

Synthesis of a spiroacetal intermediate for the synthesis of the anti-*Helicobacter pylori* agent CJ-12, 954

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Abstract

A method has been established for the synthesis of the 5,5-spiroacetal moiety of the anti-*Helicobacter pylori* agents CJ-12,954 **1** and CJ-13,014 **2** in racemic form and as a mixture of stereoisomers. Retrosynthetically the key spiroacetal **9** is derived from the acyclic protected dihydroxyketone precursor **10** or **11** which in turn are available from enynone **25** or **26**. Enynones **25** and **26** were prepared via addition of the acetylide derived from acetylenes **13** or **14** to aldehyde **12** followed by oxidation of the resultant alcohols **23** and **24** respectively. Acetylenes **13** and **14** in turn were available via [2,3]-sigmatropic rearrangement of allyl propargyl ether **16**. Extension of this reaction in an asymmetric sense by use of a chiral base would have provided acetylene **14** in enantioenriched form, however, efforts towards this end were disappointing. Enynones **25** and **26** were converted to keto epoxides **10** and **11** respectively by treatment with *meta*-chloroperbenzoic acid followed by hydrogenation of the acetylene. Attempts to effect deprotection and cyclization of bis-silyl ethers **10** and **11** to spiroacetal **9** were complicated by the presence of the epoxide. In an alternative approach enynone **26** was converted to methyl acetal **29** upon treatment with camphorsulfonic acid in methanol. Subsequent epoxidation of the terminal alkene **29** afforded epoxide **30** which then underwent smooth hydrogenation and cyclization *in situ* to the desired spiroacetal **9**.

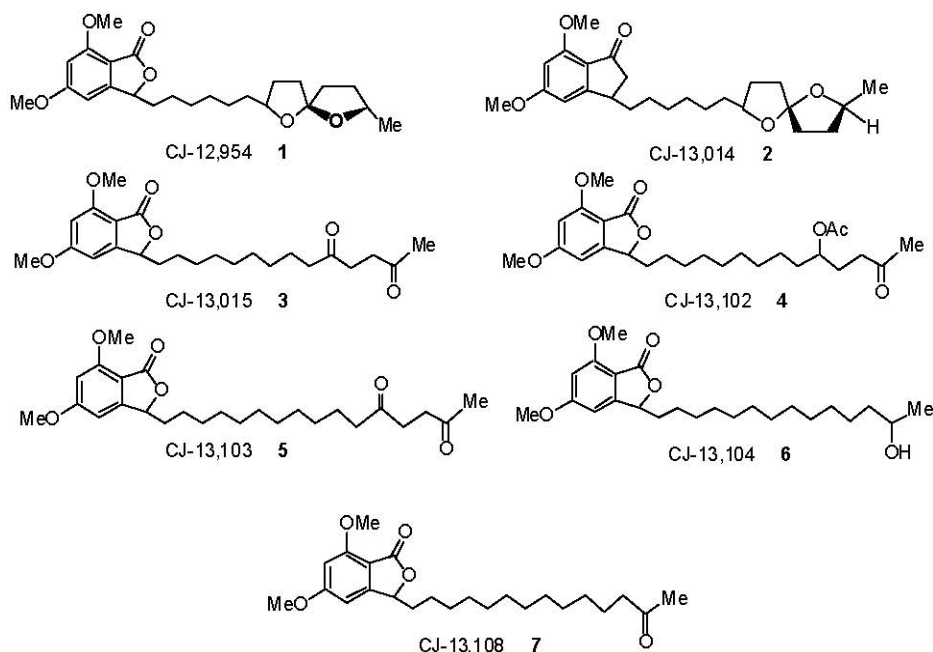
Keywords: Spiroacetals, anti-ulcer agents, *Helicobacter pylori*, Wittig rearrangement, antibiotic CJ-12,954

Introduction

Gastric and duodenal ulcers affect a significant portion of the human population worldwide. Initially they were thought to be caused by damage to stomach and duodenal tissue by digestive fluids (acid and pepsin). More recent studies have shown a relationship between the presence of the microaerophilic Gram-negative bacterium *Helicobacter pylori*, which appears to live beneath the mucus layer of the stomach, and gastric and duodenal ulcers.¹ Therapy to eliminate *Helicobacter pylori* from the gastroduodenal tract would remove the root cause of gastric and duodenal ulcers therefore antibiotics are prescribed for the treatment of *Helicobacter pylori* in addition to treatment aimed at decreasing the production of stomach acid.²

In a screening program designed to discover such compounds from microbial secondary metabolites, seven new phthalide compounds **1-7** with anti-*Helicobacter pylori* activity were isolated from the basidiomycete *Phanerochaete velutina* CL6387.³ The two most potent compounds, CJ-12, 954 **1** and CJ-13, 014 **2** have MICs of 5 ng/ml establishing that the presence of a spiro acetal moiety in addition to a phthalide unit enhances biological activity. The phthalide compounds **1-7** were specific for *Helicobacter pylori* in that they did not show antibacterial activities when tested against a panel of other microorganisms. This observed specific activity against *Helicobacter pylori* suggests that phthalides **1-7** may exhibit less side effects caused by disturbance of the normal gastro-intestinal microbial flora and may not induce drug resistance of non-target micro organisms.

The phthalides **1-7** are related to spiroloxine and sporotriacale⁴ which have also been reported to have cholesterol lowering activity.⁵ Spiroloxine has helicobactericidal activity similar to **1** and **2**. The rare 5,5-spiroacetal found in CJ-12, 954 **1** and CJ-13,014 **2** is also present in an insect pheromone⁶ and in a constituent of hop oil.⁷ We herein report a synthesis of the 5,5-spiroacetal moiety of the anti-*Helicobacter pylori* agents CJ-12,954 and **1** and CJ-13,014 **2**.

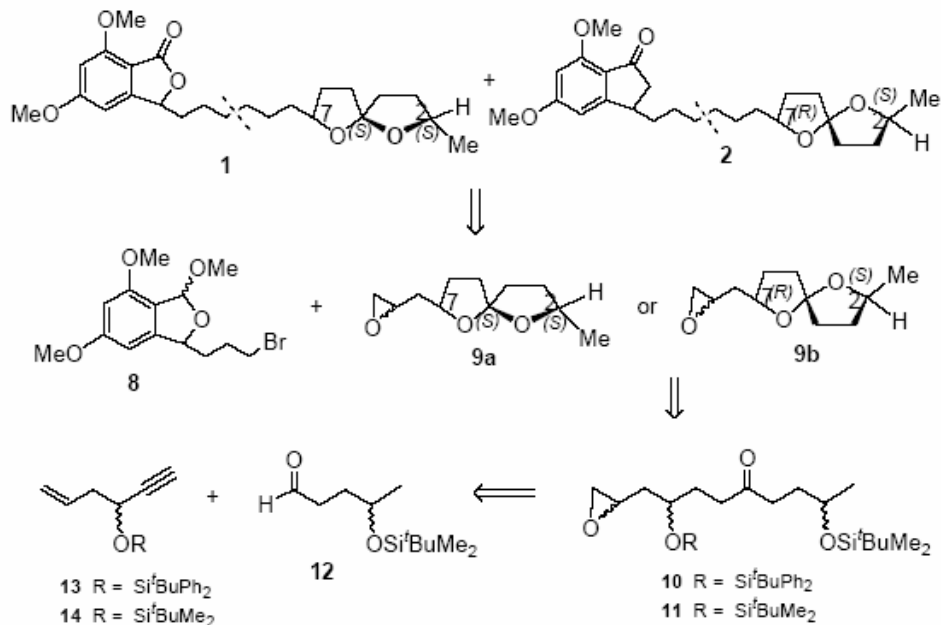


Results and Discussion

The stereochemistry of the stereogenic centre on the phthalide ring in both CJ-12,954 **1** and CJ-13,014 **2** has not been defined to date. CJ-12,954 **1** and CJ-13,014 **2** both exhibit 2*S*,7*S* stereochemistry in the spiroacetal ring and only differ in the configuration of the spirocentre. The focus of this work was on the development of a synthetic route to the spiroacetal moiety of CJ-12, 954 **1** and CJ-13,014 **2** as a mixture of stereoisomers using a synthesis that could be adapted at a later stage to control the stereochemistry at C-2 and C-7 of the spiroacetal ring system.

The key step in the retro synthesis adopted for the synthesis of CJ-12,954 **1** and CJ-13,014 **2**

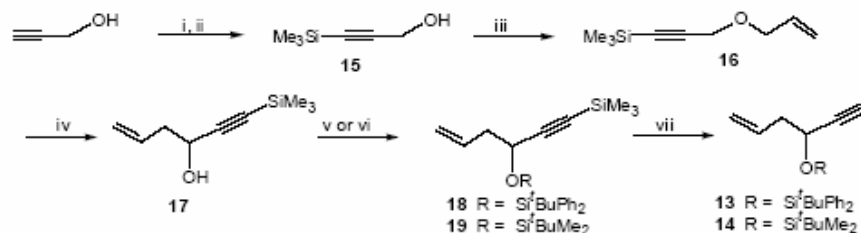
(Scheme 1) hinges on the addition of the Grignard reagent derived from bromide **8** to spiro acetal epoxide **9** followed by deoxygenation of the resultant secondary alcohol. The acyclic protected dihydroxy ketone precursor **10** or **11** to spiro acetal epoxide **9** is then constructed from addition of the acetylide of acetylene **13** or **14** to aldehyde **12**.



Scheme 1

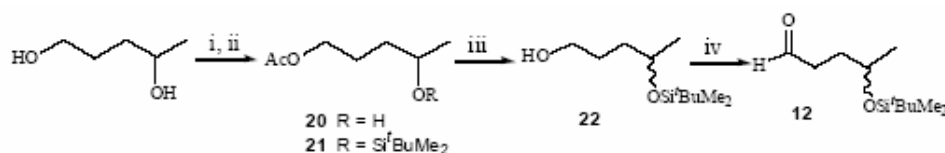
The acetylenes **13** and **14** were prepared using via [2,3]-sigmatropic rearrangement of allyl propargyl ether **16** (Scheme 2). Propargyl alcohol was converted to its *C*-trimethylsilyl derivative **15**⁸ via formation of the dianion using two equivalents of butyllithium followed by quenching with trimethylsilyl chloride. Subsequent allylation using conditions reported in the literature⁹ (ethylmagnesium bromide and HMPA) afforded allyl propargyl ether **16**. Unfortunately attempts to carry out this reaction using alternative reagents such as sodium hydride / allyl bromide, butyllithium / allyl bromide, ethyl bromide / allyl bromide were unsuccessful hence the use of the highly toxic agent HMPA could not be avoided. Treatment of allyl propargyl ether **16** with butyllithium at -78 °C for 10 min. effected smooth [2,3]-sigmatropic rearrangement to alcohol **17**.¹⁰ Subsequent *O*-silylation with *tert*-butyldimethylsilyl chloride or *tert*-butyldiphenylsilyl chloride afforded silyl ethers **18** and **19** respectively, which then underwent *C*-desilylation upon treatment with sodium methoxide to afford acetylenes **13** and **14**.

Aldehyde **12** was prepared (Scheme 3) from 1,4-pentanediol by monoacetylation of the primary alcohol using 3-acetyltetrahydrothiazole-2-thione^{11,12} to obtain acetate **20**¹³ followed by protection of the secondary alcohol as a *tert*-butyldimethyl silyl ether **21**.¹⁴ Selective removal of the acetate using potassium carbonate in methanol then afforded primary alcohol **22**¹⁴ which underwent oxidation to the required aldehyde **12**¹⁵ using Dess-Martin periodinane.¹⁶



Reagents and Conditions: (i) ^tBuLi, THF, -78 °C to room temp. (ii) 1 M, HCl, 0.5 h, 70% (iii) 1.2 M EtMgBr, HMPA (4.0 equiv.), THF, 0 °C, 5 min. Then allyl bromide, Δ, 4 h., 67%; (iv) ^tBuLi, THF, -78 °C, 10 min., 97%; (v) ^tBuPh₂SiCl, DMAP, imidazole, CH₂Cl₂ room temp., 4 h., 98%. (vi) ^tBuMe₂SiCl, DMAP, imidazole, CH₂Cl₂ room temp., 4h., 98%. (vii) NaOMe, MeOH, 1h., **13**, 88%; **14**, 96%.

Scheme 2



Reagents and Conditions: (i) 3-acetyltetrahydrothiazole-2-thione, NaH, THF, 2h, room temp., 82%. (ii) ^tBuMe₂SiCl, DMAP, imidazole, DMF, room temp., 4 h., 95%. (iii) K₂CO₃, MeOH, room temp., 18h., 92%. (iv) Dess-Martin periodinane, CH₂Cl₂, py, 1h, 94%.

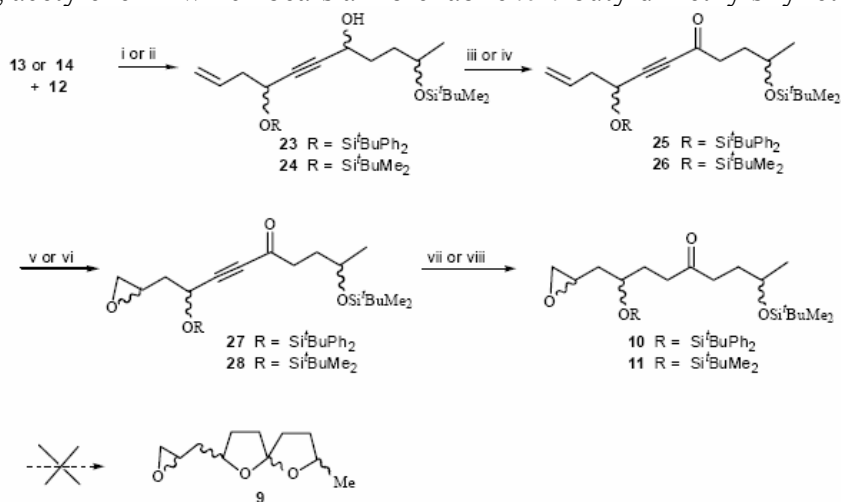
Scheme 3

With quantities of aldehyde **12** and acetylenes **13** and **14** in hand, our attention next focused on their union via formation of the lithium acetylide (Scheme 4). Treatment of acetylene **13** in which the hydroxyl group is protected as robust *tert*-butyldiphenylsilyl ether with butyllithium in THF at -78 °C for 1h Followed by treatment with aldehyde **12** failed to generate the desired alcohol **23**. In all cases unreacted acetylene **13** was recovered from the reaction.

In order to test whether butyllithium was in fact removing the acetylene proton prior to the addition of aldehyde **12**, a series of quenches with deuterium oxide were performed. As a result of these studies, it was established that both butyllithium and *tert*-butyllithium were insufficiently basic to remove the acetylenic proton. Use of Schlosser's base¹⁷ (a mixture of butyllithium and potassium *tert*-butoxide) effected deprotonation under these conditions and resulted in 100% incorporation of deuterium. Disappointingly, application of these conditions to the addition of the acetylide of acetylene **13** to aldehyde **12** only afforded the desired alcohol **23**[#] in 28% yield.

Attempts to optimise the use of Schlosser's base to effect this reaction proved uneventful. The principal side reactions observed were desilylation of acetylene **13** and aldehyde **12**. Our attention then turned to the use of butyllithium with TMEDA as a cosolvent. The efficacy of the butyllithium / TMEDA system was first demonstrated by a deuterium quench and ultimately the coupling of acetylene **13** with aldehyde **12** to afford alcohol **23** proceeded in 85% yield.

Use of a *tert*-butyldiphenylsilyl ether to protect the hydroxyl group in acetylene **13** proved problematic in the subsequent deprotection step (*vide infra*). Thus, a parallel study was also undertaken using acetylene **14** which bears a more labile *tert*-butyldimethylsilyl ether.



Reagents and Conditions: (i) **13**, ^tBuLi, TMEDA (2.5 equiv.), THF, -78 °C, 1h., then **15**, 0.5h., 85%. (ii) **14**, ^tBuLi, TMEDA (2.5 equiv.), THF, -78 °C, 50 min., then add to (**15**), 0.5h., 52%. (iii) **23**, Dess-Martin periodinane, CH₂Cl₂, room temp., 83%. (iv) **24**, TPAP, NMO, CH₂Cl₂, room temp., 0.5h., 98%. (v) **25**, *m*-CPBA, NaOAc, CH₂Cl₂, room temp., 5 days, 79%. (vi) **26**, *m*-CPBA, NaOAc, CH₂Cl₂, room temp., 5 days, 75%. (vii) **27**, 10% Pd/C, H₂, EtOAc, NaHCO₃, 2h., 98%; (viii) **28**, 10% Pd/C, H₂, EtOAc, NaHCO₃, 2h., 74%.

Scheme 4

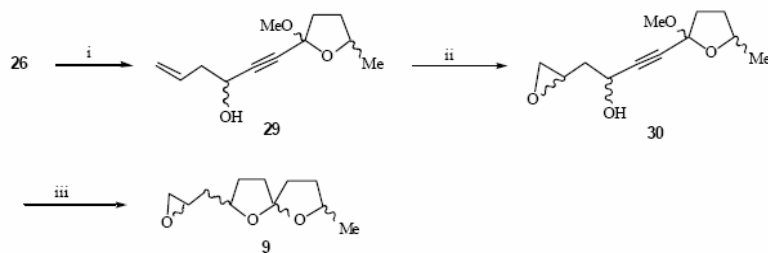
In this latter case the addition of the acetylide of acetylene **14** to aldehyde **12** was only achieved by adding the acetylide to a solution of the aldehyde (reverse addition) affording alcohol **24** in a modest 52% yield.

Alcohols **23** and **24** underwent smooth oxidation in good yield to ketones **25** and **26** using Dess-Martin periodinane or tetrapropylammonium perruthenate and *N*-methylmorpholine-*N*-oxide respectively. Subsequent selective epoxidation of the terminal alkenes **25** and **26** using *meta*-chloroperbenzoic acid buffered with sodium acetate effected smooth conversion to epoxy ynones **10** and **11** respectively. Finally removal of the triple bond by hydrogenation over palladium on charcoal afforded the key saturated keto epoxides **10** and **11** which were precursors to the desired 5,5-spiroacetal **9**.

At this stage it was envisaged that deprotection of both the silyl ethers in keto epoxides **10** and **11** would liberate a diol which would immediately undergo cyclization to the desired spiroacetal **9**. Unfortunately initial attempts to effect this transformation using silyl ether **10** which bears a robust *tert*-butyldiphenylsilyl ether at C-8, were unproductive, hence the analogous bis-silyl ether **11** was prepared which bore a more labile *tert*-butyldimethylsilyl ether at C-8. Unfortunately attempts to deprotect bis-silyl ether **11** using a variety of conditions such as tetrabutylammonium fluoride, HF/pyridine and pyridinium *p*-toluenesulfonate in dichloromethane or methanol afforded complex mixtures for which the ¹H n.m.r. spectra of the

crude product mixture clearly indicated that the epoxide had undergone reaction.

A solution to this problem was found by forming the two five membered rings of 5,5-spiroacetal **9** sequentially (Scheme 5). Treatment of bis-silyl ether **26** with a catalytic quantity of camphorsulfonic acid in methanol afforded methyl acetal **29** in 97% yield which then underwent selective epoxidation of the terminal alkene using *meta*-chloroperbenzoic acid buffered with sodium acetate affording epoxide **30** in 89% yield. The long reaction times required to effect this epoxidation and the epoxidation of alkenes **25** and **26** above, was somewhat surprising, nevertheless epoxidation of alkene **29** in the presence of the alkyne did proceed selectively. Finally hydrogenation of alkyne over palladium on charcoal in the presence of sodium bicarbonate as buffer afforded the key 5,5-spiroacetal **9** in 63% yield. The modest yield for this step was attributed to the volatility of this compound.



Reagents and Conditions: (i) camphorsulfonic acid (cat.), CH₂Cl₂, MeOH, room temp., 2h., 97%; (ii) *m*-CPBA, NaOAc, CH₂Cl₂, room temp., 2 days, 89%; (iii) 10% Pd/C, H₂, EtOAc, NaHCO₃, 2h., 63%.

[#] In all of the reactions described a mixture of stereoisomers was obtained which were not separated.

Reagents and Conditions: (i) camphorsulfonic acid (cat.), CH₂Cl₂, MeOH, room temp., 2h., 97%. (ii) *m*-CPBA, NaOAc, CH₂Cl₂, room temp., 2 days, 89%. (iii) 10% Pd/C, H₂, EtOAc, NaHCO₃, 2h., 63%.

Scheme 5

Having successfully prepared spiroacetal **9**, albeit as a mixture of all possible stereoisomers, it was next decided to extend the synthetic methodology developed herein to execute a stereocontrolled synthesis of spiroacetal **9**. In order to prepare anti-*Helicobacter pylori* agents CJ-12,954 **1** and CJ-13,014 **2** with the required 2*S*, 7*S* configuration of the 5,5-spiroacetal ring system, a synthesis of spiroacetals **9a** or **9b** which have the correct 2*S*,7*R* stereochemistry must be achieved. The stereochemistry of the spirocentre or the epoxide does not need to be controlled as the stereocentre in the epoxide is removed in a subsequent step and it was anticipated that two stereoisomers of the 5,5-spiroacetal, which differ only in the configuration of the spirocentre, would always be formed in the final spirocyclization step.

Applying the synthetic methodology reported herein to the synthesis of spiroacetal **9** with the correct 2*S*, 7*R* stereochemistry requires the synthesis of (*S*)-acetylene **14** and (*S*)-aldehyde **12**. (*S*)-Aldehyde **12** is available from (*S*)-1,4-pentanediol which in turn is readily prepared from ethyl 4-oxopentanoate by enantioselective reduction of the ketone with bakers' yeast¹⁸ followed by reduction of the ester using lithium aluminium hydride.

It was envisaged that acetylene **14** would be available in enantioenriched form by extending the key [2,3]-sigmatropic rearrangement of allyl propargyl ether **16** in an asymmetric sense.¹⁹

Towards this end, allyl propargyl ether was subjected to [2,3]-sigmatropic rearrangement using butyllithium in the presence of the chiral bases (-)-sparteine,²⁰ (1*R*,2*S*)-(-)-norephedrine and [*R*-(*R**,*R**)]-(+)-bis(α -methylbenzylamine). Disappointingly alcohol **17** was only obtained as a racemic mixture in all cases.

The successful completion of the synthesis of spiroacetal epoxide **9**, albeit as a mixture of stereoisomers, constitutes a synthesis of the spiroacetal moiety of CJ-12, 954 **1** and CJ-13, 014 **2**. It now remains to append the phthalide fragment **8** to this spiroacetal fragment. The inability to effect the key [2,3]-sigmatropic rearrangement of allyl propargyl ether **16** to alcohol **17** in an asymmetric fashion has necessitated that future work also be directed towards a synthesis of this 5,5-spiroacetal **9** using methodology that enables control of the stereochemistry at C-2 and C-7 of the spiroacetal ring system.

Experimental Section

General Procedures. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1600 series Fourier-transform infrared spectrometer as thin films between sodium chloride plates. ¹H and ¹³C n.m.r spectra were obtained using either at Bruker AC200 spectrometer or a Bruker DRX-400 spectrometer. Both ¹H and ¹³C n.m.r spectra were interpreted with the aid COSY, HETCOR and DEPT 135 experiments and are reported downfield from tetramethylsilane as standard. High-resolution mass spectra were recorded using a VG7070 spectrometer operating with an ionisation potential of 70 eV at a nominal resolution of 5000 or 10000 as appropriate. Major fragments are given as percentages of the base peak and are assigned where possible. Tetrahydrofuran and diethyl ether were dried using sodium/benzophenone and distilled prior to use. Flash chromatography was performed using Merck Kieselgel 60 or Riedel-de-Haen Kieselgel S silica gel (both 230-400 mesh) with the indicated solvents. Compounds were visualized under ultraviolet light or by staining with iodine or vanillin in methanolic sulfuric acid.

3-(Trimethylsilyl)prop-2-yn-1-ol (15). Butyllithium (21.4 mL, 10 M in hexanes, 214 mmol) was added to a solution of propargyl alcohol (5.0 g, 89.0 mmol) in dry THF (190 ml) cooled to –78 °C under nitrogen. After 0.5 h trimethylsilyl chloride (28.0 mL, 223.3 mmol) was added and the resultant mixture was warmed to room temperature and stirred for 1 h. Freshly prepared 1 M HCl (50 mL) was added, the mixture stirred vigorously for 0.5 h. and extracted with diethyl ether (50 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and evaporated *in vacuo*. Distillation of the residue under reduced pressure afforded the title compound **15** (8.0 g, 70%) as a colourless mobile liquid, bp 100-110 °C/20 mmHg (lit.⁸ bp 120 °C /20 mmHg).

1-(Allyloxy)-3-(trimethylsilyl)prop-2-yne (16). A stock solution of ethylmagnesium bromide was prepared as follows. To a stirred suspension of magnesium powder (0.30 g, 12.5 mmol) in THF (10 mL) at 25 °C was added bromoethane (1.03 mL, 13.9 mmol). The mixture was heated under reflux until initiation occurred then stirred for 1 h. at room temperature to afford a 1.2 M solution of ethylmagnesium bromide. To a stirred solution of 3-(trimethylsilyl)prop-2-yn-1-ol, **15** (0.25 g, 1.95 mmol) in THF (10 mL) and HMPA (1.36 mL, 7.8 mmol) at 0 °C under nitrogen

was added ethylmagnesium bromide (1.75 mL, 1.2 M, 2.15 mmol). The mixture was stirred for 5 min, treated with 3-bromo-1-propene (0.35 g, 2.9 mmol) then heated under reflux for 4 h. The reaction mixture was cooled to room temperature, quenched by the addition water (3 mL) and 1 M HCl (5 mL) then extracted with diethyl ether (25 mL). The organic phase was further washed with water (2 x 10 mL) and brine (10 mL) then dried over MgSO₄. Evaporation of the solvent *in vacuo* followed by flash chromatography of the residue using 2% diethyl ether - hexane as eluent afforded the title compound **16** (0.22 g, 67%) as a colourless oil for which the ¹H NMR were in agreement with the literature.⁹

1-Trimethylsilylhex-5-en-1-yn-3-ol (17). Butyllithium (2.5 mL, 1.6 M in hexanes, 4.0 mmol) was added to a stirred solution of 1-allyloxy-3-trimethylsilylprop-2-yne **16** (1.0 g, 4.0 mmol) in THF (40 mL) at -78 °C under nitrogen. The reaction was stirred for 20 min, warmed to -30 °C then quenched by the addition of 10% ammonium chloride (5 mL). The mixture was further warmed to room temperature, diluted with diethyl ether (30 mL) then washed successively with water (3 x 10 mL) and brine (10 mL). The organic extract was dried over MgSO₄ and evaporated *in vacuo* to afford the title compound (0.97 g, 97%) as light yellow oil for which the ¹H NMR data were in agreement with the literature.¹⁰

1-(Trimethylsilyl)-3-(tert-butyldiphenylsilyloxy)hex-5-en-1-yne (18). To a stirred solution of 1-(trimethylsilyl)hex-5-en-1-yn-3-ol **17** (250 mg, 1.48 mmol), imidazole (120 mg, 1.78 mmol) and 4-(dimethylaminopyridine) (18 mg, 0.15 mmol) in dichloromethane (10 mL) at room temperature was added dropwise *tert*-butyldiphenylsilyl chloride (0.49 g, 1.78 mmol). After 1 h, the reaction was quenched by the addition NaHCO₃ (2 mL) and water (10 mL) and the resultant mixture extracted with dichloromethane (3 x 10 mL). The organic extracts were dried over MgSO₄ and then evaporated *in vacuo* to afford the title compound **18**¹¹ as a light yellow oil (580 mg, 98%) that was immediately used in the next step without further purification.

1-(Trimethylsilyl)-3-(tert-butyldimethylsilyloxy)hex-5-en-1-yne (19). To a solution of alcohol **17** (6.64 g, 0.039 mol), imidazole (2.95 g, 0.043 mol) and 4-dimethylaminopyridine (0.5 g, 0.004 mmol) in dichloromethane (80 mL) at room temperature was added *tert*-butyldimethylsilyl chloride (6.23 g, 0.041 mol). After 1 h, the reaction was quenched by the addition of 10% NaHCO₃ solution (20 mL) and water (50 mL) and the resultant mixture extracted with dichloromethane (3 x 50 mL). The organic extracts were washed with brine (10 mL), dried over MgSO₄ then evaporated *in vacuo* to afford the title compound **19** as light yellow oil (10.9 g, 98%) that was immediately used in the next step without further purification.²¹

3-(tert-Butyldiphenylsilyloxy)hex-5-en-1-yne (13). To a stirred solution of acetylene **18** (70 mg, 0.17 mmol) in methanol (1 mL) at room temperature was added a freshly prepared solution of sodium methoxide (12 mg sodium in 5 mL methanol). The reaction mixture was then heated at 45 °C for 20 min. The mixture was cooled to room temperature then evaporated *in vacuo* to a volume of ~1 mL. The residue was diluted with water (5 mL), extracted with diethyl ether (3 x 10 mL), washed with brine (3 mL), dried over MgSO₄ then evaporated *in vacuo*. The title compound **13**²² (50 mg, 88%) was afforded as colorless oil. (Found: M⁺, 334.1744. C₂₂H₂₆OSi requires M⁺, 334.1753). IR: ν_{max} 3000, 1728, 1473, 1112, 1083, 701 cm⁻¹. ¹H NMR: δ (400 MHz, CDCl₃) 1.08, s, 9H, C(CH₃)₃; 2.33, d, J_{1,3} 2.1 Hz, 1H, H1; 2.31-2.39, m, 1H, H4α; 2.44, ddt, J_{4β,4α} 12.7, J_{4β,3} 7.0, and J_{4β,6} 1.3 Hz, 1H, H4β; 4.37, ddd, J_{3,4α} 5.5, J_{3,4β} 7.0, and J_{3,1} 2.1 Hz, 1H, H3; 5.03-5.08, m, 2H, H6; 5.8-5.87, m, 1H, H5; 7.35-7.7, m, 10H, 2 x Ar; ¹³C NMR

δ (100 MHz, CDCl_3) 19.3, $\text{C}(\text{CH}_3)_3$; 26.9, $\text{C}(\text{CH}_3)_3$; 42.7, C4; 63.4, C3; 72.9, C1; 84.4, C2; 117.9, C6; 127.4, 127.6, 129.7, 129.8, 135.9 and 136.0 (Ar), 133.3, C5; MS: m/z 334 (M, 6%), 277 (100), 207 (60), 199 (45).

3-(*tert*-Butyldimethylsilyloxy)hex-5-en-1-yne (14). To a stirred solution of acetylene **19** (11.0 g, 0.039 mol) in methanol (20 mL) at room temperature was added a freshly prepared solution of sodium methoxide in methanol (2.7 g sodium in 112 mL methanol). The reaction mixture was then heated to 45 °C for 20 min. The resultant mixture was cooled to room temperature then evaporated *in vacuo* to a volume of ~5 mL. The residue was diluted with water (5 mL), extracted with dichloromethane (4 x 10 mL), dried over MgSO_4 , then evaporated *in vacuo*. The title compound **14** was afforded as a colorless oil (7.86 g, 96%) for which the ^1H NMR data was in good agreement with the literature.^{23,24}

3-Acetyltetrahydrothiazole-2-thione. To a vigorously stirred solution of mercaptothiazoline (3.0 g, 26 mmol) and triethylamine (3.26 g, 33 mmol) in THF (60 ml) at room temperature was added acetyl chloride (2.28 ml, 33 mmol). An intense yellow color was immediately observed. After 18 h the reaction was diluted with water (30 ml) and the resultant mixture extracted with dichloromethane (3 x 40 mL). The combined extracts were washed with brine (30 ml), dried over MgSO_4 and evaporated *in vacuo*. Flash chromatography of the residue using 50% diethyl ether - hexane as eluent afforded the title compound (4.1 g, 98%) as a luminous yellow oil.^{11,12}

4-Hydroxy-pent-1-yl acetate (20). To a stirred solution of 1,4-pentanediol (1 g, 9.6 mmol) and 3-acetyltetrahydrothiazole-2-thione (1.6 g, 10.1 mmol) in THF (60 mL) at room temperature was added portionwise sodium hydride (240 mg, 10.1 mmol). After 2 h the reaction was quenched by the addition of 10% ammonium chloride (30 ml) and the resultant mixture extracted with dichloromethane (2 x 50 ml). The combined extracts were washed with brine (30 ml), dried over MgSO_4 and evaporated *in vacuum* to afford the title compound **20** (1.15 g, 82%) as a pale yellow solid.¹³

4-(*tert*-Butyldimethylsilyloxy)pent-1-yl acetate (21). To a stirred solution of alcohol **20** (1.15 g, 7.9 mmol), imidazole (0.72 g, 10.6 mmol) and 4-dimethylaminopyridine (117 mg, 0.96 mmol) in DMF (20 mL) at room temperature was added *tert*-butyldimethylsilyl chloride (1.44 g, 9.6 mmol) in small portions. After 4 h the reaction was quenched by the addition of saturated ammonium chloride (15 mL) and water (10 mL) then the mixture was diluted with diethyl ether (30 mL). The organic phase was separated, washed with water (2 x 10 mL), brine (5 mL) then dried over MgSO_4 . Evaporation of the organic extract *in vacuo* followed by flash chromatography of the residue using 20% diethyl ether - hexane as eluent afforded the title compound **21**¹⁴ (1.93 g, 95%) as a light yellow oil for which the ^1H NMR data was in good agreement with the literature.¹⁴

4-(*tert*-Butyldimethylsilyloxy)pentan-1-ol (22). To a stirred solution of acetate **21** (1.93 g, 7.4 mmol) in methanol (35 mL) at room temperature was added K_2CO_3 (2.0 g, 14.6 mmol) in small portions. The mixture was stirred for 18 h, filtered through a short pad of Celite™ then evaporated *in vacuo*. Flash chromatography of the residue using 40% diethyl ether - hexane as eluent afforded the title compound **22** (1.5 g, 92%) as a colorless oil for which the ^1H n.m.r. data was in good agreement with the literature.¹⁴

4-(*tert*-Butyldimethylsilyloxy)pentanal (12). Dess-Martin periodinane¹⁶ (2.1 g, 4.97 mmol) was added portionwise to a mixture of alcohol **22** (540 mg, 2.48 mmol) and pyridine (0.2 mL) in

dichloromethane (35 mL) at room temperature. After 1 h the suspension was filtered through a short pad of Celite™ (2 cm x 0.4 cm) and the filtrate diluted with NaOH (1.3 M, 10 ml). The resultant mixture was extracted with dichloromethane (3 x 10 mL) and the organic extracts dried over MgSO₄ then concentrated at reduced pressure. Flash chromatography of the residue using 5% diethyl ether - hexane as eluent afforded the title compound **12** (500 mg, 94%) as a mobile colorless liquid for which the ¹H NMR data was in good agreement with the literature.¹⁵

2-(tert-Butyldimethylsilyloxy)-8-(tert-butyldiphenylsilyloxy)undec-10-en-6-yn-5-ol (23).

Butyllithium (0.20 mL, 1.6 M in hexane, 0.32 mmol) was added to a mixture of alkyne **13** (90 mg, 0.27 mmol) and tetramethylethylenediamine (94 mg, 0.8 mmol) in THF (2.5 mL) at -78 °C under nitrogen. The mixture was stirred for 1 h then treated with a solution of aldehyde **12** (70 mg, 0.32 mmol) in THF (0.5 mL). Stirring was continued for 30 min then the reaction was quenched by the addition of 10% NaHCO₃ (1 mL) and water (3 mL). The resultant mixture was warmed to room temperature and extracted with diethyl ether (3 x 10 ml). The organic extracts were washed successively with brine (3 mL), dried over MgSO₄ then evaporated *in vacuo*. Flash chromatography of the residue using 15% diethyl ether - hexane as eluent afforded the *title compound* **23** (127 mg, 85%) as colorless oil. (Found: M⁺, 551.3375. C₃₃H₅₀Si₂O₃ requires M⁺, 551.3377). ν_{\max} 3429, 3000-2800, 1472, 1428, 1361, 1255, 1112, 835 cm⁻¹. ¹H NMR: δ (400 MHz, CDCl₃) 0.04, 2 x s, 6H, Si(CH₃)₂, 0.87, s, 9H, C(CH₃)₃; 1.06, s, 9H, C(CH₃)₃; 1.10, d, *J* 6.1 Hz, 3H, H1; 1.40-1.62, m, 4H, H3 and H4; 2.39-2.46, m, 2H, H9; 3.75-3.83, m, 1H, H2; 4.17-4.19, m, 1H, H5; 4.41-4.47, m, 1H, H8; 5.00-5.10, m, 2H, H11; 5.78-5.92, m, 1H, H10; 7.26-7.70, m, 10H, 2 x Ph. ¹³C NMR: δ (100MHz, CDCl₃) -4.75, -4.44, SiCH₃; 18.1, 19.2, C(CH₃)₃; 23.3, 23.5, 23.6, C1; 25.8, C(CH₃)₃; 26.9, C(CH₃)₃; 33.1, 33.2, 33.5, 33.6, C3; 34.5, 34.9, C4; 42.9, C9; 62.1, 62.4, C5; 63.5, C8; 68.1, 68.2, C2; 85.5, 85.7, C7; 86.1, 86.4, C6; 117.8, C11; 133.5, 133.7, 134.1, C10; 127.3, 127.6, 129.6, 129.7, 135.9, 136.1 (Ar). MS: *m/z* (CI) 551 (MH⁺, 0.5%), 361 (30), 199 (90), 159 (50), 75 (100).

2,8-Bis(tert-butyldimethylsilyloxy)undec-10-en-6-yn-5-ol (24).

Butyllithium (2 mL, 1.6 M in hexane, 3.24 mmol) was added to a mixture of acetylene **14** (570 mg, 2.7 mmol), tetramethylethylenediamine (1.21 mL, 8.1 mmol) in THF (10 mL) at -78 °C. The mixture was stirred for 50 min then transferred via cannula to a solution of aldehyde **12** (700 mg, 3.24 mmol) in THF (10 mL). Stirring was continued for a further 30 min and the reaction quenched by the addition of 10% NaHCO₃ (5 mL) and water (10 mL). The mixture was warmed to room temperature and extracted with diethyl ether (3 x 15 mL). The organic extracts were washed with brine (10 mL), dried over MgSO₄ and evaporated *in vacuo*. Flash chromatography of the residue using 10% diethyl ether - hexane as eluent afforded the *title compound* **24** (600 mg, 52%) as colorless oil. (Found: MH⁺, 427.3062. C₂₃H₄₇O₃Si₂ requires MH⁺, 427.3064). ν_{\max} 2929, 1472, 1255, 1089, 836 cm⁻¹. ¹H NMR: δ (400 MHz, CDCl₃) 0.04, 0.05, 0.09, 0.10, each s, 12H, SiCH₃; 0.88, s, 9H, C(CH₃)₃; 0.89, s, 9H, C(CH₃)₃; 1.13, d, *J* 6.1 Hz, 3H, H1; 1.55-1.77, m, 4H, H3 and H4; 2.37-2.41, m, 2H, H9; 3.80-3.89, m, 1H, H5; 4.35-4.41, m, 2H, H2 and H8; 5.05-5.10, m, 2H, H11; 5.78-5.87, m, 1H, H10. ¹³C n.m.r. δ (100 MHz, CDCl₃) -5.0, -4.8, -4.5, -4.4, SiCH₃; 18.1, C(CH₃)₃; 18.2, C(CH₃)₃; 23.1, 23.2, 23.4, C1; 25.8, C(CH₃)₃; 25.9, C(CH₃)₃; 33.1, 33.4, 33.8, 33.9, C3; 34.4, 34.5, C4; 43.2, C9; 62.1, C5; 62.5, 62.8, C8; 68.1, 68.3, C2; 85.5, C6; 85.8, C7; 117.6, C11; 134.0, C10. MS: *m/z* (CI) 427 (MH⁺, 24%) 217 (100), 159 (64), 85 (75).

2-(tert-Butyldimethylsilyloxy)-8-(tert-butyldiphenylsilyloxy)undec-10-en-6-yn-5-one (25).

Dess-Martin periodinane¹⁶ (133 mg, 0.32 mmol) was added to a mixture of alcohol **23** (0.12 g, 0.22 mmol) and pyridine (0.2 mL) in dichloromethane (5 mL) at room temperature. After 2 h the suspension was filtered through a short pad of Celite™ (1 cm x 0.2 cm) and the filtrate diluted with NaOH (1.3 M, 5 mL). The resultant mixture was extracted with dichloromethane (3 x 10 mL) and the extracts dried over MgSO₄ then concentrated at reduced pressure. Flash chromatography of the residue using 10% diethyl ether - hexane as eluent afforded the *title compound* (**25**) (99 mg, 83%) as colorless oil. (Found: M⁺, 548.3102. C₃₃H₄₈Si₂O₃ requires M⁺, 548.3142). ν_{\max} 2958, 1687, 1471, 1245, 1091, 836 cm⁻¹. ¹H NMR: δ (400 MHz, CDCl₃) 0.03, s, 3H, SiCH₃; 0.04, s, 3H, SiCH₃; 0.88, s, 9H, C(CH₃)₃; 1.08, s, 9H, C(CH₃)₃; 1.10, d, *J* 6.1 Hz, 3H, H1; 1.54-1.75, m, 2H, H3; 2.37-2.54, m, 4H, H4 and H9; 3.77-3.86, m, 1H, H2; 4.50, t, *J*_{8,9} 6.1, 1H, H8; 5.06-5.11, m, 2H, H11; 5.73-5.85, m, 1H, H10; 7.36-7.70, m, 10H, 2 x Ar. ¹³C NMR: δ (100 MHz, CDCl₃) -4.8, SiCH₃; -4.4, SiCH₃; 18.0, C(CH₃)₃; 19.3, C(CH₃)₃; 23.6, C1; 25.8, C(CH₃)₃; 26.8, C(CH₃)₃; 33.1, C3; 41.4, C9; 42.1, C4; 63.4, C8; 67.2, C2; 83.9, C6; 91.9, C7; 118.6, C11; 132.6, C10; 127.6-135.9, (Ar); 187.5, C5. MS: *m/z* 548 (M, 2%), 491 (28), 450 (65), 359 (65), 281 (40), 197 (100), 73 (75).

2,8-Bis(tert-butyl dimethylsilyloxy)undec-10-en-6-yn-5-one (26). Tetrapropylammonium perruthenate (16 mg, 0.0468 mmol), *N*-methylmorpholine-*N*-oxide (0.16 g, 1.4 mmol), and 3 Å molecular sieves (0.47 g) were added to a solution of alcohol **24** (400 mg, 0.94 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 30 min then filtered through a Celite™ pad and the solvent evaporated *in vacuo*. Flash chromatography of the residue using 10% diethylether - hexane as eluent afforded the *title compound* **26** (385 mg, 98%) as colorless oil. (Found: MH⁺, 425.2907. C₂₃H₄₅O₃Si₂ requires MH⁺, 425.2907). ν_{\max} 2956, 1682, 1472, 1255, 1136, 1088, 836 cm⁻¹. ¹H NMR: δ (400 MHz, CDCl₃) 0.01, 0.02, 0.03, 0.13, each s, 12H, SiCH₃; 0.87, s, 9H, C(CH₃)₃; 0.89, s, 9H, C(CH₃)₃; 1.12, d, *J* 6.1 Hz, 3H, H1; 1.67-1.78, m, 4H, H3 and H9; 2.45, t, *J* 6.7 Hz, 2H, H4; 2.58-2.63, m, 2H, H9; 3.79-3.84, m, 1H, H2; 4.50, t, *J* 6.4 Hz, 1H, H8; 5.10-5.15, m, 2H, H11; 5.76-5.86, m, 1H, H10. ¹³C NMR: δ (100 MHz, CDCl₃) -5.1, -4.8, -4.6, -4.4, SiCH₃; 18.0, C(CH₃)₃; 18.2, C(CH₃)₃; 23.7, C1; 25.7, C(CH₃)₃; 25.8, C(CH₃)₃; 33.2, C3; 41.9, C9; 42.3, C4; 62.7, C2; 67.2, C8; 83.4, C6; 92.3, C7; 118.4, C11; 132.9, C10; 187.5, C5. MS: *m/z* (CI) 425 (MH⁺, 60%), 293 (40), 141 (38), 75 (100).

8-(tert-Butyl dimethylsilyloxy)-2-(tert-butyl diphenylsilyloxy)-10,11-epoxyundec-6-yn-5-one (27). Meta-chloroperoxybenzoic acid (250 mg, 1.46 mmol) was added with stirring to a mixture of ketone (**25**) (200 mg, 0.36 mmol) and sodium acetate (0.12 g, 1.46 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for five days then quenched with water (10 mL). The organic layer was washed with brine (2 x 10 mL), dried over MgSO₄ and the solvent evaporated *in vacuo*. Flash chromatography of the residue using 20% diethyl ether - hexane as eluent afforded the *title compound* (**27**) (160 mg, 79%) as a colourless oil (Found: MH⁺, 565.3183. C₃₃H₄₉O₄Si₂ requires MH⁺, 565.3169). IR: ν_{\max} 2930, 2214, 1681, 1472, 1428, 1255, 1120, 836 cm⁻¹. ¹H NMR: δ (400 MHz, CDCl₃) 0.02, s, 3H, SiCH₃; 0.03, s, 3H, SiCH₃; 0.88, s, 9H, C(CH₃)₃; 1.08, s, 9H, C(CH₃)₃; 1.09, d, *J* 6.1 Hz, 3H, H1; 1.59-1.71, m, 2H, H3; 1.90-1.99, m, 2H, H9; 2.36-2.47, m, 1H, H11a; 2.36-2.47, m, 2H, H4; 2.72-2.79, m, 1H, H11b; 3.08-3.17, m, 1H, H10; 3.75-3.79, m, 1H, H2; 4.67-4.71, m, 1H, H8; 7.37-7.73, m, 10H, 2 x Ph. ¹³C NMR (100 MHz, CDCl₃): δ 4.8, SiCH₃, -4.5, SiCH₃, 18.0, C(CH₃)₃; 19.2, C(CH₃)₃; 23.6, C1 (CH₃); 25.8, C(CH₃)₃; 26.8, C(CH₃)₃; 32.9, C3; 40.9, C9; 40.9, 41.0, 41.2, 41.3, C11; 47.3, C4;

48.6, C10; 61.5, C8, 67.2, C2; 84.2, C6; 90.9, C7; 127.2-135.4, Ar; 187.2, C5. MS: m/z (CI) 565 (MH^+ , 5%), 195 (35), 135 (68), 73 (100).

2,8-Bis(*tert*-butyldimethylsilyloxy)-10,11-epoxyundec-6-yn-5-one (28). *Meta*-chloroperoxybenzoic acid (170 mg, 0.99 mmol) was added with stirring to a mixture of ketone **26** (70 mg, 0.16 mmol) and sodium acetate (81 mg, 0.99 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for five days then quenched with water (10 ml). The organic layer was washed with brine (2×10 mL), dried over $MgSO_4$ and the solvent evaporated *in vacuo*. Flash chromatography of the residue using 50% diethyl ether - hexane as eluent afforded the *title compound* **28** (55 mg, 75%) as colorless oil (Found: MH^+ , 441.2284. $C_{23}H_{45}O_4Si_2$ requires, MH^+ , 441.2856). ν_{max} 2929, 1682, 1472, 1255, 1097, 837 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$): δ 0.12, 0.14, 0.15, 0.17, each s, 12H, $SiCH_3$; 0.86, s, 9H, $C(CH_3)_3$; 0.90, s, 9H, $C(CH_3)_3$; 1.10, d, J 6.0 Hz, 3H, H1; 1.66-1.78, m, 2H, H3; 1.91-1.96, m, 2H, H9; 2.49-2.55, m, 2H, H4; 2.62-2.65, m, 1H, H11a; 2.77-2.80, m, 1H, H11b; 3.06-3.09, m, 1H, H10; 3.78-3.86, m, 1H, H2; 4.68-4.71, m, 1H, H8. ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.2, -4.9, -4.6, -4.4, $SiCH_3$; 18.0, $C(CH_3)_3$; 18.1, $C(CH_3)_3$; 23.7, C1; 25.5, $C(CH_3)_3$; 25.7, $C(CH_3)_3$; 33.1, C3; 41.1, 41.2, C9; 41.5, C4; 46.7, 47.5, C11; 48.6, C10; 60.3, 60.8, C8; 67.2, C2; 83.3, 83.8, C6; 91.3, 91.8, C7; 187.3, C5. MS: m/z (CI) 441 (MH^+ , 100%), 309 (70), 92 (40), 74 (82).

8-(*tert*-Butyldiphenylsilyloxy)-2-(*tert*-butyldimethylsilyloxy)-10,11-epoxyundecan-5-one (10). Sodium bicarbonate (50 mg, 0.57 mmol) and 10% palladium on charcoal (5 mg) were added to a solution of epoxide **27** (160 mg, 0.29 mmol) in ethyl acetate (10 mL). The reaction mixture was stirred at room temperature under a hydrogen atmosphere. After 2 h the suspension was filtered through a short pad of CeliteTM and the solvent removed under reduced pressure. Flash chromatography using 50% diethyl ether - hexane as eluent afforded the *title compound* **10** (160 mg, 98%) as colorless oil (Found: MH^+ , 569.3471. $C_{33}H_{53}O_4Si_2$ requires, MH^+ , 569.3482). IR: ν_{max} 2929, 1714, 1427, 1256, 1111 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$): δ 0.01, s, 3H, $SiCH_3$; 0.03, s, 3H, $SiCH_3$; 0.88, s, 9H, $C(CH_3)_3$; 1.03-1.08, s, 9H, $C(CH_3)_3$; 1.09, d, J 6.2 Hz, 3H, H1; 1.51-1.60, m, 2H, H3; 1.61-1.86, m, 2H, H7; 1.61-1.86, m, 2H, H9; 2.26-2.40, m, 4H, H4 and H6; 2.26-2.40, m, 1H, H11a; 2.61-2.65, m, 1H, H11b; 2.84-2.95, m, 1H, H10; 3.74-3.81, m, 1H, H2; 3.93-3.99, m, 1H, H8; 6.94-7.22, m, 10H, Ph. ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.8, $SiCH_3$; -4.4, $SiCH_3$; 18.1, $C(CH_3)_3$; 19.2, $C(CH_3)_3$; 23.7, C1 (CH_3); 25.9, $C(CH_3)_3$; 26.5, $C(CH_3)_3$; 30.4, 30.7, C9; 33.1, C3 and C7; 37.9, 38.7, 39.4, 39.9, C4 and C6; 46.8, 47.2, C11; 49.0, 49.4, C10; 67.2, C2; 70.5, 70.8, C8; 127.6-135.8, Ph; 210.6, C5. MS: m/z (CI) 568 (M, 0.16%), 379 (94), 255 (100), 199 (93), 75 (89).

2,8-Bis(*tert*-butyldimethylsilyloxy)-10,11-epoxyundecan-5-one (11). Sodium bicarbonate (21 mg, 0.25 mmol), and palladium on charcoal (2 mg) were added to a solution of epoxide **28** (50 mg, 0.12 mmol) in ethyl acetate (10 mL). The reaction mixture was stirred at room temperature under a hydrogen atmosphere. After 2 h the suspension was filtered through a short pad of CeliteTM, and the solvent removed under reduced pressure. Flash chromatography using 50% diethylether - hexane as eluent afforded the *title compound* **11** (41 mg, 74%) as colorless oil. (Found: MH^+ , 445.3180. $C_{23}H_{49}O_4Si_2$ requires, MH^+ , 445.3169). IR: ν_{max} 2929, 1716, 1472, 1236, 1072, 836 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$): δ -0.02, -0.03, 0.01, 0.05, each s, 12H, $SiCH_3$; 0.86, s, 9H, $C(CH_3)_3$; 0.87, s, 9H, $C(CH_3)_3$; 1.10, d, J 6.0 Hz, 3H, H1; 1.61-1.69, m, 4H, H3 and H7; 1.71-1.75, m, 2H, H9; 2.41-2.53, m, 1H, H11a; 2.71-2.77, m, 1H, H11b; 2.95-3.03,

m, 1H, H10; 3.77-3.84, m, 1H, H2; 3.87-3.96, m, 1H, H8. ^{13}C NMR (100 MHz, CDCl_3): δ -4.77, -4.71, -4.54, -4.38, SiCH_3 ; 17.99, $\text{C}(\text{CH}_3)_3$; 18.0, $\text{C}(\text{CH}_3)_3$; 23.7, C1; 25.8, $\text{C}(\text{CH}_3)_3$; 25.9, $\text{C}(\text{CH}_3)_3$; 30.6, 31.2, C9; 33.2, C3 and C7; 37.8, 38.3, 38.8, C4; 40.1, 40.2, C6; 46.8, 47.6, C11; 49.2, 49.6, C10; 67.5, C2; 69.1, 69.3, C8; 210.7, C5. MS: m/z (CI) 445 (MH^+ , 65%), 313 (73), 255 (100), 181 (90), 75 (58).

1-(2-Methoxy-5-methyltetrahydrofuran-2-yl)hex-5-en-1-yn-3-ol (29). Camphorsulfonic acid (12 mg, 0.047 mmol) was added to a solution of ketone **26** (100 mg, 0.236 mmol) in methanol (10 mL) and the mixture stirred at room temperature for 2 h. The methanol was removed under reduced pressure and the organic residue washed with water (2×2 mL) and brine (2×1 mL) then extracted with diethyl ether (5 mL). The organic extract was dried (MgSO_4), concentrated under reduced pressure and further purification of the residue by flash chromatography using 50% diethyl ether - hexane as eluent afforded the *title compound* **29** (491 mg, 97%) as a colorless oil. (Found: MH^+ , 211.1335. $\text{C}_{12}\text{H}_{19}\text{O}_3$ requires MH^+ , 211.1334). ν_{max} 3429, 2973, 1444, 1381, 1315, 1235, 1145, 1089, 1048, 916 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.29, d, J 6.2 Hz, 3H, CH_3 ; 1.51-1.70, m, 2H, H_4' ; 2.15-2.21, m, 2H, H_3' ; 2.47-2.51, m, 2H, H_4 ; 3.35, 3.36, 3.37, 3.38, s, 3H, OCH_3 ; 4.14-4.22, m, 1H, H_5' ; 4.31-4.39, m, 1H, H_3 ; 4.48, s, 1H, OH; 5.16-5.26, m, 2H, H_6 ; 5.85-5.92, m, 1H, H_5 . ^{13}C NMR (100 MHz, CDCl_3): δ 22.4, CH_3 ; 31.5, 31.8, C_4' ; 40.0, 40.1, C_3' ; 41.8, C4; 61.4, OCH_3 ; 75.3, C3; 77.7, C_5' ; 82.0, C1; 84.5, 84.7, C2; 101.5, 101.8, C_2' ; 118.9, C6; 132.9, C5. MS: m/z (CI) 211 (MH^+ , 6%), 179 (100), 169 (40), 137 (38), 91 (25).

5,6-Epoxy-1-(2-methoxy-5-methyltetrahydrofuran-2-yl)hex-1-yn-3-ol (30). *Meta*-chloroperoxybenzoic acid (450 mg, 2.6 mmol) was added with stirring to a mixture of methyl acetal **29** (270 mg, 1.3 mmol) and sodium acetate (210 mg, 2.6 mmol) in dichloromethane (20 mL). The reaction mixture was stirred at room temperature for two days then quenched with water (10 mL). The organic layer was washed with brine (2×5 mL), dried over MgSO_4 , and the solvent evaporated *in vacuo*. Flash chromatography of the residue using 50% diethyl ether - hexane as eluent afforded the *title compound* **30** (260 mg, 89%) as a colorless oil. (HRMS: M^{+-}OMe , 195.1012. $\text{C}_{11}\text{H}_{18}\text{O}_4$ requires M^{+-}OMe , 195.1021). IR: ν_{max} 3429, 2973, 1444, 1381, 1315, 1235, 1145, 1089, 1048, 916 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.29, d, J 6.2 Hz, 3H, CH_3 ; 1.57-1.70, m, 2H, H_4' ; 2.15-2.21, m, 2H, H_3' ; 2.22-2.29, m, 2H, H_4 ; 2.55-2.61, m, 1H, H_6a ; 2.80-2.85, m, 1H, H_6b ; 3.10-3.20, m, 1H, H_5 ; 3.35, 3.36, s, 3H, OCH_3 ; 4.14-4.22, m, 1H, H_5' ; 4.66-4.70, m, 1H, H_3 . ^{13}C NMR (100 MHz, CDCl_3): δ 20.9, CH_3 ; 31.6, 31.8, C_4' ; 39.9, 40.1, C_3' ; 41.1, C4; 46.9, C6; 49.1, C5; 60.0, 60.3, OCH_3 ; 75.4, C3; 77.2, C_5' ; 77.9, C1; 80.0, C2; 103.9, C_2' . MS: m/z (CI) 195 ($\text{M}-\text{OCH}_3$, 100%), 137 (40), 55 (68), 43 (72), 41 (94).

2-(2,3-Epoxyprop-1-yl)-7-methyl-1,6-dioxaspiro[4.4]nonane (9). Sodium bicarbonate (24 mg, 0.17 mmol) and 10% palladium on charcoal (2 mg) were added to a solution of epoxide **30** (20 mg, 0.090 mmol) in ethyl acetate (10 mL). The reaction mixture was stirred at room temperature under a hydrogen atmosphere. After 2 h the suspension was filtered through a short pad of CeliteTM and the solvent removed under reduced pressure. Flash chromatography using 50% diethyl ether - hexane as eluent afforded the *title compound* **9** (11 mg, 63%) as a colorless oil. HRMS: Found: M^{+-}H , 197.3122. $\text{C}_{11}\text{H}_{18}\text{O}_3$ requires, M^{+-}H 197.3145). IR: ν_{max} 2973, 1646, 1458, 1378, 1078, 861 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.28, d, J 6.3 Hz, 3H, CH_3 ; 1.57-1.70, m, 4H, H_3 and H_8 ; 2.03-2.10, m, 2H, H_1' ; 2.15-2.21, m, 4H, H_4 and H_9 ; 2.49-2.52, m, 1H, $\text{H}_3'\text{b}$; 2.75-2.82, m, 1H, $\text{H}_3'\text{a}$; 3.00-3.10, m 1H, H_2' ; 3.61-3.89, m, 1H, H_7 ; 4.13-4.36, m, 1H,

H2. ^{13}C NMR (100 MHz, CDCl_3): δ 21.1, 21.3, CH_3 ; 30.5, 31.6, 31.9, C8; 32.2, 32.6, C3; 35.1, 35.4, C4; 36.0, 36.2, 36.7, C9; 40.7, C1'; 47.4, 47.5, C3'; 49.5, 49.7, 49.8, 49.9, C2'; 73.9, 74.2, C2; 75.9, 76.1, C7; 102.9, 103.9, C5. MS: m/z (CI) 197 (M-H, 7%), 43 (100).

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