Found C, 70.15; H, 6.50; N, 3.21. $C_{24}H_{27}NO_5$ requires C, 70.40; H, 6.65; N, 3.42).

To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (10.23 g, 104.89 mmol) in THF (70 mL) at 0°C was added 2 M trimethylaluminium in toluene (52.5 mL,

104.89 mmol) dropwise (*caution: vigorous gas evolution*) via cannula. After 15 min at 0°C and 20 min at room temperature the clear colourless solution was re-cooled to −15°C. The aldol adduct from above (14.3 g, 34.96 mmol) in THF (150 mL) was then added dropwise via cannula. The cloudy mixture was warmed to 0°C and stirred for 2.5 h in which time gas evolution slowly ceased and the cloudy mixture became a colourless solution. The solution was transferred via cannula to a mixture of CH_2Cl_2 (330 mL) and 0.5 M HCl (170 mL) at 0°C and stirred vigorously for 18 h. The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (4×200 mL) and the volume of combined organic extracts reduced in vacuo to ca. 400 mL. After washing with brine (100 mL) the organic layer was dried ($MgSO_4$) and concentrated in vacuo. The unpurified alcohol/oxazolidinone mixture was then dissolved in *N*,*N*-dimethylformamide (120 mL) and imidazole (9.26 g, 136 mmol) was added followed by *tert*-butyldimethylsilyl chloride (10.25 g, 68 mmol). After 18 h the reaction was quenched with saturated aqueous $NaHCO_3$ (150 mL) and water (100 mL). The mixture was extracted with Et_2O (3×300 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (3:1 pet. ether/EtOAc) gave the TBS silyl ether Weinreb amide (14.1 g, 99% 2 steps) as a colourless oil $[\alpha]_D$=+5.7 (*c* 5.3, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3087–2709 (C–H), 1662 (C=O); δ_H (250 MHz, $CDCl_3$) −0.04 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.83 (9H, s, Si^{t}Bu), 1.11 (3H, d, *J*=6.7 Hz, CH*Me*), 2.80–3.00 (1H, m, C*H*Me), 3.05 (3H, s, NMe), 3.57 (3H, s, OMe), 3.83–4.00 (2H, m, CH_2OBn), 4.20 (1H, dt, *J*=8.4, 2.6 Hz, C*H*OTBS), 4.39 (2H, s, CH_2Ph), 5.59–5.75 (2H, m, C*H*=C*H*), 7.15–7.30 (5H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 14.5, 18.2, 25.7, 25.9, 32.0, 42.9, 61.5, 69.9, 71.6, 74.8, 127.5, 127.6, 128.3, 134.9, 138.4 (no C=O signal); *m*/*z* (EI^+) 407.2491 (19% M^+, $C_{22}H_{37}NO_4Si$ requires 407.2492), 392 {18% $(M-Me)^+$}, 350 {100% $(M-{}^tBu)^+$}, 91 (74% Bn^+); (Found C, 65.00; H, 9.45; N, 3.39. $C_{22}H_{37}NO_4Si$ requires C, 64.82; H, 9.15; N, 3.44).

To a solution of TBS silyl ether Weinreb amide prepared above (14.0 g, 34.2 mmol) in THF (250 mL) at −78°C was added DIBAL (24.4 mL, 136.9 mmol) dropwise via cannula. After 1 h excess DIBAL was quenched with EtOAc (5 mL) and the clear colourless solution was warmed to room temperature. Et_2O (200 mL) was then added followed by 1 M HCl (200 mL) and the two phase was mixture stirred for 18 h. The layers were separated and the aqueous layer extracted with Et_2O (2×300 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (9:1 pet. ether/EtOAc) gave aldehyde **25** (10.7 g, 89%) as a colourless oil $[\alpha]_D$=−11.8 (*c* 3.4, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3088–2710 (C–H), 1727 (C=O), 1605 (Ar), 1586 (Ar); δ_H (250 MHz, $CDCl_3$) −0.01 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.82 (9H, s, Si^{t}Bu), 1.02 (3H, d, *J*=7.0 Hz, CH*Me*), 2.42 (1H, qdd, *J*=7.0, 4.3, 1.2 Hz, C*H*Me), 3.96–4.00 (2H, m, CH_2OBn), 4.45 (2H, s, CH_2Ph), 4.50–4.56 (1H, m, C*H*OTBS), 5.61–5.82 (2H, m, C*H*=C*H*), 7.20–7.35 (5H, m, ArH), 9.71 (1H, d, *J*=1.2 Hz, CHO); δ_C (62.9 MHz, $CDCl_3$) 8.4, 18.1, 52.6, 69.8, 72.0, 127.7, 128.4, 132.8, 138.2, 204.6; *m*/*z* (CI^+) 366.2469 (100% MNH_4^+, $C_{20}H_{36}NO_3Si$ requires 366.2464), 291 (33%), 217 (33%), 91 (59% Bn^+).

(2*E*,4*R*,5*R*,6*Z*)-5-Methyl-4,8-di-(*tert*-butyldimethylsiloxy)-octa-2,6-diene-1-ol (26). To a solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate (7.20 mL, 33.83 mmol) and 18-crown-6 (40.64 g, 150.75 mmol) in THF (400 mL) at −78°C was added a 0.5 M solution of potassium hexamethyldisilazide in toluene (64.6 mL, 32.30 mmol). After 2 min, aldehyde **25** (10.70 g, 30.75 mmol) in THF (100 mL) was added dropwise via cannula. The solution was left for 30 min at −78°C before it was quenched with saturated aqueous NH_4Cl (100 mL) and warmed to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3×200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (95:5 pet. ether/EtOAc) gave the (*Z*)-α,β-unsaturated ester (11.0 g, 89%, d.s.>95:5) as a light yellow oil $[\alpha]_D$=+68.4 (*c* 3.4, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3079–2856 (C–H), 1724 (C=O), 1646; δ_H (250 MHz, $CDCl_3$) −0.09 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.87 (9H, s, Si^{t}Bu), 0.99 (3H, d, *J*=6.7 Hz, CH*Me*), 3.50–3.65 (1H, m, C*H*Me), 3.67 (3H, s, CO_2Me), 3.98–4.05 (2H, m, CH_2OBn), 4.06–4.14 (1H, m, C*H*OTBS), 4.48 (2H, s, CH_2Ph), 5.70–5.80 (3H, m, C*H*=C*H*CH$_2$OBn, C*H*CO$_2$Me), 6.12 (1H, dd, *J*=10.1, 11.6 Hz, C*H*=CHCO$_2$Me), 7.20–7.37 (5H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 14.6, 18.2, 25.9, 39.2, 51.1, 70.1, 71.7, 75.8, 118.6, 127.4, 127.6, 127.7, 128.4, 134.5, 138.4, 153.1, 166.7; *m*/*z* (CI^+) 422.2731 (100% MNH_4^+, $C_{23}H_{40}NO_4Si$ requires 422.2727), 405 (12%, MH^+), 273 (91%), 165 (57%), 52 (68%); (Found C, 68.36; H, 8.91. $C_{23}H_{36}O_4Si$ requires C, 68.27; H, 8.97).

To a solution of the (*Z*)-α,β-unsaturated ester prepared above (9.4 g, 23.3 mmol) in CH_2Cl_2 (100 mL) at −78°C was added DIBAL (10.4 mL, 58.3 mmol) dropwise. After 15 min excess DIBAL was quenched with EtOAc (10 mL) and the solution was warmed to room temperature. Saturated aqueous sodium potassium tartrate (100 mL) was added followed by water (50 mL) and the mixture was stirred vigorously for 13 h. The clear colourless layers were separated and the aqueous layer was extracted with CH_2Cl_2 (150 mL). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo and filtered through a short plug of silica (9:1 pet. ether/EtOAc) to give the (*Z*)-allylic alcohol (8.9 g, 100%) as a light yellow oil which was used without further purification $[\alpha]_D$=+28.3 (*c* 6.0, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3460 (O–H), 3089–2857 (C–H), 1606 (Ar), 1587 (Ar); δ_H (250 MHz, $CDCl_3$) 0.00 (3H, s, SiMe), 0.03 (3H, s, SiMe), 0.89 (9H, s, Si^{t}Bu), 0.96 (3H, d, *J*=6.7 Hz, CH*Me*), 1.92 (1H, s, OH), 2.52–2.68 (1H, m, C*H*Me), 3.84–4.04 (4H, m, CH_2OBn, C*H*OTBS, *H*CHOH), 4.16 (1H, ddd, *J*=12.5, 7.6, 1.4 Hz, HC*H*OH), 4.49 (2H, s, CH_2Ph), 5.20–5.34 (1H, m, CH=C*H*CHMe), 5.57–5.73 (3H, m, C*H*=CHCHMe, C*H*=C*H*CH$_2$OBn), 7.22–7.37 (5H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 11.2, 18.3, 26.0, 39.2, 58.5, 69.9, 72.1, 76.9, 127.3, 127.7, 127.8, 128.4, 129.2, 134.7, 134.8, 138.1; *m*/*z* (CI^+) 394 (24% MNH_4^+), 377.2513 (16% MH^+, $C_{22}H_{37}O_3Si$ requires 377.2512), 262 (100%), 137 (54%).

To a solution of (*Z*)-allylic alcohol prepared above (425 mg, 1.12 mmol) in *N*,*N*-dimethylformamide (10 mL) was added imidazole (311 mg, 4.50 mmol) followed by *tert*-butyldimethylsilyl chloride (340 mg, 2.25 mmol). After 10 min saturated aqueous $NaHCO_3$ (5 mL) was added followed by water (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give the crude product, which was purified by flash column chromatography (95:5 pet. ether/EtOAc) affording the fully protected diene (437 mg, 97%) as a colourless oil $[\alpha]_D$=+42.2° (*c* 4.5, CH_2Cl_2); IR (thin film) ν_{max}/cm^{-1} 2956–2857 (C–H); δ_H (250 MHz, $CDCl_3$) −0.04 (3H, s, SiMe), −0.01 (3H, s, SiMe), 0.00 (6H, s, 2×SiMe), 0.84 (9H, s, Si*t*Bu), 0.85 (9H, s, Si*t*Bu), 0.91 (3H, d, *J*=6.7 Hz, CH*Me*), 2.34–2.51 (1H, m, C*H*Me), 3.85–3.92 (1H, m, C*H*OTBS), 3.93–3.99 (2H, m, CH_2OBn), 4.09 (1H, ddd, *J*=13.1, 5.5, 1.8 Hz, *H*CHOTBS), 4.21 (1H, ddd, *J*=13.1, 6.7, 1.5 Hz, HC*H*OTBS), 4.43 (2H, s, CH_2Ph), 5.21 (1H, ddt, *J*=11.0, 10.1, 1.5 Hz, C=C*H*CHMe), 5.39–5.51 (1H, m, C*H*CH_2OTBS), 5.54–5.71 (2H, m, C*H*=C*H*CH_2OBn), 7.17–7.35 (5H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 16.5, 18.3, 25.9, 26.0, 39.3, 59.9, 70.2, 71.7, 76.7, 127.2, 127.6, 127.7, 128.4, 129.7, 133.0, 135.0, 138.4; *m*/*z* (CI^+) 508.3626 (100% MNH_4^+, $C_{28}H_{54}NO_3Si_2$ requires 508.3642), 291 (60%), 251 (47%), 91 (49% Bn^+).

To a solution of the fully protected diene prepared above (4.2 g, 8.52 mmol) in THF (70 mL) at −78°C was added the LDBB solution in THF[22] via cannula, in approximately 20 mL portions, allowing time in between additions for cooling [the mixture turns to the colour of the radical anion solution (dark green) when the reaction is complete]. Once all of the LDBB solution had been added the reaction was quenched at −78°C by the addition of pH 7 phosphate buffer (10 mL) and the mixture was allowed to warm to room temperature. The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography eluting with petroleum ether removed the biphenyl reagent (5.56 g, 80% recovery) and then eluting with 4:1 petroleum ether/EtOAc gave the desired (*E*)-allylic alcohol **26** (3.35 g, 97%) as a light yellow oil $[\alpha]_D$=+40.5 (*c* 3.7, CH_2Cl_2); IR (thin film) ν_{max}/cm^{-1} 3348 (O–H), 1472, 1463, 1255; δ_H (250 MHz, $CDCl_3$) −0.07 (3H, s, SiMe), −0.03 (3H, s, SiMe), 0.00 (6H, s, 2×SiMe), 0.83 (18H, s, 2×Si*t*Bu), 0.90 (3H, d, *J*=6.7 Hz, CH*Me*), 1.60 (1H, bs, OH), 2.30–2.47 (1H, m, C*H*Me), 3.78 (1H, t, *J*=6.3 Hz, C*H*OTBS), 3.99–4.06 (2H, m, CH_2OH), 4.12 (2H, dd, *J*=6.4, 1.5 Hz, CH_2OTBS), 5.15 (1H, ddt, *J*=11.3, 10.1, 1.5 Hz, CH=C*H*CHMe), 5.41 (1H, dt, *J*=11.0, 6.4 Hz, C*H*CH_2OTBS), 5.55 (1H, dd, *J*=15.6, 5.8 Hz, C*H*=CHCH_2OH), 5.66 (1H, dt, *J*=15.6, 4.7 Hz, C*H*CH_2OH); δ_C (62.9 MHz, $CDCl_3$) 16.7, 18.2, 18.4, 25.9, 26.0, 39.5, 60.0, 63.1, 76.6, 129.5, 133.1, 133.6; *m*/*z* (CI^+) 418 (37% MNH_4^+), 401.2892 (100% MH^+, $C_{21}H_{45}O_3Si_2$ requires 401.2907), 251 (45%), 137 (100%).

(2*R*,3*S*,4*R*,5*R*,6*Z*)-5-Methyl-4,8-di-(*tert*-butyldimethylsiloxy)-2,3-(oxirane) oct-6-en-1-ol (27). To a solution of (*E*)-allylic alcohol **26** (3.25 g, 8.08 mmol) and 4 Å molecular sieves (0.50 g) in CH_2Cl_2 (70 mL) at −40°C was added (−)-diethyltartrate (2.08 mL, 12.13 mmol) followed by titanium (IV) isopropoxide (2.89 mL, 9.70 mmol). After 10 min, TBHP (5–6 M in CH_2Cl_2; 4.85 mL, 24.24 mmol) was added dropwise and the cloudy yellow solution was warmed to −28°C. After 18 h at this temperature the mixture was warmed to −20°C and left for 3 h before dimethylsulfide (2 mL) was added. After 1 h the mixture was warmed to room temperature and then saturated aqueous Na_2SO_4 (3 mL) was added and the mixture was stirred vigorously for 1 h. The orange mixture was then filtered through a short plug of celite® and the filtrate was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (6:1 pet. ether/EtOAc) gave epoxide **27** (2.77 g, 82%) as a light yellow oil $[\alpha]_D$=+27.8 (*c* 1.8, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3450 (O–H), 1472, 1463, 1254; δ_H (250 MHz, $CDCl_3$) −0.04 (3H, s, SiMe), −0.03 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.81 (9H, s, Si*t*Bu), 0.82 (9H, s, Si*t*Bu), 0.95 (3H, d, *J*=6.7 Hz, CH*Me*), 1.91 (1H, dd, *J*=7.6, 5.8 Hz, OH), 2.47–2.64 (1H, m, C*H*Me), 2.93 (1H, dd, *J*=3.5, 2.3 Hz, C_{42}–H), 3.01–3.07 (1H, m, C_{43}–H), 3.51 (1H, dd, *J*=5.3, 3.5 Hz, C*H*OTBS), 3.59 (1H, ddd, *J*=12.5, 7.6, 4.0 Hz, *H*CHOH), 3.76 (1H, ddd, *J*=12.5, 5.8, 3.4 Hz, HC*H*OH), 4.15 (2H, dd, *J*=6.1, 1.4 Hz, CH_2OTBS), 5.30 (1H, ddt, *J*=11.3, 10.1, 1.4 Hz, CH=C*H*CHMe), 5.46 (1H, dt, *J*=11.0, 6.1 Hz, C*H*CH_2OTBS); δ_C (62.9 MHz, $CDCl_3$) 16.2, 18.3, 18.4, 25.9 (two overlapping), 37.0, 54.9, 56.8, 59.6, 61.4, 73.2, 129.4, 133.1; *m*/*z* (CI^+) 434 (10% MNH_4^+), 417.2870 (8% MH^+, $C_{21}H_{45}O_4Si_2$ requires 417.2856), 285 (100% $M-OTBS)^+$}, 217 (96%), 73 (96%); (Found C, 60.31; H, 10.65. $C_{21}H_{44}O_4Si_2$ requires C, 60.52; H, 10.64).

(2*R*,3*R*,4*R*,5*R*,6*Z*)-3-Benzoyloxy-5-methyl-4,8-di-(*tert*-butyldimethylsiloxy) oct-6-en-1,2-diol (28). To a solution of epoxide **27** (2.45 g, 5.86 mmol) in THF (25 mL) was added benzoic acid (2.14 g, 17.58 mmol) followed by titanium (IV) isopropoxide (3.49 mL, 11.72 mmol). After 18 h saturated aqueous $NaHCO_3$ (10 mL) was added followed by water (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4×30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The bulk of the benzoic acid was recrystallised from warm petrol (boiling range 40–60; 50 mL). The crystals were washed with cold petrol (50 mL) and the mother liquor was concentrated in vacuo. Purification of the concentrated mother liquor by flash column chromatography (3:1 pet. ether/EtOAc) gave diol **28** (2.52 g, 80%) as a colourless viscous oil $[\alpha]_D$=+50.0 (*c* 3.0, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3434 (O–H), 1723 (C=O), 1602 (Ar), 1586 (Ar); δ_H (250 MHz, $CDCl_3$) −0.01 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.20 (3H, s, SiMe), 0.30 (3H, s, SiMe), 0.87 (9H, s, Si*t*Bu), 1.01 (9H, s, Si*t*Bu), 1.09 (3H, d, *J*=6.7 Hz, CH*Me*), 2.67 (1H, dd, *J*=8.24, 6.1 Hz, CH_2OH), 2.75–2.93 (1H, m, C*H*Me), 3.28 (1H, d, *J*=6.4 Hz, CHO*H*), 3.54 (1H, ddd, *J*=12.5, 6.1, 2.4 Hz, *H*CHOH), 3.70 (1H, ddd, *J*=12.5, 8.24, 2.8 Hz, HC*H*OH), 3.91–4.20 (4H, m, C*H*OTBS, C*H*OH, CH_2OTBS), 5.02 (1H, dd, *J*=10.1, 2.1 Hz, C*H*OBz), 5.26 (1H, tt, *J*=10.8, 1.5 Hz, CH=C*H*CHMe), 5.46 (1H, dt, *J*=11.0, 6.1 Hz, C*H*CH_2OTBS), 7.45–7.55 (2H, m. ArH), 7.60–7.68 (1H, m, ArH), 8.05–8.12 (2H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 18.3, 18.6, 25.9, 26.0, 35.9, 59.4, 62.5, 69.5, 72.8, 74.9, 128.6, 129.2, 129.4, 130.0, 132.6,

133.6, 166.6; *m/z* (CI^+) 539.3211 (92% MH^+, $C_{28}H_{51}O_6Si_2$ requires 539.3224), 105 (100% Bz^+); (Found C, 62.29; H, 9.62. $C_{28}H_{50}O_6Si_2$ requires C, 62.41; H, 9.35).

(2*R*,3*R*,4*R*,5*R*)-3-Benzoyloxy-5-methyl-4,8-di-(*tert*-butyldimethylsiloxy)-6,7-(oxirane)octa-1,2-diol (29-*syn*). To a solution of alkene **28** (195 mg, 0.362 mmol) in CH_2Cl_2 (3 mL) at −20°C was added DMDO[25] (0.08 M in acetone; 6.8 mL, 0.544 mmol). After 10 h at this temperature the volatile material was removed in vacuo to give to give two epoxide diastereoisomers in favour of the desired epoxide **29**-*syn* (201 mg, >99%, dr 2:1), as a colourless oil $[\alpha]_D$=+12.2 (*c* 4.1, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3452 (O–H), 3064–2857 (C–H), 1725 (C=O), 1602 (Ar), 1585 (Ar); δ_H (250 MHz, $CDCl_3$) −0.04 and (−0.02) (3H, 2×s, SiMe), −0.01 and (0.00) (3H, 2×s, SiMe), 0.14 and (0.15) (3H, 2×s, SiMe), 0.19 and (0.25) (3H, 2×s, SiMe), 0.85 (9H, s, Si*t*Bu), 0.93 and (0.95) (9H, 2×s, Si*t*Bu), (1.06) and 1.21 (3H, 2×dd, *J*=6.7, 6.7 Hz, CH*Me*), 1.69–1.86 (1H, m, C*H*Me), (2.78) and 2.85 (1H, 2×dd, *J*=9.6, 4.4, 9.3, 4.1 Hz, C_{39}–H), 2.95–3.12 (1H, m, C_{38}–H), 3.40 (1H, bs, OH), 3.48–3.76 (5H, m, CH_2OH, CH_2OTBS, OH), 3.90–4.09 (1H, m, C*H*OH), (4.18) and 4.24 (1H, dd and t, *J*=6.6, 2.9, 3.5 Hz, C*H*OTBS), 5.05 and (5.14) (1H, 2×dd, *J*=9.2, 3.7, 9.3, 2.9 Hz, C*H*OBz), 7.35–8.10 (5H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 13.4, 18.2, 25.8, 25.9, 35.6, 58.2, 60.3, 61.7, 62.6, 70.2, 72.5, 72.8, 128.6, 129.2, 129.9, 133.7, 166.3; *m/z* (CI^+) 572 (27% MNH_4^+), 555 (34%), 187 (100%). Acc. Mass not within 5 ppm limits: Found 555.3115, calculated 555.3173.

(2*Z*,4*R*,5*R*,6*R*)-6-Benzyloxy-4-methyl-1,5-di-(*tert*-butyldimethylsiloxy)-7,8-(isopropylidenedioxy)oct-2-ene (30a). To a solution of diol **28** (44 mg, 0.08 mmol) in acetone (0.5 mL) was added 2,2-dimethoxypropane (0.1 mL, 0.81 mmol) followed by camphorsulfonic acid (~2 mg, ~0.01 mmol). After 5 min the volatile material was removed in vacuo. Purification by flash column chromatography (95:5 pet. ether/EtOAc) gave acetonide **30a** (48 mg, >99%) as a colourless oil $[\alpha]_D$=+56.8 (*c* 4.4, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 1725 (C=O), 1602 (Ar), 1586 (Ar); δ_H (250 MHz, $CDCl_3$) −0.01 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.12 (3H, s, SiMe), 0.13 (1H, s, SiMe), 0.85 (9H, s, Si*t*Bu), 0.95 (9H, s, Si*t*Bu), 1.03 (3H, d, *J*=7.0 Hz, CH*Me*), 1.36 (6H, s, CMe_2), 2.52–2.70 (1H, m, C*H*Me), 3.84 (1H, dd, *J*=6.7, 2.9 Hz, C*H*OTBS), 3.93 (1H, dd, *J*=8.5, 6.6 Hz, *H*–C_{44}H), 4.01 (1H, dd, *J*=8.5, 6.1 Hz, HC_{44}–*H*), 4.01–4.10 (1H, m, *H*CHOTBS), 4.13 (1H, ddd, *J*=12.8, 6.7, 1.4 Hz, HC*H*OTBS), 4.31 (1H, q, *J*=6.7 Hz, C_{43}–H), 5.22 (1H, dd, *J*=7.3, 2.7 Hz, C*H*OBz), 5.30 (1H, ddt, *J*=11.3, 9.8, 1.5 Hz, CH=C*H*CHMe), 5.48 (1H, dt, *J*=11.3, 5.9 Hz, C*H*CH_2OTBS), 7.40–7.65 (3H, m, 3×ArH), 8.01–8.11 (2H, m, 2×ArH); δ_C (62.9 MHz, $CDCl_3$) 17.4, 18.4, 25.5, 25.9, 26.1, 26.6, 36.1, 59.6, 66.8, 73.8, 74.7, 75.1, 109.4, 128.4, 129.6, 129.9, 130.1, 133.1, 165.7; *m/z* (CI^+) 596 (22% MNH_4^+), 579.3532 (92% MH^+, $C_{31}H_{55}O_6Si_2$ requires 579.3537), 447 (54%), 379 (100%), 105 (53% Bz^+); (Found C, 64.53; H, 9.54. $C_{31}H_{54}O_6Si_2$ requires C, 64.31; H, 9.40).

(2*R*,3*S*,4*S*,5*R*,6*R*)-6-Benzyloxy-4-methyl-1,5-di-(*tert*-butyldimethylsiloxy)-7,8-(isopropylidenedioxy)octa-2,3-oxirane (31a-*syn*). To a solution of alkene **30a** (34 mg, 0.06 mmol) in CH_2Cl_2 (0.75 mL) at −25°C to −20°C was added DMDO[25] (0.08 M in acetone; 1.13 mL, 0.09 mmol). After 18 h at this temperature the solution was warmed to room temperature and then the volatile material was removed in vacuo to give two epoxide diastereoisomers in favour of isomer **31a**-*syn* (35 mg, 98%, dr 4:1), as a colourless oil $[\alpha]_D$=+16.7 (*c* 1.8, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 2955–2857 (C–H), 1727 (C=O), 1602 (Ar), 1585 (Ar); δ_H (250 MHz, $CDCl_3$) −0.14 and (−0.08) (3H, 2×s, SiMe), −0.01 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.01 (3H, s, SiMe), 0.76 and (0.77) (9H, 2×s, Si*t*Bu), (0.80) and 0.84 (9H, 2×s, Si*t*Bu), (0.95) and 1.12 (3H, 2×d, *J*=7.0, 6.7 Hz, CH*Me*), (1.16) and 1.18 (3H, 2×s, OCMe), (1.20) and 1.24 (3H, 2×s, OCMe), 1.35–1.67 (1H, m, C*H*Me), (2.79–2.90) and 2.86 (1H, m and dd, *J*=9.0, 4.1 Hz, C_{39}–H), 2.92–3.01 and (3.01–3.10) (1H, 2×m, C_{38}–H), (3.54–3.65) and 3.58 {1H, m and dd, *J*=11.4, 6.0 Hz, *H*CHOTBS}, 3.71 {1H, dd, *J*=11.4, 5.6 Hz, HC*H*OTBS}, (3.78–3.87) and 3.82 (1H, m and dd, *J*=8.2, 7.0 Hz, *H*C_{44}H), (3.87–3.95) and 3.91 (1H, m and dd, *J*=8.2, 6.1 Hz, HC_{44}*H*), 3.98 and (4.03) (1H, 2×dd, *J*=6.3, 2.0, 5.8, 2.7 Hz, C*H*OTBS), 4.10–4.22 (1H, m, C_{43}–H), 5.27 (1H, t, *J*=6.3 Hz, C*H*OBz), 7.27–7.54 (3H, m, 3×ArH), 7.85–8.00 (2H, m, 2×ArH); δ_C (100.6 MHz, $CDCl_3$) (10.9), 11.9, 18.2, (25.3), 25.8, 25.9, 26.3, 29.7, 36.0, (56.9), 57.7, (58.5), 60.7, 61.5, 65.9, 66.1, (72.0), 72.4, 74.3, 74.6, (75.4), 109.6, 128.4, 129.8 (two overlapping), (130.1), 133.0, 133.1, 165.7 (minor isomer in parenthesis); *m/z* (CI^+) 612.3738 (36% MNH_4^+, $C_{31}H_{58}NO_7Si_2$ requires 612.3752), 595 (18% MH^+), 553 (31%), 300 (55%), 286 (100%), 105 (30%, Bz^+).

(2*R*,3*S*,4*S*,5*R*,6*R*)-6-Benzyloxy-4-methyl-5-(*tert*-butyldimethyl siloxy)-7,8-(isopropylidenedioxy)octa-2,3-oxirane-1-ol (32). *Conditions 1:* To a solution of acetonide **31a**-*syn* (dr 4:1, 20 mg, 0.03 mmol) in THF/water (4:1; 0.5 mL) at −5°C was added TFA (0.1 mL). The solution was stirred for 18 h before saturated aqueous $NaHCO_3$ (2 mL) was added followed by water (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was then filtered through a short plug of silica (4:1 pet. ether/EtOAc) affording two epoxide diastereoisomers in favour of epoxide **32** (12 mg, 86%, dr 4:1) as a white crystalline solid. Data is given below (Condition 2).

Conditions 2: To a solution of acetonide **31a**-*syn* (dr 4:1, 24 mg, 0.03 mmol) in MeOH/CH_2Cl_2 (1:1; 1 mL) at room temperature was added camphorsulfonic acid (~1 mg) in one portion. After 3 h the reaction was quenched with pyridine (3 drops) and the volatile material was removed in vacuo. The crude mixture was then filtered through a short plug of silica (4:1 pet. ether/EtOAc) affording two epoxide diastereoisomers in favour of epoxide **32** (15 mg, 81%, dr 4:1) as a white crystalline solid. Careful flash column chromatography (4:1 pet. ether/EtOAc) allowed isolation of the major epoxide **32** (10 mg, 54%, >95:5 by ^1H NMR) as a white crystalline solid mp 85–87°C; $[\alpha]_D$=+30.0 (*c* 1.0, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3486 (O–H), 2856–2837 (C–H), 1726 (C=O), 1602 (Ar), 1585 (Ar); δ_H (250 MHz, $CDCl_3$) 0.00 (3H, s, SiMe), 0.03 (3H, m, SiMe), 0.81 (9H, s, Si*t*Bu), 1.11 (3H, d,

J=6.7 Hz, CH*Me*), 1.26 (3H, s, CMe), 1.27 (3H, s, CMe), 1.56–1.72 (1H, m, C*H*Me), 2.45 (<1H, bs, OH), 2.78 (1H, dd, J=9.5, 4.0 Hz, C_{39}–H), 2.94 (1H, ddd, J=6.7, 5.5, 4.0 Hz, C_{38}–H), 3.50 (1H, dd, J=12.4, 6.8 Hz, *H*CHOH), 3.70 (1H, dd, J=12.4, 5.1 Hz, HC*H*OH), 3.80 (1H, dd, J=8.5, 6.4 Hz, *H*C_{44}H), 3.93 (1H, dd, J=8.5, 6.1 Hz, HC$_{44}$*H*), 3.98 (1H, dd, J=3.8, 2.9 Hz, C*H*OTBS), 4.13–4.24 (1H, m, C_{43}–H), 5.16 (1H, dd, J=7.6, 3.7 Hz, C*H*OBz), 7.30–7.60 (5H, m, ArH); *m/z* (CI^+) 498 (47%, MNH_4^+), 481.2621 (86% MH^+, $C_{25}H_{41}O_7Si$ requires 481.2622), 365 (43%), 265 (77%), 300 (55%), 105 (100%, Bz^+); X-ray crystal structure data confirmed the stereochemistry of the major epoxide as that drawn.

^{1}H NMR data for minor epoxide isomer δ_H (250 MHz, $CDCl_3$) −0.06 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.77 (9H, s, Si^{t}Bu), 0.91 (3H, d, J=7.0 Hz, CH*Me*), 1.20 (3H, s, CMe), 1.23 (3H, s, CMe), 1.38–1.55 (>1H, m, C*H*Me), 2.86 (1H, dd, J=9.6, 4.4 Hz, C_{39}–H), 3.08 (1H, dt, J=6.4, 4.3 Hz, C_{38}–H), 3.55 (1H, dd, J=12.2, 6.4 Hz, *H*CHOH), 3.75 (1H, dd, J=12.2, 3.7 Hz, HC*H*OH), 3.77–3.97 (2H, m, C_{44}–H_2), 4.02 (1H, dd, J=5.2, 3.4 Hz, C*H*OTBS), 4.16 (1H, q, J=6.5 Hz, C_{43}–H), 5.28 (1H, t, J=5.8 Hz, C*H*OBz), 7.30–7.60 (5H, m, ArH).

(2*Z*,4*R*,5*R*,6*R*,7*R*)-6-Benzoyloxy-4-methyl-1,5-di-(*tert*-butyldimethylsiloxy)-7,8-di-(trimethylsilyloxy)oct-2-ene (30b). To a solution of diol **28** (109 mg, 0.20 mmol) in *N*,*N*-dimethylformamide (2 mL) was added triethylamine (0.22 mL, 1.62 mmol) followed by trimethylsilyl chloride (0.10 mL, 0.81 mmol) resulting in a cloudy white mixture. After 5 min, water (5 mL) was added and the mixture was extracted with Et_2O (3×7 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was then filtered through a short plug of silica (9:1 pet. ether/EtOAc) to give bis-TMS protected alkene **30b** (135 mg, 99%) as a light yellow oil $[\alpha]_D$=+37.5 (*c* 2.4, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 1727 (C=O), 1604 (Ar), 1586 (Ar); δ_H (250 MHz, $CDCl_3$) −0.20 (3H, s, SiMe), −0.08 (3H, s, SiMe), −0.07 (6H, s, 2×SiMe), −0.05 (9H, s $SiMe_3$), 0.00 (9H, s, $SiMe_3$), 0.69 (9H, s, Si^{t}Bu), 0.76 (9H, s, Si^{t}Bu), 0.92 (3H, d, J=6.7 Hz, CH*Me*), 2.47–2.63 (1H, m, C*H*Me), 3.42 (1H, dd, J=10.4, 7.3 Hz, *H*CHOTMS), 3.55 (1H, dd, J=10.5, 4.1 Hz, HC*H*OTMS), 3.76 (1H, dd, J=6.1, 4.0 Hz, C*H*OTBS), 3.85 (1H, dt, J=7.0, 4.6 Hz, C*H*OTMS), 4.03 (1H, dd, J=13.1, 4.4 Hz, *H*CHOTBS), 4.14 (1H, dd, J=13.1, 6.0 Hz, HC*H*OTBS), 5.07 (1H, dd, J=6.1, 4.9 Hz, CHOBz), 5.21–5.41 (2H, m, C*H*=C*H*), 7.26–7.35 (2H, m, 2×ArH), 7.42 (1H, tt, J=6.1, 1.8 Hz, ArH), 7.86–7.93 (2H, m, 2×ArH); δ_C (62.9 MHz, $CDCl_3$) −0.61, 0.63 15.4, 16.4, 18.3, 26.0 (two overlapping), 35.5, 59.7, 63.8, 73.3, 74.0, 128.2, 129.1, 129.8, 130.0, 130.9, 132.7, 134.1, 165.8; *m/z* (CI^+) 700 (100% MNH_4^+), 683.4017 (45% MH^+, $C_{34}H_{67}O_6Si_4$ requires 683.4015), 105 (40% Bz^+).

(2*Z*,4*R*,5*R*,6*R*,7*R*)-6-Benzoyloxy-4-methyl-1,5-di-(*tert*-butyldimethylsiloxy)-7,8-di-(triethylsilyloxy)oct-2-ene (30c). To a solution of diol **28** (910 mg, 1.69 mmol) in *N*,*N*-dimethylformamide (10 mL) was added imidazole (611 mg, 10.15 mmol) followed by triethylsilyl chloride (0.852 mL, 5.07 mmol). After 18 h water (30 mL) was added and the mixture was extracted with Et_2O (3×30mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (96:4 pet. ether/EtOAc) gave bis-TES protected alkene **30c** (1.28 g, 99%) as a colourless oil $[\alpha]_D$=+42.1 (*c* 1.9, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 1728 (C=O), 1603 (Ar), 1586 (Ar); δ_H (250 MHz, $CDCl_3$) −0.16 (3H, s, SiMe), −0.02 (3H, s, SiMe), −0.00 (6H, s, 2×SiMe), 0.40–0.63 (12H, m, 6×SiCH_2Me), 0.75 (9H, s, Si^{t}Bu), 0.80–0.94 (18H, m, 6×SiCH_2*Me*), 0.84 (9H, s, Si^{t}Bu), 1.04 (3H, d, J=6.7 Hz, CH*Me*), 2.54–2.70 (1H, m, C*H*Me), 3.55 (1H, dd, J=10.4, 6.7 Hz, *H*CHOTES), 3.71 (1H, dd, J=10.4, 4.9 Hz, HC*H*OTES), 3.90 (1H, dd, J=7.0, 3.7 Hz, C*H*OTBS), 3.91–3.98 (1H, m, C*H*OTES), 4.09 (1H, dd, J=13.1, 3.4 Hz, *H*CHOTBS), 4.24 (1H, dd, J=13.1, 5.8 Hz, HC*H*OTBS), 5.19 (1H, dd, J=7.0, 4.1 Hz, C*H*OBz), 7.31–7.48 (2H, m, C*H*=C*H*), 7.32–7.53 (3H, m, 3×ArH), 7.92–8.00 (2H, m, 2×ArH); δ_C (62.9 MHz, $CDCl_3$) 4.2, 5.1, 6.4, 6.8, 6.9, 15.3, 18.3, 25.9, 26.0, 35.5, 59.6, 64.4, 73.5, 73.6, 128.2, 129.0, 129.8, 131.0, 132.6, 134.1, 165.9; *m/z* (CI^+) 784 (6% MNH_4^+), 767.4925 (11% MH^+, $C_{40}H_{79}O_6Si_4$ requires 767.4954), 567 (85%), 381 (100%); (Found C, 62.48; H, 10.43. $C_{40}H_{78}O_6Si_4$ requires C, 62.61; H, 10.24).

(2*Z*,4*R*,5*R*,6*R*,7*R*)-6-Benzoyloxy-4-methyl-1,5-di-(*tert*-butyldimethylsiloxy)-7,8-di-(triphenylsilyloxy)oct-2-ene (30d). To a solution of diol **28** (50 mg, 0.093 mmol) in *N*,*N*-dimethylformamide (1.5 mL) was added imidazole (45 mg, 0.743 mmol) followed by triphenylsilyl chloride (110 mg, 0.372 mmol). After 18 h water (5 mL) was added and the mixture was extracted with Et_2O (3×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was then filtered through a short plug of silica (95:5 pet. ether/EtOAc) to give crude bis-TPS alkene **30d** (91 mg, 96%) as a colourless viscous oil which was contaminated with TPSOH. Alkene **30d** was then used without further purification due to instability $[\alpha]_D$=+34.5 (*c* 2.9, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3070–2856 (C–H), 1727 (C=O), 1602 (Ar), 1590 (Ar); δ_H (250 MHz, $CDCl_3$) 0.18 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.01 (3H, s, SiMe), 0.69–0.85 (3H, m, CH*Me*), 0.80 (9H, s, Si^{t}Bu), 0.90 (9H, s, Si^{t}Bu), 2.46–2.62 (1H, m, C*H*Me), 3.86 (1H, dd, J=13.3, 3.7 Hz, *H*CHOTBS), 3.97–4.20 (4H, m, HC*H*OTBS, CH_2OTPS, C*H*OTBS), 4.33–4.43 (1H, m, C*H*OTPS), 5.30–5.55 (2H, m, C*H*=C*H*), 5.51 (1H, dd, J=7.3, 3.1 Hz, C*H*OBz), 7.10–8.01 (>20H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 14.9, 18.1, 25.9, 35.5, 59.5, 64.7, 73.5, 74.1, 76.8, 127.8 (two overlapping), 128.1, 129.0, 129.9, 130.0 (two overlapping), 130.8, 132.5, 133.3, 133.7, 134.0, 135.2, 135.5, 135.6, 165.6; *m/z* (FAB^+) 1055.4992 (17% MH^+, $C_{64}H_{79}O_6Si_4$ requires 1055.4954), 855 (100%), 998 {18% (M−^{t}Bu)$^+$}, {18% (M−Ph)$^+$}, 923 {37% (M−TBSO)H$^+$}; (Found C, 72.76; H, 7.36. $C_{64}H_{78}O_6Si_4$ requires C, 72.82; H, 7.45).

(2*R*,3*S*,4*R*,5*R*,6*R*,7*R*)-6-Benzoyloxy-4-methyl-1,5-di-(*tert*-butyldimethylsiloxy)-7,8-di-(trimethylsilyloxy)octa-2,3-oxirane (31b-*syn*). To a solution of alkene **30b** (95 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) at −20°C was added DMDO[25] (0.08 M in acetone; 2.6 mL, 0.21 mmol). After 18 h at this temperature the solution was warmed to room temperature and then the volatile material was removed in vacuo to give a mixture of two epoxide diastereoisomers in

favour of the desired epoxide 31b-*syn* (97 mg, 100%, dr >4:1), which existed as a light yellow oil $[\alpha]_D$=+22.7 (*c* 2.2, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 2956–2858 (C–H), 1727 (C=O), 1603 (Ar), 1586 (Ar); δ_H (250 MHz, $CDCl_3$) −0.25 and (−0.23) (3H, 2×s, Si*Me*^{t}Bu), −0.10–0.03 (27H, m, 3×Si*Me*^{t}Bu, 2×SiMe_3), (0.66) and 0.68 (9H, 2×s, Si^{t}Bu), (0.80) and 0.82 (9H, 2×s, Si^{t}Bu), (0.97) and 1.13 (3H, 2×d, *J*=7.0, 6.7 Hz, CH*Me*), 1.40–1.60 (1H, m, C*H*Me), (2.80–2.89) and 2.85 (1H, m and dd, *J*=8.9, 4.0 Hz, C_{39}–H), 2.97 and (3.06) (1H, 2×q, *J*=5.2, 5.3 Hz, C_{38}–H), 3.39–3.73 (4H, m, CH_2OTBS, CH_2OTMS), 3.72–3.81 (1H, m, C*H*OTMS), 3.97 and (4.11) (1H, 2×dd, *J*=7.6, 3.4, 8.2, 1.2 Hz, C*H*OTBS), (5.15–5.26) and 5.18 (1H, m and dd, *J*=7.6, 3.4 Hz, C*H*OBz), 7.27–7.50 (3H, m, 3×ArH), 7.85–7.97 (2H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) (−0.6), −0.5, (0.2), 0.5, (9.9), 11.8, 18.1, 25.8, 25.9, (34.9), 36.0, 58.4, 60.9, (61.5), 61.9, (63.3), 63.5, (70.9), 71.5, (73.1), 73.7, 76.7, 128.3, 129.7, 130.8, 132.7, 165.8; *m/z* (CI^+) 716 (48% MNH_4^+), 699.3941 (100% MH^+, $C_{34}H_{67}O_7Si_4$ requires 699.3964), 187 (40%).

(2*R*,3*S*,4*R*,5*R*,6*R*,7*R*)-6-Benzoyloxy-4-methyl-1,5-di-(*tert*-butyldimethylsiloxy)-7,8-di-(triethylsilyloxy)oct-2,3-oxirane (31c-*syn*). To a solution of alkene **30c** (4.80 g, 6.27 mmol; 7:1 mixture of diastereoisomers) in CH_2Cl_2 (40 mL) at −20°C was added DMDO[25] (0.08 M in acetone; 94.0 mL, 7.52 mmol). After 18 h at this temperature the solution was warmed to room temperature and then the volatile material was removed in vacuo. Purification by flash column chromatography (9:1 pet. ether/EtOAc) gave a mixture of two epoxide diastereoisomers in favour of the desired epoxide **31c**-*syn* (4.77 g, 97%, dr 7:1), which existed as a light yellow oil $[\alpha]_D$=+17.2 (*c* 2.9, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 2956–2858 (C–H), 1731 (C=O), 1603 (Ar), 1586 (Ar); δ_H (250 MHz, $CDCl_3$) (−0.23) and −0.22 (3H, 2×s, SiMe), −0.06 and (−0.04) (3H, 2×s, SiMe), (−0.02) and 0.00 (3H, 2×s, SiMe), 0.02 (3H, s, SiMe), 0.38–0.61 (12H, m, 6×SiCH_2Me), 0.69 (9H, s, Si^{t}Bu), 0.74–0.94, 0.83 (27H, m, 6×SiCH_2*Me*; s, Si^{t}Bu), (1.01) and 1.17 (3H, 2×d, *J*=6.7, 6.7 Hz, CH*Me*), 1.40–1.60 (1H, m, C*H*Me), 2.87 (1H, dd, *J*=9.2, 4.3 Hz, C_{39}–H), 3.00 and (3.03–3.12) (1H, dt and m, *J*=6.7, 4.0 Hz, C_{38}–H), 3.46–3.65 (3H, m, *H*CHOTES, CH_2OTBS), 3.66–3.90 (1H, m, C*H*OTES), 3.86 (1H, dd, *J*=12.1, 3.8 Hz, HC*H*OTES), 3.99 and (4.19) (1H, 2×dd, *J*=7.6, 1.8, 8.5, 1.0 Hz, C*H*OTBS), 5.22 and (5.30) (1H, 2×dd, *J*=7.8, 2.9, 8.6, 2.4 Hz, C*H*OBz), 7.28–7.54 (3H, m, 3×ArH), 7.86–8.02 (2H, m, 2×ArH); δ_C (62.9 MHz, $CDCl_3$) 4.2, 4.3, 4.9, 5.0, 6.8, 6.9, 11.9, 18.1, 25.8, 29.7, 36.1, 58.9, 60.8, 62.2, 64.2, 71.3, 74.1, 76.8, 128.2, 129.7, 130.8, 132.7, 165.8; *m/z* (CI^+) 783.4886 (82% MH^+, $C_{40}H_{79}O_7Si_4$ requires 783.4903), 753 (89%), 207 (100%).

(4*R*,5*R*,6*R*,7*R*)-6-Benzoyloxy-4-methyl-1,5-di-(*tert*-butyldimethylsiloxy)-7,8-di-(triphenylsilyloxy)oct-2,3-oxirane (31d-*syn*). To a solution of alkene **30d** (55 mg, 0.052 mmol) in CH_2Cl_2 (1 mL) at −20°C was added DMDO[25] (0.08 M in acetone; 1.00 mL, 0.08 mmol). After 18 h at this temperature the solution was warmed to room temperature and then the volatile material was removed in vacuo to give crude epoxide **31d**-*syn* as a mixture of diastereoisomers (48 mg, 86%, dr 8:1), which was contaminated with TPSOH and existed as an amorphous white solid $[\alpha]_D$=+2.5 (*c* 2.8, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3070–2857 (C–H), 1726 (C=O), 1603 (Ar), 1586 (Ar); δ_H (250 MHz, $CDCl_3$) −0.13 (3H, s, SiMe), −0.05 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.82 (9H, s, Si^{t}Bu), 0.90 (9H, s, Si^{t}Bu), 1.04 (3H, d, *J*=6.4 Hz, CH*Me*), 1.30–1.53 (1H, m, C*H*Me), 2.93 (1H, dd, *J*=9.0, 4.1 Hz, C_{39}–H), 2.98–3.08 and (3.11–3.20) (1H, 2×m, C_{38}–H), 3.42 and (3.53) (1H, 2×dd, *J*=11.9, 7.3, 11.7, 5.6 Hz, *H*CHOTBS), (3.59) and 3.72 (1H, 2×dd, *J*=11.6, 5.5, 11.9, 2.7 Hz, HC*H*OTBS), 4.01–4.41 (4H, m, CH_2OTPS, C*H*OTBS, C*H*OTPS), 5.50 and (5.55) (1H, 2×dd, *J*=8.2, 2.1, 8.5, 2.4 Hz, C*H*OBz), 7.19–7.79 (>33H, m, ArH), 7.86–8.01 (2H, m, ArH); *m/z* (FAB^+) 1068 (10% M^+), 1057 (12%), 923 (40%), 855 (100%); unable to verify acc. mass due to error >5 ppm.

(2*R*,3*S*,4*R*,5*R*,6*R*)-2-{[1′*R*]-2-(*tert*-Butyldimethylsiloxy)-1′-hydroxyethyl}-3-methyl-4-(*tert*-butyldimethylsiloxy)-5-benzyloxy-6-hydroxymethyl-1-tetrahydropyran (33) from 31b. To a solution of epoxide **30b** (42 mg, 0.060 mmol; 4:1 mixture of diastereoisomers) in CH_2Cl_2 (1 mL) was added camphorsulfonic acid (~1 mg, ~0.004 mmol). After 2 h TLC indicated mainly staring material was present so more CSA (~2 mg, 0.008 mmol) was added. After a further 1.5 h the reaction was quenched with pyridine (1 drop) and the volatile material was removed in vacuo. Purification by flash column chromatography (3:1 pet. ether/EtOAc) gave the desired pyran diol **33** (29 mg, 84%, dr 4:1) as an amorphous white solid. The data for the major (desired pyran) was identical to that prepared from **30c**.

(2*R*,3*S*,4*R*,5*R*,6*R*)-2-{[1′*R*]-2-(*tert*-Butyldimethylsiloxy)-1′-hydroxyethyl}-3-methyl-4-(*tert*-butyldimethylsiloxy)-5-benzyloxy-6-hydroxymethyl-1-tetrahydropyran (33) from 31c. To a solution of epoxide **31c** (4.50 g, 5.75 mmol, dr 7:1) in CH_2Cl_2 (60 mL) at −20°C was added camphorsulfonic acid (134 mg, 0.575 mmol) followed by methanol (1 mL). After 4 h more CH_2Cl_2 (20 mL) was added followed by methanol (3 mL). The solution was then stirred at −20°C for 4 h before the solution was removed from the cold bath and all of the volatile material was removed in vacuo. The crude mixture of epoxide diol, pyran **33** and camphorsulfonic acid was then dissolved in CH_2Cl_2 (50 mL) under nitrogen and then camphorsulfonic acid (120 mg, 0.517 mmol) was added. After 1 h, pyridine (0.1 mL, 1.24 mmol) was added and the volatile material was removed in vacuo. Purification by flash column chromatography (3:1 pet. ether/EtOAc then 2:1 EtOAc/pet. ether) gave the desired pyran diol **33** (2.60 g, 82%, 10:1 mixture of diastereoisomers) as an amorphous white solid, and an undesired triol secondary TBS protected epoxide of unknown configuration (58 mg, 3%) as a viscous oil.

Data for pyran diol **33** mp 65–66°C; $[\alpha]_D$=−15.8 (*c* 3.0, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3396 (O–H), 2954–2857 (C–H), 1727 (C=O); δ_H (250 MHz, $CDCl_3$) −0.25 (3H, s, SiMe), 0.00 (9H, s, 3×SiMe), 0.70 (9H, s, Si^{t}Bu), 0.83 (9H, s, Si^{t}Bu), 0.96 (3H, d, *J*=6.7 Hz, CH*Me*), 1.92–2.11 (1H, m, C*H*Me), 2.87 (2H, bs, 2×OH), 3.26 (1H, d, *J*=10.7 Hz, C_{39}–H), 3.30–3.35 (1H, m, C_{43}–H), 3.45 (1H, dd, *J*=12.8, 3.7 Hz, *H*CHOH), 3.51–3.74 (5H, m,

C*H*OTBS, HC*H*OH, C*H*OH, CH_2OTBS), 5. C*H*Me), 2.30–2.52 (2H, bs, 2×OH), 2.59 (1H, dd, *J*=9.6, 4.1 Hz, C_{39}–H), 2.80 (1H, ddd, *J*=6.1, 5.5, 4.0 Hz, C_{38}–H), 2.95 (1H, bs, OH), 3.30–3.76 (5H, m, 2×CH_2OH, C*H*OH), 4.11 (1H, dd, *J*=3.4, 2.6 Hz, C*H*OTBS), 4.85 (1H, dd, *J*=9.5, 2.4 Hz) 00 (1H, dd, *J*=9.9, 8.7 Hz, C*H*OBz), 7.23–8.05 (5H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 13.3, 18.1, 18.3, 25.8, 25.9, 38.9, 61.6, 63.6, 70.3, 73.4, 76.9, 77.9, 78.6, 128.4, 129.7, 129.9, 133.5, 166.9; *m/z* (EI^+) 555.3171 (10% MH^+, $C_{28}H_{51}O_7Si_2$ requires 555.3173), 539 {27% $(M-Me)^+$}, 514 (54%), 497 {100% $(M-{}^tBu)^+$}; (Found C, 60.60; H, 9.22. $C_{28}H_{50}O_7Si_2$ requires C, 60.72; H, 8.92).

Data for triol secondary TBS protected epoxide δ_H (250 MHz, $CDCl_3$) 0.00 (3H, s, SiMe), 0.05 (3H, SiMe), 0.78 (9H, s, Si^{t}Bu), 1.04 (3H, d, *J*=7.0 Hz, CH*Me*), 1.65 (1H, dqd, *J*=10.0, 7.0, 3.4 Hz, C*H*OBz), 7.26–7.95 (5H, m, ArH); *m/z* (CI^+) 458 (73% MNH_4^+), 441.2296 (100% MH^+, $C_{22}H_{37}O_7Si$ requires 441.2309), 105 (44% Bz^+).

(2*R*,3*S*,4*R*,5*R*,6*R*)-2-{[1′*R*]-2-(*tert*-Butyldimethylsiloxy)-1′-hydroxyethyl}-3-methyl-4-(*tert*-butyldimethylsiloxy)-5-hydroxy-6-hydroxymethyl-1-tetrahydropyran (34). To a solution of pyran-diol **33** (2.40 g, 4.33 mmol, dr 10:1) in CH_2Cl_2 (60 mL) at −78°C was added DIBAL (7.72 mL, 43.30 mmol). The solution was warmed to 0°C and left at this temperature for 30 min before it was re-cooled to −78°C. Excess DIBAL was quenched by the dropwise addition of EtOAc (5 mL) and then the solution was warmed to 0°C. The clear colourless solution was then diluted with CH_2Cl_2 (30 mL) and then water (60 mL) was added followed by saturated aqueous sodium potassium tartrate (30 mL). After stirring vigorously for 18 h the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4×60 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (1:1 pet. ether/EtOAc) gave pyran-triol **34** (1.48 g, 76%; single diastereoisomer) as a white crystalline solid mp 125–127°C; $[\alpha]_D$=+5.0 (*c* 2.0, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3387 (O–H), 3000–2856 (C–H); δ_H (250 MHz, $CDCl_3$) 0.00 (6H, s, 2×SiMe), 0.06 (3H, s, SiMe), 0.08 (3H, s, SiMe), 0.83 (9H, s, Si^{t}Bu), 0.86 (9H, s, Si^{t}Bu), 0.89 (3H, d, *J*=7.0 Hz, CH*Me*), 1.73–2.02 (2H, m, C*H*Me, OH), 2.59 (1H, d, *J*=3.4 Hz, OH), 3.05–3.25 (3H, m, CH_2OH, OH), 3.12 (1H, d, *J*=10.4 Hz, C_{39}–H), 3.44 (1H, td, *J*=8.9, 2.6 Hz, C_{43}–H), 3.50–3.84 (5H, m, CH_2OTBS, C*H*OTBS, 2×OH); δ_C (62.9 MHz, $CDCl_3$) 13.1, 18.3, 18.4, 25.9, 26.1, 38.3, 62.3, 64.1, 70.4, 71.7, 78.8, 79.9; *m/z* (CI^+) 468 (44% MNH_4^+) 451.2893 (100% MH^+, $C_{21}H_{47}O_6Si_2$ requires 451.2911), 393 {83% $(M-{}^tBu)^+$}, 243 (64%), 127 (79%), 75 (84%).

Pyran-C_{37}-alcohol (35). To a solution of pyran triol **34** (600 mg, 1.33 mmol) and 4 Å molecular sieves (50 mg) in CH_2Cl_2 (10 mL) was added benzaldehydedimethylacetal (0.22 mL, 1.47 mmol) followed by camphorsulfonic acid (31 mg, 0.13 mmol). After 2 h pyridine (5 drops) was added and the volatile material was removed in vacuo. Purification by flash column chromatography (8:1 pet. ether/EtOAc) gave the desired mono benzylidene acetal (574 mg, 80%) as a colourless oil. The ^1H NMR was contaminated (approx. 5%) with the undesired inseparable di-benzylidene acetal; $[\alpha]_D$=−22.7 (*c* 2.2, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3463 (O–H), 2953–2857 (C–H); δ_H (250 MHz, $CDCl_3$) −0.13 (3H, s, SiMe), −0.03 (3H, s, SiMe), 0.00 (6H, s, 2×SiMe), 0.77 (9H, s, Si^{t}Bu), 0.83 (9H, s, Si^{t}Bu), 0.96 (3H, d, *J*=6.7 Hz, CH*Me*), 1.87–2.05 (1H, m, C*H*Me), 3.25 (1H, d, *J*=10.7 Hz, C_{39}–H), 3.29–3.47 (3H, m, C_{43}–H, C_{44}–H_2), 3.53 (1H, dd, *J*=9.5, 7.0 Hz, *H*CHOTBS), 3.57–3.74 (3H, m, HC*H*OTBS, C*H*OTBS, C*H*OH), 4.12–4.20 (1H, m, C_{42}–H), 5.42 (1H, s, C*H*Ph), 7.20–7.49 (5H, m, ArH), the ^1H NMR was contaminated (approx. 5%) with the undesired inseparable di-benzylidene acetal; δ_C (100.6 MHz, $CDCl_3$) 13.1, 18.2, 18.3, 25.9, 26.0, 39.2, 63.9, 68.9, 70.2, 70.6, 75.8, 79.7, 83.2, 102.0, 126.3, 128.1, 128.9, 137.4; *m/z* (CI^+) 556 (10% MNH_4^+), 539.3216 (67% MH^+, $C_{28}H_{51}O_6Si_2$ requires 539.3224), 108 (100%).

To a solution of potassium hydride (33 mg, 0.82 mmol) in THF (5 mL) at 0°C was added the benzylidene acetal prepared above (400 mg, 0.74 mmol) in THF (2 mL+2×0.5 mL washes). After 10 min benzyl bromide (0.10 mL, 0.84 mmol) was added and the mixture was stirred at 0°C for 3 h. Water (10 mL) was added followed by Et_2O (10 mL) and the two layers were separated. The aqueous layer was extracted with Et_2O (3×10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (8:1 pet. ether/EtOAc) gave the globally protected pure pyran (454 mg, 98%) as a colourless oil $[\alpha]_D$=−29.5 (*c* 4.4, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 2955–2857 (C–H); δ_H (250 MHz, $CDCl_3$) −0.12 (3H, s, SiMe), −0.03 (3H, s, SiMe), −0.00 (6H, s, 2×SiMe), 0.65 (3H, d, *J*=6.7 Hz, CH*Me*), 0.78 (9H, s, Si^{t}Bu), 0.84 (9H, s, Si^{t}Bu), 1.85–2.03 (1H, m, C*H*Me), 3.18–3.30 (1H, m, C_{43}–H), 3.26 (1H, dd, *J*=10.5, 1.5 Hz, C_{39}–H), 3.33–3.46 (2H, m, C_{44}–H_2), 3.52 (1H, td, *J*=6.6, 1.5 Hz, C*H*OBn), 3.72 (2H, d, *J*=6.7 Hz, CH_2OTBS), 3.74 (1H, t, *J*=10.2 Hz, C*H*OTBS), 4.16 (1H, dd, *J*=10.4, 4.9 Hz, C_{42}–H), 4.48 (1H, d, *J*=12.2 Hz, *H*CHPh), 4.72 (1H, d, *J*=11.9 Hz, HC*H*Ph), 5.42 (1H, s, C*H*Ph), 7.20–7.46 (10H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 12.9, 18.2, 18.4, 25.9, 26.0, 39.0, 61.4, 68.9, 71.1, 73.1, 76.2, 76.9, 80.2, 83.0, 101.9, 126.4, 127.8, 128.1, 128.3, 128.4, 128.9, 137.5, 138.2; *m/z* (EI^+) 628.3634 (29% M^+, $C_{35}H_{56}O_6Si_2$ requires 628.3615), 613 {9% $(M-Me)^+$}, 571 {100% $(M-{}^tBu)^+$}, 181 (60%).

To a solution of pyran prepared above (29 mg, 0.046 mmol) in THF (1 mL) was added 0.5 mL of freshly prepared, buffered pyridinium hydrofluoride (stock solution prepared from 10 mL of THF, 5.7 mL of pyridine and 2.1 g of Fluka pyridinium hydrofluoride). After 5 h the reaction mixture was poured over saturated aqueous $NaHCO_3$ (10 mL) and then extracted with ether (3×10 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (2:1 pet. ether/EtOAc) gave alcohol **35** (21 mg, 88%) as a colourless oil $[\alpha]_D$=−15.0 (*c* 2.0, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3463 (O–H), 3035–2856 (C–H); δ_H (250 MHz, $CDCl_3$) 0.00 (3H, s, SiMe), 0.09 (3H, s, SiMe), 0.89 (3H, d, *J*=6.4 Hz, CH*Me*), 0.90 (9H, s, Si^{t}Bu), 1.86 (1H, bs, OH), 2.05–2.22 (1H, m, C*H*Me), 3.39–3.59 (3H, m, C_{43}–H, C_{44}–H_2), 3.46 (1H, dd, *J*=10.5, 2.0 Hz, C_{39}–H), 3.62–3.68 (1H, m, C*H*OBn), 3.84 (1H, t, *J*=9.9 Hz, C*H*OTBS), 3.88 (1H, dd, *J*=11.6, 4.1 Hz,

*H*CHOH), 4.00 (1H, dd, *J*=11.6, 5.2 Hz, HC*H*OH), 4.29 (1H, dd, *J*=10.4, 4.6 Hz, C_{42}–H), 4.64 (1H, d, *J*=11.9 Hz, *H*CHPh), 4.84 (1H, d, *J*=11.9 Hz, HC*H*Ph), 5.54 (1H, s, C*H*Ph), 7.36–7.56 (10H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 13.0, 18.4, 26.0, 39.4, 62.4, 68.8, 71.3, 72.0, 75.8, 76.0, 82.8, 83.6, 102.1, 126.4, 128.0, 128.1, 128.3, 128.5, 129.0, 137.4, 137.9; *m/z* (EI^+) 514.2729 (10% M^+, $C_{29}H_{42}O_6Si$ requires 514.2751), 457 {35% $(M-{}^tBu)^+$}, 91 (100% Bn^+).

Pyran-C_{37} methyl ketone (36). To a solution of oxalyl chloride (0.047 mL, 0.544 mmol) in CH_2Cl_2 (2 mL) at −78°C was added DMSO (0.077 mL, 1.088 mmol) in CH_2Cl_2 (1.5 mL) dropwise. After 5 min, alcohol **35** (140 mg, 0.272 mmol) in CH_2Cl_2 (1 mL+0.5 mL wash) was added and the white mixture stirred at −78°C for 15 min before di-*iso*-propylethyl amine (0.379 mL, 2.176 mmol) was added dropwise. After 1 h at −78°C the mixture was warmed to −40°C over a 15 min period and then quenched with pH 7 phosphate buffer (4 mL). The reaction mixture was then diluted with more pH 7 phosphate buffer (20 mL) and Et_2O (30 mL) and the layers separated. The aqueous layer was extracted with Et_2O (2×30 mL) and the combined organic layers dried (Na_2SO_4) and concentrated in vacuo to give crude the corresponding crude aldehyde (141 mg) as a yellow oil which was used without any further purification δ_H (250 MHz, $CDCl_3$) 0.00 (3H, s, SiMe), 0.08 (3H, s, SiMe), 0.79 (3H, d, *J*=6.7 Hz, CH*Me*), 0.90 (9H, s, Si^{t}Bu), 2.04–2.26 (1H, m, C*H*Me), 3.30–3.45 (1H, m, C_{43}–H), 3.46–3.59 (2H, m, C_{44}–H_2), 3.67 (1H, dd, *J*=10.5, 2.3 Hz, C_{39}–H), 3.81 (1H, t, *J*=10.1 Hz, C*H*OTBS), 3.85–3.93 (1H, m, C*H*OBn), 4.23 (1H, dd, *J*=10.4, 4.9 Hz, C_{42}–H), 5.53 (1H, s, C*H*Ph), 7.35–7.57 (5H, m, ArH), 9.78 (1H, d, *J*=1.2 Hz, C*H*O).

To a solution of the crude aldehyde prepared above (141 mg, ~0.272 mmol) in Et_2O (5 mL) at −78°C was added MeLi (1.6 M in Et_2O; 0.26 mL, 0.408 mmol) dropwise. After 30 mins the reaction had not gone to completion so more MeLi (1.6 M in Et_2O; 0.26 mL, 0.408 mmol) was added. After 30 min the reaction was quenched with pH 7 phosphate buffer (5 mL). The reaction mixture was then diluted with pH 7 phosphate buffer (25 mL) and Et_2O (30 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3×30 mL), and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. Filtration through a short plug of silica (4:1 pet. ether/EtOAc) afforded a 1:1 mixture of the two diastereomeric secondary alcohols (117 mg, 82%) as a light yellow oil which was used without further purification $[\alpha]_D$=−12.5 (*c* 1.6, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3476 (O–H); δ_H (250 MHz, $CDCl_3$) 0.00 (3H, s, SiMe), 0.09 and 0.10 (3H, 2×s, SiMe), 0.90 and 0.91 (12H, 2×s, Si^{t}Bu), 1.04 (3H, d, *J*=6.3 Hz, C_{40}–Me), 1.28 and 1.34 (3H, 2×d, *J*=6.1, 6.4 Hz, C_{36}–Me), 1.75 (1H, bs, OH), 2.00–2.30 (1H, m, C_{40}–H), 3.35–3.58 (4H, m, C_{43}–H, C_{44}–H_2, C*H*OBn), 3.66 (1H, dd, *J*=10.4, 1.8 Hz, C_{39}–H), 3.82 and 3.85 (1H, 2×t, *J*=10.1, 10.1 Hz, C*H*OTBS), 4.10–4.35 (2H, m, C_{42}–H, C*H*OH), 4.61 and 4.81 (1H, 2×d, *J*=11.9, 1.3 Hz, *H*CHPh), 4.86 and 4.87 (1H, 2×d, *J*=11.9, 11.3 Hz, HC*H*Ph), 5.54 and 5.55 (1H, 2×s, C*H*Ph), 7.30–7.60 (10H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) complex spectrum of two diastereoisomers; *m/z* (EI^+) 527.2823 (5% M^+, $C_{30}H_{43}O_6Si$ requires 527.2829), 91 (100%, Ph^+).

To a solution of the alcohol prepared above (117 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was added pyridine (0.20 mL, 2.47 mmol) followed by freshly prepared Dess–Martin periodinane[26] (94 mg, 0.24 mmol). After 1 h the volatile material was removed in vacuo and the crude material was purified by flash column chromatography (6:1 pet. ether/EtOAc) to give methyl ketone **36** (115 mg, 99%) as an amorphous white solid mp 88–90°C; $[\alpha]_D$=−22.2 (*c* 0.9, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 1716 (C=O); δ_H (250 MHz, $CDCl_3$) 0.00 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.76 (3H, d, *J*=6.7 Hz, CH*Me*), 0.91 (9H, s, Si^{t}Bu), 2.01–2.19 (1H, m, C*H*Me), 2.31 (3H, s, MeCO), 3.35 (1H, dt, *J*=10.1, 4.9 Hz, C_{43}–H), 3.45–3.59 (2H, m, C_{44}–H_2), 3.55 (1H, dd, *J*=10.4, 2.4 Hz, C_{39}–H), 3.81 (1H, t, *J*=10.2 Hz, C*H*OTBS), 3.90 (1H, d, *J*=2.1 Hz, C*H*OBn), 4.20 (1H, dd, *J*=10.4, 4.9 Hz, C_{42}–H), 4.45 (1H, d, *J*=11.9 Hz, *H*CHPh), 4.89 (1H, d, *J*=11.9 Hz, HC*H*Ph), 5.53 (1H, s, C*H*Ph), 7.37–7.56 (10H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 12.9, 18.4, 27.6, 39.2, 68.6, 71.2, 73.7, 75.8, 82.7, 83.0, 83.1, 102.1, 126.4, 128.1, 128.4, 128.6, 128.7, 129.0, 136.6, 137.4, 211.5; *m/z* (CI^+) 544 (60% MNH_4^+), 527.2806 (34% MH^+, $C_{30}H_{43}O_6Si$ requires 527.2829), 421 (100%).

5-{(4-Methoxyphenyl)methoxy}pentan-1-al (38). To a stirred suspension of NaH (346 mg, 14.4 mmol) in benzene (10 mL) at room temperature was added pentane-1,5-diol (3.0 mL, 28.8 mmol) via syringe. After 15 min the mixture was refluxed for 3 h before cooling to room temperature. PMBCl (1.95 mL, 14.4 mmol) was then added and the mixture was set to reflux for 18 h. The mixture was cooled to room temperature and the reaction was quenched with water (30 mL). The resulting slurry was extracted with CH_2Cl_2 (3×30 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a light brown oil. Distillation under reduced pressure provided the mono-protected alcohol[31] (2.45 g, 76%) as a colourless oil bp 230°C at 4 mmHg; δ_H (250 MHz, $CDCl_3$) 1.35–1.70 {7H, m, OH, $(CH_2)_3CH_2OPMB$}, 3.44 (2H, t, *J*=6.4 Hz, CH_2OPMB), 3.63 (2H, t, *J*=6.4 Hz, CH_2OH), 3.80 (2H, s, OMe), 4.42 (2H, s, CH_2OPMB), 6.83–6.90 (2H, m, ArH), 7.22–7.29 (2H, m, ArH).

To a solution of oxalyl chloride (1.18 mL, 13.60 mmol) in CH_2Cl_2 (40 mL) at −65°C was added DMSO (1.75 mL, 24.74 mmol) in CH_2Cl_2 (5 mL) dropwise via cannula. After 2 min, the mono protected alcohol from above (2.77 g, 12.37 mmol) in CH_2Cl_2 (5 mL+1 mL wash) was added over a 3 min period. After 20 min at this temperature triethylamine (8.60 mL, 61.85 mmol) was added dropwise which resulted in the formation of a thick white slurry which was kept at −65°C for 10 min then warmed to room temperature. Water (45 mL) was then added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with 1 M HCl (40 mL) and saturated aqueous $NaHCO_3$ (40 mL) then dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (5:1 pet. ether/EtOAc) gave known aldehyde **38**[30] (2.41 g, 87%) as a light yellow oil IR (thin film) ν_{max}/cm^{-1} 3530 (O–H), 3001–2723 (C–H), 1723 (C=O), 1613 (Ar), 1586 (Ar), 1513 (Ar); δ_H (250 MHz, $CDCl_3$) 1.55–1.81 {4H, $(CH_2)_2CH_2OPMB$}, 2.44 (2H, td, *J*=7.0, 1.6 Hz,

CH_2CHO), 3.44 (2H, t, J=6.0 Hz, CH_2OPMB), 3.79 (3H, s, OMe), 4.41 (2H, s, CH_2PMP), 6.87 (2H, dt, J=8.6 Hz, ArH), 7.25 (2H, dt, J=8.5, 2.7 Hz, ArH), 9.75 (1H, t, J=1.7 Hz, CHO).

(*S*)-3-{(2*S*,3*R*)-3-Hydroxyl-2-methyl-7-[(4-methoxyphenyl)methoxy]-4-heptanoyl}-4-(phenylmethyl)-2-oxazolidinone (40). To a solution of substituted auxiliary **39** (1.63 g, 7.0 mmol) in CH_2Cl_2 (30 mL) at −10°C was added dibutylboron triflate (1.94 mL, 7.7 mmol) followed by triethylamine (1.17 mL, 8.4 mmol) making sure the internal temperature did not rise above 0°C. The light yellow solution was stirred at −5°C for 20 min before cooling in an acetone/dry ice bath. Once the internal temperature had dropped to −70°C, aldehyde **247** (1.71 g, 7.7 mmol) in CH_2Cl_2 (5 mL+5 mL wash) was added over a 5 min period via cannula. The solution was kept at −70°C for 20 min then warmed to 0°C over a 30 min period and stirred for 1.5 h. The light yellow/orange solution was re-cooled to −8°C and 2 M pH 7 phosphate buffer (15 mL) was added, followed by methanol (30 mL) and 2:1 methanol/30% hydrogen peroxide (30 mL) making sure the temperature did not rise above 5°C. All volatile material was removed in vacuo, and then water (50 mL) was added. The mixture was extracted into ether (3×70 mL) and the combined organic layers washed with 5% aqueous $NaHCO_3$ (70 mL) and brine (70 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (3:2 pet. ether/EtOAc) gave **40** (3.08 g, 97%, d.s.>95:5) as a colourless oil $[\alpha]_D$=+46.7 (*c* 3.0, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3530 (O–H), 3029–2862 (C–H), 1779 (C=O), 1694 (C=O), 1612 (Ar), 1586 (Ar), 1513 (Ar); δ_H (250 MHz, $CDCl_3$) 1.24 (3H, d, J=7.0 Hz, CH*Me*), 1.34–1.72 {6H, m, $CH(CH_2)_3$}, 2.65–3.00 (1H, bs, OH), 2.77 (1H, dd, J=13.3, 9.3 Hz, *H*CHPh), 3.25 (1H, dd, J=13.4, 3.4 Hz, HC*H*Ph), 3.44 (2H, t, J=6.3 Hz, CH_2OPMB), 3.73 (1H, dq, J=7.0, 2.7 Hz, C*H*Me), 3.79 (3H, s, OMe), 3.88–4.00 (1H, m, C*H*OH), 4.14–4.27 (2H, m, CH_2CHBn), 4.42 (2H, s, CH_2PMP), 4.63–4.75 (1H, m, C*H*Bn), 6.82–6.91 (2H, m, 2×ArH), 7.16–7.39 (7H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 10.4, 22.7, 29.6, 33.6, 37.8, 42.1, 55.1, 55.3, 66.2, 69.9, 71.4, 72.6, 113.8, 127.5, 129.0, 129.3, 129.4, 130.7, 135.0, 153.0, 159.1, 177.5; *m/z* (CI^+) 455.2291 (20% M^+, $C_{26}H_{33}NO_6$ requires 455.2308), 121 (100% PMB^+); (Found C, 68.01; H, 7.50; N, 2.94. $C_{26}H_{33}NO_6$ requires C, 68.54; H, 7.31; N, 3.08).

(2*S*,3*R*)-*N*-Methoxy-*N*,2-dimethyl-7-{(4-methoxyphenyl)-methoxy}-3-(triethylsiloxy)heptanamide (41). To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.42 g, 24.8 mmol) in THF (20 mL) at 0°C was added 2 M trimethylaluminium in toluene (12.4 mL, 24.8 mmol) dropwise (*caution: vigorous gas evolution*) via syringe. After 15 min at 0°C and 10 min at room temperature the clear colourless solution was re-cooled to −15°C. Adduct **40** (3.75 g, 8.26 mmol) in THF (10 mL+5 mL wash) was then added dropwise via cannula. The cloudy mixture was warmed to 0°C and stirred for 3 h in which time gas evolution slowly ceased and the cloudy mixture became a colourless solution. The solution was transferred via cannula to a mixture of CH_2Cl_2 (200 mL) and 1 M HCl (200 mL) at 0°C and stirred vigorously for 18 h. The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (2×200 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. The unpurified alcohol/oxazolidinone mixture was then dissolved in *N*,*N*-dimethylformamide (20 mL) and imidazole (1.26 g, 20.97 mmol) was added followed by triethylsilyl chloride (1.76 mL, 10.49 mmol). After 18 h the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and water (20 mL) was added. The mixture was extracted with Et_2O (3×50 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (3:1 pet. ether/EtOAc) gave amide **41** (3.32 g, 87% 2 steps) as a colourless oil $[\alpha]_D$=+6.2 (*c* 3.2 Hz, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 2952–2876 (C–H), 1661 (C=O), 1613 (Ar), 1586 (Ar), 1514 (Ar); δ_H (250 MHz, $CDCl_3$) 0.49–0.62 (6H, m, 3×SiCH_2Me), 0.90 (9H, t, J=7.9 Hz, 3×SiCH_2*Me*), 1.09 (3H, d, J=7.0 Hz, CH*Me*), 1.28–1.60 {6H, m, $CH(CH_2)_3$}, 2.78–2.98 (1H, m, C*H*Me), 3.08 (3H, s, NMe), 3.36 (2H, t, J=6.4 Hz, CH_2OPMB), 3.57 (3H, s, NOMe), 3.73 (3H, s, PhO*Me*), 3.80–3.90 (1H, m, C*H*OTES), 4.34 (2H, s, CH_2PMP), 6.80 (2H, dt, J=8.9, 2.4 Hz, 2×ArH), 7.15–7.23 (2H, m, 2×ArH); δ_C (62.9 MHz, $CDCl_3$) 5.2, 7.0, 14.5, 21.3, 30.0, 35.8, 41.0, 55.3, 61.4, 70.1, 72.5, 73.8, 113.7, 129.2, 130.8, 159.1; *m/z* (EI^+) 453.2897 (7% M^+, $C_{24}H_{43}NO_5Si$ requires 453.2911), 121 (100% PMB^+); (Found C, 63.59; H, 9.77; N, 3.09. $C_{24}H_{43}NO_5Si$ requires C, 63.54; H, 9.55; N, 3.09).

(2*S*,3*R*)-2-Methyl-7-{(4-methoxyphenyl)methoxy}-3-triethylsilyloxy-heptanal (37). To a solution of Weinreb amide **41** (630 mg, 1.39 mmol) in THF (11 mL) at −78°C was added DIBAL (0.99 mL, 5.56 mmol) dropwise via syringe. After 1 h excess DIBAL was quenched with EtOAc (0.2 mL) and the clear colourless solution was warmed to room temperature. Et_2O (5 mL) and water (5 mL) were added followed by saturated aqueous sodium potassium tartrate (5 mL) and the mixture was stirred vigorously for 4 h. The two clear layers were separated and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Filtration of the resulting crude product through a short plug of silica (7:1 pet. ether/EtOAc) afforded aldehyde **37** (530 mg, 97%) as a colourless oil $[\alpha]_D$=+39.4 (*c* 3.3, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 2952–2876 (C–H), 1726 (C=O), 1613 (Ar), 1586 (Ar), 1514 (Ar); δ_H (250 MHz, $CDCl_3$) 0.50–0.64 (6H, m, 3×SiCH_2Me), 0.93 (9H, t, J=7.8 Hz, 3×SiCH_2*Me*), 1.04 (3H, d, J=7.1 Hz, CH*Me*), 1.15–1.70 {6H, m, $CH(CH_2)_3$}, 2.43 (1H, qdd, J=7.0, 3.7, 0.9 Hz, C*H*Me), 3.43 (2H, t, J=6.4 Hz, CH_2OPMB), 3.80 (3H, s, PhO*Me*), 4.10 (1H, dt, J=6.4, 3.7 Hz, C*H*OTES), 4.42 (2H, s, CH_2PMP), 6.81–6.86 (2H, m, 2×ArH), 7.20–7.24 (2H, m, 2×ArH), 9.75 (1H, d, J=1.2 Hz, CHO); δ_C (62.9 MHz, $CDCl_3$) 5.1, 6.9, 7.6, 22.5, 29.8, 34.5, 51.3, 55.2, 69.8, 72.1, 72.6, 113.7, 129.2, 130.6, 159.1, 205.3; *m/z* (CI^+) 412 (12% MNH_4^+), 395.2612 (12% MH^+, $C_{22}H_{39}O_4Si$ requires 395.2618), 121 (100% PMB^+).

Pyran aldol adduct (42). *Via lithium enolate:* To a 0.71 M solution of LDA in THF (0.1 mL, 0.072 mmol) at −78°C was added ketone **36** (25 mg, 0.048 mmol) in THF (0.2 mL+0.2 mL wash) via cannula. The solution was stirred for 30 min at −78°C before aldehyde **37** (38 mg,

0.096 mmol) in THF (0.2 mL) was added via cannula. After 5 min pH 7 phosphate buffer (5 mL) was added and the mixture was warmed to room temperature and then diluted with Et_2O (5 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic extracts were then dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (7:1 pet. ether/EtOAc) gave two aldol adduct diastereoisomers; major diastereoisomer (18 mg, 40%) minor isomer (14 mg, 32%) dr 1.3:1.

Via TMS enol ether: To a ~0.36 M solution of LDA in THF (0.58 mL, 0.21 mmol) at −78°C was added ketone **36** (22 mg, 0.042 mmol) in THF (0.5 mL+0.5 mL wash) via cannula. After 30 min trimethylsilyl chloride (0.011 mL, 0.084 mmol) was added. After 10 min the reaction was quenched with pH 7 phosphate buffer (2 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3×4 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was then filtered through a short plug of silica (9:1 pet. ether/EtOAc) to give the kinetic TMS enol ether **43** (25 mg, 99%) as a colourless oil which was used immediately without further purification. The ^1H NMR showed some starting material present, which could have been derived by residual HCl in the deuterochloroform during the NMR experiment. δ_H (250 MHz, $CDCl_3$) −0.07 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.23 (9H, s, 3×$SiMe_3$), 0.57 (3H, d, J=6.7 Hz, CHMe), 0.83 (9H, s, Si^{t}Bu), 1.85–2.08 (1H, m, C*H*Me), 3.18–3.34 (1H, m, C_{43}–H), 3.29 (1H, dd, J=10.6, 2.0 Hz, C_{39}–H), 3.35–3.51 (2H, m, C_{44}–H_2), 3.66–3.72 (1H, m, C*H*OBn), 3.81 (1H, t, J=10.2 Hz, C*H*OTBS), 4.18 (1H, dd, J=10.5, 5.0 Hz, C_{42}–H), 4.34–4.40 (1H, m, C═C*H*H), 4.36 (1H, dd, J=12.2 Hz, *H*CHPh), 4.52–4.58 (1H, m, C═CH*H*), 4.83 (1H, d, J=12.2 Hz, HC*H*Ph), 5.61 (1H, s, C*H*Ph), 7.27–7.50 (10H, m, ArH).

To a solution of TMS enol ether **43** (32 mg, 0.056 mmol), aldehyde **37** (44 mg, 0.112 mmol) and 4 Å molecular sieves (5 mg) at −78°C was added a 0.081 M solution of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (0.07 mL, 0.056 mmol). After 18 h the reaction was quenched at −78°C with pH 7 phosphate buffer (3 mL) and warmed to room temperature. The mixture was then diluted with Et_2O (5 mL) and pH 7 phosphate buffer (2 mL) was added. The two layers were separated and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo allowing purification by flash column chromatography (7:1 pet. ether/EtOAc) affording recovered starting material (9 mg, 28%) and the two aldol adduct diastereoisomers; major diastereoisomer (18 mg, 35%) minor isomer (9 mg, 17%) dr 2:1 in favour of the same major diasteroisomer observed in the LDA mediated aldol reaction above.

Data for major diastereoisomer $[\alpha]_D$=−27.3 (*c* 1.1, CH_2Cl_2); IR (solution in CH_2Cl_2) ν_{max}/cm^{-1} 3446 (O–H), 3000–2855 (C–H), 1716 (C═O), 1614 (Ar), 1513 (Ar); δ_H (250 MHz, $CDCl_3$) 0.00 (3H, s, SiMe), 0.08 (3H, s, SiMe), 0.60–0.80 (6H, m, 3×SiCH_2Me), 0.74 (3H, d, J=6.4 Hz, CH*Me*), 0.91 (9H, s, Si^{t}Bu), 0.97 (3H, d, J=7.0 Hz, CH*Me*), 1.04 (9H, t, J=7.8 Hz, SiCH_2*Me*), 1.25–1.85 {7H, m, C*H*Me, CH(C_2H_2)$_3$}, 2.00–2.25 (1H, m, C*H*Me), 2.75 (1H, dd, J=17.9, 4.4 Hz, *H*CHC═O), 3.00 (1H, dd, J=17.7, 7.9 Hz, HC*H*C═O), 3.26–3.63 (5H, m, C_{43}–H, C_{44}–H_2, CH_2OPMB), 3.58 (1H, dd, J=10.7, 1.8 Hz, C_{39}–H), 3.80 (1H, t, J=10.4 Hz, C*H*OTBS), 3.87 (3H, s, PhO*Me*), 3.90–4.05 (1H, m, C*H*OH), 3.93 (1H, d, J=2.1 Hz, C*H*OBn), 4.08–4.26 (1H, m, C*H*OTES), 4.17 (1H, dd, J=10.4, 4.9 Hz, C_{42}–H), 4.47 (1H, d, J=11.9 Hz, *H*CHPh), 4.50 (2H, s, CH_2PMP), 4.96 (1H, d, J=11.6 Hz, HC*H*Ph), 5.52 (1H, s, C*H*Ph), 6.90–7.59 (14H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 5.1, 6.9, 12.3, 12.7, 14.2, 18.4, 23.2, 25.9, 29.7, 29.9, 32.4, 39.1, 42.5, 44.9, 55.2, 60.4, 68.6, 69.9, 70.8, 71.3, 72.5, 73.4, 75.8, 82.1, 82.6, 83.3, 102.0, 113.7, 128.1, 128.2, 128.4, 128.9, 129.2, 130.6, 132.0, 136.9, 137.4, 159.1, 211.0; *m/z* (FAB$^+$) 922 (87%), 920.5244 (15% M^+, $C_{52}H_{80}O_{10}Si_2$ requires 920.5290), 771 (6%), 651 (7%), 211 (100%).

Data for minor diastereoisomer $[\alpha]_D$=−11.1 (*c* 0.9, CH_2Cl_2); δ_H (250 MHz, $CDCl_3$) −0.08 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.55–0.71 (9H, m, 3×SiCH_2Me; CH*Me*), 0.75 (3H, d, J=7.0 Hz, CH*Me*), 0.82 (9H, s, Si^{t}Bu), 1.14 (9H, t, J=7.8 Hz, 3×SiCH_2*Me*), 1.14–1.82 {>7H, m, C*H*Me, CH(CH_2)$_3$}, 1.92–2.15 (1H, m, C*H*Me), 2.56 (1H, dd, J=16.0, 3.5 Hz, *H*CHC═O), 2.66 (1H, dd, J=15.6, 8.5 Hz, HC*H*C═O), 3.21–3.36 (1H, m, C43–H), 3.36–3.53 (4H, m, CH_2OPMB, C_{44}–H_2), 3.58 (1H, dd, J=10.4, 1.8 Hz, C_{39}–H), 3.68–3.83 (1H, m, C*H*OTBS), 3.80 (3H, s, PhO*Me*), 3.84–3.93 (1H, m, C*H*OH), 4.02 (1H, d, J=2.1 Hz, C*H*OBn), 4.05–4.19 (2H, m, C*H*OTES, C_{42}–H), 4.38 (1H, d, J=11.9 Hz, *H*CHPh), 4.43 (2H, s, CH_2PMP), 4.85 (1H, d, J=11.9 Hz, HC*H*Ph), 5.44 (1H, s, C*H*Ph), 6.79–7.55 (14H, m, ArH); *m/z* (FAB$^+$) 922 (100%), 921.5366 (41% MH^+, $C_{52}H_{81}O_{10}Si_2$ requires 921.5368), 257 (57%), 241 (65%).

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