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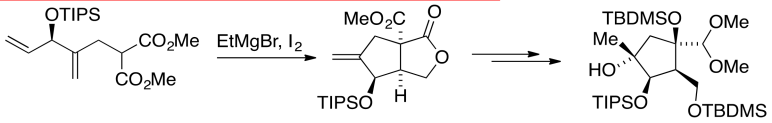

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Synthesis of the cyclopentane core of pepluanin A

Erin D. Shephed,[a] Michal S. Hallside,[a] Jack L. Sutro,[a] Amber Thompson,[a] Martin Hutchings[b] and Jonathan W. Burton[a,*]

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ABSTRACT

The jatrophane class of natural products exhibit a wide range of biological activities with certain members of this family of complex sesquiterpenes being P-glycoprotein inhibitors. Considerable attention has been paid to the synthesis of biologically active jatrophanes although very few have succumbed to total synthesis. Herein we report a synthesis of the cyclopentane core of pepluanin A, a potent P-glycoprotein inhibitor, that features an iodocarbocyclization and an invertive acetal formation as key steps.

1. Introduction

Plants of the genus *Euphorbia* produce a large number of structurally diverse terpenoid natural products that exhibit a vast array of biological activities.[1] Particularly interesting among these natural products are the jatrophane diterpenes that are characterised by a highly oxygenated *trans*-bicyclo-[10.3.0]-pentadecane scaffold.[2] These jatrophanes display a wide range of important biological activities including cytotoxicity against human cancer cell lines. However, what is most striking about certain jatrophanes is their ability to inhibit the P-glycoprotein (P-gp) and other efflux pumps that has implications for acquired multidrug resistance (MDR).[3] The selective inhibition of P-gp resulting in reduced MDR, is currently an active area of research for cancer chemotherapy given that the P-gp is overexpressed in cancer cells. As noted above the jatrophanes display wide structural variation and consequently wide variation in P-gp inhibition. Pepluanin A **1**[3a] and euphodendroidin D **2**,[4] both show inhibition of daunomycin efflux, with pepluanin A being twice as active at inhibiting the P-gp efflux of daunomycin compared with the current "gold-standard", cyclosporin A.[5] Similarly, epieuphoscopin B **3**[3c] is twice as potent as cyclosporin A at inhibiting P-gp-mediated efflux of mitoxantrone. Pepluanin A **1**, euphodendroidin D **2** and epieuphoscopin B **3** are but three of an ever-increasing number of biologically active jatrophane diterpenes being isolated from *Euphorbia* spp.[2] The structures of jatrophane diterpenes differ in the extent of oxygenation, the position of unsaturation, the type and extent of esterification and in their relative configurations as exemplified by pepluanin A **1**, euphodendroidin D **2** and epieuphoscopin **3**. The large number of jatrophane diterpenes that have been isolated has, to a certain extent, allowed a structure/activity relationship to be mapped out and leads to the potential for design of more active analogues.[6] For example, a large number of the jatrophanes that exhibit P-gp inhibition lack oxygenation at C-2. It may therefore be the case that an analogue of pepluanin A lacking a C-2 acetoxy group would show increased potency with respect to the natural product itself.

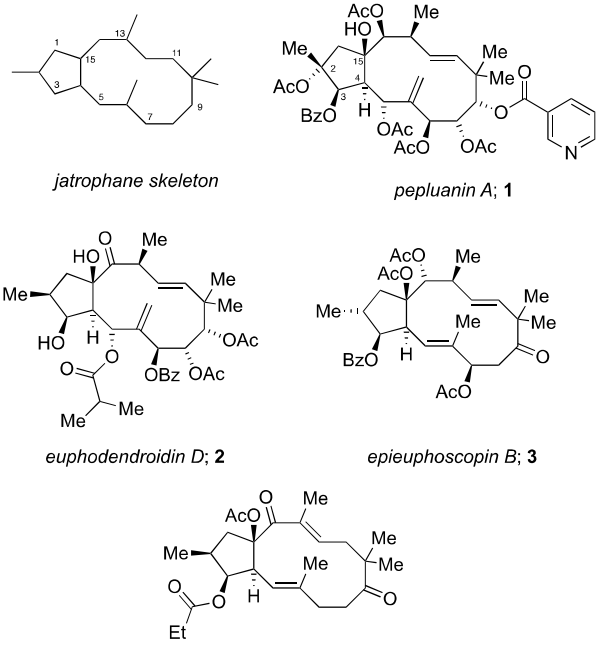


Figure 1. Jatrophane diterpene skeleton and the structure of selected jatrophane natural products.

As a result of the biological profile of these natural products and their intriguing structures, there has been significant interest from the synthetic organic chemistry community; however, there have been very few total syntheses of jatrophane natural products although many groups have reported partial syntheses.[7] The first total synthesis of a jatrophane diterpene came from the group of A. B. Smith, who prepared (±)-jatrophane and the non-natural product (±)-*epi*-jatrophane[8] as well as (+)-hydroxyjatrophanes A and B (not shown).[9] Racemic (±)-jatrophane was also prepared by Stille and Hegedus[10] with the synthesis of natural (+)-jatrophane being reported by Wiemer.[11] In 2006, Hiersemann reported the synthesis of the non-natural (–)-15-*O*-acetyl-4-*O*-propionyl-17-norcharaciol[12] (not shown) that was followed shortly after by a report from the same group on the synthesis of the natural product (-)-15-*O*-acetyl-4-*O*-propionyl-characiol **4** and a number of analogues using a carbonyl ene reaction as a key step.[6, 13] The Hiersemann syntheses represent a landmark in the total synthesis of jatrophane diterpenes. Given the ever-increasing number of biologically active jatrophanes being isolated, particularly with efflux pump inhibition properties, it is surprising that there have been so few total syntheses of these natural products and indicates the challenge these targets present to synthetic chemists.

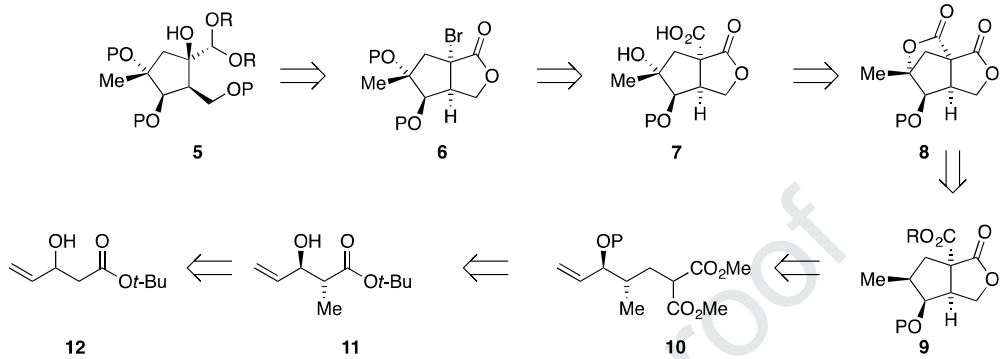
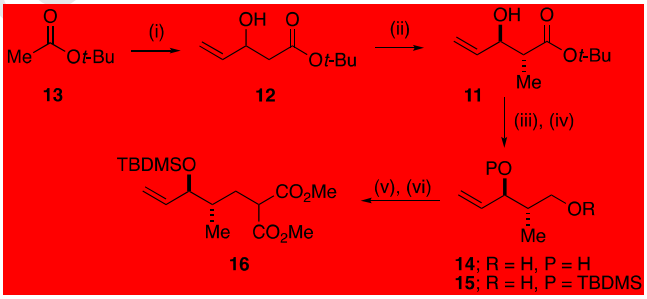


Figure 2. Retrosynthesis of the cyclopentane core of pepluanin A. P = generic protecting group, R = alkyl group.

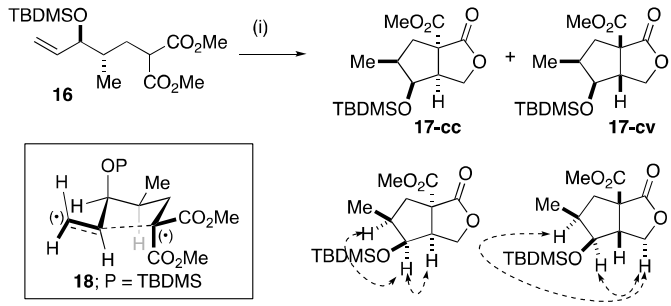
2. Results and Discussion

For a number of years, we have been interested in the oxidative radical cyclization of pentenyl malonates for the formation of [3.3.0]-bicyclic γ-lactones and have used this transformation for the synthesis of a number of natural products.[14] This oxidative radical cyclization was to be a key step in the synthesis of the cyclopentane core of pepluanin A. Our retrosynthesis of the cyclopentane core of pepluanin A is shown in Figure 2. The poly-substituted cyclopentane **5** would be derived from the bicyclic bromo-lactone **6** *via* reduction followed by bromide substitution with inversion of configuration. The bromo-lactone **6** should be readily prepared from the carboxylic acid **7**, which, in turn will be available from the tricyclic bis-lactone **8**, which itself might be synthetically available *via* an oxidative C-H insertion reaction of the carboxylic acid **9** (R = H).[15] The corresponding ester **9** (R = alkyl) was to be synthesized *via* oxidative radical cyclization from the linear malonate **10**. The malonate would be readily prepared from the known ester **11** which is itself available from the aldol product of *t*-butyl acetate and acrolein, the allylic alcohol **12**, which has been prepared in enantiopure form.[16]

The synthesis began with the aldol reaction between *t*-butyl acetate **13** and freshly distilled acrolein to give **12** (Scheme 1),[17] followed by a Frater-Seebach alkylation[18] to give the anti-aldol **11** (71%, > 20:1 dr); the relative configuration of **11** was assigned by conversion into the known diol **14**.[19] Protection of the allylic alcohol in **11** followed by ester reduction to give **15**, mesylation and reaction with sodio dimethyl malonate gave the cyclization precursor **16**. Exposure of the malonate **16** to our standard oxidative radical cyclization conditions[14b] gave a 1:1 mixture of two diastereomers **17-cc** and **17-cv**[20] in 41% yield (Scheme 2). Lowering the reaction temperature to 40 °C gave the products in 52% yield as a 1.5:1 mixture of diastereomers favoring **17-cc** where the methyl and silyloxy substituents are on the concave face of the bicyclo[3.3.0]octane. The structures of the bicyclic lactones were assigned through ^{1}H NMR nOe analysis (Scheme 2). We have previously rationalized the outcome of related oxidative radical cyclizations using the Beckwith-Houk transition state model for 5-hexenyl radical cyclizations.[14b, 21]



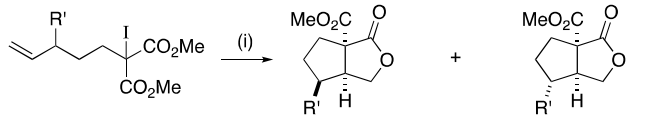
Scheme 1. Synthesis of cyclization substrate. (i) LDA, THF, –78 °C, then acrolein, quant. (ii) LDA, THF, HMPA, –78 °C, then MeI, 0 °C, 72%; (iii) TBDMSCl, imidazole, CH_2Cl_2, 98%; (iv) DIBAL, THF, –20 °C, 88%; (v) MsCl, Et_3N, CH_2Cl_2; (vi) NaH, $CH_2(CO_2Me)_2$, KI, THF, DMF, 80 °C, 89% (2 steps).



Scheme 2. Oxidative radical cyclization of malonate **16**, along with selected ^{1}H-^{1}H NMR nOe's (dotted arrows) for **17-cc** and **17-cv** and proposed cyclization transition structure **18**. (i) $Mn(OAc)_3$, $Cu(OTf)_2$, MeCN, 40 °C, 52%, **17-cc**:**17-cv** 1.5:1.

In this model it is more favorable for alkyl groups to occupy pseudo-equatorial over pseudo-axial positions in the chair-like transition state. The proposed transition state for the cyclization of **16** would position the methyl group in a pseudo-equatorial position with the alkoxy group occupying a pseudo-axial position (**18**). Taguchi has shown,[22] with iodine atom transfer reactions of

alkenyl-iodomalonates (Scheme 3), that allylic silyloxy groups impart no stereocontrol giving the product γ-lactones **20a** as a 1:1 mixtures of diastereomers.

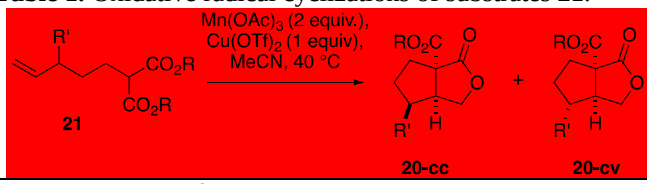


19; R' = OTBDMS **20a-cc**; R' = OTBDMS **20a-cv**; R' = OTBDMS

Scheme 3. Taguchi's atom transfer cyclization of iodomalonates. (i) benzene, 80 °C then heat, 50%, 1:1 mixture of **20a-cc** and **20a-cv**.

Surprisingly, formation of the same products **20a** from malonate **21a** under our standard oxidative radical cyclization conditions using manganese(III) acetate and copper(II) triflate gives the corresponding lactones as a mixture of diastereomers with **20a-cc** as the major product that carries the silyloxy substituent on the concave face of the bicyclic lactone (Table 1 entries 1 and 2). Indeed all of the oxidative radical cyclizations with substrates bearing allylic alkoxy groups are mildly diastereoselective with the major products formed having the alkoxy group on the inside of the [3.3.0]-bicyclic γ-lactone (**20cc**), in keeping with axial orientation in a Beckwith-Houk transition state (Table 1). The best results were with an allylic *t*-butyldimethylsilyloxy (**21a**) substituent with 0.2 M substrate concentration in acetonitrile at 40 °C to give the products **20a** as a 4:1 mixture of diastereomers in 78% yield favoring **20a-cc**. The only exception is with the benzyloxy substituted substrate **21f** where the corresponding product lactones **20f** were formed as a 1.8:1 mixture of diastereomers favoring the γ-lactone with the benzyloxy group on the convex face of the [3.3.0]-bicyclic lactone **20f-cv**.[23] Although the lactones **20f** were formed as a 1.8:1 mixture of diastereomers, dimethyl 3-hydroxy-2-methylcyclopentane-1,1-dicarboxylate (not shown) was also formed along with a number of unidentified by products making accurate determination of the diastereomeric ratio of the cyclization impossible. A control experiment with an allylic methyl group (substrate **21g)** gave the product lactones **20g** in 47% yield (22% recovered starting material) as a 1:5 mixture of stereoisomers favoring **20g-cv** in keeping with the Beckwith-Houk model. The relative configurations of the bicyclic lactones **20** were assigned using ^{1}H NMR nOe experiments. A number of the bicyclic lactone products were crystalline and single crystal X-ray structures of **20a-cv**, **20b-cc** and **20c-cc** are shown in Figure 3 confirming the ^{1}H NMR nOe assignments. Our results with allylic silyloxy substrates **21a-c** contrast with those of Taguchi. These contrasting results may potentially arise from the different solvents used and the presence of Lewis acidic metal ions under the manganese(III), copper(II) cyclization conditions.

Table 1. Oxidative radical cyclizations of substrates **21**.



Entry	R', substrate[a]	R	Products	d.r. **cc**:**cv**	Yield
1	tBuMe$_2$SiO, **21a**	Me	**20a**	2:1	78%
2	tBuMe$_2$SiO, **21a**	Me	**20a**	4:1	78%
3	tBuMe$_2$SiO, **21b**	Et	**20b**	2:1	75%
4	tBuPh$_2$SiO, **21c**	Me	**20c**	2:1	63%
5	BzO, **21d**	Me	**20d**	2:1	63%
6	AcO, **21e**	Me	**20e**	2:1	67%
7	BnO, **21f**	Me	**20f**	1:1.8	59%[b]
8	Me, **21g**	Me	**20g**	1:5	47%[c]

[a]**21a,d,f** and **g**, and **20a,d,f** and **g** are known compounds;[22] [b]dimethyl 3-hydroxy-2-methylcyclopentane-1,1-dicarboxylate was also isolated (7%); [c] 22% starting material was also isolated.

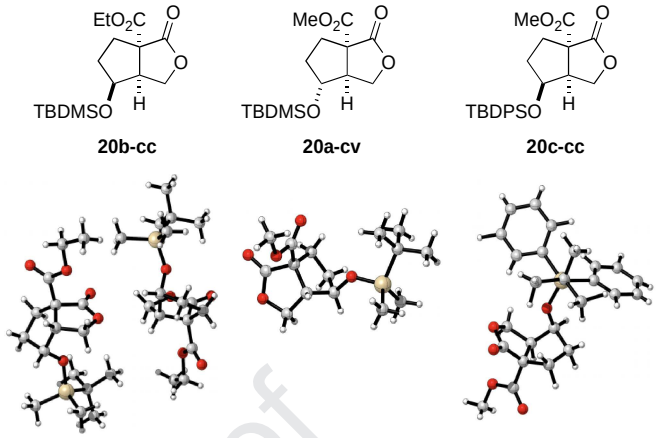
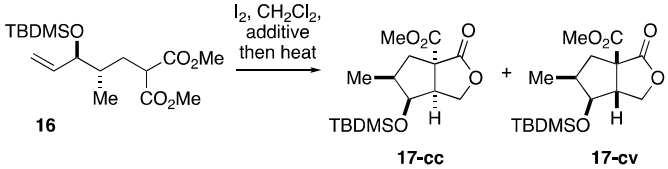


Figure 3. Structures of **20a-cv**, **20b-cc** and **20c-cc** from single crystal X-ray diffraction.

The moderate selectivity of the cyclizations of the allylic alkoxy-substituted malonates reported in Table 1 along with the known preference for alkyl groups to adopt pseudo-equatorial positions in the chair-like Beckwith-Houk transition state was one of the guiding design principles for the synthesis of the core of pepluanin A as we predicted that these two substituents would exert their effects synergistically (transition state **18**) and would lead to the formation of **17-cc** with high diastereocontrol (Scheme 2). This however turned out not to be the case. Taguchi has also shown that iodine-mediated ionic cyclizations of substituted 5-hexenyl malonates can be highly diastereoselective giving rise to the product [3.3.0]-bicyclic γ-lactones in good yields and with high levels of diastereocontrol.[22] In these iodine-mediated cyclizations substrates that bear an allylic alkoxy substituent gave the corresponding [3.3.0]-bicyclic γ-lactones with high levels of diastereocontrol favoring the diastereomer with the alkoxy substituent on the concave face of the bicyclic lactone. Use of a variety of Taguchi's conditions with substrate **16** resulted in only modest improvement in the diastereoselectivity in the formation of the lactones **17** (Table 2, entries 1-3). Use of a Grignard reagent as the base followed by addition of iodine gave the product bicyclic lactones **17** as a 1:1 mixture of diastereomers in 45% yield (Table 2, entry 4).

Table 2. Iodine mediated cyclizations of substrate **16**.



Entry	additive	base	Crude d.r. (**cc**:**cv**)	Yield
1	Ti(O*i*Pr)$_4$	CuO	1.5:1	41%
2	Ti(O*t*Bu)$_4$	CuO	2.5:1	50%
3	Ti(O*t*Bu)$_4$	2,6-dimethoxypyrdine	2:1	38%
4	none	*i*PrMgCl	1:1	45%

We reasoned that cyclization of the malonate **22** bearing a methylene unit in place of the methyl group might provide better

stereocontrol in the key oxidative cyclization due to reduced strain in the transition state (Figure 3). Furthermore, the product methylene cyclopentane **23** would offer numerous options for introduction of the C-3 tertiary alcohol in pepluanin A **1** as well as allowing access to the C-2 methyl group present in other members of the jatrophane family (e.g, **2** and **3**).

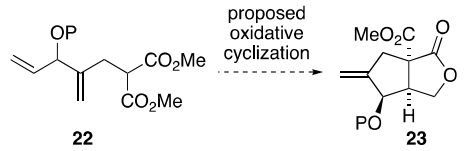
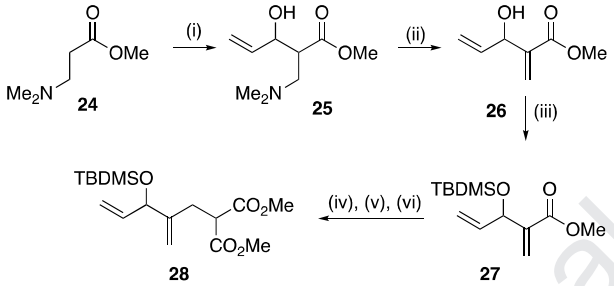


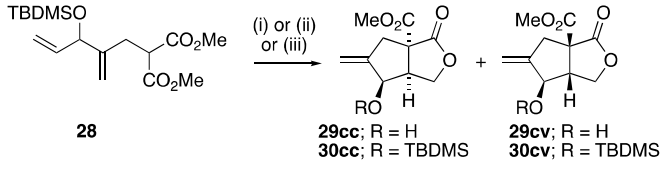
Figure 3. Proposed oxidative cyclization; P = protecting group

The cyclization substrate **28** was readily prepared using the masked acrylate chemistry developed by Drewes[24] that commenced with an aldol reaction between the enolate derived from amino-ester **24** and acrolein to give aldol **25** (Scheme 4). Transformation of the amine in **25** into an amine oxide followed by elimination on exposure to alumina gave the product alcohol **26** that was transformed into the corresponding silyl ether **27** and thence to the malonate **28**. Subjecting the malonate **28** to our standard oxidative radical conditions gave multiple products from which the deprotected lactones were isolated in 46% yield as a 2.5:1 mixture of diastereomers favoring **29cc** (Scheme 5).

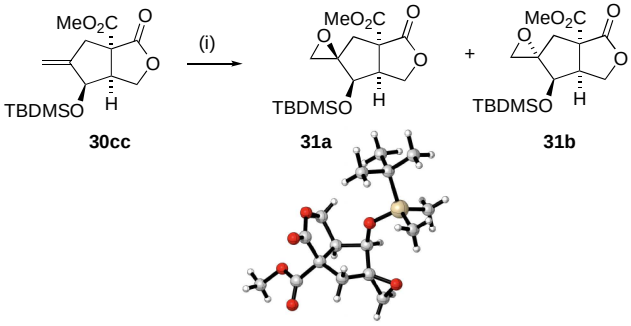


Scheme 4. Synthesis of the cyclization precursor. (i) LDA, THF, –78 °C, then acrolein, 97%; (ii) *m*-CPBA, $CHCl_3$, 5 °C then alumina, 51%; (iii) TBDMSCl, imidazole, CH_2Cl_2, 88%; (iv) DIBAL, THF, -20 °C, 86%; (v) MsCl, Et_3N, CH_2Cl_2; (v) $CH_2(CO_2Me)$, NaH, KI, THF, DMF, 80 °C, 83% (2 steps).

Using Taguchi's conditions ($Ti(Ot\text{-}Bu)_4$, CuO, I_2, CH_2Cl_2) gave the protected lactones **30** in 42% yield along with the desilylated products **29** in 42% yield with 20:1 diastereomeric ratio favoring **30cc**. Modification of Taguchi's conditions using EtMgBr as base and Cu(I)I at -78 °C followed by the addition of I_2 and then heating the crude reaction mixture to 140 °C, conditions we had developed for a conjugate addition, carbocyclization, lactonization sequence that will be reported in due course, gave the γ-lactones **30** in 92% yield as a 16:1 mixture of diastereomers favoring **30cc**. The relative configurations of the lactones **30** were assigned by ^{1}H NMR nOe analysis and confirmed by single crystal X-ray analysis of the epoxide **31a** formed from **30cc** on treatment with *m*-CPBA. Epoxidation of the lactone with *m*-CPBA gave a 3:1 mixture of epoxides **31** favoring epoxide **31a** the structures of which were assigned by ^{1}H NMR nOe analysis and single crystal X-ray analysis of the major diastereomer. Interestingly, use of DMDO resulted in reversal of the selectivity of the epoxidation.



Scheme 5. Cyclization of dienyl malonate. (i) $Mn(OAc)_3$, $Cu(OTf)_2$, MeCN, 40 °C, **29** 46%, **cc**:**cv** 2.5:1 d.r.; (ii) $Ti(Ot\text{-}Bu)_4$, CuO, I_2, CH_2Cl_2, RT, **29** 29%, **30** 42%, **cc**:**cv** 20:1 dr.; (iii) EtMgBr, CuI, CH_2Cl_2, –78 °C, then I_2, RT, then 140 °C, **30** 92%, **cc**:**cv** 16:1 d.r.



Scheme 6. Epoxidation of **30cc** along with the structure of **31a** from single crystal X-ray diffraction data. (i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, RT, **31a** 54%, **31b** 17%. (ii) dimethyldioxirane, acetone, RT, **31a** 14%, **31b** 75%

The iodocyclization using ethylmagnesium bromide and iodine is most likely ionic in nature. According to Chamberlain and Hehre,[25] the stereoselectivity of intramolecular electrophilic addition to chiral allylic alcohols can be rationalized by placing the hydroxy group on the 'inside' position resulting in a more reactive ground-state. From here cyclization takes place *via* the corresponding electrophile π-complex.[26] In our system (Figure 4), this equates to the placing the silyloxy group in a pseudo-axial orientation (as also proposed by Taguchi),[22] with a corresponding equatorial C–H bond (the inside alkoxy effect) followed by cyclization *via* the corresponding olefin iodine π-complex ultimately to give the major lactone diastereomer **30cc**. If the silyloxy group sits in a pseudo-equatorial orientation overlap between the bonding π-orbital and the $\sigma^*_{C\text{-}O}$ results in a less nucleophilic π-bond and hence a disfavoured iodine π-complex, as well as increased allylic strain with the *exo*-cyclic methylene group. This results in a lower rate of formation for the minor diastereomeric lactone **30cv**.

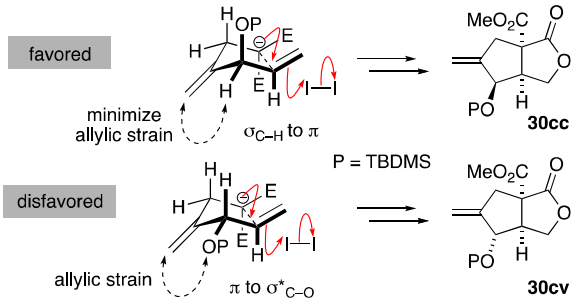


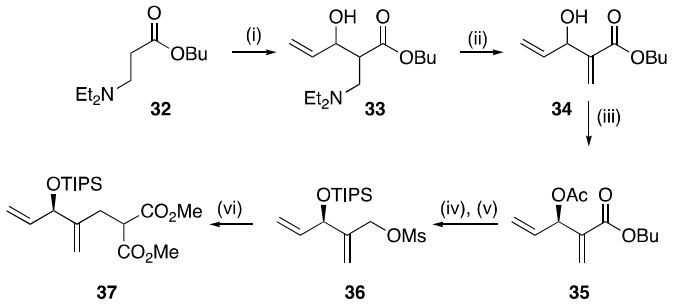
Figure 4. Proposed models for cyclization

Unfortunately, the TBDMS protecting group proved incompatible with the basic reaction conditions required for hydrolysis the methyl ester in **30cc** so that the necessary angular bromine atom could be introduced. We therefore changed the allylic protecting group to a more base-stable triisopropylsilyl group that also gave us the opportunity to synthesize the core in enantioenriched form.

2.1. Synthesis of the core in enantiopure form.

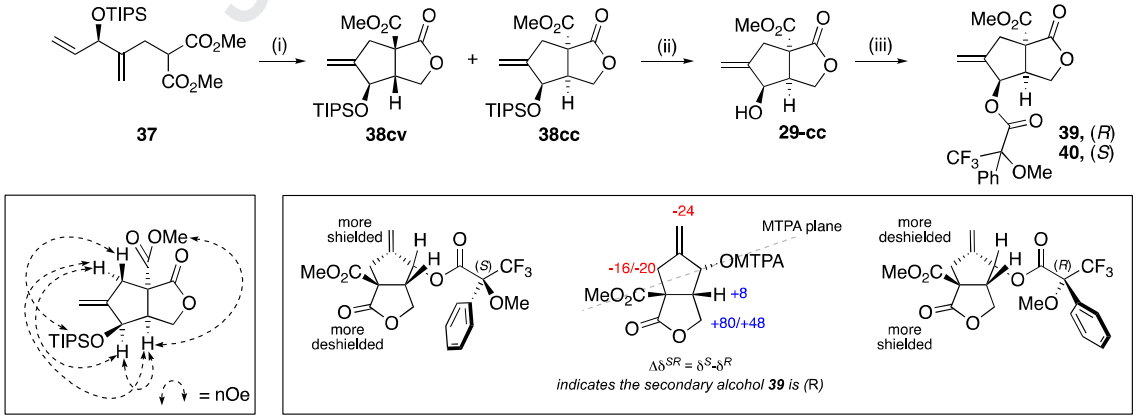
The route towards the synthesis core of pepluanin A in enantioenriched form began with the enzymatic resolution of the butyl ester **34** with *Candida Antarctica* lipase B[27] immobilized on Immobead™ in the presence of vinyl acetate that allowed isolation of the acetate **35** in 47% yield and 99% ee (Scheme 7); the absolute configuration of the acetate was tentatively assigned

as *R* on the basis precedent for the esterification of other racemic secondary alcohols with CAL-B[27] and was confirmed by Mosher ester analysis of a later intermediate (see below). The acetate in **35** could be hydrolyzed without loss of enantiomeric excess to give (+)-**34** on exposure to Amberlite IR-120 acidic resin in methanol for 4 days at room temperature. The alcohol so formed was readily converted into the silylether **36** which, in turn, was converted into the cyclization substrate **37** using standard procedures.

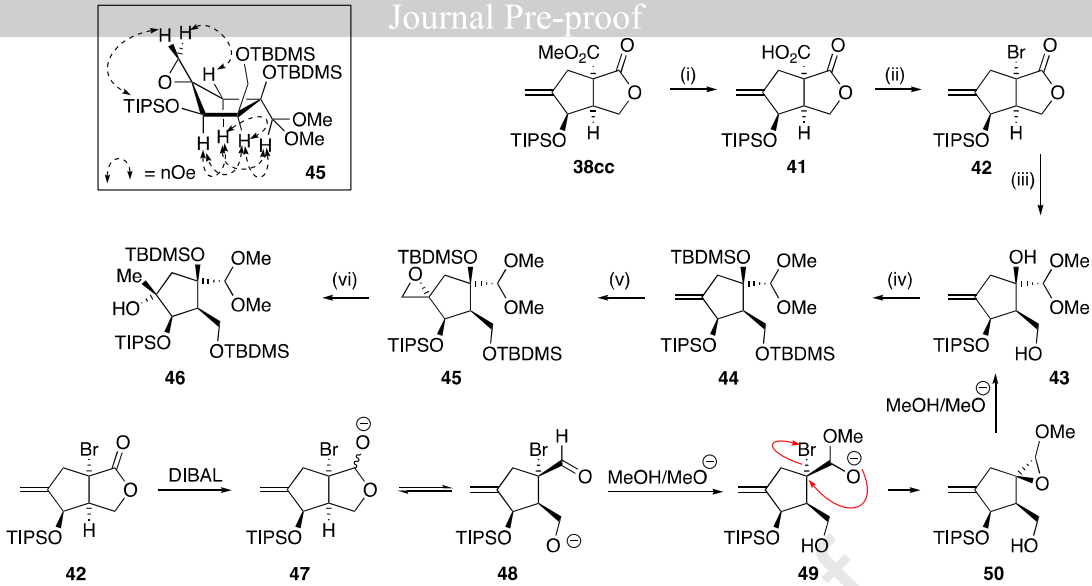


Scheme 7. Cyclization of dienyl malonate. (i) LDA, THF, –78 °C, then acrolein, 94%; (ii) *m*-CPBA, $CHCl_3$, RT, 63%; (iii) vinyl acetate, CAL-B on Immobead™, hexane, 30 °C, 47%, 99% ee; (iv) MeOH, Amberlite™ IR-120, RT, 89%, 99%ee; (v) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 93%; (vi) DIBAL, THF, -20 °C, 90%; (vi) MsCl, Et_3N, CH_2Cl_2, (vii) $CH_2(CO_2Me)$, NaH, KI, THF, DMF, 80 °C, 84% (2 steps).

Exposure of the malonate **37** to our previously optimized cyclization conditions gave the lactones **38** as a separable 5:1 mixture of diastereomers in 78% (**38cc)** and 15% (**38cv)** yields respectively (Scheme 8); the relative configurations of **38cc** and **38cv** were assigned by analogy with the configurations of **30cc** and **30cv** with the configuration of **38cc** being further supported by ^{1}H NMR nOe analysis. The absolute configuration of **38cc** was assigned using Kakisawa's extension of Mosher's method[28] with the secondary alcohol (**29-cc**) derived from treatment of the major diastereomer **38cc** with TBAF. Application of Kakisawa's method confirmed that the secondary alcohol had the expected (*R*)-configuration (Scheme 8). Having assigned the absolute configuration of the TIPS-protected lactone **38cc** we moved to convert it into the cyclopentane core of pepulanin A. Conversion of the methyl ester in **38cc** into the corresponding acid **41** was readily achieved on exposure to lithium hydroxide and water followed by acidification to pH 2 to give the corresponding carboxylic acid in **41** in quantitative yield a transformation that only proceeded in 20% yield with the TBDMS analogue **30cc** and in 42% yield with the TBDPS analogue (not shown). Decarboxylative bromination of **41** was then readily achieved using Barton chemistry.[29] Here conversion of the carboxylic acid **41** into the corresponding acid chloride followed by addition of a solution of the acid chloride in bromotrichloromethane to a suspension of 2-mercaptopyridine *N*-oxide in bromotrichloromethane heated to 130 °C (bath temperature) gave the desired bromide **42** in 79% yield as a low melting white solid. Treatment of the α-bromolactone **42** with DIBAL at –78 °C followed by the addition of MeOH and sodium methoxide gave the α-hydroxy acetal **43** in 84%. This transformation most likely proceeds *via* lactone reduction with DIBAL to give the lactol anion **47** that is in equilibrium with the corresponding alkoxy acetal **48**. Addition of methanol gives the deprotonated hemiacetal **49** that undergoes intramolecular epoxide formation with inversion of configuration. Opening of the epoxide **50** with methoxide at the electronically favored acetal position provides the acetal **43** with the tertiary hydroxyl group of pepluanin A installed. This invertive acetal formation has precedent from the groups of Shibatomi[30] and Achmatowicz[31] who showed that α-flouroaldehydes and an α-tosyloxyaldehyde respectively form α-hydroxy acetals with inversion of configuration on exposure to basic methanol; a number of other groups have also shown that α-halo acetals form α-hydroxy acetals on treatment with basic methanol but the stereochemical course of these transformations was not demonstrated.[32] The diol acetal **43** was readily protected as the bis-TBDMS ether giving **44** that on exposure to DMDO gave the epoxide **45**. The configuration of **45** was assigned on the basis of ^{1}H NMR nOe experiments. Selected nOes are shown in Scheme 9 (box), additionally, both epoxide protons show nOe's to either or both of TBDMS groups that further supports the structural assignment of the epoxide as **45**. Reductive opening of the epoxide **45** with SuperHydride™ gave the differentially protected cyclopentane core of pepluanin A **46**.



Scheme 8. Cyclization of diene **37** along determination of the relative and absolute configuration of **38**. i) EtMgBr, CuI, CH_2Cl_2, –78 °C, then I_2, RT, then 140 °C, **38cc** 78%, **38cv** 15%; (ii) TBAF, THF, 0 °C, 91%; (iii) (*R*) or (*S*)-α-methoxy-α-trifluoromethylphenylacetic, DCC, DMAP, CH_2Cl_2, (*R*)-MTPA ester (*R*)-**40** 46%, (*S*)-MTPA ester (*S*)-**40** 53%.



Scheme 9. Synthesis of the core of prepluanin A along with proposed mechanism for the formation of **43** from **42**. (i) LiOH, THF, water, RT, then HCl(aq) to pH 2; (ii) $(COCl)_2$, DMF, benzene, then concentrate, then $CBrCl_3$, add solution to mercaptopyridine *N*-oxide sodium salt in $CBrCl_3$ at 130 °C (bath temperature), 79% (2 steps); (iii) DIBAL, THF –78 °C then MeOH, NaOMe, RT, 84%; (iv) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, –78 to 0 °C, quant.; (v) DMDO, acetone, RT, 88%; (vi) $LiEt_3BH$, THF, 95%.

3. **Conclusions**

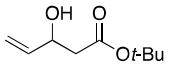
In conclusion, we have developed an enantioselective synthesis of the differentially protected cyclopentane core of pepluanin A **46** that features a diastereoseletive iodocarbocyclization and an invertive acetal formation as key steps. Future work will aim to incorporate the cyclopentane **46** in the total synthesis of pepluanin A.

4. Experimental section

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on Bruker AVC 500 (500/125 MHz), Bruker AV 400 (400/100 MHz), AVN 400 (400/100 MHz) or AVIII 400 (400/100 MHz) spectrometers. Proton and carbon chemical shifts (δ_H, δ_C) are quoted in ppm and referenced to tetramethylsilane (δ = 0 ppm) with residual protonated solvent as internal standard. Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC data and comparison with previously synthesized intermediates. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad), dd (double doublet). Coupling constants (*J*) are given in Hz, and are rounded to the nearest 0.1 Hz and averaged between corresponding coupling constants. H and H' refer to diastereotopic protons attached to the same carbon and imply no particular stereochemistry. Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ES). High resolution mass spectra were recorded by the mass spectrometry service at the Chemistry Research Laboratory, University of Oxford, using a Bruker Daltronics microTOF spectrometer (ES). *m/z* values are reported in Daltons with their percentage abundances and, where known, the relevant fragment ions in parentheses. High resolution values were calculated to four decimal places from the molecular formula, all found values being within a tolerance of 5 ppm. Infrared spectra were recorded on a Bruker Tensor 27 Fourier Transform spectrometer, using diamond ATR. Absorption maxima (ν_{max}) are described as s (strong), m (medium), w (weak) and br (broad) and quoted in wavenumbers (cm-1). Melting points: Melting points were determined using a Griffin heated metal block apparatus and are uncorrected. Optical rotations: Optical rotations were measured using a Perkin-Elmer 241 polarimeter in a cell of 1 dm path length (l). Single Crystal X-ray Diffraction: Low temperature[33] data were collected using a Nonius Kappa-CCD diffractomter and reduced using DENZO/SCALEPACK.[34] The structures were solved using SuperFlip[35] and refined using CRYSTALS.[36] Selected refinement details for each structure are given below and full details can be found in the ESI (CIF). Crystallographic data have also been deposited with the Cambridge Crystallographic Data Centre (CCDC 1963303-1963306) and copies of these data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif

Specific rotations denoted as $[\alpha]_T^D$ (T = temperature in °C, D refers to the experimental D line of a sodium lamp, where the wavelength of light = 589 nm. Compounds **21a,d,f** and **g**, and **20a,d,f** and **g** are known.[22] Compound **21b** was prepared by the same method as Taguchi used for the preparation of compound **21a**.[22]

4.1.1. tert-Butyl 3-hydroxypent-4-enoate ***12***

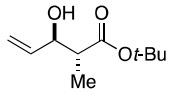


12

To a stirred solution of diisopropylamine (10.8 mL, 77.0 mmol), in THF (250 mL), at –78 °C was added BuLi (48.4 mL, 1.6 M in hexanes, 77.5 mmol) dropwise. The reaction mixture was stirred for 15 min before *tert*-butyl acetate **13** (8.90 mL, 66.4 mmol) was added and then stirred for 50 min at –78 °C. Freshly distilled acrolein (4.44 g, 66.4 mmol), in THF (10 mL + 2 mL rinse) was added rapidly and the reaction stirred for 5 min before being quenched with sat. NH_4Cl (aq) (20 mL) and extracted with Et_2O (130 mL). The separated organic layer was washed with brine (2 × 60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound **12** as a colorless oil (12.8 g, >quant); R_f 0.42 (7:1 petrol:EtOAc); δ_H (400 MHz, $CDCl_3$) 5.87 (1H, ddd, *J* = 5.9, 10.0, 17.0 Hz, C*H*=CH$_2$), 5.30 (1H, dt, *J* = 17.0, 2.0 Hz, CH=C*H*H'), 5.14 (1H, dt, *J* = 10.0, 2.0 Hz, CH=CH*H'*), 4.44–4.50 (1H, m, C*H*OH), 3.10 (1H, br s, O*H*), 2.50 (1H, dd, *J* = 16.0, 4.3 Hz, C*H*H'), 2.42 (1H, dd, *J* = 16.0, 8.1 Hz, CH*H'*), 1.47 (9H, s, CMe$_3$); δ_C (100 MHz, $CDCl_3$) 171.7

(*C*=O), 138.9 (*C*H=CH_2), 115.1 (CH=*C*H_2), 81.4 (CMe_3), 69.0 (*C*HOH), 42.0 (*C*H_2), 28.0 (CMe_3); *m/z* LRMS (ESI^+) 195 ($M+Na^+$, 100%). Data in accordance with the literature values.[17]

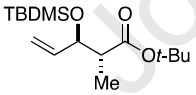
4.1.2. (2R, 3R*)-*tert*-Butyl 3-hydroxy-2-methylpent-4-enoate **11***



11

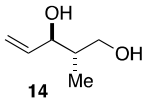
To a stirred solution of diisopropylamine (16.2 mL, 108 mmol), in THF (60 mL), at –78 °C was added BuLi (49.2 mL, 2.2 M in hexanes, 108 mmol) dropwise. The reaction mixture was stirred for 15 min before *tert*-butyl 3-hydroxypent-4-enoate **12** (8.10 g, 47.0 mmol), was added dropwise as a solution in HMPA (14 mL) and THF (30 mL). The reaction warmed to –40 °C and stirred for 20 min before cooling back to –78 °C and adding MeI (6.00 mL, 133 mmol) dropwise. The reaction was then warmed to 0 °C over 2 h quenched with sat. NH_4Cl (aq) (100 mL), followed by 1 M HCl until the aqueous layer reached neutral pH. The aqueous layer was separated and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (7:1 petrol:EtOAc) gave the title compound **11** as a colorless oil (6.30 g, 33.8 mmol, 72%); R_f 0.45 (7:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 3451br m, 2950m, 1730s; δ_H (400 MHz, $CDCl_3$) 5.86 (1H, ddd, *J* = 170, 10.0, 6.5 Hz, C*H*=CH_2), 5.33 (1H, dt, *J* = 17.0, 2.0 Hz, CH=C*H*H'), 5.22 (1H, dt, *J* = 10.0, 2.0 Hz, CH=CH*H*'), 4.16 (1H, tt, *J* = 6.5, 2.0 Hz, C*H*OH), 2.48 (1H, qn, *J* = 6.5 Hz, C*H*Me), 1.48 (9H, s, CMe_3), 1.19 (3H, d, *J* = 6.5 Hz CH*Me*); δ_C (100 MHz $CDCl_3$) 175.0 (*C*=O), 139.3 (*C*H=CH_2), 116.5 (CH=*C*H_2), 81.2 (CMe_3), 74.8 (*C*HOH), 45.8 (*C*HMe), 28.1 (CMe_3), 14.1 (CH*Me*); *m/z* LRMS (ESI^+) 209 ($M+Na^+$, 100%); HRMS (ESI^+) found 209.1144, $C_{10}H_{18}O_3Na^+$ ($M+Na^+$), requires 209.1148. In accordance with the lit. data reported for a 1:1 mixture of stereoisomers.[37] Stereochemistry assigned by conversion to known alcohol **14**.

4.1.3. (2R,3R*)-*tert*-Butyl 3-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-4-enoate*



To a stirred solution of alcohol **11** (500 mg, 2.7 mmol) in CH_2Cl_2 (5 mL) was added imidazole (460 mg, 6.8 mmol), DMAP (50 mg) and then TBDMSCl (471 mg, 3.1 mmol). The reaction was stirred at RT for 20 h, then quenched with sat. NH_4Cl (aq) (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (98:2 petrol:EtOAc) gave the title compound as a colorless oil (800 mg, 2.67 mmol, 98%). R_f 0.45 (98:2 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2971w, 1739s; δ_H (400 MHz, $CDCl_3$) 5.69 (1H, ddd, *J* = 6.7, 10.3, 17.3 Hz, C*H*=CH_2), 5.12 (1H, dt, *J* = 17.3, 1.5 Hz, CH=CHH'), 5.08 (1H, dt, *J* = 10.3, 1.5 Hz, CH=C*H*H'), 4.24 (1H, tt, *J* = 6.7, 1.5 Hz, C*H*OSi), 2.39 (1H, qn, *J* = 6.7 Hz, C*H*Me), 1.39 (9H, s, CMe_3), 0.94 (3H, d, *J* = 6.7 Hz, CH*Me*), 0.82 (9H, s, $SiCMe_3$), 0.00 (3H, Si*Me*), -0.03 (3H, Si*Me*); δ_C (100 MHz, $CDCl_3$) 173.9 (C=O), 138.6 (*C*H=CH_2), 116.3 (CH=*C*H_2), 80.1 (CMe_3), 75.7 (*C*HOSi), 47.4 CH*Me*), 28.2 (CMe_3), 25.8 (CMe_3), 18.1 ($SiCMe_3$), 12.6 (CH*Me*), -4.2 (Si*Me*), -5.0 (Si*Me*); *m/z* LRMS (ESI^+) 323 ($M+Na^+$, 100%); HRMS (ESI^+): found 323.2018, $C_{16}H_{32}O_3SiNa^+$ ($M+Na^+$), requires 323.2013.

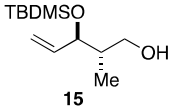
4.1.4. (2S,3R*)-2-methylpent-4-ene-1,3-diol **14***



14

To a stirred suspension of $LiAlH_4$ (1.06 g, 27.9 mmol) in Et_2O (50 mL) at 0 °C was added a solution of (2*R**,3*R**)-*tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-4-enoate (8.36 g, 27.9 mmol) in Et_2O (50 mL) and the reaction stirred at RT for 1 h. The reaction was quenched with water (1.06 mL) and aq. 2 M NaOH (1.06 mL). The mixture was stirred for 15 min then water (2.1 mL) was added and the mixture stirred for 5 min. The mixture was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5:1→1:1 Petrol:EtOAc) gave the title compound **14** as a colorless oil (2.25g, 19.4 mmol, 69%); δ_H (400 MHz, $CDCl_3$) 5.85 (1H, ddd, *J* = 17.0, 10.0, 7.0 Hz, CH_2=C*H*), 5.24 (1H, d, J = 17.0 Hz, C*H*H'=CH), 5.16 (1H, d, *J* = 10.0 Hz, CH*H*'=CH), 4.00 (1H, t, *J* = 7.0 Hz, C*H*OH), 3.70–3.80 (1H, m, C*H*H'OH), 3.63 (1H, t, *J* = 8.0 Hz, CH*H*'OH), 3.35 (2H, br s, O*H*), 1.71–1.82 (1H, m, C*H*Me), 0.84 (3H, d, *J* = 7.0 Hz, CH*Me*); δ_C (100 MHz $CDCl_3$) 139.7 (CH_2=*C*H), 116.3 (*C*H_2=CH), 78.9 (*C*HOH), 67.3 (*C*H_2OH), 39.9 (*C*HMe), 13.5 (CH*Me*). Data in accord with literature values for enantiopure material.[19]

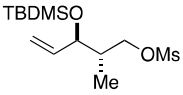
4.1.5. (2S,3R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpent-4-en-1-ol **15***



15

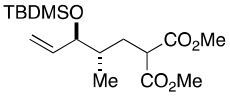
To a stirred solution of ester (2*R**,3*R**)-*tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-4-enoate (800 mg, 2.67 mmol) in THF (5 mL) at –35 °C was added DIBAL (6.7 mL, 1 M in hexane, 6.7 mmol) dropwise and the reaction was then stirred at –20 °C for 90 min. The reaction was quenched with sat. aq. Rochelle's salt (10 mL) and diluted with EtOAc (10 mL) then stirred vigorously at RT for 90 min. The aqueous layer was separated and extracted with EtOAc (3 × 10mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (4:1 petrol:EtOAc) gave the title compound **15** as a colorless oil (540 mg, 2.34 mmol, 88%); R_f 0.42 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 3325br m, 2950s; δ_H (400 MHz, $CDCl_3$) 5.83 (1H, ddd, *J* = 17.1, 10.3, 7.3 Hz, C*H*=CH_2), 5.18 (1H, dt, *J* = 17.1, 1.5 Hz, CH=C*H*H'), 5.15 (1H, dt, *J* = 10.3, 1.5 Hz, CH=CH*H*'), 4.07 (1H, ddt, *J* = 7.0, 6.3, 1.5 Hz, CHOTBDMS), 3.72 (1H, dd, *J* = 10.9, 3.6 Hz, C*H*H'OH), 3.57 (1H, dd, *J* = 10.9, 6.0 Hz, CH*H*OH), 2.59 (1H, br s, O*H*), 1.72 (1H, qddd, *J* = 7.1, 7.0, 6.0, 3.6 Hz, C*H*Me), 0.95 (3H, d, *J* = 7.1 Hz, CH*Me*), 0.91 (9H, s, CMe_3), 0.10 (3H, s, Si*Me*), 0.05 (3H, s, Si*Me*); δ_C (100 MHz $CDCl_3$) 140.2 (*C*H=CH_2), 115.5 (CH=*C*H_2), 79.4 (CMe_3), 65.9 (CHOTBDMS), 40.6 (CHMe), 25.8 (CMe_3), 18.0 ($SiCMe_3$), 14.1 (CHMe), -4.1 (SiMe), -5.0 (SiMe); *m/z* LRMS (ESI^+) 253 ($M+Na^+$, 16%); HRMS (ESI^+): found 253.1602, $C_{12}H_{26}O_2SiNa^+$ ($M+Na^+$), requires 253.1594.

4.1.6. (2S,3R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpent-4-en-1-yl methanesulfonate*



To a solution of alcohol **15** (1.66 g, 7.20 mmol) in CH_2Cl_2 (29 mL) at 0 °C was added Et_3N (1.5 mL. 1.09 g, 10.8 mmol) followed by MsCl (0.72 mL, 1.07 g, 9.4 mmol) and the reaction mixture was stirred for 10 min and then quenched with sat. aq. NH_4Cl (30 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) to yield the title compound as a yellow oil; R_f 0.42 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2930m, 1472m, 1357s; δ_H (400 MHz, $CDCl_3$) 5.76 (1H, ddd, *J* = 7.0, 10.3, 17.1 Hz, C*H*=CH_2), 5.19 (1H, dt, *J* = 17.1, 1.5 Hz, CH=C*H*H'), 5.15 (1H, dt, *J* = 10.3, 1.5 Hz, CH=CH*H*'), 4.28 (1H, dd, *J* = 10.9, 4.8 Hz, C*H*H'OMs), 4.14 (1H, *J* = dd, 10.9, 6.0 Hz, CH*H*'OMs), 4.04 (1H, ddt, *J* = 7.0, 6.3, 1.5 Hz, C*H*OTBDMS), 2.99 (3H, s, OMs), 1.90–2.04 (1H, m, C*H*Me), 0.98 (3H, d, *J* = 6.9 Hz, CH*Me*), 0.90 (9H, s, CMe_3), 0.06 (3H, s, Si*Me*), 0.02 (3H, s, Si*Me*); δ_C (100 MHz, $CDCl_3$) 139.0 (*C*H=CH_2), 116.3 (CH=*C*H_2), 75.0 (*C*HOTBDMS), 71.7 (*C*H_2OMs), 39.5 (*C*HMe), 37.1 (SO_2*Me*), 25.8 (CMe_3), 18.1 (CMe_3), 13.2 (CH*Me*), -4.1 (Si*Me*), -5.0 (Si*Me*); *m/z* LRMS (ESI^+) 331 (M+Na^+, 100%); HRMS (ESI^+): found 331.1374, $C_{13}H_{28}O_4SiSNa^+$ (M+Na^+), requires 331.1370.

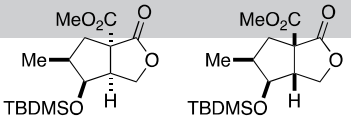
4.1.7. Dimethyl 2-((2S,3R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-4-en-1-yl)malonate* ***16***



16

To a stirred suspension of NaH (60% dispersion in mineral oil, 864 mg, 21.6 mmol) in DMF (30 mL) and THF (15 mL) at 0 °C was added dimethyl malonate dropwise (2.5 mL, 2.85g, 21.6 mmol). The reaction mixture was warmed to RT and the crude mesylate (2*S**,3*R**)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpent-4-en-1-yl methanesulfonate prepared above was added as a solution in THF (14 mL) followed by the addition of KI (358 mg, 2.16 mmol). The reaction mixture was warmed to 80 °C and stirred for 16 h, then allowed to cool to RT, quenched with sat. aq. NH_4Cl (30 mL) and petrol (30 mL) was added. The aqueous layer was extracted with petrol (2 × 30 mL), the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (9:1 petrol:EtOAc) gave the title compound **16** as a colorless oil (2.20 g, 6.40 mmol, 89%); R_f 0.62 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2956m, 1758s, 1739s, 1253s; δ_H (400 MHz, $CDCl_3$) 5.73 (1H, ddd, *J* = 6.3, 10.2, 17.0 Hz, C*H*=CH_2), 5.15 (1H, dd, *J* = 17.0, 1.5 Hz, CH=C*H*H'), 5.10 (1H, dd, *J* = 10.2, 1.5 Hz, CH=CH*H*'), 3.95 (1H, dd, *J* = 6.3, 4.9 Hz, C*H*OTBDMS), 3.72 (6H, s, CO_2Me), 3.48 (1H, dd, *J* = 9.3, 5.3 Hz, C*H*($CO_2Me)_2$), 2.11 (1H, ddd, *J* = 13.7, 9.5, 5.3 Hz, C*H*H'CHMe), 1.62 (1H, ddd, *J* = 13.7, 9.3, 6.1 Hz, CH*H*'CHMe), 1.47–1.57 (1H, m, C*H*Me), 0.88 (9H, s, CMe_3), 0.87 (3H, d, *J* = 6.6 Hz, CH*Me*), 0.03 (3H, s, Si*Me*), 0.00 (3H, s, Si*Me*); δ_C (100 MHz, $CDCl_3$) 170.2 (*C*=O), 169.9 (*C*=O), 138.9 (*C*H=CH_2), 115.6 (CH=*C*H_2), 77.4 (*C*OTBDMS) 52.5 (O*Me*), 52.4 (O*Me*), 50.0 (*C*H($CO_2Me)_2$), 37.4 (*C*HMe), 31.3 (*C*H_2), 25.9 (CMe_3), 18.2c ($SiCMe_3$), 15.0 (CH*Me*), -4.3 (Si*Me*), -5.0 (Si*Me*); *m/z* LRMS (ESI^+) 367 (M+Na^+, 100%); HRMS (ESI^+): found 367.1907, $C_{17}H_{32}O_5SiNa^+$ (M+Na^+), requires 367.1911.

4.1.8. (3aR,5S*,6S*,6aS*)-Methyl 6-((*tert*-butyldimethylsilyl)oxy)-5-methyl-3-oxohexahydro-1H- cyclopenta[c]furan-3a-carboxylate* ***17-cc*** *and (3aS*,5SR*,6S*,6aR*)-methyl 6-((*tert*-butyldimethylsilyl)oxy)-5-methyl-3-oxohexahydro-1H- cyclopenta[c]furan-3a-carboxylate* ***17-cv***

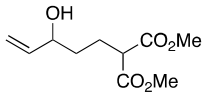


17-cc **17-cv**

To copper(II) triflate (90 mg, 0.25 mmol) and mangaese(III) acetate (201 mg, 0.75 mmol) was added malonate **16** (86 mg, 0.25 mmol) as a solution in degassed acetonitrile (1.25 mL) and the reaction mixture was stirred at 80 °C for 4 h, then allowed to coole to RT and diluted with water (2.5 mL) and EtOAc (5 mL). The aqueous layer was separated, extracted with EtOAc (2 × 5 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash column chromatography (4:1 petrol:EtOAc)gave the 2.177 as a colorless oil (35 mg, 0.11 mmol, 43%) followed by the 2.155 as a colorless oil (36 mg, 0.11 mmol, 44%); (Major **17-cc**) R_f 0.22 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2955m, 1772s, 1739s, 1255s; δ_H (400 MHz, $CDCl_3$) 4.39 (1H, dd, *J* = 9.3, 1.9 Hz, C*H*HOR), 4.34 (1H, dd, *J* = 9.3, 7.1 Hz, CH*H*OR), 4.08 (1H, t, *J* = 3.9 Hz, CHOTBDMS), 3.77 (3H, s, OMe), 3.02 (1H, ddd, *J* = 6.9, 3.9, 1.9 Hz, $CHCH_2OR$), 2.55 (1H, dd, *J* = 13.2, 7.3 Hz, CHH'CHMe), 2.08–2.16 (1H, m, CHMe), 1.93 (1H, dd, *J* = 13.2, 11.5 Hz, CHH'CHMe), 0.97 (3H, d, *J* = 6.9 Hz CHMe), 0.90 (9H, s, Si*C*Me_3), 0.09 (3H, s, SiMe), 0.07 (3H, s, SiMe); δ_C (100 MHz $CDCl_3$) 176.1 (C=O), 171.1 (C=O), 77.2 (CH_2OR), 66.5 (CHOTBDMS), 59.3 (CCO_2Me), 53.2 ($CHCH_2OR$), 52.7 (OMe), 41.8 (CH_2CHMe), 37.4 (CH_2Me), 25.8 (CMe_3), 18.0 (Si*C*Me_3), 13.8 (CHMe), -4.1 (SiMe), -4.2 (SiMe); *m/z* LRMS (ESI^+) 351 (M+Na^+, 100%); HRMS (ESI^+): found 351.1604, $C_{16}H_{28}O_5SiNa^+$ (M+Na^+), requires 351.1598.

(Minor **17-cv**) R_f 0.41 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2956 m, 1778s, 1747s, 1254m; δ_H (400 MHz, $CDCl_3$) 4.55 (1H, t, *J* = 9.5 Hz, CHH'OR), 3.99 (1H, dd, *J* = 9.5, 3.7 Hz, CHH'OR), 3.84 (1H, dd, *J* = 3.7, 1.5 Hz, CHOTBDMS), 3.76 (3H, s, CO_2Me), 3.06 (1H, ddd, *J* = 9.5, 3.7, 1.5 Hz, $CHCH_2OR$), 2.41 (1H, dd, *J* = 12.9, 12.3 Hz, CHH'CHMe), 2.20 (1H, dd, *J* = 12.9, 6.4 Hz, CHH'CHMe), 1.95–1.90 (1H, m, CHMe), 1.01 (3H, d, *J* = 6.4 Hz, CHMe), 0.86 (9H, s, CMe_3), 0.00 (3H, s, SiMe), 0.00 (3H, s, SiMe); δ_C (100 MHz $CDCl_3$) 176.4 (C=O), 169.9 (C=O), 81.0 (CHOTBDMS), 69.6 (CH_2OR), 59.8 ($CHCH_2OR$), 54.1 (CCO_2Me), 53.1 (OMe), 38.8 (CH_2CHMe), 38.6 (CHMe), 25.6 (CMe_3), 18.0 ($SiCMe_3$), 12.9 (CHMe), -4.8 (Si*Me*), -4.9 (Si*Me*).

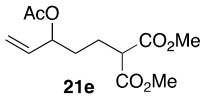
4.1.9. Dimethyl 2-(3-hydroxypent-4-en-1-yl)malonate



A mixture of hydrochloric acid (2 M, 0.1 mL, 0.3 mmol) in methanol (10 mL) was added to dimethyl 2-(3-(tert -butyldimethylsilyloxy)pent-4-enyl)malonate **21a** (2.00 g, 6.05 mmol). After 7 h of stirring at room temperature the reaction mixture was concentrated under reduced pressure. The residual oil was purified by flash column chromatography (petroleum ether:ethyl acetate, 1:1) to give the title compound as a colorless oil (1.15 g, 5.32 mmol, 88%); R_f = 0.13 (petroleum ether:ethyl acetate, 3:1); ν_{max}(neat)/cm^{-1} 3419 (O-H), 3081, 3006, 2956, 2850, 1750 (C=O), 1733 (C=O), 1645 (C=C); δ_H(400 MHz; $CDCl_3$) 5.83 (ddd, *J* = 17.2, 10.4, 6.1 Hz, 1H, C*H*=CH_2), 5.23 (d, *J* = 17.2 Hz, 1H, CH=C*H*H), 5.11 (d, *J* = 10.4 Hz, 1H, CH=CH*H*), 4.14-1.07 (m, 1H, C*H*OH), 3.72 (s, 6H, O*Me*), 3.40 (t, *J* = 7.5 Hz, 1H, C*H*($CO_2Me)_2$), 2.07-1.88 (m, 3H, C*H*$_2$CH($CO_2Me)_2$, OH), 1.58-1.50 (m, 2H, C*H*$_2$CH$_2$CH(CO_2Me)); δ_C(100 MHz, $CDCl_3$) 169.8 (CO), 169.7 (CO), 140.5 (*C*H=CH_2) 115.1 (CH=*C*H_2), 72.4 (*C*HOH), 52.5

(2×O*Me*), 51.3 (*C*H(CO$_2$Me)$_2$), 34.2 (CH_2CH(CO$_2$Me)$_2$), 24.7 (CH_2CH$_2$CH(CO$_2$Me)$_2$); *m/z* LRMS (ESI$^+$) 455.1 (2M+Na$^+$, 100%), 239.0 (M+Na$^+$, 92); HRMS (ESI+) found 239.0888, $C_{10}H_{16}NaO_5^+$ (M+Na$^+$), requires 239.0890.

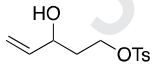
4.1.10. Dimethyl 2-(3-acetoxypent-4-en-1-yl)malonate **21e**



21e

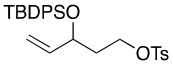
Dimethyl 2-(3-hydroxypent-4-en-1-yl)malonate (0.500 g, 2.31 mmol) was dissolved in CH_2Cl_2 (7 mL). Triethylamine (1.00 mL, 7.17 mmol) was added followed by acetic anhydride (0.650 mL, 6.87 mmol) and 4-dimethylaminopyridine (0.030 g, 0.245 mmol). After stirring at room temperature for 3 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL). 50% sat. aq. NH_4Cl (30 mL) was added and the organic layer washed with 50% sat. aq. sodium bicarbonate (30 mL). The two aqueous layers were sequentially extracted with CH_2Cl_2 (3×30 mL) and the organic layers combined, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (petrol 40-60:EtOAc, 9:1) gave the title compound **21e** as a clear oil (0.530 g, 2.05 mmol, 89%); found: C, 55.91%; H, 6.93%; $C_{12}H_{18}O_6$ requires: C, 55.81%; H, 7.02%; R_f = 0.45 (petrol:EtOAc, 3:1); $\nu_{max}(CDCl_3)/cm^{-1}$ 3088, 2991, 2956, 2848, 1736 (C=O), 1647 (C=C), 1436, 1372, 1344, 1282, 1239, 1197, 1157, 1107, 1047, 1020, 962, 931, 855; δ_H(400 MHz; $CDCl_3$) 5.74 (1H, dddd, *J* = 17.3, 10.4, 6.0, 0.7 Hz, C*H*=CH$_2$), 5.23 (1H, d, *J* = 17.3 Hz, CH=C*H*H'), 5.25-5.19 (1H, m, C*H*OAc), 5.18 (1H, d, *J* = 10.4 Hz, CH=CH*H'*), 3.72 (6H, s, 2×O*Me*), 3.36 (1H, t, *J* = 7.5 Hz, C*H*(CO$_2$Me)$_2$), 2.05 (3H, d, *J* = 0.5 Hz, C(O)*Me*), 1.96-1.88 (2H, m, CH_2CH(CO$_2$Me)$_2$), 1.68-1.60 (2H, m, CH_2CH$_2$CH(CO$_2$Me)$_2$); δ_C(100 MHz; $CDCl_3$) 170.2 (*C*O), 169.5 (2×*C*O), 135.7 (*C*H=CH$_2$), 117.2 (CH=*C*H$_2$), 73.8 (*C*HOAc), 52.5 (2×O*Me*), 51.1 (*C*H(CO$_2$Me)$_2$), 31.5 (CH_2CH(CO$_2$Me)$_2$), 24.3 (CH_2CH$_2$CH(CO$_2$Me)$_2$), 21.1 (C(O)*Me*); *m/z* LRMS (ESI$^+$) 281.1 (M+Na$^+$, 100%); HRMS (ESI$^+$) found 281.1002, $C_{12}H_{18}NaO_6^+$ (M+Na$^+$) requires 281.0996.

4.1.11. Hydroxypent-4-en-1-yl 4-methylbenzenesulfonate



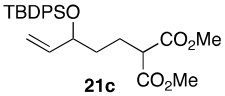
Pent-4-ene-1,3-diol[38] (0.100 g, 0.979 mmol) was dissolved in CH_2Cl_2 (10 mL), triethylamine (0.15 mL, 1.07 mmol) was added and the solution cooled to 0 °C. 4-Toluenesulfonyl chloride (0.205 g, 1.07 mmol) was added and the reaction mixture allowed to slowly warm to room temperature. After 25 h the solution was concentrated under reduced pressure and the residue purified by flash column chromatography (petroleum ether 40-60:ethyl acetate, gradient, 1:1→1:8) to give the title compound as a colorless oil (0.164 g, 0.640 mmol, 65%); R_f = 0.38 (petroleum ether:ethyl acetate, 1:1); $\nu_{max}(CDCl_3)/cm^{-1}$ 3534 (O-H), 3423 (O-H); δ_H(400 MHz; $CDCl_3$) 7.79 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.35 (2H, d, *J* = 8.0 Hz, Ar*H*), 5.80 (1H, ddd, *J* = 17.1, 10.4, 6.0 Hz, C*H*=CH$_2$), 5.20 (1H, dd, *J* = 17.1, 1.1 Hz, 1H, CH=C*H*H'), 5.10 (1H, dd, *J* = 10.4, 1.1 Hz, 1H, CH=CH*H'*), 4.27-4.18 (2H, m, CH_2OTs), 4.10 (1H, dt, *J* = 10.5, 6.0 Hz, 1H, C*H*OH), 2.44 (3H, s, *Me*), 2.21 (1H, br s, O*H*), 1.94-1.84 (1H, m, C*H*HCH$_2$OTs), 1.79 (1H, ddt, J = 14.4, 8.5, 6.0 Hz, CH*H*CH$_2$OTs); δ_C(100 MHz, $CDCl_3$) 144.8 (Ar), 139.8 (*C*H=CH$_2$), 132.9 (Ar), 129.8 (Ar), 127.9 (Ar), 115.5 (CH=*C*H$_2$), 69.0 (*C*H$_2$OTs), 67.3 (*C*HOH), 35.8 (*C*H$_2$CH$_2$OTs), 21.6 (*Me*); *m/z* LRMS (ESI$^+$) 279.1 (M+Na$^+$, 100%); HRMS (ESI$^+$) found 279.0662, $C_{12}H_{16}NaO_4S^+$ (M+Na$^+$) requires 279.0662. Further elution of the column gave the recovered starting material as a colorless oil (0.034 g, 34%)

4.1.12. 3-((tert-Butyldiphenylsilyl)oxy)pent-4-en-1-yl 4-methylbenzenesulfonate



To a solution of 3-hydroxypent-4-en-1-yl 4-methylbenzenesulfonate (1.19 g, 4.64 mmol) in *N*,*N*-dimethylformamide (10 mL), imidazole (0.948 g, 13.9 mmol) was added followed by *tert*-butyl(chloro)diphenylsilane (1.53, 5.57 mmol). The clear reaction mixture was stirred at room temperature for 5 h. sat. aq. NH_4Cl (40 mL) was added followed by Et_2O (40 mL). The organic layer was washed with water (3 × 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (petrol 30-40:EtOAc, 9:1→6:1) gave a mixture of the title compound and 4-methylbenzenesulfonic acid as a colorless oil (1.3:1, respectively, 1.91 g, approx. 65% yield of 324); R_f = 0.26 (petrol:Et_2O, 8:1); $\nu_{max}(CDCl_3)/cm^{-1}$ 3564 (O-H, acid impurity), 1644 (C=C); δ_H(400 MHz; $CDCl_3$) 7.75-7.69 (3H, m, Ar*H*), 7.64-7.56 (4H, m, Ar*H*), 7.47-7.26 (11H, m, Ar*H*), 5.68 (1H, ddd, *J* = 17.0, 10.4, 6.5 Hz, C*H*=CH$_2$), 4.92 (1H, d, *J* = 10.4 Hz, CH=C*H*H'), 4.88 (1H, d, *J* = 17.0 Hz, CH=CH*H'*), 4.26-4.21 (1H, m, C*H*OTBDPS), 4.11-4.01 (2H, m, CH$_2$OTs), 2.44 (3H s, *Me*), 1.86 (1H, dtd, *J* = 14.0, 7.1, 5.9 Hz, C*H*H'CH$_2$OTs), 1.79-1.70 (1H, m, CH*H'*CH$_2$OTs), 1.01 (9H, s, SiC*Me*$_3$); δ_C(125 MHz; $CDCl_3$) 144.6 (Ar), 139.2 (*C*H=CH$_2$), 135.8 (Ar), 135.8 (Ar), 135.2 (Ar), 134.8 (Ar), 133.6 (Ar), 133.6 (Ar), 133.0 (Ar), 129.8 (Ar), 129.7 (Ar), 129.6 (Ar), 129.6 (Ar), 127.9 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 115.6 (CH=*C*H$_2$), 71.3 (*C*HOTBDPS), 67.1 (CH$_2$OTs), 36.3 (*C*H$_2$CH$_2$OTs), 26.9 (SiC*Me*$_3$), 19.2 (Si*C*Me$_3$); *m/z* LRMS (ESI$^+$) 517.2 (M+Na$^+$, 100%); HRMS found 517.1845, $C_{28}H_{34}NaO_4SSi^+$ (M+Na$^+$) requires 517.1839.

4.1.13. *Dimethyl 2-(3-((tert-butyldiphenylsilyl)oxy)pent-4-en-1-yl)malonate* ***21c***

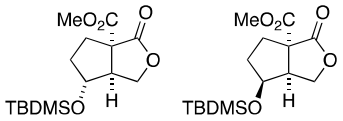


21c

To a suspension of sodium hydride (60% suspension in mineral oil, 0.072 g, 1.80 mmol) in tetrahydrofuran (2 mL), dimethyl malonate (0.200 mL, 1.75 mmol) was slowly added via syringe. 3- ((*tert*-butyldiphenylsilyl)oxy)pent-4-en-1-yl 4-methylbenzenesulfonate (0.300 g, 0.600 mmol) was added via syringe (2×0.5 mL, tetrahydrofuran rinse) followed by a small amount of potassium iodide and *N*,*N*-dimethylformamide (2 mL). The suspension was heated at 80 °C for 4 h and then cooled to room temperature and poured into 50% sat. aq. NH_4Cl (20 mL). Et_2O (40 mL) was added and the organic layer was washed with water (3 × 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography (petrol 40-60:EtOAc, 6:1) gave the title compound **21c** as a colorless oil (0.227 g, 0.499 mmol, 83%); R_f = 0.24 (petrol:EtOAc, 6:1); ν_{max}(neat)/cm^{-1} 1754 (C=O), 1737 (C=O), 1644 (C=C); δ_H(400 MHz; $CDCl_3$) 7.70-7.63 (4H, m, Ar*H*), 7.43-7.33 (6H, m, Ar*H*), 5.77 (1H, ddd, *J* = 17.0, 10.5, 6.3 Hz, C*H*=CH$_2$), 5.01 (1H, d, *J* = 17.0 Hz, CH=C*H*H'), 5.00 (1H, d, *J* = 10.5 Hz, CH=CH*H'*), 4.19 (1H, q, *J* = 6.3 Hz, C*H*OTBDPS), 3.71 (3H, s, O*Me*), 3.69 (3H, s, O*Me*), 3.24 (1H, t, *J* = 7.5 Hz, C*H*(CO$_2$Me)$_2$), 1.96-1.81 (2H, m, CH_2CH(CO$_2$Me)$_2$), 1.56-1.41 (2H, m, CH_2CH(CO$_2$Me)$_2$), 1.07 (9H, s, SiC*Me*$_3$); δ_C(100 MHz; $CDCl_3$) 169.7 (2×*C*O), 139.9 (*C*H=CH$_2$), 135.9 (Ar), 135.8 (Ar), 134.7 (Ar), 134.1 (Ar), 134.0 (Ar), 129.6 (Ar), 129.5 (Ar), 127.7 (Ar), 127.5 (Ar), 127.3 (Ar), 115.0 (CH=*C*H$_2$), 73.8

(*C*HOTBDPS), 52.4 (2×O*Me*), 51.5 (*C*H(CO$_2$Me)$_2$), 34.8 (*C*H$_2$CH$_2$CH(CO$_2$Me)$_2$), 27.0 (SiC*Me*$_3$), 23.7 (CH$_2$C*H*$_2$CH(CO$_2$Me)$_2$), 19.3 (Si*C*Me$_3$); *m/z* LRMS (ESI$^+$) 477.2 (M+Na$^+$, 72%); HRMS (ESI$^+$) found 477.2068, $C_{26}H_{34}NaO_5Si^+$ (M+Na$^+$) requires 477.2068.

4.1.14. (3aR,6R*,6aS*)-Methyl 6-(tert-butyldimethylsilyloxy)-3-oxohexahydro-1H-cyclopenta-[c]furan-3a-carboxylate **20a-cv** and (3aR*,6S*,6aS*)-methyl 6-(tert-butyldimethylsilyloxy)-3-oxohexahydro-1H-cyclopenta-[c]furan-3a-carboxylate **20a-cc***

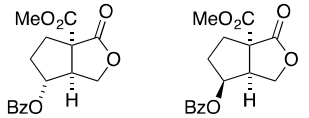


20a-cv **20a-cc**

Dimethyl 2-(3-(*tert*-butyldimethylsilyloxy)pent-4-enyl)malonate **21a** (7.0 g, 21.2 mmol) was dissolved in nitrogen sparged acetonitrile (40 mL) and added via syringe (25 mL rinse) to a mixture of manganese(III) acetate (12.0 g, 44.7 mmol) and copper(II) triflate (7.7 g, 21.3 mmol). The reaction mixture was diluted with nitrogen sparged acetonitrile (40 mL) and heated at 80 °C for 3 h 20 min under an atmosphere of nitrogen and then cooled to room temperature. Water (600 mL), EtOAc (300 mL) and brine (100 mL) were added and the aqueous layer extracted with EtOAc (3 × 300 mL). The combined organic extracts were dried (MgSO$_4$) and con- centrated under reduced pressure to yield the crude product (crude d.r. 2:1, **20a-cc**: **20a-cv**). Purification by flash column chromatography (petrol 40-60:EtOAc, gradient, 20:1→12:1→6:1→3:1 with 1% propane-2-ol) gave the title compound **20a-cv** as a white solid (1.34 g, 4.26 mmol, 20%); m.p. 38-40 °C; R_f = 0.51 (petrol 40-60:EtOAc, 3:1); found: C, 57.29%; H, 8.33%; $C_{15}H_{26}O_5Si$ requires: C, 57.35%; H, 8.24%; ν_{max}(KBr)/cm^{-1} 2955, 2929, 2893, 2858, 1772 (C=O), 1740 (C=O), 1464, 1438, 1386, 1235, 1155, 1060, 1021, 835 (Si-C), 777 (Si-C); δ_H(500 MHz; C_6D_6) 4.01 (dd, *J* = 9.6, 8.5 Hz, 1H, C*H*HO), 3.59 (dd, *J* = 7.5, 4.0 Hz, 1H, C*H*OTBDMS), 3.46 (dd, *J* = 9.6, 3.2 Hz, 1H, CH*H*O), 3.21 (s, 3H, O*CH*$_3$), 2.82 (dddd, *J* = 13.4, 9.8, 7.4, 0.5 Hz, 1H, CC*H*H), 2.81-2.77 (m, 1H, OCH$_2$C*H*), 2.18 (ddd, *J* = 13.4, 7.3, 4.5 Hz, 1H, CCH*H*), 1.45 (ddddd, *J* = 13.2, 7.4, 4.5, 4.0, 1.3 Hz, 1H, CCH$_2$C*H*H), 1.26 (dddd, *J* = 13.2, 9.8, 7.2, 4.6, Hz, 1H, CCH$_2$CH*H*), 0.86 (s, 9H, SiC*Me*$_3$), -0.11 (s, 6H, Si*Me*$_2$); δ_C(125 MHz; C_6D_6) 175.7 (*C*O), 170.0 (*C*O), 79.1 (*C*HOTBDMS), 69.2 (*C*H$_2$O), 59.9 (*C*CO$_2$Me), 55.2 (OCH$_2$*C*), 52.5 (O*Me*), 34.5 (*C*H$_2$CHOTBDMS), 31.3 (C*C*H$_2$), 25.8 (SiC*Me*$_3$), 18.0 (Si*C*Me$_3$), -4.6 (Si*Me*), -4.9 (Si*Me*); δ_H(500 MHz; $CDCl_3$) 4.52 (dd, *J* = 9.6, 8.2 Hz, 1H, C*H*HO), 4.05 (dd, *J* = 9.6, 3.0 Hz, 1H, CH*H*O), 4.05-4.03 (m, 1H, C*H*OTBDMS), 3.75 (s, 3H, O*Me*), 2.97 (dtdt, *J* = 8.2, 3.0, 1.7, 0.5 Hz, 1H, OCH$_2$C*H*), 2.69 (ddd, *J* = 13.5, 9.7, 7.4 Hz, 1H, CC*H*H), 2.14 (ddd, *J* = 13.5, 7.0, 4.6 Hz, 1H, CCH*H*), 1.81-1.74 (m, 1H, CCH$_2$C*H*H), 1.69 (dddd, *J* = 13.2, 9.7, 7.0, 4.6 Hz, 1H, CCH$_2$CH*H*), 0.83 (s, 9H, SiC*Me*$_3$), 0.03 (s, 6H, Si*Me*$_2$); δ_C(125 MHz; $CDCl_3$) 176.4 (*C*O), 170.0 (*C*O), 79.0 (*C*HOTBDMS), 70.0 (*C*H$_2$O), 59.8 (*C*CO$_2$Me), 54.8 (OCH$_2$*C*), 53.3 (O*Me*), 34.6 (*C*H$_2$CHOTBDMS), 31.2 (C*C*H$_2$), 25.7 (SiC*Me*$_3$), 18.0 (Si*C*Me$_3$), -4.5 (Si*Me*), -4.7 (Si*Me*); *m/z* LRMS (ESI$^+$) 373.3 (M+NH$_4$+MeCN$^+$, 100%); HRMS (ESI$^+$) found 337.1447, $C_{15}H_{26}NaO_5Si^+$ (M+Na$^+$) requires 337.1442. Single Crystal Data: $C_{15}H_{26}O_5Si$, triclinic, $P\bar{1}$, *a*=6.6840(2), *b*=7.2294(2), *c*=18.8432(6) Å, α=99.3709(17)°, β=90.3470(18)°, γ=97.2494(14)°, *V*=890.87(5) Å^3, Data/restraints/parameters 4008/0/194, R_{int}=0.022, Final R_1=0.0408, wR_2=0.0986 (I>2s(I)). Data in accord with literature.[22]

Further elution of the column gave the title compound **20a-cc** as a colorless oil (3.9 g, 12.4 mmol, 58%); R_f = 0.40 (petrol 40-60:EtOAc, 3:1); found: C, 57.28%; H, 8.29%; $C_{15}H_{26}O_5Si$ requires: C, 57.29%; H, 8.33%; ν_{max}(neat)/cm^{-1} 2955, 2930, 2897, 2857, 1776 (C=O), 1741 (C=O), 1471, 1464, 1436, 1407, 1381, 1362, 1313, 1251, 1215, 1158, 1135, 1102, 1076, 1056, 1028, 1008, 992, 979, 939, 925, 890, 872, 837 (Si-C), 800, 777 (Si-C); δ_H (500 MHz; C_6D_6) 4.37 (ddd, *J* = 9.0, 2.0, 0.4 Hz, 1H, C*H*HO), 4.08 (dd, *J* = 9.1, 7.7 Hz, 1H, CH*H*O), 3.90-3.85 (m, 1H, C*H*OTBDMS), 3.35 (s, 3H, O*Me*), 2.58 (ddd, *J* = 7.7, 6.2, 2.0 Hz, 1H, OCH$_2$C*H*), 2.56-2.46 (m, 2H, CC*H*$_2$), 1.59-1.44 (m, 2H, CCH$_2$C*H*$_2$), 0.98 (s, 9H, SiC*Me*$_3$), -0.02 (s, 6H, Si*Me*$_2$); δ_C(125 MHz; C_6D_6) 175.5 (*C*O), 170.7 (*C*O), 74.7 (*C*HOTBDMS), 65.8 (*C*H$_2$O), 59.9 (*C*CO$_2$Me), 52.9 (O*Me*), 50.7 (OCH$_2$*C*), 35.0 (*C*H$_2$CHOTBDMS), 30.4 (C*C*H$_2$), 25.7 (SiC*Me*$_3$), 18.0 (Si*C*Me$_3$), -4.6 (Si*Me*), -5.2 (Si*Me*); δ_H(500 MHz; $CDCl_3$) 4.49 (dd, *J* = 9.1, 2.0 Hz, 1H, C*H*HO), 4.31 (dd, *J* = 9.1, 7.7 Hz, 1H, CH*H*O), 4.28 (ddd, *J* = 6.0, 5.3, 4.4 Hz, 1H, C*H*OTBDMS), 3.75 (s, 3H, O*Me*), 3.00 (ddd, *J* = 7.7, 6.0, 2.0 Hz, 1H, OCH$_2$C*H*), 2.39 (dt, *J* = 13.3, 7.3 Hz, 1H, CC*H*H), 2.25 (dt, *J* = 13.3, 7.3 Hz, 1H, CCH*H*), 1.84 (dtd, *J* = 12.8, 7.3, 4.4 Hz, 1H, CCH$_2$C*H*H), 1.66 (dtd, *J* = 12.8, 7.3, 5.3 Hz, 1H, CCH$_2$CH*H*), 0.84 (s, 9H, SiC*Me*$_3$), 0.03 (s, 6H, Si*Me*$_2$); δ_C(125 MHz; $CDCl_3$) 176.1 (*C*O), 170.6 (*C*O), 74.4 (*C*HOTBDMS), 66.2 (*C*H$_2$O), 59.7 (*C*CO$_2$Me), 53.1 (O*Me*), 50.5 (OCH$_2$*C*), 35.0 (C*C*H$_2$), 30.3 (*C*H$_2$CHOTBDMS), 25.5 (SiC*Me*$_3$), 17.8 (Si*C*Me$_3$), -4.6 (Si Si*Me*), -5.2 (Si Si*Me*); *m/z* LRMS (ESI$^+$) 373.3 (M+NH$_4$+MeCN$^+$, 100%); HRMS (ESI$^+$) found 332.1881, $C_{15}H_{30}NO_5Si^+$ (M+NH$_4^+$) requires 332.1888. Data in accord with literature.[22]

4.1.15. (3aR,6R*,6aS*)-Methyl 6-(benzoyloxy)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate **20d-cv** and (3aR *,6S*,6aS*)-methyl 6-(benzoyloxy)-3-oxohexahydro-1H - cyclopenta[c]furan-3a-carboxylate **20d-cc***



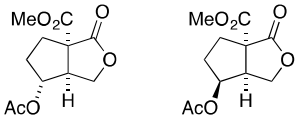
20d-cv **20d-cc**

Dimethyl 2-(3-(benzoyloxy)pent-4-en-1-yl)malonate **21d** (0.161 g, 0.500 mmol), manganese(III) acetate (0.269 g, 1.00 mmol) and copper(II) triflate (0.181 g, 0.50 mmol) were dissolved in nitrogen sparged acetonitrile (2.5 mL). The reaction mixture was heated at 40 °C for 5 h under an atmosphere of nitrogen and then cooled to room temperature. sat. aq. sodium bicarbonate (30 mL) was added followed by CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the organic layers combined, dried (Na_2SO_4) and concentrated under reduced pressure (crude product, d.r. 2:1, **20d-cc**:**20d-cv**). Purification by flash column chromatography (petrol 40-60:EtOAc, 6:1) gave the title compound **20d-cv** as a colorless oil (0.033 g, 0.108 mmol, 21%); R_f = 0.51 (petrol:EtOAc, 1:1); ν_{max}($CDCl_3$)/cm^{-1} 2978, 2957, 2919, 1778 (C=O), 1744 (C=O), 1718 (C=O), 1316, 1272, 1202, 1178, 1150, 1113, 1071, 1049, 1025, 977, 714; δ_H(500 MHz; $CDCl_3$) 8.02-7.97 (m, 2H, Ar*H*), 7.61-7.57 (m, 1H, Ar*H*), 7.48-7.42 (m, 2H, Ar*H*), 5.27 (ddd, *J* = 5.2, 2.4, 1.6 Hz, 1H, C*H*OBz), 4.67 (dd, *J* = 10.0, 8.6 Hz, 1H, H C*H*HO), 4.38 (dd, *J* = 10.0, 2.9 Hz, 1H, CH*H*O), 3.79 (s, 3H, O*Me*), 3.27 (ddt, *J* = 8.6, 2.9, 1.6 Hz, 1H, OCH$_2$C*H*), 2.76 (ddd, *J* = 13.5, 12.2, 7.0 Hz, 1H, CC*H*H), 2.43 (ddd, *J* = 13.5, 7.0, 2.4 Hz, 1H, CCH*H*), 2.20 (ddtd, *J* = 14.3, 7.0, 2.4, 1.6 Hz, 1H,

CCH_2CHH), 1.95 (dddd, *J* = 14.3, 12.2, 7.0, 5.2 Hz, 1H, CCH_2CHH); δ_C(125 MHz; $CDCl_3$) 175.3 (*C*O), 169.3 (*C*O), 166.0 (*C*O), 133.4 (Ar), 129.6 (Ar), 129.5 (Ar), 128.5 (Ar), 81.6 (*C*HOBz), 70.1 (CH_2O), 60.5 (CCO_2Me), 53.3 (O*Me*), 52.2 (OCH_2C), 32.2 (CCH_2), 31.5 (CH_2CHOBz); *m/z* LRMS (ESI^+) 327.1 ((M+Na^+, 100%); HRMS (ESI^+) found 327.0842, $C_{16}H_{16}NaO_6^+$ (M+Na^+), requires 327.0839.

Further elution of the column gave the title compound **20d-cc** as a colorless oil (0.079 g, 0.259 mmol, 52%); R_f = 0.37 (petrol:EtOAc, 1:1); $\nu_{max}(CDCl_3)/cm^{-1}$ 2982, 2957, 1775 (C=O), 1735 (C=O), 1720 (C=O), 1270, 1251, 1160, 1112, 1070, 988, 713; δ_H(500 MHz; $CDCl_3$) 8.02-7.98 (m, 2H, Ar*H*), 7.62-7.57 (m, 1H, Ar*H*), 7.49-7.43 (m, 2H, Ar*H*), 5.55 (dt, *J* = 6.3, 4.7 Hz, 1H, C*H*OBz), 4.48 (dd, *J* = 9.8, 7.2 Hz, 1H, C*H*HO), 4.43 (dd, *J* = 9.8, 2.0 Hz, 1H, CH*H*O), 3.83 (s, 3H, O*Me*), 3.43 (ddd, *J* = 7.2, 6.3, 2.0 Hz, 1H, OCH_2CH), 2.61 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1H, CC*H*H), 2.42 (ddd, *J* = 14.0, 7.4, 8.0 Hz, 1H, CCH*H*), 2.19 (dtd, *J* = 13.5, 8.0, 4.7 Hz, 1H, CCH_2CHH), 2.05 (dddd, *J* = 13.5, 7.4, 6.0, 4.7 Hz, 1H, CCH_2CHH); δ_C(125 MHz; $CDCl_3$) 175.6 (*C*O), 169.8 (*C*O), 165.7 (*C*O), 133.5 (Ar), 129.6 (Ar), 129.1 (Ar), 128.6 (Ar), 76.6 (*C*HOBz), 66.3 (CH_2O), 60.2 (CCH_2), 53.4 (O*Me*), 49.1 (OCH_2C), 32.4 CH_2CHOBz), 30.4 (CCH_2); *m/z* LRMS (ESI^+) 327.1 (M+Na^+, 100%); HRMS (ESI^+) found 327.0839, $C_{16}H_{16}NaO_6^+$ (M+Na^+), requires 327.0839.

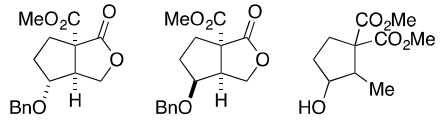
4.1.16. (3aR,6R*,6aS*)-Methyl 6-(acetoxyloxy)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate **20e-cv** and (3aR *,6S*,6aS*)-methyl 6-(acetoxyoxy)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate **20e-cc***



20e-cv **20e-cc**

A mixture of dimethyl 2-(3-acetoxypent-4-en-1-yl)malonate **21e** (0.130 g, 0.500 mmol), manganese(III) acetate dihydrate (0.269 g, 1.00 mmol) and copper(II) triflate (0.181 g, 0.500 mmol) was dissolved in nitrogen sparged acetonitrile (2.5 mL). The suspension was heated at 40 °C for 3 h 30 min under an atmosphere of nitrogen and then cooled to room temperature. Satu- rated aqueous sodium bicarbonate (30 mL) was added followed by CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the organic layers combined, dried (Na_2SO_4), and concentrated under reduced pressure (crude product, d.r. 2:1, **20e-cc**:**20e-cv**). Purification by flash column chromatography (petrol 40-60:EtOAc, 6:1) gave a mixture of the title compounds as a colorless oil (d.r. 2:1, **20e-cc**:**20e-cv**, 0.081 g, 0.334 mmol, 67%); $\nu_{max}(CDCl_3)/cm^{-1}$ 2979, 2959, 2919, 1777 (C=O), 1741 (C=O), 1436, 1377, 1268, 1240, 1156, 1131, 1090, 1048, 1020, 991, 732; δ_H(400 MHz; $CDCl_3$) 5.24 (dt, *J* = 7.3, 5.5 Hz, 1H, C*H*OAc **cc**), 4.97 (dt, *J* = 5.3, 2.0 Hz, 1H, C*H*OAc **cv**), 4.58 (ddd, *J* = 9.9, 8.4, 0.8 Hz, 1H, C*H*HO **cv**), 4.38 (ddd, *J* = 9.7, 7.6, 0.7 Hz, 1H, C*H*HO **cc**), 4.30 (dd, *J* = 9.7, 2.0 Hz, 1H, CH*H*O **cc**), 4.27 (dd, *J* = 9.9, 2.5 Hz, 1H, CH*H*O **cv**), 3.78 (s, 6H, 2×O*Me*), 3.33-3.28 (m, 1H, OCH_2CH **cc**), 3.11-3.06 (m, 1H, OCH_2CH **cv**), 2.59 (dddd, *J* = 13.4, 12.1, 7.0, 0.6 Hz, 1H, CC*H*H **cv**), 2.46 (dtd, *J* = 13.7, 7.6, 0.6 Hz, 1H, CC*H*H **cc**), 2.35-2.27 (m, 2H, CCH*H* **cc**, CCH*H* **cv**), 2.12-2.04 (m, 1H, CCH_2CHH **cc**), 2.07 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.05-1.96 (m, 1H, CCH_2CHH **cv**), 1.87-1.70 (m, 2H, CCH_2CHH **cv**, CCH_2CH, **cc**); δ_C(100 MHz; $CDCl_3$) 175.5 (*C*O), 175.2 (*C*O), 170.5 (*C*O), 170.3 (*C*O), 169.7 (*C*O), 169.3 (*C*O), 81.2 (C*H*OAc **cv**), 75.8 (C*H*OAc **cc**), 70.2 (CH_2O b), 66.1 (CH_2O **cc**), 60.4 (CCH_2), 60.0 (CCH_2), 53.3 (2×O*Me*), 52.0 (OCH_2C **cv**), 48.2 (OCH_2C **cc**), 32.0 (CH_2), 31.8 (CH_2), 31.4 (CH_2), 30.3 (CH_2), 21.0 (C(O)*Me*), 20.8 (C(O)*Me*); *m/z* LRMS (ESI^+) 265.1 (M+Na^+, 100%); HRMS (ESI^+) found 265.0689, $C_{11}H_{14}NaO_6^+$ (M+Na^+) requires 265.0683. The reaction was carried out with the same reagents and quantities at room temperature for 24 h (crude product d.r. 2:1, **20e-cc**:**20e-cc**).

4.1.17. (3aR,6R*,6aS*)-Methyl 6-(benzyloxy)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate **20f-cv** and (3aR*,6S*,6aS*)-methyl 6-(benzyloxy)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate **20f-cc** and dimethyl 3-hydroxy-2-methylcyclopentane-1,1-dicarboxylate*



20f-cv **20f-cc**

A mixture of dimethyl 2-(3-(benzyloxy)pent-4-en-1-yl)malonate **21f** (0.306 g, 1.00 mmol), manganese(III) acetate dihydrate (0.537 g, 2.00 mmol) and copper(II) triflate (0.362 g, 1.00 mmol) was dissolved in nitrogen sparged acetonitrile (5 mL). The suspension was heated at 80 °C for 13 h 30 min under an atmosphere of nitrogen and then cooled to room temperature. Water (50 mL), EtOAc (50 mL) and brine (10 mL) were added and the aqueous layer was ex- tracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure (crude product relative ratios 2:1.5:1, **20f-cv**:**20f-cc**:cyclopentane, respectively). Purification by flash column chromatography (petrol 30-40:EtOAc, gradient, 12:1→6:1→3:1→1:1) gave the title compound **20f-cv** as a colorless oil (0.084 g, 0.289 mmol, 29%); $\nu_{max}(CDCl_3)/cm^{-1}$ 1775 (C=O), 1734 (C=O); δ_H(500 MHz; $CDCl_3$) 7.39-7.27 (m, 5H, Ar*H*), 4.57 (dd, *J* = 9.6, 8.3 Hz, 1H, C*H*HO), 4.55 (d, *J* = 11.9 Hz, 1H, C*H*HPh), 4.46 (d, *J* = 11.9 Hz, 1H, CH*H*Ph), 4.11 (dd, *J* = 9.6, 2.7 Hz, 1H, CH*H*O), 3.87 (dt, *J* = 4.9, 2.7 Hz, 1H, C*H*OBn), 3.79 (m, 3H, O*Me*), 3.19 (dtd, *J* = 8.3, 2.7, 1.0 Hz, 1H, OCH_2CH), 2.68 (ddd, *J* = 13.5, 10.6, 7.2 Hz, 1H, CC*H*H), 2.28-2.22 (m, 1H, CCH*H*), 2.07-1.96 (m, 1H, CCH_2CHH), 1.73 (dddd, *J* = 13.6, 10.6, 7.0, 4.9 Hz, 1H, CCH_2CHH); δ_C(125 MHz; $CDCl_3$) 175.9 (*C*O), 169.6 (*C*O), 137.6 (Ar), 128.5 (Ar), 127.8 (Ar), 127.5 (Ar), 85.5 *C*HOBn), 71.0 (CH_2Ph), 70.3 (CH_2O), 59.9 (CCO_2Me), 53.2 (O*Me*), 51.6 (OCH_2C), 31.4 (CCH_2), 30.9 (CH_2CHOBn); *m/z* LRMS (ESI^+) 313.1 (M+Na^+, 100%), 603.2 (2M+Na^+, 80); HRMS (ESI^+) found 313.1060, $C_{16}H_{18}NaO_5^+$ (M+Na)$^+$, requires 313.1046. Data in accord with literature.[22]

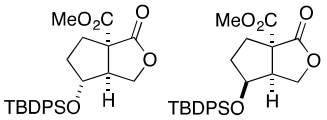
Further elution of the column gave **20f-cc** as a colorless oil (0.063 g, 0.217 mmol, 22%); $\nu_{max}(CDCl_3)/cm^{-1}$,1773 (C=O), 1732 (C=O); δ_H(400 MHz; $CDCl_3$) 7.40-7.24 (m, 5H, Ar*H*), 4.64 (dd, *J* = 9.2, 2.5 Hz, 1H, C*H*HO), 4.59 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.24 (d, *J* = 12.0 Hz, 1H, CH*H*Ph), 4.34 (dd, *J* = 9.2, 8.1 Hz, 1H, CH*H*O), 4.07 (td, *J* = 7.1, 5.0 Hz, 1H, C*H*OBn), 3.78 (s, 3H, O*Me*), 3.21-3.15 (m, 1H, OCH_2CH), 2.37 (ddd, *J* = 13.7, 9.0, 7.3 Hz, 1H), 2.34-2.28 (m, 1H), 2.03-1.94 (m, 1H), 1.83-1.73 (m, 1H); *m/z* LRMS (ESI^+) 313.1 (M+Na^+, 100%), 603.2 (2M+Na^+, 80); HRMS (ESI^+) found 313.1046, $C_{16}H_{18}NaO_5^+$ (M+Na^+), requires 313.1046. Data in accord with literature.[22]

Further elution of the column gave dimethyl 3-hydroxy-2-methylcyclopentane-1,1-dicarboxylate as a colorless oil (0.029 g, 0.134 mmol, 13%); $\nu_{max}(CDCl_3)/cm^{-1}$ 3528 (O-H), 2954, 2915, 2884, 2849, 1731 (C=O); δ_H(500 MHz; $CDCl_3$) 4.16-4.06 (m, 1H, C*H*OH), 2×3.75 (s, 3H, O*Me*), 2.64-2.54 (m, 2H, C*H*Me, CC*H*H), 2.20 (ddd, *J* = 14.4, 9.8, 4.7 Hz, 1H, CCH*H*), 1.99

(dddd, *J* = 13.8, 9.8, 8.4, 5.4 Hz, 1H, HOCHC*H*H), 1.88 (dddd, *J* = 13.8, 8.9, 4.7, 2.2 Hz, 1H, HOCHCH*H*), 1.63 (br s, 1H, O*H*), 1.13 (d, *J* = 7.2 Hz, 3H, CH*Me*); δ_C (125 MHz; $CDCl_3$) 174.5 (*C*O), 172.6 (*C*O), 76.6 (*C*HOH), 62.6 (*C*$(CO_2Me)_2$), 52.9 (O*Me*), 52.8 (O*Me*), 46.5 (*C*HMe), 34.1 (HOCH*C*$_2$), 33.0 (*C*CH_2), 10.6 (CH*Me*); *m/z* LRMS (ESI^+) 239.1 ($M+Na^+$, 100%); HMRS (ESI^+) found 239.0889, $C_{10}H_{16}NaO_5^+$ ($M+Na^+$), requires 239.0890.

The reaction was also carried out on the same scale, at 40 °C for 12 h (crude product relative ratios 2:1.5:1, **20f-cv**:**20f-cc**:cyclopentane, respectively). Purification by flash column chromatography (petrol 40-60:EtOAc, gradient, 6:1→3:1→1:1) gave the title compound **20f-cv** (0.110 g, 0.379 mmol, 38%), title compound **20f-cc** (0.062 g, 0.213 mmol, 21%) and dimethyl 3-hydroxy-2-methylcyclopentane-1,1-dicarboxylate (0.015 g, 0.069 mmol, 7%).

4.1.18. (3aR,6R*,6aS*)-Methyl 6-((tert-butyldiphenylsilyl)oxy)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate* ***20c-cv*** *and (3aR*,6S*,6aS*)-Methyl 6-((tert-butyldiphenylsilyl)oxy)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate* ***20c-cc***

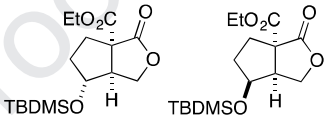


20c-cv **20c-cc**

Dimethyl 2-(3-((*tert*-butyldiphenylsilyl)oxy)pent-4-en-1-yl)malonate **21c** (0.197 g, 0.433 mmol), manganese(III) acetate dihydrate (0.233 g, 0.869 mmol) and copper(II) triflate (0.157 g, 0.434 mmol) were dissolved in nitrogen sparged acetonitrile (2.1 mL). The reaction mixture was heated at 40 °C for 13 h under an atmosphere of nitrogen and then cooled to room temperature. Water (20 mL), EtOAc (30 mL) and sat. aq. NH_4Cl (10 mL) were added and the aqueous layer extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude product (d.r. 2:1, **20c-cc**:**20c-cv**). Purification by flash column chromatography (dry loading, petrol 40-60:EtOAc, gradient, 6:1) gave the title compound **20c-cv** as a colorless oil (0.047 g, 0.107 mmol, 25%); R_f = 0.5 (petrol:EtOAc, 3:1); $\nu_{max}(CDCl_3)/cm^{-1}$ 2956, 2931, 2894, 2858, 1779 (C=O), 1746 (C=O), 1472, 1461, 1428, 1266, 1243, 1150, 1111, 1040, 822, 741, 704; δ_H(500 MHz; $CDCl_3$) 7.64-7.59 (m, 4H, Ar*H*), 7.49-7.43 (m, 2H, Ar*H*), 7.43-7.37 (m, 4H, Ar*H*), 4.24 (dd, *J* = 9.8, 8.9 Hz, 1H, C*H*HO), 4.09-4.07 (m, 1H, C*H*OTBDPS), 3.80 (s, 3H, O*Me*), 3.63 (dd, *J* = 9.8, 3.3 Hz, 1H, CH*H*O), 3.03-2.98 (m, 1H, OCH$_2$C*H*), 2.81 (ddd, *J* = 13.3, 11.0, 7.0 Hz, 1H, CC*H*H), 2.19 (ddd, *J* = 13.3, 7.0, 3.5 Hz, 1H, CCH*H*), 1.91 (ddtd, *J* = 13.4, 7.0, 3.5, 1.4 Hz, 1H, CCH$_2$C*H*H), 1.59 (dddd, *J* = 13.4, 11.0, 7.0, 4.6 Hz, 1H, CCH$_2$CH*H*), 1.06 (s, 9H, SiC*Me*$_3$); δ_C(125 MHz; $CDCl_3$) 176.1 (*C*O), 169.8 (*C*O), 135.6 (Ar), 133.5 (Ar), 133.1 (Ar), 130.0 (Ar), 127.8 (Ar), 80.1 (*C*HOTBDPS), 69.6 (*C*H$_2$O), 60.1 (*C*CO$_2$Me), 54.6 (OCH$_2$*C*), 53.1 (O*Me*), 34.3 (*C*H$_2$CHOTBDPS), 31.7 (*C*CH$_2$), 26.7 (SiC*Me*$_3$), 19.0 (Si*C*Me$_3$); *m/z* LRMS (ESI^+) 461.2 ($M+Na^+$, 100%), 899.3 ($2M+Na^+$, 78); HRMS (ESI^+) found 461.1748, $C_{25}H_{30}NaO_5Si^+$ ($M+Na^+$), requires 461.1755.

Further elution of the column gave **20c-cc** as a white solid (0.095 g, 0.216 mmol, 50%); m.p. 116-118 °C; R_f = 0.38 (petrol:EtOAc, 3:1); $\nu_{max}(CDCl_3)/cm^{-1}$ 3463, 2961, 2935, 2860, 1775 (C=O), 1742 (C=O), 1720, 1429, 1247, 1155, 1102, 1049, 1022, 976, 746, 704; δ_H(500 MHz; C_6D_6) 7.74- 7.69 (m, 4H, Ar*H*), 7.34-7.26 (m, 6H, Ar*H*), 4.69 (dd, *J* = 9.2, 2.3 Hz, 1H, C*H*HO), 4.19-4.14 (m, 1H, C*H*OTBDPS), 4.09 (dd, *J* = 9.2, 8.0 Hz, 1H, CH*H*O), 3.26 (s, 3H, O*Me*), 2.59-2.55 (m, 1H, OCH$_2$C*H*), 2.47 (ddd, *J* = 13.5, 7.0, 5.2 Hz, 1H, CC*H*H), 2.23 (ddd, *J* = 13.5, 9.0, 7.4 Hz, 1H, CCH*H*), 1.58-1.52 (m, 1H, CCH$_2$C*H*H), 1.48 (ddt, *J* = 13.0, 7.4, 5.2 Hz, 1H, CCH$_2$CH*H*), 1.20 (s, 9H, SiC*Me*$_3$); δ_C(125 MHz; C_6D_6) 175.6 (*C*O), 170.2 (*C*O), 136.0 (Ar), 136.0 (Ar), 133.8 (Ar), 133.6 (Ar), 130.3 (Ar), 75.5 (*C*HOTBDPS), 65.8 (*C*H$_2$O), 60.0 (*C*CO$_2$Me), 52.4 (O*Me*), 49.5 (OCH$_2$*C*), 34.3 (*C*H$_2$CHOTBDPS), 30.3 (*C*CH$_2$), 27.0 (SiC*Me*$_3$), 19.3 (Si*C*Me$_3$); *m/z* LRMS (ESI^+) 461.1 ($M+Na^+$, 100%), 899.3 ($2M+Na^+$, 100); HRMS (ESI^+) found 461.1757, $C_{25}H_{30}NaO_5Si^+$ ($M+Na^+$), requires 461.1755. Single Crystal Data: $C_{25}H_{30}O_5Si$, orthorhombic, $P2_12_12_1$, *a*=13.6562(5), *b*=9.7220(4), *c*=16.9985(8) Å, *V*=2256.82(16) Å^3, Data/restraints/parameters 3119/0/281, R_{int}=0.170, Flack *x*=0.2(3), Final R_1=0.0857, wR_2=0.1700 (I>2s(I)).

4.1.19. (3aR,6R*,6aS*)-Ethyl 6-(tert-butyldimethylsilyloxy)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate* ***20b-cv*** *and (3aR*,6S*,6aS*)-ethyl 6-(tert-butyldimethylsilyloxy)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate* ***20b-cc***



20b-cv **20b-cc**

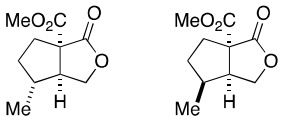
Diethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)pent-4-en-1-yl)malonate **21b** (0.196 g, 0.546 mmol), manganese(III) acetate (0.294 g, 1.09 mmol) and copper(II) triflate (0.198 g, 0.546 mmol) were dissolved in nitrogen sparged acetonitrile (2.7 mL). The reaction mixture was heated at 40 °C for 3 h under an atmosphere of nitrogen. Water (30 mL) was added followed by EtOAc (30 mL). The organic layer was washed with brine (30 mL) and the combined aqueous layers extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concetrated under reduced pressure to yield the crude product (d.r. 2:1, 204A:204B). Purification by flash column chromatography (petrol 30-40:EtOAc, gradient, 9:1→3:1→3:1) gave recovered starting material **21c** as a colorless oil (0.015 g, 0.042 mmol, 7%); R_f = 0.8 (petrol:EtOAc, 3:1).

Further elution of the column gave title compound **20b-cv** as a colorless oil (0.025 g, 0.076 mmol, 14%) R_f = 0.62 (petrol:EtOAc, 3:1); ν_{max}(KBr)/cm^{-1} 2956, 2932, 2904, 2857, 2709, 1775 (C=O), 1736 (C=O), 1248, 1159, 1058, 1029, 838 (Si-C), 776 (Si-C); δ_H(500 MHz; $CDCl_3$) 4.55 (ddd, *J* = 9.4, 8.3, 1.0 Hz, 1H, C*H*HO), 4.26-4.21 (m, 2H, OC*H*$_2$Me), 4.08 (ddd, *J* = 9.4, 3.1, 0.8 Hz, 1H, CH*H*O), 4.08-4.05 (m, 1H, C*H*OTBDMS), 2.99 (dt, *J* = 8.3, 3.1 Hz, 1H, OCH$_2$C*H*), 2.72 (ddd, *J* = 13.5, 9.5, 7.5 Hz, 1H, CC*H*H), 2.16 (ddd, *J* = 13.5, 7.0, 4.5 Hz, 1H, CCH*H*), 1.81 (ddt, *J* = 13.9, 7.5, 4.5 Hz, 1H, CCH$_2$C*H*H), 1.73 (dddd, *J* = 13.9, 9.5, 7.0, 4.8 Hz, 1H, CCH$_2$CH*H*), 1.30-1.27 (m, 3H, OCH$_2$*Me*), 0.87 (s, 9H, SiC*Me*$_3$), 0.06 (s, 6H, Si*Me*$_2$); δ_C(125 MHz; $CDCl_3$) 176.4 (*C*O), 169.3 (*C*O), 78.8 (*C*HOTBDMS), 69.8 (*C*H$_2$O), 62.1 (OCH$_2$Me), 59.7 (*C*CO$_2$Me), 54.8 (OCH$_2$*C*), 34.5 (*C*H$_2$CHOTBDMS), 30.8 (*C*CH$_2$), 25.6 (SiC*Me*$_3$), 17.8 (Si*C*Me$_3$), 14.0 (CH$_2$*Me*), -4.6 (Si*Me*), -4.9 (Si*Me*); *m/z* LRMS (ESI^+) 351.1 ($M+Na^+$, 100%); HRMS (ESI^+) found 351.1600, $C_{16}H_{28}NaO_5Si^+$($M+Na^+$), requires 351.1598.

Further elution of the column gave the title compound **20b-cc** as a white solid (0.088 g, 0.268 mmol, 49%) m.p. 44-46 °C; R_f = 0.48 (petrol:EtOAc, 3:1); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2956, 2928, 2885, 2857, 1780 (C=O), 1774 (C=O), 1248, 1055, 835 (Si-C), 776 (Si-C); δ_H(500 MHz; $CDCl_3$) 4.51 (dd, *J* = 9.1, 2.1 Hz, 1H, C*H*HO), 4.33 (dd, *J* = 9.1, 7.7 Hz, 1H, CH*H*O), 4.30 (ddd, *J* = 6.2, 5.4, 4.4

Hz, 1H, C*H*OTBDMS), 4.24-4.19 (m, 2H, OC*H*$_2$Me), 3.00 (ddd, *J* = 7.7, 6.2, 2.1 Hz, 1H, OCH$_2$C*H*), 2.41 (ddd, *J* = 13.5, 7.6, 6.8 Hz, 1H, CC*H*H), 2.26 (ddd, *J* = 13.5, 7.6, 6.8 Hz, 1H, CCH*H*), 1.86 (dtd, *J* = 12.7, 7.6, 4.4 Hz, 1H, CCH$_2$C*H*H), 1.68 (dtd, *J* = 12.7, 6.8, 5.4 Hz, 1H, CCH$_2$CH*H*), 1.29-1.25 (m, 3H, OCH$_2$*Me*), 0.87 (s, 9H, SiC*Me*$_3$), 0.06 (s, 6H, Si*Me*$_2$); δ_C (125 MHz; $CDCl_3$) 176.2 (*C*O), 170.1 (*C*O), 74.4 (*C*HOTBDMS), 66.3 (*C*H$_2$O), 62.2 (*C*H$_2$Me), 59.9 (*C*CO$_2$Me), 50.6 (OCH$_2$*C*), 35.0 (*C*H$_2$CHOTBDMS), 30.1 (C*C*H$_2$), 25.5 (SiC*Me*$_3$), 17.8 (Si*C*Me$_3$), 14.0 (CH$_2$*Me*), -4.6 (Si*Me*), -5.1 (Si*Me*); *m/z* LRMS (ESI$^+$) 679.3 (2M+Na$^+$, 100%), 351.1 (M+Na$^+$, 98); HRMS (ESI$^+$) found 351.1600, $C_{16}H_{28}O_5SiNa^+$ (M+Na$^+$), requires 351.1598. Single Crystal Data: $C_{16}H_{28}O_5Si$, monoclinic, $P2_1$, *a*=11.1296(2), *b*=7.13140(10), *c*=23.8950(5) Å, *β*=101.9519(7)°, *V*=1855.42(6) Å^3, Data/restraints/parameters 8106/1/398, R_{int}=0.055, Flack *x*=-0.15(9), Final R_1=0.0406, wR_2=0.0833 (I>2s(I)).

4.1.20. (3aR,6R*,6aS*)-Methyl 6-methyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate **20g-cv** and (3aR*,6S*,6aS*)-methyl 6-methyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate **20g-cc***



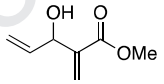
20g-cv **20g-cc**

Dimethyl 2-(3-methylpent-4-en-1-yl)malonate 176 (0.215 g, 1.00 mmol), manganese(III) acetate (0.537 g, 2.00 mmol) and copper(II) triflate (0.362 g, 1.00 mmol) were dissolved in nitrogen sparged acetonitrile (5 mL). The reaction mixture was heated at 40 °C for 3 h under an atmosphere of nitrogen and then cooled to room temperature. Water (30 mL) was added followed by EtOAc (30 mL) and sat. aq. sodium bicarbonate (10 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the organic layers combined, dried ($MgSO_4$) and concentrated under reduced pressure (crude d.r. 5:1 **20g-cv**:**20g-cc**). Purification by flash column chromatography (petrol 40-60:EtOAc, 20:1) gave recovered starting material **21g** as a colorless oil (0.048 g, 0.224 mmol, 22%).

Further elution of the column gave the title compound **20g-cv** as a colorless oil (0.070 g, 0.353 mmol, 35%); $\nu_{max}(CDCl_3)/cm^{-1}$ 2958, 2873, 1774 (C=O), 1742 (C=O), 1458, 1435, 1376, 1251, 1213, 1196, 1167, 1143, 1107, 1062, 1044, 1005, 984, 967; δ_H(400 MHz; $CDCl_3$) 4.50 (dd, *J* = 9.3, 6.7 Hz, 1H, C*H*HO), 4.14 (dd, *J* = 9.3, 1.6 Hz, 1H, CH*H*O), 3.76 (s, 3H, O*Me*), 2.61 (ddd, *J* = 13.9, 8.2, 4.3 Hz, 1H, CC*H*H), 2.55 (ddd, *J* = 7.4, 6.7, 1.6 Hz, 1H, OCH$_2$C*H*), 2.12 (ddd, *J* = 13.9, 8.7, 7.1 Hz, 1H, CCH*H*), 1.94-1.83 (m, 2H, C*H*Me, CCH$_2$C*H*H), 1.51-1.39 (m, 1H, CCH$_2$CH*H*), 1.07 (d, *J* = 6.5 Hz, 3H, CH*Me*); δ_C(100 MHz; $CDCl_3$) 176.7 (*C*O), 170.5 (*C*O), 71.0 (*C*H$_2$O), 61.4 (*C*CO$_2$Me), 54.3 (OCH$_2$*C*), 53.1 (O*Me*), 41.7 (*C*HMe), 34.5 (*C*H$_2$CHMe), 32.7 (C*C*H$_2$), 18.2 (CH*Me*); *m/z* LRMS (ESI$^+$) 221.1 (M+Na$^+$, 100%); HRMS (ESI$^+$) found 221.0792, $C_{10}H_{14}NaO_4^+$ (M+Na$^+$), requires 221.0784. Data in accord with literature.[22]

Further elution gave a mixture of compound **20g-cv** and compound **20g-cc** as a colorless oil (0.023 g, 1.5:1, **20g-cv**:**20g-cc**, 0.116 mmol, 12%); $\nu_{max}(CDCl_3)/cm^{-1}$ 2958, 2874, 1774 (C=O), 1742 (C=O), 1458, 1435, 1376, 1304, 1251, 1213, 1166, 1142, 1110, 1062, 1044, 1022, 1006, 984; δ_H(400 MHz; $CDCl_3$) 4.50 (dd, *J* = 9.3, 6.7 Hz, 1H, C*H*HO b), 4.37 (dd, *J* = 9.7, 8.1 Hz, 1H, C*H*HO a), 4.29 (dd, *J* = 9.7, 3.4 Hz, 1H, CH*H*O a), 4.14 (dd, *J* = 9.3, 1.6 Hz, 1H, CH*H*O b), 3.77 (s, 3H, O*Me* a), 3.76 (s, 3H, O*Me* b), 3.09 (td, *J* = 8.1, 3.4 Hz, 1H, OCH$_2$C*H* a), 2.61 (ddd, *J* = 13.9, 8.2, 4.3 Hz, 1H, CC*H*H b), 2.55 (ddd, *J* = 7.4, 6.7, 1.6 Hz, 1H, OCH$_2$C*H* b), 2.36 (ddd, *J* = 13.3, 11.8, 6.5 Hz, 1H, CC*H*H a), 2.36-2.25 (m, 1H, C*H*Me a), 2.29 (ddd, *J* = 13.3, 7.0, 2.1 Hz, 1H, CCH*H* a), 2.12 (ddd, *J* = 13.8, 8.7, 7.1 Hz, 1H, CCH*H* b), 1.94-1.83 (m, 3H, 2HB & 1HA, C*H*Me b, CCH$_2$C*H*H a, CCH$_2$C*H*H b), 1.51-1.39 (m, 1H, CCH$_2$CH*H* b), 1.24 (qd, *J* = 11.8, 7.1 Hz, 1H, CCH$_2$CH*H* a), 1.07 (d, *J* = 6.5 Hz, 3H, CH*Me* b), 1.04 (d, *J* = 7.0 Hz, 3H, CH*Me* a); δ_C(100 MHz; $CDCl_3$) 176.7 (*C*O b), 176.6 (*C*O a), 170.5 (*C*O a, b), 71.0 (*C*H$_2$O b), 67.0 (*C*H$_2$O a), 61.5 (*C*CO$_2$Me a), 61.4 (*C*CO$_2$Me b), 54.3 (OCH$_2$*C* b), 53.1 (O*Me* a, b), 48.4 (OCH$_2$*C* a), 41.7 (*C*HMe b), 37.4 (*C*HMe a), 34.5 (*C*H$_2$CHMe b), 33.8 (C*C*H$_2$ a), 33.3 (*C*H$_2$CHMe a), 32.7 (C*C*H$_2$ b), 18.2 (CH*Me* b), 14.5 (CH*Me* a); *m/z* LRMS (ESI$^+$) 419.2 (2M+Na$^+$, 100%), 221.1 (M+Na$^+$, 78); HRMS (ESI$^+$) found 221.0786, $C_{10}H_{14}NaO_4^+$ (M+Na$^+$), requires 221.0784. The reaction was repeated with the same reagents on the same scale at 80 °C overnight to give a mixture of the title compounds **20g-cv** and **20g-cc** (d.r. 5:1, **20g-cv**:**20g-cc**) as a colorless oil (0.151 g, 0.762 mmol, 76%).

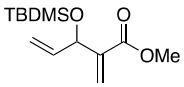
*4.1.21. Methyl 3-hydroxy-2-methylenepent-4-enoate **26***



26

To a solution of amine **25**[24] (9.95 g, 54.7 mmol) in chloroform (500 mL) at 0 °C was added dropwise a solution of purified *m*CPBA (10 g, 60 mmol) in chloroform (150 mL). The reaction was allowed to warm to RT over 16 h and then partially concentrated *in vacuo*. The solution was then passed through a column of basic alumina (deactivated with 6% w/w water) eluting with chloroform. Concentration *in vacuo* then gave a mixture of the title compound and starting amine that were separated by flash column chromatography (4:1 petrol:Et$_2$O) to give the title compound **26** as a colorless oil (4.00 g, 28.2 mmol, 51%); R_f 0.62 (4:1 petrol:EtOAc); δ_H (400 MHz $CDCl_3$) 6.28 (1H, br s, C*H*H'=C) 5.98 (1H, dddt, *J* = 17.1, 10.3, 5.4, 1.0 Hz, CH$_2$=C*H*), 5.88 (1H, br s, CH*H*'=C), 5.36 (1H, dt, *J* = 17.1, 1.0 Hz, C*H*H'=CH), 5.22 (1H, dt, *J* = 10.3, 1.0 Hz, CH*H*'=CH), 4.98 (1H, t, *J* = 5.4 Hz, C*H*OH), 3.80 (3H, s, O*Me*), 2.95 (1H, br m, CHO*H*); δ_C (100 MHz $CDCl_3$) 166.8 (*C*O), 141.1 (*C*=CH$_2$), 138.1 (CH$_2$=*C*H), 125.9 (C=*C*H$_2$), 116.1 (*C*H$_2$=CH), 72.2 (*C*HOH), 52.0 (O*Me*). In accordance with the literature values.[24] HPLC data; column: Chiralpak OD, flow rate: 0.8 mL/min, solvent: 5% IPA in hexane, retention time for (*R*) 13.20 min, (*S*) 15.20 min.

*4.1.22. Methyl 3-((tert-butyldimethylsilyl)oxy)-2-methylenepent-4-enoate **27***

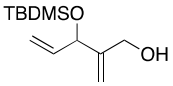


27

To a solution of alcohol **26** (3.88 g, 27.3 mmol) in CH_2Cl_2 (55 mL) was added sequentially imidazole (5.50 g, 72.6 mmol) and TBDMSCl (5.00 g, 36.3 mmol). The reaction was stirred for 16 h then quenched with sat. aq. NH_4Cl (25 mL). The aqueous layer was then separated and extracted with CH_2Cl_2 (2 × 50mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (98:2 petrol:EtOAc) gave the title compound **27** as a colorless oil (6.17 g, 24.0 mmol, 88%); R_f 0.60 (petrol); δ_H (400 MHz, $CDCl_3$) 6.21 (1H, t, *J* = 1.5 Hz, C*H*H'=C), 5.96 (1H, t, *J* = 1.5 Hz, CH*H*'=C), 5.83 (1H, ddd, *J* = 17.1, 10.1, 5.8 Hz, CH$_2$=C*H*), 5.27 (1H, dt, *J* = 17.1, 1.5 Hz, C*H*H'=CH), 5.05 (1H, dt, *J* = 10.5, 1.5 Hz, CH*H*'=CH), 5.02–5.07 (1H, m,

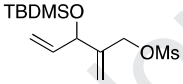
C*H*OTBDMS), 3.75 (3H, s, O*Me*), 0.84 (9H, s, C*Me*$_3$), 0.06 (3H, s, 205 Si*Me*), 0.04 (3H, s, Si*Me*); δ_C (100 MHz $CDCl_3$) 166.5 (*C*O), 142.7 (CH_2=*C*), 139.2 (CH_2=*C*H), 124.2 (*C*H_2=C), 114.5 (*C*H_2=CH), 71.4 (*C*HOTBDMS), 51.7 (O*Me*), 25.8 (SiC*Me*$_3$), 18.3 (SiCMe$_3$), -4.8 (Si*Me*), -5.1 (Si*Me*). Data in accordance with the literature values.[39]

4.1.23. 3-((tert-Butyldimethylsilyl)oxy)-2-methylenepent-4-en-1-ol



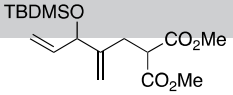
To a solution of ester **27** (6.17 g, 24.0 mmol) in THF (60 mL) at -35 °C was added DIBAL (60 mL, 1 M in hexane, 60 mmol) dropwise and the reaction stirred for 2 h at between -35 °C and -20 °C. The reaction was then quenched by the slow addition of MeOH (5 mL) followed by sat. aq. sat. aq. Rochelle's salt (60 mL), sat. aq. NH_4Cl (10 mL) and EtOAc (100 mL). The mixture was vigorously stirred for 2 h. The aqueous layer was then separated and extracted with EtOAc (2 × 150 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (6:1 petrol:EtOAc) gave the title compound as a colorless oil (4.76 g, 20.6 mmol, 86%); R_f 0.41 (6:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 3400br w, 2931m; δ_H (400 MHz $CDCl_3$) 5.83 (1H, ddd, *J* = 17.0, 10.3, 5.5 Hz, CH_2=C*H*), 5.29 (1H, dt, *J* = 17.0, 1.5 Hz, C*H*H'=CH), 5.13 (1H, dt, *J* = 10.3, 1.5 Hz, CH*H*'=CH), 5.09 (2H, br s, C*H*$_2$=C), 4.67 (1H, d *J* = 5.5 Hz, C*H*OTBDMS), 4.21 (1H, dd, *J* = 13.3, 5.5 Hz, C*H*H'OH), 4.08 (1H, dd, *J* = 13.3, 5.5 Hz, CH*H*'OH), 2.11 (1H, t, *J* = 5.5 Hz, O*H*), 0.90 (9H, s, SiC*Me*$_3$), 0.07 (3H, s, Si*Me*), 0.07 (3H, s, Si*Me*); δ_C (100 MHz $CDCl_3$) 149.1 (CH_2=*C*), 139.7 (CH_2=*C*H), 114.7 (*C*H_2=CH), 111.9 (*C*H_2=C), 76.6 (*C*HOTBDMS), 63.8 (*C*H_2OH), 25.7 (SiC*Me*$_3$), 18.3 (SiCMe$_3$), -4.8 (Si*Me*), -5.1 (Si*Me*); *m/z* LRMS (ESI$^+$) 227 (M+Na$^+$, 100); HRMS (ESI$^+$): found 251.1441, $C_{12}H_{24}O_2SiNa^+$ (M+Na$^+$), requires 251.1438.

4.1.24. 3-((tert-Butyldimethylsilyl)oxy)-2-methylenepent-4-en-1-yl methanesulfonate



To a solution of alcohol 3-((*tert*-butyldimethylsilyl)oxy)-2-methylenepent-4-en-1-ol (4.76 g, 20.8 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added Et_3N (4.3 mL. 3.1 g, 31.2 mmol) followed by MsCl (2.08 mL, 13.08 g, 27 mmol) and the reaction mixture was stirred for 10 min and then quenched with sat. aq. NH_4Cl (80 mL). The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (2 × 80 mL). The combined organic layers were washed with brine (80 mL), dried ($MgSO_4$) to yield the title compound as a yellow oil; R_f 0.41 (6:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2931m, 1359s, 1176s; δ_H (400 MHz $CDCl_3$) 5.76 (1H, ddd, *J* = 17.1, 10.3, 5.9 Hz, CH_2=C*H*), 5.36 (1H, s, C*H*H'=C), 5.30 (1H, dt, *J* = 17.1, 1.5 Hz, C*H*H'=CH), 5.28 (1H, s, CH*H*'=C), 5.15 (1H, dt, *J* = 10.3, 1.5 Hz, CH*H*'=CH), 4.68–4.73 (3H, m, C*H*OTBDMS, C*H*$_2$OMs), 3.00 (3H, s, SO$_2$*Me*), 0.89 (9H, s, SiC*Me*$_3$), 0.06 (6H, s, Si*Me*$_2$); δ_C (100 MHz $CDCl_3$) 143.4 (CH_2=*C*), 138.9 (CH_2=*C*H), 115.6 (*C*H_2=C), 115.2 (*C*H_2=CH), 74.8 (*C*HOTBDMS), 69.0 (*C*H_2OMs), 37.8 (SO$_2$*Me*), 25.7 (SiC*Me*$_3$), 18.3 (SiCMe$_3$), -4.8 (Si*Me*), -5.0 (Si*Me*); *m/z* LRMS (ESI$^+$) 329 (M+Na$^+$, 100); HRMS (ESI$^+$): found 329.1211, $C_{13}H_{26}O_4SSiNa^+$ (M+Na$^+$), requires 329.1213.

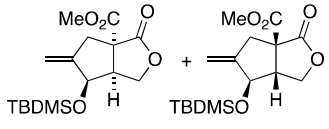
*4.1.25. Dimethyl 2-(3-((tert-butyldimethylsilyl)oxy)-2-methylenepent-4-en-1-yl)malonate **28***



28

To a stirred suspension of NaH (60% dispersion in mineral oil, 2.5 g, 62.4 mmol) in DMF (80 mL) and THF (40 mL) at 0 °C was added dimethyl malonate dropwise (7.4 mL, 8.2 g, 62.4 mmol). The reaction mixture was warmed to RT and the crude mesylate 3-((*tert*-butyldimethylsilyl)oxy)-2-methylenepent-4-en-1-yl methanesulfonate prepared above was added as a solution in THF (40 mL) followed by the addition of KI (1.04 g, 6.24 mmol). The reaction mixture was warmed to 80 °C and stirred 16 h, then allowed to cool to RT, quenched with sat. aq. NH_4Cl (80 mL) and petrol (80 mL) was added. The aqueous layer was extracted with petrol (2 × 80 mL), the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography gave the title compound **28** as a colorless oil (5.88 g, 17.2 mmol, 83%); R_f 0.43 (10:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2955w, 1740s, 1230m; δ_H (400 MHz $CDCl_3$) 5.76 (1H, ddd, *J* = 17.0, 10.3, 5.5 Hz, CH_2=C*H*), 5.29 (1H, dt, *J* = 17.0, 1.5 Hz, C*H*H'=CH), 5.13 (1H, dt, *J* = 10.3, 1.5 Hz, CH*H*'=CH), 5.12 (1H, br s, C*H*H'=C) 4.84 (1H, br s, CH*H*'=C), 4.57 (1H, d, *J* = 5.5 Hz, C*H*OTBDMS), 3.74 (1H, t, *J* = 7.8 Hz, C*H*(CO$_2$Me)$_2$), 3.73 (3H, s, O*Me*), 3.73 (3H, s, O*Me*), 2.69 (1H, dd, *J* = 15.5, 7.8 Hz, C*H*H'CH(CO$_2$Me)$_2$), 2.61 (1H, dd, *J* = 15.5, 7.8 Hz, CH*H*'CH(CO$_2$Me)$_2$), 0.91 (9H, s, SiC*Me*$_3$), 0.06 (6H, s, Si*Me*$_2$); δ_C (100 MHz $CDCl_3$) 169.6 (*C*O), 146.8 (CH_2=*C*), 139.7 (CH_2=*C*H), 114.9 (*C*H_2=CH), 111.6 (*C*H_2=C), 76.7 (*C*HOTBDMS), 52.5 (O*Me*), 52.5 (O*Me*), 50.6 (*C*H(CO$_2$Me)$_2$), 30.1 (*C*H_2CH(CO$_2$Me)$_2$) 25.8 (SiC*Me*$_3$), 18.3 (SiCMe$_3$), -4.8 (Si*Me*), -5.0 (Si*Me*); *m/z* LRMS (ESI$^+$) 365 (M+Na$^+$, 100); HRMS (ESI$^+$): found 365.1754, $C_{17}H_{30}O_5SiNa^+$ (M+Na$^+$), requires 365.1755.

4.1.26. Methyl (3aR,6R*,6aS*)-6-((tert-butyldimethylsilyl)oxy)-5-methylene-3-oxotetrahydro-1H-cyclopenta[c]furan-3a(3H)-carboxylate **30cc** and methyl (3aS*,6R*,6aR*)-6-((tert-butyldimethylsilyl)oxy)-5-methylene-3-oxotetrahydro-1H- cyclopenta[c]furan-3a(3H)-carboxylate **30cv***



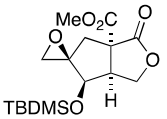
30cc **30cv**

To a solution of malonate **28** (500 mg, 1.46 mmol) and CuI (25 mg, 0.125 mmol) in CH_2Cl_2 (15 mL) cooled to –78 °C was added ethylmagnesium bromide (0.70 mL, 3 M in Et_2O, 2.1 mmol) and the mixture then stirred for 15 min. Iodine was added (1.8 g, 5.8 mmol) and the reaction warmed to RT and stirred for 16 h. The reaction was quenched with sat. aq. $Na_2S_2O_3$ (25 mL), then diluted with H_2O (100 mL) and CH_2Cl_2 (200 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude solid was then heated to 140 °C for 20 min before being cooled to RT and purified by flash column chromatography (7:1 petrol:EtOAc) to give **30cv** as a colorless oil (26.5 mg, 0.08 mmol, 6%) followed by **30cc** as a colorless oil (412 mg, 1.26 mmol, 87%); (Major **30cc**) R_f 0.52 (7:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2963m, 1775s, 1734s, 1249s; δ_H (400 MHz C_6D_6) 5.01 (1H, br m, C*H*H'=C), 4.80 (1H, br m, CH*H*'=C), 4.32 (1H, dd, *J* = 9.3, 3.4 Hz, C*H*H'O), 4.25 (1H, dt, *J* = 7.2, 1.8 Hz, C*H*OTBDMS), 4.04 (1H, dd, *J* = 9.3, 8.2 Hz, CH*H*'O), 3.33 (3H,

s, O*Me*), 3.23 (1H, dt, *J* = 16.2, 2.3 Hz, C*H*H'C=CH_2), 3.04 (1H, dt, *J* = 16.2, 2.3 Hz, CH*H*'C=CH_2), 2.86 (1H, td, *J* = 7.2, 3.4 Hz, C*H*CHOTBDMS), 0.94 (9H, s SiC*Me*$_3$), 0.00 (3H, s, Si*Me*), -0.06 (3H, s, Si*Me*); δ_C (100 MHz $CDCl_3$) 175.7 (*C*=O), 170.2 (*C*=O), 147.8 (CH_2=*C*), 109.2 (*C*H_2=C), 74.4 (*C*HOTBDMS), 66.0 (*C*H_2OR), 57.4 (*C*CO_2Me), 53.4 (O*Me*), 48.3 (*C*HCH_2OR), 35.8 (*C*H_2C=CH_2), 25.8 (C*Me*$_3$), 18.1 (SiCMe_3), -4.8 (Si*Me*), -5.1 (Si*Me*); *m/z* LRMS (ESI^+) 344 ($M+NH_4^+$, 100); HRMS (ESI^+): found 349.1434, $C_{16}H_{26}O_5SiNa^+$ ($M+Na^+$), requires 349.1442.

(Minor **30cv**) R_f 0.55 (7:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2956m, 1777s, 1733s, 1249s; δ_H (400 MHz $CDCl_3$) 5.05 (1H, q, *J* = 1.5 Hz, C*H*H'=C), 5.02 (1H, q, *J* = 1.5 Hz, CH*H*'=C), 4.53 (1H, dd, *J* = 9.5, 7.7 Hz, C*H*H'O), 4.18 (1H, dd, *J* = 3.8, 1.5 Hz, C*H*OTBDMS), 4.06 (1H, dd, *J* = 9.5, 3.8 Hz, CH*H*'O), 3.76 (3H, s, O*Me*), 3.38 (1H, dt, *J* = 16.8, 1.5 Hz, C*H*H'C=CH_2), 3.02 (1H, td, *J* = 7.7, 3.6 Hz, C*H*CHOTBDMS), 2.71 (1H, dt, *J* = 16.8, 1.5 Hz, CH*H*'C=CH_2), 0.85 (9H, s, SiC*Me*$_3$), 0.06 (3H, s, Si*Me*), 0.05 (3H, s, Si*Me*); δ_C (100 MHz $CDCl_3$) 175.7 (*C*O), 169.4 (*C*O), 148.5 (CH_2=*C*), 110.1 (*C*H_2=C), 79.0 (*C*HOTBDMS), 69.5 (*C*H_2O), 57.4 (*C*CO_2Me), 53.76 (*C*HCH_2O), 53.3 (O*Me*), 35.9 (*C*H_2C=CH_2), 25.6 (SiC*Me*$_3$), 17.9 (Si*C*Me$_3$), -4.5 (*SiMe)*, -4.7 (Si*Me*);

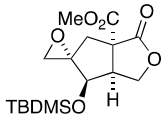
4.1.27. Methyl (3aS,4R*,5R*,6aR*)-4-((tert-butyldimethylsilyl)oxy)-1-oxodihydro-1H,3H-spiro[cyclopenta[c]furan-5,2'-oxirane]-6a(6H)-carboxylate* ***31a***



31a

To a stirred solution of alkene **30cc** (50 mg, 0.15 mmol) in CH_2Cl_2 (1.5 mL) was added $NaHCO_3$ (38 mg, 0.45 mmol) and *m*CPBA (57 mg, 70% wt/wt, 0.23 mmol). The reaction was stirred for 48 h before being quenched with sat. aq. $Na_2S_2O_3$ (1 mL). The mixture was diluted with sat. aq. $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) and then the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (4:1 petrol:EtOAc) gave recovered starting material (7 mg, 21 μmol, 14%), epoxide **31b** (see below) (9 mg, 26 μmol, 17%) and the title compound **31a** (28 mg, 81 μmol, 54%) as a white solid; m.p. 59–62 °C; R_f 0.35 (6:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2955w, 1777s, 1744s, 1253m; δ_H (400 MHz $CDCl_3$) 4.55 (1H, dd, *J* = 9.2, 2.5 Hz, C*H*H'O), 4.40 (1H, dd, *J* = 9.2, 7.8 Hz, CH*H*'O), 3.94 (1H, d, *J* = 5.5 Hz, C*H*OTBDMS), 3.80 (3H, s, O*Me*), 3.14 (1H, ddd, *J* = 8.0, 5.6, 2.5 Hz, C*H*CH_2O), 2.86 (1H, d, *J* = 4.9 Hz, CC*H*H'OC), 2.77 (1H, d, *J* = 4.9 Hz, CCH*H*'OC), 2.57 (1H, d, *J* = 14.3 Hz, C*H*H'CCO_2Me), 2.47 (1H, d, *J* = 14.3 Hz, CH*H*'CCO_2Me), 0.88 (9H, s, SiC*Me*$_3$), 0.10 (3H, s, Si*Me*), 0.04 (3H, s, Si*Me*); δ_C (100 MHz $CDCl_3$) 175.2 (*C*O), 170.2 (*C*O), 74.5 (C*H*OTBDMS), 66.1 (*C*H_2O), 64.8 (CH_2O*C*), 56.7 (*C*CO_2Me), 53.5 (O*Me*), 50.5 (*C*H_2OC), 48.3 (*C*HCH_2O), 33.7 (*C*H_2CCO_2Me), 25.7 (SiC*Me*$_3$), 18.1 (Si*C*Me$_3$), -4.5 (Si*Me*), -5.3 (Si*Me*); *m/z* LRMS (ESI^+) 365 ($M+Na^+$, 100); HRMS (ESI^+): found 365.1386, $C_{16}H_{26}O_6SiNa^+$ ($M+Na^+$), requires 365.1391. Single Crystal Data: $C_{16}H_{26}O_6Si$, monoclinic, $P2_1/c$, *a*=20.7306(4), *b*=7.96400(10), *c*=11.4367(2) Å, β=99.7675(6)°, *V*=1860.81(5) $Å^3$, Data/restraints/parameters 4222/26/221, R_{int}=0.017, Final R_1=0. 0431, wR_2=0.1157 (I>2s(I)).

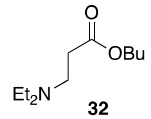
4.1.28. Methyl (3aS,4R*,5S*,6aR*)-4-((tert-butyldimethylsilyl)oxy)-1-oxodihydro-1H,3H-spiro[cyclopenta[c]furan-5,2'-oxirane]-6a(6H)-carboxylate* ***31b***



31b

To a solution of alkene **30cc** (40 mg, 0.125 mmol) in acetone (0.5 mL) was added a solution of DMDO (3.0 mL, 0.08 M, 0.24 mmol) and the reaction was left to stand for 5 h. The reaction was then concentrated *in vacuo*, followed by azeotropic drying with isopropanol *in vacuo*. Purification by flash column chromatography (6:1 petrol:EtOAc) gave the title compound **31b** as a colorless oil (32 mg, 94 μmol, 75%) and epoxide **31a** (6 mg, 18 μmol, 14%); R_f 0.42 (6:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2955w, 1777s, 1744s, 1253m; δ_H (400 MHz $CDCl_3$) 4.55 (1H, dd, *J* = 9.3, 2.3 Hz, C*H*H'O), 4.41 (1H, dd, *J* = 9.3, 8.0 Hz, CH*H*'O), 4.13 (1H, d, *J* = 8.0 Hz, C*H*OTBDMS), 3.81 (3H, s, O*Me*), 3.26 (1H, td, *J* = 8.0, 2.3 Hz, C*H*CH_2O), 2.97 (1H, d, *J* = 5.0 Hz, CC*H*H'OC), 2.73 (1H, d, *J* = 5.0 Hz, CCH*H*'OC), 2.63 (1H, d, *J* = 14.4 Hz, C*H*H'CCO_2Me), 2.38 (1H, d, *J* = 14.4 Hz, CH*H*'CCO_2Me), 0.87 (9H, s, SiC*Me*$_3$), 0.05 (6H, s, Si*Me*$_2$); δ_C (100 MHz $CDCl_3$) 175.2 (*C*O), 169.4 (*C*O), 73.2 (*C*HOTBDMS), 65.8 (*C*H_2O), 64.7 (CH_2O*C*), 56.5 (*C*CO_2Me), 53.6 (O*Me*), 49.2 (*C*H_2OC), 46.9 (*C*HCH_2O), 34.2 (*C*H_2CCO_2Me), 25.6 (SiC*Me*$_3$), 18.0 (Si*C*Me$_3$), -4.6 (Si*Me*), -5.1 (Si*Me*);

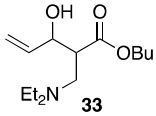
4.1.29. Butyl 3-(diethylamino)propanoate ***32***



32

To vigorously stirred water (500 mL) was added butyl acrylate (82.0 mL, 570 mmol) and diethylamine (65.0 mL, 630 mmol). The reaction was stirred for 1 h and then extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were dried (Na_2SO_4), filtered and then concentrated *in vacuo* to give the title compound **32**as a yellow oil (102 g, 505 mmol, 89%); R_f 0.45 (9:1 CH_2Cl_2:MeOH); ν_{max}/cm^{-1} (thin film) 2964m, 1735s, 1197m; δ_H (400 MHz $CDCl_3$) 4.08 (2H, t, *J* = 6.7 Hz, CH_2Pr), 2.79 (2H, t, *J* = 7.3 Hz, Et_2NCH_2), 2.51 (4H, q, *J* = 7.3 Hz, MeCH_2), 2.44 (2H, t, *J* = 7.3 Hz, CH_2CO_2Bu), 1.60 (2H, quin, *J* = 6.7 Hz, CH_2Et), 1.31 (2H, sept, *J* = 6.7 Hz, CH_2CH_2Me), 1.02 (6H, t, *J* = 7.3 Hz, NCH_2*Me*), 0.92 (3H, t, *J* = 6.7 Hz, *Me*); δ_C (100 MHz $CDCl_3$) 173.0 (*C*O), 64.3 (*C*H_2Pr), 48.1 (Et_2NCH_2), 46.8 (N*C*H_2Me), 32.3 (*C*H_2CO_2Bu), 30.7 (*C*H_2Et), 19.2 (CH_2*C*H_2Me), 13.7 (*C*H_2CH_2*Me*), 11.9 (NCH_2*Me*); *m/z* LRMS(ESI^+) 202 (M+H+, 100); HRMS (ESI^+): found 202.1799, $C_{11}H_{24}O_2N^+$ ($M+H^+$), requires 202.1802.

4.1.30. Butyl 2-((diethylamino)methyl)-3-hydroxypent-4-enoate ***33***



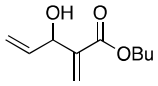
33

To solution of diisopropylamine (21.9 mL, 156 mmol) in THF (200 mL) at -78 °C was added BuLi (61.4mL, 2.5 M in hexane, 154mmol) and the reaction stirred for 15min. Butyl 3-(dimethylamino)propionate **32** (26.5 g, 132 mmol) was then added dropwise and the reaction stirred for 30 min at -78 °C then warmed to RT for 30 min over which time a white precipitate formed. The reaction was then cooled back to –78 °C and freshly distilled acrolein (7.37 g, 132 mmol) was added dropwise as a solution in THF (60 mL) and the reaction stirred for 1 h. The reaction was quenched with NH_4Cl (150 mL) and diluted with

EtOAc (300 mL). The aqueous layer was separated was separated and extracted with EtOAc (3 × 200 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude title compound **33** as a yellow oil (31.8 g, 124 mmol, 94%, d.r. 2:1); R_f 0.42 (10:1 EtOAc:MeOH); ν_{max}/cm^{-1} (thin film) 3300br w, 2964m, 1730s, 1180s; data for major diastereomer: δ_H (400 MHz $CDCl_3$) 5.78 (1H, ddd, *J* = 17.0 Hz, 10.3, 6.8 Hz, CH_2=C*H*), 5.26 (1H, ddd, *J* = 17.0, 1.6, 1.2 Hz, C*H*H'=CH), 5.09 (1H, ddd, *J* = 10.3, 1.7, 0.9 Hz, CH*H*'=CH), 4.35–4.41 (1H, m, C*H*OH), 3.96–4.08 (2H, m, CH_2Pr), 2.98–3.05 (1H, m, C*H*H'NEt_2), 2.60–2.80 (4H, m, C*H*CH*H*'NCH_2Me), 2.35–2.45 (2H, m, NCH_2Me), 1.52–1.63 (2H, m, CH_2Et), 1.30–1.41 (2H, m, CH_2CH_2Me), 1.06 (6H, t, *J* = 7.1 Hz, NCH_2*Me*), 0.91 (3H, t, *J* = 7.4 Hz, CH_2CH_2*Me*); δ_C (100 MHz $CDCl_3$) 171.9 (*C*O), 138.3 (CH_2=*C*H), 116.2 (*C*H_2=CH), 76.6 (*C*HOH), 64.5 (*C*H_2Pr), 55.9 (*C*HCO), 48.6 (CH*C*H_2N), 46.7 (N*C*H_2), 30.5 (*C*H_2Et), 19.1 (CH_2*C*H_2Me), 13.7 (CH_2CH_2*Me*), 11.3 (NCH_2*Me*);

data for the minor diastereomer: δ_H (400 MHz $CDCl_3$) 5.87 (1H, ddd, *J* = 17.0, 10.5, 4.4 Hz, CH_2=C*H*), 5.40 (1H, dd, *J* = 17.0, 1.8 Hz, C*H*H'=CH), 5.23 (1H, dt, *J* = 10.5, 1.9 Hz, CH*H*'=CH), 4.60–4.65 (1H, m, C*H*OH), 3.96–4.08 (2H, m, CH_2Pr), 3.11 (1H, dt, *J* = 11.3, 4.2 Hz, C*H*CH_2NEt_2), 2.93 (1H, dd, *J* = 13.0, 11.3 Hz, C*H*H'NEt_2), 2.60–2.80 (3H, m, CHCH*H*'NCH_2Me), 2.35–2.45 (2H, m, NCH_2Me), 1.52–1.63 (2H, m, CH_2Et), 1.30–1.41 (2H, m, CH_2CH_2Me), 1.01 (6H, t, *J* = 7.1 Hz, NCH_2*Me*), 0.91 (3H, t, *J* = 7.4 Hz, CH_2CH_2*Me*); δ_C (100 MHz $CDCl_3$) 172.1 (*C*O), 137.8 (CH_2=*C*H), 116.2 (*C*H_2=CH), 73.5 (*C*HOH), 64.5 (*C*H_2Pr), 51.7 (*C*HCO), 47.0 (NCH_2), 45.8 (CH*C*H_2N), 30.5 (*C*H_2Et), 19.1 (CH_2*C*H_2Me), 13.7 (CH_2CH_2*Me*), 11.3 (NCH_2*Me*); *m/z* LRMS (ESI^+) 258 ($M+H^+$, 100); HRMS (ESI^+): found 258.2058, $C_{14}H_{28}O_3N^+$ ($M+H^+$), requires 258.2064.

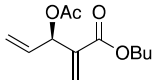
4.1.31. Butyl 3-hydroxy-2-methylenepent-4-enoate ***34***



34

To a stirred suspension of amine **33** (27.7 g, 108 mmol) and $NaHCO_3$ (24.1 g, 287 mmol) in CH_2Cl_2 (500 mL) cooled to 0 °C was added a solution of *m*CPBA (43.5 g, 50% wt/wt, 126 mmol) in CH_2Cl_2 (250 mL). The reaction was then warmed to RT and stirred vigorously for 4 h. The mixture was concentrated *in vacuo* to approximately 40 mL and diluted with pentane (300 mL), H_2O (150 mL) and sat. aq. NaHCO3 (150 mL). The aqueous layer was separated and extracted with pentane (2 × 300 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (6:1 petrol:Et_2O) gave the title compound **34** as a colorless oil (12.5 g, 67.8 mmol, 63%); R_f 0.56 (6:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 3423br w, 2948w, 1712s; δ_H (400 MHz $CDCl_3$) 6.25 (1H, s, C=C*H*H'), 5.96 (1H, ddd, *J* = 17.3, 10.5, 5.6 Hz, CH_2=C*H*), 5.83 (1H, t, *J* = 1.0 Hz, C=CH*H*'), 5.33 (1H, dt, *J* = 17.3, 1.0 Hz, C*H*H'=CH), 5.20 (1H, dt, *J* = 10.5, 1.0 Hz, CH*H*'=CH), 4.94 (1H, t, *J* = 5.6 Hz, C*H*OH), 4.18 (2H, t, *J* = 6.8 Hz, CH_2Pr), 2.95 (1H, d, *J* = 5.6 Hz, CHO*H*), 1.66 (2H, quin, *J* = 6.8 Hz, CH_2Et), 1.40 (2H, sept, *J* = 6.8 Hz, CH_2Me), 0.94 (3H, t, *J* = 6.8 Hz, *Me*); δ_C (100 MHz $CDCl_3$) 166.4 (*C*O), 141.3 (*C*=CH_2), 138.2 (CH_2=*C*H), 125.6 (C=*C*H_2), 116.0 (*C*H_2=CH), 72.3 (*C*HOH), 64.9 (*C*H_2Pr), 30.6 (*C*H_2Et), 19.2 (*C*H_2Me), 13.7 (*Me*); *m/z* LRMS (ESI^+) 207 ($M+Na^+$, 100); HRMS (ESI^+): found 207.0990, $C_{10}H_{16}O_3Na^+$ ($M+Na^+$), requires 207.0992. HPLC data: column: Chiralpak AD, flow rate: 0.8 mL/min, solvent: 1.5% IPA in hexane, retention time for (*S*) 19.7 min, (*R*) 21.3 min.

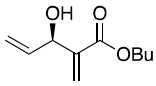
4.1.32. Butyl (R)-3-acetoxy-2-methylenepent-4-enoate ***35***



35

To a stirred solution of alcohol **34** (13.9 g, 75.5 mmol) and vinyl acetate (43 mL, 460 mmol) in hexane (400 mL) was added *Candida Antarctica* lipase B immobilised on immobead™ recombinant from yeast (8.52 g, 7244 U/kg). The reaction was warmed to 31 °C and stirred for 3 d. The reaction mixture was then filtered and concentrated *in vacuo*. Purification by flash column chromatography (12:1→6:1 petrol:Et_2O) gave the acetate **35** as a colorless oil (8.03 g, 35.4 mmol, 47%, >99% e.e) followed by alcohol (–)-**34** (7.02 g, 38.1 mmol, 50%); R_f 0.42 (20:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2947w, 1744s, 1721s; δ_H (400 MHz $CDCl_3$) 6.34 (1H, s, C=C*H*H'), 6.10 (1H, br d, *J* = 6.4 Hz, C*H*OAc), 5.89 (1H, ddd, *J* = 17.0, 10.4, 6.4 Hz, CH_2=C*H*), 5.83 (1H, s, C=CH*H*'), 5.33 (1H, dt, *J* = 17.0, 1.0 Hz, C*H*H'=CH), 5.24 (1H, dt, *J* = 10.4, 1.0 Hz, CH*H*'=CH), 4.17 (2H, t, *J* = 6.7 Hz, CH_2Pr), 2.09 (3H, s, C(O)*Me*), 1.59 (2H, quin, *J* = 6.7 Hz, CH_2Et), 1.39 (2H, sept, *J* = 6.7 Hz, CH_2Me), 0.93 (3H, t, *J* = 6.7 Hz, CH_2*Me*); δ_C (100 MHz $CDCl_3$) 169.5 (*CO*), 165.1 (*C*O), 139.0 (*C*=CH_2), 134.3 (CH_2=*C*H), 126.3 (C=*C*H_2), 117.9 (*C*H_2=CH), 71.9 (*C*HOAc), 64.9 (*C*H_2Pr), 30.6 (*C*H_2Et), 21.1 (C(O)*Me*), 19.2 (*C*H_2Me), 13.7 (CH_2*Me*); *m/z* LRMS (ESI^+) 249 ($M+Na^+$, 100); HRMS (ESI^+): found 249.1091, $C_{12}H_{18}O_4Na^+$ ($M+Na^+$), requires 249.1097; $[\alpha]_D^{25}$ –31.7 (*c* = 1.0 in $CHCl_3$). HPLC data of racemate formed from the acetylation of (±)-**34** using Ac_2O and NEt_3: column: Chiralpak OD, flow rate: 0.8 mL/min, solvent: 1% IPA in hexane, retention time for (*S*) 13.8 min, (*R*) 15.9 min.

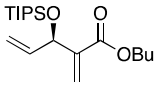
*4.1.33. Butyl (R)-3-hydroxy-2-methylenepent-4-enoate (+)-****34***



(+)-**34**

To a solution of acetate **35** (6.35 g, 23.1 mmol) in MeOH (100 mL) was added IR-120 Amberlite™ resin (50 g). The mixture was stirred for 4 d and then filtered and concentrated *in vacuo*. Purification by flash column chromatography (12:1→6:1 petrol:Et_2O) gave recovered starting material **35** (440 mg, 1.9 mmol, 7%) and the title compound (+)-**34** as a colorless oil (4.61 g, 25.1 mmol, 89%, >99% e.e.); physical data as above for racemic alcohol **34**; $[\alpha]_D^{25}$ +13.5 (c = 1.0 in $CHCl_3$).

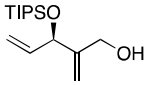
4.1.34. Butyl (R)-2-methylene-3-((triisopropylsilyl)oxy)pent-4-enoate



To a solution of alcohol (+)-**34** (4.61 g, 25.1 mmol) in CH_2Cl_2 (75 mL) at 0 °C was added sequentially 2,6-lutidine (4.40 mL, 37.6 mmol) and TIPSOTf (8.08 mL, 30.6 mmol). The reaction was stirred for 30 min and then quenched with sat. aq. $NaHCO_3$ (25 mL). The aqueous layer was then separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (98:2 petrol:EtOAc) gave the title compound butyl (*R*)-2-methylene-3-((triisopropylsilyl)oxy)pent-4-enoate as a colorless oil (7.91 g, 23.2 mmol, 93%); R_f 0.65 (petrol); ν_{max}/cm^{-1} (thin film) 2959m, 1716s, 1463m; δ_H (400 MHz $CDCl_3$) 6.24 (1H, dd, *J* = 1.8, 1.0 Hz, C*H*H'=C), 6.02 (1H, t, *J* = 1.2 Hz, CH*H*'=C), 5.82 (1H, ddd, *J* = 17.1, 10.3, 5.9 Hz, CH_2=C*H*), 5.28 (1H, dt, *J* = 17.1, 1.0 Hz,

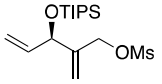
C*H*H'=CH), 5.05 (1H, dt, *J* = 5.9, 1.0 Hz, C*H*OTIPS), 5.04 (1H, dt, *J* = 10.3, 1.4 Hz, CH*H'*=CH), 4.16 (2H, dt, *J* = 6.7, 1.9 Hz, OCH_2), 1.61–1.69 (2H, m, OCH_2CH_2), 1.35–1.45 (2H, m, CH_2Me), 1.03–1.15 (21H, m, TIPS), 0.94 (3H, t, *J* = 7.4 Hz, *Me*); δ_C (100 MHz $CDCl_3$) 166.0 (*C*O), 143.5 (CH_2=*C*), 139.8 (CH_2=*C*H), 123.9 (*C*H_2=C), 114.3 (*C*H_2=CH), 71.6 (*C*HOTIPS), 64.5 (O*C*H_2), 30.6 (OCH$_2$*C*H_2), 19.2 (CH2Me), 18.0 (CMe2), 12.2 (SiCHMe2). *m/z* LRMS (ESI^+) 363 ($M+Na^+$, 100); HRMS (ESI^+): found 363.2322, $C_{19}H_{36}O_3SiNa^+$ ($M+Na^+$), requires 363.2326; $[\alpha]_D^{25}$ -7.8 (*c* = 1.0 in $CHCl_3$).

4.1.35. (R)-2-Methylene-3-((triisopropylsilyl)oxy)pent-4-en-1-ol



To a solution of (*R*)-2-methylene-3-((triisopropylsilyl)oxy)pent-4-enoate (9.42 g, 25.6 mmol) in THF (140 mL) at –78 °C was added DIBAL (71.6 mL, 1 M in hexane, 71.6 mmol) dropwise and the reaction was then warmed to between - 35 °C and -20 °C for 2 h. The reaction was quenched by the slow addition of MeOH (5 mL) followed by sat. aq. sat. aq. Rochelle's salt (60 mL), sat. aq. NH_4Cl (10 mL) and EtOAc (100 mL) and stirred vigorously until two clear phases formed on standing. The aqueous layer was then separated and extracted with EtOAc (2 × 150 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (6:1 petrol:EtOAc) gave the title compound (*R*)-2-methylene-3-((triisopropylsilyl)oxy)pent-4-en-1-ol as a colour oil (6.23 g, 23.1 mmol, 90%); R_f 0.45 (6:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 3430br m, 2867s, 1464m; δ_H (400 MHz $CDCl_3$) 5.86 (1H, ddd, *J* = 17.2, 10.3, 5.5 Hz, CH_2=C*H*), 5.30 (1H, dt, *J* = 17.2, 1.5 Hz, C*H*H'=CH), 5.13 (1H, dt, *J* = 10.3, 1.5 Hz, CH*H'*=CH), 5.09–5.13 (2H, br s, C*H*$_2$=C), 4.84 (1H, d *J* = 5.9 Hz, C*H*OTIPS), 4.25 (1H, dd, *J* = 13.6, 4.0 Hz, C*H*H'OH), 4.12 (1H, dd, *J* = 13.6, 6.4 Hz, CH*H'*OH), 2.06 (1H, dd, *J* = 6.4, 4.0 Hz, O*H*), 1.03–1.15 (21H, m, TIPS); δ_C (100 MHz $CDCl_3$) 149.3 (CH_2=*C*), 140.2 (CH_2=*C*H), 114.5 (*C*H_2=CH), 111.6 (*C*H_2=C), 77.0 (*C*HOTIPS), 63.3 (*C*H_2OH), 18.0 (SiCH*Me*$_2$), 12.2 (Si*C*H*Me*$_2$); *m/z* LRMS (ESI^+) 293 ($M+Na^+$, 100); HRMS (ESI^+): found 293.1909, $C_{15}H_{30}O_2SiNa^+$ ($M+Na^+$), requires 293.1907; $[\alpha]_D^{25}$ +11.3 (*c* = 1.0 in CHCl3).

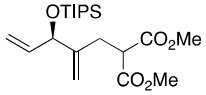
*4.1.36. (R)-2-Methylene-3-((triisopropylsilyl)oxy)pent-4-en-1-yl methanesulfonate **36***



36

To a solution of (*R*)-2-methylene-3-((triisopropylsilyl)oxy)pent-4-en-1-ol alcohol **26** (5.36 g, 19.8 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added Et_3N (4.3 mL. 3.1 g, 31.2 mmol) followed by MsCl (2.08 mL, 13.08 g, 27 mmol) and the reaction mixture was stirred for 10 min and then quenched with sat. aq. NH_4Cl (80 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 80 mL). The combined organic layers were washed with brine (80 mL), dried ($MgSO_4$) to give the title compound **27** as a crude yellow oil; R_f 0.45 (6:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2931m, 1359s, 1176s; δ_H (400 MHz $CDCl_3$) 5.77 (1H, ddd, *J* = 17.1, 10.3, 5.9 Hz, CH_2=C*H*), 5.40 (1H, s, C*H*H'=C), 5.32 (1H, dt, *J* = 17.1, 1.4 Hz, C*H*H'=CH), 5.28 (1H, s, CH*H'*=C), 5.16 (1H, dt, *J* = 10.3, 1.4 Hz, CH*H'*=CH), 4.81 (1H, d, *J* = 5.9 Hz, C*H*OTIPS), 4.73 (2H, s, CH_2OMs), 3.00 (3H, s, SO_2*Me*), 1.02–1.06 (21H, m, TIPS); δ_C (100 MHz $CDCl_3$) 149.6 (CH_2=*C*), 139.4 (CH_2=*C*H), 115.4 (*C*H_2=C), 114.9 (*C*H_2=CH), 75.2 (*C*HOTIPS), 68.7 (*C*H_2OMs), 37.7 (SO_2*Me*), 18.0 (SiCH*Me*$_2$), 12.2 (Si*C*H*Me*$_2$).

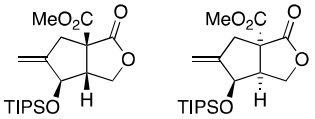
*4.1.37. Dimethyl (R)-2-(2-methylene-3-((triisopropylsilyl)oxy)pent-4-en-1-yl)malonate **37***



37

To a stirred suspension of NaH (60% dispersion in mineral oil, 2.4 g, 60 mmol) in DMF (80 mL) and THF (40 mL) at 0 °C was added dimethyl malonate dropwise (6.85 mL, 7.9 g, 60 mmol). The reaction mixture was warmed to RT and the crude mesylate **36** prepared above was added as a solution in THF (40 mL) followed by the addition of KI (1 g, 6.6 mmol). The reaction mixture was warmed to 80 °C and stirred 16 h, then allowed to cool to RT, quenched with sat. aq. NH_4Cl (80 mL) and petrol (80 mL) was added. The aqueous layer was extracted with petrol (2 × 80mL), the combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (15:1 petrol:EtOAc) gave the title compound **37** as a colorless oil (6.40 g, 16.6 mmol, 84%); R_f 0.49 (10:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2955w, 1740s, 1230m; δ_H (400 MHz $CDCl_3$) 5.75 (1H, ddd, *J* = 17.1, 10.3, 5.7 Hz, CH_2=C*H*), 5.28 (1H, dt, *J* = 17.1, 1.5 Hz, C*H*H'=CH), 5.14 (1H, t, *J* = 0.9 Hz, C*H*H'=C), 5.11 (1H, dt, *J* = 10.3, 1.5 Hz, CH*H'*=CH), 4.84 (1H, t, *J* = 1.5 Hz, CH*H'*=C), 4.65 (1H, d, *J* = 5.8 Hz, C*H*OTIPS), 3.68–3.73 (1H, m, C*H*(CO_2Me)$_2$), 3.71 (3H, s, O*Me*), 3.71 (3H, s, O*Me*), 2.58–2.72 (2H, m, CH_2CH(CO_2Me)$_2$), 1.01–1.11 (21H, m, TIPS); δ_C (100 MHz $CDCl_3$) 169.6 (*C*O), 147.0 (CH_2=*C*), 140.2 (CH_2=*C*H), 114.7 (*C*H_2=CH), 111.2 (*C*H_2=C), 74.5 (*C*HOTIPS), 52.5 (O*Me*), 50.5 (*C*H(CO_2Me)$_2$), 29.8 (*C*H_2CH(CO_2Me)$_2$, 18.0 (SiCH*Me*$_2$), 12.3 (Si*C*H*Me*$_2$); *m/z* LRMS(ESI^+) 407 ($M+Na^+$, 100); HRMS (ESI^+): found 407.2223, $C_{20}H_{36}OSiNa^+$ ($M+Na^+$), requires 407.2224; $[\alpha]_D^{25}$ +11.6 (c = 1.0 in $CHCl_3$).

*4.1.38. Methyl (3aR,6R,6aS)-5-methylene-3-oxo-6-((triisopropylsilyl)oxy)tetrahydro-1H-cyclopenta[c]furan-3a(3H)-carboxylate **38cc** and methyl (3aS,6R,6aR)-5-methylene-3-oxo-6-((triisopropylsilyl)oxy)tetrahydro-1H-cyclopenta[c]furan-3a(3H)-carboxylate **38cv***



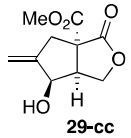
38cv **38cc**

To a solution of malonate **37** (6.38 g, 16.6 mmol) and CuI (158 mg, 0.83 mmol) in CH_2Cl_2 (150 mL) at -78 °C was added ethylmagnesium bromide (8.30 mL, 3 M in Et_2O, 24.9 mmol). The reaction was stirred for 15 min, and then iodine (16.9 g, 66.4 mmol) was added. The reaction was warmed to RT and stirred for 16 h and then quenched by the addition of sat. aq. NH_4Cl (50 mL) and $Na_2S_2O_3$ (25 mL), and then diluted with H_2O (100 mL) and CH_2Cl_2 (200 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was then heated to 140 °C for 30 min before being cooled to RT and purified by flash column chromatography (6:1 petrol:Et_2O) to give **38cv** as a colorless oil (0.91 g, 2.5 mmol, 15%) followed by **38cc** as a colorless oil (4.81 g, 13.1 mmol, 78%); (Major **38cc**) R_f 0.52 (7:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2945m, 1776s, 1743s, 1150s; δ_H (400 MHz $CDCl_3$) 5.18 (1H, s, C*H*H'=C), 5.05 (1H, s, CH*H'*=C), 4.70 (1H, d, *J* = 7.7 Hz, C*H*OTIPS), 4.46 (1H, dd, *J* =

9.4, 4.5 Hz, C*H*H'O), 4.31 (1H, dd, *J* = 9.4, 8.8 Hz, CH*H*'O), 3.79 (3H, s, O*Me*), 3.24 (1H, ddd, *J* = 8.8, 7.7, 4.5 Hz, C*H*CH$_2$O), 3.08 (1H, dtd, *J* = 16.0, 2.4, 0.9 Hz, C*H*H'C=CH$_2$), 2.78 (1H, d, *J* = 16.0 Hz, CH*H*'C=CH$_2$), 1.03–1.12 (21H, m, TIPS); δ_C (100 MHz CDCl$_3$) 175.7 (*C*O), 170.2 (*C*O), 147.0 (CH$_2$=*C*), 109.2 (*C*H$_2$=C), 74.2 (*C*HOTIPS), 65.9 (*C*H$_2$O), 56.9 (*C*CO$_2$Me), 53.4 (O*Me*), 47.7 (*C*HCH$_2$OR), 35.9 (*C*H$_2$C=CH$_2$), 18.0 (CH*Me*$_2$), 12.2 (Si*C*HMe$_2$); *m/z* LRMS (ESI$^+$) 391 (M+Na$^+$, 100); HRMS (ESI$^+$): found 391.1930, $C_{19}H_{32}O_5SiNa^+$ (M+Na$^+$), requires 391.1911; $[\alpha]_D^{25}$ -69.6 (c = 1.0 in CHCl$_3$).

(Minor **38cv**) R_f 0.55 (7:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2956m, 1777s, 1747s, 1061s; δ_H (400 MHz CDCl$_3$) 5.12 (1H, s, C*H*H'=C), 5.07 (1H, s, CH*H*'=C), 4.56 (1H, dd, *J* = 9.4, 8.8 Hz, C*H*H'O), 4.29 (1H, dd, *J* = 2.5, 0.8 Hz, C*H*OTIPS), 3.94 (1H, dd, *J* = 9.4, 5.0 Hz, CH*H*'O), 3.78 (3H, s, O*Me*), 3.51 (1H, ddt, *J* = 16.4, 2.5, 0.8 Hz, C*H*H'C=CH$_2$), 3.20 (1H, ddd, *J* = 8.8, 5.0, 2.5 Hz, C*H*CHOTIPS), 2.70 (1H, d, *J* = 16.4 Hz, CH*H*'C=CH$_2$), 1.00–1.10 (21H, m, TIPS); δ_C (100 MHz CDCl$_3$) 175.8 (*C*O), 169.5 (*C*O), 148.4 (CH$_2$=*C*), 111.2 (*C*H$_2$=C), 79.9 (*C*HOTIPS), 69.3 (C*H*$_2$OR), 58.4 (*C*CO$_2$Me), 54.2 (*C*HCH$_2$O), 53.3 (O*Me*), 36.8 (*C*H$_2$C=CH$_2$), 17.9 (CH*Me*$_2$), 12.2 (Si*C*HMe$_2$); $[\alpha]_D^{25}$ +11.3 (c = 1.0 in CHCl$_3$).

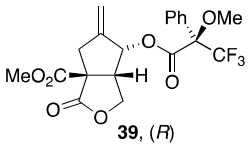
4.1.39. Methyl (3aR,6R,6aS)-6-hydroxy-5-methylene-3-oxotetrahydro-1H-cyclopenta[c]furan-3a(3H)-carboxylate ***29-cc***



29-cc

To a stirred solution of **38cc** (0.368 g, 1.00 mmol) in THF (5 mL) at 0 °C was added TBAF(1.30 mL, 1 M in THF, 1.30 mmol) and the reaction mixture was stirred for 5 min. sat. aq. NH$_4$Cl (2 mL) was added followed by EtOAc (10 mL) and the mixture was allowed to warm to RT. The organic phase was separated, and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$), filtered, and concentrated *in vacuo*. Purification by flash column chromatography (3:1 petrol:EtOAc) gave the title compound **29-cc** as a colorless oil (0.193 g, 0.91 mmol, 91%);R_f 0.10 (3:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 3478 (OH), 1766 (CO), 1737(CO); δ_H (500 MHz, CDCl$_3$) 5.19 (1H, q, *J* = 1.9 Hz, *H*H'C=C), 5.12 (1H, q, *J* = 2.0 Hz, H*H*'C=C), 4.63 – 4.66 (1H, 1H, C*H*OH), 4.55 (1H, dd, *J* = 9.5, 3.1 Hz, COOC*H*H'C), 4.41 (1H, dd, *J* = 9.5, 7.7 Hz, COOCH*H*'C), 3.80 (3H, s, O*Me*), 3.27 (1H, td, *J* = 7.6, 3.1 Hz, COOCHH'C*H*), 3.13 (1H, dt, *J* = 16.7, 2.2 Hz, H$_2$C=CC*H*H'), 2.95 (1H, dd, *J* = 16.6, 1.6 Hz, H$_2$C=CCH*H*'); δ_C (126 MHz, CDCl$_3$) 175.6 (*C*COOCH$_2$), 169.9 (*C*COOMe), 148.7 (CH$_2$=*C*), 109.8 (*C*H$_2$=C), 73.7 (*C*OH), 66.1 (COO*C*H$_2$C), 58.0 (C(COOMe)COOCH$_2$), 53.5 (O*Me*), 48.4 (COH*C*HCH$_2$), 36.2 (CH$_2$=C*C*H$_2$); *m/z* HRMS (ESI$^+$) 235.0578 found, $C_{10}H_{12}O_5Na^+$ (M+Na$^+$), requires 235.0577.

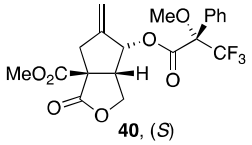
4.1.40. Methyl (3aR,6R,6aS)-5-methylene-3-oxo-6-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)tetrahydro-1H-cyclopenta[c]furan-3a(3H)-carboxylate ***39***



39, (*R*)

To a stirred solution of the alcohol **39** (0.015 g, 0.07 mmol) in CH$_2$Cl$_2$ (1 mL) was added DCC (0.043 g, 0.21 mmol), DMAP (0.024 g, 0.21 mmol), (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (0.048 g, 0.21 mmol), and the reaction was stirred for 16 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (4:1 petrol:EtOAc) gave the title compound **39** as a colorless oil (0.014 g, 0.03 mmol, 46%); 0.12 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1778s (CO) 1749(CO); δ_H (400 MHz, CDCl$_3$) δ 7.38 (5H, m, Ar*H*), 5.74 (1H, d, *J* = 7.2 Hz, C*H*OMPTA), 5.23 (1H, q, 1.9 Hz, *H*HC=C), 5.20 (1H, q, 1.9 Hz, H*H*C=C), 4.22 (1H, dd, *J* = 9.8, 8.0 Hz, COOC*H*H'C), 3.93 (1H, dd, *J* = 9.8, 3.5 Hz, COOCH*H*'C), 3.81 (3H, s, COO*Me*), 3.53 (3H, q, *J* = 1.3 Hz, ROOCCO*Me*), 3.51 (1H, dt, *J* = 7.7, 3.4 Hz, COOCH$_2$C*H*), 3.21 (1H, dt, *J* = 17.0, 2.3 Hz, H$_2$C=CC*H*H'), 2.89 (1H, ddq, *J* = 17.0, 2.7, 1.5, Hz, H$_2$C=CCH*H*'); δ_C (126 MHz, CDCl$_3$) 174.4 (*C*COOCH$_2$), 169.1 (*C*COOMe), 166.0 (F$_3$CCR$_2$*C*OOR), 142.8 (CH$_2$=*C*), 131.6, 129.9, 128.6, 127.0, 123.1 (q, *J* = 288.8 Hz, *C*F$_3$), 113.2 (*C*H$_2$=C), 84.5 (q, *J* = 28.1 Hz, F$_3$C*C*), 77.1 (*C*OMPTA), 65.4 (COO*C*H$_2$C), 58.0 (*C*(COOMe)COOCH$_2$), 55.5 (ROOCCR$_2$O*Me*), 53.6 (COO*Me*), 46.9 (C(OMPTA)*C*HCH$_2$), 35.8 (CH$_2$=C*C*H$_2$); *m/z* HRMS (ESI$^+$) 451.0973 found, $C_{20}H_{19}F_3O_7Na^+$ (M+Na$^+$), requires 451.0975.

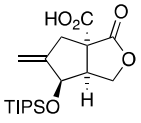
4.1.41. Methyl (3aR,6R,6aS)-5-methylene-3-oxo-6-(((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)tetrahydro-1H-cyclopenta[c]furan-3a(3H)-carboxylate ***40***



40, (*S*)

To a stirred solution of the alcohol **39** (0.015 g, 0.07 mmol) in CH$_2$Cl$_2$ (1 mL) was added DCC (0.043 g, 0.21 mmol), DMAP (0.024 g, 0.21 mmol), (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (0.048 g, 0.21 mmol), and the reaction was stirred for 16 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (4:1 petrol:EtOAc) to give the title compound **40** as a colorless oil (0.016 g, 0.04 mmol, 53%); 0.11 (4:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 1779(CO), 1749(CO); δ_H (400 MHz, CDCl$_3$) δ 7.46 (5H, m, Ar*H*), 5.76 (1H, d, *J* = 7.5 Hz, C*H*OMPTA), 5.16 (2H, q, *J* = 1.9 Hz, *H*$_2$C=C), 4.34 (1H, dd, *J* = 9.8, 8.0 Hz, COOC*H*H'C), 4.12 (1H, dd, *J* = 9.8, 3.4 Hz, COOCH*H*'C), 3.81 (3H, s, COO*Me*), 3.52 (1H dt, *J* = 7.7, 3.9 Hz, COOCH$_2$C*H*), 3.49 (3H, q, *J* = 1.3 Hz, ROOCCO*Me*), 3.17 (1H, dt, *J* = 17.1, 2.2 Hz, H$_2$C=CC*H*H'), 2.82 (1H, m, H$_2$C=CCH*H*'); δ_C (126 MHz, CDCl$_3$) 174.4 (*C*COOCH$_2$), 169.1 (*C*COOMe), 166.0 (F$_3$CCR$_2$*C*OOR), 142.8 (CH$_2$=*C*), 131.2, 130.0 128.7, 127.35 (*C*-Ar), 123.19 (q, *J* = 288.6 Hz, *C*F$_3$), 113.11 (*C*H$_2$=C), 84.8 (q, *J* = 28.1 Hz, F$_3$C*C*), 77.1 (*C*OMPTA), 65.7 (COO*C*H$_2$C), 58.0 (*C*(COOMe)COOCH$_2$), 55.4 (ROOCCR$_2$O*Me*), 53.7 (COO*Me*), 47.1 (C(OMPTA)*C*HCH$_2$), 35.9 (CH$_2$=C*C*H$_2$); *m/z* HRMS (ESI$^+$) 451.0972 found, $C_{20}H_{19}F_3O_7Na^+$ (M+Na$^+$), requires 451.0975.

4.1.42. (3aR,6R,6aS)-5-Methylene-3-oxo-6-((triisopropylsilyl)oxy)tetrahydro-1H-cyclopenta[c]furan-3a(3H)-carboxylic acid ***41***

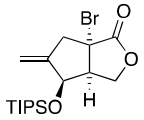


41

To a rapidly stirred solution of ester **38cc** (4.60 g, 12.5 mmol) in THF:H$_2$O (35 mL:35 mL) was added LiOH•H$_2$O (2.61 g, 62.0 mmol). The reaction was stirred for 16 h and then carefully acidified to pH 2 using 2 M aq. HCl (ca. 35 mL). The mixture was then extracted with EtOAc (4 × 50 mL). The combined

organic layers were dried ($MgSO_4$), filtered and then concentrated *in vacuo* to give the crude acid (4.43 g, 12.5 mmol, quant.). The acid was used as the crude mixture for all further reactions but an analytical sample can be obtained by purification by flash column chromatography (2:1:0.01 petrol:EtOAc:AcOH) to give the title compound **41** as a colorless oil; R_f 0.38 (2:1:0.01 petrol:EtOAc:AcOH); ν_{max}/cm^{-1} (thin film) 3089br w, 2943m, 1774s, 1645s; δ_H (400 MHz $CDCl_3$) 10.08 (1H, br s, CO_2H), 5.21 (1H, s, C*H*H'=C), 5.08 (1H, s, CH*H*'=C), 4.76 (1H, d, *J* = 7.4 Hz, C*H*OTIPS), 4.47 (1H, dd, *J* = 9.5, 4.8 Hz, C*H*H'O), 4.36 (1H, dd, *J* = 9.5, 8.8 Hz, CH*H*'O), 3.36 (1H, ddd, *J* = 8.8, 7.4, 4.8 Hz, C*H*CH_2O), 3.06 (1H, dt, *J* = 16.2, 2.0 Hz, C*H*H'CCO_2H), 2.81 (1H, d, *J* = 16.2 Hz, CH*H*'CCO_2H), 1.03–1.16 (21H, m, TIPS); δ_C (100 MHz $CDCl_3$) 176.2 (*C*O), 174.2 (*C*O), 146.7 (CH_2=*C*), 109.6 (*C*H_2=C), 74.3 (*C*HOTIPS), 66.4 (*C*H_2O), 47.5 (*C*CO_2H), 17.9 (CH*Me*$_2$), 12.2 (Si*C*HMe_2); *m/z* LRMS (ESI^+) 377 ($M+Na^+$, 100); HRMS (ESI^+): found 377.1755, $C_{18}H_{30}O_5SiNa^+$ ($M+Na^+$), requires 377.1754; $[\alpha]_D^{25}$ -20.8 (*c* = 1.0 in $CHCl_3$).

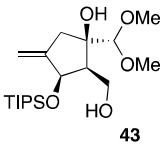
*4.1.43. (3aS,4R,6aS)-6a-Bromo-5-methylene-4-((triisopropylsilyl)oxy)hexahydro-1H-cyclopenta[c]furan-1-one **42***



42

To a solution of the crude acid **42** (4.43 g, 12.5 mmol) from the previous step in benzene (40 mL) at 0 °C was added oxalyl chloride (5.4 mL) followed by DMF (50 μL). The reaction was warmed to RT and stirred for 1 h by which point gas evolution had ceased. The mixture was then concentrated *in vacuo* before being redissolved in $CBrCl_3$ (62 mL). The solution was then added dropwise down the side of reflux condenser over a period of approximately 1 h into a suspension of 2-mercaptopyridine *N*-oxide sodium salt (2.28 g, 15.2 mmol) in $CBrCl_3$ (62 mL) heated to 130 °C (external oil bath temperature). The reaction was stirred for a further 10 min and then cooled to RT and filtered, washing with CH_2Cl_2. The solution was then concentrated *in vacuo*. Purification by flash column chromatography (15:1 petrol:EtOAc) gave the title compound **42** as a white solid (3.74 g, 9.90 mmol, 79%); m.p. 38–40 °C; R_f 0.42 (15:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2944m, 1781s, 1464m; δ_H (400 MHz $CDCl_3$) 5.21 (1H, s, C*H*H'=C), 5.06 (1H, s, CH*H*'=C), 4.85 (1H, d, *J* = 7.7 Hz, C*H*OTIPS), 4.48 (1H, dd, *J* = 9.6, 3.3 Hz, C*H*H'O), 4.38 (1H, dd, *J* = 9.6, 8.0 Hz, CH*H*'O), 3.24 (1H, d, *J* = 16.6 Hz, C*H*H'CBr), 3.21 (1H, td, *J* = 8.0, 3.3 Hz, C*H*CH_2O), 2.94 (1H, dd, *J* = 16.6, 2.0 Hz, CH*H*'O), 1.02–1.18 (21H, m, TIPS); δ_C (100 MHz $CDCl_3$) 175.5 (*C*O), 146.7 (CH_2=*C*), 110.0 (*C*H_2=C), 74.2 (*C*HOTIPS), 65.1 (*C*H_2OR), 53.7 (*C*Br), 53.6 (*C*HCH_2O), 43.6 (*C*H_2CBr), 18.0 (SiCH*Me*$_2$), 12.3 (Si*C*HMe_2); *m/z* LRMS (ESI^+) 411 ($M^{79}+Na^+$, 50) 413 (M^{81}+Na+, 50); HRMS (ESI^+): found 411.0962, 413.0941, $C_{17}H_{29}O_3BrSiNa^+$ ($M+Na^+$), requires 411.0962, 413.0941; $[\alpha]_D^{25}$ -36.8 (*c* = 1.0 in $CHCl_3$).

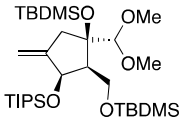
*4.1.44. (1R,2S,3R)-1-(Dimethoxymethyl)-2-(hydroxymethyl)-4-methylene-3-((triisopropylsilyl)oxy)cyclopentan-1-ol **43***



43

To a stirred solution of lactone **42** (3.70 g, 9.50 mmol) in THF (95 mL) at -78 °C was added DIBAL (37 mL, 1 M in hexane, 37 mmol) dropwise. The reaction was stirred for 16 h at -78 °C and then quenched by the addition of MeOH (95 mL). NaOMe (16.9 mL, 25% wt/wt in MeOH, 74 mmol) was added and the reaction was warmed to RT and stirred for 2 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (50 mL) and sat. aq. sat. aq. Rochelle's salt (50 mL). The mixture was vigorously stirred for 1 h and then diluted with H_2O (100 mL) and EtOAc (100 mL). The aqueous layer was separated and extracted with EtOAc (2 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Purification by flash column chromatography (2:1 petrol:EtOAc) gave the title compound **43** as a colorless oil (2.98 g, 7.96 mmol, 84%); R_f 0.34 (2:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 3400br m, 2943w, 1079s; δ_H (400 MHz $CDCl_3$) 5.06–5.08 (1H, m, C*H*H'=C), 4.88–4.90 (1H, m, CH*H*'=C), 4.65 (1H, d, *J* = 5.7 Hz, C*H*OTIPS), 4.18 (1H, s, C*H*$(OMe)_2$), 3.98 (1H, ddd, *J* = 11.5, 7.4, 3.0 Hz, C*H*H'OH), 3.83 (1H, ddd, *J* = 11.5, 9.1, 4.1 Hz CH*H*'OH), 3.74 (1H, s, O*H*), 3.56 (3H, s, O*Me*), 3.49 (3H, s, O*Me*), 3.10 (1H, dd, *J* = 9.1, 3.0 Hz, OH), 2.71 (1H, dt, *J* = 17.2, 2.2 Hz, C*H*H'COH), 2.43 (1H, ddt, *J* = 17.2, 2.0, 0.6 Hz, CH*H*'COH), 2.24 (1H, ddd, *J* = 7.4, 5.7, 4.1 Hz, C*H*CH_2OH), 1.02–1.06 (21H, m, TIPS); δ_C (100 MHz $CDCl_3$) 150.2 (CH_2=*C*), 108.9 (*C*H$(OMe)_2$), 108.2 (*C*H_2=C), 82.5 (*C*OH), 78.1 (*C*HOTIPS), 59.4 (*C*H_2OH), 58.4 (O*Me*), 57.5 (O*Me*), 50.0 (*C*HCH_2OH), 41.4 (*C*H_2COH), 18.1 × (SiCH*Me*$_2$), 12.4 (Si*C*HMe_2); *m/z* LRMS(ESI^+) 397 ($M+Na^+$, 100); HRMS (ESI^+): found 397.2378, $C_{19}H_{38}O_5SiNa^+$ ($M+Na^+$), requires 397.2381; $[\alpha]_D^{25}$ -19.3 (c = 1.0 in $CHCl_3$).

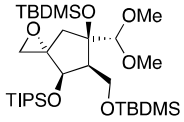
*4.1.45. tert-Butyl(((1S,2R,5R)-2-((tert-butyldimethylsilyl)oxy)-2-(dimethoxymethyl)-4-methylene-5-((triisopropylsilyl)oxy)cyclopentyl)methoxy)dimethylsilane **44***



44

To a solution of diol **43** (2.89 g, 7.72 mmol) in CH_2Cl_2 (38 mL) at -78 °C was added 2,6-lutidine (4.04 mL, 35.0 mmol), and TBSOTf (5.30 mL, 23 mmol). The reaction was then warmed to 0 °C and stirred for 1 h before being quenched with sat. aq. NaHCO3 (50 mL) and diluted with petrol (70 mL). The aqueous layer was separated and extracted with 10:1 petrol:EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Purification by flash column chromatography (20:1 petrol:EtOAc) gave the title compound **44** as a colorless oil (4.65 g, 7.71 mmol, quant); R_f 0.67 (20:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2987m, 1463m; δ_H (400 MHz $CDCl_3$) 4.96–4.99 (1H, m, C*H*H'=C), 4.84–4.87 (1H, m, CH*H*'=C), 4.63 (1H, d, *J* = 6.7 Hz, C*H*OTIPS), 4.19 (1H, s, C*H*$(OMe)_2$), 3.95 (1H, dd, *J* = 10.0, 7.2 Hz, C*H*H'OTBDMS), 3.86 (1H, dd, *J* = 10.0, 6.2 Hz, CH*H*'OTBDMS), 3.53 (3H, s, O*Me*), 3.44 (3H, s, O*Me*), 2.52–2.54 (2H, m, CH_2COTBDMS), 2.28 (1H, q, *J* = 6.7 Hz, C*H*CH_2OTBS), 1.04–1.10 (21H, m, TIPS), 0.89 (9H, s, SiC*Me*$_3$), 0.85 (9H, s, SiC*Me*$_3$), 0.10 (3H, s, Si*Me*), 0.04 (6H, s, Si*Me*), 0.03 (3H, s, Si*Me*); δ_C (100 MHz $CDCl_3$) 152.5 (CH_2=*C*), 110.1 (*C*H$(OMe)_2$), 107.7 (*C*H_2=C), 84.2 (*C*OTBDMS), 75.6 (*C*HOTIPS), 60.0 (*C*H_2OTBDMS), 58.9 (O*Me*), 56.9 (O*Me*), 52.2 (*C*HCH_2OTBDMS), 41.0 (*C*H_2COTBDMS), 26.2 (SiC*Me*$_3$), 26.1 (SiC*Me*$_3$), 18.8 (SiCMe$_3$), 18.4 (SiCH*Me*$_2$), 18.3 (SiCH*Me*$_2$), 12.8 (Si*C*HMe_2), -2.5 (Si*Me*), -2.8 (Si*Me*), -5.2 (Si*Me*), -5.5 (Si*Me*); *m/z* LRMS (ESI^+) 625 ($M+Na^+$, 100); HRMS (ESI^+): found 625.4108, $C_{31}H_{66}O_5Si_3Na^+$ ($M+Na^+$), requires 625.4110; $[\alpha]_D^{25}$ -19.6 (*c* = 1.0 in $CHCl_3$).

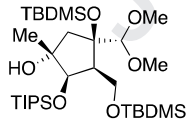
4.1.46. tert-Butyl(((3S,4R,5S,6R)-6-((tert-butyldimethylsilyl)oxy)-6-(dimethoxymethyl)-4-((triisopropylsilyl)oxy)-1-oxaspiro[2.4]heptan-5-yl)methoxy)dimethylsilane ***45***



45

DMDO (80 mL, 0.08 M in acetone, 6.4 mmol) cooled to -20 °C was added to alkene **44** (3.68 g, 6.10 mmol) at RT. The reaction was stirred for 4 h at RT and then concentrated *in vacuo* to approximately 10 mL and then diluted with petrol (90 mL), dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Purification by flash column chromatography (20:1 petrol:EtOAc) gave the title **45** compound as a colorless oil (3.34 g, 5.4 mmol, 88%); R_f 0.32 (20:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2949m, 1471w; δ_H (400 MHz $CDCl_3$) 4.29 (1H, s, C*H*(OMe)$_2$), 4.25 (1H, d, *J* = 7.9 Hz, C*H*OTIPS), 4.00 (1H, dd, *J* = 10.1, 8.2 Hz, C*H*H'OTBDMS), 3.81 (1H, dd, *J* = 10.1, 5.8 Hz, CH*H*'OTBDMS), 3.59 (3H, s, O*Me*), 3.42 (3H, s, O*Me*), 3.06 (1H, d, *J* = 5.0 Hz, C*H*H'OC), 2.72 (1H, d, *J* = 5.0 Hz, CH*H*'OC), 2.42 (1H, ddd, *J* = 8.2, 7.9, 5.8 Hz, C*H*CH$_2$OTBDMS), 2.07 (1H, d, *J* = 14.3 Hz, C*H*H'COTBDMS), 1.97 (1H, d, *J* = 14.3 Hz, CH*H*'COTBS), 1.06 (21H, s, TIPS), 0.89 (9H, s, SiC*Me*$_3$), 0.86 (9H, s, SiC*Me*$_3$), 0.08 (3H, s, Si*Me*), 0.04 (3H, s, Si*Me*), 0.03 (6H, s, Si*Me*); δ_C (100 MHz $CDCl_3$) 108.9 (*C*H(OMe)$_2$), 84.1 (*C*OTBDMS), 75.5 (*C*HOTIPS), 67.1 (CH$_2$O*C*), 59.8 (*C*H$_2$OTBDMS), 59.6 (O*Me*), 56.2 (O*Me*), 51.2 (*C*H$_2$OC), 50.5 (*C*HCH$_2$OTBDMS), 38.4 (*C*H$_2$COTBDMS), 26.2 (SiC*Me*$_3$), 26.1 (SiC*Me*$_3$), 18.9 (Si*C*Me$_3$), 18.4 (Si*C*Me$_3$), 18.2 (SiCH*Me*$_2$), 18.1 (SiCH*Me*$_2$), 12.9 (Si*C*HMe$_2$), -2.8 (Si*Me*), -2.9 (Si*Me*), -5.2 (Si*Me*), -5.4 (Si*Me*); *m/z* LRMS (ESI$^+$) 641 (M+Na$^+$, 100); HRMS (ESI$^+$): found 641.4058, $C_{31}H_{66}O_6Si_3Na^+$ (M+Na$^+$), requires 641.4059; $[\alpha]_D^{25}$ -16.3 (c = 1.0 in $CHCl_3$).

4.1.47. (1R,2R,3S,4R)-4-((tert-Butyldimethylsilyl)oxy)-3-(((tert-butyldimethylsilyl)oxy)methyl)-4-(dimethoxymethyl)-1-methyl-2-((triisopropylsilyl)oxy)cyclopentan-1-ol ***46***



46

To a solution of epoxide **45** (800 mg, 1.29 mmol) in THF (8 mL) was added $LiHEt_3$ (3.87 mL, 1 M in THF, 3.87 mmol). The reaction was stirred for 16 h, and then quenched by the careful addition of sat. aq. NH_4Cl (10 mL), and then diluted with H_2O (20 mL) and petrol (20 mL). The aqueous layer was separated and extracted with petrol (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and then concentrated *in vacuo*. Purification by flash column chromatography (15:1 petrol:EtOAc) gave the title compound **46** as a colorless oil (764 mg, 1.23 mmol, 95%); R_f 0.33 (15:1 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 3485br m, 2948m; δ_H (400 MHz $CDCl_3$) 4.27 (1H, br s, O*H*), 4.16 (1H, s, C*H*(OMe)$_2$), 4.02 (1H, dd, *J* = 4.7, 1.0 Hz, C*H*OTIPS), 3.96 (1H, dd, *J* = 9.9, 6.6 Hz, C*H*H'OTBDMS), 3.77 (1H, dd, *J* = 9.9, 6.6 Hz, CH*H*'OTBDMS), 3.59 (3H, s, O*Me*), 3.51 (3H, s, O*Me*), 2.37 (1H, td, *J* = 6.6, 4.8 Hz, C*H*CH$_2$OTBDMS), 2.13 (1H, dd, *J* = 14.6, 1.0 Hz, C*H*H'COTBDMS), 1.99 (1H, d, *J* = 14.6 Hz, CH*H*'COTBDMS), 1.29 (3H, s, *Me*COH), 1.09–1.14 (21H, m, TIPS), 0.89 (9H, s, SiC*Me*$_3$), 0.85 (9H, s, SiC*Me*$_3$), 0.09 (3H, s, Si*Me*), 0.03 (3H, s, Si*Me*), 0.03 (3H, s, Si*Me*), 0.02 (3H, s, Si*Me*); δ_C (100 MHz $CDCl_3$) 110.7 (*C*H(OMe)$_2$), 84.6 (quat), 83.0 (quat), 81.5 (*C*HOTIPS), 60.4 (*C*H$_2$OTBS), 59.5 (O*Me*), 57.9 (O*Me*), 51.0 (*C*HCH$_2$OTBS), 48.9 (*C*H$_2$COTBS), 26.1 (SiC*Me*$_3$), 22.2 (*Me*COH), 18.6 (*C*Me$_3$), 18.6 (CH*Me*$_2$), 18.6 (CH*Me*$_2$), 18.4 (*C*Me$_3$), 13.5 (Si*C*HMe$_2$), -2.0 (Si*Me*), -2.5 (Si*Me*), -5.1 (Si*Me*), -5.4 (Si*Me*); *m/z* LRMS (ESI$^+$) 643 (M+Na$^+$, 100); HRMS (ESI$^+$): found 643.4213, $C_{31}H_{68}O_6Si_3Na^+$ (M+Na$^+$), requires 643.4216; $[\alpha]_D^{25}$ -8.7 (*c* = 1.0 in $CHCl_3$).

Acknowledgments

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Dedication

Dedicated to Professor Steve Davies, an inspirational teacher and researcher.

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Supplementary Material

^{1}H and ^{13}C NMR of synthetic intermediates. Chiral HPLC traces.

Synthesis of the core of the P-glycoprotein inhibitor pepluanin A reported

Key methods involve selective iodocyclization and invertive acetal formation

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: