Tetrahedron 65 (2009) 4201–4211

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of precursors of phomactins using [2,3]-Wittig rearrangements

Peter D.P. Shapland, Eric J. Thomas *

The School of Chemistry, The University of Manchester, Manchester, M13 9PL, UK

ARTICLE INFO

Article history:
Received 8 January 2009
Received in revised form 12 March 2009
Accepted 13 March 2009
Available online 21 March 2009

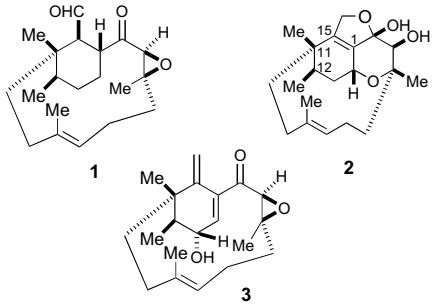
ABSTRACT

o-Toluic acid has been converted into methyl (8*RS*,9*SR*)-7-(bromomethyl)-8,9-dimethyl-1,4-dioxaspiro-[4.5]dec-6-ene-8-carboxylate, the stereochemical defining step being a conjugate addition of lithium dimethylcuprate to a cyclohexadienone prepared using a Birch reduction followed by an allylic oxidation. Displacement of the bromide with various propargylic alcohols followed by reduction of the ester and protection of the primary alcohol so formed then gave a series of propargyl cyclohexenylmethyl ethers. [2,3]-Wittig rearrangements of these and related propargylic ethers were studied as an approach to precursors of phomactins. The rearrangements were found to proceed by regioselective deprotonation of the propargylic side-chain to give substituted methylenecyclohexanes but mixtures of stereoisomers were obtained.

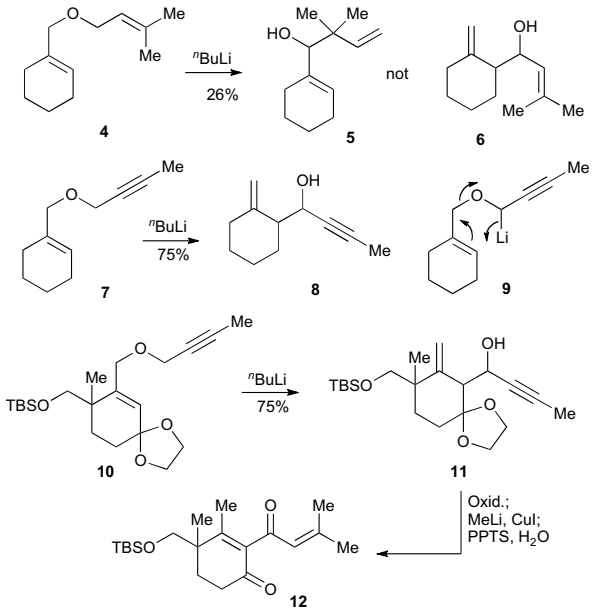
Aspects of the chemistry of the Wittig rearrangement products were investigated including epoxidation, oxidation of the side-chain hydroxyl groups to give 2-ynones and reactions of the 2-ynones with lithium dimethylcuprate. The propargyl side-chain of a Wittig rearrangement precursor was elaborated to prepare an intermediate, which was fully functionalised for incorporation into a phomactin.

1. Introduction

The phomactins are a group of diterpenes, which have interesting biological activity and which have attracted considerable interest from synthetic organic chemists.[1] Phomactin D **1** was the first member of the series to succumb to total synthesis,[2] and since then two syntheses of phomactin A **2**[3,4] and syntheses of phomactins B2 **3**[5] and G[6] have been reported, along with many contributions on alternative approaches to phomactins.[7] The chemistry of phomactins has been reviewed.[8]



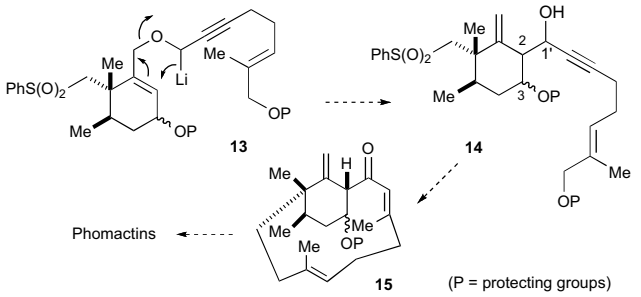
In planning a new approach to phomactins, [2,3]-Wittig rearrangements[9] were considered for the synthesis of suitably substituted methylenecyclohexanes. Preliminary studies,[10] see Scheme 1, showed that 1-(3-methylbut-2-enyloxymethyl)cyclohex-1-ene **4** rearranged on treatment with *n*-butyllithium with



Scheme 1. Preliminary studies of the synthesis of 2-(1-hydroxyalk-2-ynyl)-1-methylenecyclohexanes by [2,3]-rearrangements.

* Corresponding author.
E-mail address: e.j.thomas@manchester.ac.uk (E.J. Thomas).

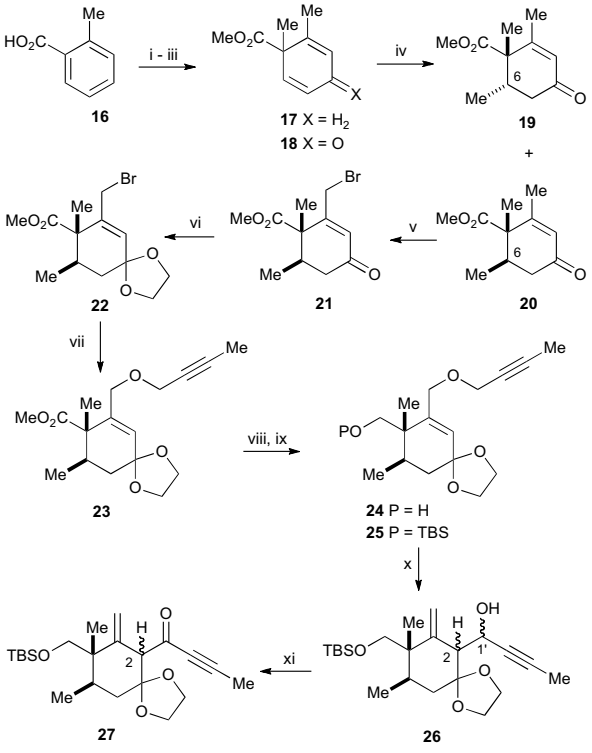
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.03.031



Scheme 2. An approach to precursors of phomactins using a [2,3]-Wittig rearrangement.

deprotonation of the more acidic ethereal methylene group next to the six-membered ring to give 1-(2,2-dimethyl-1-hydroxybut-3-en-1-yl)cyclohexene **5** and not 2-(1-hydroxy-3-methylbut-2-enyl)-1-methylenecyclohexane **6**.[10] However, the corresponding alkyne **7** rearranged via the lithiated intermediate **9** to give the 2-(1-hydroxybut-2-ynyl)-1-methylenecyclohexane **8**, and rearrangement of the slightly more complex propargyl allyl ether **10** gave the methylenecyclohexane **11**. In both cases mixtures of stereoisomers were obtained. Alcohol **11** was taken through to the unsaturated diketone **12** by oxidation, conjugate addition and hydrolysis of the acetal with migration of the exocyclic double-bond.[10]

Based on these preliminary observations, a synthetic approach to the phomactins was envisaged in which a [2,3]-Wittig rearrangement of a lithiated 1-(alk-2-yn-1-yloxymethyl)cyclohexene, e.g., **13**, would be used to prepare a 2-(1-hydroxyalk-2-yn-1-yl)-1-methylenecyclohexane **14**, see Scheme 2. Further modification, e.g.,



Scheme 3. Reagents and conditions (i) (a) Li, liq. NH_3, THF, −78 °C, then MeI (99%); (ii) $SOCl_2$, MeOH, reflux, 1 h (98%); (iii) ^tBuOOH, PDC, benzene, 0 °C, 3.5 h (68%); (iv) MeLi, CuI, ether, 0 °C, 30 min, add **18**, 30 min (89%: **19**/**20**=23:77); (v) NBS, AIBN (trace), CCl_4, reflux, 24 h (**21**; 67%); (vi) ethylene glycol, PPTS, benzene, reflux, Dean–Stark (95%); (vii) but-2-ynol, NaH, THF, rt, 30 min, add **22**, rt, 24 h (53%); (viii) $LiEt_3BH$, THF, 0 °C, 1 h (80%); (ix) TBSOTf, Et_3N, DCM, rt, 6 h (67%); (x) ^nBuLi, THF, −78 °C, 3 h (50%; two isomers, 70:30); (xi) DMSO, $(COCl)_2$, DCM, −78 °C, 3 h, Et_3N, rt, 2 h (65%; 70:30).

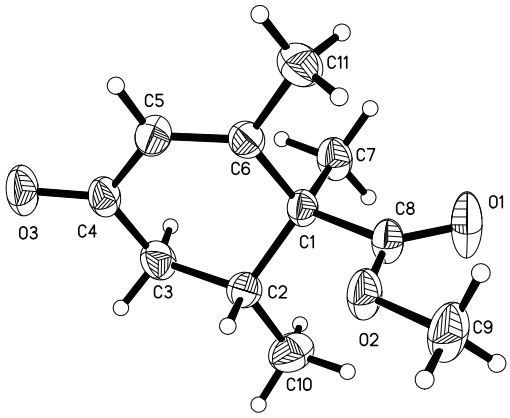
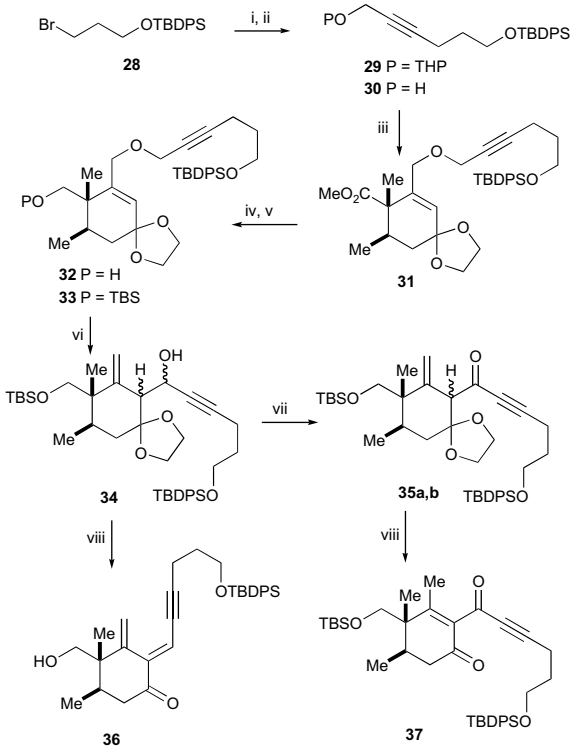


Figure 1. An ORTEP representation of the structure of the methyl ester **20** as determined by X-ray crystallography.

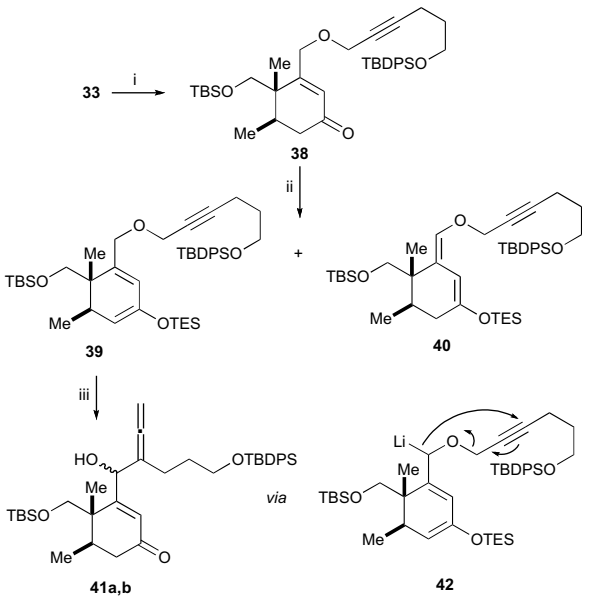
with macrocycle formation by sulfone alkylation,[2] could then give access to bicyclic precursors of phomactins, e.g., the ketone **15**. We now report studies into Wittig rearrangements of several 1-(alk-2-ynyloxymethyl)cyclohexenes and aspects of the chemistry of the products so formed. Of interest in the context of a phomactin synthesis is the stereoselectivity of these Wittig rearrangements with respect to the newly formed stereogenic centres at C(2) and C(1′), and the subsequent conversion of the alkyne into a trisubstituted alkene.

2. Discussion

The synthesis and Wittig rearrangement of the propargyl ether **25** is outlined in Scheme 3. Using lithium rather than sodium, reductive methylation[11] of *o*-toluic acid **16** followed by esterification



Scheme 4. Reagents and conditions: (i) $THPOCH_2CCH$, ^nBuLi, THF, 0 °C, 30 min, add **28**, THF, reflux, 16 h (99%); (ii) PPTS, MeOH, rt, 2 days (58%); (iii) NaH, THF, reflux 1 h, add **21**, THF, reflux, 5 h (50%); (iv) $LiEt_3BH$, THF, 0 °C, 30 min (91%); (v) TBSCl, imid., DCM, rt, 44 h (80%); (vi) ^nBuLi, −78 °C, 3 h (82%; two isomers, 67:33); (vii) DMSO, $(COCl)_2$, DCM, 3 h, Et_3N, rt, 9 h (**35a**, 28%; **35b**, 42%); (viii) aq HCl (10%), acetone, H_2O, rt (**36**, 46%; **37**, 44%).



Scheme 5. Reagents and conditions: (i) PPTS, acetone–H_2O, reflux, 3 h (92%); (ii) Et_3SiOTf, Et_3N, DCM, rt, 21 h (**40**, 10%; **39**, 69%); (iii) ^nBuLi, THF, −78 °C, 2 h (**41a**, 25%; **41b**, 25%).

gave methyl 1,2-dimethylcyclohexa-2,5-diene-1-carboxylate **17**, and allylic oxidation to the ketone **18** was carried out using pyridinium dichromate and *tert*-butyl hydroperoxide.[12]

Preliminary studies of free-radical bromination of the 2-methyl group of dienone **18** were complicated by bis-bromination, and conversion of dienone **18** into methyl 2-hydroxymethyl-1-methyl-4-oxocyclohexa-2,5-diene-1-carboxylate by oxidation of the exocyclic double-bond of its *tert*-butyldimethylsilyl dienol ether using dimethyl dioxirane[13] was difficult to scale up. However, conjugate addition[14] of lithium dimethylcuprate to dienone **18** was found to be regioselective for the less substituted double-bond and was stereoselective in favour of diastereoisomer **20** in which the two methyl groups were cis-disposed about the six-membered ring, **19**:**20**=23:77 (89% combined yield). The structure of the major isomer **20** was established by X-ray crystallography, see Figure 1.

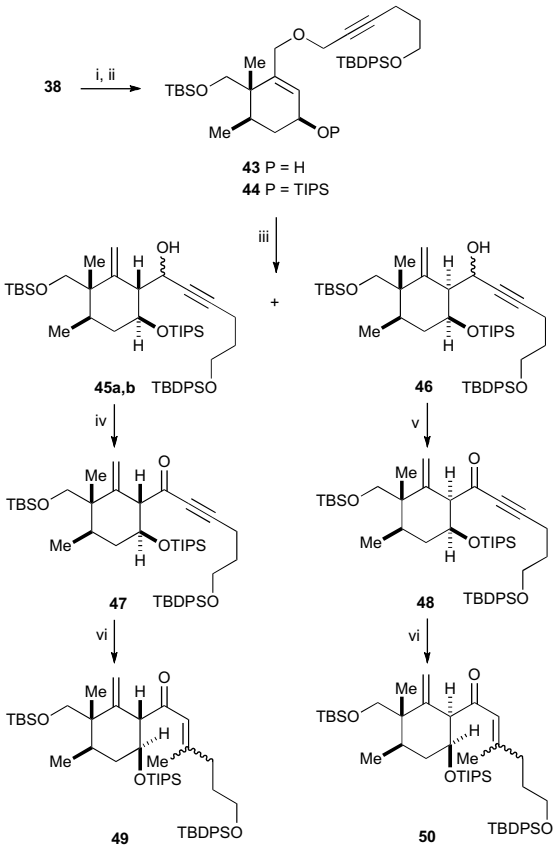
Although the stereoselectivity of this conjugate addition was only modest, the major isomer **20** had the relative stereochemistry at its two stereogenic centres corresponding to that at C(11) and C(12) of the phomactins. Preliminary studies of the analogous conjugate addition using the isopropyl ester corresponding to **18**, or by using different reaction solvents, did not reveal significant improvements in the stereoselectivity, and so the conjugate addition of lithium dimethylcuprate to the dienone **18** was retained for the preparation of ester **20**, although, for convenience, a mixture of the epimers **19** and **20** was taken through to the next step.

Allylic bromination of the mixture of epimeric esters **19** and **20** was carried out using *N*-bromosuccinimide and the required bromomethyl ester **21** was isolated from the mixture of products in a 67% yield based on the amount of ester **20** in the starting material. Following protection of the ketone **21** as its acetal **22**, which was found to be rather unstable, displacement of the bromide using the sodium salt of but-2-ynol gave ether **23** (53%). Reduction of the methoxycarbonyl group was then carried out using lithium triethylborohydride and the alcohol **24** was protected as its *tert*-butyldimethylsilyl ether **25**.

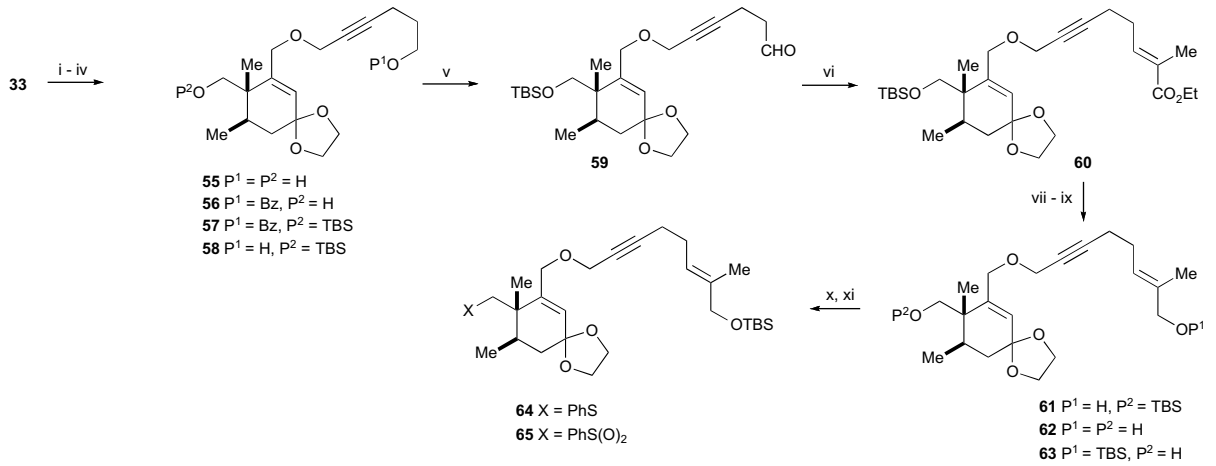
The Wittig rearrangement of ether **25** using *n*-butyllithium gave a mixture of only two of the four possible stereoisomers of the homoallylic alcohol **26** (50%), and oxidation of this mixture gave a mixture of both epimeric ketones **27**, ratio 70:30, showing the two alcohols had the opposite configuration at C(2). Although considerations of steric interactions in the transition structures for Wittig rearrangements of ether **25** indicated the likely preferred relative configurations at C(2) and C(1′) in the rearrangement products **26**,[15] these were not confirmed.[16] Instead [2,3]-Wittig rearrangements of substrates with more developed side-chains were investigated.

The tetrahydropyranyl ether of prop-2-ynol was alkylated using bromide **28** to give alkyne **29**, which was deprotected selectively to give the hexynol **30**. This was alkylated using bromide **21** to give the propargylic ether **31**, which was reduced and the resulting primary alcohol **32** protected as its *tert*-butyldimethylsilyl ether **33**. The Wittig rearrangement was carried out using *n*-butyllithium and gave a good yield, 82%, of a mixture of two inseparable stereoisomers of the propargylic alcohol **34**, ratio 67:33. Oxidation of this mixture under Swern conditions gave a mixture of the two ketones **35a**,**b**, 70% combined yield, which could be separated. As before, considerations of likely steric interactions in the transition structures of the Wittig rearrangements of ether **33** indicated the likely relative configurations at C(2) and (1′), but these were not confirmed although preliminary NMR data did indicate the probable stereochemistry at C(2).[17]

Attempts to hydrolyse the acetal protecting group of the mixture of rearrangement products **34** was accompanied by dehydration and deprotection giving the hydroxydienone **36**, the geometry of the exocyclic double-bond being provisionally assigned by the lack of an NOE enhancement of either of the methylene protons on irradiation of H(1′).[18] Hydrolysis of the major keto-acetal **35b** led to migration of the exocyclic double-bond and gave the conjugated diketone **37**, cf. the formation of enedione **12** (Scheme 4).[10]



Scheme 6. Reagents and conditions: (i) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, rt, 1 min (98%); (ii) TIPSCl, imid., DCM, rt, 46 h (99%); (iii) ^nBuLi, THF, −78 °C, 4 h (**45a**, 29%; **45b**, 19%; **46**, 21%); (iv) TPAP, **45a**, NMO, 4 Å sieves, DCM, rt, 70 h (77%); (v) DMSO, $(COCl)_2$, DCM, **46**, −78 °C, 7 h, Et_3N, 14 h (81%); (vi) MeLi, CuI, Et_2O, 0 °C, 30 min, add **47** or **48**, 30 min [(*Z*)-**49**, 50%; (*E*)-**49**, 49%; (*Z*)-**50**, 35%; (*E*)-**50**, 57%).



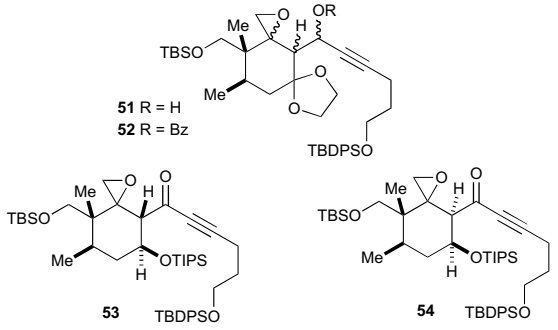
Scheme 7. Reagents and conditions: (i) TBAF, THF, rt, 1 h (94%); (ii) PhCOCl, Et_3N, DCM, 0 °C, 1 h, rt, 16 h (89%); (iii) TBSCl, imid., DCM, rt, 51 h (55%); (iv) NaOH, H_2O, MeOH, rt, 90 min (97%); (v) NMO, 4 Å sieves, DCM, **58**, rt, 30 min, add TPAP, 30 min (70%); (vi) $Ph_3P{=}C(Me)CO_2Et$, DCM, rt, 12 h (80%); (vii) $LiEt_3BH$, THF, 0 °C, 30 min (98%); (viii) TBAF, THF, rt, 5 h (75%); (ix) TBSCl, imid., DCM, rt, 14 h (84%); (x) (a) MsCl, py, rt, 20 h (b) PhSH, NaH, DMF, 60 °C, 26 h (79%); (xi) DMDO, acetone, rt, 30 min (50%).

To avoid the complications due to the dehydration and isomerisation observed during hydrolysis of the acetals **34** and **35b**, it was decided to look at [2,3]-Wittig rearrangements of other derivatives of the ketone **38** prepared by hydrolysis of acetal **33** (92%). Reaction of the ketone with triethylsilyl trifluoromethanesulfonate in the presence of triethylamine gave mainly the cross-conjugated enol ether **39** although a small amount of its separable regioisomer **40** was also formed. However, the [2,3]-Wittig rearrangement of enol ether **39** with an acidic work-up, proceeded with the unwanted regioselectivity via the lithiated ether **42** and gave the allenes **41** as a mixture of epimers (50%), see Scheme 5.

Ketone **38** was therefore reduced under Luche conditions to give alcohol **43** as a single diastereoisomer. The configuration of the alcohol at C(1) was initially assigned on the basis that the incoming hydride would approach the ketone on its less hindered face away from the axial methyl group at C(4), and was subsequently confirmed by later work.[16] Following protection of the alcohol as its tri-isopropylsilyl ether **44**, the Wittig rearrangement was found to give the three diastereoisomeric products **45a**,**b** and **46**. In these cases the configurations of the products at C(2) were assigned on the basis of the diaxial coupling, ca. 10 Hz, observed between H(2) and H(3) for products **45a**,**b**, the analogous coupling for isomer **46** being ca. 4.5 Hz. The configurations of the products at C(1′) were not formally established but could be tentatively assigned on the basis of likely steric interactions in the transition structures for the rearrangements.[19] Oxidation of alcohols **45a** and **b** gave the same ketone **47**, whereas alcohol **46** gave the epimeric ketone **48**.

At this stage, preliminary studies were carried out into the reactions of the conjugated ynones **47** and **48** with lithium dimethylcuprate to see whether this procedure could be used for the preparation of intermediates with a conjugated trisubstituted (*E*)-double-bond corresponding to the C(2′)-C(3′) double-bond present in potential precursors of the phomactins. However, reactions of ketones **47** and **48** with lithium dimethylcuprate gave rise to mixtures of (2′*E*)- and (2′*Z*)-enones **49** and **50** (82–99%). Surprisingly, subsequent isomerisation with iodine gave predominantly the (2′*Z*)-isomer, (2′-*Z*)-**49**, from the (*E*,*Z*)-mixture **49** and the (2′*E*)-isomer, (2′-*E*)-**50**, from the (*E*,*Z*)-mixture **50**. The origin of this dichotomy was not investigated (Scheme 6).

During the course of this work, preliminary studies were carried out on the epoxidation of the exocyclic methylene groups of the Wittig rearrangement products **34** and **45** with a view to subsequent isomerisation to introduce the C(1)–C(15) double-bond and the hydroxyl group at C(20) of the phomactins. However, epoxidation of the mixture of rearrangement products **34** gave a complex mixture of epoxides **51**, and attempts to hydrolyse the acetal, in some cases after preparation of the 1′-benzoate **52**, led to decomposition. Single isomers of the keto-epoxides **53** and **54** were prepared from the alcohols **45a** and **46** followed by oxidation, but attempts to isomerise these under basic conditions to give the corresponding conjugated allylic alcohols either led to returned starting material (triethylamine, LDA) or decomposition (DBU).



Finally, the Wittig precursor **33** was modified to prepare a more advanced intermediate **65**, see Scheme 7. Desilylation followed by selective benzoylation of the more accessible hydroxyl group in the side-chain, protection of the 8-hydroxymethyl group as a *tert*-butyldimethylsilyl ether, and saponification of the ester gave alcohol **58**, which was oxidised to the aldehyde **59**. A Wittig condensation of this aldehyde and reduction of the resulting ester **60** then gave the alcohol **61**, which on deprotection gave diol **62**. Selective protection of the more accessible hydroxyl group provided the alcohol **63**, which was taken through to the sulfone **65** by displacement of the corresponding mesylate followed by oxidation. Sulfone **65** corresponds to the sulfone **13** identified as a possible precursor of the phomactins, see Scheme 2.

3. Conclusions

This work provided results, which have underpinned a synthetic approach to phomactins. The usefulness of [2,3]-Wittig rearrangements for the synthesis of suitably substituted methylenecyclohexanes has been confirmed and stereoselective syntheses of Wittig rearrangement precursors, i.e., the propargylic ethers **44** and **65**, which have the functionality required for incorporation into a phomactin, have been developed. However, more efficient syntheses of Wittig rearrangement precursors with fully developed

side-chains, i.e., sulfones **13** and **65**, and control of the stereoselectivity of the Wittig rearrangements, were required before this work could be incorporated into a stereoselective synthesis of phomactins. Both of these problems have been overcome and this approach has now been used to prepare macrocyclic precursors of the phomactins.[16,18]

4. Experimental section

4.1. General procedures

Melting points were recorded on a Gallenkamp apparatus. Proton NMR spectra were recorded using Varian Unity A300 and 500 spectrometers. Coupling constants are given in hertz and chemical shifts relative to Me_4Si. IR spectra were recorded on a Perkin Elmer 1710FT spectrometer and were run as liquid films, KBr discs or as solutions in chloroform. Low resolution mass spectra were measured on a Micromass Trio 200 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 before use and all non-aqueous reactions were performed under an atmosphere of dry argon or nitrogen.

4.2. Methyl 1,2-dimethylcyclohexa-2,5-diene-1-carboxylate 17

o-Toluic acid (30.19 g, 0.22 mol) was dissolved in tetrahydrofuran (50 cm^3) and liquid ammonia (~600 cm^3), freshly distilled from sodium, at −78 °C. Lithium was added in portions until a blue colour persisted for 15 min. Iodomethane (27.6 cm^3, 0.44 mol) was added dropwise. After 90 min, the cooling bath was removed and the ammonia was allowed to evaporate overnight. The white residue was dissolved in water (400 cm^3) and acidified with concentrated hydrochloric acid. The aqueous solution was extracted with ether (3×400 cm^3). The extracts were washed with brine (2×500 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield 1,2-dimethylcyclohexa-2,5-diene-1-carboxylic acid (33.25 g, 99%) as a yellow solid. An analytical sample was recrystallised from light petroleum to yield a colourless solid. Mp 64–65 °C (light petroleum) (found: M^+, 152.0835; $C_9H_{12}O_2$ requires *M*, 152.0837); ν_{max}/cm^{-1} 3310, 1710, 1256 and 840; δ_H 10.65 (1H, br s, CO_2H), 5.89 (1H, dtd, *J* 10, 3, 1, 5-*H*), 5.64 (2H, m, 3-*H* and 6-*H*), 2.83–2.62 (2H, m, 4-H_2), 1.79 (3H, d, *J* 1, 2-CH_3) and 1.40 (3H, s, 1-CH_3); δ_C 181.0, 132.7, 128.9, 125.2, 121.7, 47.4, 26.7, 23.6 and 19.6; *m*/*z* (EI) 152 (M^+, 5%), 107 (100) and 91 (85).

A solution of the acid (33.25 g, 0.22 mol) in thionyl chloride (160 cm^3, 2.2 mol) was heated under reflux for 1 h. After cooling to ambient temperature, the excess thionyl chloride was removed under reduced pressure. Methanol (200 cm^3) followed by triethylamine (61 cm^3, 0.43 mol) was added slowly at 0 °C. After 30 min, water (100 cm^3) was added and the mixture extracted with ether (3×200 cm^3). The extracts were washed with brine (200 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the *title compound* **17** (35.53 g, 98%) as a yellow liquid. An analytical sample was distilled to yield the ester **17** as a colourless liquid. Bp 58–60 °C (1.5 mmHg); R_f=0.65 (10% ether in light petroleum) (found: M^+, 166.0994; $C_{10}H_{14}O_2$ requires *M*, 166.0994); ν_{max}/cm^{-1} 1732, 1436, 1232, 1102 and 706; δ_H 5.84 (1H, dtd, *J* 10, 3, 1, 5-*H*), 5.60 (2H, m, 3-*H* and 6-*H*), 3.71 (3H, s, 1-CO_2CH_3), 2.73 (2H, m, 4-H_2), 1.72 (3H, d, *J* 1, 2-CH_3) and 1.38 (3H, s, 1-CH_3); δ_C 175.2, 133.2, 129.3, 124.4, 121.1, 52.2, 47.1, 26.7, 23.9 and 19.6; *m*/*z* (CI) 166 (M^+, 9%), 107 (100) and 91 (71).

4.3. Methyl 1,2-dimethyl-4-oxocyclohexa-2,5-diene-1-carboxylate 18

An aqueous solution of *tert*-butyl hydroperoxide (70% w/v, 47 cm^3, 0.345 mol) was added dropwise at 0 °C to a mechanically stirred mixture of diene **17** (19.08 g, 0.115 mol), pyridinium dichromate (129.7 g, 0.345 mol) and Celite® (48 g) in benzene (500 cm^3). After 3.5 h, the mixture was filtered and the solids were washed with ether (5×200 cm^3). The extracts were concentrated to ~200 cm^3 then washed with saturated aqueous sodium metabisulfite (200 cm^3) and brine (200 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether/light petroleum (1:8 to 2:3) gave the *title compound* **18** (14.09 g, 68%) as a pale yellow solid. An analytical sample was crystallised from ether at −78 °C, mp 52.6–53.6 °C (ether); R_f=0.1 (10% ether in light petroleum) (found: C, 66.98; H, 7.01%; M^+, 180.0788; $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71%; *M*, 180.0876); ν_{max}/cm^{-1} 1738, 1667, 1438, 1227, 1104 and 888; δ_H 6.82 (1H, d, *J* 10, 6-*H*), 6.34 (1H, dd, *J* 10, 1, 5-*H*), 6.22 (1H, qn, *J* 1, 3-*H*), 3.73 (3H, s, 1-CO_2CH_3), 2.02 (3H, d, *J* 1, 2-CH_3) and 1.56 (3H, s, 1-CH_3); δ_C 185.6, 170.9, 157.6, 148.7, 128.7, 128.3, 53.1, 51.5, 22.2 and 20.2; *m*/*z* (CI) 198 (M^++18, 14%), 181 (100), 136 (8) and 121 (7); *m*/*z* (EI) 180 (M^+, 35%), 136 (30), 121 (100), 91 (96), 77 (92) and 49 (92).

4.4. Methyl (1*RS*,6*RS*)- and (1*RS*,6*SR*)-1,2,6-trimethyl-4-oxocyclohex-2-ene-1-carboxylates 19 and 20

Methyllithium (1.6 M in ether, 100 cm^3, 0.16 mol) was added to a suspension of copper(I) iodide (17.65 g, 0.093 mol) in ether (180 cm^3) at 0 °C. After 30 min, a solution of dienone **18** (11.72 g, 0.065 mol) in ether (80 cm^3) was added dropwise. After 30 min, a mixture of concentrated aqueous ammonia and saturated aqueous ammonium chloride (1:1, 500 cm^3) was added. The blue aqueous layer was extracted with ether (3×200 cm^3). The extracts were washed with water (250 cm^3), brine (250 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether/light petroleum (1:4) gave the *title compounds* **19** and **20** (9.02 g, 89%; **19**:**20**=23:77). The two diastereoisomers were separated by HPLC to yield first the (1*RS*,6*SR*)-*isomer of the title compound* **20** as a colourless solid, mp 63–65 °C (light petroleum/ether); R_f=0.3 (50% ether in light petroleum) (found: M^+, 196.1093; $C_{11}H_{16}O_3$ requires *M*, 196.1099); ν_{max}/cm^{-1} 2959, 1737, 1667, 1628, 1248, 1192, 1118 and 1013; δ_H 5.93 (1H, s, 3-*H*), 3.79 (3H, s, 1-CO_2CH_3), 2.77 (1H, m, 6-*H*), 2.42 (1H, dd, *J* 17, 4, 5-*H*), 2.23 (1H, dd, *J* 17, 13, 5-*H*′), 1.91 (3H, s, 2-CH_3), 1.32 (3H, s, 1-CH_3) and 0.97 (3H, d, *J* 7, 6-CH_3); δ_C 197.8, 174.8, 162.7, 127.2, 52.4, 52.3, 40.9, 35.9, 20.4, 16.4 and 14.6; *m*/*z* (CI) 214 (M^++18, 100%) and 197 (73); *m*/*z* (EI) 196 (M^+, 17%), 154 (32), 109 (56), 86 (100), 84 (100) and 49 (100). The second fraction was the (1*RS*,6*RS*)-*isomer of the title compound* **19** isolated as a colourless solid, mp 55–56.5 °C (light petroleum/ether); (found M^+, 196.1095; $C_{11}H_{16}O_3$ requires *M*, 196.1099); ν_{max}/cm^{-1} 2954, 1730, 1671, 1629, 1438, 1237, 1167, 1106 and 1015; δ_H 5.99 (1H, s, 3-*H*), 3.75 (3H, s, 1-CO_2CH_3), 2.60 (1H, dd, *J* 17, 13, 5-*H*′), 2.36 (1H, dd, *J* 17, 4, 5-*H*), 2.20 (1H, m, 6-*H*), 1.94 (3H, s, 2-CH_3), 1.46 (3H, s, 1-CH_3) and 1.05 (3H, d, *J* 7, 6-CH_3); δ_C 198.6, 172.5, 160.3, 128.4, 52.1, 51.5, 42.1, 38.2, 21.3, 21.1 and 16.9; *m*/*z* (CI) 214 (M^++18, 100%) and 197 (94); *m*/*z* (EI) 196 (M^+, 31%), 154 (30), 109 (59), 83 (100) and 67 (60).

4.5. Methyl (1*RS*,6*SR*)-2-(bromomethyl)-1,6-dimethyl-4-oxocyclohex-2-ene-1-carboxylate 21

2,2′-Azobis(2-methylpropionitrile) (0.45 g, 2.73 mmol) and *N*-bromosuccinimide (5.35 g, 30.1 mmol) were added to a solution of a mixture of enones **19** and **20** (**19**/**20**=25:75; 5.36 g, 27.3 mmol) in degassed (N_2 flow; 30 min) carbon tetrachloride (125 cm^3). The

mixture was heated under reflux for 24 h, cooled to ambient temperature and filtered. The filtrate was concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:6 to 1:5) gave the *title compound* **21** (3.75 g, 67%) as a yellow liquid, R_f=0.4 (50% ether in light petroleum) (found: M^++H, 275.0285; $C_{11}H_{16}O_3^{79}Br$ requires *M*, 275.0283); ν_{max}/cm^{-1} 2955, 1732, 1676, 1628, 1453, 1251, 1191, 1116 and 1013; δ_H 6.21 (1H, s, 3-*H*), 4.00 (1H, d, *J* 12, 2-C*H*), 3.88 (1H, d, *J* 12, 2-C*H*′), 3.70 (3H, s, 1-CO_2CH_3), 2.67 (1H, m, 6-*H*), 2.38 (1H, dd, *J* 17.5, 4.5, 5-*H*), 2.20 (1H, dd, *J* 17.5, 11.5, 5-*H*′), 1.36 (3H, s, 1-CH_3) and 0.90 (3H, d, *J* 7, 6-CH_3); δ_C 197.6, 174.0, 158.7, 130.2, 52.7, 51.8, 41.3, 36.6, 29.8, 16.3 and 16.0; *m*/*z* (CI) 294 (M^++18, 100%), 292 (M^++18, 92), 277 (M^+, 37), 275 (M^+, 35), 214 (34), 197 (35) and 195 (39).

4.6. Methyl (8*RS*,9*SR*)-7-(bromomethyl)-8,9-dimethyl-1,4-dioxaspiro[4.5]dec-6-ene-8-carboxylate 22

Ethylene glycol (4.45 cm^3, 79.85 mmol) was added to a solution of the ketobromide **21** (5.49 g, 19.96 mmol) and pyridinium toluene-4-sulfonate (0.50 g, 2.00 mmol) in benzene (60 cm^3) and the mixture was heated under reflux in a Dean–Stark apparatus for 14 h. After cooling to ambient temperature, the benzene was removed under reduced pressure below 30 °C. The residue was taken up in ether (100 cm^3) and the ethereal solution was washed with saturated aqueous sodium bicarbonate (50 cm^3), water (50 cm^3), brine (50 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure below 30 °C to yield the acetal **22** (6.05 g, 95%) as a yellow liquid. Chromatography of a sample on silica eluted with ether in light petroleum (8:1) gave the *title compound* **22** as a colourless liquid, R_f=0.2 (20% ether in light petroleum) (found: M^++H, 319.0552; $C_{13}H_{20}O_4^{79}Br$ requires *M*, 319.0545); ν_{max}/cm^{-1} 2995, 1730, 1665, 1453, 1252, 1147, 1084, 1026 and 969; δ_H 5.83 (1H, s, 6-*H*), 4.06 (4H, m, 2-H_2 and 3-H_2), 3.97 (1H, d, *J* 11.5, 7-C*H*), 3.81 (1H, d, *J* 11.5, 7-C*H*′), 3.76 (3H, s, CO_2CH_3), 2.60 (1H, m, 9-*H*), 1.77 (2H, m, 10-H_2), 1.30 (3H, s, 8-CH_3) and 0.93 (3H, d, *J* 7, 9-CH_3); δ_C 175.1, 141.7, 129.8, 105.1, 64.8, 64.5, 52.3, 51.2, 37.0, 34.5, 30.7, 16.3 and 15.1; *m*/*z* (CI) 338 (M^++18, 24%), 336 (26), 321 (89) and 319 (100); *m*/*z* (EI) 319 (M^+, 3%), 239 (100), 197 (37) and 179 (54).

Methyl (8*RS*,9*SR*)-7-[1-bromomethylidene]-8,9-dimethyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (10%) was also isolated from the column (found: M^++H, 319.0545; $C_{13}H_{20}O_4^{79}Br$ requires *M*, 319.0545); ν_{max}/cm^{-1} 2953, 1729, 1455, 1242, 1133, 1102 and 1078; δ_H 5.82 (1H, d, *J* 1.5, 7-C*H*Br), 4.02–3.84 (4H, m, 2-H_2 and 3-H_2), 3.67 (3H, s, 8-CO_2CH_3), 2.83 (1H, dd, *J* 14.5, 2, 6-*H*), 2.49 (1H, m, 9-*H*), 2.31 (1H, d, *J* 14.5, 6-*H*′), 1.64 (2H, m, 10-H_2), 1.19 (3H, s, 8-CH_3) and 0.78 (3H, d, *J* 7, 9-CH_3); δ_C 175.3, 142.8, 108.1, 103.6, 64.6, 64.5, 54.6, 52.1, 39.0, 37.0, 34.8, 16.4 and 16.3; *m*/*z* (CI) 338 (M^++18, 26%), 336 (M^++18, 28), 321 (M^++1, 100), 319 (M^++1, 91) and 239 (79).

4.7. Methyl (8*RS*,9*SR*)-7-(but-2-ynyloxy)methyl-8,9-dimethyl-1,4-dioxaspiro[4.5]dec-6-ene-8-carboxylate 23

But-2-ynol (0.274 cm^3, 3.67 mmol) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 147 mg, 3.67 mmol) in tetrahydrofuran (10 cm^3) followed, after 30 min, by the bromide **22** (390 mg, 1.22 mmol) in tetrahydrofuran (5 cm^3). After 24 h, saturated aqueous ammonium chloride (15 cm^3) was added. The layers were separated and the aqueous layer was extracted with ether (2×15 cm^3). The extracts were washed with water (15 cm^3), brine (15 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:4) gave the *title compound* **23** (201 mg, 53%) as a yellow liquid, R_f=0.15 (20% ether in light petroleum) (found: M^+, 308.1624; $C_{17}H_{24}O_5$ requires *M*, 308.1624); ν_{max}/cm^{-1} 2953, 1730, 1669, 1437, 1252, 1145, 1103 and 1074; δ_H 5.74 (1H, s, 6-*H*), 4.09–3.89 (8H, m, 2-H_2, 3-H_2, 7-CH_2 and 1′-H_2), 3.71 (3H, s, 8-CO_2CH_3), 2.56 (1H, m, 9-*H*), 1.87 (3H, m, 4′-H_3), 1.74 (2H, m, 10-H_2), 1.22 (3H, s, 8-CH_3) and 0.89 (3H, d, *J* 7, 9-CH_3); δ_C 175.5, 142.1, 124.7, 105.4, 82.5, 74.8, 68.9, 64.7, 64.4, 57.8, 52.0, 49.6, 37.4, 34.4, 16.3, 14.6 and 3.5; *m*/*z* (CI) 326 (M^++18, 11%) and 309 (M^++1, 100).

4.8. (8*RS*,9*SR*)-7-(But-2-ynyloxy)methyl-8,9-dimethyl-8-hydroxymethyl-1,4-dioxaspiro[4.5]dec-6-ene 24

A solution of lithium triethylborohydride (1.0 M in tetrahydrofuran, 2.73 cm^3, 2.73 mmol) was added dropwise at 0 °C to a solution of the ester **23** (382 mg, 1.24 mmol) in tetrahydrofuran (4 cm^3). After 1 h, the reaction was poured into water/ether (1:1) and the aqueous layer was extracted with ether (2×6 cm^3). The extracts were washed with brine (10 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (2:1) gave the *title compound* **24** (278 mg, 80%) as a colourless liquid, R_f=0.15 (50% ether in light petroleum) (found: M^++H, 281.1755; $C_{16}H_{25}O_4$ requires *M*, 281.1753); ν_{max}/cm^{-1} 3484, 2961, 2222, 1665, 1357, 1177, 1096, 1069 and 965; δ_H 5.70 (1H, s, 6-*H*), 4.16–3.28 (10H, m, 2-H_2, 3-H_2, 7-CH_2O, 1′-H_2 and 8-CH_2O), 2.72 (1H, dd, *J* 10 and 5, 8-CH_2O*H*), 2.35 (1H, m, 9-*H*), 1.79 (3H, t, *J* 2, 4′-CH_3), 1.66 (2H, m, 10-H_2), 0.86 (3H, d, *J* 7, 9-CH_3) and 0.70 (3H, s, 8-CH_3); δ_C 143.8, 132.4, 105.2, 83.3, 74.2, 70.5, 64.7, 64.6, 64.4, 58.3, 43.1, 37.7, 30.1, 15.4, 14.8 and 3.5; *m*/*z* (CI) 298 (M^++18, 4%), 282 (19), 281 (100) and 181 (69).

4.9. (8*RS*,9*SR*)-8-(*tert*-Butyldimethylsilyloxymethyl)-7-(but-2-ynyloxy)methyl-8,9-dimethyl-1,4-dioxaspiro-[4.5]dec-6-ene 25

Triethylamine (0.17 cm^3, 1.184 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.20 cm^3, 0.868 mmol) was added to a solution of the alcohol **24** (221 mg, 0.789 mmol) in dichloromethane (2.5 cm^3). After 6 h, the reaction was diluted with dichloromethane (5 cm^3), washed with saturated aqueous sodium bicarbonate (5 cm^3) then concentrated under reduced pressure. The residue was taken up in ether (25 cm^3) and the mixture filtered. The filtrate was passed through a plug of anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:20 to 1:4) gave the *title compound* **25** (206 mg, 67%) as a colourless liquid, R_f=0.85 (50% ether in light petroleum) (found: M^+, 394.2527; $C_{22}H_{38}O_4Si$ requires *M*, 394.2539); ν_{max}/cm^{-1} 2954, 1671, 1466, 1360, 1254, 1099, 1074, 840 and 776; δ_H 5.63 (1H, d, *J* 1, 6-*H*), 4.15–3.80 (8H, m, 2-H_2, 3-H_2, 7-CH_2 and 1′-H_2), 3.51 (1H, d, *J* 10.5, 8-C*H*), 3.40 (1H, d, *J* 10.5, 8-C*H*′), 2.20 (1H, m, 9-*H*), 1.81 (3H, t, *J* 2, 4′-H_3), 1.72 (2H, m, 10-H_2), 0.84 (12H, m, SiC(CH_3)$_3$ and 9-CH_3), 0.80 (3H, s, 8-CH_3) and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 144.8, 124.4, 105.6, 82.1, 75.2, 69.4, 65.2, 64.4, 64.2, 57.7, 42.1, 37.9, 30.8, 25.8, 18.1, 15.3, 14.9, 3.5, −3.7 and −5.7; *m*/*z* (EI) 394 (M^+, 3%), 193 (22), 83 (80) and 73 (100).

4.10. (8*RS*,9*SR*)-8-(*tert*-Butyldimethylsilyloxymethyl)-6-(1-hydroxybut-2-ynyl)-8,9-dimethyl-7-methylene-1,4-dioxaspiro[4.5]decane 26

n-Butyllithium (1.6 M in hexanes; 1.06 cm^3, 1.698 mmol) was added dropwise at −78 °C to a solution of the ether **25** (134 mg, 0.340 mmol) in tetrahydrofuran (2.5 cm^3). After 3 h, saturated aqueous ammonium chloride (3 cm^3) was added and the aqueous layer was extracted with ether (2×4 cm^3). The extracts were washed with brine (10 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:3) gave the *title compound* **26** (68 mg, 50%), a 70:30 mixture of diastereoisomers, as a colourless liquid, R_f=0.4 (50% ether in light petroleum) (found:

M^++H, 395.2626; $C_{22}H_{39}O_4Si$ requires *M*, 395.2617); ν_{max}/cm^{-1} 3507, 2954, 2229, 1639, 1467, 1254, 1096, 1034, 840 and 776; δ_H 5.77 (0.7H, s, 7-C*H*), 5.44 (0.3H, s, 7-C*H*), 5.22 (0.3H, s, 7-C*H*′), 5.19 (0.7H, s, 7-C*H*′), 4.95 (0.7H, m, 1′-*H*), 4.81 (0.3H, m, 1′-*H*), 3.98 (4H, m, 2-H_2 and 3-H_2), 3.63 (0.3H, s, 1′-O*H*), 3.54 (0.7H, m, 1′-O*H*), 3.48 (2H, m, 8-CH_2), 2.82 (0.7H, br s, 6-*H*), 2.79 (0.3H, m, 6-*H*), 2.00 (1H, m, 9-*H*), 1.82 (0.9H, d, *J* 2.3, 4′-H_3), 1.79 (2.1H, d, *J* 2.3, 4′-H_3), 1.77–1.49 (2H, m, 10-H_2), 0.95 (2.1H, s, 8-CH_3), 0.86 [12.9H, m, 8-CH_3, 9-CH_3 and SiC(CH_3)$_3$], 0.04 [1.8H, s, Si(CH_3)$_2$], 0.00 [4.2H, s, Si(CH_3)$_2$]; δ_C 146.5, 145.0, 114.4, 112.8, 112.3, 111.0, 80.6, 80.4, 79.7, 79.2, 69.8, 67.6, 65.8, 64.4, 64.3, 64.0, 63.8, 61.3, 61.0, 52.4, 51.2, 45.0, 44.0, 39.7, 38.5, 32.0, 30.7, 25.8, 25.8, 18.7, 18.2, 16.8, 16.0, 15.6, 15.2, 3.8, −5.6 and −5.7; *m*/*z* (CI) 412 (M^++18, 2%), 395 (6), 391 (27), 377 (42), 327 (100) and 283 (24).

4.11. (8*RS*,9*SR*)-8-(*tert*-Butyldimethylsilyloxymethyl)-8,9-dimethyl-7-methylene-6-(1-oxobut-2-ynyl)-1,4-dioxaspiro[4.5]decane 27

Dimethyl sulfoxide (60 μL, 0.85 mmol) in dichloromethane (0.25 cm^3) was added dropwise at −78 °C to oxalyl chloride (30 μL, 0.34 mmol) in dichloromethane (1 cm^3). After 15 min, the alcohols **26** (a 75:25 mixture of diastereoisomers; 67 mg, 0.17 mmol) in dichloromethane (0.5 cm^3) was added. After a further 3 h, triethylamine (118 μL, 0.85 mmol) was added and the reaction was warmed to ambient temperature then stirred for 2 h. Water (3 cm^3) was added and the aqueous layer extracted with dichloromethane (2×5 cm^3). The extracts were washed with water (5 cm^3), brine (5 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:3) gave the *title compound* **27** (43 mg, 65%), a 70:30 mixture of diastereoisomers, as a pale yellow liquid, R_f=0.45 (50% ether in light petroleum) (found: M^++H, 393.2455; $C_{22}H_{36}O_4Si$ requires *M*, 393.2461); ν_{max}/cm^{-1} 2955, 2218, 1680, 1468, 1254, 1099, 838 and 776; δ_H 5.20 (0.7H, s, 7-C*H*), 5.14 (0.3H, s, 7-C*H*), 5.10 (0.7H, s, 7-C*H*′), 4.87 (0.3H, d, *J* 1.5, 7-C*H*′), 3.86 (4H, m, 2-H_2 and 3-H_2), 3.57 (3H, m, 8-CH_2 and 6-*H*), 1.98 (1H, m, 9-*H*), 1.96 (0.9H, s, 4′-H_3), 1.95 (2.1H, s, 4′-H_3), 1.61 (2H, m, 10-H_2), 0.83 [15H, m, SiC(CH_3)$_3$, 8-CH_3 and 9-CH_3] and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 185.8, 147.4, 146.4, 115.9, 111.3, 109.3, 108.7, 90.0, 80.7, 67.6, 67.0, 65.8, 65.2, 65.0, 64.8, 63.9, 62.1, 44.4, 44.1, 40.6, 38.0, 32.3, 31.5, 25.8, 25.8, 18.2, 17.5, 16.4, 15.8, 4.2, 4.1, −5.6 and −5.7; *m*/*z* (CI) 393 (M^+ +1, 100%) and 168 (17).

4.12. Methyl (8*RS*,9*SR*)-7-[(6-*tert*-butyldiphenylsilyloxyhex-2-yn-1-yloxy)methyl]-8,9-dimethyl-1,4-dioxaspiro[4.5]dec-6-ene-8-carboxylate 31

Alcohol **30** (14.27 g, 40.54 mmol) in tetrahydrofuran (100 cm^3) was added via a cannula to a suspension of sodium hydride (60% in mineral oil, 1.62 g, 40.54 mmol) in tetrahydrofuran (75 cm^3) and the mixture was heated under reflux for 1 h. After cooling to 0 °C, a solution of bromide **21** (6.05 g, 18.96 mmol) in tetrahydrofuran (50 cm^3) was added. The mixture was heated under reflux for 5 h, cooled to ambient temperature and saturated aqueous ammonium chloride (100 cm^3) was added. The aqueous layer was extracted with ether (2×100 cm^3) and the extracts were washed with water (100 cm^3), brine (100 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted using ether in light petroleum (1:6 to 1:3) gave the *title compound* **31** (5.61 g, 50%) as a pale yellow liquid, R_f=0.2 (20% ether in light petroleum) (found: M^++H, 591.3136; $C_{35}H_{47}O_6Si$ requires *M*, 591.3142); ν_{max}/cm^{-1} 2951, 1731, 1667, 1430, 1252, 1143, 1105, 1075 and 705; δ_H 7.70 (4H, m, Ar–*H*), 7.44 (6H, m, Ar–*H*), 5.74 (1H, s, 6-*H*), 4.07 (6H, m, 2-H_2, 3-H_2 and 1′-H_2), 3.95 (2H, m, 7-CH_2), 3.76 (2H, t, *J* 6, 6′-H_2), 3.70 (3H, s, 8-CO_2CH_3), 2.59 (1H, m, 9-*H*), 2.40 (2H, tt, *J* 7.5, 2, 4′-H_2), 1.76 (4H, m, 10-H_2 and 5′-H_2), 1.22 (3H, s, 8-CH_3), 1.08 [9H, s, SiC(CH_3)$_3$] and 0.90 (3H, d, *J* 7, 9-CH_3); δ_C 175.5, 142.1, 135.5, 133.7, 129.5, 127.6, 124.8, 105.4, 86.7, 75.7, 68.9, 65.8, 64.7, 64.4, 62.3, 57.8, 52.0, 49.6, 37.4, 34.4, 31.5, 26.8, 19.2, 16.3, 15.3 and 14.6; *m*/*z* (CI) 608 (M^++18, 7%), 591 (29) and 391 (100).

4.13. (8*RS*,9*SR*)-7-[(6-*tert*-Butyldiphenylsilyloxyhex-2-yn-1-yloxy)methyl]-8,9-dimethyl-8-hydroxymethyl-1,4-dioxaspiro[4.5]dec-6-ene 32

Lithium triethylborohydride (1.0 M in tetrahydrofuran, 10.59 cm^3, 10.59 mmol) was added dropwise to the ester **31** (2.50 g, 4.24 mmol) in tetrahydrofuran (20 cm^3) at 0 °C. After 30 min, the reaction was poured into ether/water (1:1; 30 cm^3). Water (10 cm^3) was added and the aqueous layer was extracted with ether (2×20 cm^3). The extracts were washed with water (15 cm^3), brine (2×20 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:3 to 1:2) gave the *title compound* **32** (2.17 g, 91%) as a colourless liquid, R_f=0.1 (50% ether in light petroleum) (found: M^+, 562.3119; $C_{34}H_{46}O_5Si$ requires *M*, 562.3114); ν_{max}/cm^{-1} 3434, 3069, 2957, 1664, 1467, 1428, 1107, 1068, 966, 823 and 705; δ_H 7.70 (4H, m, Ar–*H*), 7.44 (6H, m, Ar–*H*), 5.79 (1H, s, 6-*H*), 4.22–3.90 (8H, m, 2-H_2, 3-H_2, 7-CH_2 and 1′-H_2), 3.77 (2H, t, *J* 6, 6′-H_2), 3.62 (1H, dd, *J* 11, 5, 8-C*H*), 3.43 (1H, dd, *J* 11, 10.5, 8-C*H*′), 2.80 (1H, dd, *J* 10.5, 4.5, O*H*), 2.42 (3H, m, 4′-H_2 and 9-*H*), 1.80 (4H, m, 10-H_2 and 5′-H_2), 1.09 [9H, s, SiC(CH_3)$_3$], 0.96 (3H, d, *J* 7, 9-CH_3) and 0.78 (3H, s, 8-CH_3); δ_C 143.8, 135.5, 133.7, 132.6, 129.5, 127.7, 127.6, 105.2, 87.5, 75.1, 70.4, 64.7, 64.7, 64.4, 62.3, 58.3, 43.2, 37.7, 31.5, 30.1, 26.8, 19.2, 15.4, 15.2 and 14.8; *m*/*z* (CI) 563 (M^++1, 100%), 211 (64) and 181 (83); *m*/*z* (EI) 562 (M^+, 8%), 532 (30), 505 (34) and 199 (100).

4.14. (8*RS*,9*SR*)-8-(*tert*-Butyldimethylsilyloxy)methyl-7-[(6-*tert*-butyldiphenylsilyloxyhex-2-yn-1-yloxy)methyl]-8,9-dimethyl-1,4-dioxaspiro[4.5]dec-6-ene 33

Imidazole (61 mg, 0.89 mmol) followed by *tert*-butyldimethylsilyl chloride (84 mg, 0.556 mmol) was added to the alcohol **33** (250 mg, 0.445 mmol) in dichloromethane (1.5 cm^3). After 44 h, aqueous saturated ammonium chloride solution (3 cm^3) was added and the mixture extracted with ether (3×5 cm^3). The extracts were washed with water (10 cm^3), brine (10 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:4) gave the *title compound* **33** (242 mg, 80%) as a colourless liquid, R_f=0.85 (50% ether in light petroleum) (found: M^++H, 677.4052; $C_{40}H_{61}O_5Si_2$ requires *M*, 677.4057); ν_{max}/cm^{-1} 2954, 1468, 1254, 1104, 1073, 839 and 704; δ_H 7.64 (4H, m, Ar–*H*), 7.37 (6H, m, Ar–*H*), 5.64 (1H, d, *J* 1, 6-*H*), 4.15–3.82 (8H, m, 2-H_2, 3-H_2, 7-CH_2 and 1′-H_2), 3.69 (2H, t, *J* 6, 6′-H_2), 3.51 and 3.40 (each 1H, d, *J* 10.5, 8-C*H*), 2.34 (2H, tt, *J* 7.5, 2, 4′-H_2), 2.22 (1H, m, 9-*H*), 1.74 (4H, m, 10-H_2 and 5′-H_2), 1.02 [9H, s, SiC(CH_3)$_3$], 0.84 [12H, m, SiC(CH_3)$_3$ and 9-CH_3], 0.80 (3H, s, 8-CH_3) and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 144.7, 135.5, 133.7, 129.5, 127.6, 124.5, 105.6, 86.3, 76.1, 69.4, 65.2, 64.4, 64.2, 62.4, 57.6, 42.2, 38.0, 31.5, 30.8, 26.8, 25.8, 19.2, 18.1, 15.4, 14.9 and −5.6; *m*/*z* (CI) 677 (M^++1, 63%), 391 (62), 341 (31), 168 (100) and 157 (75).

4.15. (8*RS*,9*SR*)-8-*tert*-Butyldimethylsilyloxymethyl-6-(1-hydroxy-6-*tert*-butyldiphenylsilyloxyhex-2-yn-1-yl)-8,9-dimethyl-7-methylene-1,4-dioxaspiro[4.5]decane 34

n-Butyllithium (1.75 M in hexanes, 7.37 cm^3, 12.9 mmol) was added dropwise at −78 °C to ether **33** (1.74 g, 2.58 mmol) in tetrahydrofuran (14 cm^3). After 3 h, saturated aqueous ammonium

chloride (25 cm^3) was added and the aqueous layer extracted with ether (3×25 cm^3). The extracts were washed with water (25 cm^3), brine (25 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:4) gave the *title compounds* **34** (1.435 g, 82%), a 67:33 mixture of diastereoisomers, as a colourless liquid, R_f=0.8 (50% ether in light petroleum) (found: M^++H, 677.4059; $C_{40}H_{61}O_5Si_2$ requires *M*, 677.4057); ν_{max}/cm^{-1} 3510, 2953, 1469, 1254, 1104, 839 and 704; δ_H 7.65 (4H, m, Ar–*H*), 7.37 (6H, m, Ar–*H*), 5.74 (0.67H, d, *J* 1.5, 7-C*H*), 5.47 (0.33H, s, 7-C*H*), 5.20 (0.33H, s, 7-C*H*′), 5.17 (0.67H, s, 7-C*H*′), 4.95 (0.67H, m, 1′-*H*), 4.87 (0.33H, m, 1′-*H*), 3.97 (4H, m, 2-H_2 and 3-H_2), 3.72 (0.66H, m, 6′-H_2), 3.70 (1.34H, t, *J* 6, 6′-H_2), 3.48 (3H, m, 8-CH_2 and 1′-O*H*), 2.83 (0.67H, t, *J* 1.5, 6-*H*), 2.76 (0.33H, d, *J* 3.5, 6-*H*), 2.33 (2H, td, *J* 7.5, 2, 4′-H_2), 2.02 (0.67H, m, 9-*H*), 1.90 (0.33H, m, 9-*H*), 1.66 (4H, m, 10-H_2 and 5′-H_2), 1.03 [9H, s, SiC(CH_3)$_3$], 0.96 (2.01H, s, 8-CH_3), 0.86 [12.99H, m, SiC(CH_3)$_3$, 8-CH_3 and 9-CH_3], 0.04 [1.98H, s, Si(CH_3)$_2$] and 0.00 [4.02H, s, Si(CH_3)$_2$]; δ_C 146.2, 145.0, 135.5, 133.8, 129.5, 127.5, 114.4, 112.8, 112.3, 111.0, 84.7, 84.3, 80.6, 80.2, 69.8, 67.5, 65.8, 64.4, 64.3, 64.0, 63.8, 62.6, 62.5, 61.3, 61.1, 52.3, 51.4, 45.0, 44.0, 39.7, 38.5, 31.9, 31.7, 30.8, 26.8, 25.8, 19.2, 18.7, 18.2, 18.2, 16.8, 16.1, 15.6, 15.6, 15.5, 15.2, −5.6 and −5.7; *m*/*z* (CI) 694 (M^++18, 2%), 677 (3), 582 (11), 565 (10), 368 (33) and 327 (100).

4.16. (8*RS*,9*SR*)-8-*tert*-Butyldimethylsilyloxymethyl-6-(6-*tert*-butyldiphenylsilyloxy-1-oxohex-2-yn-1-yl)-8,9-dimethyl-7-methylene-1,4-dioxaspiro[4.5]decane 35a,b

Dimethyl sulfoxide (72 μL, 1.02 mmol) in dichloromethane (0.25 cm^3) was added dropwise to oxalyl chloride (36 μL, 0.408 mmol) in dichloromethane (0.5 cm^3) at −78 °C. After 15 min, the alcohols **34** (138 mg, 0.204 mmol) in dichloromethane (1 cm^3) were added. After 3 h, triethylamine (142 μL, 1.02 mmol) was added and the reaction was allowed to warm to ambient temperature. After 9 h, water (3 cm^3) was added and the aqueous layer extracted with ether (2×5 cm^3). The extracts were washed with water (5 cm^3), brine (5 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:6) gave *minor diastereoisomer of the title compound* **35a** (39 mg, 28%) as a colourless liquid, R_f=0.35 (20% ether in light petroleum) (found: M^++H, 675.3913; $C_{40}H_{59}O_5Si_2$ requires *M*, 675.3901); ν_{max}/cm^{-1} 2955, 2213, 1682, 1468, 1428, 1254, 1184, 1104, 837 and 704; δ_H 7.61 (4H, m, Ar–*H*), 7.36 (6H, m, Ar–*H*), 5.13 and 4.87 (each 1H, s, 7-C*H*), 4.08 (1H, m, 2-*H*), 3.88 (3H, m, 2-*H*′ and 3-H_2), 3.74 (1H, s, 6-*H*), 3.68 (2H, t, *J* 5.5, 6′-H_2), 3.65 and 3.55 (each 1H, d, *J* 10.5, 8-C*H*), 2.48 (2H, t, *J* 7, 4′-H_2), 1.94 (1H, m, 9-*H*), 1.81–1.43 (4H, m, 10-H_2 and 5′-H_2), 1.00 [9H, s, SiC(CH_3)$_3$], 0.88 (3H, s, 8-CH_3), 0.83 [12H, m, SiC(CH_3)$_3$ and 9-CH_3] and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 185.7, 147.2, 135.4, 133.5, 129.6, 127.6, 111.4, 109.2, 93.2, 82.5, 66.9, 65.2, 64.9, 62.2, 62.1, 44.1, 40.6, 32.3, 30.7, 26.8, 25.8, 19.2, 18.2, 16.4, 15.7, 15.7 and −5.6; *m*/*z* (CI) 675.5 (M^++1, 84%), 327.2 (66), 283.1 (100) and 256.1 (69). The second fraction corresponded to the *major diastereoisomer of the title compound* **35b** (58 mg, 42%) as a colourless liquid, R_f=0.3 (20% ether in light petroleum) (found: M^++H, 675.3908; $C_{40}H_{59}O_5Si_2$ requires *M*, 675.3901); ν_{max}/cm^{-1} 2955, 2211, 1680, 1468, 1428, 1253, 1104, 836 and 704; δ_H 7.61 (4H, m, Ar–*H*), 7.36 (6H, m, Ar–*H*), 5.19 and 5.07 (each 1H, s, 7-C*H*), 3.88 (4H, m, 2-H_2 and 3-H_2), 3.68 (2H, t, *J* 6, 6′-H_2), 3.59 and 3.49 (each 1H, d, *J* 10, 8-C*H*), 3.49 (1H, br s, 6-*H*), 2.47 (2H, t, *J* 7, 4′-H_2), 2.02 (2H, m, 10-*H* and 9-*H*), 1.75 (2H, m, 5′-H_2), 1.56 (1H, m, 10-*H*′), 1.00 [9H, s, SiC(CH_3)$_3$], 0.84 [12H, m, SiC(CH_3)$_3$ and 9-CH_3], 0.77 (3H, s, 8-CH_3) and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 185.8, 146.5, 135.4, 133.5, 129.6, 127.7, 116.1, 108.5, 94.0, 81.2, 67.4, 66.3, 65.0, 63.8, 62.1, 44.4, 37.8, 31.5, 30.6, 26.8, 25.8, 19.2, 18.2, 17.4, 15.7, 15.6, −5.6 and −5.6; *m*/*z* (CI) 675.5 (M^++1, 100%), 327.2 (61), 283.2 (38), 168.1 (70) and 88.1 (87).

4.17. (4*RS*,5*SR*)-2-[(*E*)-(6-*tert*-Butyldiphenylsilyloxy-hex-2-ynylidene)]-4-hydroxymethyl-4,5-dimethyl-3-methylenecyclohexanone 36

Aqueous hydrogen chloride (10%, 100 μL) was added to the acetals **34** (125 mg, 0.186 mmol) in acetone/water (10:1; 4.4 cm^3). After 15 h, the reaction was diluted with ether (10 cm^3) and saturated aqueous sodium bicarbonate (10 cm^3) was added. The aqueous layer was extracted with ether (2×10 cm^3) and the extracts were washed with brine (2×10 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:1) gave the *title compound* **36** (43 mg, 46%) as a yellow liquid, R_f=0.4 (50% ether in light petroleum) (found: M^+, 500.2749; $C_{32}H_{40}O_3Si$ requires *M*, 500.2746); ν_{max}/cm^{-1} 3464, 3069, 2956, 2205, 1684, 1611, 1564, 1468, 1427, 1386, 1108, 965, 908, 822, 738 and 704; δ_H 7.59 (4H, m, Ar–*H*), 7.33 (6H, m, Ar–*H*), 6.44 (1H, t, *J* 2.5, 1′-*H*), 5.88 and 5.25 (each 1H, s, 3-C*H*), 3.67 (2H, m, 6′-H_2), 3.48 (2H, m, 4-CH_2), 2.51 (2H, m, 4′-H_2), 2.25 (1H, m, 6-*H*), 2.08 (1H, m, 5-*H*), 1.73 (1H, m, 6-*H*′), 1.71 (2H, m, 5′-H_2), 1.02 (3H, s, 4-CH_3), 1.97 [9H, s, SiC(CH_3)$_3$] and 0.87 (3H, d, *J* 7, 5-CH_3); δ_C 135.5, 135.5, 129.6, 129.5, 127.6, 127.5, 117.4, 116.9, 68.8, 62.2, 44.8, 43.4, 31.6, 31.2, 26.8, 19.2, 18.4, 16.8 and 16.1; *m*/*z* (CI) 518 (M^++18, 100%), 501 (M^++1, 98) and 423 (30).

4.18. (4*RS*,5*SR*)-4-*tert*-Butyldimethylsilyloxymethyl-2-(6-*tert*-butyldiphenylsilyloxy-1-oxohex-2-ynyl)-3,4,5-trimethylcyclohex-2-enone 37

Toluene-4-sulfonic acid (ca. 1 mg) was added to the acetal **35b** (9 mg, 13 mmol) in acetone (1 cm^3) and water (100 μL). After 25 h, saturated aqueous sodium bicarbonate (1 cm^3) was added and the mixture extracted with ether (3×2 cm^3). The extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:3) gave the *title compound* **37** (4 mg, 44%) as a colourless liquid, R_f=0.65 (50% ether in light petroleum) (found: M^+, 630.3545; $C_{38}H_{54}O_4Si_2$ requires *M*, 630.3560); ν_{max}/cm^{-1} 3070, 2930, 2209, 1675, 1615, 1467, 1254, 1106, 839 and 704; δ_H 7.64 (4H, Ar–*H*), 7.40 (6H, m, Ar–*H*), 3.70 (2H, t, *J* 6, 6′-H_2), 3.66 and 3.56 (each 1H, d, *J* 10.5, 4-C*H*), 2.52 (3H, m, 6-*H* and 4′-H_2), 2.30 (1H, dd, *J* 17.5, 12.5, 6-*H*′), 1.95 (3H, s, 3-CH_3), 1.80 (2H, m, 5′-H_2), 1.04 [9H, s, SiC(CH_3)$_3$], 0.96 (3H, d, *J* 6.5, 5-CH_3), 0.92 (3H, s, 4-CH_3), 0.86 [9H, s, SiC(CH_3)$_3$] and 0.04 [6H, s, Si(CH_3)$_2$]; δ_C 195.6, 182.3, 164.4, 140.0, 135.5, 133.6, 129.6, 127.7, 96.4, 81.9, 65.3, 62.2, 44.9, 41.8, 31.9, 30.7, 29.7, 26.8, 25.8, 19.2, 16.3, 16.0, 15.6, 14.7 and −5.7; *m*/*z* (CI) 631 (M^++1, 88%), 553 (6), 391 (22), 283 (32), 94 (64) and 58 (100).

4.19. (4*RS*,5*SR*)-4-*tert*-Butyldimethylsilyloxymethyl-3-(6-*tert*-butyldiphenylsilyloxyhex-2-ynyloxy)methyl-4,5-dimethylcyclohex-2-enone 38

Pyridinium toluene-4-sulfonate (106 mg, 0.42 mmol) was added to the acetal **33** (946 mg, 1.40 mmol) in acetone (20 cm^3) and water (0.4 cm^3). The reaction was heated under reflux for 3 h, then cooled to ambient temperature and concentrated under reduced pressure. The residue was taken up in ether (25 cm^3) and washed with saturated aqueous sodium bicarbonate (10 cm^3), water (10 cm^3) and brine (10 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the *title compound* **38** (815 mg, 92%) as a colourless liquid, R_f=0.75 (50% ether in light petroleum) (found: M^++H, 633.3782; $C_{38}H_{57}O_4Si_2$ requires *M*, 633.3795); ν_{max}/cm^{-1} 2932, 1671, 1626, 1467, 1255, 1107, 840, 778 and 705; δ_H 7.62 (4H, m, Ar–*H*), 7.35 (6H, m, Ar–*H*), 6.16 (1H, s, 2-*H*), 4.23 (2H, d, *J* 1.5, 1′-H_2), 4.08 (2H, d, *J* 2, 3-CH_2), 3.68 (2H, t, *J* 6, 6′-H_2), 3.55 and 3.50 (each 1H, d, *J* 11, 4-C*H*), 2.33 (5H, m, 5-*H*, 6-H_2 and 4′-H_2), 1.73 (2H, m, 5′-H_2), 1.01 [9H, s, SiC(CH_3)$_3$], 0.90 (6H, m, 8-CH_3

and 9-CH_3), 0.83 [9H, s, SiC(CH_3)$_3$], 0.02 (3H, s, SiCH_3) and 0.00 (3H, s, SiCH_3); δ_C 199.0, 165.2, 135.5, 133.7, 129.5, 127.6, 125.5, 87.0, 75.5, 68.2, 65.2, 62.3, 58.4, 43.2, 41.9, 32.9, 31.5, 26.8, 25.7, 19.2, 18.0, 15.4, 15.3, 15.1 and −5.7; *m*/*z* (CI) 650 (M^++18, 9%), 633 (13), 555 (57), 391 (80) and 168 (100).

4.20. (5*RS*,6*SR*)-5-*tert*-Butyldimethylsilyloxymethyl-4-(6-*tert*-butyldiphenylsilyloxyhex-2-ynyloxy)methyl-5,6-dimethyl-2-triethylsilyloxycyclohexa-1,3-diene 39 and (4*RS*,5*SR*)-4-*tert*-butyldimethylsilyloxymethyl-3-(6-*tert*-butyldiphenylsilyloxyhex-2-ynyloxy)methylidene-4,5-dimethyl-1-triethylsilyloxycyclohexa-1,3-diene 40

The enone **38** (241 mg, 0.381 mmol) in dichloromethane (2 cm^3) was added dropwise to a solution of triethylsilyl trifluoromethanesulfonate (86 μL, 0.381 mmol) and triethylamine (106 μL, 0.761 mmol) in dichloromethane (1 cm^3) and, after 21 h, the reaction was diluted with ether (25 cm^3). The solution was washed with saturated aqueous sodium hydrogen carbonate (10 cm^3), water (10 cm^3) and brine (10 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with light petroleum containing ether (2%) and triethylamine (1%) gave the *title compound* **40** (27 mg, 10%) as a colourless liquid, R_f=0.6 (10% ether in light petroleum) (found: M^+, 746.4553; $C_{44}H_{70}O_4Si_3$ requires *M*, 746.4582); ν_{max}/cm^{-1} 2955, 1618, 1471, 1426, 1361, 1190, 1105, 1068, 1010, 835, 779 and 701; δ_H 7.66 (4H, m, Ar–*H*), 7.37 (6H, m, Ar–*H*), 5.82 (1H, s, 3-C*H*), 5.74 (1H, d, *J* 1.5, 2-*H*), 4.30 (2H, t, *J* 2, 1′-H_2), 3.73 (2H, t, *J* 6, 6′-H_2), 3.58 and 3.17 (each 1H, d, *J* 9.5, 4-C*H*), 2.46 (1H, m, 6-*H*), 2.38 (2H, m, 4′-H_2), 2.01 (1H, m, 5-*H*), 1.77 (3H, m, 5′-H_2 and 6-*H*′), 1.05 [9H, s, SiC(CH_3)$_3$], 0.97 [12H, m, Si(CH$_2$CH_3)$_3$ and 1-CH_3], 0.88 [9H, s, SiC(CH_3)$_3$], 0.85 (3H, d, *J* 7, 6-CH_3), 0.69 [6H, q, *J* 8, Si(CH_2CH$_3$)$_3$], 0.01 (3H, s, SiCH_3) and 0.00 (3H, s, SiCH_3); δ_C 149.6, 140.4, 135.9, 134.2, 130.0, 128.0, 119.5, 101.8, 87.4, 76.1, 70.3, 62.8, 60.0, 40.9, 35.9, 32.9, 32.0, 27.2, 26.3, 20.2, 19.6, 18.6, 16.3, 15.9, 7.1, 5.4, −5.6 and −5.7; *m*/*z* (ES^+) 764.6 (M^++18, 5%), 747.6 (5) and 164.1 (100). The second fraction was the *title compound* **39** (195 mg, 69%) as a colourless liquid, R_f=0.55 (10% ether in light petroleum) (found: M^+, 746.4572; $C_{44}H_{70}O_4Si_3$ requires *M*, 746.4582); ν_{max}/cm^{-1} 3037, 2954, 1471, 1428, 1360, 1248, 1196, 1104, 1006, 969, 836, 778, 739 and 702; δ_H 7.64 (4H, m, Ar–*H*), 7.37 (6H, m, Ar–*H*), 5.73 (1H, d, *J* 2, 3-*H*), 4.73 (1H, dd, *J* 5.5, 2.2, 1-*H*), 4.06 (2H, t, *J* 2, 1′-H_2), 4.03 (2H, s, 4-CH_2), 3.72 (2H, t, *J* 6, 6′-H_2), 3.49 and 3.43 (each 1H, d, *J* 9.5, 5-C*H*), 2.44 (1H, m, 6-*H*), 2.36 (2H, m, 4′-H_2), 1.75 (2H, m, 5′-H_2), 1.03 [9H, s, SiC(CH_3)$_3$], 0.96 [12H, m, Si(CH$_2$CH_3)$_3$ and 5-CH_3], 0.86 [12H, m, SiC(CH_3)$_3$ and 6-CH_3], 0.64 [6H, q, *J* 8, Si(CH_2CH$_3$)$_3$], 0.00 (3H, s, SiCH_3) and −0.01 (3H, s, SiCH_3); δ_C 146.5, 140.4, 135.9, 134.2, 130.0, 128.0, 124.6, 109.2, 86.8, 76.6, 67.2, 57.8, 40.6, 33.9, 32.0, 27.2, 26.3, 19.6, 18.7, 16.3, 15.8, 14.5, 7.1, 5.1 and −5.7; *m*/*z* (ES^+) 764.6 (M^++18, 8%), 747.6 (17), 316.2 (9) and 162.0 (100).

4.21. (4*RS*,5*SR*)-4-*tert*-Butyldimethylsilyloxymethyl-3-(5-*tert*-butyldiphenylsilyloxy-1-hydroxy-2-vinylidene-pent-1-yl)-4,5-dimethylcyclohex-2-enones 41a, b

n-Butyllithium (1.6 M in hexanes, 0.81 cm^3, 1.30 mmol) was added dropwise to the enol ether **39** (194 mg, 0.26 mmol) in tetrahydrofuran (2.5 cm^3) at −78 °C. After 2 h, aqueous hydrochloric acid (1 N; 3 cm^3) was added and the mixture was allowed to warm to ambient temperature. After stirring for 1 h, the mixture was diluted with water (10 cm^3) and extracted with ether (3×10 cm^3). The extracts were washed with brine (10 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:2) gave the *title compound* **41a** (41 mg, 25%) as a yellow liquid, R_f 0.45 (50% ether in light petroleum) (found: M^+, 632.3678; $C_{38}H_{56}O_4Si_2$ requires *M*, 632.3717); ν_{max}/cm^{-1} 3399, 3072, 2931, 1952, 1660, 1471, 1428, 1252, 1098, 1007, 836, 777 and 702; δ_H 7.56 (4H, m, Ar–*H*), 7.32 (6H, m, Ar–*H*), 6.24 (1H, s, 2-*H*), 4.82 (3H, m, 1′-*H* and 2′-C=CH_2), 3.73 (1H, d, *J* 10.5, 4-C*H*), 3.59 (3H, m, 4-C*H*′ and 5′-H_2), 3.03 (1H, br s, O*H*), 2.38 (2H, m, 3′-H_2), 2.19 (1H, m, 6-*H*), 1.87 (2H, m, 5-*H* and 6-*H*′), 1.62 (2H, m, 4′-H_2), 0.97 [9H, s, SiC(CH_3)$_3$], 0.87 (3H, d, *J* 6.5, 5-CH_3), 0.85 (3H, s, 4-CH_3), 0.80 [9H, s, SiC(CH_3)$_3$], 0.01 (3H, s, SiCH_3) and 0.00 (3H, s, SiCH_3); δ_C 206.3, 199.7, 135.7, 133.8, 129.8, 128.1, 127.8, 105.2, 77.5, 70.7, 66.6, 62.7, 44.2, 42.0, 33.7, 30.1, 27.1, 25.9, 23.3, 20.4, 19.4, 15.7, 15.5 and −5.7; *m*/*z* (ES^+) 650.4 (M^++18, 100%), 633.4 (64), 615.4 (68), 555.3 (39) and 283.2 (5). The second fraction was the *title compound* **41b** (41 mg, 25%) as a yellow liquid, R_f=0.25 (50% ether in light petroleum) (found: M^+, 632.3723; $C_{38}H_{56}O_4Si_2$ requires *M*, 632.3717); ν_{max}/cm^{-1} 3392, 3052, 2928, 1952, 1662, 1471, 1428, 1389, 1251, 1105, 836, 777 and 703; δ_H 7.59 (4H, m, Ar–*H*), 7.35 (6H, m, Ar–*H*), 6.08 (1H, s, 2-*H*), 4.91 (2H, m, 2′-C=CH_2), 4.79 (1H, m, 1′-*H*), 3.82 (1H, d, *J* 10.5, 4-C*H*), 3.64 (2H, m, 5′-H_2), 3.54 (1H, d, *J* 10.5, 4-C*H*′), 2.44 (2H, m, 3′-H_2), 2.20 (1H, m, 6-*H*), 1.88 (2H, m, 5-*H* and 6-*H*′), 1.66 (2H, m, 4′-H_2), 0.99 [9H, s, SiC(CH_3)$_3$], 0.90 (3H, d, *J* 6.5, 5-CH_3), 0.84 (3H, s, 4-CH_3), 0.82 [9H, s, SiC(CH_3)$_3$] and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 203.1, 198.2, 164.6, 133.9, 132.2, 127.8, 126.3, 125.9, 104.8, 79.0, 70.6, 65.0, 61.6, 42.6, 40.3, 32.2, 28.8, 25.2, 24.1, 22.5, 17.5, 16.5, 15.4, 13.8, −5.6 and −5.7; *m*/*z* (ES^+) 650.4 (M^++18, 100%), 633.4 (29), 615.3 (57), 555.3 (28) and 317.2 (4).

4.22. (1*RS*,4*RS*,5*SR*)-4-(*tert*-Butyldimethylsilyloxymethyl)-3-[(6-*tert*-butyldiphenylsilyloxyhex-2-ynyloxy)-methyl]-4,5-dimethylcyclohex-2-en-1-ol 43

Sodium borohydride (0.35 g, 9.15 mmol) was added in portions to the enone **38** (5.78 g, 9.15 mmol) and cerium(III) chloride heptahydrate (3.41 g, 9.15 mmol) in methanol (50 cm^3). After 1 min, aqueous hydrogen chloride (10%) was added until effervescence ceased. Water (100 cm^3) was then added and the mixture was extracted with ether (3×100 cm^3). The extracts were washed with water (100 cm^3) and brine (100 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:2) gave the *title compound* **43** (5.7 g, 98%) as a colourless liquid, R_f=0.5 (50% ether in light petroleum) (found: M^++NH_4, 652.4217; $C_{38}H_{62}NO_4Si_2$ requires *M*, 652.4217); ν_{max}/cm^{-1} 3340, 3071, 2930, 1468, 1254, 1106, 843, 776 and 704; δ_H 7.65 (4H, m, Ar–*H*), 7.38 (6H, m, Ar–*H*), 5.77 (1H, s, 2-*H*), 4.22 (1H, m, 1-*H*), 4.11 (1H, dt, *J* 13, 1.5, 3-C*H*), 4.08 (2H, m, 1′-H_2), 3.96 (1H, dt, *J* 13, 1.5, 3-C*H*′), 3.71 (2H, t, *J* 6, 6′-H_2), 3.49 and 3.38 (each 1H, d, *J* 10, 4-C*H*), 2.36 (2H, tt, *J* 7, 2, 4′-H_2), 2.01 (1H, m, 5-*H*), 1.82 (1H, m, 6-*H*), 1.75 (2H, pent, *J* 7, 5′-H_2), 1.41 (1H, m, 6-*H*′), 1.03 [9H, s, SiC(CH_3)$_3$], 0.83 [15H, m, Si(CH_3)$_3$, 4-CH_3 and 5-CH_3] and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 141.2, 135.5, 133.7, 130.0, 129.5, 127.6, 86.3, 76.2, 69.8, 67.6, 64.8, 62.4, 57.6, 42.2, 36.8, 31.5, 30.6, 26.8, 25.7, 19.2, 18.1, 16.1, 15.5, 15.3, −5.6 and −5.7; *m*/*z* (CI) 652 (M^++18, 9%), 617 (38), 485 (32), 335 (89) and 704 (100).

4.23. (1*RS*,4*RS*,5*SR*)-4-(*tert*-Butyldimethylsilyloxymethyl)-3-[(6-*tert*-butyldiphenylsilyloxyhex-2-ynyloxy)-methyl]-4,5-dimethyl-1-tri-isopropylsilyloxycyclohex-2-ene 44

Tri-isopropylsilyl chloride (0.42 cm^3, 1.98 mmol) was added to the alcohol **43** (1.254 g, 1.98 mmol) and imidazole (0.27 g, 3.96 mmol) in dichloromethane (5 cm^3). After 46 h at ambient temperature, water (15 cm^3) was added and the mixture was extracted with ether (3×30 cm^3). The extracts were washed with water (30 cm^3) and brine (30 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:20) gave the *title compound* **44** (1.552 g, 99%) as a colourless oil, R_f=0.95 (10%

ether in light petroleum) (found: M^++NH_4, 808.5540; $C_{47}H_{82}NO_4Si_3$ requires *M*, 808.5551); ν_{max}/cm^{-1} 2934, 1465, 1253, 1103, 1067, 840, 776 and 703; δ_H 7.66 (4H, m, Ar–*H*), 7.40 (6H, m, Ar–*H*), 5.75 (1H, s, 2-*H*), 4.32 (1H, m, 1-*H*), 4.11 (1H, d, *J* 13, 3-C*H*), 4.07 (2H, m, 1′-H_2), 3.98 (1H, d, *J* 13, 3-C*H*′), 3.72 (2H, t, *J* 6, 6′-H_2), 3.50 and 3.40 (each 1H, d, *J* 11, 4-C*H*), 2.36 (2H, m, 4′-H_2), 1.98 (1H, m, 5-*H*), 1.76 (3H, m, 5′-H_2 and 6-*H*), 1.52 (1H, m, 6-*H*′), 1.07 [30H, m, Si(C*H*(CH_3)$_2$)$_3$ and SiC(CH_3)$_3$], 0.85 [15H, m, SiC(CH_3)$_3$, 5-CH_3 and 4-CH_3] and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 139.2, 135.5, 133.8, 132.2, 129.5, 127.5, 86.1, 70.1, 68.1, 65.0, 62.4, 57.0, 42.2, 37.2, 31.6, 30.7, 26.8, 25.8, 19.2, 18.1, 16.1, 15.7, 15.3, 12.3, −5.6 and −5.7; *m*/*z* (CI) 808 (M^++18, 52%), 791 (6), 617 (48), 455 (61), 439 (72), 281 (96) and 135 (100).

4.24. (2*RS*,3*RS*,5*SR*,6*RS*)- and (2*SR*,3*RS*,5*SR*,6*RS*)-6-(*tert*-Butyldimethylsilyloxymethyl)-2-(1-hydroxy-6-*tert*-butyldiphenylsilyloxyhex-2-ynyl)-5,6-dimethyl-3-(tri-isopropylsilyloxy)-1-methylenecyclohexanes 45a,b and 46

n-Butyllithium (1.6 M in hexanes, 6.13 cm^3, 9.81 mmol) was added dropwise at −78 °C to the ether **44** (1.552 g, 1.96 mmol) in tetrahydrofuran (20 cm^3). After 4 h, water (10 cm^3) was added and the aqueous layer was extracted with ether (2×15 cm^3). The extracts were washed with water (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:30 to 1:10) gave the *title compound* **45a** (450 mg, 29%) as a colourless liquid, R_f=0.65 (10% ether in light petroleum) (found: M^++NH_4, 808.5527; $C_{47}H_{82}NO_4Si_3$ requires *M*, 808.5551); ν_{max}/cm^{-1} 3497, 3050, 2932, 1636, 1467, 1428, 1253, 1108, 1035, 838, 776 and 704; δ_H 7.62 (4H, m, Ar–*H*), 7.36 (6H, m, Ar–*H*), 4.98 and 4.89 (each 1H, s, 1-C*H*), 4.52 (1H, dd, *J* 9, 3, 1′-*H*), 4.36 (1H, d, *J* 9.5, O*H*), 4.09 (1H, td, *J* 9.5, 5, 3-*H*), 3.66 (2H, t, *J* 6, 6′-H_2), 3.57 and 3.49 (each 1H, d, *J* 10.5, 6-C*H*), 2.55 (1H, dd, *J* 9, 3, 2-*H*), 2.30 (2H, m, 4′-H_2), 1.81 (1H, m, 5-*H*), 1.76–1.50 (4H, m, 4-H_2 and 5′-H_2), 1.08 [21H, m, Si(C*H*(CH_3)$_2$)$_3$], 1.01 [9H, s, SiC(CH_3)$_3$], 0.82 [15H, m, SiC(CH_3)$_3$, 5-CH_3 and 6-CH_3] and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 148.6, 135.5, 133.8, 129.5, 127.5, 110.1, 86.2, 80.2, 74.7, 66.9, 64.5, 62.6, 52.8, 44.1, 39.8, 32.3, 31.7, 26.8, 25.8, 19.2, 18.2, 17.1, 16.0, 15.6, 13.1, −5.7 and −5.7; *m*/*z* (CI) 792 (6%), 618 (23), 439 (29), 368 (64) and 135 (100). The second fraction was the *title compound* **46** (322 mg, 21%), a colourless liquid, R_f=0.6 (10% ether in light petroleum) (found: M^++NH_4, 808.5561; $C_{47}H_{82}NO_4Si_3$ requires *M*, 808.5551); ν_{max}/cm^{-1} 3582, 3472, 3050, 2935, 1640, 1466, 1428, 1388, 1253, 1103, 838, 776 and 703; δ_H 7.65 (4H, m, Ar–*H*), 7.37 (6H, m, Ar–*H*), 5.15 and 5.06 (each 1H, s, 1-C*H*), 4.76 (1H, m, 1′-*H*), 4.44 (1H, m, 3-*H*), 3.69 (2H, t, *J* 6, 6′-H_2), 3.43 (2H, s, 6-CH_2), 2.63 (1H, dd, *J* 8.5, 4.5, 2-*H*), 2.34 (2H, m, 4′-H_2), 1.90–1.69 (4H, m, 5-*H*, 4-*H* and 5′-H_2), 1.43 (1H, m, 4-*H*′), 1.05 [21H, m, Si(C*H*(CH_3)$_2$)$_3$], 1.03 [9H, s, SiC(CH_3)$_3$], 0.93 (3H, s, 6-CH_3), 0.86 [12H, m, SiC(CH_3)$_3$ and 5-CH_3] and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 148.5, 135.5, 133.8, 129.5, 127.5, 111.3, 85.9, 80.2, 71.2, 69.7, 62.7, 62.6, 52.4, 44.9, 38.5, 31.7, 30.9, 26.8, 25.9, 19.2, 18.2, 18.2, 16.8, 16.7, 15.6, 12.9, −5.6 and −5.6; *m*/*z* (CI) 809 (2%), 774 (19), 600 (18), 439 (42), 368 (94) and 135 (100). The third fraction was the *title compound* **45b** (288 mg, 19%), a pale yellow liquid, R_f=0.4 (10% ether in light petroleum) (found: M^++NH_4, 808.5539; $C_{47}H_{82}NO_4Si_3$ requires *M*, 808.5551); ν_{max}/cm^{-1} 3457, 3071, 2954, 1636, 1466, 1253, 1105, 1066, 838 and 703; δ_H 7.62 (4H, m, Ar–*H*), 7.35 (6H, m, Ar–*H*), 5.19 and 5.09 (each 1H, s, 1-C*H*), 4.86 (1H, td, *J* 6.5, 2, 1′-*H*), 3.69 (3H, m, 3-*H* and 6′-H_2), 3.62 and 3.48 (each 1H, d, *J* 10.5, 6-C*H*), 2.54 (1H, dd, *J* 10, 6.5, 2-*H*), 2.29 (2H, td, *J* 7.5, 1.5, 4′-H_2), 1.82–1.42 (5H, m, 5-*H*, 4-H_2 and 5′-H_2), 1.05 [21H, m, Si(C*H*(CH_3)$_2$)$_3$], 1.00 [9H, s, SiC(CH_3)$_3$], 0.83 [9H, s, SiC(CH_3)$_3$], 0.80 (6H, m, 5-CH_3 and 6-CH_3) and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 148.5, 135.5, 133.8, 129.5, 127.5, 109.6, 86.5, 80.1, 75.6, 67.0, 63.5, 62.6, 52.9, 44.4, 40.9, 32.9, 31.7, 26.8, 25.7, 19.2, 18.2, 18.1, 16.3, 15.8, 15.5, 12.9 and −5.7; *m*/*z* (CI) 809 (3%), 792 (6), 618 (66), 368 (81) and 135 (100).

4.25. (2*RS*,3*RS*,5*SR*,6*RS*)-6-(*tert*-Butyldimethylsilyloxymethyl)-2-(6-*tert*-butyldiphenylsilyloxy-1-oxohex-2-ynyl)-5,6-dimethyl-3-(tri-isopropylsilyloxy)-1-methylenecyclohexane 47

Tetra-*n*-propylammonium perruthenate (9 mg, 0.025 mmol) was added to a stirred suspension of alcohol **45a** (202 mg, 0.25 mmol), *N*-methylmorpholine *N*-oxide (59 mg, 0.501 mmol) and crushed 4 Å molecular sieves in dichloromethane (2 cm^3). After 70 h, the reaction was diluted with dichloromethane (20 cm^3). The organic layer was washed with saturated aqueous sodium thiosulfate (10 cm^3), brine (10 cm^3) and saturated aqueous copper(II) sulfate (10 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:19) gave the *title compound* **47** (156 mg, 77%) as a colourless oil, R_f=0.75 (10% ether in light petroleum) (found: M^++H, 789.5135; $C_{47}H_{77}O_4Si_3$ requires *M*, 789.5129); ν_{max}/cm^{-1} 3071, 2951, 2214, 1675, 1466, 1252, 1106, 840, 776 and 703; δ_H 7.61 (4H, m, Ar–*H*), 7.36 (6H, m, Ar–*H*), 4.99 and 4.68 (each 1H, d, *J* 1, 1-C*H*), 4.15 (1H, td, *J* 10.5, 4.5, 3-*H*), 3.67 (2H, t, *J* 6, 6′-H_2), 3.64 and 3.46 (each 1H, d, *J* 10.5, 6-C*H*), 3.37 (1H, d, *J* 10, 2-*H*), 2.46 (2H, t, *J* 6.5, 4′-H_2), 1.76 (4H, m, 5′-H_2, 4-*H* and 5-*H*), 1.46 (1H, m, 4-*H*′), 1.01 [30H, m, Si(C*H*(CH_3)$_2$)$_3$ and SiC(CH_3)$_3$], 0.82 [15H, m, SiC(CH_3)$_3$ 5-CH_3 and 6-CH_3] and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 189.2, 148.0, 135.4, 133.6, 129.6, 127.6, 110.1, 93.7, 82.0, 71.9, 66.1, 64.1, 62.2, 44.1, 39.4, 31.9, 30.8, 26.8, 25.8, 19.2, 18.2, 16.4, 15.9, 15.7, 12.7 and −5.7; *m*/*z* (CI) 790 (24%), 616 (4), 440 (6), 168 (71), 135 (72) and 58 (100).

4.26. (2*SR*,3*RS*,5*SR*,6*RS*)-6-(*tert*-Butyldimethylsilyloxymethyl)-2-(6-*tert*-butyldiphenylsilyloxy-1-oxohex-2-ynyl)-5,6-dimethyl-3-(tri-isopropylsilyloxy)-1-methylenecyclohexane 48

Dimethyl sulfoxide (60 μL, 0.85 mmol) in dichloromethane (0.25 cm^3) was added at −78 °C to a solution of oxalyl chloride (30 μL, 0.34 mmol) in dichloromethane (0.5 cm^3). After 15 min, the alcohol **46** (54 mg, 0.068 mmol) in dichloromethane (1 cm^3) was added. After stirring at −78 °C for 7 h, triethylamine (118 μL, 0.850 mmol) was added. After a further 14 h, water (3 cm^3) was added and the mixture extracted with ether (3×5 cm^3). The extracts were washed with water (5 cm^3), brine (5 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica eluted with ether in light petroleum (1:19) gave the *title compound* **48** (43 mg, 81%) as a colourless oil, R_f=0.7 (10% ether in light petroleum) (found: M^++H, 789.5113; $C_{47}H_{77}O_4Si_3$ requires *M*, 789.5129); ν_{max}/cm^{-1} 3071, 2952, 2209, 1682, 1623, 1465, 1253, 1107, 837, 776 and 703; δ_H 7.61 (4H, m, Ar–*H*), 7.35 (6H, m, Ar–*H*), 5.08 (2H, m, 1-CH_2), 3.82 (1H, dt, *J* 12, 6, 3-H), 3.69 (2H, t, *J* 6, 6′-H$_2$), 3.65 (1H, d, *J* 6, 2-H), 3.59 and 3.40 (each 1H, d, *J* 10.5, 6-C*H*), 2.46 (2H, t, *J* 7.5, 4′-H_2), 2.32 (1H, m, 4-*H*), 1.75 (3H, m, 5′-H_2 and 5-*H*), 1.58 (1H, m, 4-*H*′), 1.01 [30H, m, Si(C*H*(CH_3)$_2$)$_3$ and SiC(CH_3)$_3$], 0.83 [12H, m, SiC(CH_3)$_3$ and 5-CH_3], 0.73 (3H, s, 6-CH_3) and 0.00 [6H, s, Si(CH_3)$_2$]; δ_C 186.4, 147.3, 135.4, 133.6, 129.6, 127.6, 116.0, 92.5, 81.9, 71.6, 66.3, 65.2, 62.2, 44.1, 36.5, 31.9, 30.7, 26.8, 25.8, 19.2, 18.2, 18.1, 18.0, 17.6, 15.7, 15.5, 12.3 and −5.6; *m*/*z* (CI) 790 (19%), 616 (6), 538 (5), 439 (5), 168 (53) and 135 (100).

4.27. Crystal data for methyl (1*RS*,6*SR*)-1,2,6-trimethyl-4-oxocyclohex-2-ene-1-carboxylate 20

$C_{11}H_{16}O_3$, MW 196.24, triclinic, space group *P*−1, *a*=8.170(1), *b*=11.691(2), *c*=6.381(2) Å, α=91.35(2), β=109.51(2), γ=107.39(1)°, *V*=543.0(2) Å^3, *Z*=2, D_c=1.200 g cm^{-3}, μ(Cu Kα)=0.704 mm^{-1}, *F*(000)=212, *T*=296 K. Crystal dimensions were 0.4×0.4×0.35 mm;

2379 reflections measured, 2225 independent reflections (R_{int}=0.042), R_1=0.057 for the 1717 reflections with $I>2\sigma(I)$, $wR(F^2)$=0.1817 (all data). CCDC 714071. X-ray data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax (+44) 122 333 6033.

Acknowledgements

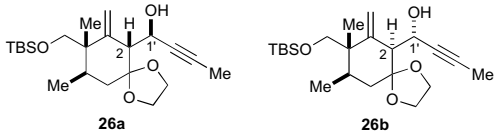
We thank GlaxoSmithKline for support through the CASE scheme (to P.D.P.S.) and Dr. M. Helliwell for the X-ray crystal structure.

Supplementary data

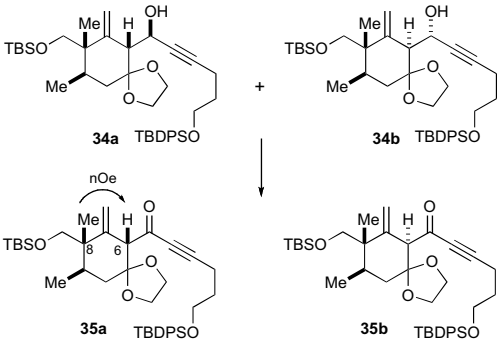
Supplementary data with full experimental procedures for the synthesis of intermediates **28**–**30** and **49**, **50**, **53**–**65**, can be found in the online version. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.03.031.

References and notes

1. (a) Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 5463; (b) Chu, M.; Patel, M. G.; Gullo, V. P.; Truumees, I.; Puar, M. S.; McPhail, A. T. *J. Org. Chem.* **1992**, *57*, 5817; (c) Chu, M.; Truumees, I.; Gunnarsson, I.; Bishop, W. R.; Kreutner, W.; Horan, A. C.; Patel, M. G.; Gullo, V. P.; Puar, M. S. *J. Antibiot.* **1993**, *46*, 554; (d) Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Haruyama, H.; Yoda, K.; Hata, T. *J. Org. Chem.* **1994**, *59*, 564; (e) Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Kuwano, H.; Hata, T. *J. Antibiot.* **1995**, *48*, 1188; (f) Koyama, K.; Ishino, M.; Takatori, K.; Sugita, T.; Kinoshita, K.; Takahashi, K. *Tetrahedron Lett.* **2004**, *45*, 6947.
2. Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107.
3. (a) Goldring, W. P. D.; Pattenden, G. *Chem. Commun.* **2002**, 1736; (b) Diaper, C. M.; Goldring, W. P. D.; Pattenden, G. *Org. Biomol. Chem.* **2003**, *1*, 3949.
4. (a) Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712.
5. Huang, J.; Wu, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 13366.
6. Goldring, W. P. D.; Pattenden, G. *Org. Biomol. Chem.* **2004**, *2*, 466.
7. (a) Foote, K. M.; Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275; (b) Chen, D.; Wang, J.; Totah, N. I. *J. Org. Chem.* **1999**, *64*, 1776; (c) Seth, P. P.; Totah, N. I. *J. Org. Chem.* **1999**, *64*, 8750; (d) Seth, P. P.; Chen, D.; Wang, J.; Gao, X.; Totah, N. I. *Tetrahedron* **2000**, *56*, 10185; (e) Seth, P. P.; Totah, N. I. *Org. Lett.* **2000**, *2*, 2507; (f) Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695; (g) Chemler, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949; (h) Foote, K. M.; John, M.; Pattenden, G. *Synlett* **2001**, 365; (i) Mi, B.; Maleczka, R. E., Jr. *Org. Lett.* **2001**, *3*, 1491; (j) Houghton, T. J.; Choi, S.; Rawal, V. H. *Org. Lett.* **2001**, *3*, 3615; (k) Mohr, P. J.; Halcomb, R. L. *Org. Lett.* **2002**, *4*, 2413; (l) Cheing, J. W. C.; Goldring, W. P. D.; Pattenden, G. *Chem. Commun.* **2003**, 2788; (m) Foote, K. M.; Hayes, C. J.; John, M. P.; Pattenden, G. *Org. Biomol. Chem.* **2003**, *1*, 3917; (n) Cole, K. P.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4843; (o) Cole, K. P.; Hsung, R. P. *Chem. Commun.* **2005**, 5784; (p) Ryu, K.; Cho, Y.-S.; Jung, S.-I.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3343; (q) Teng, D.; Wang, B.; Augatis, A. J.; Totah, N. I. *Tetrahedron Lett.* **2007**, *48*, 4605; (r) Huang, J.; Wang, H.; Wu, C.; Wulff, W. D. *Org. Lett.* **2007**, *9*, 2799; (s) Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687; (t) Goldring, W. P. D.; Alexander, S. P. H.; Kendall, D. A.; Pattenden, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3263.
8. Goldring, W. P. D.; Pattenden, G. *Acc. Chem. Res.* **2006**, *39*, 354.
9. (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885; (b) Nakai, T.; Mikami, K. *Synthesis* **1991**, 594; (c) Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105.
10. Marsden, A.; Thomas, E. J. *Arkivoc* **2002**, *ix*, 78.
11. (a) Acheson, R. M.; Flowerday, R. F. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2339; (b) Linker, T.; Frohlich, L. *J. Am. Chem. Soc.* **1995**, *117*, 2694.
12. (a) Shultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1992**, *114*, 1824; (b) Shultz, A. G.; Taveras, A. G.; Harrington, R. E. *Tetrahedron Lett.* **1988**, *29*, 3907.
13. (a) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087; (b) Murray, R. W.; Shiang, D. L. *J. Chem. Soc., Perkin Trans. 2* **1990**, 349; (c) Troisi, L.; Cassidei, L.; Lopez, L.; Mello, R.; Curci, R. *Tetrahedron Lett.* **1989**, *30*, 257.
14. Mori, S.; Nakamura, E. *Chem.—Eur. J.* **1999**, *5*, 1534.
15. On the basis of steric interactions between the alkynyl group and the acetal in the transition state for the [2,3]-Wittig rearrangements, it is suggested that the two products were diastereoisomers **26a** and **26b**. This is consistent with the formation of two diastereomeric products from the rearrangement of acetal **33** and the formation of three products from the rearrangement of the protected alcohol **44**. Moreover, the major product isolated from a [2,3]-Wittig rearrangement of an analogous albeit slightly more complex system en route to the phomactin nucleus was shown to have the relative configuration at C(2) and C(1′) as shown here for products **26a** and **26b** (see Ref. 16).



16. Balnaves, A. S.; McGowan, G.; Shapland, P. D. P.; Thomas, E. J. *Tetrahedron Lett.* **2003**, *44*, 2713.
17. Following the provisional stereochemical assignments to products **26**, it is suggested that the two products from the rearrangement of ether **33** had the relative stereochemistry at C(2) and C(1′) as shown for **34a** and **34b**, oxidation giving the corresponding ketones **35a** and **35b**. An NOE observed for H(6) on irradiation of 8-CH_3 for the minor ketone **35a** suggested that this had the structure shown below. The major rearrangement product was therefore provisionally assigned as alcohol **34b**. This assignment was not confirmed in this series but is consistent with results obtained later for analogous systems (see Ref. 18).



18. Blackburn, T. J.; Helliwell, M.; Kilner, M. J.; Lee, A. T. L.; Thomas, E. J. *Tetrahedron Lett.*, in press.
19. Following the discussion above, the major and minor isomers of product **45** are believed to be epimers **45a** and **45b**, respectively, and the C(2)-epimer is assigned the structure **46**, the configuration at C(2) in these compounds being unambiguously established by $J_{2,3}$.