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Synthesis of the C(1)–C(16) fragment of bryostatins using an 'ene' reaction between an allylsilane and an alkynone

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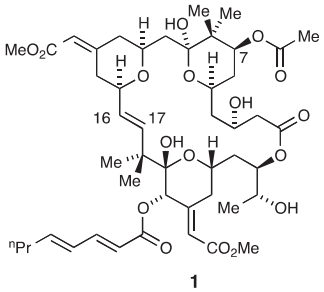
ABSTRACT

The zinc(II) iodide mediated 'ene' reaction between (4*R*)-4,5-bis-(*tert*-butyldimethylsilyloxy)-2-(trimethylsilylmethyl)pent-1-ene (**43**) and (5*S*,7*R*,9*S*)-5,11-dibenzyloxy-4,4-dimethyl-7,9-dihydroxy-7,9-*O*-isopropylideneundec-1-yn-3-one (**53**) gave the (*E*)-vinylsilane **54** with excellent stereoselectivity. Simultaneous deprotection and cyclisation via a stereoselective oxy-Michael reaction gave the bicyclic acetal **57** after treatment with trimethyl orthoformate. A synthesis of the ester **60** corresponding to the C(1)–C(16) fragment of the bryostatins was then completed by O-silylation, oxidative cleavage of the methylene group and a stereoselective condensation of the resulting ketone **59** with the chiral phosphonate **61**.

1. Introduction

The bryostatins as represented by bryostatin **1** are a group of marine natural products with potent biological activity partially due to inhibition of protein kinase Cs.[1] They have been involved in clinical trials for the treatment of various cancers and also display memory enhancement in animal models. However, they are difficult to access from natural sources.

Considerable work has been carried out on the synthesis of bryostatins because of their novel structures and potentially important biological activities. Six total syntheses of natural products have been reported to date[2] together with a formal total synthesis.[3] Close analogues,[4–6] some of which retain biological activities,[7] have also been prepared.



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Convergent syntheses of bryostatins can be envisaged, which involve the formation of the 16,17-double-bond followed by macrolactonisation. Indeed this strategy was used in the early total syntheses of bryostatins with a classical Julia reaction being used for assembly of the 16,17-double-bond.[2a–c] In a recent synthesis of a 20-deoxybryostatin, the use of a modified Julia reaction for formation of this double-bond was found to be advantageous.[5]

We recently reported a synthesis of the 4-methylenetetrahydropyran **5** in which the key step was the stereoselective 'ene' reaction between the allylsilane **2** and the alkynone **3**.[8,9] This gave the (*E*)-vinylsilane **4**[8,9] and simultaneous deprotection and cyclisation via a stereoselective oxy-Michael reaction, induced by hydrogen fluoride in pyridine, gave the 2,6-*cis*-disubstituted 4-methylenetetrahydropyran **5**, after reprotection of the primary hydroxyl group. Moreover, oxidation of this diene was found to be selective for the exocyclic methylene group; for example, epoxidation gave a mixture of the diastereoisomeric epoxides **6**, ratio ca. 85:15.

We now report the use of this chemistry to complete a synthesis of an ester corresponding to the C(1)–C(16)-fragment of bryostatins. This, via assembly of the 16,17-alkene, could be incorporated into a bryostatin synthesis.[10]

2. Results and discussion

Initial studies were concerned with the elaboration of the 4-methylenetetrahydropyran **7**, which had been prepared earlier.[8] Epoxidation using *m*-chloroperbenzoic acid gave the epoxide **8** as a mixture of diastereoisomers, see Scheme 1. Cleavage of the

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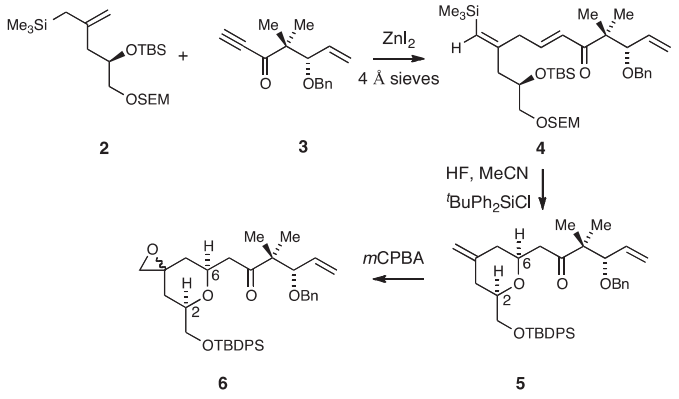
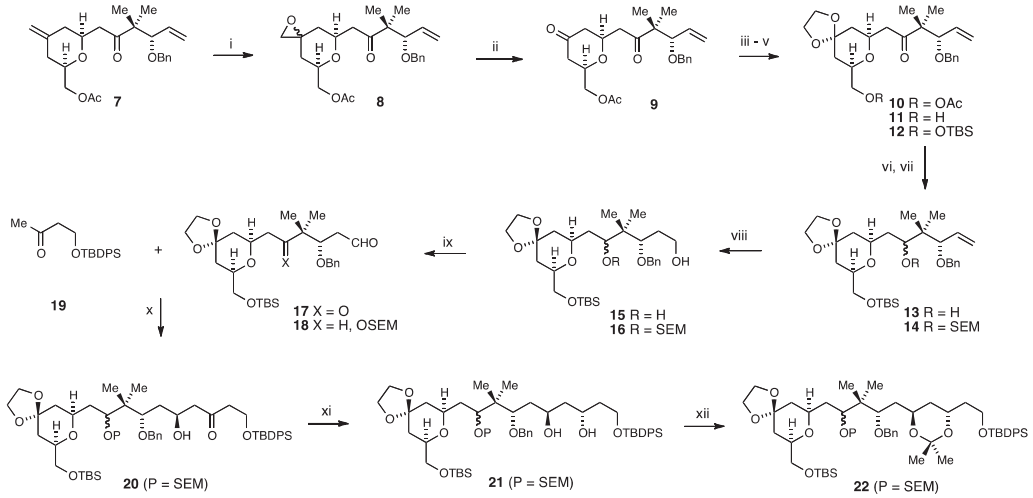


and conversion into the acetonide **22** was achieved using 2,2-dimethoxypropane. In the ^{13}C NMR spectrum of the acetonide **22** the proximity of the acetonide methyl groups at δ 25.24 and 25.36 supported the *anti*-configuration assigned to the 1,3-diol **21** from the reduction of the hydroxyketone **20**.[13]

To complete a synthesis of the C(1)–C(16)-fragment of a bryostatin from the acetonide **22** it remained to introduce the exocyclic methoxycarbonyl group and to carry out modifications of the protecting groups. However, because the ketone at C(9) (bryostatin numbering) had interfered with the hydroboration and aldol steps the overall synthesis was rather long. For this reason it was decided to see whether the hydroboration and aldol steps could be carried out earlier in the synthesis. This would require the zinc(II) iodide mediated 'ene' reaction to be compatible with more advanced intermediates.

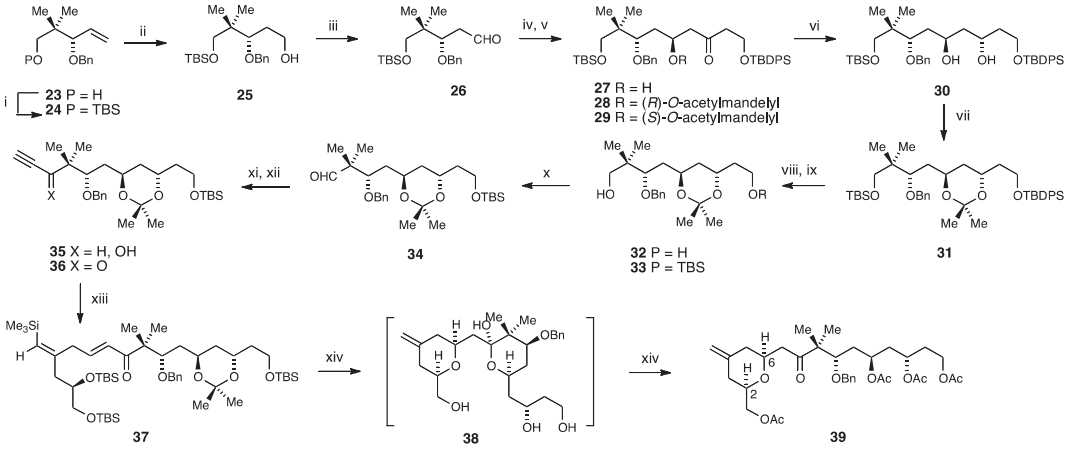


Scheme 1. Reagents and conditions: i, *m*-CPBA, DCM, rt 18 h (61%) ii, H_5IO_6, ether, rt, 18 h (91%); iii, $(CH_2OH)_2$, PPTS benzene, reflux, 2 h (89%); iv, K_2CO_3, MeOH, H_2O, rt, 1.5 h (85%); v, TBSCl, imid., DCM, rt, 30 min (72%); vi, $LiEt_3BH$,THF, −78 °C to rt, 30 min (**13a**, 81%; **13b**, 10%); vii, $^iPr_2NEt$, DCM, SEMCl, rt, 1 h (82%); viii, BH_3. THF, rt, 18 h, then NaOH, 30% aq H_2O_2, rt, 1 h (**15**, 58%; **16**, 66%); ix, $(COCl)_2$, DCM, DMSO, −78 °C, 20 min, Et_3N, −78 °C to rt; x, **19**, LDA, THF, −78 °C, 30 min, add **18**,2 min (60% from **16**); xi, $Me_4N(AcO)_3BH$, MeCN, −40 °C to −20 °C, 18 h (94%); xii, 2,2-DMP, PPTS, rt, 24 h (99%).

epoxide to the ketone **9** was achieved using periodic acid and the ketone was protected as its acetal **10**. Saponification of the acetate then gave the alcohol **11** that was protected as its *tert*-butyldimethylsilyl ether **12**. Preliminary attempts to hydroborate the unsaturated ketone **12** gave complex mixtures of products and so the ketone was reduced to the corresponding alcohol **13**. Lithium triethylborohydride gave an 89:11 mixture of epimers and the synthesis was continued using the major epimer although the configuration at its hydroxyl bearing carbon was not established. Hydroboration–oxidation then gave the diol **15** and this was oxidized into the keto-aldehyde **17**. However, this aldehyde was found to be rather unstable and attempts to effect an aldol condensation with the lithium enolate generated from the ketone **19**[11] were unsuccessful. The unsaturated alcohol **13** was therefore protected as its (trimethylsilylethoxy)methyl (SEM) ether **14** and hydroboration gave the alcohol **16** after oxidation. Further oxidation gave the aldehyde **18** that underwent a stereoselective aldol condensation with the lithium enolate of the ketone **19** following Vanderwalle's procedure[11] to give the hydroxyketone **20**. This aldol reaction was highly stereoselective. The structure of the product in this case was assigned by analogy with the literature[11] although the stereoselectivities of later examples were confirmed by ^{1}H NMR, vide infra. Reduction using tetramethylammonium triacetoxyborohydride[11,12] then gave the 1,3-*anti*-diol **21** selectively

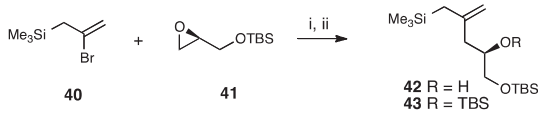
Alcohol **23**, which is available from (*R*)-pantolactone in three steps,[8] was protected as its *tert*-butyldimethylsilyl ether **24**, see Scheme 2. Hydroboration and oxidation gave the primary alcohol **25** and further oxidation gave the aldehyde **26**. The aldol reaction of this aldehyde with the lithium enolate of the methyl ketone **19** was again stereoselective and gave essentially a single hydroxyketone identified as the diastereoisomer **27** by analogy with the literature.[11] In this case, the configuration of the hydroxyl bearing stereogenic centre was confirmed by comparison of the ^{1}H NMR spectra of the (*R*)- and (*S*)-*O*-acetylmandelates **28** and **29**.[14] Reduction to the 1,3-*anti*-diol **30** was carried out using lithium tris-*tert*-butoxyaluminium hydride in the presence of lithium iodide[11,15] and the diol was protected as its acetonide **31**. Again the ^{13}C NMR spectrum of the acetonide **31**, in which the acetonide methyl groups were observed at δ 25.22 and 25.41, supported the 1,3-*anti*-configuration assigned to the 1,3-diol **30**.[13] Removal of both silyl groups gave the diol **32** that was reprotected as its mono-*tert*-butyldimethylsilyl ether **33**. Oxidation, addition of ethynylmagnesium bromide and further oxidation then gave the alkynone **36** ready for the crucial 'ene' reaction.

In the event the 'ene' reaction of the alkynyl ketone **36** with the (bis-*tert*-butyldimethylsilyloxyalkyl)allylsilane **43**, prepared from the epoxide **41** in two steps, see Scheme 3, gave the (*E*)-vinylsilane **37** with excellent stereoselectivity, see Scheme 2. In this case, the geometry of the vinylsilane was assigned on the basis of earlier



Scheme 2. Reagents and conditions: i, TBSCl, imid., DMAP, TBAI, DCM, rt, 30 min (97%); ii, BH_3. THF, 18 °C to rt, 18 h, then NaOH, aq H_2O_2, 50 °C, 3 h (67%); iii, $(COCl)_2$, DCM, DMSO, DCM, −78 °C, 20 min, then Et_3N, rt; iv, **19**, LDA, THF, −78 °C, 30 min, add **26**, −78 °C, 2 min (76%); v, (*R*)- or (*S*)-*O*-acetylmandelyl chloride, $CHCl_3$, DMAP, −10 °C to rt, 1 h (**28**, 82%; **29**, 70%); vi, LiI, $Li(^tBuO)_3AlH$, ether, −78 °C, 18 h (95%); vii, DMP, PPTS, rt, 18 h (93%); viii, TBAF, THF, rt, 18 h (99%); ix, TBSCl, imid., DCM, rt, 2 h (94%); x, Dess–Martin periodinane, DCM, rt 30 min; xi, HCCMgBr, THF, −78 °C to rt; xii, Dess–Martin periodinane, DCM, rt, 20 min (ca. 100%); xiii, ZnI_2, 4 Å sieves, DCM, **43**, rt, 48 h (64%); xiv, (a) aq HF, MeCN, rt, 18 h; (b) Ac_2O, py, DMAP, rt, 18 h (**39**, 65%).

work.[8] The reaction with aqueous hydrogen fluoride under conditions that had previously been used to effect the simultaneous deprotection and oxy-Michael addition now gave a crude product that was difficult to characterize but which was believed to be the hemi-acetal **38**. However, treatment of this crude product with acetic anhydride in pyridine gave the 2,6-*cis*-disubstituted 4-methylenetetrahydropyran **39** that was isolated in an overall yield of 65% based on the enone **37**. The 2,6-*cis*-configuration of the tetrahydropyran was confirmed by a strong NOE enhancement of H(2) on irradiation of H(6) and vice versa.



Scheme 3. Reagents and conditions; i, **40**, Mg, THF, reflux, 5 min, **41**, CuI, −10 °C, 1 h (60%); ii, TBSOTf, Et_3N, DCM, 0 °C, 5 min (96%).

This synthesis of the 4-methylenetetrahydropyran **39** confirmed that the proposed assembly strategy was viable and that the 'ene' reaction could be carried out on more advanced intermediates. However, the protecting group strategy had now to be modified to facilitate better differentiation of the hydroxyl groups. Since it was intended to trap the 5-hydroxyl group as its acetal with the ketone at C(9), and it was thought that it would be possible to differentiate between the primary hydroxyl group at C(16) and the secondary hydroxyl group at C(3), it was decided to look at alternative protecting groups for the hydroxyl group at C(1) (bryostatin numbering).

The aldol reaction between 4-benzyloxybutan-2-one **44** and the aldehyde **26** gave only a modest, 51%, yield of the required adduct **45**. In this case minor side-products were detected, which were not fully characterized but which were believed to be branched isomers formed by non-regiospecific deprotonation of the ketone **44**. Nevertheless the configuration of the major product was shown to correspond to the required isomer **45** by comparison of the ^1H NMR spectra of the (*R*)- and (*S*)-*O*-acetylmandelates **46** and **47**.[14] Following reduction of the aldol product, protection of the resulting diol **48** gave the acetonide **49**, the acetonide methyl groups being observed at δ 25.15 and 25.32 in its ^{13}C NMR spectrum so confirming the *anti*-selective reduction of the hydroxyketone **45**.[13] Desilylation gave the alcohol **50** and this was taken though to the alkynone **53** by oxidation, addition of ethynylmagnesium bromide and further oxidation, see Scheme 4.

The zinc di-iodide mediated 'ene' reaction between the alkynyl ketone **53** and the allylsilane **43** proceeded as expected and gave the (*E*)-vinylsilane **54** in a reasonable yield (55%). In this case the (*E*)-configuration of the vinylsilane was confirmed by a significant NOE enhancement observed for 13-CH on irradiation of one of the hydrogens at C(14). Treatment with aqueous hydrogen fluoride then initiated deprotection and the required oxy-Michael addition to generate what was believed to be the hemi-acetal **55**. To confirm the structure of this intermediate, the crude product was treated with acetic anhydride in pyridine. This gave the tri-acetate **56** albeit in only a modest overall yield (35%) based on the alkynone **54**. Again in this case a significant NOE enhancement of H(2) was observed on irradiation of H(6) and vice versa so confirming the 2,6-*cis*-configuration assigned to the tetrahydropyran.

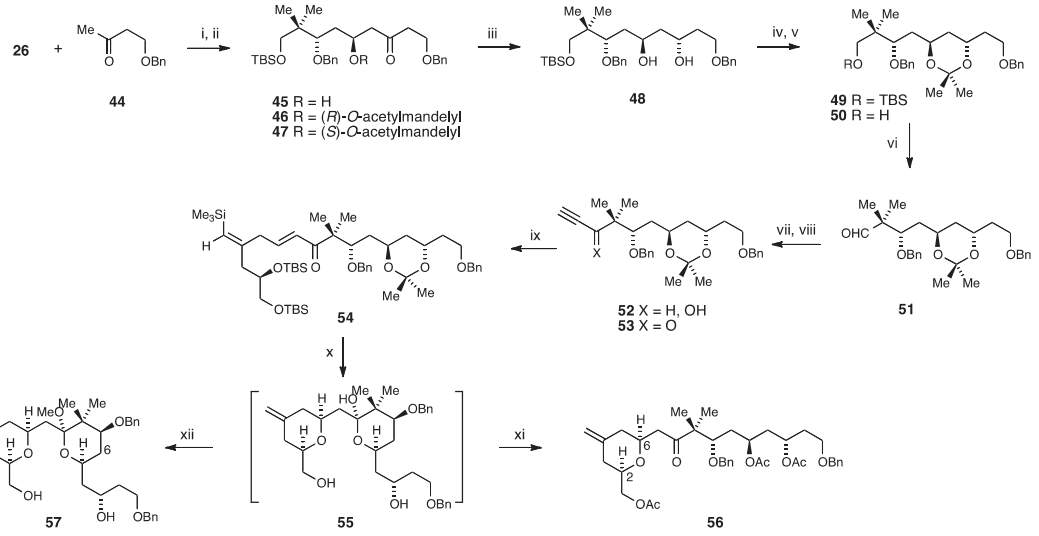
To progress the synthesis, the crude hemi-acetal **55** was reacted with trimethyl orthoformate in methanol in the presence of pyridinium toluene *p*-sulfonate. This gave the methoxyacetal **57** in an overall yield of 49% based on the starting alkynone **54**.

A characteristic feature of the ^1H NMR spectrum of acetal **57**, and of similar acetals prepared later, was the apparent quartet at δ 1.42 (J 12 Hz) attributed to 6-H_{ax}. In the ^{13}C NMR spectrum of acetal **57**, the acetal carbon, C(9), was observed at δ 103.92.

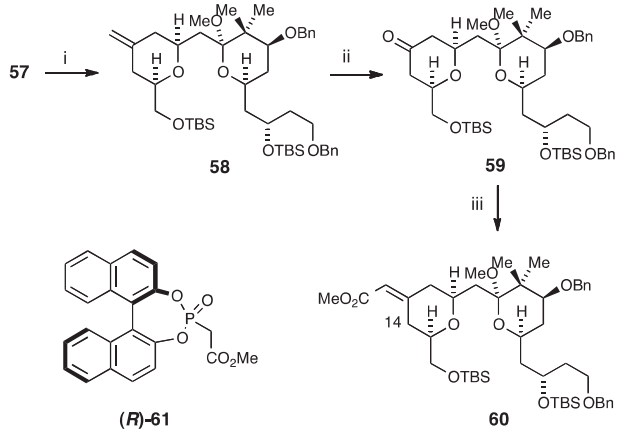
To complete a synthesis of the C(1)–C(16) fragment of a bryostatin, it remained to introduce the methoxycarbonylmethylene side chain. Following silylation of the two free hydroxyl groups of the methoxyacetal **57**, oxidative cleavage of the methylene group of the resulting silyl ether **58** gave the ketone **59**. Treatment of this ketone with the (*R*)-phosphonate **61**, which had been used before in synthetic approaches to bryostatins,[2b,16] gave the (*Z*)-alkene **60** together with its (*E*)-isomer, ratio 72:28, see Scheme 5. The geometry of the major alkene was confirmed as the (*Z*)-isomer **60** on the basis of precedent[16] and was consistent with ^1H NMR studies, in particular, the marked deshielding of the equatorial proton at C(14), which was observed at δ 3.76,[5] due to the proximity of the methoxycarbonyl group. COSY spectra were consistent with the assignments of H(12) and H(14).

3. Summary and conclusions

Ester **60** corresponds to the C(1)–C(16) fragment of bryostatins and is ready for incorporation into a convergent synthesis of



Scheme 4. Reagents and conditions: i, **44**, LDA, THF, −78 °C, 2 min (51%); ii, (*R*)- or (*S*)-*O*-acetylmandelyl chloride, py, DMAP, DCM, 0 °C to rt, 10 h (**46**, 75%; **47**, 85%); iii, $Me_4N(AcO)_3BH$, MeCN, −40 °C to −20 °C, 18 h (95%); iv, 2,2-DMP, PPTS, rt, 18 h (74%); v, TBAF, THF, rt, 18 h (95%); vi, $(COCl)_2$, DCM, DMSO, −78 °C, 20 min, add **50**, −78 °C, 20 min, Et_3N; vii, HCCMgBr, THF, −78 °C to rt; viii, Dess-Martin periodinane, DCM, rt, 4 h (99%); ix, 4 Å sieves, ZnI_2, DCM, **43**, rt, 18 h (55%); x, aq HF, MeCN, rt, 18 h; xi, Ac_2O, py, DMAP, rt, 18 h (35%); xii, $HC(OMe)_3$, PPTS, MeOH, rt, 3 h (49%).



Scheme 5. Reagents and conditions: i, TBSCl, imid., DCM, TBAI, rt, 1 h (ca. 100%); ii, (a) OsO_4 (cat.), *N*-methylmorpholine-*N*-oxide, acetone, H_2O, *tert*-BuOH, Na_2CO_3, rt, 18 h (55%) (b) $NaIO_4$, Na_2CO_3, THF, MeOH, H_2O, rt, 30 min (69%); iii, **61**, NaHMDS, THF, −78 °C, 30 min, add **59**, −50 °C to −15 °C, 18 h [49%; (*Z*)/(*E*)=72:28].

bryostatins. This synthesis features the (*E*)-selective, zinc(II) iodide promoted 'ene' reaction between the alkynones **36** and **53**, and the allylsilane **43**, together with formation of 2,6-*cis*-disubstituted 4-methylenetetrahydropyrans by stereoselective oxy-Michael reactions. However, although the chiral phosphonate **61** provided the required alkene **60** as the major product from its reaction with ketone **59**, the stereoselectivity of this reaction was only modest and the two geometrical isomers were very difficult to separate. For this reason, an alternative approach to the C(1)–C(16) fragment of bryostatins was developed in which the exocyclic trisubstituted double-bond was introduced stereoselectively earlier in the synthesis. This work,[17] together with studies of syntheses of the C(17)-C(27) fragments of bryostatins and procedures for the assembly of intact bryostatins[4b,5] will be described in full elsewhere.

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 Hz and chemical shifts relative to Me_4Si. IR spectra were recorded on a 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. All optical rotations were measured at 22 °C.

4.2. Experimental procedures

*4.2.1. (2R,4RS,6S)-2-Acetoxymethyl-6-[(4S)-4-benzyloxy-3,3-dimethyl-2-oxohex-5-enyl]-4-methyl-4,1″-epoxytetrahydropyran (**8**).* 3-Chloroperbenzoic acid (ca. 80%; 1.78 g, 8.25 mmol) was added to the diene **7** (3 g, 7.5 mmol) in DCM (25 mL) and the mixture stirred at room temperature for 18 h. Saturated aqueous sodium thiosulfate (30 mL) was added and the mixture was extracted with ether (3×40 mL). The organic extracts were washed with water (40 mL) and brine (40 mL), then dried over magnesium sulfate. The solution was filtered and the filtrate concentrated

under reduced pressure. Chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **8** (1.9 g, 61%) as a colourless oil, $[\alpha]_D$ +12 (*c* 0.2 in Et_2O); ν_{max}/cm^{-1} 3010, 2975, 2912, 2872, 1741, 1707, 1455, 1369, 1237 and 1068; δ_H (300 MHz, $CDCl_3$) 1.04 (3H, s, 3′-C*H*$_3$), 1.23 (5H, s, 3-*H*$_{eq}$, 5-*H*$_{eq}$, 3′-C*H*$_3$′), 1.74 (1H, dd, *J* 13.5 and 11.7, 5-*H*$_{ax}$), 1.91 (1H, dd, *J* 13.5 and 12.0, 3-*H*$_{ax}$), 2.09 (3H, s, COC*H*$_3$), 2.58 (1H, dd, *J* 17.2 and 6.6, 1′-*H*), 2.66 (1H, d, *J* 4.5, 1″-*H*), 2.70 (1H, d, *J* 4.5, 1″-*H*′), 2.96 (1H, dd, *J* 17.2 and 5.6, 1′-*H*′), 3.98 (2H, m, 2-*H*, 4′-*H*), 4.08 (2H, m, 2-C*H*$_2$), 4.18 (1H, m, 6-*H*), 4.28 and 4.57 (each 1H, d, *J* 11.8, HC*H*Ar), 5.32 (1H, d, *J* 17.2, 6′-*H*), 5.40 (1H, dd, *J* 10.4 and 1.6, 6′-*H*′), 5.76 (1H, ddd, *J* 17.3, 10.4 and 8.1, 5′-*H*) and 7.20–7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.72, 20.79, 21.84, 30.86, 34.37, 37.96, 44.76, 51.17, 52.77, 55.86, 70.44, 71.89, 73.09, 85.93, 120.21, 127.30, 127.47, 128.12, 134.14, 138.35, 170.79 and 212.05; *m*/*z* (CI^+) 434 (M^++18, 100%), 417 (19), 309 (30) and 108 (28); HRMS (CI^+): M^++H, found 417.2288. $C_{24}H_{33}O_6$ requires 417.2278.

*4.2.2. (2R,4RS,6S)-2-Acetoxymethyl-6-[(4S)-4-benzyloxy-3,3-dimethyl-2-oxohex-5-enyl]tetrahydropyran-4-one (**9**).* Periodic acid (1.28 g, 5.6 mmol) was added to the epoxide **8** (2.33 g, 5.6 mmol) in ether (50 mL) and the mixture stirred at room temperature for 18 h. Saturated aqueous sodium thiosulfate (20 mL) was added after which the mixture gave a negative result with starch/potassium iodide paper. The mixture was extracted with ether (3×20 mL) and the organic extracts were washed with water (20 mL) and brine (20 mL), then dried over magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **9** (2.1 g, 91%) as a colourless oil, $[\alpha]_D$ +4.6 (*c* 1.4 in Et_2O); ν_{max}/cm^{-1} 2963, 2920, 2855, 1741, 1719, 1455, 1367, 1234 and 1067; δ_H (300 MHz, $CDCl_3$) 1.05 and 1.23 (each 3H, s, 3′-C*H*$_3$), 2.10 (4H, m, COC*H*$_3$, 5-*H*$_{ax}$), 2.30 (1H, dd, *J* 14.8 and 11.3, 3-*H*$_{ax}$), 2.39 (1H, ddd, *J* 14.8, 3.4 and 1.6, 3-*H*$_{eq}$), 2.49 (1H, dt, *J* 14.6 and 1.8, 5-*H*$_{eq}$), 2.67 (1H, dd, *J* 17.6 and 6.5, 1′-*H*), 3.06 (1H, dd, *J* 17.4 and 5.9, 1′-*H*′), 3.90 (1H, m, 2-*H*), 3.96 (1H, d, *J* 8.1, 4′-*H*), 4.14 (3H, m, 6-*H*, 2-C*H*$_2$), 4.24 and 4.57 (each 1H, d, *J* 11.5, HC*H*Ar), 5.33 (1H, d, *J* 17.2, 6′-*H*), 5.42 (1H, dd, *J* 10.3, 6′-*H*′), 5.77 (1H, ddd, *J* 17.2, 10.3 and 8.1, 5′-*H*) and 7.20–7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.65, 20.70, 21.92, 43.34, 45.08, 46.81, 51.14, 65.86, 70.49, 73.04, 74.26, 86.03, 120.45, 127.44, 127.55, 128.18, 133.96, 138.16, 170.55, 205.16 and 211.42; *m*/*z* (CI^+) 420 (M^++18, 100%) and 403 (27); HRMS (CI^+): M^++H, found 403.2131. $C_{23}H_{31}O_6$ requires 403.2120.

*4.2.3. (7R,9S,)-7-Acetoxymethyl-9-[(4S)-4-benzyloxy-3,3-dimethyl-2-oxohex-5-enyl]-1,4,8-trioxaspiro[4.5]decane (**10**).* Ketone **9** (2.1 g, 5.24 mmol), ethylene glycol (30 mL) and PPTS (50 mg) were dissolved in benzene (150 mL) and the solution heated under reflux in a Dean–Stark apparatus for 2 h before being cooled to room temperature. Water (100 mL) was added, the mixture was extracted with ether and the organic extracts were washed with water then dried over magnesium sulfate. Concentration under reduced pressure gave the *title compound* **10** (2.08 g, 89%) as a colourless oil, $[\alpha]_D$ +5.7 (*c* 0.7 in Et_2O); ν_{max}/cm^{-1} 2964, 2924, 2879, 1740, 1706, 1454, 1382, 1369, 1245, 1069, 1044, 1004, 945 and 700; δ_H (300 MHz, $CDCl_3$) 1.04 and 1.21 (each 3H, s, 3′-C*H*$_3$), 1.36 (1H, t, *J* 11.7, 10-*H*$_{ax}$), 1.57 (1H, t, *J* 12.8, 6-*H*$_{ax}$), 1.66 (1H, dt, *J* 12.8 and 2.5, 6-*H*$_{eq}$), 1.85 (1H, dt, *J* 12.9 and 2.2, 10-*H*$_{eq}$), 2.05 (3H, s, COC*H*$_3$), 2.59 (1H, dd, *J* 17.3 and 7.1, 1′-*H*), 2.95 (1H, dd, *J* 17.3 and 5.6, 1′-*H*′), 3.86 (1H, m, 7-*H*), 3.99 (5H, m, 2-*H*$_2$, 3-*H*$_2$, 4′-*H*), 4.08 (3H, m, 7-C*H*$_2$, 9-*H*), 4.29 and 4.56 (each 1H, d, *J* 11.8, HC*H*Ar), 5.31 (1H, dd, *J* 17.2 and 1.0, 6′-*H*), 5.40 (1H, dd, *J* 10.3 and 1.7, 6′-*H*′), 5.75 (1H, ddd, *J* 17.2, 10.3 and 8.0, 5′-*H*) and 7.20–7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.74, 20.82, 21.77, 37.16, 40.37, 44.55, 51.24, 64.26, 64.41, 66.59, 70.37, 71.73, 73.03, 85.69, 106.64, 120.24, 127.32, 127.48, 128.13, 134.17, 138.29, 170.83 and 212.08; *m*/*z* (CI^+) 464 (M^++18, 24%) and 108 (100); HRMS (CI^+): M^++NH_4, found 464.2653. $C_{25}H_{38}NO_7$ requires 464.2648.

*4.2.4. (7R,9S,)-9-[(4S)-4-Benzyloxy-3,3-dimethyl-2-oxohex-5-enyl]-7-hydroxymethyl-1,4,8-trioxaspiro[4.5]decane (**11**).* Potassium carbonate (20 g) was added to an emulsion of the acetate **10** (2.08 g, 4.66 mmol) in methanol (20 mL) and water (20 mL) and the mixture stirred vigorously for 1.5 h. Water (100 mL) was added, the mixture was extracted with ether and the organic extracts were washed with water then dried over magnesium sulfate. Concentration under reduced pressure gave the *title compound* **11** (1.6 g, 85%) as a colourless oil, R_f=0.3 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ +8.8 (*c* 1.5 in Et_2O); ν_{max}/cm^{-1} 3480, 3064, 2966, 2923, 2878, 1706, 1469, 1455, 1384, 1367, 1209, 1151, 1068, 1003, 944 and 737; δ_H (300 MHz, $CDCl_3$) 0.95 and 1.09 (each 3H, 3′-C*H*$_3$), 1.25 (1H, dd, *J* 12.8 and 11.5, 10-*H*$_{ax}$), 1.46 (1H, t, *J* 12.9 and 6-*H*$_{ax}$), 1.51 (1H, m, 6-*H*$_{eq}$), 1.73 (1H, dt, *J* 12.9 and 2.1, 10-*H*$_{eq}$), 1.89 (1H, m, O*H*), 2.48 (1H, dd, *J* 17.5 and 6.7, 1′-*H*), 2.79 (1H, dd, *J* 17.5 and 5.9, 1′-*H*′), 3.40 and 3.52 (each 1H, m, 7-HC*H*), 3.65 (1H, m, 7-*H*), 3.88 (5H, m, 4′-*H*, 2-*H*$_2$, 3-*H*$_2$), 4.00 (1H, m, 9-*H*), 4.19 and 4.46 (each 1H, d, *J* 11.7, HC*H*Ar), 5.21 (1H, ddd, *J* 18.0, 1.9 and 0.8, 6′-*H*), 5.29 (1H, ddd, *J* 10.4, 1.9 and 0.7, 6′-*H*′), 5.64 (1H, m, 5′-*H*) and 7.15–7.35 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.80, 21.87, 36.75, 40.56, 44.51, 51.24, 64.21, 64.37, 65.68, 70.38, 71.33, 75.47, 85.53, 106.85, 120.26, 127.35, 127.53, 128.15, 134.15, 138.24 and 211.69; *m*/*z* (CI^+) 422 (M^++18, 100%), 405 (63) and 344 (49); HRMS (CI^+): M^++H, found 405.2277. $C_{23}H_{33}O_6$ requires 405.2279.

*4.2.5. (7R,9S,)-9-[(4S)-4-Benzyloxy-3,3-dimethyl-2-oxohex-5-enyl]-7-tert-butyldimethysilyloxymethyl-1,4,8-trioxaspiro[4.5]-decane (**12**).* The alcohol **11** (1.6 g, 3.96 mmol) and imidazole (1.35 g, 19.8 mmol) were dissolved in DCM (20 mL) and *tert*-butyldimethylsilyl chloride (658 mg, 4.36 mmol) in DCM (20 mL) was added. The mixture was stirred at room temperature for 30 min then water (20 mL) was added. Following extraction with ether (3×20 mL), the organic extracts were washed with water (20 mL) and brine (20 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **12** (1.5 g, 72%) as a colourless oil, R_f=0.7 (9:1 light petroleum/ethyl acetate), $[\alpha]_D$ −5.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2953, 2927, 2855, 1709, 1638, 1470, 1384, 1363, 1253, 1115, 1069, 1027, 1006, 942, 837 and 778; δ_H (300 MHz, $CDCl_3$) 0.00 (6H, s, 2× SiC*H*$_3$), 0.84 [9H, s, SiC(C*H*$_3$)$_3$], 0.98 and 1.14 (each 3H, s, 3′-C*H*$_3$), 1.27 (1H, t, *J* 11.8, 10-*H*$_{ax}$), 1.45 (1H, dd, *J* 13.0 and 10.8, 6-H$_{ax}$), 1.69 (1H, dt, *J* 13.0 and 1.9, 6-*H*$_{eq}$), 1.77 (1H, dt, *J* 12.8 and 2.3, 10-*H*$_{eq}$), 2.51 (1H, dd, *J* 17.4 and 7.1, 1′-*H*), 2.91 (1H, dd, *J* 17.4 and 5.6, 1′-*H*′), 3.48 (1H, m, 7-*H*), 3.61 (2H, m, 7-C*H*$_2$), 3.92 (5H, m, 4′-*H*, 2-*H*$_2$, 3-*H*$_2$), 4.02 (1H, m, 9-*H*), 4.23 and 4.49 (each 1H, d, *J* 11.7, HC*H*Ar), 5.26 (1H, dd, *J* 17.2 and 1.1, 6′-*H*), 5.33 (1H, dd, *J* 10.3 and 1.5, 6′-*H*′), 5.69 (1H, ddd, *J* 17.2, 10.3 and 8.0, 5′-*H*) and 7.15–7.30 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.35, −5.31, 18.27, 18.77, 21.79, 25.84, 37.53, 40.58, 44.68, 51.24, 64.11, 64.32, 66.11, 70.43, 71.31, 75.67, 85.64, 107.10, 120.11, 127.29, 127.46, 128.12, 134.22, 138.32 and 212.02; *m*/*z* (CI^+) 536 (M^++18, 4%), 519 (M^++1, 4), 373 (16), 108 (96) and 91 (100%); HRMS (CI^+): M^++H, found 519.3133. $C_{29}H_{47}O_6Si$ requires 519.3142.

*4.2.6. (7R,9R)-9-[(2R,4S)- and (7R,9R)-9-[(2S,4S)-4-Benzyloxy-3,3-dimethyl-2-hydroxyhex-5-enyl]-7-tert-butyldimethylsilyloxymethyl-1,4,8-trioxaspiro[4.5]decane (**13**).* Ketone **12** (1.1 g, 2.12 mmol) was dissolved in THF (6.5 mL) and the solution was cooled to −78° C. Lithium triethylborohydride ('super Hydride®') (1 M in THF, 6.4 mL) was added dropwise and the mixture allowed to warm to room temperature. After 30 min, saturated aqueous sodium-potassium tartrate (10 mL) was added and the mixture extracted with ether (3×10 mL) The organic extracts were washed with water (10 mL) and brine (10 mL), then dried over magnesium sulfate. After

concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the major diastereoisomer of the *title compound* **13** (895 mg, 81%) as colourless oil, R_f=0.8 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −6.7 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3500, 3030, 2955, 2928, 2857, 1638, 1471, 1385, 1334, 1257, 1150, 1112, 1066, 1007, 947, 927, 838, 777, 734 and 699; δ_H 0.00 (300 MHz, $CDCl_3$) (6H, s, 2× SiC*H*$_3$), 0.79 and 0.80 (each 3H, s, 3′-C*H*$_3$), 0.83 [9H, s, SiC(C*H*$_3$)$_3$], 1.35–1.80 (6H, m, 1′-*H*$_2$, 6-*H*$_2$, 10-*H*$_2$), 3.35–3.85 (7H, m, 2′-*H*, 4′-*H*, 7-*H*, 9-*H*, 7-C*H*$_2$, O*H*), 3.90 (4H, s, 2-*H*$_2$, 3-*H*$_2$), 4.29 and 4.53 (each 1H, d, *J* 11.7, HC*H*Ar), 5.19 (1H, dd, *J* 17.2 and 1.9, 6′-*H*), 5.28 (1H, dd, 10.4 and 1.8, 6′-*H*′), 5.77 (1H, ddd, *J* 17.2, 10.4 and 8.1, 5′-*H*) and 7.20–7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.42, −5.37, 18.23, 19.20, 19.57, 25.83, 37.08, 37.45, 40.91, 41.11, 64.19, 64.39, 66.02, 70.59, 74.35, 75.65, 75.82, 85.67, 107.05, 119.04, 127.23, 127.49, 128.15, 135.18 and 138.74; *m*/*z* (CI^+) 521 (M^++1, 10%), 391 (15) and 58 (100); HRMS (CI^+): M^++H, found 521.3291. $C_{29}H_{49}O_6Si$ requires 521.3298. The minor diastereoisomer of the *title compound* **13** (110 mg, 10%) was then eluted as a colourless oil, R_f=0.7 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ +18.3 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3497, 3029, 2926, 2855, 1473, 1459, 1388, 1362, 1330, 1255, 1151, 1109, 1063, 1027, 1005, 940, 836 and 778; δ_H (300 MHz, $CDCl_3$) 0.00 (6H, s, 2× SiC*H*$_3$), 0.71 (3H, s, 3′-C*H*$_3$), 0.83 [9H, s, SiC(C*H*$_3$)$_3$], 0.89 (3H, s, 3′-C*H*$_3$′), 1.30–1.70 (6H, m, 1′-*H*$_2$, 6-*H*$_2$, 10-*H*$_2$), 3.25–3.95 (11H, m, 2′-*H*, 4′-*H*, 7-*H*, 9-*H*, 7-C*H*$_2$, 2-*H*$_2$, 3-*H*$_2$, O*H*), 4.25 and 4.54 (each 1H, d, *J* 11.7, HC*H*Ar), 5.19 (1H, dd, *J* 17.2 and 1.6, 6′-*H*), 5.29 (1H, dd, *J* 10.4 and 1.9, 6′-*H*′), 5.75 (1H, ddd, *J* 17.3, 10.3 and 8.2, 5′-*H*) and 7.20–7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.31, −5.29, 16.51, 18.26, 20.88, 25.84, 37.22, 37.44, 40.90, 40.96, 64.10, 64.29, 66.19, 70.28, 72.53, 73.71, 75.75, 88.21, 107.48, 119.45, 127.33, 127.53, 128.21, 135.10 and 138.34; *m*/*z* (CI^+) 521 (M^++1, 10%) and 391 (100); HRMS (CI^+): M^++H, found 521.3299. $C_{29}H_{49}O_6Si$ requires 521.3298.

*4.2.7. (7R,9R)-9-[(2R/2S,4S)-4-Benzyloxy-3,3-dimethyl-2-(2-trimethylsilylethoxy)methoxyhex-5-enyl]-7-tert-butyldimethylsilyloxymethyl-1,4,8-trioxaspiro[4.5]decane (**14**).* (2-Trimethylsilylethoxy)methyl chloride (610 μL, 3.44 mmol) was added dropwise to the major diastereoisomer of the alcohol **13** (895 mg, 1.72 mmol) and di-isopropylethylamine (2.1 mL, 12.04 mmol) in DCM (4 mL) at 0° C and the mixture stirred at room temperature for 1 h. Water (5 mL) was added, the mixture was extracted with ether (3×5 mL) and the organic extracts were washed with water (5 mL) and brine (5 mL), then dried over magnesium sulfate. After concentration under reduced pressure chromatography of the residue eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **14** (920 mg, 82%) as a colourless oil, R_f=0.8 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −7.0 (1.0 in DCM); ν_{max}/cm^{-1} 3072, 2954, 2882, 1471, 1384, 1250, 1150, 1110, 1059, 1028, 930 and 837; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, 3× SiC*H*$_3$), 0.03 (6H, s, 2× SiC*H*$_3$), 0.82 (3H, s, 3′-C*H*$_3$), 0.82 [12H, s, SiC(C*H*$_3$)$_3$, 3′-C*H*$_3$′], 0.95 (2H, m, SiC*H*$_2$), 1.32 (1H, t, *J* 12.1, 6- or 10-*H*$_{ax}$), 1.44 (1H, t, *J* 11.7, 10- or 6-*H*$_{ax}$), 1.60 (1H, m, 1′-*H*), 1.79 (3H, m, 6-*H*$_{eq}$, 10-*H*$_{eq}$, 1′-*H*′), 3.50 (1H, dd, *J* 9.62 and 5.91, 7-HC*H*), 3.56–3.79 (7H, m, 7-*H*, 9-*H*, 2′-*H*, 4′-*H*, 7-HC*H*, C*H*$_2$CH$_2$Si), 3.95 (4H, s, 2-*H*$_2$, 3-*H*$_2$), 4.28 and 4.53 (each 1H, d, *J* 11.8, HC*H*Ar), 4.63 (2H, m, OC*H*$_2$O), 5.22 (1H, dd, *J* 17.3 and 1.5, 6′-*H*), 5.32 (1H, dd, *J* 10.4 and 1.9, 6′-*H*′), 5.75 (1H, ddd, *J* 17.3, 10.3 and 8.5, 5′-*H*) and 7.20–7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.36, −5.32, −1.49, 17.88, 18.27, 18.54, 18.71, 25.85, 37.81, 38.02, 40.70, 42.23, 64.05, 64.24, 65.63, 60.18, 69.62, 73.37, 75.62, 79.78, 84.32, 96.44, 107.32, 119.41, 127.01, 127.12, 128.07, 135.47 and 139.21; *m*/*z* (CI^+) 668 (M^++18, 1%), 533 (4) and 90 (100); HRMS (CI^+): M^++NH_4, found 668.4376. $C_{35}H_{67}NO_7Si_2$ requires 668.4377.

*4.2.8. (7R,9R)-9-[(2R/2S,4S)-4-Benzyloxy-3,3-dimethyl-2,6-dihydroxyhexyl]-7-tert-butyldimethylsilyloxymethyl-1,4,8-trioxaspiro[4.5]decane (**15**).* Borane (1.0 M in THF, 0.14 mL, 0.138 mmol) was added dropwise to the major diastereoisomer of the alkene **13** (60 mg, 0.115 mmol) in THF (0.3 mL) at room temperature. The mixture was stirred for 18 h then added to aqueous sodium hydroxide (3 M, 5 mL). After the effervescence had abated, a solution of aqueous hydrogen peroxide (30%; 5 mL) was added and the mixture was stirred vigorously for 1 h. The mixture was extracted with ether (3×10 mL) and the organic fractions were washed with water (10 mL) and brine (10 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **15** (36 mg, 58%) as a colourless oil. R_f=0.2 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −5.3 (*c* 1.01 in DCM); ν_{max}/cm^{-1} 3480, 2957, 2928, 2882, 1471, 1257, 1151, 1112, 1066, 946, 838 and 778; δ_H (300 MHz, $CDCl_3$) 0.00 (6H, s, 2× SiC*H*$_3$), 0.78 (3H, s, 3′-C*H*$_3$), 0.83 [9H, s, SiC(C*H*$_3$)$_3$], 0.84 (3H, s, 3′-CH$_3$′), 1.10–1.90 (10H, m, 5′-*H*$_2$, 1′-*H*$_2$, 6-*H*$_2$, 10-*H*$_2$, 2× O*H*), 3.40–4.00 (12H, m, 6′-*H*$_2$, 2′-*H*, 4′-*H*, 7-*H*, 9-*H*, 7-C*H*$_2$), 4.61 and 4.78 (each 1H, d, *J* 11.3, HC*H*Ar) and 7.20–7.35 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.48, −5.40, 18.22, 18.34, 19.21, 25.81, 33.29, 36.72, 37.22, 41.42, 42.02, 61.08, 64.23, 64.41, 65.99, 74.40, 74.74, 76.06, 76.57, 81.81, 106.88, 127.43, 127.70, 128.28 and 138.83; *m*/*z* (CI^+) 539 (M^++1, 100%); HRMS (CI^+): M^++H, found 539.3404. $C_{29}H_{51}O_7Si$ requires 539.3404.

*4.2.9. (7R,9R)-9-[(2R/2S,4S)-4-Benzyloxy-3,3-dimethyl-6-hydroxy-2-(2-trimethylsilylethoxy)methoxyhexyl]-7-tert-butyldimethylsilyloxymethyl-1,4,8-trioxaspiro[4.5]decane (**16**).* Borane (1 M in THF, 0.77 mL) was added to the alkene **14** (100 mg, 0.154 mmol) in THF (100 μL) at −18° C. The mixture was stirred for 18 h at room temperature then added to aqueous sodium hydroxide (3 M, 20 mL). Aqueous hydrogen peroxide (30%, 20 mL) was added followed by THF (20 mL) and the mixture was stirred for 3 h at room temperature. The mixture was extracted with ether (3×20 mL) and the organic extracts were washed with water (20 mL) and brine (20 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with petroleum to light petroleum/ether (1:1) gave the *title compound* **16** (68 mg, 66%) as a colourless oil, R_f=0.3 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −4.0 (*c* 2.3 in DCM); ν_{max}/cm^{-1} 3460, 2954, 2928, 2882, 1471, 1362, 1330, 1250, 1148, 1109, 1058, 1028, 938, 926, 837 and 778; δ_H (300 MHz, C_6D_6) 0.01 (9H, s, 3× SiC*H*$_3$), 0.07 (6H, s, 2× SiC*H*$_3$), 0.95 [9H, s, SiC(C*H*$_3$)$_3$], 0.97–1.04 (8H, 2×3′-C*H*$_3$, SiC*H*$_2$), 1.60 (3H, m, 5′-*H*$_2$, 10-*H*$_{ax}$), 1.73 (1H, m, 6-H$_{ax}$), 1.83 (1H, m, 1′-*H*), 1.89 (1H, m, 6-*H*$_{eq}$), 1.94 (1H, m, 10-*H*$_{eq}$), 2.04 (1H, m, 1′-*H*′), 3.50–3.57 (5H, m, 6′-*H*, 2-*H*$_2$, 3-*H*$_2$), 3.58–3.68 (2H, m, 6′-*H*′, 4′-*H*), 3.69–3.82 (5H, m, SiCH$_2$C*H*$_2$, 2′-*H*, 7-C*H*$_2$), 3.91 (1H, m, 7-*H*), 3.99 (1H, m, 9-*H*), 4.61 (2H, s, C*H*$_2$Ar), 4.74 and 4.83 (each 1H, d, *J* 6.7, OHC*H*O) and 7.10–7.35 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.38, −5.33, −1.48, 17.89, 18.28, 19.01, 19.18, 25.86, 33.55, 37.72, 38.03, 40.95, 43.76, 60.81, 64.09, 64.28, 65.65, 66.16, 73.27, 74.36, 75.69, 79.72, 81.31, 95.72, 107.27, 127.24, 127.31, 128.23 and 138.90; *m*/*z* (CI^+) 685 (M^++17, 17%), 568 (55) and 551 (100); HRMS (CI^+): M^++NH_4, found 686.4477. $C_{35}H_{68}NO_8Si_2$ requires 686.4483.

*4.2.10. (7R,9R)-9-[(2R/2S,4S)-4-Benzyloxy-3,3-dimethyl-5-formyl-2-(trimethylsilylethoxy)methoxypentyl]-7-tert-butyldimethylsilyloxymethyl-1,4,8-trioxaspiro[4.5]decane (**18**).* DMSO (53 μL, 0.75 mmol) in DCM (0.5 mL) was added dropwise to oxalyl chloride (33 μL, 0.38 mmol) in DCM (0.5 mL) at −78° C. The mixture was stirred for 20 min and then the alcohol **16** (169 mg, 0.25 mmol) in DCM (0.5 mL) was added dropwise. After stirring at −78° C for a further 20 min, triethylamine (210 μL, 1.5 mmol) was added and the mixture was allowed to warm to room temperature then extracted with ether (3×2 mL). The organic extracts were washed with water (3×2 mL), brine (2 mL) then dried over magnesium sulfate.

Concentration under reduced pressure gave the title compound **18** (168 mg, 100%) used without further purification; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, 3× SiCH_3), 0.04 (6H, s, 2× SiCH_3), 0.75 [17H, m, 2×3′-CH_3, CH_2Si, SiC(CH_3)$_3$], 1.1–1.85 (6H, m, 6-H_2, 10-H_2, 1′-H_2), 3.66 (2H, m, 5′-H_2), 3.4–3.75 (5H, m, 7-*H*, 9-*H*, 2′-*H*, CH_2CH$_2$Si), 4.92 (4H, m, 2-H_2, 3-H_2), 4.14 (1H, m, 4′-*H*), 4.53 and 4.55 (each 1H, d, *J* 11.5, HC*H*Ar), 4.66 (2H, s, OCH_2O), 7.20–7.35 (5H, m, Ar*H*) and 9.86 (1H, br s, C*H*O).

*4.2.11. (5S,7S,9R/9S,)-7-Benzyloxy-10-{(7R,9R)-9-tert-butyldimethylsilyloxymethyl-1,4,8-trioxaspiro[4.5]dec-7-yl}-1-(tert-butyldiphenylsilyloxy)-5-hydroxy-8,8-dimethyl-9-(2-trimethylsilylethoxy)methoxydecan-3-one (**20**).* *n*-Butyllithium (1.60 M in hexanes, 191 μL, 0.305 mmol) was added dropwise to di-isopropylamine (46 μL, 0.33 mmol) in THF (300 μL) at −78° C and the mixture was allowed to warm to room temperature then cooled back to −78° C. The ketone **19** (91 mg, 0.279 mmol) in THF (300 μL), precooled to −78° C, was added dropwise. The mixture was stirred at −78° C for 30 min and the aldehyde **18** (169 mg, 0.254 mmol) in THF (300 μL) was added. After 2 min, methanol (300 μL) was added followed by saturated aqueous ammonium chloride (300 μL). The mixture was allowed to warm to room temperature and extracted with ether (3×5 mL) and the organic extracts were washed with water (5 mL) and brine (5 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **20** (150 mg, 60%) as a colourless oil, R_f=0.6 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ +24.0 (*c* 0.1 in Et_2O); ν_{max}/cm^{-1} 3515, 3069, 2954, 2930, 2883, 2859, 1708, 1471, 1428, 1387, 1362, 1250, 1110, 1027, 939, 836, 778 and 737; δ_H (300 MHz, acetone-d_6) 0.00 (9H, s, 3× SiCH_3), 0.05 (6H, s, 2× SiCH_3), 0.87 [18H, s, 2× SiC(CH_3)$_3$], 0.94 (2H, m, SiCH_2) 0.99 (6H, s, 2× 8-CH_3), 1.28 (1H, m, 6′-H_{ax}), 1.39 (1H, dd, *J* 12.6 and 11.4, 10′-H_{ax}), 1.54 (2H, m, 6-H_2), 1.71 (3H, m, 10-H_2, 10′-H_{eq}), 1.83 (1H, dt, *J* 12.9 and 2.1, 6′-H_{eq}), 2.66 (2H, m, 4-H_2), 2.75 (2H, m, 2-H_2), 3.50–3.78 (7H, m, 9-*H*, 7′-*H*, 9′-*H*, 9′-CH_2, SiCH$_2$CH_2), 3.83 (1H, m, 7-*H*), 3.90 (4H, m, 2′-H_2, 3′-H_2), 3.94 (2H, t, *J* 6.3, 1-H_2), 4.32 (1H, m, 5-*H*), 4.63 (1H, d, *J* 6.6, OHC*H*O), 4.69 (1H, d, *J* 11.5, HC*H*Ar), 4.71 (1H, d, *J* 6.5, OHC*H*O), 4.82 (1H, d, *J* 11.5, HC*H*Ar) and 7.18–7.75 (15H, m, Ar*H*); δ_C (75 MHz, benzene-d_6) −5.48, −1.66, 17.81, 18.16, 18.93, 19.31, 19.60, 25.75, 26.58, 38.02, 38.34, 41.28, 43.63, 45.42, 50.18, 59.22, 63.76, 64.01, 64.41, 65.51, 66.46, 73.37, 75.79, 79.83, 80.12, 95.63, 107.45, 126.92, 127.70, 128.05, 129.66, 133.37, 135.52, 139.82 and 209.73; *m*/*z* (ES$^+$) 1010 (M^++18, 25%) and 526 (100); HRMS (CI$^+$): M^++NH_4, found 1010.6037. $C_{55}H_{92}NO_{10}Si_3$ requires 1010.6029.

*4.2.12. (3S,5R,7S,9R/9S)-7-Benzyloxy-10-{(7R,9R)-9-(tert-butyldimethylsilyloxymethyl)-1,4,8-trioxaspiro[4.5]dec-7-yl}-1-tert-butyldiphenylsilyloxy-8,8-dimethyl-9-(2-trimethylsilylethoxy)-methoxydecane-3,5-diol (**21**).* Tetramethylammonium triacetoxyborohydride (171 mg, 0.65 mmol) was dissolved in acetonitrile (430 μL) and acetic acid (430 μL) was added. This mixture was stirred at room temperature for 30 min then cooled to −40° C. The ketone **20** (80 mg, 0.081 mmol) in acetonitrile (130 μL) was added at this temperature and the mixture was stirred at −20° C for 18 h. Saturated aqueous sodium bicarbonate (1 mL) was added dropwise and the mixture was allowed to warm to room temperature then extracted with ether (3×5 mL). The organic extracts were washed with water (5 mL) and brine (5 mL), then dried over magnesium sulfate. Concentration under reduced pressure gave the *title compound* **21** (75 mg, 94%) as a colourless oil, $[\alpha]_D$ +8.0 (*c* 0.2 in Et_2O); ν_{max}/cm^{-1} 3468, 3071, 2954, 2884, 2859, 1472, 1428, 1362, 1250, 1143, 1111, 1027, 938, 837, 778 and 737; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, 3× SiCH_3), 0.03 (6H, s, 2× SiCH_3), 0.87 [9H, s, SiC(CH_3)$_3$], 0.90–0.98 (8H, m, 2× 8-CH_3, SiCH_2), 1.04 [9H, s, SiC(CH_3)$_3$], 1.30–1.90 (12H, 2-H_2, 4-H_2, 6-H_2, 10-H_2, 6′-H_2, 10′-H_2), 3.20–4.00 (14H, m), 4.15 (1H, m), 4.24 (1H, m), 4.60–4.80 (4H, m, CH_2Ar, OCH_2O) and 7.20–7.70 (15H, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.32, −1.46, 17.89, 18.27, 18.96, 19.42, 25.88, 26.76, 30.25, 37.70, 38.02, 38.24, 38.33, 40.92, 43.13, 43.62, 63.41, 64.03, 64.24, 65.65, 66.15, 69.87, 73.35, 74.77, 75.61, 80.23, 80.33, 95.80, 107.37, 125.43, 127.13, 127.27, 127.74, 128.16, 129.80, 132.78, 132.87, 135.45, 139.42; *m*/*z* (ES$^+$) 1033 (M^++39, 100%), 1017 (M^++23, 60), 1012 (M^++18, 78), 877 (58) and 433 (22).

*4.2.13. (3S,5R,7S,9R/9S)-7-Benzyloxy-10-{(7R,9R)-9-(tert-butyldimethylsilyloxymethyl)-1,4,8-trioxaspiro[4.5]dec-7-yl}-1-tert-butyldiphenylsilyloxy-3,5-O-isopropylidene-8,8-dimethyl-9-(2-trimethylsilylethoxy)methoxydecane-3,5-diol (**22**).* The diol **21** (38 mg, 0.038 mmol) and PPTS (1 mg) were dissolved in 2,2-dimethoxypropane and the mixture was stirred at room temperature for 24 h then added to saturated aqueous sodium bicarbonate (1 mL). The mixture was then extracted with ether (3×2 mL) and the organic extracts were washed with water (2 mL), brine (2 mL) then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **22** (39 mg, 99%) as a colourless oil, $[\alpha]_D$ −8.5 (*c* 2.4 in Et_2O); δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, 3× SiCH_3), 0.03 (6H, s, 2× SiCH_3), 0.87 [9H, s, SiC(CH_3)$_3$], 0.88–1.02 (2H, m, SiCH_2), 0.90 and 0.95 (each 3H, s, 8-CH_3), 1.01 [9H, s, SiC(CH_3)$_3$], 1.32 (6H, s, 2× CH_3), 1.34–1.60 (6H, m), 1.62–1.85 (6H, m), 3.40–3.53 (2H, m), 3.54–3.80 (8H, m), 3.92 (4H, s, 2′-H_2, 3′-H_2), 3.96–4.08 (2H, m), 4.63 (2H, s, CH_2Ar), 4.67 (2H, s, OCH_2O) and 7.10–7.70 (15H, m, Ar*H*); δ_C (75 MHz, benzene-d_6) −5.37, −5.39, −1.56, 17.85, 18.27, 19.12, 19.27, 19.61, 25.24, 25.36, 25.83, 26.80, 38.13, 38.48, 38.79, 38.93, 39.13, 41.38, 43.89, 60.31, 63.13, 63.84, 64.09, 65.55, 66.57, 73.33, 74.87, 75.79, 80.04, 80.64, 95.85, 100.04, 107.56, 126.83, 127.02, 128.18, 129.58, 134.00, 135.64 and 139.78; *m*/*z* (ES$^+$) 1073 (M^++39, 83%) and 1052 (M^++18, 100).

*4.2.14. (3S)-3-Benzyloxy-4,4-dimethyl-5-tert-butyldimethylsilyloxypent-1-ene (**24**).* *tert*-Butyldimethylsilyl chloride (21.5 g, 143 mmol) was added to the alcohol **23** (21 g, 95.4 mmol), imidazole (32.5 g, 477 mmol), DMAP (20 mg) and TBAI (20 mg) in DCM (163 mL) and the reaction mixture stirred at room temperature for 30 min. Saturated aqueous sodium bicarbonate (100 mL) was added and the mixture was extracted with ether (3×100 mL). The organic extracts were washed with water (100 mL) and brine (100 mL), dried over magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **24** (30.8 g, 97%) as a colourless oil, R_f=0.9 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ +14.2 (*c* 1.8 in Et_2O); ν_{max}/cm^{-1} 3067, 3031, 2956, 2930, 2857, 1472, 1390, 1361, 1254, 1093, 1004, 926, 852, 838 and 776; δ_H (300 MHz, $CDCl_3$) 0.01 and 0.02 (each 3H, s, SiCH_3), 0.82 (3H, s, 4-CH_3), 0.89 [12H, s, SiC(CH_3)$_3$ and 4-CH_3′], 3.29 and 3.49 (each 1H, d, *J* 9.3, 5-*H*), 3.69 (1H, d, *J* 8.0, 3-*H*), 4.29 and 4.52 (each 1H, d, *J* 11.8, HC*H*Ar), 5.22 (1H, ddd, *J* 17.2, 2.1 and 0.7, 1-*H*), 5.28 (1H, dd, *J* 10.3 and 2.1, 1-*H*′), 5.80 (1H, ddd, *J* 17.2, 10.4 and 8.0, 2-*H*) and 7.30–7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.61, 18.18, 19.89, 21.03, 25.83, 39.53, 69.12, 70.47, 84.27, 118.22, 127.02, 127.37, 128.03, 135.70 and 139.26; *m*/*z* (CI$^+$) 335 (M^++1, 100%); HRMS (CI$^+$): M^++H, found 335.2412. $C_{20}H_{35}O_2Si$ requires 335.2406.

*4.2.15. (3S)-3-Benzyloxy-5-tert-butyldimethylsilyloxy-4,4-dimethylpentan-1-ol (**25**).* Borane (1 M in THF, 69.2 mL) was added at −18° C to the alkene **24** (21 g, 62.9 mmol) in THF (88 mL) and the mixture stirred at room temperature for 18 h. It was then added dropwise to aqueous sodium hydroxide (3 M) with the evolution of copious amounts of gas. When the evolution had abated, aqueous hydrogen peroxide (30%, 150 mL) was added and the mixture was stirred at 50° C for 3 h. The mixture was extracted with ether

(3×100 mL) and the combined organic extracts were washed with water (100 mL) and brine (100 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **25** (14.83 g, 67%) as a colourless oil, R_f=0.3 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ +2.5 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3409, 3030, 2956, 2930, 2858, 1472, 1391, 1361, 1255, 1095, 938, 851, 838 and 776; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.01 (each 3H, s, SiCH_3), 0.84 (3H, s, 4-CH_3), 0.89 [12H, s, SiC(CH_3)$_3$, 4-CH_3′], 1.72 (2H, m, 2-H_2), 1.99 (1H, s, O*H*), 3.23 and 3.51 (each 1H, d, *J* 9.6, 5-*H*), 3.59 (1H, dd, *J* 8.8 and 4.3, 3-*H*), 3.71 (2H, m, 1-H_2), 4.57 and 4.66 (each 1H, d, *J* 11.4, HC*H*Ar) and 7.20–7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.57, −5.50, 18.21, 19.95, 21.57, 25.86, 33.10, 40.55, 61.15, 69.59, 74.50, 81.09, 127.43, 127.56, 128.29 and 138.88; *m*/*z* (CI^+) 353 (M^++1, 100%); HRMS (CI^+): M^++H, found 353.2519. $C_{20}H_{37}O_3Si$ requires 353.2512.

*4.2.16. (3S)-3-Benzyloxy-5-tert-butyldimethylsilyloxy-4,4-dimethylpentanal (**26**).* Dimethyl sulfoxide (8.88 mL, 125.4 mmol) in DCM (75 mL) was added dropwise to oxalyl chloride (5.3 mL, 62.7 mmol) in DCM (75 mL) at −78° C and the mixture stirred at this temperature for 20 min. The alcohol **25** (14.71 g, 41.8 mmol) in DCM (75 mL) was added at −78° C and the mixture was stirred for another 20 min before triethylamine (35 mL, 251 mmol) was added. The mixture was allowed to warm to room temperature, extracted with ether (3×150 mL) and the organic extracts were washed with water (3×100 mL) and brine (100 mL), then dried over magnesium sulfate. Concentration under reduced pressure gave the aldehyde **26** used without further purification; ν_{max}/cm^{-1} 1727; δ_H (300 MHz, $CDCl_3$) 9.78 (1H, t, *J* 2, C*H*O).

*4.2.17. (5S,7S)-7-Benzyloxy-9-tert-butyldimethylsilyloxy-1-tert-butyldiphenylsilyloxy-5-hydroxy-8,8-dimethylnonan-3-one (**27**).* *n*-Butyllithium (1.45 M in hexanes, 15.6 mL, 22.6 mmol) was added to di-isopropylamine (3.16 mL, 22.6 mmol) in THF (30 mL) at −78° C. The mixture was allowed to warm to room temperature then cooled back to −78° C. The ketone **19** (7.37 g, 22.6 mmol) in THF (30 mL) precooled to −78° C was added and the mixture stirred at −78° C for 30 min. The aldehyde **26** (6.6 g, 18.9 mmol) in THF (30 mL) precooled to −78° C was then added dropwise and the reaction mixture stirred for 2 min. Methanol (5 mL) then saturated aqueous ammonium chloride (5 mL) were added and the mixture allowed to warm to room temperature. The mixture was extracted with ether (3×50 mL) and the organic extracts were washed with water (50 mL) and brine (50 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compou*nd **27** (9.8 g, 76%) as a colourless oil, R_f=0.4 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −3.2 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3542, 3071, 2953, 2858, 1712, 1471, 1428, 1391, 1361, 1255, 1107, 851, 776, 737 and 700; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.02 (each 3H, s, SiCH_3), 0.85–0.90 [15H, m, 2× 8-CH_3, SiC(CH_3)$_3$], 1.01 [9H, s, SiC(CH_3)$_3$], 1.45 and 1.60 (each 1H, m, 6-*H*), 2.58 (4H, m, 2-H_2, 4-H_2), 3.14 (1H, d, *J* 3.6, O*H*), 3.27 and 3.54 (each 1H, d, *J* 9.6, 9-*H*), 3.75 (1H, dd, *J* 10.3 and 2.2, 7-*H*), 3.90 (2H, t, *J* 6.3, 1-H_2), 4.22 (1H, m, 5-*H*), 4.68 (2H, s, CH_2Ar) and 7.20–7.75 (15H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.53, −5.48, 18.24, 19.07, 19.90, 21.80, 25.90, 26.73, 37.44, 40.39, 46.02, 50.67, 59.39, 64.70, 69.57, 74.75, 79.09, 127.27, 127.54, 127.68, 128.24, 129.70, 133.23, 135.48, 139.29 and 210.90; *m*/*z* (CI^+) 677 (M^++1, 20%), 351 (35) and 344 (100); HRMS (CI^+): M^++H, found 677.4052. $C_{40}H_{61}O_5Si_2$ requires 677.4057.

*4.2.18. (5S,7S)-7-Benzyloxy-9-tert-(butyldimethylsilyloxy)-1-tert-butyldiphenylsilyloxy-5-[(R)-2-acetoxy-2-phenylacetoxy]-8,8-dimethylnonan-3-one (**28**).* 4-Dimethylaminopyridine (55 mg, 0.45 mmol) was added to the alcohol **27** (20 mg, 0.03 mmol) in chloroform (200 μL) and the mixture was cooled to −10 °C under nitrogen. (*R*)-*O*-Acetylmandelyl chloride (19 mg, 0.09 mmol) in chloroform (200 μL) was added and the mixture allowed to warm to room temperature. After 1 h, it was added to saturated aqueous sodium bicarbonate (10 mL), the mixture was extracted with ether (4×10 mL) and the organic extracts were washed with water (10 mL) and brine (10 mL), then dried over magnesium sulfate. After concentration under reduced pressure, HPLC reverse phase chromatography of the residue eluting with MeCN/DCM (4:1) gave the *title compound* **28** (21 mg, 82%) as a colourless oil, $[\alpha]_D$ −34.4 (*c* 0.5 in Et_2O), ν_{max}/cm^{-1} 3070, 2957, 2930, 2857, 1745, 1720, 1472, 1456, 1372, 1233, 1210, 1176, 1088, 852, 837, 776, 738 and 701; δ_H (300 MHz, $CDCl_3$) 0.00 (6H, s, 2× SiCH_3), 0.68 and 0.72 (each 3H, s, 8-CH_3), 0.88 and 1.00 [each 9H, s, SiC(CH_3)$_3$], 1.65 and 1.78 (each 1H, m, 6-*H*), 2.17 (3H, s, COCH_3), 2.60 (2H, m, 2-H_2), 2.75 and 2.82 (each 1H, dd, *J* 16, 7, 4-*H*), 2.87 (1H, m, 7-*H*), 3.22 and 3.26 (each 1H, d, *J* 9.5, 9-*H*), 3.88 (2H, t, *J* 6.3, 1-H_2), 3.98 and 4.01 (each 1H, d, *J* 11.5, HC*H*Ar), 5.36 (1H, m, 5-*H*), 5.83 (1H, s, C*H*OAc) and 7.20–7.70 (20H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.55, 18.27, 19.04, 20.14, 20.61, 21.26, 25.91, 26.71, 35.76, 40.45, 45.75, 48.38, 59.38, 69.20, 70.12, 74.54, 74.68, 80.08, 127.10, 127.30, 127.60, 127.63, 128.08, 128.78, 129.30, 129.58, 133.38, 133.66, 135.46, 138.88, 168.39, 170.17 and 205.71; *m*/*z* (CI^+) 551 (4%), 473 (5), 403 (3) and 212 (100); HRMS (CI^+): M^++NH_4, found 870.4808. $C_{50}H_{72}NO_8Si_2$ requires 870.4796.

*4.2.19. (5S,7S)-7-Benzyloxy-9-tert-(butyldimethylsilyloxy)-1-tert-butyldiphenylsilyloxy-5-[(S)-2-acetoxy-2-phenylacetoxy]-8,8-dimethylnonan-3-one (**29**).* 4-Dimethylaminopyridine (73 mg, 0.60 mmol) was added the alcohol **27** (20 mg, 0.03 mmol) in chloroform (200 μL) and the mixture cooled to −10 °C under nitrogen. (*S*)-*O*-Acetylmandelyl chloride (19 mg, 0.09 mmol) in chloroform (200 μL) was added and the mixture was allowed to warm to room temperature. After 1 h, it was added to saturated aqueous sodium bicarbonate (10 mL), the mixture was extracted with ether (4×10 mL) and the organic extracts were washed with water (10 mL) and brine (10 mL), then dried over magnesium sulfate. After concentration under reduced pressure, HPLC reverse phase chromatography of the residue eluting with MeCN/DCM (4:1) gave the *title compound* **29** (18 mg, 70%) as a colourless oil, $[\alpha]_D$ +8.0 (*c* 0.8 in Et_2O); ν_{max}/cm^{-1} 3070, 3033, 2957, 2930, 2886, 2857, 1746, 1720, 1497, 1472, 1428, 1372, 1257, 1232, 1209, 1176, 1092, 1030, 1006, 852, 837, 776, 737 and 701; δ_H (300 MHz, $CDCl_3$) 0.00 (6H, m, 2× SiCH_3), 0.84 and 0.85 (each 3H, s, 8-CH_3), 0.91 and 0.99 [each 9H, s, SiC(CH_3)$_3$], 1.65 and 1.90 (each 1H, m, 6-*H*), 2.16 (3H, s, CH_3CO), 2.32 (2H, m, 2-H_2), 2.57 (2H, t, *J* 6.2, 4-H_2), 3.28 (1H, d, *J* 9.5, 9-*H*), 3.44 (1H, m, 7-*H*), 3.46 (1H, d, *J* 9.5, 9-*H*′), 3.70 (2H, t, *J* 6.3, 1-H_2), 4.44 and 4.50 (each 1H, d, *J* 11.3, HC*H*Ar), 5.44 (1H, m, 5-*H*), 5.82 (1H, s, C*H*OAc) and 7.20–7.65 (20H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.56, 18.22, 19.02, 20.10, 20.57, 21.51, 25.90, 26.70, 35.73, 40.54, 45.56, 48.01, 59.18, 69.39, 70.15, 74.59, 74.69, 79.69, 127.09, 127.46, 127.60, 128.11, 128.64, 129.12, 129.59, 133.51, 135.44, 139.19, 168.27, 169.98 and 205.37; *m*/*z* (CI^+) 551 (5%), 473 (5), 295 (15), 274 (10) and 212 (100); HRMS (CI^+): M^++NH_4, found 870.4809. $C_{50}H_{72}NO_8Si_2$ requires 870.4796.

*4.2.20. (3S,5R,7S)-7-Benzyloxy-9-tert-butyldimethylsilyloxy-1-tert-butyldiphenylsilyloxy-8,8-dimethylnonane-3,5-diol (**30**).* Lithium iodide (10 mesh 99.99%, 3.96 g, 29.6 mmol) was added to the ketone **27** (2 g, 2.96 mmol) in ether (30 mL) at 0° C and the solution cooled to −78° C with rapid stirring to give a fine white suspension. Lithium tri-(*tert*-butoxy)aluminohydride (1 M in THF, 29.6 mL) was added and the mixture stirred for 18 h at −78° C. Methanol (15 mL) was added followed by saturated aqueous ammonium chloride (15 mL). The mixture was extracted with ether (5×50 mL) and the organic extracts were washed with water (50 mL) and brine (50 mL), then dried over magnesium sulfate. After concentration

under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **30** (1.9 g, 95%) as a colourless oil, R_f=0.2 (9:1 light petroleum/ethyl acetate), $[\alpha]_D$ −6.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3428, 3071, 2954, 2857, 1471, 1428, 1390, 1361, 1254, 1091, 837, 775, 736 and 701; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.01 (each 3H, s, SiCH_3), 0.86 (3H, s, 8-CH_3), 0.87 [12H, s, 8-CH_3′, SiC(CH_3)$_3$], 1.02 [9H, s, SiC(CH_3)$_3$], 1.40–1.90 (6H, m, 2-H_2, 4-H_2, 6-H_2), 3.15 (1H, s, O*H*), 3.27 and 3.52 (each 1H, d, *J* 9.5, 9-*H*), 3.68 (1H, s, O*H*′), 3.72 (1H, dd, *J* 9.8 and 2.1, 7-*H*), 3.83 (2H, m, 1-H_2), 4.09 and 4.21 (each 1H, m, 3- or 5-*H*), 4.67 and 4.68 (each 1H, d, *J* 11.5, HC*H*Ar) and 7.20–7.70 (15H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.54, −5.50, 18.23, 18.96, 20.15, 21.65, 25.88, 26.74, 38.04, 38.12, 40.46, 43.29, 63.55, 66.33, 69.69, 74.56, 79.71, 127.24, 127.58, 127.73, 128.21, 129.79, 132.76, 132.88, 135.45, 135.48 and 139.36; *m*/*z* (CI^+) 679 (M^++1, 35%), 249 (68), 196 (47), 108 (75), 106 (63) and 91 (100); HRMS (CI^+): M^++H, found 679.4213. $C_{40}H_{63}O_5Si_2$ requires 679.4214.

*4.2.21. (3S,5R,7S)-7-Benzyloxy-9-tert-butyldimethylsilyloxy-1-tert-butyldiphenylsilyloxy-8,8-dimethyl-3,5-O-isopropylidenenonane-3,5-diol (**31**).* A solution of the diol **30** (230 mg, 0.33 mmol) and PPTS (5 mg) in 2,2-dimethoxypropane (3 mL) was stirred for 18 h then added to saturated aqueous sodium bicarbonate (5 mL). The mixture was extracted with ether (3×5 mL) and the organic extracts were washed with water (5 mL) and brine (5 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **31** (220 mg, 93%) as a colourless oil, R_f=0.7 (9:1 light petroleum/ethyl acetate), $[\alpha]_D$ −7.1 (*c* 1.4 in Et_2O); ν_{max}/cm^{-1} 3070, 2932, 2858, 1589, 1471, 1428, 1379, 1252, 1224, 1175, 1100, 837, 775, 736, 701 and 613; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.02 (each 3H, s, SiCH_3), 0.85 and 0.87 (each 3H, s, 8-CH_3), 0.89 and 1.20 [each 9H, s, SiC(CH_3)$_3$], 1.32 (6H, s, 2× CH_3), 1.40–1.80 (6H, m, 2-H_2, 4-H_2, 6-H_2), 3.30 and 3.49 (each 1H, d, *J* 9.5, 9-*H*), 3.60–3.80 (3H, m, 7-*H*, 1-H_2), 4.04 (2H, m, 3-*H*, 5-*H*), 4.62 (2H, s, CH_2Ar) and 7.15–7.75 (15H, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.58, −5.52, 18.16, 19.13, 20.03, 21.71, 25.22, 25.41, 25.84, 26.77, 38.06, 38.82, 38.97, 40.47, 60.03, 63.25, 63.71, 69.54, 74.47, 79.30, 100.02, 127.10, 127.52, 127.74, 127.97, 128.19, 129.45, 133.84, 133.88, 135.47 and 139.44; *m*/*z* (CI^+) 719 (M^++1, 1%), 274 (29), 216 (28), and 91 (100); HRMS (CI^+): M^++H, found 719.4516. $C_{43}H_{67}O_5Si_2$ requires 719.4527.

*4.2.22. (3S,5R,7S)-7-Benzyloxy-8,8-dimethyl-3,5-O-isopropylidenenonane-1,3,5,9-tetraol (**32**).* Tetra-*n*-butylammonium fluoride (1 M in THF, 2.33 mL) was added to the silyl ether **31** (250 mg, 0.33 mmol) in THF (2.5 mL) and the mixture stirred at room temperature for 18 h. It was then filtered though a bed of silica gel, washing the filter cake with ether several times, and the filtrate was concentrated under reduced pressure to give the *title compound* **32** (120 mg, 99%) as a colourless oil, R_f=0.1 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −13.8 (*c* 1.3 in Et_2O); ν_{max}/cm^{-1} 3412, 2935, 2875, 1470, 1384, 1202, 1198, 1069, 1053, 1029, 736 and 698; δ_H (300 MHz, $CDCl_3$) 0.84 and 0.96 (each 3H, s, 8-CH_3), 1.33 and 1.39 (each 3H, s, CH_3), 1.20–1.80 (6H, m, 2-H_2, 4-H_2, 6-H_2), 3.07 (2H, s, 2× O*H*), 3.30 and 3.49 (each 1H, d, *J* 10.9, 9-*H*), 3.63 (1H, dd, *J* 9.2, 1, 7-*H*), 3.78 (1H, dd, *J* 11.5 and 5.2, 1-*H*), 3.91 (1H, td, *J* 12.0 and 2.7, 1-*H*′), 4.04 and 4.15 (each 1H, m, 3- or 5-*H*), 4.41 (2H, s, CH_2Ar) and 7.20–7.40 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.96, 21.44, 22.14, 29.92, 30.10, 38.56, 39.55, 42.28, 59.83, 65.74, 67.55, 70.21, 75.01, 83.01, 98.44, 127.59, 127.73, 128.35 and 138.57; *m*/*z* (CI^+) 310 (100%) and 309 (81); HRMS (CI^+): $M^+-H_2O+NH_4$, 368.2803. $C_{21}H_{38}NO_4$ requires 368.2801.

*4.2.23. (3S,5R,7S)-3-Benzyloxy-9-tert-butyldimethylsilyloxy-2,2-dimethyl-5,7-O-isopropylidenenonane-1,5,7-triol (**33**).* *tert*-Butyldimethylsilyl chloride (163 mg, 1.08 mmol) in DCM (5 mL) was added to the diol **32** (397 mg, 1.08 mmol) and imidazole (370 mg, 5.42 mmol) in DCM (5 mL) at 0° C. After 1.5 h, more TBSCl (30 mg) was added and, after 30 min, water (10 mL) was added. The mixture was extracted with ether and the organic extracts were washed with water then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **33** (491 mg, 94%) as a colourless oil, R_f=0.8 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −5.1 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 3476, 2953, 2930, 2858, 1471, 1380, 1253, 1224, 1170, 1099, 1048, 836, 776 and 733; δ_H (300 MHz, $CDCl_3$) 0.00 (6H, s, 2× SiCH_3), 0.85 [9H, s, SiC(CH_3)$_3$], 0.87 and 0.95 (each 3H, s, 2-CH_3), 1.29 (6H, s, 2× CH_3), 1.45–1.80 (6H, m, 4-H_2, 6-H_2, 8-H_2), 2.78 (1H, t, *J* 6.0, O*H*), 3.33 (1H, dd, *J* 11.1 and 5.9, 1-*H*), 3.48 (2H, m, 1-*H*′, 3-*H*), 3.61 (2H, m, 9-H_2), 3.95 (2H, m, 5-*H*, 7-*H*), 4.52 and 4.63 (each 1H, d, *J* 11.3, HC*H*Ar) and 7.20–7.35 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.44, −5.42, 18.18, 21.52, 21.67, 25.03, 25.29, 25.85, 38.17, 38.87, 39.70, 59.10, 63.24, 64.61, 70.28, 74.32, 82.66, 100.26, 127.27, 127.52, 128.35 and 138.50; *m*/*z* (CI^+) 423 (100%); HRMS (CI^+): M^++H, found 481.3346. $C_{27}H_{49}O_5Si$ requires 481.3349.

*4.2.24. (5S,7R,9S)-5-Benzyloxy-11-tert-butyldimethylsilyloxy-4,4-dimethyl-7,9-dihydroxy-7,9-O-isopropylideneundec-1-yne-3-one (**36**).* The Dess–Martin periodinane (20 mg, 0.048 mmol) was added to the alcohol **33** (20 mg, 0.042 mmol) in DCM (1 mL) and the mixture was stirred at room temperature for 30 min. Saturated aqueous sodium bicarbonate (2 mL) was added followed by aqueous sodium thiosulfate (10%, 2 mL) and ether (2 mL). After 20 min, the mixture was extracted with ether (3×3 mL) and the organic extracts were washed with water (3 mL) and brine (3 mL), then dried over magnesium sulfate. Concentration under reduced pressure gave the aldehyde **34** used without further purification.

Ethynylmagnesium bromide (0.5 M in THF, 84 μL, 0.17 mmol) was added to this aldehyde **34** (20 mg, 0.042 mmol) dropwise at −78° C under an atmosphere of nitrogen. The mixture was allowed to warm to room temperature then saturated aqueous ammonium chloride (1 mL) was added. The mixture was extracted with ether (3×2 mL) and the organic extracts were washed with water (2 mL) and brine (2 mL), then dried over magnesium sulfate. Concentration under reduced pressure gave the alcohol **35** (21 mg, 100%) as a mixture of epimers, used without further purification.

The Dess–Martin periodinane (20 mg, 0.047 mmol) was added to the alcohol **35** (20 mg, 0.040 mmol) in DCM (1 mL). After stirring at room temperature for 20 min, saturated aqueous sodium bicarbonate (1 mL), 10% aqueous sodium thiosulfate (1 mL) and ether (1 mL) were added and the suspension was stirred for 30 min. The mixture was extracted with ether (3×1 mL) and the organic extracts were washed with water (1 mL) and brine (1 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **36** (20 mg, 100%) as a colourless oil, R_f=0.6 (9:1 light petroleum/ethyl acetate), $[\alpha]_D$ +66.0 (*c* 1.0 in DCM); ν_{max}/cm^{-1} 2928, 2857, 2088, 1679, 1470, 1380, 1256, 1224, 1098, 1029, 836 and 776; δ_H (300 MHz, $CDCl_3$) 0.00 (6H, s, 2× SiCH_3), 0.83 [9H, s, SiC(CH_3)$_3$], 1.13 and 1.22 (each 3H, s, 4-CH_3), 1.31 and 1.33 (each 3H, s, CH_3), 1.40–1.70 (6H, m, 6-H_2, 8-H_2, 10-H_2), 3.24 (1H, s, 1-*H*), 3.62 (2H, m, 11-H_2), 3.90–4.05 (2H, m, 7-*H*, 9-*H*), 4.08 (1H, m, 5-*H*), 4.59 (2H, s, CH_2Ar) and 7.18–7.35 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.43, 18.18, 18.93, 20.85, 25.10, 25.36, 25.85, 38.39, 38.75, 38.88, 53.16, 59.12, 63.18, 63.47, 74.40, 79.72, 80.16, 80.28, 100.14, 127.18, 127.38, 128.21, 138.45 and 192.20; *m*/*z* (CI^+) 503 (M^++1, 2%), 445 (5), 376 (7) and 58 (100); HRMS (CI^+): M^++H, found 503.3196. $C_{29}H_{47}O_5Si$ requires 503.3192.

*4.2.25. (3S,5R,7S,15R,10E)-7-Benzyloxy-1,15,16-tris-(tert-butyldimethylsilyloxy)-3,5-dihydroxy-8,8-dimethyl-3,5-O-isopropylidene-13-[((E)-trimethylsilylmethylidene)hexadeca-10-en-9-one (**37**).* Molecular sieves (4 Å, 500 mg) were added to the alkynone **36** (200 mg, 0.4 mmol) in DCM (2 mL) and the mixture stirred at room temperature for 5 min. Zinc(II) iodide (dried at 250° C, 3 mmHg, 18 h; 254 mg, 0.78 mmol) was added and the flask was filled with nitrogen and wrapped in aluminium foil. The allylsilane **43** (495 mg, 1.19 mmol) in DCM (2 mL) was added and the mixture was stirred at room temperature for 48 h. The orange solution was filtered on a bed of Celite washing the bed with ether. Saturated aqueous ammonium chloride (10 mL) was added to the filtrate and the mixture was shaken in a separating funnel, which caused decolourisation of the organic layer. The mixture was extracted with ether (3×10 mL) and the organic extracts were washed with water (10 mL) and brine (10 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **37** (236 mg, 64%) as a colourless oil, R_f=0.4 (1:1 light petroleum/ethyl acetate), ν_{max}/cm^{-1} 2954, 2932, 2859, 1691, 1620, 1471, 1381, 1362, 1252, 1244, 1100, 837 and 776; δ_H (300 MHz, $CDCl_3$) 0.03 (18H, m, 6× SiCH_3), 0.08 (9H, m, 3× SiCH_3), 0.88 [27H, m, 3× SiC(CH_3)$_3$], 1.14 and 1.19 (each 3H, s, 8-CH_3), 1.34 and 1.35 (each 3H, s, CH_3), 1.45–1.75 (6H, m, 2-H_2, 4-H_2, 6-H_2), 2.05 (1H, dd, *J* 13.5 and 7.6, 14-*H*), 2.35 (1H, dd, *J* 13.5 and 4.3, 14-*H*′), 3.05 (2H, d, *J* 6.5, 12-H_2), 3.37 (1H, dd, *J* 9.9 and 6.3, 16-*H*), 3.49 (1H, dd, *J* 9.9 and 5.2, 16-*H*′), 3.65 (2H, m, 1-H_2), 3.75 (1H, m, 15-*H*), 3.86–4.09 (3H, m, 3-*H*, 5-*H*, 7-*H*), 4.58 and 4.60 (each 1H, d, *J* 11.2, HC*H*Ar), 5.42 (1H, s, 13-C*H*), 6.61 (1H, d, *J* 15.3, 10-*H*), 6.89 (1H, dt, *J* 15.3 and 6.5, 11-*H*) and 7.10–7.35 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.43, −5.41, −4.68, −4.36, 0.20, 18.02, 18.18, 18.27, 20.61, 21.16, 25.16, 25.38, 25.84, 25.90, 25.98, 38.68, 38.75, 38.92, 39.18, 43.86, 51.30, 59.14, 63.17, 63.27, 67.02, 72.75, 74.69, 80.44, 100.10, 126.54, 127.12, 127.29, 128.20, 129.81, 138.64, 144.70, 151.75 and 202.94.

*4.2.26. (2R,6S)-2-Acetoxymethyl-4-methylene-6-[(4S,6R,8S)-6,8,10-triacetoxy-4-benzyloxy-3,3-dimethyl-2-oxodecyl]tetrahydropyran (**39**).* Aqueous hydrogen fluoride (56%, 200 μL) was added to the enone **37** (10 mg, 0.011 mmol) in acetonitrile (200 μL) in a Teflon tube and the mixture was stirred at room temperature for 18 h then added slowly to an excess of saturated aqueous sodium bicarbonate (10 mL). The mixture was extracted with ethyl acetate (5×10 mL) and the organic extracts were washed with water (5 mL) and brine (10 mL), then dried over magnesium sulfate. After concentration under reduced pressure, the residue was dissolved in pyridine (2 mL) and acetic anhydride (1 mL). DMAP (1 mg) was added and the mixture was stirred at room temperature for 18 h then added to powdered ice (5 mL). The mixture was extracted with ether (3×5 mL) and the organic extracts were washed with water (5 mL) and brine (5 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **39** (5 mg, 65%) as a colourless oil, R_f=0.6 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −9.3 (*c* 0.3 in Et_2O); ν_{max}/cm^{-1} 3073, 2975, 2951, 1740, 1731, 1658, 1453, 1370, 1245, 1109, 1047, 1027, 942 and 715; δ_H (300 MHz, $CDCl_3$) 1.02 and 1.14 (each 3H, s, 3′-CH_3), 1.53 (2H, m, 5′-H_2), 1.68–1.85 (5H, m, 5-H_{ax}, 7′-H_2, 9′-H_2), 1.87 (1H, m, 3-H_{ax}), 1.90, 1.95, 1.98 and 2.01 (each 3H, s, COCH_3), 2.12 (1H, d, *J* 13.0, 3-H_{eq}), 2.20 (1H, d, *J* 13.7, 5-H_{eq}), 2.35 (1H, dd, *J* 17.2 and 6.0, 1′-*H*), 2.92 (1H, dd, *J* 17.2 and 6.3, 1′-*H*′), 3.48 (1H, m, 2-*H*), 3.64 (1H, dd, *J* 8.5 and 2.6, 4′-*H*), 3.74 (1H, m, 6-*H*), 3.98 (4H, 2-CH_2, 10′-H_2), 4.45 and 4.58 (each 1H, d, *J* 11.0, HC*H*Ar), 4.66 (2H, s, 4-CH_2), 4.91 (1H, m, 8′-*H*), 5.13 (1H, m, 6′-*H*) and 7.20–7.30 (5H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 20.18, 20.82, 20.84, 20.90, 20.92, 21.12, 33.42, 36.49, 37.78, 39.70, 39.99, 44.81, 52.62, 60.54, 66.65, 67.26, 67.95, 74.45, 74.94, 75.86, 80.90, 109.94, 127.39, 127.46, 128.24, 138.55, 142.50, 170.71, 170.85 and 212.44; *m*/*z* (CI^+) 650 (M^++18, 15%) and 91 (100); HRMS (CI^+): M^++18, found 650.3550. $C_{34}H_{52}NO_{11}$ requires 650.3539.

*4.2.27. (2R)-1-tert-Butyldimethylsilyloxy-4-(trimethylsilylmethyl)-pent-4-en-2-ol (**42**).* The bromopropenylsilane **40** (12.05 g, 62.4 mmol) and two small crystals of iodine were added to a suspension of magnesium (1.67 g, 68.7 mmol) in THF (10 mL). After 10 min, the iodine colouration disappeared and the reaction mixture became warm. After the reflux stopped, the mixture was heated under reflux for 5 min. The resulting green/brown solution was allowed to cool to room temperature and added dropwise via cannula to a mixture of the epoxide **41** (11.73 g, 62.4 mmol) and copper(I) iodide (1.19 g, 6.24 mmol) in THF (40 mL) at −10° C. More THF (10 mL) was added to the residual magnesium and this was also added to the reaction mixture that was stirred at −10° C for 1 h. Saturated aqueous ammonium chloride (30 mL) was added and the mixture exposed to the air. After 1 h, the mixture was extracted with ether (3×30 mL) and the organic extracts were washed with water (30 mL) and brine (30 mL) then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **42** (11.1 g, 60%) as a colourless oil, R_f=0.5 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −0.1 (*c* 2.6 in Et_2O); ν_{max}/cm^{-1} 3468, 2954, 2930, 2859, 1632, 1463, 1417, 1250, 1114, 1039, 840 and 777; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, 3× SiCH_3), 0.04 (6H, s, 2× SiCH_3), 0.88 [9H, s, SiC(CH_3)$_3$], 1.54 and 1.55 (each 1H, d, *J* 13.3, 4-C*H*), 2.09 (2H, m, 3-H_2), 2.32 (1H, d, *J* 3.1, O*H*), 3.47 (1H, dd, *J* 9.9 and 6.5, 1-*H*), 3.57 (1H, dd, *J* 9.9 and 4.3, 1-*H*′), 3.76 (1H, m, 2-*H*) and 4.61 and 4.66 (each 1H, s, 5-*H*); δ_C (75 MHz, $CDCl_3$) −5.45, −5.42, −1.46, 18.20, 25.81, 26.65, 42.02, 66.62, 69.68, 109.88 and 144.02.

*4.2.28. (4R)-4,5-bis-(tert-Butyldimethylsilyloxy)-2-(trimethylsilylmethyl)pent-1-ene (**43**).* Triethylamine (24 mL, 175 mmol) and TBSOTf (8.05 mL, 35.1 mmol) were added dropwise to the alcohol **42** (10.6 g, 35.1 mmol) in DCM (150 mL) at 0° C. After 5 min, saturated aqueous sodium bicarbonate (30 mL) was added and the mixture was extracted with ether (3×150 mL). The organic extracts were washed with water (150 mL) and brine (150 mL) then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue on basic alumina eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **43** (14 g, 96%), R_f=0.8 (9:1 light petroleum/ethyl acetate), $[\alpha]_D$ −5.8 (*c* 1.6 in Et_2O); ν_{max}/cm^{-1} 2954, 2930, 2895, 2858, 1632, 1472, 1361, 1251, 1112, 1080, 988, 837 and 776; δ_H (300 MHz, $CDCl_3$) 0.00 (9H, s, 3× SiCH_3), 0.03 (12H, s, 4× SiCH_3), 0.86 and 0.88 [each 9H, s, SiC(CH_3)$_3$], 1.53 (2H, m, 2-CH_2), 1.97 (1H, dd, *J* 13.6 and 7.3, 3-*H*), 2.23 (1H, dd, *J* 13.6 and 5.0, 3-*H*′), 3.42 (1H, dd, *J* 10, 6.2, 5-*H*), 3.51 (1H, dd, *J* 9.9, 5.4, 5-*H*′), 3.75 (1H, m, 4-*H*), 4.55 (1H, s, 1-*H*) and 4.62 (1H, d, *J* 1.0, 1-*H*′); δ_C (75 MHz, $CDCl_3$) −5.39, −5.40, −4.74, −4.42, −1.47, 18.09, 18.29, 25.84, 25.92, 26.94, 43.30, 67.19, 72.22, 109.91 and 144.07; *m*/*z* (CI^+) 417 (M^++1, 2%), 285(45) and 90 (100); HRMS (CI^+): M^++H, found 417.3050. $C_{21}H_{49}O_2Si_3$ requires 417.3040.

*4.2.29. (5S,7S)-1,7-Dibenzyloxy-9-tert-butyldimethylsilyloxy-5-hydroxy-8,8-dimethylnonan-3-one (**45**).* *n*-Butyllithium (1.60 M in hexanes, 17.1 mL, 112 mmol) was added dropwise to di-*iso*propylamine (16.3 mL, 117 mmol) in THF (34 mL) at −78° C The mixture was allowed to warm to room temperature and was then cooled back down to −78° C. The ketone **44** (17.1 mL, 99 mmol) in THF (38 mL), precooled to −78° C, was added and the mixture was stirred for 30 min before the aldehyde **26** (31.4 g, 90 mmol) in THF (47 mL) was added. After 2 min, methanol (10 mL) was added followed by saturated aqueous ammonium chloride (20 mL). The mixture was allowed to warm to room temperature and was extracted with ether (3×300 mL). The organic extracts were

washed with water (200 mL) and brine (200 mL) then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **45** (24.0 g, 51%) as a colourless oil, R_f=0.2 (4:1 light petroleum/ethyl acetate), $[\alpha]_D$ +6.0 (*c* 0.4 in Et_2O); ν_{max}/cm^{-1} 3442, 3030, 2958, 2872, 1713, 1496, 1454, 1365, 1274, 1099, 1028, 842 and 739; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.01 (each 3H, s, SiCH_3), 0.85 (6H, s, 2× 8-CH_3), 0.88 [9H, s, SiC(CH_3)$_3$], 1.46 and 1.56 (each 1H, m, 6-*H*), 2.55 (1H, d, *J* 8.4, 4-*H*), 2.58 (1H, d, *J* 3.4, 4-*H*′), 2.64 (2H, m, 2-H_2), 3.09 (1H, m, O*H*), 3.25 and 3.52 (each 1H, d, *J* 9.5, 9-*H*), 3.71 (2H, t, *J* 1-H_2), 3.74 (1H, m, 7-*H*), 4.22 (1H, m, 5-*H*), 4.47 and 4.65 (each 2H, s, CH_2Ar) and 7.20–7.40 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.57, −5.52, 18.21, 19.88, 21.77, 25.86, 37.44, 40.37, 43.37, 50.65, 64.78, 65.05, 69.55, 73.20, 74.72, 79.14, 127.26, 127.54, 127.66, 128.22, 128.35, 137.79, 139.25 and 210.35; *m*/*z* (CI^+) 529 (M^++1, 11%), 421 (12), 403 (14), 295 (15), 260 (20), 243 (20) and 91 (100); HRMS (CI^+): M^++H, found 529.3339. $C_{31}H_{49}O_5Si$ requires 529.3349.

*4.2.30. (5S,7S)-1,7-Dibenzyloxy-9-tert-(butyldimethylsilyloxy)-5-[(R)-2-acetoxy-2-phenylacetoxy]-8,8-dimethylnonan-3-one (**46**).* (*R*)-*O*-Acetylmandelyl chloride (60 mg, 0.28 mmol) in DCM (150 μL) was added to pyridine (77 μL, 0.95 mmol), DMAP (1 mg, 0.008 mmol) and the alcohol **45** in DCM (250 μL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 10 h. Ether (2 mL) and water (2 mL) were added and the mixture was extracted with ether (3×2 mL). The organic extracts were washed with water (2 mL) and brine (2 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **46** (50 mg, 75%) as a colourless oil, $[\alpha]_D$−41.8 (*c* 2.5 in Et_2O); ν_{max}/cm^{-1} 3064, 3032, 2956, 2929, 2857, 1745, 1716, 1455, 1370, 1233, 1176, 1090, 851, 838 and 737; δ_H 0.00 (300 MHz, $CDCl_3$) (6H, s, 2× SiCH_3), 0.69 and 0.72 (each 3H, s, 8-CH_3), 0.88 [9H, s, SiC(CH_3)$_3$], 1.62 and 1.78 (each 1H, m, 6-*H*), 2.18 (3H, s, COCH_3), 2.67 (2H, t, *J* 6.2, 2-H_2), 2.74 (1H, d, *J* 6.6, 4-*H*), 2.78 (1H, d, *J* 5.4, 4-*H*′), 2.86 (1H, m, 7-*H*), 3.23 and 3.24 (each 1H, d, *J* 7.5, 9-*H*), 3.68 (2H, t, *J* 6.3, 1-H_2), 3.97 and 4.03 (each 1H, d, *J* 11.26, HC*H*Ar), 4.46 (2H, s, CH_2Ar), 5.35 (1H, m, 5-*H*), 5.81 (1H, s, C*H*OAc) and 7.15–7.55 (15H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.54, −5.53, 18.27, 20.18, 20.63, 21.29, 25.91, 35.76, 40.45, 43.26, 48.15, 64.97, 69.19, 70.14, 73.07, 74.56, 74.69, 80.09, 127.14, 127.33, 127.51, 127.67, 128.10, 128.28, 128.69, 128.80, 129.32, 133.62, 138.08, 138.84, 168.43, 170.23 and 205.37; *m*/*z* (CI^+) 722 (M^++18, 2%), 403 (35) and 212 (100); HRMS (CI^+): M^++NH_4, found 722.4090. $C_{41}H_{60}NO_8Si$ requires 722.4088.

*4.2.31. (5S,7S)-1,7-Dibenzyloxy-9-tert-(butyldimethylsilyloxy)-5-[(S)-2-acetoxy-2-phenylacetoxy]-8,8-dimethylnonan-3-one (**47**).* (*S*)-*O*-Acetylmandelyl chloride (60 mg, 0.28 mmol) in DCM (150 μL) was added to pyridine (77 μL, 0.95 mmol), DMAP (1 mg, 0.008 mmol) and the alcohol **45** in DCM (250 μL) at 0 °C. The mixture was warmed to room temperature and stirred for 10 h. Ether (2 mL) and water (2 mL) were added and the mixture was extracted with ether (3×2 mL). The organic extracts were washed with water (2 mL) and brine (2 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography on silica gel eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **47** (57 mg, 85%) as a colourless oil, $[\alpha]_D$+32.9 (*c* 1.7 in Et_2O); ν_{max}/cm^{-1} 3088, 3032, 2955, 2929, 2857, 1746, 1715, 1496, 1455, 1371, 1232, 1176, 1096, 851, 838, 776 and 736; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.01 (each 3H, s, SiCH_3), 0.82 and 0.89 (each 3H, s, 8-CH_3), 0.90 [9H, s, SiC(CH_3)$_3$], 1.62 (1H, ddd, *J* 14.7, 10.6 and 2.9, 6-*H*), 1.88 (1H, ddd, *J* 14.6, 9.9 and 1.8, 6-*H*′), 2.16 (3H, s, COCH_3), 2.35 (2H, m, 2-H_2), 2.54 (2H, m, 4-H_2), 3.26 (1H, d, *J* 9.6, 9-*H*), 3.41 (1H, dd, *J* 10.4 and 1.8, 7-*H*), 3.43 (1H, d, *J* 9.6, 9-*H*′), 3.47 (2H, t, *J* 6.5, 1-H_2), 4.38 (2H, s, CH_2Ar), 4.42 and 4.48 (each 1H, d, *J* 11.4, HC*H*Ar), 5.43 (1H, m, 5-*H*), 5.80 (1H, s, C*H*OAc) and 7.15–7.50 (15H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.55, 18.22, 20.13, 20.56, 21.52, 25.91, 35.73, 40.54, 43.01, 47.86, 64.81, 69.39, 70.18, 73.03, 74.61, 74.60, 79.74, 127.11, 127.47, 127.58, 128.13, 128.27, 128.67, 129.14, 133.54, 138.03, 139.16, 168.28, 170.00 and 205.03; *m*/*z* (CI^+) 722 (M^++18, 1.5%), 403 (55) and 212 (100); HRMS (CI^+): M^++NH_4, found 722.4088. $C_{41}H_{60}NO_8Si$ requires 722.4088.

*4.2.32. (3S,5R,7S)-1,7-Dibenzyloxy-9-(tert-butyldimethylsilyloxy)-8,8-dimethylnonane-3,5-diol (**48**).* Tetramethylammonium triacetoxyborohydride (95 g, 362 mmol) was dissolved in acetonitrile (240 mL) and acetic acid (240 mL) and the mixture was stirred at room temperature for 30 min then cooled to −40° C. The ketone **45** (23.9 g, 45.2 mmol) in acetonitrile (240 mL) was added dropwise. The solution was stirred at −20° C for 18 h then saturated aqueous sodium bicarbonate (300 mL) was added slowly. After warming to room temperature, the mixture was extracted with ethyl acetate (5×200 mL) and the organic extracts were washed with water (100 mL) and brine (100 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **48** (22.8 g, 95%) as a colourless oil, R_f=0.2 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −10.9 (*c* 0.7 in Et_2O); ν_{max}/cm^{-1} 3443, 3064, 3030, 2952, 2858, 1496, 1471, 1454, 1361, 1253, 1207, 1098, 838, 777 and 734; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.01 (each 3H, s, SiCH_3), 0.85 (3H, s, 8-CH_3), 0.87 [12H, s, 8-CH_3′, SiC(CH_3)$_3$], 1.40–1.75 (5-H, m), 1.90 (1H, m), 3.20 (1H, s, O*H*), 3.27 (1H, d, *J* 9.6, 9-*H*), 3.42 (1H, s, O*H*), 3.51 (1H, d, *J* 9.6, 9-*H*′), 3.57–3.74 (3H, m, 1-H_2, 7-*H*), 4.12 (2H, m, 3-*H*, 5-*H*), 4.50 and 4.66 (each 2H, s, CH_2Ar) and 7.10–7.40 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.55, −5.50, 18.23, 20.18, 21.63, 25.87, 36.16, 38.06, 40.45, 43.21, 66.40, 69.29, 69.64, 69.68, 73.32, 71.51, 79.72, 127.27, 127.58, 127.63, 127.72, 128.22, 128.40, 137.74 and 139.30; *m*/*z* (CI^+) 531 (M^++1, 40%) and 417 (100); HRMS (CI^+): M^++H, found 531.3513. $C_{31}H_{51}O_5Si$ requires 531.5306.

*4.2.33. (3S,5R,7S)-1,7-Dibenzyloxy-9-(tert-butyldimethylsilyloxy)-3,5-O-isopropylidene-8,8-dimethylnonane-3,5-diol (**49**).* A solution of the diol **48** (22.8 g, 43 mmol) and PPTS (500 mg, 2.0 mmol) in 2,2-dimethoxypropane (1.2 L) was stirred for 18 h at room temperature. Saturated aqueous sodium bicarbonate (200 mL) was added and the aqueous layer extracted with ether (3×100 mL). The organic extracts were washed with water (200 mL) and brine (200 mL), dried over magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **49** (18.06 g, 74%) as a colourless oil, R_f=0.7 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −7.0 (*c* 0.8 in Et_2O); ν_{max}/cm^{-1} 3064, 3030, 2953, 2857, 1471, 1454, 1379, 1363, 1252, 1224, 1164, 1098, 838, 775 and 734; δ_H (300 MHz, $CDCl_3$) 0.00 and 0.02 (each 3H, s, SiCH_3), 0.84 and 0.86 (each 3H, s, 8-CH_3), 0.88 [9H, s, SiC(CH_3)$_3$], 1.31 and 1.33 (each 3H, s, CH_3), 1.48–1.68 (4H, m, 4-H_2, 6-H_2), 1.74 (2H, m, 2-H_2), 3.25 (1H, d, *J* 9.5, 9-*H*), 3.42–3.59 (3H, m, 9-*H*′, 1-H_2), 3.63 (1H, dd, *J* 9.8 and 2.1, 7-*H*), 4.00 (2H, m, 3-*H*, 5-*H*), 4.44 (2H, s, CH_2Ar), 4.61 and 4.62 (each 1H, d, *J* 11.5, HC*H*Ar) and 7.19–7.39 (10H, m, Ar*H*); δ_C −5.57, −5.50, 18.18, 20.04, 21.71, 25.15, 25.32, 25.86, 35.94, 38.11, 38.96, 40.48, 63.58, 63.77, 66.63, 69.54, 73.03, 74.48, 79.32, 100.00, 127.08, 127.13, 127.46, 127.62, 128.21, 128.28, 138.47 and 139.45; *m*/*z* (CI^+) 513 (40%), 405 (61), 91 (95) and 90 (100); HRMS (CI^+): M^++H, found 571.3800. $C_{34}H_{55}O_5Si$ requires 571.3819.

*4.2.34. (3S,5R,7S)-3,9-Dibenzyloxy-5,7-O-isopropylidene-2,2-dimethylnonane-1,5,7-triol (**50**).* Tetra-*n*-butylammonium fluoride (1.0 M in THF, 48 mL) was added to the silyl ether **49** (9.11 g,

16 mmol) in THF (100 mL) and the mixture was stirred at room temperature for 18 h. Water (200 mL) was added, the mixture was extracted with ether (3×200 mL) and the organic extracts were washed with water (100 mL) and brine (100 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **50** (6.9 g, 95%) as a colourless oil, R_f=0.3 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −13.3 (*c* 0.9 in Et_2O); ν_{max}/cm^{-1} 3466, 3030, 2928, 2872, 1454, 1379, 1224, 1170, 1100, 1029, 901 and 735; δ_H (300 MHz, $CDCl_3$) 0.84 and 0.92 (each 3H, s, 2-CH_3), 1.25 and 1.26 (each 3H, s, CH_3), 1.42–1.74 (6H, m, 4-H_2, 6-H_2, 8-H_2), 2.70 (1H, br s, O*H*), 3.30 (1H, d, *J* 11.1, 1-*H*), 3.38–3.54 (4H, m, 1-*H*′, 3-*H*, 9-H_2), 3.93 (2H, m, 5-*H*, 7-*H*), 4.42 (2H, s, CH_2Ar), 4.54 and 4.59 (each 1H, d, *J* 11.3, HC*H*Ar) and 7.15–7.35 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 21.45, 21.71, 24.99, 25.22, 35.89, 38.22, 38.84, 39.75, 63.59, 64.57, 66.50, 70.23, 73.04, 74.35, 82.50, 100.33, 127.27, 127.50, 127.53, 127.63, 128.30, 128.36, 138.42 and 138.58; *m*/*z* (CI^+) 474 (M^++18, 0.5%), 455 (1) and 399 (100); HRMS (CI^+): M^++H, found 457.2957. $C_{28}H_{40}O_5$ requires 457.2953.

*4.2.35. (5S,7R,9S)-5,11-Dibenzyloxy-4,4-dimethyl-7,9-dihydroxy-7,9-O-isopropylideneundec-1-yn-3-one (**53**).* Dimethyl sulfoxide (4.29 mL, 60.6 mmol) in DCM (50 mL) was added dropwise to oxalyl chloride (2.56 mL, 4.26 mmol) in DCM (50 mL) at −78° C. The mixture was stirred at this temperature for 20 min before the alcohol **50** (6.9 g, 15.1 mmol) in DCM (50 mL) was added. After stirring at −78° C for 20 min, triethylamine (21 mL, 151 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was extracted with ether (3×200 mL) and the organic extracts were washed with water (3×100 mL) and brine (100 mL), then dried over magnesium sulfate. Concentration under reduced pressure gave the aldehyde **51** (7.0 g, 100%) as a colourless oil, used without further purification; δ_H (300 MHz, $CDCl_3$) 1.10 and 1.18 (each 3H, s, 2-CH_3), 1.38 and 1.40 (each 3H, s, CH_3). 1.55–1.85 (6H, m, 4-H_2, 6-H_2, 8-H_2), 3.55 (2H, m, 9-H_2), 3.87 (1H, m, 3-*H*), 4.07 (2H, m, 5-*H*, 7-*H*), 4.54 (2H, s, CH_2Ar), 4.62 and 4.69 (each 1H, d, *J* 11.5, HC*H*Ar), 7.2–7.45 (10H, m, Ar*H*) and 9.69 (1H, s, 1-*H*).

Ethynylmagnesium bromide (0.5 M in THF, 62 mL, 31 mmol) was added to the aldehyde **51** (7.0 g, 15.4 mmol) in THF (160 mL) at −78° C. The mixture was allowed to warm to room temperature and saturated aqueous ammonium chloride (100 mL) was added carefully at 0° C. The mixture was extracted with ether (3×100 mL) and the organic extracts were washed with water (100 mL) and brine (100 mL), then dried over magnesium sulfate. Concentration under reduced pressure gave the alcohol **52** (8.0 g, 100%), a mixture of epimers, as a colourless oil, used without further purification.

Dess–Martin periodinane (8.6 g, 20.3 mmol) was added in portions to the alcohol **52** (7.39 g, 15.4 mmol) in DCM (200 mL) saturated with water. The mixture was stirred at room temperature for 4 h and saturated aqueous sodium bicarbonate (200 mL) and aqueous sodium thiosulfate (10%, 100 mL) were added slowly. Ether (200 mL) was added and the mixture was stirred vigorously for 30 min then extracted with ether (3×200 mL). The organic extracts were washed with water (200 mL) and brine (200 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **53** (7.25 g, 99%) as a colourless oil, R_f=0.4 (4:1 light petroleum/ethyl acetate), $[\alpha]_D$ −0.3 (*c* 1.2 in Et_2O); ν_{max}/cm^{-1} 3063, 3030, 2985, 2939, 2870, 2088, 1679, 1454, 1380, 1224, 1100, 1062 and 737; δ_H (300 MHz, $CDCl_3$) 1.10 and 1.19 (each 3H, s, 4-CH_3), 1.27 and 1.29 (each 3H, s, CH_3), 1.40–1.60 (4H, m, 6-H_2, 8-H_2), 1.69 (2H, m, 10-H_2), 3.22 (1H, s, 1-*H*), 3.47 (2H, m, 11-H_2), 3.96 (2H, m, 7-*H*, 9-*H*), 4.05 (1H, m, 5-*H*), 4.42 and 4.56 (each 2H, s, CH_2Ar) and 7.15–7.35 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) 18.98, 20.86, 25.04, 25.27, 35.88, 38.43, 38.71, 53.17, 63.48, 63.54, 66.53, 73.03, 74.43, 79.74, 80.18, 80.36, 100.23, 127.18, 127.41, 127.48, 127.62, 128.24, 128.29, 138.43, 139.46 and 192.20; *m*/*z* (CI^+) 479 (M^++1, 16%), 421 (100) and 108 (97); HRMS (CI^+): M^++H, found 479.2806. $C_{30}H_{39}O_5$ requires 479.2797.

*4.2.36. (3S,5R,7S,15R,10E)-1,7-Dibenzyloxy-15,16-bis-(tert-butyldimethylsilyloxy)-3,5-dihydroxy-8,8-dimethyl-3,5-O-isopropylidene-13-[((E)-trimethylsilylmethylidene)hexadeca-10-en-9-one (**54**).* Crushed molecular sieves (4 Å, 1.8 g) were added to the alkynone **53** (4.56 g, 10.8 mmol) in DCM (2.3 mL) and the mixture stirred at room temperature for 5 min. Zinc(II) iodide (dried at 250° C, 3 mmHg, for 18 h, 5.17 g, 16.2 mmol) was added and the flask was filled with nitrogen and wrapped in aluminium foil. The allylsilane **43** (9.0 g, 21.6 mmol) in DCM (2.3 mL) was added and the mixture was stirred at room temperature for 18 h. Ether (10 mL) was added and the mixture was filtered on a bed of Celite washing the bed several times with small amounts of ether. Saturated aqueous ammonium chloride (30 mL) was added and the mixture was extracted with ether (3×30 mL). The organic extracts were washed with water (30 mL) and brine (30 mL) then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **54** (5.35 g, 55%) as a colourless oil, R_f=0.6 (4:1 light petroleum/ethyl acetate), $[\alpha]_D$ −2.4 (*c* 0.5 in Et_2O); ν_{max}/cm^{-1} 3067, 3030, 2954, 2929, 2857, 1723, 1689, 1496, 1470, 1380, 1364, 1251, 1224, 1102, 1028, 838 and 777; δ_H (300 MHz, $CDCl_3$) 0.00 (3H, s, SiCH_3), 0.01 (6H, s, 2× SiCH_3), 0.02 (3H, s, SiCH_3), 0.07 (9H, s, 3× SiCH_3), 0.85 and 0.86 [each 9H, s, SiC(CH_3)$_3$], 1.12 and 1.18 (each 3H, s, 8-CH_3), 1.32 and 1.33 (each 3H, s, CH_3), 1.40–1.63 (4H, m, 4-H_2, 6-H_2), 1.73 (2H, m, 2-H_2), 2.03 (1H, dd, *J* 13.6 and 7.6, 14-*H*), 2.34 (1H, dd, *J* 13.6 and 4.3, 14-*H*′), 3.06 (2H, d, *J* 6.3, 12-H_2), 3.35 (1H, dd, *J* 9.9 and 6.3, 16-*H*), 3.43–3.58 (3H, m, 16-*H*′, 1-H_2), 3.73 (1H, m, 15-*H*), 3.88 (1H, m, 7-*H*), 3.99 (2H, m, 3-*H*, 5-*H*), 4.47 and 4.56 (each 2H, s, CH_2Ar), 5.41 (1H, s, 13-C*H*), 5.59 (1H, d, *J* 15.3, 10-*H*), 6.89 (1H, dt, *J* 15.3 and 6.3, 11-*H*) and 7.20–7.35 (10H, m, Ar*H*); δ_C (75 MHz, $CDCl_3$) −5.40, −5.38, −4.68, −4.35, 0.21, 18.03, 18.28, 20.60, 21.18, 25.07, 25.26, 25.84, 25.91, 29.63, 35.86, 38.68, 39.18, 43.85, 51.29, 63.26, 63.50, 66.53, 67.02, 72.74, 73.01, 74.70, 80.41, 100.18, 126.51, 127.12, 127.31, 127.46, 127.60, 128.21, 128.28, 129.83, 138.39, 138.61, 144.76, 151.73 and 202.96; *m*/*z* (ES^+) 912 (M^++18, 100%); HRMS (CI^+): M^++H, found 895.5752. $C_{51}H_{87}O_7Si_3$ requires 895.5759.

*4.2.37. (2R,6S)-2-Acetoxymethyl-4-methylene-6-[(4S,6R,8S)-6,8-diacetoxy-4,10-dibenzyloxy-3,3-dimethyl-2-oxodecyl]tetrahydropyran (**56**).* Aqueous hydrogen fluoride (56%, 2.8 mL) was added to the enone **54** (1.0 g, 1.12 mmol) in acetonitrile (20 mL) in a Teflon flask and the mixture stirred at room temperature for 18 h then added carefully to saturated aqueous sodium bicarbonate (50 mL). The mixture was extracted with ethyl acetate (6×50 mL) and the organic extracts were washed with brine (50 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in pyridine (130 mL) and acetic anhydride (64 mL). 4-Dimethylaminopyridine (5 mg) was added and the mixture was stirred at room temperature for 18 h then poured onto crushed ice (100 mL). The mixture was extracted with ether (3×100 mL) and the organic extracts were washed with water (100 mL) and brine (100 mL), dried over magnesium sulfate and concentrated under reduced pressure. Chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **56** (238 mg, 35%) as a colourless oil, R_f=0.6 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ −14.2 (*c* 1.3 in Et_2O); ν_{max}/cm^{-1} 3065, 3031, 2942, 2871, 1739, 1706, 1655, 1497,

1454, 1370, 1243, 1101, 1027 and 739; δ_H (500 MHz, $CDCl_3$) 1.09 and 1.22 (each 3H, s, 3′-CH_3), 1.54–1.66 (2H, m, 5′-H_2), 1.76–1.90 (5H, m, 5-H_{ax}, 7′-H_2, 9′-H_2), 1.95 (3H, s, COCH_3), 1.97 (1H, m, 3-H_{ax}), 2.05 and 2.08 (each 3H, COCH_3), 2.19 (1H, m, 3-H_{eq}), 2.27 (1H, m, 5-H_{eq}), 2.47 (1H, dd, *J* 17.3 and 6.0, 1′-*H*), 2.98 (1H, dd, *J* 17.3 and 6.4, 1′-*H*′), 3.47 (2H, m, 10′-H_2), 3.55 (1H, m, 2-*H*), 3.72 (1H, dd, *J* 9.2 and 2.1, 4′-*H*), 3.81 (1H, m, 6-*H*), 4.03 (1H, dd, *J* 11.5 and 4.1, 2-HC*H*), 4.07 (1H, dd, *J* 11.7 and 6.2, 2-HC*H*′), 4.45 and 4.46 (each 1H, d, *J* 11.5, HC*H*Ar), 4.52 and 4.66 (each 1H, d, *J* 10.9, HC*H*Ar), 4.78 (2H, narrow m, 4-CH_2), 5.05 (1H, m, 8′-*H*), 5.22 (1H, m, 6′-*H*) and 7.20–7.40 (10H, m, Ar*H*); δ_C (75 MHz, benzene-d_6) 19.58, 19.98, 20.43, 20.46, 21.12, 34.91, 36.36, 38.25, 39.89, 39.97, 44.63, 52.49, 66.32, 67.55, 67.74, 72.65, 74.44, 75.02, 75.90, 81.15, 109.39, 127.26, 127.39, 127.45, 127.90, 128.09, 138.67, 139.07, 142.91, 169.52, 169.64, 170.14 and 210.73; *m*/*z* (CI^+) 698 (M^++18, 34%) and 91 (100); HRMS (CI^+): M^++NH_4, found 698.3893. $C_{39}H_{56}NO_{10}$ requires 698.3904.

*4.2.38. (3S,5SR,7S,9S,11S,15R)-1,7-Dibenzyloxy-5,9-epoxy-11,15-epoxy-13-methylidene-9-methoxy-8,8-dimethylhexadecane-3,16-diol (**57**).* Aqueous hydrogen fluoride (56%, 5.6 mL) was added to the enone **54** (1 g, 1.11 mmol) in acetonitrile (40 mL) in a Teflon flask and the mixture was stirred at room temperature for 24 h. The reaction was then added to an excess of saturated aqueous sodium bicarbonate (50 mL) and the mixture extracted with ethyl acetate (5×50 mL). The organic extracts were washed with brine (20 mL), dried over magnesium sulfate and concentrated under reduced pressure. Following azeotropic distillation of benzene (2×10 mL), the residue was dissolved in methanol (25 mL) and trimethyl orthoformate (3.76 mL) and PPTS (50 mg) were added. This mixture was stirred at room temperature for 3 h and saturated aqueous sodium bicarbonate (20 mL) was added rapidly. After extraction with ethyl acetate (5×20 mL), the organic extracts were washed with brine (10 mL) then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the *title compound* **57** (217 mg, 34%), R_f=0.3 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ +47.5 (*c* 0.9 in Et_2O); ν_{max}/cm^{-1} 3439, 3066, 3030, 2943, 1652, 1496, 1454, 1362, 1092, 890, 736; δ_H (500 MHz, acetone-d_6) 1.01 and 1.08 (each 3H, s, 8-CH_3), 1.42 (1H, q, *J* 12, 6-H_{ax}), 1.57 (1H, ddd, *J* 14.0, 9.6 and 3.2, 4-*H*), 1.64 (1H, ddd, *J* 14.0, 8.9 and 2.4, 4-*H*′), 1.68–1.80 (4H, m), 1.86–1.94 (3H, m), 2.07 (1H, dd, *J* 16.0 and 5.8, 10-*H*′), 2.17 (1H, d, *J* 13.4, 12-H_{eq}), 2.45 (1H, d, *J* 13.1, 14-H_{eq}), 3.23 (3H, s, OCH_3), 3.31 (1H, m), 3.48 (2H, m), 3.51–3.70 (4H, m), 3.74 (1H, dd, *J* 11.6 and 4.7), 3.92 (1H, m, 3-*H*), 4.11 (1H, m, 5-*H*), 4.44 (1H, d, *J* 11.9, HC*H*Ar), 4.51 (2H, s, CH_2Ar), 4.65 (1H, d, *J* 11.9, HC*H*Ar), 4.70 and 4.74 (each 1H, d, *J* 2.0, 13-C*H*) and 7.20–7.40 (10H, m, Ar*H*); δ_C (75 MHz, benzene-d_6) 16.92, 20.61, 31.27, 36.28, 37.50, 40.02, 41.12, 41.38, 42.98, 48.80, 66.17, 66.33, 67.14, 67.59, 71.08, 72.81, 74.53, 78.11, 80.24, 103.92, 108.26, 127.25, 127.43, 127.58, 127.75, 127.90, 128.09, 138.78, 139.43 and 144.34; *m*/*z* (CI^+) 537 (M^+–31, 37%) and 182 (100); HRMS (CI^+): M^+–CH_3OH, found 536.3128. $C_{33}H_{44}O_6$ requires 536.3138. The column was flushed with ethyl acetate and the material isolated taken through the reaction sequence again to provide more product **57** (total yield, 310 mg, 49%).

*4.2.39. (3S,5R,7S,9S,11S,15R)-1,7-Dibenzyloxy-3,16-bis-(tert-butyldimethylsilyloxy)-5,9-epoxy-11,15-epoxy-13-methylidene-9-methoxy-8,8-dimethylhexadecane (**58**).* *tert*-Butyldimethylsilyl chloride (33 mg, 0.22 mmol), DMAP (5 mg) and TBAI (5 mg) were added to the diol **57** (113 mg, 0.20 mmol) and imidazole (68 mg, 1.0 mmol) in DCM (2.5 mL) and the mixture stirred at room temperature for 1 h. Ether was added (5 mL) followed by water (5 mL) and the mixture was extracted with ether (3×5 mL). The organic extracts were washed with water (5 mL) and brine (5 mL), dried over magnesium sulfate and concentrated under reduced pressure. This process was then repeated several times until TLC indicated complete conversion to the bis-TBS ether **58**. Chromatography of the residue eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **58** (160 mg, ca. 100%) as a colourless oil, R_f=0.8 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ +55.6 (*c* 1.0 in Et_2O); ν_{max}/cm^{-1} 3066, 3030, 2930, 2857, 1652, 1496, 1471, 1361, 1255, 1110, 888, 836, 776 and 734; δ_H (500 MHz, benzene-d_6) 0.15 and 0.18 (each 6H, s, 2× SiCH_3), 1.04 and 1.06 [each 9H, s, SiC(CH_3)$_3$], 1.35 and 1.40 (each 3H, s, 8-CH_3), 1.57 (1H, q, *J* 12.0, 6-H_{ax}), 1.78 (1H, dt, *J* 14.0 and 5.3, 4-*H*), 1.85–2.15 (7H, m), 2.30 (1H, d, *J* 12.8, 14-H_{eq}), 2.39 (1H, ddd, *J* 15.9 and 4.6, 10-*H*′), 2.54 (1H, d, *J* 13.0, 12-H_{eq}), 3.29 (3H, s, OCH_3), 3.50 (1H, m, 15-*H*), 3.58 (1H, m, 11-*H*), 3.63–3.68 (2H, m, 1-*H*, 16-*H*), 3.78 (1H, dd, *J* 10.4 and 5.2, 16-*H*′), 3.80–3.88 (2H, m, 5-*H*, 1-*H*′), 3.90 (1H, dd, *J* 11.6 and 4.7, 7-*H*), 4.26 (1H, m, 3-*H*), 4.32, 4.42, 4.46 and 4.51 (each 1H, d, *J* 11.7, HC*H*Ar), 4.84 and 4.89 (each 1H, d, *J* 1.4, 13-C*H*), and 7.10–7.45 (10H, m, Ar*H*); δ_C (75 MHz, benzene-d_6) −5.53, −4.44, −4.37, 16.63, 17.89, 18.14, 20.88, 25.73, 33.36, 36.96, 38.33, 39.26, 42.61, 43.28, 44.84, 47.89, 66.23, 66.52, 66.58, 68.02, 71.27, 72.75, 75.03, 78.67, 78.83, 104.12, 108.25, 126.71, 126.99, 127.25, 127.58, 127.89, 128.09, 138.84, 139.49 and 144.92; *m*/*z* (CI^+) 765 (M^+–31, 15%) and 91 (100); HRMS (CI^+): M^+–CH_3O, found 765.4934. $C_{45}H_{73}O_6Si_2$ requires 765.4945.

*4.2.40. (3S,5R,7S,9S,11S,15R)-1,7-Dibenzyloxy-3,16-bis-(tert-butyldimethylsilyloxy)-5,9-epoxy-11,15-epoxy-9-methoxy-8,8-dimethylhexadecan-13-one (**59**).* *N*-Methylmorpholine-*N*-oxide (60 mg, 0.50 mmol) and osmium tetroxide (1 small crystal) were added to the alkene **58** (202 mg, 0.25 mmol) and sodium carbonate (65 mg) suspended in acetone (3.3 mL), *tert*-butanol (3.3 mL) and water (1.6 mL). The mixture was stirred for 18 h at room temperature then aqueous sodium sulfite (10%, 5 mL) was added. The mixture was extracted with ethyl acetate (5×5 mL) and the organic extracts were washed with brine (5 mL), then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (1:1) gave the corresponding vicinal diols (114 mg, 55%), a mixture of epimers, as a colourless oil.

Sodium periodate (400 mg, 1.86 mmol) was added to a suspension of these diols (114 mg, 0.14 mmol) and sodium carbonate (53 mg) in THF (663 μL), methanol (663 μL) and water (800 μL). The mixture was stirred at room temperature for 30 min followed by the addition of aqueous sodium thiosulfate (10% 3 mL). The mixture was extracted with ether (3×5 mL) and the organic extracts were washed with water (5 mL), and brine (5 mL) then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **59** (76 mg, 69%) as a colourless oil, R_f=0.8 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ +58.0 (*c* 0.4 in Et_2O); ν_{max}/cm^{-1} 3030, 2952, 2929, 2857, 1721, 1471, 1361, 1253, 1112, 836, 776 and 734; δ_H (500 MHz, acetone-d_6) 0.09 (12H, overlapping s, 4× SiCH_3), 0.89 and 0.91 [each 9H, s, SiC(CH_3)$_3$], 1.03 and 1.05 (each 3H, s, 8-CH_3), 1.35 (1H, q, *J* 12, 6-H_{ax}), 1.63 (1H, dt, *J* 14.0 and 5.0), 1.75 (1H, m), 1.80–1.88 (2H, m), 1.91–2.00 (2H, m), 2.18 (1H, dd, *J* 16.0 and 5.0, 10-*H*′), 2.21 (1H, d, *J* 15.0, 14-H_{eq}), 2.25 (1H, dd, *J* 14.0 and 11.5, 12-H_{ax}), 2.33 (1H, dd, *J* 14.5 and 11.5, 14-H_{ax}), 2.49 (1H, d, *J* 14.5, 12-H_{eq}), 3.17 (3H, s, CH_3O), 3.54–3.62 (2H, m, 7-*H*, 16-*H*), 3.63–3.75 (5H, m, 1-H_2, 3-*H*, 15-*H*, 16-*H*′), 3.91 (1H, m, 11-*H*), 4.09 (1H, m, 5-*H*), 4.43 (1H, d, *J* 12.0, HC*H*Ar), 4.50 (2H, s, CH_2Ar), 4.64 (1H, d, *J* 12.0, HC*H*Ar) and 7.20–7.40 (10H, m, Ar*H*); δ_C (75 MHz, benzene-d_6) −5.57, −4.38, 16.53, 17.86, 17.89, 18.07, 20.78, 25.64, 25.75, 33.33, 38.41, 39.00, 43.20, 43.38, 44.76, 47.68, 49.08, 65.79, 66.46, 66.59, 68.19, 71.24, 72.75, 73.52, 76.91, 78.44, 103.74, 127.04, 127.39,

128.01, 128.09, 138.90, 139.38 and 204.92; m/z (CI^+) 784 (35%), 767 (M^+-31, 15) and 91 (100); HRMS (ES^+): $M^+ + NH_4$, 816.5265. $C_{45}H_{78}NO_8Si_2$ requires 816.5266.

*4.2.41. (3S,5R,7S,9S,11S,15R)-1,7-Dibenzyloxy-3,16-bis-(tert-butyldimethylsilyloxy)-5,9-epoxy-11,15-epoxy-9-methoxy-13-[(Z)-methoxycarbonylmethylidene]-8,8-dimethylhexadecane (**60**).* Sodium hexamethyldisilazide (1 M THF, 182 μL) was added dropwise at −78° C to the (*R*)-phosphonate **61** (78 mg, 0.193 mmol) in THF (200 μL). This mixture was stirred for at 30 min at −78 °C then the ketone **59** (77 mg, 0.096 mmol) in THF (200 μL) was added. The mixture was stirred for 18 h at −50 °C and allowed to warm to −15 °C. The mixture was stirred at this temperature for a further 18 h then allowed to warm to room temperature. Saturated aqueous ammonium chloride (3 mL) was added and the mixture was extracted with ether (3×5 mL). The organic extracts were washed with water (5 mL) and brine (5 mL) then dried over magnesium sulfate. After concentration under reduced pressure, chromatography of the residue eluting with light petroleum to light petroleum/ether (9:1) gave the *title compound* **60** (40 mg, 49%) as a colourless oil, a 72:28 mixture of (*Z*)/(*E*)-isomers, R_f=0.9 (1:1 light petroleum/ethyl acetate), $[\alpha]_D$ +51.6 (*c* 2.0 in Et_2O); ν_{max}/cm^{-1} 3030, 2950, 2929, 2885, 2857, 1721, 1651, 1471, 1435, 1361, 1253, 1200, 1150, 1112, 1005, 836, 776 and 734; δ_H (500 MHz, $CDCl_3$) 0.04–0.09 (12H, overlapping s, 4× SiCH_3), 0.87 [2.5H, s, SiC(CH_3)$_3$], 0.88 [6.5H, s, SiC(CH_3)$_3$], 0.89 [2.5H, s, SiC(CH_3)$_3$], 0.99 (2.2H, s, 8-CH_3), 1.01 (0.8H, s, 8-CH_3), 1.05 (2.2H, s, 8-CH_3'), 1.06 (0.8H, s, 8-CH_3'), 1.35 (1H, q, *J* 12.2, 6-H_{ax}), 1.60 (1H, m), 1.72–1.79 (2H, m), 1.80–1.93 (4H, m), 2.02–2.09 (2H, m), 2.23 (0.28H, m, 14-H_{eq}), 2.43 (0.72H, d, *J* 13.3, 12-H_{eq}), 3.14 (2.2H, s, CH_3O), 3.17 (0.8H, s, CH_3O), 3.38 (0.72H, m, 15-*H*), 3.42 (0.28H, m, 15-*H*), 3.52–3.61 (4H, m), 3.62–3.71 (6H, m), 3.76 (0.72H, d, *J* 14.0, 14-H_{eq}), 3.97 (1H, m), 4.01 (0.28H, d, *J* 13.9, 12-H_{eq}), 4.43, 4.49, 4.50 and 4.60 (each 1H, d, *J* 11.8, HC*H*Ar), 5.64 (0.72H, s, 13-C*H*), 5.65 (0.28H, s, 13-C*H*), and 7.20–7.40 (10H, m, Ar*H*); δ_C (75 MHz, benzene-d_6) (*Z*)-isomer **60** −5.51, −4.42, −4.34, 16.53, 17.89, 18.13, 20.86, 25.72, 30.02, 32.11, 33.31, 38.37, 38.66, 38.99, 43.26, 44.27, 44.81, 47.78, 47.82, 50.12, 66.34, 66.51, 67.99, 71.28, 72.77, 74.82, 78.30, 78.54, 103.99, 114.31, 127.25, 127.43, 127.57, 127.74, 127.90, 138.82, 139.42, 157.99 and 166.15; distinct peaks for the minor (*E*)-isomer 16.77, 33.43, 38.17, 39.66, 44.55, 74.43 and 165.98; m/z (CI^+) 823 (M^+-31, 8%), 105 (81) and 91 (100); HRMS (CI^+): M^+-CH_3O, found 823.4993. $C_{47}H_{75}O_8Si_2$ requires 823.5000.

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