Diastereocontrolled Synthesis of Hetero- and Carbocycles via Manganese(III) and Copper(II): Towards a Novel Prostaglandin Total Synthesis

Paul H. Docherty

Trinity College, University of Oxford

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ABSTRACT

Paul H. Docherty, Trinity College, University of Oxford

D.Phil. Thesis

The prostaglandins are a unique family of natural products found in all mammalian life, including humans. Their biological significance is profound, and they are responsible for a vast array of bodily functions. This importance, coupled with their low concentration *in vivo*, has made them attractive targets for total chemical synthesis.

The work herein describes synthetic efforts towards their synthesis using an oxidative radical cyclisation to construct the key [3.3.0]-bridged bicyclic lactone, from which the prostaglandin skeleton may be derived. Key to this was the development of manganese(III) acetate and copper(II) triflate as optimal reagents for this cyclisation of unsaturated malonate/malonic acid derivatives. To study this, several model substrates for this crucial cyclisation were synthesised, and their cyclisation analysed.

Chapter 5 describes the design and synthesis of several model substrates containing malonate groups for the oxidative radical cyclisation. The results of the cyclisation with manganese(III) and various copper(II) salts influenced the design of the substrates, and led to the use of malonic acids as more effective substrates for the formation of [3.3.0]-bicyclic lactones. A catalytic process, in which atmospheric oxygen is the terminal oxidant was also developed.

Chapter 6 describes the studies towards a total synthesis of the prostaglandin family. Two potential routes are followed, the first of which used a key asymmetric epoxidation to install asymmetry. A Suzuki coupling was used to deliver the desired diene required for the cyclisation substrate, which was successfully cyclised using manganese(III) acetate and copper(II) triflate, creating the desired [3.3.0]-bicyclic lactone in good yield and with excellent diastereomeric control. A second, shorter route to the same lactone was also developed, using a novel asymmetric deconjugative aldol condensation to establish asymmetry. Cyclisation of this analogous substrate was also successful, delivering the same lactone after olefin metathesis.

Acknowledgements

I must thank many people for their contributions towards this work, and will start with my academic supervisor. Dr. Jonathan Burton has designed what I feel to be an outstanding project, which I feel privileged to have worked on. His support and unvarying enthusiasm has profoundly changed my attitude towards chemistry, and guided me to career in the science.

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Contents

Abbreviations

Ac	Acetyl	m/z	mass-to-charge ratio
AIBN	Azobisisobutyronitrile	nOe	Nuclear Overhauser effect
Aq.	Aqueous	NOESY	Nuclear Overhauser effect spectroscopy
Ar	Aromatic		
Bn	Benzyl	P	Generic protecting group
Br	Broad	*p*	*para*
Bu	Butyl	PG	Prostaglandin
c	Concentration	Ph	Phenyl
Cat.	Catalytic	PMB	*para*-methoxy benzyl
COSY	Correlated Spectroscopy	PMP	*para*-methoxy phenyl
1D	One Dimensional	ppm	Parts per million
2D	Two Dimensional	PPTS	Pyridinium p-toluenesulfonate
d	Doublet		
DCM	Dichloromethane	Pr	Propyl
dd	Doublet-doublet	PTSA	*p*-toluenesulphonic acid
DEM	Diethyl malonate	Py.	Pyridine
DEPT	Distortionless enhancement by polarisation transfer	q	Quartet
		R	Generic Organic Group
DIBAL-H	Diisobutylaluminium hydride	R_f	Retention factor
		RT	Room Temperature
DMAP	Dimethylaminopyridine	s	Singlet/strong
DMF	*N*,*N*-Dimethylformamide	SAE	Sharpless Asymmetric Epoxidation
DMM	Dimethyl malonate		
DMS	Dimethylsulphide	sat.	Saturated
DMSO	Dimethyl sulphoxide	SET	Single electron transfer
dt	Double-triplet	S_N2	Bimolecular nucleophillic substitution
EDDA	Ethylene diamine diacetate		
eq.	Equivalents	SOMO	Singly occupied molecular orbital
ESI	Electrospray ionisation		
Et	Ethyl	t	Triplet
h	hours(s)	TBAF	Tetrabutylammonium fluoride
HWE	Horner-Wadsworth-Emmons		
		TBDPS	*tert*-Butyldiphenylsilyl
HSQC	Heteronuclear single-quantum correlation	TBS	*tert*-Butyldimethylsilyl
		Tf	Trifluromethanesulphonyl
IR	Infra-Red	TFA	Trifluroacetic acid
J	Scalar coupling constant	THF	Tetrahydrofuran
LAH	Lithium aluminium hydride	t.l.c.	Thin layer chromatography
m	multiplet / medium		
Me	Methyl	TMS	Trimethylsilyl
min	minute(s)	TOCSY	Total correlation spectroscopy
mol	Mole(s)		
m.p.	Melting Point	tol.	Tolene
Ms	Methanesulfonyl	Ts	*para*-Toluenesulphonyl
m.s.	Molecular Sieves	UV	Ultra-violet
MS	Mass spectroscopy	w	Weak
NMR	Nuclear magnetic resonance	% w.t.	% by weight

1 The Prostaglandin Family

1.1 History of the prostaglandins

First discovered by Von Euler in the 1930s,[1] the members of the prostaglandin (PG) family are considered amongst the most important of regulatory biomolecules. Found in the majority of human cells, their high concentration in the prostate and reproductive glands of humans led to their discovery and (erroneously attributed) name. Primarily investigated by Bergstrom *et al.*,[2] the members of the prostaglandin family are based on the parent structure prostanoic acid, **1.1** (Figure 1.1).

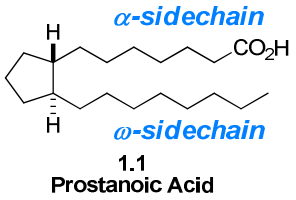


Figure 1.1: Prostanoic Acid

There are ten subclasses of prostaglandin, each differing in chemical functionality, biological activity and synthetic challenge. Prostaglandins *A*-*J* each perform a different role in the human body (selected examples, Figure 1.2). The nomenclature is extended by a subscript (generally *1*-*3*) denoting the number of *exo*-cyclic double bonds present in the class. In the F-class of PGs, a subscript α or β is used to define the stereochemistry at the C-9 position. Further possible structural variations are possible, generally through inversion of a stereocentre, and many such diastereomers

are found to be naturally occurring in other species. The organic chemist has extended this range far further, varying the functionality of the series to produce a variety of synthetic analogues, often for a specific therapeutic purpose.[3]

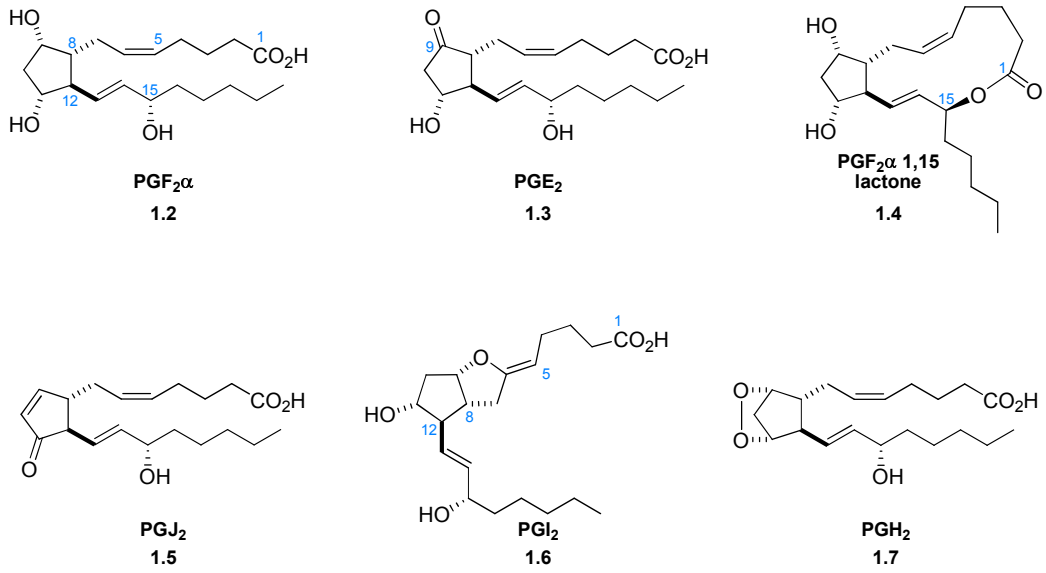


Figure 1.2: Selected members of the prostaglandin family.

The multifarious roles of prostaglandins are frequently contradictory; pairs of variants often have opposing effects when regulating bodily processes. Some of these processes include inflammation, blood clotting, sleep, labour and blood pressure.[4] PGE_2 (**1.3**) is known to induce fever and dilate blood vessels during inflammation, whereas $PGF_{2\alpha}$ (**1.2**) causes vasoconstriction.[5,6] PGD_2, however, is known to eliminate inflammation entirely.[7]

1.2 Biosynthesis

Prostaglandins are biosynthesised on demand; none are stored in the body for any length of time. Whilst this fact precipitated their low concentration *in vitro*, this has not prevented a detailed understanding of the biosynthetic pathway to the series (Figure 1.3).

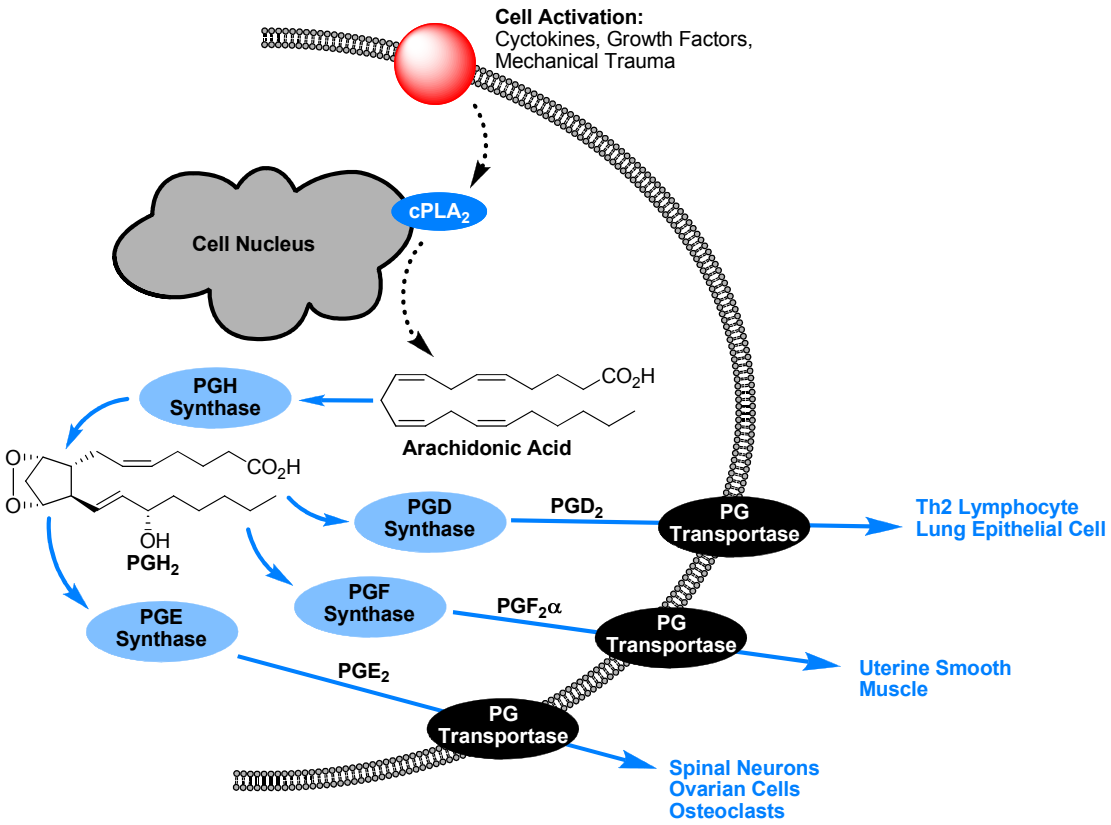


Figure 1.3: Prostaglandins Biosynthesis and Transfer.[8]

Although prostaglandins are found at a low concentration in the body, they are synthesised in almost all cells, on demand at the required site. Prostaglandins act as autocrine and paracrine lipid mediators, acting at or close to the site of biosynthesis.[8] The process can be considered to start with the release of arachidonic acid, from the cell membrane by phospholipase A_2 (PLA_2). The PLA_2 enzyme hydrolyses arachidonic acid ester, a process controlled by a wide variety of PLA_2 enzymes,[9] but generally attributed to type IV cytosolic PLA_2 ($cPLA_2$). This is commonly prompted by mechanical trauma, cytokines, growth factors or inflammatory stimuli, which cause cell-specific and agonist-dependent translocation of the $cPLA_2$ to the nuclear envelope, endoplasmic reticulum (ER) and Golgi apparatus.[10]

At the ER and nuclear membrane, free arachidonic acid released by $cPLA_2$ is presented to prostaglandin H synthase (PGHS, also known as COX -

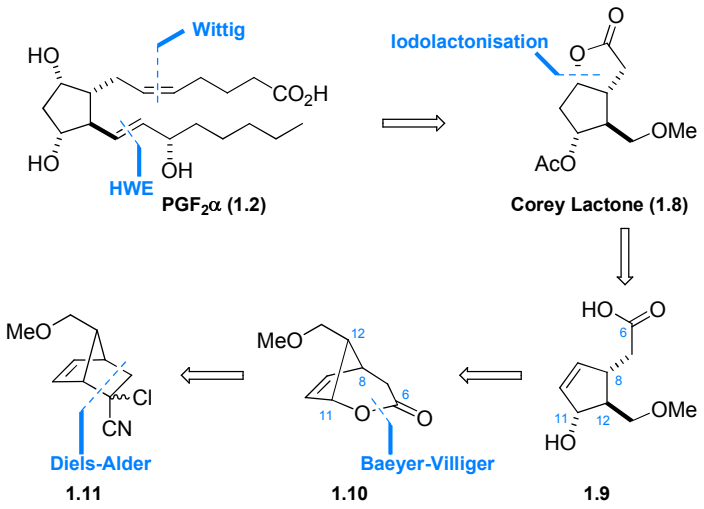
cyclooxygenase),[11] where it is metabolised to prostaglandin H_2 (**1.7**). Coupling of PGH_2 biosynthesis to metabolism by downstream enzymes is cell specific. For example, PGF synthase, responsible for the synthesis of PGF structures from PGH_2, is found only in the uterus, the site of PGF activity, whereas PGE structures are formed *via* microsomal PGE synthase (mPGES).[4]

1.3 Total Synthesis of the Prostaglandins

The prostaglandins have attracted much attention from the synthetic community, owing to their highly functionalised cyclopentane core and impressive biological profile. A multitude of total syntheses of various members of the prostaglandin class have been reported,[12] both in academic and industrial contexts. The field is too vast to review here; however, the syntheses from the groups and Corey, Kobayashi and Shibasaki are discussed below to give context to the results presented in Chapter 6.

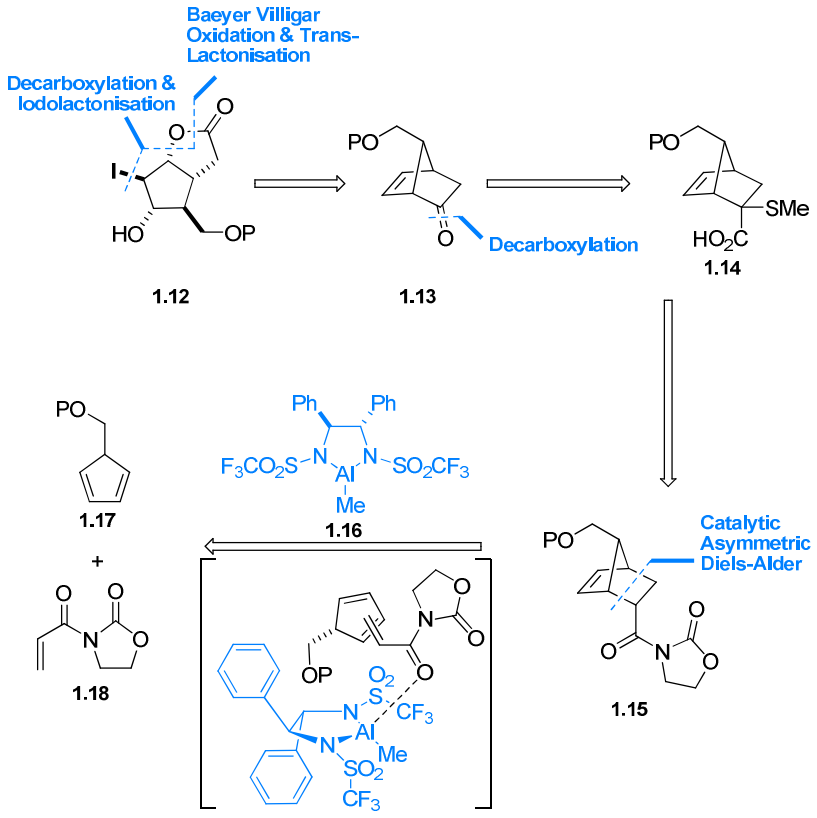
1.3.1 The Corey Synthesis

Acknowledged as a major pioneer of prostaglandin synthesis, E. J. Corey is renowned for his constantly evolving route to these molecules, which encompasses major developments in organic chemistry, such as the use of catalytic asymmetric synthesis.[13] In his seminal 1969 publication, a single resolved precursor was used to develop a key bicyclic intermediate which could be elaborated to the whole prostaglandin family (Scheme 1.1).



Scheme 1.1: Partial retrosynthesis, showing key steps in Corey's route to $PGF_{2\alpha}$.[14]

The key to this synthesis was an early Diels-Alder cycloaddition of a cyclopentadiene with 2-chloroacrylonitrile giving **1.11** and setting three stereocenters in one transformation. The cycloadduct **1.11** was readily transformed into the hydroxyacid **1.9** which underwent iodolactonisation, deiodination and acetylation to complete the synthesis of the so-called "Corey Lactone" (**1.8**), a precursor which has the completed cyclopentane moiety at its core. Elaboration of **1.8** required two olefinations to append the α- and ω- sidechains. Despite some drawbacks, the synthesis itself was groundbreaking, and represents the first total synthesis of a member of the prostaglandin family. Many years and revisions later, Corey published a very elegant alternative route to the lactone **1.12** (an analogue of lactone **1.8**), this time employing a recently developed catalytic asymmetric process (Scheme 1.2).[8,15]



Scheme 1.2: Partial retrosynthesis showing a modernised route to Corey Lactone.[8]

This route again contains a key Diels-Alder reaction early in the synthesis on a protected hydroxymethylenecyclopentadiene. However, in contrast to the former route, Corey used the C_2–symmetric catalyst **1.16**, which allowed an enantioselective synthesis of adduct **1.15** in excellent yield and enantiomeric excess (93%; >95% *ee*, Scheme 1.2.) Following similar procedures to those in Scheme 1.1, Baeyer-Villiger oxidation, saponification and iodolactonisation delivered **1.12**, which can be converted to the prostaglandin series using similar methodology as outlined previously.

1.3.2 The Kobayashi Synthesis

Also notable for his contributions to the field of prostanoid synthesis is Kobayashi, who has published several elegant methodologies relevant to this research area. Most remarkable is his 2002 synthesis of several 11-deoxy prostaglandins using borate nucleophiles.[16] In this work, enantiomerically enriched monoacetate **1.19** was treated with $NiCl_2(PPh_3)_2$, forming a π-allyl complex, which was attacked by borate **1.20**. Hard nucleophiles, such as this borate, attack π-allyl complexes at the metal centre, and following reductive elimination, resulted in the *trans*- product **1.22**.[17]

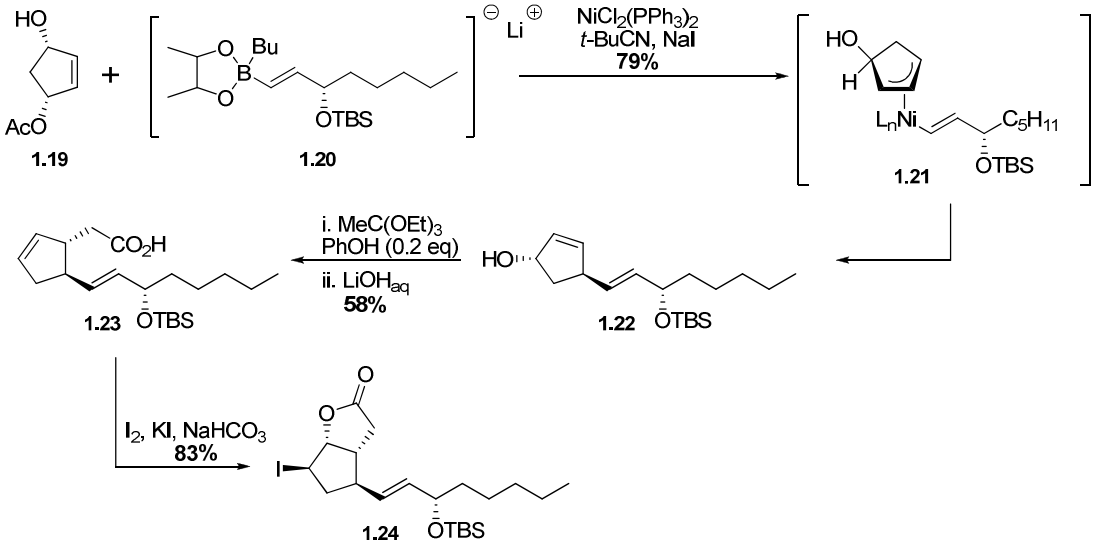
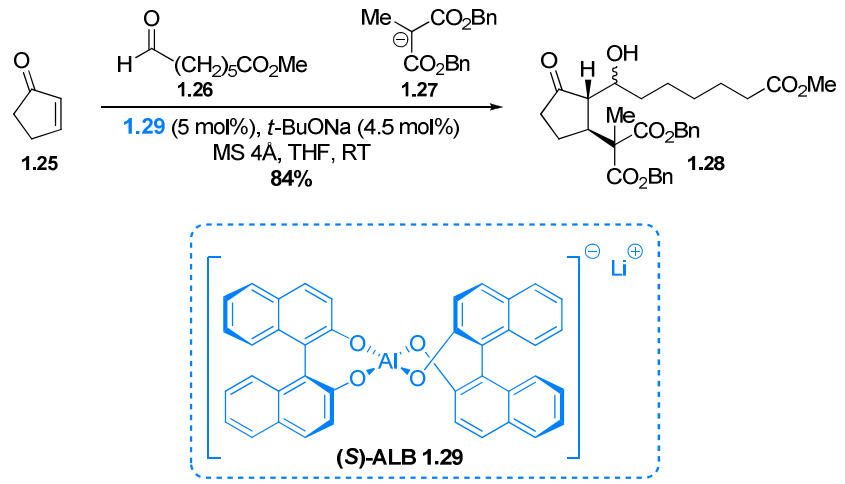


Figure 1.4. Key reactions in the Kobayashi synthesis of 11-deoxy prostanoids.

Cyclopent-2-enol **1.22** was then treated under Johnson-Claisen conditions and the resulting ester hydrolysed to provide acid **1.23**, which upon iodolactonisation gave lactone **1.24**. This advanced intermediate is analogous to lactone **1.12**, and was used to synthesise precursors to 11-deoxy PGE_2 and 11-deoxy PGA_2.

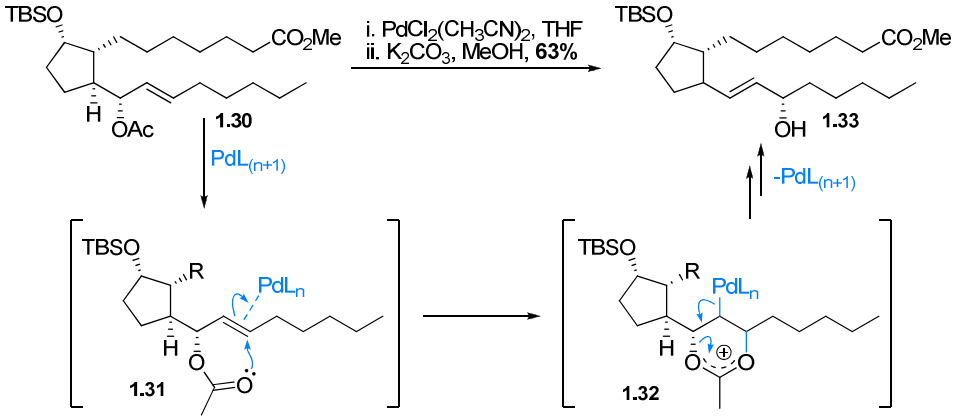
1.3.3 The Shibasaki Synthesis

Shibasaki *et al* used a similar retrosynthesis in their synthesis of 11-deoxy-$PG_{1\alpha}$, performing a three-component coupling on a related cyclopentenone, **1.25** (Scheme 1.3).[18] In contrast, however, they derived asymmetry for this process *via* the chiral aluminium binaphthoxide catalyst **1.29**. This allowed controlled delivery of the methyl dibenzyl malonate anion (**1.27**), and trapping of the enolate onto aldehyde **1.26**.



Scheme 1.3 Catalytic asymmetric three component coupling used by Shibasaki.

To introduce the C-15 stereocentre, Shibasaki used an Overman-type rearrangement to transpose the C-13 acetate in **1.30** (major diastereomer shown) to the required C-15 acetate (Scheme 1.4).[19,20] This reaction proceeds *via* a [3,3]-sigmatropic rearrangement when thermally induced, but in metal catalysed conditions is proposed to occur *via* an acetoxonium ion such as **1.32**..[21]



Scheme 1.4 Overman-type rearrangement of an allylic acetate.

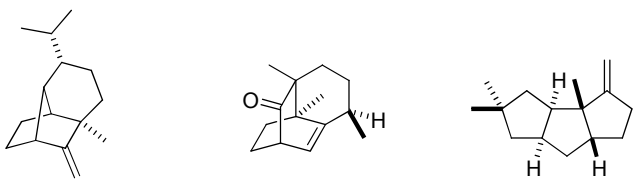
This approach allowed completion of the target with reasonable control over the C-15 stereocentre, which is significant as many previous approaches had relied upon resolution or the chiral pool to establish this allylic stereocentre.

2 Manganese Triacetate Cyclisations

2.1 Radical Reactions

At this point it is pertinent to discuss the general character of radical reactions, and in specific, radical cyclisation methodology. Historically, radical reactions have been a key component of the synthetic chemist's toolkit. In general, radical reactions involve relatively benign reagents, and can often lead more directly to a carbocyclic skeleton without extraneous and elaborate functionalisation compared with traditional ionic reactions. Radical reactions can also exhibit complementary chemoselectivity to their ionic counterparts; this may negate the need for protection of sensitive functional groups, such as hydroxy and amino groups. Some radical reactions are tolerant to water, and thus to wet solvents.

Radical cyclisation reactions have long been used in total synthesis of natural products; early examples include Bakuzis's synthesis of sativene and copacamphene,[22] Stork's syntheses of norseychellanone[23], and Curran's synthesis of hirsutene[24] (Figure 2.1).



copacamphene (2.1) **norseychellanone (2.2)** **hirsutene (2.3)**

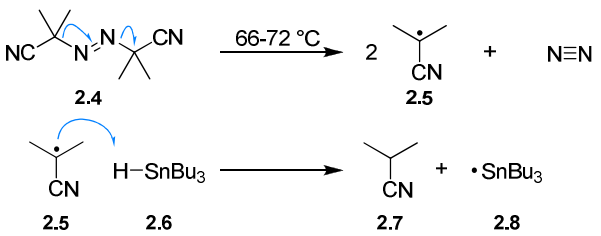
Figure 2.1: Natural products synthesised *via* radical cyclisations.

To be synthetically useful, radical reactions require two fundamental elements; the generation of a reactive entity (initiation), and a controlled sequence of propagation reactions to lead to the desired product.

2.1.1 Radical Generation

Radicals may be generated in a molecule *via* a range of processes, including thermolysis, photolysis, use of radical initiators or a redox system; of these, the last two are most regularly used in organic synthesis.[25] Typically, radical initiators are species with a particularly weak bond, which may be broken easily in a homolytic fashion. This leaves at least two separate products, each a radical. Each of the radicals formed can generate a substrate-based radical, generally by abstraction of a group or atom.

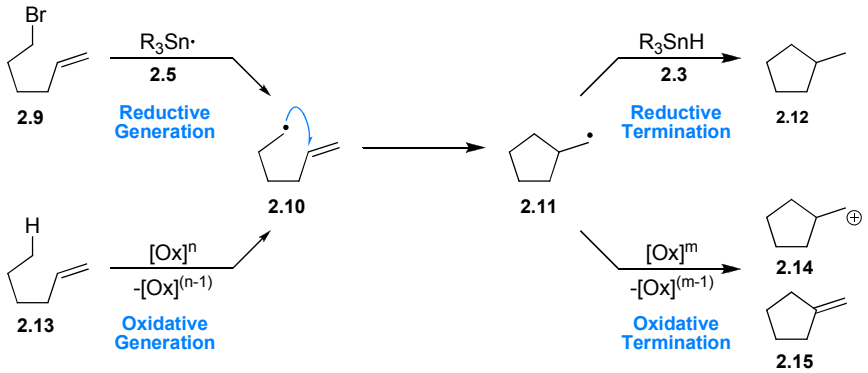
This process is described as *initiation*, and is followed by *propagation* and *termination* steps in the radical process. An example is initiation by thermolysis of the weak C–N single bonds in AIBN (**2.4**), eliminating a molecule of nitrogen gas, and leaving a pair of nitrile-stabilised radicals (**2.5**) (Scheme 2.1). These radicals can then selectively homolyse the weak Sn–H bond in tributyltin hydride (**2.6**), producing a chain-carrying tributyltin radical (**2.8**). Although rather expensive, the initiating species is only used in sub-stoichiometric quantities.



Scheme 2.1: Initiation process for AIBN / Bu_3SnH

The tin radical **2.8** is then capable of interacting with the substrate. In the case of alkyl halide **2.10**, abstraction of the halogen atom then generates substrate-based radical **2.11**, and tributyltin halide by-product (Scheme 2.2). The substrate radical is then capable of regenerating tin radical **2.8** by hydrogen atom abstraction, and leaves the cycle as the reduced alkane. Thus, the cycle continues, as another unit of tributyltin radical has been formed.

Tributyl tin hydride has its flaws as a reagent. It is relatively expensive, highly toxic (as are its by-products), and produces and terminates substrate radicals in a reductive manner. This is shown in Scheme 2.2, where halide **2.9** is reduced by tributyl tin hydride to radical **2.10**. This species then undergoes 5-*exo*-trig cyclisation to generate adduct radical **2.11**, which in the presence of tributyl tin hydride, undergoes a second reduction to give alkane **2.12**.



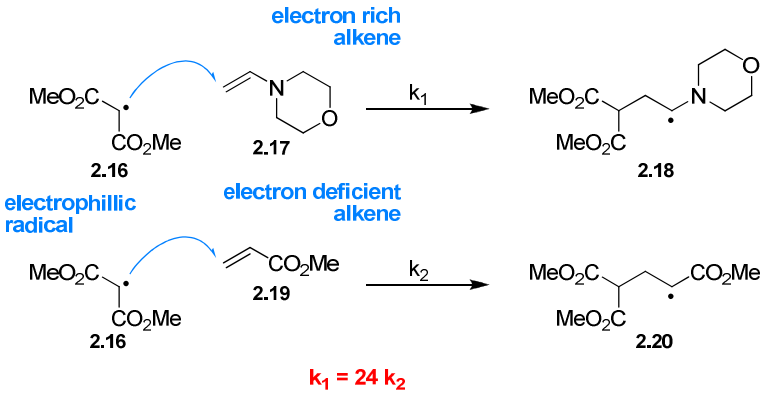
Scheme 2.2: Mechanisms of oxidative and reductive radical generation and termination.

Under oxidative conditions, the same radical **2.10** can be generated *via* hydrogen atom abstraction, leading again to radical **2.11**. Oxidation of **2.11** may occur *via* single

electron transfer, resulting in carbocation **2.14**, which can react with other reagents or groups present to form a more functionalised product, or eliminate a proton to generate an olefin such as **2.15**.

2.1.2 Reaction Control

Generally, 5-*exo*-trig cyclisations are favoured over their 6-*endo*-trig counterparts in due to kinetic considerations,[26] with the stereochemical outcome of these cyclisations being predicted by the models proposed by Houk[27] and Beckwith.[28] The *exo* mode of cyclisation is preferred over *endo* due to its lower entropy of activation and better orbital overlap. Other factors which influence radical reactions include electronic nature of the radical site, and of the intended site of attack. Both nucleophilic and electrophilic radical types exist, and react fastest with electron poor and electron rich alkenes respectively. The nature of the radical generated manifests itself noticeably when comparing the reaction rates of polarity matched radicals and acceptors and the converse (Scheme 2.3).



Scheme 2.3: Electronic nature of various radicals.

2.2 Manganese Triacetate

Manganese(III) acetate generates electrophilic *C*-centred radicals from malonates and related CH-acidic compounds. It is an oxidative radical generator, and has been widely used in organic synthesis.[43] The structure of $Mn(OAc)_3$ is based around an oxo-centred triangle of manganese atoms, with six bridging acetates (Figure 2.2).[29] This structural motif is not unique to manganese(III) acetate, and is common for a number of transition metal acetates.[30]

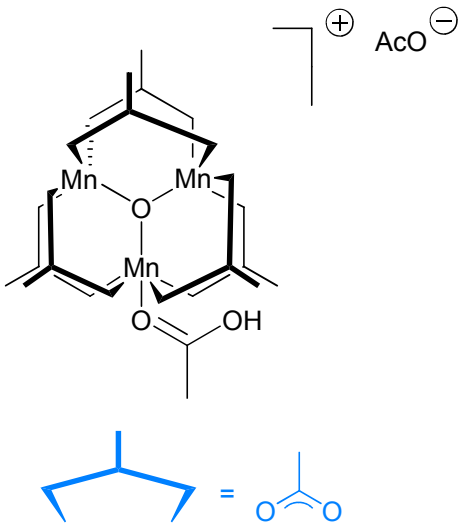
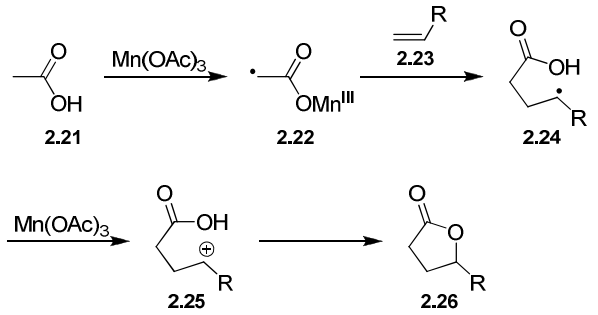


Figure 2.2: Structure of Manganese Acetate.

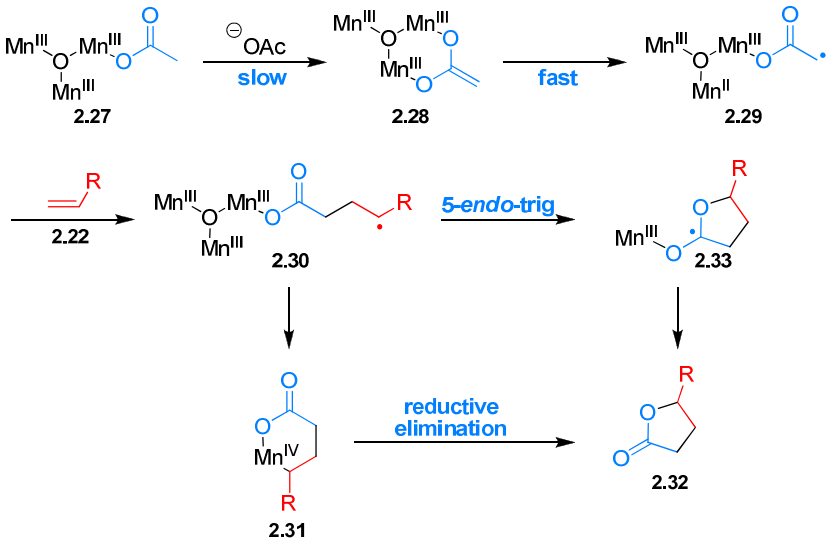
2.2.1 Cyclisation of Carbonyl Compounds

Manganaese(III) acetate was initially used for the synthesis of γ-lactones from alkenes and acetic acids (Scheme 2.4), with the reaction being postulated to occur *via* the mechanism shown.[31,32]



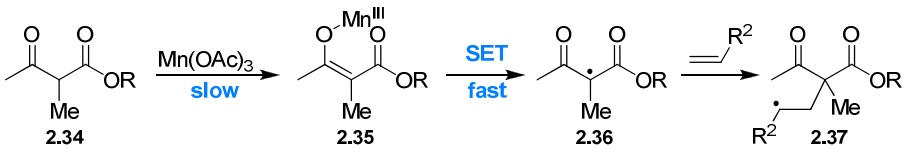
Scheme 2.4: Intermolecular cyclisation of AcOH with alkenes.

This mechanism, however, is unlikely, as in cases where the nature of R should cause rearrangement of the carbocation **2.25**, no such reaction occurs. The alternative mechanism, proposed by Fristad,[33] is thought to begin with formation of the manganese(III) enolate from **2.27** (Scheme 2.5). Deprotonation by an acetate anion (the slow, rate determining step) forms enolate **2.28**, which undergoes fast single electron transfer from one of the manganese centres to give radical **2.29.** Addition to an olefin, such as **2.22** forms the adduct radical **2.30**, from which there are two postulated routes to γ-lactone **2.32**. One involves cyclisation of the adduct radical onto the oxygen atom of the carbonyl group to provide **2.33**, which, following loss of manganese(II), gives **2.32**. This 5-*endo*-trig process, however, is very unlikely due to poor overlap of the radical SOMO with the carbonyl π-system. The other (more likely) possibility is formation of metallocycle **2.31**, and reductive elimination of Mn(II).[34] The adduct radical may also undergo other reactions such as hydrogen atom transfer and polymerisation as lactone formation can be inefficient when manganese(III) acetate is the only oxidant present.



Scheme 2.5: Mechanism of intermolecular cyclisation of AcOH with alkenes.

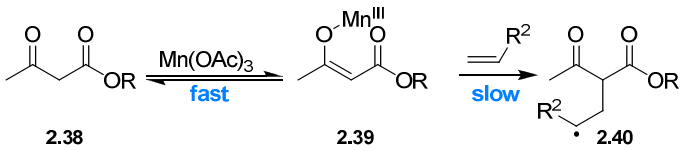
β-Dicarbonyl compounds are commonly used in manganese(III)-mediated reactions. β-Keto esters and malonates have been widely used,[35] and are found to be more readily oxidised than acetic acid because their lower pKa allows more facile enolisation.[36] The mechanism for α-substituted β-dicarbonyl compounds proceeds through a similar mechanism to that with acetic acid (Scheme 2.6).[37]



Scheme 2.6: Intermolecular cyclisation of α-substituted-β-dicarbonyls.

In this mechanism, although faster than in the reaction of alkenes with acetic acid, the rate determining step is the enolisation (leading to Mn(III) enolate **2.35**), as opposed to the electron transfer step, which is relatively fast. This means that the reaction rate is independent of the concentration of alkene, and is also independent of the type of tether used if the reaction is intramolecular.[33]

However, the mechanism for the cyclisation of α-unsubstituted-β-dicarbonyl compounds is different. In this case, enolisation is reversible and fast, with respect to the SET step (Scheme 2.7). The manganese(III) enolate, **2.39** then reacts directly with the alkene to give the adduct radical **2.40**, and the overall rate is dependent upon the concentration of the alkene, or the length of the tether if the reaction is intramolecular. This change in mechanism can be explained as follows; α-substitution decreases the acidity of the α-proton by electron donation and by steric hindrance, in turn decreasing the enolisation propensity.[38]



2.38 **2.39** **2.40**

Scheme 2.7: Cyclisation of α-unsubstituted-β-dicarbonyl compounds.

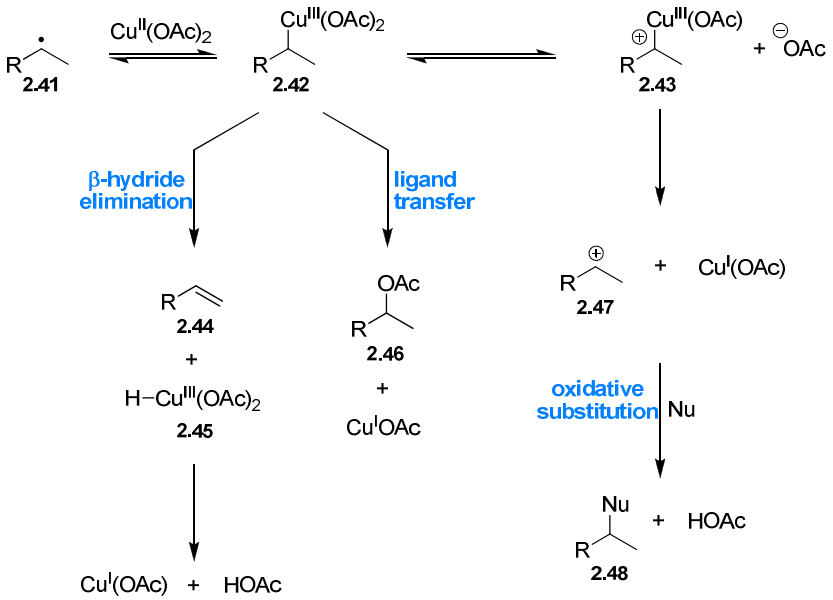
2.2.2 Termination

The fate of the adduct radical intermediate depends on the metal salts present in the reaction mixture, and the solvent system used. In a series of experiments, Mn(III), Ce(IV) and Cu(II) salts were used in reactions between ketones and olefins, leading to γ-keto esters.[39,40]. It was found that manganese(III) acetate can oxidise tertiary or allylic adduct radicals to cations, but not primary or secondary radicals, whereas the other metal salts were capable of performing these oxidations.[41] This is due to a kinetic effect, as manganese(III) is a considerably more powerful oxidant [E_0 = 1.51 V] than copper(II) [E_0 = 0.16 V].[42]

2.2.3 Copper(II) Salts

Because of the limitations of manganese(III), to oxidise primary, secondary or vinylic radicals, a co-oxidant must be present. Because of their enhanced reaction rate, and compatibility with manganese salts, copper(II) salts are often used in this manner. Manganese(III) acetate is able to re-oxidise copper(I) to copper(II), and thus a catalytic quantity of copper may be used when a sufficient quantity of the manganese(III) salt is present.

In the presence of Cu(II) salts, an organocopper(III) intermediate (**2.42**) is formed by the trapping of the adduct radical with Cu(II).[43] Three pathways can then be followed from this intermdiate, as shown in Scheme 2.8. The olefin product (**2.44**) arises by oxidative elimination; only possible if β-hydrogen elimination is possible, whereas ligand transfer or oxidative substitution may also occur. The reaction rates of each pathway vary with the nature of the ligand on copper and the substrate.[44]

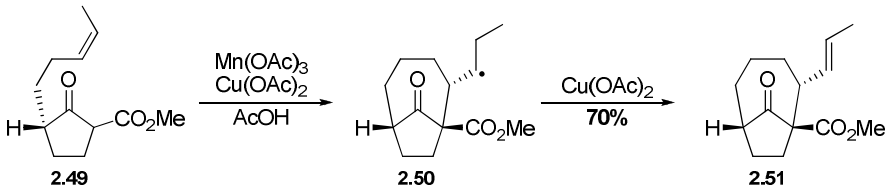


Scheme 2.8: Mechanisms of oxidative termination.

2.2.4 Copper(II) Acetate

The most common choice of copper(II) salt for use with manganese(III) acetate is copper(II) acetate. The acetate ligand strongly coordinates to the metal centre, and studies have shown that copper(II) acetate exists predominately as an undissociated inner-sphere complex.[45] This tight coordination renders co-ordinately unsaturated intermediates such as **2.43** disfavoured, and hence products resulting from oxidative substitution are not favoured and unsaturated products arising from β-hydride elimination tend to be the major products. The oxidation/elimination sequence is under kinetic control, leading to a predominance of the least substituted alkene (Hofmann elimination), with the (*E*)-configured alkene generally predominating.[46]

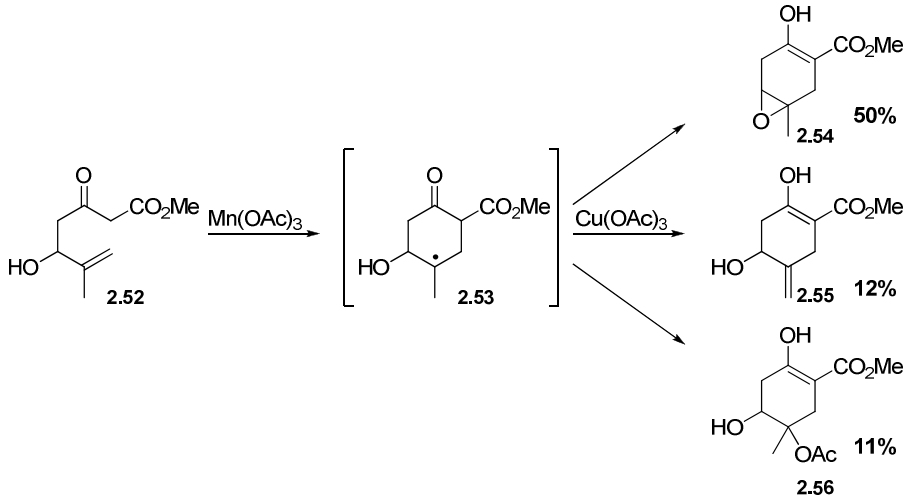
This combination of reagents is very powerful, and has been used by Snider to construct bicyclic olefins such as **2.51** (Scheme 2.9).



Scheme 2.9 Use of manganese acetate and copper acetate in tandem

In this reaction, the radical generated by manganese(III) acetate cyclises in an intramolecular reaction onto the *cis*-olefin *via* a 6-*exo*-trig process. The adduct radical, **2.50**, is then trapped by copper(II) acetate, with β-hydrogen elimination resulting in product **2.51**.

However, should a suitable nucleophile be present, inter- or intramolecular substitution can occur, leading to a more structurally complex product. Snider has shown that oxidative substitution by a β-hydroxyl can result in useful yields of epoxide **2.54** (Scheme 2.10). Other products from this reaction include the β-hydrogen elimination product, alkene **2.55**, and the ligand transfer product, acetate **2.56**.

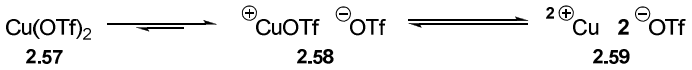


Scheme 2.10: Possible termination of adduct radicals.

2.2.5 Other Copper(II) Salts

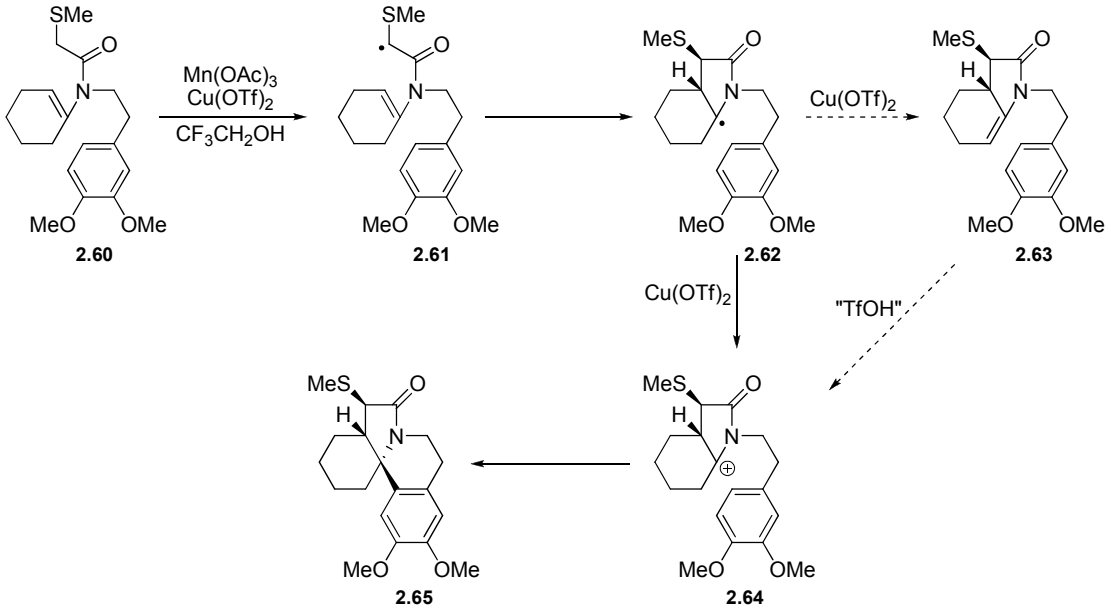
Studies of alkyl radicals generated in the presence of copper salts have shown that the ratio of substitution to elimination products varies according to the copper(II) salt present, when used as co-oxidant, and that the presence of a carbocation stabilising group can greatly increase the proportion of substitution. Copper(II) salts with poorly coordinating ligands, such as triflate or tetrafluoroborate were found to give increased substitution/elimination ratios, as these complexes readily favour the formation of intermediates analogous to **2.43**.[45] This leads to a greater degree of dissociation in the organocopper(III) intermediates, and thus, follows pathways similar to that of **2.43**.

Copper(II) triflate exists predominately as a dissociated salt, **2.58**, and the triflate ligands are bound in the outer co-ordination sphere (Scheme 2.11).



Scheme 2.11 Dissociation of ligands from copper(II) triflate.

Examples of the use of outer-sphere copper complexes in conjunction with manganese(III) acetate are rare; one such result has been published in Ishibashi's synthesis of the erythrinane skeleton.



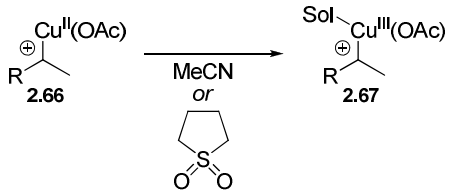
Scheme 2.12 Use of copper(II) triflate in the oxidation of adduct radicals.

Ishibashi's proposed mechanism (Scheme 2.12) for the formation of the 6,5,6-ring system involves oxidation of substrate **2.60** to radical **2.61**. This then attacks the cyclohexene moiety in a 5-*endo*-trig manner, to give adduct radical **2.62**. Ishibashi then proposes that the copper triflate promotes a β-hydrogen elimination to give alkene **2.63**, and that triflic acid produced *in situ* protonates this olefin to give

carbocation **2.64**. However, previous work and the work detailed in this thesis suggest that direct oxidation by copper(II) of **2.62** to the carbocation **2.64** will occur.[47,48]

2.2.6 Solvent Effects

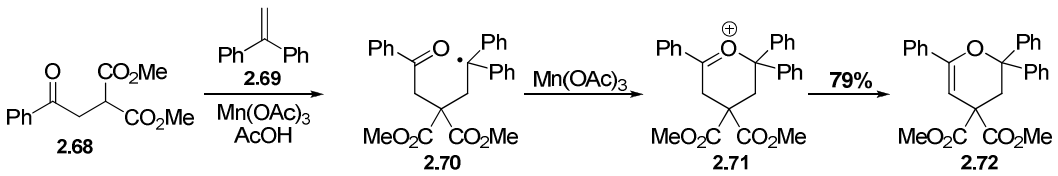
Solvents such as acetonitrile and tetramethylene sulfone also enhance substitution, by stabilising the co-ordinately unsaturated copper(III) species **2.66**. The resulting co-ordinately saturated complex is more stable, and also a more effective leaving group (Scheme 2.13).[44]



Scheme 2.13: Stabilisation of copper(III) intermediates by solvent

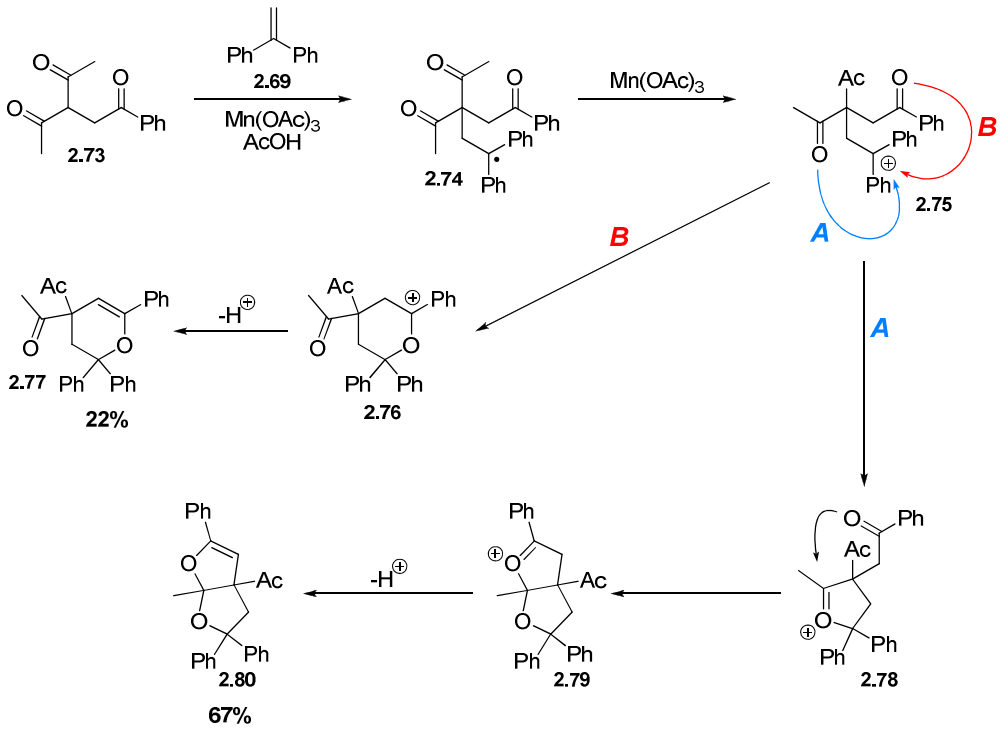
2.2.7 Heteroatom Termination

Key to this project and to other examples in the literature is the generation of more functionalised products by conversion of the adduct radical into a C-X bond i.e. heteroatom trapping. This is particularly desirable in the case of intramolecular reactions, as a heterocycle may be produced. In a relatively simple case, malonate **2.68** was treated with $Mn(OAc)_3$, generating a radical which added across olefin **2.69** (Scheme 2.14). The adduct radical **2.70** was oxidised to the cabocation by $Mn(OAc)_3$, to which the aryl ketone added giving an oxonium ion **2.71** which gave a good yield of dihydropyran **2.72**.[49]



Scheme 2.14: Termination of adduct radicals by heteroatoms.

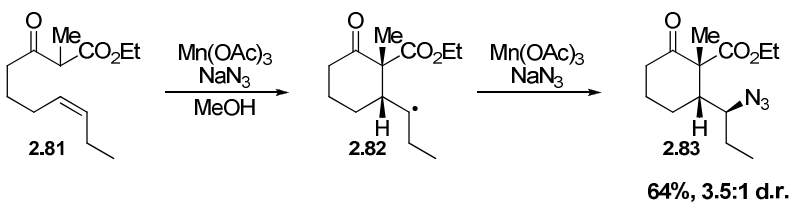
In a more complex example, Nishino *et al*. were able to show a competitive heteroatom termination, where two ketone moieties in the substrate **2.75** were both able to trap a stabilised carbocation. The carbocation was produced *via* Mn(III)-mediated combination of the 1,3 diketone **2.73** and the olefin **2.69** giving the stabilised adduct radical **2.74** which was then oxidised by Mn(III) to give the key carbocation (Scheme 2.15). It was found that trapping of the carbocation by the acetyl group *via* pathway A led to the major product, dioxabicylco[3.3.0]oct-3-ene **2.80**. Intermediate oxonium ion **2.78** is trapped by the aryl ketone to form a second oxonium ion, **2.79**, creating two fused five membered rings. The resulting oxonium ion then loses a proton generating major product **2.80**.



Scheme 2.15: Synthesis of dihydropyrans and dioxabicylco[3.3.0]oct-3-enes.

Snider has also shown that termination by trapping with hydroxyl groups is also possible as discussed previously (Scheme 2.10)

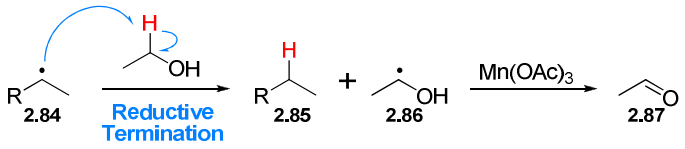
Snider has shown that intermolecular heteroatom termination by azide is also possible. In this example, manganese(III) acetate was used to generate an acetoacetyl radical which trapped onto the olefin in an intramolecular reaction. The resulting adduct radical is then oxidised by a second unit of manganese(III) acetate, which undergoes oxidative substitution by azide.[50]



Scheme 2.16: Trapping of azide by cabocations.

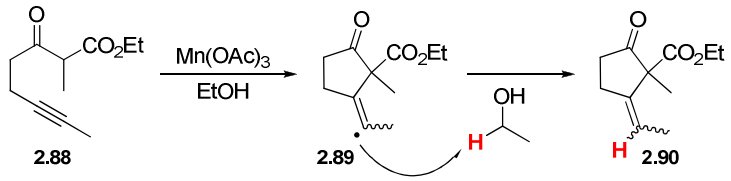
2.2.8 Reductive Termination

A third termination pathway has also been observed – that of reductive termination. In this case, the adduct radical abstracts a hydrogen atom from other species present, typically solvent or the parent substrate. Particularly good yields of product derived from reductive termination have been achieved when using ethanol as the solvent, as the hydroxyl group stabilises the resulting radical **2.86**, which in itself is oxidised by $Mn(OAc)_3$ to acetaldehyde **2.87** (Scheme 2.17).



Scheme 2.17: Mechanism of reductive termination.

An example of this pathway in synthesis comes from Snider's study of the addition of acetoacetyl radicals onto acetylenes (Scheme 2.18).[51] In this scheme, radical generation on substrate **2.88** resulted in 5-*exo*-dig cyclisation to give vinyl radical adduct **2.89**. As oxidation of vinyl radicals by Mn(III) (and by Cu(II)) is inefficient, reductive termination occurs to give olefin **2.90**.



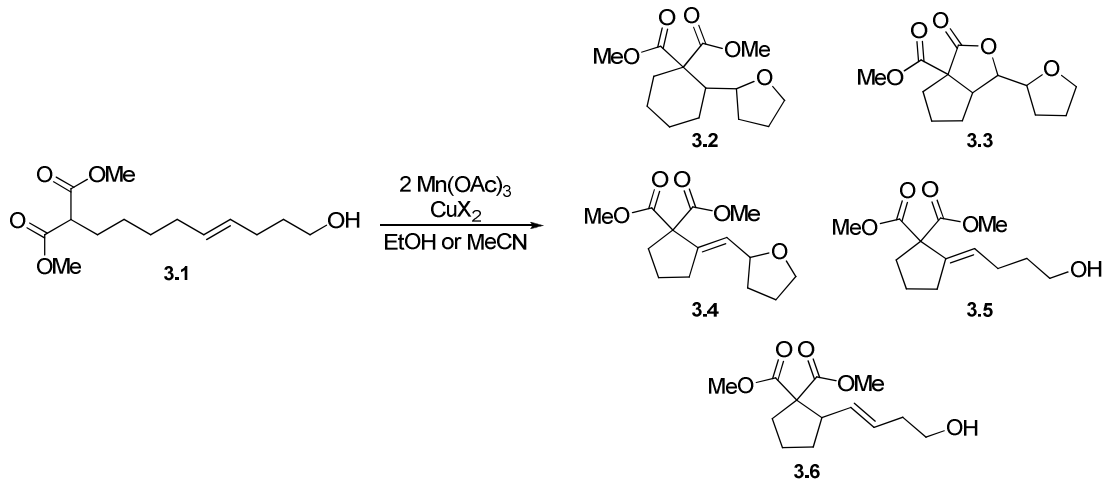
Scheme 2.18: Example of reductive termination using ethanol.

2.3 Summary

The studies outlined highlight the breadth of chemistry possible using manganese(III) acetate. A number of C-H acidic compounds undergo oxidiation by manganese(III) and a diverse array of products may be formed depending on the reaction conditions. Whilst the mechanisms of radical generation discussed above are generally accepted, the mechanisms of oxidation of the adduct radicals and in particular oxidative substitution are less well understood. Although the role of copper(II) acetate in conjunction with manganese(III) acetate is well precedented, few example of the use of other copper salts have been documented, and this area deserves further attention.

3 Previous Work

Previous work within our laboratory has shown that exposure of unsaturated malonate derivatives such as **3.1** to manganese(III) acetate and copper(II) salts can give rise to a variety of products (**3.2**-**3.6**, Scheme 3.1), with the ratio of products dependent upon the nature of the copper(II) additives used (Table 3.1).[47,48]

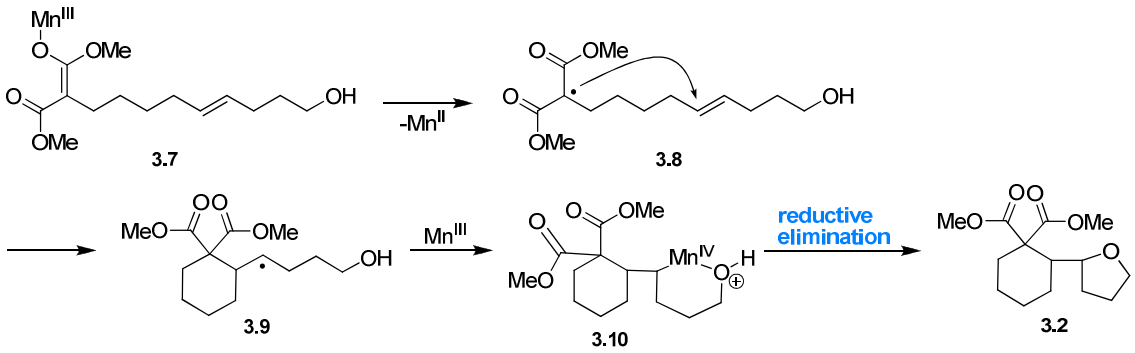


Scheme 3.1: Product mixture from $Mn(OAc)_3/CuX_2$ cyclisation of unsaturated malonates.

Expt.	Solvent	Co-oxidant	Reaction Time	**3.1** %	**3.2** %	**3.4** %	**3.3** %	**3.5** %	**3.6** %
1	MeCN	$Cu(OAc)_2$	72 h	53	35	7	-	-	-
2	EtOH	$Cu(OTf)_2$	3 h	53	45	19	-	-	-
3	MeCN	$Cu(OTf)_2$	48 h	0	40	22	**10**	9	8
4	MeCN	$Cu(BF_4)_2$	30 h	0	51	9	**15**	6	6
5	MeCN	$Cu(ClO_4)_2$	48 h	0	47	14	**15**	10	-
6	MeCN	$Cu(SbF_6)_2$	12 h	0	47	2	**4**	6	-

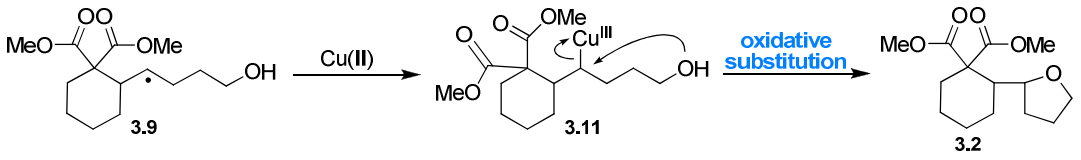
Table 3.1: Products from cyclisation of 3.1, highlighting lactone 3.3.

A diverse range of products are formed under the reaction conditions and the mechanisms of product formation will be discussed below. The ether **3.2** is formed in reasonable yield in the presence or absence of copper(II) additives. The postulated mechanism for formation of **3.2** begins with the expected 6-*exo*-trig cyclisation of the edduct radical derived from the substrate **3.1** onto the double bond to give free radical **3.9**. A possible pathway to **3.2** is formation of a Mn(IV) metallocycle **3.10**, from which reductive elimination gives **3.2** (Scheme 3.2).



Scheme 3.2: Postulated mechanism for formation of 3.2 in the absence of CuX_2.

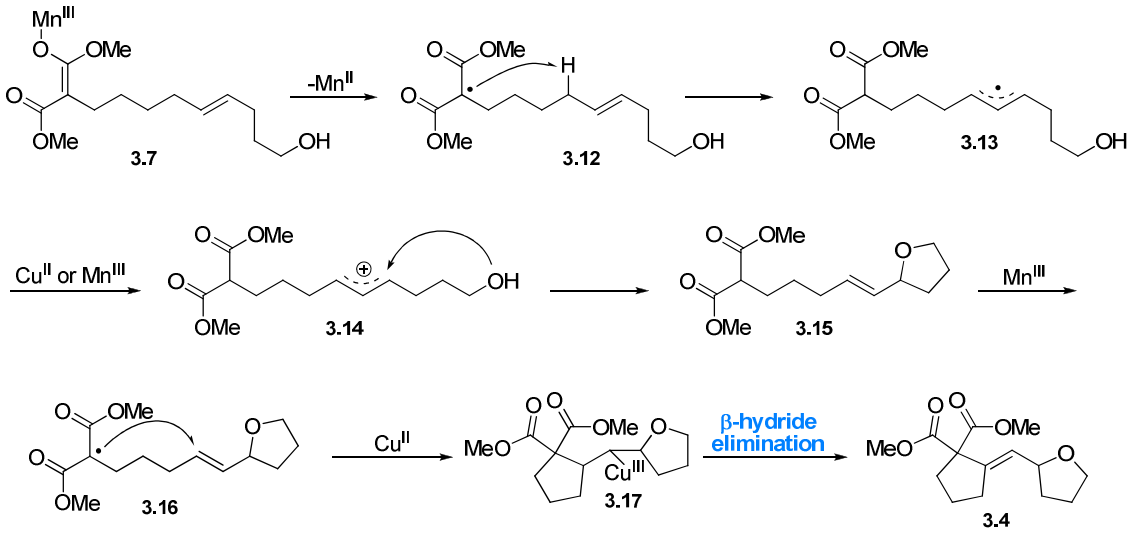
However, Cu(II) may play a role in product formation when present, since the yield of **3.2** increases as the ligands on the copper salt become less coordinating (AcO^- > TfO^- > ClO_4^- > BF_4^- > SbF_6^-) although this is a relatively minor effect. Thus, an alternative mechanism is possible (Scheme 3.3).



Scheme 3.3: Alternative mechanism for formation of 3.2 with CuX_2.

In this mechanism, adduct radical **3.9** is formed as before, and is oxidised to **3.11** by copper(II). Oxidative substitution of copper(III) by the pendant alcohol and loss of a proton then provides tetrahydrofuran **3.2**.

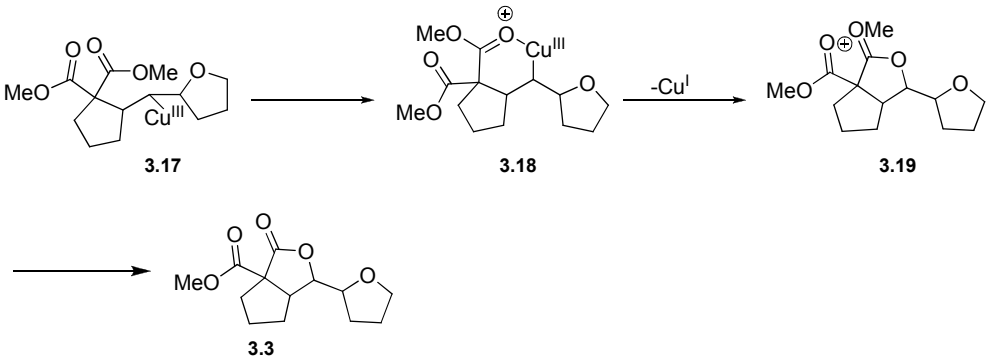
Unsaturated ether **3.4** is most likely formed by a rather different mechanism, in which the initial malonate free radical performs a 1,5-hydrogen atom abstraction, leaving an allylic free radical which is oxidised to the corresponding allylic cation (**3.14**) by Cu^{II} or Mn^{III}. The pendant alcohol then traps the cation to form tetrahydrofuran, **3.15** (in preference to the less favoured 7-membered ring). The intermediate **3.15** is oxidised by $Mn(OAc)_3$ for a second time to form free radical **3.16**, which preferentially undergoes 5-*exo*-trig cyclisation, giving the corresponding adduct radical, which rapidly reacts with Cu(II) generating the Cu(III) intermediate **3.17**. β–Hydride elimination from **3.17** finally leaves the alkene **3.4** (Scheme 3.4).



Scheme 3.4: Mechanism for formation of unsaturated tetrahydrofuran 3.4.

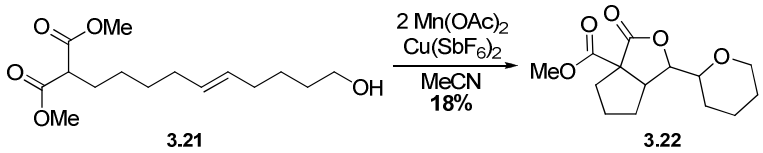
Most relevant to this project was the formation of lactone **3.3**, which was formed in rather poor yield. The lactone formation step is thought to proceed *via* copper(III)

intermediate **3.18**. Generally, Cu(II) salts with less coordinating ligands (other than $Cu(SbF_6)_2$) gave improved yields of the lactone **3.3**.



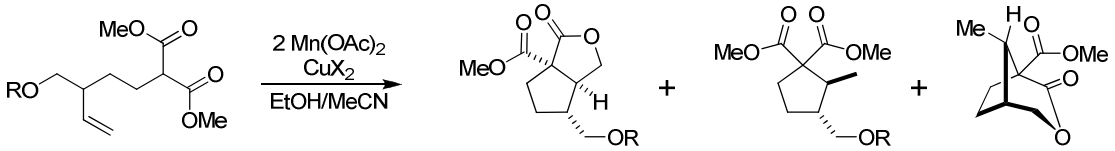
Scheme 3.5: Mechanism for the formation of lactone 3.3.

Similar results were observed with the analogous substrate, **3.21** (Scheme 3.6), presumably *via* a similar mechanism to that in Scheme 3.5.



Scheme 3.6: Analogous results.

Far better yields of lactone were achieved using substrates **3.23** and **3.24**, which contain a terminal olefin (Scheme 3.7, Table 3.2) which may account for the increased lactonisation efficiency. In the case in which a free alcohol is present in the substrate, a small amount of bicyclic lactone **3.29** was observed, presumably formed by transesterification from cyclopentane **3.28**. Conversely, in the case where R is a silyl protecting group (**3.23**), bicyclic lactone **3.29** cannot form, and thus does not feature in the product mixture.



3.23 R = TBDPS
3.24 R = H

3.25 R = TBDPS
3.26 R = H

3.27 R = TBDPS
3.28 R = H

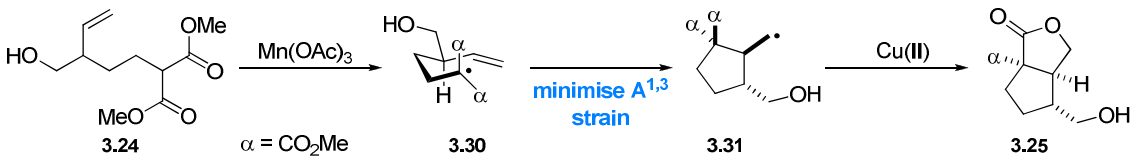
3.29

Scheme 3.7: Analogous results with terminal alkenes.

Expt.	Substrate	Solvent	Co-oxidant	**3.25** %	**3.27** %	**3.29** %
7	**3.23**	MeCN	$Cu(BF_4)_2$	64	9	0
8	**3.23**	MeCN	$Cu(OTf)_2$	52	0	0
9	**3.23**	EtOH	None	76	0	0
Expt.	Substrate	Solvent	Co-oxidant	**3.26** %	**3.28** %	**3.29** %
10	**3.24**	MeCN	$Cu(BF_4)_2$	60	0	0
11	**3.24**	MeCN	$Cu(OTf)_2$	51	0	0
12	**3.24**	EtOH	None	20	48	17

Table 3.2: Product distribution from cyclisation of substrates 3.23 and 3.24.

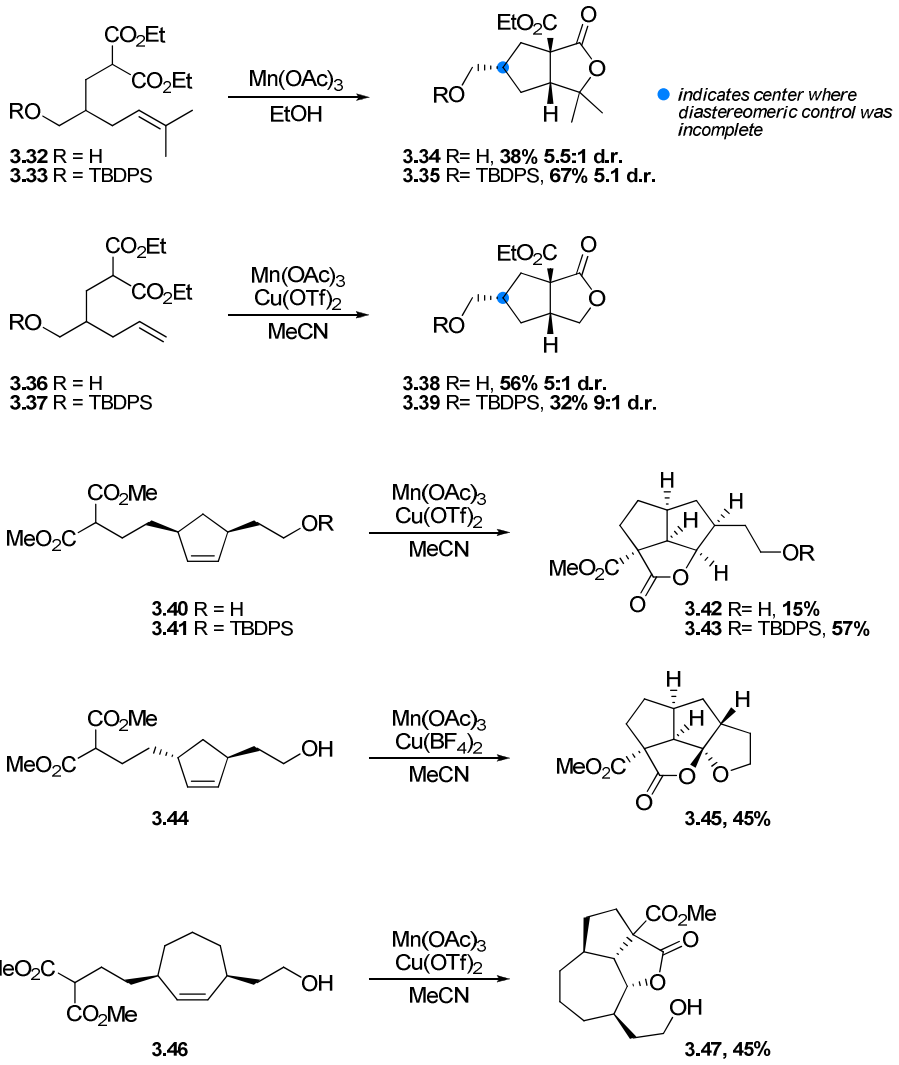
The cyclopentanes **3.27** and **3.28** are clearly formed by reductive termination, which is negligible when using copper salts. Tetrahydrofurans were also formed by cyclisation of **3.24**, but use of a silyl protecting group on the hydroxyl (as in **3.23)** prevented this. Lactones **3.25** and **3.26** were produced in good yield, and with complete diastereoselectivity for a *trans*- relationship between the ring junction and the hydroxy-methyl group. The Houk-Beckwith model predicts that the initial cyclisation occurs *via* a chair conformation accounting for the observed stereoselectivity (Scheme 3.8).[27,28]



Scheme 3.8: Application of Houk-Beckwith model for 5-*exo*-trig radical cyclisations.

Malonate radical **3.30** is produced from the substrate **3.24** by the action of manganese(III) acetate as before. 5-*exo*-Trig cyclisation then occurs from the chair conformation shown giving the primary adduct radical **3.31**, which undergoes Cu(II) oxidation, and lactonisation as before to produce lactone **3.25**.

Further examples of lactone formation from a variety of substrates are illustrated in scheme 3.9. In each case, the system (e.g. solvent, copper salt) with best yield of lactone is shown, although many other reaction conditions were screened. Although lactones were not always produced in particularly high yields, it is anticipated that further studies would allow optimisation of these reactions to give good yields of lactone-containing products.

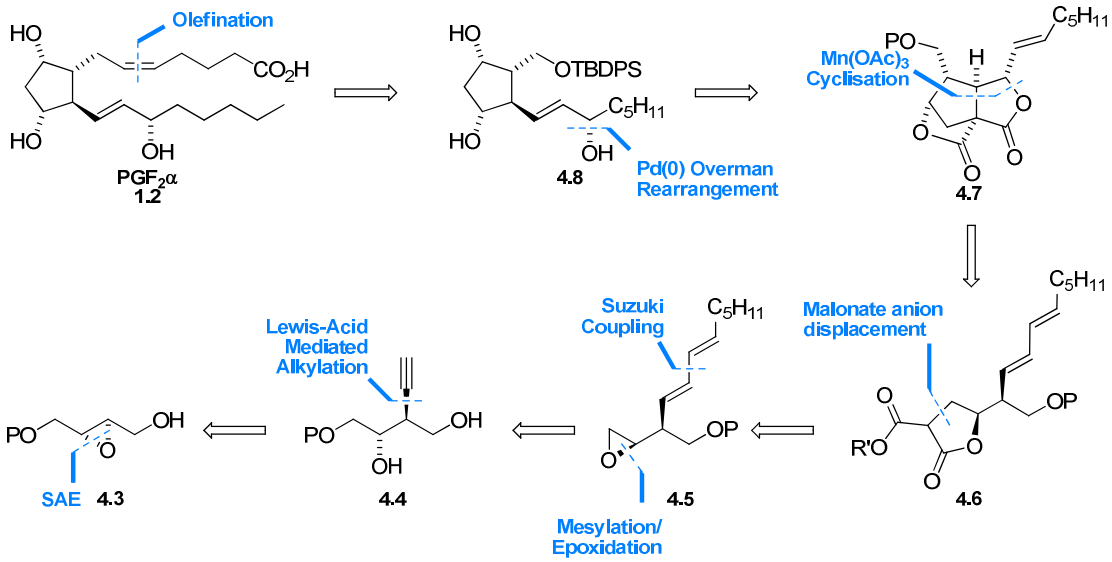


Scheme 3.9: Selected examples of lactone formation.

4 Aims & Synthetic Strategy

4.1 Proposed Synthesis of the Prostaglandin Family

Synthesis of lactones by the procedure shown previously should allow a novel route to the prostaglandin skeleton, and is the subject of the second phase of this project. The retrosynthetic analysis of the prostaglandins is shown below.



Scheme 4.1 Retrosynthetic analysis of total synthesis strategy

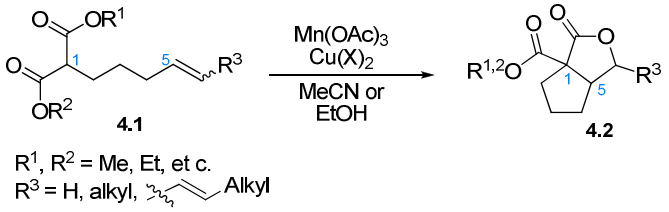
Sharpless asymmetric epoxidation[52] of mono-protected (*E*)-butene diol will give the enantioenriched epoxide **4.3**. Opening of the epoxide with an aluminium acetylide following the procedure of Miyashita[53] will provide diol **4.4** (Scheme 4.1). After hydroboration of the acetylene, Suzuki coupling[54] with a suitable vinyl halide partner (containing the ω-sidechain) will install the requisite diene functionality. Tosylation

and epoxide formation will give **4.5**, which when treated with dimethyl malonate anion will leave **4.6**, the desired cyclisation substrate.

Treatment of 1,3-dicarbonyl substrate **4.6** with manganese(III) acetate will allow cyclisation to form the [3.3.0] tricyclic lactone **4.7**, in which three new stereocenters will have been generated with diastereocontrol being predicted using the Houk-Beckwith model.[27,28] The allylic lactone moiety will then undergo transfer of stereochemistry using an Overman rearrangement to provide the C-15 hydroxyl group.[55] The malonate will be oxidatively cleaved using lead(IV) acetate, which on reduction will provide the C-11 hydroxyl group. Deprotection of the primary hydroxyl will then allow oxidation and olefination to append the α-sidechain, providing the general prostaglandin skeleton.

4.2 Methodology Development

To effect the total synthesis outlined above, it will be necessary to further develop the methodology for the synthesis of γ-lactones using manganese(III) acetate. The results detailed in the preceding chapter illustrate progress towards suitable conditions for the cyclisation of unsaturated malonates to produce a variety of complex carbo- and heterocycles. However, it is expected that optimisation of these conditions towards lactone-bearing products will allow an efficient synthesis of these molecules. Thus, a variety of substrates will be constructed, and the optimised cyclisation conditions developed in this first phase of the project.



Scheme 4.2: Structural motif of cyclisation substrates

As shown in Scheme 4.2, the substrate will be constructed such that the olefin is separated from the malonate group by three methylene units, allowing facile 5-*exo*-trig cyclisation. The effect of different alkyl malonates should be tested, along with the possibility of unsymmetric malonates, in which $R^1 \neq R^2$.

Of critical importance to this project is the study of substitution on the olefin. Study of terminal olefins should be continued, along with a variety of 1,2-disubstituted olefins. The geometry of such olefins should also be varied. Lastly, and most importantly for the anticipated total synthesis of the prostaglandin family, substrates containing dienes should also be studied. Once such studies have been completed, and conditions for cyclisation optimised, synthesis of the prostaglandin family will commence.

5 Synthesis of Bicyclic [3.3.0] Lactones

5.1 Terminal Olefin Substrates

5.1.1 Retrosynthesis of Terminal Olefin Substrates

As detailed above, previous work had already shown that malonate **3.23** could cyclise to give lactone **3.25**. It was anticipated that increasing the electron donating ability of the malonate esters could favour the formation of oxocarbenium ion **5.3** (Figure 5.1), and thus favour the formation of lactone products. Substrate **5.1** was therefore designed to contain a diethyl malonate moiety whose cyclisation could be compared with that of **3.23**.

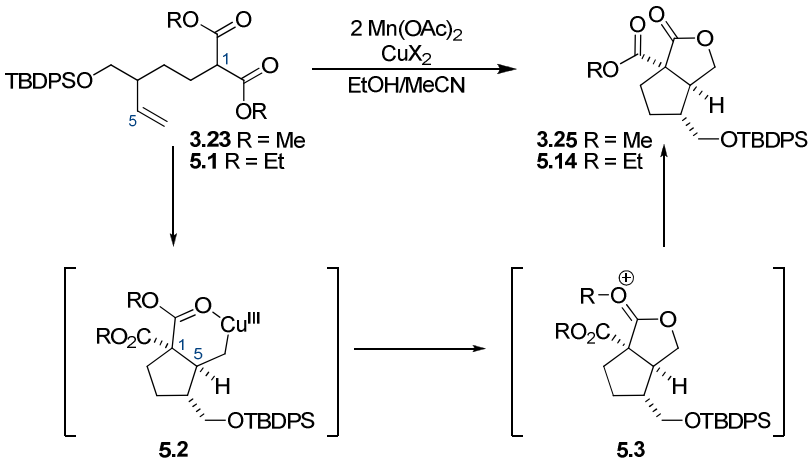


Figure 5.1: Proposed stabilisation of oxocarbenium ion by alkyl group.

Retrosynthetic analysis of substrate **5.1** shows that disconnection of a dialkyl malonate reveals a primary alcohol, **5.5** (Figure 5.2). This can be introduced by

reduction of ethyl ester **5.6**, a product of the Johnson-Claisen rearrangement of mono-protected butene-1,4-diol **5.7** and triethylorthoacetate (**5.8**). Although the geometry of olefin in **5.7** is undefined, this is of no consequence, as the Johnson-Claisen rearrangement results in a terminal olefin.

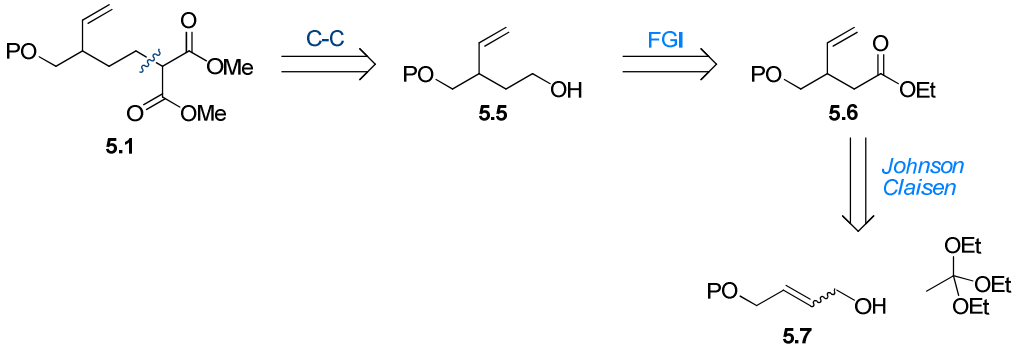
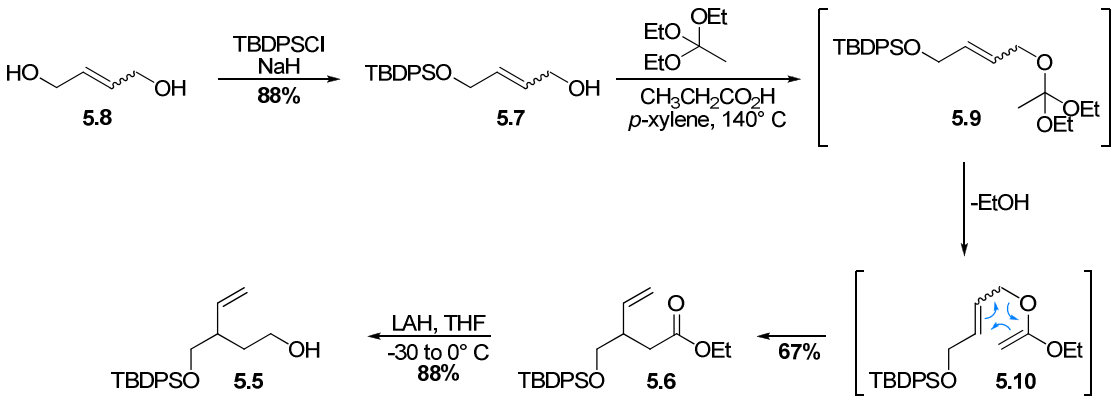


Figure 5.2: Retrosynthesis of terminal olefin substrate 5.1

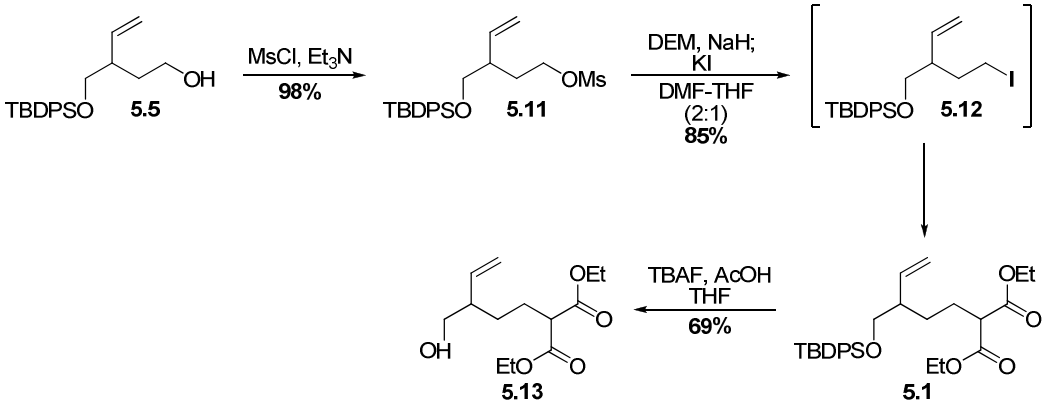
5.1.2 Synthesis of Terminal Olefin Substrates

Synthesis of this substrate commenced with McDougal mono-protection of commercially available butene-1,4-diol.[56] Sodium hydride was used to generate a suspension of the mono-sodium salt of butene-1,4-diol in THF; TBDPSCl was then added to generate the mono-protected diol **5.7** in greater than statistical yield (Scheme 5.1) . The monoprotected diol was then heated to reflux (140 °C) in *para*-xylene with triethylorthoacetate and a catalytic quantity of distilled propionic acid. This led to the formation of a the corresponding orthoacetate, which after elimination of ethanol allowed [3,3]-sigmatropic rearrangement to give the desired ethyl ester.[57] Reduction of the ethyl ester then proceeded using lithium aluminium hydride (powder or suspension in THF) to give the primary alcohol **5.5**. The LAH reduction was found to be very batch-dependent; some commercial LAH was found to be considerably more potent and was capable of removing the silyl protecting group. The over-activity of such batches could be counteracted by cooling the reaction further to -30 °C.



Scheme 5.1: Synthesis of primary alcohol 5.5

With desired primary alcohol **5.5** in hand, a protocol similar to the one used in previous work was envisaged for the formation of the malonate **5.1**, involving transformation of the free hydroxy group into an iodide, providing a good leaving group.[48] However, transformation of alcohol **5.6** into an iodide led to rapid elimination and loss of the required functionality. Alcohol **5.5** was therefore first converted to mesylate **5.11** using methane sulfonyl chloride and triethylamine (Scheme 5.2).[58] This reaction was essentially quantitative, and the product was used directly in the displacement reaction.



Scheme 5.2 Completion of terminal olefin substrate synthesis

The mesylate group was then to be displaced by the anion of diethyl malonate. It was found in an analogous case that the solvent used in this reaction was critical – a polar, aprotic solvent such as DMF was required for anion solubility, but gave a poor yield of the product.[48] Optimisation of solvent conditions led to a favoured ratio of 2:1 DMF:THF. An excess of anion was generated to reduce dialkylation, which was also found to be a problem in analogous systems. If a catalytic quantity of potassium iodide was included in the reaction mixture, the displacement was found to be higher yielding.[59] Presumably this involves formation of a small quantity of iodide **5.12** which is subsequently displaced by the diethyl malonate. The malonate **5.1** could then be functionalised further by removing the silyl protecting group with buffered TBAF in THF, thus generating a third substrate, **5.13**.[60]

5.2 Cyclisation of Terminal Olefin Substrates

Cyclisation conditions previously developed in the group were applied to these substrates. The product mixtures were first analysed by crude NMR, and then separated by flash column chromatography for further analysis.

Cyclisation of substrates (**5.1**, **5.13**) was carried out using the same conditions used previously for dimethyl malonate analogue **3.23**. As shown in Table 4.1, the yield of lactones **5.14** and **5.16** was moderate and comparable to that formed by cyclisation of **3.23**. These lactones were formed as a single diastereoisomer in each case most probably reflecting the favoured Houk-Beckwith chair-like transition state for cyclisation which places the alkoxymethyl group in a *pseudo*-equatorial position.[27,28]

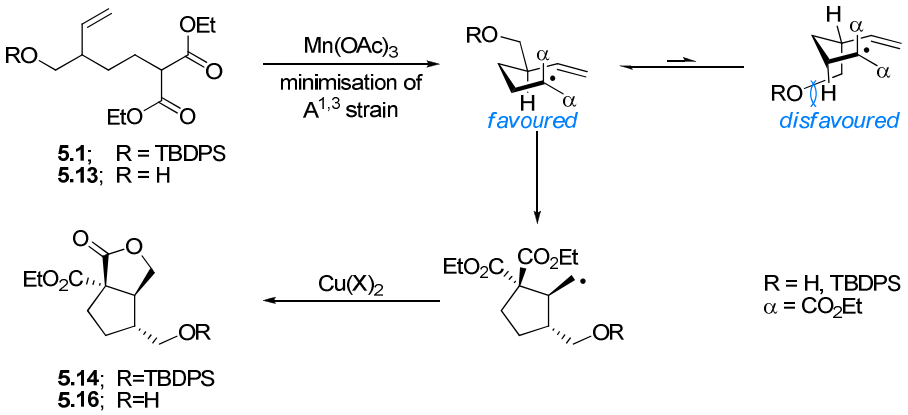
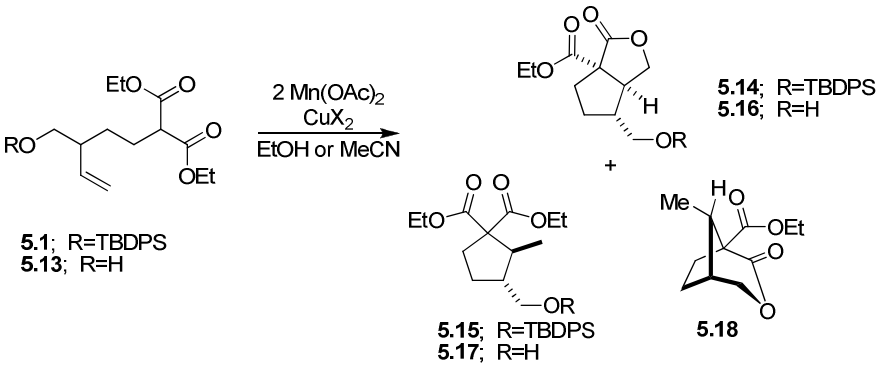


Figure 5.3: Postulated Houk-Beckwith model for cyclisation.

It is perhaps interesting that the relatively small hydroxymethyl group is as capable of controlling this cyclisation as the more bulky TBDPS protected analogue.



Scheme 5.3: Products resulting from cyclisation of 5.1 and 5.13.

Expt.	Substrate	Solvent	Co-oxidant	**5.15** %	**5.18** %	**5.14** %
13	**5.1**	EtOH	None	0	0	21
14	**5.1**	EtOH	$Cu(OTf)_2$	0	0	55
15	**5.1**	MeCN	$Cu(OTf)_2$	0	0	34
Expt.	Substrate	Solvent	Co-oxidant	**5.17** %	**5.18** %	**5.16** %
16	**5.13**	EtOH	None	0	0	28
17	**5.13**	EtOH	$Cu(OTf)_2$	0	0	40
18	**5.13**	MeCN	$Cu(OTf)_2$	0	0	56

Table 5.1: Results of cyclisation experiments of substrates 4.2 and 4.1.

As expected, no bridged, bicyclic lactone **5.18** was detected when substrate **5.1** was used, as this would require loss of the protecting group. However, such a structure would be a likely by-product in the cyclisation of substrate **5.13**, and thus it was slightly surprising that none was isolated. This might be explained by the greater stability of ethyl esters with regard to trans-esterification compared to the corresponding methyl esters.

Also of note was the lack of cyclopentane products **5.15** and **5.17**; both had been produced in the cyclisations of the dimethyl malonyl analogues, **3.23** and **3.24**.

The stereochemistry of lactones **5.14** and **5.16** was assigned primarily by comparison with the methyl-ester analogue, **3.25**, which was unambiguously characterised and assigned in previous work. However, extensive NMR studies were completed, and key nOes are shown for lactone **5.14** (Figure 5.4). Key nOes present include that of the H-1β proton with the H-6β proton and the H-5β proton. The H-1α proton also showed a nOe to the bridgehead proton (H-6a). This was found to be entirely consistent with **5.16**, and that of analogue **3.25**.

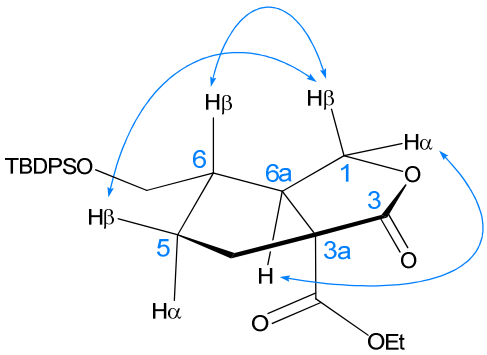
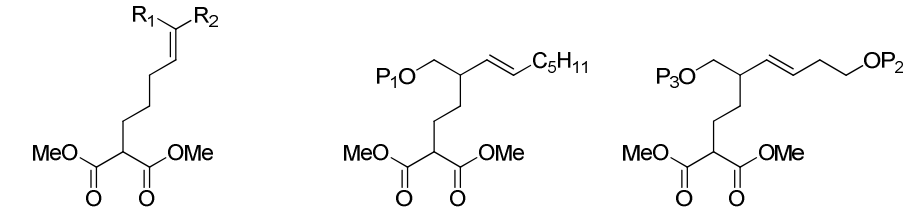


Figure 5.4 Stereochemical assignment of lactone 5.14

In summary, it has been shown that cyclisation substrates containing terminal olefins can cyclise effectively and produce lactones in moderate to excellent yields. When present, functionality on the tether between the malonate group can result in a highly diastereocontrolled cyclistation. However, using a more bulky malonate group does not increase the yield of lactone produced.

5.3 1,2-Disubstituted Olefin Substrates

Investigation of terminal olefin substrates had shown that cyclisation to form lactones was possible for a range of substrates. In order to investigate the cyclisation mechanism and tolerance of olefin substitution, three substrate skeletons were designed (Figure 5.5). The most simple substrates, **5.19** and **5.20** bear a short alkyl chain on the olefin, and are geometric isomers. Their cyclisation will investigate the effect of olefin geometry on the cyclisation. The remaining substrates, **5.21** – **5.25**, are analogues of the terminal olefin substrate **5.1** containing either an alkyl chain or an alkoxy side chain.



5.19 : $R_1 = C_5H_{11}$, $R_2 = H$
5.20 : $R_1 = H$, $R_2 = C_5H_{11}$

5.21 : P_1 = TBDPS
5.22 : $P_1 = H$

5.23 : P_1 = TBDPS, P_2 = Bn
5.24 : $P_1 = H$, P_2 = Bn
5.25 : P_1 = TBDPS, $P_2 = H$

Figure 5.5: Model substrates for secondary olefin cyclisations.

5.3.1 Retrosynthesis of Secondary Olefin Substrates

The simplest substrate, **5.19**, was envisaged to come from commercially available (*Z*)-dec-4-en-1-ol (Figure 5.6). This alcohol is available exclusively as the *Z* isomer, which would be mesylated allowing alkylation with dimethyl malonate to give the desired substrate.

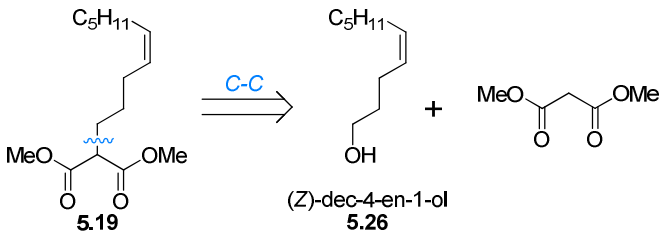


Figure 5.6: Retrosynthesis of substrate 5.19

(*E*)-dec-4-en-1-ol, required for the analogous synthesis of related substrate **5.20**, is not commercially available. However, a synthesis of this alcohol was designed in which it would be prepared from corresponding acetylene **5.28**. This in turn could be synthesised by alkylation of the commercially available heptyne with iodide **5.29**, made by monoprotection and iodination of propane-1,3-diol.

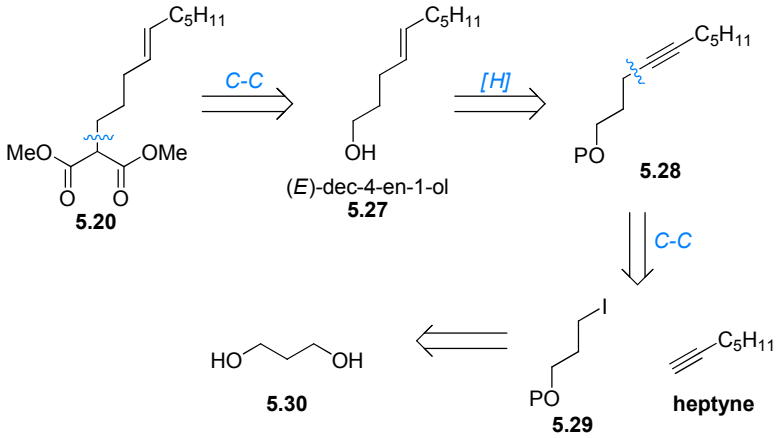


Figure 5.7: Retrosynthesis of substrate 5.20.

The more complex substrates **5.21** and **5.22** were envisaged to be available from a similar strategy to the terminal olefin substrates **5.1** and **5.13** (Figure 5.8). Disconnection of the malonate group back to a primary alcohol was planned. Using the same methodology as before, the alcohol would be obtained from reduction of an ethyl ester, introduced in the Johnson-Claisen reaction of alcohol **5.33**. This more complex allylic alchol could be made by a reduction of the corresponding propargyl

alcohol **5.34**, which could be itself made by alkylation of hexanal with a protected propargyl alcohol, 5.35.

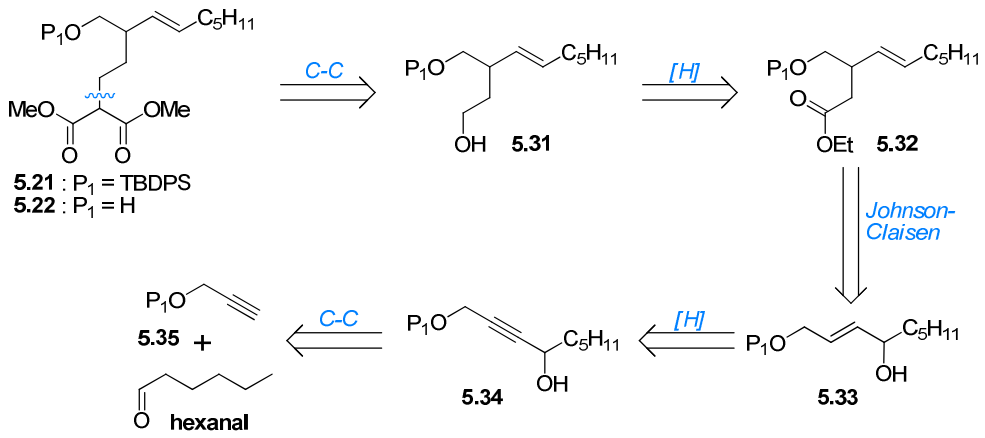


Figure 5.8: Retrosynthesis of substrate 5.21 & 5.22

A retrosynthesis of the final substrates, **5.23** – **5.25**, can be envisaged in the same manner, using very similar chemistry (Figure 5.9). Again, a key disconnection is that of displacement of a suitable leaving group by a malonate, for which triol **5.36** would be a suitable parent. The free primary alcohol can again be developed from the ester present in the Johnson-Claisen rearrangement product **5.37**. The allylic alcohol required for the Johnson-Claisen (**5.38**) can again be introduced by reduction of a propargyl alcohol, **5.39**. This can be made *via* alkylation of the same protected propargyl alcohol as used before (**5.35**), with a different aldehyde, **5.40**. The aldehyde is known in the chemical literature, and can be made by oxidation of a mono-protected symmetrical diol, **5.30**.[61]

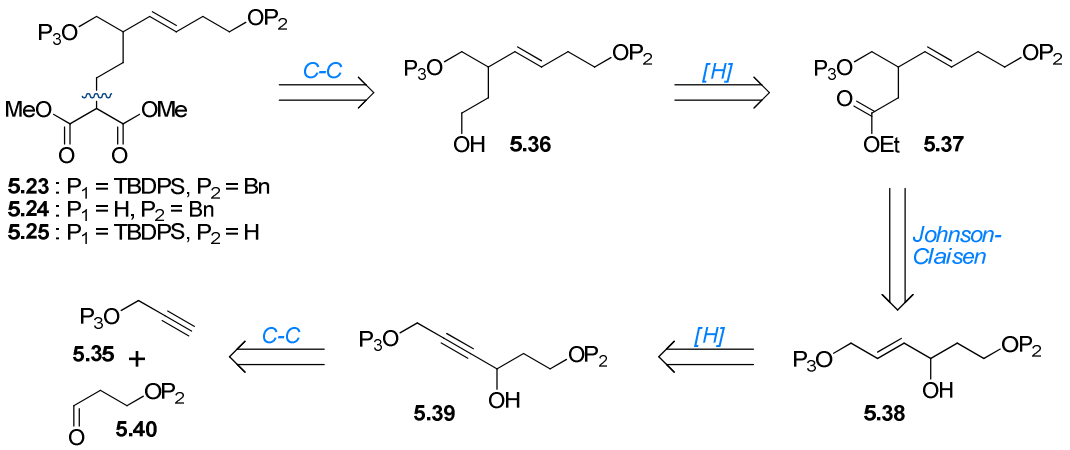
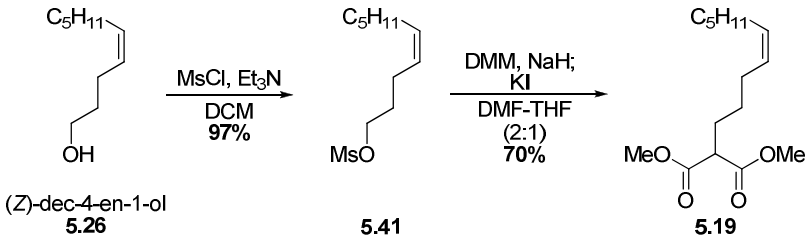


Figure 5.9: Retrosynthesis of substrates 5.23-5.25

5.3.2 Synthesis of 1,2-Disubstituted Olefin Substrates

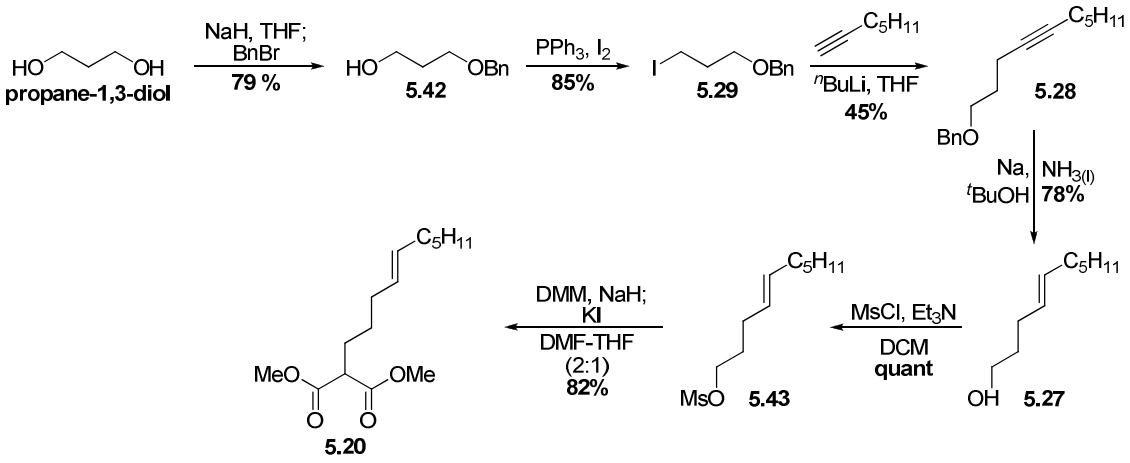
Synthesis of the alkene **5.19**, proceeded as planned, using commercial (*Z*)-dec-4-en-1-ol as the starting material. This was mesylated in excellent yield, and the mesylate **5.41** displaced by dimethyl malonate using iodide catalysis as in other examples to give cyclisation substrate in excellent overall yield (Figure 5.5).



Scheme 5.4: Synthesis of *cis*- isomer 5.19

The (*E*)-isomer **5.20** was the product of a more lengthy synthesis, which began with mono-protection of propane-1,3-diol with benzyl bromide. This material was available from other co-workers in the laboratory, with the yield shown indicative of their results. Iodination of the free alcohol was completed with ease, using triphenyl phosphine and iodine. Conveniently, the product could be separated from the

remaining phosphine and phosphine oxide produced in the reaction by trituration with hexane. The primary iodide was then displaced by the lithiated heptyne which gave the disubstituted acetylene **5.28** in moderate yield.



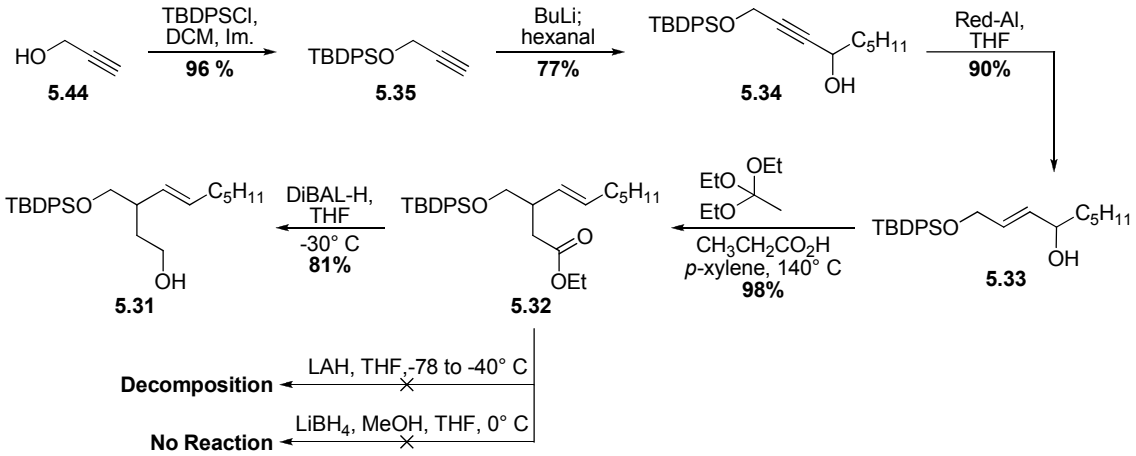
Scheme 5.5: Synthesis of *trans*- isomer 5.20

The acetylene was then reduced to the corresponding (*E*)-olefin under Birch conditions. This procedure was particularly convenient, as the benzyl protecting group was also removed under the strongly reducing conditions.

The product of this reduction, alcohol **5.27**, is a geometric isomer of the (*Z*)-olefin, **5.26**, and was treated with the same conditions of mesylation and displacement to complete the cyclisation substrate **5.20**.

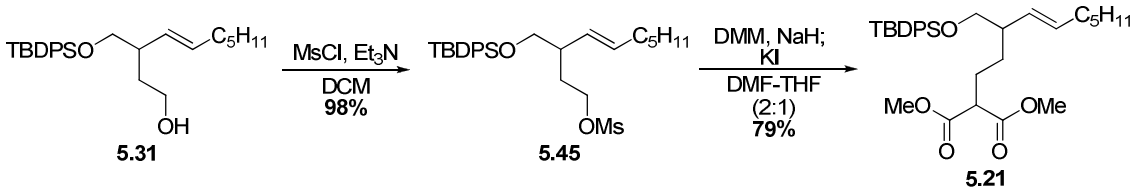
For substrate **5.21**, the TBDPS protecting group was chosen for its ease of introduction, removal and robustness. The synthesis began with protection of propargyl alcohol **5.44** with TBDPSCl (Scheme 5.6), which was completed in good yield. The product was then deprotonated using a slight excess of *n*-butyl lithium and freshly distilled hexanal added - hexanal was found to auto-oxidise to caproic acid

after storage for even a short time at low temperature. This reaction gave the desired product in a good yield, along with the mass-balance of starting material. Addition of an increased amount of base was found to be ineffective at increasing the yield of this step, as the product was prone to desilylation in excess base.



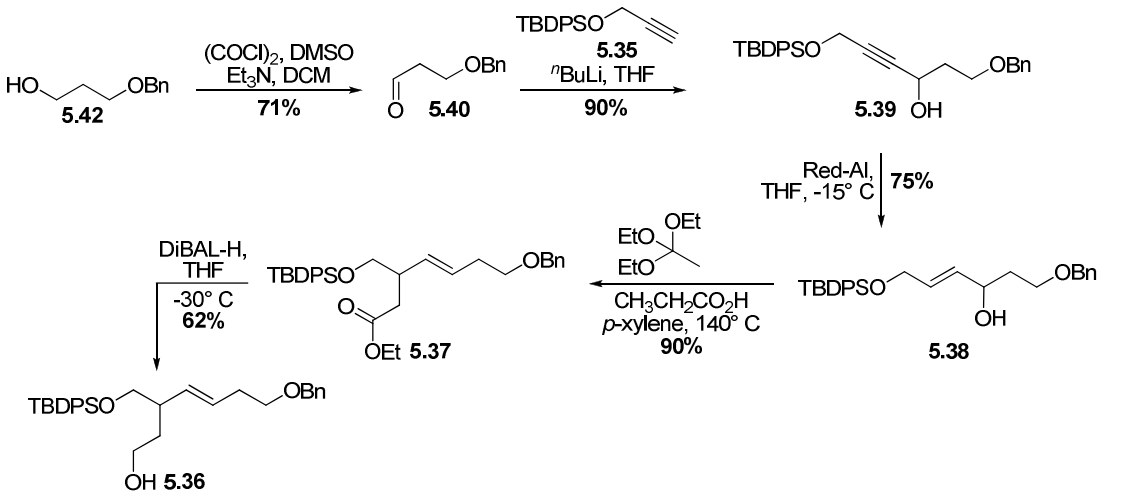
Scheme 5.6 Route towards substrate 5.21

Reduction of **5.34** to the corresponding allylic alcohol was performed in good yield with Red-Al®, providing a substrate for Johnson-Claisen reaction. The rearrangement proceeded in excellent yield as before to give ester **5.32**. Reduction of the resulting ethyl ester **5.32** proved once again problematic. Initially, the reduction was attempted with LAH, but was found to lead to decomposition, even at reduced temperature. Next, an attempt was made with lithium borohydride, but after extended reaction time, no reaction was observed. Eventually, it was found that ester **5.32** was reduced cleanly and efficiently with DIBAL-H; the primary alcohol obtained was then mesylated (Scheme 5.7) and the mesylate group displaced with dimethyl malonate anion using iodide catalysis, completing substrate **5.21**.



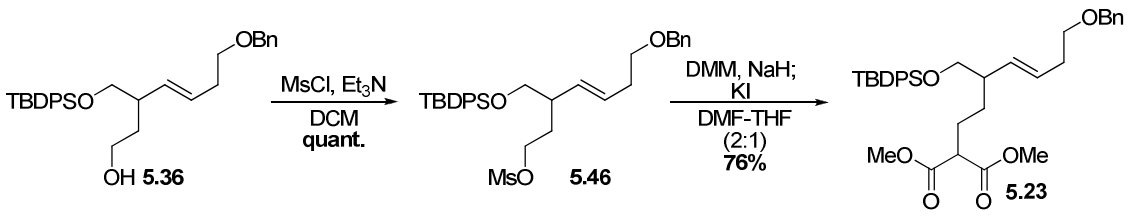
Scheme 5.7: Completion of substrate 5.21

Starting with the alternative aldehyde **5.40**, a similar alkylation with **5.35** allowed construction of an analogous propargyl alcohol, **5.39** (Scheme 5.8); the aldehyde was produced from monoprotected diol **5.42**, in a Swern oxidation.[62,63] Reduction of the propargyl alcohol **5.39** was again effected with Red-Al®, but the reaction had be carried out at -15 °C to avoid deprotection of the silyl ether. A Johnson-Claisen rearrangement then provided ester **5.37** in good yield, which was reduced to the primary alcohol **5.36** using DIBAL-H as in previous syntheses.



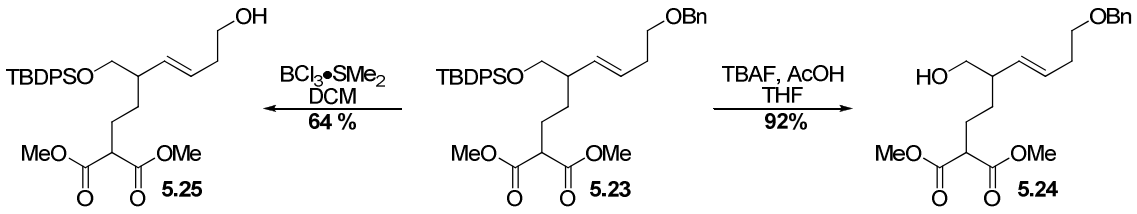
Scheme 5.8: Synthesis of primary alcohol 5.36

As before, the primary hydroxyl was mesylated and displaced with dimethyl malonate anion to provide malonate **5.23** (Scheme 5.9).



Scheme 5.9 Completion of parent substrate 5.23

The other cyclisation substrates based on this skeleton could be made by selective deprotection of the orthogonally-protected parent substrate. Thus, AcOH-buffered TBAF was capable of removing the silyl protecting group to provide substrate **5.24**, whereas boron trichloride–dimethyl sulphide complex was selective for the benzyl protecting group and hence synthesis of substrate **5.25** was completed (Scheme 5.10).

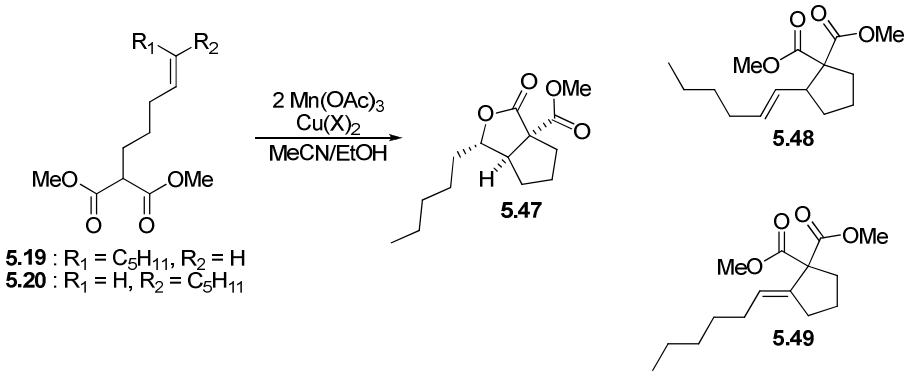


Scheme 5.10: Differential deprotection of substrate 5.23

5.4 Cyclisation of 1,2-Disubstituted Olefin Substrates

Cyclisation of substrates **5.19** and **5.20** gave a moderate yield of lactone **5.47** when copper salts $Cu(OTf)_2$ and $Cu(BF_4)_2$ were employed as co-oxidants. However, unlike the cyclisation of terminal alkene substrates (**5.2**, **5.13**), the products were not formed as single diastereoisomers. In each case, the lactones **5.47** were isolated as a 3:1 mixture of diastereoisomers at the lactone stereocentre (major diastereoisomer shown). The ratio of diastereoisomers is independent of the copper(II) salt used and

of the geometry of the starting alkene. Also isolated from these reactions was alkene **5.49**, along with an inseparable trace of **5.48**.



Scheme 5.11: Cyclisation of substrate 5.19

Expt.	Substrate	Solvent	Co-oxidant	**5.47** %	d.r.	**5.48**/**5.49** %
19	5.19	EtOH	None	0	-	trace
20	5.19	MeCN	$Cu(OTf)_2$	55	3:1	11%
21	5.19	MeCN	$Cu(BF_4)_2$	52	3:1	10%
Expt.	Substrate	Solvent	Cu Salt	**5.47** %	d.r.	**5.48**/**5.49** %
22	5.20	EtOH	None	0	-	trace
23	5.20	MeCN	$Cu(OTf)_2$	58	3:1	12%
24	5.20	MeCN	$Cu(BF_4)_2$	56	3:1	10%

Table 5.2 Results from cyclisation of substrates 5.19 & 5.20.

The configuration of lactone **5.47** was assigned by examining key nOes (Figure 5.10). However, as **5.47** was isolated as a mixture of diastereoisomers, many signals were found to overlap. Using 1-dimensional ^{1}H NMR TOCSY experiments, protons corresponding to only one diastereoisomer were resolved. The configuration of the major diastereomer of **5.47** was then assigned by ^{1}H NMR NOESY experiments on

the mixture of diastereomers. Most notable was the nOe between the H-1 proton and the H-6β. HSQC assignment of C-6 allowed identification of H-6α, which showed a strong nOe to H-6a. This nOe data is entirely consistant with the stereochemistry of **5.47** depicted in the Figure.

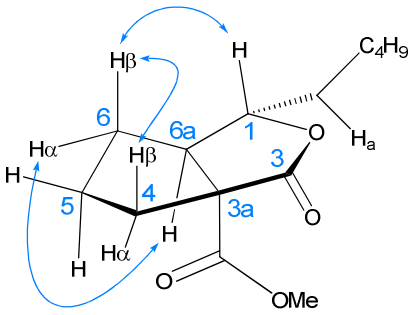
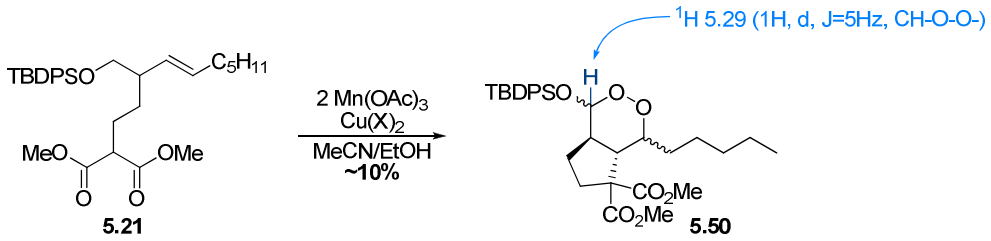


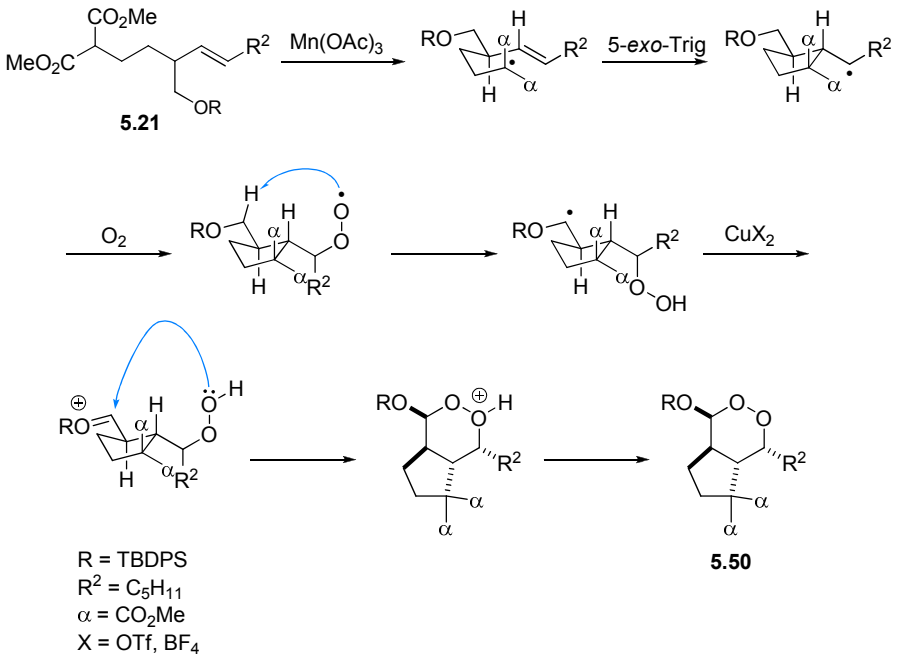
Figure 5.10: Stereochemical assignment of lactone 5.47.

Exposure of **5.21** to the typical cyclisation conditions led to unexpected results – very little lactone was produced, with a high percentage of starting material being isolated. Surprisingly though, an unknown compound, conceivably peroxide **5.50**, was also isolated (***m/z*** (ESI+) Found: $(M+NH_4)^+$, 586.3195; $C_{32}H_{48}NO_7Si$ requires 586.3200).



Scheme 5.12: Cyclisation of substrate 5.21 and postulated product

The NMR spectrum of **5.50** was quite distinct from the expected product mixture, but bore some similarities to a peroxide produced *via* previous work within the group. A postulated mechanism for the formation of this species is shown (Scheme 5.13).



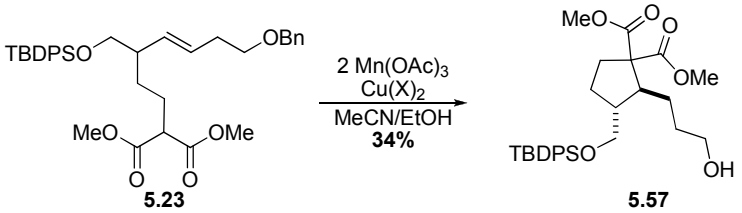
Scheme 5.13: Proposed mechanism of peroxide formation

Treatment of malonate precursor **5.21** with manganese(III) acetate generates educt-radical **5.51**, which then performs a 5-*exo*-trig cyclisation to produce adduct radical **5.52**. This then traps triplet oxygen from the atmosphere, forming peroxy radical **5.53**. 1,5-Hydrogen transfer then provides the more stable radical **5.54**, which is oxidised by copper(II) to the oxocarbenium ion **5.55**. Attack of the hydro-peroxide group then leads to endo-peroxide **5.56**, which need only lose a proton to provide peroxide **5.50**.

Peroxides are incredibly powerful synthetic intermediates, easily converted to a variety of functionalities, so are an appealing target. Work by Kurosawa *et al*,[64] Snider[65] and Nishino[66] has shown that their formation in $Mn(OAc)_3$ cyclisations is known, but can be inefficient. Thus, reactions on the same substrate were conducted both in an open atmosphere, and in an oxygen atmosphere. The yield of peroxide **5.50**, however, was unchanged in either, remaining around 10%. This left little hope for efficient peroxide synthesis, so this approach was set-aside for the moment.

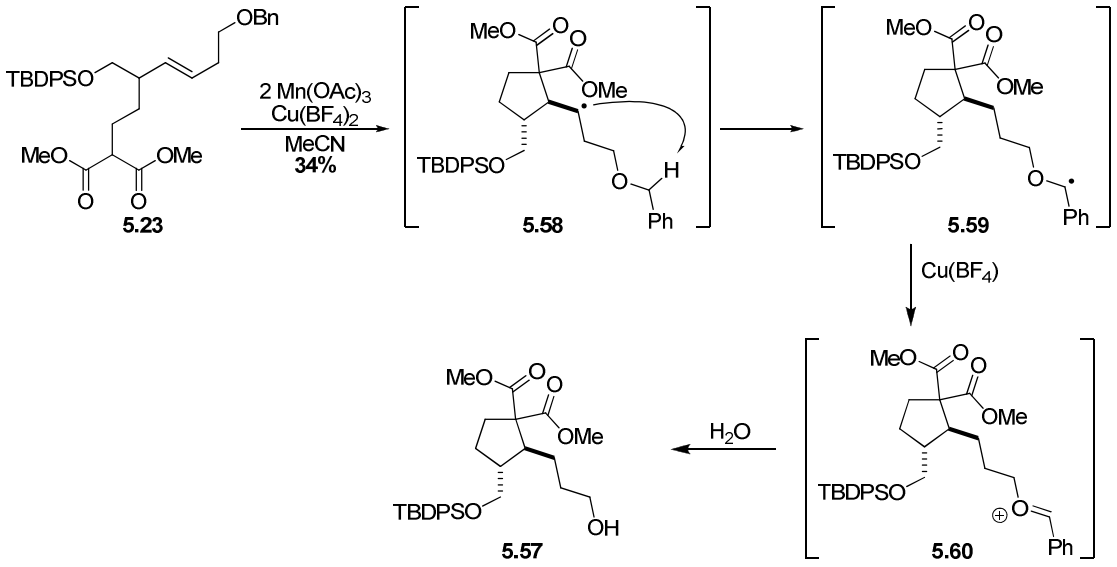
Of greater concern was the absence of lactone formed by cyclisation in this system. The fact that the adduct radical is capable of trapping oxygen in preference to lactonisation suggests that the conformation required for lactonisation is unfavourable. However, the reaction conformation does not appear more congested that proposed for other substrates, so it is still unknown as to why this substrate is unwilling to cyclise to give the desired lactone.

Substrate **5.23** also gave no lactone product on cyclisation (Scheme 5.14). A modest yield of cyclopentane **5.57** was isolated. This product is interesting as it has lost the benzyl protecting group present in the starting material.



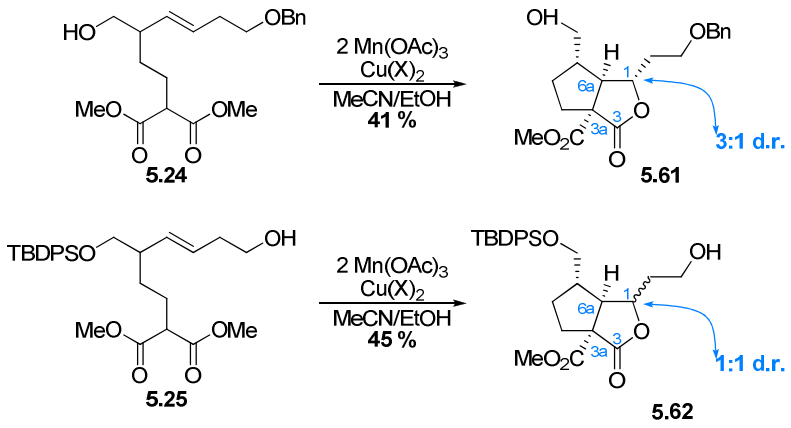
Scheme 5.14: Cyclisation of substrate 5.23

Examination of the structure of the adduct radical **5.58** reveals the possibility of 1,5 hydrogen atom transfer to give the more stable benzylic radical, **5.59** (Scheme 5.15). This can then be oxidised by either metal oxidant present to generate the stabilised oxocarbenium ion **5.60**. This could then hydrolysed by water (commercial manganese(III) acetate is used as the dihydrate) to give the free primary alcohol.



Scheme 5.15: Postulated mechanism for loss of benzyl group.

Cyclisation of the similar substrates **5.24** and **5.25** were more successful (Scheme 5.16). Both returned starting material, but also moderate and similar yields of the corresponding lactones. Interestingly, the substrates displayed different degrees of diastereoselectivity. The lactones derived from substrate **5.24** were formed in a 3:1 ratio, favouring the all-syn diastereomer as in previous examples. However, the lactones formed from cyclisation of substrate **5.25** were isolated as a 1:1 mixture of diastereomers at the lactone stereocentre. Rationalising this result is complicated, as the transition states for cyclisation are very similar; the selective deprotections clearly remove bulk from the cyclisation substrates, but in positions that are relatively remote.



Scheme 5.16 Cyclisation of substrates 5.24 & 5.25

The stereochemistry of lactone **5.61** and **5.62** was assigned by extensive 1-D and 2-D NMR spectroscopy. Comparison of chemical shifts with other [3.3.0] γ-lactones aided identification of key resonances, which were then unambiguously assigned by ^{1}H NMR COSY experiments. Key nOes are shown below, as taken from NOESY spectra (Figure 5.11).

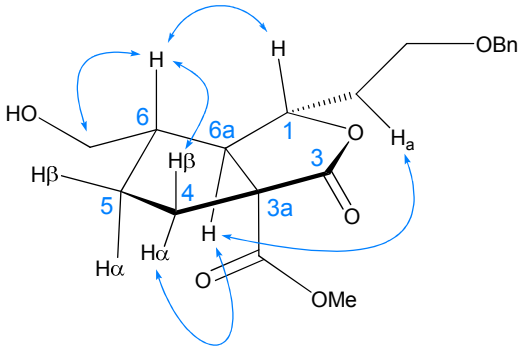


Figure 5.11: Stereochemical assignment of 5.61

Lactone **5.61** was isolated as a mixture of diastereoisomers, in 3:1 ratio. Nevertheless the stereochemistry of the major diastereomer could be assigned by ^{1}H NMR COSY and NOESY experiments. Key to the stereochemical assignment of **5.61** were nOes between the H-1 and the H-6 (Figure 5.11), which also showed an nOe to H-4β. H-4β has an nOe H-6a proton which also showed an nOe to the benxyloxy sidechain.

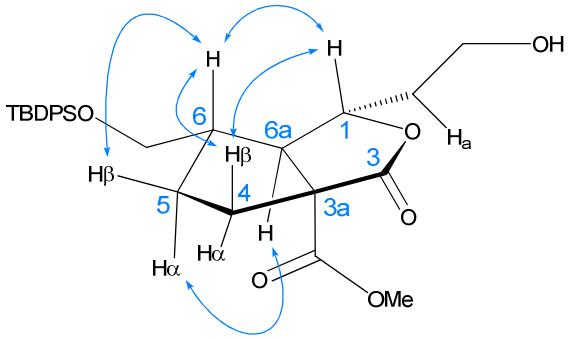
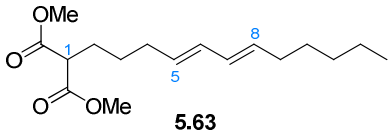


Figure 5.12: Stereochemical assignment of 5.62

For **5.62**, which was isolated as a 1:1 mixture of diastereoisomers, ^{1}H NMR COSY experiment was used to identify signals in the ^{1}H NMR belonging to a single diastereoisomer. The stereochemistry of this diastereomer was then analysed using NOESY spectra. ^{1}H NMR nOes were observed between the proton H-6 and H-1, H-5β, and H-4β, indicating that they were on the same face of the molecule (Figure 5.12). Furthermore, an nOe was again present between the H-5α and H-6a proton, both of which must be on the α face.

5.5 Diene Substrate

The studies on secondary olefin substrates has shown that the increased stability of the adduct radicals does not appear to encourage lactone formation. However, modest diastereoselectivity in the lactones formed had been demonstrated. The product desired in the planned synthesis of the prostaglandin family contains an allylic lactone, proposed to arise from cyclisation of a diene-containing substrate. Since the allylic lactone required contains an olefin exocyclic to the [3.3.0] ring system, the required cyclisation needed to contain a 5,6-7,8-diene. The synthesis of a simplified model substrate, **5.63** was therefore attempted (Figure 5.13).



5.63

Figure 5.13: Model substrate for diene cyclisation.

A consequence of the added complexity in this system is that the substrate may cyclise onto the diene in several modes (Figure 5.14). Of these cyclisation modes, the 7-*exo*-trig is the most unlikely, due to poor orbital overlap and product (**5.66**) features an (*E*)-olefin constrained within a seven-membered ring. Although (*E*)-cycloheptenes have been produced, they are exceptionally unstable. Also less likely is the 8-*endo*-trig cyclisation leaving an (*E*)-olefin within an eight-membered ring (the adduct radical can be predicted to rearrange to give the corresponding *Z*-olefin). The desired 5-*exo*-trig is most likely, with the 6-*endo*-trig cyclisation also a possibility.

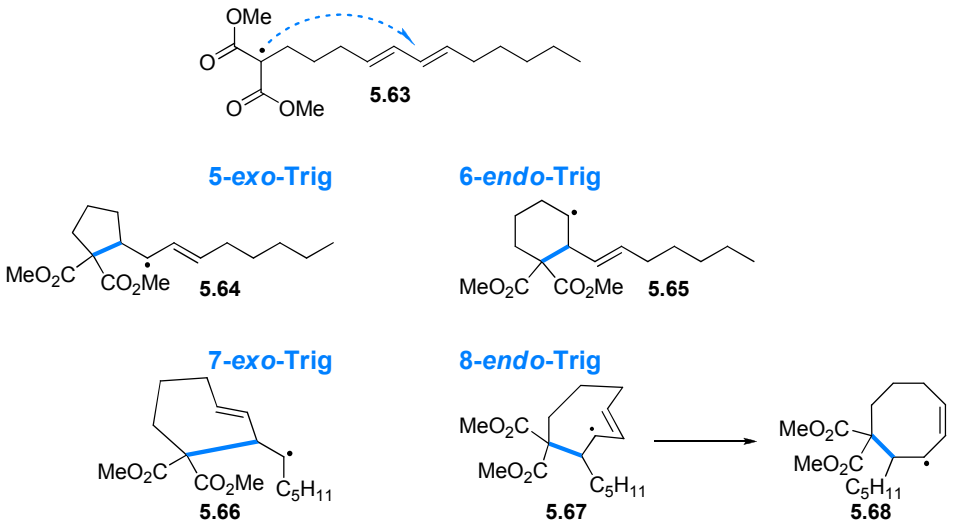


Figure 5.14: Putative cyclisation modes of substrate 5.63

5.5.1 Retrosynthesis of the Diene Substrate

The diene **5.63** was envisaged to come from primary alcohol **5.76**. The diene moiety would be installed *via* a key Suzuki coupling,[54] which would provide the (*E*,*E*)-diene functionality required. The partners for the palladium-mediated coupling would both be made from acetylenes, with hydroboration providing the boronic acid partner, and hydroalumination producing the iodide after workup with iodine.

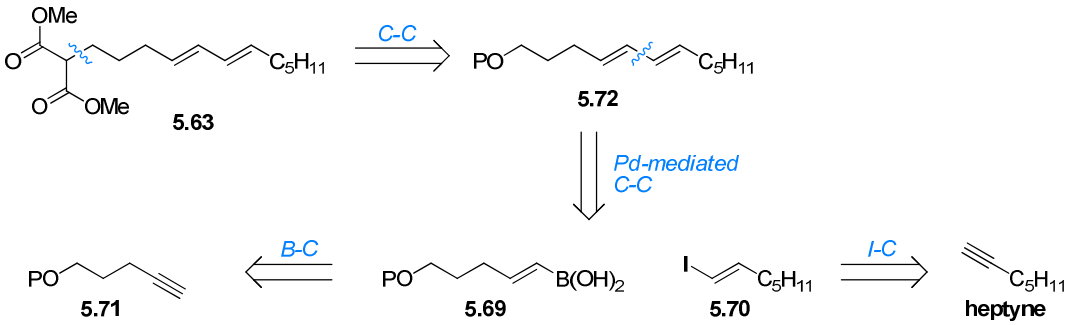
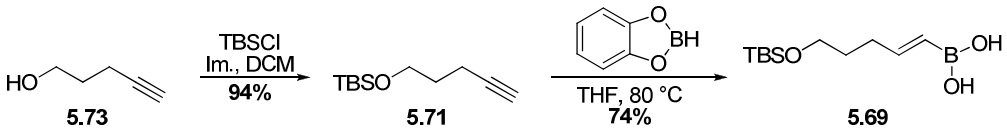


Figure 5.15: Retrosynthesis of diene model substrate

5.5.2 Synthesis of the Diene Substrate

The synthesis of diene substrate **5.63** began with synthesis of the boronic acid, **5.69**. A literature survey highlights a synthesis of a similar diene using the same boronic acid.[67] Using the protocol described by Pattenden, pentyn-1-ol was therefore protected as the TBS ether using standard conditions. Hydroboration was then completed using catechol borane.



Scheme 5.17: Hydroboration of TBS-protected pentynol

Work then began on synthesis of the remaining coupling partner, the vinyl iodide. Several methods of converting an acetylene such as heptyne into the corresponding vinyl iodide, **5.70**, exist. The general process involves hydrometallation with a suitable metal-hydride species, and then formal displacement of the metal by iodine (Figure 5.16). A commonly used metal hydride is Schwartz reagent, which generates a vinyl-zirconium intermediate (**5.74** where M = Zr).[68] Although broadly applicable, a stoichiometric amount of Schwartz reagent is required, which can be very costly. Alternatives include hydroboration and hydrostannylation, but these methods are also costly and in the case of tin, produce undesirable biproducts.

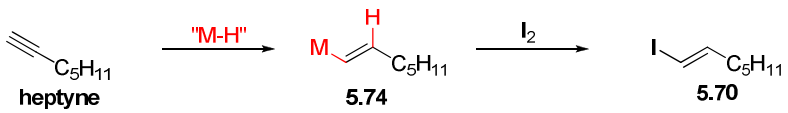
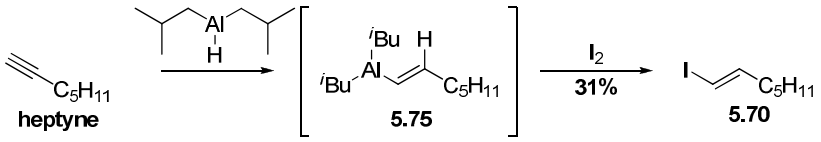


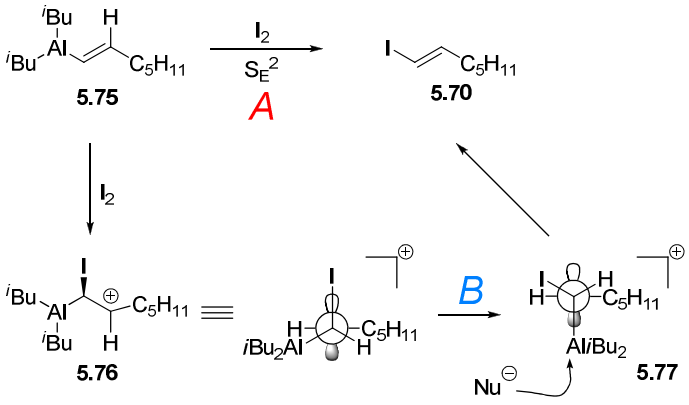
Figure 5.16: General procedure for formation of vinyl iodides from alkynes

Thus, attention was turned to hydroalumination, which has been demonstrated to be effective with commercial DIBAL-H, and is therefore relatively inexpensive.[69] Previous studies in the literature have shown that this reaction can be troublesome if the acetylene starting material is oxygenated (perhaps owing to co-ordination of the aluminium hydride by the oxygen), but heptyne has proven to be an effective substrate.



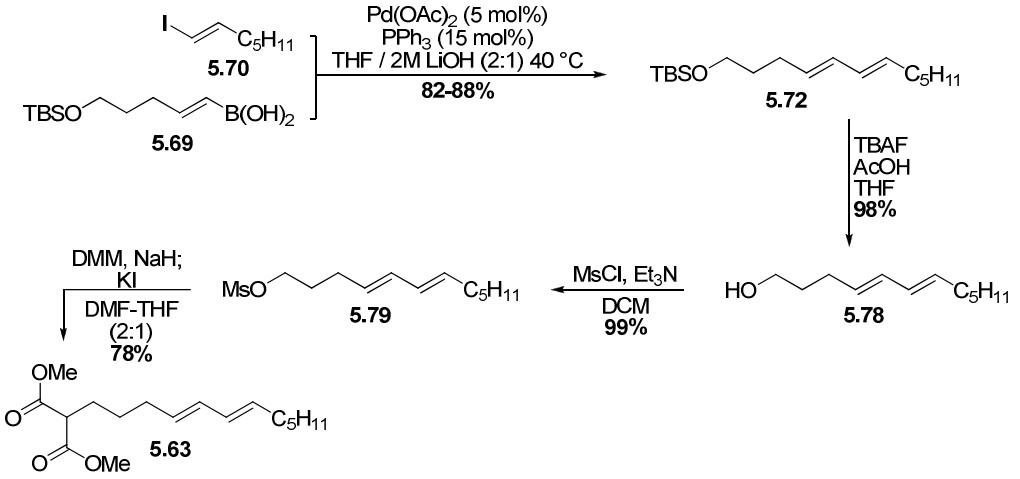
Scheme 5.18: Hydroalumination and iodation of heptyne

Indeed, conversion of heptyne to vinyl iodide **5.70** was achieved, albeit in modest yield (Scheme 5.18). The procedure involved addition of DiBAL-H in hexane to the substrate, and then removal of solvent to isolate the vinyl-alane. Iodine, as a solution in THF was then added to the vinyl alane which generated the product as a single stereoisomer (δ_H (400 MHz, $CDCl_3$) 6.51 (1H, dt, *J* = 18.0, 6.2, ICH=C*H*CH_2), 6.17 (1H, d, *J* = 18.0, IC*H*=CH)). There are two possible mechanistic pathways from the vinyl alane to the vinyl iodide and both may operate in this example (Scheme 5.19).



Scheme 5.19: Iodination pathways of vinyl-aluminium species 5.75

Both mechanisms begin with the expected stereospecific *syn*-addition of the aluminium hydride across the acetylene to generate intermediate **5.75**. In mechanism A, a direct S_E2 displacement of the aluminium occurs, directly providing the product. Alternatively, mechanism B involves formation of β-metal stabilised carbenium ion **5.76**. The 'least motion' movement of the C-Al bond to allow full stablisation of the carbenium ion gives conformation **5.77**. Elimination of aluminium then delivers the *trans*- vinylidoide **5.70**.



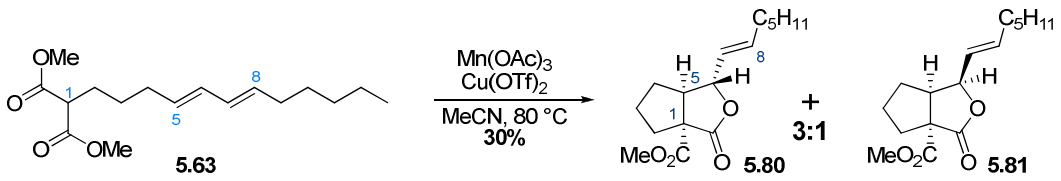
Scheme 5.20: Suzuki coupling and completion of substrate synthesis

Suzuki coupling conditions used successfully by Pattenden *et al*,[67] in a similar system were applied to the coupling of boronic ester **5.69** and iodide **5.70**. The substrates were dissolved in THF / 2M LiOH(aq) in 2:1 ratio (Scheme 5.20). As in the literature system, palladium(II) acetate and triphenyl phosphine were used as the pre-catalyst, forming palladium(0) bis(diphenylphosphine) *in* situ. This system operated particularly well, and excellent yields of diene **5.72** were obtained without the need for further optimisation. No longer required, the TBS protecting group was removed efficiently in AcOH buffered TBAF, leaving the free primary alcohol **5.78**. The now

familiar strategy of mesylation (**5.79**) to provide a good leaving group, and displacement of the mesylate group by dimethyl malonate anion provided the required cyclisation substrate **5.63** in excellent overall yield.

5.6 Cyclisation of the Diene Substrate

With a short and effective synthesis of cyclisation substrate **5.63** complete, cyclisation of this material using the standard conditions was attempted. The reaction was completed in acetonitrile using either copper(II) triflate or copper(II) tetrafluoroborate in conjunction with manganese(III) acetate.



Scheme 5.21: Cyclisation of diene substrate 5.63

Cyclisation of the diene proceeded to yield a complex mixture of products, as well as returned starting material (Scheme 5.21). Unfortunately, the desired lactone **5.80** was only present in 30%, as a 3:1 mixture of diastereomers (the minor isomer being epimer **5.81**). The stereochemistry of the lactones produced was determined by extensive NMR spectroscopy. The individual peaks corresponding to each isomer were first assigned by ^{1}H NMR COSY experiments, and then the stereochemistry analysed by ^{1}H NMR NOESY experiment.

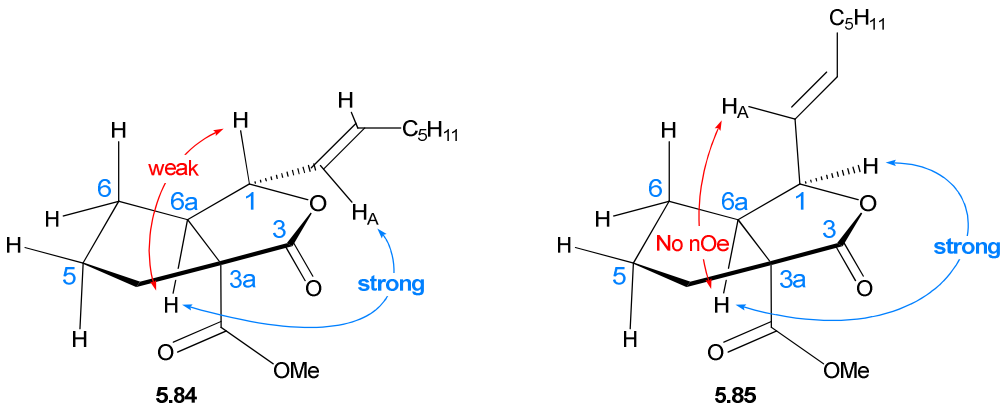


Figure 5.17: Stereochemical analysis of lactone 5.80 and 5.85.

In both lactones, an nOe was present between the H-1 and the bridgehead proton H-6a (Figure 5.17). However, in the isomer presumed to be **5.80**, this nOe was far weaker than in the other epimer. Also, in **5.80**, a strong nOe was seen between the bridgehead proton H-6a and the alkene proton H_A. This would suggest that these protons are on the same face of the molecule. In the other isomer (**5.81**), no contact was observed between these protons, suggesting that they are on opposite faces of the molecule.

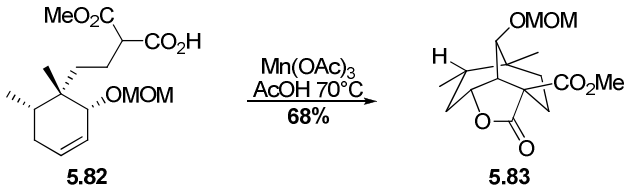
Correlating this result with those obtained for the substituted olefins, it can be observed that as the adduct radical (or analogous carbocation) becomes more stable, the overall yield of product decreases. This is against the original postulate, which proposed that lactone yield might increase as the adduct radical is stablised. However, it is possible that instead of favouring lactonisation, stabilisation of the reactive intermediates is promoting side reactions, such as fragmentation or trapping of other species present. It is particularly notable that some of the by-products contain the desired cyclopentane moiety. This would suggest that the initial radical formation, and cyclisation onto the alkene/diene proceeds readily. However, the

modest yield of lactone would suggest that the lactonisation event is not efficient. A method of increasing the rate of lactonisation was therefore necessary.

5.7 Malonic Acid Substrates – Initial Studies

As discussed above, a more efficient lactonisation step was required. The general mechanism proposed for lactonisation shows that trapping of the adduct radical by copper is essential. The ester groups in the malonate moiety ligate the copper, and a formal Cu(III)-C bond is formed.[70] Reductive elimination of Cu(I) then follows, forming the oxocarbenium ion, **5.3**. Hydrolysis of this intermediate then delivers the desired product. If a malonic acid were used in place of the malonate, the ligation of copper by the carboxylic acids seemed likely to be more effective. Secondly, hydrolysis of the oxocarbenium ion formed from reductive elimation of copper(I) from intermediate **5.3** is now not required. Malonic acid derivatives of the substrates described above therefore fell under scrutiny.

A literature survey showed that the use of carboxylic acids as substrates for manganese(III) acetate cyclisations is known. In his synthesis of (±)-14-epiupial, Paquette used a β-carboxy ester as the substrate for an intramolecular cyclisation (Scheme 5.22).[71]



5.82 **5.83**

Scheme 5.22: Use of carboxylic acid substrates by Paquette

A simple substrate, based on the secondary olefin substrate, **5.19,** was designed to test the viability of these cyclisations. Rather than attempt a synthesis of the β-carboxy

ester as in Paquette's work, it was decided to make the malonic acid derivative, **5.84**. However, as in the aforementioned studies, there was concern that the basic hydrolysis conditions required to saponify **5.19** to **5.84** directly might also lead to competing decarboxylation or a retro-Claisen condensation. A strategy of acid hydrolysis of a Meldrum's acid derivative was therefore adopted.

5.7.1 Retrosynthesis of the Malonic Acid Substrate

The retrosynthesis of malonic acid **5.84** hinges upon an acid hydrolysis of Meldrum's acid derivative **5.85** (Figure 5.18). This substrate should be available from a Knoevenagel condensation of Meldrum's acid **5.87** and aldehyde **5.86**, both readily available.

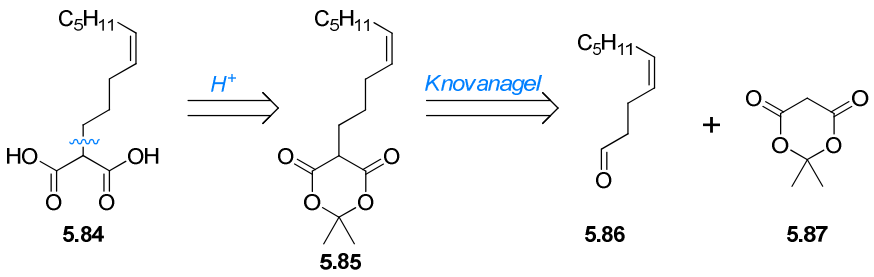
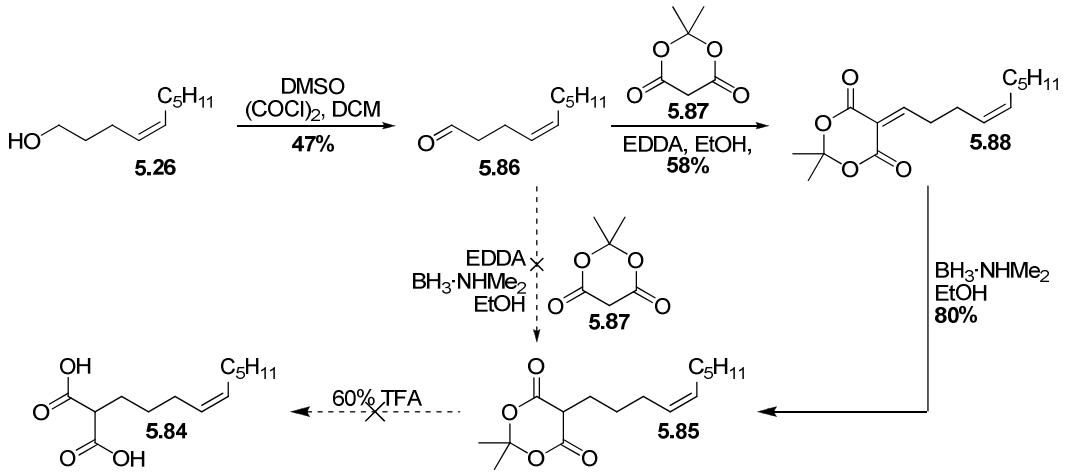


Figure 5.18: Retrosynthesis of substrate 5.84 from Meldrum's Acid

A study of the literature highlighted a prior synthesis of intermediate **5.85** in such a manner, so was the starting point for this synthesis.[72,73] Again, (*Z*)-dec-4-en-1-ol was used as the initial starting material, and was oxidised using Swern conditions to aldehyde **5.86** (Scheme 5.23). This isolated yield of the aldehyde was modest even though TLC analysis of the reaction mixture indicated efficient reaction. Most likely this is due to decomposition of the product during purification. However, the reaction

was conducted on such a scale that work continued with the Knoevenagel condensation.



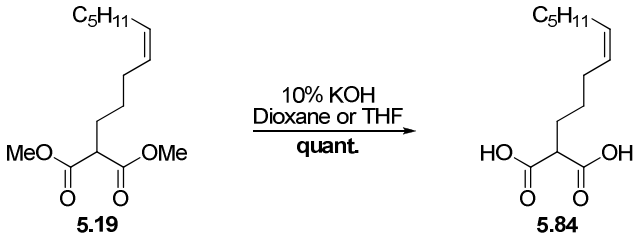
Scheme 5.23: Initial route towards malonic acid 5.88

Previous studies suggested that the condensation might be completed in tandem with reduction.[72] A system of Meldrum's acid, ethylene diamine diacetate and borane-dimethyl amine was prepared in ethanol, but disappointingly, none of the desired product was evident in either the crude NMR or after flash column chromatography. However, completion of the transformation in a stepwise manner was successful, although again only in moderate overall yield. Addition of Meldrum's acid to (*Z*)-dec-4-en-1-al in ethanol with EDDA delivered the unsaturated derivative **5.88**, which was somewhat troublesome in isolation owing to its propensity for enolisation. This material was then reduced with borane-dimethylamine complex to give the desired Meldrum's acid derivative **5.85**,

Our attention then turned to the crucial hydrolysis of the acetonide group in the Meldrum's acid moiety. Initially, relatively mild conditions were employed, using 20% acetic acid in water. However, only starting material **5.85** was recovered after 24

hours. Increasing the concentration of acetic acid and increasing the reaction temperature was unsuccessful. Similarly the use of trifluoroacetic acid was also unsuccessful and resulted in some decomposition of the starting material.

Ultimately it was found that basic hydrolysis of the dimethyl malonate **5.19** gave the desired product **5.84** in quantitative yield after acidic workup. Thus, dissolution of the substrate in dioxane or THF followed by addition of a stoichiometric quantity of potassium hydroxide solution allowed quantitative saponification without any decomposition *via* the retro-Claisen condensation or decarboxylation pathways (Scheme 5.24).

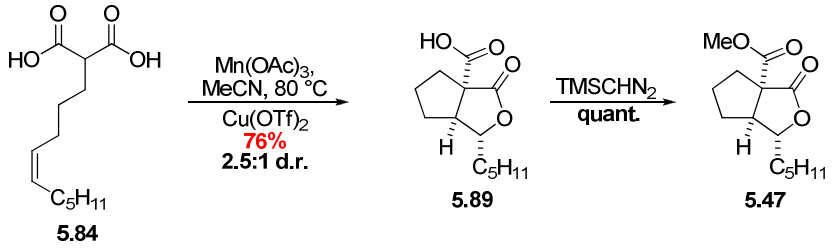


Scheme 5.24: Successful transformation of 5.19 into 5.84.

Initially, saponifications were performed in dioxane, and were considerably faster than the corresponding reactions in THF. This can be rationalised by considering that dioxane has a better miscibility with aqueous systems than THF, and therefore the concentration of hydroxide anions in dioxane is higher than that of THF. However, removal of dioxane from the substrate without loss of malonic acid into aqueous media was considerably more difficult than with THF.

5.8 Cyclisation of the Malonic Acid Substrate

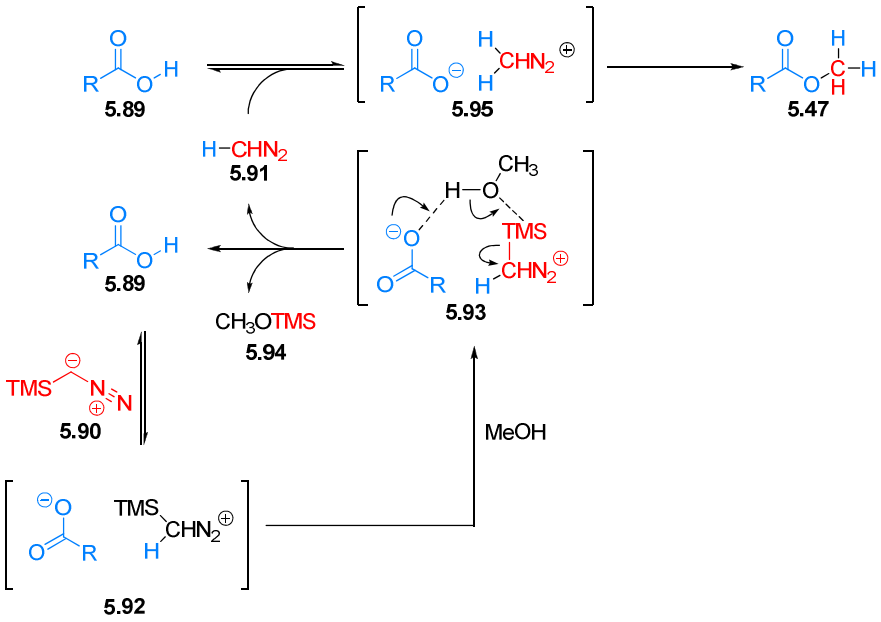
With a single-step transformation of malonate substrate **5.19** to malonic acid substrate **5.84** now possible, cyclisation of this material was investigated (Scheme 5.25). Conditions identical to those used for malonate-based substrates were employed, in which the substrate was dissolved in acetonitrile, and metal salts added as required. The solution was then brought to reflux and allowed to stir for eighteen hours as before. As the product contained a free carboxylic acid group, care was taken to acidify the aqueous layer when working-up the reactions, and thus a quantitative mass recovery was possible.



Scheme 5.25: Cyclisation of malonic acid substrate 5.83

Purification of the crude products on silica proved arduous, so it was decided to methylate the crude reaction mixture with TMS-diazomethane (**5.89**).[74] This simple procedure converted all carboxylic acid moieties to the analogous methyl esters, thus providing a material which was readily purifiable on silica (Scheme 5.25). TMS-diazomethane is far safer and operationally simpler to work with than its parent compound, diazomethane (**5.91**). However, the reaction mechanism for TMS-diazomethane has only recently been unravelled by the work of Lloyd-Jones.[74] The mechanism proposed by this work suggests that a termolecular reaction between the

carboxylate, methanol and protonated TMS-diazomethane generates diazomethane *in situ* (Scheme 5.27).



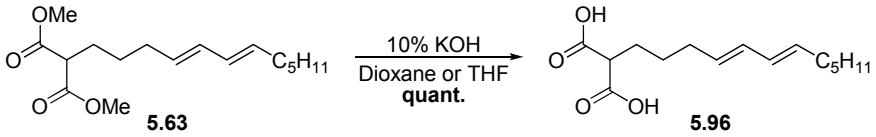
Scheme 5.26: Lloyd-Jones mechanism for methylation with TMS-diazomethane

After methylation, the crude product mixture of methyl esters was analysed first by ^{1}H NMR, and then purified to isolate the lactone products. Pleasingly, it was found that the desired lactone **5.47** was obtained in a 76% yield, which when compared with the 58% yield achieved for the cyclisation of the malonate substrate **5.19** shows that the malonic acids are better substrates for this cyclisation.

5.9 Further Malonic Acid Substrates

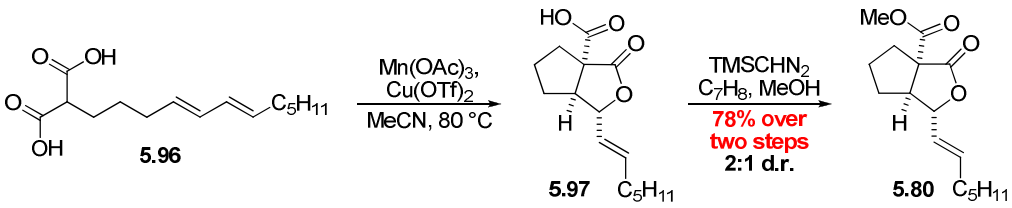
With a successful cyclisation of malonic acid substrate **5.84** achieved, attention was turned to the poorly-performing cyclisation of the diene substrate, **5.63**. It was anticipated that the faster rate of lactonisation of malonic acid substrates might allow an analogous cyclisation of substrate **5.95** to be performed to generate β-carboxylic

lactone product **5.96**. As in the cyclisation of **5.84**, methylation of the carboxylic acid would follow cyclisation to aid purification of the product, and would also lead directly to the same lactone **5.80**.



Scheme 5.27: Conversion of malonate 5.63 into corresponding malonic acid 5.96

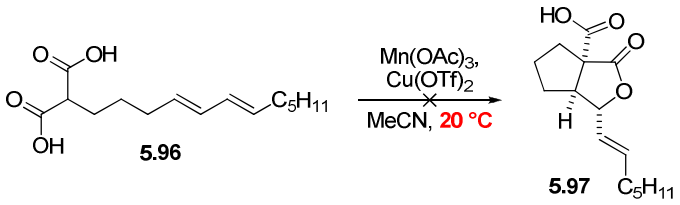
Using the methodology described above, malonate **5.63** was converted to the required cyclisation substrate **5.96** by saponification (Scheme 5.27). Treatment of this substrate under our standard cyclisation conditions resulted in isolation of impure β-carboxylic lactone **5.97**. This was then converted to methyl ester analogue **5.80** in what is assumed to be a quantitative reaction. This structure shared characterisation data with the previously isolated sample.



Scheme 5.28: Cyclisation of diene 5.96

The overall yield of lactone **5.80** over these two steps was 78%, a vast improvement over the result achieved for the malonate **5.63** (Scheme 5.28). The success of malonic acid substrates in these cyclisations led to consideration of reaction temperature, and that the reaction might operate at a lower temperature than the 80 °C. Thus, the reaction was repeated at room-temperature, and analysed by TLC after the usual

eighteen hours. Unfortunately, only starting material was observed, and even after a further day, no β-carboxylic lactone was observed (Scheme 5.29).



Scheme 5.29 Attempt at room-temperature cyclisation of diene 5.96

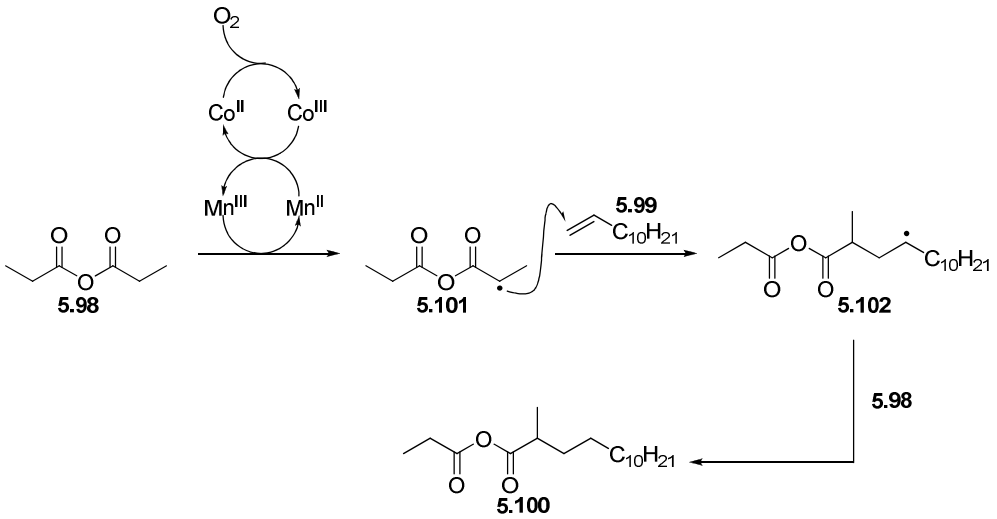
5.10 Catalytic Studies

A possible limitation of the methodology discussed thus far has been that the cyclisations rely upon a stoichiometric quantity of the metal reagents. Although manganese(III) acetate and copper(II) triflate are relatively inexpensive reagents, recovery of metals from the crude product mixture can be challenging, and becomes more difficult as the scale of the reaction increases.

Thus, attention was drawn to the work of Ishii, who demonstrated the use of a O_2/Co/Mn oxidation cycle, in which Mn(II) was oxidised to Mn(III) by Co(II).[75] The Co(II) is initially oxidised to Co(III) by dioxygen. Co(III) than takes Mn(II) to Mn(III) which then initiates the reaction. In this manner, it was possible to use a catalytic quantity of both manganese(II) acetate and cobalt(II) acetate to perform an intermolecular radical reaction (Scheme 5.30).

Scheme 5.30: Catalytic intermolecular reaction shown by Ishii.

The researchers found that the optimal reaction conditions were to use a 0.5 mol% loading of Mn(II) acetate, 0.1 mol% loading of Co(II) acetate, and to conduct the reaction without solvent at 130 ºC. As manganese(II) acetate is incapable of oxidative radical generation, the first step must be oxidation of Mn(II) to Mn(III) by Co(II) (Scheme 5.31). This provides the redox radical initiator to generate educt radical **5.101** from anhydride **5.98**. The radical generated then reacts in the familiar fashion, adding to the more sterically-accessible side of the terminal olefin **5.99** to form the more stable of the possible adduct radicals **5.102**, leading to product.



Scheme 5.31: Proposed catalytic cycle and mechanism for addition of 5.98 to 5.99.

Application of this appealing catalytic process to the formation of lactones required consideration of the differences between the system used by Ishii, and that used in the stoichiometric lactonisation chemistry described above. Most pressing was the use of

copper as a co-oxidant in the lactone formation step, which was unnecessary in Ishii's work. Fortunately, examination of the oxidation potentials of Mn(III) and Cu(I) indicate that manganese(III) will be able to oxidise copper(I) to the required copper(II), bringing copper into the catalysis redox cycle (Figure 5.19).

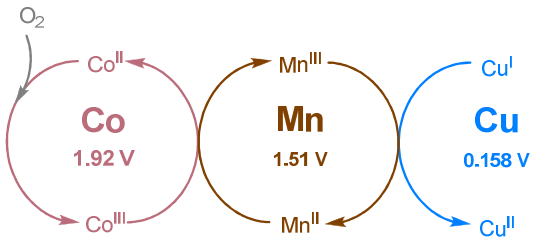


Figure 5.19: Cartoon redox cycle

Also of concern was the lack of solvent in the Ishii system; the malonic acids which would be the preferred cyclisation substrates were solids, and thus would be incompatible with neat reaction conditions. It was decided to attempt the cyclisation of malonic acids in acetonitrile at 80° C as in the stoichiometric studies. In order to test the procedure, malonic acid substrate **5.103** was used, as the substrate was most readily accessible, and was known to lactonise efficiently when using stoichiometric conditions (Figure 5.20).

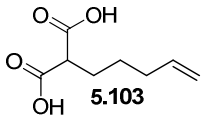


Figure 5.20: Model substrate for catalysis methodology

Investigation of the catalytic cyclisation of malonic acids began with the design of a simple substrate, **5.103**. Like substrate **5.1**, this compound features a terminal olefin, so was hoped to be a good substrate for the manganese(III) acetate cyclisation. The synthesis of **5.103** is relatively simple, requiring only an alkylation of dialkyl

malonate with 5-bromopent-1-ene, followed by saponificiation of the malonate to provide the desired substrate (Figure 5.21).

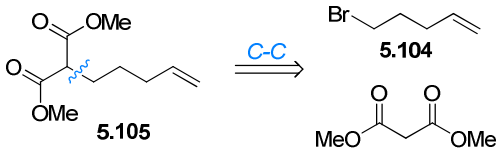
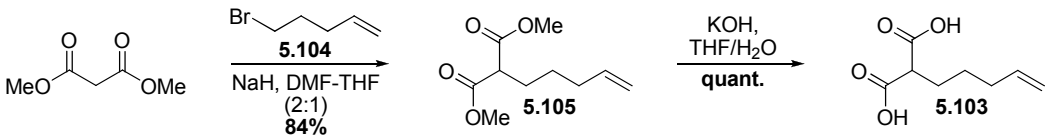


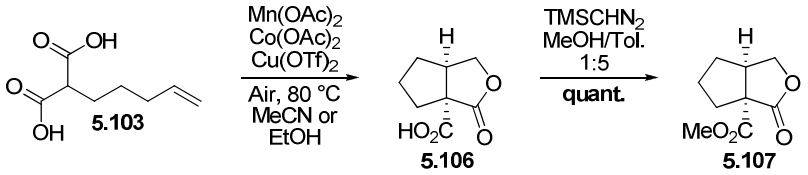
Figure 5.21: Retrosynthesis of substrate 5.107

Synthesis of substrate **5.103** was completed by alkylation of dimethyl malonate with commercially available 5-bromopent-1-ene. Quantitative generation of the anion of dimethyl malonate anion by addition of the malonate to a suspension of washed sodium hydride in DMF provided the alkylation partner to which the alkyl bromide was added (Scheme 5.33).



Scheme 5.32: Synthesis of substrate 5.103

A series of reactions was then performed, varying the metal salts used, loading of metals and the solvent system. To compare the catalytic reaction, the familiar stoichiometric conditions were used, along with a stoichiometric loading of metals in which the loading of metal catalysts was lowered from 50 mol% to 1 mol% of each (Scheme 5.33). The reactions were heated in acetonitrile at 80° C for eighteen hours (as in the stoichiometric studies), and the crude reaction products were treated with TMS-diazomethane to generate a mixture of methyl esters rather than acids.



Scheme 5.33: Cyclisation of substrate 5.103

Expt.	Solvent	$Mn(OAc)_2$	$Co(OAc)_2$ Molar Equivalents	$Cu(OTf)_2$	**5.107** %
24	MeCN	2	1	1	66
25	EtOH	2	1	1	88
26	MeCN	0.5	0.5	0.5	75
27	MeCN	0.1	0.1	0.1	74
28	MeCN	0.05	0.05	0.05	81
29	MeCN	0.02	0.02	0.02	85
30	MeCN	0.01	0.01	0.01	86
31	MeCN	2	1	-	56
32	MeCN	0.1	0.1	-	57

Table 5.3: Results of cyclisation of 5.103 using stoichiometric and catalysts systems

The cyclisation was found to occur in all cases, but the yield of lactone was variable (Table 5.3). Most importantly, catalytic turn-over was evident in all cases where a substoichiometric quantity of metal salts was used. Significantly, it is interesting that in the case of runs 8 and 9, the reaction proceeded to give a reasonable yield of lactone *in the absence of copper(II) salts*. However, it is possible that any trace amounts of copper(II) present in the system could perform the key lactonisation and then be reoxidised.

A proposed catalysis cycle is shown in "cartoon" schematic (Figure 5.22). The cycle begins with oxidation of the manganese(II) acetate precatalyst to manganese(III)

acetate by cobalt(II) acetate. The resulting cobalt(I) acetate is then reoxidised back to cobalt(II) acetate by oxygen. Meanwhile, the generated manganese(III) performs the usual oxidation of the substrate **5.103**, regenerating manganese(II) acetate which can re-enter the redox cycle. Educt radical **5.108** performs the expected 5-*exo*-trig cyclisation to yield adduct radical **5.109**, which is oxidised to the product by copper(II) triflate. The reduced copper(I) triflate then enters the redox cycle and is reoxidised back to copper(II) triflate by manganese(III) acetate or cobalt(III) acetate.

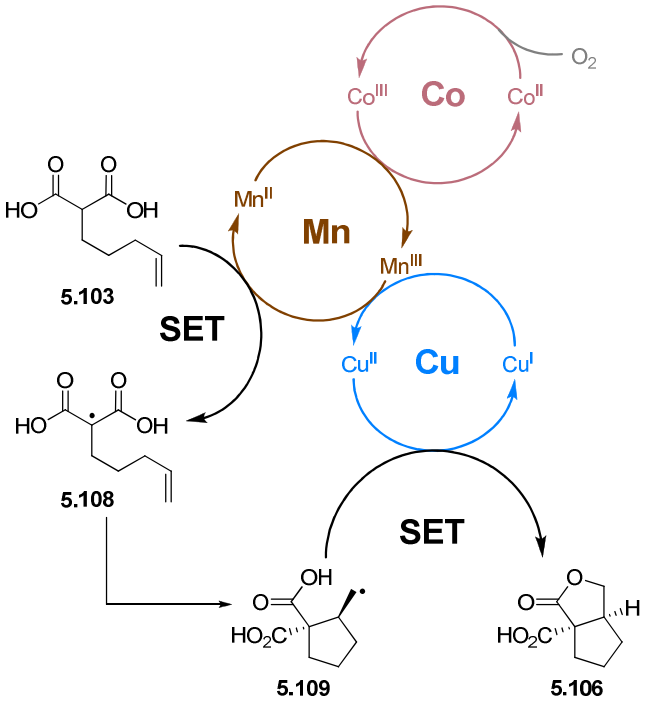
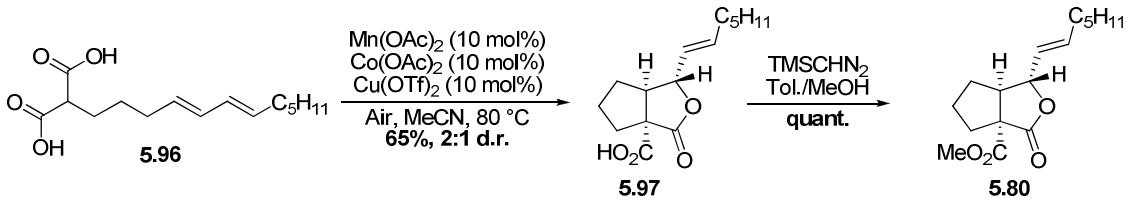


Figure 5.22: Cartoon represention of the cyclisation of 5.103

With a successful catalytic cyclisation possible for the simple substrate **5.103**, attention was turned to cyclisation of other substrates under the same conditions. A significant test of this methodology was to attempt cyclisation of diene **5.63**, for which cyclisation had proven more difficult. Using the malonic acid substrate **5.96**, previously found to be an effective substrate for cyclisation with stoichiometric metal conditions, a cyclisation was perfomed using 10 mol% of metal salt (Scheme 5.34).

Again, the crude mixture was treated with TMS-diazomethane to facilitate purification. The yield for the reaction was not quite as high as the stoichiometric system, but still provided lactone **5.80** in a 65% yield, as a 2:1 mixture of diastereoisomers.



Scheme 5.34: Cyclisation of diene 5.96 using catalytic system

5.11 Summary

In this chapter it has been demonstrated that δ,ε- unsaturated malonate derivatives are suitable substrates for cyclisation, with manganese(III) acetate and copper(II) triflate giving optimal reagents. Most effective were substrates bearing a terminal olefin moiety (**5.2**, **5.13**), but some successful reactions were carried out using secondary olefins (**5.19**, **5.20**, **5.24**, **5.25**). This reaction created two new rings and displayed a reasonable degree of diastereoselectivity .

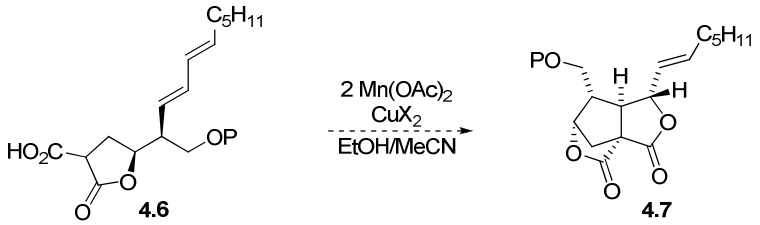
However, a 5,6-7,8-unsaturated malonate (**5.63**) did not cyclise efficiently. The problem was resolved by using a malonic acid derivative (**5.96**), which returned a good yield of the desired allylic lactone. Other substrates containing a malonic acid were found to cyclise more readily than the malonate derivatives, but the diene substrate was the most pronounced case.

Most recently, a catalytic variant of the cyclisation conditions has been developed, in which a redox cycle involving atmospheric oxygen has been demonstrated. This system returned a similar yield of the desired lactone product (**5.107**), using as little as 1 mol% of three different metal salts. This methodology was found to be effective in the cyclisation of a more complex diene substrate.

6 Studies Towards the Total Synthesis of the Prostaglandins

6.1 First Generation Approach to Key Substrate

The results detailed in the preceding chapter show that the cyclisation of a diene bearing a pendant malonic acid moiety was efficient, and could deliver the desired [3.3.0]-bicyclic lactone with reasonable degree of diastereomeric control. As a result, it was reasonable to assume that a substrate such as **4.6** would cyclise in the same manner to deliver the desired bis-lactone, **4.7**, ideally with the same efficiency (Scheme 6.1). Work therefore began on a synthesis of the lactone **4.6** using the approach detailed in the previously discussed retrosynthesis.

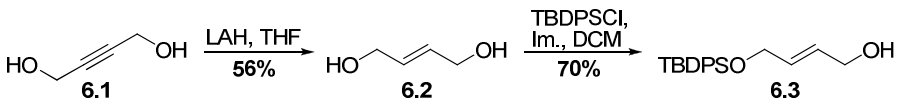


Scheme 6.1: Proposed cyclisation of substrate 6.35 to key lactone 6.36

The synthesis began with preparation of known epoxide **6.4**, which derived from a Sharpless asymmetric epoxidation of monoprotected diol **6.3**. This alcohol is a geometric isomer of the *cis*-butene-1,4-diol **5.7**, but the required *trans*-butene-1,4-diol, unlike *cis*-butene-1,4-diol, is not commercially available. *Trans*-butene-1,4-diol

was therefore produced *via* a vigorous reduction of butyne-1,4-diol with lithium aluminium hydride.[76] Although this procedure has been carried-out by many research groups, and is well documented, it was found difficult to reproduce. An initial problem was a lack of substrate solubility in the desired reaction solvent, THF. Purification of butyne-1,4-diol by hot filtration in THF did improve the yield of the reduction.

Attempts to reduce the purified acetylene were made using both powdered LAH, as well as the commercially-available solution (which delivered more reproducible results), but at no point did the isolated yield approach the literature values of 85-95%.[76] Performing the reduction on a larger scale was not a desirable option, as such large-scale hydride reductions can be rather hazardous. However, enough material was generated to proceed to the mono-protection step, which used the McDougal protocol familiar from previous work.[56] The TBDPS protecting group was chosen once again, owing to its ease of use and resilience to routine procedures. It was found that the *trans*- isomer of butene-1,4-diol was as effective a substrate as the *cis*-isomer, and that monoprotection proceeded smoothly.



Scheme 6.2: Synthesis of mono-protected *trans*-butene-1,4-diol

The substrate for the important Sharpless asymmetric epoxidation[52] was now complete, and the reaction was attempted using the optimised literature procedure.[77] It is not an overstatement that this reaction is one of the most important asymmetric processes. Using an inexpensive and naturally available ligand and a cheap metal centre allows the synthesis of a broad range of enantioenriched epoxides from allylic

alcohol substrates. In the case of the epoxidation of allylic alcohol **6.3**, the epoxide **6.4** was synthesised in excellent yield and enantiomeric excess (Scheme 6.3). The expected transition state is shown (Figure 6.1).

Scheme 6.3: Sharpless Epoxidation of allylic alcohol.

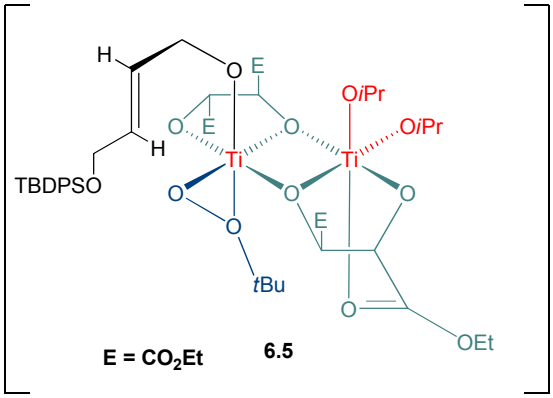
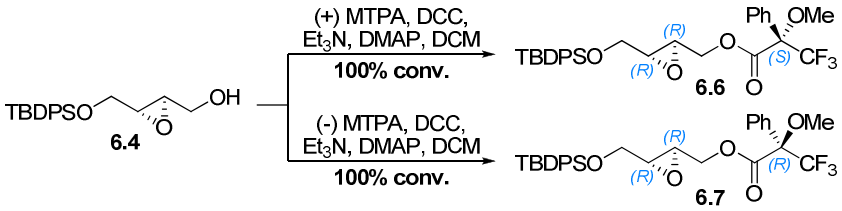


Figure 6.1: Proposed transition state for Sharpless asymmetric epoxidation

Diethyl tartrate was chosen as the source of chirality, as this was the simplest and cheapest option, and commercially available titanium isopropoxide was used without further purification. The yield of this reaction was found to be very reproducible, and no optimisation was required to achieve this. The enantiomeric excess was measured by conversion of the free epoxy alcohol to a pair of Mosher's esters. This was performed using commercially available MPTA acid chlorides; care was taken to ensure completion of reaction before analysis, eliminating the possibility of kinetic resolution (Scheme 6.4).[78] Analysis of the crude reaction mixture by both ^{1}H and ^{19}F NMR showed a predominance of one diastereoisomer in both cases (Figure 6.2), and comparison of integrals showed that the ratio of isomers was greater than 95:5, thus

implying that the epoxide **6.4** had been formed with at least a 90% enantiomeric excess (^{1}H NMR (500 MHz, $CDCl_3$) 4.63 (1H, dd, *J* = 12.3 Hz, 3.1 Hz, C*H*HO(C=O)), 4.63 (1H, dd, *J* = 12.3 Hz, 5.5 Hz, C*H*HO(C=O)), 3.83 (1H, dd, *J* = 12.1 Hz, 3.1 Hz, C*H*HOTBDPS), 3.77 (1H, dd, *J* = 12.1 Hz, 4.1 Hz, C*H*HOTBDPS), 3.56 (3H, s, *OMe*), 3.21-3.19 (1H, m, C*H*-O-CH), 3.06 (1H, td, *J* = 3.6 Hz, 2.1 Hz, C*H*-O-CH),). The absolute stereochemistry of **6.4** was assumed to be as shown and was proven by X-ray crystal structure analysis of a later intermediate.



Scheme 6.4: Formation of MTPA esters for determination of enantiomeric excess

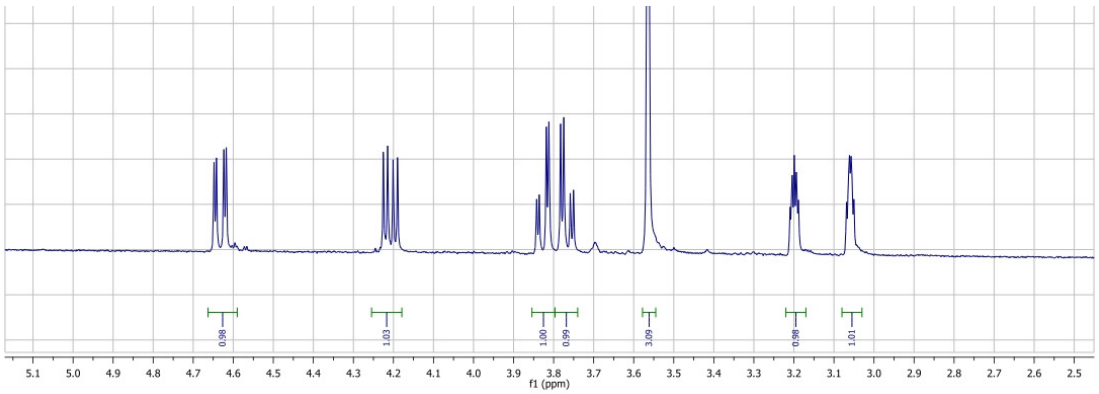


Figure 6.2: ^{1}H NMR spectrum for Mosher's ester 6.6 from 5.1ppm to 2.5 ppm

After achieving excellent enantioselectivity, attention was turned to control of the regioselectivity in the opening of the newly installed epoxide. In such a system, the epoxide may be opened by a carbon-centred nucleophile at either the C-2 or C-3 position, depending upon the reagent used and the reaction conditions. It has been shown that the use of aluminium Lewis acids promotes addition at C-3 to generate the 1,2-diol;[79] conversely, the use of Gilman-type cuprates results in 1,3-diols (Figure

6.3).[80] However, in our synthesis the use of an acetylene anion (or equivalent) was required; however Gilman-type reagents derived from acetylenes are very unreactive – indeed acetylenes are often used as dummy ligands in heterocuprates.[81]

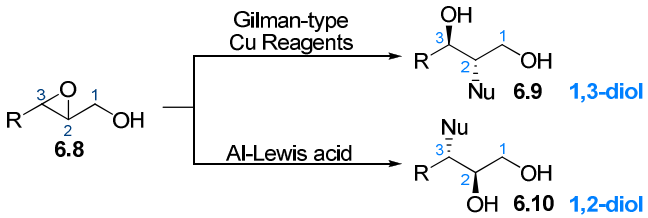
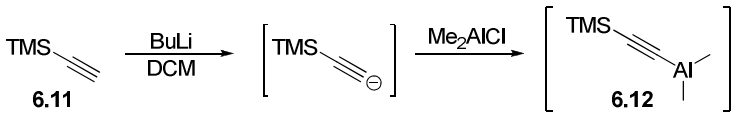


Figure 6.3: Opening of epoxy alcohols by organometallics

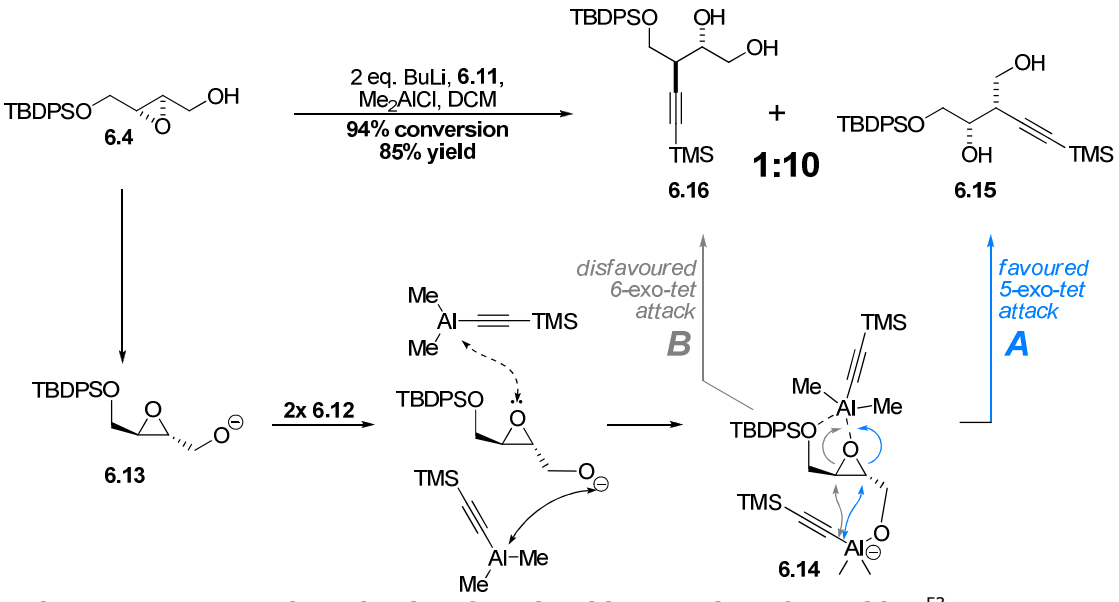
The recent publication of a new method for the opening of epoxy alcohols with aluminium Lewis acids in the desired manner (C-2 opening) was therefore of great interest. Miyashita's protocol was followed using TMS-acetylene as the nucleophile, and dimethyl aluminium chloride as the Lewis acid.[53] The first step of this reaction involves the formation of the aluminium based nucleophile, **6.12**, by addition of dimethyl aluminium chloride to a solution of deprotonated TMS-acetylene (**6.11**) (Scheme 6.5).



Scheme 6.5: Miyashita protocol for regio-controlled opening of epoxides.

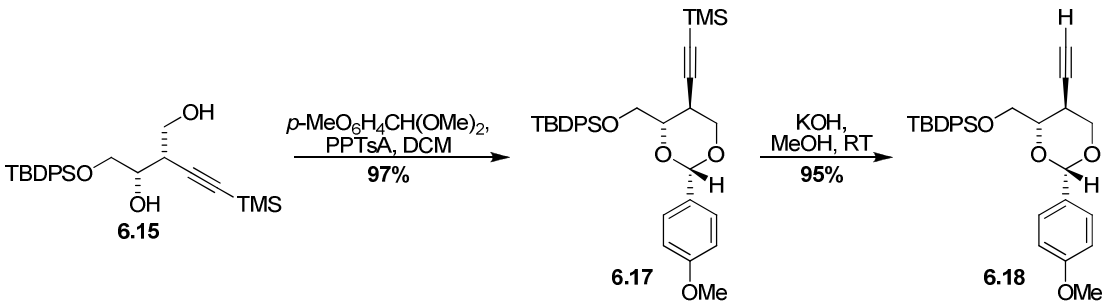
The nucleophile was then added to a solution of deprotonated epoxide (**6.13**). In the original publication, Miyashita postulates that an "ate" complex (in this case) **6.14** is formed between the deprotonated epoxide and the aluminium acetylide. A second equivalent of the aluminium acetylide **6.12** then activates the epoxide for ring-opening. The "ate" complex can then break-down in two ways; pathway A results in a favoured 5-*exo*-tet attack of the acetylene-aluminium bond into the epoxide,

resulting in 1,3-diol **6.15**. Conversely, the acetylene-aluminium bond may attack in a less favoured 6-*exo*-tet manner to form 1,2-diol **6.16**; pathway B.



Scheme 6.6 Proposed mechanism for Miyashita opening of epoxides.[53]

The epoxide opening proceeded in good yield, returning an excellent 10:1 ratio of the desired 1,3-diol to the unwanted 1,2-diol isomer, which was easily removed by flash column chromatography. The regiochemistry of the opening of the epoxide was proven by X-ray crystal structure analysis of a later intermediate (*vide infra*).



Scheme 6.7: Protecting group manipulation of diol 6.15

To proceed with the planned hydroboration of the acetylene, protection of the diol was necessary. The *para*-methoxybenzylidine acetal group was chosen, which would subsequently offer the opportunity for selective conversion to a *para*-methoxybenzyl ether and a free alcohol. Treatment of diol **6.15** with a solution of *para*-methoxybenzylidine dimethyl acetal resulted in clean protection, and the crystalline intermediate **6.17** was isolated. A crystal of this acetal was grown, and X-ray diffraction led to confirmation of the relative and absolute stereochemistry (Figure 6.4).

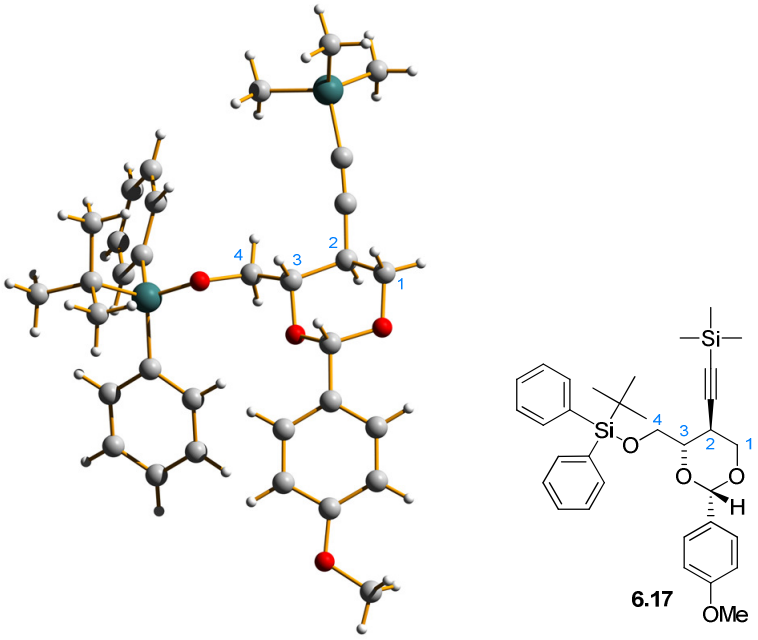
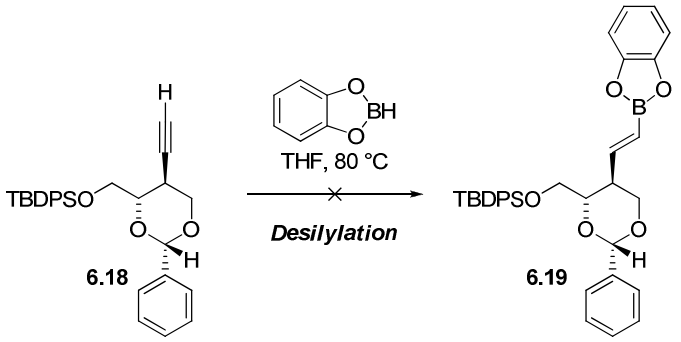


Figure 6.4: X-Ray structure of acetal 6.17

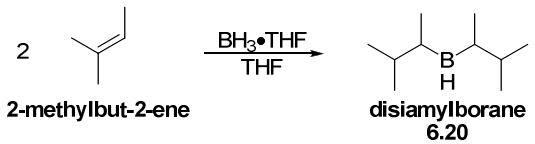
Removal of the TMS group was initially performed on a small scale using Amberlyst-26. However, this reaction was exceptionally slow when working on a larger scale (>500mg), so potassium hydroxide was then chosen as the base for this deprotection, which then proceeded efficiently (Scheme 6.7).

With the synthesis of the terminal acetylene **6.18** was complete attention was turned to its hydroboration. Success with catechol borane as a hydroboration reagent in the methodology phase of this project suggested that it might be employed in this case, but unfortunately a significant loss of the TBDPS protecting group occurred with this reagent (Scheme 6.8).



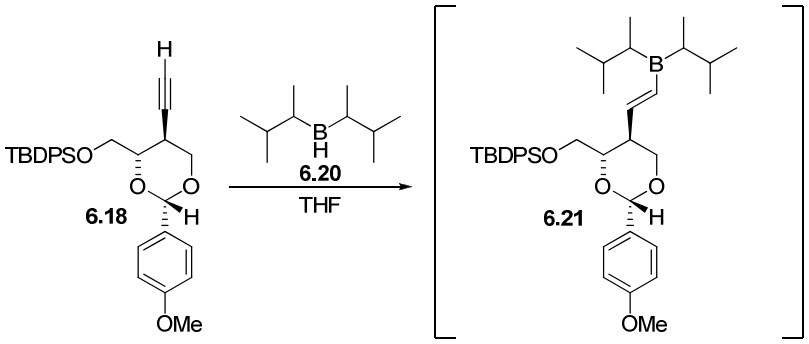
Scheme 6.8: Attempted hydroboration of acetylene 6.18

Although numerous alternatives are available for this transformation, many are expensive, so the first considered was the cheap and commonly used disiamyl borane.[82] This reagent is not commercially available, as it decomposes in a relatively short time, but can be purchased as a kit compromised of borane-THF complex solution and 2-methylbut-2-ene solution. Combination of these reagents in a 1:2 ratio at 0 °C, resulted in a 0.5 M solution of disiamyl borane solution which was used directly (Scheme 6.9).



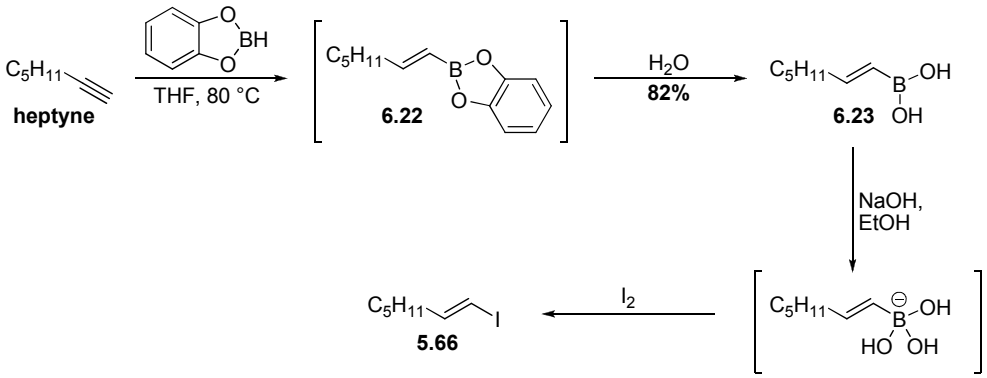
Scheme 6.9: Preparation of disiamylborane

Addition of this solution to acetylene **6.18** at room temperature, followed by warming to 80 °C, resulted in apparent clean conversion of the acetylene (Scheme 6.10). Rather than attempting to isolate the borane, it was used directly in the Suzuki coupling.



Scheme 6.10: Hydroboration of acetylene 6.18 with disiamylborane

Although the vinyl iodide partner, **5.66**, had previously been produced *via* a hydroalumination/iodination protocol in the methodology phase of this project, the hazardous nature of this procedure and the low yield led us to examine an alternative. An alternative hydrometallation might be perfomed, such as hydroboration, and then conversion to the vinyl iodide would provide the same product *via* a potentially milder procedure.[83,84]

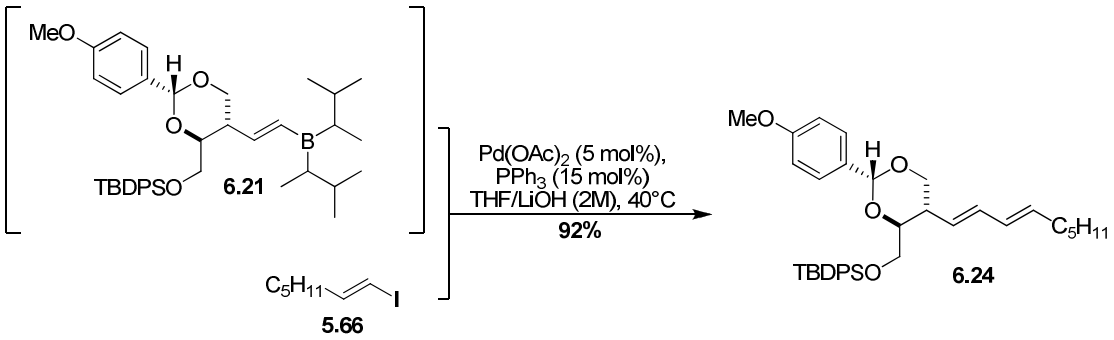


Scheme 6.11: Alternative synthesis of vinyl iodide 5.66

Thus, heptyne was treated with catechol borane in the usual manner to produce catechol-boronic ester **6.22**, which was immediately treated with water to hydrolyse the boronic ester and deliver vinyl boronic acid **6.23** (Scheme 6.11). However, as in earlier work, difficulty arose in removing the liberated catechol from this boronic acid which resulted in low yields for the subsequent iodination reaction.

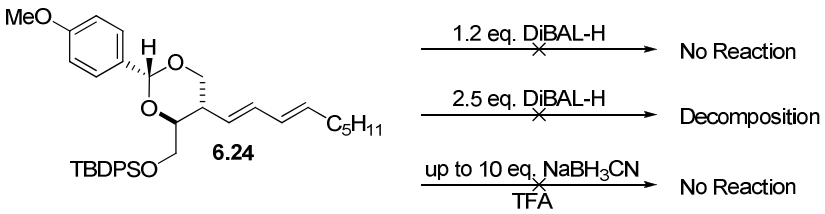
Nevertheless, it was found that the boronic acid **6.23** from commercial sources was very pure and readily underwent iodination in good yield to generate a clean sample of the desired vinyl iodide **5.66**. This reaction follows the same general process shown in the previous chapter, but is more likely to follow mechanism B.

With a convenient preparation of vinyl iodide **5.66** developed, and an efficient route to vinyl borane **6.21** in place, the Suzuki coupling was attempted using the same protocol as before, developed from a procedure by Pattenden (Scheme 6.12).[67] Initially, the reaction was attempted using the same ratio of iodide to borane as was previously successful; 1:1.2. This gave an excellent yield of diene **6.24**, the configuration of which was shown to be the desired (*E*,*E*)-isomer by ^{1}H NMR analysis (δ_H (400 MHz, $CDCl_3$) 6.20 (1H, dd, *J* = 15.2 Hz, 10.3 Hz, CH=*C*H), 5.97 (1H, dd, *J* = 15.0 Hz, 10.3 Hz, C*H*=CH), 5.67 (1H, dt, *J* = 15.2 Hz, 7.0 Hz, CH=C*H*), 5.49 (1H, s, ArC*H*), 5.18 (1H, dt, *J* = 15.3 Hz, 9.1 Hz, C*H*=CH). However, in this system, the borane partner is the more valuable, and thus the reaction was attempted using the converse ratio, and with success. Unfortunately, using a 1:1 ratio of both partners was not as well tolerated, and a significant proportion of proto-deborylation was evident.



Scheme 6.12: Suzuki coupling of vinyl borane and vinyl iodide

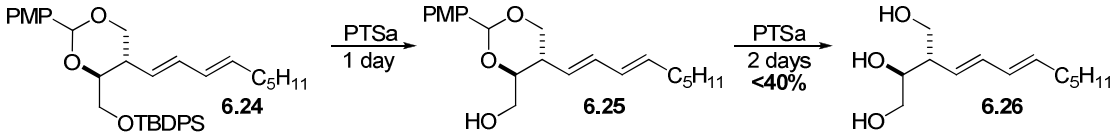
With a successful synthesis of the diene now in place, attention turned to the selective deprotection of the PMP-acetal. Examples in the literature suggest that reductive conditions (DiBAL-H, $NaBH_3CN$, Bu_3SnH) can effect this transformation,[85] to give either regioisomer of the product. Unfortunately, using DiBAL-H proved ineffective; addition of 1.1 eq. of reagent resulted in returned starting material, whereas an increased quantity led to substrate decomposition (Scheme 6.13). Sodium cyanoborohydride (with TFA) was also unsuccessful; even ten equivalents of reductant returned only starting material.



Scheme 6.13: Attempted reductive clevage of acetal 6.24

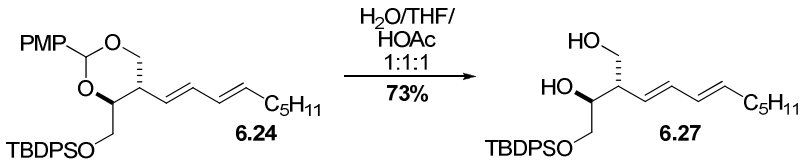
Because substrate **6.24** was the product of an eight-step sequence, and therefore rather precious, it was decided to simply remove the PMP acetal completely under acidic conditions, and then selectively protect the 1,3-diol using more conventional means. Treatment of **6.24** with PTSA, however, gave an unexpected desilylation product (**6.25**) rather than the expected diol **6.27** formed by hydrolysis of the PMP acetal

(Scheme 6.14). Resubmission of this material to the reaction conditions, and increasing the amount of PTSA to five equivalents eventually led to triol **6.26**, but in a poor yield. No remaining starting material **6.24** or alcohol **6.25** was present, so it is suspected that decomposition of the diene had occurred.



Scheme 6.14: Deprotection of PMP acetal with PTSA

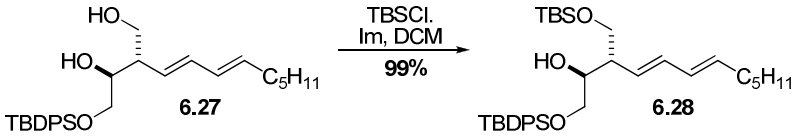
A survey of the literature found descriptions of several protocols for the deprotection of acetals such as **6.24**, and thus the same reaction was attempted using a 1:1:1 solution of H_2O/THF/AcOH (Scheme 6.15).[86] Under these conditions the desired diol **6.27** was the only isolated product. It is not clear why one organic acid favours desilylation but the other acetal hydrolysis.



Scheme 6.15: Alternative conditions for deprotection of PMP acetal

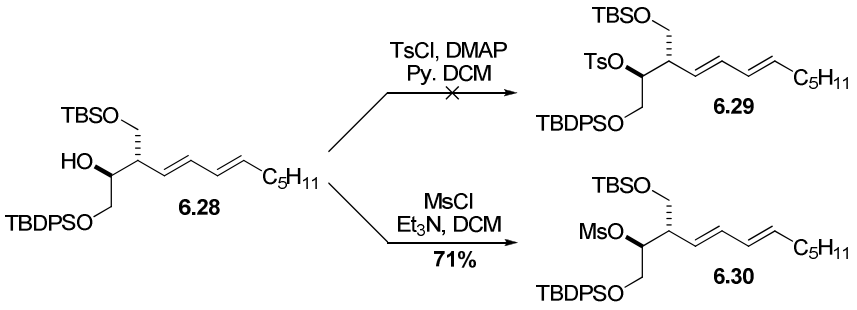
With complete deprotection of the acetal now possible, attention turned to monoprotection of the resultant diol. This was expected to be straightforward, as the primary hydroxyl should react far faster than the secondary alcohol, resulting in the desired protection. This manipulation was completed with ease – using 1 equivalent of TBSCl, a reasonable yield (72 %) of TBS ether **6.28**; the mass-balance was made up of unreacted starting material (Scheme 6.16). No bis-protection was evident, so

the amount of TBSCl used was increased to 1.5 equivalents, which increased the yield of **6.28** to 99% without evidence of bis-protection.



Scheme 6.16: Monoprotection of diol 6.27

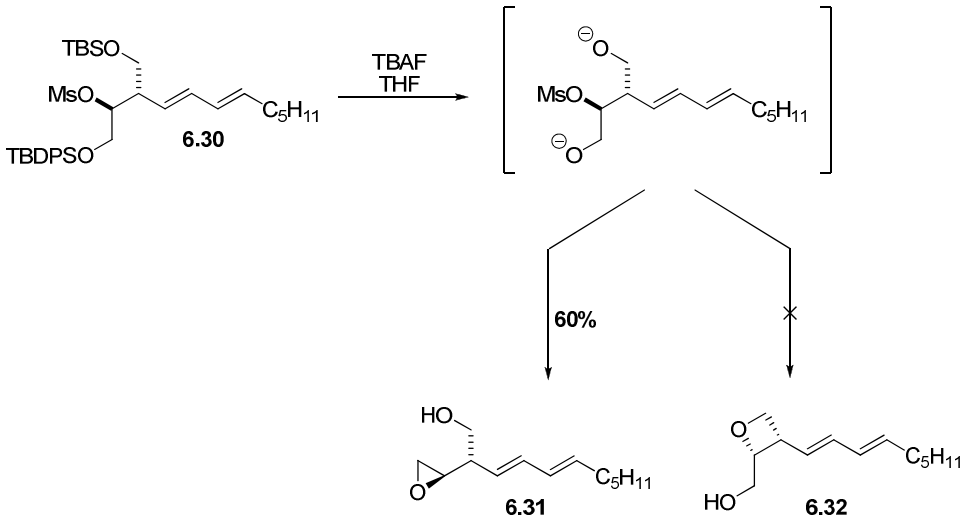
The next procedure required was conversion of the free secondary alcohol in **6.28** into the corresponding sulfonate ester using tosyl chloride or mesyl chloride. Initial attempts to install a tosyl group, using standard reaction conditions, failed with none of tosylate **6.29** isolated (Scheme 6.17). However, mesylation was far more successful, and a good yield of mesylate **6.30** was isolated. Presumably, this is because of the rather hindered nature of the secondary alcohol.



Scheme 6.17: Sulfonation of alcohol 6.28

Treatment of mesylate **6.30** with TBAF was expected to remove both silyl protecting groups, and, in the absence of an acid buffer, provide a basic environment for epoxide formation. This proposal was reduced to practice, using 2.5 equivalents of TBAF in THF with no AcOH buffer returned epoxide **6.31** as a single diastereoisomer in good

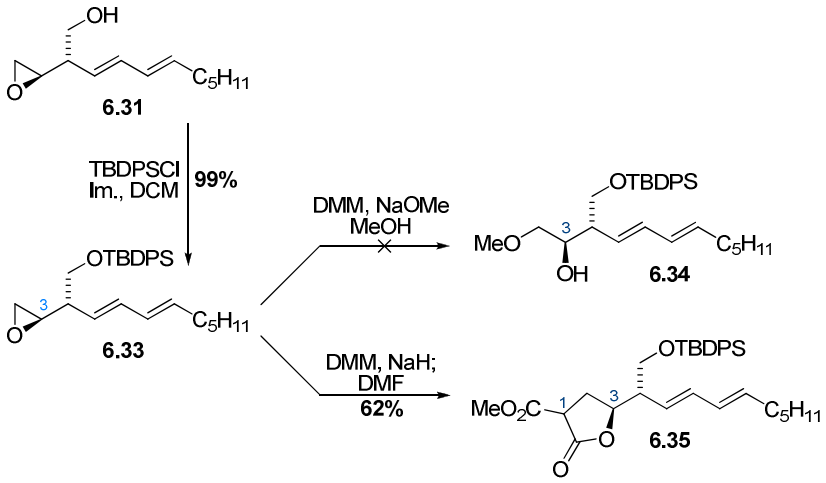
yield (Scheme 6.18). No oxetane product **6.32** was isolated, presumably as three-membered ring formation is kinetically faster than four-membered ring formation.



Scheme 6.18: Formation of epoxide 6.31 *via* deprotection

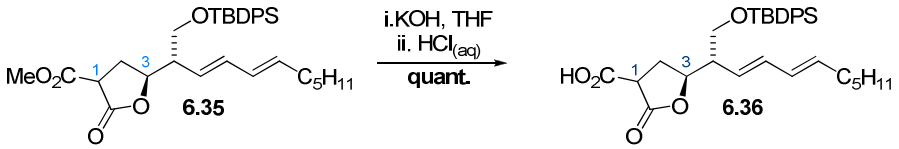
To proceed with the planned malonate opening of the newly installed epoxide, the free primary alcohol required reprotection. Again, the TBDPS group was chosen, and the protection reaction proceeded in good yield (Scheme 6.19). A survey of the literature then suggested that the best conditions for the epoxide opening would be to use an alkoxide base and dialkyl malonate, e.g. sodium methoxide and dimethyl malonate.[87] These conditions were attempted, but surprisingly, the only product isolated was methyl ether **6.34**, along with returned starting material (Scheme 6.19). Varying the number of equivalents of base or malonate used did not improve this result. Our previous success in the alkylation of malonates with mesylates had involved quantitative generation of the malonate anion and these conditions were successful with the epoxide **6.33**. Thus, an excess of malonate anion was prepared in DMF using sodium hydride, and a solution of epoxide added to this at 0 °C. This produced a reasonable yield of lactone **6.35**, along with returned epoxide. The lactone

was isolated as a 1:1 mixture of epimers at the C-1 position, but this was inconsequential as this stereochemistry was lost in the manganse(III) acetate radical formation. The yield could be increased by heating the reaction to 80 °C for sixteen hours, but the reaction could not be forced to completion by further heating or by increasing the amount of either dimethyl malonate or base employed.



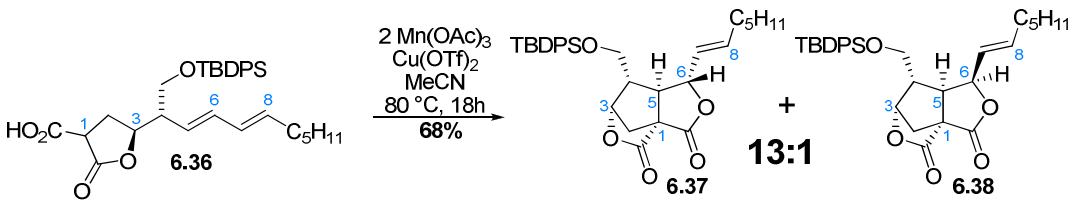
Scheme 6.19: Opening of epoxide with dimethyl malonate

As in the model systems, saponification of the ester moiety was required to generate a free carboxylic acid for efficient lactone formation in the manganese(III) acetate cyclisation. In this case, though, the starting material was no longer a symmetrical dialkyl malonate, but a β-methyl ester γ-lactone. It was expected that treatment of **6.35** with base would both saponify the ester and the lactone, and that the latter would reform upon acidification. In practice, hydrolysis of the **6.35** under basic conditions followed by acidification delivered the desired β-carboxylic lactone **6.36** as a mixture of epimers at the C-1 position (Scheme 6.20). The fact that the lactones were not diastereomerically pure was inconsequential, as the manganese(III) mediated cyclisation begins with enolisation of the β-dicabonyl compound and hence all stereochemical information at this centre is lost.



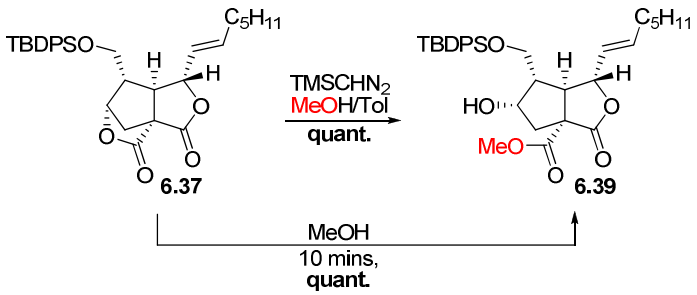
Scheme 6.20: Completion of key substrate

This transformation completed the synthesis of the desired cyclisation precursor, and thus the stage was set for the key cyclisation. This was performed using the same conditions as before, with two equivalents of manganese(III) acetate and one equivalent of copper(II) triflate in acetonitrile. After heating at 80 °C for eighteen hours, the reaction appeared to be complete; the lactone **6.37** (Scheme 6.21) was isolated in good yield (68% yield), with crude NMR indicating excellent diastereomeric control (13:1 **6.37**:**6.38**). The structure of **6.37** was assigned by extensive proton and carbon NMR experiments. Moreover, the infra-red spectrum of **6.37** showed the presence of two gamma-lactones (ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 1813 s (C=O *bridged lactone*), 1727 s (C=O *lactone*)). The bridged gamma-lactone in **6.37** is more strained and hence has a higher ν_{max}. High resolution mass spectrometry is fully consistent with the proposed structure (***m/z*** (ESI+) Found: $(M+Na)^+$, 555.2335; $C_{25}H_{34}NaO_3Si$ requires *M*, 555.2335).



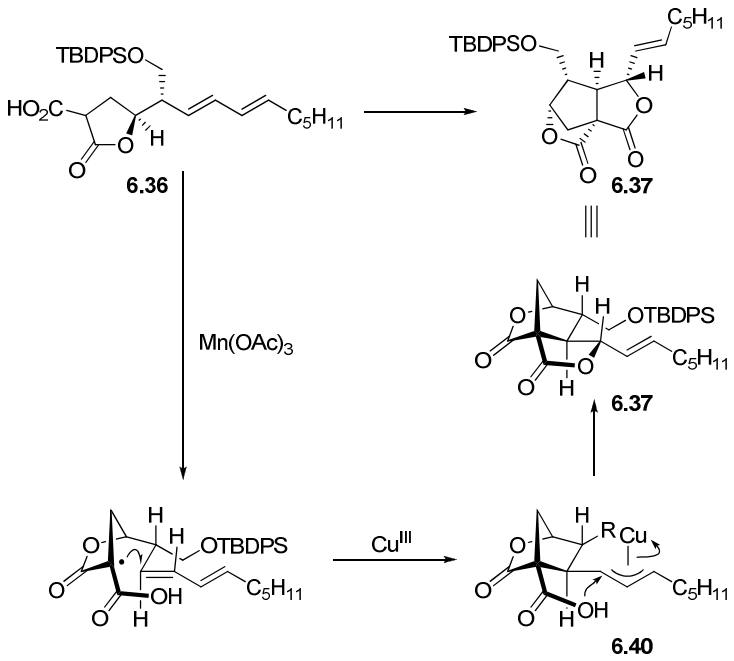
Scheme 6.21: Cyclisation of key substrate 6.35

Analysis by TLC indicated very polar material which was suspected to be either remaining starting material or carboxylic acid-containing products. The product mixture was therefore treated with TMS-diazomethane in toluene/methanol, which removed the baseline spots (Scheme 6.22). However, the major product from this reaction was ester **6.39**, which was later produced by simply stirring bis-lactone **6.37** in methanol. It is therefore likely that the TMS-diazomethane was unnecessary, and that more strained, and therefore more labile lactone is opened by methanol to create **6.39**. This was later confirmed by simple solvolysis of **6.37** in methanol, which delivered a quantitiative yield of **6.39**.



Scheme 6.22 Opening of labile lactone by methanol

It seems reasonable to conclude that the base-line spots evident on TLC analysis of **6.37** corresponded to a small proportion of the bis-lactone which was ring-opened on the (slightly acidic) TLC plate. The crude reaction mixture was then submitted to flash column chromatography to obtain a purified sample, which was found to be a mixture of epimers **6.37** and **6.38**, with a 13:1 ratio in favour of the desired diastereoisomer **6.37**. This particularly high degree of stereochemical control may result from the lactone moiety already present in **6.36**, which rigidifies the transition state for the conversion of **6.36** to **6.37** (Scheme 6.23).



Scheme 6.23: Postulated mechanism of cyclisation accounting for high d.r.

It was planned to make several derivatives of **6.36** to probe this transition state, and of course to bring more material through this route towards total synthesis, but thus far the route had been rather lengthy and low yielding. Of the problems encountered, many could be overcome through a revised protecting group strategy, but it was decided at this point to consider an alternative route.

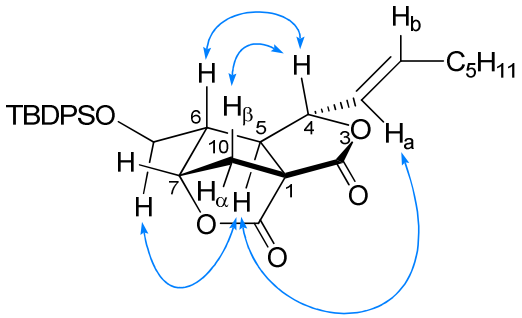


Figure 6.5: Stereochemical Analysis of 6.37 and 6.39

The stereochemistry of both **6.37** and **6.39** were assigned on the basis of extensive ^{1}H and ^{13}C NMR analysis (Figure 6.5). The stereochemical analysis of **6.37** was

complicated by the the fact that the resonances corresponding to H-6 and one of the protons attached to C-10 were overlapping. Nevertheless the stereochemistry of **6.39** could be assigned as shown according due to the following key ^{1}H-^{1}H nOes. Thus, H-4 showed a strong reciprocal nOe to the resonance consisting of both H-6 and one of the protons attached to C-10. Furthermore, H-4 showed a strong reciprocal nOe to the other proton attached to C-10. There is no possibility that H-4 can see both H-10β and H-10α and hence H-4 shows nOes to H-6 and H-10β. Furthermore, H-5 shows nOes to H-4, Ha and C*H*$_2$OSi – indicating that the CH$_2$OSi, H-5 and the alkene side chain are on the same face of the molecule. The stereochemical assignment for the tricyclic lactone **6.37** was further confirmed by ^{1}H-^{1}H nOe analysis of the bicylic lactone **6.39** where all of the key resonances are clearly separated. .

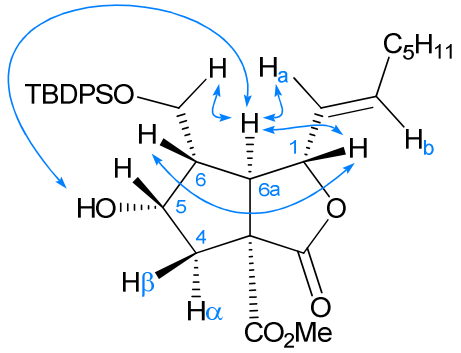


Figure 6.6: Stereochemical of 6.39

Thus, in **6.39**, H-1 shows a strong reciprocal nOe to H-6 (and to H-6a). Furthermore, H-6 sees a strong nOe to H-4β but not to H-4α, and a weak nOe to the H-6a. Similarly to the tricylic lactone **6.36**, the bridgehead proton H-6a has strong reciprocal nOes to the alkene proton Ha, C*H*$_2$OSi, and H-1, and a weak nOe to the OH proton. The above nOe data are consistant with the assigned structures for **6.37** and **6.39**.

6.2 Second Generation Approach Retrosynthesis

When examining the desired cyclisation precursor, **6.36**, it seems that displacement of a sulphonate ester such as **6.41** with dimethyl malonate anion would be an appropriate disconnection (Figure 6.7). Such a triol-derivative contains a pair of contiguous stereocentres, which could be created in an asymmetric alkylation. Further manipulation suggests that an asymmetric aldol reaction could allow introduction of these stereocentres, and that reduction of a suitable chiral auxiliary would leave one of the desired primary alcohols. Thus, an aldehyde such as **6.44** could react with diene **6.43** in a deconjugative manner, creating adduct **6.42** which contains both of the required stereocentres along with the key diene moiety.

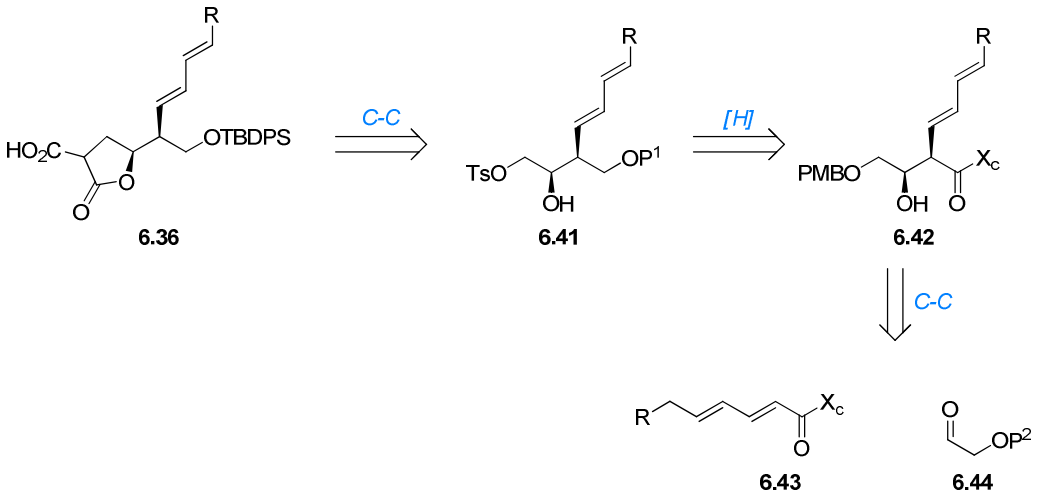
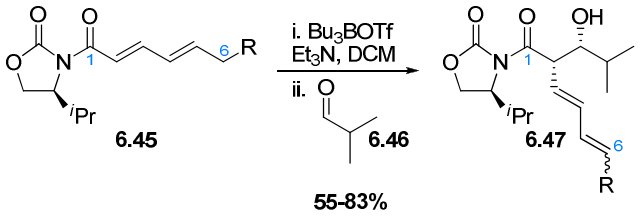


Figure 6.7: Second-generation retrosynthetic analysis of key substrate 6.40

In 1998, Takacs reported the regio- and diastereoselective boron-mediated aldol reaction of chiral dienoic *N*-acyl oxazolidinones, using the familiar Evans-type auxiliaries.[88,89]



Scheme 6.24: Aldol condensation of diene 6.45 with isobutyraldehyde

This procedure provides the two stereocentres required in the synthesis of the cyclisation substrate, but unfortunately, the control of diene geometry was not complete. It was found the aldol reaction of dienonic acid derivatives such as **6.45** with a suitable aldehyde such as isobutyraldehyde **6.46** resulted in the adduct **6.47** as a 1:1 mixture of geometric isomers at the C-6 position. The transition state for such a reaction is likely to be represented by chair-like TS **6.48**, in which the approach of the aldehyde **6.46** is controlled by the isopropyl group on the oxazolidinone and the dipole of the oxazolidinone and the aldehyde are opposed.[90] This results in an "Evans syn" addition,[89] with both the diene and the newly formed hydroxyl on the same face of **6.47** as drawn.

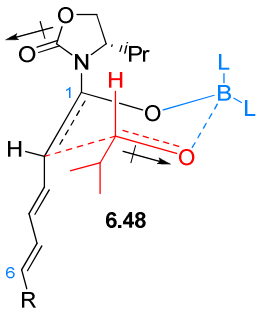


Figure 6.8: Stereochemical rationale of Evan's Aldol

However, a method of generating the required (*E*,*E*)-diene was suggested by Takacs, in which a skipped diene, such as **6.49**, might be used as the substrate. In this substrate, the desired (*E*)-configuration between C-5 and C-6 is already in place, and

following work by Schneider,[91] is likely to retain this geometry during the aldol reaction. Utilising this idea in a retrosynthesis of the desired cyclisation substrate leads to two partners for the aldol; skipped dienoic acid substrate **6.49**, containing the required auxiliary, and aldehyde **6.50** (Figure 6.9).

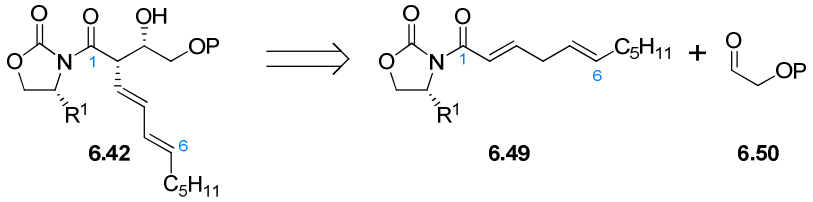


Figure 6.9: Retrosynthesis of aldol product 6.51

However, a synthesis of the skipped diene fragment appeared to be quite lengthy, and although this method would result in the same cyclisation substrate as used previously, **6.36**, it was decided to make an analogous substrate, **6.51**. The substrate benefits from a reduced complexity, as the terminal diene moiety has no possibility of geometrical isomerism analogous to that in **6.47**. The cyclisation of **6.51** should result in tricyclic bis-lactone **6.52**, analogous to cyclisation product **6.36**, to which it could be converted into **6.37** using cross-metathesis (Figure 6.10).

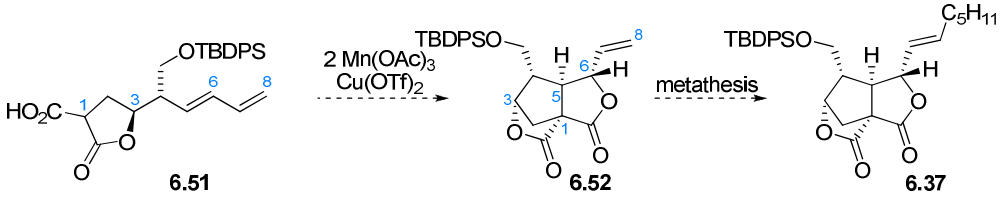


Figure 6.10: Proposed cyclisation of substrate 6.51 and olefin metathesis of product

A retrosynthetic analysis of substrate **6.51** then suggests that this substrate could be constructed in far fewer steps than the original substrate, **6.36** (Figure 6.11). Displacement of a suitable leaving group, such as tosylate, in **6.52** with dimethyl

malonate anion would give the lactone **6.51** after saponification/acidification. Reduction of the chiral auxiliary, followed by protection and tosylation would convert **6.53** into **6.52**, which itself is a product of an aldol condensation between diene **6.54** and aldehyde **6.55**. This aldehyde is known in the literature,[92] and can be made from ozonolysis of protected diol **6.56**. Most succinctly, the diene **6.54** can be made by simple acylation of sorbic acid with the desired auxiliary.

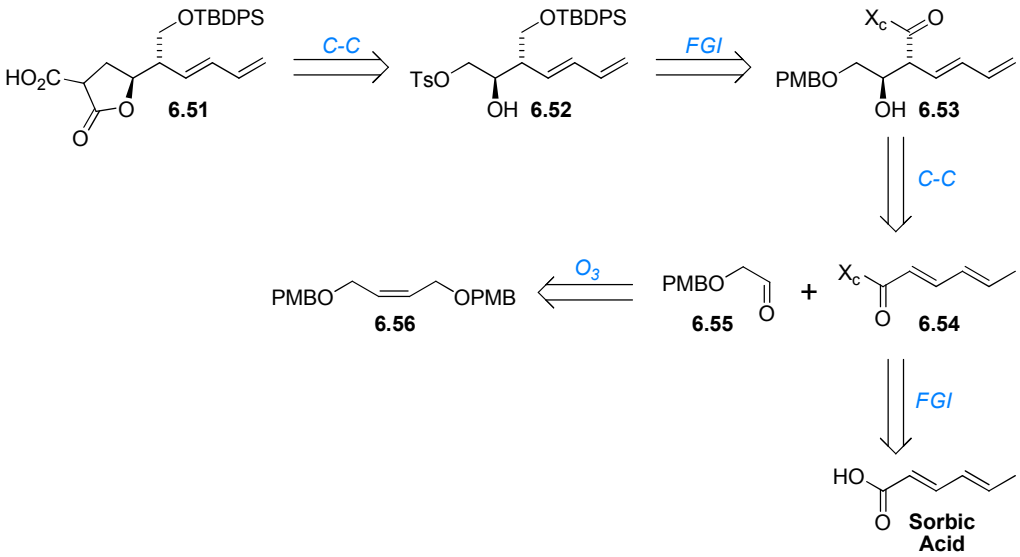
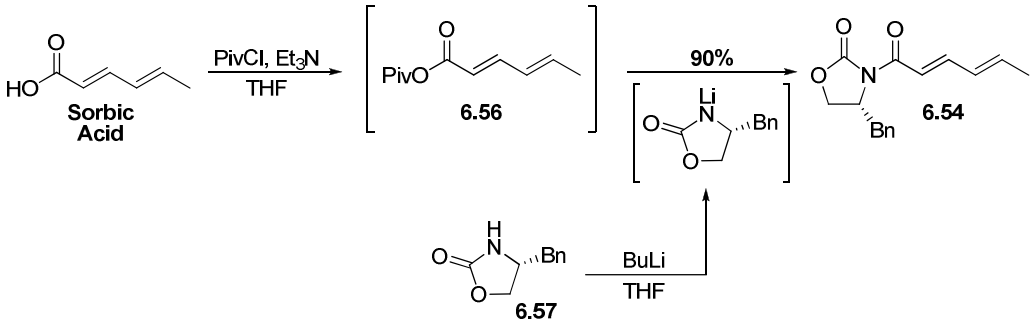


Figure 6.11: Retrosynthesis of cyclisation substrate 6.51

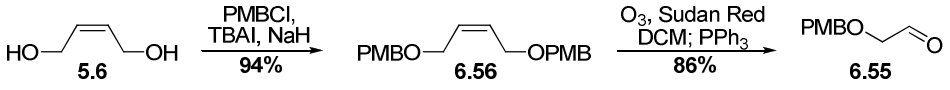
6.3 Second Generation Approach

With a new retrosynthesis planned, the first priority was the asymmetric deconjugative aldol required to set the two stereocentres required. Thus, sorbic acid was coupled with the desired auxiliary by firstly forming the pivaloyl mixed anhydride, followed by the addition of the metalated oxazolidinone (Scheme 6.25).[85] This convenient, one-pot procedure yielded the desired aldol substrate **6.54** as a crystalline solid in good yield.



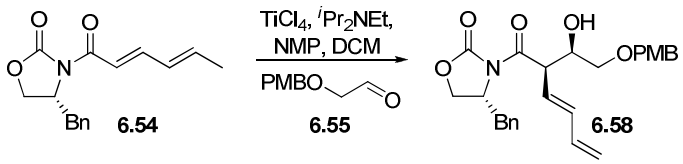
Scheme 6.25: Synthesis of N-acyl oxazolidinone 6.54

The aldehyde **6.55** was produced *via* bis-protection of *cis*-butene diol with PMBCl, using TBAI-mediated iodide catalysis, followed by ozonolysis of the alkene (Scheme 6.26).[92] A small amount of sudan red dye was used in the ozonolysis to indicate completion of alkene cleavage so as to avoid oxidation of the PMB groups. To quench the reaction, an excess of triphenylphosphine was added, from which the aldehyde was separated by distillation shortly before the aldol reaction.



Scheme 6.26: Synthesis of aldehyde 6.55

Initially, conditions similar to those used by Takacs were employed for the deconjugative aldol reaction. Rather than prepare dibutylboron triflate, though, the more easily prepared diethylboron triflate was used.[93] This was easily made by treating a commercially available solution of triethyl borane with neat triflic acid and stirring at 40 °C for a few minutes. Addition of the diene and triethylamine or Hunig's base, was followed by the freshly distilled aldehyde. However, no product was isolated from this reaction. Thus, it was decided to investigate a Crimmins[94] aldol reaction using titanium(IV) chloride as the Lewis acid in conjunction with one equivalent of NMP ligand. The initial run showed a reasonable yield of product, but it was found that lowering the amount of Lewis Acid used, along with the reaction temperature, resulted in an optimal yield (Scheme 6.27, **Error! Reference source not found.**Table 6.1).

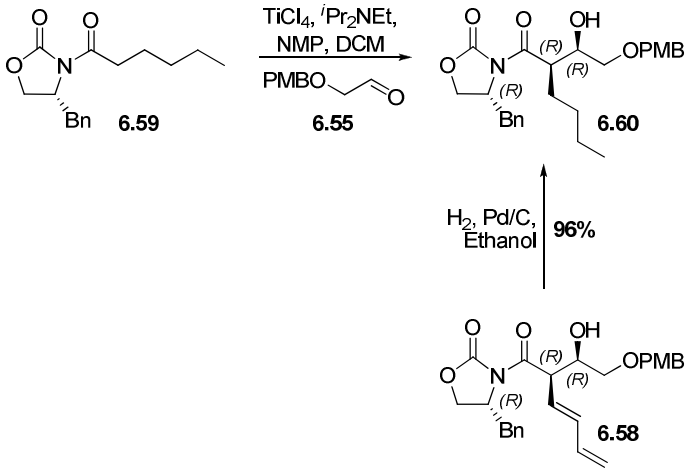


Scheme 6.27: Ti-mediated aldol addition

Expt.	Lewis Acid Equivalents	Reaction Temperature	d.r.	**6.58** %
1	1.0	0 °C	1.25:1	54
2	0.8	0 °C	5:1	68
3	1.0	-78 °C → -40 °C	7:1	80
4	0.9	-78 °C → -40 °C	18:1	84

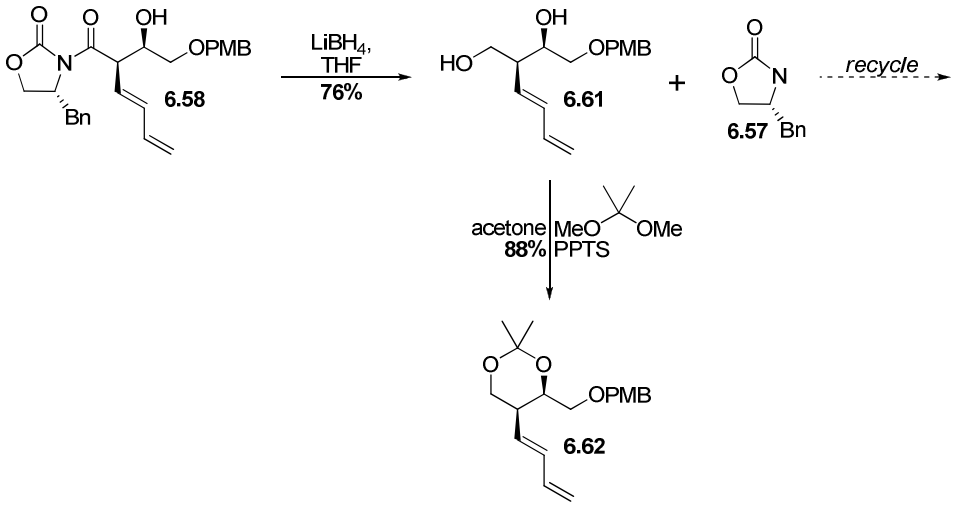
Table 6.1: Optimisation of aldol conditions

The stereochemistry of the aldol product was determined by extensive NMR analysis and by chemical derivation. Key to this was the aldol reaction of an analogous substrate, **6.59**. This substrate bears no unsatuaration, and thus is a standard substrate for the Crimmins conditions used, and was reacted in the same manner as substrate **6.54** to produce adduct **6.60**. This alcohol could also be produced *via* hydrogenation of **6.58**, confirming that the stereochemistry of **6.58** must be the same as **6.60** (Scheme 6.28). Further proof for the stereochemistry of the aldol product **6.58** is given below.



Scheme 6.28: Studies to assign stereochemistry of deconjugative aldol

With the deconjugative aldol reaction proceeding in good yield and with good diastereocontrol, attention now turned to the elaboration of **6.58** into the desired cyclisation substrate. This began with reductive cleavage of the chiral auxiliary. This diol **6.61** was formed in good yield and the auxiliary was recovered and could be recycled. Diol **6.61** was then treated with 2,2-dimethoxypropane to form acetonide **6.62**, which gave further stereochemical evidence (Scheme 6.29).



Scheme 6.29: Removal of auxiliary and further assignment of stereochemistry

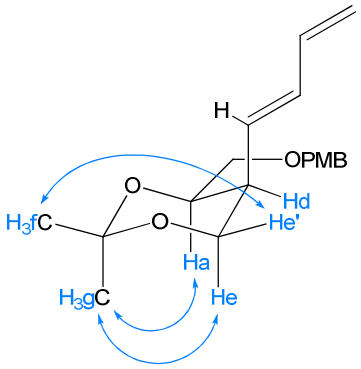


Figure 6.12: Selected nOe couplings for acetonide 6.62

The methyl groups containing protons H_3f and H_3g show different NOE contacts. H_3f shows a contact with He', whereas H_3g shows contacts with Ha and He, indicating that both protons are axial (Figure 6.12). Furthermore, extensive coupling constant analysis (Figure 6.14) confirmed the stereochemical assignment.

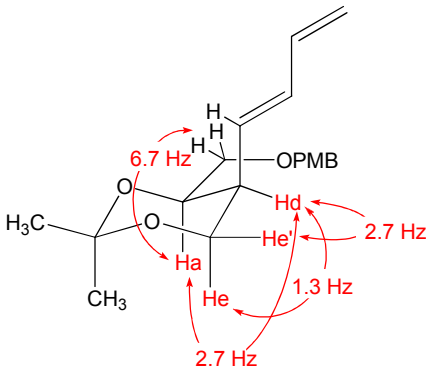
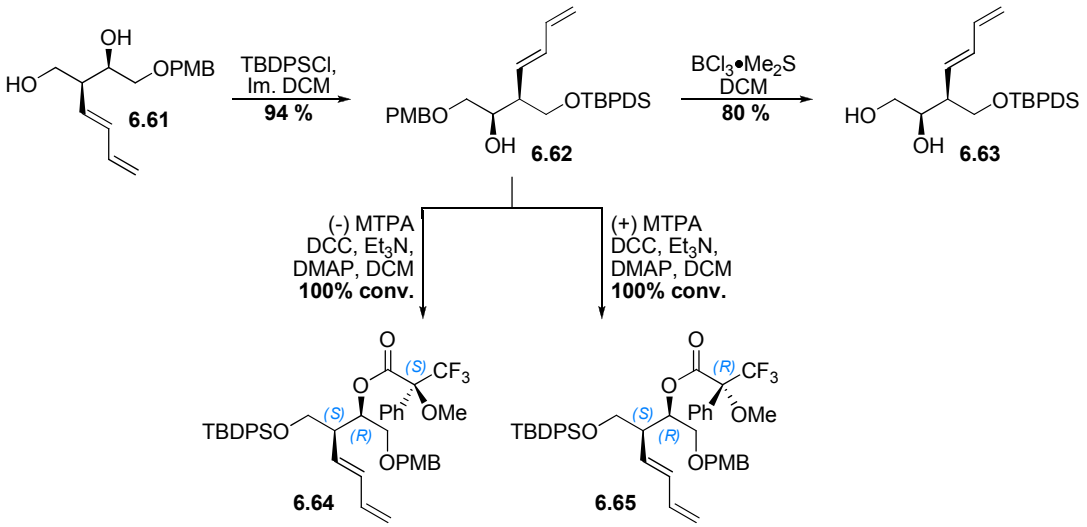


Figure 6.13: Selected coupling constants present in acetonide 6.62

The free primary alcohol **6.61** was then protected as the TBDPS ether **6.62**, with good regioselectivity and yield (Scheme 6.30). The silyl ether **6.62** was then treated with both enantiomers of Mosher's acid, using DCC to form a pair of diastereomeric esters. Analysis of these esters by NMR confirmed the absolute stereochemistry of the alcohol using the methods of Kakisawa.[95] The relative configuration of **6.61** had been established by coupling constant analysis and ^{1}H NMR nOe experiments and absolute configuration of the secondary alcohol in **6.62** had been confirmed by Kakisawa's extension of Mosher's method and hence the absolute configuration of the deconjugative Crimmins aldol reaction had been fully established.

The protecting group manipulations were then finalised by Lewis acid-mediated deprotection of **6.62** using the convenient Holmes procedure,[96] to give diol **6.63** in good yield.



Scheme 6.30: Protection of diol 6.59 and formation of MTPA esters.

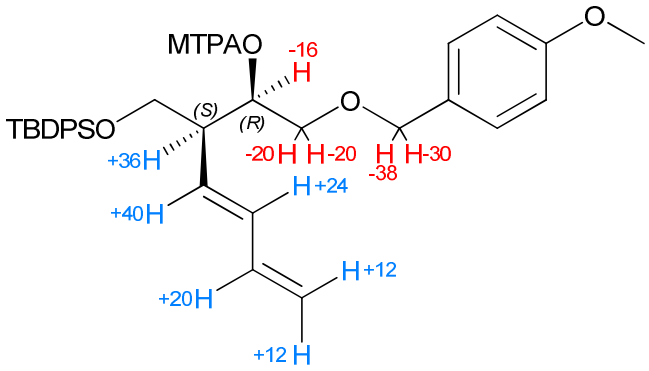
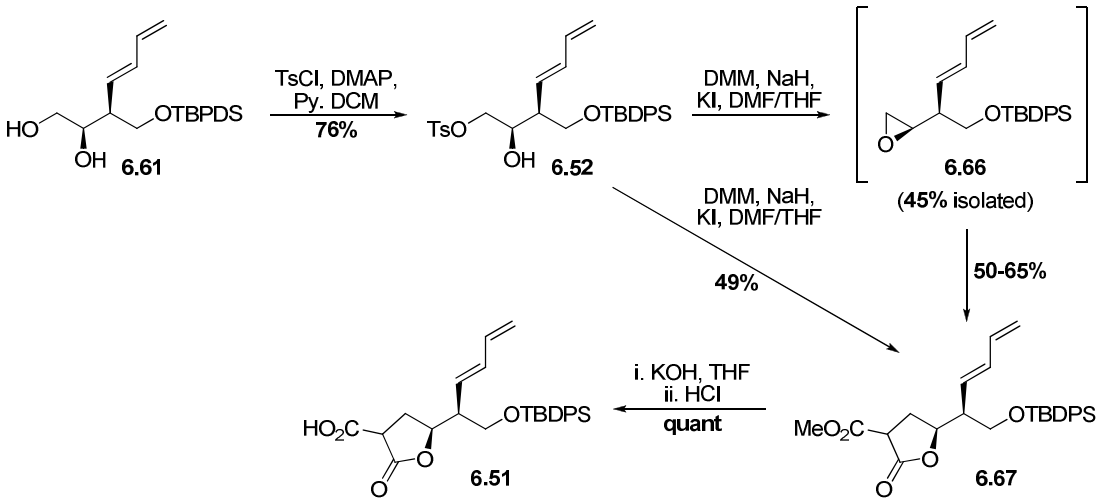


Figure 6.14: Assignment of configuration at C-3 by the technique of Kakisawa. The numbers are Δδ values for δ_S - δ_R for the two Mosher esters.

Diol **6.63** was sulfonated with tosyl chloride; care was taken as bis-tosylation was evident if an excess of tosyl chloride was used, unlike the mono TBS protection of the corresponding diol **6.27** (Scheme 6.31). The tosylate was then displaced with malonate anion, much in the same way as was used in the methodology phase of the project. Again, iodide catalysis was used to enhance the rate of reaction. An excess of sodium hydride was employed to allow *in situ* generation of the epoxide **6.66** from the tosylate **6.52**. The lactone **6.67** was isolated in 49% yield along with a 45% yield of the epoxide **6.66**. Unfortunately, this ratio of epoxide to lactone could not be

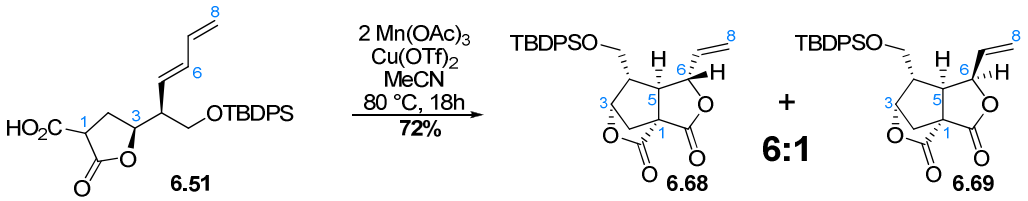
improved, but the epoxide could be converted to lactone by resubmission to the reaction conditions in a 50-65% yield



Scheme 6.31: Completion of synthesis of substrate 6.51

Saponifiction of the lactone-ester was carried out as before, completing the synthesis of the cyclisation substrate **6.51** in eight steps from sorbic acid.

Cyclisation of substrate **6.51** was very similar to the related **6.36** cyclised earlier; a slightly better combined yield of C-6 epimers was isolated with lower diastereocontrol (Scheme 6.32). The stereochemistry of the major, desired epimer **6.68** was ascertained by extensive nmr; a digram illustrating key nOe contacts is shown (Figure 6.15).



Scheme 6.32: Cyclisation of substrate 6.51

Several nOe contacts can be seen to proton H-4, most notably to protons H-10β, H-7, and H-6, all of which reside on the same face, suggesting that H-4 also does.

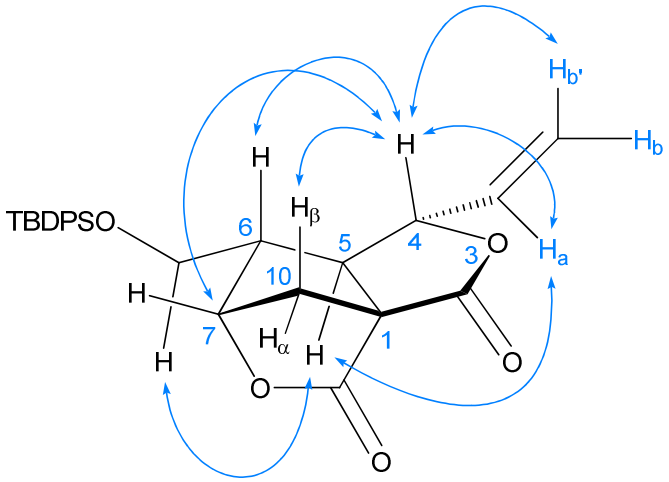
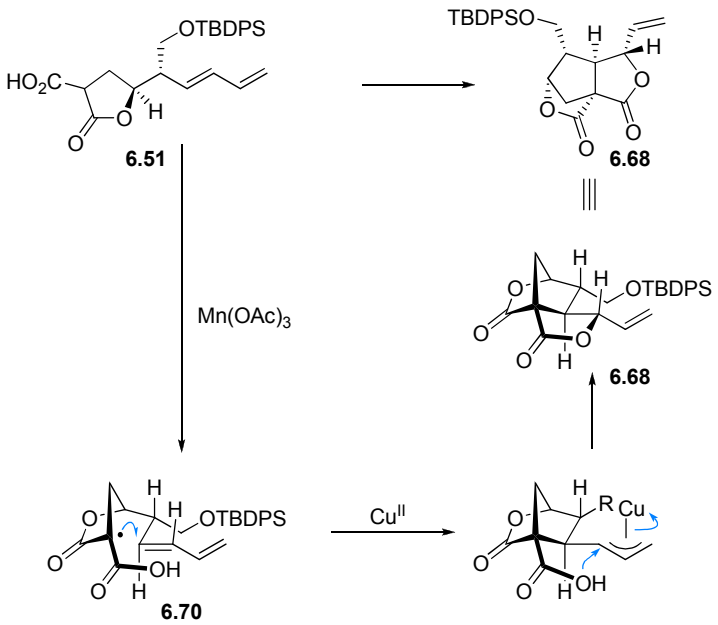


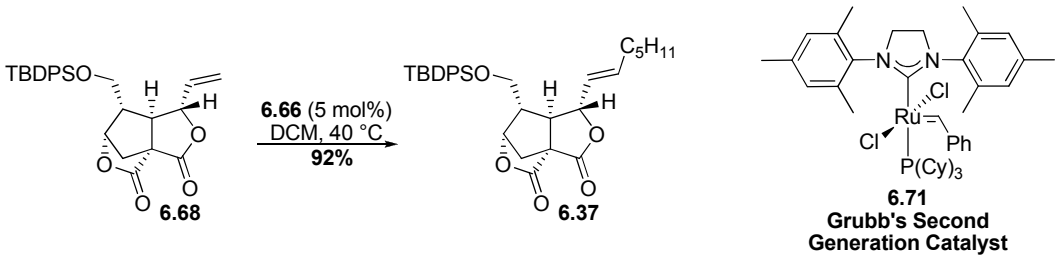
Figure 6.15: Stucture of lactone 6.68 showing selected nOes

The postulated mechanism for this cyclisation is similar to that proposed for substrate **6.35** and is postulated to occur from conformation **6.70**. As the substrate used in this case is a terminal diene, the reduced steric bulk in the substrate may be responsible for the reduced diastereoselectivity in the formation of **6.64** (Scheme 6.33).



Scheme 6.33: Proposed cyclisation mechanism and stereochemical rationale

Conversion of cyclisation product **6.68** into the previously synthesised **6.37** was performed using olefin cross-metathesis.[97] In this case, terminal olefin **6.68** would react with hept-1-ene to add on the required C_5H_{11} side chain and complete the synthesis of this intermediate. However, analysis of work published on cross-metathesis suggested that hept-1-ene will dimerise quickly under metathesis conditions to yield dodec-6-ene. Fortunately, it was thought that this dimer would also be metathesis active, and would participate in cross-metathesis with **6.64**.[98] A solution of hept-1-ene, Grubbs second-generation catalyst (**6.66**) and tricyclic bis-lactone **6.64** in DCM was found to produce **6.36** (along with a mass-balance of dodecene) after only two hours (Scheme 6.34).



Scheme 6.34: Metathesis of substrate 6.64 to give original product 6.37.

6.4 Analogous Cyclisations

With the second generation route proven to be a more succinct route to a cyclisation substrate, and the cyclisation completed successfully, two analogous substrates were designed to investigate the scope of the cyclisation process (Figure 6.16).

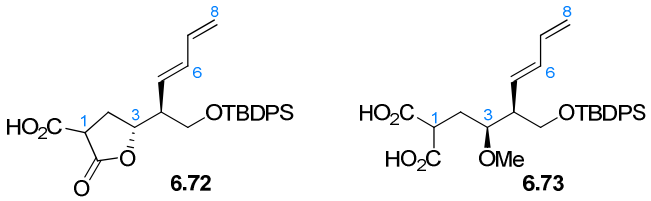


Figure 6.16: Analogous cyclisation substrates

The first, **6.72**, is a diastereoisomer of the previously used substrate **6.51**. The second, **6.73**, is a variant of **6.51** in which there is no longer a lactone moiety, but a malonic acid. The secondary hydroxyl in this substrate has been methylated to prevent lactone formation. Cyclisation of **6.73** will investigate the role of the lactone moiety in **6.53**, and whether, as suspected, it aids diastereomeric control by providing additional constraint in the cyclisation transition state. Retrosynthetic analysis of both substrates suggests that they can be made from an intermediate in the synthesis of **6.51** (Figure 6.17):

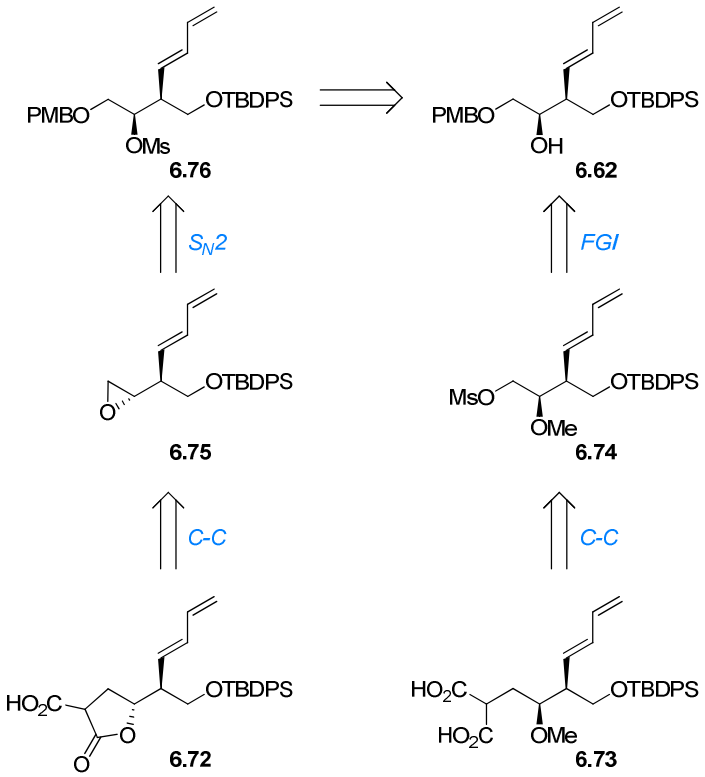
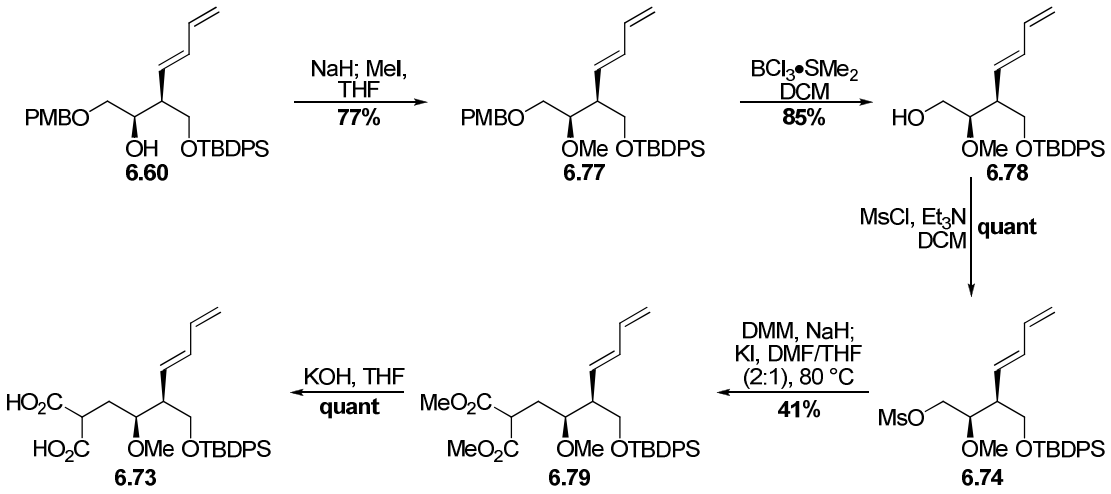


Figure 6.17: Retrosynthetic analysis of substrates 6.72 & 6.73

Manipulation of the free secondary alcohol in bis-protected triol **6.62** will generate mesylate **6.76**. Removal of the PMB protecting group then permits manipulation of the now free primary alcohol, allowing intramolecular cyclisation and displacement to provide epoxide **6.75**, a diastereoisomer of epoxide **6.66**. This can then be converted to substrate **6.72** by opening of the epoxide by dimethyl malonate and saponification in a similar manner as before.

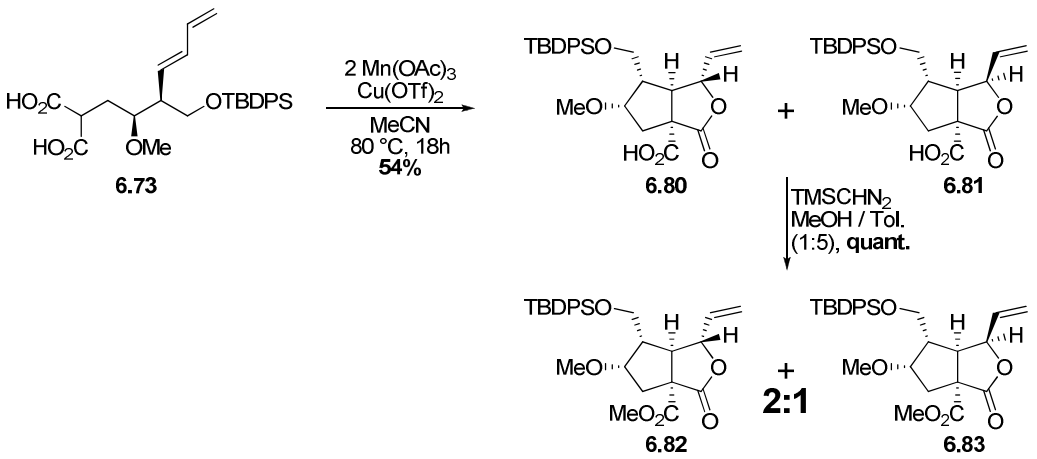
Methylation of the free secondary alcohol in **6.62** effectively provides a small and resilient protecting group for this position. The PMB group can be removed and replaced by a mesylate to provide **6.74**, which can be displaced in usual manner by dimethyl malonate anion. Saponification will then provide malonic-acid based substrate **6.73**.

Synthesis of cyclisation substrate **6.73** then began with methylation of the alcohol **6.62**, which was completed simply by quantitative deprotonation with sodium hydride and then treatment with methyl iodide (Scheme 6.35). The methyl ether **6.77** was then treated with BCl_3•SMe_2 complex, which efficiently removed the PMB protecting group. The resulting primary alcohol **6.78** was mesylated in excellent yield to provide the mesylate **6.74**, which was displaced with dimethyl malonate anion using the same conditions that were found to be successful before.



Scheme 6.35: Synthesis of substrate 6.73

Using the same cyclisation protocol as for **6.51**, substrate **6.73** was treated with manganese(III) acetate and copper(II) triflate in acetonitrile at 80 °C for eighteen hours. The crude reaction mixture was analysed by NMR, and was found to contain a mixture of products (Scheme 6.36). The product mixture was treated with TMS diazomethane as before to generate a mixture of methyl esters which could be more easily analysed. This mixture was found to contain a reasonable yield of the desired lactone, again as a mixture of diastereoisomers, but in this case in a considerably less favourable ratio.



Scheme 6.36: Cyclisation of substrate 6.71

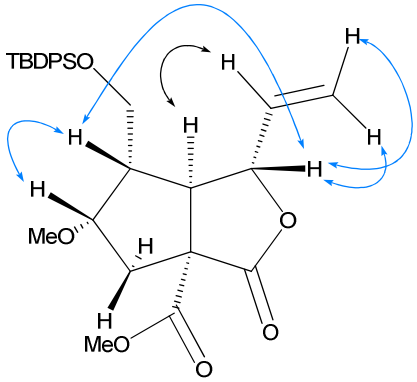
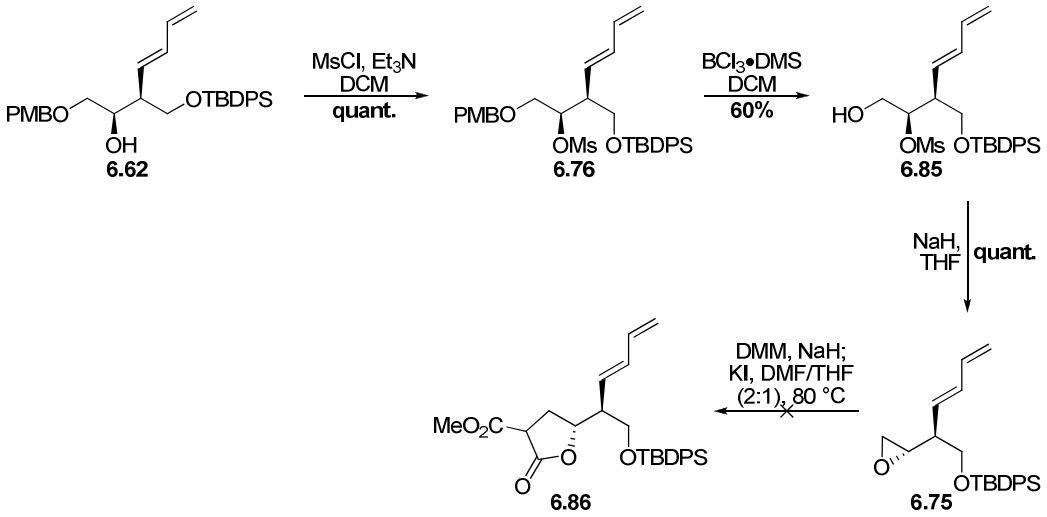


Figure 6.18: Structure of lactone 6.82 including key nOes

A possible rationale for the reduced degree of diastereoselectivity in the cyclisation is that there is no longer a lactone moiety in the starting material. This lack of rigidity suggests a more flexible mechanism / transistion state and thus may manifest in a lower diastereomeric ratio.

Synthesis of substrate **6.73** began with the same starting material as the previous synthesis (Scheme 6.37). In this case, the free secondary alcohol in **6.62** was mesylated using standard conditions, and then the PMB group was removed from mesylate **6.76** using Holmes' conditions to deliver mesylate **6.85**. The relatively poor

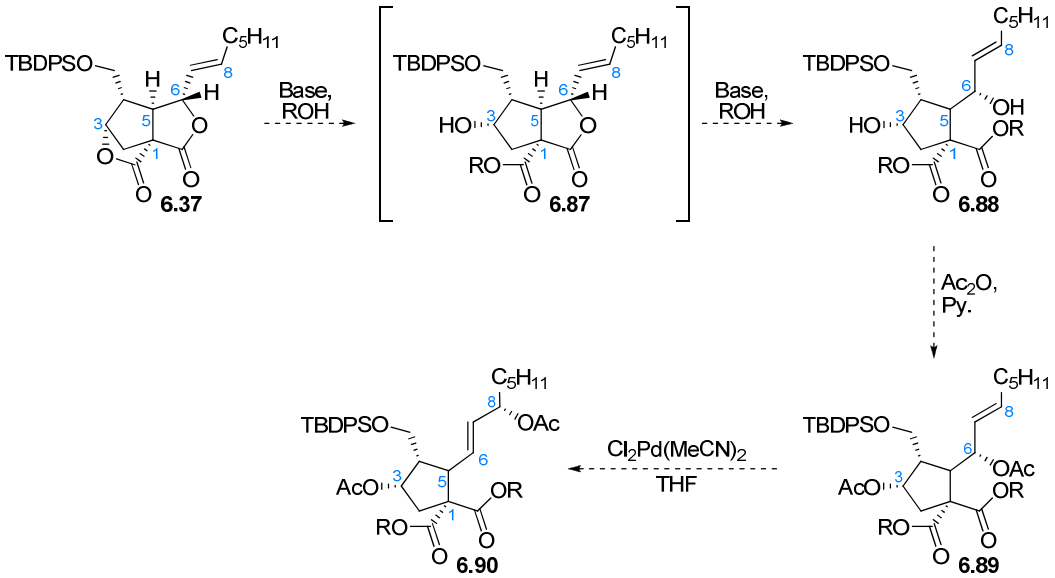
yield for this deprotection can be accounted for by the sensitivity of the mesyl group to the strong Lewis Acid conditions. Nevertheless, enough mesylate **6.85** was produced to continue; this was treated with sodium hydride to induce intramolecular cyclisation. Epoxide **6.75**, a diastereoisomer of epoxide **6.66**, was produced in good yield, and was then treated with the same conditions as **6.66** in an attempt to form lactone **6.86**. However, this reaction behaved entirely differently, and rather than opening the epoxide to form the lactone, the epoxide decomposed. Two further attempts were made, in which a small excess of malonate and sodium hydride were used, but the result disappointingly remained the same.



Scheme 6.37: Attempted synthesis of lactone 6.86.

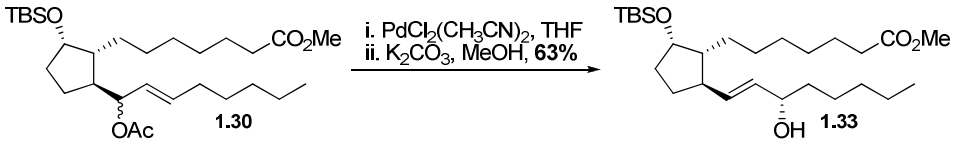
6.5 Elaboration Of Key Lactones

With an efficient synthesis of the key lactone **6.37** now possible, our attention was turned to transformation of the lactone into a substrate suitable for the planned Overman-type rearrangement. This required opening of the lactone to provide allylic acetate **6.89**, which could be treated with a catalyst such as dichloro bis-acetonitrile palladium(II) to induce a formal [3,3] sigmatropic rearrangement (Scheme 6.38).



Scheme 6.38: Proposed forward synthesis allylic acetate 6.90

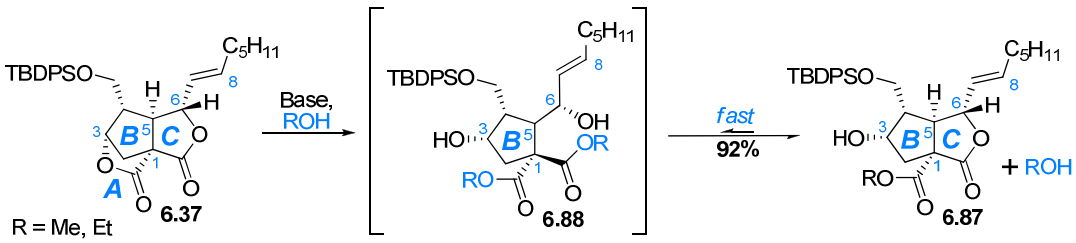
Such rearrangements are reasonably well known, and have been used in the course of a total synthesis of the prostaglandin family, as shown in Shibasaki's synthesis of 11-deoxy-$PG_{1\alpha}$ (Scheme 6.39 - reproduced from Chapter 1.).



Scheme 6.39: Overman rearrangement featured in Shibasaki's work

First, however, it was required to open the lactones to allow installation of the acetate group onto C-6. Dissolution of the bis-lactone in alcoholic solvent and addition of base would presumably form the desired product **6.88**, but only mono-lactone **6.87** was isolated; presumably any diol formed had relactonised. Extended reaction times, increased quantities of base and/or heated could not alleviate this problem.

This can be rationalised by considering that the lactone ring labelled **C** is far less strained that that of lactone ring **A**. Indeed, under the basic conditions, lactone **6.87** will be in fast equilibrium with opened species **6.89**, but reformation of the five-membered ring is far more favourable than protonation (Scheme 6.40).



Scheme 6.40: Attempted opening of C-ring lactone

Although alternatives to alcohol solvents are known to be more effective, a lack of time meant that the synthetic efforts towards the prostaglandin family were halted at this point.

6.6 Summary

The first-generation approach was proven to be an effective route towards the desired cyclisation substrate, but the protecting group strategy was found to be imperfect. Cyclisation of the key diene substrate gave the desired allylic lactone in good yield and with excellent diastereomeric control. However, it was decided that this route was too lengthy, and a second generation approach was then designed.

This route relied upon a key chiral-auxiliary controlled deconjugative aldol. Although similar work has been demonstrate in the literature, this was the first successful deconjugative Crimmins-type aldol reaction, which provided the desired aldol product in good yield. Elaboration of this product to the desired cyclisation substrate was completed quickly and easily, and the cyclisation proved to be almost as effective as that produced in the first generation approach. This allylic lactone was then transformed into the product from the first generation approach using Grubbs olefin metathesis in excellent yield.

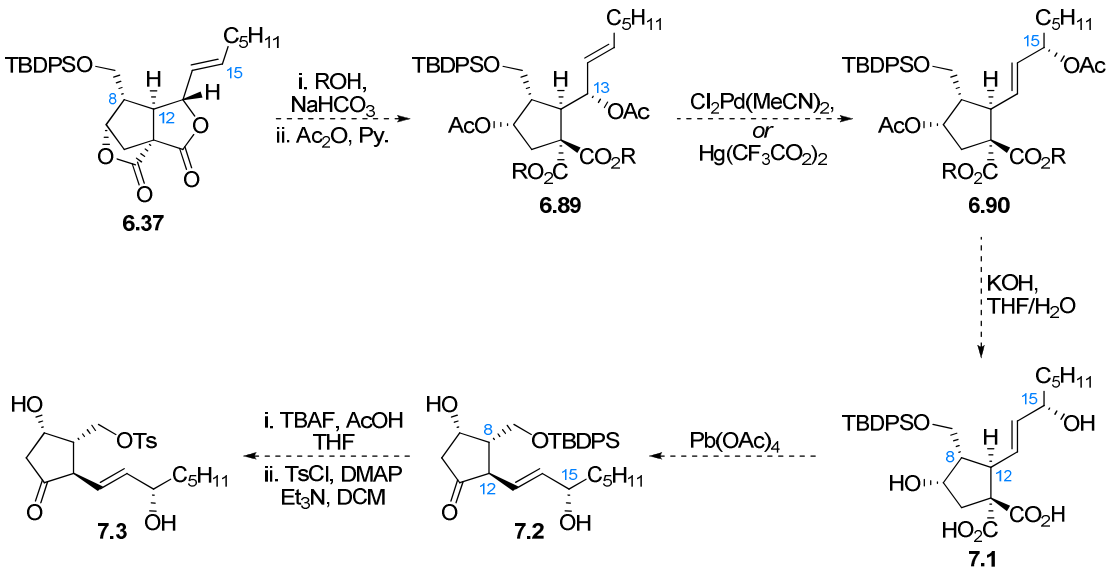
Elaboration of this lactone (now available from both routes) towards the natural product was unfortunately halted, as the lactone could not be opened irreversibly. Lack of time meant that this reaction was not optimised, but it is expected that this transformation will be possible in the future.

7 Future Work

7.1 Total Synthesis

Although a total synthesis of the prostaglandin family was not completed, it is still eminently possible. The first boundary to overcome is the opening of the C-ring lactone to allow acetate formation. Attempts were made to perform this transformation using simple alcohols (methanol and ethanol), which were unsuccessful. However, use of a more bulky alcohol such as *tert*-butanol or perhaps an amine (thus forming the analogous amide) might permit this transformation (Scheme 7.1).

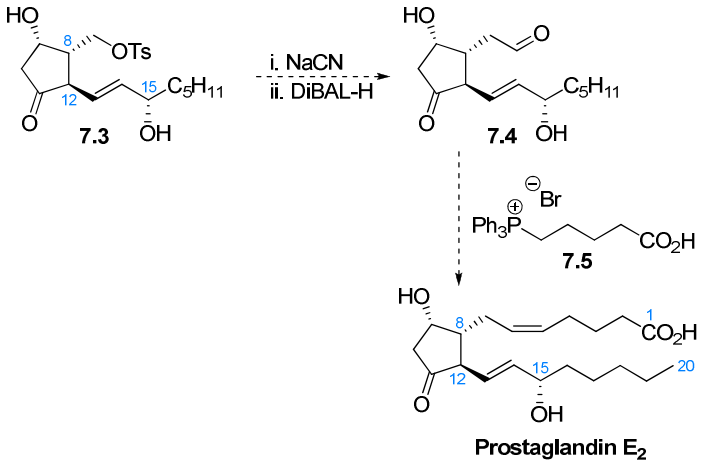
With the allylic alcohol freed from the lactone, it should be possible to acetylate this using standard conditions. It is likely that the C-9 alcohol will also be acetylated under these conditions, but this is of no consequence. Treatment of the allylic alcohol with either a palladium(II) catalyst, or less attractively, mercuric trifluoroacetate, will promote an Overman-type [3,3]-sigmatropic rearrangement.[99,100] The resulting allylic acetate resembles the product of a 1,3-acetate shift, and contains the desired C-15 hydroxyl, with the desired stereochemistry. The transfer of stereochemistry results from the suprafacial cyclic transition state predicted for the [3,3]-sigmatropic rearrangement.



Scheme 7.1: Proposed opening of lactone, rearrangement and oxidative cleavage.

Following rearrangement, the acetate group is no longer required, and thus can be saponified by base. The basic conditions will also saponify the C-9 acetate, along with both esters, resulting in a geminal bis-carboxylic acid. Such species are known to be cleaved by lead(IV) acetate to generate a geminal bis-acetate, which can be hydrolysed to the corresponding ketone in work-up.[101]

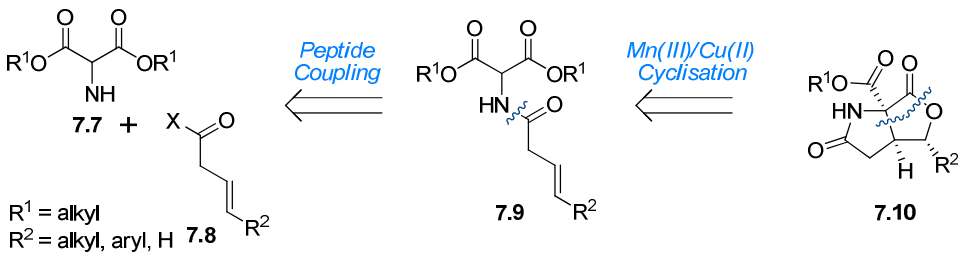
With the cyclopentane core of the prostaglandin complete, and the ω-sidechain installed, only the α-sidechain need be introduced. The most promising strategy involves homologation, beginning with cleavage of the silyl ether, and selective tosylation of the now free primary alcohol (**7.3**, Scheme 7.2). Displacement of the tosyl group with cyanide will provide the required one-carbon homologation, which can be reduced to the required aldehyde **7.4** with DiBAL-H. The sidechain may then be installed *via* a Wittig olefination using the commercially available salt. As this substrate is a non-stabilised Wittig salt, the reaction should be *Z*-selective, generating the required *cis*-double bond required, and completing the synthesis of prostaglandin E_2.



Scheme 7.2: Appendage of α-sidechain.

7.2 Methodology

In the course of this project, it has been demonstrated that the manganese(III) acetate cyclisation of unsaturated malonates can be used for the efficient construction of both carbocycles and lactones. However, to extend this methodology further, it would be advantageous to widen this methodology into the construction of other heterocycles. A logical method of introducing heteroatoms would be to build them into the starting material. Thus, an amide such as **7.9** could be constructed using standard peptide coupling of amino malonate **7.7** and a suitable unsaturated acyl equivalent **7.8** (Scheme 7.3).



Scheme 7.3: Construction and cyclisation of amide containing malonates.

Cyclisation of amides such as **7.9** should be similar to the results obtained for carbocycles, resulting in a bicyclic lactam-lactone **7.10**. Such substructures can be found in the core of several natural products, including the biologically active species neooxazolomycin[102,103] and salinosporamide A[104,105] (Figure 7.1). Development of this methodology should provide a concise route to these appealing natural products.

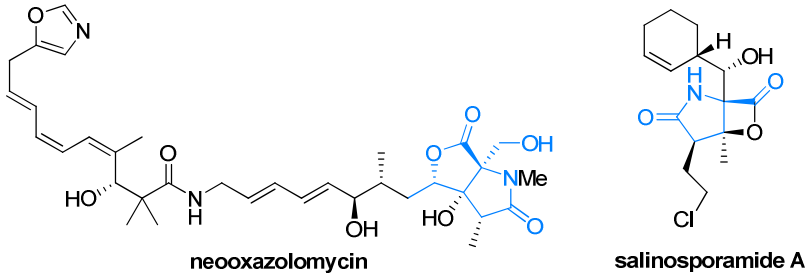
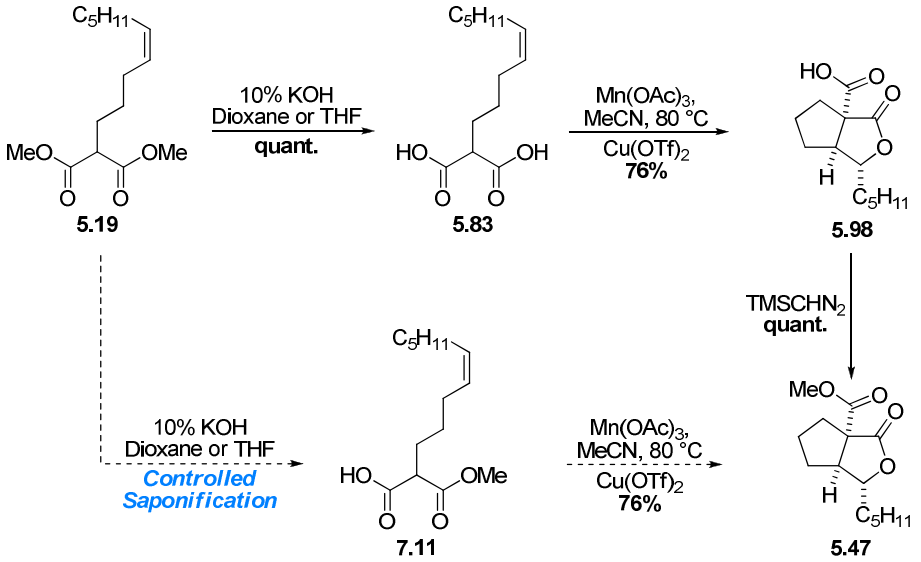


Figure 7.1: Two lactam/lactone containing natural products.

Further development of the catalysis methodology briefly examined within this project holds exciting prospects for this type of radical cyclisation. A more thorough understanding of the metal salts required, their role in the cyclisation, and optimisation of the reaction conditions is essential. After this has been developed, a screen of substrates similar to those used in this project will allow a comparison of both methodologies.

Related to this study would be the controlled saponification of malonates to give β-carboxyl esters (Scheme 7.4). Cyclisation of these substrates should proceed in the same manner (and yield) as the malonic acids, but will not require methylation to give the desired product. Thus, an appealing model would be saponification of malonate **5.19** using only one equivalent of base allowing only one saponification, and generation of β-carboxyl esters **7.11**. Successful cyclisation should lead directly to lactone-ester **5.47** with no requirement for subsequent esterification reactions.



Scheme 7.4: Proposed cyclisation of β-carboxyl esters.

8 Experimental Section

General Experimental Techniques

NMR spectra were recorded on Bruker DRX-400 (400 MHz), DRX-500 (500 MHz) and Avance 500 TCI-ATM Cryo (500 MHz) spectrometers at Cambridge University. Bruker DPX-400 (400 MHz), DQX-400 (400 MHz) and AV-500 (500 MHz) machines were used at Oxford University. Bruker AV-400 (400 MHz), and AV-500 (500 MHz) instruments were utilised at AstraZeneca, Alderley Park. Chemical shifts are quoted in ppm relative to tetramethylsilane (δ=0 ppm) and referenced to the solvent residual. For convenience, the following abbreviations are used; s – singlet, d – doublet, t – triplet, q – quartet, qn – quintet, m – multiplet, dd – doublet of doublets etc. Coupling constants (*J*) are given in Hertz. Where useful, the FID was zero filled (128 K), and sine-bell shifted (SSB = 30) prior to Fourier transformation to provide baseline resolved multiplets, and therefore more easily identifiable and measurable coupling constants.

Two dimensional (2D) spectra were recorded on instruments fitted with gradient coils. Double Quantum Filtered (DQF) and magnitude COSY spectra were typically acquired with 256 slices in F_1 and 2048 in F_2 (acquisition time approximately 20 min).

Infra-red spectra were recorded on a Perkin-Elmer 1600 FT IR spectrometer. Samples were prepared as solutions in the solvent indicated.

Analytical thin layer chromatography (tlc) was carried out on Merck pre-coated 0.23 mm thick plates of Keiselgel 60 F_{254}. Flash column chromatography[106] was carried out using Merck 9385 Keiselgel 60 SiO_2 (230-400 mesh) unless otherwise stated.

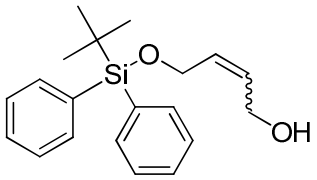
Non-aqueous reactions were carried out under an atmosphere of dry nitrogen unless indicated to the contrary.

Dry THF was distilled from potassium in a recycling still using benzophenone ketyl as indicator or by passage through activated alumina. Other dry solvents were purified using standard techniques.[107] Water used experimentally was deionised.

THF refers to tetrahydrofuran. DCM refers to dichloromethane. DMF refers to *N,N*-dimethylformamide. PE refers to light petroleum ether, the fraction boiling between 40°C and 60°C. Brine refers to a saturated solution of sodium chloride in water.

Optical rotations are quoted in deg cm^2 g^{-1}.

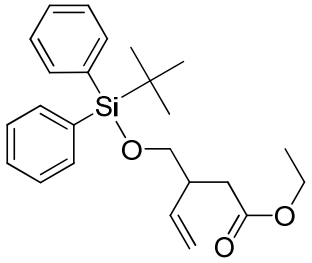
5.7 (*E*/*Z*)-4-(*tert*-Butyldiphenylsilyloxy)but-2-en-1-ol[108]



Mono-protection of the diol was performed using the McDougal procedure.[56] Sodium hydride (2.61 g, 60% dispersion in mineral oil, 68.18 mmol) was suspended in THF (130 mL), and allowed to stir at RT for 2 h. (*E*/*Z*)-But-2-ene-1,4-diol (6.00g, 68.18 mmol) was then added dropwise over 15 min, and the reaction mixture was allowed to stir for a further 20 min. The reaction was cooled to 0 °C, and TBDPSCl (18.71 g, 68.18 mmol) was added dropwise over 15 min, before being allowed to warm to RT and left to stir overnight. The reaction was then quenched with aqueous sodium bicarbonate solution (10%, 20 mL), the organic phase separated, and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and the solvent was removed *in vacuo*. The remaining residue was purified using flash column chromatography (20:1 PE:EtOAc) to give (*E*/*Z*)-4-(*tert*-butyldiphenylsilyloxy)but-2-en-1-ol as an off-white, clear oil (19.63 g, 60.13 mmol, 88%),

$\boldsymbol{R_f}$ = 0.39 (PE:EtOAc, 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.70-7.65 (4H, m, Ar*H*), 7.45-7.35 (6H, m, Ar*H*), 5.74-5.68 (1H, m, C*H*=CH), 5.67-5.58 (1H, m, CH=C*H*), 4.26 (2H, d, *J* = 6.0 Hz, OCH_2), 4.01 (2H, t, *J* = 6.4 Hz, CH_2OH), 1.50 (1H, t, *J* = 5.9 Hz, O*H*), 1.04 (9H, s, SiC$(CH_3)_3$); ***m/z*** (ESI+) Found: $[M+Na]^+$, 349.1595; $C_{20}H_{26}O_2SiNa$ requires *M*, 349.1600.

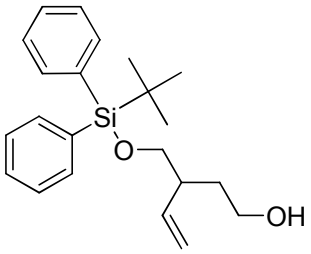
5.6 Ethyl 3-((*tert*-Butyldiphenylsilyloxy)methyl)pent-4-enoate[109]



To a stirred solution of (*E*/*Z*)-4-(*tert*-butyldiphenylsilyloxy)but-2-en-1-ol (3.00 g, 9.20 mmol) in *para*-xylene (30 mL) was added triethylorthoacetate (7.45 g, 46.00 mmol) and propionic acid (6.8 mg, 0.09 mmol). The solution was then heated under reflux overnight. The solvent, and remaining reagents were removed *in vacuo*. The crude product was then purified by flash column chromatography (7:1 PE:EtOAc), to give ethyl 3-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enoate as a clear, colourless oil, (2.46 g, 6.204 mmol, 67%);

$\boldsymbol{R_f}$ = 0.65 (hexane:EtOAc, 3:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.67-7.62 (4H, m, Ar*H*), 7.44-7.33 (6H, m, Ar*H*), 5.75 (1H, ddd, *J* = 18.0 Hz, 10.2 Hz, 7.8 Hz, *H*C=CH_2), 5.10-5.02 (2H, m, HC=CH_2), 4.10 (2H, q, *J* = 6.8 Hz, OC$H_2$$CH_3$), 3.65 (1H, dd, *J* = 10.0 Hz, 5.2 Hz, OC*H*HCH), 3.55 (1H, dd, *J* = 10.0 Hz, 6.6 Hz, OCH*H*CH), 2.84-2.74 (1H, m, C*H*), 2.67 (1H, dd, *J* = 14.6 Hz, 5.6 Hz, CH*H*), 2.38-2.29 (1H, m, C*H*H), 1.22 (3H, t, *J* = 6.8 Hz, OCH_2CH_3), 1.04 (9H, s, $SiC(CH_3)_3$); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CHCl_3$) 3072 s, 2932 m, 2859 m, 1736 s (C=O); ***m/z*** (ESI+) Found $[M+Na]^+$ 419.2019; $C_{24}H_{32}O_3SiNa$ requires 419.2018.

5.5 3-((*tert*-Butyldiphenylsilyloxy)methyl)pent-4-en-1-ol[48]

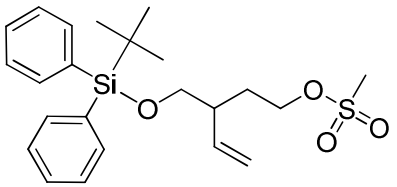


To a solution of lithium aluminium hydride (0.287 g, 7.56 mmol) in THF (20 mL) was added a solution of ethyl 3-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enoate (1.50 g, 3.78 mmol) in THF (10 mL) dropwise, at -30 °C and the reaction mixture was allowed to stir at -30 °C for 2.5 h. The reaction was then quenched with aqueous KOH solution (10%, 6 mL), and allowed to stir for a further 1 h. The so formed precipitate was then filtered through Celite™, washing with Et_2O (4 × 100 mL) and pH 7 buffer (60 mL). The organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was further purified by flash column chromatography (2:1 PE:EtOAc), to give 3-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-en-1-ol as a clear, colourless oil (1.18 g, 3.33 mmol, 88%);

$\boldsymbol{R_f}$ = 0.24 (hexane:EtOAc, 3:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.68-7.63 (4H, m, Ar*H*), 7.45-7.34 (6H, m, Ar*H*), 5.74-5.64 (1H, m, C*H*=CH_2), 5.12-5.04 (2H, dt, *J* = 5.2 Hz, 0.8 Hz, CH=CH_2), 3.74-3.60 (2H, m, OCH_2), 3.60 (2H, t, *J* = 6.0 Hz, CH_2OH), 2.41-2.34 (1H, m, C*H*CH=CH_2), 1.86-1.77 (1H, m), 1.70 (1H, t, *J* = 6.0 Hz, O*H*), 1.66-1.58 (1H, m), 1.04 (9H, s, ^tBu); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CHCl_3$) 3340 br (O-H), 3071 w, 2931 m, 2894

m, 2858 m; ***m/z*** (ESI+) Found: $[M+Na]^+$, 377.1927 $C_{22}H_{30}O_2SiNa$ requires M, 377.1913.

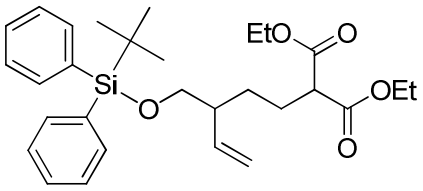
5.11 3-((*tert*-Butyldiphenylsilyloxy)methyl)pent-4-enyl methanesulfonate[48]



To a solution of 3-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-en-1-ol (0.101 g, 0.282 mmol) in DCM (10 mL) at 0°C was added triethylamine (0.086 g, 0.846 mmol) and methanesulfonyl chloride (0.097 g, 0.846 mmol). The reaction mixture was warmed to RT, stirred for 1 h, after which it was quenched by addition of HCl (10 mL, 1.0 M). The organic phase was separated, and the aqueous phase extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried ($MgSO_4$), and the solvent removed *in vauco* to give 3-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enyl methanesulfonate as a clear, colourless oil (0.120 g, 0.278 mmol, 99%);

$\boldsymbol{R_f}$ = 0.50 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.69-7.67 (2H, m, Ar*H*), 7.67-7.65 (2H, m, Ar*H*), 7.45-7.36 (6H, m, Ar*H*), 5.64 (1H, ddd, *J* = 16.6 Hz, 10.0 Hz, 8.2 Hz, C*H*=CH_2), 5.11-5.02 (2H, m, CH=C*HH*), 4.24 (2H, m, $CH_2OSO_2CH_3$), 3.63 (1H, dd, *J* = 10.0, 5.3, SiOC*H*H), 3.58 (1H, dd, *J* = 10.0, 6.3, SiOCH*H*), 2.95 (3H, s, SO_2CH_3), 2.43-2.34, (1H, m, C*H*CH=CH_2), 1.77-1.68 (2H, m, CH*H*CH_2OSO_2) 1.06 (9H, s, $SiC(CH_3)_3$).

5.1 *Diethyl 2-(3-((tert-butyldiphenylsilyloxy)methyl)pent-4-enyl)malonate*



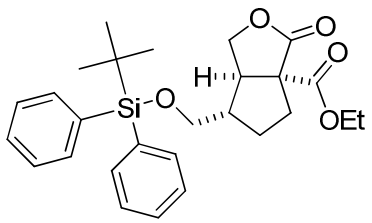
Dry DMF (10 mL) was added to sodium hydride (60% suspension in mineral oil, 0.083 g, 2.076 mmol) at 0 °C, and the suspsension allowed to stir for 15 min. Diethyl malonate (0.333 g, 2.076 mmol) was then added dropwise, the solution was allowed to warm to RT and stirred for a further 20 min. A solution of 3-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enyl methanesulfonate (0.300 g, 0.692 mmol) in THF (10 mL) was added dropwise, followed by potassium iodide (0.172 g, 1.038 mmol), and the reaction mixture was heated under reflux for 18 h.

The reaction was then quenched with sat. aq. NH_4Cl solution (10 mL), the organic phase separated, and the aqueous phase extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (8:1 PE:EtOAc), to give diethyl 2-(3-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enyl)malonate as a clear, colourless oil (0.2903 g, 0.5849 mmol, 85%);

$\boldsymbol{R_f}$ = 0.60 (PE:EtOAc, 8:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.69-7.67 (2H, m, Ar*H*), 7.67-7.65 (2H, m, Ar*H*), 7.45-7.36 (6H, m, Ar*H*), 5.62 (1H, ddd, *J* = 16.8 Hz, 10.7 Hz, 8.5 Hz, C*H*=CH_2), 5.04 (2H, m, CH=CH_2), 4.19 (2H, q, *J* = 7.0 Hz, OC$H_2$$CH_3$), 4.17 (2H, q, *J* = 7.0 Hz, OC$H_2$$CH_3$), 3.65 (2H, m, SiOC$H_2$), 3.29 (1H, t, *J* = 7.6 Hz, C*H*$(C=O)_2$), 2.30 (1H, m, C*H*CH=CH_2), 1.95 (1H, m, C*H*HCH$(C=O)_2$), 1.81 (1H, m,

CH*H*CH(C=O)$_2$), 1.62 (1H, m, SiOCH$_2$CHCH*H*), 1.31 (1H, m, SiOCH$_2$CHC*H*H), 1.25 (6H, t, J = 6.5 Hz, 2 × OCH$_2$CH_3), 1.04 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (125 MHz, CDCl$_3$) 169.6 (*C*=O), 169.5 (*C*=O), 135.6 (*Ar*), 133.9 (C=C), 132.7 (C=C), 130.5 (*Ar*), 129.5 (*Ar*), 127.5 (*Ar*), 67.5 (SiO*C*H$_2$), 61.2 (O*C*H$_2$CH$_3$), 61.2 ((O*C*H$_2$CH$_3$), 52.1 ((C=O)$_2$*C*H), 45.2 (*C*HCH=CH$_2$), 32.6 (CH$_2$), 31.4 (CH$_2$), 26.8 ((*C*H$_3$)$_3$C), 22.5 ((CH$_3$)$_3$*C*), 14.1 (OCH$_2$*C*H$_3$), 14.0 (OCH$_2$*C*H$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ (Et$_2$O) 2960 m (CH), 2929 m (CH), 1752 s (C=O), 1734 s (C=O); ***m/z*** (ESI+) Found: $[M+Na]^+$, 519.2539; $C_{13}H_{22}O_5Na$ requires 519.2543.

5.14 *(±)-(3*aS**,6*S**,6*aR**)-Ethyl 6-((tert-butyldiphenylsilyloxy)methyl)-3-oxo-hexahydro-1*H*-cyclopenta[*c*]furan-3*a*-carboxylate*



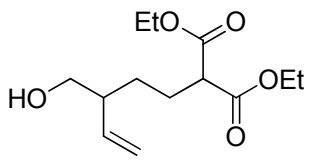
A solution of 2-(3-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enyl)malonate (0.040 g, 0.0806 mmol) in acetonitrile (2 mL) was prepared in a reaction carousel. Manganese(III) acetate (0.043 g, 0.1613 mmol) was added, along with copper(II) triflate (0.029 g, 0.0806 mmol). The reaction tube was degassed, and heated under reflux for 18 h.

After addition of water (5 mL), the organic phase was separated, and the aqueous phase extracted with Et$_2$O (5 × 5 mL). The combined organic extracts were washed with brine and dried (MgSO$_4$), and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (20:1 → 6:1 PE:EtOAc)to give (±)-

(3a*S**,6*S**,6a*R**)-ethyl 6-((*tert*-butyldiphenylsilyloxy)methyl)-3-oxo-hexahydro-1H-cyclopenta[c]furan-3a-carboxylate as a clear, colourless oil (highest yield 0.0110 g, 55%);

R_f = 0.52 (PE:EtOAc 2:1); δ_H (500 MHz, $CDCl_3$) 7.69-7.67 (2H, m, Ar*H*), 7.67-7.65 (2H, m, Ar*H*), 7.45-7.36 (6H, m, Ar*H*), 4.50 (1H, dd, *J* = 9.2 Hz, 6.6 Hz, C*H*HO(C=O)), 4.26 (1H, dd, *J* = 9.2 Hz, 1.2 Hz, CH*H*O(C=O)), 4.23 (2H, m, CH_2CH$_3$), 3.72 (1H, dd, *J* = 10.3 Hz, 5.7 Hz, SiOCH*H*), 3.58 (1H, dd, *J* = 10.3 Hz, 7.3 Hz, SiOC*H*H), 2.86 (1H, ddd, *J* = 6.6 Hz, 6.4 Hz, 1.2 Hz, C*H*CH$_2$O(C=O)), 2.57 (1H, ddd, *J* = 13.8 Hz, 8.3 Hz, 5.4 Hz, CH$_2$C*H*HC), 2.15 (1H, m, CH$_2$CH*H*C), 2.15 (1H, m, C*H*CH$_2$CH$_2$C), 1.80 (1H, dq, *J* = 5.7 Hz, 7.1 Hz, CHC*H*HCH$_2$C) , 1.61 (1H, m, CHCH*H*CH$_2$C), 1.29 (3H, t, *J* = 7.1 Hz, (C=O)OCH$_2$CH_3), 1.07 (9H, s, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 176.6 (*C*(=O)OCH), 169.8 (*C*(=O)OCH$_2$CH$_3$), 135.5 (*Ar*), 133.1 (*Ar*), 129.9 (*Ar*), 127.8 (*Ar*), 72.0 (C(=O)O*C*H), 65.6 (*C*H$_2$OTBDPS), 62.2 (O*C*H$_2$CH$_3$), 61.4 (C), 50.2 (*C*HCHCH$_2$OTBDPS), 49.5 (*C*HCH$_2$OTBDPS), 32.5 (*C*H$_2$C(C(=O))$_2$), 29.2 (*C*H$_2$HCH$_2$OTBDPS), 26.9 (C(*C*H$_3$)$_3$), 19.2 (*C*(CH$_3$)$_3$), 14.1 (CH$_2$*C*H$_3$); ν_{max}/cm^{-1} (Et_2O) 2959 m (C-H), 2959 m (C-H), 2931 m (C-H), 2858 m (C-H), 1779 s (C=O γ-lactone), 1740.4 (C=O ester); ***m/z*** (ESI+) Found: $[M+Na]^+$, 484.2519; $C_{13}H_{22}O_5Na$ requires 484.2515.

5.13 *Diethyl 2-(3-((*tert-*butyldiphenylsilyloxy)methyl)pent-4-enyl)malonate*



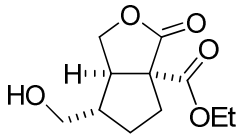
2-(3-((*tert*-Butyldiphenylsilyloxy)methyl)pent-4-enyl)malonate (0.220 g, 0.443 mmol) was dissolved in THF (20 mL), and acetic acid (0.080 mL, 1.329 mmol) was added

dropwise at 0 °C with stirring. Tetrabutylammonium fluoride (1.0 M, 1.33 mL, 1.329 mmol) was added, and the reaction was stirred for a further 15 min. The reaction was then allowed to warm to RT and stirred for a further 18 h.

The reaction was quenched by addition of water (20 mL), the organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo* leaving the crude product which was purified by flash column chromatography (1:1 PE:EtOAc) to give diethyl 2-(3-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enyl)malonate as a clear, colourless oil, (0.079 g, 0.306 mmol, 69%),

$\boldsymbol{R_f}$ = 0.47 (PE:EtOAc 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.59 (1H, ddd, *J* = 17.0 Hz, 10.4 Hz, 8.7 Hz, C*H*=CH_2), 5.19 (1H, d, *J* = 10.4 Hz, CH=C*H*H), 5.19 (1H, d, *J* = 17.0 Hz, CH=C*H*H), 4.24-4.16 (4H, m, (C=O)OC$H_2$$CH_3$), 3.57 (1H, dd, *J* = 10.4 Hz, 5.3 Hz, HOCH*H*), 3.45 (1H, dd, *J* = 10.4 Hz, 3.7 Hz, HOC*H*H), 3.31 (1H, t, *J* = 7.4 Hz, (C*H*(CO_2Et)$_2$), 2.29-2.20 (1H, m, C*H*CH=CH_2), 2.02-2.92 (1H, m, C*H*HCH(CO_2Et)$_2$), 1.90-1.80 (1H, m, C*H*HCH(CO_2Et)$_2$), 1.49-1.43 (1H, m, $HOCH_2CHCH$*H*), 1.35-1.29 (1H, m, $HOCH_2CHC$*H*H), 1.27 (6H, t, *J* = 7.1 Hz, (C=O)OCH_2C*H*$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.4 (C(=O)), 169.4 (C(=O)), 138.9 (*C*H=CH_2), 118.1 (CH=*C*H_2), 65.4 (HO*C*H_2), 61.4 ((C=O)*C*H_2CH_3), 51.9 (C*H*(C=O)$_2$), 46.7 (*C*HCH=CH_2), 28.2 ($HOCH_2CHCH_2$), 26.3 (*C*H_2CH(C=O)$_2$), 14.1 ((C=O)CH_2*C*H_3); ***m/z*** (ESI+) Found: $[M+Na]^+$, 281.1359; $C_{13}H_{22}O_5Na$ requires 281.1365; $\boldsymbol{\nu_{max}}$**/cm^{-1}** (Et_2O) 3454 br (O-H), 2982 m (C-H), 2928 m (C-H), 1728 s (C=O ester), 1641 (C=C).

5.16 ± *(3a*S*,*6*S*,*6a*R**)-Ethyl 6-(hydroxymethyl)-3-oxo-hexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate*



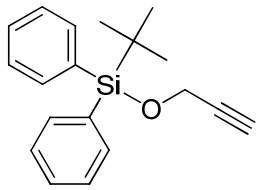
A solution of 2-(3-((*tert*-butyldiphenylsilyloxy)methyl)pent-4-enyl)malonate (0.040 mg, 0.155 mmol) in acetonitrile (2 mL) was prepared in a reaction carousel. Manganese(III) acetate (0.083 g, 0.301 mmol) was added along with copper(II) triflate (0.056 g, 0.155 mmol). The reaction tube was degassed, and heated under reflux for 18 h.

After addition of water (5 mL), the organic phase was separated, and the aqueous phase extracted with Et_2O (5 × 5 mL). The combined organic extracts were washed with brine (5 × 5 mL) and dried ($MgSO_4$), and solvent was removed (±)-(3a*S**,6*S**,6a*R**)-ethyl 6-(hydroxymethyl)-3-oxo-hexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate. The crude product was purified by flash chromatography (20:1→ 6:1 PE:EtOAc), to give the title compound as a clear, colourless oil (highest yield 0.0110 g, 56%);

$\boldsymbol{R_f}$ = 0.05 (PE:EtOAc 10:1); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 4.50 (1H, dd, *J* = 9.3 Hz, 6.9 Hz, CHC*H*HO(C=O)), 4.25 (1H, dd, *J*= 9.3 Hz, 1.75 Hz, CHCH*H*O(C=O)), 4.21 (1H, qd, *J* = 7.1, 1.3, (OCH_2CH$_3$), 3.70 (1H, dd, *J* = 10.4 Hz, 5.8 Hz, HOC*H*H), 3.56 (1H, dd, *J* = 9.9 Hz, 7.6 Hz, HOCH*H*), 2.89 (1H, dt, *J* = 6.9 Hz, 1.7 Hz, C*H*CH$_2$O(C=O)), 2.57 (1H, ddd, *J* = 13.8 Hz, 7.8 Hz, 1.8 Hz, CH$_2$C*H*HC), 2.15 (2H, m, CH$_2$CH*H*C, C*H*CH$_2$CH$_2$C), 1.85 (1H, ddt, *J* = 13.2 Hz, 6.8 Hz, 6.5 Hz, CHCH*H*CH$_2$C), 1.64 (1H, m, CHC*H*HCH$_2$C), 1.27 (3H, t, *J* = 7.6 Hz, (C=O)OCH$_2$C*H*$_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 176.7 (*C*(=O)OCH$_2$CH), 169.9 (*C*(=O)OCH$_2$CH$_3$), 72.1 (C(=O)O*C*H$_2$CH), 64.6 (HO*C*H$_2$), 62.3 (C(=O)O*C*H$_2$CH$_3$), 61.5 (*C*(CO$_2$)$_2$), 49.8 (C*H*CH$_2$O(C=O)), 49.3

(*C*HCH$_2$O(C=O)), 32.5 (CH$_2$*C*H$_2$C(CO$_2$)$_2$), 29.0 (*C*H$_2$CH$_2$C(CO$_2$)$_2$), 14.0 (C(=O)OCH$_2$*C*H$_3$); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 3380 br (O-H), 2979 m (C-H), 2938 m (C-H), 2876 m (C-H), 1773 s (C=O γ-lactone), 1738 s (C=O ester); ***m/z*** (ESI+) Found: $[M+H]^+$, 251.0890; $C_{29}H_{43}O_3$ requires 251.0895.

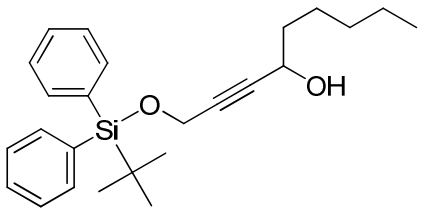
5.35 *tert*-Butyldiphenyl(prop-2-ynyloxy)silane[110]



To a stirred solution of propargyl alcohol (5.43 g, 97.8 mmol) in DCM (25 mL) were added imidazole (6.66 g, 97.8 mmol) and *tert*-butyldiphenylsilyl chloride (27.7 mL, 87.3 mmol). After 18 h, the reaction was quenched with water (50 mL), the organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed *in vacuo* to give *tert*-butyldiphenyl(prop-2-ynyloxy)silane as an off-white viscous oil, (24.75 g, 96%);

$\boldsymbol{R_f}$ = 0.63 (PE:EtOAc 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.71 (2H, m, Ar*H*), 7.69 (2H, m, Ar*H*), 7.45-7.36 (6H, m, Ar*H*), 4.31 (2H, d, *J* = 2.4 Hz, CH_2), 2.37 (1H, t, *J* = 2.4 Hz, *H*C≡C), 1.06 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 2960 m (C-H), 2932 m (CH), 2893 m (C-H), 2859 m (C-H).

5.34 *1-(*tert*-Butyldiphenylsilyloxy)non-2-yn-4-ol*

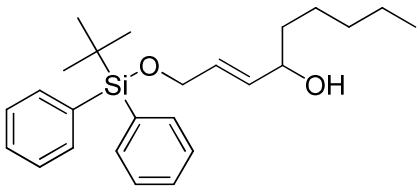


n-BuLi (6.36 mL, 1.6 M in hexanes, 10.18 mmol) was added to a stirred solution of *tert*-butyldiphenyl(prop-2-ynyloxy)silane (3.0 g, 10.18 mmol) in THF (40 mL) at -78 °C. After 30 min, freshly distilled hexanal (1.25 mL, 10.18 mmol) was added dropwise, and the reaction allowed to stir for a further 1 h. The reaction was then quenched with HCl (1.0 M, 12 mL), and the organic phase separated; the aqueous phase was then extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and solvent was removed *in vacuo*, to give the crude product, which was purified by flash column chromatography (4:1 DCM:PE → neat DCM) to give 1-(*tert*-butyldiphenylsilyloxy)non-2-yn-4-ol as a clear, colourless oil (3.079 g, 7.83 mmol, 77%);

$\boldsymbol{R_f}$ = 0.44 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.71 (2H, m, Ar*H*), 7.69 (2H, m, Ar*H*), 7.45-7.36 (6H, m, Ar*H*), 4.36 (2H, d, *J* = 1.7 Hz, SiOCH_2), 4.27 (1H, tt, *J* = 6.5 Hz, 1.7 Hz, OHC*H*), 1.58 (2H, q, *J* = 6.5 Hz, HOCHCH_2), 1.52 (1H. s, OH), 1.38 (2H, qn, *J* = 6.9 Hz, CHCH_2CH_2), 1.29 (4H, m, CH_2CH_2CH_3), 1.06 (9H, s, SiC(CH_3)$_3$), 0.88 (3H, t, *J* = 6.8, CH_3); $\boldsymbol{\delta_C}$ (125 MHz, CDCl3) 135.7 (Ar), 134.8 (Ar), 133.2 (Ar), 129.8 (Ar), 129.6 (Ar), 127.7 (Ar), 86.3 (C≡*C*CHOH), 83.2 (SiOCH_2*C*≡C), 62.5 (C≡C*C*HOH), 52.7 (SiO*C*H_2C≡C), 37.5 (CHOH*C*H_2), 31.4 (*C*H_2CH_2CH_3), 26.8 (*C*H_3C), 26.7 (*C*H_3C), 26.5 (*C*H_3C), 24.7 (*C*H_2CH_3), 22.5 (CHOHCH_2*C*H_2), 19.1 (CH_3*C*), 14.0 (CH_2*C*H_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3375 br (O-H) 2956 m (C-H), 2932m (C-

H), 2859 m (C-H), 2220 w (C≡C); ***m/z*** (ESI+) Found: $[M+H]^+$,417.2221; $C_{29}H_{43}O_3$ requires 417.2226.

5.33 1-(*tert*-Butyldiphenylsilyloxy)non-2-en-4-ol[111]

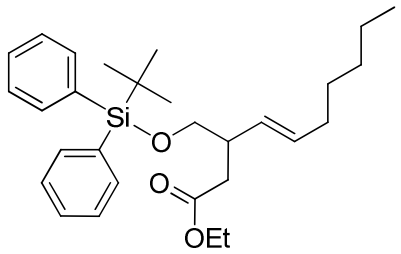


Red-Al® (65% wt. in toluene, 1.828 mL, 6.08 mmol) was added to THF (80 mL) at 0°C. A solution of 1-(*tert*-butyldiphenylsilyloxy)non-2-yn-4-ol (1.60 g, 4.05 mmol) in THF (10 mL) was added dropwise with stirring, and the reaction mixture was warmed to RT and stirred for 1 h . The reaction mixture was then quenched with sat. aq. NH_4Cl solution (10 mL), and a saturated solution of Rochelle's salt (10 mL) was added. The mixture was left to stir until homogeneous, the organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (5:1 PE:EtOAc,) to give 1-(*tert*-butyldiphenylsilyloxy)non-2-en-4-ol as a clear, colourless oil (1.43 g, 3.64 mmol, 90 %),

$\boldsymbol{R_f}$ = 0.33 (PE:EtOAc 5:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.69-7.65 (4H, m, Ar*H*), 7.43-7.34 (6H, m, Ar*H*), 5.74-5.71 (2H, m, C*H*=C*H*), 4.21 (2H, m, SiOCH_2), 4.08 (1H, dt, *J* = 6.3 Hz, 4.6 Hz, OHC*H*), 1.58-1.42 (2H, m, (HO)CHCH_2CH$_2$), 1.40-1.24 (6H, m,

CH_2CH_2CH_2CH$_3$), 1.06 (9H, s, SiC(CH_3)$_3$), 0.89 (3H, t, J = 6.8 Hz, CH_3); $\boldsymbol{\nu_{max}}$**/cm^{-1}** (CDCl$_3$) 3358 br (O-H) 2956 m (C-H), 2931 m (C-H), 2858 m (C-H).

5.32 *(*E*)-Ethyl 3-((*tert*-butyldiphenylsilyloxy)methyl)dec-4-enoate*

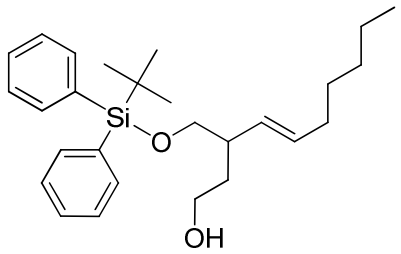


To a stirred solution of 1-(*tert*-butyldiphenylsilyloxy)non-2-en-4-ol (1.43 g, 3.64 mmol) in *para*-xylene (80 mL) was added triethylorthoacetate (3.45 g, 18.18 mmol) and propionic acid (13 μL, 13 mg, 0.18 mmol). The solution was then heated to reflux overnight. The solvent, and remaining reagents were removed *in vacuo*. The crude product was then purified by flash column chromatography (10:1 PE:EtOAc), to give (*E*)-ethyl 3-((*tert*-butyldiphenylsilyloxy)methyl)dec-4-enoate as a clear, colourless oil, (1.61g, 3.56 mmol, 98%);

$\boldsymbol{R_f}$ = 0.52 (PE:EtOAc 2:1); $\boldsymbol{\delta_H}$ (400 MHz, CDCl$_3$) 7.71 (2H, m, ArH), 7.69 (2H, m, ArH), 7.45-7.36 (6H, m, ArH), 5.47 (1H, dt, J = 15.3 Hz, 7.0 Hz, CHCH=CH), 5.28 (1H, ddt, J = 15.3 Hz, 7.0 Hz, 1.2 Hz CHCH=CH), 4.08 (2H, q, J = 7.1 Hz, (C=O)OCH_2CH$_3$), 3.61 (1H, dd, J = 9.8 Hz 4.6 Hz, SiOCH_2), 3.51 (1H, dd, J = 9.8 Hz, 7.1 Hz, SiOCH_2), 2.74 (1H, m, SiOCH$_2$CH), 2.65 (1H, dd, J = 14.8 Hz, 5.6 Hz, CHCHH(C=O)), 2.28 (1H, dd, J = 14.8 Hz, 8.8 Hz, CHCHH(C=O)), 1.94 (2H, q, J = 6.7 Hz, CH=CHCH_2), 1.34-1.22 (2H, m, CH=CHCH$_2$CH_2), 1.22 (3H, t, J = 7.2 Hz, (C=O)OCH$_2$CH_3), 1.06 (2H, m, CH$_2$CH_2CH$_3$), 1.06 (9H, s, SiC(CH_3)$_3$), 0.89 (3H, t, J

= 6.8 Hz, $CH_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$) 172.9 (*C*=O), 135.6 (Ar), 133.7 (Ar), 132.6 (CH*C*=C), 129.6 (CHC=*C*), 127.6 (Ar), 127.6 (Ar), 66.8 (SiOCH_2), 60.1 ((C=O)OCH_2CH_3), 41.9 (*C*HC=C), 36.8 (CH_2(C=O)), 32.6 (CH=CHCH_2), 31.3 ($CH_2CH_2CH_3$), 29.0 (CH=CHCH$_2CH_2$), 26.9 ((CH_3)$_3$C), 26.8 ((CH_3)$_3$C), 26.7 ((CH_3)$_3$C), 22.5 (CH_2CH_3), 19.1 ((CH_3)$_3$*C*), 14.3 ((C=O)OCH$_2CH_3$), 14.0 (CH_2CH_3); ν_{max}/cm^{-1} ($CDCl_3$) 2958 m (C-H), 2930 m (C-H), 2858 m (C-H) , 1736 m (C=O ester); ***m/z*** (ESI+) Found: $[M+H]^+$ 466.2909; $C_{29}H_{43}O_3$ requires *M*, 466.2903.

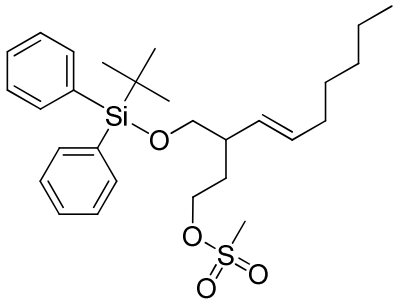
5.31 *(*E*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)dec-4-en-1-ol*



DIBAL-H (1.5 M in THF, 0.941 mL, 1.412 mmol) was added to a stirred solution of (*E*)-ethyl 3-((*tert*-butyldiphenylsilyloxy)methyl)dec-4-enoate (0.200 g, 0.428 mmol) in THF (20 mL) at -78 °C. The reaction mixture was then warmed to 0 °C, and quenched with a saturated solution of Rochelle's salt (20 mL) after 1 h. The organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was then purified by flash column chromatography (DCM) to give (*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)dec-4-en-1-ol as a clear, colourless oil (0.142 g, 0.347 mmol, 81%);

$\boldsymbol{R_f}$ = 0.29 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.71 (2H, m, Ar*H*), 7.69 (2H, m, Ar*H*), 7.45-7.36 (6H, m, Ar*H*), 5.47 (1H, dt, *J* = 15.3 Hz, 7.0 Hz, CHCH=C*H*), 5.28 (1H, ddt, *J* = 15.3 Hz, 7.0 Hz, 1.2 Hz, CHC*H*=CH), 3.68 (2H, m, HOCH_2), 3.55 (2H, m, SiOCH_2), 2.33-2.29 (1H, m, *J* = 6.1 Hz, $SiOCH_2CH$), 1.95 (2H, dt, *J* = 6.7 Hz, 6.7 Hz, CH=CHCH_2), 1.81 (1H, ddt, *J* = 12.7 Hz, 5.2 Hz, $HOCH_2CH$*H*), 1.57 (1H, ddt, *J* = 8.7 Hz, 5.2 Hz, 2.8 Hz, $HOCH_2CH$H), 1.35-1.18 (6H, m, CH_2CH_2CH_2CH_3), 1.04 (9H, s, $SiC(CH_3)_3$), 0.86 (3H, t, *J* = 6.8 Hz, $CH_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 135.6 (Ar), 133.6 (Ar), 132.4 (CH*C*=C), 130.8 (CHC=*C*), 129.6 (Ar), 127.6 (Ar), 67.9 (SiO*C*H_2), 61.5 (*C*H_2OH), 42.8 (*C*HC=C), 34.9 (*C*H_2CH_2OH), 32.6 (CH=CH*C*H_2), 31.4 (*C*$H_2CH_2CH_3$), 29.1 (CH=CHCH_2*C*H_2), 26.8 ((*C*H_3)$_3$C), 22.5 (*C*H_2CH_3), 19.2 ((CH_3)$_3$*C*), 14.0 (CH_2*C*H_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3342 br (O-H), 2957 m (C-H), 2957 m (C-H), 2857 m (C-H); ***m/z*** (ESI+) Found: $[M+Na]^+$, 424.2791; $C_{27}H_{40}O_2HSi$ requires 424.2798.

5.45 *(*E*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)dec-4-enyl methanesulfonate*

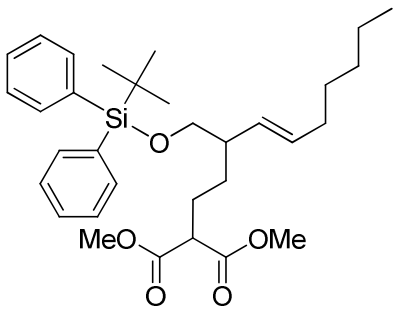


Alcohol (*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)dec-4-en-1-ol (0.136 g, 0.321 mmol) was dissolved in DCM (20 mL), and triethylamine (0.067 mL, 0.481 mmol) and methanesulfonyl chloride (0.037 mL, 54.7 mg, 0.481 mmol) added at 0 °C. The reaction mixture was warmed to RT, and stirred for 1 h, after which it was quenched

by addition of HCl (10 mL, 1 M). The organic phase was separated, and the aqueous phase extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*, to give (*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)dec-4-enyl methanesulfonate as a clear, colourless oil (0.161 g, 0.321 mmol, 100%);

$\boldsymbol{R_f}$ = 0.63 (DCM:PE 1:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.71 (2H, m, Ar*H*), 7.69 (2H, m, Ar*H*), 7.45-7.36 (6H, m, Ar*H*), 5.48 (1H, dt, *J* = 15.3 Hz, 7.0 Hz, CHCH=C*H*), 5.19 (1H, ddt, *J* = 15.3 Hz, 7.0 Hz, 1.2 Hz, CHC*H*=CH), 4.23 (2H, m, SO_2OCH_2), 3.59 (1H, dd, *J* = 10.1 Hz, 7.0 Hz, SiOC*H*H), 3.53 (1H, dd, *J* = 10.1 Hz, 7.5 Hz, SiOCH*H*), 2.94 (3H, s, CH_3SO_2), 2.31 (1H, m, *J* = 5.3 Hz, $SiOCH_2CH$), 2.07 (1H, m, SO_2OCH_2CHH), 1.95 (2H, q, *J* = 6.7, CH=CHC*HH*), 1.65 (1H, m, $SO_2OCH_2CH_2$), 1.35-1.18 (6H, m, $CH_2CH_2CH_2CH_3$), 1.04 (9H, s, ^tBu), 0.86 (3H, t, *J* = 6.8 Hz, $CH_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 135.6 (Ar), 133.7 (Ar), 133.6 (CH*C*=C), 129.6 (CHC=*C*), 129.2 (Ar), 127.6 (Ar), 68.7 (CH_2OMs), 67.4 ($SiOCH_2$), 41.8 (*C*HC=C), 37.3 (SO_2CH_3), 32.6 (CH_2CH_2OMs), 31.4 ($CH=CHCH_2$), 30.7 ($CH_2CH_2CH_3$), 29.1 ($CH=CHCH_2CH_2$), 26.8 ($(CH_3)_3C$), 22.5 (CH_2CH_3), 19.3 ($(CH_3)_3C$), 14.0 (CH_2CH_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 2929 m (C-H), 2858 m (C-H); ***m/z*** (ESI+) Found: $[M+Na]^+$, 525.2462; $C_{28}H_{42}O_4NaSiS$ requires 525.2471.

5.21 *(*E*)-Dimethyl 2-(3-((*tert*-butyldiphenylsilyloxy)methyl)dec-4-enyl)malonate*

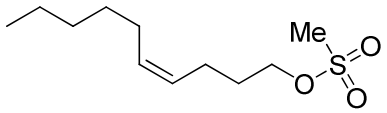


Dry DMF (4 mL) was added to sodium hydride (60% suspension in mineral oil, 0.048 g, 1.20 mmol) at 0°C, and the suspension allowed to stir for 10 min. Dimethyl malonate (0.137 mL, 1.20 mmol) was then added dropwise, the solution was allowed to warm to RT, and stirred for a further 20 min. A solution of (*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)dec-4-enyl methanesulfonate (0.200 g, 0.400 mmol) in THF (2 mL) was added dropwise, followed by potassium iodide (0.199 g, 1.20 mmol), and the mixture was heated at 80 °C for 18 h. After 30 min, the reaction mixture became thick and viscous. The reaction was quenched with sat. aq. NH_4Cl (10 mL); the organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (3:1 DCM:PE), to give the (*E*)-dimethyl 2-(3-((*tert*-butyldiphenylsilyloxy)methyl)dec-4-enyl)malonate as a clear, pale yellow oil, (0.179 g, 0.334 mmol, 85%);

$\boldsymbol{R_f}$ = 0.41 (DCM:PE 3:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.71 (2H, m, Ar*H*), 7.69 (2H, m, Ar*H*), 7.45-7.36 (6H, m, Ar*H*), 5.48 (1H, dt, *J* = 15.3 Hz, 7.0 Hz, CHCH=C*H*), 5.19 (1H, ddt, *J* = 15.3 Hz, 7.0 Hz, 1.2 Hz, CHC*H*=CH), 3.71 (6H, s, OCH_3), 3.52 (1H, dd, *J* = 10.0 Hz, 5.4 Hz, SiOCH*H*), 3.49 (1H, dd, *J* = 10.0 Hz, 6.2 Hz, SiOC*H*H), 3.33 (1H, t, *J* = 7.6 Hz, $CH(CO_2Me)_2$), 2.15 (1H, d, *J* = 5.4, $SiOCH_2CH$), 1.95 (2H, m), 1.93 (1H, m), 1.80 (1H, m), 1.57 (2H, m), 1.36-1.17 (6H, m, $CH_2CH_2CH_2CH_3$), 1.02 (9H, s, $SiC(CH_3)_3$), 0.86 (3H, t, *J* = 6.8 Hz, $CH_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 169.9 (*C*=O), 169.9 (*C*=O), 135.6 (Ar), 134.9 (C=*C*), 133.9 (*C*=C), 132.7 (Ar), 130.4 (Ar), 67.5 ($SiOCH_2$), 52.4 (OCH_3), 52.4 (OCH_3), 51.8 ($CH(CO_2Me)_2$)), 45.2 (*C*HCH=CH), 32.6 (CH_2), 31.4 (CH_2), 29.1 (CH_2), 28.8 (CH_2), 26.8 (CH_2), 26.6 ($C(CH_3)_3$), 22.5 (CH_2), 19.3 ($C(CH_3)_3$), 14.0 (CH_2CH_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 2955 m

(C-H), 2929 m (C-H), 2857 m (C-H), 1755 s (C=O malonate), 1737 (C=O malonate); ***m/z*** Found: $[M+Na]^+$,561.3012; $C_{13}H_{22}O_5Na$ requires 561.3002.

5.41 (*Z*)-Dec-4-enyl methanesulfonate[112]

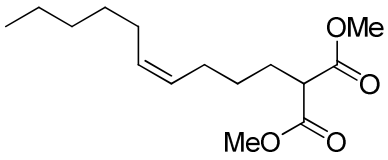


cis-4-Decen-1-ol (5.0 g, 32.0 mmol) was dissolved in DCM (50 mL), and triethylamine (6.70 mL, 48.0 mmol) and methanesulfonyl chloride (3.72 mL, 48.0 mmol) were added at 0 °C. The reaction was allowed to warm to RT and stirred for a further 1 h, after which it was quenched by addition HCl (2.0 M, 20 mL). The organic phase was separated, and the aqueous phase extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*, to give the (*Z*)-dec-4-enyl methanesulfonate as a clear, pale brown oil (7.29 g, 31.1 mmol, 97%),

$\boldsymbol{R_f}$ = 0.78 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.43 (1H, dtt, *J* = 11.0 Hz, 7.3 Hz, 1.8 Hz, C*H*=CH), 5.30 (1H, dtt, *J* = 11.0 Hz, 7.3 Hz, 2.0 Hz, C*H*=CH), 4.21 (2H, t, *J* = 6.5 Hz, CH_2OMs), 2.98 (3H, s, SO_2CH_3), 2.14 (2H, q, *J* = 7.3 Hz, CH_2), 2.00 (2H, q, *J* = 6.8 Hz, CH_2), 1.79 (2H, qn, *J* = 7.6 Hz, CH_2), 1.29 (6H, m, CH_2, CH_2, CH_2), 0.87 (3H, t, *J* = 6.8 Hz, CH_2CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 131.9 (*C*=C), 127.2 (C=*C*), 69.5 (*C*H_2OSO_2Me), 37.3 (SO_2CH_3), 31.5 (*C*H_2), 29.1 (*C*H_2), 28.9 (*C*H_2), 27.2 (*C*H_2), 23.0 (*C*H_2), 22.5 (*C*H_2), 14.0 (*C*H_3CH_2); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 2956 m (C-H), 2927 m

(C-H), 2957 m (C-H); ***m/z*** (ESI+) Found: $[M+Na]^+$, 257.1190; $C_{15}H_{26}O_4Na$ requires *M*, 257.1182.

5.19 *(Z)-Dimethyl 2-(dec-4-enyl)malonate*



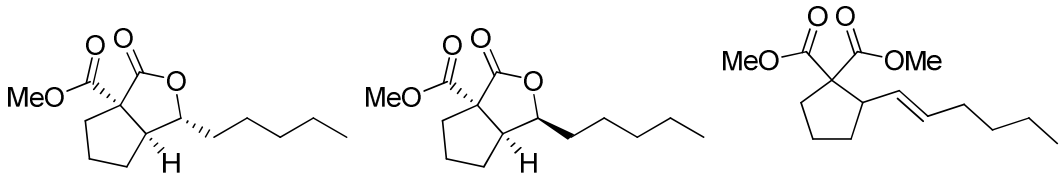
Dry DMF (8 mL) was added to sodium hydride (60% suspension in mineral oil, 0.256 g, 6.4 mmol) at 0 °C, and the suspension allowed to stir for 10 min. Dimethyl malonate (0.846 g, 6.4 mmol) was then added dropwise, and the solution allowed to warm to RT. Stirring was continued for a further 20 min and then a solution of (*Z*)-dec-4-enyl methanesulfonate (0.500 g, 2.13 mmol) in THF (10 mL) was added dropwise, followed by potassium iodide (1.06 g, 6.4 mmol). The mixture was heated to reflux (80°C) for 18 h; after 30 min, the solution solidified into a light-yellow gel. The reaction was quenched with sat. aq. NH_4Cl (10 mL), and extracted (3 × 30 mL Et_2O, brine wash). The organic phase was dried ($MgSO_4$) and solvent removed *in vacuo* to leave the crude product residue. Further purification by flash column chromatography (3:1 DCM:PE) furnished (*Z*)-dimethyl 2-(dec-4-enyl)malonate as a clear, colourless oil, (0.402g, 1.49 mmol, 70%);

$\boldsymbol{R_f}$ = 0.47 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.42 (1H, dt, *J* = 10.8 Hz, 7.1 Hz, CH=C*H*), 5.31 (1H, dt, *J* = 10.8 Hz, 7.1 Hz, CH=C*H*), 3.72 (6H, s, OCH_3), 3.35 (1H, t, *J* = 7.6 Hz, C*H*($CO_2Me)_2$), 2.05 (2H, q, *J* = 7.1 Hz, CH_2), 1.99 (2H, q, *J* = 6.8 Hz,

C*H*$_2$), 1.90 (2H, dt, *J* = 8.0 Hz, 7.1 Hz, C*H*$_2$), 1.31 (8H, m, C*H*$_2$, C*H*$_2$, C*H*$_2$, C*H*$_2$), 0.87 (3H, t, *J* = 6.8 Hz, C*H*$_3$CH$_2$); δ_C (125 MHz, $CDCl_3$) 169.9 (*C*=O), 169.9 (*C*=O), 130.8 (*C*=C), 128.5 (C=*C*), 52.4 (O*C*H$_3$), 51.6 (*C*H(CO$_2$Me)$_2$), 31.5 (*C*H$_2$), 29.3 (*C*H$_2$), 28.4 (*C*H$_2$), 27.4 (*C*H$_2$), 26.7 (*C*H$_2$), 22.5 (*C*H$_2$), 14.0 (CH$_2$*C*H$_3$) – *Note there is one accidental equivalence in the ^{13}C spectrum.*

ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 2955 m (CH), 2928 m (CH), 2858 m (CH), 1745 s (C=O), 1738 s (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 293.1723; $C_{15}H_{26}O_4Na$ requires *M*, 293.1729); **EA** Found C 66.72; H 66.64. $C_{15}H_{26}O_4$ requires C, 66.64; H, 9.69;

5.47 *(±)(1*R/S*,3a*R**,6a*S**)-methyl 3-oxo-1-pentylhexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate* , *(1S*,3aR*,6aS*)-methyl 3-oxo-1-pentylhexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate* and **5.48** *(*E*)-dimethyl 2-(hex-1-enyl)cyclopentane-1,1-dicarboxylate*



A solution of (*Z*)-dimethyl 2-(dec-4-enyl)malonate (40.0 mg, 0.148 mmol) in acetonitrile (2 mL) was prepared in a reaction carousel. Manganese(III) acetate (79.3 mg, 0.296 mmol) was added along with copper(II) triflate (53.4 mg, 0.148 mmol). The reaction tube was degassed, and heated to reflux for 18h, after which the reaction was quenched by addition of water (4 mL). The organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic extracts were

washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by column chromatography (20:1 PE:EtOAc → 2:1) gave (3a*R*,6a*S*)-methyl 3-oxo-1-pentylhexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate (21.7 mg, 0.081 mmol, 55%) which was isolated as a 2:1 mixture of C-1 diastereomers , along with (*E*)-dimethyl 2-(hex-1-enyl)cyclopentane-1,1-dicarboxylate (4.6 mg, 0.016 mmol, 11%;

$\boldsymbol{R_f}$ = 0.45 (PE:EtOAc 1:1);

[major isomer] $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.63 (1H, dt, *J* = 7.2 Hz, 5.4 Hz, (C=O)OC*H*CH_2), 3.71 (3H, s, OCH_3), 2.89 (1H, dt, *J* = 13.2 Hz, 6.3 Hz, (C=O)OCHC*H*), 2.81-2.78 (1H, m, (C=O)OCHCH*H*), 2.36-2.31 (C*H*HC(CO_2)), 2.26-2.22 (CH*H*C(CO_2)), 2.00-1.44 (4H, m, CHCHCH_2CH_2), 1.75-1.70 (OCHCH*H*CH_2), 1.52-1.77 (OCHC*H*HCH_2), 1.44-1.24 (6H, m, CH_2CH_2C$H_2$$CH_3$), 0.88 (3H, t, *J* = 7.2 Hz, CH_2CH_3);

[minor isomer] $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.06 (1H, ddd, *J* = 7.9 Hz, 5.6 Hz, 4.0 Hz, (C=O)OC*H*CH_2), 3.71 (3H, s, OCH_3), 2.75 (1H, ddd, *J* = 8.3 Hz, 3.7 Hz, 2.7 Hz, C*H*CHO(C=O)), 2.33-2.26 (1H, m, CH*H*C(CO_2)$_2$), 2.24-2.19 (1H, m, CH*H*C(CO_2)$_2$), 1.95-1.92 (1H, m, C*H*HCHCHO(C=O)), 1.78-1.69 (1H, m, (C=O)OCHC*H*HCH_2) 1.67-1.60 (1H, m, CH*H*CHCHO(C=O)), 1.67-1.57 (1H, m, (C=O)OCHCH*H*CH_2) 1.60-1.43 (2H, m (CO_2)$_2$CH_2C$H_2$$CH_2$), 1.43-1.23 (6H, m, C$H_2CH_2CH_2$$CH_3$), 0.90 (3H, t, *J* = 6.2 Hz, CH_2CH_3);

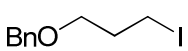
$\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 176.1 (C=O, *ester* [d1]), 175.9 (C=O, *ester* [d2]), 171.1 (C=O, *lactone* [d2]), 170.7 (C=O, *lactone* [d1]), 86.2 ((C=O)O*C*HCH_2 [d2]), 81.2 ((C=O)O*C*HCH_2 [d1]), 63.6 (C(CO_2)$_2$ [d1]), 62.3 (C(CO_2)$_2$ [d2]), 53.1 (CO_2*Me* [d2]), 53.0 (CO_2*Me* [d1]), 50.8 (OCHC*H*CH_2 [d2]), 50.1 (OCHC*H*CH_2 [d1]), 36.2

(*C*H_2C(CO_2) [d2]), 35.5 (*C*H_2C(CO_2) [d1]), 34.2 (*C*HCHCH$_2$ [d1]), 34.1 (*C*HCHCH$_2$ [d2]), 31.6 (CH$_2$ [d1]), 31.4 (CH$_2$ [d1]), 30.7 (*C*H$_2$ [d]), 27.1 (*C*H$_2$ [d]), 26.4 (*C*H$_2$ [d]), 25.8 (*C*H$_2$ [d]), 25.7 (*C*H$_2$ [d]), 25.0 (*C*H$_2$ [d]), 22.5 (*C*H$_2$ [d2]), 22.4 (*C*H$_2$ [d1]), 13.9 (2 x CH$_2$*C*H$_3$ [d1 + d2]); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 2952 m (C-H), 2871 m (C-H), 1773 s (C=O, *lactone*), 1742 s (C=O*, ester*); ***m/z*** Found: $(M+Na)^+$, 277.1410; $C_{14}H_{22}O_4Na$ requires *M*, 483. 277.1416).

5.48 *(E)-Dimethyl 2-(hex-1-enyl)cyclopentane-1,1-dicarboxylate*

$\boldsymbol{R_f}$ = 0.59 (PE:EtOAc 1:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.48 (1H, dt, *J* = 15.2 Hz, 6.8 Hz, CH$_2$C*H*=CHCH), 5.35 (1H, dd, *J* = 15.2 Hz, 8.3 Hz, CH$_2$CH=C*H*CH), 3.70 (3H, s, O*Me*), 3.61 (3H, s, O*Me*), 3.19 (1H, dt, *J* = 7.6 Hz, 7.4 Hz, ((CO_2)$_2$CC*H*CH=CH), 2.45 (1H, dt, *J* = 13.7, 8.3, C*H*HC(CO_2)$_2$), 2.07 (1H, m, CH*H*C(CO_2)$_2$), 1.98-1.94 (3H, m, CH=CHC*H*$_2$, C*H*HCHCH=CH), 1.84-1.79 (1H, m, C*H*HCH$_2$C(CO_2)$_2$), 1.61 (2H, m, CH*H*CHCH=CH, CH*H*CH$_2$C(CO_2)$_2$), 1.29-1.23 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 0.87 (3H, t, *J* = 7.2 Hz, C*H*$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 172.9 (*C*(=O)OMe), 171.4 (*C*(=O)OMe), 132.4 (CH=*C*HCH$_2$), 128.9 (CH*C*H=CHCH$_2$), 64.4 (*C*(CO_2Me)$_2$), 52.5 (OMe), 52.0 (OMe), 49.0 (*C*HCH=CH), 33.8 ((CO_2)$_2$C*C*H$_2$), 32.5 (*C*H$_2$), 31.6 (*C*H$_2$), 31.4 (*C*H$_2$), 23.1 (*C*H$_2$), 22.2 (*C*H$_2$), 13.9 (CH$_2$*C*H$_3$); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 2955 m (C-H), 2929 m (C-H), 1732 s (C=O*, malonate*), 1667 w (C=C, *trans*), 1267 w (C-O), 973 w (C=C-H, *trans*); ***m/z*** (ESI+) Found: $(M+Na)^+$, 291.1567; $C_{15}H_{24}O_4Na$ requires *M*, 291.1572.

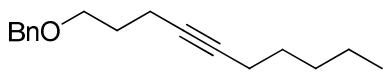
5.29 1-((3-Iodopropoxy)methyl)benzene[113]



To a mixture of acetonitrile (30 mL) and Et_2O (80 mL) was added 3-(benzyloxy)propan-1-ol (2.0g, 12 mmol), imidazole (1.375g, 20.2 mmol) and iodine (4.85g, 19.1 mmol), and the solution left to stir in the absence of light. After 1 h, TLC analysis indictated the reaction was complete, and the mixture was quenched with saturated sodium thiosulfate solution (30 mL). The organic layer was concentrated *in vacuo*, and triturated with hexane (5 × 50 mL). The hexane fractions were combined and evapourated *in vacuo*, leaving crude iodide which was purified by passing through a silica plug (3:1 PE:EtOAc), and the solvent removed *in vacuo*, furnishing 1-((3-iodopropoxy)methyl)benzene as a clear, colourless oil, (2.8253g, 10.21 mmol, 85%),

$\boldsymbol{R_f}$ = 0.68 (1:1 PE:EA); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.33 (5H, m, Ar*H*), 4.51 (2H, s, PhCH_2), 3.53 (2H, t, *J* = 5.8 Hz, CH_2OBn), 3.30 (2H, t, *J* = 6.8 Hz, CH_2I), 2.09 (2H, tt, *J* = 6.8 Hz, 5.8 Hz, $CH_2CH_2CH_2$).

5.28 *1-((dec-4-ynyloxy)methyl)benzene*

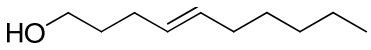


To a solution of heptyne (1.22 mL, 9.28 mmol) in THF (50 mL) was added *n*-BuLi (5.8 mL, 1.6 M in hexanes9.8 mmol) at -78 °C, and the reaction mixture warmed to 0 °C. 1-((3-Iodopropoxy)methyl)benzene (2.28 g, 10.21 mmol in 10 mL THF) was added dropwise over 15 min, and the reaction heated overnight at 30 °C. The reaction was then quenched with sat. aq. NH_4Cl (10 mL), extracted with EtOAc (3 × 25 mL), and the solvent removed *in vacuo*, leaving crude product. which was purified by flash

column chromatography (20:1 PE:EtOAc), furnishing 1-((dec-4-ynyloxy)methyl)benzene as a clear, colourless oil, (1.02g, 4.1 mmol, 45%),

$\boldsymbol{R_f}$ = 0.45 (20:1 PE:EA); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.32 (5H, m, Ar*H*), 4.50 (2H, s, PhCH_2), 3.59 (2H, t, *J* = 5.8 Hz, CH_2OBn), 2.26 (2H, tt, *J* = 7.0 Hz, 4.6 Hz, CH_2), 2.11 (2H, tt, *J* = 7.0 Hz, 4.6 Hz, CH_2), 1.78 (2H, qn, *J* = 6.6 Hz, CH_2), 1.46 (2H, qn, *J* = 6.3 Hz, CH_2), 1.32 (4H, m, CH_2), 0.89 (3H, t, *J* = 7.0 Hz, CH_3); $\boldsymbol{\delta_C}$ (500 MHz, $CDCl_3$), 138.6 (*Ar*), 128.3 (*Ar*), 127.6 (*Ar*), 127.5 (*Ar*), 80.6 (*C*≡C), 79.3 (*C*≡C), 72.9 (Ar*C*H_2O), 69.0 (O*C*H_2CH_2), 31.1 (*C*H_2), 29.2 (*C*H_2), 28.8 (*C*H_2), 22.2 (*C*H_2), 18.7 (*C*H_2), 15.6 (*C*H_2), 14.0 (*C*H_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CHCl_3$) 3029 w (C-H), 2930 m (C-H), 2858 m (C-H); ***m/z*** (ESI+) Found: $(M+H)^+$, 245.1901; $C_{15}H_{24}O_4Na$ requires *M*, 245.1905.

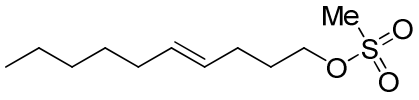
5.27 (*E*)-Dec-4-en-1-ol[114]



Ammonia (125 mL) was condensed into a round-bottomed flask at -78 °C. Sodium metal (0.23 g, 10 mmol) was added portiowise to give a dark blue solution. 1-((Dec-4-ynyloxy)methyl)benzene (1.0g, 4.1 mmol) in Et_2O (4 mL) and *tert*-butanol were then added. After 1 h, TLC analysis indicated that the reaction was complete, and the reaction mixture was warmed to RT and the ammonia allowed to evaporate overnight. The residue was quenched by the addition of water at 0 °C, extracted with Et_2O (3 × 100 mL) and the solvent removed *in vacuo*, leaving crude product. This was purified by flash column chromatography (2:1 PE:EtOAc), furnishing (*E*)-dec-4-en-1-ol as a clear, colourless oil, (504 mg, 3.22 mmol, 78%);

$\boldsymbol{R_f}$ = 0.40 (2:1 PE:EA); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.42 (2H, m, C*H*=C*H*), 3.64 (2H, t, *J* = 6.4 Hz, HOCH_2), 2.06 (2H, m, CH_2), 1.96 (2H, q, *J* = 6.8 Hz, CH_2), 1.62 (2H, q, *J* = 7.5 Hz, CH_2), 1.30 (6H, m, CH_2), 0.87 (3H, t, *J* = 7.0 Hz, CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$), 131.3 (*C*=C), 129.3 (*C*=C), 62.6 (*C*H_2OH), 32.5 (*C*H_2C=C), 32.4 (C=C*C*H_2), 31.4 (*C*H_2), 29.2 (*C*H_2), 28.9 (*C*H_2), 22.5 (*C*H_2), 14.0 (CH_2*C*H_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CHCl_3$) 3326.5 br (O-H), 3955 w (C-H), 2924 m (C-H), 2856 m (C-H).

5.43 *(*E*)-Dec-4-enyl methanesulfonate*

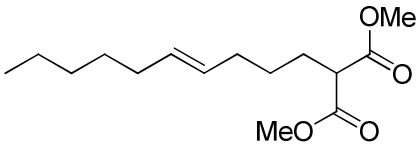


(*E*)-Dec-4-en-1-ol (300 mg, 1.92 mmol) was dissolved in DCM (10 mL), and triethylamine (375 µL, 2.88 mmol) and methanesulfonyl chloride (223 µL, 2.88 mmol) added. The reaction mixture was warmed to RT and left to stir for 1 h, after which it was quenched by addition of HCl (5 mL, 1 M). The organic phase was separated, and the aqueous phase extracted with DCM (3 × 25 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*, leaving (*E*)-dec-4-enyl methanesulfonate as a clear, colourless oil (460 g, 1.92 mmol, 100%);

$\boldsymbol{R_f}$ = 0.78 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.46 (1H, dtt, *J* = 15.2 Hz, 6.7 Hz, 1.5 Hz, C*H*=CH), 5.34 (1H, dtt, *J* = 15.2 Hz, 6.7 Hz, 1.3 Hz, CH=C*H*), 4.21 (2H, t, *J* = 6.5 Hz, CH_2OMs), 2.98 (3H, s, SO_2CH_3), 2.10 (2H, dt, *J* = 6.7 Hz, 6.5 Hz, HC=CHCH_2), 1.97 (2H, dt, *J* = 6.9, 6.7 Hz, CH_2HC=CH), 1.80 (2H, qn, *J* = 7.5 Hz, CH_2), 1.29 (6H, m, CH_2, CH_2, CH_2), 0.87 (3H, t, *J* = 6.7, CH_2CH_3); $\boldsymbol{\delta_C}$ (125 MHz,

$CDCl_3$), 132.4 (*C*H=CH), 127.7 (*C*H=CH), 69.5 (MsO*C*H_2), 37.2 (*C*H_3SO_2), 32.5 (*C*H_2), 31.4 (*C*H_2), 29.1 (*C*H_2), 28.9 (*C*H_2), 28.2 (*C*H_2), 22.5 (*C*H_2), 14.0 (*C*H_3); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CHCl_3$) 2980 m (C-H), 2958 m (C-H), 2926 (C-H), 2858 (C-H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 257.1183; $C_{11}H_{22}O_3NaS$ requires *M*, 257.1187.

5.20 *(Z)-dimethyl 2-(non-4-enyl)malonate*

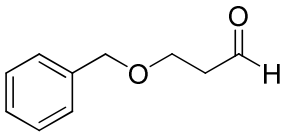


DMF (8 mL, anhydrous) was added to sodium hydride (60% dispersion in mineral oil, 0.130 g, 1.1 mmol) at 0°C and the suspension allowed to stir for 10 min. Dimethyl malonate (0.4 mL, 3.33 mmol) was then added dropwise, and the solution allowed to warm to RT. Stirring was continued for a further 20 min and then a solution of (*E*)-dec-4-enyl methanesulfonate (0.260 g, 3.33 mmol) in THF (4 mL) was added dropwise, followed by potassium iodide (552 g, 3.3 mmol), and the mixture was heated to reflux (80°C) for 18 h. The reaction was then quenched with sat. aq. NH_4Cl (5 mL), and extracted (3 × 25 mL Et_2O, brine wash). The organic phase was dried and solvent removed *in vacuo* to leave a crude product residue which was purified by flash column chromatography (5:1 PE:EtOAc), leaving (*Z*)-dimethyl 2-(non-4-enyl)malonate as a clear, colourless oil, (0.204g, 0.75 mmol, 68%),

$\boldsymbol{R_f}$ = 0.47 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.37 (2H, m, C*H*=C*H*), 3.72 (6H, s, OCH_3), 3.35 (1H, t, *J* = 7.5 Hz, C*H*C($CO_2Me)_2$), 2.03-1.88 (6H, m, 3 × CH_2), 1.39-1.18 (8H, m, CH_2, CH_2, CH_2, CH_2), 0.87 (3H, t, *J* = 6.8 Hz, CH_3CH_2); $\boldsymbol{\delta_C}$ (125 MHz,

$CDCl_3$) 169.9 (*C*=O), 131.4 (*C*=C), 129.0 (C=*C*), 52.4 (O*C*H_3), 51.6 (*C*HC(CO_2Me)$_2$), 32. 5 (*C*H_2) 32.1 (*C*H_2), 31.4 (*C*H_2), 29.2 (*C*H_2), 28.3 (*C*H_2), 27.2 (*C*H_2), 22.5 (*C*H_2), 14.0 (CH_2*C*H_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 2980 m (C-H), 2957 m (C-H), 2926 m (C-H), 2858 m (C-H), 1749 s (C=O), 1731 s (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 293.1725; $C_{15}H_{26}O_4Na$ requires *M*, 293.1729.

5.40 3-(benzyloxy)propanal[115]

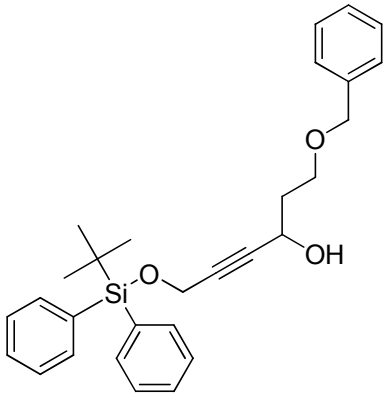


To DCM (200 mL) at -78 °C was added oxalyl chloride (2.0 mL, 23 mmol) with constant stirring. DMSO (3.2 mL, 45 mmol) was then added dropwise, keeping the temperature of the reaction mixture below -65 °C, and the solution was allowed to stir for 5 min. of 3-(Benzyloxy)propan-1-ol (3.32 g, 20 mmol) was then added dropwise, and stirring was continued at -78 °C for a further 30 min. Triethylamine (14mL, 50 mmol) was added and the reaction mixture warmed to 10 °C before pouring onto 2 M HCl (200 mL). The organic phase was separated, and the aqueous phase extracted with DCM (3 × 100 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*. The residue was then purified by kugelrohr distillation (0.05 mmHg, 125 °C), to furnish the 3-(benzyloxy)propanal (2.35 g, 71%);

$\boldsymbol{R_f}$ = 0.41 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.79 (1H, t, *J* = 1.8 Hz, C*H*O), 7.36-7.26 (5H, m, Ar*H*), 4.52 (2H, s, CH_2Ph), 3.81 (2H, t, *J* = 6.1 Hz, CH_2OBn), 2.69 (2H, td, *J*

= 6.1 Hz, 1.8 Hz, CH_2CHO); δ_C (125 MHz, $CDCl_3$) 201.3 (*C*HO), 137.8 (Ar), 128.5 (Ar), 127.8 (Ar), 127.7 (Ar), 73.3 (*C*H_2Ph), 63.8 (*C*H_2OBn), 43.9 (*C*H_2CHO); ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 2967 m (C-H), 2866 m (C-H), 1721 s (C=O).

5.39 *1-(Benzyloxy)-6-(*tert*-butyldiphenylsilyloxy)hex-4-yn-3-ol*

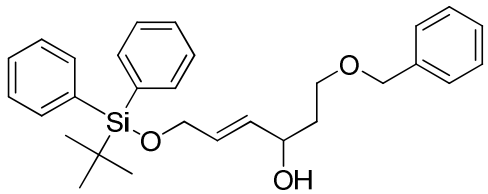


n-BuLi (6.3 mL, 1.6 M in hexanes, 10.19 mmol) was added to a stirred solution of *tert*-butyldiphenyl(prop-2-ynyloxy)silane (3.0 g, 10.19 mmol) in THF (40 mL) at -78°C. After 30 min, 3-(benzyloxy)propanal (1.67 g, 10.19 mmol) was added dropwise, and the reaction mixture allowed to stir for a further 1 h. The reaction was then quenched with HCl (1 M, 12 mL); the organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 300 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*. The residue was purified by flash column chromatography (4:1 DCM:PE → DCM), to give 1-(benzyloxy)-6-(*tert*-butyldiphenylsilyloxy)hex-4-yn-3-ol as a clear, colourless oil (4.191 g, 90%);

R_f = 0.42 (10:1 DCM:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.70-7.69 (4H, m, Ar*H*), 7.44-7.25 (12H, m, Ar*H*), 4.54 (1H, t, *J* = 4.9 Hz, HOC*H*), 4.50 (2H, s, OCH_2Ph), 4.35

(2H, d, *J* = 1.7 Hz, CH_2C≡C), 3.76 (1H, m, CH_2OBn), 3.60 (1H, m, CH_2OBn), 2.68 (1H, dt, *J* = 6.0 Hz, 2.0 Hz, OH); 1.99 (1H, ddt, *J* = 14.3 Hz, 6.3 Hz, 3.5 Hz, HOCH$_2$CH_2) 1.85 (1H, m, HOCH$_2$CH_2) 1.05 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$) 137.8 (Ar), 135.6 (Ar), 133.1 (Ar), 129.8 (Ar), 128.55 (Ar), 127.8 (Ar), 127.7 (Ar), 127.7 (Ar), 127.0 (Ar), 85.5 (C≡C), 83.3 (C≡C), 73.3 (O*C*H$_2$Ph), 67.6 (*C*H$_2$OBn), 61.3 (*C*HOH), 60.4 (SiO*C*H$_2$), 36.6 (*C*H$_2$CHOH), 26.7 (C(*C*H$_3$)$_3$), 19.1 (*C*(CH$_3$)$_3$); ν_{max}/**cm^{-1}** ($CDCl_3$) 3422 br (O-H), 2959 m (C-H), 2930 m (C-H), 2858 m (C-H); 2325 w (C≡C); ***m/z*** (ESI+) Found: (M+Na)$^+$, 481.2164; $C_{29}H_{34}O_3NaSi$ requires *M*, 483. 481.2175.

5.38 *(*E*)-1-(Benzyloxy)-6-(*tert*-butyldiphenylsilyloxy)hex-4-en-3-ol*

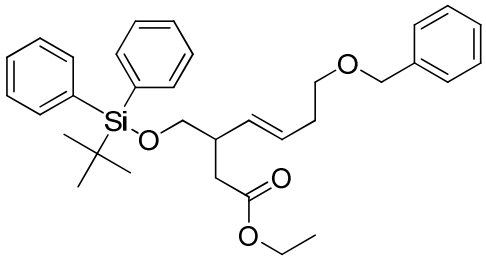


Red-Al® (65% wt. in toluene, 0.10 mL, 0.327 mmol) was added to THF (10 mL), at -15°C. To the resulting solution was added a solution of 1-(benzyloxy)-6-(*tert*-butyldiphenylsilyloxy)hex-4-yn-3-ol (100 mg, 0.218 mmol) in THF (10 mL), and the reaction mixture left to stir for 1.5 h. The reaction was then quenched with sat. aq. NH_4Cl (5 mL, saturated), and a saturate solution of Rochelle's salt was added (5 mL). The mixture was stirred until homogeneous and then the organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*. The residue was purified by flash column chromatography (1:10 EtOAc:DCM),

leaving (*E*)-1-(benzyloxy)-6-(*tert*-butyldiphenylsilyloxy)hex-4-en-3-ol as a clear, colourless oil (74 mg, 70%);

$\boldsymbol{R_f}$ = 0.40 (10:1 DCM:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.67-7.65 (4H, m, Ar*H*), 7.43-7.25 (11H, m, Ar*H*), 5.77-7.76 (2H, m, C*H*=C*H*), 4.50 (2H, s, OCH_2Ph), 4.35 (1H, m, C*H*OH), 4.20 (2H, m, CH_2CH=CH), 3.69 (1H, ddd, *J* = 14.8, 9.0, 5.5, C*H*HOBn), 3.61 (1H, ddd, *J* = 14.8, 9.5, 6.2, CH*H*OBn), 2.69 (1H, s, br, OH), 1.82 (1H, m, CH_2CH$_2$OBn), 1.05 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 137.9 (Ar), 135.5 (Ar), 133.7 (Ar), 132.1 (Ar), 129.6 (Ar), 129.4 (Ar), 128.4 (Ar), 127.7 (Ar), 127.7 (Ar), 127.6 (Ar), 73.3 (OCH_2Ph), 71.1 (*C*HOH), 68.4 (*C*H$_2$OCH$_2$Ph), 63.8 (SiOCH_2), 36.5 (HOCH*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 19.2(*C*(CH$_3$)$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3727 br (O-H), 2960 m (C-H), 2929 m (C-H), 2857 m (C-H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 483.2339; $C_{29}H_{34}O_3NaSi$ requires *M*, 483.2331.

5.37 *(*E*)-Ethyl 7-(benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-enoate*

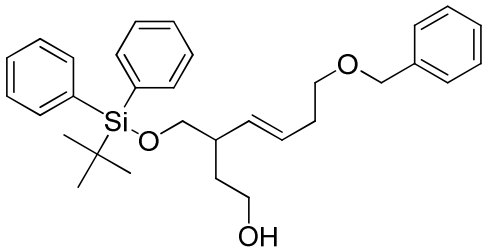


To a solution of (*E*)-1-(benzyloxy)-6-(*tert*-butyldiphenylsilyloxy)hex-4-en-3-ol (100 mg, 0.219 mmol) in *para*-xylene (10 mL) was added triethylorthoacetate (0.21 mL, 1.09 mmol) and propionic acid (3 drops). The solution was then heated to reflux (140 °C) overnight. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (10:1 PE:EtOAc), leaving (*E*)-ethyl 7-(benzyloxy)-3-((tert-

butyldiphenylsilyloxy)methyl)hept-4-enoate as a clear, colourless oil, (1.61g, 3.56 mmol, 98%).

$\boldsymbol{R_f}$ = 0.69 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.67-7.65 (4H, m, Ar*H*), 7.43-7.25 (11H, m, Ar*H*), 5.50 (1H, dt, *J* = 15.5 Hz, 6.5 Hz, C*H*=CH), 5.38 (1H, dd, *J* = 15.5 Hz, 8.0 Hz, CH=C*H*), 4.46 (2H, s, OCH_2Ph), 4.07 (2H, q, *J* = 7.1 Hz, (C=O)OCH_2CH$_3$), 3.62 (1H, dd, *J* = 9.8 Hz, 5.3 Hz, C*H*HOPh), 3.51 (1H, dd, *J* = 9.8 Hz, 6.8 Hz, OCH*H*Ph), 3.42 (2H, t, *J* = 7.1 Hz, CH_2O), 2.79-2.72 (1H, m, C*H*HCO$_2$Et), 2.65 (1H, dd, *J* = 15.0 Hz, 5.7 Hz, CH*H*CO$_2$Et), 2.32-2.25 (3H, m, C*H*CH=CHCH_2), 1.19 (3H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 1.03 (9H, s, SiC(CH_3)$_3$; $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 172.7 (*C*=O), 138.4 (*Ar*), 135.6 (*Ar*), 133.6 (*Ar*), 131.5 (*C*=C), 129.6 (C=*C*), 129.3 (*Ar*), 129.1 (*Ar*), 128.3 (*Ar*), 127.7 (*Ar*), 127.6 (*Ar*), 127.5 (*Ar*), 72.9 (O*C*H$_2$Ph), 70.0 (*C*H$_2$O), 66.6 (*C*H$_2$O), 60.2 ((C=O)*C*H$_2$), 41.8 (*C*HCH=CHCH$_2$) 36.6 (*C*H$_2$), 33.1 (*C*H$_2$), 26.8 (SiC(*C*H$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$), 14.2 (*C*H$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 2958 m (C-H), 2930 m (C-H), 2858 m (C-H), 1736 (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 533.2744; $C_{29}H_{34}O_3NaSi$ requires *M*, 533.2745.

5.36 *(*E*)-7-(Benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-en-1-ol*

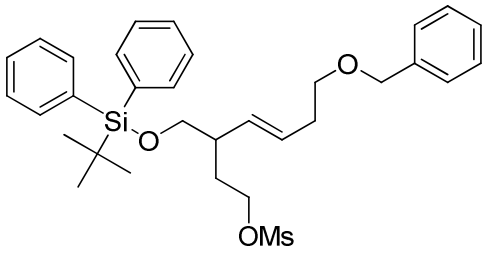


DIBAL-H (1.5 mol L^{-1}, 1.19 mL, 1.51 mmol) was added to a solution of (*E*)-7-(benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-en-1-ol (0.200 g, 0.377

mmol) in THF (20 mL) at -78°C with stirring. The reaction mixture was then warmed to 0 °C, stirred for 1 h and then quenched with a saturated solution of Rochelle's salt solution (20 mL). The organic phase was separated, and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and solvent removed *in vacuo*. The residue was then purified by flash column chromatography (DCM) to give (*E*)-7-(benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-en-1-ol as a clear, colourless oil (0.116 g, 0.238 mmol, 62%);

$\boldsymbol{R_f}$ = 0.41 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.67-7.65 (4H, m, Ar*H*), 7.43-7.25 (11H, m, Ar*H*), 5.46 (1H, dt, *J* = 15.4 Hz, 6.4 Hz, CH=C*H*CH_2), 5.38 (1H, dd, *J* = 15.4 Hz, 8.5 Hz, CHC*H*=CH), 4.48 (2H, s, OCH_2Ph), 3.66 (2H, m, CH_2OBn), 3.56 (2H, m, CH_2), 3.44 (2H, t, *J* = 6.6 Hz, CH_2OH), 2.35 (1H, m, C*H*CH=CH), 2.29 (2H, dt, *J* = 6.4, 5.9, CH=CHCH_2), 1.79 (1H, m, C*H*H), 1.56, (1H, m), 1.05 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (500 MHz, $CDCl_3$), 135.6 (*Ar*), 134.8 (*Ar*), 133.3 (C=*C*), 129.6 (*Ar*), 129.4 (*Ar*), 128.4 (*Ar*), 128.2 (*C*=C), 127.8 (*Ar*), 127.8 (*Ar*), 127.6 (*Ar*), 72.9 (O*C*H_2Ph), 69.8 (*C*H_2O), 67.7 (*C*H_2O), 61.4, (*C*H_2O) 43.2 (*C*HCH=CH), 34.8 (*C*H_2), 33.2 (*C*H_2), 26.9 (SiC(*C*H_3)$_3$), 19.4 (Si*C*(CH$_3$)$_3$); $\boldsymbol{\nu_{max}}$**/cm^{-1}**3423 br (O-H), 3069 w (C-H), 2930 m (C-H), 2857 m (C-H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 483.2339; $C_{29}H_{36}NaO_3Si$ requires *M*, 483.2331.

5.46 *(*E*)-7-(Benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-enyl methanesulfonate*

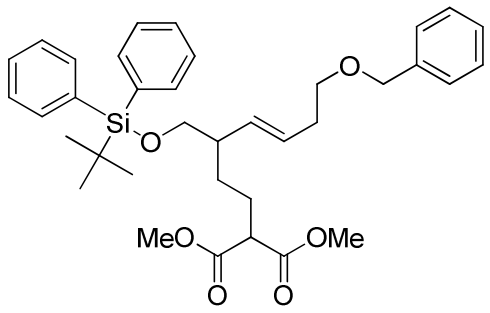


(*E*)-7-(Benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-en-1-ol (0.130 g, 0.266 mmol) was dissolved in DCM (10 mL), and triethylamine (0.056 mL, 0.40 mmol) and methanesulfonyl chloride (0.031 mL, 0.40 mmol) added at 0 °C. The reaction mixture was warmed to RT, the reaction was left to stir for 1 h, after which it was quenched by addition of HCl (5 mL, 1 mol L^{-1}). The organic phase was separated, and the aqueous phase extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*, furnishing (*E*)-7-(benzyloxy)-3-((*tert*-butyldiphenyl- silyloxy)methyl)hept-4-enyl methanesulfonate as a clear, colourless oil (0.154 g, 0.266 mmol, 100%);

$\boldsymbol{R_f}$ = 0.51 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.67-7.65 (4H, m, Ar*H*), 7.43-7.25 (11H, m, Ar*H*), 5.50 (1H, dt, *J* = 15.4 Hz, 6.6 Hz, C*H*=CH), 5.29 (1H, dd, *J* = 15.4 Hz, 8.7 Hz, CH=C*H*), 4.48 (2H, s, OCH_2Ph), 4.21 (2H, m, CH_2OSO_2), 3.59 (1H, dd, *J* = 14.1 Hz, 9.9 Hz, CH*H*OSi), 3.54 (1H, dd, *J* = 14.1 Hz, 9.9 Hz C*H*HOSi), 3.46 (2H, t, *J* = 6.8 Hz, CH_2OBn), 2.90 (3H, s, CH_3SO_2), 2.33 (3H, m, C*H*CH=CH, CH=CHCH_2), 2.06 (1H, m, C*H*HOSO$_2$), 1.65 (1H, m, C*H*HOSO$_2$), 1.05 (9H, s, Si(C(*C*H_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 138.7 (*Ar*), 138.4 (*Ar*), 135.6 (*Ar*), 133.1 (*C*H=CH), 131.4 (*Ar*), 129.7 (*Ar*), 128.4 (CH=*C*H), 127.7 (*Ar*), 127.6 (*Ar*), 72.9, 69.9, 68.6, 67.2, 41.8, 37.2, 33.1, 30.6, 26.9, 19.3; $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 3070 w (C-H), 3030

w (C-H), 2998 w (C-H), 2956 m (C-H), 2931 m (C-H), 2897 w (C-H), 2857 m (C-H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 589.2414; $C_{32}H_{42}NaO_5SSi$ requires *M*, 589.2420.

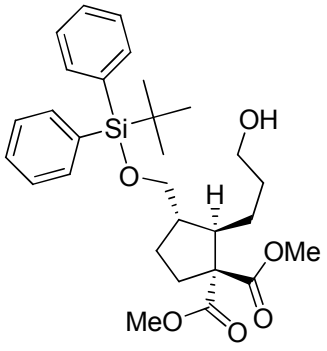
5.23 *(±) (*E*)-Dimethyl 2-(7-(benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-enyl)malonate*



DMF (16 mL, anhydrous) was added to sodium hydride (60% suspension in mineral oil, 69 mg, 1.63 mmol) at 0 °C, and the suspension was allowed to stir for 10 min. Dimethyl malonate (0.20 mL, 1.72 mmol) was then added dropwise, and the solution allowed to warm to RT and was stirred for a further 20 min. A solution of (*E*)-7-(benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-enyl methanesulfonate in THF (0.326 g, 0.575 mmol in 8 mL) was added dropwise, followed by potassium iodide (0.287 g, 1.72 mmol), and the mixture was heated to reflux (80 °C) for 18h. The reaction was quenched with sat. aq. NH_4Cl (10 mL); the organic phase was separated, and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*. Further purification by flash column chromatography (3:1 PE:EtOAc), left (*E*)-dimethyl 2-(7-(benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-enyl)malonate as a clear, light-yellow oil, (0.263g, 76%);

R_f = 0.57 (3:1 PE:EtOAc); δ_H (500 MHz, $CDCl_3$) 7.67-7.65 (4H, m, Ar*H*), 7.43-7.25 (11H, m, Ar*H*), 5.50 (1H, dt, *J* = 15.4 Hz, 6.8 Hz, CHCH=C*H*CH_2), 5.29 (1H, dd, *J* = 15.4 Hz, 8.7 Hz, CHC*H*=$CHCH_2$), 4.48 (2H, s, OCH_2Ph), 3.70 (6H, s, OCH_3), 3.57 (1H, dd, *J* = 10.0 Hz, 5.8 Hz, C*H*HOTBDPS), 3.51 (1H, dd, *J* = 10.0 Hz, 6.8 Hz, CH*H*OTBDPS), 3.48 (2H, t, *J* = 7.1 Hz, CH_2OBn), 3.35 (1H, t, *J* = 7.7 Hz, C*H*($CO_2Me)_2$), 2.30 (2H, td, *J* = 7.1 Hz, 6.8 Hz, CH=CHCH_2), 2.20 (1H, m, C*H*CH=CH), 1.95 (1H, m, C*H*HCH($CO_2Me)_2$), 1.83 (1H, m, CH*H*CH($CO_2Me)_2$), 1.61 (1H, m, CH*H*CH_2CH($CO_2Me)_2$), 1.25 (1H, m, C*H*HCH$_2$CH($CO_2)_2$Me), 1.05 (9H, s, Si(C(C$H_3)_3$); δ_C (100 MHz, $CDCl_3$) 169.9 (2 × *C*O_2Me), 138.5 (*Ar*), 135.6 (*Ar*), 134.8 (*Ar*), 133.8 (*Ar*), 132.7 (CH*C*H=$CHCH_2$), 129.6 (*Ar*), 128.5 (*Ar*), 128.4 (CHCH=*C*HCH_2), 127.6 (*Ar*), 72.9 (O*C*H_2Ph), 70.2 (*C*H_2OBn), 67.1 (*C*H_2OTBDPS), 52.3 (CO_2*Me*), 51.7 (*C*H($CO_2Me)_2$), 45.2 (*C*HCH=$CHCH_2$), 33.3 (CHCH=CH*C*H_2), 28.7 (*C*H_2CH($CO_2Me)_2$, 26.9 (*C*($CH_3)_3$), 26.6 (*C*H_2CH_2CH($CO_2Me)_2$), 19.3 (C(*C*$H_3)_3$); ν_{max}/**cm**$^{-1}$ 2940 m (C-H), 2873 m (C-H), 1755 m (C=O), 1733 m (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 625.2956; $C_{36}H_{46}NaO_6Si$ requires *M*, 625.2961.

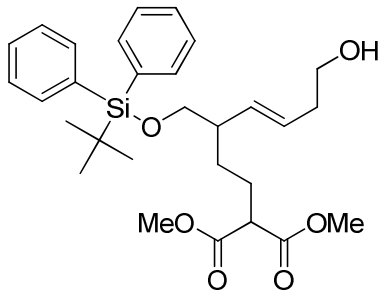
5.57 *(±) (2*R**,3*S**)-Dimethyl 3-((*tert-*butyldiphenylsilyloxy)methyl)-2-(3-hydroxypropyl)cyclopentane-1,1-dicarboxylate*



A solution of (*E*)-dimethyl 2-(7-(benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-enyl)malonate (20.0 mg, 0.034 mmol) in either EtOH or acetonitrile (2 mL) was prepared in a reaction carousel. Manganese(III) acetate (18.2 mg, 0.068 mmol) was added to each, along with copper(II) triflate (12.3 mg, 0.034 mmol) or copper(II) tetrafluroborate (8.1 mg, 0.034 mmol) as necessary. The reaction tubes were degassed, and heated to reflux for 18h, after which the reaction was quenched by addition of water (4 mL). The organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by column chromatography (20:1 PE:EtOAc → 4:1), returned (*E*)-dimethyl 2-(7-(benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-enyl)malonate (5.9 mg, 0.011 mmol, 34%) as a clear, colourless oil;

$\boldsymbol{R_f}$ = 0.25 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.76-7.62 (4H, m, Ar*H*), 7.43-7.34 (6H, m, Ar*H*), 3.82 (1H, dd, *J* = 10.0 Hz, 5.3 Hz, C*H*HOSi), 3.70 (1H, dd, *J* = 10.0 Hz, 6.5 Hz, C*H*HOSi), 3.40 (2H, m, CH_2OH), 3.38 (3H, s, CO_2CH_3), 3.35 (3H, s, CO_2CH_3), 2.70 (1H, dt, *J* = 7.8 Hz, 5.9 Hz, C*H*CHCH$_2$OSi), 2.55 (1H, dt, *J* = 13.2 Hz, 7.8 Hz, C*H*HC$(CO_2Me)_2$), 2.17 (2H, m, CH*H*C$(CO_2Me)_2$, C*H*HCH$_2$C$(CO_2Me)_2$), 2.03 (1H, m, C*H*CH$_2$OSi), 1.62 (2H, m, CH*H*CH$_2$C$(CO_2Me)_2$, C*H*HCH$_2$CH$_2$OH), 1.43 (3H, m, CH*H*C*H*$_2$CH$_2$OH), 1.23 (9H, s, Si(C(C*H*$_3$)$_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 173.1 (*C*=O), 171.8 (*C*=O), 135.67 (Ar), 133.8 (Ar), 129.6 (Ar), 127.6 (Ar), 66.4 (*C*H$_2$OSi), 64.5 (*C*H$_2$OH), 62.8 (*C*$(CO_2Me)_2$), 52.5 (CO_2CH_3), 52.1 (CO_2CH_3), 47.3 (*C*H), 46.0 (*C*H), 34.1 (*C*H$_2$), 31.3 (*C*H$_2$), 27.8 (*C*H$_2$), 27.6 (*C*H$_2$), 26.9 (*C*$(CH_3)_3$), 19.3 (C(*C*H$_3$)$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3422 br (O-H), 3071 w (C-H), 3049 w (C-H), 2998 w (C-H), 2952 m (C-H), 2932 m (C-H), 2859 m (C-H), 1731 s (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 535.2484; $C_{29}H_{40}NaO_6Si$ requires *M*, 535.2492.

5.25 *(±) (*E*)-Dimethyl 2-(3-((*tert*-butyldiphenylsilyloxy)methyl)-7-hydroxyhept-4-enyl)malonate*

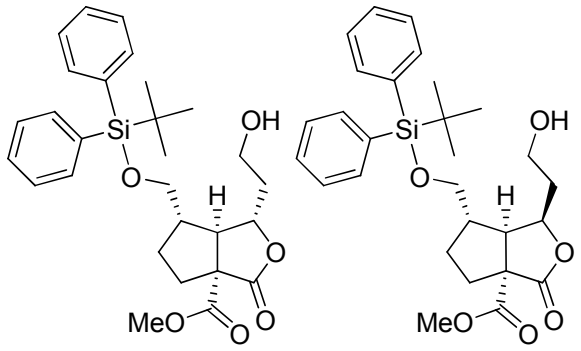


(±)-(*E*)-Dimethyl 2-(7-(benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-hept-4-enyl)malonate (0.238 g, 0.395 mmol) was dissolved in DCM (10 mL), and boron trichloride-dimethyl sulfide complex solution (2 M solution in DCM, 2.37 mL, 4.73 mmol) added dropwise at 0 °C and stirring was continued for a further 3 days at RT. The reaction was quenched by addition of sat. aq. NH_4Cl (5 mL), the organic phase was separated, and the aqueous phase extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo* leaving an impure residue which was further purified by flash column chromatography (1:1 PE:EtOAc), to give (±)-(*E*)-dimethyl 2-(3-((*tert*-butyldiphenylsilyloxy)methyl)-7-hydroxyhept-4-enyl)malonate as a clear, colourless oil (138mg, 0.269 mmol, 68%);

$\boldsymbol{R_f}$ = 0.41 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.76-7.62 (4H, m, Ar*H*), 7.43-7.34 (6H, m, Ar*H*), 5.41 (1H, dt, *J* = 15.4, 6.8, CH_2CH=CH), 5.31 (1H, dd, *J* = 15.4 Hz, 8.7 Hz, CH_2CH=C*H*), 3.71 (6H, s, OCH_3), 3.61 (2H, t, *J* = 6.2 Hz, CH_2OH), 3.52 (2H, m, CH_2OSi), 3.32 (1H, t, *J* = 7.6 Hz, $CH(CO_2Me)_2$), 2.25 (2H, q, *J* = 7.0 Hz, $CH_2CH(CO_2Me)_2$), 2.20 (1H, m, C*H*CH=CH), 1.92 (1H, m), 1.80 (1H, m), 1.60 (1H, m), 1.20 (1H, m), 1.05 (9H, s, $Si(C(CH_3)_3)$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.9 (*C*=O), 169.8

(*C*=O), 135.8 (*Ar*), 135.6 (*Ar*), 135.4 (*Ar*), 134.9 (*Ar*), 134.3 (*Ar*), 133.7 (*Ar*), 129.9 (*Ar*), 129.6 (*Ar*), 128.3 (*C*H=CH), 127.8 (CH=*C*H), 127.4 (*Ar*), 67.2 (*C*H_2OTBDPS), 61.9 (*C*H_2OH), 52.5 (CO_2*Me* × 2), 51.8 (*C*H(CO_2Me)$_2$), 45.2 (*C*HCH=CH), 36.2 (CH=CH*C*H_2), 28.6 (*C*$H_2$$CH_2$CH($CO_2$Me)$_2$), 26.9 (SiC(*C*$H_3$)$_3$), 26.6 (C*H*$_2$CH($CO_2$Me)$_2$), 19.3, (Si*C*($CH_3$)$_3$); $\boldsymbol{\nu_{max}}$**/cm^{-1}** 3441 br (O-H), 2952 m (C-H), 2862 m (C-H), 1733 m (C=O). ***m/z*** (ESI+) Found: $[M+Na]^+$, 535.2486; $C_{29}H_{40}NaO_6Si$ requires *M*, 535.2492.

5.62 *(±)-(1*S**,3a*S**,6*S**,6a*R**)-methyl 6-((*tert*-butyldiphenylsilyloxy)methyl)-1-(2-hydroxyethyl)-3-oxohexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate and (±)-(1*R**,3a*S**,6*S**,6a*R**)-methyl 6-((*tert*-butyldiphenylsilyloxy)methyl)-1-(2-hydroxyethyl)-3-oxohexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate*



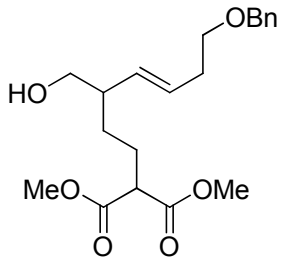
A solution of (±)-(*E*)-dimethyl 2-(3-((*tert*-butyldiphenylsilyloxy)methyl)-7-hydroxyhept-4-enyl)malonate (20.0 mg, 0.039 mmol) in acetonitrile (2 mL) was prepared in a reaction carousel. Manganese(III) acetate (21 mg, 0.078 mmol) was added along with copper(II) triflate (14 mg, 0.039 mmol). The reaction tube was degassed, and heated to reflux for 18h, after which the reaction was quenched by addition of water (4 mL). The organic phase was separated, and the aqueous phase

extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by column chromatography (20:1 PE:EtOAc → 4:1), delivered (±)-(1*S*,3a*S*,6*S*,6a*R*)-methyl 6-((*tert*-butyldiphenylsilyloxy)methyl)-1-(2-hydroxyethyl)-3-oxohexahydro-1*H*-cyclopenta- [*c*]furan-3a-carboxylate (9.3 mg, 0.0023, mmol, 46%) as a 1:1 mixture of diastereoisomers.

$\boldsymbol{R_f}$ = 0.26 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.76-7.62 (4H [d1], 4H [d2], m, Ar*H*), 7.43-7.34 (6H [d1], 6H [d2] m, Ar*H*), 4.83 (1H [d1], ddd, *J* = 9.8 Hz, 6.2 Hz, 3.2 Hz, C*H*CH_2CH_2OH), 4.46 (1H [d2], ddd, *J* = 12.8 Hz, 8.4 Hz, 4.6 Hz, C*H*CH_2CH_2OH), 3.78-3.75 (1H, m, C*H*HOH [d2]), 3.78, (3H [d], s, CO_2*Me*), 3.77, (3H [d], s, CO_2*Me*), 3.77-3.74 (1H [d1], m, C*H*HOH), 3.74-3.71 (1H [d1], m, C*H*HOH), 3.72-3.69 (1H [d2], m, C*H*HOH), 3.63-3.60 (2H [d2], m, C*H*HOTBDPS) , 3.55-3.52 (2H [d1], m, C*H*HOTBDPS), 2.82 (1H [d2], dd, *J* = 5.2 Hz, 3.5 Hz, CHC*H*CH *bridgehead*), 2.80 (1H [d1], dd, *J* = 5.9 Hz, 5.8 Hz, CHC*H*CH *bridgehead*), 2.35-2.23 (3H [d1], m, CH_2C$(CO_2)_2$, C*H*CH_2OTBDPS) 2.16 (1H [d2], m, C*H*CH_2OTBDPS), 2.00 (1H [d2], m, CH_2CH_2OH), 1.89 (1H [d2], m, CH_2CH_2OH) 1.79 (1H [d1], m, CH_2CH_2OH), 1.05 (9H [d1], 9H [d2], s, Si(C(C$H_3)_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$), 175.6 (C=O, *ester* [d]), 175.4 (C=O, *ester* [d], 175.6 (C=O, *lactone* [d]), 175.4 (C=O, *lactone* [d]), 135.6 (*Ar*), 135.5 (*Ar*), 133.2 (*Ar*), 129.9 (*Ar*), 127.8 (*Ar*), 82.9 (*C*HCH_2CH_2OH [d2]), 78.6 (*C*HCH_2CH_2OH [d1]), 59.9 (C$(CO_2)_2$), 59.1 (C$(CO_2)_2$), 54.2 (CH*C*HCH *bridgehead* [d2]), 53.2 (CO_2*Me* [d]), 53.1 (*C*H_2OH [d2]), 53.1 (CO_2*Me* [d]), 52.9 (*C*H_2OH [d2]), 51.5 (CH*C*HCH *bridgehead* [d2]), 38.5 (*C*H_2CH_2OH [d2]), 33.8 (*C*H_2CH_2OH [d2]), 33.7 (*C*HCH_2OTBDPS [d2]), 33.5 (CH_2C$(CO_2)_2$ [d2]) 32.6 (*C*HCH_2OTBDPS [d1]), 32.3 (CH_2C$(CO)_2$ [d1]), 29.0 (2 × $CH_2CH_2(CO_2)_2$), 26.9 (2 × SiC(*C*$H_3)_3$), 19.2 (2 × Si*C*$(CH_3)_3$). $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 3454

br (O-H), 3071 w (C-H), 3049 w (C-H), 2955 m (C-H), 2932 m (C-H), 2891 m (C-H), 2858 m (C-H), 1775 s (C=O), 1740 s (C=O). ***m/z*** (ESI+) Found: $(M+Na)^+$, 519.2180; $C_{28}H_{36}NaO_6Si$ requires *M*, 519.2179.

5.24 *(*E*)-dimethyl 2-(7-(benzyloxy)-3-(hydroxymethyl)hept-4-enyl)malonate*

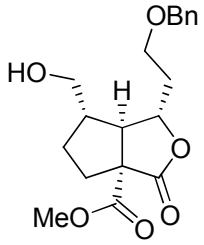


(*E*)-Dimethyl 2-(7-(benzyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)hept-4-enyl)malonate (0.152 g, 0.258 mmol) was dissolved in THF (20 mL), and acetic acid (0.044 mL, 0.775 mmol) was added dropwise at 0°C whilst stirring. Addition of tetrabutylammonium fluoride (1.0 M, 0.775 mL, 0.775 mmol) followed, and stirring was continued for a further 15 min. The reaction mixture was then before warmed to RT and stirred for a further 18h. The reaction was quenched by addition of water (10 mL), the organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and solvent removed *in vacuo* leaving an impure residue. Purification by flash column chromatography (1:1 PE:EtOAc) gave (*E*)-dimethyl 2-(7-(benzyloxy)-3-(hydroxymethyl)hept-4-enyl)malonate as a clear, colourless oil, (0.083 g, 0.237 mmol, 92%);

$\boldsymbol{R_f}$ = 0.37 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.35-7.25 (5H, m, Ar*H*), 5.57 (1H, dt, *J* = 15.4 Hz, 7.0 Hz, CH_2CH=CH), 5.22 (1H, dd, *J* = 15.4 Hz, 8.8 Hz,

$CH_2CH{=}CH$), 4.49 (2H, s, OCH_2Ph), 3.71 (6H, s, OCH_3), 3.48 (2H, m, CH_2OBn), 3.35 (1H, t, J = 7.6 Hz, $CH(CO_2Me)_2$), 2.35 (2H, q, J = 7.0 Hz, $CH_2CH(CO_2Me)_2$), 2.18 (1H, m, $CHCH{=}CH$), 1.95-1.75 (2H, m), 1.40 (1H, m), 1.24 (1H, m); δ_C (100 MHz, $CDCl_3$) 169.7 ($C{=}O$ × 2), 138.3 (*Ar*), 132.4 (*Ar*), 130.8 (*Ar*), 128.4 ($CH{=}CH$), 127.7 ($CH{=}CH$), 127.6 (*Ar*), 72.9 (OCH_2Ph), 69.6 (CH_2OBn), 65.5 (CH_2OH), 52.5 (CO_2Me × 2), 51.6 ($CH(CO_2Me)_2$), 45.7, ($CHCH{=}CH$), 33.1 ($CH{=}CHCH_2$), 28.5 ($CH_2CH_2CH(CO_2Me)_2$), 26.5 ($CH_2CH(CO_2Me)_2$); ν_{max}/**cm**$^{-1}$ 3328 m (O-H), 2941 m (C-H), 2873 m (C-H), 1734 m (C=O); ***m/z*** (ESI+) Found: $[M+Na]^+$, 387.1778; $C_{20}H_{28}NaO_6$ requires *M*, 387.1784.

5.61 *(±)(1S*,3aS*,6S*,6aR*)-Methyl 1-(2-(benzyloxy)ethyl)-6-(hydroxymethyl)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate*

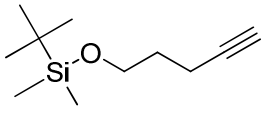


A solution of (*E*)-dimethyl 2-(7-(benzyloxy)-3-(hydroxymethyl)hept-4-enyl)malonate (20.0 mg, 0.057 mmol) in acetonitrile (2 mL) was prepared in a reaction carousel. Manganese(III) acetate (31 mg, 0.114 mmol) was added along with copper(II) triflate (21 mg, 0.057 mmol). The reaction tube was degassed, and heated to reflux for 18h, after which the reaction was quenched by addition of water (4 mL). The organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by column chromatography (20:1 PE:EtOAc → 2:1), returned

(1*S*,3a*S*,6*S*,6a*R*)-methyl 1-(2-(benzyloxy)ethyl)-6-(hydroxymethyl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (8.6 mg, 0.023 mmol, 41%);

$\boldsymbol{R_f}$ = 0.24 (2:1 PE:EtOAc); [Major isomer] $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.39-7.30 (5H, m, Ar*H*), 4.55 (1H, d, *J* = 11.8 Hz, OC*H*HPh), 4.50 (1H, d, *J* = 11.8 Hz, OCH*H*Ph), 4.50-4.48 (1H, m, C*H*CH_2CH_2OBn), 3.63 (2H, m, C*H*$_2$OBn), 3.78 (3H, s, CO_2*Me*), 3.58 (1H, dd, *J* = 10.3 Hz, 5.6 Hz, C*H*HOH), 3.41 (1H, m, CH*H*OH), 2.81 (1H, dd, *J* = 4.9, 3.5, CHC*H*CH *bridgehead*), 2.56 (1H, m $CHCH_2OH$), 2.14 (2H, m, CH*H*C$(CO_2)_2$), 2.07 (2H, m, C*H*$_2CH_2$OBn), 1.81 (1H, ddd, *J* = 14.0 Hz, 7.2 Hz, 7.0 Hz, C*H*HC$CH_2(CO_2)_2$), 1.65 (1H, ddd, *J* = 14.0 Hz, 7.2 Hz, 6.8 Hz, CH*H*CH_2C$(CO_2)_2$); [Minor isomer, selected resonances] $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 4.91 (1H, dd, *J* = 7.7 Hz, 5.9 Hz, C*H*CH_2CH_2OBn), 2.86 (1H, dd, *J* = 5.9 Hz, 4.1 Hz, CHC*H*CH *bridgehead*), 2.16-2.13 (1H, m, SiOCH_2C*H*). [Major isomer] $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 175.6 (*C*=O), 171.1 (*C*=O), 137.7 (Ar), 128.6 (Ar), 128.4 (Ar), 128.4 (Ar), 83.0 (*C*HO(C=O)), 73.4 (O*C*H_2Ph), 66.9 (*C*H_2OBn), 63.0 (*C*H_2/C), 54.3 ((C=O)O*C*H_3), 53.3 (*C*H_2/C), 51.9 (CH), 50.1 (CH), 36.3 (CH_2), 33.8 (CH_2), 28.8 (CH_2); ***m/z*** (ESI+) Found: $(M+Na)^+$, 371.1465; $C_{19}H_{24}NaO_6$ requires *M*, 371.1471; $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3447 br (O-H), 3031 m (C-H), 2954 m (C-H), 2925 m (C-H), 2856 m (C-H), 1771 s (C=O), 1738 s (C=O).

5.71 *tert*-Butyldimethyl(pent-4-ynyloxy)silane[67]

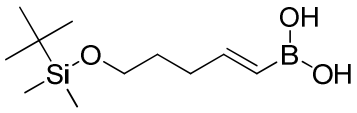


tert-Butyldimethylsilyl chloride (9.55 g, 63.4 mmol) was added dropwise over 10 min to a stirred solution of pent-4-yn-1-ol (5.0 g, 59.4 mmol) and imidazole (4.45 g, 65.4

mmol) in DCM (25 ml) at 0 °C. The solution was then allowed to warm to RT where it was stirred for a further 3 h. The solution was then diluted with DCM (50 ml) and then washed with sat. aq. NH_4Cl (100 ml). The organic layer was separated and the aqueous layer was re-extracted with DCM (2 × 70 ml). The combined organic extracts were washed with brine (80 ml), dried ($MgSO_4$), and solvent removed *in vacuo* to give a colourless oil, which was purified by flash column chromatography (10:1 PE:Et_2O) to give the *tert*-butyl(pent-4-ynyloxy)diphenylsilane (11.0 g, 55.8 mmol, 94%) as a colourless oil;

$\boldsymbol{R_f}$ = 0.85 (PE:EtOAc 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 3.65 (2H, t, *J* = 6.6 Hz, SiOCH_2), 2.23 (2H, td, *J* = 7.2 Hz, 2.3 Hz, CH_2C≡CH), 1.90 (1H, t, *J* = 2.3, CH_2C≡C*H*), 1.71 (2H, tt, *J* = 7.2 Hz, 6.8 Hz, SiOCH_2CH_2), 0.89 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$);

5.69 (*E*)-5-(*tert*-butyldimethylsilyloxy)pent-1-enylboronic acid[67]

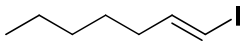


Catechol borane (5g, 4.4 mL, 25.18 mmol) was added dropwise to a solution of *tert*-butyldimethyl(pent-4-ynyloxy)silane (3.22g, 30.2 mmol) in THF (20 mL) at 0 °C. The mixture was then heated to reflux (80 °C) for 8 h, after which time the reaction was cooled and solvent removed *in vacuo*. The crude boronic ester was then purfied by kugelrohr distillation (180 °C, 0.2 mmHg), and then promptly poured onto water (30 mL), and the mixture stirred vigourously for 1 h. After this time, the (E)-5-(tert-

butyldimethylsilyloxy)pent-1-enylboronic acid was collected by filtration as a white powder (4.42g, 18.1 mmol, 72%) m.p. 66.9-72.3 °C [lit.[67] m.p. 68 °C],

$\boldsymbol{R_f}$ = 0.05 (5:1 EA:PE); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.98 (1H, dt, *J* = 17.7 Hz, 6.5 Hz, BCH=C*H*CH_2), 5.58 (1H, d, *J* = 17.7 Hz, BC*H*=CH), 3.61 (2H, dt *J* = 6.5 Hz, 6.0 Hz, C*H*$_2$OSi), 2.25 (2H, m, CHC*H*$_2$CH$_2$), 1.69 (2H, m, CH$_2$C*H*$_2$CH$_2$), 0.91 (9H, s, SiC(CH$_3$)$_3$), 0.06 (6H, s, Si(CH$_3$)$_2$;

5.70 (*E*)-1-Iodohept-1-ene[116]



Method 1: [117]

To 1-heptyne (1.0g, 10.4 mmol) in 20 ml of *n*-hexane was added DIBAL-H (10.4 mL, 1 M in hexane) at 0 °C. When the initial exothermic reaction had subsided, the reaction mixture was heated for 4 hr at 50 °C. The hexane was then removed under reduced pressure (0.5 mmHg), and the residue obtained diluted with THF (10 mL). To this vinylalane solution at -50 °C was added iodine (2.64 g, 10.0 mmol) as a solution in THF (5 mL). After allowing the reaction mixture to warm up to RT, the diisobutylalane was decomposed at 0 °C by dropwise addition of 20% H_2SO_4 (8 mL). When the isobutane evolution had diminished, the reaction mixture was poured into ice-20% H_2SO_4. The vinyl iodide was extracted into hexane (2 × 20 mL) and the combined extracts were washed first with solutions of sodium thiosulfate (20 mL), then with sodium bicarbonate (20 mL). The combined organic extracts were washed with brine (80 ml) and then dried and evaporated *in vacuo* to a light yellow oil, which

was purified by flash column chromatography (20:1 PE:Et_2O) to give the (*E*)-1-iodohept-1-ene (0.72 g, 31%) as a yellow oil;

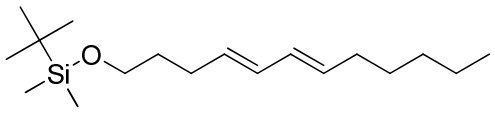
Method 2:[118]

To a solution of (*E*)-hept-1-enylboronic acid (0.5 g, 3.52 mmol) in Et_2O, NaOH (3 M, 3.52 mL) was added, and the solution cooled to 0 ºC. To this was added iodine (1.075 g, 4.23 mmol) as a solution in Et_2O (10 mL), dropwise, over 5 min. The reaction mixture turned a deep yellow/red upon addition of the iodine, but the colour quickly faded; however, after ~80% of addition completed a deep red colour persisted. The reaction was then allowed to stir at 0 ºC for 1.5 h.

A saturated solution of sodium thiosulphate (10 mL) was added and the organic phase was washed with water and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the crude iodide as a light yellow oil, which was purified by flash chromatography on silica, (20:1 PE:EtOAc) to give the (*E*)-1-iodohept-1-ene (630 mg, 2.8 mmol, 80%) as a light yellow liquid.

$\boldsymbol{R_f}$ = 0.61 (20:1 PE:EA); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.51 (1H, dt, *J* = 18.0 Hz, 6.3 Hz, ICH=C*H*CH_2), 6.17 (1H, d, *J* = 18.0 Hz, IC*H*=CH), 1.96 (2H, dt, *J* = 6.9 Hz, 6.3 Hz ICH=CHC*H*$_2$), 1.32 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.96 (3H, t, *J* = 7.1, CH_2CH_3).

5.72 tert-*butyl((4*E*,6*E*)-dodeca-4,6-dienyloxy)dimethylsilane*

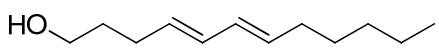


Triphenylphosphine (25 mg, 0.088 mmol) was added in one portion to a stirred solution of palladium(II) acetate (5 mg, 0.022 mmol) in degassed THF (10 ml) under

an atmosphere of argon, and the mixture was then stirred for 20 min. The resultant yellow solution was added dropwise over 10 min to a stirred mixture of (*E*)-1-iodohept-1-ene (100 mg, 0.44 mmol), (*E*)-5-(*tert*-butyldimethylsilyloxy)pent-1-enylboronic acid (151 mg, 0.62 mmol) and degassed aqueous lithium hydroxide solution (10 ml, 2 M) in degassed THF (10 ml) under an atmosphere of argon. The mixture was stirred at 40 °C for 16 h, then cooled and partitioned between Et_2O (100 ml) and water (20 ml). The separated aqueous layer was extracted with Et_2O (3 × 50 ml), and the combined organic extracts were then washed successively with sat. aq. NH_4Cl (100 ml), water (75 ml) and brine (50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to leave a pale brown oil. The oil was purified by column chromatography on silica gel using 10% EtOAc–light petroleum as eluant to give *tert*-butyl((4E,6E)-dodeca-4,6-dienyloxy)dimethylsilane (115 mg, 88%) as a colourless oil;

$\boldsymbol{R_f}$ = 0.79 (2:1 PE:EA); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.99 (2H, m, CH_2CH=C*H*C*H*=$CHCH_2$), 5.56 (1H, ddd, *J* = 16.4 Hz, 7.3 Hz, 6.9 Hz, CH_2C*H*=CHCH=C*H*CH_2), 5.55 (1H, ddd, *J* = 16.6 Hz, 7.3 Hz, 6.8 Hz, CH_2C*H*=CHCH=C*H*CH_2), 3.60 (2H, t, *J* = 6.3 Hz, SiOC*H*$_2$), 2.10 (2H, dt, *J* = 7.3 Hz, 7.1 Hz, CH=CHC*H*$_2$), 2.04 (2H, dt, *J* = 7.3 Hz, 7.0 Hz, C*H*$_2$CH=CH), 1.63-1.55 (2H, m, $SiOCH_2C$*H*$_2$), 1.40-1.23 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2CH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 0.87 (3H, t, *J* = 7.1 Hz, CH_2C*H*$_3$), 0.03 (6H, s, $Si(CH_3)_2$; $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 132.6 (*C*=C), 131.6 (*C*=C), 130.7 (C=*C*), 130.2 (C=*C*), 62.6 (*C*H_2OTBDPS), 32.6 (CH=CH-*C*H_2), 31.4 (*C*H_2-CH=CH), 29.1 (*C*H_2), 28.8 (*C*H_2), 28.4 (*C*H_2), 25.9 ($SiC(CH_3)_3$), 22.5 (*C*H_2), 18.3 ($SiC(CH_3)_3$), 14.0 (CH_2CH_3), -5.0 ($Si(CH_3)_2$), $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3071.0 (C-H), w 2956 m (C-H), 2928 m (C-H), 2857m (C-H); ***m/z*** (ESI+) Found: $(M+H)^+$, 319.2437; $C_{18}H_{36}NaOSi^+$ requires *M*, 319.2433.

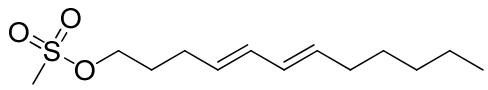
5.78 *(4*E*,6*E*)-Dodeca-4,6-dien-1-ol*



tert-butyl((4*E*,6*E*)-dodeca-4,6-dienyloxy)dimethylsilane (20 mg, 0.067 mmol) was dissolved in THF (10 mL), and acetic acid (12.5 μL, 0.2 mmol) was added dropwise at 0°C. Tetrabutylammonium fluoride (0.2 mL, 1.0 M, 0.2 mmol) was added and stirring continued for a further 15 min, before allowing the reaction mixture to warm to RT and stir 18h. The reaction was quenched by addition of water (10 mL), the organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and the solvent removed *in vacuo* Purification by flash column chromatography (2:1 PE:EtOAc) gave (4*E*,6*E*)-dodeca-4,6-dien-1-ol (12 mg, 0.065 mmol, 98%) as a clear, colourless oil,

$\boldsymbol{R_f}$ = 0.38 (2:1 PE:EA); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$); 6.01 (2H, m), 5.57 (2H, m), 3.64 (2H, t, *J* = 6.3 Hz, CH_2OH), 2.14 (2H, dt, *J* = 6.8 Hz, 6.6 Hz, CH=CHCH_2), 2.04 (2H, dt, *J* = 6.8, 6.6 Hz, CH=CHCH_2), 1.65 (2H, m, CH_2CH$_2$OH) 1.43-1.26 (6H, m, CH_2CH_2CH_2CH$_3$), 0.91 (3H, t, *J* = 7.1 Hz, CH$_2$CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 133.1 (*C*=*C*), 131.1 (*C*=*C*), 131.0 (*C*=*C*), 130.0 (*C*=*C*), 62.5 (HOCH_2), 32.5 (CH_2), 32.3 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 22.5 (CH_2CH$_3$), 14.0 (CH$_2$CH_3); ***m/z*** Found: $(M-H)^-$, 181.1591; $C_{12}H_{21}O$ requires *M*, 181.1592; $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3374 br (O-H), 2929 m (C-H), 2860 m (C-H);

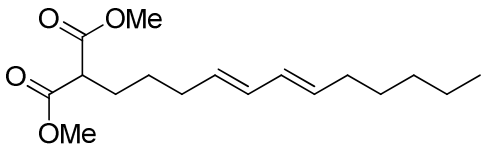
5.79 *(4*E*,6*E*)-Dodeca-4,6-dienyl methanesulfonate*



(4*E*,6*E*)-Dodeca-4,6-dien-1-ol (0.150 g, 0.808 mmol) was dissolved in DCM (10 mL), and triethylamine (0.162 mL, 1.212 mmol) and methanesulfonyl chloride (0.096 mL, 1.212 mmol) were added at 0 °C. The reaction mixture was warmed to RTand stirred for 1 h, after which it was quenched by addition of aqueous HCl (10 mL, 1 M). The organic phase was separated, and the aqueous phase extracted with DCM (3 × 40 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*, furnishing (4*E*,6*E*)-dodeca-4,6-dienyl methanesulfonate as a clear, colourless oil (182 mg, 0.7 mmol, 87%);

$\boldsymbol{R_f}$ = 0.71 (2:1 PE:EA); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$); 6.00 (2H, m), 5.55 (2H, m), 4.22 (2H, t, *J* = 6.6 Hz, CH_2OMs), 2.98 (3H, s, SO_2CH_3), 2.18 (2H, dt, *J* = 6.8 Hz, 6.6 Hz, CH=CHCH_2), 2.04 (2H, dt, *J* = 6.8 Hz, 6.6 Hz, CH=CHCH_2), 1.83 (2H, m, CH_2CH$_2$OMs) 1.40-1.24 (6H, m, CH_2CH_2CH_2CH$_3$), 0.87 (3H, t, *J* = 7.1 Hz, CH$_2$CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 133.8 (*C*=*C*), 132.0 (*C*=*C*), 129.7 (*C*=*C*), 129.2 (*C*=*C*), 69.4 (SO_2CH_3), 37.3 (*C*H$_2$), 32.5 (*C*H$_2$), 31.4 (*C*H$_2$), 29.0 (*C*H$_2$), 28.7 (*C*H$_2$), 28.3 (*C*H$_2$), 22.5 (*C*H$_2$CH$_3$), 14.0 (CH$_2$*C*H$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 2957 m (CH), 2929 m (CH), 2872 m (CH); ***m/z*** (ESI+) Found: $(M+Na)^+$, 283.1347; $C_{13}H_{24}NaO_3S$ requires *M*, 283.1338.

5.63 *Dimethyl 2-((4E,6E)-dodeca-4,6-dienyl)malonate*

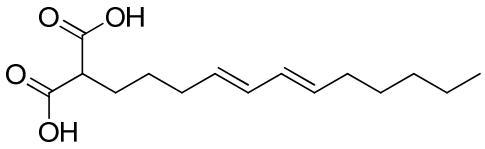


DMF (12 mL, anhydrous) was added to sodium hydride (60% suspension in mineral oil, 0.25 g, 6.27 mmol) at 0°C, and the suspension allowed to stir for 10 min. Dimethyl malonate (0.72 mL, 6.27 mmol) was then added dropwise, and the solution allowed to warm to RT and was stirred for a further 20 min. (4*E*,6*E*)-Dodeca-4,6-dienyl methanesulfonate (0.55 g, 2.10 mmol) was added dropwise as a solution in THF (6 mL), followed by potassium iodide (1.05 g, 6.27 mmol), and the mixture was heated at 80 °C for 18h. The reaction was quenched with sat. aq. NH_4Cl (10 mL); the organic phase was separated, and the aqueous phase extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*. The crude product mixture was then purified by flash column chromatography (5:1 PE:EtOAc) to give dimethyl 2-((4*E*,6*E*)-dodeca-4,6-dienyl)malonate as a clear, colourless oil, (0.485g, 78%).

$\boldsymbol{R_f}$ = 0.55 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.01-5.93 (2H, m), 5.56 (1H, ddd, *J* = 19.3 Hz, 12.6 Hz, 6.8 Hz, CH_2CH=CHCH=CH), 5.50 (1H, ddd, *J* = 19.3 Hz, 13.7 Hz, 7.2 Hz, CH_2CH=C*H*CH=CH), 3.72 (6H, s, (C=O)OCH_3), 3.34 (1H, t, *J* = 7.6 Hz, C*H*$(CO_2Me)_2$), 2.05 (2H, m), 1.98 (2H, m), 1.38 (4H, m, CH_2) 1.27 (4H, m, $CH_2CH_2CH_2CH_3$), 0.87 (3H, t, *J* = 7.1 Hz, CH_2CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 169.8 (*C*=O), 133.1 (*C*H), 131.1 (*C*H), 130.8 (*C*H), 130.0 (*C*H), 52.5 (O*C*H_3), 51.6 (*C*H$(CO_2Me)_2$), 32.5 (*C*H_2), 32.1 (*C*H_2), 31.1 (*C*H_2), 29.0 (*C*H_2), 28.4 (*C*H_2), 27.2

(*C*H_2), 22.5 (*C*H_2*C*H_3), 14.0 (CH_2*C*H_3); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 2954 m (CH), 2926 m (CH), 2859 m (CH), 1745 s (C=O), 1734 s (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 319.1883; $C_{13}H_{24}NaO_3S$ requires *M*, 319.1885.

5.96 *2-((4*E*,6*E*)-Dodeca-4,6-dienyl)malonic acid*

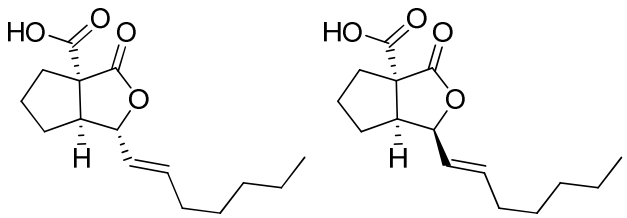


To a solution dimethyl 2-((4*E*,6*E*)-dodeca-4,6-dienyl)malonate (185 mg, 0.62 mmol) in dioxane (10 mL) was added KOH (5mL, 10% aqueous solution) at 0 °C with constant stirring. The reaction was allowd to warm to RT and stirred for 3 h. HCl (10% aqueous solution) was added until the reaction mixture was at pH 2. The reaction mixture was extracted with DCM (3 × 20 mL), and solvent removed *in vacuo* to give 2-((4*E*,6*E*)-dodeca-4,6-dienyl)malonic acid (161 mg, 97%) as a white crystalline solid (MP_{decomp} = 61 °C);

δ_H (400 MHz, $CDCl_3$); 5.99 (m, 2H), 5.54 (m, 2H), 3.43 (1H, t, *J* = 7.6 Hz, C*H*$(CO_2H)_2$), 2.10 (2H, dt, *J* = 7.2 Hz, 7.1 Hz, CH_2CH=CH), 2.04 (2H, dt, *J* = 7.3 Hz, 7.2 Hz, CH_2CH=CH), 1.95 (2H, dt, *J* = 7.3 Hz, 7.6 Hz, CH_2 $CH(CO_2H)_2$), 1.49 (2H, m, CH_2), 1.37 (2H, m, CH_2), 1.28 (4H, m, CH_2C$H_2$$CH_3$), 0.87 (3H, t, *J* = 6.7 Hz, CH_2CH_3); **δ_C** (125 MHz, $CDCl_3$); 174.6 (*C*O_2H), 133.2 (*C*H), 131.3 *C*H), 130.4 (*C*H), 129.9 (*C*H), 51.3 (*C*$(CO_2H)_2$), 32.5 (CH=CH*C*H_2), 32.0 (CH=CH*C*H_2), 31.4 (*C*H_2), 29.0 (*C*H_2), 28.2 (*C*H_2), 26.9 (*C*H_2), 22.5 (*C*H_2), 14.0 (CH_2*C*H_3); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$)

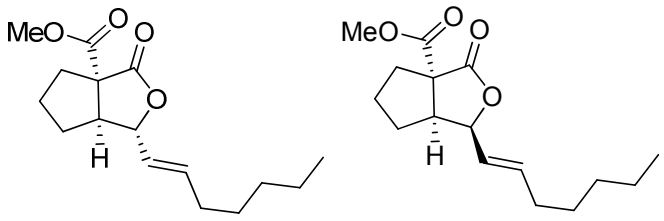
3051 br (CO_2H), 2921 m (CH), 2857 m (CH), 1703 s (CO_2H); ***m/z*** (ESI-) Found: $(M+Na)^+$, 291.1564; $C_{15}H_{24}NaO_4$ requires *M*, 291.1572.

5.97 *(±)(1S*,3aS*,6aR*,E)-1-(Hept-1-enyl)-3-oxo-hexahydro-1H-cyclopenta[c]furan-3a-carboxylic acid* and *(1S*,3a*R,6aS*)-1-((E)-hept-1-enyl)-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylic acid*



A solution of 2-((4*E*,6*E*)-dodeca-4,6-dienyl)malonic acid (40.0 mg, 0.15 mmol) in either EtOH or acetonitrile (2 mL) was prepared in a reaction carousel. Manganese(III) acetate (80.0 mg, 0.30 mmol) was added along with copper(II) triflate (54 mg, 0.15 mmol). The reaction tube was degassed, and heated to reflux for 18h, after which the reaction was quenched by addition of water (4 mL). The mixture was acidified to pH2 with HCl (10% aqueous) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*, leaving crude (±)(1*S**,3a*S**,6a*R**,*E*) -1- (hept-1-enyl) -3-oxo-hexahydro -1*H*- cyclopenta[c]furan-3a-carboxylic acid, which was used directly in the next reaction without further analysis;

5.80 *(1*S**,3a*S**,6a*R**,*E*)-Methyl 1-(hept-1-enyl)-3-oxo-hexahydro-1*H*-cyclopenta[c]-furan-3a-carboxylate*, *(1*S**,3a*R**,6a*S**)-methyl 1-((*E*)-hept-1-enyl)-3-oxohexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate*

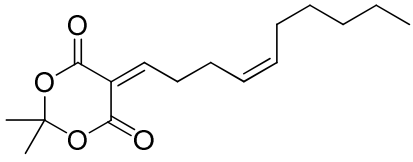


To a crude solution of (1*S**,3a*S**,6a*R**,*E*)-1-(hept-1-enyl)-3-oxo-hexahydro-1*H*-cyclopenta[c]furan-3a-carboxylic acid (40 mg, 0.150 mmol) in toluene/methanol (10 ml/2 mL) was added TMS-diazomethane (124 μL, of a 2.0 M solution in hexanes, 0.247 mmol). The reaction mixture was allowed to stir at RT for 14 h, and then quenched by addition of acetic acid (1 mL). Solvent was removed *in vacuo*, and the crude mixture purified by column chromatography (20:1 PE:EtOAc → 4:1) to leave (1*S**,3a*S**,6a*R**,*E*)- methyl 1-(hept-1-enyl)-3-oxo-hexahydro-1*H*-cyclopenta[c]-furan-3a-carboxylate (30.8 mg, 0.112 mmol, 78%) as a 2:1 mixture of diasteroisomers;

$\boldsymbol{R_f}$ = 0.34 (3:1 PE:EtOAc); [Major isomer] $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 5.75 (1H, dt, *J* = 15.4 Hz, 6.8 Hz, CH=C*H*CH_2CH_2), 5.51 (1H, ddt, *J* = 15.4 Hz, 8.0 Hz, 1.6Hz, CHC*H*=$CHCH_2$), 4.44 (1H, dd, *J* = 7.8 Hz, 3.8 Hz, (C=O)OC*H*CH=CH), 3.75 (3H, s, CH_3O(C=O)), 2.87 (1H, dt, *J* = 8.2 Hz, 3.1 Hz, (C=O)OCHC*H*CH_2), 2.34 (2H, m, CH_2C(C=O)), 2.24 (2H, m, CH_2CH_2C(C=O)), 2.05 (2H, m, CH=CHCH_2CH_2), 1.68 (2H, m, CH_2CHCHCH=CH), 1.39-1.22 (6H, m, $CH_2CH_2CH_2$), 0.86 (3H, t, *J* = 6.7 Hz, $CH_2CH_2CH_3$); [Minor isomer – selected resonances] $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 5.84 (1H, dt, *J* = 15.4 Hz, 6.3 Hz, CH=C*H*CH_2CH_2), 5.44 (1H, ddt, *J* = 15.4 Hz, 7.3 Hz,

1.4 Hz, CHC*H*=CHCH$_2$), 5.10 (1H, dd, *J* = 6.9 Hz, 6.7 Hz, (C=O)OC*H*CH=CH), 3.75 (3H, s, C*H*$_3$O(C=O)), 2.98 (1H, dt, *J* = 7.9 Hz, 6.6 Hz, (C=O)OCHC*H*CH$_2$), 1.39-1.22 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$), 0.86 (3H, t, *J* = 6.7 Hz, CH$_2$CH$_2$C*H*$_3$); [Both isomers] δ_C (125 MHz, $CHCl_3$) 175.9 (*C*(=O)OCH), 175.8 (*C*(=O)OCH), 171.0 (*C*(=O)OCH$_3$), 170.5(*C*(=O)OCH$_3$), 136.9 (CH=*C*H-CH$_2$), 135.8 (CH=*C*H-CH$_2$), 127.6 (*C*H=CH-CH$_2$), 123.6 (*C*H=CH-CH$_2$), 86.4 (C(=O)O*C*H), 81.5 (C(=O)O*C*H), 63.4 (*C*(CO$_2$)$_2$), 62.2 (*C*(CO$_2$)$_2$), 53.1 (2 × OMe), 51.7 (*C*HCH-O-C(=O)), 50.9 (*C*HCH-O-C(=O)), 35.3 (*C*H$_2$*C*(CO$_2$)$_2$), 34.3 (*C*H$_2$*C*(CO$_2$)$_2$), 32.2 (CH=CH*C*H$_2$), 32.0 (CH=CH*C*H$_2$), 31.3 (*C*H$_2$CH$_2$CH$_3$), 31.2 (*C*H$_2$CH$_2$CH$_3$), 28.4 (*C*H$_2$CHCH-O-C(=O)), 28.2 (*C*H$_2$CHCH-O-C(=O)), 26.2 (*C*H$_2$CH$_2$*C*(CO$_2$)$_2$), 25.6 (*C*H$_2$CH$_2$*C*(CO$_2$)$_2$), 22.4 (2 × CH$_2$*C*H$_3$), 14.0 (2 × CH$_2$*C*H$_3$); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 2955 m (CH), 2828 m (CH), 2858 m (CH), 1771 m (C=O *lactone*), 1740 m (C=O *ester*); ***m/z*** (ESI+) Found: (M+Na)$^+$, 303. 1568; $C_{13}H_{22}O_5Na$ requires *M*, 303.1572.

5.88 5-(*Z*)-4-Decenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[119]

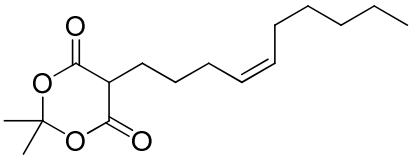


Ethylene diammonium diacetate (176 mg, 0.98 mmol) was added to a solution of Meldrum's acid (842 mg, 5.8 mmol) and (*Z*)-4-decenal (570 mg, 3.69 mmol) in absolute EtOH (8 mL) at RT and the resulting solution was stirred for 1 h. Water

(10 mL), 5% aqueous HCl solution (3 mL) and DCM (20 mL) were added and the aqueous phase extracted with DCM (3×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (9:1 hexanes:EtOAc) gave 5-(*Z*)-4-decenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione as an oil (0.602g, 2.15 mmol, 58%);

$\boldsymbol{R_f}$ = 0.41 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.89 (1H, t, *J* = 7.5 Hz, C=C*H*), 5.50-5.30 (2H, m, C*H*=C*H*), 3.00 (2H, dt, *J* = 7.5 Hz, 7.3 Hz, C=CHCH_2), 2.34 (2H, dt, *J* = 7.3 Hz, 7.2 Hz, C=CHCH_2), 2.03 (2H, dt, *J* = 7.9 Hz, 6.1 Hz, C=CHCH_2), 1.70 (6H, s, (CH_3)$_2$C) 1.38-1.21 (6H, m, CH_2CH_2CH_2CH_3), 0.88 (3H, t, *J* = 6.6 Hz, CH_2CH_3).

5.85 5-(*Z*)-4-Decenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[119]

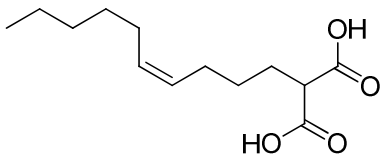


5-(*Z*)-4-Decenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (50 mg, 0.18 mmol) was dissolved in dry absolute EtOH, and borane-dimethylamine complex was added. The reaction was stirred overnight, and was quenched by the addition of sat. aq. NH_4Cl (3 mL). The mixture was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried ($MgSO_4$) and concentrated. Purfication by flash chromatography

(2:1 PE:EtOAc) gave 5-(*Z*)-4-Decenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione as an oil: (41 mg, 0.145 mmol, 80%);

$\boldsymbol{R_f}$ = 0.28 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.46-5.29 (2H, m, C*H*=C*H*), 3.50 (1H, t, *J* = 5.1, C*H*$(CO_2)_2$), 2.09 (2H, q, *J* = 7.1, CH_2), 2.01 (2H, q, *J* = 6.9, CH_2), 1.95 (2H, dt, *J* = 8.0,7.2, CH_2), 1.76 (3H, s, CCH_3), 1.74 (3H, s, CCH_3), 1.36-1.17 (6H, m, CH_2, CH_2, CH_2), 0.87 (3H, t, *J* = 7.0, CH_3CH_2).

5.84 *(Z)-2-(Non-4-enyl)malonic acid*

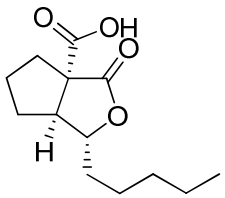


To a solution of (*Z*)-dimethyl 2-(dec-4-enyl)-malonate (250 mg, 0.9 mmol) in dioxane (10 mL) was added KOH (5 mL, 10% aqueous solution) at 0 °C with constant stirring. The reaction was then warmed to RT and left to stir for 3 h. HCl (10% aqueous solution) was added until the reaction mixture was pH 2. DCM (20 mL) was added and the aqueous phase was extracted with futher DCM (3 × 20 mL). The organic phases were combined and concentrated *in vacuo* to give (*Z*)-2-(non-4-enyl)malonic acid (204 mg, 91%);

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.40-5.30 (2H, m, C*H*=C*H*), 3.42 (1H, t, *J* = 7.4 Hz, C*H*$(CO_2H)_2$), 2.07 (2H, dt, *J* = 7.1 Hz, 7.0 Hz, CH_2CH=CH), 2.00 (2H, dt, *J* = 6.9 Hz, 6.8 Hz, CH_2CH=CH), 1.95 (2H, m, CH_2CH), 1.45 (2H, qn, *J*=7.6 Hz, $CH_2CH_2CH_2$) 1.31 (6H, m, CH_2, CH_2, CH_2,), 0.87 (3H, t, *J* = 6.8 Hz, CH_2CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 174.5 (*C*=O), 131.1 (*C*=*C*), 128.3 (*C*=*C*), 51.3 (*C*H$(CO_2H)_2$), 31.5

(*C*H_2), 29.3 (*C*H_2), 28.3 (*C*H_2), 27.2 (*C*H_2), 26.6 (*C*H_2), 22.5 (*C*H_2), 14.0 (CH_2CH_3); *Note there is one accidental equivalence in the carbon spectrum.* ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 3050 br (O-H), 2924 m (C-H), 2857 m (C-H), 1708 s (C=O). ***m/z*** (ESI+) Found: $(M+Na)^+$, 265.1422; $C_{13}H_{22}NaO_4$ requires *M*, 265.1416; **EA** Found C 64.38, H 9.21, $C_{13}H_{22}NaO_4$ requires C 64.44, H 9.15.

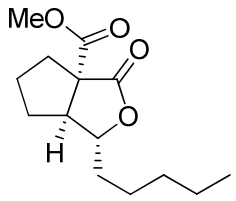
5.89 *(1*S**,3a*S**,6a*R**)-1-butyl-3-oxo-hexahydro-1*H*-cyclopenta[c]furan-3a-carboxylic acid*



A solution of (*Z*)-2-(non-4-enyl)malonic acid (40.0 mg, 0.16 mmol) in acetonitrile (2 mL) was prepared in a reaction carousel. Manganese(III) acetate (89.0 mg, 0.33 mmol) was added along with copper(II) triflate (60 mg, 0.16 mmol). The reaction tube was degassed, and heated to reflux for 18h, after which the reaction was quenched by addition of water (4 mL). The mixture was acidified to pH=2 with HCl (10% aqueous) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed, to leave crude (1*S**,3a*S**,6a*R**)-1-butyl-3-oxo-hexahydro-1*H*-cyclopenta[c]furan-3a-carboxylic acid as a impure oil, which was passed directly to the next reaction for further purificiation (2:1 mixture of diastereoisomers, 30.2 mg, 74% yield),

δ_H (500 MHz, $CDCl_3$) 9.27 (2H, s, br, CO_2H), 4.70 (1H, dt, *J* = 8.5 Hz, 5.6 Hz, (C=O)OC*H*CH_2), 3.00 (1H, dt, *J* = 7.9 Hz, 6.6 Hz, (C=O)OCHC*H*CH_2), 2.35 (2H, m, CH_2C(C=O)), 2.28 (2H, m, CH_2CH_2C(C=O)), 1.95 (1H, m, CHC*H*HCH_2CH_2), 1.84 (1H, m, CHCH*H*CH_2CH_2), 1.69 (2H, m, CH_2CHCHCH_2CH_2), 1.35 (2H, m, CH_2CH-$_2CH_3$), 1.30 (2H, m, $CH_2CH_2CH_3$), 0.87 (3H, t, *J* = 6.7 Hz, $CH_2CH_2CH_3$); **δ_C** (500 MHz, $CDCl_3$) 176.2 (*C*O_2H), 175.5 (*C*O_2CH), 86.6 (CO_2*C*H), 63.7 (*C*CO_2H), 50.6 (*C*HCHO(C=O)) 36.2 (*C*H_2CCO_2H), 36.0 (CH_2), 31.5 (CH_2), 30.7 (CH_2), 27.2 (CH_2), 26.4 (CH_2), 25.7 (CH_2), 24.9 (CH_2), 22.5 (CH_2), 13.9 (CH_3); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 3125 br (O-H), 2955 m (C-H), 2871 m (C-H), 1767 s (C=O *acid*), 1711.6 (C=O *lactone*);

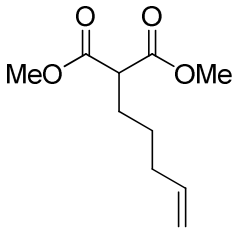
5.47 *(1*S**,3a*S**,6a*R**)-methyl 3-oxo-1-pentyl-hexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate*



A solution of the crude (1*S**,3a*S**,6a*R**)-1-butyl-3-oxo-hexahydro-1*H*-cyclopenta[c]furan-3a-carboxylic acid (40.0 mg, 0.16 mmol) was dissolved in methanol : toluene (2 mL : 8 mL), and cooled in ice. TMS-diazomethane (0.124 mL, 2 M in hexanes) was then added dropwise whilst stirring, and the RM warmed to RT. After 18hrs, TLC analysis indicated completion of reaction; the RM was cooled in ice, and acetic acid (30 μL, 0.5 mmol) added dropwise. The reaction was warmed to RT, and allowed to stir for 15 min after. The solvent was then removed *in vacuo*, leaving impure product as a colourless oil; this was then purified by column chromatography

(20:1 PE:EtOAc → 4:1), returning (±)-(1*S*,3a*S*,6a*R*)-methyl 3-oxo-1-pentyl-hexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate (31.2 mg, 98%, 2:1 d.r. by nmr), whose spectra were consistent with the material produced independently in this study.

5.105 Dimethyl 2-(pent-4-enyl)malonate[120]

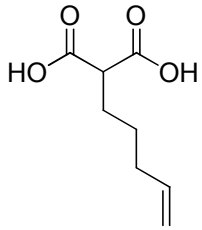


Dimethyl malonate (11.8 mL, 90.0 mmol) was added to a suspension of sodium hydride (3.6g, 90.0 mmol, 60% dispersion in mineral oil) in DMF (50 mL) at 0 °C. 5-bromo-1-pentene was then added as a solution in THF (25 mL), followed by potassium iodide (5g, 30.0 mmol). The reaction was then warmed to 80 °C, and allowed to stir for 16 h. After this time, the reaction was quenched by addition of sat. aq. NH_4Cl (20 mL), and the biphasic mixture extracted with Et_2O (3 × 150 mL). The organic fractions were combined, dried ($MgSO_4$), and solvent removed *in vacuo* to leave crude product, which was purified by distillation (kugelrohr, 90 °C, 2 mmHg). This removed the excess dimethyl malonate to leave dimethyl 2-(pent-4-enyl)malonate as a light yellow oil (5.45g, 27.25 mmol, 91%).

$\boldsymbol{R_f}$ = 0.41 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.77 (1H, dddd, *J* = 17.1 Hz, 10.4 Hz, 7.7 Hz, 3.6 Hz, CH=C*H*H), 5.01 (1H, dd, *J* = 17.1 Hz, 1.7 Hz, CH=C*H*H), 4.96 (1H, dd, *J* = 10.4 Hz, 1.7 Hz, CH=C*H*H), 3.73 (6H, s, CO_2*Me*), 3.35 (1H, t, *J* = 7.7 Hz, C*H*($CO_2Me)_2$), 2.08 (2H, td, *J* = 7.2 Hz, 6.9 Hz, $CH_2CH{=}CH_2$), 1.91 (2H, dt, *J* =

8.2 Hz, 7.6 Hz $CH_2CH(CO_2Me_2)$, 1.41 (2H, m, $CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 169.8 (*C*=O), 137.8 (H*C*=CH_2), 115.1 (HC=*C*H_2), 52.3 (CO_2*Me*) 51.5 (*C*H$(CO_2Me)_2$), 33.3 (*C*H_2CH=CH_2), 28.2 (*C*H_2CH$(CO_2Me)_2$), 26.5 ($CH_2CH_2CH_2$).

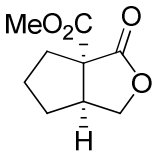
5.103 2-(Pent-4-enyl)malonic acid[121]



To a solution of dimethyl 2-(pent-4-enyl)malonate (1g, 5 mmol) in dioxane (20 mL) was added aqueous potassium hydroxide solution (10%, 10 mL), and the biphasic mixture allowed to stir for 3 h. The solution was then acidified to pH=2 with aqueous HCl (2M, ~8 mL) and extracted with DCM (3 × 25 mL), the organic extracts combined and solvent removed *in vacuo* to leave 2-(pent-4-enyl)malonic acid as white needle-like crystals, (834 mg, 4.85 mmol, 97%);

MP = 83.3-85.1 °C; δ_H (400 MHz, $CDCl_3$) 8.38 (2H, br, CO_2*H*), 5.78 (1H, m, C*H*=CH_2), 5.02 (2H, m, CH=CH_2), 3.45 (1H, t, *J* = 7.4 Hz, C*H*$(CO_2H)_2$), 2.11 (2H, q, *J* = 7.1 Hz, CH_2CH=CH_2), 1.96 (2H, dt, *J* = 8.4 Hz, 7.5 Hz, $CH_2CH(CO_2H)_2$), 1.51 (2H, m, $CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 174.9 (*C*=O), 137.6 (H*C*=CH_2), 115.3 (HC=*C*H_2), 51.4 (*C*H$(CO_2H)_2$), 33.2 (*C*H_2CH=CH_2), 28.1 (*C*H_2CH$(CO_2H)_2$), 26.4 ($CH_2CH_2CH_2$).

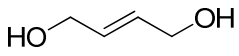
5.107 (3a*R**,6a*S**)-Methyl 3-oxohexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate[122]



A solution of (*Z*)-2-(non-4-enyl)malonic acid (40.0 mg, 0.22 mmol) in either EtOH or acetonitrile (2 mL) was prepared in a reaction carousel. Manganese(II) acetate (5.4 mg, 0.022 mmol, 0.1 eq.) was added along with copper(II) triflate (8.2 mg, 0.022 mmol, 0.1 eq.) and cobalt(II) acetate (5.48 mg, 0.022 mmol, 0.1 eq.). The reaction tube was degassed, and heated to reflux for 18 h, after which the reaction was quenched by addition of water (4 mL). The mixture was acidified to pH=2 with HCl (10% aqueous) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*, to leave an impure mixture of carboxylic acids. A solution of the crude acids (approx. 40. mg, 0.22 mmol) was dissolved in EtOH : toluene (2 mL : 8 mL), and cooled in ice. TMS-diazomethane (0.170 mL, 2 M in hexanes) was then added dropwise whilst stirring, and the reaction mixture warmed to RT. After 18hrs, TLC analysis indicated completion of reaction; the reaction mixture was cooled in ice, and acetic acid (45 μL, 0.75 mmol) added dropwise. The reaction was warmed to RT, and allowed to stir for 15 min after the cessation of effervescence. The solvent was then removed *in vacuo*, leaving impure product as a colourless oil; this was then purified by column chromatography (20:1 PE:EtOAc → 4:1) to leave (3a*R**,6a*S**)-methyl 3-oxohexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate as an impure oil (32.8 mg, 0.18 mmol, 80% yield);

R_f = 0.38 (2:1 PE:EtOAc); δ_H (400 MHz, $CDCl_3$) 4.56 (1H, dd, *J* = 9.3 Hz, 7.7 Hz, C*H*HO(C=O)), 4.08 (1H, dd, *J* = 9.3 Hz, 2.5 Hz CH*H*O(C=O)), 3.77 (3H, s, CO_2*Me*), 3.14-3.06 (1H, m, C*H bridgehead*), 2.43-2.33 (1H, m, C*H*HC(C=O), 2.30-2.22 (1H, m, CH*H*C(C=O)), 2.12-2.00 (1H, m, CH*H*CH_2C), 1.83 (1H, m, CH*H*CH_2C) 1.72-1.57 (2H, m, $CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 176.4 (C=O), 170.0 (*C*=O), 73.2 (*C*H_2O(C=O)), 61.6 (*C*$(CO_2Me)_2$), 53.1 (*C*O_2Me), 45.6 (CH_2C(C=O)), 34.6 (*C*H_2CH_2C), 34.1 (*C*H *bridgehead*), 25.9 ($CH_2CH_2CH_2$).

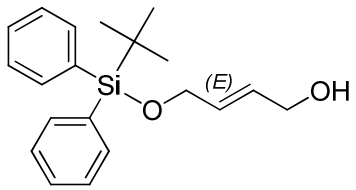
6.2 (*E*)-but-2-ene-1,4-diol[123]



But-2-yne-1,4-diol (8.7g, 100 mmol) was dissolved in THF (30 mL) and was added dropaies to a lithium aluminium hydride solution in THF (100 mL, 1 M, 100 mmol) at 0 ºC. The mixture was allowed to warm to RT, and was then heated at reflux overnight. The reaction mixture was allowed to cool to RT and then further cooled to 0 ºC, and water (3.8 mL), NaOH solution (15% w.t., 3.8 mL), and further water (11 mL) were added. The mixture was stirred at RT for 3 h, after which time aluminium salts were removed by filtration and the filtrate dried ($MgSO_4$). The solvent was removed *in vacuo*, and purification by automated flash column chromatography (120 g pre-packed column; neat EtOAc) gave (*E*)-but-2-ene-1,4-diol as a colourless oil, (4.9 g, 56 mmol, 56%);

$\boldsymbol{R_f}$ = 0.08 (EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.88 (2H, m, C*H*=C*H*), 4.17 (4H, m, CH_2CH=$CHCH_2$), 1.89 (2H, m, O*H*); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 130.5 (*C*H=*C*H), 62.9 (CH_2CH=$CHCH_2$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3350 (O-H), 2951 m (C-H).

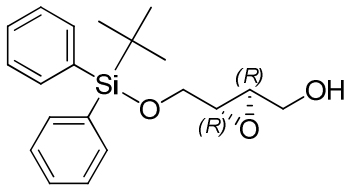
6.3 (*E*)-4-(*tert*-Butyldiphenylsilyloxy)but-2-en-1-ol[124]



Mono-protection of the diol was performed using the McDougal procedure.[56] Sodium hydride (1.01 g, 60% dispersion in mineral oil, 2.26 mmol) was suspended in THF (80 mL), and allowed to stir for 2 h. (*E*)-But-2-ene-1,4-diol (2.34 g, 2.26 mmol) was then added dropwise over 15 min, and the reaction mixture was allowed to stir for a further 20 min. TBDPSCl (6.91 g, 26.6 mmol) was added dropwise over 15 min at 0 °C, and stitting was continued at RT for 18 h. Aqueous sodium bicarbonate was added (10% w.t., 20 mL), the organic phase separated, and the aqueous phase extracted with DCM (3 × 100 mL). The solvent was removed *in vacuo* and purification *via* automated flash chromatography (120 g pre-packed column; 0-50% hexanes:EtOAc) gave the title compound. (6.1g, 18.67 mmol, 70%);

$\boldsymbol{R_f}$ = 0.37 (PE:EtOAc, 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.71-7.68 (4H, m, Ar*H*), 7.46-7.37 (6H, m, Ar*H*), 5.94 (1H, dtt, *J* = 15.4 Hz, 5.5 Hz, 1.7 Hz C*H*=CH), 5.80 (1H, dtt, *J* = 15.4 Hz, 4.4 Hz, 1.4 Hz CH=C*H*), 4.25-4.22 (2H, m, OCH_2), 4.16 (2H, t, *J* = 4.4 Hz, OCH_2), 1.31 (1H, t, *J* = 5.8 Hz, O*H*), 1.08 (9H, s, $SiC(CH_3)_3$); ***m/z*** (ESI+) Found: $(M+Na)^+$, 349.1595; $C_{20}H_{26}O_2SiNa$ requires *M*, 349.1600.

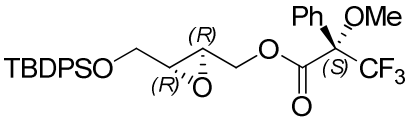
6.4 ((2*R*,3*R*)-3-((tert-Butyldiphenylsilyloxy)methyl)oxiran-2-yl)methanol[125]



To a stirred suspension of powdered 4 Å molecular sieves (3 g) in DCM (100 mL) at -20 °C was added $Ti(OiPr)_4$ (4.64 mL, 15.70 mmol, 0.54 eq) and D-(-)-diethyl tartrate (3.22 mL, 18.72 mmol, 0.36 eq). *t*-Butylhydroperoxide (11.36 mL, 5-6 M in decane, 58.16 mmol, 2 eq.), predried over 4A molecular sieves, was then added dropwise. Upon complete addition of the hydroperoxide, the reaction mixture was stirred for 35 min and a solution of monosilylated *trans*-2-butene-l,4-diol (9.5 g, 29.1 mmol) in DCM (10 mL) was added dropwise. The reaction mixture was then warmed to 0 °C and allowed to stir for 16 h. The resulting mixture was poured into a freshly prepared, stirred solution of ferrous sulfate (17.0 g, 61.1 mmol) and tartaric acid (5.2 g, 34.6 mmol) in of water (50 mL) at 0 ° C. The ice bath was removed and stirring was continued for 10 min. After this time the layers were separated and the aqueous back extracted with Et_2O (2 × 100 mL). The combined organic extracts were then treated with a precooled solution of 30% NaOH (w/v) in brine (7 mL) and stirred vigorously for 1 h at 0 °C. The layers were separated, the aqueous layer was extracted with Et_2O (2 × 100 mL), and the combined extracts dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The impure epoxide was purified by automated column chromatography (120 g pre-packed column; 0-50% hexanes:Et_2O) to give ((2*R*,3*R*)-3-((*tert*-butyldiphenylsilyloxy)methyl)oxiran-2-yl)methanol (8.37g, 24.4 mmol, 84%) as a colourless oil;

R_f = 0.25 (PE:EtOAc, 2:1); δ_H (400 MHz, $CDCl_3$) 7.71-7.67 (4H, m, Ar*H*), 7.47-7.38 (m, 6 H, Ar*H*), 3.94 (1H, m, CH*H*O), 3.89 (1H, dd, *J* = 12.2 Hz, 3.2 Hz C*H*HO), 3.79 (1H, dd, *J* = 12.2 Hz, 4.3 Hz, CH*H*O), 3.63 (1H, dd, *J* = 12.0 Hz, 7.9 Hz, 4.4 Hz), 3.19 (1H, dt, *J* = 2.6 Hz, 2.1 Hz, C*H*(O)CH), 3.11 (1H, dt, *J* = 2.6 Hz, 1.9 Hz, C*H*(O)CH), 1.71 (1H, dd, *J* = 7.5 Hz, 5.5 Hz, O*H*), 1.04 (9H, s, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 135.6 (Ar), 133.2 (Ar), 129.8 (Ar), 127.8 (Ar), 63.2 (CH_2O), 61.2 (CH_2O), 55.7 (*C*H(O)CH), 55.6 (*C*H(O)CH), 26.7 (C(CH_3)$_3$), 19.2 ($C(CH_3)_3$); ν_{max}/cm^{-1} ($CDCl_3$) 3424 br (O-H), 3071 m (C-H), 3049 m (C-H), 2957 m (C-H), 2931 m (C-H), 2893 m (C-H), 2893 m (C-H), 871 w (*epoxide*); ***m/z*** (ESI+) Found: $(M+Na)^+$, 365.1539; $C_{20}H_{26}O_3SiNa$ requires *M*, 365.1543; $[\alpha]_D$ = +15.9 (*c* 1.00, DCM).

6.6 *(*S*)-((2*R*,3*R*)-3-((*tert*-butyldiphenylsilyloxy)methyl)oxiran-2-yl)methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate*

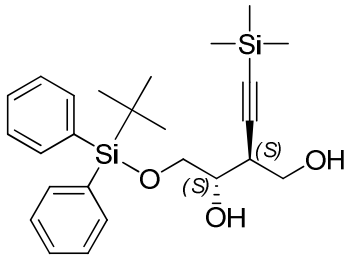


To solution of ((2*R*,3*R*)-3-((*tert*-butyldiphenylsilyloxy)methyl)oxiran-2-yl)methanol (10 mg, 0.029 mmols) in DCM (10 mL) was added DMAP (5 mg, 0.041 mmols) and triethylamine (0.036 mL, 0.247 mmols). To this solution was added (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (19 µL, 0.1 mmols), and the solution allowed to stir for 18 hours. The reaction mixture was then quenched by addition of water (10 mL), and the biphasic mixture extracted with DCM (3 x 10 mL). The organic fractions were combined, dried ($MgSO_4$) and solvent removed *in vacuo* to leave a residue, which was passed through a silica plug (EtOAc). The solvent was

removed *in vacuo* to leave crude product, (16 mg, 0.029 mmols, 99%), as a clear, colourless gum.

$\boldsymbol{R_f}$ = 0.52 (PE:EtOAc, 2:1); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.68-7.64 (4H, m, Ar*H*), 7.55-7.52 (2H, m, Ar*H*), 7.46-7.36 (9H, m, Ar*H*), 4.63 (1H, dd, *J* = 12.3 Hz, 3.1 Hz, C*H*HO(C=O)), 4.21 (1H, dd, *J* = 12.3 Hz, 5.5 Hz, C*H*HO(C=O)), 3.83 (1H, dd, *J* = 12.1 Hz, 3.1 Hz, C*H*HOTBDPS), 3.77 (1H, dd, *J* = 12.1 Hz, 4.1 Hz, C*H*HOTBDPS), 3.56 (3H, s, *OMe*), 3.21-3.19 (1H, m, C*H*-O-CH), 3.06 (1H, td, *J* = 3.6 Hz, 2.1 Hz, C*H*-O-CH), 1.04 (9H, s, Si(C(CH_3)$_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 166.3 (C=O), 135.6 (*Ar*), 135.5 (*Ar*), 133.1 (*Ar*), 132.9 (*Ar*), 133.1 (*Ar*), 129.8 (*Ar*), 129.7 (*Ar*), 128.5 (*Ar*), 127.8 (*Ar*), 127.3 (*Ar*), 65.2 (*C*H_2O(C=O)), 62.6 (*C*H_2OTBDPS), 56.0 (*C*H-O-CH), 55.5 (O*Me*), 52.1 (CH-O-*C*H), 29.7 (*C*(C=O)(CF_3)(Ph)(OMe)), 26.7 (SiC(*C*H_3)$_3$), 19.2 (Si*C*(CH_3)$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 2960 w (C-H), 2931 m (C-H), 2857 m (C-H), 1751 s (C=O), 1170 s (C-F), 1082 m (C-F), 1113 s (C-F); ***m/z*** (ESI+) Found: $[M+Na]^+$, 581.1939; $C_{30}H_{33}F_3NaO_5Si$ requires *M*, 581.1942; $\boldsymbol{[\alpha]_D}$ = -11.0 (*c* 0.8, $CDCl_3$).

6.15 *(2*S*,3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-2-((trimethylsilyl)ethynyl)butane-1,3-diol*

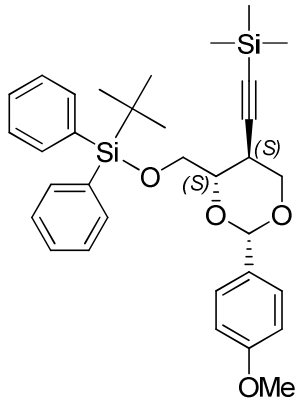


To a solution of ((2*R*,3*R*)-3-((tert-Butyldiphenylsilyloxy)methyl)oxiran-2-yl)methanol (7.4 g, 21.60 mmol) in DCM (40 mL) was added *n*-BuLi (14.8 mL, 1.6 M in hexanes, 23.76 mmol) at 0 ºC. In a separate flask, *n*-BuLi (53.57 mL, 1.6 M in hexanes, 86.40

mmol) was added to a solution of TMS-acetylene (12.14 mL, 86.40 mmol) in DCM (100 mL) at 0 ºC.. After stirring for 30 min, dimethyl aluminium chloride solution was added (86.40 mL, 86.40 mmol, 1.0 M) to the lithiated acetylene, and stirring continued for a further 30 min. The solution was then cooled to –78 ºC, and the lithium alkoxide solution previously prepared was added. The reaction mixture was stirred for a further 30 min at -78 ºC and then warmed to 0 ºC and stirring was continued for 1.5 h. The reaction was then quenched by addition of water (10 mL), followed by aqueous HCl (10 mL, 2 M). The organic layer was separated and the aqueous phase extracted with EtOAc (2 × 80 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by automated flash chromatorgraphy, (120 g pre-packed column; 0-50% hexanes:EtOAc) gave (2S,3S)-4-(*tert*-butyldiphenylsilyloxy)-2-((trimethylsilyl) ethynyl)butane-1,3-diol, (8.1g, 18.4 mmol, 85%) as a clear, colourless oil;

$\boldsymbol{R_f}$ = 0.20 (10:1 DCM:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.70-7.65 (4H, m, Ar*H*), 7.45-7.35 (6H, m, Ar*H*), 3.90 (1H, dd, *J* = 6.2 Hz, 2 Hz, O*H*), 3.86-3.75 (4H, m, CH_2OH, CH_2OSi), 2.81 (1H, d, *J* = 6.4 Hz, O*H*), 2.76 (1H, dt, *J* = 8.1 Hz, 6.1 Hz, C*H*C≡C), 2.61 (1H, dd, *J* = 6.1 Hz, 4.9 Hz, CH_2O*H*), 1.04 (9H, s, ^tBu), 0.08 (9H, s, Si(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 135.5 (Ar), 135.5 (Ar), 132.8 (Ar), 132.9 (Ar), 129.9 (Ar), 129.9 (Ar), 127.8 (Ar), 102.9 (C≡*C*Si), 89.5 (*C*≡CSi), 73.4 (*C*HOH), 66.3 (*C*H_2OSi), 64.1 (*C*H_2OH), 38.5 (*C*HC≡CSi), 26.9 (C(*C*H_3)$_3$), 19.3 (*C*(CH_3)$_3$), 0.0 (Si(*C*H_3)$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3406 br (O-H), 3071 m (C-H), 3050 m (C-H), 2958 m (C-H), 2931 m (C-H), 2893 m (C-H), 2857 m (C-H), 2170 w (C≡C); ***m/z*** (ESI+) Found: $(M+Na)^+$, 463.2090; $C_{20}H_{26}O_2SiNa$ requires *M*, 463.2095; $\boldsymbol{[\alpha]_D}$ = +24.2 (*c* 0.19, DCM).

6.17 tert-*Butyl((((4*S*,5*S*)-2-(4-methoxyphenyl)-5-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)methoxy)diphenylsilane*

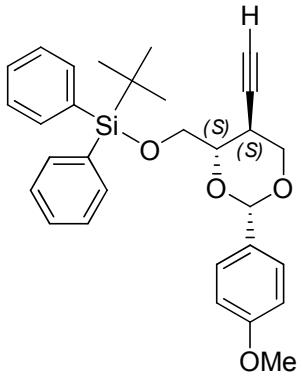


(2S,3S) - 4 - (*tert*-Butyldiphenylsilyloxy) - 2 - ((trimethylsilyl) ethynyl) butane-1,3-diol (7.94 g, 18.0 mmol) was dissolved in DCM (50 mL) and *p*-toluenesulphonic acid (50 mg, 0.26 mmol) and anisaldehyde dimethylacetal (4.60 mL, 27.0 mmol) were added. The resulting solution was stirred at RT overnight and then concentrated. The residue was purified by automated flash chromatography (5% EtOAc/hexanes) to deliver *tert*-butyl(((4*S*,5*S*) - 2 - (4-methoxyphenyl) - 5 - ((trimethylsilyl)ethynyl) - 1,3 - dioxan-4-yl)methoxy)diphenylsilane as a white, crystalline solid (9.76g, 14.47 mmol, 97%);

$\boldsymbol{R_f}$ = 0.41 (DCM); δ_H (400 MHz, d_6-DMSO) 7.68-7.65 (4H, m, Ar*H*), 7.47-7.34 (8H, m, Ar*H*), 6.94 (2H, d, *J* = 7 Hz, Ar*H*), 5.59 (1H, s, C*H*OPMP), 4.26 (1H, dd, *J* = 10.1 Hz, 4.7 Hz), 4.03 (2H, m, $SiOCH_2CH$), 3.98 (1H, dd, *J* = 10.9 Hz, 4.7 Hz SiOC*H*H), 3.94-3.90 (2H, m, SiOCH*H* CH*H*OPMP) 3.80 (1H, t, *J* = 10.9 Hz, CH*H*OPMP), 3.76 (3H, s, OCH_3), 3.02 (1H, td, *J* = 9.7 Hz, 4.5 Hz, C*H*C≡CH), 2.49 (1H, d, *J* = 2.1 Hz, CHC≡C*H*), 0.98 (9H, s, $SiC(CH_3)_3$), 0.18 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz, d_6-DMSO) 159.8 (Ar), 135.7 (Ar), 133.7 (Ar), 132.8 (Ar) 130.8 (Ar), 130.0 (Ar), 127.6 (Ar), 127.6 (Ar), 114.3 (Ar), 101.8 (C≡*C*$SiMe_3$), 101.3 ((Ar*C*$H(O)_2$), 88.9 (*C*≡C$SiMe_3$),

70.0 (*C*H_2OSi), 70.0 (*C*HOCH), 64.1 (*C*H_2OCH), 55.3 (*C*HC≡CH), 26.8 (C(*C*H_3)$_3$), 19.4 (*C*(CH$_3$)$_3$), 0.01 (*Si*(CH$_3$)$_3$); ν_{max}/**cm^{-1}** ($CDCl_3$) 2999 m (CH), 2958 m (CH), 2931 m (CH), 2895 m (CH), 2173 w (C≡CSi); ***m/z*** (ESI+) Found: $(M+Na)^+$, 581.2512; $C_{33}H_{42}O_4Si_2Na$ requires *M*, 581.2514; **[α]$_D$** = 56.2 (*c* 1.00, DCM); **MP** = 76.5 – 78.0 °C; **EA** Found C 71.00; H 7.65. $C_{33}H_{42}O_4Si_2$ requires C, 70.92; H, 7.58;

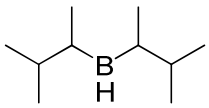
6.18 tert-*Butyl(((4*S*,5*S*)-5-ethynyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)methoxy) diphenylsilane*



To *tert*-butyl(((4*S*,5*S*)-2-(4-methoxyphenyl)-5-((trimethylsilyl)ethynyl)-1,3-dioxan-4-yl)methoxy)diphenylsilane (5.7 mg, 10.2 mmol) in DCM (20 mL) was added KOH in MeOH (10%, 20 mL). The reaction was then allowed to stir at RT until TLC analysis indicated completion of reaction (3 h). Water (40 mL) was added, and the biphasic mixture separated. The aqueous layer was washed with DCM (2 × 50 mL), and the combined organic phases were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by automated flash chromatography (120 g pre-packed column; 0-20% hexanes:EtOAc) gave *tert*-butyl(((4*S*,5*S*)-5-ethynyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl) methoxy) diphenylsilane (4.71 g, 9.7 mmol, 95%) as a clear, colourless oil;

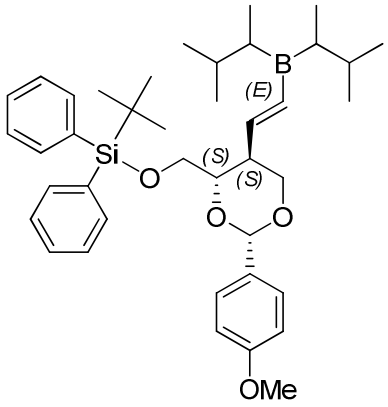
$\boldsymbol{R_f}$ = 0.33 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.70-7.65 (4H, m, Ar*H*), 7.50-7.32 (8H, m, Ar*H*), 6.90 (2H, d, *J* = 7.2 Hz, Ar*H*), 5.47 (1H, s, C*H*PMP), 4.38 (1H, dd, *J* = 11.1 Hz, 4.3 Hz, $SiOCH_2CH$), 3.98 (2H, m, CH_2OPMP), 3.88-3.80 (5H, m, $SiOCH_2$, OCH_3), 3.05 (1H, td, *J* = 8.1 Hz, 5.8 Hz, C*H*C≡CH), 2.09 (1H, d, *J* = 2.2 Hz, CHC≡C*H*) 1.08 (9H, s, $SiC(CH_3)_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 160.0 (Ar), 135.7 (Ar), 133.6 (Ar), 132.7 (Ar) 130.6 (Ar), 130.0 (Ar), 127.9 (Ar), 127.5 (Ar), 114.3 (Ar), 101.3 (Ar), 81.2 (C≡*C*H), 79.8 (*C*≡CH), 72.3 (CH_2OSi), 70.0 (*C*HOCH), 64.1 (CH_2OCH), 55.6 (*C*HC≡CH), 26.8 ($SiC(CH_3)_3$), 19.4 ($SiC(CH_3)_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3289 m (C≡C-H), 2931 m (C-H), 2856 m (C-H), 844 w (C-O-C); ***m/z*** (ESI+) Found: $(M+Na)^+$, 509.2118; $C_{33}H_{42}O_4Si_2Na$ requires *M*, 509.2124; $\boldsymbol{[\alpha]_D}$ = 39.6 (*c* 1.00, DCM); **EA** Found C 74.13; H 7.12. $C_{30}H_{34}O_4Si$ requires C, 74.04; H, 7.04;

6.20 Disiamylborane[126]



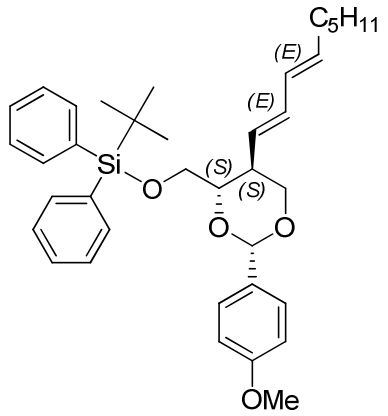
Disiamylborane was produced from a kit purchased from the Sigma-Aldich company. To a solution of borane-THF complex (20 mL, 1 mol L^{-1} in THF, 10 mmol) at 0 °C was added 2-methyl-2-butene solution (20 mL, 2 mol L^{-1} in THF, 20 mmol). The solution was allowed to stir at 0 °C for a further 2 h, and the disiamylborane (40 mL, 0.5 mol L^{-1}) used directly in the next reaction.

6.21 *(((4*S*,5*S*)-5-((*E*)-2-(Bis(3-methylbutan-2-yl)boryl)vinyl)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)methoxy)(*tert*-butyl)diphenylsilane*



To a solution of *tert*-butyl(((4*S*,5*S*)-5-ethynyl-2-(4-methoxyphenyl)-1,3-dioxan-4-yl) methoxy) diphenylsilane (2.0 g, 4.1 mmol) in THF (20 mL) was added disiamyl borane solution (22 mL, 0.5 mol L^{-1} in THF, 11 mmol) at 0 °C. After 30 min, the reaction was warmed to RT, and allowed to stir overnight. The solvent was then removed *in vacuo*, providing crude (((4*S*,5*S*)-5-((*E*)-2-(bis(3-methylbutan-2-yl)boryl)vinyl)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)methoxy)(tert-butyl)diphenylsilane, which was used directly without further analysis or purification in the Suzuki coupling.

6.24 tert-*Butyl(((4*S*,5*S*)-2-(4-methoxyphenyl)-5-((1*E*,3*E*)-nona-1,3-dienyl)-1,3-dioxan-4-yl)methoxy)diphenylsilane*

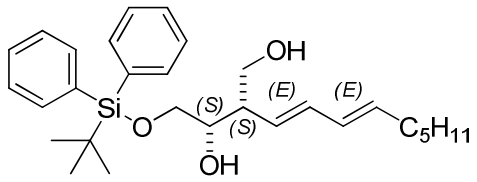


Triphenylphosphine (75 mg, 0.268 mmol) was added in one portion to a stirred solution of palladium(II) acetate (15 mg, 0.067 mmol) in degassed THF (10 ml) under an atmosphere of argon, and the mixture was then stirred for 20 min. To the yellow solution was added dropwise the vinyl iodide (320 μL, 1.428 mmol) and the vinyl borane (1.31g, 2.056 mmol) in degassed THF (10 mL). Degassed aqueous lithium hydroxide solution (10 mL, 2 M) was added and the mixture was stirred at 40 °C for 16 h, then cooled and partitioned between Et_2O (100 ml) and water (20 ml). The separated aqueous layer was extracted with Et_2O (3 × 50 ml), and the combined organic extracts were then washed successively with sat. aq. NH_4Cl (100 ml), water (75 ml) and brine (50 ml), dried and evaporated *in vacuo* to leave a pale brown oil. The oil was purified by column chromatography (10% EtOAc:PE) to give *tert*-butyl(((4*S*,5*S*)-2-(4-methoxyphenyl)-5-((1*E*,3*E*)-nona-1,3-dienyl)-1,3-dioxan-4-yl)methoxy)diphenylsilane (0.76 g, 1.30 mmol 92%) as a colourless oil;

$\boldsymbol{R_f}$ = 0.45 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.76-7.69 (4H, m, Ar*H*), 7.50-7.32 (8H, m, Ar*H*), 6.93 (2H, m, Ar*H*), 6.20 (1H, dd, *J* = 15.2 Hz, 10.3 Hz, CH=*C*H), 5.97 (1H, dd,

J = 15.3 Hz, 10.3 Hz, C*H*=CH), 5.67 (1H, dt, *J* = 15.2 Hz, 7.0 Hz, CH=C*H*), 5.49 (1H, s, ArC*H*), 5.18 (1H, dt, *J* = 15.3 Hz, 9.1 Hz, C*H*=CH), 4.14 (1H, dd, *J* = 11.2 Hz, 5.0 Hz, C*H*OCHAr), 3.88-3.80 (5H, m, CH_2OSi, OCH_3), 3.65 (2H, m, CH_2O), 2.82 (1H, ddd, *J* = 10.3 Hz, 10.1 Hz, 4.5 Hz, C*H*CH=CH), 2.11 (2H, dt, *J* = 7.2, 7.1, CH=CHCH_2), 1.47-1.30 (8H, m, *alkyl chain*), 1.08 (9H, s, ^tBu), 0.93 (3H, t, *J* = 6.7 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 159.9 (*Ar*-OMe), 135.8 (*Ar*), 135.7 (*Ar*), 135.0 (CH=CH-CH=*C*HCH$_2$), 134.5 (CH=*C*H-CH=CHCH$_2$), 133.7 (*Ar*), 133.6 (*Ar*), 131.2 (CH=*C*H), 129.7 (CH=CH-*C*H=CHCH$_2$), 129.5 (*Ar*), 127.6 (*C*H=CH-CH=CHCH$_2$), 127.5 (*Ar*), 125.9 (CH=*C*H), 113.5 (*Ar*), 101.1 (Ar*C*H), 81.8 (*C*HOCHAr), 71.0 (*C*H$_2$O), 65.0 (*C*H$_2$OH), 55.3 (O*C*H$_3$), 39.6 (*C*HCH=*C*H), 32.6 (*C*H$_2$CH=CH), 31.4 (*C*H$_2$), 29.0 (*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 22.6 (*C*H$_2$), 19.4 (*C*(CH$_3$)$_3$), 14.1 (*C*H$_3$); ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 3071 m (C-H), 3048 m (CH), 3015 m (CH), 2957 m (CH), 2929 m (CH), 2856 m (CH), 1616 w (C=H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 607.3214; $C_{25}H_{34}NaO_3Si$ requires *M*, 607.3214; $[\alpha]_D$ = 17.0 (*c* 3.2, DCM).

6.27 *(2*S*,3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-2-((1*E*,3*E*)-nona-1,3-dienyl)butane-1,3-diol*

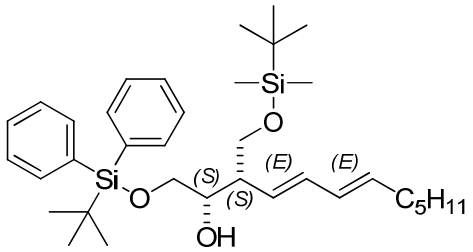


To a solution of *tert*-butyl(((4*S*,5*S*)-2-(4-methoxyphenyl)-5-((1*E*,3*E*)-nona-1,3-dienyl)-1,3-dioxan-4-yl)methoxy)diphenylsilane (500 mg, 0.856 mmol) in THF (10 mL) was added acetic acid (10 mL) and water (10 mL). The solution was then

warmed to 40 °C, and allowed to stir overnight. The reaction mixture was then diluted DCM, and the phases separated. The aqueous phase was washed with further DCM (3 × 20 mL), and the organic fractions combined, dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash column chromatography (3:1 hexane : EtOAc), gave (2*S*,3*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-((1*E*,3*E*)-nona-1,3-dienyl)butane-1,3-diol as a clear, colourless oil (290 mg, 0.62 mmol, 73%);

$\boldsymbol{R_f}$ = 0.10 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.67-7.63 (4H, m, Ar*H*), 7.45-7.35 (6H, m, Ar*H*), 6.06 (1H, dd, *J* = 15.2 Hz, 10.3 Hz, CH=C*H*), 5.90 (1H, dd, *J* = 15.0 Hz, 10.4 Hz, C*H*=CH), 5.61 (1H, dt, *J* = 15.0 Hz, 6.9 Hz, CH=C*H*), 5.18 (1H, dd, *J* = 15.3 Hz, 9.2 Hz, C*H*=CH), 4.87-3.54 (5H, m, C*H*OH, CH_2OH, CH_2OSi), 2.89 (1H, br, O*H*), 2.78 (1H, br, O*H*), 2.43 (1H, dt, *J* = 8.7 Hz, 5.8 Hz, CH=CH-C*H*), 2.06 (2H, dt, *J* = 7.2 Hz, 7.0 Hz, CH=CH-CH_2), 1.45-1.23 (6H, m, CH_2CH_2CH_2), 1.07 (9H, s, SiC(CH_3)$_3$), 0.93 (3H, t, *J* = 6.7 Hz, CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 135.5 (*Ar*), 134.9 (*C*H), 134.1 (*C*H), 132.9 (*Ar*), 129.9 (*C*H), 127.8 (*C*H), 129.6 (*Ar*), 127.8 (*Ar*), 127.2 (*Ar*), 74.8 (*C*HO), 66.3 (*C*H_2OSi), 65.4 (*C*H_2OH), 47.3 (*C*H), 39.6 (*C*HCH=*C*H), 32.6 (*C*H_2CH=*C*H), 31.4 (*C*H_2), 28.9 (*C*H_2), 26.9 (C(*C*H_3)$_3$), 22.5 (*C*H_2), 22.6 (*C*H_2), 19.2 (*C*(CH$_3$)$_3$), 14.1 (*C*H_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3384 br (O-H), 3071 m (C-H), 3049 m (C-H), 3017 m (C-H), 2957 m (C-H), 2857 m (C-H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 489.2795; $C_{29}H_{42}NaO_3Si$ requires *M*, 489.2801; $\boldsymbol{[\alpha]_D}$ = 17.0 (*c* 3.2, DCM).

6.28 *(6*S*,7*S*)-2,2,10,10,11,11-hexamethyl-7-((1*E*,3*E*)-nona-1,3-dienyl)-3,3-diphenyl-4,9-dioxa-3,10-disiladodecan-6-ol*

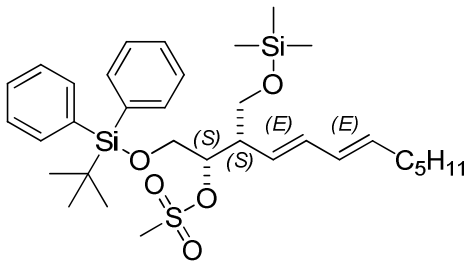


To a solution of (2*S*,3*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-((1*E*,3*E*)-nona-1,3-dienyl)butane-1,3-diol (200 mg, 0.43 mmol) in dry DMF (10 mL) was added imidazole (29 mg, 0.43 mmol) and DMAP (5 mg, 0.053 mmol). The reaction mixture was then cooled to 0 °C, and TBSCl (65 mg, 0.43 mmol) was. The solution was allowed to stir for 30 min and then warmed to RT, and stirred overnight. The reaction was then quenched by addition of water (10 mL), and extracted with Et_2O (5 × 10 mL). The organic fractions were combined, dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash column chromatography (5:1 PE:EtOAc) gave (6*S*,7*S*)-2,2,10,10,11,11-hexamethyl-7-((1*E*,3*E*)-nona-1,3-dienyl)-3,3-diphenyl-4,9-dioxa-3,10-disiladodecan-6-ol as a clear, colourless oil, (250 mg, 0.43 mmol, 99%);

$\boldsymbol{R_f}$ = 0.69 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.71-7.64 (4H, m, Ar*H*), 7.43-7.36 (6H, m, Ar*H*), 6.08 (2H, dd, *J* = 15.2 Hz, 10.4 Hz, CH=C*H*CH=CHCH$_2$), 5.95 (2H, dd, *J* = 15.0 Hz, 10.4 Hz, CH=CHC*H*=CHCH$_2$), 5.59 (1H, dt, *J* = 15.0 Hz, 7.2 Hz, CH=CH-CH=C*H*CH$_2$), 5.38 (1H, dd, *J* = 15.2 Hz, 9.0 Hz, CHC*H*=CH-CH=CH), 3.83 (1H, dd, *J* = 10.0, 4.8, C*H*HOTBS), 3.78 (1H, m, C*H*OH), 3.74 (1H, dd, *J* = 10.0, 4.2, CH*H*OTBS), 3.71 (1H, dd, *J* = 10.4, 4.2, CH*H*OTBDPS), 3.67 (1H, dd, *J* = 10.4, 5.4, CH*H*OTBDPS), 3.29 (1H, d, *J* = 4.8 O*H*), 2.48 (1H, m, CH=CHC*H*), 2.07 (2H, dt, *J* = 7.3, 7.0, CH=CHC*H*$_2$), 1.44-1.24 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$), 1.07 (9H, s, SiC(C*H*$_3$)$_3$), 0.83

(12H, m, *alkyl chain*, *TBS group*), 0.04 (6H, s, Si(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 135.6 (*Ar*), 134.8 (CH=*C*H), 134.0 (CH=*C*H), 133.4 (*Ar*), 133.3 (*Ar*), 133.0 (*Ar*), 130.1 (*C*H=CH), 129.7 (*Ar*), 128.8 (*Ar*), 127.7 (*C*H=CH), 73.6 (*C*HOH), 66.2 (*C*H_2OTBS), 65.0 (*C*H_2OTBDPS), 47.1 (*C*HCH=CH), 32.6 (CH=CH*C*H_2), 31.4 (*C*H_2), 29.03 (*C*H_2), 26.9 (SiC(*C*H_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 22.6 (*C*H_2), 19.3 (Si*C*(CH$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 14.1 (CH$_2$*C*H$_3$), -5.5 (Si*C*H$_3$); ν_{max}/**cm^{-1}** ($CDCl_3$) 3385 br (OH), 2929 m (CH), 2857 m (CH); ***m/z*** (ESI+) Found: $(M+Na)^+$, 649.3646; $C_{29}H_{42}NaO_3Si$ requires *M*, 649.3666; $[\alpha]_D$ = 11.9 (*c* 0.21, DCM).

6.30 *(5*S*,6*S*)-2,2,10,10-Tetramethyl-5-((1*E*,3*E*)-nona-1,3-dienyl)-9,9-diphenyl-3,8-dioxa-2,9-disilaundecan-6-yl methanesulfonate*

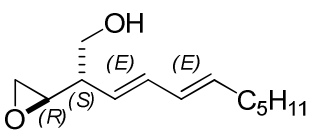


(6*S*,7*S*)-2,2,10,10,11,11-hexamethyl-7-((1*E*,3*E*)-nona-1,3-dienyl)-3,3-diphenyl-4,9-dioxa-3,10-disiladodecan-6-ol (650mg, 1.08 mmol) was dissolved in DCM (20 mL), triethylamine (0.608 mL, 4.34 mmol) and methanesulfonyl chloride (0.333 mL, 4.34 mmol) were added at 0 °C and the reaction mixture was then allowed to warm to RT and was stirred overnight. HCl (10 mL, 1 M solution) was added, the organic phase was separated, and the aqueous phase extracted with DCM (3 × 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and solvent

removed *in vacuo* to give (5*S*,6*S*)-2,2,10,10-tetramethyl-5-((1*E*,3*E*)-nona-1,3-dienyl)-9,9-diphenyl-3,8-dioxa-2,9-disila undecan-6-yl methanesulfonate as a clear, colourless oil (508 mg, 0.77 mmol, 71%);

$\boldsymbol{R_f}$ = 0.41 (1:2 PE:DCM); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.74-7.63 (4H, m, Ar*H*), 7.50-7.34 (6H, m, Ar*H*), 6.18 (1H, dd, *J* = 15.3 Hz, 10.3 Hz, CH=C*H*), 5.97 (1H, dd, *J* = 15.3 Hz, 10.3 Hz, C*H*=CH), 5.61 (1H, dt, *J* = 15.3 Hz, 6.9 Hz, CH=C*H*), 5.36 (1H, dd, *J* = 15.3, 9.4, C*H*=CH), 4.85 (1H, ddd, *J* = 7.6, 5.1, 5.3, C*H*OMs), 3.91 (1H, dd, *J* = 12.1, 2.6, C*H*HOTBDPS), 3.84 (1H, dd, *J* = 12.1, 5.1, CH*H*OTBDPS), 3.78 (1H, dd, *J* = 10.2, 4.5, C*H*HOTBS), 3.78 (1H, dd, *J* = 10.2, 4.7, CH*H*OTBS), 2.99 (3H, s, O*Ms*), 2.77 (1H, m, C*H*CH=CH), 2.08 (2H, td, *J* = 7.5, 7.2, CH=CHCH_2), 1.45-1.23 (8H, m, *alkyl chain*), 1.09 (9H, s, SiC(CH_3)$_3$), 0.87 (12H, m, *alkyl chain*, *TBS group*), 0.02 (6H, s, Si(CH_3)$_2$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 135.6 (*Ar*), 135.5 (*Ar*), 135.0 (CH=*C*H), 134.5 (CH=*C*H), 133.0, 132.6 (*Ar*), 129.9 (*C*H=CH), 129.7 (*Ar*), 129.7 (*Ar*), 127.8 (*Ar*), 127.7 (*Ar*), 126.4 (*C*H=CH), 83.7 (*C*HOMs), 64.2 (*C*H_2OTBDPS), 63.0 (*C*H_2OTBS), 46.3 (*C*HCH=CH), 38.4 (*OMs*), 32.6 (CH=CH*C*H_2), 31.4 (*C*H_2), 28.9 (*C*H_2), 26.8 (SiC(*C*H_3)$_3$), 25.9 (SiC(*C*H_3)$_3$), 22.5 (*C*H_2), 19.2 (Si*C*(CH$_3$)$_3$), 18.9 (Si*C*(CH$_3$)$_3$), 14.1 (CH$_2$*C*H$_3$), -5.4 (Si*C*H$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 2929.61 cm^{-1} (CH), 2857.72 cm^{-1} (CH); $\boldsymbol{[\alpha]_D}$ = +11.3 (*c* 0.21, DCM).

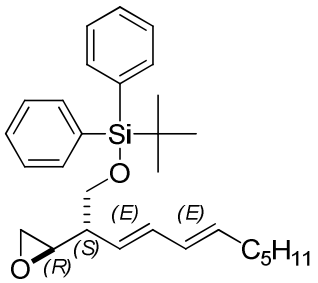
6.31 *(*S,*3*E*,5*E*)-2-((*R*)-Oxiran-2-yl)undeca-3,5-dien-1-ol*



(5*S*,6*S*)-2,2,10,10-tetramethyl-5-((1*E*,3*E*)-nona-1,3-dienyl)-9,9-diphenyl-3,8-dioxa-2,9-disila undecan-6-yl methanesulfonate (500 mg, 0.76 mmol) was dissolved in THF (20 mL), and tetrabutylammonium fluoride (3.8 mL, 3.8 mmol, 1.0 M, in THF) was added dropwise at 0 °C. The reaction mixture was allowed to warm to RT and stirred for a further 16h. The reaction was quenched by addition of water (10 mL), the organic phase was separated, and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed in vacuo leaving an impure residue. The crude epoxide was purified by flash column chromatography (3:1 PE:EtOAc) to give (*S*,3*E*,5*E*)-2-((*R*)-oxiran-2-yl)undeca-3,5-dien-1-ol as a clear, colourless oil (95mg, 0.452 mmol, 60%);

$\boldsymbol{R_f}$ = 0.18 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (200 MHz, $CDCl_3$) 6.20 (1H, dd, *J* = 15.1 Hz, 10.2 Hz, CH=C*H*), 6.00 (1H, dd, *J* = 14.8 Hz, 10.2 Hz, C*H*=CH), 5.68 (1H, dt, *J* = 14.8 Hz, 6.9 Hz, CH=C*H*), 5.36 (1H, dd, *J* = 15.1 Hz, 8.4 Hz, C*H*=CH), 3.64 (2H, m, CH_2OH), 3.09 (1H, m, CH=CH-C*H*), 2.80 (1H, dd, *J* = 4.7 Hz, 4.0 Hz, C*H*H(O)CH), 2.69 (1H, dd, *J* = 4.7 Hz, 1.8 Hz, CH*H*(O)CH), 2.53 (1H, dt, *J* = 7.2 Hz, 6.2Hz, CH_2(O)C*H*), 2.06 (2H, dt, *J* = 6.9, 6.8, CH=CH-CH_2), 1.45-1.24 (8H, m, *alkyl chain*), 0.89 (3H, t, *J* = 6.6 Hz, *alkyl chain*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 135.9 (*C*H_2=*C*H_2), 135.1 (*C*H_2=*C*H_2), 130.0 (*C*H_2=*C*H_2), 126.3 (*C*H_2=*C*H_2), 63.9 (*C*H_2OH), 53.5 (*C*H), 46.5 (*C*H), 45.5 (*C*H_2), 33.0 (*C*H_2), 31.9 (*C*H_2), 29.3 (*C*H_2), 23.0 (*C*H_2), 14.5 (CH_2*C*H_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3110 br (O-H), 2929 m (C-H), 2857 m (C-H), 917 w (*epoxide*); ***m/z*** (ESI+) Found: $(M+Na)^+$, 233.1513; $C_{13}H_{22}NaO_2$ requires *M*, 233.1517; $\boldsymbol{[\alpha]_D}$ = +22.9 (*c* 0.135, DCM).

6.33 tert-*Butyl((*S*,3*E*,5*E*)-2-((*R*)-oxiran-2-yl)undeca-3,5-dienyloxy)diphenylsilane*

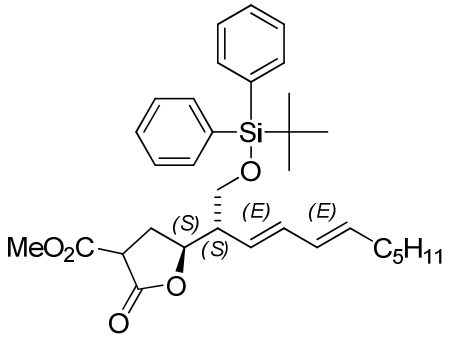


To a solution of (*S*,3*E*,5*E*)-2-((*R*)-oxiran-2-yl)undeca-3,5-dien-1-ol (95 mg, 0.452 mmol) in DCM (10 mL) was added imidazole (93 mg, 1.36 mmol, 3.0 eq.) and TBDPSCl (0.363 mL, 1.36 mmol). The reaction was allowed to stir at RT for 12 h and was quenched with sat. aq. NH_4Cl (10 mL). The phases were separated, and the aqueous layer washed with DCM (3 × 10 mL); the organic fractions were combined, dried ($MgSO_4$), and solvent removed *in vacuo*. The remaining residue was then purified by flash column chromatography (10:1 PE:EtOAc) to give *tert*-butyl((*S*,3*E*,5*E*)-2-((*R*)-oxiran-2-yl)undeca-3,5-dienyloxy)- diphenylsilane as a clear, colourless oil (201mg, 0.452 mmol, 99%),

$\boldsymbol{R_f}$ = 0.21 (10:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.74-7.63 (4H, m, Ar*H*), 7.50-7.34 (6H, m, Ar*H*), 6.12 (1H, dd, *J* = 14.7 Hz, 9.9 Hz, C*H*=CH), 5.98 (1H, dd, *J* = 14.7 Hz, 10.5 Hz, CH=C*H*), 5.62 (1H, dt, *J* = 14.6 Hz, 6.8 Hz, CH=C*H*CH_2), 5.31 (1H, dd, *J* = 14.6 Hz, 7.9 Hz, CHC*H*=CH), 3.73 (2H, m, CH_2OSi), 3.11 (1H, C*H*(O)CH_2), 2.79 (1H, dd, *J* = 5.0 Hz, 4.0 Hz, C*H*H(O)CH), 2.62 (1H, dd, *J* = 5.0 Hz, 2.8 Hz, C*H*H(O)CH), 2.27 (1H, tt, *J* = 7.2 Hz, 6.6 Hz, C*H*CH_2OSi), 2.05 (2H, dt, *J* = 6.7, 6.5, CH=CHCH_2), 1.45-1.24 (6H, m, CH_2CH_2CH_2), 1.07 (9H, s, SiC(CH_3)$_3$), 0.89 (3H, t, J = 6.6 Hz, CH_2CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 135.6 (*Ar*), 134.6 (*C*H_2=*C*H_2), 133.5 (*Ar*),

133.4 (*Ar*), 129.9 (*C*H_2=*C*H), 129.7 (*C*H_2=*C*H), 127.7 (*Ar*), 126.9 (*C*H=*C*H_2), 65.0 (*C*H_2OTBDPS), 53.2, (*C*H-O-CH_2), 47.4, (*C*HCH=CH), 46.3, (CH-O-*C*H_2), 32.6 (CH=CH*C*H_2), 31.4 (*C*$H_2CH_2CH_3$), 29.0 (CH=CHCH_2*C*H_2), 26.8 (C(*C*H_3)$_3$), 22.5 (*C*H_2CH_3), 19.22 (*C*$(CH_3)_3$), 14.1 (CH_2*C*H_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 2928 m (C-H), 2857 m (C-H), 919 (*epoxide*); ***m/z*** (ESI+) Found: $(M+Na)^+$, 471.2690; $C_{29}H_{40}NaO_2Si$ requires *M*, 471.2695; $\boldsymbol{[\alpha]_D}$ = +19.4 (*c* 0.19, DCM).

6.35 *(5*S*)-Methyl 5-((*S*,3*E*,5*E*)-1-(*tert*-butyldiphenylsilyloxy)undeca-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylate*

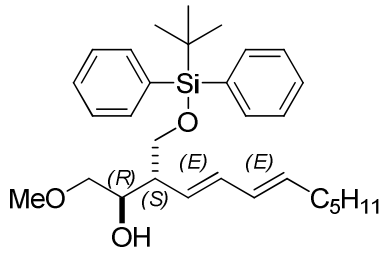


Sodium hydride (50 mg, 60% dispersion in mineral oil, 1.24 mmol) was washed with pentane (3 × 10 mL), and solvent removed *in vacuo*. To the dry, white powder was added DMF (1 mL), and the suspension allowed to stir at RT for 15 min. To this was added dimethyl malonate (141 μL, 1.24 mmol), dropwise, and the solution allowed to stir for a further 15 min. *tert*-Butyl((*S*,3*E*,5*E*)-2-((*R*)-oxiran-2-yl)undeca-3,5-dienyloxy)-diphenylsilane (111 mg, 0.248 mmol, 1 eq.) was added as a solution in THF (1 mL), and stirring continued at RT for 15 min. The reaction mixure was then heated at 80 °C for 14 hrs. After cooling to ambient temperature, the reaction was quenched with sat. aq. NH_4Cl (10 mL). The phases were separated, and the aqueous layer washed with Et_2O (3 × 10 mL); the organic fractions were combined, dried

($MgSO_4$), and solvent removed *in vacuo*. The remaining residue was then purified by flash column chromatography (5:1 PE:EtOAc) to give (5*S*)-methyl 5-((*S*,3*E*,5*E*)-1-(*tert*-butyldiphenyl-silyloxy)undeca-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylate as a clear, colourless oil (84 mg, 0.154 mmol, 62%, 1:1 mixture of diastereomers), along with recovered starting material (38 mg, 0.084 mmol, 34%).

$\boldsymbol{R_f}$ = 0.30 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.77-7.64 (4H, m, Ar*H*), 7.45-7.34 (6H, m, Ar*H*), 6.01 (2H, m, C*H*=CH-CH=C*H*), 5.62 (2H, m, CH=C*H*-C*H*=CH), 3.81 (3H, s, CO_2Me), 3.78-3.51 (3H, m, C*H*O(C=O), CH_2OSi), 2.79-2.68 (1H, m, C*H*CH=CH), 2.60-2.38 (2H, m ($(C=O)_2CHCH_2$), 2.10 (2H, dt, *J* = 6.8 Hz, CH=CH-CH_2), 1.45-1.24 (6H, m, *alkyl chain*), 1.07 (9H, s, Si(^tBu)), 0.89 (3H, t, *J* = 6.6 Hz, CH_2CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 172.5 (*C*(=O)OH), 172.3 (*C*(=O)OH), 170.9 (CO_2CH), 170.7 (CO_2CH), 136.2 (*Ar*), 136.0 (*Ar*), 136.0 (*Ar*), 136.2 ($CH_2=CH_2$), 135.7 ($CH_2=CH_2$), 135.6 ($CH_2=CH_2$), 135.4 ($CH_2=CH_2$), 135.0 (*Ar*), 133.6 (*Ar*), 133.1 (*Ar*), 133.1 (*Ar*), 129.9 ($CH_2=CH_2$), 129.8 ($CH_2=CH_2$), 129.6 (*Ar*), 129.5 ($CH_2=CH_2$), 129.5 ($CH_2=CH_2$), 127.9 (*Ar*), 124.3 (*Ar*), 123.5 (*Ar*), 80.1 (*C*HO(C=O)), 79.8 (*C*HO(C=O)), 64.1 (CH_2OTBDPS), 63.8 (CH_2OTBDPS), 54.2 (C(=O)OCH_3), 53.6 (C(=O)OCH_3), 50.7 ($CH(CO_2)_2$), 49.2 ($CH(CO_2)_2$), 46.7 (*C*HCH=CH), 46.6 (*C*HCH=CH), 32.2 (CH=CHCH_2), 31.5 (CH=CHCH_2), 28.9 ($CH_2CH_2CH_3$), 28.9 ($CH_2CH_2CH_3$), 26.8 ($CH_2CH_2CH_2CH_3$), 26.6 ($CH_2CH_2CH_2CH_3$), 26.5 (C(CH_3) × 2), 25.8 (CH_2CH_3), 23.5 (CH_2CH_3), 19.3 ($C(CH_3)$), 19.2 ($C(CH_3)$), 14.0 (CH_3) , 13.9 (CH_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 2928 m (C-H), 2857 m (C-H), 1782 s (C=O *ester*), 1742 s (C=O *lactone*); $\boldsymbol{[\alpha]_D}$ = +11.6 (*c* 0.75, DCM).

6.34 *(2*S*,3*R*)-4-methoxy-2-((1*E*,3*E*)-nona-1,3-dienyl)butane-1,3-diol*

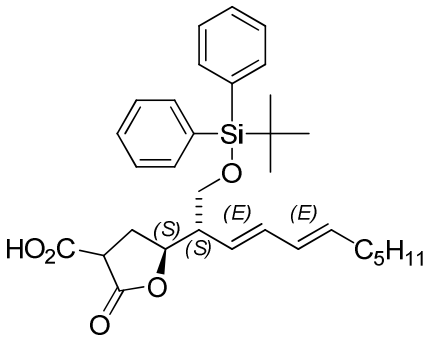


To a solution of *tert*-butyl((*S*,3*E*,5*E*)-2-((*R*)-oxiran-2-yl)undeca-3,5-dienyloxy)-diphenylsilane (100 mg, 0.22 mmol) in methanol (2 mL) was added dimethyl malonate (126 μL, 1.11 mmol.) followed by sodium methoxide (60 mg, 1.11 mmol). After stirring at RT for 1 day, the reaction mixture was heated at reflux for 12 h. The reaction mixture was allowed to cool and was quenched with sat. aq. NH_4Cl (10 mL). The phases were separated, and the aqueous layer washed with Et_2O (3 × 10 mL); the organic fractions were combined, dried ($MgSO_4$), and solvent removed *in vacuo*. The remaining residue was then purified by flash column chromatography (5:1 PE:EtOAc) to give (2*S*,3*R*)-4-methoxy-2-((1*E*,3*E*)-nona-1,3-dienyl)butane-1,3-diol as a clear, colourless oil (58 mg, 0.121 mmol, 55%), along with recovered starting material (30 mg, 0.066 mmol, 30%).

$\boldsymbol{R_f}$ = 0.46 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.69-7.65 (4H, m, Ar*H*), 7.47-7.36 (6H, m, Ar*H*), 6.07-6.95 (2H, m), 5.67-5.55 (2H, m), 4.16 (1H, ddt, *J* = 7.4Hz, 4.0 Hz, 3.0 Hz C*H*OH), 3.82 (1H, dd, *J* = 10.1 Hz, 6.9, C*H*HOSi), 3.72 (1H, dd, *J* = 10.1 Hz, 4.9, CH*H*OSi), 3.40-3.32 (2H, m, CH_2OMe), 3.37 (3H, s, O*Me*), 2.67 (d, *J* = 3.0 Hz, O*H*), 2.35 (1H, m, C*H*CH_2OSi), 2.06 (2H, dt, *J* = 7.3 Hz, 7.0 Hz, CH=CHCH_2), 1.42-1.24 (6H, m, CH_2CH_2CH_2), 0.89 (3H, t, *J* = 7.1, CH_2CH_3); $\boldsymbol{\delta_C}$ (400 MHz, $CDCl_3$) 135.7 (*Ar*), 135.6 (*Ar*), 134.2 (*C*=C), 134.1 (*Ar*), 133.9 (*C*=C), 130.0 (*C*=C), 129.7

(*C*=C), 129.5 (*Ar*), 127.7 (*Ar*), 127.0 (*Ar*), 75.5 (CH_2O), 70.6 (*C*HOH), 65.9 (CH_2O), 59.1 (O*Me*), 47.2 (*C*HCH=CHCH=$CHCH_2$), 32.6 (CHCH=CHCH=*C*HCH_2), 31.5 (CH_2), 29.8 (CH_2), 28.9 (CH_2), 26.8 (SiC(CH_3)$_3$), 19.2 (Si*C*(CH_3)$_3$); ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 2928 m (C-H), 2857 m (C-H), 1782 s (C=O *ester*), 1742 s (C=O *lactone*); ***m/z*** (ESI+) Found: $(M+Na)^+$, 557.2689; $C_{25}H_{34}NaO_3Si$ requires *M*, 557.2699; $[\alpha]_D$ = +5.1 (*c* 0.41, DCM).

6.36 *(5*S*)-5-((*S*,*3*E*,5*E*)-1-(*tert-*Butyldiphenylsilyloxy)undeca-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylic acid*



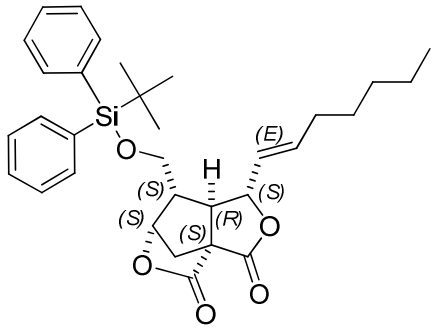
To a solution of (5*S*)-methyl 5-((*S*,3*E*,5*E*)-1-(*tert*-butyldiphenylsilyloxy)undeca-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylate (110 mg, 0.20 mmol) in THF (15 mL) was added potassium hydroxide solution (10% in water, 5 mL). The solution was allowed to stir for 16 h, and then acidified by addition of aqueous sulphate buffer (0.25 M H_2SO_4 / 0.75 M Na_2SO_4). Once the solution had been brought to pH = 2, it was washed with DCM (5 × 10 mL); the organic fractions were combined, dried ($MgSO_4$), and solvent removed *in vacuo*. The remaining residue was then purified by flash column chromatography (3:1 PE:EtOAc, 5% AcOH) to return (5*S*)-5-((*S*,3*E*,5*E*)-1-(*tert*-butyldiphenyl-silyloxy)undeca-3,5-dien-2-yl)-2-

oxotetrahydrofuran-3-carboxylic acid as a light-yellow gum (84 mg, 0.157 mmol, 78%, 1:1 mixture of diastereomers);

δ_H (400 MHz, $CDCl_3$) 7.69-7.65 (4H [d1], 4H [d2], m, Ar*H*), 7.45-7.34 (6H [d1], 6H [d2], m, Ar*H*), 6.16-6.05 (1H [d1], 1H [d2], m, C*H*=CH), 6.03-5.92 (1H [d1], 1H [d2], m, C*H*=CH), 5.71-5.61 (1H [d1], 1H [d2], m, C*H*=CH), 5.37 (1H [d1], dd, *J* = 15.3 Hz, 8.9 Hz, CHC*H*=CHCH=CHCH$_2$), 5.26 (1H [d2], dd, *J* = 15.3 Hz, 9.3 Hz, CHC*H*=CHCH=CHCH$_2$), 5.16 (1H [d1], td, *J* = 7.2 Hz, 3.2 Hz, CH$_2$C*H*O(C=O)), 4.89 (1H [d1], td, *J* = 7.2 Hz, 4.1 Hz, CH$_2$C*H*O(C=O)), 3.77-3.64 (2H [d1], 2H [d2], m, C*H*$_2$OSi), 3.59 (1H [d], dd, *J* = 10.0 Hz, 6.1 Hz, C*H*(CO$_2$)$_2$), 3.40 (1H [d], dd, *J* = 7.2 Hz, 4.6 Hz, C*H*(CO$_2$)$_2$), 2.71 (1H [d1], ddd, *J* = 13.5 Hz, 7.4 Hz, 5.8 Hz, C*H*HCH(CO$_2$)$_2$), 2.55-2.39 (4H, m, C*HH*CH(CO$_2$)$_2$, C*H*CH$_2$OSi), 2.32 (1H [d], ddd, *J* = 13.5 Hz, 7.1 Hz, 3.3 Hz, C*H*CH$_2$OSi), 2.11-2.04 (2H [d1], 2H [d2], m, CH=CHC*H*$_2$ [d1 + d2]), 1.43-1.25 (6H [d1], 6H [d2], m, C*H*$_2$C*H*$_2$C*H*$_2$), 1.08 (9H [d1], 9H [d2], s, Si(C(C*H*$_3$)$_3$), 0.90 (3H [d1], 3H [d2], t, *J* = 6.8 Hz, CH$_2$C*H*$_3$); **δ_C** (100 MHz, $CDCl_3$) 172.4 (*C*O$_2$H), 172.3 (*C*O$_2$H), 171.2 (*C*O$_2$CH), 170.7 (*C*O$_2$CH), 136.4 (*Ar*), 136.1 (*Ar*), 136.1 (*Ar*), 135.7 (*C*H$_2$=*C*H$_2$), 135.6 (*C*H$_2$=*C*H$_2$), 135.6 (*C*H$_2$=*C*H$_2$), 135.5 (*C*H$_2$=*C*H$_2$), 134.8 (*Ar*), 133.4 (*Ar*), 133.3 (*Ar*), 133.1 (*Ar*), 129.8 (*C*H$_2$=*C*H$_2$), 129.8 (*C*H$_2$=*C*H$_2$), 129.7 (*Ar*), 129.6 (*C*H$_2$=*C*H$_2$), 129.4 (*C*H$_2$=*C*H$_2$), 127.8 (*Ar*), 124.1 (*Ar*), 123.5 (*Ar*), 78.9 (*C*H(CO$_2$)), 78.6 (*C*H(CO$_2$)), 64.2 (*C*H$_2$OTBDPS), 64.0 (*C*H$_2$OTBDPS), 50.3 (*C*H(CO$_2$)), 49.2 (*C*H(CO$_2$)), 46.9 (*C*HCH=CH), 46.6 (*C*HCH=CH), 32.6 (CH=CH*C*H$_2$), 31.4 (CH=CH*C*H$_2$), 28.7 (*C*H$_2$CH$_2$CH$_3$), 28.9 (*C*H$_2$CH$_2$CH$_3$), 26.9 (*C*H$_2$CH$_2$CH$_2$CH$_3$), 26.9 (*C*H$_2$CH$_2$CH$_2$CH$_3$), 26.6 (C(*C*H$_3$)), 25.6 (*C*H$_2$CH$_3$), 22.5 (*C*H$_2$CH$_3$), 19.2 (*C*(CH$_3$)), 19.0 (*C*(CH$_3$)), 14.2 (*C*H$_3$) , 14.0 (*C*H$_3$); **ν_{max}/cm^{-1}** ($CDCl_3$) 3523 br (CO$_2$H), 3072 m (CH), 3048 m (CH), 2958 m (CH), 2929

m (CH), 2856 m (CH), 1779 s (C=O *lactone*), 1738 s (C=O *acid*), 1727 w (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 557.2689; $C_{25}H_{34}NaO_3Si$ requires *M*, 557.2699; $[\alpha]_D$ = 15.4 (*c* 0.92, DCM).

6.37 *(1*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-((*E*)-hept-1-enyl)-3,8-dioxa-tricyclo[5.2.1.0^{1,5}]decane-2,9-dione*



Method 1:

A solution of the malonic acid (5*S*)-5-((*S*,3*E*,5*E*)-1-(*tert*-butyldiphenyl-silyloxy)undeca-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylic acid (20.0 mg, 0.037 mmol) in degassed acetonitrile (2 mL, 18.5 mmol L^{-1}) was prepared in a reaction carousel. Manganese(III) acetate (20.0 mg, 0.75 mmol) was added, along with copper(II) triflate (14 mg, 0.037 mmol). The reaction tube was degassed, and heated to reflux for 18 h, after which the reaction was quenched by addition of water (4 mL). The mixture was acidified to pH = 2 with HCl (10% aqueous) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine dried ($MgSO_4$), and the solvent removed *in vacuo*. The remaining residue was then purified

by flash column chromatography (5:1 PE:EtOAc, 5% AcOH), to give (1*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-((*E*)-hept-1-enyl)-3,8-dioxa-tricyclo[5.2.1.$0^{1,5}$]decane-2,9-dione as a colourless gum (12 mg, 0.022 mmol, 68%).

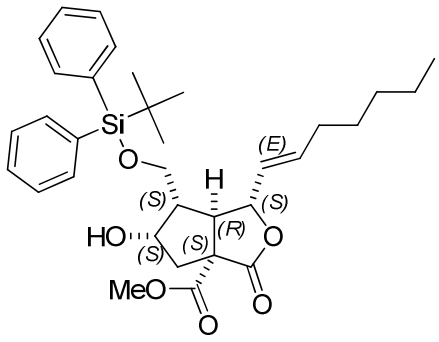
Method 2:

A solution of (1*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-vinyl-3,8-dioxa-tricyclo[5.2.1.$0^{1,5}$]decane-2,9-dione (15 mg, 0.0324 mmol) in distilled, degassed DCM (10 mL) was prepared, to which Grubbs second-generation catalyst ((1,3-bis(2,4,6- trimethyl phenyl) -2- imidazolidinylidene) dichloro (phenyl methylene) (tricyclohexylphosphine) ruthenium) was added (1.4 mg, 0.00016 mmol). The reaction was warmed to 40° C, and allowed to stir for 30 min. At this point, hept-1-ene (64 mg, 91 μL, 0.649 mmol) was added to the reaction mixture, and the gold-coloured solution allowed to stir for a further 3 h. The reaction mixture was allowed to cool and solvent removed *in vacuo*. Purification by flash column chromatography, (PE 40-60 → 2:1 Et_2O:PE 40-60) gave (1*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-((E)-hept-1-enyl)-3,8-dioxa-tricyclo[5.2.1.$0^{1,5}$]decane-2,9-dione (16 mg, 0.0298 mmol, 92%) as a clear, colourless oil with spectroscopic data consistent with the earlier isolated sample.

$\boldsymbol{R_f}$ = 0.23 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.63-7.62 (4H, m, Ar*H*), 7.48-7.38 (6H, m, Ar*H*), 5.83 (1H, dt, *J* = 15.3 Hz, 6.7 Hz, CH=C*H*CH_2), 5.40 (1H, dd, *J* = 15.3 Hz, 7.5 Hz, CHC*H*=CH), 5.12 (1H, s, C*H*(O)CH_2), 4.72 (1H, dd, *J* = 8.2 Hz, 1.2 Hz, OC*H*CH=CH), 3.70 (1H, dd, *J* = 10.4 Hz, 1.3 Hz, C*H*HOTBDPS), 3.60 (1H, dd, *J* = 10.4 Hz, 6.7 Hz, C*H*HOTBDPS), 2.62-2.58 (2H, m, C*H*CH_2OTBDPS, C*H*HCHCHCH_2OTBDPS), 2.43 (1H, d, *J* = 10.9 Hz, CH*H*CHCHCH_2OTBDPS), 2.26

(1H, dd, *J* = 9.6 Hz, 4.7 Hz, C*H*CHCH=CH), 1.98 (2H, dt, *J* = 8.2 Hz, 6.9 Hz, CH=CHCH_2), 1.34-1.18 (6H, m, CH_2CH_2CH_2), 1.06 (9H, s, SiC(CH_3)$_3$), 0.86 (3H, t, *J* = 7.1, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 169.1 (*C*(=O)OCHCH=CH), 167.3 (*C*(=O)OCHCHCH$_2$), 138.7 (CH*C*H=CH), 135.5 (*Ar*), 135.4 (*Ar*), 133.0 (*Ar*), 130.0 (*Ar*), 127.9 (*Ar*), 124.7 (CH=*C*HCH$_2$), 84.2 (O*C*HCH=CH), 82.2 (*C*H(O)CH$_2$), 62.2 (*C*H$_2$OTBDPS), 56.8 (*C*(CO$_2$)$_2$), 50.2 (*C*HCHCH=CH), 49.4 (C*H*CH$_2$OTBDPS), 40.6 (*C*H$_2$CHCHCH$_2$OTBDPS), 32.1 (C*H*$_2$CH=CH), 31.3 (C*H*$_2$), 28.2 (*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 22.4 ((CO$_2$)$_2$C*C*H$_2$), 19.2 (*C*(CH$_3$)$_3$), 14.0 (CH_2CH_3); ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 2959 m (C-H), 2928 m (C-H), 2859 m (C-H), 1813 s (C=O *bridged lactone*), 1727 s (C=O *lactone*), 1600 w (C=C); ***m/z*** (ESI+) Found: $(M+Na)^+$, 555.2335; $C_{25}H_{34}NaO_3Si$ requires *M*, 555.2335; $[\alpha]_D$ = +11.3 (*c* 1.1, DCM).

6.39 *(1*S*,3a*S*,5*S*,6*S*,6a*R*)-Methyl 6-((*tert*-butyldiphenylsilyloxy)methyl)-1-((*E*)-hept-1-enyl)-5-hydroxy-3-oxohexahydro-1*H*-cyclopenta[c]furan-3a-carboxylate*

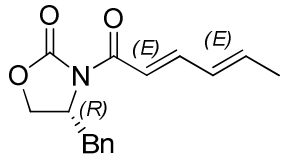


A crude sample of (1*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-((*E*)-hept-1-enyl)-3,8-dioxa-tricyclo[5.2.1.0^{1,5}]decane-2,9-dione was dissolved in methanol (5 mL), and allowed to stir for 1 h at RT. The solvent was then removed *in vacuo*, and the remaining residue purified by flash column chromatography (5:1 PE:EtOAc) to

give (1S,3aS,5S,6S,6aR)-methyl 6-((tert-butyldiphenylsilyloxy)methyl)-1-((E)-hept-1-enyl) -5 -hydroxy- 3- oxohexahydro- 1H –cyclopenta [c] furan -3a -carboxylate as a colourless gum (14 mg, 0.026 mmol, 70%);

R_f = 0.21 (2:1 PE:EtOAc); δ_H (400 MHz, $CDCl_3$) 7.66-7.63 (4H, m, Ar*H*), 7.48-7.38 (6H, m, Ar*H*), 5.66 (1H, dt, *J* = 15.4 Hz, 6.6 Hz, CH=C*H*CH_2), 5.55 (1H, dd, *J* = 15.4 Hz, 7.2 Hz, C*H*=$CHCH_2$), 4.66 (1H, d, *J* = 7.0 Hz, C*H*CH=CH), 4.42 (1H, d, *J* = 6.8 Hz, 3.5 Hz, C*H*OH), 3.96 (1H, dd, *J* = 10.8 Hz, 6.4 Hz, C*H*HOTBDPS), 3.96 (1H, dd, *J* = 10.8 Hz, 6.0 Hz, CH*H*OTBDPS), 3.80 (3H, s, O*Me*), 2.98 (1H, dd, *J* = 9.9 Hz, 2.0 Hz, C*H*CHOC(=O)), 2.67 (1H, dd, *J* = 14.8 Hz, 1.4 Hz, CH(OH)C*H*HC$(CO_2)_2$), 2.52 (1H, d, *J* = 4.2 Hz, O*H*), 2.28 (1H, dd, *J* = 14.8 Hz, 4.1 Hz, CH(OH)CH*H*C$(CO_2)_2$), 2.07 (1H, m, C*H*CH_2OTBDPS), 2.01 (2H, dt, *J* = 7.1 Hz, 6.8 Hz, CH=CHCH_2), 1.37-1.20 (6H, m, *alkyl chain*), 1.06 (9H, s, SiC(CH_3)$_3$), 0.88 (3H, t, *J* = 6.6 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 175.3 (*C*(=O)OCH), 171.5 (*C*(=O)OCH_3), 135.7 (*Ar*), 135.6 (*Ar*), 135.5 (CH=*C*HCH_2), 135.5 (*Ar*), 132.9 (*Ar*), 132.7 (*Ar*), 130.0 (*Ar*), 127.9 (*Ar*), 127.4 (*C*H=$CHCH_2$), 84.7 (*C*HCH=CH), 74.9 (C*H*OH), 62.5 (*C*H_2OTBDPS), 60.4 (*C*$(CO_2)_2$), 54.5 (*C*HCH_2OTBDPS), 53.5 (O*Me*), 52.8 (*C*HCHOC(=O)), 43.1 (CH(OH)*C*$H_2C(CO_2)_2$), 32.0 (CH=CH*C*H_2), 31.3 (*alkyl chain*), 28.4 (*alkyl chain*), 26.8 (C(*C*H_3)$_3$), 22.5 (*alkyl chain*), 19.1 (*C*$(CH_3)_3$), 14.0 (*C*H_3). ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 3507 br (O-H), 3071 m (C-H), 3049 m (C-H), 2957 m (C-H), 2929 m (C-H), 2856 m (C-H), 1772 s (C=O *lactone*), 1737 s (C=O *ester*), 1670 w (C=C); ***m/z*** (ESI+) Found: $(M+Na)^+$, 587.2791; $C_{28}H_{34}NaO_6Si$ requires *M*, 587.2805; $[\alpha]_D$ = +22.0 (*c* 0.53, DCM).

6.54 *(*R*)-4-Benzyl-3-((2*E*,4*E*)-hexa-2,4-dienoyl)oxazolidin-2-one*

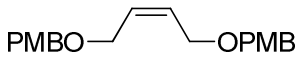


To a stirred solution of sorbic acid (0.86 g, 7.7 mmol) and triethylamine (1.34 mL, 9.62 mmol) in THF (40 mL) at -78 °C was added pivolyl chloride (1.00 mL, 8.08 mmol). The resulting slurry was left to stir for a further 15 min, and then warmed to 0 °C, and stirring continued for 1 h before cooling the reaction mixture to -78 °C. In a separate flask, a solution of (*R*)-4-benzyloxazolidin-2-one (1.5 g, 8.46 mmol) in THF (40 mL) was deprotonated with *n*-BuLi (5.3 mL, 1.6 M in hexanes, 8.46 mmol) at -78 °C. The metalated oxazolidinone was then added to the dienoate slurry *via* canula over 10 min, with the temperature at a constant -78 °C. Stirring of the slurry continued for a further 20 min, and the reaction mixture was then warmed to RT and stirred for 14 h. The reaction was quenched by addition of water, and the solvent removed *in vacuo*. The residue was taken up in DCM (100 mL), and washed with HCl (50 mL, 0.5 M), a saturated solution of sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$) and evaporated *in vacuo* to leave an impure oil. The oil was recrystalised from Et_2O/DCM to give (*R*)-4-benzyl-3-((2*E*,4*E*)-hexa-2,4-dienoyl)oxazolidin-2-one as white needles (7.1g, 23.14 mmol, 90.2%)

$\boldsymbol{R_f}$ = 0.61 (10:1 DCM:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.51 (1H, dd, *J* = 15.0 Hz, 10.4 Hz, C(O)CH=C*H*), 7.27 (6H, m, Ar*H*, C*H*=CH), 6.29 (2H, m, C(O)C*H*=CHCH=C*H*CH_3), 4.74 (1H, ddd, *J* = 10.6 Hz, 6.9 Hz, 3.2 Hz, C*H*CH_2Ph), 4.17 (2H, m, OCH_2CHN), 3.32 (1H, dd, *J* = 13.4 Hz, 3.2 Hz C*H*HPh), 2.82 (1H, dd, *J*

= 13.4 Hz, 9.4 Hz, CH*H*Ph), 1.89 (3H, d, *J*=6.3, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 165.5 (*C*=O), 153.5 (*C*=O), 147.0 (C(=O)CH=*C*H), 141.3 (CH=*C*HCH$_3$), 135.4 (*Ar*), 130.4 (*C*=C), 129.5 (*Ar*), 128.9 (*Ar*), 127.3 (*Ar*), 117.9 (C=*C*), 66.1 (O*C*H$_2$CHN), 55.4 (OCH$_2$*C*HN), 37.9 (*C*H$_2$), 18.9 (*C*H$_3$); ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 3087 m (CH), 3062 m (CH), 3028 m (CH), 2931 m (CH), 2850 m (CH), 1789 s (C=O *oxazolidinone*), 1681 s (C=O *amide*); ***m/z*** (ESI+) Found: $(M+Na)^+$, 294.1091; $C_{16}H_{17}NO_3Na$ requires *M*, 294.1101; **EA** Found C 70.76, H 6.39, N 5.21, $C_{16}H_{17}NO_3$ requires C 70.83, H 6.32, N 5.16; $[\alpha]_D$ = -129.1 (*c* 1.04, DCM); **MP** = 101.9-104.1 °C

6.56 (*Z*)-1,4-Bis(4-methoxybenzyloxy)but-2-ene[92]

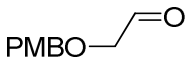


To a washed suspension of sodium hydride (2.8g, 60% dispersion in mineral oil, 69.5 mmol) in DMF (100 mL) was added (*Z*)-1,4-but-2-ene diol (2.66 g, 30.21 mmol) dropwise at 0 °C, and the resulting suspension was allowed to stir for 15 min. After this time, the reaction was warmed to 60 °C, and TBAI (0.55g, 1.51 mmol, 5 mol%) was added in one portion. PMBCl (9.4 mL) was then added dropwise, monitoring reaction temperature with an internal thermometer. The reaction was then allowed to stir at 60 °C for a further 15 h. The reaction was cooled to RT, and quenched by the slow addition of sat. aq. NH_4Cl (10 mL). EtOAc (100 mL) was added and the aqueous phase was extracted with further EtOAc (3 × 100 mL). The organic fractions were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by

flash column chromatography (1:1 PE : Et_2O) gave (*Z*)-1,4-*bis*(4-methoxybenzyloxy)but-2-ene as a colourless oil (6.1 g, 18.57 mmol, 61%);

$\boldsymbol{R_f}$ = 0.56 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.25 (4H, d, *J* = 8.7 Hz, Ar*H*), 6.87 (4H, d, *J* = 8.7 Hz, Ar*H*), 5.77 (2H, m), 4.42 (4H, s), 4.04 (4 H, d, *J* = 3.7 Hz), 3.80 (6 H, s); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 2934 m (C-H), 2836 m (C-H), 1612 m (C=C), 1586 m (Ar), 1513 m (Ar), 1464 m (Ar), 1248 m (C-O);

6.55 2-(4-Methoxybenzyloxy)acetaldehyde[92]

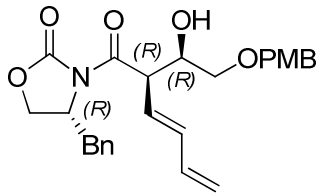


A solution of (*Z*)-1,4-bis(4-methoxybenzyloxy)but-2-ene (3.00 g, 9.12 mmol) and Sudan III dye (<1 mg) in DCM (80 mL) was cooled to –78 °C and a stream of (generated at 230V, 100 flow rate) ozone was bubbled through the orangish/pink solution for 10 min. until a yellowish/brown color persisted. After purging the reaction with oxygen, a solution of triphenylphosphine (3.60 g, 13.71 mmol, 1.5 equiv.) in DCM (20 mL) was added dropwise over 5 min. and the solution was allowed to slowly warm to RT. After 0.5 h, the orange solution was concentrated *in vacuo* and purified *via* kugelrohr distillation (bp ~185 °C (1.5 mmHg)) to afford 2-(4-methoxybenzyloxy)acetaldehyde (3.07 g, 8.48 mmol, 93%) yield) as a faint yellow oil;

$\boldsymbol{R_f}$ = 0.48 (10:1 DCM:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.70 (1H, s), 7.28 (2H, d, *J* = 8.6 Hz, Ar*H*), 6.89 (2H, d, *J* = 8.6 Hz, Ar*H*), 4.56 (2H, s), 4.05 (2H, s), 3.80 (3H, s);

ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 2837 m (C-H), 3001 w (C-H), 2925 m (C-H), 2856 m (C-H), 1735 s (C=O), 1613 m (Ar), 1586 (Ar);

6.58 *(*R*)-4-Benzyl-3-((*R,E*)-2-((*R*)-1-hydroxy-2-(4-methoxybenzyloxy)ethyl)hexa-3,5-dienoyl)oxazolidin-2-one*[127]

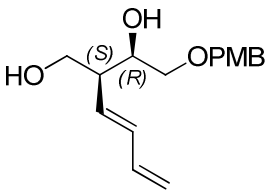


To a solution of (*R*)-4-benzyl-3-((2*E*,4*E*)-hexa-2,4-dienoyl)oxazolidin-2-one (1.81 g, 7.06 mmol) in DCM (20 mL) at -78 °C was added titanium(IV) chloride (1.2 g, 0.7mL). The reaction mixture was stirred for 15 min, Hünig's base (3.074 mL, 17.65 mmol) was added, and stirring was continued for a further 1 h. NMP (0.67mL, 7.06 mmol) was added, and stirring was continued for 10 min, before freshly distilled 2-(4-methoxybenzyloxy)acetaldehyde (1.4g, 7.7 mmol) in DCM (5 mL) was added. The reaction mixture was stirred at -78 °C for a futher 2 h, after which time the reaction was warmed to -40 °C and stirred at that temperature for 2 h. The reaction mixture was quenched by addition of half-saturated NH_4Cl solution (10 mL) at 0 °C, and extracted with DCM (3 × 20 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to leave an impure residue, which was purified by flash column chromatography (10:1 DCM:Et_2O) to give (*R*)-4-benzyl-3-

((*R*,*E*)-2-((*R*)-1-hydroxy-2-(4-methoxybenzyloxy)ethyl)hexa-3,5-dienoyl)oxazolidin-2-one (2.68g, 5.93 mmol, 84%) as a light yellow gum;

$\boldsymbol{R_f}$ = 0.40 (10:1 DCM:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.32-7.23 (5H, m, Ar*H*), 7.14-7.12 (2H, m, Ar*H*), 6.88-6.83 (2H, m, Ar*H*), 6.43-6.34 (2H, m, CH=C*H*C*H*=CH_2), 5.83 (1H, dd, *J* = 14.5 Hz, 9.4 Hz, C*H*=CHCH=CH_2), 5.29-5.23 (1H, m, CH=CHCH=C*H*H), 5.16 (1H, d, *J* = 8.1 Hz, CH=CHCH=CH*H*), 4.76 (1H, dd, *J* = 9.5 Hz, 5.5 Hz, (C=O)C*H*CHOH), 4.55 (1H, tt, *J* = 8.5 Hz, 3.2 Hz, C*H*Bn), 4.46 (1H, d, *J* = 11.5 Hz, C*H*HPMP), 4.43 (1H, d, *J* = 11.5 Hz, C*H*HPMP), 4.26 (1H, q, *J* = 5.8 Hz, C*H*OH), 4.07 (1H, dd, *J* = 9.1 Hz, 3.1 Hz, OC*H*HCHBn), 3.98 (1H, t, *J* = 8.4 Hz, OCH*H*CHBn), 3.78 (3H, s, PMB O*Me*), 3.55 (1H, dd, *J* = 9.6 Hz, 5.9 Hz, C*H*HOPMB), 3.50 (1H, dd, *J* = 9.6 Hz, 5.8 Hz, C*H*HOPMB), 3.14 (1H, dd, *J* = 13.5 Hz, 3.4 Hz, C*H*HPh), 2.91 (1H, *br*, O*H*), 2.76 (1H, dd, *J* = 13.5 Hz, 8.9 Hz, C*H*HPh); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.0 (N*C*(=O)CH), 159.2 (*Ar*-OMe), 152.9 (O*C*(=O)N), 137.0 (*Ar*), 136.3 (*C*=C), 134.9 (*Ar*), 129.5 (C=*C*), 129.4 (*Ar*), 128.9 (*Ar*), 127.3 (*Ar*), 126.8 (*C*H=CHCH=CH_2), 118.3 (CH=CHCH=*C*H_2), 113.8 (*Ar*), 72.9 (*C*H_2PMP), 71.4 (*C*H_2PMB), 70.8 (*C*HOH), 65.8 (OCH_2CHBn), 55.2 (PMB O*Me*), 54.9 (*C*HBn), 49.3 ((C=O)*C*HCHOH), 37.5 (*C*H_2Ph); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3483 br (O-H), 3062 m (C-H), 3029 m (C-H), 3002 m (C-H), 2916 m (C-H) 2865 m (C-H), 1778 s (C=O, *oxazolidinone*), 1693 s (C=O, *amide*); ***m/z*** (ESI+) Found: $(M+Na)^+$, 474.1886; $C_{26}H_{29}NO_6Na$ requires *M*, 474.1887; **EA** Found C 69.23, H 6.42, N 3.22, $C_{26}H_{29}NO_6$ requires C 69.16 H 6.47 N 3.10; $\boldsymbol{[\alpha]_D}$ = +14.2 (*c* 0.69, DCM).

6.61 *(2*S*,3*R*)-2-((*E*)-Buta-1,3-dienyl)-4-(4-methoxybenzyloxy)butane-1,3-diol*

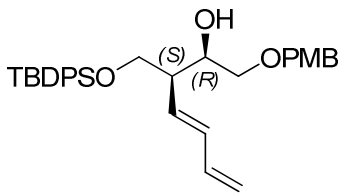


To a solution of (*R*)-4-benzyl-3-((*R*,*E*)-2-((*R*)-1-hydroxy-2-(4-methoxybenzyloxy) ethyl)hexa-3,5-dienoyl)oxazolidin-2-one (1.63 g, 3.61 mmol) in THF (50 mL) was added methanol (0.175 mL, 4.33 mmol). The reaction was then cooled to 0 °C, and a solution of lithium borohydride (2.17 mL, 2.0 M in THF, 4.33 mmol) was added dropwise. The reaction was allowed to stir for a further 2 h, after which time it was quenched by addition of 15% NaOH and the organic solvents were reomved *in vacuo*. Et_2O was added and the organic phase was separated. The aqueous layer was extracted further with Et_2O, and the combined extracts were washed with brine, dried ($MgSO_4$), and the solvent reomved *in vacuo*. Purification by flash column chromatography (5:1 DCM:Et_2O) gave (2*S*,3*R*)-2-((*E*)-buta-1,3-dienyl)-4-(4-methoxybenzyloxy)butane-1,3-diol as a clear, colourless oil (760 mg, 2.73 mmol, 76%);

$\boldsymbol{R_f}$ = 0.20 (10:1 DCM:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.25 (2H, d, *J* = 8.6 Hz, Ar*H*), 6.89 (2H, d, *J* = 8.6 Hz, Ar*H*), 6.34 (1H, dt, *J* = 16.9 Hz, 10.3 Hz, CH=CHC*H*=CH_2), 6.16 (1H, dd, *J* = 15.5 Hz, 10.3 Hz, CH=C*H*CH=CH_2), 5.77 (1H, dd, *J* = 15.4 Hz, 9.3 Hz, C*H*=CHCH=CH_2), 5.17 (1H, d, *J* = 15.5 Hz, CH=CHCH=C*H*H), 5.07 (1H, d, *J* = 10.1 Hz, CH=CHCH=CH*H*), 4.49 (1H, d, *J* = 11.5 Hz, OC*H*HPMP), 4.45 (1H, d, *J* = 11.5 Hz, OCH*H*PMP), 4.04 (1H, m, C*H*OH), 3.81 (3H, s, *OPMB*), 3.75 (2H, t, *J* = 6.0 Hz, CH_2OH), 3.44 (2H, m, CH_2OPMB), 2.67 (1H, m, CHO*H*), 2.40 (1H, m, CH=CH-

C*H*-CH_2OH), 2.33 (1H, m, CH_2OH); δ_C (100 MHz, $CDCl_3$) 159.3 (*Ar*-OMe), 136.7 (*C*=C), 134.6 (C=*C*), 130.2 (*Ar*), 129.8 (*C*=C), 129.5 (*Ar*), 116.7 (C=*C*), 113.9 (*Ar*), 73.1 (CH_2O), 72.5 (CH_2O), 71.4 (*C*HOH), 64.5 (CH_2O), 55.3 (OMe), 47.4 (*C*HCH=CHCH=CH_2); ν_{max}/**cm**$^{-1}$ (($CDCl_3$) 3416 br (O-H), 3083 m (C-H), 3037 m (C-H), 3001 m (C-H), 2909 m (C-H) 2869 m (C-H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 301.1410; $C_{16}H_{22}NaO_4$ requires *M*, 301.1411; $[\alpha]_D$ = +4.7 (*c* 1.23, DCM).

6.62 *(2*R,*3*S,E*)-3-((*tert-*Butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyloxy)hepta-4,6-dien-2-ol*

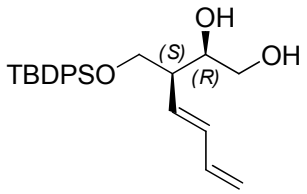


To a solution of (2*S*,3*R*)-2-((*E*)-buta-1,3-dienyl)-4-(4-methoxybenzyloxy)butane-1,3-diol (760 mg, 2.73 mmol) in DCM (40 mL) at 0 °C was added imidazole (204 mg, 3.00 mmol) followed by *tert*-butyldiphenylsilylchloride (0.78 mL, 3.00 mmol) and the reaction mixture stirred for 15 min at that temperature before being stirred at RT for 15 h. The reaction was quenched by the addition of saturated sodium hydrogen carbonate solution (15 mL), and the mixture was extracted with DCM (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo*. Purifcation by flash column chromatography (10:1 DCM:Et_2O) gave

(2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyloxy)hepta-4,6-dien-2-ol as a clear colourless oil (1.32g, 2.55 mmol, 94%);

$\boldsymbol{R_f}$ = 0.48 (10:1 DCM:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.68-7.64 (4H, m, Ar*H*), 7.46-7.36 (6H, m, Ar*H*), 7.26 (2H, d, *J* = 9.4 Hz, Ar*H*), 6.88 (2H, d, *J* = 6.6 Hz, Ar*H*), 6.31 (1H, dt, *J* = 17.0 Hz, 10.1 Hz, CHC*H*=CH_2), 6.05 (1H, dd, *J* = 15.4 Hz, 10.4 Hz, CH=C*H*CH=CH_2), 5.77 (1H, dd, *J* = 15.4 Hz, 9.2 Hz, CHC*H*=CHCH=CH_2), 5.12 (1H, d, *J* = 17.0 Hz, CH=CHCH=C*H*H), 5.03 (1H, d, *J* = 10.1 Hz CH=CHCH=CH*H*), 4.49 (1H, d, *J* = 11.5 Hz, OC*H*HPMP), 4.44 (1H, d, *J* = 11.5 Hz, OCH*H*PMP), 4.19 (1H, m, C*H*OH), 3.84 (1H, dd, *J* = 10.0 Hz, 6.5 Hz, C*H*HOSi), 3.81 (3H, s, OPMB CH_3), 3.74 (1H, dd, *J* = 10.0 Hz, 5.2 Hz, CH*H*OSi), 3.47-3.40 (2H, m, CH_2OPMB), 2.7 (1H, d, *J* = 2.7 Hz, O*H*), 2.40 (1H, m, CH=CH-C*H*-CH_2OSi), 1.06 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 159.2 (*Ar*-OMe), 137.0 (CH*C*H=CHCH=CH_2), 135.6 (*Ar*), 135.6 (*Ar*), 134.2 (CH*C*H=CHCH=CH_2), 133.3 (*Ar*), 133.1 (*Ar*), 130.6 (*Ar*), 130.2 (*Ar*), 129.7 (CHCH=*C*HCH=CH_2), 129.4 (*Ar*), 127.7 (*Ar*), 116.1 (CHCH=CHCH=*C*H_2), 113.8 (*PMB-Ar*), 73.0 (*C*H_2OPMB), 72.6 (*C*H_2Ar), 70.7 (*C*HOH), 65.8 (*C*H_2OSi), 55.3 (OMe), 47.2 (*C*HCH=CHCH=CH_2), 26.8 (SiC(*C*H_3)$_3$), 19.2 (Si*C*$(CH_3)_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3474 br (O-H), 3134 m (C-H) 3071 m (C-H), 3045 m (C-H), 2999 m (C-H), 2955 m (C-H), 2930 m (C-H), 2857 m (C-H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 539.2580; $C_{32}H_{40}NaO_4Si$ requires *M*, 539.2588; $\boldsymbol{[\alpha]_D}$ = +19.8 (*c* 0.65, DCM).

6.63 *(2*R,*3*S,E*)-3-((*tert-*Butyldiphenylsilyloxy)methyl)hepta-4,6-diene-1,2-diol*

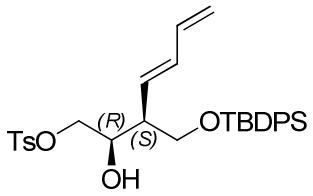


To a solution of (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-(4-methoxy benzyloxy)hepta-4,6-dien-2-ol (1.23 g, 2.38 mmol) in DCM (30 mL) was added a solution of boron trichloride-dimethylsulphide complex (2.38 mL, 2.0 M in DCM, 4.76 mmol). After 5 min, the reaction was quenched by pouring onto rapidly stirred saturated aqueous sodium hydrogen carbonate solution (30 mL). THF (20 mL) was added immediately, and the biphasic mixture allowed to stir for 30 min. The mixture was extracted with DCM (3 × 30 mL), the combined extracts dried ($MgSO_4$), and solvent removed *in vacuo* to Purification by flash column chromatography (5:1 DCM:Et_2O) gave (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)hepta-4,6-diene-1,2-diol as a clear colourless oil (760 mg, 1.92 mmol, 81%);

$\boldsymbol{R_f}$ = 0.22 (10:1 DCM:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.67-7.65 (4H, m, Ar*H*), 7.48-7.38 (6H, m, Ar*H*), 6.30 (1H, dt, *J* = 17.0 Hz, 10.3 Hz, CH_2=C*H*-CH), 6.08 (1H, dd, *J* = 15.3 Hz, 10.2 Hz, CH_2=CH-C*H*=CH), 5.73 (1H, dd, *J* = 15.3 Hz, 9.2 Hz, C*H*=CHCH=CH_2), 5.14 (1H, dd, *J* = 17.0 Hz, 1.7 Hz, CH=C*H*H), 5.06 (1H, dd, *J* = 10.2 Hz, 1.4 Hz, CH=CH*H*), 4.01 (1H, m, C*H*OH), 3.79 (2H, d, *J* = 5.5 Hz, C*H*HOSi), 3.62 (2H, t, *J* = 5.9 Hz, CH_2OH), 2.73 (1H, d, *J* = 2.73 Hz, CHO*H*), 2.41 (1H, dt, *J* = 9.5 Hz, 5.2 Hz, CH=CH-C*H*-CH_2OSi), 2.11 (1H, t, *J* = 6.0 Hz, CH_2O*H*), 1.06 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 136.7 (CH*C*H=CHCH=CH_2), 135.6 (*Ar*), 135.6 (*Ar*), 134.4 (*Ar*) (CH*C*H=CHCH=CH_2) 132.9 (*Ar*), 132.8 (*Ar*), 130.3 (*Ar*),

129.9 (*Ar*) (CHCH=*C*HCH=CH_2), 127.8 (*Ar*), 116.7 (CHCH=CHCH=*C*H_2), 72.8 (*C*HOH), 65.8 (*C*H_2OH), 65.0 (*C*H_2OSi), 47.2 (*C*HCH=CHCH=CH_2), 26.9 (SiC(*C*H_3)$_3$), 19.2 (Si*C*(CH_3)$_3$); ν_{max}/**cm^{-1}** ($CDCl_3$) 3385 br (O-H), 3071 m (C-H), 3048 m (C-H), 2999 m (C-H), 2957 m (C-H), 2930 m (C-H), 2889 m (C-H), 2857 m (C-H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 419.2011; $C_{24}H_{32}NaO_3Si$ requires *M*, 419.2013; **[α]$_D$** = -17.9 (*c* 3.05, DCM)

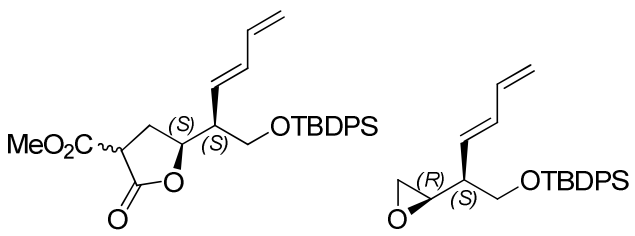
6.52 *(2*R*,3*S*,*E*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)-2-hydroxyhepta-4,6-dienyl 4-methylbenzenesulfonate*



A solution of (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)hepta-4,6-diene-1,2-diol (600 mg, 1.51 mmol) in DCM (30 mL) was cooled to 0 °C, and tosyl chloride (288 mg, 1.51 mmol), DMAP (184 mg, 1.51 mmol) and TEA (0.316 mL, 2.27 mmol.). The reaction mixture was stirred for 15 min at 0 °C and then a RT for 15 h. The reaction was quenched by addition of aqueous HCl (10 mL, 1.0M), and the mixture extracted with DCM (3 × 30 mL). The combined extracts were dried ($MgSO_4$), and the solvent removed *in vacuo*. Purification by flash column chromatography (10:1 DCM:Et_2O) gave (2R,3S,E)-3- ((tert-butyldiphenylsilyloxy)methyl) -2- hydroxyhepta-4,6-dienyl 4-methyl benzenesulfonate as a clear colourless oil (632 mg, 1.15 mmol, 76%);

R_f = 0.44 (10:1 DCM:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.81-7.79 (2H, d, *J* = 8.3 Hz, SO_2Ar), 7.65-7.63 (4H, m, Ar*H*), 7.48-7.38 (6H, m, Ar*H*), 7.35-7.33 (2H, d, *J* = 8.3 Hz, SO_2Ar), 6.25 (1H, dt, *J* = 16.9 Hz, 10.2 Hz, CH_2=C*H*-CH), 6.01 (1H, dd, *J* = 15.4 Hz, 10.6 Hz, CH_2=CH-C*H*=CH), 5.64 (1H, dd, *J* = 15.4 Hz, 9.3 Hz, C*H*=CHC=CH_2), 5.11 (1H, dd, *J* = 17.1 Hz, 1.4 Hz, CH=C*H*H), 5.05 (1H, dd, *J* = 10.2 Hz, 1.4 Hz, CH=CH*H*), 4.27-4.22 (1H, m, C*H*OH), 4.01 (2H, d, *J* = 6.0 Hz, C*H*OTs), 3.81-3.73 (2H, m, CH_2OSi), 2.75 (1H, d, *J* = 3.5 Hz, O*H*), 2.45 (3H, s, ArCH_3), 2.39 (1H, m, CH=CH-C*H*-CH_2OSi), 1.06 (9H, s, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 144.9 (SO_2*Ar*), 136.6 (CH*C*H=CHCH=CH_2), 135.6 (*Ar*), 135.5 (*Ar*), 135.0 (CHCH=CH*C*H=CH_2), 132.9 (*Ar*), 132.7 (*Ar*), 129.9 (CHCH=*C*HCH=CH_2), 128.7 (*Ar*), 128.0 (*Ar*), 127.8 (*Ar*), 117.0 (CHCH=CHCH=*C*H_2), 72.2 (*C*H_2OTs), 70.0 (*C*HOH), 65.5 (*C*H_2OSi), 46.6 (*C*HCH=CHCH=CH_2), 26.9 (SiC(*C*H_3)$_3$), 21.7 (Ar*C*H_3), 19.2 (Si*C*(CH_3)$_3$); ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 3385 br (O-H), 3071 m (C-H), 3047 m (C-H), 2998 m (C-H), 2961 m (C-H), 2931 m (C-H), 2891 m (C-H), 2857 m (C-H), 1363 w (OSO_2), 1177 s (OSO_2); ***m/z*** (ESI+) Found: $(M+Na)^+$, 573.2101; $C_{31}H_{38}NaO_5SSi$ requires *M*, 573.2107); $[\alpha]_D$ = +15.6 (*c* 0.41, DCM).

6.67 *(*S*)-Methyl 5-((*S,E*)-1-(*tert-*butyldiphenylsilyloxy)hexa-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylate* and **6.66** tert-*butyl((*S,E*)-2-((*R*)-oxiran-2-yl)hexa-3,5-dienyloxy)diphenylsilane*



Sodium hydride (98 mg, 60% dispersion in mineral oil, 2.45 mmol) was washed with pentane (3 × 10 mL) and dried; DMF (5 mL) was added, and the suspension allowed to stir at RT for 15 min. The flask was cooled to 0 °C, and dimethyl malonate (0.186 mL, 1.63 mmol, 3.0 eq.) added dropwise. Stirring was continued for 15 min, and a solution of (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-2-hydroxyhepta-4,6-dienyl-4-methyl- benzenesulfonate (300 mg, 0.54 mmol) in THF (5 mL) was added dropwise. The reaction was allowed to stir for a further 15 min, after which potassium iodide (271 mg, 1.63 mmol) was added and the reaction was heated at 80 °C for 15 h. The reaction was then cooled to ambient temperature, and quenched by cautious addition of saturated aqueous sodium hydrogen carbonate solution (10 mL). The layers were separated, and the aqueous layer washed with Et_2O (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), and solvent removed *in vacuo*. Purificaiton by flash column chromatography (1:1 PE 40-60:Et_2O) gave (*S*)-methyl 5-((*S*,*E*)-1-(*tert*-butyldiphenylsilyloxy)hexa-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylate as 1:1 mixture of diastereoisomers and as a clear colourless oil (127 mg, 0.265 mmol, 49%); *tert*-Butyl((*S*,*E*)-2-((*R*)-oxiran-2-yl)hexa-3,5-dienyloxy)diphenylsilane (92 mg, 0.243 mmol, 45%), was also isolated.

6.67 *(*S*)-Methyl 5-((*S,E*)-1-(*tert-*butyldiphenylsilyloxy)hexa-3,5-dien-2-yl)-2-oxotetrahydro furan-3-carboxylate:*

$\boldsymbol{R_f}$ = 0.42 (1:1 PE 40-60 : Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.68-7.63 (4H [d1], 4H [d2], m, Ar*H*), 7.47-7.38 (6H [d1], 6H [d2], m, Ar*H*), 6.35-6.25 (1H [d1], 1H [d2], m, CH=CHC*H*=CH_2), 6.19-6.11 (1H [d1], 1H [d2], m, CH=C*H*CH=CH_2), 5.56 (1H [d1], dd, *J* = 15.3 Hz, 9.1 Hz, C*H*=CHCH=CH_2), 5.45 (1H [d2], dd, *J* = 15.1 Hz, 9.4 Hz,

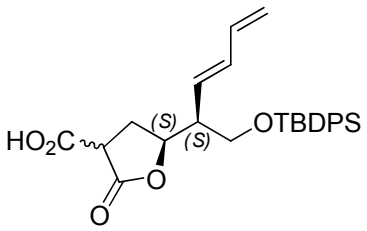
C*H*=CHCH=CH_2), 5.21-5.06 (3H [d1], 2H [d2], m, CH=CHCH=CH_2, CH_2C*H*O(C=O), 4.84 (1H [d2], dd, *J* = 10.4 Hz, 6.3 Hz, 4.4 Hz, CH_2C*H*O(C=O)), 3.84-3.79 (1H [d], m, SiOC*H*H), 3.81 (3H [d], s, CO_2*Me*), 3.80 (3H [d], s, CO_2*Me*), 3.77-3.63 (1H [d1], 2H [d2], m, SiOC*HH*, CH(CO_2Me)$_2$), 3.56 (1H [d2], dd, *J* = 9.9 Hz, 5.2 Hz, CH(CO_2Me)$_2$), 2.69 (1H [d1], ddd, *J* = 13.0 Hz, 7.5 Hz, 5.2 Hz, C*H*CH=CHCH=CH_2), 2.54-2.41 (2H [d1], 2H [d2], m, C*H*CH=CHCH=CH_2, C*HH*CH(CO_2Me)$_2$, 2.27 (1H [d2], ddd, *J* = 13.3 Hz, 9.9 Hz, 7.1 Hz, CH*H*CH(CO_2Me)$_2$), 1.07 (9H [d1], 9H [d2], s, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 171.9 (*C*(=O)OCH), 171.5 (*C*(=O)OCH), 168.2 (*C*(=O)OCH_3), 168.0 (*C*(=O)OCH_3), 136.5 (CH*C*H=CHCH=CH_2), 136.5 (CH*C*H=CHCH=CH_2), 136.3 (*Ar*), 136.1 (*Ar*), 135.6 (CH*C*H=CHCH=CH_2), 135.5 (CH*C*H=CHCH=CH_2), 133.3 (*Ar*), 133.3 (*Ar*), 133.1 (*Ar*), 129.8 (CHCH=*C*HCH=CH_2), 129.9 (CHCH=*C*HCH=CH_2), 127.9 (*Ar*), 127.8 (*Ar*), 127.7 (*Ar*), 127.3 (*Ar*), 117.8 (CHCH=CHCH=*C*H_2), 117.4 (CHCH=CHCH=*C*H_2), 78.7 (C(=O)O*C*H), 78.1 (C(=O)O*C*H), 64.1 (*C*H_2OSi), 63.9 (*C*H_2OSi), 53.2 (C(=O)O*C*H_3), 53.1 (C(=O)O*C*H_3), 50.1 (C(=O)C*H*C(=O)), 49.3 (C(=O)C*H*C(=O)), 47.1 (*C*HCH=CHCH=CH_2), 46.7 (*C*HCH=CHCH=CH_2), 30.0 (C(=O)CH*C*H_2CHO), 29.7 (C(=O)CH*C*H_2CHO), 26.9 (SiC(*C*H_3)$_3$), 26.9 (SiC(*C*H_3)$_3$), 19.3 (Si*C*(CH_3)$_3$), 19.3 (Si*C*(CH_3)$_3$); ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 3071 m (C-H), 3046 m (C-H), 2999 m (C-H), 2955 m (C-H), 2931 m (C-H), 2931 m (C-H), 2857 m (C-H), 1728 s (C=O), 1741 s (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 501.2058; $C_{28}H_{34}NaO_5Si$ requires *M*, 501.2068; $[\alpha]_D$ = +15.0 (*c* 0.85, DCM)

6.66 tert-*butyl((*S,E*)-2-((*R*)-oxiran-2-yl)hexa-3,5-dienyloxy)diphenylsilane:*

R_f = 0.51 (1:1 PE 40-60 : Et_2O); δ_H (400 MHz, $CDCl_3$) 7.69-7.66 (4H, m, Ar*H*), 7.48-7.38 (6H, m, Ar*H*), 6.31 (1H, dt, *J* = 16.6 Hz, 10.0 Hz, CH-C*H*=CH_2), 6.17 (1H, dd, *J*

= 15.4 Hz, 10.6 Hz, CH_2=CH-C*H*=CH), 5.58 (1H, dd, *J* = 15.3 Hz, 8.0 Hz, C*H*=CH-CH=CH_2), 5.16 (1H, dd, *J* = 16.6 Hz, 1.6 Hz, CH=C*H*H), 5.05 (1H, dd, *J* = 10.0 Hz, 1.6 Hz, CH=CH*H*), 3.78 (1H, dd, *J* = 10.2 Hz, 7.4 Hz, SiOC*H*H), 3.74 (1H, dd, *J* = 10.2 Hz, 5.9 Hz, SiOC*H*H), 3.12 (1H, ddd, *J* = 6.3 Hz, 4.0 Hz, 2.8 Hz, CH_2(-O-)C*H*CH), 2.80 (1H, dd, *J* = 5.0 Hz, 4.0 Hz, C*H*H(-O-)C*H*CH), 2.80 (1H, dd, *J* = 5.0 Hz, 2.7 Hz, C*H*H(-O-)C*H*CH), 2.30 (1H, m, CH=CH-C*H*-CH_2OSi), 1.08 (9H, s, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 136.8 (CH-*C*H=CH_2), 135.6 (*Ar*), 133.9 (CH_2=CH-C*H*=CH), 133.4 (*Ar*), 130.3 (C*H*=CH-CH=CH_2), 129.8 (*Ar*), 127.7 (*Ar*), 116.6 (CH=*C*H_2), 64.9 (SiO*C*H_2), 53.1 (CH_2(-O-)*C*HCH), 47.34 (CH=CH-C*H*-CH_2OSi), 46.26 (C*H*H(-O-)*C*HCH), 26.83 (SiC(*C*H_3)$_3$), 19.24 (Si*C*(CH_3)$_3$); ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 3072 m (C-H), 3048 w (C-H), 2998 w (C-H), 2957 m (C-H), 2930 m (C-H), 2982 w (C-H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 401.1907; $C_{25}H_{34}NaO_3Si$ requires *M*, 401.1913; $[\alpha]_D$ = +8.7 (*c* 0.24, $CDCl_3$).

6.51 *(*S*)-5-((*S,E*)-1-(*tert*-Butyldiphenylsilyloxy)hexa-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylic acid*



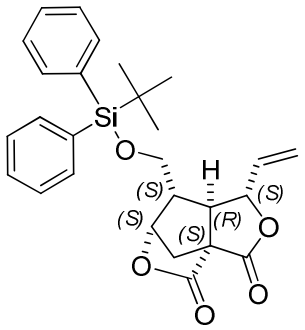
To a solution of (*S*)-methyl 5-((*S,E*)-1-(*tert*-butyldiphenylsilyloxy)hexa-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylate (72 mg, 0.15 mmol) in THF (10 mL) was added aqueous potassium hydroxide (2.5 mL, 10%), and the reaction mixture was strirred for 18 h. The reaction was then acidified by addition of pH 2 sulphate buffer

(15 mL). The mixture was then extracted with DCM (3 × 15 mL), the organic layers combined and dried ($MgSO_4$) and solvent removed *in vacuo* to leave (*S*)-5-((*S*,*E*)-1-(*tert*-butyldiphenylsilyloxy)hexa-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylic acid (1:1 mixture of diastereoisomers, 70 mg, 150 mmol, quant.) as a faint yellow oil which used directly in the next reaction.

δ_H (400 MHz, $CDCl_3$) 7.67-7.63 (4H [d1], 4H [d2], m, Ar*H*), 7.47-7.36 (6H [d1], 6H [d2], m, Ar*H*), 6.33-6.22 (1H [d1], 1H [d2], m, C*H*=CH_2), 6.18 (1H [d1], d, *J* = 14.8 Hz, C*H*CH=CH_2), 6.15 (1H, [d2], d, 15.0 Hz, C*H*CH=CH_2), 5.51 (1H [d1], dd, *J* = 15.4 Hz, 9.2 Hz, C*H*=CHCH=CH_2), 5.42 (1H [d2], d, *J* = 15.1 Hz, 9.2 Hz, C*H*=CHCH=CH_2), 5.22-5.07 (3H [d1], 2H [d2], m, CH=CH_2, CH_2C*H*O(C=O)), 4.9 (1H [d2], ddd, *J* = 10.2 Hz, 6.5 Hz, 4.5 Hz, CH_2C*H*O(C=O)), 3.84-3.78 (2H [d1], 1H [d2], m, SiOC*HH*), 3.75-3.66 (1H [d1], 1H[d2], SiOCH*H*, CH($CO_2Me)_2$), 3.58 (1H [d2], dd, *J* = 10.1 Hz, 6.0 Hz, CH($CO_2Me)_2$), 2.71 (1H [d1], ddd, *J* = 13.6 Hz, 6.9 Hz, 6.1 Hz, C*H*HCH($CO_2Me)_2$), 2.56-2.42 (1H [d2], 1H [d1], m, C*H*HCH($CO_2Me)_2$, C*H*CH=CHCH=CH_2), 2.32 (1H [d2], ddd, *J* = 13.5 Hz, 10.1 Hz, 6.4 Hz, C*H*CH=CHCH=CH_2), 1.07 (9H [d1], 9H, [d2], s, SiC(C$H_3)_3$); δ_C (100 MHz, $CDCl_3$) 172.3 (*C*(=O)OH), 172.2 (*C*(=O)OH), 171.4 (*C*(=O)OCH), 170.6 (*C*(=O)OCH), 136.6 (CH*C*H=CHCH=CH_2), 136.5 (CH*C*H=CHCH=CH_2), 136.4 (*Ar*), 136.3 (*Ar*), 136.2 (*Ar*), 135.6 (CH*C*H=CHCH=CH_2), 135.5 (CH*C*H=CHCH=CH_2), 134.8 (*Ar*), 133.3 (*Ar*), 133.2 (*Ar*), 133.0 (*Ar*), 129.9 (CHCH=*C*HCH=CH_2), 129.9 (CHCH=*C*HCH=CH_2), 127.9 (*Ar*), 127.8 (*Ar*), 127.4 (*Ar*), 127.0 (*Ar*), 118.1 (CHCH=CHCH=*C*H_2), 117.7 (CHCH=CHCH=*C*H_2), 78.9 (C(=O)O*C*H), 78.5 (C(=O)O*C*H), 64.0 (*C*H_2OSi), 63.8 (*C*H_2OSi), 50.1 (C(=O)C*H*C(=O)), 49.2 (C(=O)C*H*C(=O)), 46.7 (*C*HCH=CHCH=CH_2), 46.4 (*C*HCH=CHCH=CH_2), 29.6 (C(=O)CH*C*H_2CHO), 29.2 (C(=O)CH*C*H_2CHO), 26.9 (SiC(*C*$H_3)_3$), 26.9 (SiC(*C*$H_3)_3$),

19.3 (Si*C*$(CH_3)_3$); ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 3200 br (CO_2H), 3071 m (C-H), 3047 m (C-H), 3014 m (C-H), 2998 m (C-H), 2957 m (C-H), 2931 m (C-H), 2931 m (C-H), 2857 m (C-H), 1728 s (C=O), 1741 s (C=O); ***m/z*** (ESI+) Found: $[M+Na]^+$, 487.1911; $C_{27}H_{32}NaO_5Si$ requires *M*, 487.1917; $[\alpha]_D$ = +9.7 (*c* 1.15, DCM).

6.68 *(1*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-vinyl-3,8-dioxa-tricyclo[5.2.1.0^{1,5}]decane-2,9-dione*

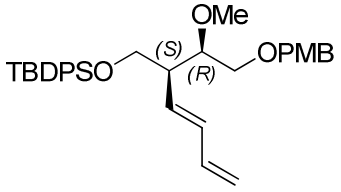


A solution of the (*S*)-5-((*S*,*E*)-1-(*tert*-butyldiphenylsilyloxy)hexa-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylic acid (73 mg, 0.157 mmol) in degassed acetonitrile (2 mL, 78.5 mmol L^{-1}) was prepared in a reaction carousel. Manganese(III) acetate (85 mg, 0.314 mmol) was added, along with copper(II) triflate (14 mg, 0.157 mmol). The reaction tube was degassed, and heated to reflux for 18h, after which the reaction was quenched by addition of water (4 mL). The mixture was acidified to pH = 2 with HCl (10 mL, 2 M) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by flash column chromatography (5:1 PE 40-60:Et_2O) gave (1*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-vinyl-3,8-dioxa-

tricyclo[5.2.1.01,5]decane-2,9-dione as a clear colourless oil (52 mg, 0.113 mmol, 72%);

$\boldsymbol{R_f}$ = 0.19 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.65-7.61 (4H, m, Ar*H*), 7.48-7.37 (6H, m, Ar*H*), 5.79 (1H, ddd, *J* = 17.1 Hz, 10.4 Hz, 6.7 Hz, C*H*=CH_2), 5.40 (1H, d, *J* = 17.1 Hz, CH=C*H*H (*trans*)), 5.28 (1H, d, *J* = 10.4 Hz, CH=CH*H* (*cis*)), 5.11 (1H, m, OC*H*CH_2), 4.75 (1H, dd, *J* = 9.6 Hz, 6.7 Hz, (C=O)OC*H*CHCH$_2$OSi), 3.72 (1H, dd, *J* = 10.4 Hz, 8.7 Hz, C*H*HOSi), 3.61 (1H, dd, *J* = 10.4 Hz, 6.9 Hz, C*H*HOSi), 2.61 (2H, m, C*H*CH_2OSi, C*H*HCO_2), 2.45 (1H, d, *J* = 10.9 Hz, C*H*HCO_2), 2.30 (1H, dd, *J* = 9.6 Hz, 4.7 Hz, C*H*CHCH=CH_2), 1.06 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.0 (*C*(=O)), 167.1 (*C*(=O)), 135.5 (*Ar*), 135.4 (*Ar*), 132.9 (*C*H=CH_2), 132.8 (*Ar*), 132.6 (*Ar*), 130.0 (*Ar*), 127.9 (*Ar*), 120.2 (CH=CH_2), 83.8 ((C=O)O*C*HCHCH$_2$OSi), 82.3 (O*C*HCH=CH_2), 62.2 (*C*H_2OSi), 56.6 (C(=O)*C*C(=O), 50.1 (*C*HCHCH=CH_2), 49.5 (*C*H_2CO_2), 40.7 (*C*HCH$_2$OSi), 26.8 (SiC(*C*H_3)$_3$), 19.2 (Si*C*(CH_3)$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3071 m (C-H), 3049 m (C-H), 2957 m (C-H), 2931 m (C-H), 2931 m (C-H), 2858 m (C-H), 1813 s (C=O), 1778 s (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 485.1762; $C_{27}H_{30}NaO_5Si$ requires *M*, 485.1755; $\boldsymbol{[\alpha]_D}$ = +13.5 (*c* 1.35, DCM).

6.77 tert-*Butyl((*S,E*)-2-((*R*)-1-methoxy-2-(4-methoxybenzyloxy)ethyl)hexa-3,5-dienyloxy)diphenylsilane*

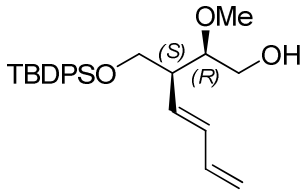


Sodium hydride (58 mg, 60% dispersion in mineral oil, 1.44 mmol) was washed with pentane (3 × 5 mL) and suspended in THF (5 mL). (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-(4-methoxy-benzyloxy)hepta-4,6-dien-2-ol (250 mg, 0.48 mmol) was added as a solution in THF (5 mL) and the mixture was stirred for 30 min. Methyl iodide (0.150 mL, 2.40 mmol) was then added slowly, and stirring was continued for 16 h.. The reaction was quenched with sat. aq. NH_4Cl solution (5 mL), and extracted with DCM (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash column chromatography (DCM) gave *tert*-butyl((*S*,*E*)-2-((*R*)-1-methoxy-2-(4-methoxybenzyloxy)ethyl)hexa-3,5-dienyloxy) diphenylsilane as a clear colourless oil (195 mg, 0.367 mmol, 77%);

$\boldsymbol{R_f}$ = 0.45 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.66 (4H, m, Ar*H*), 7.45-7.35 (6H, m, Ar*H*), 7.26 (2H, d, *J* = 7.3 Hz, Ar*H*), 6.88 (2H, d, *J* = 8.7 Hz, *PMB*), 6.26 (1H, dt, *J* = 17.0 Hz, 10.4 Hz, CH_2=C*H*-CH), 6.02 (1H, dd, *J* = 15.4 Hz, 10.4 Hz, CH_2=CH-C*H*=CH), 5.56 (1H, dd, *J* = 15.4 Hz, 9.3 Hz, C*H*=CHCH=CH_2), 5.07 (1H, d, *J* = 17.0 Hz, CH*H*=CH-CH), 4.98 (1H, d, *J* = 17.0, CH*H*=CH-CH), 4.49 (1H, d, *J* = 11.6 Hz, OC*H*HPMP), 4.44 (1H, d, *J* = 11.6 Hz, OCH*H*PMP), 3.82 (3H, s, ArOCH_3), 3.79 (2H, m, CH_2OSi), 3.60 (1H, dd, *J* = 9.9 Hz, 5.9 Hz, C*H*OMe), 3.51 (1H, dd, *J* = 10.0 Hz, 6.2 Hz, C*H*HOPMB), 3.46 (3H, s, OMe), 3.43 (1H, dd, *J* = 10.0 Hz, 5.2 Hz, C*H*HOPMB), 2.52 (1H, m, CH=CH-C*H*-CH_2OSi), 1.06 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 159.5 (*Ar*-OMe), 137.1 (CH*C*H=CHCH=CH_2), 135.6 (*Ar*), 134.8 (*Ar*), 134.14(CHCH=CH*C*H=CH_2), 133.7 (*Ar*), 130.9 (*Ar*), 129.6 (*Ar*), 129.2 (*Ar*), 127.6 (*Ar*), 115.7 (CHCH=CHCH=*C*H_2), 113.7 (*PMB-Ar*), 78.8 (*C*HOH), 72.9 (*C*H_2OPMB), 71.3 (*C*H_2Ar), 63.9 (*C*H_2OSi), 59.2 (OMe), 55.3 (OMe), 47.6 (*C*HCH=CHCH=CH_2), 26.9 (SiC(*C*H_3)$_3$), 19.3 (Si*C*(CH_3)$_3$); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 3071

m (C-H), 3046 m (C-H), 2998 m (C-H), 2930 m (C-H), 2857 m (C-H), 1652 w (Ph), 1612 w (Ph); ***m/z*** (ESI+) Found: $(M+Na)^+$, 553.2745; $C_{27}H_{30}NaO_5Si$ requires *M*, 553.2750; $[\alpha]_D$ = +36.6 (*c* 0.3, DCM).

6.78 *(2*R,*3*S,E*)-3-((*tert-*Butyldiphenylsilyloxy)methyl)-2-methoxyhepta-4,6-dien-1-ol*

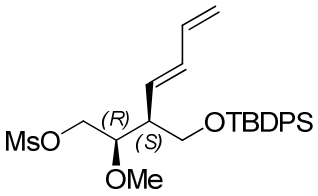


To a solution of *tert*-butyl((*S*,*E*)-2-((*R*)-1-methoxy-2-(4-methoxy benzyl oxy) ethyl) hexa-3,5-dienyloxy)diphenylsilane (175 g, 0.329 mmol) in DCM (10 mL) was added a solution of boron trichloride-dimethylsulphide complex (0.5 mL, 2.0 M, 0.99 mmol). After 5 min, the reaction was quenched rapidly by pouring the solution onto rapidly stirred saturated aqueous sodium hydrogen carbonate solution (20 mL). THF (10 mL) was added immediately, and the biphasic mixture allowed to stir for 30 min. The mixture was extracted with DCM (3 × 30 mL), the combined extracts dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by flash column chromatography (10:1 DCM:Et_2O) gave (2*R*,3*S*,E)-3-((*tert*-butyldiphenylsilyloxy)methyl)-2-methoxyhepta-4,6-dien-1-ol as a clear colourless oil (115 mg, 0.279 mmol, 85%);

R_f = 0.41 (10:1 DCM:Et_2O); δ_H (400 MHz, $CDCl_3$) 7.68-7.64 (4H, m, Ar*H*), 7.46-7.37 (6H, m, Ar*H*), 6.28 (1H, dt, *J* = 17.0 Hz, 10.2 Hz, CH_2=C*H*-CH), 6.07 (1H, dd, *J* = 15.4 Hz, 10.3 Hz, CH_2=CH-C*H*=CH), 5.56 (1H, dd, *J* = 15.4 Hz, 9.0 Hz,

C*H*=CHCH=CH_2), 5.10 (1H, d, *J* = 17.0 Hz, CH_2=C*H*-CH), 5.01 (1H, d, *J* = 10.2 Hz, CH_2=C*H*-CH), 3.76 (1H, dd, *J* = 10.2 Hz, 7.5 Hz, CH*H*OSi), 3.66 (1H, dd, *J* = 10.2 Hz, 5.3 Hz, C*H*HOSi), 3.66 (2H, m, CH_2OH), 3.60 (1H, m, C*H*OMe), 3.45 (3H, s, OMe), 2.49 (1H, ddd, *J* = 12.8 Hz, 9.1 Hz, 4.7 Hz, CH=CH-C*H*-CH_2OSi), 2.01 (1H, dd, *J* = 5.9 Hz, 4.7 Hz, O*H*), 1.06 (9H, s, SiC(CH_3)$_3$); **δ_C** (100 MHz, $CDCl_3$) 136.9 (CH*C*H=CHCH=CH_2), 136.9 (*Ar*), 135.6 (*Ar*), 133.9 (CHCH=CH*C*H=CH_2), 133.4 (*Ar)*, 131.3 (*Ar*), 129.7 (CHCH=*C*HCH=CH_2), 127.7 (*Ar*), 127.6 (*Ar*), 116.2 (CHCH=CHCH=*C*H_2), 81.2 (*C*HOMe), 63.9 (*C*H_2OH), 63.1 (*C*H_2OSi), 59.0 (OMe), 47.1 (*C*HCH=CHCH=CH_2), 26.9 (SiC(*C*H_3)$_3$), 19.3 (Si*C*(CH_3)$_3$); ***ν_{max}*/cm^{-1}** ($CDCl_3$) 3726 (O-H), 3071 (C-H), 3047 (C-H), 2998 (C-H), 2931 (C-H), 2890 (C-H), 2858 (C-H); ***m/z*** (ESI+) Found: $(M+Na)^+$, 433.2159; $C_{25}H_{34}NaO_3Si$ requires *M*, 433.2169; **$[\alpha]_D$** = +13.0 (*c* 0.3, DCM).

6.74 *(2R,3S,E)-3-((*tert-*Butyldiphenylsilyloxy)methyl)-2-methoxyhepta-4,6-dienyl methanesulfonate*

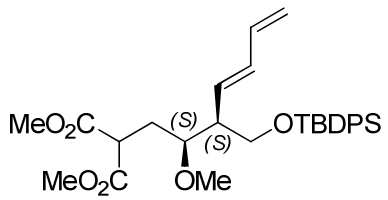


A solution of (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)hepta-4,6-diene-1,2-diol (312 mg, 0.76 mmol) in DCM (20 mL) was cooled to 0 °C. Methanesulfonyl chloride (117 mL, 1.52 mmol) and triethylamine (0.210 mL, 1.52 mmol) were added, and stirring was continued for 15 min at 0 °C and 15 h at RT. The reaction was

quenched by addition of aqueous HCl (10 mL, 1.0 M), and the mixture extracted with DCM (3 × 50 mL). The combined extracts were dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by flash column chromatography (10:1 DCM:Et_2O) gave (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-2-methoxyhepta-4,6-dienyl methanesulfonate as a clear colourless oil (319 mg, 0.653 mmol, 86%);

$\boldsymbol{R_f}$ = 0.40 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.68-7.64 (4H, m, Ar*H*), 7.47-7.37 (6H, m, Ar*H*), 6.28 (1H, dt, *J* = 16.9 Hz, 10.4 Hz, CH_2=C*H*-CH), 6.04 (1H, dd, *J* = 15.4 Hz, 10.6 Hz, CH_2=CH-C*H*=CH), 5.55 (1H, dd, *J* = 15.4 Hz, 9.4 Hz, C*H*=CHCH=CH_2), 5.12 (1H, d, *J* = 15.4 Hz, C*H*H=C*H*-CH), 5.03 (1H, d, *J* = 10.1 Hz, CH*H*=C*H*-CH), 4.24 (1H, dd, *J* = 10.7 Hz, 6.8 Hz, CH*H*OMs), 4.20 (1H, dd, *J* = 10.7 Hz, 4.5 Hz, CH*H*OMs), 3.91 (1H, ddd, *J* = 7.5 Hz, 4.5 Hz, 3.2 Hz, C*H*OMe), 3.79 (1H, dd, *J* = 10.1 Hz, 8.6 Hz, CH*H*OSi), 3.62 (1H, dd, *J* = 10.1 Hz, 5.4 Hz, C*H*HOSi), 3.49 (3H, s, O*Me*), 3.01 (3H, s, O*Ms*), 2.45 (1H, m, CH=CH-C*H*-CH_2OSi), 1.08 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 136.5 (CH*C*H=CHCH=CH_2), 135.6 (*Ar*), 135.0 (*Ar*), 133.4 (CHCH=CH*C*H=CH_2), 133.3 (*Ar*), 129.8 (*Ar*), 129.8 (CHCH=*C*HCH=CH_2), 129.1 (*Ar*), 127.8 (*Ar*), 116.9 (CHCH=CHCH=*C*H_2), 77.8 (*C*HOMe), 71.0 (*C*H_2OMs), 63.4 (C*H*$_2$OSi), 59.7 (O*Ms*), 47.3 (CH=CH-*C*H-CH_2OSi), 37.4 (O*Me*), 26.9 (SiC(*C*H_3)$_3$), 19.3 (Si*C*(CH_3)$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3071 m (C-H), 2932 m (C-H), 2932 m (C-H), 2891 m (C-H), 2858 m (C-H), 1359 m (OSO_2), 1177 m (OSO_2); ***m/z*** (ESI+) Found: $(M+Na)^+$, 511.1942; $C_{25}H_{34}NaO_3Si$ requires *M*, 511.1945; $\boldsymbol{[\alpha]_D}$ = +9.1 (*c* 0.53, DCM).

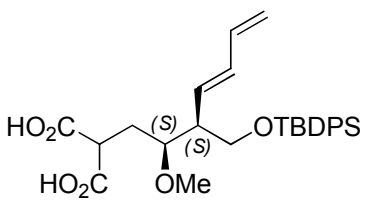
6.79 *Dimethyl 2-((2*S,*3*S,E*)-3-((*tert-*butyldiphenylsilyloxy)methyl)-2-methoxyhepta-4,6-dienyl)malonate*



Sodium hydride (80 mg, 60% dispersion in mineral oil, 1.96 mmol) was washed with pentane (3 × 10 mL) and dried; DMF (8 mL) was added, and the suspension allowed to stir at RT for 15 min. The flask was cooled to 0 °C, and dimethyl malonate (0.232 mL, 1.96 mmol) added dropwise. The reaction mixture was stirred for a further 15 min and then a solution of (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-2-methoxyhepta-4,6-dienyl methanesulfonate (319 mg, 0.65 mmol) in THF (4 mL) was added dropwise. The reaction was allowed to stir for a further 15 min, after which time potassium iodide (325 mg, 1.96 mmol, 3 eq.) was added and the reaction was heated 80 °C for 15 h. The reaction was then cooled to ambient temperature, and quenched by cautious addition of saturated aqueous sodium hydrogen carbonate solution (5 mL). The layers were separated, and the aqueous layer washed with Et_2O (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by flash column chromatography (2:1 PE 40-60:Et_2O) was used to separate the product mixture, leaving dimethyl 2-((2*S*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-2-methoxyhepta-4,6-dienyl)malonate as a clear colourless oil (132 mg, 0.251 mmol, 39%), along with recovered starting material (153 mg, 0.313 mmol, 48%).

$\boldsymbol{R_f}$ = 0.36 (2:1 PE:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.68-7.63 (4H, m, Ar*H*), 7.46-7.36 (6H, m, Ar*H*), 6.28 (1H, dt, *J* = 17.0 Hz, 10.2 Hz, CH-C*H*=CH_2), 6.05 (1H, dd, *J* = 15.4 Hz, 10.2 Hz, CH=C*H*CH=CH_2), 5.57 (1H, dd, *J* = 15.4 Hz, 9.2 Hz, C*H*=CHCH=CH_2), 5.10 (1H, dd, *J* = 17.0 Hz, 1.5 Hz, C*H*H=CH-CH), 5.00 (1H, dd, *J* = 10.2 Hz, 1.4 Hz, CH*H*=CH-CH), 3.77 (1H, m, SiOC*H*H), 3.75 (3H, s, CO_2*Me*), 3.72 (3H, s, CO_2*Me*), 3.62 (1H, dd, *J* = 10.1 Hz, 6.1 Hz, SiOCH*H*), 3.57-3.51 (2H, m, C*H*OMe, C*H*($CO_2Me)_2$), 3.35 (1H, s, O*Me*), 2.38 (1H, m, CH=CH-C*H*-CH_2OSi), 2.10 (1H, ddd, *J* = 14.8 Hz, 8.8 Hz, 6.7 Hz, C*H*HCH($CO_2Me)_2$), 2.00 (1H, ddd, *J* = 14.8 Hz, 8.2 Hz, 4.5 Hz, C*H*HCH($CO_2Me)_2$), 1.05 (9H, s, SiC($CH_3)_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.9 (C(=O)), 169.8 (C(=O)), 137.0 (CH*C*H=CHCH=CH_2), 135.6 (*Ar*), 134.5 (*Ar*), 133.6 (*Ar*), (CHCH=CH*C*H=CH_2), 130.60 (CHCH=*C*HCH=CH_2), 129.7 (*Ar*), 129.7 (*Ar*), 127.7 (*Ar*), 116.1 (CHCH=CHCH=*C*H_2), 78.0 (*C*HOMe), 63.7 (CH_2OSi), 59.0 (OMe), 52.5 (*C*H($CO_2Me)_2$), 49.2 (CO_2*Me*), 48.8 (CH=CH-*C*H-CH_2OSi), 32.1 (*C*H_2CH(C=O)$_2$), 26.9 (SiC(*C*$H_3)_3$), 19.2 (Si*C*($CH_3)_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3071 m (C-H), 3046 m (C-H), 2999 m (C-H), 2953 m (C-H), 2931 m (C-H), 2891 m (C-H), 2857 m (C-H), 1754 s (C=O), 1737 s (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 547.2477; $C_{25}H_{34}NaO_3Si$ requires *M*, 547.2486; $\boldsymbol{[\alpha]_D}$ = +10.5 (*c* 0.38, DCM).

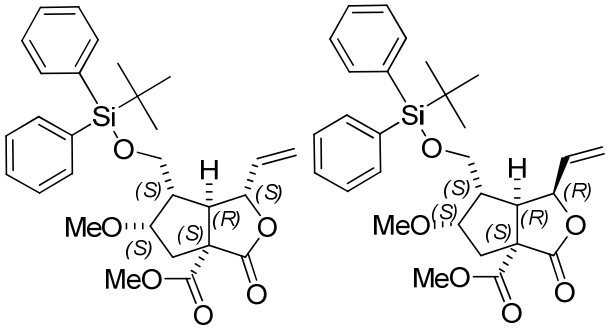
6.73 *2-((2*S,*3*S,E*)-3-((*tert-*Butyldiphenylsilyloxy)methyl)-2-methoxyhepta-4,6-dienyl)malonic acid*



To a solution of dimethyl 2-((2*S*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-2-methoxyhepta-4,6-dienyl)malonate (132 mg, 0.266 mmol) in THF (10 mL) was added aqueous potassium hydroxide (2.5 mL, 10%), and the reaction mixture was stirred for 18 h. The reaction acidified by addition of pH 2 sulphate buffer (15 mL) and extracted with DCM (3 × 15 mL). The organic layers combined and dried ($MgSO_4$) and solvent removed *in vacuo* to give 2-((2*S*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-2-methoxyhepta-4,6-dienyl)malonic acid (132 mg, 0.266 mmol, quant.) which was used in the next reaction without further purification;

δ_H (400 MHz, $CDCl_3$) 9.53 (CO_2H), 7.69-7.64 (4H, m, Ar*H*), 7.47-7.37 (6H, m, Ar*H*), 6.28 (1H, dt, *J* = 17.1 Hz, 10.1 Hz, CH_2=C*H*-CH), 6.05 (1H, dd, *J* = 15.4 Hz, 10.5 Hz, CH_2=CH-C*H*=CH), 5.58 (1H, dd, *J* = 15.4 Hz, 9.1 Hz, C*H*=CHCH=CH_2), 5.11 (1H, d, *J* = 17.1 Hz, C*H*H=C*H*-CH), 5.01 (1H, d, *J* = 10.1 Hz, CH*H*=C*H*-CH), 3.78 (1H, m, SiOC*H*H), 3.69-3.57 (3H, m, SiOCH*H*, C*H*OMe, C*H*($CO_2Me)_2$), 3.37 (3H, s, O*Me*), 2.38 (1H, m, CH=CH-C*H*-CH_2OSi), 2.20-2.00 (2H, m, C*H*$_2$CH($CO_2Me)_2$), 1.05 (9H, s, SiC(C*H*$_3)_3$); δ_C (100 MHz, $CDCl_3$) 174.7 (*C*O_2H), 174.6 (*C*O_2H), 136.9 (CH*C*H=CHCH=CH_2), 135.6 (*Ar*), 134.7 (*Ar*), 133.5 (CHCH=CH*C*H=CH_2), 133.4 (*Ar*), 130.3 (CHCH=*C*HCH=CH_2), 129.8 (*Ar*), 129.7 (*Ar*), 127.7 (*Ar*), 116.4 (CHCH=CHCH=*C*H_2), 78.2 (*C*HOMe), 63.6 (*C*H_2OTBDPS), 59.2 (CHO*Me*), 52.8 (*C*H($CO_2H)_2$), 49.1 (*C*HCH=CHCH=*C*H_2) 48.8, 32.2 (*C*H_2CH($CO_2H)_2$), 26.8 (C(*C*$H_3)_3$), 26.8 (*C*$(CH_3)_3$); ν_{max}/**cm**$^{-1}$ ($CDCl_3$) 3072 m (C-H), 3048 m (C-H), 2961 m (C-H), 2930 m (C-H), 2856 m (C-H), 1757 s (C=O); ***m/z*** (ESI+) Found: $(M-H)^-$, 495.2208; $C_{28}H_{35}O_6Si$ requires *M*, 495.2203; $[\alpha]_D$ = +2.5 (*c* 1.68, DCM).

6.80 *(1*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-vinyl-3,8-dioxa-tricyclo[5.2.1.0^{1,5}]decane-2,9-dione* and **6.81** *(1*S*,4*R*,5*R*,6*S*,7*S*)-6-(*tert*-Butyl-diphenyl-silanyloxymethyl)-4-vinyl-3,8-dioxa-tricyclo[5.2.1.0^{1,5}]decane-2,9-dione*

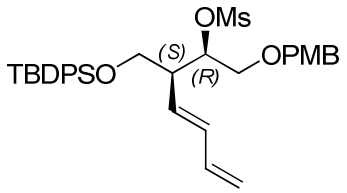


A solution of the (*S*)-5-((*S*,*E*)-1-(*tert*-butyldiphenylsilyloxy)hexa-3,5-dien-2-yl)-2-oxotetrahydrofuran-3-carboxylic acid (73 mg, 0.157 mmol) in degassed acetonitrile (2 mL, 78.5 mmol L^{-1}) was prepared in a reaction carousel. Manganese(III) acetate (85 mg, 0.314 mmol) was added, along with copper(II) triflate (14 mg, 0.157 mmol). The reaction tube was degassed, and heated to reflux for 18h, after which the reaction was quenched by addition of water (4 mL). The mixture was acidified to pH 2 with HCl (2 M) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and solvent removed *in vacuo*. The crude product mixture was dissolved in toluene:methanol (4:1, 10 mL), and cooled to 0 °C. TMS-diazomethane (0.159 mL, 2M, 0.317 mmol) was then added dropwise. A colour change from light yellow to grey-blue was observed. The reaction was then warmed to RT, and allowed to stir for 15 h. The light-yellow reaction mixture was quenched by addition of acetic acid at 0 °C. The solvent was removed *in vacuo*, leaving crude product as a yellow oil. Purification by flash column chromatography (5:1 PE 40-

60:Et_2O) to leave (1*S*,4*S*,5*R*,6*S*,7*S*)-6-(*tert*-butyl-diphenyl-silanyloxymethyl)-4-vinyl-3,8-dioxa-tricyclo[5.2.1.$0^{1,5}$]decane-2,9-dione as a clear colourless oil (34 mg, 0.084 mmol, 54%) as a 2.5:1 mixture of diastereoisomers.

$\boldsymbol{R_f}$ = 0.35 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ [major] (400 MHz, $CDCl_3$) 7.66-7.63 (4H, m, Ar*H*), 7.47-7.36 (6H, m, Ar*H*), 5.94 (1H, ddd, *J* = 17.1 Hz, 10.5 Hz, 6.4 Hz, C*H*=CH_2), 5.22 (1H, d, *J* = 17.1 Hz, CH=C*H*H), 5.17 (1H, d, *J* = 10.5 Hz, CH=CH*H*), 4.73 (1H, d, *J* = 6.4 Hz, C*H*CH=CH_2), 3.92 (1H, dd, *J* = 10.3 Hz, 6.7 Hz, SiOC*H*H), 3.84 (1H, td, *J* = 3.8 Hz, 2.3 Hz, C*H*OMe), 3.73 (3H, s, CO_2*Me*), 3.67 (1H, dd, *J* = 10.3 Hz, 7.3 Hz, SiOCH*H*), 3.20 (3H, s, OMe), 2.95 (1H, dd, *J* = 3.9 Hz, 2.1 Hz, CHC*H*CHCH=CH_2), 2.89 (1H, dd, *J* = 14.6 Hz, 2.1 Hz, C*H*HC(CO_2)$_2$), 2.18 (1H, m, SiOCH_2C*H*), 2.06 (1H, dd, *J* = 14.6 Hz, 4.0 Hz, CH*H*C(CO_2)$_2$), 1.04 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_H}$ [minor, selected resonances] (400 MHz, $CDCl_3$) 5.54 (1H, ddd, *J* = 17.2 Hz, 10.6 Hz, 6.8 Hz, C*H*=CH_2 [d2]), 4.01 (1H, m, C*H*HOSi [d2]), 3.78 (3H, s, CO_2*Me* [d2]), 3.35 (3H, s, O*Me*, [d2]), $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.6 (*C*=O), 170.0 (*C*=O), 135.9 (*C*=C), 135.5 (*Ar*), 131.4 (*Ar*), 129.8 (*Ar*), 127.8 (*Ar*), 127.6 (*Ar*), 119.2 (*Ar*), 117.5 (C=*C*), 85.0 (*C*HCH=CH_2), 82.3 (C*H*OMe), 62.0 (SiO*C*H_2), 56.4 (CHO*Me*), 54.5 (SiOCH_2*C*H) 53.1 (CO_2*Me*), 52.8 (CH*C*HCHCH=CH_2), 37.6 (*C*H_2(CO_2)$_2$), 26.8 (SiC(CH_3)$_3$), 26.8 (SiC(CH_3)$_3$), 19.1 (SiC(CH_3)$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ (DCM) 3078 w (C-H), 3049 w (C-H), 2954 m (C-H), 2932 m (C-H), 2892 m (C-H), 2858 m (C-H), 1778 s (C=O), 1744 s (C=O); ***m/z*** (ESI+) Found: $(M+Na)^+$, 531.2173; $C_{29}H_{36}NaO_6Si$ requires *M*, 531.2179; $\boldsymbol{[\alpha]_D}$ = +15.7 (*c* 1.7, DCM)

6.76 *(2*R,*3*S,E*)-3-((*tert-*Butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyloxy)hepta-4,6-dien-2-yl methanesulfonate*

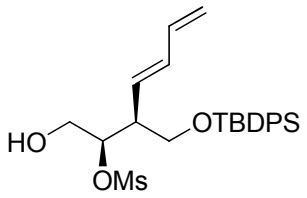


To a solution of (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-(4-methoxy-benzyloxy)hepta-4,6-dien-2-ol (500 mg, 0.96 mmol) in DCM (20 mL) at 0 °C was added methanesulfonyl chloride (0.224 mL, 2.90 mmol), followed by triethylamine (0.404 mL, 2.90 mmol). The solution was allowed to stir at 0 °C for 15 min, after which time it was allowed to stir overnight at RT. The reaction was quenched by addition of aqueous HCl (1M, 10 mL), and the biphasic system extracted with DCM (3 × 20 mL). The organic extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to give a crude residue of (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy) methyl)-1-(4-methoxybenzyloxy) hepta-4,6-dien-2-yl methane-sulfonate. The crude yellow oil was used directly in the next reaction without further purification (570 mg, quant.);

$\boldsymbol{R_f}$ = 0.41 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.67-7.63 (4H, m, Ar*H*), 7.46-7.36 (6H, m, Ar*H*), 7.23 (2H, d, *J* = 8.6 Hz, *PMB*), 6.87 (2H, d, *J* = 8.6 Hz, *PMB*), 6.25 (1H, dt, *J* = 16.9 Hz, 10.1 Hz, CH_2=C*H*-CH), 6.02 (1H, dd, *J* = 15.3 Hz, 10.5 Hz, CH_2=CH-C*H*=CH), 5.54 (1H, dd, *J* = 15.3 Hz, 9.3 Hz, C*H*=CHCH=CH_2), 5.18 (1H, dd, *J* = 7.2 Hz, 4.1 Hz, 3.5 Hz, C*H*OMs), 5.13 (1H, dd, *J* = 16.9 Hz, 1.4 Hz, C*H*H=C*H*-CH (*trans*)), 5.06 (1H, dd, *J* = 10.1 Hz, 1.4 Hz, C*H*H=C*H*-CH (*cis*)), 4.48 (1H, d, *J* = 11.5 Hz, OC*H*HPMP), 4.44 (1H, d, *J* = 11.5 Hz, OCH*H*PMP), 3.81 (3H, s, ArO*Me*), 3.76

(1H, dd, *J* = 10.4 Hz, 7.8 Hz, C*H*HOSi), 3.68 (1H, dd, *J* = 10.9 Hz, 7.4 Hz, C*H*HOPMB), 3.65 (1H, dd, *J* = 10.4 Hz, 5.2 Hz, CH*H*OSi) , 3.57 (1H, dd, *J* = 10.9 Hz, 4.3 Hz, CH*H*OPMB), 3.00 (3H, s, *Ms*), 2.59 (1H, m, CH=CH-C*H*-CH_2OSi), 1.07 (9H, s, SiC(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 136.4 (CH*C*H=CHCH=CH_2), 135.7 (*Ar*), 135.6 (*Ar*), 134.8 (*Ar*), 133.3 (CHCH=CH*C*H=CH_2), 129.8 (CHCH=*C*HCH=CH_2), 129.5 (*Ar*), 128.5 (*Ar*), 127.7 (*Ar*), 117.2 (CHCH=CHCH=*C*H_2), 113.8 (*PMB-Ar*), 80.8 (*C*HOMs), 72.8 (*C*H_2OPMB), 70.1 (*C*H_2Ar), 63.2 (*C*H_2OSi), 55.3 (O*Me*), 46.8 (*C*HCH=CHCH=CH_2), 38.5 (O*Ms*), 26.6 (SiC(*C*H_3)$_3$), 19.2 (Si*C*(CH_3)$_3$); ν_{max}/cm^{-1} ($CDCl_3$) 3071 w (C-H), 3046 w (C-H), 3015 w (C-H), 3000 w (C-H), 2956 m (C-H), 2932 m (C-H), 2892 m (C-H), 2858 m (C-H); ***m/z*** (ESI+) Found: $[M+Na]^+$, 617.2364; $C_{33}H_{42}NaO_6SSi$ requires *M*, 617.2369; $[\alpha]_D$ = +1.3 (*c* 7.4, DCM).

6.85 *(2R,3S,E)-3-((*tert*-Butyldiphenylsilyloxy)methyl)-1-hydroxyhepta-4,6-dien-2-yl methanesulfonate*

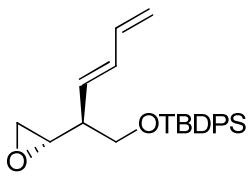


To a solution of (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyloxy)hepta-4,6-dien-2-yl methanesulfonate (570 mg, 0.96 mmol) in DCM (20 mL) was added a solution of boron trichloride-dimethylsulphide complex (1.92 mL, 2.0 M, 0.99 mmol). After 5 min, the reaction was quenched by pouring the solution onto rapidly stirred saturated aqueous sodium hydrogen carbonate solution (20 mL). THF (10 mL) was added immediately, and the biphasic mixture allowed to stir for 30 min. The mixture was then extracted with DCM (3 × 30 mL), the

combined extracts dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by flash column chromatography (10:1 DCM:Et_2O) to leave (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-hydroxyhepta -4,6 –dien -2-yl methanesulfonate as a clear colourless oil (275 mg, 0.58 mmol, 60%);

$\boldsymbol{R_f}$ = 0.36 (10:1 DCM:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.67-7.63 (4H, m, Ar*H*), 7.48-7.38 (6H, m, Ar*H*), 6.25 (1H, dt, *J* = 17.0 Hz, 10.3 Hz, CH_2=C*H*-CH), 6.03 (1H, dd, *J* = 15.2 Hz, 10.5 Hz, CH_2=CH-C*H*=CH), 5.53 (1H, dd, *J* = 15.2 Hz, 9.3 Hz, C*H*=CHCH=CH_2), 5.15 (1H, d, *J* = 17.0 Hz, C*H*H=C*H*-CH (*cis*)), 5.06 (1H, d, *J* = 10.3 Hz, C*H*H=C*H*-CH (*trans*)), 5.06 (1H, m, C*H*OMs), 3.85 (1H, dd, *J* = 12.7 Hz, 6.7 Hz, C*H*HOH), 3.78 (1H, dd, *J* = 12.7 Hz, 3.7 Hz, C*H*HOH), 3.73 (1H, dd, *J* = 10.6 Hz, 7.8 Hz, C*H*HOSi), 3.67 (1H, dd, *J* = 10.6 Hz, 5.1 Hz), 3.05 (3H, s, *Ms*), 2.58 (1H, m, CH=CHC*H*CH_2OSi), 1.08 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (400 MHz, $CDCl_3$) 136.2 (CH*C*H=CHCH=CH_2), 135.6 (*Ar*), 135.5 (*Ar*), 135.4 (*Ar*) 130.0 (CHCH=CH*C*H=CH_2), 129.9 (*Ar*), 128.2 (CHCH=*C*HCH=CH_2), 127.8 (*Ar*), 117.6 (CHCH=CHCH=*C*H_2), 83.1 (*C*HOMs), 63.8 (*C*H_2O), 63.3 (*C*H_2O), 46.8 (*C*HCH=CHCH=CH_2), 38.3 (O*Ms*), 26.9 (SiC(*C*H_3)$_3$), 19.2 (Si*C*(CH_3)$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3530 m (O-H), 3071 m (C-H), 3046 m (C-H), 2956 m (C-H), 2932 m (C-H), 2989 m (C-H), 2858 m (C-H), 1346 m (OSO_2), 1174 m (OSO_2); ***m/z*** (ESI+) Found: $(M+Na)^+$, 497.1784; $C_{25}H_{34}NaO_3Si$ requires *M*, 497.1788; $\boldsymbol{[\alpha]_D}$ = +3.3 (*c* 0.27, DCM).

6.75 tert-*Butyl((*S,E*)-2-((*S*)-oxiran-2-yl)hexa-3,5-dienyloxy)diphenylsilane*



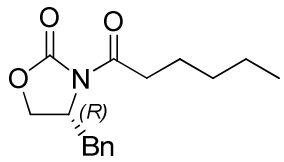
A suspension of washed (3 x 10 mL pentane) sodium hydride (46 mg, 1.16 mmols, 2.0 eq.) was prepared in THF (10 mL). After cooling to 0 °C, a solution of (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-hydroxyhepta-4,6-dien-2-yl methanesulfonate (275 mg, 0.58 mmols) in THF (10 mL) was added dropwise. The solution was then allowed to warm to RT, and left to stir for 16 hours.

The reaction was quenched by addition of sat. aq. NH_4Cl (10 mL), and the mixture extracted with DCM (3 x 20 mL). The organic extracts were combined, dried ($MgSO_4$) and solvent removed *in vacuo* to leave a crude residue, which was further purified by flash column chromatography to leave (10:1 DCM:Et_2O) to leave *tert*-butyl((*S*,*E*)-2-((*S*)-oxiran-2-yl)hexa-3,5-dienyloxy)diphenylsilane at a clear, colourless oil (230 mg, 0.60 mmols, quant.)

$\boldsymbol{R_f}$ = 0.48 (DCM); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.67-7.65 (4H, m, Ar*H*), 7.46-7.36 (6H, m, Ar*H*), 6.32 (1H, dt, *J* = 16.6 Hz, 10.5 Hz, CH_2=C*H*-CH), 6.14 (1H, dd, *J* = 15.3 Hz, 10.4 Hz, CH_2=CH-C*H*=CH), 5.69 (1H, dd, *J* = 15.3 Hz, 9.4 Hz, C*H*H=C*H*-CH), 5.16 (1H, d, *J* = 16.6 Hz, C*H*H=C*H*-CH (*cis*)), 5.05 (1H, d, *J* = 10.5 Hz, C*H*H=CH-CH (*trans*)), 3.88 (1H, dd, *J* = 9.9 Hz, 5.2 Hz, C*H*HOSi), 3.81 (1H, dd, *J* = 9.9 Hz, 4.7 Hz, C*H*HOSi), 3.12 (1H, ddd, *J* = 6.9 Hz, 4.0 Hz, 2.8 Hz, C*H*(O)CH_2), 2.80 (1H, dd, *J* = 5.0 Hz, 4.1 Hz, CH(O)CH*H*), 2.57 (1H, dd, *J* = 5.0 Hz, 2.8 Hz, CH(O)CH*H*), 2.16 (1H, m, CH=CH-C*H*-CH_2OSi), 1.08 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (400 MHz, $CDCl_3$) 136.9 (CH*C*H=CHCH=CH_2), 135.6 (*Ar*), 133.4 (*Ar*), 130.7 (CHCH=CH*C*H=CH_2), 129.7 (*Ar*), 127.7 (*Ar*), 116.6 (CHCH=CHCH=*C*H_2), 64.8 (CH_2OSi), 52.4 (*C*H(O)CH_2), 47.5 (CH(O)*C*H_2), 46.2 (*C*HCH=CHCH=CH_2), 26.8 (SiC(*C*H_3)$_3$), 19.3 (Si*C*(CH_3)$_3$); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3134 m (C-H), 3071 m (C-H), 2047 m (C-H), 2998 m (C-H), 2958

m (C-H), 2930 m (C-H), 2892 m (C-H), 2857 m (C-H), 1260 w (*epoxide*), 868 w (*epoxide*); ***m/z*** (ESI+) Found: $(M+Na)^+$, 401.1900; $C_{25}H_{34}NaO_3Si$ requires *M*, 401.1907; $[\alpha]_D$ = +10.5 (*c* 0.35, CH_2Cl_2).

6.59 (*R*)-4-Benzyl-3-hexanoyloxazolidin-2-one[128]

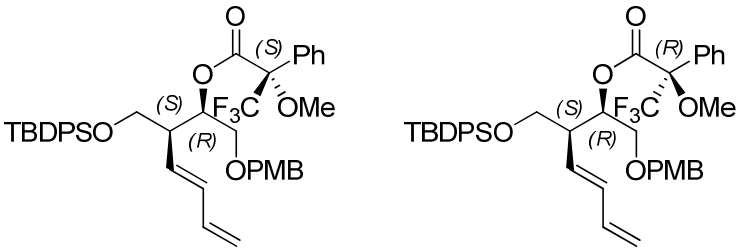


To a stirred solution of hexanoic acid acid (0.128 mL, 1.02 mmol) and triethylamine (0.177 mL, 1.28 mmol) in THF (10 mL) at -78 °C was added pivolyl chloride (0.132 mL, 1.28 mmol). The resulting slurry was left to stir for a further 15 min, and then warmed to 0 °C, stirred for 1 h and recooled to -78 °C. In a separate flask, a solution of (*R*)-4-benzyloxazolidin-2-one (0.2 g, 1.13 mmol) in THF (10 mL) was deprotonated with *n*-BuLi (0.7 mL, 1.6 M in hexanes, 1.13 mmol) at -78 °C. The metalated oxazolidinone was then added to the dienoate slurry *via* canula over 10 min, with the temperature at a constant -78 °C. The reaction mixture was stirred 20 min at -78 °C and then at RT for 14 h. The reaction was then quenched by addition of water, and the solvent removed *in vacuo*. The residue was taken up in DCM (20 mL), and washed with HCl (20 mL, 0.5 M), sodium bicarbonate (20 mL, sat.) and brine (20 mL). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. Purification by flash chromatography (DCM) gave (*R*)-4-benzyl-3-hexanoyloxazolidin-2-one (280 mg, 1.01 mmol, quant.) as a clear, colourless oil;

$\boldsymbol{R_f}$ = 0.61 (10:1 DCM:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.36-7.21 (5H, m, Ar*H*), 4.68 (1H, ddd, *J* = 10.6 Hz, 6.9 Hz, 3.3 Hz, $(C{=}O)_2NCH$), 4.19 (2H, m, $(C{=}O)OCH_2$), 3.31 (1H, dd, *J* = 3.4 Hz, 3.3 Hz, C*H*HPh), 2.94 (2H, m, $NC(=O)CH_2$), 2.77 (1H, dd, *J* = 13.4 Hz, 9.6 Hz, C*H*HPh) 1.71 (2H, m, $NC(=O)CH_2CH_2$), 1.38 (4H, m, $CH_2CH_2CH_2$), 0.93 (3H, t, *J* = 7.0 Hz, CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.5 ($NC(=O)CH_2$), 153.5 ($OC(=O)N$, 135.3 (*Ar*), 129.4 (*Ar*), 128.9 (*Ar*), 127.3 (*Ar*), 66.1 (OCH_2CHN), 55.2 (OCH_2CHN), 37.9 (CH_2Bn), 35.5 ($C(=O)CH_2$), 31.3 ($C(=O)CH_2CH_2CH_2$), 23.9 ($C(=O)CH_2CH_2CH_2$), 22.4 (CH_2CH_2), 13.9 (CH_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$), 3063 m (C-H), 3029 m (C-H), 2956 m (C-H), 2931 m (C-H) 2870 m (C-H), 1783 s (C=O, *oxazolidinone*), 1700 s (C=O, *amide*); $\boldsymbol{[\alpha]_D}$ = -69.7 (*c* 0.43, DCM).

6.64 *(*S*)-((2*R,*3*S,E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyloxy)hepta-4,6-dien-2-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate*

and **6.65** (R*)-((2*R,*3*S,E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyloxy)hepta-4,6-dien-2-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate*



To a solution of DMAP (2.3 mg, 0.0193 mmol) and DCC (12 mg, 0.0580 mmol) in DCM (1.5 mL) was added Mosher's acid ((*R*)- or (*S*)- 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid, 9 mg, 0.0387 mmol), followed by (2*R*,3*S*,*E*)-3-((*tert*-butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyloxy)hepta-4,6-dien-2-ol (10 mg,

0.0193 mmol). The reaction was allowed to stir for 15 h; after this time, water was added (10 ml) and the solution diluted with further DCM (10 mL). The biphasic mixture was separated, and aqueous layer washed with DCM (3 x 10 mL), recombining the organic extracts and drying ($MgSO_4$). The solvent was removed *in vacuo* to leave crude product, (14 mg, 0.0191 mmol, 99% in both cases).

6.64 *(S)-((2R,3S,E)-3-((tert-butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyloxy)hepta-4,6-dien-2-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate*

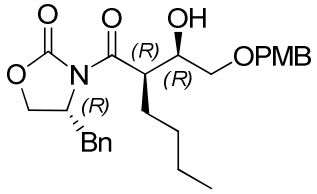
$\boldsymbol{R_f}$ = 0.45 (DCM); δ_H (400 MHz, $CDCl_3$) 7.64-7.60 (2H, m, Ar), 7.53-7.50 (2H, m, Ar), 7.5-7.29 (11H, m, Ar), 7.17 (2H, m, Ar), 6.84 (2H, m, Ar), 6.24 (1H, dt, *J* = 16.9 Hz, 10.3 Hz, CH_2=C*H*-CH), 6.03 (1H, dd, *J* = 15.3 Hz, 10.4 Hz, CH_2=CH-C*H*=CH), 5.75 (1H, dt, *J* = 6.5 Hz, 4.7 Hz, C*H*O(C=O), 5.51 (1H, dd, *J* = 15.3 Hz, 6.0 Hz, C*H*=CHCH=CH_2), 5.10 (1H, dd, *J* = 15.3 Hz, 6.0 Hz, CH=CHCH=C*H*H), 5.03 (2H, m, CH=CHCH=CH*H*), 4.37 (2H, s, OPMB *CH_2*), 3.81 (3H, s, OPMB *OMe*), 3.65 (1H, dd, *J* = 10.3 Hz, 7.3 Hz, SiOC*H*H), 3.59 (1H, dd, *J* = 10.3 Hz, 5.7 Hz, SiOC*H*H), 3.53 (1H, dd, *J* = 10.7 Hz, 6.7 Hz, C*H*HOPMB), 3.50 (1H, dd, *J* = 10.7 Hz, 4.7 Hz, C*H*HOPMB), 3.43 (3H, s, *OMe*), 2.68-2.61 (1H, m, CH=CH-C*H*-CH_2OSi), 1.06 (9H, s, SiC(C*H_3*)$_3$); δ_C (125 MHz, $CDCl_3$) 166.0 (*C*=O), 159.1 (*Ar*), 136.5 (CH-C*H*=CH_2), 135.6 (*Ar*), 135.2 (CH=C*H*-CH=CH_2), 133.3 (*Ar*), 133.2 (*Ar*), 132.2 (*Ar*), 129.9 (*Ar*), 129.7 (C*H*=CH-CH=CH_2), 129.4 (*Ar*), 129.4 (*Ar*), 129.2 (*Ar*), 128.2 (*Ar*), 127.7 (*Ar*), 116.9 (CH=C*H*-CH=*C*H_2), 113.7 (*Ar*), 73.9 (*C*HCH_2OPMB), 72.6 (O*C*H_2PMP), 69.2 (*C*H_2OPMB), 63.7 (*C*H_2OSi), 55.4 (O*Me*), 55.3 (O*Me*), 46.1 (*C*HCH_2OSi), 29.7 (*C*(C=O)(CF_3)(Ph)(OMe)), 26.8 (SiC(*C*H_3)$_3$), 19.2 (Si*C*(CH_3)$_3$); δ_F (377 MHz, $CDCl_3$) -71.45 (3F, s, CF_3); $\boldsymbol{\nu_{max}}$**/cm^{-1}** ($CDCl_3$) 3071 m (C-H), 3000 m (C-H), 2954 m (C-H), 2931 m (C-H), 2858 m (C-H), 1749 m (C=O), 1249 s (C-F), 1171 s (C-F),

1111 s, (C-F); ***m/z*** (ESI+) Found: $(M+Na)^+$, 755.2998; $C_{25}H_{34}NaO_3Si$ requires *M*, 755.2992; $[\alpha]_D$ = -2.3 (*c* 0.55, CH_2Cl_2).

6.65 (R*)-((2*R,*3*S,E*)-3-((*tert-*butyldiphenylsilyloxy)methyl)-1-(4-methoxybenzyloxy)hepta-4,6-dien-2-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate*

R_f = 0.45 (DCM); δ_H (400 MHz, $CDCl_3$) 7.64-7.59 (4H, m, Ar), 7.57-7.52 (2H, m, Ar), 7.46-7.30 (7H, m, Ar), 7.26-7.20 (4H, m, Ar), 6.88-6.84 (2H, m, Ar), 6.18 (1H, ddd, *J* = 16.9 Hz, 10.5 Hz, 10.3 Hz, CHC*H*=CH_2), 5.97 (1H, dd, *J* = 15.3 Hz, 10.5 Hz, CH=C*H*-CH=CH_2), 5.79 (1H, dt, *J* = 7.5 Hz, 4.1 Hz, C*H*O(C=O)), 5.41 (1H, dd, *J* = 15.3 Hz, 9.3 Hz, C*H*=C*H*-CH=CH_2), 5.08 (1H, dd, *J* = 16.9 Hz, 1.3 Hz, CHCH=C*H*H), 5.01 (2H, dd, *J* = 10.3 Hz, 1.3 Hz, CHCH=CH*H*), 4.48 (1H, d, *J* = 11.5 Hz, OPMB CH_2), 4.44 (1H, d, *J* = 11.5 Hz, OPMB CH_2), 3.81 (3H, s, OPMB *OMe*), 3.63 (1H, dd, *J* = 10.8 Hz, 7.6 Hz, C*H*HOPMB), 3.57 (1H, dd, *J* = 10.8 Hz, 4.0 Hz, CH*H*OPMB), 3.56-3.48 (2H, m, SiOCH_2), 3.50 (3H, s, *OMe*), 2.58-2.51 (1H, m, CH=CH-C*H*-CH_2OSi), 1.06 (9H, s, SiC(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 165.9 (*C*=O), 159.2 (*Ar*), 136.6 (CH-C*H*=CH_2), 135.6 (*Ar*), 135.1 (CH=C*H*-CH=CH_2), 133.4 (*Ar*), 133.3 (*Ar*), 129.71 (C*H*=CH-CH=CH_2), 129.3 (*Ar*), 128.2 (*Ar*), 127.7 (*Ar*), 127.4 (*Ar*), 116.8 (CH=C*H*-CH=*C*H_2), 113.8 (*Ar*), 73.6 (*C*HCH$_2$OPMB), 72.5 (O*C*H$_2$PMP), 69.6 (*C*H$_2$OPMB), 63.5 (*C*H$_2$OSi), 55.4 (O*Me*), 55.3 (O*Me*), 46.5 (*C*HCH$_2$OSi), 29.7 (*C*(C=O)(CF_3)(Ph)(OMe)), 26.8 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*(CH$_3$)$_3$); δ_F (377 MHz, $CDCl_3$) -71.32 (3F, s, CF_3); ν_{max}/**cm^{-1}** ($CDCl_3$) 3072 m (C-H), 3000 m (C-H), 2955 m (C-H), 2932 m (C-H), 2858 m (C-H), 1750 m (C=O), 1249 s (C-F), 1172 s (C-F), 1112 s, (C-F); ***m/z*** (ESI+) Found: $[M+Na]^+$, 755.2986; $C_{42}H_{47}F_3NaO_6Si$ requires *M*, 755.2992; $[\alpha]_D$ = +7.5 (*c* 0.65, CH_2Cl_2).

6.60 *(*R*)-4-Benzyl-3-((*R*)-2-((*R*)-1-hydroxy-2-(4-methoxybenzyloxy) ethyl)hexanoyl)oxazolidin-2-one*[127]



Method 1:

To a solution of (*R*)-4-benzyl-3-hexanoyloxazolidin-2-one (100 mg, 0.369 mmol) in DCM (20 mL) at -78 °C was added titanium(IV) chloride (36 μL, 0.332 mmol). The reaction mixture was stirred 15 min, and then Hünig's base (0.158 mL, 0.922 mmol) was added, and stirring continued for a further 1 h. After this time, NMP (35.6 μL, 0.369 mmol) and, after stirring for 10 min, freshly distilled 2-(4-methoxybenzyloxy)acetaldehyde (66 μL, 0.406 mmol) in DCM (1 mL). The reaction mixture was stirred at -78 °C for 2 h and then at -40 °C for 2 h. The reaction was quenched by addition of half-saturated NH_4Cl (5 mL) at 0 °C, and extracted with DCM (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash column chromatography (10:1 DCM:Et_2O) gave (*R*)-4-benzyl-3-((R)-2-((R)-1-hydroxy-2-(4 methoxybenzyloxy) ethyl)hexanoyl) oxazolidin-2-one as a colourless gum (138 mg, 0.305 mmol, 83%);

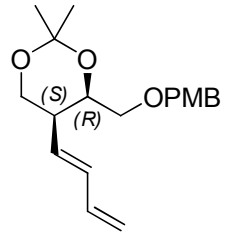
Method 2:

To a solution of (*R*)-4-benzyl-3-((*R*,*E*)-2-((*R*)-1-hydroxy-2-(4-methoxybenzyloxy) ethyl)hexa-3,5-dienoyl)oxazolidin-2-one (50 mg, 0.1107 mmol) in EtOH (10 mL) was

added palladium on carbon (10% wt, 1.2 mg, 0.0011 mmol) under nitrogen atmosphere. The atmosphere was then exchanged for hydrogen, and the reaction allowed to stir for 2 h. After this time, TLC analysis indicated completion of reaction, the hydrogen was removed and the reaction mixture filtered through Celite™. The solvent was removed *in vacuo* to give (*R*)-4-benzyl-3-((R)-2-((R)-1-hydroxy-2-(4 methoxybenzyloxy) ethyl)hexanoyl) oxazolidin-2-one as a colourless gum (50 mg, 0.1107 mmol, quantitative);

$\boldsymbol{R_f}$ = 0.40 (10:1 DCM:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.37-7.18 (7H, m, Ar*H*), 6.89-6.84 (2H, m, Ar*H*), 4.57 (1H, C*H*CH_2Ph), 4.47 (1H, d, *J* = 11.4 Hz, OCH*H*Ar), 4.47 (1H, d, *J* = 11.4 Hz, OC*H*HAr), 4.17 (1H, m, (C=O)C*H*), 4.08 (2H, m, C*H*OH, OC*H*HCHCH_2Ph), 3.98 (1H, m, OCH*H*CHCH_2Ph), 3.78 (3H, s, OMe), 3.57 (1H, dd, *J* = 9.7 Hz, 4.3 Hz, CH*H*OPMB), 3.51 (1H, dd, *J* = 9.7 Hz, 6.6 Hz, CH*H*OPMB), 3.32 (1H, dd, *J* = 13.3 Hz, 3.5 Hz, C*H*HPh), 2.67 (1H, dd, *J* = 13.3 Hz, 10.0 Hz, C*H*HPh), 2.53 (1H, 3.9 Hz, O*H*), 1.92-1.80 (1H, m, C*H*HCH_2CH_2CH_3), 1.77-1.67 (1H, m, CH*H*CH_2CH_2CH_3), 1.40-1.28 (4H, m, CH_2CH_2CH_3), 0.90 (3H, t, *J* = 6.7 Hz, CH_2CH_2CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.0 (N(*C*=O)CH_2), 159.3 (OPMB *Ar*), 153.3 (O(*C*=O)N), 135.3 (*Ar*), 130.0 (*Ar*), 129.5 (*Ar*), 129.4 (*Ar*), 128.9 (*Ar*), 127.3 (*Ar*), 113.8 (*Ar*), 73.0 (PMB *C*H_2), 71.8 (*C*H_2OPMB), 71.2 (*C*HOH), 65.84 (OCH_2CHCH_2Ph), 55.53 (*C*HCH_2Ph), 55.27 (PMB O*Me*), 45.48 ((C=O)*C*H), 38.05 (*C*H_2Ph), 29.22 (*C*H_2), 28.15 (*C*H_2CH_2CH_2CH_3), 22.88 (*C*H_2), 13.97 (CH_2*C*H_3); $\boldsymbol{\nu_{max}/cm^{-1}}$ ($CDCl_3$) 3473 br (O-H), 3965 m (C-H), 2930 m (C-H), 2867 m (C-H), 1778 s (C=O, *oxazolidinone*), 1693 s (C=O, *amide*); ***m/z*** (ESI+) Found: $(M+Na)^+$, 478.2198; $C_{26}H_{33}NNaO_6$ requires *M*, 478.2206; $\boldsymbol{[\alpha]_D}$ = -22.3 (*c* 0.43, DCM).

6.62 *(4*R,5S*)-5-((*E*)-Buta-1,3-dienyl)-4-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxane*



To a solution of (2*S*,3*R*)-2-((*E*)-buta-1,3-dienyl)-4-(4-methoxybenzyloxy)butane-1,3-diol (10 mg, 0.036 mmol) in acetone (4 mL) was added PPTS (6.8 mg, 0.036 mmol), followed by 2,2 dimethoxy propane (22 μL, 0.180 mmol). The solution was allowed to stir at RT for 12 h, after which time it was diluted with DCM (15 mL) and water (15 mL). The layers were separated, and the aqueous layer washed with DCM (2 × 15 mL). The organic extracts were combined, dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by flash column chromatography (DCM) gave (4*R*,5*S*)-5-((*E*)-buta-1,3-dienyl)-4-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxane as a clear, colourless oil (9.3 mg, 0.029 mmol, 81%);

$\boldsymbol{R_f}$ = 0.44 (10:1 DCM:Et_2O); δ_H (500 MHz, $CDCl_3$) 7.24 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.87 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.37 (1H, dt, *J* = 17.0 Hz, 9.9 Hz, CHCH=CHC*H*=CH_2), 6.11 (2H, m, CHC*H*=C*H*CH=CH_2), 5.14 (1H, dd, *J* = 17.0 Hz, 1.6 Hz, CHCH=CHCH=CH*H*), 5.04 (1H, dd, *J* = 10.1 Hz, 1.6 Hz, CHCH=CHCH=CH*H*), 4.50 (1H, d, *J* = 11.6 Hz, OC*H*HAr), 4.37 (1H, d, *J* = 11.6 Hz, OC*H*HAr), 4.23 (1H, td, *J* = 6.2 Hz, 2.6 Hz, C*H*CH_2OPMB), 4.18 (1H, dd, *J* = 11.5 Hz, 2.9 Hz, C*H*HCHCH), 3.81 (3H, s, PMB *OMe*), 3.71 (1H, dd, *J* = 11.5 Hz, 1.7 Hz, CH*H*CHCH), 3.37 (1H, dd, *J* = 9.6 Hz, 6.1 Hz, C*H*HOPMB), 3.30 (1H, dd, *J* = 9.6

Hz, 6.4 Hz, C*H*HOPMB), 2.16 (1H, m, CHCH=CHCH=CH_2), 1.50 (3H, s, C(CH_3)), 1.44 (3H, s, C(CH_3)); δ_C (125 MHz, $CDCl_3$) 159.2 (*Ar*), 137.2 (CHCH=CH*C*H=CH_2), 133.2 (*C*=C), 131.2 (*C*=C), 130.2 (*Ar)*, 129.4 (*Ar)*, 115.9 (CHCH=CHCH=*C*H_2), 113.7 (*Ar)*, 98.9 (*C*(CH_3)$_2$), 73.1 (O*C*H_2Ar), 71.2 (*C*H_2OPMB), 70.6 (*C*HCH$_2$OPMB), 65.3 (CH_2CHCH), 55.3 (OPMB *OMe*), 39.9 (*C*HCH=CHCH=CH_2), 29.6 (C(*C*H_3)), 19.0 (C(*C*H_3)); ν_{max}/cm^{-1} ($CDCl_3$) 3084 w (C-H), 2997 m (C-H), 2969 m (C-H), 2915 w (C-H), 2848 m (C-H), 2870 m (C-H), 2846 w (C-H), 2806 w (C-H), 1615 (C=C); *m/z* (ESI+) Found: $(M+Na)^+$, 341.1734; $C_{26}H_{33}NNaO_6$ requires *M*, 341.1729; $[\alpha]_D$ = +27.1 (*c* 0.46, CH_2Cl_2).

9 Bibliography

1 N-S. von Euler; *Arch. Exp. Path. Pharmak.* **1934**, *175*, 78

2 a) S. Bergström, J. Sjövall; *Acta Chem. Scand.* **1957**, *11*, 1086. b) S. Bergström, J. Sjövall; *Acta Chem. Scand.*, **1960**, *14*, 1693 – 1700. c) S. Bergström, J. Sjövall; *Acta Chem. Scand*. **1960**, *14*, 1701 – 1705. d) S. Bergström, R. Ryhase, B. Samuelsson, J. Sjövall; *Acta Chem. Scand.*, **1962**, 16, 501 – 502. e) S. Bergström, R. Ryhase, B. Samuelsson, J. Sjövall; *J. Biol. Chem.* **1963**, 238, 3555-3564.

3 For a review of therapeutically useful prostaglandin analogues, see: P. W. Collins, S. W. Djuric; *Chem. Re*v. **1993**, *93*, 1533

4 M.D. Mitchell; *Bailliere Clin. Obstet. Gynaecol.* **1992**, *6*, 687–706.

5 J.E. Brian Jr., S.A. Moore, F.M. Faraci; *Stroke*, **1998**, *29*, 2600–2606.

6 G. Haugen, I. Helland; *Gynecol. Obstet. Invest*. **2001**, *52*, 75–81

7 O. Hayaishi, H. Matsumura; *Adv. Neuroimmunol*. **1995**, *5*, 211–216.

8 C. D. Funk; *Science*, **2000**, *294*, 1871-1875

9 D. A. Six, E. A. Dennis; *Biochim. Biophys. Acta.*, **2000**, *1*, 1488

10 J. H. Evans, D. M. Spencer, A. Zweifach, C. C. Leslie; *J. Biol. Chem.*, **2001**, *276*, 30150

11 W. L. Smith, D. L. DeWitt, R. M. Garavito; *Annu. Rev. Biochem.*, **2000**, *69*, 145

12 S. Das, S. Chandrasekhar, J. S. Yadav, R. Gree; *Chem. Rev.* **2007**, *107*, 3286-3337.

13 a) E.J. Corey, I. Vlattas, N.H, Andersen, K. Harding; *J. Am. Chem. Soc*.,**1968**, *90*, 3247. b) E.J. Corey, K.B. Becker, R.K. Verma; *J. Am. Chem. Soc*., **1972**, *94*, 8616. c) E.J. Corey, H.E. Ensley, J.W. Suggs; *J. Am. Chem. Soc*., **1975**, *97*, 6908

14 Guidelines for a suitable retrosynthesis taken from K. C. Nicolaou, E. J. Sorensen; *Classics in Total Synthesis*, Wiley/VCH, New York, **1996**.

15 a) E. J. Corey, T. P. Loh; *J. Am. Chem. Soc.*, **1991**, *113*, 8966. b) E. J. Corey, T. P. Loh, T. D. Roper, M. D. Azimioara, M. C. Noe; *J. Am. Chem. Soc.*, **1992**, *114*, 8290

16 Y. Kobayashi, M. G. Murugesh, M. Nakano, E. Takahisa, S. B. Usmani, T. Ainai; *J. Org. Chem.* **2002**, *67*, 7110-7123

17 M. Ito, M. Matsuumi, M. G. Murugesh, Y. Kobayashi; *J. Org. Chem.* **2001**, *66*, 5881-5889

18 K.-I. Yamada, T. Arai, H. Sasai, M. Shibasaki; *J. Org. Chem*. **1998**; *63*, 3666-3672

19 L. E. Overman, C. B. Campbell; *J. Org. Chem*. **1976**; *41*, 3338-3340

20 The first acknowledged use of this transformation in a total synthesis of the prostaglandins was by Grieco *et al*. P. A. Grieco, T. Takigawa, S. L. Bongers, H. Tanaka; *J. Am. Chem. Soc.,* **1980**, *102*, 7587-7588

21 L. E. Overman, C. B. Campbell, F. M. Knoll; *J. Am. Chem. Soc.,* **1978**, *100*, 4822-4834

22 P. Bakuzis; O. O. S. Campos; M. L. F. Bakuzis; *J. Org. Chem.,* **1976**, *41*, 3261

23 G. Stork, N. H. Baine; *Tetrahedron Lett.* **1985**, *26*, 5927.

24 D. P. Curran, D. M. Rakiewicz; *J. Am. Chem. Soc.*, **1985**, *107*, 1448

25 B. Geise; *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, London, **1986.**

26 (a) J. E. Baldwin; *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, R. C. Thomas; *J. Chem. Soc., Chem. Commun.* **1976**, 736. (c) J. E. Baldwin, R. C. Thomas, L. Kruse, L. Silberman; *J. Org. Chem*, **1977**, *42*, 3846.

27 D. C. Spellmeyer, K. N. Houk; *J. Org. Chem.*, **1987**, *52*, 959-974

28 A. L. J. Beckwith, C. H. Schiesser; *Tetrahedron Lett.*, **1985**, *26*, 373-376

29 L. W. Hessel, C. Romers; *Recl. Trav. Chim. Pays-Bas*, **1969**, *88*, 545

30 Examples include: Fe: M. E. Holt, S. L. Holt, W. Tucker, R. O. Aspland, K. J. Wabou; *J. Am. Chem. Soc.* **1974**, *96*, 2621-2623. Mo: A. Bino, F. A. Cotton, Z. Dori; *J. Am. Chem. Soc*. **1981**, *103*, 243-244. Ru: F. A. Cotton, J. G.Norman, Jr.; *Inorg. Chim. Acta*, **1972**, *6*, 411-419.

31 J. B. Bush, H. Finkbeiner; *J. Am. Chem. Soc.*, **1968**, *90*, 5903-5905

32 E. I. Heiba, R. M. Dessau; *J. Am. Chem. Soc.*, **1968**, *90*, 5905-5906

33 W. E. Fristad, J. R. Peterson; *J. Org. Chem.*, **1985**, *50*, 10-18

34 B. B. Snider; In *Radicals In Organic Synthesis*, P. Renaud, M. P. Sibi, Eds. Wiley VCH, New York, **2001**; Vol 1, pp 198-216.

35 G. G. Melikyan; *Synthesis*, **1993**, 833-860

36 E. I. Heiba, R. M. Dessau; *J. Org. Chem.*, **1974**, *39*, 3456

37 B. B. Snider, J. J. Patricia, S. A. Kates; *J. Org. Chem.*, **1988**, *53*, 2137.

38 a) J. M. Kern, P Federlin; *Tetrahedron Lett.,* **1977**, *10*, 837-840. b) J. M. Kern, P. Federlin. Tetrahedron. **1978**, *34*, 661-670

39 E. I. Heiba, R. M. Dessau; *J. Am. Chem. Soc.*, **1970**, *93*, 524-527

40 E. I. Heiba, R. M. Dessau; *J. Am. Chem. Soc.*, **1972**, *94*, 2888-2889

41 B. B. Snider; *Chem. Rev.*, **1996**, *96*, 339-363

42 R. C. Weast; *Handbook of Chemistry and Physics*, CRC Press, Boca Ranton, Florida, **1981**

43 a) B. B. Snider, R. Mohan, S. A. Kates; *Tetrahedron Lett.,* **1987**, *28*, 841. b) R. Mohan, S. A. Kates, M. A. Dombroski, B. B. Snider; *Tetrahedron Lett.* **1987**, *28*, 845. c) J. E. Merritt, M. Sasson, S. A. Kates, B. B. Snider; *Tet. Lett.* **1988**, *29*, 5209. d) S. A. Kates, M. A. Dombroski, B. B. Snider; *J. Org. Chem.*, **1990**, *55*, 2427. e) M. A. Dombroski, S. A. Kates, B. B. Snider; *J. Am. Chem. Soc.*, **1990**, *112*, 2759. f) B. B. Snider, J. E. Merritt; *Tetrahedron* **1991**, *47*, 8663. g) B. B. Snider, B. O. Buckman; *J. Org. Chem.*, **1992**, *57*, 322. h) B. B. Snider, Q. Zhang, M. A. Dombroski; *ibid*. **1992**, *57*, 4195. i) B. B. Snider, Q. Zhang; *Tetrahedron Lett.*, **1992**, *33*, 5921.

44 J. K. Kochi; In *Free Radicals Vol 1*. J. K. Kochi, Ed., Wiley/VCH, New York, **1973**, pp 549-623.

45 J. K. Kochi, R. V. Subramanian; *Inorganic Chemistry*, **1965**, *4*, 1527.

46 B. B. Snider, T. Kwon; *J. Org. Chem.*, **1990**, *55*, 1965-1968

47 (a) D. G. Hulcoop, H. M. Sheldrake, J. W. Burton; *Org. Biomol. Chem.*, **2004**, *2*, 965. (b) D. G. Hulcoop, J. W. Burton; *Chem. Commun*, **2005**, 4688.

48 D. G. Hulcoop; *Thesis*, Cambridge University, **2005**.

49 V. –H. Nguyen, H. Nishino; *Tetrahedron Lett.,* **2004**, *45*, 3373-3377.

50 B. B. Snider, J. R. Duvall; *Org. Lett.* **2004**, *6*, 1265-1268

51 B. B. Snider; T. Kwon; *J. Org. Chem.*, **1991**, *56*, 5544-5553

52 (a) T. Katsuki, K. B. Sharpless; *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976. (b) S. S, Woodard, M. G. Finn, K. B. Sharpless; *J. Am. Chem. Soc.* **1991**, *113*, 106-113. (c) For reviews of the Sharpless asymmetric epoxidation, see: R. A. Johnson, K.

B. Sharpless; *Comp. Org. Syn.* **1991**, *7*, 389-436 and (d) A. Pfenninger; *Synthesis*, **1986**, 89-116.

53 M. Sasaki, K. Tanino, M. Miyashita; *Org. Lett.*, **2001**, *3*, 1765-1767.

54 (a) N. Miyaura, K. Yamada, A. Suzuki; *Tetrahedron Lett.* **1979**, 3437 (b) For a review of the Suzuki coupling, see: N. Miyaura, A. Suzuki; *Chem. Rev.* **1995**, *95*, 2457-2483.

55 (a) L. E. Overman; *J. Am. Chem. Soc.* **1974**, *96*. 597. (b) L. E. Overman, *J. Am. Chem. Soc.* **1976**, *98*. 2901.

56 P. G McDougal, J. G. Rico, Y.-I. Oh, B. D. Condon; *J. Org. Chem.* **1986**, *51*, 3388.

57 (a) K. Kondo, F. Mori; *Chemisty Lett.* **1974**, 741. (b) J. S. Sabol, G. A. Flynn, D. Friedrich, E. W. Huber; *Tetrahedron Lett.* **1997**, *38*, 3687.

58 S. Mahboobi, K. Bernauer; *Helv. Chim. Acta.* **1988**, *71*, 2034.

59 D. G. Hall, R. Mueller, P. Deslongchamps. *Tetrahedron. Lett.* **1992**, *33*, 5221.

60 A. B. Smith, S. S.-Y. Chen, F. C. Nelson, J. M. Reichert, B. A. Salvatore; *J. Am. Chem. Soc.* **1995**, *117*, 12013.

61 M. T. Crimmins, D. G. Washburn; *Tetrahedron Lett.*, **1998**, 7487-7490.

62 K. Omura, D. Swern; *Tetrahedron*, **1978**, *34*, 1651.

63 A. J. Mancuso, D. Swern; *Synthesis*, **1981**, 165-185.

64 a) C. Y. Qian, T. Yamada, H. Nishino, K. Kurosawa; *Bull. Chem. Soc. Jap.,* **1992**, *65*, 1371-1378. b) S. Tategami, T. Yamada, H. Nishino, J. D. Korp, K. Kurosawa; *Tetrahedron Lett.*, **1990**, *31*, 6371-6374.

65 B. B. Snider, B. Y. F. Wan, B. O. Buckman, B. M. Foxman; *J. Org. Chem.*, **1991**, *56*, 328-334.

66 a) M. T. Rahman, H. Nishino; *Org. Lett.*, **2003**, *5*, 2887-2890. b) R. Kumabe, H. Nishino; *Tetrahedron Lett.*, **2004**, *45*, 703-706. c) M. T. Rahman, H. Nishino; *Tetrahedron Lett.*, **2003**, *44*, 5225-5228.

67 J. C. Muir, G. Pattenden, T. Ye; *J. Chem. Soc., Perkin Trans. I*, **2002**, 2243-2250.

68 (a) D. W. Hart, J. Schwartz; *J. Am. Chem. Soc.*, **1974**, *96*, 8115 – 8116, (b) J. Schwartz, J. A. Labinger; *Angew. Chem. Int. Ed.*, **2003**, *15*, 333-340

69 J-M. Duffault, J. Einhorn, A. Alexakis; *Tetrahedron Lett.,* **1991**, *30*, 3701, C. Hamdouchi, C. Sanchez-Martinez; Synthesis, **2001**, 833-340

70 M. Freiberg, D. Meyerstein, *J. Chem. Soc., Faraday Trans. 1*, **1980**, *76*, 1825

71 L. A. Paquette, A. G. Schaefer, J. P. Springer, *Tetrahedron* **1987**, *43*, 5567

72 B. B. Snider, R. B. Smith, *Tetrahedron*; **2002**, *58*, 25-34.

73 Original procedure described by D. M. Hrabowchak, F. X. Smith. *Tetrahedron Lett*, **1983**, *24*, 4951.

74 E. Kühnel, D. D. P. Laffan, G. C. Lloyd-Jones, T. Martínez del Campo, I. R. Shepperson, J. L. Slaughter; *Angew. Chem. Int. Ed.,* **2007***, 46,* 7075-7078.

75 (a) K. Hirase, T. Iwahama, S. Sakaguchi, Y.Ishii; *J. Org. Chem.*, **2002**, *67*, 970-973. (b) K. Hirase, S. Sakaguchi, Y. Ishii; *J. Org. Chem.*, **2003**, *68*, 5974-5976.

76 M. T. Crimmins, A.C. DeBaillie; *J. Am. Chem. Soc.,* **2006**, *128*, 4936 -4937.

77 J. G. Hill, K. B. Sharpless, C. M. Exon, R. Regenye; *Org. Syn.*, *Annual Volume 63*, 66; *Collective Volume 7,* 461.

78 T. R. Hoye, C. S Jeffrey, F. Shao; *Nature Protocols*, **2007**, 2, 2451-2458

79 T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima, H. Nozaki; *Tetrahedron Lett*, **1982**, *23*, 3597-3600

80 M. Johnson, T. Nakata, Y. Kishi; *Tetrahedron Lett*, **1979**, *20*, 4343-4346

81 R. J. K. Taylor; *Organocopper Reagents*, Oxford University Press, Oxford, **1994**, 41-43

82 (a) H. C. Brown, G. Zweifel; *J. Am. Chem. Soc.*, **1961**, *83*, 3834-3840, (b) T. D. Parsons, M. B. Silverman, D. M. Ritter; *J. Am. Chem. Soc.*, **1957**, *79*, 5091-5098

83 H. C. Brown, T. Hamaoka, N. Ravindran; *J. Am. Chem. Soc.*, **1973**, *95*, 5786-5788

84 D. J. Comeskeya, B. J. Bunna, S. Fielder; *Tet. Lett.* **2004**, *45*, 7651-7654

85 D. A. Evans, W. C. Trenkle, J. Zhang, J. D. Burch; *Org. Lett.*, **2005**, *7*, 3335-3338, R. Barth, J. Mulzer; *Angew. Chem. Int. Ed.*; **2007**, *46*, 5791-5794.

86 B. Tse; *J. Am. Chem. Soc.*; **1996**, *118*, 7094-7100

87 K. Engstrom, R. Henry, L. S. Hollis, B. Kotecki, I. Marsden, Y. Pu, S. Wagaw, W. Wang; *J. Org. Chem.*; **2006**, *71*, 5369-5372

88 J. M. Takacs, M. R. Jaber, B. J. Swanson, S. J. Mehrman; *Tetrahedron: Asymmetry*, **1998**, *9*, 4313-4324.

89 D. A. Evans, J. Bartroli, T. L. Shih; *J. Am. Chem. Soc.*, **1981**, *103*, 2127-2129

90 D. A. Evans; *Aldrichimica Acta*, **1982**, *15*, 23-32

91 C. Schneider, M Rehfeuter; *Tetrahedron.*, **1997**, *53*, 133-144

92 A. B. Smith, R. J. Fox; *Org. Lett.*, **2004**, *6*, 1477-1480

93 R. K. Boeckman Jr., T. J. Clark, B. C. Shook; *Helv. Chim. Acta.*, **2002**, *85*, 4532-4560

94 (a) M. T. Crimmins, J. She; *Synlett*, **2004**, 1371-1374 (b) M. T. Crimmins, B. W. King, E. A. Tabet, K. Chaudhary; *J. Org. Chem.*, **2001**, *66*, 894-902.

95 (a) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa; *J. Org. Chem.*, **1991**, *56*, 1296-1298. (b) T. Kusumi, T. Hamada, M. O. Ishitsuka, I. Ohtani, H. Kakisawa; *J. Org. Chem.*, **1992**, *57*, 1033-1035.

96 M. S. Congreve, E. C. Davison, M-A. M. Fuhry, A. B. Holmes, A. N. Payne, R. A. Robinson, S. E. Ward; *Synlett*., **1993**, *9*, 663-665

97 D. Astruc; *New J. Chem.*, **2005**, *29*, 42-56

98 A. K. Chatterjee, T. L. Choi, D. P. Sanders, R. H. Grubbs; *J. Am. Chem. Soc.*, **2003**, *125*, 11360-11370

99 Initial Studies: L. E. Overman, F. M. Knoll; *Tetrahedron Lett.* **1979**, *20*, 321-324 Reviews: L. E. Overman; *Acc. Chem. Res.* **1980**, *13*, 218-224, L. E. Overman; *Angew. Chem. lnt. Ed.* **1984**, *23* 579-586.

100 B. M. Trost, J. M. Timko, J. L. Stanton; *J. Chem. Soc. Chem. Commun.*, **1978,** 436.

101 J. J. Tufariello, W. J. Kissel; *Tetrahedron Lett.* **1966**, *7*, 6145-6150

102 a) T. Mori, K. Takahashi, M. Kashiwabara, D. Uemura; *Tetrahedron Lett.* **1985**, *26*, 1073 - 1076; b) K. Takahashi, M. Kawabata, D. Uemura; *Tetrahedron Lett.* **1985**, *26*, 1077 - 1078.

103 (a) A. S. Kende, K. Kawamura, R. J. DeVita; *J. Am. Chem. Soc.* **1990**, *112*, 4070 – 4072 (b) E. O. Onyango, J. Tsurumoto, N. Imai, K. Takahashi, J. Ishihara, S. Hatakeyama; *Angew. Chem. Int. Ed.* **2007**, *119*, 6823 – 6825

104 R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical; *Angew. Chem. Int. Ed.* **2003**, *42*, 355-357.

105 (a) L. R. Reddy, P. Saravanan, E. J. Corey; *J. Am. Chem. Soc.*, **2004**, *126*, 6230-6231. (b) A. Endo, S. J. Danishefsky; *J. Am. Chem. Soc.*, **2005**, *127*, 8298-8299. (c) T. Ling, V. R. Macherla, R. R. Manam, K. A. McArthur, B. C. M. Potts; *Org. Lett.* **2007**, *9*, 2289-2292.

106 W.C. Still, M. Kahn and A. Mitra; *J. Org. Chem.*, 1978, 43, 2923-2925

107 D. D. Perin, W. L. F. Amerego and D. R. Perrin, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, **1980**

108 Y. Tang, Y. Zhang, M. Dai, T. Luo, L. Deng, J. Chen, Z. Yang, *Org. Lett.*, **2005**, *7*, 885 - 888

109 A. Christopher, D. Brandes, S. Kelly, T. Minehan; *Org. Lett*., **2006**, 8, 451-454.

110 I. Larrosa, M. I. Da Silva, P. M. Gómez, P. Hannen, E. Ko, S. R. Lenger, S. R. Linke, A. J. P. White, D. Wilton, A. G. M. Barrett; *J. Am. Chem. Soc.*, **2006**, *128*, 14042 -14043

111 D. J. Critcher, S. Connolly, M. Wills; *J. Org. Chem.* **1997**, *62*, 6638-6657

112 E. Wenkert, V. F. Ferreira, E. L. Michelotti, M. Tingoli; *J. Org. Chem.* **1985**, *50*, 719-721

113 J. M. Schomaker, V. R. Pulgam, B. Borhan; *J. Am. Chem. Soc.*, **2004**, *126*, 13600 - 13601

114 T. Zheng, R. S. Narayan, J. M. Schomaker, B. Borhan; *J. Am. Chem. Soc.*, **2005**, *127*, 6946 - 6947

115 J. Burton; University of Cambridge, unpublished work.

116 C. Hamdouchi, C. Sanchez-Martinez; *Synthesis*, **2001**, *6*, 833-841

117 G. Zweifel; *J. Am. Chem. Soc.* **1967**, *89*, 2753 - 2754

118 L. Crombie, A. Hobbs, M. A. Horsham; *Tet. Lett.*, **1987**, *28*, 4875-1987.

119 B. B. Snider, R. B. Smith; *Tetrahedron*, **2002***,* 25-34.

120 G. Fournet, G. Balme, J. Gore; *Tetrahedron*, **1990**, *46*, 7763-7774

121 K. T. Potts, T. Rochanapruk, S. J. Coats, L. Hadjiarapoglou, A. Padwa; J. *Org. Chem.* **1993**, *58*, 5040-5042

122 D. P. Curran, C. T. Chang; *J. Org. Chem.*, **1989**, *54*, 3140-3157

123 S. Röttger, H. Waldmann; *Eur. J. Org. Chem.*, **2006**, *9*, 2093-2099.

124 H. Corlay, W. B. Motherwell, A. M. K. Pennell, M. Shipman, A. M. Z. Slawin, D. J. Williams, P. Binger, M. Stepp; *Tetrahedron*, **1996**, *52*, 4883.

125 J. A. McCauley, K. Nagasawa, P. A. Lander, S. G. Mischke, M. A. Semones Y. Kishi, *J. Am. Chem. Soc.*, **1998**, *120*, 7647.

126 G. Zweifel, H.C. Brown, *Org. React.* **1963**, *13*, 1.

127 Adapted from the procedure in reference 95 (a).

128 J. L. Belelie, J. M. Chong. *J. Org. Chem.,* **2001**, *66*, 5552 -5555.