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ARTICLE

Some limitations of an approach to the assembly of bryostatins by ring-closing metathesis

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Preliminary studies into the use of ring-closing metathesis (RCM) in a convergent approach for the total synthesis of bryostatins are described. An ester that would have provided an advanced intermediate for a synthesis of a 20-deoxybryostatin by a RCM was prepared from an unsaturated acid and alcohol corresponding to the C1-C16 and C17-C27 fragments. However, studies of the formation of the C16-C17 double-bond by RCM were not successful and complex mixtures of products were obtained. To provide a insight into factors that may be involved in hindering RCM in this system, a slightly simplified C1-C16 acid and modified C17-C25 alcohols were prepared and their use for the synthesis of analogues of bryostatins was investigated. Although only low yields were obtained, it appeared that macrolides analogous to the bryostatins can be prepared by RCM, using the Grubbs II catalyst, if the precursors lack the two methyl groups at C18. RCM was not observed, however, for substrates in which these methyl groups were present.

Introduction

As discussed in earlier papers,[1,2] approaches to the synthesis of the bryostatins, as exemplified by bryostatin 1 (**1**) and 10 (**2**), see Figure 1, are of interest because of their biological activities and relative inaccessibility from natural sources. Indeed several outstanding total syntheses have been reported[3] and synthetic analogues have been discovered that have potent biological effects,[4,5] some with tumour suppressing bryostatin-like activity. Overall this work has been a significant contribution to natural product synthesis and may lead to improved cancer chemotherapy.

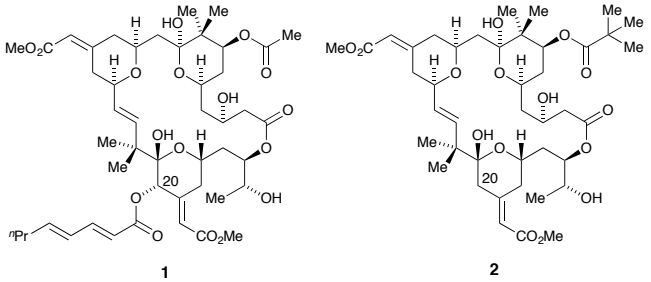

Figure 1 Representative bryostatins

We identified the 20-deoxybryostatins, e.g. bryostatin 10 (**2**),[6] as initial targets for our synthetic work in this area because they have received less attention from synthetic chemists than their C20-oxygenated counterparts such as bryostatin 1 (**1**). In planning our synthesis, it was recognised that the use of synthetic intermediates that corresponded to the C1-C16 and C17-C27 fragments could lead to convergent approaches, see Figure 2. Indeed, the early syntheses of bryostatins[3a-d] used Julia reactions to assemble the C16-C17 double bond from an aldehyde that corresponded to C1-C16 fragment and a sulfone that matched the C17-C27 component. However, in these syntheses several functional group interconversions had to be deferred until after the assembly steps because of the vigorous conditions required for conventional Julia reactions and this undermined the convergency of these syntheses.

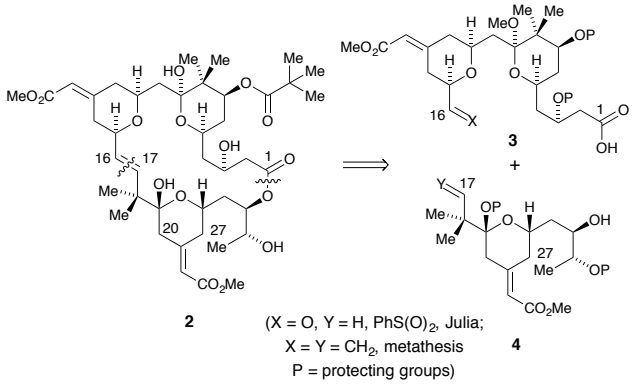

Figure 2 Disconnections of 20-deoxybryostatins

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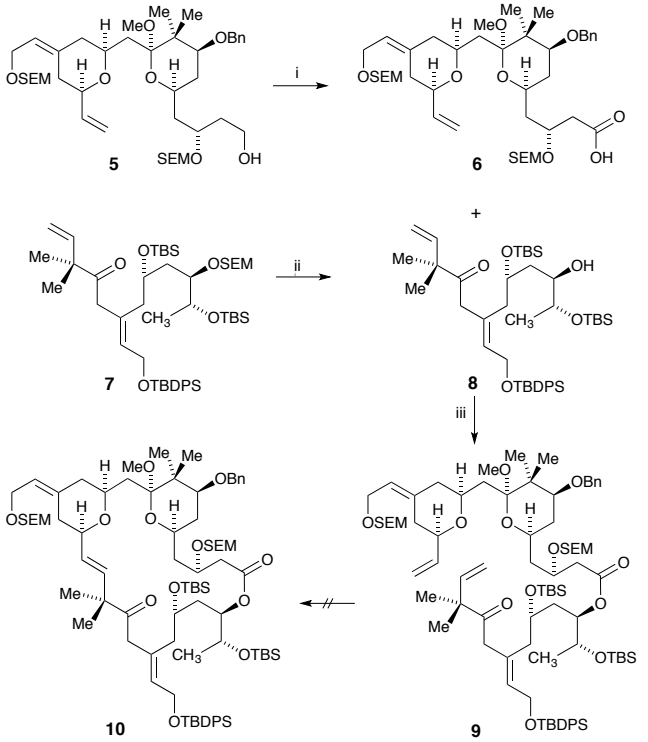
As an alternative, It was thought that a late-stage ring-closing metathesis (RCM)[7] could provide a better convergent approach for assembly of bryostatins by being compatible with more of the complex functionality present in these challenging natural products. We have reported full details of syntheses of C1-C16[1] and C17-C27[2] fragments that could be incorporated into both Julia and RCM-based syntheses, see Figure 2. We now describe full details of some preliminary studies into the use of RCM for the synthesis of bryostatins.[8]

Results and discussion

Unsuccessful attempts to prepare a fully functionalised precursor of a bryostatin by ring-closing metathesis

The alcohol **5**[1] was oxidised to the acid **6** that was esterified using the alcohol **8** prepared by selective deprotection of the SEM-ether **7**[2] to give ester **9** (Scheme 1). However, attempts to carry out a RCM of this ester to give the macrolide **10** using the Grubbs II catalyst were unsuccessful and gave mixtures of products that could not be properly characterised. It appeared that some isomerisation of the double bond attached to the tetrahydropyran had taken place along with partial loss of the methoxy acetal, and only traces of an (*E*)-disubstituted alkene were detected in the crude product mixtures (^{1}H NMR).



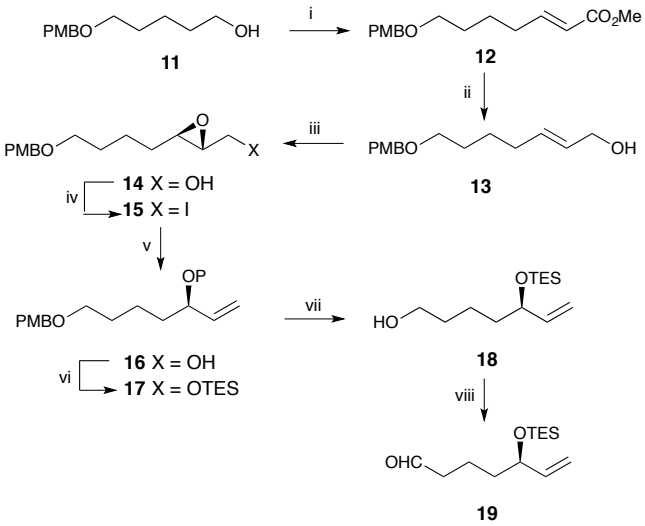
Scheme 1 Unsuccessful attempts at ring-closing metathesis Reagents and conditions i, (a) Dess-Martin periodinane, py., DCM, rt, 5 min; (b) $NaH_2PO_4.2H_2O$, 2-methylbut-2-ene, THF, $NaClO_2$, ^{t}BuOH, H_2O, rt, 5 min; ii, K_2CO_3, $MgBr_2.Et_2O$, ^{n}BuSH, ether, rt, 20 min (64%); iii, **6**, 2,4,6-$C_6H_2C(O)Cl$, tol., Et_3N, rt, 1 h, add **8**, DMAP (cat.), rt, 10 min (57% from **5**).

These results were very disappointing especially as the ester **9** was available in fewer than 25 linear steps from (*R*)-pantolactone. Several reasons were considered for the lack of success in this ring-closing metathesis. The ketone at C19 may have been coordinating to organometallic intermediates formed by metathesis of the proximal terminal double bond so inhibiting the catalytic cycle. Alternatively steric hindrance due to the two geminal methyl groups at C18 may have been a critical factor although there are examples of alkenes with geminal allylic methyl groups successfully engaging in ring-closing metathesis.[9]

It was decided not to study the ring-closing metathesis of ester **9** any further at this stage. Instead RCM of simpler analogues was investigated to see what could be learnt about the structural factors that might be involved in impeding RCM in this series.

Studies of ring-closing metathesis for the preparation of simplified analogues of bryostatins

The slightly simplified C1-C16 fragment **26** was synthesised as outlined in Schemes 2 and 3. Oxidation of the alcohol **11**[10] with an *in situ* Wittig reaction gave the (*E*)-alkene **12** that was reduced to the alcohol **13**. A Sharpless asymmetric oxidation using (–)-di-isopropyl tartrate gave the hydroxyepoxide **14** that was converted into the iodide **15**. Treatment of this with *tert*-butyllithium initiated iodide-lithium exchange and subsequent epoxide ring-opening[11] to give the allyl alcohol **16** that was shown to have an ee of >95% by comparison of the ^{1}H NMR spectra of its (*R*)- and (*S*)-*O*-acetylmandelates.[12] After *O*-silylation, selective removal of the *p*-methoxybenzyl ether gave the alcohol **18** that was oxidised using the Dess-Martin periodinane to the aldehyde **19** (Scheme 2).



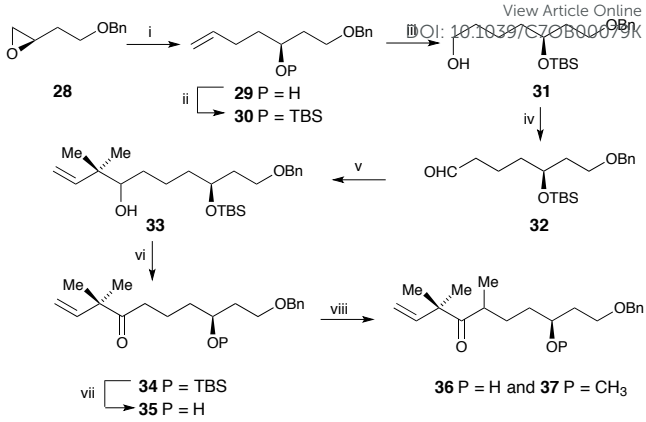
Scheme 2 Synthesis of aldehyde **19** Reagents and conditions i, DMSO, $(COCl)_2$, DCM, –78 °C, 20 min, **11**, –78 °C, 20 min, Et_3N, –78 °C to rt, 20 min, –78 °C, Ph_3PCHCO_2Me, DCM, rt, 14 h (*ca*. 99%); ii, DIBAL-H, hexanes, THF, –78 °C to rt, 4 h (98%); iii, (–)-DIPT, 4Å sieves, $Ti(O^iPr)_4$, 10 min, –20 °C, ^{t}BuOOH, decanes, 30 min, **13**, –20 °C, 4 h (*ca*. 99%); iv, Ph_3P, I_2, imid., THF, rt, 2 h (92%); v, ^{t}BuLi, hexanes, THF, –78 °C, 15 min (95%); vi, TESCl, imid., DCM, 0 °C to rt, 16 h (*ca*. 100%); vii, pH 7 buffer, DCM, DDQ, rt, 10 min (73%); viii, Dess-Martin periodinane, py., DCM, rt, *ca*. 2 h (94%).

The aldehyde **19** was condensed with the ketophosphonate **20**[1] to give the enone **21**. Deprotection using hydrogen fluoride-pyridine complex removed the triethylsilyl group selectively to give the alcohol **22** that on treatment with potasium *tert*-butoxide cyclised to the 2,6-*cis*-disubstituted tetrahydropyran **23** in an excellent yield. Alternatively, removal of both of the silyl protecting groups from the bis-silyl ether **21** followed by in situ treatment with base gave the primary alcohol **24** in a 62% yield based on the phosphonate **20**, see Scheme 3.

The silyl ether **23** was taken through to the methoxyacetal **25** using pyridinium toluene *p*-sulfonate and trimethyl orthoformate in methanol, and a protection-deprototection sequence gave the primary alcohol **27** *via* the SEM-ether **26**. In this synthesis, the yields in the steps between the phosphonate **20** and the C1-C17 alcohol **27** were significantly better than those in the synthesis of the fully functionalised C1-C16 fragment **5** and the alcohol **27** was available in a >30% overall yield from alcohol **11**, see Scheme 3.

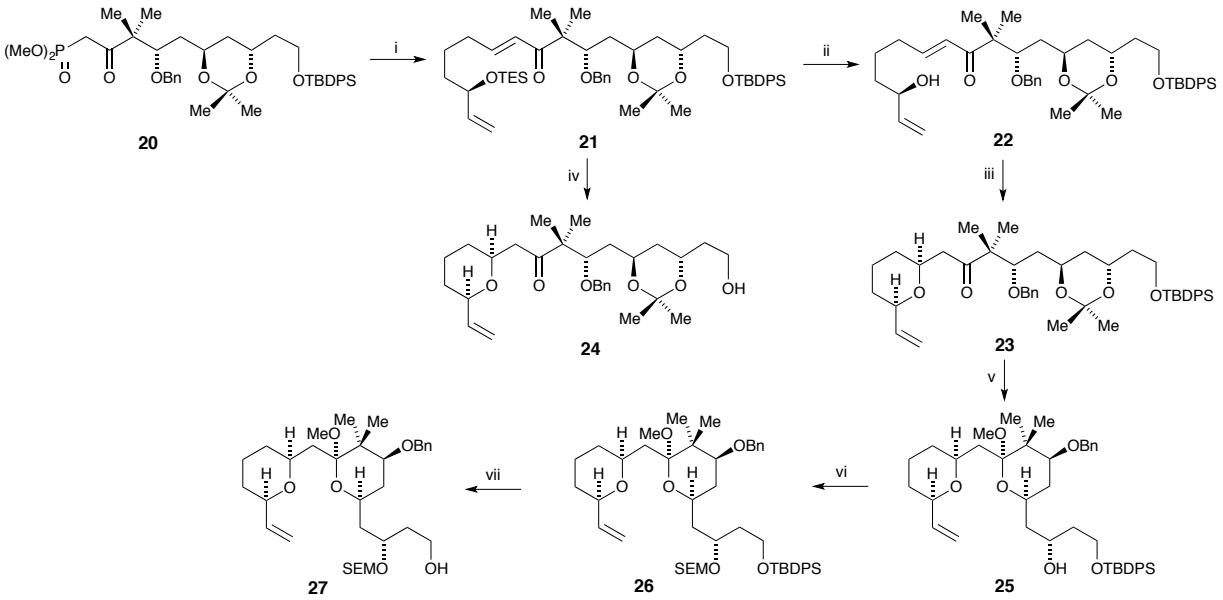
Products corresponding to simplified C17-C27 fragments of bryostatins were now prepared, one with and one without two geminal allylic methyl groups.

Reaction of the epoxide **28**[13] with allylmagnesium bromide, catalysed by copper(I) iodide, gave the alcohol **29** that was protected as its *tert*-butyldimethylsilyl ether **30**, see Scheme 4. Hydroboration-oxidation gave the alcohol **31** that was oxidised to the aldehyde **32**. Addition of the organozinc reagent prepared from dimethylallyl bromide then gave a mixture of the epimers of the alcohol **33** that was oxidised to the ketone **34**. Desilylation gave the hydroxyketone **35** with traces of its cyclic hemiacetal. Treatment of this hydroxyketone with base and methyl iodide led to methylation of the corresponding enolate to give ketone **36**, essentially as a single diastereoisomer, although the configuration at C5 was not established, together with some of the corresponding methyl ether **37**, see Scheme 4.



Scheme 4 Synthesis of hydroxyketone **35** Reagents and conditions i, CuI, CH_2=$CHCH_2Br$, THF, –40 °C to –30 °C, 20 min, **28**, THF, –40 °C, 1 h (83%); ii, TBSCl, imid., DCM, 0 °C to rt, 22 h (93%); iii, BH_3.THF, THF, –25 °C to rt, 16 h, NaOH, 30% H_2O_2 (86%); iv, DMSO, $(COCl)_2$, –78 °C, 10 min, **31**, –78 °C, 20 min, Et_3N, –78 °C to rt 30 min; v, 1-bromo-3-methylbut-2-ene, Zn, THF, rt, 10 min, **32**, rt, 15 h (67% from **31**); vi, DMSO, $(COCl)_2$, DCM, –78 °C, 10 min, **33**, DCM, –78 °C, 20 min, Et_3N, –78 °C to rt, 30 min; vii, TBAF, THF, rt, 16 h (85% from **33**); viii, NaH, DMF, 0 °C, 30 min, MeI, 30 min (**36**, 39%; **37**, 18%).

Cyclisation of the hydroxyketone **35** under acidic conditions gave the enol ether **38** and oxidation in methanol using *m*-chloroperoxybenzoic acid gave the hydroxyacetal **39** together with *ca*. 25% of a side product that may have been an isomer, but which was not purified. However, oxidation of the mixture gave the tetrahydropyranone **40** and this on reduction using lithium triethylborohydride gave the alcohol **39** essentially as a single diastereoisomer. This was converted into its methyl ether **41** and debenzylation gave the primary alcohol **42**, see Scheme 5.



Scheme 3 Synthesis of a simplified C1-C16 fragment Reagents and condtions i, $Ba(OH)_2$, THF, rt, 30 min, **19**, wet THF, 18 h; ii, HF.py., THF, py., rt, 15 min (87% from **20**); iii, KO^{t}Bu, THF, rt, 40 min (81%); iv, (a) TBAF, THF, rt, 16 h; (b) KO^{t}Bu, THF, 40 min (**24**, 62% from **20** via **21**); v, $HC(OMe)_3$, PPTS, MeOH, rt, 17 h (86%); vi, SEMCl, $^i Pr_2NEt$, DCM, 0 °C to rt, DMAP (86%); vii, TBAF, THF, rt, 14 h (93%).

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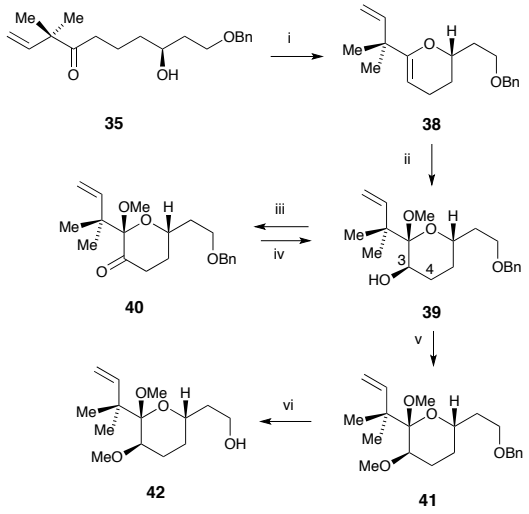
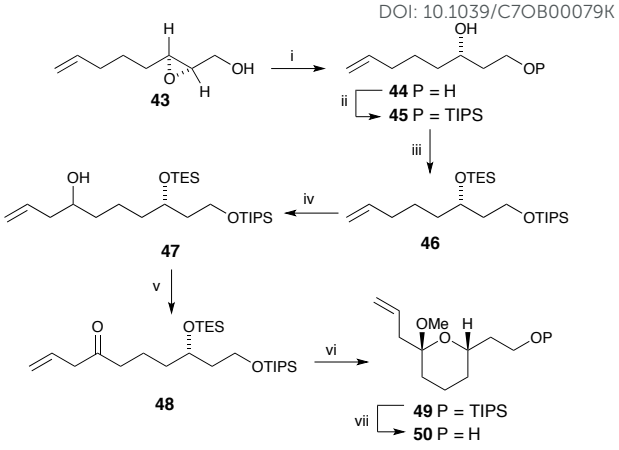


Scheme 5 Synthesis of the C17-C25 fragment **42** Reagents and conditions: i, TsOH, benzene, 50 °C, 3 h, 4Å sieves, CSA, rt, 16 h (*ca*. 100%); ii, *m*CPBA, MeOH, 4Å sieves, rt, 1 h (89%); iii, Dess-Martin periodinane, py., DCM, 0 °C to rt, 4 h (86% from **38**); iv, (a) $LiBHEt_3$, THF, –10 °C to rt, 15 h (b) NaH, MeI, ether, –10 °C to rt, 15 h (76% from **40**); v, Na, liq. NH_3, EtOH, –78 °C, 2 h (97%).



Scheme 6 Synthesis of the methoxy acetal **50** Reagents and conditions: i, Red-Al, tol., THF, 0 °C, 4 h (94%); ii, TIPSCl, imid., DCM, 0 °C to rt, 16 h (99%); iii, TESCl, imid., DCM, rt, 1 h (99%); iv, (a) ozone, DCM, –78 °C, *ca*. 45 min, Me_2S, rt (b) CH_2=$CHCH_2Br$, THF, rt, 16 h (67% from **46**); v, Dess-Martin periodinane, py., DCM, rt, 50 min (76%); vi, $HC(OMe)_3$, PPTS, MeOH, rt, 17 h (64%); vii, TBAF, THF, rt, 16 h (*ca*. 100%).

The structures shown were assigned to the products in Schemes 4 and 5 on the basis of spectroscopic data. In particular, for the alcohol **39**, H-3 was shown to be axial since it had coupling constants of 11.4 Hz and 4.7 Hz with the axial and equatorial protons at H-4. Similar coupling constants were found for the methyl ethers **41** and **42**. The alkyl substituents at C-2 and C-6 in the alcohol **39** were equatorial with the methoxy group at C-2 in the anomerically preferred axial position. The configuration at C-3 shown for alcohol **39** was also consistent with the reduction of ketone **40** from the less hindered direction.

The acetal **50** was prepared to evaluate RCM with a substrate that lacked the two geminal allylic methyl groups, see Scheme 6.

Epoxide **43**[14] was prepared from the corresponding diene using a Sharpless asymmetric epoxidation with (+)-diethyl tartrate. Reduction with sodium bis-(2-methoxyethoxy)aluminium hydride[15] gave the diol **44** that was protected as its tri-isopropylsilyl ether **45**. This was converted into its triethylsilyl ether **46** that was taken through to the alcohol **47** as a mixture of epimers by ozonolysis and reaction of the ensuing aldehyde with allylmagnesium bromide. Oxidation gave the ketone **48** that was converted into the methoxy acetal **49** in one step using pyridinium toluene *p*-sulfonate and triethyl orthoformate in methanol. The acetal was isolated essentially as a single anomer that was assigned the configuration shown at C-2 on the basis of the anomeric effect. Finally, desilylation gave the alcohol **50** ready for studies of ring closing metathesis, see Scheme 6.

The C1-C16 alcohol **27** was oxidised to the acid **51** via the corresponding aldehyde and the acid was esterified with the C17-C25 alcohols **50** and **42** to give the esters **52** and **54**. Using the Grubbs II catalyst, a modest, 17%, yield of the (*E*)-alkene **53** was obtained from the ester **52** but no cyclised product was isolated under similar reaction conditions from the reaction with ester **54**, see Scheme 7. The metathesis product **53** was identified from its spectroscopic data with the newly formed (*E*)-double-bond being clearly evident in its ^{1}H NMR spectrum (16-H, δ 5.68, 1 H, dd, *J* 15.3, 7.5; 17-H, δ 6.07, 1 H, ddd, *J* 15.3, 8.0, 5.4). Although the yield of this RCM product was only modest, the reaction was not optimised. Apart from the product **53**, complex mixtures of other products were isolated that were not characterised. For the ester **54**, only very minor traces of a product with an (*E*)-double-bond were detected in the crude product mixtures from attempted RCM. The formation of dimeric products and the loss of the double bond next to the tetrahydropyran were significant as indicated by MS and ^{1}H NMR, see experimental.

Summary and conclusions

The paper reports only a few preliminary results on the use of RCM for the synthesis of bryostatins. However, the results obtained are consistent with the geminal methyl groups at C18 providing additional hindrance that helps to prevent effective RCM for the esters **9** and **54**. In contrast, under the same reaction conditions using the Grubbs II catalyst, the ester **52** that lacked these methyl substituents, gave some of the metathesis product **53**, albeit in only a very modest, albeit unoptimised, yield. In a parallel study, Trost and his collaborators found, during a study of the synthesis of bryostatin 1 using a relay RCM to form the C16-C17 double-bond, that a ring-expanded bryostatin was formed but this did not undergo the relay metathesis reaction to give a macrolide corresponding to the naturally occurring bryostatins.[16]

Clearly the low yield obtained for the cyclisation of ester **52** mitigates against firm conclusions being drawn from our work since further studies using a wider range of catalysts and reaction conditions are really required for the scope of this approach to be

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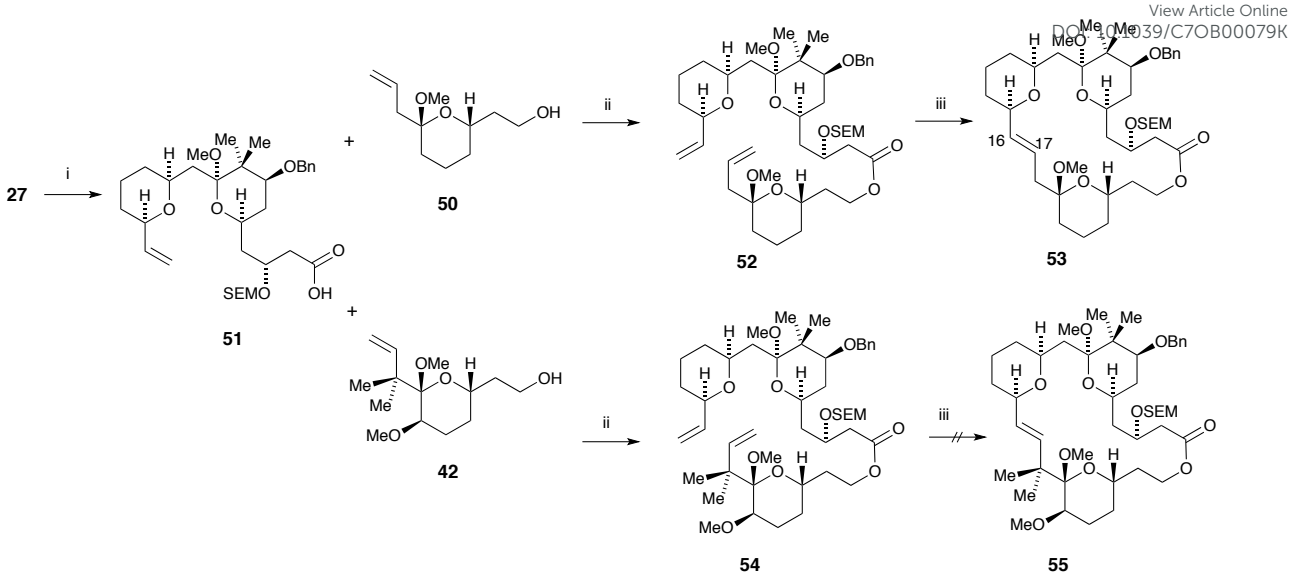

Scheme 7 Synthesis of analogues of bryostatins using RCM Reagents and conditions i, (a) Dess-Martin periodinane, py., DCM, rt, 15 min; (b) $NaH_2PO_4.2H_2O$, 2-methylbut-2-ene, ^{t}BuOH, water, THF, $NaClO_2$, 0 °C, 5 min; ii, 2,4,6-$Cl_3C_6H_2C(O)Cl$, tol., Et_3N, rt, 1 h, **50** or **42**, tol., DMAP, rt, 30 min (**52**, 47% from **27**); iii, Grubbs II cat., tol., 60 °C, ca. 12 h (**53**, 17%).

properly delineated. Of interest in this context, is the recent isolation of naturally occurring bryostatins in which there is only one methyl group at C18.[17] Whether these natural products could be synthesised by RCM is a tantalising prospect. However, at this point, we chose not to continue with investigations of RCM reactions for the synthesis of naturally occuring bryostatins. Instead we decided to study the synthesis of 20-deoxybryostatins using the C1-C16 and C17-C27 fragments we already had available, but using the modified Julia reaction to assemble the 16,17-double-bond. This work eventually led to a successful synthesis of a 20-deoxybryostatin.[18,19]

Experimental

General experimental details

Flash column chromatography was performed using Merck silica gel (60H; 40-60μ, 230-240 mesh). Light petroleum refers to the fraction boiling between 40 and 60 °C and was redistilled before use. Tetrahydrofuran was dried over sodium-benzophenone and was distilled under nitrogen prior to use. Dichloromethane was dried over CaH_2 and was distilled before use. Ether refers to diethyl ether. Reactions under non-aqueous conditions were carried out under an atmosphere of nitrogen or argon.

Mass spectra used electron impact ionisation (EI^+), chemical ionisation using ammonia (Cl^+), electrospray ionisation in the positive mode (ES^+) and atmospheric pressure chemical ionisation in the positive or negative mode ($APCI^+$ or $APCI^-$). Low and high resolution mass spectra were recorded using a Micromass Trio 200 and a Kratos Concept IS spectrometer, respectively. Infra-red spectra were measured using a Genesis FTIR spectrometer on NaBr plates, either neat or as evaporated films. Nuclear magnetic resonance spectra were recorded using a Varian Unity 300 (300 Mz) spectrometer. Spectra were recorded at 300 Mz (^{1}H) and at 75 Mz (^{13}C) and were in in deuteriated chloroform unless otherwise indicated. Coupling constants (*J*) are given in Hertz (Hz) and chemical shifts are relative to tetramethylsilane. Residual non-deuteriated solvent was used as the internal standard.

Epoxide **43** was prepared from oct-2,7-dien-1-ol as desecribed for its enantiomer[14] but using L-(+)-diethyl tartrate, and had $[\alpha]_D^{20}$ –28.7 (*c* 3.1, $CHCl_3$), [lit.[14] for the enantiomer, $[\alpha]_D^{23}$ +38.6 (*c* 1.8, $CHCl_3$)].

(8*S*,10*R*,11*R*)-8,11-Bis-(*tert*-butyldimethylsilyloxy)-6-[(*E*)-(2-*tert*-butyldiphenylsilyloxyethylidene]-3,3-dimethyl-10-hydroxydodec-1-en-4-one (8). Solid potassium carbonate (278 mg, 2.01 mmol), magnesium bromide diethyl etherate (437 mg, 1.69 mmol) and *n*-butanethiol (0.18 mL, 1.68 mmol) were added to the SEM-ether **7** (181 mg, 0.20 mmol) in ether (4 mL) and the mixture stirred for 30 min then poured into water (100 mL) and ether (100 mL). The aqueous layer was extracted with ether (3 × 50 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (10:1 light petroleum:ether with 1% triethylamine) of the residue gave the title compound **8** as a colourless oil (99 mg, 64%), R_f = 0.5 (1:10 ether:light petroleum), $[\alpha]_D^{20}$ +3.0 (*c* 7.8, $CHCl_3$) (Found: M^+ + Na, 789.4728. $C_{44}H_{74}O_5Si_3Na$ requires M, 789.4736); ν_{max}/cm^{-1} 3570, 3071, 3051, 2954, 2931, 2892, 2857, 1713, 1635, 1471, 1428, 1256, 1110, 1069, 1006, 836, and 777; δ_H 0.02, 0.05, 0.06 and 0.08 (each 3 H, s, $SiCH_3$), 0.87, 0.90 and 1.07 [each 9 H, s, $SiC(CH_3)_3$], 1.11 (3 H, d, *J* 6.2, 12-H_3), 1.18 (1 H, m, 9-H), 1.27 (6 H, s, 2 × 3-CH_3), 1.42 (1 H, m, 9-H′), 2.15 (1 H, dd, *J* 13.5, 8.3, 7-H), 2.20 (1 H, dd, *J* 13.5, 5.9, 7-H′), 2.41 (1 H, d, *J* 5.0, OH), 3.18 and 3.28 (each 1 H, d, *J* 16.4, 5-H), 3.40-3.60 (2 H, m, 8-H, 10-H), 3.95 (1 H, m, 11-H), 4.27 (2 H, d, *J* 6.3, 2′-H_2), 5.17-5.25 (2 H, m, 1-H_2), 5.47 (1 H, t, *J* 6.2, 1′-H), 5.96 (1 H, dd, *J* 17.6, 10.5, 2-H), 7.35-7.50 (6 H, m, ArH) and 7.60-7.75 (4 H, m, ArH); δ_C –4.6(2), –4.0, –3.9, 18.2(2), 19.4, 20.2, 23.9, 26.1, 26.2, 27.1, 39.6, 40.4,

46.0, 51.4, 61.1, 68.7, 72.2, 114.8, 127.9, 129.9, 131.6, 132.2, 134.0, 134.1, 135.8, 135.9, 142.7 and 210.7; *m/z* (ES^+) 790 (100%).

(8*S*,10*R*,11*R*)-8,11-Bis-(*tert*-butyldimethylsilyloxy)-6-[(*E*)-(2-*tert*-butyldiphenylsilyloxyethylidene]-3,3-dimethyl-4-oxododec-1-en-10-yl (3*R*,5*R*,7*S*,9*S*,11*S*,15*R*)-7-Benzyloxy-13-[(*Z*)-2-(2-trimethylsilylethoxymethoxy)ethylidene]-5,9-epoxy-11,15-epoxy-8,8-dimethyl-9-methoxy-3-(2-trimethylsilylethoxymethoxy)heptadec-16-enoate (9). Pyridine (28 mL, 7.5 eq.) and then, afer 5 min, the alcohol **5** (33 mg, 0.043 mmol) in DCM (2 mL) were added to a suspension of the Dess-Martin periodinane (29 mg, 1.5 eq.) in DCM (1 mL). After 5 min, saturated aqueous sodium bicarbonate (10 mL) and Et_2O (10 mL) were added and the aqueous phase extracted with Et_2O (3 × 10 mL). The organic extracts were washed with saturated aqueous sodium thiosulfate (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford the aldehyde that was used in the next step.

Solid $NaH_2PO_4.2H_2O$ (67 mg, 10 eq.) and 2-methylbut-2-ene in THF (2 M in THF, 0.43 mL, 20 eq.) were added to this aldehyde in a mixture of *t*-BuOH:water (2:1, 0.5 mL). The mixture was cooled to 0 °C and $NaClO_2$ (24.5 mg) in *t*-BuOH:water (2:1, 0.5 mL) was added. After stirring for 5 min, saturated sodium hydrogen carbonate in brine (1:1, 2 mL) and ethyl acetate (5 mL) were added. The aqueous phase was extracted with EtOAc (4 × 2 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the acid **6** that was used as soon as possible in the next step; δ_H (C_6D_6) 1.02 and 1.05 [each 9 H, s, $SiCH_3)_3$], 0.80-1.10 (4 H, m, 2 × $SiCH_2$), 1.28 and 1.32 (each 3 H, s, 8-CH_3), 1.55-1.95 (6 H, m, 4-H_2, 6-H_2, 10-H, 12-H), 2.04 (1 H, br. t, *J* 11.0, 14-H_{ax}), 2.25-2.45 (2 H, m, 10-H′, 12-H′), 2.63 (1 H, br. d, *J* 11.0, 14-H_{eq}), 2.68 and 2.88 (each 1 H, dd, *J* 16.0, 5.0, 2-H), 3.17 (3 H, s, OCH_3), 3.50-3.95 (8 H, m, 3-H, 5-H, 7-H, 11-H, 2 × C*H*$_2$$CH_2$Si), 4.51 (1 H, dd, *J* 11.9, 7.0, 2′-H), 4.27 (1 H, m, 2′-H′), 4.28 (1 H, d, *J* 11.8, Ph*H*CH), 4.42 (1 H, m, 15-H), 4.47 (1 H, d, *J* 11.8, PhHC*H*), 4.70, 4.77, 4.79 and 4.80 (each 1 H, d, *J* 6.9, O*H*CHO), 5.07 (1 H, dt, *J* 10.5, 1.5, 17-H), 5.42 (1 H, dt, *J* 17.3, 1.6, 17-H′), 5.67 (1 H, br. t, *J* 6.4, 1′-H), 5.94 (1 H, ddd, *J* 17.3, 10.4, 5.4, 16-H), 7.05-7.25 (3 H, m, ArH) and 7.33 (2 H, d, *J* 7.0, ArH).

Triethylamine (12 μL) and 2,4,6-trichlorobenzoyl chloride (8 μL) were added to the acid **6** (from 33 mg, 0.043 mmol of the alcohol **5**) in toluene (1 mL) and the reaction mixture was stirred at rt for 1 h. The alcohol **8** (33 mg) in toluene (1.4 mL) and 4-dimethylaminopyridiine (8 mg) were added and the mixture was stirred for a further 10 min. Saturated aqueous sodium hydrogen carbonate (10 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with ether (3 × 10 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (15:1 light petroleum:ether with 1% Et_3N) of the residue gave the title compound **9** (38 mg, 57 %); δ_H (C_6D_6) 0.02 and 0.05 [each 9 H, s, $Si(CH_3)_3$], 0.14, 0.17, 0.20 and 0.25 (each 3 H, s, $SiCH_3$), 1.00 and 1.03 [each 9 H, s, $SiC(CH_3)_3$], 0.98-1.06 (4 H, m, 2 × $SiCH_2$), 1.22 [9 H, s, $SiC(CH_3)_3$], 1.00-1.15 (9 H, m, 2 × 8-CH_3, 12′-H_3), 1.26 and 1.34 (each 3 H, s, 3′-CH_3), 1.75-2.95 (18 H, m, 2-H_2, 4-H_2, 6-H_2, 10-H_2, 12-H_2, 14-H_2, 5′-H_2, 7′-H_2, 9′-H_2), 3.34 (3 H, s, OCH_3), 3.7-4.08 (9 H, m, 3-H, 5-H, 7-H, 11-H, 8′-H, 2 × O*C*$H_2$$CH_2$Si), 4.14-4.26 (3 H, m, 11′-H, 2′′-H_2), 4.32 (1 H, d, *J* 11.2, Ph*H*CH), 4.40-4.60 (4 H, m, 15-H, 2′′′-H_2, PhHC*H*), 4.70, 4.73, 4.82 and 4.86 (each 1 H, d, *J* 6.5, O*H*CHO), 5.02-5.12 (3 H, m, 17-H, 1′-H_2), 5.24 (1 H, m, 10′-H), 5.39 (1 H, dt, *J* 17.0, 1.5, 17-H′), 5.63 and 5.72 (each 1 H, br. t, *J* 6.5, 1′′-H, 1′′′-H), 5.88 (1 H, dd, *J* 17.6, 10.5, 2′-H), 5.93 (1 H, ddd, *J* 17.3, 10.4, 5.4, 16-H), 7.1-7.40 (11 H, m, ArH) and 7.80-7.90 (4 H, m, ArH); δ_C (C_6D_6) –4.6, –4.5, –3.8, –1.3, 15.5, 18.2, 18.3, 19.4, 23.7, 26.1, 26.3, 27.0, 43.5, 48.5, 51.4, 62.6, 65.1, 65.6, 65.8, 71.6, 75.3, 78.2, 79.1, 93.9, 104.5, 114.3, 120.5, 127.5, 128.4(2), 129.9, 130.0, 132.6, 135.9, 139.4 and 170.7; *m/z* (ES^+) 1550 (M^+ + 23, 100%).

Methyl (*E*)-7-(4-methoxybenzyloxy)hept-2-enoate (12). Dimethyl sulfoxide (7.1 mL, 100 mmol) was added dropwise to oxalyl chloride (7 mL, 80 mmol) at –78 °C in DCM (150 mL). The mixture was stirred for 20 min at –78 °C and the alcohol **11** (12 g, 53 mmol) in DCM (50 mL) was added dropwise. After stirring for 20 minutes, triethylamine (42.8 mL, 320 mmol) was added and stirring was continued at –78 °C for 20 min. The mixture was allowed to warm to 0 °C and stirred for 20 min then cooled to –78 °C and methyl (triphenylphosphoranylidene)acetate (1.5 g, 4.5 mmol) in DCM (75 mL) was added. The solution was allowed to warm to rt and stirred for 16 h. Saturated aqueous ammonium chloride (100 mL) was added and the organic layer diluted with ether (200 mL). The organic phase was washed with water (150 mL) and brine (150 mL). A conventional work-up gave the title compound **12**, a colourless oil (14.9 g, 99%) with just traces of its (*Z*)-isomer (Found: $M^+ + NH_4$, 296.1855. $C_{16}H_{26}O_4N$ requires M, 296.1856); ν_{max}/cm^{-1} 2999, 2940, 2860, 1722, 1655, 1613, 1586, 1513, 1459, 1438, 1302, 1202, 1172, 1099, 1036, 983 and 821; δ_H 1.50-1.70 (4 H, m, 5-H_2, 6-H_2), 2.21 (2 H, q, *J* 6.4, 4-H_2), 3.67 (2 H, t, *J* 6.4, 7-H_2), 3.77 and 3.82 (each 3 H, s, OCH_3), 4.47 (2 H, s, $ArCH_2$), 5.82 (1 H, dt, *J* 15.2, 1.5, 2-H), 6.99 (1 H, dt, *J* 15.8, 7.5, 3-H) and 6.90 and 7.29 (each 2 H, d *J* 8.8, ArH); δ_C 25.0, 29.5, 32.2, 51.6, 55.5, 69.8, 72.8, 114.0, 121.3, 129.5, 130.9, 149.6, 159.4, 167.4; *m/z* (Cl^+) 296 (M^+ + 18, 100%).

(*E*)-7-(4-Methoxybenzyloxy)hept-2-en-1-ol (13). Di-isobutylaluminium hydride (1 M in hexanes, 200 mL, 200 mmol) was added to the ester **12** (22.3 g, 80 mmol) in THF (100 mL) at –78 °C and the solution stirred at rt for 4 h. After cooling to –78 °C, methanol (60 mL) was added over 30 min before warming to rt and pouring into a vigorously stirred mixture of saturated aqueous sodium potassium tartrate (350 mL) and ether (700 mL) at 0 °C. The mixture was stirred for 30 min and then the aqueous layer was extracted with ether (3 × 300 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (1 : 8 ethyl acetate:hexane then 1:1 ether:light petroleum) afforded the title compound **13** as a colourless oil (18.5 g, 98%) (Found: M^+, 250.1570. $C_{15}H_{22}O_3$ requires M, 250.1563); ν_{max}/cm^{-1} 3401, 3000, 2935, 2858, 1670, 1613, 1586, 1514, 1463, 1363, 1302, 1245, 1174, 1097, 1035, 972 and 821; δ_H 1.40-1.70 (4 H, m, 5-H_2, 6-H_2), 2.05-2.209 (2 H, m, 4-H_2), 2.40 (1 H, s, OH), 3.44 (2 H, t, *J* 6.4, 7-H_2), 3.80 (3 H, s, OCH_3), 4.07 (2 H, d, *J* 6.5, 1-H_2), 4.42 (2 H, s, $ArCH_2$), 5.60-5.80 (2 H, m, 2-H, 3-H) and 6.90 and 7.29 (each 2 H, d, *J* 8.8, ArH); δ_C 26.0, 29.5, 32.2, 55.5, 64.0, 70.2, 72.8, 114.0, 128.5, 129.5, 131.0, 133.2 and 159.4; *m/z* (Cl^+) 268 (M^+ + 18, 100%), 251 (M^+ + 1, 10), 138 (70) and 121 (70).

(2*R*,3*R*)-7-(4-Methoxybenzyloxy)-2,3-epoxyheptan-1-ol (14). (–)-Di-isopropyl tartrate (0.32 mL, 2.1 mmol) and $Ti(O^iPr)_4$ (0.29 mL, 2 mmol) were added to a suspension of 4Å molecular sieves (1 g) and the mixture stirred for 10 min at rt then cooled to –20 °C. *tert*-Butyl hydroperoxide (5 M in decanes, 6 mL, 30 mmol) was added and the suspension stirred for 0.5 h before the alcohol **13** (5 g, 20 mmol) was added. After stirring at –20 °C for 4 h, brine containing sodium

hydroxide (3 M) was added and solution allowed to warm to rt then extracted with ether (3 × 100 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound **14** as a colourless oil (5.3 g, 99%) (Found: $M^+ + NH_4$, 284.1859. $C_{15}H_{26}O_4N$ requires M, 284.1856); δ_H 1.50-1.75 (6 H, m, 4-H_2, 5-H_2, 6-H_2), 1.95 (1 H, br. s, OH), 2.95-3.00 (2 H, m, 2-H, 3-H), 3.48 (2 H, t, *J* 6.3, 7-H_2), 3.63 (1 H, dd, *J* 12.5, 4.4, 1-H), 3.83 (3 H, s, OCH_3), 3.91 (1 H, dd, *J* 12.6, 2.6, 1-H′), 4.45 (2 H, s, $ArCH_2$) and 6.90 and 7.29 (each 2 H, d, *J* 8.8, Ar-H); δ_C 23.0, 26.1, 29.7, 31.6, 55.5, 56.2, 58.8, 62.0, 70.0, 72.9, 114.0, 129.5, 130.8 and 159.4; *m/z* (Cl^+) 284 (M^+ + 18, 100%).

(2*R*,3*R*)-7-(4-Methoxybenzyloxy)-2,3-epoxy-1-iodoheptane (15). Imidazole (0.33 g, 4.80 mmol), triphenylphosphine (0.75 g, 2.80 mmol) and iodine (0.70 g, 2.80 mmol) were added to the alcohol **14** (0.50 g, 2.40 mmol) in THF (7.5 mL) at rt. The solution was stirred at rt for 2 h, saturated aqueous sodium thiosulfate (10 mL) was added and the stirring was continued until the reaction mixture became clear. Ether was added and the aqueous layer was extracted with ether (3 × 10 mL). The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (15:1 light petroleum:ether) of the residue gave the title compound **15** as a colourless oil (0.69 g, 92%), $[\alpha]_D^{20}$ +25 (*c*, 1.2, $CHCl_3$) (Found: M^+ + Na, 399.0430. $C_{15}H_{21}O_3INa$ requires M, 399.0428); δ_H 1.40-1.80 (6 H, m, 4-H_2, 5-H_2, 6-H_2), 2.83 (1 H, m, 3-H), 3.04 (2 H, m, 1-H_2), 3.23 (1 H, m, 2-H), 3.48 (2 H, t, *J* 6.3, 7-H_2), 3.83 (3 H, s, OCH_3), 4.46 (2 H, s, $ArCH_2$) and 6.90 and 7.29 (each 2 H, d, *J* 7.8, ArH); δ_C 5.3, 22.9, 29.7, 31.8, 55.6, 58.5, 62.8, 69.9, 72.8, 114.0, 129.5, 130.9 and 159.4; *m/z* (ES^+) 399 (M^+ + 23, 100%).

(*R*)-7-(4-Methoxybenzyloxy)hept-1-en-3-ol (16). *tert*-Butyllithium (1.7 M in hexanes, 0.89 mL) was added to the iodide **15** (260 mg, 0.69 mmol) in THF (5 mL) at –78 °C and the solution stirred for 15 mins at –78 °C. Saturated aqueous ammonium chloride was added and the mixture extracted with ether (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (4:1 ether:light petroleum) of the residue gave the title compound **16** as a colourless oil (164 mg, 95%), $[\alpha]_D^{20}$ 32.6 (*c* 5.7, $CHCl_3$) (Found: M^+ + H, 251.1638. $C_{15}H_{23}O_3$ requires M, 251.1642); ν_{max}/cm^{-1} 3392, 2934, 2859, 1686, 1613, 1586, 1514, 1463, 1363, 1302, 1245, 1174, 1097, 1035, 972 and 821; δ_H 1.20-1.80 (6 H, m, 4-H_2, 5-H_2, 6-H_2), 3.48 (2 H, t, *J* 6.5, 7-H_2), 3.84 (3 H, s, OCH_3), 4.13 (1 H, q, *J* 6.4, 3-H), 4.46 (2 H, s, $ArCH_2$), 5.14 (1 H, dt, *J* 10.4, 1.3, 1-H), 5.25 (1 H, dt, *J* 17.1, 1.3, 1-H′), 5.89 (1 H, ddd, *J* 17.1, 10.4, 6.2, 2-H) and 6.90 and 7.29 (each 2 H, d, *J* 7.8, ArH); δ_C 22.3, 29.8, 37.0, 55.5, 70.1, 72.8, 73.3, 114.0, 114.8, 129.5, 130.9, 141.4 and 159.3; *m/z* (Cl^+) 268 (M^+ + 18, 100%), 251 (M^+ + 1, 50), 138 (60) and 121 (90).

(*R*)-*O*-Acetylmandelic acid (34 mg) and 4-dimethylaminopyridine (cat.) were added to the alcohol **16** (59 mg, 0.086 mmol) in THF (0.6 mL) and the solution cooled to 0 °C. Dicyclohexyl carbodi-imide (45 mg) in THF (0.5 mL) was added and the mixture stirred at rt for 16 h. After dilution with ether (15 mL), filtration and concentration under reduced pressure followed by chromatography (1:2 ether:light petroleum) of the residue afforded the (*R*)-*O*-acetyl mandelate of the alcohol **16** as a colourless oil (65 mg, 88%), R_f = 0.50 (1:1 ether:light petroleum) (Found: M^+, 426.2042. $C_{25}H_{30}O_6$ requires M, 426.2037); δ_H 1.10-1.90 (6 H, m, 4-H_2, 5-H_2, 6-H_2), 2.21 (3 H, s, CH_3CO_2), 3.45 (2 H, t, *J* 6.6, 7-H_2), 3.82 (3 H, s, OCH_3), 4.45 (2 H, s, $ArCH_2$), 4.93 (1 H, dt, *J* 17.1, 1.3, 1-H), 5.02 (1 H, dt, *J* 10.7, 1.2, 1-H′), 5.29 (1 H, q, *J* 5.4, 3-H), 5.62 (1 H, ddd, *J* 17.0, 10.6, 5.1, 2-H), 5.95 (1 H, s, 2′-H), 6.90 and 7.28 (each 2 H, d, *J* 7.8, ArH), 7.40 (3 H, m, ArH) and 7.49 (2 H, m, ArH); *m/z* (Cl^+) 444 (M^+ + 18, 10 %), 341 (50) and 121 (100).

Following the same procedure, (*S*)-*O*-acetylmandelic acid (34 mg), the alcohol **16** (59 mg, 0.086 mmol) and dicyclohexylcarbodi-imide 45 mg), after chromatography (1:2, ether:light petroleum), gave (*S*)-*O*-acetylmandelate of the alcohol **16** as a colourless oil (65 mg, 88%), R_f = 0.50 (1:1, ether:light petroleum) (Found: M^+, 426.2041. $C_{25}H_{30}O_6$ requires M, 426.2037); δ_H 1.10-1.90 (6 H, m, 4-H_2, 5-H_2, 6-H_2), 2.22 (3 H, s, CH_3CO_2), 3.27 (2 H, t, *J* 6.6, 7-H_2), 3.80 (3 H, s, OCH_3), 4.39 (2 H, s, $ArCH_2$), 5.20-5.35 (3 H, m, 1-H_2, 3-H), 5.79 (1 H, ddd, *J* 17.1, 10.5, 6.2, 2-H), 5.94 (1 H, s, 2′-H), 6.90 and 7.25 (each 2 H, d, *J* 7.8, ArH), 7.38 (3 H, m, ArH) and 7.49 (2 H, m, ArH); *m/z* (Cl^+) 444 (M^+ + 18, 10 %), 341 (30) and 121 (100).

(*R*)-7-(4-Methoxybenzyloxy)-3-triethylsilyloxyhept-1-ene (17). The alcohol **16** (1.4 g, 5.6 mmol) in DCM (10 mL) was added to triethylsilyl chloride (1 mL, 5.6 mmol) and imidazole (700 mg, 8.4 mmol) in DCM (40 mL) at 0 °C and the mixture stirred at rt for 16 h. The mixture was washed with brine (80 mL, and the aqueous layer extracted with DCM (50 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (1:9 ether:light petroleum) of the residue to yield the title compound **17** as a clear oil (2.24 g, *ca*. 100%), $[\alpha]_D^{20}$ +17 (*c* 2.1, $CHCl_3$) (Found: $M^+ + NH_4$, 382.2773. $C_{21}H_{40}O_3NSi$ requires M, 382.2772); δ_H 0.62 (6 H, q, *J* 7.6, 3 × $SiCH_2$), 0.97 (9 H, t, *J* 7.6, 3 × CH_3), 1.25-1.70 (6 H, m, 4-H_2, 5-H_2, 6-H_2), 3.46 (2 H, t, *J* 6.7, 7-H_2), 3.83 (3 H, s, OCH_3), 4.09 (1 H, q, *J* 7.1, 3-H), 4.46 (2 H, s, $ArCH_2$), 5.05 (1 H, dt, *J* 10.2, 1.5, 1-H), 5.25 (1 H, dt, *J* 18.4, 1.5, 1-H′), 5.89 (1 H, ddd, *J* 16.8, 10.4, 6.4, 2-H) and 6.90 and 7.27 (each 2 H, d, *J* 8.8, ArH); δ_C 5.2, 7.1, 22.2, 30.0, 38.2, 55.5, 70.3, 72.8, 74.1, 114.0, 129.5, 131.0, 142.0 and 159.3; *m/z* (Cl^+) 382 (M^+ + 18, 25%), 138 (62) and 121 (100).

(*R*)-5-Triethylsilyloxyhept-6-en-1-ol (18). An aqueous pH 7 buffer (2 mL) was added to the 4-methoxybenzyl ether **17** (2.2 g, 6 mmol) in DCM (20 mL) followed by dichlorodicyanoquinone (1.39 g, 6.12 mmol) and the mixture stirred for 10 min. Saturated aqueous sodium bicarbonate (250 mL) and ether (250 mL) were added and the aqueous phase extracted with ether (3 × 100 mL). The organic extracts were washed with saturated aqueous sodium bicarbonate (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (1:4 to 1:3 to 1:2 ether:light petroleum containing 0.5% triethylamine) of the residue gave the title compound **18** (1.08 g, 73%) as a colourless, highly viscous oil, R_f = 0.16 (1:3 ether:light petroleum), $[\alpha]_D^{20}$ 8.7 (*c* 3.9, $CHCl_3$) (Found: M^+ - H, 243.1786. $C_{13}H_{27}O_2Si$ requires M, 243.1775); δ_H 0.63 (6 H, q, *J* 7.5, 3 × $SiCH_2$), 0.98 (9 H, t, *J* 7.8, 3 × CH_3), 1.30-1.65 (6 H, m, 2-H_2, 3-H_2, 4-H_2), 2.74 (1 H, br. s, OH), 3.67 (2 H, t, *J* 6.6, 1-H_2), 4.12 (1 H, q, *J* 7.1, 5-H), 5.06 (1 H, dt, *J* 10.4, 1.5, 7-H), 5.25 (1 H, dt, *J* 17.1, 1.5, 7-H′) and 5.89 (1 H, ddd, *J* 16.8, 10.3, 6.4, 6-H); δ_C 5.1, 7.1, 21.6, 32.9, 38.0, 63.0, 74.1, 114.1 and 141.8; *m/z* (Cl^+) 245 (M^+ + 1, 100%).

(*R*)-5-Triethylsilyloxyhept-6-enal (19). Pyridine (5 mL) and the alcohol **18** (500 mg, 2.0 mmol) in DCM (5 mL) were added to a suspension of the Dess-Martin periodinane (852 mg, 2.0 mmol) in DCM (25 mL) at rt. After 50 min, a second portion of the periodinane (852 mg, 2.0 mmol) was added and the resulting

solution stirred for 1 h. Saturated aqueous sodium bicarbonate (100 mL) and ethyl acetate (100 mL) were added and the organic phase washed with saturated aqueous sodium thiosulfate (100 mL). The aqueous washings were extracted with ethyl acetate (3 × 200 mL) and the organic extracts were washed with brine (30 mL) and dried ($MgSO_4$). Chromatography of the residue gave the title compound **19** colourless oil (468 mg, 94 %), R_f = 0.3 (1:4 ether:light petroleum) (Found: $M^+ - H$, 241.1619, $C_{13}H_{25}O_2Si_2$ requires M, 241.1618); δ_H 0.61 (6 H, q, *J* 7.8, 3 × $SiCH_2$), 0.95 (9 H, t, *J* 7.8, 3 × CH_3), 1.45-1.80 (4 H, m, 3-H_2, 4-H_2), 2.45 (2 H, td, *J* 7.3, 1.8, 2-H_2), 4.12 (1 H, q, *J* 6.2, 5-H), 5.06 (1 H, d, *J* 10.4, 7-H), 5.17 (1 H, d, *J* 17.1, 7-H'), 5.89 (1 H, ddd, *J* 17.0, 10.4, 6.0, 6-H) and 9.76 (1 H, t, *J* 1.8, 1-H); δ_C 5.1, 7.1, 18.0, 37.6, 44.1, 73.7, 114.4, 141.5 and 202.8; *m/z* (CI^+) 243 (M^+ + 1, 20%), 137 (50), 127 (90) and 102 (100).

(3*R*,7*E*,11*S*,13*R*,15*S*)-11-Benzyloxy-17-*tert*-butyldiphenylsilyloxy-3-hydroxy-10,10-dimethyl-13,15-di-*O*-isopropylideneheptadeca-1,7-dien-9-one (22). The ketophosphonate **20** (254 mg, 0.35 mmol) in dry THF (2.5 mL) was added to a suspension of barium hydroxide (37 mg, 0.88 mmol) in dry THF (2.5 mL) and the mixture stirred for 30 min before the crude aldehyde **19** (277 mg, 0.46 mmol) in THF:water (40:1, 2 mL) was added. The mixture was stirred for 18 h and saturated aqueous ammonium chloride (60 mL) and ether (60 mL) were added. The aqueous phase was extracted with ether (3 × 40 mL) and the organic extracts were washed with brine (120 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the enone **21** as a viscous oil that was used immediately, R_f = 0.84 (1:1 ether:light petroleum) (Found: M^+ + Na, 863.5086, $C_{51}H_{76}O_6NaSi_2$ requires M, 863.5073); δ_H 0.69 (6 H, q, *J* 7.5, 3 × $SiCH_2$), 1.10 (9 H, t, *J* 7.8, 3 × CH_3), 1.26 [9 H, s, $SiC(CH_3)_3$], 1.29 and 1.39 (each 3 H, s, 10-CH_3), 1.47 and 1.51 (each 3 H, s, CCH_3), 1.31-1.94 (10 H, m, 4-H_2, 5-H_2, 12-H_2, 14-H_2, 16-H_2), 2.02 (2 H, br q, *J* 7.0, 6-H_2), 3.83 (1 H, m, 11-H), 3.96 (1 H, m, 13-H), 4.07 (1 H, m, 15-H), 4.21 (3 H, m, 3-H, 17-H_2), 4.77 and 4.85 (each 1 H, d, *J* 12.0, Ar*H*CH), 5.04 (1 H, dt, *J* 10.4, 1.0, 1-H), 5.21 (1 H, dt, *J* 17.3, 1.1, 1-H'), 5.82 (1 H, ddd, *J* 16.5, 10.3, 6.2, 2-H), 6.76 (1 H, d, *J* 15.2, 8-H), 7.10-7.40 (9 H, m, 7-H, ArH), 7.47 (2 H, d, *J* 7.5, ArH) and 7.87 (5 H, m, ArH); *m/z* (ES^+) 864 (M^+ + 23, 100%).

Pyridine (0.13 mL) and then the HF-pyridine complex (0.065 mL) were added to the triethylsilyl ether **21** (100 mg, 0.12 mmol) in THF (1.5 mL) at 0 °C. After for stirring 15 min, saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was warmed to rt. Ether (40 mL) and saturated aqueous ammonium chloride (20 mL) were added and the aqueous phase was extracted with ether (3 × 30 mL). The organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (4:5 ether:light petroleum) of the residue gave the title compound **22** as a highly viscous colourless oil (76 mg, 87 %), R_f = 0.21 (1:1 ether:light petroleum) (Found: M^+ + Na, 749.4201. $C_{45}H_{62}O_6NaSi$ requires M, 749.4208); ν_{max}/cm^{-1} 3505, 2932, 2892, 2857, 1686, 1616, 1588, 1513, 1467, 1428, 1383, 1364, 1302, 1249, 1224, 1173, 1109, 1037, 910 and 823; δ_H (C_6D_6) 1.17 [9 H, s, $SiC(CH_3)_3$], 1.21 and 1.31 (each 3 H, s, 10-CH_3), 1.39 and 1.43 (each 3 H, s, CCH_3), 1.00-1.80 (10 H, m, 4-H_2, 5-H_2, 12-H_2, 14-H_2, and 16-H_2), 1.89 (2 H, br. q, *J* 5.4, 6-H_2), 3.75 (2 H, m, 11-H, 13-H), 3.87 (1 H, m, 15-H), 4.05-4.20 (3 H, m, 17-H_2, 3-H), 4.68 and 4.76 (each 1 H, d, *J* 11.6, Ar*H*CH), 5.04 (1 H, dt, *J* 10.4, 1.8, 1-H), 5.21 (1 H, dt, *J* 17.3, 1.6, 1-H'), 5.64 (1 H, ddd, *J* 17.1, 10.3, 5.7, 2-H), 6.66 (1 H, dt, *J* 15.2, 1.5, 8-H), 7.00-7.25 (9 H, m, 7-H, ArH), 7.37 (2 H, d, *J* 7.5, ArH) and 7.78 (5 H, m, ArH); δ_C (C_6D_6) 12.0, 19.3, 21.0, 21.1, 24.2, 25.4, 25.7, 27.0, 32.4, 36.8, 38.8, 39.3, 46.5, 51.5, 60.4, 63.3, 63.6, 72.4, 75.1, 81.0, 100.3, 113.7, 126.2, 127.3, 128.5, 129.9, 134.2, 135.9, 139.4, 141.9, 146.7 and 201.8; *m/z* (ES^+) 750 (M^+ + 23, 100%).

(4*S*,6*R*,8*S*)-4-Benzyloxy-10-*tert*-butyldiphenylsilyloxy-1-[(2*S*,6*R*)-6-ethenyltetrahydropyran-2-yl]-6,8-di-*O*-isopropylidene-3,3-dimethyldecan-2-one (23). Potassium *tert*-butoxide (0.092 M in THF, 1.0 mL, 0.092 mmol) was added to the alcohol **22** (259 mg, 0.35 mmol) in THF (2.1 mL) at rt and the mixture stirred for 40 min. Saturated aqueous ammonium chloride (30 mL) and ether (50 mL) were added and the aqueous phase extracted with ether (2 × 50 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound **23** (210 mg, 81 %), R_f = 0.43 (1:2 ether:light petroleum), $[\alpha]_D^{21}$ +17.6 (*c* 3.6, $CHCl_3$) (Found: M^+ + Na, 749.4211. $C_{45}H_{62}O_6NaSi$ requires M, 749.4208); ν_{max}/cm^{-1} 2932, 2890, 2857, 1704, 1611, 1587, 1512, 1468, 1427, 1381, 1363, 1302, 1247, 1224, 1172, 1108, 1039, 822 and 738; δ_H (C_6D_6) 1.27 [9 H, s, $SiC(CH_3)_3$], 0.90-1.80 (24 H, m, 5-H_2, 7-H_2, 9-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 4 × CH_3), 2.49 (1 H, dd, *J* 17.4, 6.3, 1-H), 3.04 (1 H, dd, *J* 17.3, 6.0, 1-H'), 3.72 (2 H, m, 4-H, 6-H), 3.88 (1 H, m, 8-H), 4.00-4.15 (4 H, m, 10-H_2, 2'-H, 6'-H), 4.65 and 4.74 (each 1 H, d, *J* 11.6, Ar*H*CH), 5.01 (1 H, dt, *J* 10.8, 1.8, 2''-H), 5.26 (1 H, dt, *J* 17.4, 1.9, 2''-H'), 5.64 (1 H, ddd, *J* 17.4, 10.8, 5.0, 1''-H), 7.00-7.40 (11 H, m, ArH) and 7.78 (4 H, m, ArH); δ_C (C_6D_6) 19.4, 20.6, 21.2, 23.6, 25.3, 25.6, 27.0, 30.1, 30.4, 31.5, 31.7, 38.9, 39.3, 45.6, 52.8, 60.5, 63.3, 63.8, 74.0, 75.0, 78.1, 81.1, 100.3, 113.4, 127.3, 128.5, 129.9, 134.2, 135.9 and 140.2; *m/z* (ES^+) 749.5 (M^+ + 23, 100%).

(4*S*,6*R*,8*S*)-4-Benzyloxy-1-[(2*S*,6*R*)-6-ethenyltetrahydropyran-2-yl]-10-hydroxy-6,8-di-*O*-isopropylidene-3,3-dimethyldecan-2-one (24). Tetra-*n*-butylammonium fluoride (1 M in THF, 0.43 mL, 0.43 mmol) was added to the enone **21** (150 mg, 0.18 mmol) in THF (5 mL) at rt and the mixture stirred for 16 h. Water (50 mL) was added and the mixture extracted with ether (4 × 50 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in THF (2.1 mL), potassium *tert*-butoxide (0.092 M in THF, 1.0 mL, 0.092 mmol) was added and the mixture stirred for 40 min. Saturated aqueous ammonium chloride (30 mL) and ether (50 mL) were added and the aqueous phase extracted with ether (2 × 50 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue gave the title compound **24** as a colourless oil (54 mg, 62 % from ketophosphonate **20**) containing ca. 10% of the 2'-epimer (Found: M^+ + Na, 511.3033. $C_{29}H_{44}O_6Na$ requires M, 511.3030); ν_{max}/cm^{-1} 2932, 2890, 2857, 1704, 1611, 1587, 1512, 1468, 1427, 1381, 1363, 1302, 1247, 1224, 1172, 1108, 1039, 822 and 738; δ_H (C_6D_6) 1.00-1.68 (24 H, m, 5-H_2, 7-H_2, 9-H_2, 3'-H_2, 4'-H_2, 5'-H_2, 4 × CH_3), 2.48 and 3.04 (each 1 H, dd, *J* 17.3, 6.0, 1-H), 3.50-3.70 (2 H, m, 4-H, 6-H), 3.72 (1 H, m, 8-H), 3.86 (1 H, m, 2'-H), 4.00-4.15 (3 H, m, 10-H_2, 6'-H), 4.63 and 4.70 (each 1 H, d, *J* 11.6, ArHC*H*), 5.00 (1 H, dt, *J* 10.8, 1.8, 2''-H), 5.25 (1 H, dt, *J* 17.4, 1.9, 2''-H'), 5.85 (1 H, ddd, *J* 17.4, 10.8, 5.0, 1''-H), 7.00-7.25 (3 H, m, ArH) and 7.35 (2 H, m, ArH); δ_C (C_6D_6) 20.5, 21.3, 23.6, 25.2, 25.3, 26.7, 30.1, 30.4, 31.2, 31.7, 38.4, 38.6, 39.4, 45.6, 52.9, 60.5, 63.8, 66.0, 74.0, 75.1, 78.1, 81.0, 100.4, 113.4, 127.2, 127.3, 128.5, 135.2, 140.2 and 211.4; *m/z* (ES^+) 511 (M^+ + 23, 100%).

(3*S*,5*R*,7*S*,9*S*,11*S*,15*R*)-7-Benzyloxy-1-*tert*-butyldiphenylsilyloxy-

5,9-epoxy-11,15-epoxy-8,8-dimethyl-9-methoxyheptadec-16-en-3-ol (25). Anhydrous methanol (5 mL) and trimethyl orthoformate (0.5 mL) were added to the hydroxyketone **23** (210 mg 0.29 mmol) followed by oven-dried pyridinium toluene *p*-sulfonate (13 mg, 0.11 mmol). The mixture was stirred for 17 h, saturated aqueous sodium bicarbonate (50 mL) and ether (50 mL) were added and the aqueous phase was extracted with ether (2 × 50 mL). The organic extracts were washed with saturated aqueous sodium bicarbonate (2 × 20 mL) and concenrated under reduced pressure. Chromatography (1:3 light petroleum:ether with 1% triethylamine) of the residue gave the title compound **25** as a colourless oil (174 mg, 86 %), R_f = 0.78 (1:1 ether:light petroleum), $[\alpha]_D^{20}$ +27 (*c* 3.5, $CHCl_3$) (Found: M^+ + Na, 723.4055, $C_{43}H_{60}O_6NaSi$ requires M, 723.4051); ν_{max}/cm^{-1} 3514, 3071, 2932, 2858, 1644, 1589, 1472, 1454, 1428, 1382, 1361, 1337, 1260, 1199, 1092, 1028, 983, 921 and 823; δ_H (C_6D_6) 1.15 [9 H, s, $SiC(CH_3)_3$], 1.34 and 1.45 (each 3 H, s, 8-CH_3), 0.90-1.80 (12 H, m, 2-H_2, 4-H_2, 6-H_2, 12-H_2, 13-H_2, and 14-H_2), 1.92 (1 H, dd, *J* 16.4, 2.6, 10-H), 2.22 (1 H, dd, *J* 16.3, 6.4, 10-H'), 3.27 (3 H, s, OCH_3), 3.60-3.75 (2 H, m, 3-H, 5-H), 3.80-3.95 (3 H, m, 1-H_2, 7-H), 4.08 (1 H, m, 11-H), 4.65 (2 H, m, 15-H, Ar*H*CH), 4.74 (1 H, d, *J* 11.6, ArHC*H*), 5.02 (1 H, dt, *J* 10.7, 1.9, 17-H), 5.36 (1 H, dt, *J* 17.3, 1.9, 17-H', 5.84 (1 H, ddd, *J* 17.4, 10.7, 4.5, 16-H), 7.00-7.40 (11 H, m, ArH) and 7.78 (4 H, m, ArH); δ_C (C_6D_6) 17.1, 19.3, 20.0, 24.2, 27.0, 30.4, 31.4, 33.2, 40.1, 40.6, 43.5, 43.7, 48.3, 63.0, 65.5, 67.1, 71.6, 73.8, 77.7, 79.5, 104.6, 113.4, 127.3, 127.5, 128.3, 128.4, 130.0, 133.7, 133.8, 135.9 and 140.0; *m/z* (ES^+) 745 (90%), 723 (M^+ + 23, 100) and 670 (80).

(3*S*,5*R*,7*S*,9*S*,11*S*,15*R*)-7-Benzyloxy-5,9-epoxy-11,15-epoxy-8,8-dimethyl-9-methoxy-3-(2-trimethylsilylethoxymethoxy)heptadec-16-en-1-ol (27). Di-isopropylethylamine (140 µL, 0.32 mmol) and 2-trimethylsilylethoxymethyl chloride (0.18 mL, 0.976 mmol) were added to the alcohol **25** (120 mg, 0.21 mmol) in DCM (1.0 mL) at 0 °C before adding 4-dimethylaminopyridine (cat.) at rt. The mixture was stirred at rt and saturated aqueous sodium bicarbonate (4 mL) and ether (4 mL) were added. After 30 min, more saturated aqueous sodium bicarbonate (20 mL) and ether (20 mL) were added and the aqueous phase extracted with ether (2 × 15 mL). The organic extracts were washed with saturated aqueous sodium bicarbonate (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (1:20 then 1:4 ether:light petroleum with 1 % triethylamine) of the residue gave the 2-trimethylsilylethoxymethyl ether **26** as a colourless oil (122 mg, 86%), R_f = 0.77 (1:1 ether:light petroleum) (Found: M^+ + Na, 853.4869. $C_{49}H_{74}O_7NaSi_2$ requires M, 853.4865); *m/z* (ES^+) 854 (M^+ + 23, 100%).

Tetra-*n*-butylammonium fluoride (1 M in THF, 0.43 mL, 0.43 mmol) was added to the 2-trimethylsilylethoxymethyl ether **26** (180 mg, 0.22 mmol) in THF (5 mL) at rt and the mixture stirred for 16 h at rt before water (50 mL) was added. The mixture was extracted with ether (4 × 50 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (1:1 light petroleum:ether) of the residue gave the title compound **27** as a clear oil (120 mg, 93%), R_f = 0.20 (1:1 ether:light petroleum), $[\alpha]_D^{20}$ +27 (*c* 3.5, $CHCl_3$) (Found: M^+ + Na, 615.3686. $C_{33}H_{56}O_7NaSi$ requires M, 615.3688); ν_{max}/cm^{-1} 3413, 2922, 2850, 1463, 1425, 1381, 1359, 1248, 1108, 1057, 1026, 856 and 835; δ_H (C_6D_6) –0.01 [9 H, s, $Si(CH_3)_3$], 0.98 (2 H, m, $SiCH_2$), 1.29 and 1.42 (each 3 H, s, 8-CH_3), 0.90-1.80 (12 H, m, 2-H_2, 4-H_2, 6-H_2, 12-H_2, 13-H_2, and 14-H_2), 1.92 (1 H, dd, *J* 16.3, 3.4, 10-H), 2.22 (1 H, dd, *J* 16.1, 6.0, 10-H'), 3.23 (3 H, s, OCH_3), 3.50-3.95 (8 H, m, 1-H_2, 3-H, 5-H, 7-H, 11-H, OCH_2CH_2Si), 4.08 (1 H, m, 15-H), 4.34 and 4.71 (each 1 H, d, *J* 11.9, Ar*H*CH), 4.69 and 4.79 (each 1 H, d, *J* 6.9, OHC*H*O), 5.05 (1 H, dt, *J* 10.7, 1.8, 17-H), 5.36 (1 H, dt *J* 17.3, 1.9, 17-H'), 5.88 (1 H, ddd, *J* 17.4, 10.7, 4.7, 16-H), 7.00-7.25 (3 H, m, ArH) and 7.78 (2 H, m, ArH); δ_C (C_6D_6) –1.4, 17.1, 18.2, 20.1, 24.2, 30.1, 31.6, 33.2, 33.6, 38.6, 40.6, 42.5, 43.4, 48.6, 59.5, 65.7, 66.0, 71.6, 73.9, 74.8, 77.9, 79.2, 95.1, 104.6, 113.4, 127.4, 127.5, 128.4, 139.9 and 140.1; *m/z* (ES^+) 616 (M^+ + 23, 100%).

(*S*)-1-Benzyloxyhept-6-en-3-ol (29). Prop-2-enylmagnesium bromide (1 M in ether, 28.5 mL, 28.5 mmol) was added to a suspension of copper(I) iodide (542 mg, 2.85 mmol) in THF (10 mL) at –40 °C. The mixture was warmed to –30 °C and stirred for 20 min before cooling to –40 °C. The epoxide **28**[13] (3.38 g, 18.99 mmol) in THF (34 mL) was added and the stirring continued for 1 h. Saturated aqueous ammonium chloride (60 mL) and ether (60 mL) were added and the mixture was allowed to warm to rt before partitioning between water and ether. The aqueous layer was extracted with ether (2 × 50 mL) and the organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (4:1 light petroleum:ether) of the residue afforded the title compound **29** (3.48 g, 83%), R_f = 0.35 (1:1 light petroleum:ether), $[\alpha]_D^{20}$ +5.9 (*c* 2.3, $CHCl_3$) (Found: M^+ + NH_4, 238.1803. $C_{14}H_{24}O_2N$ requires M, 238.1802); ν_{max}/cm^{-1} 3417, 3065, 3031, 2935, 2922, 2861, 1640, 1453, 1416, 1363, 1206, 1098, 1028, 997, 912 and 737; δ_H 1.52-1.72 (2 H, m, 4-H_2), 1.78-1.85 (2 H, m, 2-H_2), 2.09-2.34 (2 H, m, 5-H_2), 2.89 (1 H, br. s, OH), 3.66-3.82 (2 H, m, 1-H_2), 3.87 (1 H, m, 3-H), 4.58 (2 H, s, $ArCH_2$), 5.02 (1 H, ddt, *J* 10.2, 2.0, 1.2, 7-H), 5.10 (1 H, ddt, *J* 17.1, 2.0, 1.6, 7-H'), 5.90 (1 H, ddt, *J* 16.9, 10.1, 6.6, 6-H) and 7.29-7.44 (5 H, m, ArH); δ_C 30.2, 36.7, 36.8, 69.5, 71.1, 73.6, 114.9, 128.0, 128.1, 128.8, 138.2 and 138.9; *m/z* (CI^+) 238 (M^+ + 18, 66%) and 221 (M^+ + 1, 100%).

(*S*)-1-Benzyloxy-3-*tert*-butyldimethylsilyloxyhept-6-ene (30). *tert*-Butyldimethylsilyl chloride (2.86 g, 18.95 mmol) was added to imidazole (3.22 g, 47.37 mmol) in DCM (60 mL) at 0 °C followed by the alcohol **29** (3.48 g, 15.79 mmol) in DCM (20 mL). The mixture was allowed to warm to rt and was stirred for 22 h. Saturated aqueous sodium hydrogen carbonate (80 mL) was added and the mixture partitioned between water and DCM. The aqueous layer was extracted with ether (3 × 80 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (light petroleum to 15:1 light petroleum:ether) of the residue afforded the title compound **30** (4.93 g, 93%), R_f = 0.48 (1:9 ether:light petroleum), $[\alpha]_D^{23}$ –0.7 (*c* 2.4, $CHCl_3$) (Found: M^+ + H, 335.2399. $C_{20}H_{35}O_2Si$ requires M, 335.2401); ν_{max}/cm^{-1} 3065, 3032, 2952, 2931, 2889, 2857, 1461, 1363, 1253, 1097, 1056, 1006, 836 and 775; δ_H 0.10 and 0.11 (each 3 H, s, $SiCH_3$), 0.94 [9 H, s, $SiC(CH_3)_3$], 1.56-1.65 (2 H, m, 4-H_2), 1.78-1.87 (2 H, m, 2-H_2), 2.09-2.20 (2 H, m, 5-H_2), 3.60 (2 H, t, *J* 6.6, 1-H_2), 3.93 (1 H, dq, *J* 6.6, 5.8, 3-H), 4.53 and 4.57 (each 1 H, d, *J* 11.9, ArHC*H*), 5.00 (1 H, ddt, *J* 10.1, 2.0, 1.3, 7-H), 5.06 (1 H, ddd, *J* 17.2, 3.6, 1.6, 7-H'), 5.87 (1 H, ddt, *J* 16.9, 10.2, 6.6, 6-H) and 7.30-7.43 (5 H, m, ArH); δ_C –4.3, –4.1, 18.4, 26.2, 29.6, 36.9, 37.2, 67.4, 69.2, 73.2, 114.6, 127.8, 127.9, 128.6, 138.8 and 139.1; *m/z* (CI^+) 335 (M^+ + 1, 100%).

(*S*)-7-Benzyloxy-5-*tert*-butyldimethylsilyloxyheptan-1-ol (31). Borane in THF (1 M, 16.2 mL, 16.2 mmol) was added to the alkene **30** (4.93 g, 14.74 mmol) in THF (50 mL) at –25 °C dropwise over 10 min. The mixture was warmed to rt over 1 h, stirred for 16 h, then added to a mixture of aqueous sodium hydroxide (3 M, 100 mL) and hydrogen peroxide (30%, 100 mL). The temperature rose to 65 °C and the mixture was cooled to 45 °C using an ice bath then stirred with heating at 50 °C for 30 min before being cooled to rt and extracted with ether (3 × 50 mL). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (2:8 to 1:1 ether:light petroleum) of the residue gave the title compound **31** (4.45 g, 86%), R_f = 0.33 (3:7 ether:light petroleum), $[\alpha]_D^{20}$ +4.6 (*c* 4.0, $CHCl_3$) (Found: M^+ + H 353.2501. $C_{20}H_{37}O_3Si$ requires M, 353.2506); ν_{max}/cm^{-1} 3356, 2930, 2883, 2857, 1471, 1461, 1361, 1254, 1100, 1061, 836, 775 and 736; δ_H 0.10 (6 H, s, 2 × $SiCH_3$), 0.93 [9 H, s, $Si(CH_3)_3$], 1.37-1.72 (7 H, m, 2-H_2, 3-H_2, 4-H_2, OH), 1.73-1.89 (2 H, m, 6-H_2), 3.60 (2 H, t, *J* 6.6, 7-H_2), 3.66 (2 H, t, *J* 6.6, 1-H_2), 3.90 (1 H, dq, *J* 6.8, 5.3, 5-H), 4.52 and 4.57 (each 1 H, d, *J* 11.9, ArHCH) and 7.31-7.43 (5 H, m, ArH); δ_C –4.3, –4.1, 18.4, 21.4, 26.2, 33.2, 37.1, 37.5, 63.1, 67.4, 69.6, 73.3, 127.8, 128.0, 128.6 and 138.8; *m/z* (Cl^+) 353 (M^+ + 1, 100%) and 221 (86).

(*S*)-7-Benzyloxy-5-*tert*-butyldimethylsilyloxyheptanal (32). Dimethyl sulfoxide (1.83 mL, 25.24 mmol) was added to oxalyl chloride (1.15 mL, 13.25 mmol) in DCM (42 mL) at –78 °C over 5 min. The solution was stirred for 10 min at –78 °C before the alcohol **31** (4.45 g, 12.62 mmol) in DCM (14 mL) was added. The mixture stirred for 20 min, triethylamine (8.4 mL, 59.32 mmol) was added and the stirring was continued for 15 min before the reaction was allowed to warm to rt for 30 min. Saturated aqueous ammonium chloride was added and the mixture partitioned between water and ether. The aqueous layer was extracted with ether (3 × 50 mL) and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound **32** that was used directly in the next reaction, R_f = 0.40 (3:7 ether:light petroleum) (Found: M^+ + H, 351.2345. $C_{20}H_{35}O_3Si$ requires M, 351.2350); ν_{max}/cm^{-1} 2952, 2929, 2884, 2857, 1727, 1471, 1462, 1455, 1361, 1255, 1100, 1064, 836, 775 and 736; δ_H 0.10 (6 H, s, 2 × $SiCH_3$), 0.93 [9 H, s, $Si(CH_3)_3$], 1.47-1.57 (2 H, m, 4-H_2), 1.65-1.78 (2 H, m, 3-H_2), 1.81 (2 H, q, *J* 6.3, 6-H_2), 2.47 (2 H, td, *J* 7.3, 1.8, 2-H_2), 3.58 (2 H, t, *J* 6.5, 7-H_2), 3.94 (1 H, m, 5-H), 4.51 and 4.56 (each 1 H, d, *J* 11.9, ArHC*H*), 7.31-7.43 (5 H, m, ArH) and 9.80 (1 H, t, *J* 1.8, 1-H); δ_C –4.3, –4.1, 17.9, 18.3, 26.1, 37.0, 37.1, 44.3, 67.2, 69.3, 73.3, 127.8, 127.9, 128.6, 138.8 and 202.9; *m/z* (Cl^+) 368 (M^+ + 18, 10%), 351 (M^+ + 1, 42) and 219 (100).

(4*RS*,8*S*)-10-Benzyloxy-8-*tert*-butyldimethylsilyloxy-3,3-dimethyldec-1-en-4-ol (33). 1-Bromo-3-methylbut-2-ene (90%, 2.45 mL, 18.93 mmol) was added to a suspension of non-activated powdered zinc (2.446 g, 37.87 mmol) in THF (60 mL) at rt. After stirring for 10 min, the aldehyde **32** (from 4.45 g of the alcohol **31**) in THF (18 mL) was added and the mixture stirred for 16 h. Saturated aqueous ammonium chloride was added and the mixture filtered through celite then partitioned between water and ether. The aqueous layer was extracted with ether and the organic extracts washed with brine, dried $MgSO_4$) and concentrated under reduced pressure. Chromatography (2:8 ether:light petroleum) of the residue gave the title compound **33** as an oil (3.56 g, 67% from alcohol **31**) as a 60:40 mixture of epimers, R_f = 0.36 (3:7 ether:light petroleum) (Found: M^+ + H, 421.3128. $C_{25}H_{45}O_3Si$ requires M, 421.3132); ν_{max}/cm^{-1} 3445, 2952, 2929, 2857, 1471, 1432, 1361, 1255, 1098, 1054, 1006, 836, 774 and 735; δ_H 0.08 (6 H, s, 2 × $SiCH_3$), 0.92 [9 H, s, $SiC(CH_3)_3$], 1.04 and 1.05 (each 3 H, s, 3-CH_3), 1.26-1.86 (9 H, m, 5-H_2, 6-H_2, 7-H_2, 9-H_2, OH), 3.27 (0.6 H, br. d, *J* 10.1, 4-H), 3.59 (2.4 H, m, 4-H, 10-H_2), 3.89 (1 H, dq, *J* 6.0, 5.2, 8-H), 4.51 and 4.55 (each 1 H, d, *J* 11.9, ArHC*H*), 5.09 (1 H, dd, *J* 17.3, 1.6, 1-H), 4.55 (1 H, dd, *J* 10.7, 1.6, 1-H'), 5.85 (1 H, dd, *J* 10.8, 17.5, 2-H) and 7.30-7.41 (5 H, m, ArH); δ_C –4.3, –4.1, 18.4, 22.3, 22.8, 22.9, 23.4, 26.2, 28.6, 31.8, 31.9, 37.1, 37.3, 37.7, 37.8, 41.9, 67.4, 69.6, 69.8, 73.2, 78.5, 113.6, 127.8, 127.9, 128.6, 138.9 and 145.7; *m/z* (Cl^+) 421 (M^+ + 1, 30%) and 289 (100).

(8*S*)-10-Benzyloxy-8-*tert*-butyldimethylsilyloxy-3,3-dimethyldec-1-en-4-one (34). Dimethyl sulfoxide (0.25 mL) was added to oxalyl chloride (0.15 mL) in DCM (6 mL) at –78 °C dropwise over 5 min. After 10 min at –78 °C the alcohol **33** (0.438 g) in DCM (4 mL) was added and the mixture stirred for 20 min. Triethylamine (1.1 mL) was added and the mixture was stirred for 15 min at –78 °C then allowed to warm to rt and stirred for 30 min. Saturated aqueous ammonium chloride was added and the mixture was partitioned between water and ether. The aqueous layer was extracted with ether and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound **34** that was used directly in the next reaction, R_f = 0.65 (3:8 ether:light petroleum), $[\alpha]_D^{20}$ + 7.3 (*c* 3.3, $CHCl_3$) (Found: M^+ + H, 419.2971. $C_{25}H_{43}O_3Si$ requires M, 419.2976); ν_{max}/cm^{-1} 2953, 2931, 2889, 2857, 1710, 1464, 1363, 1253, 1098, 1008, 836, 775 and 736; δ_H 0.09 and 0.10 (each 3 H, s, $SiCH_3$), 0.93 [9 H, s, $SiC(CH_3)_3$], 1.27 (6 H, s, 2 × 3-CH_3), 1.38-1.51 (2 H, m, 7-H_2), 1.53-1.70 (2 H, m, 6-H_2), 1.71-1.89 (2 H, m, 9-H_2), 2.49 (2 H, dt, *J* 7.4, 1.8, 5-H_2), 3.58 (2 H, t, *J* 6.5, 10-H_2), 3.88 (1 H, dq, *J* 6.6, 5.7, 8-H), 4.51 and 4.57 (each 1 H, d, *J* 11.9, ArHC*H*), 5.15-5.25 (2 H, m, 1-H_2), 5.96 (1 H, dd, *J* 17.6, 10.5, 2-H) and 7.31-7.41 (5 H, m, ArH); δ_C –4.4, –4.1, 18.4, 19.9, 23.8, 26.2, 37.2(2), 37.8, 51.0, 67.4, 69.5, 73.2, 114.5, 127.8, 127.9, 128.6, 138.4, 142.9 and 210.2; *m/z* (Cl^+) 436 (M^+ + 18, 2%), 419 (M^+ + 1, 2) and 287 (100).

(8*S*)-10-Benzyloxy-8-hydroxy-3,3-dimethyldec-1-en-4-one (35). Tetra-*n*-butylammonium fluoride (1 M in THF, 19 mL) was added to the silyl ether **34** (8.3 mmol) in THF (50 mL) at rt and the mixture stirred for 16 h. Saturated aqueous sodium hydrogen carbonate (50 mL) was added and the mixture partitioned between water and ether. The aqueous layer was extracted with ether and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (4:6 ether:light petroleum to 6:4 ether:light petroleum) of the residue gave the title compound **35** (2.15 g, 85% from alcohol **33**) containing traces of the corresponding hemiacetal, R_f = 0.17/0/59 (1:1 ether:light petroleum) (Found: M^+ + Na, 327.1928. $C_{19}H_{28}O_3Na$ requires M, 327.1931); ν_{max}/cm^{-1} 3422, 2929, 2867, 1708, 1454, 1412, 1365, 1262, 1205, 1097, 1026, 920 and 739; δ_H (C_6D_6) 1.08 (6 H, s, 2 × 3-CH_3), 1.24-1.82 (6 H, m, 6-H_2, 7-H_2, 9-H_2), 2.24 (2 H, t, *J* 7.0, 5-H_2), 3.36 (1 H, ddd, *J* 9.2, 7.6, 4.7, 10-H), 3.45 (1 H, ddd, *J* 9.2, 6.1, 4.8, 10-H'), 3.71 (1 H, m, 8-H), 4.23 (2 H, s, $ArCH_2$), 4.93 (1 H, dd, *J* 10.7, 1.0, 1-H), 4.95 (1 H, dd, *J* 17.4, 1.0, 1-H'), 5.74 (1 H, dd, *J* 17.4, 10.7, 2-H) and 7.01-7.26 (5 H, m, ArH); δ_C (C_6D_6) 20.2, 23.5, 37.1, 37.3,

50.6, 69.0, 70.5, 73.1, 113.8, 127.6, 127.7, 128.5, 138.7, 143.1 and 211.4; *m/z* (ES^+) 327 (M^+ + 23, 100%).

(8*S*)-10-Benzyloxy-8-hydroxy-3,3,5-trimethyldec-1-en-4-one (36) and (8*S*)-10-benzyloxy-8-methoxy-3,3,5-trimethyldec-1-en-4-one (37). Sodium hydride (60% in mineral oil, 6.3 mg, 0.16 mmol) was added to the hydroxyketone **35** (32 mg, 0.105 mmol) in DMF (1 mL) at 0 °C. After stirring for 30 min, methyl iodide was added (13 µL, 0.21 mmol) and the mixture was stirred for 30 min. Saturated aqueous ammonium chloride was added and the mixture partitioned between water and ether. The aqueous layer was extracted with ether and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (2:8 then 1:1 ether:light petroleum with 1% Et_3N) of the residue gave the title compound **37** (6 mg, 18%), R_f = 0.50 (1:1 ether:light petroleum) (Found: M^+ + Na, 355.2241. $C_{21}H_{32}O_3Na$ requires M, 355.2244); ν_{max}/cm^{-1} 2968, 2932, 2870, 1706, 1634, 1455, 1365, 1260, 1095, 1027, 1013, 993, 919, 737; δ_H 0.96 (3 H, d, *J* 6.8, 5-CH_3), 1.12 (6 H, s, 2 × 3-CH_3), 1.29-1.49 and 1.67-1.83 (6 H, m, 6-H_2, 7-H_2 and 9-H_2), 2.70 (1 H, hex, *J* 6.7, 5-H), 3.15 (3 H, s, OCH_3), 3.26 (1 H, pent, *J* 6.8, 8-H), 3.38-3.55 (2 H, m, 10-H_2), 4.33 (2 H, s, $ArCH_2$), 4.95 (1 H, dd, *J* 10.6, 1.1, 1-H), 4.98 (1 H, dd, *J* 17.4, 1.1, 1-H′), 5.79 (1 H, dd, *J* 17.4, 10.6, 2-H) and 7.07-7.33 (5 H, m, ArH); *m/z* (ES^+) 355 (M^+ + 23, 100%). The more polar product was the title compound **36** (13 mg, 39%), R_f = 0.19 (1:1 ether:light petroleum) (Found: M^+ + Na, 341.2087. $C_{20}H_{30}O_3Na$ requires M, 341.2087); ν_{max}/cm^{-1} 3481, 2968, 2932, 2871, 1705, 1634, 1454, 1414, 1365, 1262, 1099, 1013, 921, 803 and 738; δ_H (C_6D_6) 0.97 (3 H, d, *J* 6.8, 5-CH_3), 1.14 and 1.15 (each 3 H, s, 3-CH_3), 1.19-1.83 (6 H, m, 6-H_2, 7-H_2 and 9-H_2), 2.61 (1 H, br. s, OH), 2.76 (1 H, hex, *J* 6.8, 5-H), 3.32 (1 H, ddd, *J* 9.2, 8.8, 4.4, 10-H), 3.47 (1 H, ddd, *J* 9.2, 5.9, 4.7, 10-H′), 3.65 (1 H, m, 8-H), 4.20 (2 H, s, $ArCH_2$), 4.97 (1 H, dd, *J* 10.6, 1.0, 1-H), 4.99 (1 H, dd, *J* 17.4, 1.0, 1-H′), 5.82 (1 H, dd, *J* 17.4, 10.6, 2-H) and 7.04-7.23 (5 H, m, ArH); δ_C (C_6D_6) 18.8, 23.4, 30.6, 35.7, 37.0, 40.4, 51.2, 69.1, 70.9, 73.2, 114.1, 127.6, 127.9, 128.5, 138.6, 142.6 and 214.9; *m/z* (ES^+) 341 (M^+ + 23, 100%).

(2*S*)-2-(2-Benzyloxyethyl)-6-(2-methylbut-3-en-2-yl)-3,4-dihydro-2*H*-pyran (38). Toluene *p*-sulfonic acid (5.5 mg, 32 µmol) was added to the hydroxyketone **35** (68 mg, 0.16 mmol) in benzene (0.7 mL) and the solution was heated at 50 °C for 3 h. Molecular sieves (4Å, 200 mg) and chlorosulfonic acid (10 mg, 64 µmol) were added and the mixture stirred for 16 h. More molecular sieves (4Å, 200 mg) were added and the mixture heated at 80 °C for 1.5 h. The mixture was allowed to cool and was filtered through a basic alumina plug with ether washings. Concentration under reduced pressure gave the title compound **38** (68 mg, *ca*. 100%), R_f = 0.73 (1:1 ether:light petroleum), $[\alpha]_D^{20}$ +39.9 (*c* 3.0, $CHCl_3$) (Found: M^+ + Na, 309.1827. $C_{19}H_{26}NaO_2$ requires M, 309.1830); ν_{max}/cm^{-1} 2962, 2946, 2923, 2851, 1663, 1453, 1359, 1291, 1091, 1003, 911 and 735; δ_H (C_6D_6) 1.25 and 1.26 (each 3 H, s, CH_3), 1.36 and 1.49 (each 1 H, m, 3-H), 1.67-1.98 (4 H, m, 1′-H_2 and 4-H_2), 3.49 (1 H, ddd, *J* 9.1, 6.3, 5.2, 2′-H), 3.60 (1 H, ddd, *J* 9.0, 8.2, 5.7, 2′-H′), 3.92 (1 H, dddd, *J* 9.3, 8.6, 4.2, 2.4, 2-H), 4.35 (2 H, s, $ArCH_2$), 4.60 (1 H, ddd, *J* 4.5, 2.9, 0.8, 5-H), 5.01 (1 H, dd, *J* 10.7, 1.5, 4′′-H), 5.10 (1 H, dd, *J* 17.5, 1.5, 4′′-H′), 6.07 (1 H, dd, *J* 17.5, 10.6, 3′′-H), 7.06-7.21 (3 H, m, ArH) and 7.28-7.33 (2 H, m, ArH); δ_C 20.6, 25.5(2), 27.8, 35.7, 41.6, 66.9, 72.4, 73.1, 93.4, 110.9, 127.5, 127.6, 128.4, 139.3, 146.3 and 159.1; *m/z* (ES^+) 309 (M^+ + 23, 43%) and 186 (100).

(2*S*,6*S*)-6-(2-Benzyloxyethyl)-2-methoxy-2-(2-methylbut-3-en-2-yl)tetrahydropyran-3-one (40). Molecular sieves (4Å, 900 mg) then *m*-chloroperoxybenzoic acid (70% pure, 633 mg, 2.56 mmol) were added to the dihydropyran **38** (615 mg, 2.147 mmol) in anhydrous MeOH (20 mL) and the mixture stirred for 1 h at rt. Saturated aqueous sodium hydrogen carbonate and then saturated aqueous sodium sulfite were added and the mixture was partitioned between water and ether. The aqueous layer was extracted with ether and the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (16% ether and 1% Et_3N in light petroleum) of the residue afforded the alcohol **39** containing ca. 25% of a minor side product probably an isomer (640 mg, 89%), R_f = 0.44 (1:1 ether:light petroleum) (Found: M^+ + Na, 357.2039. $C_{20}H_{30}O_4Na$ requires M, 357.2036); δ_H (C_6D_6) 1.00 (1 H, m, 1′′-H), 1.15 and 1.22 (each 0.75 H, s, CH_3), 1.30 and 1.33 (each 2.25 H, s, CH_3), 1.49-1.76 (5 H, m, 1′′-H′, 4-H_2, 5-H_2), 3.19 (2.25 H, s, OCH_3), 3.24 (0.75 H, s, OCH_3), 3.33-3.68 (3 H, m, 2′′-H_2, 6-H), 3.72 (0.75 H, dd, *J* 11.4, 4.7, 3-H), 3.82 (0.25 H, t, *J* 3.0, 3-H), 4.26-4.37 (2 H, m, $ArCH_2$), 4.82 (0.25 H, dd, *J* 10.9, 1.6, 4′-H), 4.91 (0.25 H, dd, *J* 17.7, 1.7, 4′-H′), 4.99 (0.75 H, dd, *J* 10.9, 1.6, 4′-H), 5.10 (0.75 H, dd, *J* 17.7, 1.7, 4′-H′), 6.45 (0.75 H, dd, *J* 17.7, 10.9, 3′-H), 6.52 (0.25 H, dd, *J* 17.9, 10.8, 3′-H) and 7.07-7.30 (5 H, m, ArH); δ_C (C_6D_6) 21.5, 24.0, 24.5, 24.8, 24.9, 27.3, 30.3, 31.0, 36.2, 36.8, 45.9, 46.7, 50.5, 51.6, 66.5, 66.8, 67.4, 68.0, 69.0, 70.1, 73.1, 101.1, 103.0, 110.1, 110.4, 127.8, 127.9, 128.4, 139.0, 147.1 and 148.1; *m/z* (ES^+) 357 (M^+ + 23, 100%).

Pyridine (1.05 mL) and the Dess-Martin periodinane (1.09 g) were added to this mixture of alcohols **39** (640 mg) in DCM (20 mL) at 0 °C and the mixture was allowed to warm to rt and stirred for 4 h. Saturated aqueous sodium hydrogen carbonate was added and the mixture was partitioned between water and ether. The aqueous layer was extracted with ether and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (9:1 light petroleum:ether with 1% Et_3N) of the residue gave the title compound **40** (614 mg, 86% from **38**), R_f = 0.47 (1:1 ether:light petroleum) (Found: M^+ + Na, 355.1878. $C_{20}H_{28}O_4Na$ requires M, 355.1880); ν_{max}/cm^{-1} 2942, 2866, 1727, 1453, 1413, 1363, 1112, 1052, 915 and 739; δ_H (C_6D_6) 1.24 and 1.45 (each 1 H, m, 5-H), 1.27 and 1.34 (each 3 H, s, CH_3), 1.54-1.61 (2 H, m, 1′′-H_2), 2.06 (1 H, ddd, *J* 17.3, 7.3, 3.2, 4-H), 2.17 (1 H, ddd, *J* 17.4, 10.7, 7.5, 4-H′), 3.16 (3 H, s, OCH_3), 3.35 (1 H, dt, *J* 9.1, 5.2, 2′′-H), 3.52 (1 H, dt, *J* 9.4, 6.7, 2′′-H′), 3.83 (1 H, m, 6-H), 4.25 (2 H, s, $PhCH_2$), 4.95 (1 H, dd, *J* 10.9, 1.5, 4′-H), 5.01 (1 H, dd, *J* 17.7, 1.5, 4′-H′), 6.35 (1 H, dd, *J* 17.7, 10.9, 3′-H) and 7.03-7.26 (5 H, m, ArH); δ_C (C_6D_6) 22.4, 22.8, 30.2, 36.1, 37.3, 45.0, 51.5, 66.4, 69.4, 73.1, 103.7, 112.1, 127.8, 128.5, 138.9, 145.0 and 204.3; *m/z* (ES^+) 355 (M^+ + 23, 100%).

(2*S*,3*R*,6*S*)-6-(2-Benzyloxyethyl)-2,3-dimethoxy-2-(2-methylbut-3-en-2-yl)tetrahydropyran (41). Lithium triethyborohydride (1 M in THF, 2.21 mL, 2.21 mmol) was added to the ketone **40** (614 mg, 1.85 mmol) in THF (6 mL) at –10 °C and the mixture was allowed to warm to rt and stirred overnight. Saturated aqueous sodium hydrogen carbonate and ether and were added and the aqueous layer was extracted with ether. The organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the (3*R*)-alcohol **39** containing <3% of minor somers.

Sodium hydride (90 mg) and methyl iodide (0.18 mL) were added to this alcohol in THF (10 mL) at –10 °C and the mixture stirred for 16 h at rt. Saturated aqueous sodium hydrogen carbonate was added and the mixture partitioned between water and ether. The aqueous layer was extracted with ether and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (9:1 light petroleum:ether with 1% Et_3N) afforded the title compound **41** (487 mg, 76% from **40**) containing <3% of minor isomers; δ_H (C_6D_6) 0.97-1.12 (2 H, m, 1''-H_2), 1.37 and 1.39 (each 3 H, s, CH_3), 1.60-1.72 (3 H, m, 4-H, 5-H_2), 1.85 (1 H, dddd, *J* 13.5, 12.0, 11.4, 4.2, 4-H'), 3.07 (3 H, s, OCH_3), 3.21 (1 H, dd, *J* 11.7, 4.5, H-3), 3.26 (3 H, s, OCH_3), 3.48 (1 H, dt, *J* 6.9, 4.8, 2''-H), 3.62 (1 H, m, 2''-H'), 3.7 (1 H, dddd, *J* 11.7, 8.7, 3.9, 2.7, H-6); 4.38 (2 H, s, $PhCH_2$), 5.02 (1 H, dd, *J* 10.8, 1.5, 3'-H); 5.1 (1 H, dd, *J* 17.7, 1.5, 3'-H'), 6.58 (1 H, dd, *J* 17.7, 10.8, 2'-H) and 7.45-7.15 (5 H, m, ArH).

(2*S*,3*R*,6*S*)-6-(2-Hydroxyethyl)-2,3-dimethoxy-2-(2-methylbut-3-en-2-yl)tetrahydropyran (42). Ethanol (4 mL) was added to liquid ammonia (30 mL) followed by the benzyl ether **41** (487 mg) in THF (4 mL) at –78 °C. Small pieces of sodium were added until the solution turned blue. The mixture was stirred for 2 h at –78 °C during which time it remained blue and then solid ammonium chloride (1 g) was added followed by saturated aqueous ammonium chloride (10 mL) and ether (10 mL). The mixture was allowed to warm to rt and, after allowing the ammonia to evaporate, the aqueous layer was extracted with ether. The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography gave the title compound **42** (350 mg, 97%); δ_H (C_6D_6) 0.97-1.12 (2 H, m, 1''-H_2) 1.37 and 1.39 (each 3 H, s, CH_3), 1.20-1.72 (3 H, m, 4-H, 5-H_2), 1.95 (1 H, dddd, *J* 13.5, 12.0, 11.1, 4.2, 4-H'), 1.97 (1 H, br. s, OH), 3.07 (3 H, s, OCH_3), 3.22 (1 H, dd, *J* 11.4, 4.5, 3-H), 3.26 (3 H, s, OCH_3), 3.50-3.72 (3 H, m, 6-H, 2''-H_2), 5.02 (1 H, dd, *J* 10.8, 1.5, 3'-H), 5.1 (1 H, dd, *J* 17.7, 1.5, 3'-H') and 6.5 (1 H, dd, *J* 17.7, 11.1, 2'-H); δ_C (C_6D_6) 23.3, 24.5, 24.7, 30.1, 31.1, 38.4, 45.7, 50.5, 54.7, 60.2, 69.3, 80.2, 101.7, 110.2 and 147.4.

(3*S*)-Oct-7-ene-1,3-diol (44). The hydroxyepoxide **43**[14] (4 g, 28.2 mmol) in THF (20 mL) was added to sodium bis-(2-methoxyethoxy)aluminium hydride (65 wt % in toluene, 2.8 mL) in THF (12 mL) at 0 °C and the solution stirred at 0 °C for 4 h. Ether and saturated aqueous Rochelle's salt (30 mL) were added and the aqueous phase extracted with ethyl acetate (3 × 100 mL). After drying ($MgSO_4$) the organic extracts, concentration under reduced pressure gave the title compound **44** as a clear oil (3.8 g, 94 %), $[\alpha]_D^{20}$ –31 (*c* 5.9, $CHCl_3$) (Found: $M^+ + NH_4$, 162.1486. $C_8H_{20}O_2N$ requires M, 162.1489; ν_{max}/cm^{-1} 3345, 3078, 2935, 1641, 1438, 1056, 996 and 910; δ_H 1.55-1.60 (4 H, m, 4-H_2, 5-H_2), 1.60-1.80 (2 H, m, 6-H_2), 2.00-2.20 (2 H, m, 2-H_2), 3.22 (2 H, s, 2 × OH), 3.75-3.95 (3 H, m, 1-H_2, 3-H), 4.95-5.10 (2 H, m, 8-H_2) and 5.84 (1 H, ddt, *J* 16.8, 10.2, 6.6, 7-H); δ_C 25.0, 33.9, 37.3, 38.4, 61.7, 72.1, 114.9 and 138.8; *m/z* (Cl^+) 162 (M^+ + 18, 100%) and 145 (M^+ + 1, 90).

(3*S*)-1-Tri-isopropylsilyloxyoct-7-en-3-ol (45). The diol **44** (1.44 g, 10 mmol) was added to a suspension of tri-isopropylsilyl chloride (2.2 mL, 10 mmol) and imidazole (1.02 g, 15 mmol) in DCM (40 mL) at 0 °C and the reaction mixture allowed to warm to rt then stirred for 16 h. The mixture was washed with brine (80 mL) and the aqueous layer extracted with DCM (50 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (1:1 ether:light petroleum) of the residue gave the title compound **45** as a clear oil (3.1 g, 99 %), $[\alpha]_D^{20}$ –13 (*c* 7.3, $CHCl_3$) (Found: M^+ + H, 301.2552. $C_{17}H_{37}O_2Si$ requires M, 301.2557); ν_{max}/cm^{-1} 3430, 3078, 2935, 1641, 1463, 1095, 996, 910 and 883; δ_H 1.11 [21 H, m, 3 × $SiCH(CH_3)_2$], 1.40-1.65 (4 H, m, 4-H_2, 5-H_2), 1.71 (2 H, m, 6-H_2), 2.12 (2 H, m, 2-H_2), 3.57 (1 H, s, OH), 3.85-4.10 (3 H, m, 1-H_2, 3-H), 4.95-5.10 (2 H, m, 8-H_2) and 5.86 (1 H, ddt, *J* 16.6, 10.1, 6.8, 7-H); δ_C 12.0, 18.2, 25.1, 34.1, 37.3, 38.5, 63.9, 72.7, 114.7 and 139.1; *m/z* (Cl^+) 301 (M^+ + 1, 100%).

(8*S*)-8-Triethylsilyloxy-10-tri-isopropylsilyloxydec-1-en-4-ol (47). The alcohol **45** (3 g, 10 mmol) was added to a suspension of triethylsilyl chloride (1.85 mL, 11 mmol) and imidazole (1.02 g, 15 mmol) in DCM (40 mL) at rt and the reaction mixture stirred for 1 h then washed with brine (80 mL). Following extraction of the aqueous layer with DCM (50 mL), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (40:60 ether:light petroleum) of the residue gave the bis-silyl ether **46** as a clear oil (4.2 g, 99 %); δ_H 0.64 (6 H, q, *J* 7.5, 3 × $SiCH_2$), 1.04 (9 H, t, *J* 7.5, 3 × $SiCH_2CH_3$), 1.13 [21 H, m, 3 × $SiCH(CH_3)_2$], 1.40-1.60 (4 H, m, 4-H_2, 5-H_2), 1.73 (2 H, q, *J* 6.7, 6-H_2), 2.11 (2 H, m, 2-H_2), 3.81 (2 H, t, *J* 6.4, 1-H_2), 3.92 (1 H, m, 3-H), 4.96-5.15 (2 H, m, 8-H_2) and 5.87 (1 H, m, 7-H); δ_C 5.3, 7.2, 12.3, 18.3, 24.9, 34.2, 37.2, 40.7, 60.5, 69.5, 114.6 and 139.2.

The bis-silyl ether **46** (3.8 g, 9.18 mmol) was dissolved in DCM (40 mL) and the solution cooled to –78 °C. Ozone was bubbled through the solution at –78 °C until the solution turned blue (approx 45 min) and then oxygen was bubbled through for a further 5 min. Dimethyl sulphide (1.35 mL, 18.36 mmol) was added and the solution was allowed to warm to rt then concentrated under reduced pressure to leave (5*S*)-5-triethylsilyloxy-7-tri-isopropylsilyloxyheptanal.

Prop-2-enylmagnesium bromide (1 M in THF, 13 mL, 13 mmol) was added to this aldehyde in THF (20 mL) at rt and the solution stirred for 16 h. Saturated aqueous ammonium chloride (50 mL) and ether (50 mL) were added. The aqueous phase was extracted with ether (3 × 100 mL) and the organic extracts dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (3:1 ether:light petroleum) of the residue gave the title compound **47** as a colourless oil (2.65 g, 67 % from **45**), as a mixture of epimers, $[\alpha]_D^{20}$ –13 (*c* 1.0, $CHCl_3$) (Found: M^+ + H, 459.3688. $C_{25}H_{55}O_3Si_2$ requires M, 459.3684); ν_{max}/cm^{-1} 3362, 2951, 2868, 1460, 1415, 1239, 1064, 1013 and 883; δ_H 0.64 (6 H, q, *J* 8.1, 3 × $SiCH_2$), 0.90 (2 H, m, 6-H_2), 0.99 (9 H, t, *J* 8.2, 3 × $SiCH_2CH_3$), 1.09 [21 H, m, 3 × $SiCH(CH_3)_2$], 1.40-1.60 (4 H, m, 5-H_2, 7-H_2), 1.72 (2 H, q, *J* 6.3, 9-H_2), 2.10-2.40 (2 H, m, 3-H_2), 3.68 (1 H, m, 8-H), 3.78 (2 H, t, *J* 6.6, 10-H_2), 3.91 (1 H, m, 4-H), 5.17 (2 H, br. d, *J* 12.7, 1-H_2) and 5.86 (1 H, m, 2-H); δ_C 5.3, 7.2, 12.2, 18.3, 21.6, 37.2, 37.7, 40.6, 42.1, 60.5, 69.6, 70.9, 118.4 and 135.1; *m/z* (Cl^+) 459 (M^+ + 1, 30%), 419 (25) and 132 (100).

(8*S*)-8-Triethylsilyloxy-10-tri-isopropylsilyloxydec-1-en-4-one (48). Pyridine (6 mL, 74.6 mmol) and the alcohol **47** (2.5 g, 5.46 mmol) in DCM (5 mL) were added to a suspension of the Dess-Martin periodinane (2.5 g, 5.87 mmol) in DCM (10 mL) at rt and the mixture stirred for 50 min. Saturated aqueous sodium bicarbonate (50 mL) and ethyl acetate (50 mL) were added and the organic phase was washed with saturated aqueous sodium thiosulfate (20 mL). The aqueous layers were extracted with ethyl acetate (3 × 100

mL) and the organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue gave the title compound **48** as a colourless oil (1.9 g, 76 %), R_f = 0.48 (1:1 ether:light petroleum), $[\alpha]_D^{21}$ –6.1 (*c* 2.4, $CHCl_3$) (Found: M^+ + H, 457.3532. $C_{25}H_{53}O_3Si_2$ requires M, 457.3528); ν_{max}/cm^{-1} 2868, 1735, 1463, 1383, 1242, 1101, 1069, 1014, 882 and 843; δ_H 0.63 (6 H, q, *J* 7.5, 3 × $SiCH_2$), 0.99 (9 H, t, *J* 7.6, 3 × $SiCH_2CH_3$), 1.09 [21 H, m, 3 × $SiCH(CH_3)_3$], 1.49 (2 H, m, 6-H_2), 1.60-1.80 (4 H, m, 7-H_2, 9-H_2), 2.47 (2 H, m, 5-H_2), 3.19 (2 H, m, 3-H_2), 3.77 (2 H, t, *J* 6.3, 10-H_2), 3.91 (1 H, m, 8-H), 5.15-5.24 (2 H, m, 1-H_2) and 5.96 (1 H, ddt, *J* 17.0, 10.3, 7.0, 2-H); *m/z* (Cl^+) 457 (M^+ + 1, 10%), 325 (30) and 132 (100).

(2*R*,6*S*)-2-Methoxy-2-(prop-2-enyl)-6-(2-tri-isopropylsilyloxyethyl)tetrahydropyran (49). Anhydrous methanol (10.5 mL) and trimethyl orthoformate (0.1 mL) were added to the ketone **48** (1.30 g, 2.85 mmol) followed by oven dried pyridinium toluene 4-sulfonate (72 mg, 0.29 mmol). The mixture was stirred for 17 h, saturated aqueous sodium bicarbonate (50 mL) and ether (50 mL) were added and the aqueous phase was extracted with ether (2 × 20 mL). The organic extracts were washed with saturated aqueous sodium bicarbonate (2 × 20 mL), dried and concentrated under rediced pressure. Chromatography (1:3 light petroleum:ether with 1% triethylamine) of the residue gave the title compound **49** as a colourless oil (650 mg, 64 %), R_f = 0.8 (1:9 ether:light petroleum), $[\alpha]_D^{21}$ +3.1 (*c* 10.1, $CHCl_3$) (Found: M^+ + Na, 379.2641. $C_{20}H_{40}O_3NaSi$ requires M, 379.2639); ν_{max}/cm^{-1} 3077, 2867, 1642, 1464, 1096, 1057, 1039, 1009 and 882; δ_H (C_6D_6) 0.95-1.05 (2 H, m, 4-H_2), 1.11 [21 H, m, 3 × $SiCH(CH_3)_3$], 1.35-1.45 (2 H, m, 5-H_2), 1.60-2.00 (4 H, m, 3-H_2, 1''-H_2), 2.32 (1 H, ddt, *J* 15.2, 7.3, 1.0, 1'-H), 2.52 (1 H, ddt, *J* 15.2, 7.0, 1.0, 1'-H'), 3.21 (3 H, s, OCH_3), 3.75-3.95 (3 H, m, 6-H, 2''-H_2), 4.98-5.10 (2 H, m, 3'-H_2) and 5.87 (1 H, ddt, *J* 17.7, 10.5, 7.0, 2'-H); δ_C (C_6D_6) 12.3, 18.2, 19.3, 31.3, 33.1, 40.1, 41.7, 47.1, 60.1, 66.9, 98.8, 117.3 and 134.0; *m/z* (ES^+) 379 (M^+ + 23, 60%) and 325 (100).

(2*R*,6*S*)-2-Methoxy-2-(prop-2-enyl)-6-(2-hydroxyethyl)tetrahydropyran (50). Tetra-*n*-butylammonium fluoride (1 M in THF, 1.4 mL, 1.4 mmol) was added to the tri-isopropylsilyl ether **49** (450 mg, 1.26 mmol) in THF (10 mL) at rt and the mixture stirred for 16 h at rt. Water (50 mL) was added, the mixture was extracted into ether (4 × 50 mL) and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (20:80 light petroleum:ether with 1 % Et_3N) of the residue gave the title compound **50** as a clear oil (253 mg, ca. 100 %), $[\alpha]_D^{21}$ +3.1 (*c* 5.2, $CHCl_3$) (Found: M^+ + Na, 223.1300. $C_{11}H_{20}O_3Na$ requires M, 223.1305); ν_{max}/cm^{-1} 3351, 2954, 2926, 2873, 1699, 1453 and 1049; δ_H (C_6D_6) 1.05 and 1.19 (each 1 H, m, 4-H), 1.25-1.45 (2 H, m, 3-H_2), 1.50-1.75 (3 H, m, 1''-H, 5-H_2), 1.83 (1 H, m, 1''-H'), 2.16 (1 H, ddt, *J* 14.3, 7.0, 1.3, 1'-H), 2.23 (1 H, br. s, OH), 2.36 (1 H, ddt, *J* 14.3, 7.0, 1.3, 1'-H'), 3.07 (3 H, s, OCH_3), 3.50-3.85 (3 H, m, 6-H, 2''-H_2), 4.92-5.05 (2 H, m, 3'-H_2) and 5.75 (1 H, ddt, *J* 17.3, 10.3, 7.0, 2-H); δ_C (C_6D_6) 18.9, 31.0, 32.8, 38.6, 41.5, 47.1, 60.9, 70.3, 99.0, 117.6 and 133.5; *m/z* (ES^+) 223 (M^+ + 23, 100 %).

2-[(2*R*,6*S*)-2-Methoxy-2-(prop-2-enyl)tetrahydropyran-6-yl]ethyl (3*R*,5*R*,7*S*,9*S*,11*S*,15*R*)-7-benzyloxy-5,9-epoxy-11,15-epoxy-8,8-dimethyl-9-methoxy-3-(2-trimethylsilylethoxymethoxy)heptadec-16-enoate (52). Pyridine (80 μL) followed after 5 min by the alcohol **27** (75 mg, 0.127 mmol) in DCM (3.5 mL) were added to a suspension of the Dess-Martin periodinane (81 mg) in DCM (2 mL) and the mixture stirred for 15 min. Saturated aqueous sodium bicarbonate (10 mL) and ether (10 mL) were added and the aqueous phase was extracted with ether (3 × 10 mL). The organic extracts were washed with saturated aqueous sodium thiosulfate (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford the corresponding aldehyde; δ_H (C_6D_6) 0.00 [9 H, s, $Si(CH_3)_3$], 0.85-1.70 (18 H, m, 4-H_2, 6-H_2, 12-H_2, 13-H_2, 14-H_2, 2 × 8-CH_3, $SiCH_2$), 1.91 (1 H, dd, *J* 16.0, 3.2, 10-H), 2.16 (1 H, dd, *J* 16.0, 5.5, 10-H'), 2.45 (1 H, ddd, *J* 16.0, 4.8, 1.6, 2-H), 2.52 (1 H, ddd, *J* 16.0, 6.4, 2.5, 2-H'), 3.19 (3 H, s, OCH_3), 3.50 (1 H, m, 11-H), 3.60-3.88 (5 H, m, 3-H, 5-H, 7-H, OCH_2CH_2Si), 4.32 (1 H, m, 15-H), 4.33 and 4.49 (each 1 H, d, *J* 12.0, Ar*H*CH), 4.67 and 4.75 (each 1 H, d, *J* 7.0, OHC*H*O), 5.05 (1 H, dt, *J* 10.7, 1.8, 17-H), 5.35 (1 H, dt, *J* 17.4, 1.8, 17-H'), 5.87 (1 H, ddd, *J* 17.4, 10.7, 4.7, 16-H), 7.03-7.40 (5 H, m, ArH) and 9.70 (1 H, dd, *J* 2.5, 1.6, 1-H); δ_C (C_6D_6) –1.4, 17.1, 18.1, 20.2, 24.2, 26.7, 30.4, 31.6, 33.1, 33.4, 40.5, 42.5, 43.5, 48.4, 50.3, 65.5, 71.6, 72.0, 73.8, 78.0, 79.1, 95.3, 104.5, 113.4, 127.4, 128.4, 129.7, 135.2, 140.1 and 199.8.

Solid $NaH_2PO_4.2H_2O$ (195 mg, 10 equiv) and 2-methyl-but-2-ene in THF (2 M, 1.25 mL, 20 equiv) were added to this aldehyde in a mixture of *tert*-butanol:water (2:1, 1.5 mL) and the mixture cooled to 0 °C. A solution of $NaClO_2$ (72 mg) in *tert*-butanol:water (2:1, 1.5 mL) was added and the mixture stirred for 5 min. A mixture of saturated aqueous sodium hydrogen carbonate and brine (1:1, 5 mL) was added followed by ethyl acetate (10 mL). The aqueous phase was extracted with ethyl acetate (4 × 5 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the carboxylic acid **51**; *m/z* (ES^-) 605 (M^+ – 1, 100%).

This acid was dissolved in toluene (3 mL) and triethylamine (36 μL) and 2,4,6-trichlorobenzoyl chloride (24 μL) were added. The reaction mixture was stirred at rt for 1 h and the alcohol **50** (27 mg, 0.135 mmol) in toluene (4 mL) and 4-dimethylaminopyridine (24 mg) were added. The mixture was stirred for 15 min before saturated sodium hydrogen carbonate (15 mL) and EtOAc (15 mL) were added. The aqueous phase was extracted with ether (3 × 15 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography (15:1 to 1:1 light petroleum:ether with 1% Et_3N) gave the title compound **52** (47 mg, 47%) as a pale yellow oil (Found: M^+ + Na, 811.4796. $C_{44}H_{72}O_{10}NaSi$ requires M, 811.4787); δ_H (C_6D_6) 0.02 [9 H, s, $Si(CH_3)_3$], 0.84-2.00 (21 H, m, 4-H_2, 6-H_2, 10-H, 12-H_2, 13-H_2, 14-H_2, 2'-H_2, 3''-H_2, 4''-H_2, 5''-H_2, $SiCH_2$), 1.27 and 1.40 (each 3 H, s, 8-CH_3), 2.14-2.37 (2 H, m, 10-H', 1'''-H), 2.46 (1 H, dd, *J* 14.3, 7.5, 1'''-H'), 2.70 (1 H, dd, *J* 15.5, 5.5, 2-H), 2.84 (1 H, dd *J* 15.5, 6.3, 2-H'), 3.00-3.15 (2 H, m, OCH_2CH_2Si), 3.13 and 3.24 (each 3 H, s, OCH_3), 3.55-4.00 (5 H, m, 3-H, 5-H, 7-H, 11-H, 6''-H), 4.27-4.53 (5 H, m, 15-H, 1'-H_2, $PhCH_2$), 4.82 and 4.88 (each 1 H, d, *J* 7.0, OHC*H*O), 4.97-5.09 (3 H, m, 17-H, 3'''-H_2), 5.37 (1 H, dt, *J* 17.3, 1.6, 17-H'), 5.72-5.97 (2 H, m, 16-H, 2'''-H), 7.06-7.24 (3 H, m, ArH) and 7.33 (2 H, m, ArH); δ_C (C_6D_6) –1.4, 17.1, 18.2, 19.1, 20.1, 24.2, 31.1, 31.6, 32.9, 33.2, 33.5, 35.6, 40.6, 41.5, 41.9, 42.3, 43.4, 47.2, 48.5, 61.3, 65.5, 65.6, 65.8, 66.9, 71.5, 73.7, 73.9, 78.0, 79.2, 95.4, 98.9, 104.5, 113.4, 117.4, 127.3, 127.5, 128.4, 133.8, 139.9, 140.2 and 171.0; *m/z* (ES^+) 812 (M^+ + 23, 60%).

25-(3*R*,5*S*,7*S*,9*S*,11*S*,15*R*,19*R*,23*S*,16*E*)-7-Benzyloxy-5(9),11(15),19(23)-tris-epoxy-3-(2-trimethylsilylethoxymethoxy)-9,19-bis-methoxy-8,8-dimethylpentacos-16-enolide (53). Solid

Grubbs' II catalyst (1.8 mg) was added to the dienyl ester **52** (35 mg, 0.044 mmol) in toluene (5.5 mL) and the mixture was warmed to 60 ^{o}C and stirred for 3 h. More catalyst (1 mg) was added and the heating continued for 5.5 h. After cooling to rt, chromatography on neutral alumina (15:1 light petroleum:ether with 1% Et_3N) gave the title compound **53** (6 mg, 17%) (Found: M^+ + Na, 783.4481. $C_{42}H_{68}O_{10}NaSi$ requires M, 783.4474); δ_H (C_6D_6) –0.02 [9 H, s, $Si(CH_3)_3$], 0.80-2.15 (29 H, m, 4-H_2, 6-H_2, 10-H_2, 12-H_2, 13-H_2, 14-H_2, 18-H, 20-H_2, 21-H_2, 22-H_2, 24-H_2, 2 × 8-CH_3, $SiCH_2$), 2.42 (1 H, m, 18-H'), 2.60 (1 H, dd, *J* 16.7, 9.2, 2-H), 2.92 (1 H, m, 2-H'), 3.02-3.23 (2 H, m, OC$H_2$$CH_2$Si), 3.34 (6 H, s, 2 × OCH_3), 3.40-4.20 (7 H, m, 3-H, 5-H, 7-H, 11-H, 15-H, 23-H, 25-H), 4.32 and 4.49 (each 1 H, d, *J* 11.7, Ph*H*CH), 4.49 (1 H, m, 25-H'), 4.78 and 4.97 (each 1 H, d, *J* 7.0, OHC*H*O), 5.68 (1 H, dd, *J* 15.3, 7.5, 16-H), 6.07 (1 H, ddd, *J* 15.3, 8.0, 5.4, 17-H) and 7.10-7.35 (5 H, m, ArH); δ_C (C_6D_6) –1.5, 16.7 18.3, 19.1, 21.3, 24.3, 30.1, 30.3, 32.2, 32.4, 33.6, 34.3, 39.1, 40.2, 41.2, 42.6, 43.9, 46.6, 48.2, 48.4, 60.1, 64.9, 65.2, 67.5, 71.4, 74.2, 79.3, 79.25 96.6, 98.9, 104.3, 127.3, 128.3, 128.9, 134.5, 140.0 and 171.0; *m/z* (ES^+) 784 (M^+ + 23, 100%).

2-[(2*S*,3*R*,6*S*)-2,3-Dimethoxy-2-(2-methylbut-3-en-2-yl)tetrahydropyran-6-yl]ethyl (3*R*,5*R*,7*S*,9*S*,11*S*,15*R*)-7-benzyloxy-5,9-epoxy-11,15-epoxy-8,8-dimethyl-9-methoxy-3-(2-trimethylsilylethoxymethoxy)heptadec-16-enoate (54). Following the procedure outlined above, the alcohol **27** (75 mg, 0.127 mmol) gave the carboxylic acid **51**. This acid was dissolved in toluene (3 mL) and triethylamine (36 μL) and 2,4,6-trichlorobenzoyl chloride (24 μL) were added. The mixture was stirred at rt for 1 h and then the alcohol **40** (33 mg) in toluene (4 mL) and 4-dimethylaminepyridine (24 mg) were added. The mixture was stirred for 30 min and saturated aqueous sodium hydrogen carbonate (15 mL) and EtOAc (15 mL) were added. The aqueous phase was extracted with ether (3 × 15 mL) and the organic extracts were dried (Na_2SO_4) then concentrated under reduced pressure. Chromatography (15:1 to 1:1 light petroleum:ether + 1% Et_3N) of the residue gave the title compound **54**; δ_H (C_6D_6) 0.02 [9 H, s, $Si(CH_3)_3$], 0.85-1.85 (18 H, m, 4-H_2, 6-H_2, 12-H_2, 13-H_2, 14-H_2, 2'-H_2, 4''-H_2, 5''-H_2, $SiCH_2$), 1.26, 1.32, 1.36 and 1.40 (each 3 H, s, CH_3), 1.95 (1 H, dd, *J* 16.0, 3.5, 10-H), 2.20 (1 H, dd, *J* 16.0, 5.5, 10-H'), 2.69 (1 H, dd, *J* 15.3, 5.3, 2-H), 2.86 (1 H, dd *J* 15.3, 6.7, 2-H'), 3.04, 3.24 and 3.30 (each 3 H, s, OCH_3), 3.40-3.95 (8 H, m, 3-H, 5-H, 7-H, 11-H, 3''-H, 6''-H, OC$H_2$$CH_2$Si), 4.25-4.40 (2 H, m, 1'-H_2), 4.32 and 4.48 (each 1 H, d, *J* 11.8, Ph*H*CH), 4.49 (1 H, m, 15-H), 4.82 and 4.90 (each 1 H, d, *J* 7.0, OHC*H*O), 5.02 (1 H, dd, *J* 10.8, 1.6, 4'''-H), 5.02-5.14 (2 H, m, 17-H, 4'''-H'), 5.37 (1 H, dt, *J* 17.3, 1.9, 17-H'), 5.90 (1 H, ddd, *J* 17.4, 10.7, 4.7, 16-H), 6.53 (1 H, dd, *J* 17.7, 10.8, 3'''-H), 7.04-7.25 (3 H, m, ArH) and 7.34 (2 H, d, *J* 7.0, ArH); δ_C (C_6D_6) –1.4, 17.1, 18.2, 20.1, 23.2, 24.2, 24.5, 24.6, 30.1, 31.1, 33.3, 33.5, 35.2, 40.6, 42.0, 42.4, 43.5, 45.7, 48.5, 50.5, 54.7, 61.5, 65.6, 65.8, 67.3, 71.6, 73.7, 73.9, 78.0, 79.2, 80.2, 95.5, 101.4, 104.5, 109.8, 113.4, 127.3, 127.5, 128.4, 139.9, 140.2, 147.5 and 171.0; *m/z* (ES^+) 865 (M^+ + 18, 70%) and 816 (40).

Attempts to carry out RCM using the conditions outlined for the synthesis of the macrolide **53**, led to mixtures of compounds containing only traces of a product containing a disubstituted (*E*)-double-bond; δ_H (C_6D_6) 6.31 (1 H, dd, *J* 16.0, 5.5, 16-H) and 6.78 (1 H, br. d, *J* 16.0, 17-H). The major products appeared to have retained the double-bond next to the geminal methyl groups but to have lost the double-bond attached to the tetrahydropyran; δ_H (C_6D_6) 5.01 (1 H, dd, *J* 10.8, 1.6, 4'''-H), 5.51 (1 H, dd, *J* 17.7, 1.6, 4'''-H'), 5.98 (1 H, narrow m, 16/17-H) and 6.55 (1 H, dd, *J* 17.7, 10.8, 3'''-H). Some dimeric products were evident from the low resolution MS; *m/z* (ES^+) 1689 (M^+ + 23, 100%).

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