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Synthesis of 2,6-*cis*-disubstituted 4-methylenetetrahydropyrans by oxy-Michael addition

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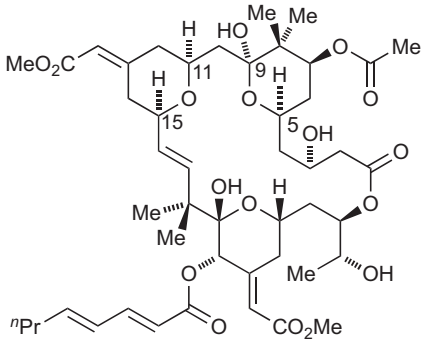
ABSTRACT

The combination of an 'ene' reaction between a 2-(2-trialkylsilyloxyalkyl)prop-2-enyl(trimethyl)silane and an alk-1-yn-3-one mediated by zinc(II) iodide, and an intramolecular oxy-Michael reaction, provides an efficient synthesis of *cis*-2,6-disubstituted 4-methylenetetrahydropyrans of interest in the context of a synthesis of bryostatins. The stereoselective formation of (*E*)-vinylsilanes in the 'ene' reaction is of interest.

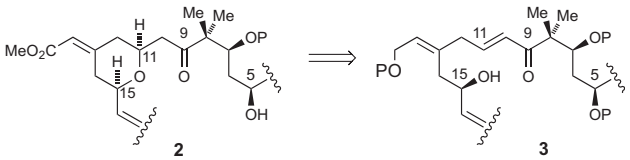
1. Introduction

The bryostatins, as represented by bryostatin 1 (**1**), are a group of important natural products of interest because of their anti-cancer and other biological activities.[1] However, the supply of bryostatins from natural sources is limited and this has led to a considerable body of work being carried out on their synthesis including the completion of several total syntheses[2] and the synthesis of analogues.[3,4] The synthesis of fragments has also been of interest.[1]



1

The hemiacetal at C(9) in bryostatins is synthetically equivalent to the corresponding hydroxyketone, see partial structure **2**. When planning a synthesis of this fragment, the formation of the *O*—C(11) bond by an intramolecular oxy-Michael reaction was considered an attractive option since many alternatives would be available for the synthesis of the oxy-Michael precursor **3**. However, these oxy-Michael reactions involve skipped dienes conjugated to a ketone that might be prone to double bond migration and isomerisation. There was also the question as to the stereoselectivity of the cyclisation reaction. We here report studies into the assembly of 4-methylenetetrahydropyrans corresponding to the C(7)—C(16) fragment of brysotatins, albeit lacking the methoxycarbonyl moiety, using the oxy-Michael approach.[5,6]



2 **3**

(P = protecting groups)

2. Results and discussion

In preliminary studies, a Stille reaction was used to synthesize an oxy-Michael precursor **13**, see Scheme 1. 2-(Acetoxymethyl) prop-2-enylstannane **6**[7] was prepared by stannylation of 2-methylprop-2-enol **4** followed by acetylation of the resulting 2-hydroxymethylpropenylstannane **5**. The boron trifluoride mediated

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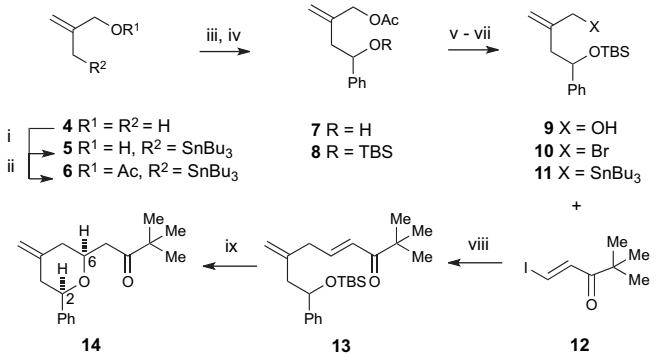
reaction of this stannane with benzaldehyde gave the homoallylic alcohol **7**[7] that was converted into its *tert*-butyldimethylsilyl ether **8**. This was taken though to the Stille precursor **11** by saponification and conversion of the resulting alcohol **9** into the stannane **11** via a Barbier reaction of the corresponding bromide **10**. The Stille coupling of the propenylstannane **11** with 4,4-dimethyl-1-iodopent-1-en-3-one (**12**)[8] was more effective using $PdCl_2(MeCN)_2$ as the catalyst and gave the dienone **13**. Desilylation of this dienone with in situ cyclisation using HF·pyridine gave the 2,6-*cis*-disubstituted 4-methylenetetrahydropyran **14** in a 79% yield.



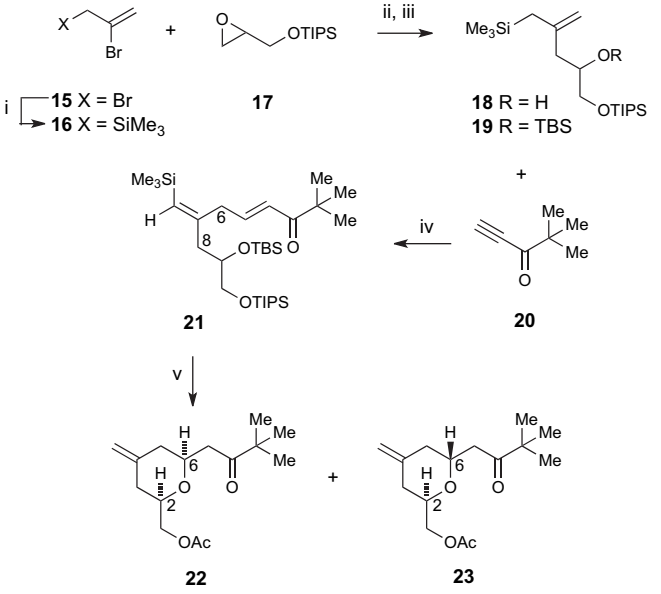
Scheme 1. Reagents and conditions: i, ^{n}BuLi, TMEDA, Et_2O, −30 °C to rt, 20 h, $^{n}Bu_3SnCl$, 0 °C to rt, 15 min (59%); ii, Ac_2O, Et_3N, DMAP, DCM, rt, 10 h (88%); iii, $BF_3{\cdot}Et_2O$, PhCHO, DCM, −78 °C, 1.5 h (99%); iv, $^{t}BuMe_2SiOTf$, 2,6-lutidine, DCM, 0 °C then rt, 3 h; v, K_2CO_3, H_2O, MeOH, rt, 2 h (91% from **7**); vi, (a) MsCl, Et_3N, DCM, 0 °C to rt, 3 h (b) NaBr, DMF, rt, 18 h (64%); vii, $(^{n}Bu_3Sn)_2O$, Mg, 1,2-dibromoethane, 35 °C, sonicate, 1 h (73%); viii, $PdCl_2(MeCN)_2$, DMF, 80 °C, 4 h (45%); ix, HF·pyridine, MeCN, rt, 12 h (79%).

The structure assigned to the methylenetetrahydropyran **14** was supported by spectroscopic data. In particular, the relative stereochemistry at C(2) and C(6) was assigned on the basis of a significant NOE enhancement of H(6) on irradiation of H(2) and vice versa. The axial hydrogens at C(3) and C(5) were also clearly observable as triplets with coupling constants of 11.5 Hz consistent with diaxial coupling to the hydrogens at C(2) and C(6).

The formation of this 2,6-*cis*-disubstituted stereoisomer **14** was not unexpected since its 2- and 6-substituents are both equatorial with respect to the six-membered ring, but whether this was due to kinetic or thermodynamic control was not clear at this stage. However, this reaction was usefully stereoselective in that the 2,6-*trans*-isomer was not isolated.

The stereoselective formation of the 4-methylenetetrahydropyran **14** from dienone **13** by deprotection and a subsequent oxy-Michael reaction shows that this chemistry is compatible with a skipped diene. However, a more efficient synthesis of oxy-Michael precursors was required. Using mild Lewis acids, allyl(trimethyl)silanes have been shown to undergo 'ene' reactions with propargylic ketones in a reaction, which preserves the trimethylsilyl group,[9] and this chemistry was investigated for the synthesis of oxy-Michael precursors with additional functionality.

2-Bromo-3-trimethylsilylpropene (**16**) was prepared from 2,3-dibromopropene **15** by treatment with trichlorosilane in the presence of triethylamine and copper(I) chloride followed by the reaction with methylmagnesium bromide.[10] Treatment of the racemic epoxide **17**, in the presence of copper(I) iodide, with the Grignard reagent generated from the bromide **16**, gave the homoallylic alcohol **18**, which was protected as its *tert*-butyldimethylsilyl ether **19**. The zinc(II) iodide-catalysed 'ene' reaction of this allylsilane with 4,4-dimethylpent-1-yn-3-one (**20**) retained the trimethylsilyl group and gave the (*E*)-vinylsilane **21** as the only isolated product. The one-pot deprotection–cyclisation of the dienone **21** was then carried out using hydrogen fluoride in acetonitrile and, after acetylation, gave the separable 2,6-*cis*- and 2,6-*trans*-disubstituted 4-methylenetetrahydropyrans **22** and **23** in overall isolated yields of 61% and 11%. Similar results were obtained using toluene 4-sulfonic acid in acetonitrile or pyridinium toluene 4-sulfonate in ethanol for the deprotection–cyclisation (Scheme 2).



Scheme 2. Reagents and conditions: i, Cl_3SiH, Et_3N, CuCl, Et_2O, 0 °C to rt, 15 h, then MeMgBr, Et_2O, rt, 15 h (70%); ii, **16**, Me_3SiCl, Mg, THF, reflux, then **17**, CuI, THF, rt, 1 h (95%); iii, $^{t}BuMe_2SiOTf$, 2,6-lutidine, DCM, rt, 18 h (90%); iv, 4 Å sieves, ZnI_2, DCM, rt, 24 h (52%); iv, HF, MeCN, rt, 18 h, then Ac_2O, py, DCM, rt, 18 h (**22**, 61%; **23**, 11%).

The structure of the (*E*)-vinylsilane **21** formed during the 'ene' reaction was assigned on the basis of ^{1}H NMR NOE studies in that a significant enhancement of the methylene proton was observed on irradiation of 8-H_2 but not on irradiation of 6-H_2 and was consistent with later studies of similar reactions. The retention of the silyl group has precedent, indeed the reaction conditions chosen were known to result in retention of the silyl group. However, the literature examples[9] involve cyclohexenylmethylsilanes and the high stereoselectivity of the 'ene' process in an open-chain system was not expected. Mechanistic aspects of the reaction were not studied, but a two-step process via the silicon stabilized carbenium ion **24** may be involved. If this is the case, the observed stereoselectivity is consistent with an intramolecular proton transfer to the enolate carbon via a six-membered chair-like transition structure, see structure **25** in Fig. 1. A similar transition structure could be drawn for a concerted process.

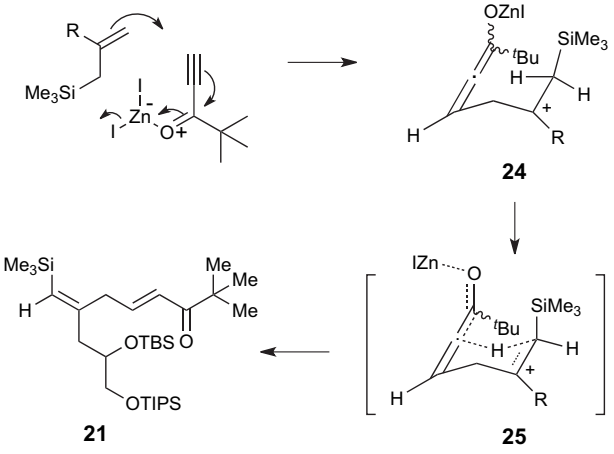
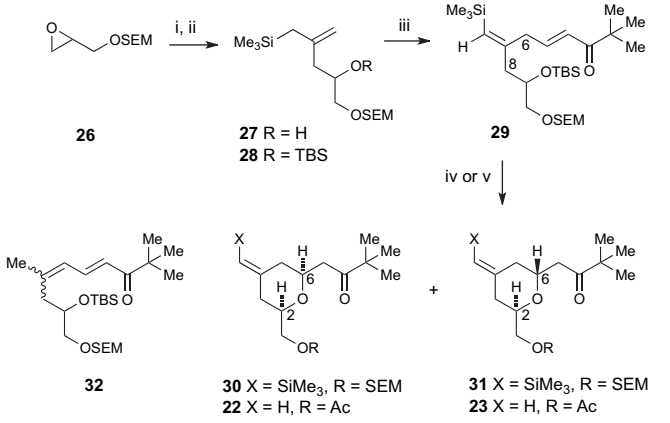


Fig. 1. Formation of (*E*)-vinylsilane **21**.

The major product from the oxy-Michael reaction of dienone **21** was identified as the 2,6-*cis*-diastereoisomer **22** from ^{1}H NMR data. In particular, axial-axial coupling was observed between H(2) and H(3)$_{ax}$ and between H(6) and H(5)$_{ax}$.

The analogous cyclisation of the 2-(trimethylsilylethoxy)-methoxy (SEM) protected hydroxyketone **29** was also investigated, see Scheme 3. Copper(I)-catalysed ring-opening of the SEM-protected epoxide **26** using the Grignard reagent derived from the bromopropenylsilane **16** gave the alcohol **27**, which was protected as its *tert*-butyldimethylsilyl ether **28**. The 'ene' reaction of this allylsilane with the alkynyl ketone **20** gave the (*E*)-vinylsilane **29** with excellent stereoselectivity although other Lewis acids, including zinc(II) chloride and bromide, trimethylsilyl trifluoromethanesulfonate and bis(cyclopentadienyl)titanium(II) trifluoromethanesulfonate gave complex mixtures of products.

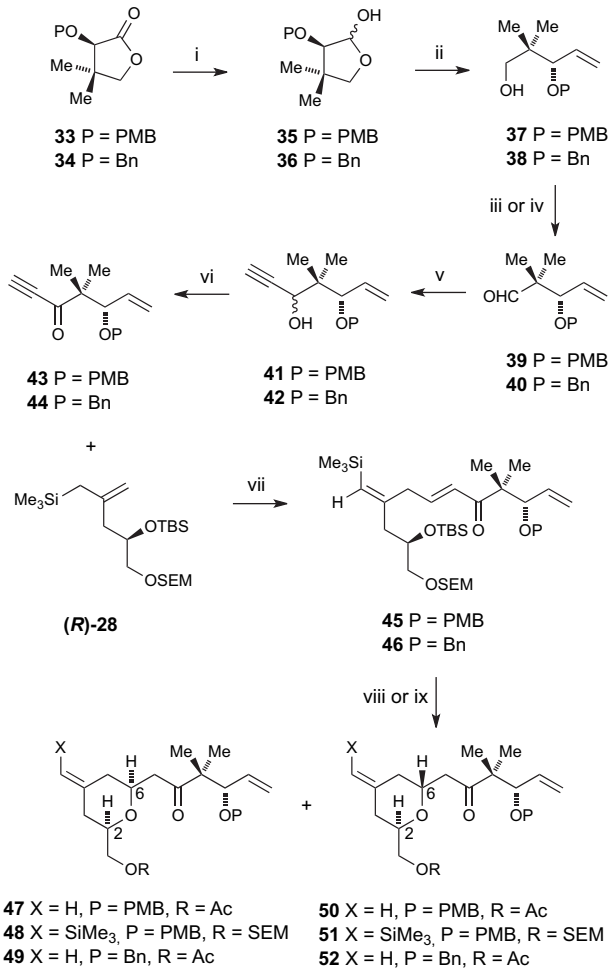


Scheme 3. Reagents and conditions: i, **16**, Me_3SiCl, Mg, THF, reflux, then **26**, CuI, THF, rt, 1 h (88%); ii, $^tBuMe_2SiOTf$, 2,6-lutidine, DCM, rt, 18 h (77%); iii, 4 Å sieves, ZnI_2, DCM, rt, 24 h (62%); iv, HF·pyridine, THF, 0 °C to rt, 18 h (**30**, 38%; **31**, 38%); v, HF, MeCN, rt, 18 h, then Ac_2O, py, DCM, rt, 18 h (**22**, 62%; **23**, 10%).

Desilylation of the dienylketone **29** was studied under various conditions. With HF·pyridine in tetrahydrofuran, a 50:50 mixture of the 2,6-*cis*- and 2,6-*trans*-disubstituted 4-(trimethylsilylmethylene)tetrahydropyrans **30** and **31** was obtained in which the vinylic trimethylsilyl and the SEM groups had been retained. Tetra-*n*-butylammonium fluoride effected desilylation and double bond migration but no cyclisation to give the open-chain product **32** as a mixture of (*E*)- and (*Z*)-isomers (82%). However, hydrogen fluoride in acetonitrile with in situ acetylation of the products gave the previously obtained 2,6-*cis*- and 2,6-*trans*-disubstituted methylenetetrahydropyrans **22** and **23**, ratio **22**/**23**=85:15, as before.

The geometry of the vinylsilane **29** was assigned by analogy with geometry of vinylsilane **21** and was consistent with later work. The less polar 4-(trimethylsilylmethylene)tetrahydropyran was provisionally identified as the 2,6-*cis*-epimer **30** by analogy with other series. The (*E*)-geometry of its exocyclic double bond was confirmed by NOE studies since the exocyclic methylene proton, 4-CH, was significantly enhanced on irradiation of one of the hydrogens at C(3) but was not affected by either of the hydrogens at C(5).

The less stereoselective desilylation and cyclisation of dienylketone **29** induced by HF·pyridine, may reflect kinetic control, whereas the more stereoselective reactions of both dienylketones **21** and **29** using hydrogen fluoride in acetonitrile may be due to thermodynamic control under the more acidic conditions. This point was not investigated further at this stage. Rather it was decided to study the use of slightly more complex alkynylketones, which would allow for the subsequent development of the C(1)–C(8) fragment of bryostatins. The synthesis and cyclisations of the dienylketones **45** and **46** are outlined in Scheme 4.



Scheme 4. Reagents and conditions: i, DIBAL-H, THF, −78 to −35 °C, 5 h (**35**, 87%; **36**, 88%); ii, Ph_3PMeBr, THF, ^{n}BuLi, −78 to 0 °C, 30 min., −78 °C, add **35** or **36**, rt, 15 h (**37**, 59%; **38**, 82%); iii, TPAP, NMO, 4 Å sieves, DCM, rt, 3 h (**39**, 77%); iv, DMSO, $(COCl)_2$, DCM, −78 °C, 1 h, Et_3N (**40**, 94%); v, HCCMgBr, THF, −78 °C, rt, 18 h (**41**, 50:50, 96%; **42**, 54:46, 93%); vi, Dess–Martin periodinane, DCM, 0 °C, rt, 3 h (**43**, 92%; **44**, ca. 100%); vii, 4 Å sieves, ZnI_2, DCM, rt, 24 h (**45**, 66%; **46**, 75%); viii, HF, MeCN, rt, 18 h, then Ac_2O, py, rt, 18 h (**47**, 46%; **50**, <6%; **49**, 66%; **52**, 6%); ix, HF·pyridine, THF, 0 °C, rt, 18 h (**48**, 21%; **51**, 21%).

Protection of (*R*)-pantolactone as its 4-methoxybenzyl ether **33** followed by reduction gave the lactol **35** that was converted into the pentenol **37**[11] via a Wittig condensation. Oxidation and addition of ethynylmagnesium bromide to the resulting aldehyde **39** gave the propargylic alcohol **41** as a 50:50 mixture of separable epimers. Oxidation gave the ketone **43** and the zinc(II) iodide promoted 'ene' reaction of this ketone with the (*R*)-enantiomer of the allylsilane **28** gave the trienylketone **45** with excellent stereoselectivity.

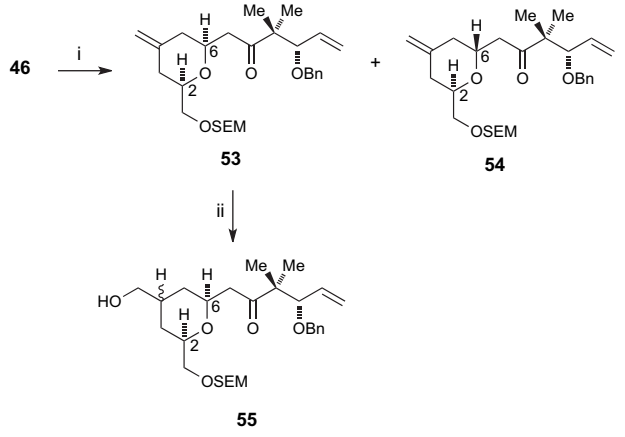
The one-pot deprotection and cyclisation of ketone **45** using HF in acetonitrile gave predominantly the 2,6-*cis*-4-methylenetetrahydropyrans **47** after acetylation, the 2,6-*cis*-**47**/2,6-*trans*-**50** ratio being ca. 85:15, but only in a modest yield (52%) perhaps due to the lability of the 4-methoxybenzyl group under these conditions. The 2,6-*cis*-configuration of the major isomer **47** was confirmed by ^{1}H NMR, axial–axial coupling being observed between H(2) and H(3)$_{ax}$ and between H(6) and H(5)$_{ax}$.

With HF·pyridine, deprotection and cyclisation of ketone **45** proceeded with retention of the trimethylsilyl and SEM groups but, as observed for the cyclisation of dienone **29**, a 50:50 mixture of the epimeric (*E*)-4-(trimethylsilylmethylene)tetrahydropyrans **48** and **51** was obtained.

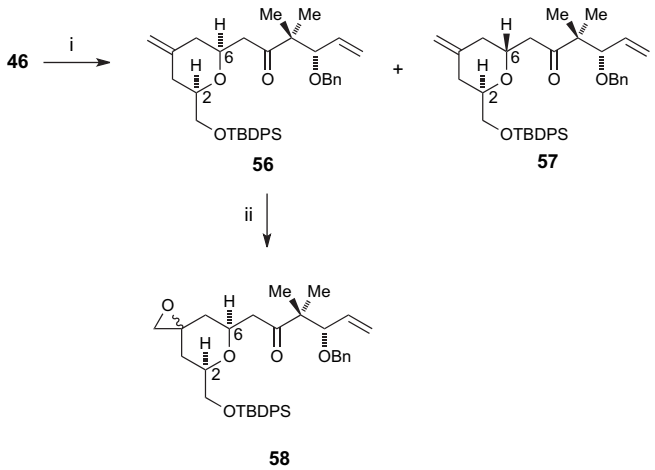
At this stage, since the cyclisation of dienone **45** using HF in acetonitrile had given only a modest yield of the cyclised products

47 (and **50**), the benzyl protected cyclisation precursor **46** was prepared from benzyl protected (*R*)-pantolacone, see Scheme 4. In this case, the configuration of the vinylsilane **46**, prepared from the zinc(II) iodide promoted reaction between the allylsilane (***R***)-**28** and the alkynyl ketone **44** was confirmed by NOE. Cyclisation of dienone **46** using HF in acetonitrile gave the desilylated 4-methylenetetrahydropyrans **49** and **52** in a 78% yield, ratio 90:10. The 2,6-*cis*-configuration assigned to the major isomer **49** was confirmed by ^{1}H NMR in that a significant NOE enhancement of H(2) was observed on irradiation of H(6) and vice versa. Moreover, both the 2- and 6-substituents were shown to be equatorial in this major isomer by the observation of *trans*-diaxial coupling between H(2) and H(3)$_{ax}$ and between H(6) and H(5)$_{ax}$.

To complete a synthesis of the C(1)–C(16) fragment of the bryostatins, the exocyclic methylene group of the 2,6-disubstituted 4-methylenetetrahydropyrans would need to be converted stereoselectively into the required 4-(methoxycarbonylmethylene) moiety and the terminal double-bond elaborated into the C(1)–C(5) fragment. Since it was possible that the primary acetate substituent would limit the chemistry, which could be used for these conversions the analogous SEM- and *tert*-butyldiphenylsilyl-protected 4-methylenetetrahydropyrans **53**/**54** and **56**/**57** were prepared by cyclisation of dienone **46** using HF in acetonitrile followed by protection of the primary alcohol using either SEM or *tert*-butyldiphenylsilyl chloride, see Schemes 5 and 6.



Scheme 5. Reagents and conditions: i, HF, MeCN, rt, 18 h, then SEMCl, ^{i}Pr$_2$NEt, DCM, rt, 15 h (**53**, 48%; **54**, 9%); ii, 9-BBN, THF, rt, 18 h, aq NaOH (3 M), H_2O_2 (30%), rt, 3 h (73%, 70:30 mixture of epimers).



Scheme 6. Reagents and conditions: i, HF, MeCN, rt, 18 h, then ^{t}BuPh$_2$SiCl, imid., DCM, rt, 18 h (**56**, 57%; **57**, 10%); ii, *m*-CPBA, DCM, 0 °C, 5 h (95%, 85:15 mixture of epimers).

Hydroboration of the 2,6-*cis*-disubstituted methylenetetrahydropyran **53** took place preferentially on the exocyclic methylene group to give a mixture of epimeric primary alcohols **55** after oxidation of the intermediate organoborane. Similarly, epoxidation of the analogous *tert*-butyldiphenylsilyl ether **56** also took place on the exocyclic methylene group to give a mixture of the exocyclic epoxides **58**. Although it is likely that these reactions took place selectively from the equatorial direction on the less hindered face of the methylenetetrahydropyrans **53** and **56**, the configurations of the major products **55** and **58** were not formally confirmed although reasonable stereoselectivities were observed.

3. Summary and conclusions

The oxy-Michael reaction of skipped dienones has proved useful for the synthesis of 4-methylenetetrahydropyrans that may be useful in the context of a synthesis of bryostatins.[5,6] Deprotection with in situ cyclisation of the hydroxyl protected dienones **13**, **21**, **29**, **45** and **46**, under acidic conditions using hydrogen fluoride in acetonitrile, gave 2,6-*cis*-disubstituted 4-methylenetetrahydropyrans preferentially. The analogous deprotection and cyclisation reactions of dienones **29** and **45** under less acidic conditions using hydrogen fluoride in pyridine were less stereoselective. It is suggested that the cyclisations in acetonitrile are under thermodynamic control since the 2,6-*cis*-disubstituted tetrahydropyrans, in which the 2- and 6-substituents are both equatorial, are believed to be the more stable. Also of interest in this work are the stereoselective 'ene' reactions between 2-substituted allylsilanes and propargylic ketones, which gave (*E*)-vinylsilanes with excellent stereoselectivity even for the acyclic systems.[9] Although giving the wrong stereoisomer in these cases for conversion with retention of configuration into the 4-(methoxycarbonylmethylene)tetrahydropyran present in bryostatins,[2g] these reactions may be useful in the general context of the stereoselective synthesis of skipped dienes. Finally, the exocyclic epoxide **58**, prepared by regioselective epoxidation of diene **56**, after cleavage to the corresponding ketone, should provide access to the required 4-(methoxycarbonylmethylene)tetrahydropyran on treatment with the appropriate enantiomerically enriched phosphine oxide.[2d] Details of the completion of a synthesis of the C(1)–C(16) fragment of a bryostatin using this chemistry will be reported elsewhere.[12]

4. Experimental

4.1. General

Melting points were recorded on a Gallenkamp apparatus, and optical rotations measured on an AA-100 polarimeter at 589 nm. Proton NMR spectra were recorded using Varian Unity Inova 300 and Varian Unity 500 spectrometers. Coupling constants are given in hertz and chemical shifts relative to Me_4Si. IR spectra were recorded on an ATI Mattson Genesis FTIR spectrometer and were run as liquid films unless otherwise stated. Low resolution mass spectra were measured on a Fisons Trio 2000 spectrometer and high resolution spectra on a Kratos Concept-IS spectrometer.

Chromatography refers to flash chromatography using Merck silica gel 60H (40–63 nm[3], 230–400 mesh). Light petroleum refers to the fraction boiling at 40–60 °C and ether to diethyl ether. All solvents and reagents were purified by standard techniques and all non-aqueous reactions were performed under an atmosphere of dry argon or nitrogen.

4.2. Experimental procedures

*4.2.1. 3-Acetoxymethyl-1-phenylbut-3-en-1-ol (**7**)*[7]. Stannane **6** (5.73 g, 14 mmol) and boron trifluoride diethyletherate (4.4 mL,

36 mmol) were added to benzaldehyde (1.2 mL, 12 mmol) in dichloromethane (22 mL) at −78 °C. After 1.5 h, the reaction mixture was poured into saturated aqueous ammonium chloride. The aqueous solution was extracted with ether and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue using petrol/ether (2:1) gave the *title compound* **7** (2.60 g, 99%) as a colourless oil; ν_{max} 1050, 1235, 1375, 1739, 3447 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.15 (3H, s, C*H*$_3$CO), 2.31 (1H, s, O*H*), 2.54 (2H, m, 2-*H*$_2$), 4.61 and 4.63 (each 1H, d, *J* 15.0, 13.0, 3-C*H*), 4.90 (1H, t, *J* 6.5, 1-*H*), 5.13 and 5.23 (each 1H, s, 4-*H*), 7.41 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 21.0, 38.2, 43.7, 66.7, 72.5, 115.9, 125.6, 127.6, 128.4, 140.5, 143.7; *m*/*z* (EI) 220 (M^+, 10%), 203 (75), 143 (100), 107 (99), 79 (62), 72 (64), 43 (55); HRMS (CI): M^++NH_4, found 238.1437. $C_{13}H_{20}NO_3$ requires 238.1443.

*4.2.2. 4-tert-Butyldimethylsilyloxy-2-methylene-4-phenylbut-1-yl(tributyl)stannane (**11**).* *tert*-Butyldimethylsilyl trifluoromethane/sulfonate (2.52 g, 9.52 mmol) was added to the alcohol **7** (1.40 g, 6.36 mmol) and 2,6-lutidine (1.36 g, 12.7 mmol) in dichloromethane (20 mL) at 0 °C and the mixture allowed to warm to ambient temperature, stirred for 3 h, then poured into saturated aqueous ammonium chloride (50 mL). The aqueous layer was separated and extracted with dichloromethane (2×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the acetate **8** as a colourless oil; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.17 (each 3H, s, SiC*H*$_3$), 1.03 [9H, s, SiC(C*H*$_3$)$_3$], 2.25, (3H, s, C*H*$_3$CO), 2.56 (1H, dd, *J* 13.5, 5, 3-*H*), 2.63 (1H, dd, *J* 13.5, 6.3, 3-*H*′), 4.65 and 4.72 (each 1H, d, *J* 10, 1-*H*), 4.95 (1H, m, 4-*H*), 5.07 and 5.24 (each 1H, m, 2-C*H*), 4.72 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.11, −4.78, 18.09, 20.85, 25.73, 44.75, 67.09, 74.35, 115.46, 125.83, 127.04, 127.96, 140.40, 144.74, 170.57. This acetate was dissolved in methanol (20 mL) and saturated aqueous potassium carbonate (2 mL) was added. The mixture was stirred at ambient temperature for 2 h then concentrated under reduced pressure. Ethyl acetate (20 mL) was added and the mixture was washed with saturated aqueous ammonium chloride (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using petrol/ether (95:5) as eluent gave the alcohol **9** (1.69 g, 5.78 mmol, 91%) as a colourless oil. Methane sulfonic anhydride (2.02 g, 11.6 mmol) was added to the alcohol **9** (1.70 g, 5.82 mmol) and triethylamine (2.94 g, 29.1 mmol) in dichloromethane (20 mL) at 0 °C and the mixture stirred at ambient temperature for 3 h then poured into saturated aqueous ammonium chloride (20 mL). The aqueous layer was extracted with dichloromethane (2×50 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the corresponding methanesulfonate as a brown oil. This sulfonate was dissolved in *N*,*N*-dimethylformamide (10 mL) and sodium bromide (2.40 g, 23.3 mmol) was added. The mixture was stirred at ambient temperature for 18 h then poured into water (50 mL). The mixture was extracted with ether (3×50 mL) and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using petrol/ether (99:1) as eluent gave the bromide **10** (1.32 g, 3.71 mmol, 64%) as a colourless oil; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.19 (each 3H, s, SiC*H*$_3$), 1.04 [9H, s, SiC(C*H*$_3$)$_3$], 2.73 (2H, d, *J* 6.0, 3-*H*$_2$), 4.10 (2H, s, 2-C*H*$_2$), 4.99 (1H, t, *J* 6.0, 4-*H*), 5.08 and 5.37 (each 1H, s, 1-*H*), 7.45 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.06, −4.75, 18.10, 25.76, 37.54, 44.46, 74.50, 118.27, 125.84, 127.10, 128.00, 142.20, 144.54. Magnesium turnings (0.155 g, 6.48 mmol) was added to 1,2-dibromoethane (0.583 g, 3.10 mmol), the bromide **10** (1.00 g, 2.82 mmol) and bis(tributyltin) oxide (1.68 g, 2.82 mmol) in tetrahydrofuran (10 mL) and the mixture sonicated at 35 °C for 1 h. It was then poured into saturated aqueous ammonium chloride (20 mL) and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography using petrol as eluent gave the *title compound* **11** (1.17 g, 2.06 mmol, 73%) as a colourless oil; ν_{max} 669, 776, 835, 944, 1069, 1085, 1255, 1463, 1627 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.19 (each 3H, s, SiC*H*$_3$), 0.98−1.38 [24H, m, 3×C*H*$_3$CH$_2$CH$_2$C*H*$_2$Sn and SiC(C*H*$_3$)$_3$], 1.38−1.50 (6H, m, 3×CH$_3$CH$_2$C*H*$_2$CH$_2$Sn), 1.58−1.68 (6H, m, 3×CH$_3$C*H*$_2$-CH$_2$CH$_2$Sn), 1.85 and 2.00 (each 1H, d, *J* 11, 1-*H*), 2.31 and 2.49 (each 1H, dd, *J* 13.5, 5.0, 3-*H*), 4.60 and 4.72 (each 1H, t, *J* 9.5, 2-C*H*), 4.92 (1H, dd, *J* 8.0, 5.0, 4-*H*) and 7.35−7.47 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.03, −4.76, 9.37, 13.62, 18.14, 19.40, 25.79, 27.29, 28.90, 50.01, 74.79, 107.87, 125.87, 126.75, 127.83, 145.68, 146.32; *m*/*z* (EI) 509 (M^+−57, 20%), 507 (15), 451 (10), 449 (7), 291 (90), 289 (80), 41 (100).

*4.2.3. (E)-9-tert-Butyldimethylsilyloxy-2,2-dimethyl-7-methylene-9-phenylnon-4-en-3-one (**13**).* Vinyl iodide **12**[8] (44 mg, 0.177 mmol), allylstannane **11** (100 mg, 0.177 mmol) and bis(acetonitrile) dichloropalladium(II) (9 mg, 0.036 mmol) were heated at 80 °C in degassed *N*,*N*-dimethylformamide (5 mL) for 4 h. The mixture was allowed to cool to ambient temperature, water (10 mL) was added and the mixture was extracted with ether (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using petrol/ether (99:1) as eluent gave the *title compound* **13** (31 mg, 0.080 mmol, 45%) as a colourless oil; ν_{max} 700, 777, 836, 1069, 1091, 1256, 1364, 1473, 1623, 1692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.19 (each 3H, s, SiC*H*$_3$), 1.04 [9H, s, SiC(C*H*$_3$)$_3$], 1.33 [9H, s, C(C*H*$_3$)$_3$], 2.48 (1H, dd, *J* 13.5, 5.0, 8-*H*), 2.61 (1H, dd, *J* 13.5, 8.0, 8-*H*′), 3.04 (2H, d, *J* 7.0, 6-*H*$_2$), 4.92 (1H, dd, *J* 8.0, 5.0, 9-*H*), 5.00 (2H, s, 7-C*H*$_2$), 6.64 (1H, d, *J* 15.0, 4-*H*), 7.08 (1H, dt, *J* 15.0, 7.0, 5-*H*), 7.38−7.48 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.06, −4.73, 18.11, 25.75, 26.09, 39.58, 42.74, 47.41, 74.68, 114.76, 125.57, 125.84, 127.00, 127.95, 142.94, 144.31, 144.98, 204.02.

*4.2.4. (2RS,6SR)-6-(2-Oxo-3,3-dimethylbutyl)-4-methylene-2-phenyltetrahydropyran (**14**).* Hydrogen fluoride−pyridine complex (0.1 mL) was added to the dienone **13** (25 mg, 0.065 mmol) in acetonitrile (0.5 mL) at ambient temperature and the mixture stirred for 12 h. Saturated aqueous sodium hydrogen carbonate (10 mL) was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with saturated copper(II) sulfate solution (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using petrol/ether (98:2) gave the *title compound* **14** (14 mg, 0.051 mmol, 79%) as a colourless oil; δ_H (300 MHz, $CDCl_3$) 1.34 [9H, s, C(C*H*$_3$)$_3$], 2.21 (1H, t, *J* 11.5, 5-*H*), 2.42 (1H, t, *J* 11.5, 3-*H*), 2.64 (2H, m, 3-*H*′ and 5-*H*′), 2.79 and 3.22 (each 1H, dd, *J* 16.5, 6.5, 1′-*H*), 4.20 (1H, dtd, *J* 11.5, 6.5, 2.5, 6-*H*), 4.56 (1H, dd, *J* 11.5, 2.5, 2-*H*), 5.03 (2H, m, 4-C*H*$_2$), 7.40−7.60 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 25.99, 40.17, 42.49, 43.12, 44.25, 75.12, 80.12, 109.35, 125.67, 127.30, 128.19, 142.29, 143.77, 213.45; *m*/*z* (CI) 290 (M^++18, 80%), 273 (M^++1, 100), 255 (M^+−17, 50); HRMS (CI): M^+, found 272.1774. $C_{18}H_{24}O_2$ requires 272.1776.

*4.2.5. 2-(Tri-iso-propylsilyloxymethyl)oxirane (**17**).* Imidazole (9.2 g, 149 mmol) was added to (±)-glycidol (2 g, 27 mmol) in DCM (50 mL), followed by tri-*iso*-propylsilyl chloride (5.8 mL, 27 mmol) and the solution stirred at rt for 18 h. Saturated aqueous ammonium chloride (20 mL) was added and the organic layer was washed with DCM (40 mL). The combined organic extracts were washed with water (40 mL) and brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/petrol (4:96) as eluent gave the *title compound* **17** (5.28 g, 86%) as a colourless oil; ν_{max} 684, 780, 843, 883, 918, 991,

1103, 1254, 1385, 1164 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.11 [21H, m, 3×SiC*H*(CH_3)$_2$], 2.71 (1H, dd, *J* 3, 5, 3-*H*), 2.82 (1H, dd, *J* 4, 5, 3-*H*′), 3.16 (1H, m, 2-*H*), 3.80 (1H, dd, *J* 4.5, 11.5, 1′-*H*) and 3.96 (1H, dd, *J* 3.5, 11.5, 1′-*H*′); δ_C (75 MHz, $CDCl_3$) 11.87, 17.82, 44.38, 52.50, 63.86; *m*/*z* (CI) 248 (M^++18, 100%), 231 (48), 162 (11); HRMS (CI): M^++NH_4, found 248.2053. $C_{12}H_{30}NO_2Si$ requires 248.2046.

*4.2.6. 1-(Tri-iso-propylsilyloxy)-4-(trimethylsilylmethyl)pent-4-en-2-ol (**18**).* Trimethylsilyl chloride (170 μl, 1.6 mmol) was added to a flask containing magnesium (423 mg, 17.4 mmol) and THF (10 mL). The mixture was heated under reflux for 1 min then cooled to rt. The remaining solution was removed and the magnesium washed with THF (5×10 mL). THF (10 mL) was added to the flask followed by 2-bromo-3-trimethylsilylpropene **16** (306 mg, 1.6 mmol). The mixture was heated until the reaction was initiated and then the remaining 2-bromo-3-trimethylsilylpropene **16** (2.75 g, 14.2 mmol) in THF (10 mL) was added at a rate so as to maintain gentle reflux. On completion of addition, the solution was heated under reflux for 0.5 h then allowed to cool to rt. Copper(I) iodide (301 mg, 1.6 mmol) was added to the epoxide **17** (3.52 g, 15.3 mmol) in THF (10 mL) at −10 °C followed by the solution of 2-bromo-3-trimethylsilylpropenylmagnesium bromide. The mixture was stirred at this temperature for 1 h and saturated aqueous ammonium chloride (15 mL) was added. The organic layer was washed with ether (3×10 mL) and the combined organic extracts were washed with aqueous ammonia (10%, 20 mL), water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/petrol (3:97) as the eluent gave the *title compound* **18** (5.26 g, 95%) as a colourless oil; ν_{max} 685, 795, 853, 955, 1065, 1117, 1249, 1385, 1418, 1464, 1632, 3465 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, Si(CH_3)$_3$], 1.04 [21H, m, 3×SiC*H*(CH_3)$_2$], 1.56 (2H, m, 4-CH_2), 2.12 (2H, m, 3-*H*$_2$), 2.42 (1H, d, *J* 3, O*H*), 3.55 (1H, dd, *J* 7.5, 10, 1-*H*), 3.65 (1H, dd, *J* 4.5, 10, 1-*H*′), 3.79 (1H, m, 2-*H*), 4.61 and 4.66 (each 1H, m, 5-*H*); δ_C (75 MHz, $CDCl_3$) −1.46, 11.84, 17.89, 26.71, 42.06, 67.01, 69.91, 109.82 and 144.09; *m*/*z* (CI) 345 (M^++1, 7%), 327 (50), 289 (42), 255 (95), 234 (20), 216 (50), 174 (21), 132 (42) and 90 (100); HRMS (CI): M^++H, found 345.2641. $C_{18}H_{41}O_2Si_2$ requires 345.2645.

*4.2.7. 2-(tert-Butyldimethylsilyloxy)-1-(tri-iso-propylsilyloxy)-4-(trimethylsilylmethyl)pent-4-ene (**19**).* 2,6-Lutidine (960 μl, 8.7 mmol) was added to the pentenol **18** (1.5 g, 4.35 mmol) in DCM (10 mL), followed by *tert*-butyldimethylsilyl trifluoromethane sulfonate (1 mL, 4.35 mmol). The solution was stirred at rt for 18 h then saturated ammonium chloride (10 mL) was added. The aqueous layer was washed with DCM (2×10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using petrol as the eluent gave the *title compound* **19** (1.79 g, 90%) as a colourless oil; ν_{max} 684, 776, 838, 878, 992, 1066, 1115, 1251, 1465, 1633 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, Si(CH_3)$_3$], 0.03 (6H, s, 2×SiCH_3), 0.86 [9H, s, SiC(CH_3)$_3$], 1.05 [21H, m, 3×SiC*H*(CH_3)$_2$], 1.53 (2H, d, *J* 4, 4-CH_2), 1.99 (1H, dd, *J* 7.5, 13.5, 3-*H*), 2.30 (1H, dd, *J* 4.5, 13.5, 3-*H*′), 3.48 (1H, dd, *J* 6.5, 9.5, 1-*H*), 3.60 (1H, dd, *J* 5, 9.5, 1-*H*′), 3.78 (1H, m, 2-*H*), 4.55 and 4.63 (each 1H, m, 5-*H*); δ_C (75 MHz, $CDCl_3$) −4.73, −4.48, −1.49, 11.88, 17.95, 25.85, 26.94, 43.42, 67.37, 72.38, 109.93 and 144.12; *m*/*z* (CI) 459 (M^++1, 0.2%), 403 (30), 327 (88), 216 (36), 174 (70), 170 (29) and 90 (100); HRMS (CI): M^++H, found 459.3517. $C_{24}H_{55}O_2Si_3$ requires 459.3510.

*4.2.8. (E)-9-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-10-(tri-iso-propylsilyloxy)-7-[(E)-trimethylsilylethylidene]dec-4-en-3-one (**21**).* Activated powdered 4 Å molecular sieves (500 mg) were added to the allylsilane **19** (1.79 g, 3.9 mmol) and ketone **20** (857 mg, 7.8 mmol) in DCM (1 mL). The flask was screened from light and zinc(II) iodide (1.87 g, 5.8 mmol) was added. The mixture was stirred for 24 h, then the orange solution was filtered though Celite and the filtrate washed with DCM (2×20 mL) and ethyl acetate (10 mL). After dilution with DCM (30 mL) and water (50 mL), the mixture was shaken until the orange colour had faded. The aqueous layer was washed with DCM (2×20 mL) and the combined organic extracts were washed with water (20 mL), brine (20 mL), ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/petrol (1:99) as the eluent gave the *title compound* **21** (1.15 g, 52%) as a colourless oil; ν_{max} 683, 775, 838, 990, 1087, 1116, 1250, 1364, 1466, 1621, 1693 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.01 (each 3H, s, SiCH_3), 0.07 [9H, s, Si(CH_3)$_3$], 0.83 [9H, s, SiC(CH_3)$_3$], 1.02 [21H, m, 3×SiC*H*(CH_3)$_2$], 1.11 (9H, s, 1-*H*$_3$ and 2×2-CH_3), 2.06 (1H, dd, *J* 8, 13.5, 8-*H*), 2.40 (1H, dd, *J* 4, 13.5, 8-*H*′), 3.04 (2H, dd, *J* 1.5, 6.5, 6-*H*$_2$), 3.42 (1H, dd, *J* 7, 9.5, 10-*H*), 3.58 (1H, dd, *J* 5, 9.5, 10-*H*′), 3.76 (1H, m, 9-*H*), 5.45 (1H, s, 7-C*H*), 6.46 (1H, dt, *J* 15, 1.5, 4-*H*), 6.88 (1H, dt, *J*, 15, 6.5, 5-*H*); δ_C (75 MHz, $CDCl_3$) −4.66, −4.39, 0.17, 11.87, 17.96, 18.04, 25.85, 26.08, 39.20, 42.82, 44.08, 67.18, 72.77, 125.05, 129.91, 144.90, 151.83, 203.82; *m*/*z* (CI) 586 (M^++18, 26%), 569 (M^++1, 44), 174 (18), 132 (17), 90 (100) and 58 (26); HRMS (CI): M^++H, found 569.4248. $C_{31}H_{65}O_3Si_3$ requires 569.4241.

*4.2.9. (2RS,6SR)- and (2RS,6RS)-2-Acetoxymethyl-4-methylene-6-(3,3-dimethyl-2-oxobutyl)tetrahydropyrans (**22**) and (**23**).* Aqueous hydrogen fluoride (58–62%, 100 μl) was added dropwise to the dienone **21** (40 mg, 0.07 mmol) in acetonitrile (1 mL) in a Teflon tube and the solution stirred for 18 h. Saturated aqueous sodium hydrogen carbonate was added until effervescence ceased and the mixture diluted with DCM (10 mL) and water (10 mL). The aqueous layer was washed with DCM (2×10 mL) and the combined organic extracts were washed water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Pyridine (100 μl), DCM (500 μl) and acetic anhydride (300 μl) were added and the solution was stirred at rt for 18 h. Saturated aqueous ammonium chloride (10 mL) and DCM (10 mL) were added and the organic layer was washed with DCM (2×10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/petrol (5:95) as the eluent gave the major diastereoisomer of the *title compound* **22** (11.5 mg, 61%) as a colourless oil; ν_{max} 769, 840, 895, 992, 1049, 1108, 1169, 1329, 1333, 1368, 1475, 1655, 1706, 1741 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.08 (9H, s, 4"-*H*$_3$ and 2×3"-CH_3), 1.85 (1H, t, *J* 11.5, 5-*H*), 2.00 (1H, br t, *J* 11.5, 3-*H*), 2.02 (3H, s, CH_3CO), 2.22 (1H, d, *J* 12.5, 3-*H*′), 2.28 (1H, d, *J* 12, 5-*H*′), 2.47 (1H, dd, *J* 6.5, 16.5, 1"-*H*), 2.88 (1H, dd, *J* 6, 16.5, 1"-*H*′), 3.59 (1H, m, 2-*H*), 3.85 (1H, ddt, *J* 2.5, 6, 12, 6-*H*), 4.06 (1H, dd, *J* 4, 11.5, 1′-*H*), 4.12 (1H, dd, *J* 6.5, 11.5, 1′-*H*′), 4.81 and 4.83 (each 1H, d, *J* 2, 4-C*H*); δ_C (75 MHz, $CDCl_3$) 20.78, 25.96, 36.49, 40.03, 42.89, 44.78, 66.64, 74.89, 75.81, 109.87, 142.57, 170.81, 213.38; *m*/*z* (CI) 286 (M^++18, 68%), 269 (M^++1, 100) and 169 (2); HRMS (CI): M^++H, found 269.1748. $C_{15}H_{25}O_4$ requires 269.1753. The minor diastereoisomer of the *title compound* **23** (2 mg, 11%) was isolated as a colourless oil; δ_H (300 MHz, $CDCl_3$) 1.06 (9H, s, 4"-*H*$_3$ and 2×3"-CH_3), 1.94 (1H, dd, *J* 6, 13, 5-*H*), 2.02 (4H, m, CH_3CO and 3-*H*), 2.25 (1H, dd, *J* 4, 13, 3-*H*′), 2.38 (1H, dd, *J* 4.5, 13, 5-*H*′), 2.61 (1H, dd, *J* 5, 17, 1"-*H*), 2.70 (1H, dd, *J* 7, 17, 1"-*H*′), 3.88 (1H, dq, *J* 4.5, 11.5, 2-*H*), 3.98 and 4.11 (each 1H, dd, *J* 7, 11.5, 1′-*H*), 4.35 (1H, m, 6-*H*), 4.72 and 4.76 (each 1H, s, 4-C*H*); δ_C (75 MHz, $CDCl_3$) 20.84, 26.11, 36.02, 38.73, 39.74, 44.29, 65.05, 69.29, 70.35, 111.41, 140.52, 170.89 and 212.99.

Alternatively, toluene 4-sulfonic acid (1 mg, 0.01 mmol) was added to a stirred solution of dienone **21** (40 mg, 0.07 mmol) in acetonitrile (1 mL) and water (one drop) and the solution was heated to 50 °C overnight. DCM (10 mL) and water (10 mL) were added and the aqueous layer was washed with DCM (2×10 mL). The combined organic extracts were washed water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure.

Alternatively, pyridinium toluene 4-sulfonate (10 mg, 0.02 mmol) was added to the dienone **21** (40 mg, 0.07 mmol) in ethanol (1 mL) and the solution was heated to 60 °C overnight. DCM (10 mL) and water (10 mL) were added and the aqueous layer was washed with DCM (2×10 mL). The combined organic extracts were washed water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure.

Following the procedure outlined for the synthesis of tetrahydropyrans **22** and **23** from dienone **21**, treatment of the dienone **29** (80 mg, 0.15 mmol) in acetonitrile (2 mL) with aqueous hydrogen fluoride (58–62%, 200 μl) and acetylation using pyridine (500 μl), DCM (500 μl) and acetic anhydride (500 μl) gave the tetrahydropyran **22** (24 mg, 62%) as a colourless oil and the tetrahydropyran **23** (4 mg, 61%) also as a colourless oil.

*4.2.10. 2-(2-Trimethylsilylethoxymethoxy)methyloxirane (**26**).* Di-*iso*propylethylamine (36 mL, 135 mmol) and 2-trimethylsilylethoxymethyl chloride (12 mL, 67.6 mmol) were added to (±)-glycidol (5.00 g, 64.1 mmol) at 0 °C in DCM (100 mL) and the solution stirred at rt for 16 h. Saturated aqueous ammonium chloride (50 mL) was added and the organic layer was washed with DCM (50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (11:89) as eluent gave the *title compound* **26** (9.55 g, 73%) as a colourless oil; ν_{max} 694, 762, 837, 859, 1056, 1109, 1156, 1194, 1249, 1378, 1409 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, $Si(CH_3)_3$], 0.92 (2H, m, $SiCH_2$), 2.61 (1H, dd, *J* 3, 5, 3-*H*), 2.79 (1H, dd, *J* 4, 5, 3-*H*′), 3.15 (1H, m, 2-*H*), 3.50 (1H, dd, *J* 6, 11.5, 2-C*H*), 3.62 (2H, m, OCH_2CH_2Si), 3.77 (1H, dd, *J* 3.5, 11.5, 2-C*H*′), 4.68 (2H, s, OCH_2O); δ_C (75 MHz, $CDCl_3$) −1.50, 18.01, 44.44, 50.58, 65.21, 68.16, 94.95; *m*/*z* (CI) 222 (M^++18, 38%), 205 (M^++1, 4), 164 (10), 131 (22), 90 (100); HRMS (CI): M^++NH_4, found 222.1522. $C_9H_{24}NO_3Si$ requires 222.1525. (*S*)-(−)-Glycidol gave the (*R*)-enantiomer (***R***)-**26** with $[\alpha]_D^{20}$−2.3 (*c* 1.0 in DCM).

*4.2.11. 1-(2-Trimethylsilylethoxy)methoxy-4-(trimethylsilylmethyl) pent-4-en-2-ol (**27**).* Trimethylsilyl chloride (330 μl, 2.6 mmol) was added to magnesium (996 mg, 40.1 mmol) and THF (20 mL). The mixture was heated under reflux for 1 min then cooled to rt. The remaining solution was removed and the magnesium washed with THF (5×20 mL). THF (20 mL) was added followed by 2-bromo-3-trimethylsilylpropene (0.55 g, 2.85 mmol). The mixture was heated until the reaction was initiated and the 2-bromo-3-trimethylsilylpropene **16** (4.95 g, 25.6 mmol) in THF (10 mL) was added at a rate so as to maintain gentle reflux. On completion of the addition the solution was heated under reflux for 0.5 h then allowed to cool to rt. Copper iodide (494 mg, 2.6 mmol) was added to the epoxide **26** (5.3 g, 26 mmol) in THF (20 mL) at −10 °C followed by the solution of 2-bromo-3-trimethylsilylpropylmagnesium bromide. The mixture was stirred at this temperature for 1 h then saturated aqueous ammonium chloride (30 mL) was added. The organic layer was washed with ether (3×30 mL) and the combined organic extracts were washed aqueous ammonia (10%, 20 mL), water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (1:10) as the eluent gave the *title compound* **27** (7.2 g, 88%) as a colourless oil; ν_{max} 694, 840, 857, 1033, 1055, 1114, 1157, 1249, 1417, 1632, 3465 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [18H, s, 2×$Si(CH_3)_3$], 0.93 (2H, m, CH_2Si), 1.55 and 1.56 (each 1H, d, *J* 13.5, 4-C*H*), 2.12 (2H, m, 3-H_2), 2.60 (1H, d, *J* 3, O*H*), 3.44 (1H, dd, *J* 5, 10.5, 1-*H*), 3.62 (3H, m, 1-*H*′ and OCH_2CH_2Si), 3.90 (1H, m, 2-*H*), 4.66 (4H, m, 5-H_2 and OCH_2O); δ_C (75 MHz, $CDCl_3$) −1.50, −1.46, 18.02, 26.58, 42.30, 65.32, 68.36, 72.71, 95.38, 110.21, 143.73; *m*/*z* (CI) 336 (M^++18, 0.5%), 132 (9) and 90 (100); HRMS (CI): M^++NH_4, found 336.2386. $C_{15}H_{38}NO_3Si_2$ requires 336.2390. The (*R*)-epoxide (***R***)-**26** gave the (*R*)-enantiomer of alcohol **27**; $[\alpha]_D^{20}$ − 0.6 (*c* 1.0 in DCM).

*4.2.12. 2-tert-Butyldimethylsilyloxy-1-(trimethylsilylethoxy)methoxy-4-(trimethylsilylmethyl)pent-4-ene (**28**).* 2,6-Lutidine (5.3 mL, 45.6 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.8 mL, 25.1 mmol) were added to the alcohol **27** (7.2 g, 22.7 mmol) in DCM (50 mL) at 0 °C and the solution stirred at rt for 18 h. Saturated aqueous ammonium chloride (30 mL) was added and the organic layer was washed with DCM (2×20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether in petrol (2:98) as the eluent gave the *title compound* **28** (7.55 g, 77%) as a colourless oil; ν_{max} 693, 775, 836, 992, 1058, 1109, 1156, 1251, 1468, 1633; δ_H (300 MHz, $CDCl_3$) 0.00 [18H, s, 2×$Si(CH_3)_3$], 0.04 (6H, s, 2×$SiCH_3$), 0.86 [9H, s, $SiC(CH_3)_3$], 0.92 (2H, m, CH_2Si), 1.52 (2H, s, 4-CH_2), 2.07 (1H, dd, *J* 6.5, 14, 3-*H*), 2.18 (1H, dd, *J* 6.0, 14, 3-*H*′), 3.40 (1H, dd, *J* 6, 10, 1-*H*), 3.46 (1H, dd, *J* 4.5, 10, 1-*H*′), 3.59 (2H, m, OCH_2CH_2Si), 3.91 (1H, m, 2-*H*), 4.56 and 4.62 (each 1H, m, 5-*H*), 4.65 (2H, m, OCH_2O); δ_C (75 MHz, $CDCl_3$) −4.76, −4.56, −1.49, −1.45, 18.05, 25.83, 26.99, 43.55, 64.93, 70.57, 71.89, 95.05, 110.09, 128.25, 143.76; *m*/*z* (CI) 450 (M^++18, 1%), 301 (9), 243 (11) and 90 (100); HRMS (CI): M^++NH_4, found 450.3262. $C_{21}H_{52}NO_3Si_3$ requires 450.3255. The (*R*)-alcohol (***R***)-**27** gave the (*R*)-enantiomer of the silyl ether **28**; $[\alpha]_D^{20}$− 0.2 (*c* 1.0 in DCM).

*4.2.13. (E)-9-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-10-(trimethylsilylethoxy)methoxy-7-[(E)-trimethylsilylethylidene]dec-4-en-3-one (**29**).* Activated powdered 4 Å molecular sieves (1 g) were added to the allylsilane **28** (1.53 g, 3.56 mmol) and the alkynone **20** (200 mg, 1.78 mmol) in DCM (1.5 mL). The flask was screened from light and zinc(II) iodide (0.58 g, 1.82 mmol) was added. The mixture was stirred for 24 h, then the resulting orange solution was filtered though Celite and the filtrate washed with DCM (20 mL) and ethyl acetate (10 mL). The solution was diluted with DCM (20 mL) and water (30 mL) and shaken until the orange colour had faded. The aqueous layer was washed with DCM (2×20 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/petrol (3:97) as the eluent gave the *title compound* **29** (610 mg, 62%) as a colourless oil; ν_{max} 692, 775, 838, 936, 987, 1057, 1110, 1195, 1251, 1366, 1471, 1619, 1692 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, $Si(CH_3)_3$], 0.01 and 0.04 (each 3H, s, $SiCH_3$), 0.08 [9H, s, $Si(CH_3)_3$], 0.85 [9H, s, $SiC(CH_3)_3$], 0.91 (2H, m, CH_2Si), 1.12 (9H, s, 1-H_3 and 2×2-CH_3), 2.12 (1H, dd, *J* 7, 13, 8-*H*), 2.31 (1H, dd, *J* 4, 13, 8-*H*′), 3.04 (2H, dd, *J* 1.5, 6.5, 6-H_2), 3.40 (2H, m, 10-H_2), 3.58 (2H, m, CH_2CH_2Si), 3.89 (1H, m, 9-*H*), 4.63 (2H, s, OCH_2O), 5.45 (1H, s, 7-*CH*), 6.48 (1H, d, *J* 15, 4-*H*), 6.87 (1H, dt, *J* 15, 6.5, 5-*H*); δ_C (75 MHz, $CDCl_3$) −4.69, −4.47, −1.48, −0.15, 18.03, 25.82, 26.05, 39.09, 42.83, 44.27, 64.99, 70.84, 71.97, 95.08, 125.23, 130.06, 144.62, 151.26; *m*/*z* (CI) 560 (M^++18, 8%), 203 (3), 174 (9), 132 (21) and 90 (100); HRMS (CI): M^++NH_4, found 560.3977. $C_{28}H_{62}NO_4Si_3$ requires 560.3986.

*4.2.14. (2RS,6SR)- and (2RS,6RS)-6-(3,3-Dimethyl-2-oxobutyl)-2-(trimethylsilylethoxymethoxy)methyl-4-[(E)-trimethylsilylmethylene]tetrahydropyrans (**30**) and (**31**).* A Teflon tube was charged with the dienone **29** (200 mg, 0.37 mmol) in dry THF (7 mL) and the solution cooled to 0 °C. HF·pyridine (250 μl) was added and the mixture stirred for 0.5 h at 0 °C and at rt for 18 h. Ether (20 mL) was added followed by saturated aqueous sodium hydrogen carbonate until effervescence ceased. The organic layer was washed with ether (2×10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and

concentrated under reduced pressure. Chromatography of the residue using ether/petrol (6:94) as eluent gave the 2,6-*cis*-diastereoisomer of the *title compound* **30** (60 mg, 38%) as a colourless oil; ν_{max} 692, 725, 838, 936, 987, 1057, 1110, 1195, 1251, 1366, 1410, 1471, 1619 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.09 [each 9H, s, Si(CH_3)$_3$], 0.92 (2H, m, CH_2Si), 1.11 (9H, s, 4″-H_3 and 2×3″-CH_3), 1.80 (1H, br t, *J* 12, 5-*H*), 2.13 (2H, m, 3-H_2), 2.53 (1H, m, 5-*H*′), 2.59 (1H, dd, *J* 6.5, 17, 1″-*H*), 2.92 (1H, dd, *J* 5, 17, 1″-*H*′), 3.52 (5H, m, 2-*H*, 1′-H_2 and CH_2CH_2Si), 3.77 (1H, m, 6-*H*), 4.67 (2H, s, OCH_2O), 5.26 (1H, s, 4-C*H*); δ_C (75 MHz, $CDCl_3$) −1.47, 0.14, 18.00, 26.04, 39.48, 41.55, 43.19, 44.14, 64.96, 70.44, 74.68, 77.51, 94.95, 124.04, 152.17, 213.11; *m*/*z* (CI) 446 (M^++18, 31%), 211 (23), 179 (12), 90 (100); HRMS (CI): M^++NH_4, found 446.3122. $C_{22}H_{48}NO_4Si_3$ requires 446.3122. The 2,6-*trans*-diastereoisomer of the *title compound* **31** (60 mg, 38%) was isolated as a colourless oil; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.06 [each 9H, s, Si(CH_3)$_3$], 0.92 (2H, m, CH_2Si), 1.11 (9H, s, 2×3″-CH_3 and 4″-H_3), 2.16 (2H, m, 3-*H* and 5-*H*), 2.32 (1H, dd, *J* 3.5, 13.5, 3-*H*′), 2.52 (1H, dd, *J* 4.5, 13.5, 5-*H*′), 2.61 (1H, dd, *J* 5, 17.5, 1″-*H*), 2.87 (1H, dd, *J* 4.5, 17.5, 1″-*H*′), 3.51 (1H, dd, *J* 5, 10.5, 1′-*H*), (3H, m, 1′-*H*′ and CH_2CH_2Si), 3.90 (1H, m, 2-*H*), 4.32 (1H, br dq, *J* 4.5, 9, 6-*H*), 4.67 (2H, s, OCH_2O), 5.32 (1H, s, 4-C*H*); δ_C (75 MHz, $CDCl_3$) −1.44, 0.17, 18.04, 26.30, 38.16, 40.58, 40.97, 44.21, 65.06, 68.73, 69.19, 71.95, 95.02, 126.00, 150.04, 213.30.

*4.2.15. 9-tert-Butyldimethylsilyloxy-2,2,7-trimethyl-10-[(trimethylsilylethoxy)methoxy]deca-4,6-dien-3-one (**32**).* TBAF (1 M in THF, 55 μl, 0.055 mmol) was added to the dienone **29** (30 mg, 0.055 mmol) in THF (500 μl) and the solution stirred for 4 h. Water (10 mL) and ether (10 mL) were added and the organic layer was washed with ether (2×10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/petrol (3:97) as eluent gave the *title compound* **32** (21 mg, 82%) as a colourless oil, a 66:33 mixture of geometrical isomers; ν_{max} 776, 836, 1062, 1109, 1250, 1365, 1471, 1587, 1626, 1679 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 (3H, s, SiCH_3), 0.02 [6H, s, Si(CH_3)$_3$], 0.05 (3H, s, SiCH_3), 0.08 [3H, s, Si(CH_3)$_3$], 0.83 [3H, s, SiC(CH_3)$_3$], 0.85 [6H, s, SiC(CH_3)$_3$], 0.91 (2H, m, CH_2Si), 1.15 (3H, s, 1-H_3 and 2-CH_3), 1.16 (6H, s, 1-H_3 and 2-CH_3), 1.91 (3H, m, 7-CH_3), 2.22–2.62 (2H, m, 8-H_2), 3.43 (2H, m, 10-H_2), 3.61 (2H, m, CH_2CH_2Si), 3.91 (1H, m, 9-*H*), 4.66 (0.66H, s, OCH_2O), 4.67 (1.34H, s, OCH_2O), 6.06 (0.66H, d, *J* 12, 6-*H*), 6.11 (0.34H, d, *J* 12, 6-*H*), 6.45 (0.33H, d, *J* 15, 4-*H*), 6.47 (0.66H, d, *J* 15, 4-*H*), 7.58 (0.66H, dd, *J* 15, 12, 5-*H*), 7.60 (0.34H, dd, *J* 15,12, 5-*H*); δ_C (75 MHz, $CDCl_3$) −4.90, −4.67, −1.46, 17.97, 18.07, 25.52, 25.74, 25.77, 26.32, 38.09, 42.86, 45.75, 65.09, 70.06, 70.34, 71.80, 72.01, 95.15, 122.40, 122.53, 126.83, 138.69, 139.23, 146.89, 147.20, 204.98; *m*/*z* (CI) 488 (M^++18, 8%), 471 (M^++1, 4), 443 (31), 413 (24), 353 (24), 130 (24), 130 (21), 90 (100); HRMS (CI): M^++H, found 471.3331. $C_{25}H_{51}O_4Si_2$ requires 471.3326.

*4.2.16. (3R)-3-Benzyloxy-4,4-dimethyltetrahydrofuran-2-ol (**36**).* DIBAL-H (1 M in THF, 107 mL, 107 mmol) was added dropwise to the lactone **34** (15.7 g, 71 mmol) in THF (100 mL) at −78 °C over 1 h and the solution warmed to −35 °C and stirred for 5 h. The mixture was cooled to −78 °C and precooled methanol (10 mL) was added. The mixture was allowed to warm slowly to 0 °C, then saturated aqueous ammonium chloride (100 mL) was added. Celite (20 g) was stirred into the mixture and the suspension stirred until a gel formed exothermically. The gel was broken up and ether (100 mL) added. The mixture was filtered and the filter cake washed twice with methanol in ethyl acetate (1%, 3×50 mL). The organic layer was separated and the aqueous layer extracted with ether (3×50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (1:2) as eluent gave the *title compound* **36** (13.8 g, 88%) as a colourless oil, a 75:25 mixture of diastereoisomers; ν_{max} 699, 739, 909, 1042, 1132, 1204, 1361, 1394, 1463, 3356 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.11 (0.75H, s, 4-CH_3), 1.15 and 1.16 (each 2.25H, s, 4-CH_3), 1.17 (0.75H, s, 4-CH_3), 3.05 (0.75H, br s, O*H*), 3.48 (0.25H, d, *J* 10, 3-*H*), 3.52 (0.25H, m, O*H*), 3.57 (0.75H, d, *J* 3, 3-*H*), 3.69 (0.75H, d, *J* 8.5, 5-*H*), 3.77 (0.25H, d, *J* 8, 5-*H*), 3.86 (0.75H, d, *J* 8.5, 5-*H*), 4.04 (0.25H, d, *J* 8, 5-*H*), 4.63 (0.75H, d, *J* 12, *H*CHAr), 4.68 and 4.72 (each 0.25H, d, *J* 12, *H*CHAr), 4.75 (0.75H, d, *J* 12, *H*CHAr), 5.42 (0.75H, t, *J* 3.5, 2-*H*), 5.51 (0.25H, dd, *J* 4.5, 10, 2-*H*), 7.37 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 19.76, 20.33, 21.49, 24.01, 25.70, 42.02, 72.30, 74.31, 78.59, 78.85, 85.26, 91.39, 97.50, 102.77, 127.37, 127.48, 127.75, 127.88, 128.09, 128.24, 128.44, 128.50; *m*/*z* (CI) 240 (M^++18, 29%), 223 (M^++1, 13), 222 (M^+, 100), 205 (7), 108 (9); HRMS (CI): M^+, 222.1261. $C_{13}H_{18}O_3$ requires 222.1256.

*4.2.17. (3S)-3-(4-Methoxybenzyloxy)-2,2-dimethylpent-4-en-1-ol (**37**).* ^{n}Butyllithium (1.61 M in hexanes, 172 mL, 276 mmol) was added dropwise to methyltriphenylphosphonium bromide (81 g, 227 mmol) in THF (300 mL) at −78 °C. The solution was allowed to warm to 0 °C, stirred for 0.5 h then cooled to −78 °C. The lactol **35** (20 g, 79.3 mmol) in THF (100 mL) was added dropwise and the mixture was allowed to warm to rt and was stirred overnight. Aqueous ammonium chloride (100 mL) was added and the mixture diluted with DCM (200 mL) and water (200 mL). The aqueous layer was washed with DCM (3×100 mL) and the combined organic extracts were washed with water (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (25:75) as the eluent gave the *title compound* **37** (11.8 g, 59%) as a colourless oil, $[\alpha]_D^{20}$+41.9 (*c* 1.0 in DCM); ν_{max} 823, 1037, 1175, 1248, 1301, 1465, 1513, 1613, 3439 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.91 (6H, s, 2×2-CH_3), 2.92 (1H, br m, O*H*), 3.55 and 3.58 (each 1H, dd, *J* 5, 11, 1-*H*), 3.63 (1H, d, *J* 8.5, 3-*H*), 3.84 (3H, s, OCH_3), 4.26 and 4.58 (each 1H, d, *J* 11.5, *H*CHAr), 5.27 and 5.41 (each 1H, m, 5-*H*), 5.84 (1H, ddd, J 8.5, 10.5, 17.5, 4-*H*), 6.91 and 7.27 (each 2H, d, *J* 9.5, Ar*H*); δ_C (75 MHz, $CDCl_3$) 19.70, 22.56, 38.44, 55.18, 69.93, 71.31, 87.72, 113.76, 119.58, 129.37, 130.05, 134.93, 159.12; *m*/*z* (EI) 250 (M^+, 9%), 194 (41), 137 (16), 122 (22), 121 (100); HRMS (EI): M^+, found 250.1573. $C_{15}H_{22}O_3$ requires 250.1569.

*4.2.18. (3S)-3-Benzyloxy-2,2-dimethylpent-4-en-1-ol (**38**).* ^{n}Butyllithium (1.63 M, 95 mL, 154 mmol) was added dropwise to methyltriphenylphosphonium bromide (47.6 g, 133 mmol) in THF (200 mL) at −78 °C. The solution was allowed to warm to 0 °C, stirred for 0.5 h, then cooled to −78 °C and the lactol **36** (13.7 g, 61.7 mmol) in a THF (50 mL) was added dropwise. The mixture was allowed to warm to rt overnight then saturated aqueous ammonium chloride (50 mL) was added dropwise. Ether (100 mL) and water (100 mL) were added and the aqueous was layer washed with ether (3×50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (1:3) as eluent gave the *title compound* **38** (11 g, 82%) as a colourless oil, $[\alpha]_D^{20}$+17.8 (*c* 1.0 in DCM); ν_{max} 698, 737, 826, 930, 1058, 1389, 1422, 1458, 1604, 1640, 1710, 3396 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.95 and 0.96 (each 3H, s, 2-CH_3), 2.92 (1H, br m, O*H*), 3.41 (1H, dd, *J* 4.5, 11, 1-*H*), 3.58 (1H, dd, *J* 6, 11, 1-*H*′), 3.68 (1H, d, *J* 8.5, 3-*H*), 4.35 and 4.66 (each 1H, d, *J* 12, *H*CHAr), 5.30 (1H, ddd, *J* 0.5, 2, 17, 5-*H*), 5.43 (1H, ddd, *J* 0.5, 2, 10.5, 5-*H*′), 5.86 (1H, ddd, *J* 8.5, 10.5, 17, 4-*H*), 7.30–7.45 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 19.79, 22.48, 39.56, 70.37, 71.13, 88.01, 119.67, 127.61, 127.74, 128.34, 134.88, 138.07; *m*/*z* (CI) 238 (M^++18, 100%), 221 (M^++1, 19), 220 (M^+, 3); HRMS (CI): M^++H, 220.1465. $C_{14}H_{20}O_2$ requires 220.1463.

*4.2.19. (3S)-3-(4-Methoxybenzyloxy)-2,2-dimethylpent-4-enal (**39**).* 4-Methylmorpholine *N*-oxide (5.58 g, 47.7 mmol), 4 Å molecular sieves (500 mg) and tetrapropylammonium perruthenate (558 mg, 1.6 mmol) were added to the alcohol **37** (7.95 g, 31.8 mmol) in DCM (70 mL) and the solution stirred for 3 h. The reaction mixture was then filtered and the filter cake washed with DCM (3×20 mL). The filtrate was diluted with water (30 mL) and the aqueous layer was washed with DCM (2×20 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (17:83) as eluent gave the *title compound* **39** (6.12 g, 77%) as a colourless oil, $[\alpha]_D^{20}$+4.8 (*c* 1.0 in DCM); ν_{max} 822, 934, 1035, 1069, 1175, 1248, 1301, 1464, 1513, 1612, 1728 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.00 and 1.12 (each 3H, s, 2-C*H*$_3$), 3.82 (4H, m, 3-*H* and OC*H*$_3$), 4.27 and 5.33 (each 1H, d, *J* 11.5, *H*CHAr), 5.35 (1H, m, 5-*H*), 5.45 (1H, dd, *J* 2.5, 10, 5-*H*′), 5.78 (1H, ddd, *J* 7.5, 10, 18.5, 4-*H*), 6.90 and 7.23 (each 2H, d, *J* 7, Ar*H*), 9.54 (1H, s, 1-*H*); δ_C (75 MHz, $CDCl_3$) 16.50, 19.44, 49.55, 55.18, 69.76, 83.48, 113.64, 120.51, 129.27, 130.06, 133.66, 159.04, 205.61; *m*/*z* (CI) 266 (M^++18, 27%), 138 (25), 121 (100); HRMS (CI): M^++NH_4, found 266.1757. $C_{15}H_{24}NO_3$ requires 266.1756.

*4.2.20. (3S)-3-Benzyloxy-2,2-dimethylpent-4-enal (**40**).* DMSO (6.3 mL, 88.9 mmol) in DCM (20 mL) was added dropwise to a solution of oxalyl chloride (3.81 mL, 44.4 mmol) in DCM (50 mL) at −78 °C over 10 min. The solution was stirred for 10 min then the alcohol **38** (8.9 g, 40.4 mmol) in DCM (30 mL) was added. After 1 h, triethylamine (28.2 mL, 202 mmol) was added and the solution stirred at −78 °C for 10 min then warmed to rt. Saturated aqueous ammonium chloride, water (150 mL) and DCM (50 mL) were added and the aqueous layer was washed with DCM (2×50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (14:86) as eluent gave the *title compound* **40** (8.36 g, 94%) as a colourless oil, $[\alpha]_D^{20}$+3.5 (*c* 1.0 in DCM); ν_{max} 699, 741, 800, 934, 1071, 1270, 1390, 1457, 1706 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.22 and 1.26 (each 3H, s, 2-C*H*$_3$), 4.00 (1H, d, *J* 8, 3-*H*), 4.41 and 4.67 (each 1H, d, *J* 12, *H*CHAr), 5.37 (1H, dd, *J* 1, 17, 5-*H*), 5.45 (1H, dd, *J* 1.5, 10.5, 5-*H*′), 5.82 (1H, ddd, *J* 8, 10.5, 17, 4-*H*), 7.35 (5H, m, Ar*H*), 9.6 (1H, s, 1-*H*); δ_C (75 MHz, $CDCl_3$) 19.64, 22.39, 46.56, 70.61, 85.00, 120.82, 127.47, 127.77, 128.20, 133.62, 137.91, 181.28; HRMS (CI): M^++NH_4, found 236.1640. $C_{14}H_{22}NO_2$ requires 236.1650.

*4.2.21. (3RS,5S)-5-(4-Methoxybenzyloxy)-4,4-dimethylhept-6-en-1-yn-3-ol (**41**).* Ethynylmagnesium bromide (0.5 M in THF, 62 mL, 31 mmol) was added dropwise to the aldehyde **39** (5.14 g, 20.7 mmol) in THF (30 mL) at −78 °C and the mixture stirred for 18 h at rt. Saturated aqueous ammonium chloride (50 mL) was added and the aqueous layer extracted with ether (3×100 mL). The combined organic fractions were washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (12:88) as the eluent gave one diastereoisomer of the *title compound* **41a** (2.73 g, 48%) as a colourless oil, $[\alpha]_D^{20}$+8.3 (*c* 1.0 in DCM); ν_{max} 824, 934, 1053, 1175, 1249, 1302, 1386, 1418, 1465, 1514, 1586, 1612, 3463 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.95 and 1.12 (each 3H, s, 4-C*H*$_3$), 2.46 (1H, d *J* 2, 1-*H*), 3.53 (1H, d, *J* 3.5, O*H*), 3.78 (1H, d, *J* 8.5, 5-*H*), 3.85 (3H, s, OC*H*$_3$), 4.29 (1H, d, *J* 11.5, *H*CHAr), 4.43 (1H, m, 3-*H*), 5.58 (1H, d, *J* 11.5, *H*CHAr), 5.32 (1H, dd, *J* 1.5, 18, 7-*H*), 5.44 (1H, dd, *J* 1.5, 10.5, 7-*H*′), 5.86 (1H, ddd, *J* 8.5, 10.5, 18, 6-*H*), 6.92 and 7.29 (each 2H, d, *J* 7, Ar*H*); δ_C (75 MHz, $CDCl_3$) 16.33, 21.21, 41.64, 55.19, 70.02, 73.62, 83.00, 87.30, 113.77, 120.11, 129.45, 129.85, 134.72, 159.15; *m*/*z* (CI) 292 (M^++18, 4%), 275 (M^++1, 10%), 121 (100); HRMS (CI): M^++H, found 275.1651. $C_{17}H_{23}O_3$ requires 275.1647. The other diastereoisomer of the *title compound* **41b** (2.73 g, 48%) was isolated as a colourless oil; $[\alpha]_D^{20}$ +39.8; δ_H (300 MHz, $CDCl_3$) 0.97 and 1.08 (each 3H, s, 4-C*H*$_3$), 2.49 (1H, d, *J* 2, 1-*H*), 3.85 (3H, s, OC*H*$_3$), 4.02 (1H, d, *J* 8, 3-*H*), 4.12 (1H, d, *J* 8, 5-*H*), 4.22 (1H, d, *J* 8, O*H*), 4.34 and 4.55 (each 1H, d, *J* 11.5, *H*CHAr), 5.35 (1H, d, *J* 16, 7-*H*), 5.44 (1H, dd, *J* 2, 10.5, 7-*H*′), 5.83 (1H, ddd, *J* 8, 10.5, 16, 6-*H*), 6.91 and 7.30 (each 2H, d, *J* 7, Ar*H*); δ_C (75 MHz, $CDCl_3$) 19.16, 22.04, 41.12, 55.20, 70.31, 70.90, 73.55, 83.55, 86.12, 113.79, 120.01, 129.69, 129.75, 134.30, 159.25.

*4.2.22. (3RS,5S)-5-Benyloxy-4,4-dimethylhept-6-en-1-yn-3-ol (**42**).* Ethynylmagnesium bromide in THF (0.5 M, 74 mL, 37.1 mmol) was added dropwise to the aldehyde **40** (5.42 g, 24.9 mmol) in THF (50 mL) at −78 °C. The mixture was warmed to rt and stirred for 18 h, then saturated aqueous ammonium chloride (50 mL) was added. The aqueous layer was extracted with ether (3×50 mL) and the combined organic extracts washed with water (50 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (1:2) as eluent gave the *title compound* **42** (5.65 g, 93%) as a colourless oil, a 54:46 mixture of diastereoisomers; ν_{max} 699, 743, 934, 1056, 1210, 1388, 1417, 1461, 1640, 1709, 3299, 3435 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.97, 0.99, 1.10 and 1.13 (each 1.5H, s, 4-C*H*$_3$), 2.46 and 2.48 (each 0.5H, d, *J* 2, 1-*H*), 3.33 (0.5H, d, *J* 4, O*H*), 3.81 (0.5H, d, *J* 8.5, 5-*H*), 3.93 (0.5H, d, *J* 8.5, O*H*), 4.14 (0.5H, d, *J* 8, 5-*H*), 4.25 (0.5H, dd, *J* 2, 8.5, 3-*H*), 4.36 and 4.41 (each 0.5H, d, *J* 11.5, *H*CHAr), 4.44 (0.5H, dd, *J* 2, 4, 3-*H*), 4.62 and 4.64 (each 0.5H, d, *J* 11.5, *H*CHAr), 5.25–5.50 (2H, m, 7-*H*$_2$), 5.86 (1H, m, 6-*H*), 7.29 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 16.57, 19.14, 20.91, 21.89, 41.20, 41.80, 70.02, 70.41, 70.65, 70.74, 73.60, 73.69, 83.00, 83.51, 86.33, 87.42, 120.10, 120.15, 127.58, 127.75, 128.06, 128.32, 128.39, 134.22, 134.71, 137.62, 137.90; *m*/*z* (CI) 262 (M^++18, 100%), 245 (M^++1, 47); HRMS (CI): M^++NH_4, found 262.1802. $C_{16}H_{24}NO_2$ requires 262.1806.

*4.2.23. (5S)-5-(4-Methoxybenzyloxy)-4,4-dimethylhept-6-en-1-yn-3-one (**43**).* Dess–Martin periodinane (7.9 g, 18.9 mmol) was added slowly to the mixture of epimeric alcohols **41** (5.17 g, 18.9 mmol) in DCM (50 mL) at 0 °C and the solution stirred for 3 h at rt. Aqueous sodium hydroxide (3 M, 10 mL) was added and the mixture stirred for 10 min. The organic layer was washed with aqueous sodium hydroxide (3 M, 10 mL), water (30 mL) and brine (30 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (11:89) as eluent gave the *title compound* **43** (4.73 g, 92%) as a colourless oil, $[\alpha]_D^{20}$−5.3 (*c* 1.0 in DCM); ν_{max} 823, 936, 1064, 1175, 1248, 1464, 1513, 1615, 1679, 2089 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.14 and 1.23 (each 3H, s, 4-C*H*$_3$), 3.19 (1H, s, 1-*H*), 3.82 (3H, s, OC*H*$_3$), 4.22 (1H, d, *J* 8, 5-*H*), 4.32 and 4.54 (each 1H, d, *J* 11.5, *H*CHAr), 5.39 (1H, d, *J* 17.5, 7-*H*), 5.46 (1H, dd, *J* 1.5, 10.5, 7-*H*′), 5.78 (1H, ddd, *J* 8, 10.5, 17.5, 6-*H*), 6.88 and 7.27 (each 2H, d, *J* 7, Ar*H*); δ_C (75 MHz, $CDCl_3$) 17.21, 21.45, 52.17, 55.19, 70.20, 79.31, 84.01, 113.49, 120.65, 129.28, 130.91, 133.80, 158.96, 191.42; *m*/*z* (CI) 290 (M^++18, 1%), 273 (M^++1, 0.3), 153 (12), 121 (100); HRMS (CI): M^+, found 272.1413. $C_{17}H_{20}O_3$ requires 272.1412.

*4.2.24. (5S)-5-Benzyloxy-4,4-dimethylhept-6-en-1-yn-3-one (**44**).* Dess–Martin periodinane (10.8 g, 23.2 mmol) was added slowly to the alcohol **42** (5.65 g, 23.2 mmol) in DCM (50 mL) at 0 °C. The solution was allowed to warm to rt and was stirred for 3 h. Aqueous sodium hydroxide (3 M, 20 mL) was added and the mixture stirred for 10 min. The organic layer was then washed with aqueous sodium hydroxide (3 M, 20 mL), water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (1:9) as eluent gave the *title compound* **44** (5.6 g, 100%) as a colourless oil, $[\alpha]_D^{20}$−12.6 (*c* 1.0 in DCM); ν_{max} 694, 739, 935, 1061, 1212, 1240, 1317, 1386, 1460, 1678, 2089 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.15

and 1.25 (each 3H, s, 4-CH_3), 3.18 (1H, s, 1-*H*), 4.25 (1H, d, *J* 8, 5-*H*), 4.39 and 4.61 (each 1H, d, *J* 12, *H*CHAr), 5.40 (1H, d, *J* 17, 7-*H*), 5.46 (1H, d, *J* 10.5, 7-*H*′), 5.79 (1H, ddd, *J* 8, 10.5, 17, 6-*H*), 7.34 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 17.25, 21.43, 52.17, 70.54, 79.36, 79.75, 84.37, 120.73, 127.32, 127.66, 128.09, 133.70, 138.08, 191.33; *m*/*z* (CI) 260 (M^++18, 100%), 243 (M^++1, 5); HRMS (CI): M^++NH_4, found 260.1645. $C_{16}H_{22}NO_2$ requires 260.1650.

*4.2.25. (3S,11R,6E)-11-tert-Butyldimethylsilyloxy-4,4-dimethyl-3-(4-methoxybenzyloxy)-12-(2-trimethylsilylethoxy)methoxy-9-[(E)-trimethylsilylmethylidene]dodeca-1,6-dien-5-one (**45**).* Activated powdered 4 Å molecular sieves (500 mg) were added to alkynone **43** (1 g, 3.7 mmol) and allylsilane (***R***)-**28** (2.84 g, 6.6 mmol) in DCM (4 mL). The flask was protected from light and zinc(II) iodide (1.6 g, 4.9 mmol) was added. The mixture was stirred for 24 h, filtered and the filtrate washed with DCM (20 mL) and ethyl acetate (5 mL). DCM (20 mL) and water (20 mL) were added and the mixture was shaken until the orange colour had faded. The aqueous layer was washed with DCM (2×20 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/petrol (3:97) as eluent gave the *title compound* **45** (1.71 g, 66%) as a colourless oil, $[\alpha]_D^{20}$+1.8 (*c* 1.0 in DCM); ν_{max} 774, 836, 1039, 1249, 1466, 1513, 1615, 1688 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.02 [9H, s, Si(CH_3)$_3$], 0.03 and 0.05 (each 3H, s, SiCH_3), 0.09 [9H, s, Si(CH_3)$_3$], 0.87 [9H, s, SiC(CH_3)$_3$], 0.93 (2H, m, CH_2Si), 1.05 and 1.15 (each 3H, s, 4-CH_3), 2.12 (1H, dd, *J* 8, 13, 10-*H*), 2.31 (1H, dd, *J* 4.5, 13, 10-*H*′), 3.03 (2H, m, 8-H_2), 3.38 and 3.42 (each 1H, dd, *J* 5, 10, 12-*H*), 3.60 (2H, m, CH_2CH$_2$Si), 3.80 (3H, s, OCH_3), 3.91 (1H, m, 11-*H*), 3.92 (1H, d, *J* 8.5, 3-*H*), 4.20 and 4.49 (each 1H, d, *J* 11.5, *H*CHAr), 4.64 (2H, s, OCH_2O), 5.26 (1H, d, *J* 18, 1-*H*), 5.34 (1H, dd, *J* 1.5, 10.5, 1-*H*′), 5.45 (1H, s, 9-C*H*), 5.70 (1H, ddd, *J* 8, 10.5, 18, 2-*H*), 6.50 (1H, d, *J* 15, 6-*H*), 6.84 (3H, m, 7-*H* and Ar*H*), 7.17 (2H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −4.68, −4.47, −1.47, 0.18, 18.02, 19.47, 21.33, 25.83, 39.18, 44.18, 50.31, 55.12, 64.98, 70.10, 70.90, 72.01, 84.68, 95.08, 113.48, 119.64, 126.56, 129.07, 129.86, 130.40, 134.53, 143.98, 151.42, 158.87, 202.39; *m*/*z* (CI) 722 (M^++18, 33%), 705 (M^++1, 28), 137 (100), 121 (78); HRMS (CI): M^++NH_4, found 722.4675. $C_{38}H_{72}NO_6Si_3$ requires 722.4667.

*4.2.26. (3S,11R,6E)-3-Benzyloxy-11-tert-butyldimethylsilyloxy-4,4-dimethyl-12-(2-trimethylsilylethoxy)methoxy-9-[(E)-trimethylsilylmethylidene]dodeca-1,6-dien-5-one (**46**).* Activated powdered 4 Å molecular sieves (1 g) were added to the alkynone **44** (2.53 g, 10.45 mmol) and allylsilane (***R***)-**28** (8.98 g, 20.79 mmol) in DCM (10 mL). The flask was protected from light and zinc(II) iodide (5 g, 15.67 mmol) was added. The mixture was stirred for 24 h, filtered, and the filtrate washed with DCM (20 mL) and ethyl acetate (5 mL). DCM (20 mL) and water (20 mL) were added and the mixture shaken until the orange colour had faded. The aqueous layer was washed with DCM (2×20 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/petrol (2:98) then ethyl acetate/petrol (6:94) as eluent gave the *title compound* **46** (5.26 g, 75%) as a colourless oil, $[\alpha]_D^{20}$− 1.3 (*c* 1.0 in DCM); ν_{max} 695, 775, 837, 932, 989, 1059, 1107, 1250, 1466, 1615, 1690 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.02 [9H, s, Si(CH_3)$_3$], 0.03 and 0.06 (each 3H, s, SiCH_3), 0.10 [9H, s, Si(CH_3)$_3$], 0.87 [9H, s, SiC(CH_3)$_3$], 0.94 (2H, m, CH_2Si), 1.08 and 1.18 (each 3H, s, 4-CH_3), 2.13 (1H, dd, *J* 8, 13.5, 10-*H*), 2.30 (1H, ddd, *J* 1, 4.5, 13.5, 10-*H*′), 3.01 (1H, ddd, *J* 1.5, 7, 12.5, 8-*H*), 3.05 (1H, ddd, *J* 1.5, 7, 12.5, 8-*H*′), 3.38 (1H, dd, *J* 5, 10, 12-*H*), 3.42 (1H, dd, *J* 5.5, 10, 12-*H*′), 3.60 (2H, m, CH_2CH$_2$Si), 3.90 (1H, br dq, *J* 5, 8, 11-*H*), 3.95 (1H, d, *J* 8, 3-*H*), 4.29 and 4.56 (each 1H, d, *J* 12, *H*CHAr), 4.64 (2H, s, OCH_2O), 5.28 (1H, d, *J* 17.5, 1-*H*), 5.35 (1H, dd, *J* 1.5, 10.5, 1-*H*′), 5.45 (1H, s, 9-C*H*), 5.72 (1H, ddd, *J* 8, 10.5, 17.5, 2-*H*), 6.51 (1H, d, *J* 15, 6-*H*), 6.85 (1H, dt, *J* 15, 7, 7-*H*), 7.20–7.35 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −4.68, −4.66, −1.46, 0.18, 18.04, 19.45, 21.38, 25.83, 39.21, 44.18, 50.34, 64.99, 70.45, 70.94, 72.01, 85.07, 95.09, 119.77, 126.52, 127.24, 127.48, 128.08, 129.86, 134.44, 138.34, 144.08, 151.42, 202.33; *m*/*z* (CI) 692 (M^++18, 1%), 675 (M^++1, 1), 90 (100); HRMS (CI): M^++H, found 675.4290. $C_{37}H_{67}O_5Si_3$ requires 675.4296.

*4.2.27. (2R,6S)- and (2R,6R)-2-Acetoxymethyl-6-[(4S)-3,3-dimethyl-4-(4-methoxybenzyloxy)-2-oxohex-5-enyl]-4-methylenetetrahydropyrans (**47**) and (**50**).* Aqueous hydrogen fluoride (58–62%, 300 μl) was added to the trienone **45** (100 mg, 1.42 mmol) in acetonitrile (1 mL) in Teflon tube. The solution was stirred for 18 h, then ether (10 mL) was added followed by the dropwise addition of a saturated aqueous sodium hydrogen carbonate until effervescence ceased. The aqueous layer was washed with ethyl acetate (4×10 mL) and the combined organic fractions were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The mixture was filtered though a short pad of silica using ethyl acetate/petrol (30:70) as eluent. The residue was taken up in acetic anhydride (500 μl) and pyridine (500 μl) was added. The solution was stirred for 18 h then saturated aqueous ammonium chloride (10 mL) was added. The aqueous layer was washed with DCM (2×10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (6:94) as eluent gave the (6*S*)-epimer of the *title compound* **47** (28 mg, 46%) as a colourless oil, $[\alpha]_D^{20}$ +5.9 (*c* 1.0 in DCM); ν_{max} 824, 936, 1038, 1174, 1246, 1368, 1465, 1513, 1611, 1706, 1740 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.89 and 1.05 (each 3H, s, 3″-CH_3), 1.69 (1H, br t, *J* 12, 5-*H*), 1.86 (1H, br t, *J* 12, 3-*H*), 1.95 (3H, s, CH_3CO), 2.06 (1H, d, *J* 12, 3-*H*′), 2.18 (1H, d, *J* 12, 5-*H*′), 2.44 (1H, dd, *J* 7, 17, 1″-*H*), 2.79 (1H, dd, *J* 6.5, 17, 1″-*H*′), 3.44 (1H, m, 2-*H*), 3.68 (4H, m, 6-*H* and OCH_3), 3.82 (1H, d, *J* 8, 4″-*H*), 3.95 (2H, m 2-CH_2), 4.06 and 4.35 (each 1H, d, *J* 11.5, *H*CHAr), 4.61 (2H, m, 4-CH_2), 5.15 (1H, dd, *J* 2, 17.5, 6″-*H*), 5.25 (1H, dd, *J* 2, 10.5, 6″-*H*′), 5.60 (1H, ddd, *J* 8, 10.5, 17.5, 5″-*H*), 6.73 and 7.10 (each 2H, d, *J* 7, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.80, 20.83, 21.80, 36.60, 40.13, 45.02, 51.26, 55.20, 66.78, 70.17, 74.76, 75.92, 85.53, 109.73, 113.59, 120.05, 129.17, 130.45, 134.37, 142.79, 159.00, 170.86, 212.38; *m*/*z* (CI) 448 (M+18, 25%), 241 (4), 138 (26), 121 (100); HRMS (CI): M^++NH_4, found 448.2704. $C_{25}H_{38}NO_6$ requires 448.2699. An impure sample tentatively identified as containing the (6*R*)-epimer of the *title compound* **50** (4 mg, 6%) was isolated as a colourless oil.

*4.2.28. (2R,6S)- and (2R,6R)-6-[(4S)-3,3-Dimethyl-4-(4-methoxybenzyloxy)-2-oxohex-5-enyl]-2-(2-trimethylsilylethoxymethoxy)methyl-4-[(E)-trimethylsilylmethylene]tetrahydropyrans (**48**) and (**51**).* HF·pyridine (125 μl) was added dropwise to the trienone **45** (100 mg, 1.42 mmol) in dry THF (4 mL) at 0 °C in a Teflon tube. The mixture was stirred for 0.5 h, allowed to warm to rt, and stirred for 18 h. Ether (10 mL) was added followed by saturated aqueous sodium hydrogen carbonate until effervescence ceased. The organic layer was washed with ether (2×10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/petrol (2:98) as eluent gave the (6*S*)-epimer of the *title compound* **48** (19 mg, 21%) as a colourless oil, $[\alpha]_D^{20}$+5.9 (*c* 1.0 in DCM); ν_{max} 838, 935, 1037, 1058, 1108, 1249, 1466, 1514, 1616, 1706 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 and 0.11 [each 9H, s, Si(CH_3)$_3$], 0.92 (2H, m, CH_2Si), 1.08 and 1.17 (each 3H, s, 3″-CH_3), 1.74 (1H, br t, *J* 13, 5-*H*), 2.12 (2H, m, 3-H_2), 2.58 (1H, d, *J* 13, 5-*H*′), 2.67 (1H, dd, *J* 8, 17.5, 1″-*H*), 2.94 (1H, dd, *J* 4.5, 17.5, 1″-*H*′), 3.45–3.65 (5H, m, 1′-H_2, 2-*H* and CH_2CH$_2$Si), 3.74 (1H, m, 6-*H*), 3.76 (3H, s, OCH_3), 3.95 (1H, d, *J* 8, 4″-*H*), 4.18 and 4.44 (each 1H, d, *J* 11.5, *H*CHAr), 4.67 (2H, s, OCH_2O), 5.25 (1H, d, *J* 17, 6″-*H*), 5.26 (1H,

s, 4-C*H*), 5.34 (1H, d, *J* 10.5, 6″-*H*′), 5.69 (1H, ddd, *J* 8, 10.5, 17, 5″-*H*), 6.82 and 7.16 (each 2H, d, *J* 7, Ar*H*). The (6*R*)-epimer of the *title compound* **51** (19 mg, 21%) was isolated as a colourless oil, $[\alpha]_D^{20}$ +17.5 (*c* 1.0 in DCM); ν_{max} 838, 933, 1038, 1058, 1106, 1249, 1379, 1466, 1513, 1615, 1706 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 and 0.08 [9H, s, Si(CH_3)$_3$], 0.94 (2H, m, CH_2Si), 1.02 and 1.14 (each 3H, s, 3″-CH_3), 2.08 (1H, dd, *J* 6.5, 13, 5-*H*), 2.19 (1H, dd, *J* 6, 13.5, 3-*H*), 2.35 (1H, dd, *J* 4.5, 13, 3-*H*′), 2.55 (1H, m, 1″-*H* and 5-*H*′), 2.90 (1H, dd, *J* 5, 17.5, 1″-*H*′), 3.58 (4H, m, 1′-H_2 and CH_2CH_2Si), 3.80 (3H, s, OCH_3), 3.90 (2H, m, 4″-*H* and 2-*H*), 4.10 (1H, d, *J* 11.5, *H*CHAr), 4.28 (1H, m, 6-*H*), 4.46 (1H, d, *J* 11.5, *H*CHAr), 4.67 (2H, s, OCH_2O), 5.26 (1H, d, *J* 17, 6″-*H*), 5.32 (1H, s, 4-C*H*), 5.35 (1H, dd, *J* 1.5, 11, 6″-*H*′), 5.69 (1H, ddd, *J* 8, 11, 17, 5″-*H*), 6.84 and 7.17 (each 2H, d, *J* 7, Ar*H*).

*4.2.29. (2R,6S)- and (2R,6R)-2-Acetoxymethyl-6-[(4S)-4-benzyloxy-3,3-dimethyl-2-oxohex-5-enyl]-4-methylenetetrahydropyrans (**49**) and (**52**).* Aqueous hydrogen fluoride (58–62%, 200 μl) was added to the trienone **46** (100 mg, 0.14 mmol) in acetonitrile (1 mL) in a Teflon tube, and the solution stirred for 18 h. Ether (10 mL) was added followed by the dropwise addition of saturated aqueous sodium hydrogen carbonate until effervescence ceased. The aqueous layer was washed with ethyl acetate (4×10 mL) and the combined organic fractions were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was filtered though a short pad of silica using ethyl acetate/petrol (30:70) as eluent. The residue was then taken up in acetic anhydride (500 μl) and pyridine (100 μl) was added. The solution was stirred for 18 h then saturated aqueous ammonium chloride (10 mL) was added. The aqueous layer was washed with DCM (2×10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/petrol (6:94) as eluent gave the (6*S*)-epimer of the *title compound* **49** (39 mg, 66%) as a colourless oil, $[\alpha]_D^{20}$–6.2 (*c* 1.0 in DCM); ν_{max} 699, 737, 896, 934, 1047, 1237, 1370, 1461, 1654, 1707, 1742 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.00 and 1.17 (each 3H, s, 3″-CH_3), 1.79 (1H, br t, *J* 12.5, 5-*H*), 1.95 (1H, br t, *J* 12.5, 3-*H*), 2.04 (3H, s, CH_3CO), 2.16 (1H, br dt, *J* 13, 2, 3-*H*′), 2.29 (1H, br dt, *J* 13, 2, 5-*H*′), 2.56 (1H, dd, *J* 7, 17, 1″-*H*), 2.90 (1H, dd, *J* 5.5, 17, 1″-*H*′), 3.53 (1H, dddd, *J* 3.5, 6, 11.5, 13, 2-*H*), 3.77 (1H, m, 6-*H*), 3.94 (1H, d, *J* 8, 4″-*H*), 4.03 (2H, m, 2-CH_2), 4.24 and 4.52 (each 1H, d, *J* 12, *H*CHAr), 4.75 (2H, m, 4-CH_2), 5.32 (1H, d, *J* 17, 6″-*H*), 5.35 (1H, dd, *J* 1.5, 10.5, 6″-*H*′), 5.71 (1H, ddd, *J* 8, 10.5, 17, 5″-*H*), 7.26 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.74, 20.80, 21.78, 36.54, 40.06, 44.97, 51.25, 66.73, 70.46, 74.10, 75.88, 85.81, 109.72, 120.15, 127.31, 127.49, 128.12, 134.20, 138.32, 142.71, 170.82, 212.30; *m*/*z* (CI) 418 (M^++18, 100%), 401 (M^++1, 30); HRMS (CI): M^++NH_4, found 418.2592. $C_{14}H_{36}NO_5$ requires 418.2593. The (6*R*)-epimer of the *title compound* **52** (4 mg, 6%) was isolated as a colourless oil, $[\alpha]_D^{20}$–41 (*c* 1.0 in DCM); δ_H (300 MHz, $CDCl_3$) 1.04 and 1.14 (each 3H, s, 3″-CH_3), 1.96 (1H, dd, *J* 6, 13, 5-*H*), 2.06 (4H, m, CH_3CO and 3-*H*), 2.27 (1H, dd, *J* 4, 13, 3-*H*′), 2.40 (1H, dd, *J* 4, 13, 5-*H*′), 2.58 (1H, dd, *J* 7, 17, 1″-*H*), 2.78 (1H, dd, *J* 5, 17, 1″-*H*′), 3.92 (2H, m, 4″-*H* and 2-*H*), 4.02 (1H, dd, *J* 4, 11.5, 2-C*H*), 4.16 (1H, dd, *J* 7, 11.5, 2-C*H*′), 4.26 (1H, d, *J* 11.5, *H*CHAr), 4.37 (1H, m, 6-*H*), 4.54 (1H, d, *J* 11.5, *H*CHAr), 4.71 and 4.78 (each 1H, m, 4-C*H*), 5.29 (1H, ddd, *J* 1, 2, 17, 6″-*H*), 5.38 (1H, dd, *J* 1, 10, 6″-*H*′), 5.71 (1H, ddd, *J* 8, 10, 17, 5″-*H*), 7.28 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.82, 20.88, 21.96, 29.66, 35.98, 38.77, 41.52, 51.44, 65.01, 69.07, 70.27, 85.21, 111.36, 120.35, 127.40, 127.57, 128.19, 134.22, 138.18, 140.54, 170.94, 211.50.

*4.2.30. (2R,6S)- and (2R,6R)-6-[(4S)-4-Benzyloxy-3,3-dimethyl-2-oxohex-5-enyl]-4-methylene-2-[(2-trimethylsilylethoxymethoxy) methyl]tetrahydropyrans (**53**) and (**54**).* Aqueous hydrogen fluoride (58–62%, 1.5 mL) was added to the trienone **46** (1 g, 1.5 mmol) in acetonitrile (7.5 mL) in a Teflon tube and the solution stirred for 18 h. Ether (50 mL) was added followed by aqueous saturated sodium hydrogen carbonate until effervescence ceased. The aqueous layer was washed with ethyl acetate (4×20 mL) and the combined organic fractions were washed with water (30 mL) and brine (30 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was filtered though a short pad of silica using ethyl acetate/petrol (30:70) as the eluent. The residue was then taken up in DCM (2 mL) and SEM-chloride (345 μl, 1.39 mmol) and di-*iso*-propylethylamine (490 μl, 1.84 mmol) was added. The solution was stirred overnight then saturated aqueous ammonium chloride (10 mL) was added. The aqueous layer was washed with DCM (2×10 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (6:94) as eluent gave the (6*S*)-epimer of the *title compound* **53** (355 mg, 48%) as a colourless oil, $[\alpha]_D^{20}$–1.1 (*c* 1.0 in DCM); ν_{max} 697, 738, 836, 858, 934, 1059, 1105, 1249, 1379, 1465, 1654, 1706 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 [9H, s, Si(CH_3)$_3$], 0.92 (2H, m, CH_2Si), 0.99 and 1.16 (each 3H, s, 3″-CH_3), 1.77 (1H, br t, *J* 12, 5-*H*), 2.01 (1H, br t, *J* 11.5, 3-*H*), 2.17 (1H, br d, *J* 12, 3-*H*′), 2.30 (1H, br d, *J* 13, 5-*H*′), 2.63 (1H, dd, *J* 7.5, 17.5, 1″-*H*), 2.91 (1H, dd, *J* 5, 17.5, 1″-*H*′), 3.49 (3H, m, 2-CH_2 and 2-*H*), 3.59 (2H, m, CH_2CH_2Si), 3.78 (1H, m, 6-*H*), 3.95 (1H, d, *J* 8, 4″-*H*), 4.23 and 4.51 (each 1H, d, *J* 11.5, *H*CHAr), 4.66 (2H, s, OCH_2O), 4.75 (2H, m, 4-CH_2), 5.26 (1H, d, *J* 17, 6″-*H*), 5.39 (1H, dd, *J* 1.5, 10.5, 6″-*H*′), 5.70 (1H, ddd, *J* 8, 10.5, 17, 5″-*H*), 7.26 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) –1.48, 18.01, 18.74, 21.77, 36.93, 40.19, 45.20, 51.22, 64.98, 70.44, 74.63, 76.51, 85.72, 94.96, 109.25, 120.14, 127.29, 127.47, 128.11, 134.20, 138.33, 143.39, 212.33; *m*/*z* (CI) 506 (M^++18, 100%); HRMS (CI): M^++NH_4, found 506.3300. $C_{28}H_{48}NO_5Si$ requires 506.3301. The (6*R*)-epimer of the *title compound* **54** (63 mg, 9%) was isolated as a colourless oil, $[\alpha]_D^{20}$–6.15 (*c* 1.0 in DCM); δ_H (300 MHz, $CDCl_3$) 0.00 [9H, s, Si(CH_3)$_3$], 0.91 (2H, m, CH_2Si), 1.02 and 1.12 (each 3H, s, 3″-CH_3), 1.95 (1H, br dd, *J* 5.5, 13, 5-*H*), 2.09 (1H, br dd, *J* 7.5, 13.5, 3-*H*), 2.26 (1H, br dd, *J* 4, 13.5, 3-*H*′), 2.40 (1H, br dd, *J* 4.5, 13.5, 5-*H*′), 2.67 (1H, dd, *J* 8, 17.5, 1″-*H*), 2.77 (1H, dd, *J* 5, 17.5, 1″-*H*′), 3.56 (4H, m, 2-CH_2 and CH_2CH_2Si), 3.83 (1H, m, 2-*H*), 3.92 (1H, d, *J* 8, 4″-*H*), 4.23 (1H, d, *J* 12, *H*CHAr), 4.34 (1H, m, 6-*H*), 4.52 (1H, d, *J* 12, *H*CHAr), 4.64 (2H, s, OCH_2O), 4.73 (2H, m, 4-CH_2), 5.27 (1H, dd, *J* 1.5, 17.5, 6″-*H*), 5.35 (1H, dd, *J* 1.5, 10.5, 6″-*H*′), 5.69 (1H, ddd, *J* 8, 10.5, 17.5, 5″-*H*), 7.26 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) –1.48, 18.01, 18.91, 21.91, 36.36, 38.81, 41.64, 51.44, 65.03, 68.78, 69.10, 70.31, 71.51, 85.21, 95.00, 110.89, 120.19, 127.32, 127.50, 128.13, 134.27, 138.20, 141.18, 211.66.

*4.2.31. (2R,4RS,6S)-6-[(4S)-4-Benzyloxy-3,3-dimethyl-2-oxohex-5-enyl]-4-(hydroxymethyl)-2-[(2-trimethylsilylethoxymethoxy)-methyl]tetrahydropyran (**55**).* 9-BBN (0.5 M in THF, 1.8 mL, 0.88 mmol) was added to an ice cooled solution of the methylenetetrahydropyran **53** (288 mg, 0.59 mmol) in THF. The solution was stirred at rt for 18 h then ice cooled water (1 mL), aqueous sodium hydroxide (3 M, 800 μl) and aqueous hydrogen peroxide (30%, 500 μl) were added. The mixture was allowed to warm to rt and was stirred for 3 h. Water (5 mL) and ether (5 mL) were added and the aqueous layer was washed with ether (3×5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (30:70) as eluent gave the *title compound* **55** (218 mg, 73%) as a colourless oil, a 75:25 mixture of epimers; ν_{max} 698, 741, 837, 859, 933, 1057, 1106, 1249, 1381, 1466, 1705, 3475 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.01 [9H, s, Si(CH_3)$_3$], 0.91 (2H, m, CH_2Si), 0.98 and 1.15 (each 3H, s, 3″-CH_3), 1.20–1.90 (5H, m, 3-H_2, 4-*H* and 5-H_2), 2.05 (0.3H, s, O*H*), 2.57 (0.3H, dd, *J* 8, 17.5, 1″-*H*), 2.63 (0.7H, dd, *J* 8, 17.5, 1″-*H*), 2.86 (0.3H, dd, *J* 5, 17.5, 1″-*H*′), 2.87 (0.7H, dd, *J* 5, 17.5, 1″-*H*′), 3.39 (0.7H, d, *J* 5, 2-C*H*), 3.53 (4.3H, m, 4-CH_2, 2-C*H* and CH_2CH_2Si), 3.77

(1.7H, m, 6-*H* and 4″-*H*), 3.95 (1.3H, m, 2-*H* and 4″-*H*), 4.22 (0.7H, d, *J* 12, *H*CHAr), 4.23 (0.3H, d, *J* 12, *H*CHAr), 4.51 (0.7H, d, *J* 12, *H*CHAr), 4.52 (0.3H, d, *J* 12, *H*CHAr), 4.64 (0.6H, s, OCH_2O), 4.66 (1.4H, s, OCH_2O), 5.27 (1H, m, 6″-*H*), 5.39 (1H, m, 6″-*H*′), 5.70 (1H, m, 5″-*H*), 7.26 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −1.46, 18.01, 18.67, 18.71, 21.75, 21.85, 28.38, 30.85, 31.91, 33.44, 34.04, 37.52, 45.40, 45.56, 51.17, 51.23, 63.21, 64.95, 67.63, 69.13, 70.43, 70.79, 71.10, 72.06, 73.25, 76.09, 85.73, 85.89, 94.95, 120.11, 127.24, 127.28, 127.35, 127.45, 128.09, 134.15, 138.33, 138.42, 212.75, 213.02; *m*/*z* (CI) 524 (M^++18, 100%); HRMS (CI): M^++NH_4, found 524.3406. $C_{28}H_{50}NO_6Si$ requires 534.3407.

*4.2.32. (2R,6S)- and (2R,6R)-6-[(4S)-4-Benzyloxy-3,3-dimethyl-2-oxohex-5-enyl]-2-(tert-butyldiphenylsilyloxy)methyl-4-methylenetetrahydropyrans (**56**) and (**57**).* Aqueous hydrogen fluoride (58–62%, 3 mL) was added to the trienone **46** (2 g, 3.1 mmol) in acetonitrile (15 mL) in a Teflon tube and the solution was stirred for 18 h. Ether (100 mL) was added followed by saturated aqueous sodium hydrogen carbonate, which was added dropwise until effervescence ceased. The aqueous layer was washed with ethyl acetate (4×30 mL) and the combined organic fractions were washed with water (40 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was filtered though a short pad of silica using ethyl acetate/petrol (30:70) as eluent and the residue was taken up in ice cooled DCM (3 mL). Imidazole (190 mg, 2.8 mmol) and *tert*-butyldiphenylsilyl chloride (544 μl, 2.1 mmol) were added and the solution stirred for 18 h. Saturated aqueous ammonium chloride (5 mL) was added and the organic layer was washed with DCM (5 mL). The combined organic extracts were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (3:97) as eluent gave the (6*S*)-epimer of the *title compound* **56** (1.07 g, 57%) as a colourless oil, $[\alpha]_D^{20}$ +2.3 (*c* 1.0 in DCM); ν_{max} 703, 740, 822, 891, 934, 1111, 1362, 1386, 1426, 1467, 1652, 1706 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.93 (3H, s, 3″-CH_3), 0.97 [9H, s, SiC(CH_3)$_3$], 1.10 (3H, s, 3″-CH_3), 1.70 (1H, br t, *J* 12.5, 5-*H*), 1.88 (1H, br t, *J* 12.5, 3-*H*), 2.22 (2H, m, 5-*H*′ and 3-*H*′), 2.49 (1H, dd, *J* 7, 17.5, 1″-*H*), 2.75 (1H, dd, *J* 5.5, 17.5, 1″-*H*′), 3.54 (2H, m, 2-*H* and 2-C*H*), 3.66 (2H, m, 2-C*H*′ and 6-*H*), 3.88 (1H, d, *J* 8, 4″-*H*), 4.17 and 4.44 (each 1H, d, *J* 11.5, *H*CHAr), 4.66 (2H, s, 4-CH_2), 5.22 (1H, d, *J* 17, 6″-*H*), 5.28 (1H, d, *J* 10.5, 6″-*H*′), 5.64 (1H, ddd, *J* 8, 10.5, 17, 5″-*H*), 7.18 (6H, m, Ar*H*), 7.30 (5H, m, Ar*H*), 7.59 (4H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.74, 19.22, 21.80, 26.76, 37.17, 40.45, 45.08, 51.23, 66.96, 70.48, 74.35, 78.56, 85.72, 109.04, 120.11, 127.30, 127.50, 128.12, 129.49, 133.62, 134.22, 135.54, 135.60, 138.29, 143.81, 212.32; *m*/*z* (CI) 614 (M^++18, 100%); HRMS (CI): M^++NH_4, found 614.3667. $C_{38}H_{52}NO_4Si$ requires 614.3665. The (6*R*)-epimer of the *title compound* **57** (176 mg, 10%) was isolated as a colourless oil,$[\alpha]_D^{20}$ −19.2 (*c* 1.0 in DCM); δ_H (300 MHz, $CDCl_3$) 1.06 (3H, s, 3″-CH_3), 1.10 [9H, s, SiC(CH_3)$_3$], 1.18 (3H, s, 3″-CH_3), 1.98 (1H, br dd, *J* 5.5, 13.5, 5-*H*), 2.20 (1H, br dd, *J* 6.5, 13, 3-*H*), 2.38 (2H, m, 3-*H*′ and 5-*H*′), 2.64 (1H, dd, *J* 8, 17.5, 1″-*H*), 2.78 (1H, dd, *J* 5, 17.5, 1″-*H*′), 3.75 (3H, m, 2-*H* and 2-CH_2), 3.97 (1H, d, *J* 8, 4″-*H*), 4.30 (2H, m, 6-*H* and *H*CHAr), 4.58 (1H, *J* 12, *H*CHAr), 4.73 and 4.79 (each 1H, s, 4-C*H*), 5.33 (1H, d, *J* 17, 6″-*H*), 5.41 (1H, dd, *J* 1.5, 10.5, 6″-*H*′), 5.75 (1H, ddd, *J* 8, 10.5, 17, 5″-*H*), 7.30 (5H, m, Ar*H*), 7.43 (6H, m, Ar*H*), 7.71 (4H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.82, 19.20, 21.84, 26.79, 36.26, 39.04, 41.78, 51.44, 65.00, 69.24, 70.31, 73.12, 85.15, 110.75, 120.19, 127.35, 127.56, 128.14, 129.54, 133.51, 134.27, 135.52, 135.55, 138.16, 141.41, 211.73.

*4.2.33. (2R,6S)-6-[(4S)-4-Benzyloxy-3,3-dimethyl-2-oxohex-5-enyl]-2-(tert-butyldiphenylsilyloxy)methyl-4-methyl-4,1″-epoxytetrahydropyran (**58**).* *m*-CPBA (207 mg, 0.84 mmol) was added portionwise to the methylenetetrahydropyran **56** (457 mg, 0.77 mmol) in DCM (3 mL) at 0 °C and the mixture stirred for 5 h. Aqueous sodium thiosulfate (10%, 2 mL), water (5 mL) and DCM (5 mL) were added and the aqueous layer was washed with DCM (3×5 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/petrol (6:94) as eluent gave the *title compound* **58** (448 mg, 95%) as a colourless oil, an 85:15 mixture of diastereoisomers; ν_{max} 703, 740, 823, 933, 1111, 1366, 1387, 1426, 1467, 1707, 2360 cm^{-1}; δ_H (300 MHz, $CDCl_3$) major isomer 0.97 (3H, s, 3‴-CH_3), 1.05 [9H, s, SiC(CH_3)$_3$], 1.16 (3H, s, 3‴-CH_3), 1.21 (2H, m, 3-*H* and 5-*H*), 1.66 (1H, m, 5-*H*′), 1.82 (1H, m, 3-*H*′), 2.51 (1H, dd, *J* 16, 8, 1‴-*H*), 2.58 and 2.66 (each 1H, d, *J* 5, 1″-*H*), 2.82 (1H, dd, *J* 16, 7, 1‴-*H*′), 3.54 and 3.69 (each 1H, m, 2-C*H*), 3.83 (1H, m, 2-*H*), 3.92 (1H, m, 4‴-*H*), 4.13 (1H, m, 6-*H*), 4.21 and 4.49 (each 1H, d, *J* 11.5, *H*CHAr), 5.25 (1H, d, *J* 17, 6‴-*H*), 5.33 (1H, m, 6‴-*H*′), 5.69 (1H, m, 5‴-*H*), 7.21 (5H, m, Ar*H*), 7.36 (6H, m, Ar*H*), 7.63 (4H, m, Ar*H*); distinctive peaks for the minor isomer 1.14 (3H, s, 3‴-CH_3), 1.35 (1H, t, *J* 16, 5-*H*), 1.82 (1H, t, *J* 16, 3-*H*), 2.68 (1H, d, *J* 5, 1″-*H*); δ_C (75 MHz, $CDCl_3$) major isomer 18.75, 19.21, 21.84, 26.74, 35.02, 38.34, 44.91, 51.15, 52.83, 56.18, 66.71, 70.49, 71.46, 75.58, 85.83, 120.07, 127.28, 127.47, 127.49, 127.52, 128.11, 129.50, 135.53, 135.59, 138.33, 211.86; *m*/*z* (CI) 630 (M^++18, 100%); HRMS (CI): M^++NH_4, found 630.3615. $C_{38}H_{52}NO_5Si$ requires 630.3614.

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