An approach to the synthesis of phomactins using a Wittig rearrangement

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Dedicated to Professor J. R. Bull on his retirement from the University of Cape Town

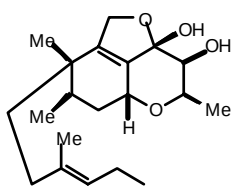
Abstract

Preliminary studies to evaluate the feasability of an approach to the synthesis of the phomactin diterpenes are outlined. The key step is the 2,3-Wittig rearrangement of the propargylic ether **32** which gives a mixture of the diastereoisomeric alcohols **33**. Oxidation to the ketones **34** and **35** followed by conjugate addition of lithium dimethylcuprate and deprotection gives the unsaturated diketone **37** so providing a strategy for the synthesis of the cyclohexenyl core of the phomactins.

Keywords: 2,3-Wittig rearrangement, phomactins, propargylic ether

Introduction

The phomactins are a group of diterpenes some of which are of interest as platelet activating factor antagonists.[1] Representative structures include phomactins A **1**, D **2**, E **3** and Sch. 49028 **4**. Because of their novel structures and biological activities, several groups have reported synthetic studies in this area[2] including a total synthesis of phomactin D **2**[3] and, very recently, of phomactin A **1**.[4]



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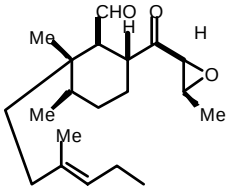

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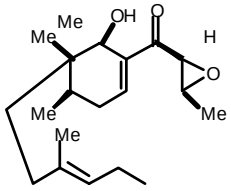

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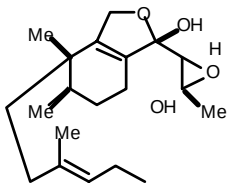
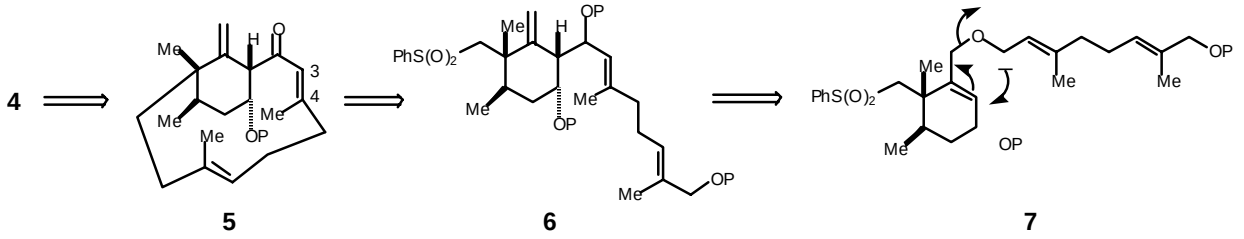


4

The isolation of the hydroxyepoxide **4**, Sch.49028, which is isomeric with phomactin A **1** suggests that **4** may be an intermediate in the biosynthesis of **1** and that isomerisation of a

hydroxyepoxide similar to Sch. 49028 could provide a synthetic route to phomactin A; indeed this chemistry featured in the first synthesis of phomactin A which was reported very recently.[4]

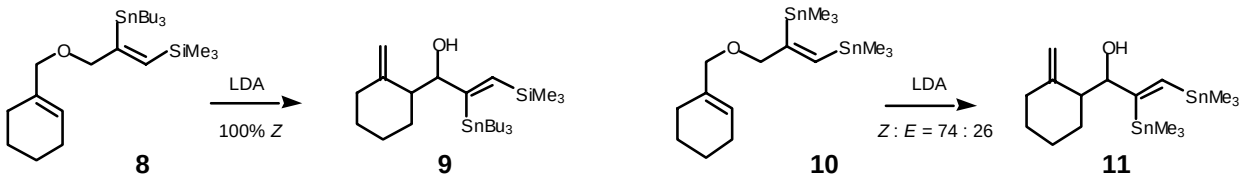
With this in mind, an approach to the phomactins was conceived with Sch. 49028 **4** as the initial target, see Scheme 1. Sch. 49028 is to be prepared from the trienyl ketone **5** by stereoselective reduction to give an alcohol which would then be used to direct epoxidation to the adjacent 3,4-double-bond. Further directed epoxidation of the exocyclic methylene group, followed by reoxidation to the ketone and isomerisation of the exocyclic β,γ-epoxyketone should then provide the cyclic hemiacetal and **4** on deprotection.§ The trienyl ketone **5** is to be prepared from the cyclohexylmethyl sulfone **6** by a precedented[3] intramolecular sulfone alkylation, and a convergent route to methylenecyclohexane **6** was envisaged based on a 2,3-Wittig rearrangement of a bis-allylic ether, e.g. **7**. Although the 2,3-Wittig rearrangement has been widely studied,[5] several uncertainties needed to be clarified before the synthesis of the ether **7** was undertaken. For example, what would be the regioselectivity of rearangement of unsymmetric bis-allyl ethers related to **7**? Would the rearrangement of **7** be stereoselective? We here report the results of a study of 2,3-Wittig rearrangements undertaken to validate this approach to the phomactins.



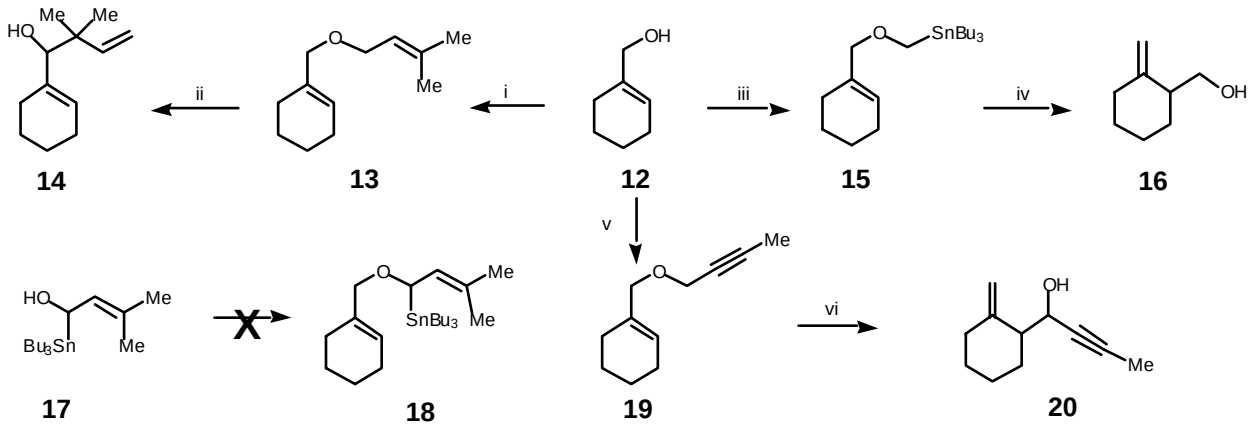
Scheme 1. Outline of a proposed synthesis of the phomactins.

Results and Discussion

Ethers **8** and **10** have been shown to undergo 2,3-Wittig rearrangements to give alcohols **9** and **11** on treatment with lithium diisopropylamide[6] so providing a precedent for the proposed rearrangement, and related 3,3-Claisen rearrangements are known.[7,8] However, Wittig rearrangements of unsymmetrical bis-allylic ethers tend to involve deprotonation of the less alkylated, presumably more acidic and accessible, allylic system,[9] and so initial studies were carried out to establish the regioselectivity of rearrangement of ethers analogous to **7**.

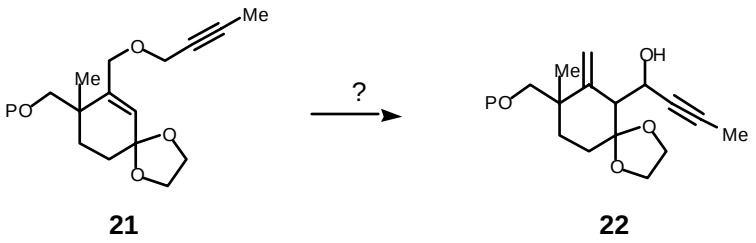


Rearrangement of 3-methylbut-2-enyl ether **13**, prepared by alkylation of cyclohexenylmethanol **12**,[7] was found to proceed by deprotonation of the methylene group attached to the cyclohexenyl ring and gave the isomer **14** of the required product, albeit in only modest yield. Tin-lithium exchange and 2,3-rearrangement of the alkoxymethylstannane **15**[10] was successful and gave the 2-(hydroxymethyl)methylenecyclohexane **16**, but attempts to prepare the 1-alkoxy-3-methylbut-2-enylstannane **18**[11] were thwarted by the instability of the hydroxystannane **17**. However, Wittig rearrangement of the propargylic ether **19**[13] took place with the required regioselectivity and gave the alcohol **20** as mixture of diastereoisomers.



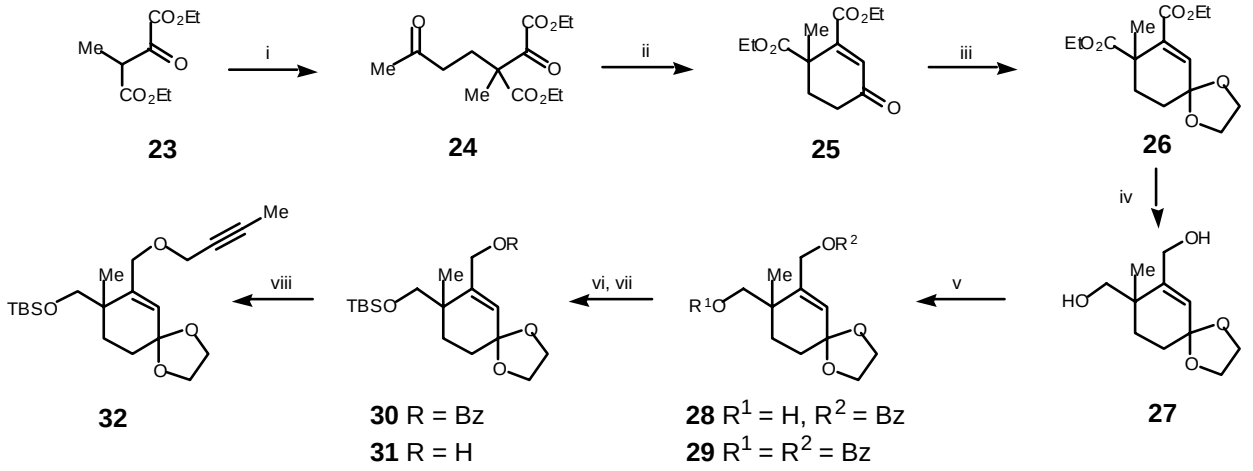
Scheme 2. Preliminary studies; *Reagents and conditions:* i, NaH, 1-bromo-3-methylbut-2-ene, THF (96%); ii, *n*-BuLi, THF, -78 to r.t , 1 h (26%); iii, NaH, Bu_3SnCH_2I (47%); iv, *n*-BuLi, THF, -78 ^oC, 2 h (60%); v, NaH, 1-bromobut-2-yne (90%); vi, *n*-BuLi, -78 ^oC, 8 h (75% together with unchanged **19**, 19%).

On the basis of these preliminary studies it was decided to study further the 2,3-rearrangement of propargylic ethers. Specifically it was decided to prepare the protected keto-ether **21** and to study its rearrangement, hopefully to the alcohol **22**. Further chemistry to convert the alkyne group into the require trisubstituted alkene would then be studied to establish the suitability of these compounds for incorporation into a synthesis of phomactin analogues.



The synthesis of the 2,3-rearrangement precursor **32** is outlined in Scheme 3. Michael addition of the keto-diester **23** to methyl vinyl ketone gave the adduct **24** which was cyclised using piperidine to complete the Dieckmann synthesis[14] of cyclohexenone **25**. After protection of

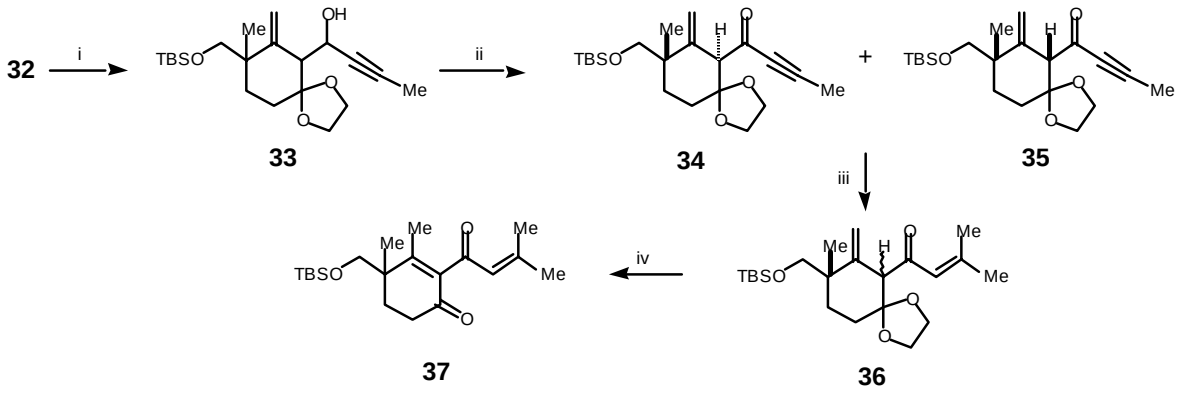
the ketone as ketal **26**, reduction to the diol **27** was best effected using lithium triethylborohydride. It now was necessary to distinguish between the two primary hydroxyl groups. This was accomplished by esterification using benzoyl chloride which gave a mixture of the mono- and bis-benzoates **28** (67%) and **29** (20%) the latter being reduced back to the diol **27** for recycling. Protection of the monobenzoate **28** as its *tert*-butyldimethylsilyl ether **30** followed by reductive removal of the benzoyl group gave the monoprotected diol **31** which was alkylated using 1-bromobut-2-yne to give the required ether **32**.



Scheme 3. Synthesis of the rearrangement precursor; *Reagents and conditions*: i, KO^{t}Bu, methyl vinyl ketone, toluene (93%); ii, piperidine, HOAc (glacial), toluene (88%); iii, 1,2-ethanediol, *p*-TsOH, benzene, heat under reflux (Dean Stark) (98%); iv, $LiEt_3BH$, THF (91%); v, BzCl, Et_3N, cat. DMAP, CH_2Cl_2 (**28**, 67%; **29**, 20%); vi, TBSCl, imid., CH_2Cl_2 (97%); vii, $LiEt_3BH$ (96%); viii, NaH, 1-bromobut-2-yne, THF (91%).

The 2,3-Wittig rearrangement of the propargyl ether **32** was carried out by treatment with *n*-butyllithium in tetrahydrofuran, and gave a mixture of diastereomeric products **33** (75%). This mixture wasn't separated, rather it was oxidised to give the two ketones **34** and **35**, combined yield 82%, ratio 55: 45, respectively. The structures of these ketones were assigned on the basis of spectroscopic data including nOe difference experiments.[15]

The formation of the ketones **34** and **35** confirms that the Wittig rearrangement of propargylic ethers can provide a route to intermediates which may be useful for the synthesis of phomactins since the regioselectivity is controlled in the required sense by use of the alkynyl ether. Although the rearrangement of ether **32** was not usefully stereoselective, it was thought that in the case of the more heavily functionalised cyclohexene **7**, the facial selectivity of the rearrangement would be more significant.



Scheme 4. Completion of the Wittig rearrangement chemistry; *Reagents and conditions*; i, *n*-butyllithium, THF (75%); ii, $(COCl)_2$, DMSO, Et_3N (82%); iii, MeLi, CuI, THF (77%); iv, PPTS, H_2O-acetone (40%).

Moreover, the mixture of ketones **34** and **35** was reacted with lithium dimethylcuprate to give the dienyl ketone **36** which on treatment with pyridinium toluene *p*-sulfonate in acetone-water was converted into the 2-(3-methylbut-2-enoyl)cyclohex-2-enone **37**. During this hydrolysis of the ketal, the exocyclic alkene had migrated inside the ring and so the ketone **37** was formed as a single (racemic) stereoisomer having lost both of the stereogenic centres introduced during the Wittig rearrangment.

Conclusions

This synthesis of the ketone **37** shows that the 2,3-Wittig rearrangement of cyclohexenylmethyl propargyl ethers is regioselective and provides access to intermediates which may be useful for a synthesis of the phomactins. The functionality around the cyclohexene ring in **37** parallels that present in the phomactins apart from the missing 12-methyl substituent, and the side-chain has the required C(1) carbonyl and trisubstituted 2,3-alkene. Present work is concerned with applying the chemistry reported in this paper to complete a synthesis of a phomactin.

Experimental Section

General Procedures. Low resolution mass spectra were recorded on a VG Trio 200 spectrometer and high resolution mass spectra were recorded on a Kratos Concept IS spectrometer. Infrared spectra were recorded as evaporated films on a Genesis FTIR or Perkin-Elmer 1710 FT spectrometers. ^{1}H NMR spectra were recorded on Varian Unity INOVA300 or Bruker AC300 (300MHz) spectrometers with residual non-deuterated solvent as the internal standard. Proton-decoupled ^{13}C NMR spectra were recorded on Bruker AC300 (75MHz) or

Varian Unity 500 (125MHz) spectrometers with residual non-deuterated solvent as internal standard.

Flash column chromatography was carried out using Merck silica gel 60H (40-60μ, 230-240 mesh). Thin layer chromatography (TLC) was performed using glass plates coated with Merck $HF_{254/366}$ silica gel. Analytical high pressure liquid chromatography (HPLC) was performed on a Waters 600A pump using a μBondapak cartridge, 8mm x 100mm with a Gilson 131 refractive index detector. Preparative HPLC was performed on a Gilson 712 pump control system running Gilson HPLC software, using an ODS Rainin Dynamex 60A column, 21.4mm x 250mm with a Gilson 131 refractive index detector.

Petrol refers to light petroleum ether which distills between 40 ˚C and 60 ˚C and was redistilled before use. Ether refers to diethyl ether. All reactions were performed under an atmosphere of dry nitrogen or argon with solvents and reagents purified and dried by standard techniques.

1-(3-Methylbut-2-enyloxymethyl)cyclohexene (13). To a suspension of sodium hydride (360 mg of a 60% dispersion in mineral oil, 8.93 mmol), previously washed with hexane (3x5 cm^3), in tetrahydrofuran (9 cm^3) was added 1-cyclohexenylmethanol **12**[7] (500 mg, 4.46 mmol) in tetrahydrofuran (1 cm^3). The reaction mixture was stirred for 1.5 h and then 1-bromo-3-methylbut-2-ene (1.00 g, 6.70 mmol) was added dropwise. The mixture was stirred for 1 h then satd. aq. ammonium chloride (2 cm^3) added. The aqueous layer was extracted with ether (2x5 cm^3). The combined organic extracts were washed with water (2x5 cm^3) and brine (5cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 3:1 petrol:ether, yielded the *title compound* **13** (770 mg, 96 %) as a colourless oil (Found: M^+, 180.1516; $C_{12}H_{20}O$ requires *M*, 180.1514); ν_{max}/cm^{-1} 2926, 2856, 2838, 1674, 1447, 1089, 1070; δ_H (300MHz, $CDCl_3$) 1.63 (4H, m, 4-H_2 and 5-H_2), 1.69 (3H, s, 4'-H_3), 1.76 (3H, s, 3'-CH_3), 2.03 (4H, m, 3-H_2 and 6-H_2), 3.83 (2H, s, 1-CH_2), 3.92 (2H, d, *J* 7, 1'-H_2), 5.38 (1H, m, 2'-H), 5.70 (1H, narrow multiplet, 2-H); δ_C (75MHz, $CDCl_3$) 18.0, 22.5, 22.6, 25.1, 25.8, 26.0, 66.1, 74.9, 121.4, 124.9, 135.2, 136.6; *m/z* (E.I.) 180 (M^+, 13%), 95 (62), 55 (67), 41 (100); *m/z* (C.I., NH_3) 198 ($M^+ + NH_4$, 99%), 181 ($M^+ + H$, 71), 163 (100).

1-(2,2-Dimethyl-1-hydroxybut-3-enyl)cyclohexene (14). To a solution of ether **13** (100 mg, 0.56 mmol) in tetrahydrofuran (2 cm^3), at –78 ˚C, was added *n*-butyllithium (0.42 cm^3 of a 1.6 M solution in hexane, 0.67 mmol). The reaction mixture was stirred for 1 h, warmed to room temperature and stirred for a further 1 h. Water (0.5 cm^3) was added and the aqueous layer was extracted with ether (2x0.5 cm^3). The combined organic extracts were washed with water (0.5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 10:1 petrol:ether, yielded the *title compound* **14** (26 mg, 26%) as a colourless oil (Found: M^+ - OH, 163.1490; $C_{12}H_{19}$ requires *M*, 163.1487); ν_{max}/cm^{-1} 3462 (OH), 2959, 2930, 2858, 1636, 1022, 909; δ_H (300MHz, $CDCl_3$) 1.04 (3H, s, 2'-CH_3), 1.07 (3H, s, 2'-CH_3), 1.63 (5H, m, 4-H_2, 5-H_2 and 1'-OH), 2.02 (4H, m, 3-H_2 and 6-H_2), 3.72 (1H, d, *J* 3, 1'-H), 5.08

(2H, m, 4'-H_2), 5.65 (1H, narrow multiplet, 2-H), 5.96 (1H, m, 3'-H); δ_C (75MHz, $CDCl_3$) 22.6, 22.8, 25.0, 25.1, 26.8, 42.0, 82.8, 112.9, 125.5, 138.1, 145.7; *m/z* (E.I.) 111 (49%), 50 (71), 42 (100), 40 (68); *m/z* (C.I., NH_3) 163 (M^+ - OH, 100%), 128 (19). Starting ether **13** was also recovered (38 mg, 38%).

1-(Tributylstannylmethoxymethyl)cyclohexene (15). To a suspension of sodium hydride (185 mg of a 60% dispersion in mineral oil, 4.63 mmol), previously washed with hexane (3x5 cm^3), in tetrahydrofuran (10 cm^3) was added the alcohol **12** (259 mg, 2.31 mmol). The reaction mixture was stirred for 2 h and then iodomethyl(tributyl)tin[16] (1.80 g, 3.47 mmol) was added. The mixture was stirred for a further 3 days then water (2 cm^3) was added. The aqueous layer was extracted with ether (2x5 cm^3). The combined organic extracts were washed with water (2x5 cm^3) and brine (5 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, using petrol as the eluant, yielded the *title compound* **15** (455 mg, 47%) as a colourless oil (Found: M^+ - C_4H_9, 359.1398; $C_{16}H_{31}O^{120}Sn$ requires *M*, 359.1397); ν_{max}/cm^{-1} 2955, 2925, 1461, 1065, 1045; δ_H (300MHz, $CDCl_3$) 0.92 (15H, m, ($CH_3CH_2CH_2CH_2$)$_3$Sn), 1.34 (6H, m, ($CH_3CH_2CH_2CH_2$)$_3$Sn), 1.58 (10H, m, 4-H_2, 5-H_2 and ($CH_3CH_2CH_2CH_2$)$_3$Sn) 2.03 (4H, m, 3-H_2 and 6-H_2), 3.70 (2H, s, OCH_2Sn), 3.75 (2H, s, 1-CH_2), 5.68 (1H, narrow multiplet, 2-H); δ_C (75MHz, $CDCl_3$) 9.0, 13.7, 22.5, 22.6, 25.0, 25.8, 27.4, 29.2, 60.7, 79.9, 124.5, 135.3; *m/z* (E.I.) 359 [M(^{120}Sn)$^+$ - C_4H_9, 45%], 291 (85), 289 (55), 235 (100), 233 (68), 179 (83), 177 (82); *m/z* (C.I., NH_3) 359 [M(^{120}Sn)$^+$ - C_4H_9, 100%], 357 (83), 355 (47). Starting alcohol **12** (65 mg, 25%) was also recovered.

2-Hydroxymethyl-1-methylenecyclohexane (16). To a solution of stannyl ether **15** (438 mg, 1.05 mmol) in tetrahydrofuran (3 cm^3), at –78 ˚C, was added *n*-butyllithium (0.79 cm^3 of a 1.61M solution in hexane, 1.27 mmol). The reaction mixture was stirred for 2 h, water (0.5 cm^3) was added and the mixture warmed to room temperature. The aqueous layer was extracted with ether (2x1 cm^3). The combined organic extracts were washed with water (1 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 5:1 petrol:ether, yielded the *title compound* **16** (79 mg, 60%) as a colourless oil (Found: M^+, 126.1043; $C_8H_{14}O$ requires *M*, 126.1045); ν_{max}/cm^{-1} 3365 (OH), 2928, 2855, 1644, 1027; δ_H (300MHz, $CDCl_3$) 1.49-2.38 (10H, m, 2-H, 3-H_2, 4-H_2, 5-H_2, 6-H_2 and 2-CH_2OH), 3.68 (1H, dd, *J* 11 and 6, 2-C*H*HO), 3.83 (1H, dd, *J* 11 and 8, 2-CH*H*O), 4.71 (1H, s, 1-C*H*H), 4.83 (1H, s, 1-CH*H*); δ_C (75MHz, $CDCl_3$) 24.0, 28.3, 34.3, 45.6, 64.0, 107.5, 149.7; *m/z* (E.I.) 126 (M^+, 5%), 95 (100), 93 (59), 79 (38), 67 (68). Starting ether **15** was also recovered (86 mg, 20%).

1-(But-2-ynyloxymethyl)cyclohexene (19). To a suspension of sodium hydride (2.14 g of a 60% dispersion in mineral oil, 0.054 mol), previously washed with hexane (3x30 cm^3), in tetrahydrofuran (120 cm^3) was added the alcohol **12** (3.00 g, 0.027 mol). The reaction mixture was stirred for 1 h and then 1-bromobut-2-yne (4.28 g, 0.032 mol) was added. The mixture was stirred for a further 15 h and satd. aq. ammonium chloride (20 cm^3) was added. The aqueous layer was extracted with dichloromethane (2x20 cm^3). The combined organic extracts were washed with water (2x20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and concentrated under

reduced pressure. Flash column chromatography, 2:1 petrol:ether, yielded the *title compound* **19** (3.96 g, 90%) as a colourless oil (Found: $M^+ + H$, 165.1275; $C_{11}H_{17}O$ requires *M*, 165.1279); ν_{max}/cm^{-1} 2922, 2855, 1670, 1440, 1355, 1157, 1136, 1090, 1072, 921, 898, 830, 802; δ_H (300MHz, $CDCl_3$) 1.64 (4H, m, 4-H_2 and 5-H_2), 1.88 (3H, t, *J* 2, 4'-H_3), 2.04 (4H, m, 3-H_2 and 6-H_2), 3.90 (2H, s, 1-CH_2), 4.06 (2H, q, *J* 2, 1'-H_2), 5.73 (1H, narrow multiplet, 2-H); δ_C (75MHz, $CDCl_3$) 3.6, 22.4, 22.5, 25.1, 26.0, 57.2, 74.4, 75.4, 82.1, 125.8, 134.4; *m/z* (C.I., NH_3) 182 ($M^+ + NH_4$, 100%), 165 ($M^+ + H$, 9%), 147 (21), 112 (18), 95 (28).

2-(1-Hydroxybut-2-ynyl]methylenecyclohexane (20). To a solution of ether **19** (5.6 g, 0.034 mol) in tetrahydrofuran (56 cm^3), at –78 ˚C, was added *n*-butyllithium (16.39 cm^3 of a 2.5M solution in hexane, 0.041 mol) dropwise over 40 min. The reaction mixture was stirred for 8 h, water (20 cm^3) was added and the mixture warmed to room temperature. The aqueous layer was extracted with ether (2x20 cm^3). The combined organic extracts were washed with water (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 10:1 petrol:ether, yielded the *title compound* **20** as a mixture of diastereoisomers (4.21 g, 75%) as a colourless oil (Found: $M^+ + NH_4$, 182.1540; $C_{11}H_{20}NO$ requires *M*, 182.1545); ν_{max}/cm^{-1} 3406 (OH), 2929, 2856, 1646, 1446, 1013, 890; δ_H (300MHz, $CDCl_3$) 1.57 (4H, m, 4-H_2 and 5-H_2), 1.87 (5H, m, 3-H_2 and 4'-H_3), 2.17 (2H, m, 6-H_2), 2.32 (1H, m, 2-H), 4.56 (1H, m, 1'-H), 4.86 (2H, m, 1-CH_2); δ_C (75MHz, $CDCl_3$) 3.7, 23.0, 24.1, 28.1, 28.2, 29.5, 33.5, 35.5, 49.5, 50.3, 62.5, 63.2, 78.8, 79.9, 81.7, 82.0, 108.1, 110.1, 148.5, 148.7; *m/z* (C.I., NH_3) 182 ($M^+ + NH_4$, 100%), 164 (80), 147 (85). Starting ether **19** was also recovered (1.08 g, 19%).

Diethyl 2-methyl-3-oxo-2-(3-oxobutyl)butanedioate (24). To a suspension of potassium *tert*-butoxide (3.57 g, 0.032 mol) stirring in toluene (140 cm^3) was added diethyl 3-methyl-2-oxo-1,2-butanedioate (64.38 g, 0.318 mol). The reaction mixture was stirred until a yellow solution was produced and methyl vinyl ketone (21.05 g, 0.300 mol) then added. The mixture was stirred for 90 h and satd. aq. ammonium chloride (60 cm^3) was added. The aqueous layer was extracted with ether (3x60 cm^3). The organic extracts were washed with water (2x60 cm^3) and brine (60 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Distillation (129-132 ˚C, 0.1 mbar) yielded the *title compound* **24** (75.66 g, 93%) as a pale yellow oil (Found: $M^+ + H$, 273.1342; $C_{13}H_{21}O_6$ requires *M*, 273.1338); ν_{max}/cm^{-1} 2986, 1754 (C=O), 1727 (C=O), 1300, 1246, 1178, 1028; δ_H (300MHz, $CDCl_3$) 1.20 (3H, t, *J* 7, 1-$CO_2CH_2CH_3$), 1.34 (3H, t, *J* 7, 4-$CO_2CH_2CH_3$) , 1.41 (3H, s, 2-CH_3), 2.10 (3H, s, 4'-H_3), 2.17 (2H, m, 1'-H_2), 2.42 (2H, m, 2'-H_2), 4.14 (2H, q, *J* 7, 1-$CO_2CH_2CH_3$), 4.29 (2H, q, *J* 7, 4-$CO_2CH_2CH_3$); δ_C (75MHz, $CDCl_3$) 13.8, 19.8, 28.4, 29.8, 38.0, 55.3, 61.5, 62.5, 160.1, 171.6, 191.2, 206.9; *m/z* (E.I.) 273 ($M^+ + H$, 5%), 199 (87), 129 (40), 125 (100), 97 (35), 43 (58); *m/z* (C.I., NH_3) 290 ($M^+ + NH_4$, 100%), 273 ($M^+ + H$, 37).

Diethyl 1-methyl-4-oxocyclohex-2-ene-1,2-dicarboxylate (25). Piperidine (0.99 cm^3, 10.0 mmol) and glacial acetic acid (1.15 cm^3, 20.0 mmol), in toluene (175 cm^3), were heated at 80 ˚C. The diester **24** (16 g, 0.059 mol) was added dropwise and the mixture heated under reflux

for 2 h. The solution was cooled and the solvent removed under reduced pressure. The residue was taken up in dichloromethane (30 cm^3) and washed with water (3x10 cm^3). After drying ($MgSO_4$), the organic layer was concentrated under reduced pressure and distilled (118-122 ˚C, 0.3mbar) yielding the *title compound* **25** (13.17 g, 88%) as a yellow oil (Found: M^+, 254.1150; $C_{13}H_{18}O_5$ requires *M*, 254.1154); ν_{max}/cm^{-1} 2941, 1739 (C=O), 1725 (C=O), 1691 (C=O), 1620, 1253, 1181, 1113, 1098, 1055, 1024; δ_H (300MHz, $CDCl_3$) 1.21 (3H, t, *J* 7, 1-$CO_2CH_2\mathit{CH_3}$), 1.30 (3H, t, *J* 7, 2-$CO_2CH_2\mathit{CH_3}$), 1.59 (3H, s, 1-CH_3), 2.04 (1H, m, 6-*H*H), 2.33 (1H, m, 6-H*H*), 2.54 (2H, m, 5-H_2), 4.10-4.29 (4H, m, 1-$CO_2\mathit{CH_2}CH_3$ and 2-$CO_2\mathit{CH_2}CH_3$), 6.71 (1H, s, 3-H); δ_C (75MHz, $CDCl_3$) 14.0, 21.2, 33.5, 34.1, 44.6, 61.3, 61.7, 132.5, 150.8, 165.6, 174.4, 198.5; *m/z* (E.I.) 254 (M^+, 13%), 181 (38), 179 (100), 105 (53); *m/z* (C.I., NH_3) 272 ($M^+ + NH_4$, 100%), 255 ($M^+ + H$, 32).

7,8-Diethoxycarbonyl-8-methyl-1,4-dioxa-spiro[4.5]dec-6-ene (26). To a solution of the diester **25** (5 g, 0.02 mol) in benzene (40 cm^3) was added 1,2-ethanediol (2.74 cm^3, 0.020 mol) and toluene *p*-sulphonic acid (cat., ~50 mg). The mixture was heated under reflux for 3 hours under a Dean Stark trap, cooled and the solvent removed under reduced pressure. The residue was taken up in dichloromethane (20 cm^3) and washed with water (20 cm^3) and brine (20 cm^3). The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 1:1 petrol:ether, afforded the *title compound* **26** (5.75 g, 98%) as a yellow oil (Found: M^+, 298.1415; $C_{15}H_{22}O_6$ requires *M*, 298.1416); ν_{max}/cm^{-1} 2982, 1723 (C=O), 1650, 1257, 1199, 1126, 1057, 1029; δ_H (300MHz, $CDCl_3$) 1.21 (3H, t, *J* 7, 8-$CO_2CH_2\mathit{CH_3}$), 1.28 (3H, t, *J* 7, 7-$CO_2CH_2\mathit{CH_3}$), 1.46 (3H, s, 8-CH_3), 1.85 (3H, m, 10-H_2 and 9-*H*H), 2.14 (1H, m, 9-H*H*), 4.09 (8H, m, 8-$CO_2\mathit{CH_2}CH_3$, 7-$CO_2\mathit{CH_2}CH_3$, OCH_2CH_2O), 6.69 (1H, s, 6-H); δ_C (75MHz, $CDCl_3$) 14.1, 14.1, 21.9 , 29.6, 33.4, 43.8, 60.8, 60.9, 64.9, 65.0, 104.6, 136.1, 137.0, 165.8, 175.6; *m/z* (E.I.) 298 (M^+, 4%), 252 (40), 225 (94), 224 (100), 86 (79), 84 (78), 49 (62); *m/z* (C.I., NH_3) 316 ($M^+ + NH_4$, 69%), 299 ($M^+ + H$, 100).

(8-Hydroxymethyl-8-methyl-1,4-dioxa-spiro[4.5]dec-6-en-7-yl)-methanol (27). To a solution of diester **26** (5.35 g, 0.018 mol) with stirring at 0˚C in tetrahydrofuran (50 cm^3) was added, dropwise, lithium triethylborohydride (81 cm^3 of a 1 M solution in tetrahydrofuran, 0.081 mol). The reaction mixture was stirred for 1 h and then poured into ether:brine (1:1; 100 cm^3). The layers were separated and the aqueous layer was extracted with ether (2x50 cm^3). The combined organic extracts were washed with brine (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 25:1 ether:methanol, yielded the *title compound* **27** (3.51 g, 91%) as a colourless gum (Found: M^+, 214.1203; $C_{11}H_{18}O_4$ requires *M*, 214.1205); ν_{max}/cm^{-1} 3401 (OH), 2952, 2935, 2878, 1656, 1090, 1020; δ_H (300MHz, $CDCl_3$) 1.07 (3H, s, 8-CH_3), 1.49 (1H, m, 9-*H*H), 2.05 (3H, m, 10-H_2 and 9-H*H*), 3.06 and 3.29 (both 1H, br s, 7-$CH_2O\mathit{H}$ and 8-$CH_2O\mathit{H}$), 3.43 (1H, d, *J* 11, 8-C*H*HOH), 3.65 (1H, d, *J* 11, 8-CH*H*OH), 4.03 (5H, m, 7-C*H*HOH, OCH_2CH_2O), 4.25 (1H, d, *J* 12, 7-CH*H*OH), 5.71 (1H, s, 6-H); δ_C (75MHz, $CDCl_3$) 21.3, 30.0, 32.1, 39.4, 63.6, 64.5, 64.7, 69.7, 105.8, 128.5, 147.0; *m/z* (E.I.) 214 (M^+, 12%), 184 (100), 166 (51), 55 (53); *m/z* (C.I., NH_3) 215 ($M^+ + H$, 100%).

(7-Benzoyloxymethyl-8-methyl-1,4-dioxa-spiro[4.5]dec-6-en-8-yl)-methanol (28) and 7,8-dibenzoyloxymethyl-8-methyl-1,4-dioxa-spiro[4.5]dec-6-ene (29). To a solution of diol **27** (6.5 g, 0.031 mol), triethylamine (10.71 cm^3, 0.077 mol) and 4-dimethylaminopyridine (cat., ~40 mg) stirring in dichloromethane (75 cm^3) benzoyl chloride (3.99 cm^3, 0.034mol) was added dropwise. The reaction mixture was stirred for 5 min and water (13 cm^3) was added. The aqueous layer was extracted with ether (2x13 cm^3). The combined organic extracts were washed with water (13 cm^3) and brine (13 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 3:1 petrol:ether yielded the *title compound* **29** (2.57 g, 20%) as a colourless oil (Found: M^+, 422.1725; $C_{22}H_{26}O_6$ requires *M*, 422.1729); ν_{max}/cm^{-1} 2955, 1720 (C=O), 1601, 1271, 1108, 1070, 710; δ_H (300MHz, $CDCl_3$) 1.33 (3H, s, 8-CH_3), 1.75 (1H, m, 9-*H*H), 1.99 (2H, m, 10-H_2), 2.15 (1H, m, 9-H*H*), 4.02 (4H, m, OCH_2CH_2O), 4.33 (1H, d, *J* 11, 8-C*H*HO), 4.40 (1H, d, *J* 11, 8-CH*H*O), 4.91 (1H, d, *J* 11, 7-C*H*HO), 4.97 (1H, d, *J* 11, 7-CH*H*O), 5.91 (1H, s, 6-H), 7.44 (4H, m, 4xAr-H), 7.57 (2H, m, 2xAr-H), 8.05 (4H, m, 4xAr-H); δ_C (75MHz, $CDCl_3$) 22.2, 29.9, 32.3, 37.6, 64.5, 64.6, 64.7, 69.7, 105.3, 128.4, 128.4, 128.8, 129.7, 129.9, 130.0, 133.0, 141.1, 166.0, 166.4*; m/z* (E.I.) 422 (M^+, 13%), 301 (28), 105 (100); *m/z* (C.I., NH_3) 423 (*(*M^+ + H, 100%). Further elution with 1:1 petrol:ether, yielded the *title compound* **28** (6.45 g, 67%) as a colourless oil (Found: M^+ + H, 319.1537; $C_{18}H_{23}O_5$ requires *M*, 319.1545); ν_{max}/cm^{-1} 3477 (OH), 2954, 2880, 1720 (C=O), 1665, 1272, 1112, 1086, 1071, 1026, 713; δ_H (300MHz, $CDCl_3$) 1.13 (3H, s, 8-CH_3), 1.60 (1H, m, 9-*H*H), 2.04 (4H, m, 10-H_2, 9-H*H* and 8-CH_2O*H*), 3.51 (1H, dd, *J* 11 and 7, 8-C*H*HOH), 3.77 (1H, dd, *J* 11 and 4, 8-CH*H*OH), 3.99 (4H, m, OCH_2CH_2O), 4.81 (1H, dd, *J* 14 and 1, 7-C*H*HO), 4.96 (1H, dd, *J* 14 and 1, 7-CH*H*O), 5.83 (1H, s, 6-H), 7.48 (2H, t, *J* 7, 2xAr-H), 7.61 (1H, t, *J* 7, 1xAr-H), 8.08 (2H, d, *J* 7, 2xAr-H); δ_C (75MHz, $CDCl_3$) 21.6, 30.0, 32.0, 39.4, 64.2, 64.6, 69.3, 105.5, 128.2, 128.5, 129.7, 129.8, 133.2, 142.0, 166.3; *m/z* (E.I.) 288 (4%), 122 (62), 105 (100), 77 (99); *m/z* (C.I., NH_3) 319 (M^+ + H, 49%), 292 (100), 172 (55).

7-Benzoyloxymethyl-8-*tert*-butyldimethylsilyloxymethyl-8-methyl-1,4-dioxa-spiro[4.5]dec-6-ene (30). To a solution of alcohol **28** (6.45 g, 0.020 mol) and imidazole (4.14 g, 0.061 mol) stirring in dichloromethane (100 cm^3), at 0˚C, *tert*-butyldimethylsilyl chloride (3.06 g, 0.020 mol) was added. The reaction mixture was stirred for 18 h then satd. aq. ammonium chloride (30 cm^3) was added. The aqueous layer was extracted with dichloromethane (3x25 cm^3). The combined organic extracts were washed with water (25 cm^3) and brine (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, using petrol as the eluent, yielded the *title compound* **30** (8.52 g, 97%) as a colourless oil (Found: M^+, 432.2332; $C_{24}H_{36}O_5Si$ requires *M*, 432.2332); ν_{max}/cm^{-1} 2954, 2932, 1723 (C=O), 1665, 1602, 1585, 1268, 1094, 838, 712; δ_H (300MHz, $CDCl_3$) 0.07 (6H, s, $Si(CH_3)_2$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.18 (3H, s, 8-CH_3), 1.58 (1H, m, 9-*H*H), 1.94 (3H, m, 10-H_2 and 9-H*H*), 3.57 (2H, s, 8-CH_2), 4.01 (4H, m, OCH_2CH_2O), 4.90 (2H, d, *J* 1, 7-CH_2), 5.77 (1H, s, 6-H), 7.48 (2H, t, *J* 8, 2xAr-H), 7.60 (1H, t, *J* 8, 1xAr-H), 8.10 (2H, dd, *J* 8 and 1, 2xAr-H); δ_C (75MHz, $CDCl_3$) -5.6, -5.5, 18.3, 21.8, 25.9, 30.0, 31.6, 39.2, 64.5, 64.5, 68.7, 105.7,

125.9, 128.4, 129.7, 130.2, 133.0, 143.2, 166.1; *m/z* (E.I.) 432 (M^+, 5%), 378 (18), 179 (100), 105 (53), 77 (26), 73 (44); *m/z* (C.I., NH_3) 433 (M^+ + H, 100%).

(8-*tert*-Butyldimethylsilyloxymethyl-8-methyl-1,4-dioxa-spiro[4.5]dec-6-en-7-yl)-methanol (31). To a solution of ester **30** (8.52 g, 0.020 mol) in tetrahydrofuran (160 cm^3), at 0 ˚C, was added lithium triethylborohydride (43.4 cm^3, 1M in tetrahydrofuran, 0.043 mol). The reaction mixture was stirred for 30 min then water (40 cm^3) was added. The aqueous layer was extracted with ether (2x40 cm^3). The combined organic extracts were washed with water (40 cm^3) and brine (40 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 3:1 petrol:ether, yielded the *title compound* **31** (6.19 g, 96%) as a colourless oil (Found: M^+, 328.2074; $C_{17}H_{32}O_4Si$ requires *M*, 328.2070); ν_{max}/cm^{-1} 3432 (OH), 2953, 1663, 1255, 1090, 838, 776; δ_H (300MHz, $CDCl_3$) 0.11 (6H, s, $Si(CH_3)_2$), 0.94 (9H, s, $SiC(CH_3)_3$), 1.10 (3H, s, 8-CH_3), 1.50 (1H, m, 9-*H* H), 1.88 (3H, m, 10-H_2 and 9-H*H*), 2.87 (1H, m, 7-CH_2O*H*), 3.55 (2H, s, 8-CH_2O), 4.00 (5H, m, 7-C*H* HOH, OCH_2CH_2O), 4.22 (1H, dd, *J* 13 and 4, 7-CH*H* O), 5.68 (1H, s, 6-H); δ_C (75MHz, $CDCl_3$) -5.5, 18.3, 21.7, 25.8, 30.1, 32.4, 39.1, 63.7, 64.5, 64.6, 70.1, 105.8, 125.6, 147.6; *m/z* (E.I.) 329 (M^+ + H, 51%), 328 (M^+, 69), 271 (40), 179 (77), 75 (97), 73 (100); *m/z* (C.I., NH_3) 329 (M^+ + H, 100%).

8-*tert*-Butyldimethylsilyloxymethyl-7-but-2-ynyloxymethyl-8-methyl-1,4-dioxa-spiro[4.5]-dec-6-ene (32). To a suspension of sodium hydride (1.75 g of a 60% dispersion in mineral oil, 0.044 mol), previously washed with hexane (3x20 cm^3), in tetrahydrofuran (40 cm^3) was added the alcohol **31** (5.77 g, 0.018 mol) in tetrahydrofuran (40 cm^3). The reaction mixture was stirred for 1 h and then 1-bromobut-2-yne (5.85 g, 0.044 mol) was added. The mixture was stirred for a further 28 h and water (40 cm^3) added. The aqueous layer was extracted with ether (2x30 cm^3). The combined organic extracts were washed with water (30 cm^3) and brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 3:1 petrol:ether, yielded the *title compound* **32** (6.09 g, 91%) as a colourless oil (Found: M^+, 380.2375; $C_{21}H_{36}O_4Si$ requires *M*, 380.2383); ν_{max}/cm^{-1} 2953, 2930, 1094, 837, 775; δ_H (300MHz, $CDCl_3$) 0.06 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.08 (3H, s, 6-CH_3), 1.50 (1H, m, 9-*H* H), 1.90 (6H, m, 10-H_2, 9-H*H* and 4'-H_3), 3.50 (2H, s, 1'-H_2), 4.03 (8H, m, 7-CH_2O, 8-CH_2O, OCH_2CH_2O), 5.69 (1H, s, 6-H); δ_C (75MHz, $CDCl_3$) -5.6, -5.5, 3.6, 18.2, 21.6, 25.9, 30.1, 31.7, 39.0, 57.8, 64.5, 64.5, 68.6, 69.2, 75.2, 82.3, 105.9, 124.8, 144.2; *m/z* (E.I.) 380 (M^+, 6%), 323 (24), 223 (40), 179 (68), 89 (71), 75 (68), 73 (100); *m/z* (C.I., NH_3) 381 (M^+ + H, 100%).

8-*tert*-Butyldimethylsilyloxymethyl-6-(1-hydroxybut-2-ynyl)-8-methyl-7-methylene-1,4-dioxa-spiro[4.5]decane (33). To a solution of ether **32** (6.04 g, 0.016 mol) in tetrahydrofuran (40 cm^3), at –78 ˚C, was added *n*-butyllithium (11.92 cm^3 of a 1.6M solution in hexane, 0.091 mol). The reaction mixture was stirred for 48 h at –78 ˚C then water (25 cm^3) was added. The aqueous layer was extracted with ether (2x25 cm^3). The combined organic extracts were washed with water (25 cm^3) and brine (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 3:1 petrol:ether, yielded the *title compound* **33** as a

mixture of diastereoisomers (4.52 g, 75%) as a colourless oil (Found: M^+ + H, 381.2457; $C_{21}H_{37}O_4Si$ requires *M*, 381.2461); ν_{max}/cm^{-1} 3502 (OH), 2953, 2857, 1679, 1639, 1090, 838, 776; δ_H (300MHz, $CDCl_3$) 0.03, 0.05, 0.06 and 0.06 (6H in total, all s, $Si(CH_3)_2$), 0.89 (4H, s, 0.44x$SiC(CH_3)_3$), 0.90 (5H, s, 0.56x$SiC(CH_3)_3$), 1.09 (0.67H, s, 0.22x8-CH_3), 1.11 (1.5H, s, 0.5x8-CH_3), 1.13 (0.83H, s, 0.28x8-CH_3), 1.35 (1H, m, 9-*H* H), 1.69 (3H, m, 9-H*H* and 10-H_2), 1.88 (3H, m, 4'-H_3), 2.89 (1H, m, 6-H), 3.40-3.85 (3H, m, 8-CH_2O and 1'-H), 4.05 (4H, m, OCH_2CH_2O), 4.66 (0.3H, br s, 0.3x1'-OH), 4.90 (0.7H, br s, 0.7x1'-OH), 5.05 (0.42H, m, 0.21x7-CH_2), 5.16 (0.66H, d, *J* 1, 0.33x7-CH_2), 5.29 (0.26H, s, 0.13x7-H_2), 5.52 (0.66H, d, *J* 2, 0.33x7-CH_2); δ_C (75MHz, $CDCl_3$) -5.6, -5.5, -5.5, 3.9, 4.0, 4.3, 15.3, 18.2, 18.2, 23.3, 23.6, 23.9, 25.8, 25.9, 30.2, 30.3, 31.4, 31.5, 31.7, 32.1, 40.5, 41.2, 41.8, 50.9, 54.9, 61.5, 61.7, 63.2, 64.2, 64.3, 64.5, 64.7, 65.3, 65.9, 68.1, 69.1, 69.5, 79.2, 80.1, 80.2, 81.4, 110.0, 111.1, 112.4, 112.5, 115.1, 146.7, 146.8; *m/z* (E.I.) 99 (100%), 75 (37), 73 (32); *m/z* (C.I., NH_3) 381 (M^+ + H, 5%), 313 (100), 99 (37). Starting ether **32** (656 mg, 11%) was also recovered.

(6*RS*,8*RS*)]- and (6*SR*,8*RS*)]-8-*tert*-Butyldimethylsilyloxymethyl-6-(1-oxobut-2-ynyl)-8-methyl-7-methylene-1,4-dioxa-spiro[4.5]decanes (34) and (35). To oxalyl chloride (0.98 cm^3, 11.20 mmol) with stirring at –78 ˚C, in dichloromethane (50 cm^3) was added, dropwise, dimethyl sulphoxide (1.99 cm^3, 27.99 mmol) in dichloromethane (10 cm^3). The mixture was stirred for 15 min after which the alcohol **33** (2.13 g, 5.60 mmol) in dichloromethane (10 cm^3) was added. After a further 3 h triethylamine (3.9 cm^3, 27.99 mmol) was added and the reaction mixture slowly warmed to room temperature. The reaction mixture was stirred for a further 2 h then water (70 cm^3) was added. The aqueous layer was extracted with dichloromethane (2x20 cm^3) and the combined organic extracts were washed with water (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 3:1 petrol:ether, yielded the *title compounds* **34** and **35** (1.74 g, 82%) as a colourless oil. Preparative HPLC, 70:30 acetonitrile:water, separated the two diastereoisomers, **34**:**35** = 55:45. Major diastereoisomer **34** (Found: M^+, 378.2224; $C_{21}H_{34}O_4Si$ requires *M*, 378.2226); ν_{max}/cm^{-1} 2954, 2930, 2894, 2857, 2217, 1680 (C=O), 1658, 1253, 1089, 838, 776; δ_H (300MHz, $CDCl_3$) 0.07 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.11 (3H, s, 8-CH_3), 1.55 (1H, m, 9-*H* H), 1.73 (2H, m, 10-H_2), 1.87 (1H, m, 9-H*H*), 2.04 (3H, s, 4'-H_3), 3.53 (1H, d, *J* 10, 8-C*H* HO), 3.56 (1H, d, *J* 10, 8-CH*H* O), 3.79 (1H, s, 6-H), 4.05 (4H, m, OCH_2CH_2O), 5.04 (1H, d, *J* 2, 7-C*H* H), 5.11 (1H, s, 7-CH*H*); δ_C (75MHz, $CDCl_3$) -5.5, 4.3, 18.2, 23.3, 25.5, 31.4, 31.7, 41.2, 63.2, 64.7, 65.3, 69.1, 81.6, 90.2, 110.0, 113.0, 147.2, 186.2; *m/z* (E.I.) 378 (M^+, 4%), 321 (37), 99 (100), 86 (38), 73 (54), 67 (65); *m/z* (C.I., NH_3) 379 (M^+ + H, 100%). Minor diastereoisomer **35** (Found: M^+, 378.2227; $C_{21}H_{34}O_4Si$ requires *M*, 378.2226); ν_{max}/cm^{-1} 2953, 2929, 2888, 2857, 2218, 1679 (C=O), 1631, 1257, 1092, 838, 776; δ_H (300MHz, $CDCl_3$) 0.49 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.17 (3H, s, 8-CH_3), 1.62 (4H, m, 9-H_2 and 10-H_2), 2.04 (3H, s, 4'-H_3), 3.42 (1H, d, *J* 10, 8-C*H* HO), 3.52 (1H, d, *J* 10, 8-CH*H* O), 3.68 (1H, s, 6-H), 3.75 (4H, m, OCH_2CH_2O), 5.16 (2H, s, 7-CH_2); δ_C (75MHz, $CDCl_3$) -5.5, 4.2, 18.3, 23.7, 25.9, 30.2, 31.2,

41.3, 64.3, 64.9, 65.1, 67.9, 81.1, 90.5, 109.6, 115.7, 146.4, 185.5; *m/z* (E.I.) 378 (M^+, 6%), 321 (62), 99 (100), 73 (64), 67 (62); *m/z* (C.I., NH_3) 379 (M^+ + H, 100%).

8-*tert*-Butyldimethylsilyloxymethyl-6-(3-methyl-1-oxobut-2-enyl)-8-methyl-7-methylene-1,4-dioxa-spiro[4.5]decane (36). To copper(I) iodide (1.56 g, 8.19 mmol) in tetrahydrofuran (11 cm^3) at 0 ˚C, was added methyllithium (9.93 cm^3 of a 1.65M solution in ether, 16.38 mmol). The reaction mixture was stirred for 15 min during which time the solution changed from colourless to yellow in colour and then back to colourless. A mixture of the alkynes **34** and **35** (619 mg, 1.64 mmol) in tetrahydrofuran (5 cm^3) was added and the reaction mixture stirred for 30 min. A mixture of satd. aq. ammonium chloride and 10% aq. ammonia (1 : 1, 10 cm^3) was added over 30 min and the mixture warmed to room temperature. The aqueous layer was extracted with ether (3x10 cm^3). The combined organic extracts were washed with brine (3x10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 3:1 petrol:ether, yielded the *title compound* **36** (494 mg, 77%) as a colourless oil (Found: M^+, 394.2534; $C_{22}H_{38}O_4Si$ requires *M*, 394.2539); ν_{max}/cm^{-1} 2954, 2930, 2858, 1691 (C=O), 1622, 1254, 1091, 838, 776; δ_H (300MHz, $CDCl_3$) 0.00, 0.03 and 0.06 (1H, 1H and 4H, s, $Si(CH_3)_2$), 0.88 and 0.91 (3H and 6H, s, $SiC(CH_3)_3$), 1.09 and 1.14 (2H and 1H, s, 8-CH_3), 1.26 (1H, m, 9-*H*H), 1.62 (3H, m, 9-H*H* and 10-H_2), 1.89 (3H, s, 3'-CH_3), 2.17 (3H, s, 4'-H_3), 3.47 (3H, m, 6-H, 8-CH_2O), 4.00 (4H, m, OCH_2CH_2O), 4.90 (0.7H, s, 0.35x7-H_2), 5.07 (1.3H, m, 0.65x7-H_2), 6.23 (1H, s, 2'-H); δ_C (75MHz, $CDCl_3$) -5.6, -5.6, -5.5, -5.5, 18.2, 20.8, 23.2, 24.9, 25.9, 27.7, 27.8, 29.9, 31.5, 31.8, 41.2, 41.5, 62.3, 64.0, 64.3, 64.6, 65.0, 65.2, 67.7, 69.1, 110.1, 110.4, 112.6, 114.8, 124.1, 125.2, 148.3, 148.6, 154.4, 155.3, 197.8, 198.6; *m/z* (E.I.) 394 (M^+, 5%), 337 (18), 127 (100), 99 (47), 83 (45); *m/z* (C.I., NH_3) 395 (M^+ + H, 100%), 127 (47).

4-(*tert*-Butyldimethylsilyloxymethyl)-3,4-dimethyl-2-(3-methyl-1-oxobut-2-enyl)cyclohex-2-enone (37). To a solution of the ketal **36** (100 mg, 0.254 mmol) in 10:1 acetone:water (3.8 cm^3) was added pyridinium toluene *p*-sulphonate (cat., ~5 mg). The reaction mixture was heated under reflux for 27 h then diluted with water:ether (1 : 1, 2 cm^3). The aqueous layer was extracted with ether (2x2 cm^3). The combined organic extracts were washed with water (2 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography, 3:1 petrol:ether, yielded the *title compound* **37** (35 mg, 40%) as a colourless oil (Found: M^+ + H, 351.2360; $C_{20}H_{35}O_3Si$ requires *M*, 351.2355); ν_{max}/cm^{-1} 2954, 2930, 2857, 1666 (C=O), 1616, 1254, 1097, 839, 777; δ_H (300MHz, $CDCl_3$) 0.08, (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.14 (3H, s, 4-CH_3), 1.72 (1H, m, 5-*H*H), 1.87 and 1.93 (3H each, s, 3-CH_3 and 3'-CH_3), 2.27 (4H, m, 5-H*H* and 4'-H_3), 2.54 (2H, m, 6-H_2), 3.46 (1H, d, *J* 10, 4-C*H*HO), 3.74 (1H, d, *J* 10, 4-CH*H*O), 6.08 (1H, s, 2'-H); δ_C (75MHz, $CDCl_3$) -5.6, 16.4, 18.2, 20.7, 21.0, 25.8, 28.0, 32.1, 34.3, 41.0, 69.0, 125.4, 142.0, 156.4, 161.3, 196.5, 197.1; *m/z* (E.I.) 293 (31%), 263 (44), 218 (37), 89 (47), 83 (71), 75 (60), 73 (100); *m/z* (C.I., NH_3) 351 (M^+ + H, 100%). Starting ketal **36** (25 mg, 25%) was also recovered.

§ In the schemes, P refers to an undefined protecting group.

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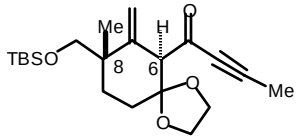
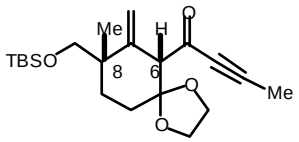


34



35

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