

Studies Towards the Total Synthesis of FR182877

**A thesis submitted by Frederick Woolf Goldberg in partial fulfilment of the
requirements for the degree of Doctor of Philosophy**

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Abstract

FR182877 is a novel hexacyclic natural product isolated from a soil sample, and is a promising anti-cancer lead. The structural highlight of FR182877 is a tricyclic motif that includes a highly strained bridgehead olefin and a vinylogous carbonate. Chapter one presents the isolation, biosynthesis and biological action of FR182877, then goes on to review the two total syntheses and three model studies that have been reported in the literature. Chapter two presents the model studies that we have undertaken to synthesise the strained tricycle. Specifically, we discuss our approach to the bicyclic tetrahydropyranopyranone unit, including a successful route which utilised an aldol reaction between a dihydropyran and a range of carbonyl compounds. We then go on to discuss our approaches to the tricyclic motif. Firstly, we investigated an intramolecular aldol reaction, although no degree of desired reaction was observed. Intramolecular radical cyclisation reactions have also been investigated, although only reduced uncyclised products were obtained. Two different ring-closing metathesis approaches are also presented, and have been supported by computational investigations to predict which cyclisations are likely to succeed. The first approach attempted to form a bridgehead olefin compound directly, but although some degree of cyclisation was observed this route was not pursued. An alternative ring-closing metathesis approach where the bridgehead carbons were saturated was successful, and showed an interesting dependence on stereochemistry that was supported by the computational investigations. However, our efforts to dehydrogenate the ring-closed products to give the bridgehead olefin failed as the resulting bridgehead olefin was found to be prone to ring-opening and epoxidation reactions. Chapter three reviews the findings presented in chapter two and discusses avenues for future research. Chapter 4 gives full experimental details and spectroscopic and physical data for all new compounds prepared.

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Finally, I would like to thank Alice and my family for everything.

Abbreviations

abs.	Absolute
Ac	Acetyl
AIBN	2,2'-Azobis- <i>iso</i> -butyronitrile
aq.	Aqueous
Ar	Aryl substituent
ⁿ Bu	<i>n</i> -Butyl
^t Bu	<i>tert</i> -Butyl
Bn	Benzyl
BTI	[Bis(trifluoroacetoxy)iodo]benzene
Bz	Benzoyl
¹³ C	Carbon 13
CI	Chemical ionisation
Conc ⁿ	Concentration
(±)-CSA	(±)-Camphor-10-sulfonic acid
Cy	Cyclohexyl
d	Doublet
Dabco TM	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets
DIBAL	Di- <i>iso</i> -butylaluminium hydride
DMAP	4- <i>N</i> -dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMSO	Dimethyl sulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereoisomeric ratio
dt	Doublet of triplets

EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide HCl salt
eq.	Equivalent(s)
Et	Ethyl
g	Gram(s)
GC	Gas chromatography
HF	Hartree-Fock
Hz	Hertz
IBX	<i>o</i> -Iodoxybenzoic acid
IC ₅₀	Concentration at which 50% of the test sample is incapacitated
im	Imidazole
ⁱ Pr	<i>iso</i> -Propyl
IR	Infrared
<i>J</i>	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminium hydride
LCMS	Liquid chromatography mass spectroscopy
LHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium di- <i>iso</i> -propylamide
m	Multiplet
M	Molar
<i>m</i> CPBA	<i>meta</i> -Chloroperbenzoic acid
Me	Methyl
mg	Milligram(s)
MHz	Megahertz
min(s)	Minute(s)
ml	Millilitre(s)
MM	Molecular mechanics
mmol	Millimole(s)
mol	Mole(s)
m.p.	Melting point
MPO	4-Methoxypyridine- <i>N</i> -oxide
MS	Mass spectrometry
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	<i>N</i> -Bromosuccinimide

NMO	4-Methylmorpholine <i>N</i> -oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NPSP	<i>N</i> -(Phenylseleno)phthalimide
PEG	Polyethylene glycol
petrol	Petroleum ether (40-60°C)
Ph	Phenyl
ppm	Part(s) per million
PPTS	Pyridinium <i>p</i> -toluenesulfonate
ⁱ Pr	<i>iso</i> -propyl
py	Pyridine
q	Quartet
qn	Quintet
RCM	Ring-closing metathesis
s	Singlet
sat.	Saturated
sol.	Solution
t	Triplet
T	Temperature
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBAI	Tetra- <i>n</i> -butylammonium iodide
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMS	Trimethylsilyl
Tf	Trifluoromethanesulfonyl
triflic	Trifluoromethanesulfonic
Ts	<i>p</i> -Toluenesulfonyl

Chapter 1: Introduction

1.1 Isolation and structure of FR182877

The natural product FR182877 **1** was first reported in 1996¹ by scientists at Fujisawa (Figure 1). It was isolated from the culture broth of *Streptomyces* sp. No. 9885, and was shown to have potent antitumour activities against murine ascitic tumour and murine solid tumour *in vivo*.² Note that **1** has also been designated as WS9885B in some reports.³

The structure and relative stereochemistry of FR182877 were solved through the application of a series of 2D NMR spectroscopy techniques and X-ray crystallographic analysis of an epoxidised derivative.⁴ The absolute stereochemistry in this report was assigned as shown for (+)-**1** (Figure 1) by Mosher ester analysis. However, the absolute stereochemistry was later corrected by scientists at Fujisawa⁵ as being as shown for (-)-**1**. The absolute stereochemistry was confirmed when Sorensen completed the total synthesis of (+)-**1** and showed that the optical rotation was opposite to that exhibited by the natural product.⁶ Further confirmation was obtained when Evans completed the total synthesis of (-)-**1**⁷ and showed it to have the same sign of optical rotation as the natural product, and when Sorensen then also completed the total synthesis of (-)-**1**.⁸

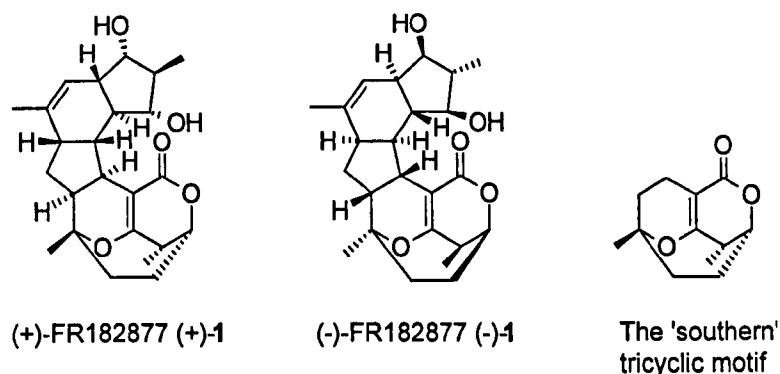


Figure 1

FR182877 has an unusual hexacyclic structure. Of particular interest is the 'southern' portion, which consists of a tricycle made up of a bicyclic tetrahydropyranopyranone bridged by a 7-membered ring. This tricyclic portion contains a highly strained bridgehead olefin. Indeed, this bridgehead olefin can be epoxidised by air, or more

efficiently by bubbling oxygen through a solution of **1**.⁴ Sorensen has also shown that a wide variety of nucleophiles undergo clean conjugate addition reactions with **1**, including amines, thiols and imidazole.⁸

1.2 Biosynthesis of FR182877

To date no studies investigating the biosynthesis of FR182877 have been conducted. However, a study has been published by Zeeck⁹ which investigated the biosynthesis of a closely related natural product, hexacyclinic acid **2** (Figure 2). In this report he used feeding experiments with ¹³C-labelled acetate and propionate and analysed the ¹³C spectra of the resulting hexacyclinic acid. His conclusion was that hexacyclinic acid is derived biosynthetically from a polyketide chain that incorporates 7 acetate and 4 propionate units as shown in Figure 2. Given the close structural similarities between **1** and **2** it seems plausible that FR182877 could be derived from a similar polyketide chain. Although Zeeck discussed how this polyketide chain could furnish hexacyclinic acid he provided no experimental evidence as to the nature of the biosynthetic pathway.

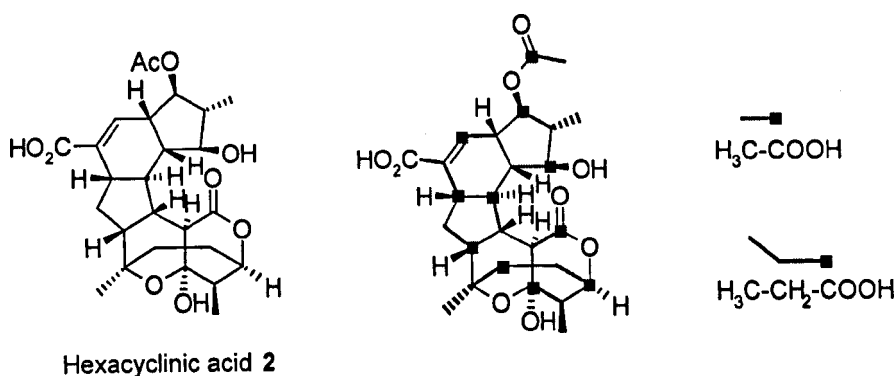


Figure 2: Labelling pattern of **2**, showing incorporation of acetate (red) and propionate (blue) units

Sorensen and Evans have discussed the possibility that FR182877 could be the biosynthetic product of two tandem Diels-Alder cyclisations,^{8,10,11} which could form the natural product from a macrocycle derived from a polyketide chain. They have both completed total syntheses of **1** by using this strategy (see section 1.4).

1.3 Biological properties of FR182877

1.3.1 Tubulin polymerisation and cancer

The anti-cancer properties of FR182877 have been attributed to the fact that it stabilises microtubules in the cell,¹² in a similar manner to paclitaxel (Taxol®).¹³ Microtubules are dynamic, polymeric structures consisting of filaments of ca. 240 Å diameter. They form a crucial component of the cytoskeleton, giving structure and form to the cell. They are also important for cell mobility, for transport of vesicles within the cell and for organization of organelles such as the Golgi and endoplasmic reticulum. More crucially for cancer chemotherapy, however, they form the mitotic spindles that separate the chromatids during mitosis.¹⁴

Microtubules are composed of tubulin polymer. Tubulin is a heterodimer, composed of α -tubulin and β -tubulin subunits (Figure 3). These heterodimers polymerise to form protofilaments, and then these protofilaments (usually 13, although between 12-15 have been observed) can aggregate to form microtubules. The microtubules thus have a polarity, and consequently the two ends can extend or contract (by polymerisation or depolymerisation) independently. Controlling the polymerisation and depolymerisation of these microtubules is crucial to the process of cell division, as the mitotic spindles that separate the sister chromatids need to be rapidly formed and broken down during mitosis. Both microtubule-stabilising and microtubule-destabilising drugs have been used successfully for cancer chemotherapy.^{15,16}

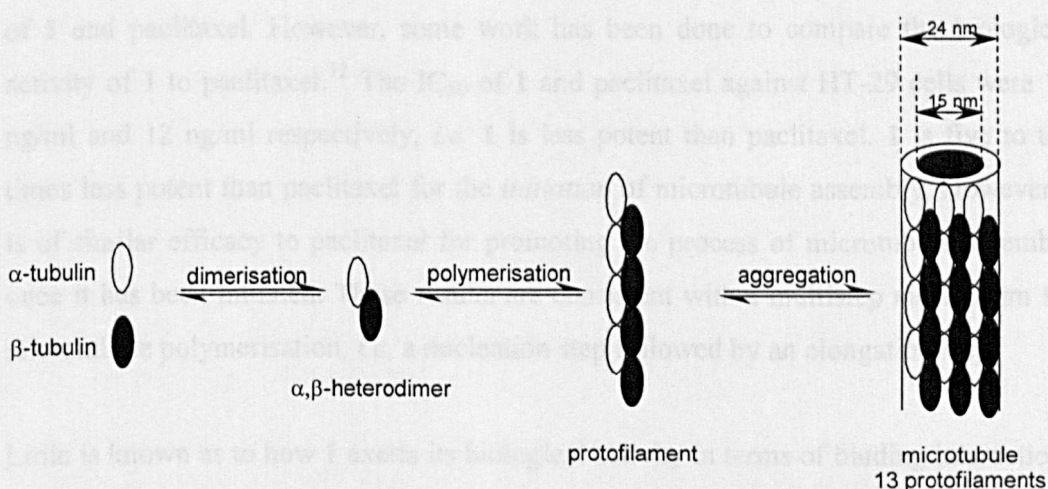


Figure 3: The formation of microtubules from tubulin polymerisation

Paclitaxel is a well-known example of a microtubule-stabilising drug, and unlike FR182877 many studies have been conducted to investigate its biological action.^{13,15,17} It is known that paclitaxel binds to microtubules *in vitro* with a stoichiometry of 1 mole of paclitaxel to 1 mole of tubulin. However, paclitaxel binds to free tubulin with little or no affinity and thus stabilises microtubules. This stabilisation disrupts the process of cell division, and eventually leads to apoptosis (programmed cell death). Paclitaxel is therefore selectively cytotoxic for cells that are undergoing rapid cell division, such as tumour cells.

It should be noted that this explanation of the cytotoxicity of paclitaxel and other microtubule-stabilising drugs such as FR182877 might be an oversimplification. It has been shown¹⁸ that paclitaxel can disrupt spindle organisation at a much lower concentration than it stabilises microtubule polymerisation, so providing another explanation for the observed mitotic arrest. There is also some evidence¹⁸ that paclitaxel causes microtubules to aggregate together, and thus it may be that the cytotoxicity of paclitaxel is enhanced by the formation of persistent microtubule bundles during interphase.

1.3.2 Biological properties of FR182877

FR182877 **1** has been shown to promote microtubule polymerisation *in vitro*, in a similar manner to paclitaxel. No studies have been reported to compare the binding sites of **1** and paclitaxel. However, some work has been done to compare the biological activity of **1** to paclitaxel.¹² The IC₅₀ of **1** and paclitaxel against HT-29 cells were 73 ng/ml and 12 ng/ml respectively, *i.e.* **1** is less potent than paclitaxel. **1** is five to ten times less potent than paclitaxel for the *initiation* of microtubule assembly. However **1** is of similar efficacy to paclitaxel for promoting the process of microtubule assembly once it has been initiated. These results are consistent with a multistep mechanism for microtubule polymerisation, *i.e.* a nucleation step followed by an elongation step.

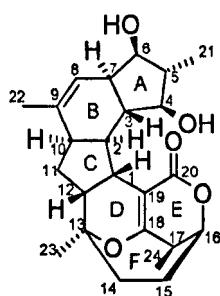
Little is known as to how **1** exerts its biological activity in terms of binding interactions with specific proteins. However, Sorensen and Cravatt have recently co-published a study¹⁹ where a tagged form of **1** was incubated with a mouse-heart proteome. This

study concluded that (-)-1 is a selective inhibitor of mouse carboxylesterase-1 (CE-1), a serine hydrolase that has been implicated in lipid metabolism and detoxification of xenobiotics.²⁰ The complex of (-)-1 with CE-1 was stable to protein denaturation, suggesting that the interaction is due to a covalent modification. Also, no binding occurred with either tagged (+)-1, or with (-)-1 and denatured CE-1, suggesting a specific interaction between the natural product and a structured binding site in the protein. However, it is not clear whether there is a connection between CE-1 inhibition and the observed antitumour effects of (-)-1.

1 may prove to be a fruitful lead for finding new leads for cancer chemotherapy. At the very least, studies on the biological action of 1 should improve our understanding of how microtubule stabilisers work in general.

1.4 Review of current literature approaches

To date two groups have completed total syntheses of FR182877, those of Evans and Sorensen. This short review will present their closely related synthetic strategies and will also present model approaches taken by Clarke, Nakada and Roush. Throughout the review the rings will be referred to as A-F and the carbons numbered 1-24 as shown in Figure 4 below.



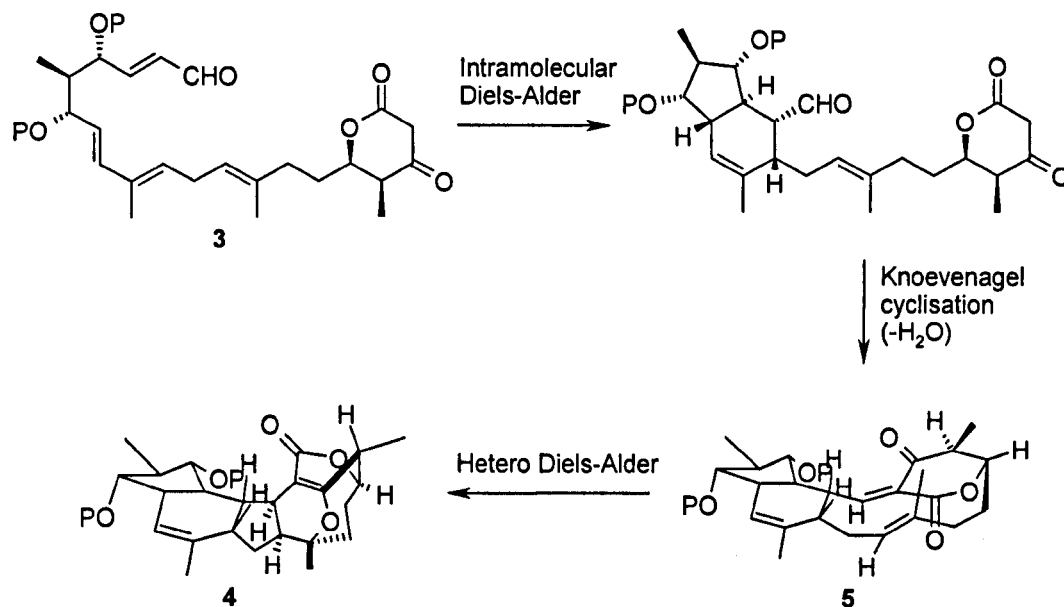
(-)-FR182877 (-)-1

Figure 4

1.4.1 Sorensen's total synthesis

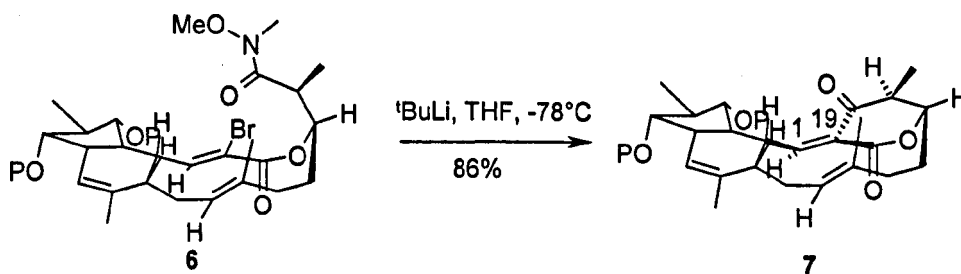
Sorensen has used a 'biomimetic' approach to complete the total synthesis of 1, in that he disconnects the natural product to a linear starting material. This strategy was first

reported in 1999,³ when he suggested that two intramolecular Diels-Alder reactions and a Knoevenagel cyclisation could take a synthetically accessible extended chain **3** to the desired hexacyclic structure **4** (Scheme 1). In this communication an elegant enantioselective synthesis of such a linear precursor **3** was also reported.



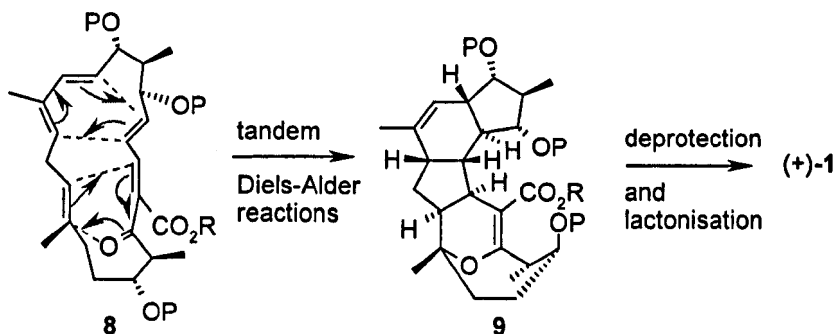
Scheme 1

A later communication reported²¹ that although the first intramolecular Diels-Alder step proceeded efficiently, efforts to perform a Knoevenagel condensation to form the desired hetero Diels-Alder substrate **5** failed. As an alternative, it was found that a substrate such as **6** (Scheme 2) could be lithiated to form a transitory allenolate that then proceeds to react with the Weinreb amide to give **7**. Unfortunately, although this represents an interesting approach, the C19-C1 alkene of **7** possessed the wrong stereochemistry for a synthesis of the natural product.



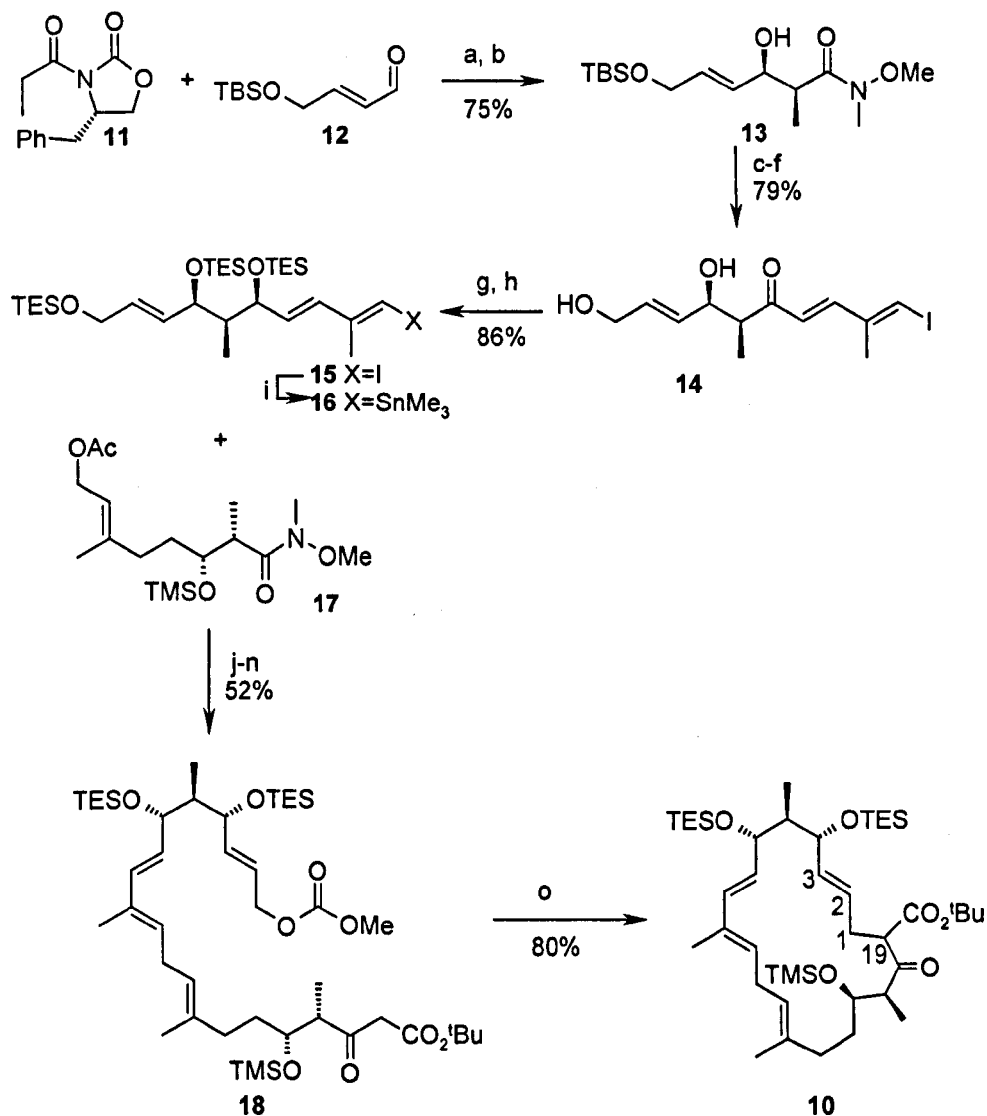
Scheme 2

The total synthesis of **1** was reported by Sorensen in 2002,⁶ and relied upon a subtly different strategy to that followed in the previous approaches. The strategy was to form a 19-membered macrocycle **8** first (Scheme 3), which should then undergo two spontaneous Diels-Alder reactions to form a pentacycle **9** that could provide the hexacyclic natural product upon lactonisation.



Scheme 3

The successful route to the desired 19-membered macrocycle **10** is summarised below (Scheme 4). To establish the desired absolute and relative stereochemistry of C5 and C6 Sorensen utilised an asymmetric aldol reaction between **11** and TBS-protected hydroxy-but-2-enal **12**, then Weinreb amidation to form **13** (Scheme 4). TMS protection of the hydroxyl group, followed by displacement with an excess of dimethyl lithiomethylphosphonate, a Horner-Wadsworth-Emmons reaction with (*E*)- β -iodomethylacrolein, and removal of the silicon protecting groups gave **14**. A chelation-controlled reduction established the stereochemistry of C4, and then TES protection of both hydroxy groups and a palladium-catalysed stannylation of the resulting iodide **15** gave **16**. It was found that **16** underwent a smooth Stille coupling with **17**. **17** was synthesised from geranyl acetate by dihydroxylation, periodate cleavage, an Evans aldol reaction, Weinreb amidification and TMS protection. The Stille product was converted to the desired Trost-Tsuji substrate **18**, which underwent a palladium catalysed cyclisation to give the desired 19-membered macrocycle **10** in excellent yield. Note that this substrate did not spontaneously undergo the first Diels-Alder reaction, as the C2-C3 alkene was not sufficiently activated without the C19-C1 unsaturation that was introduced in the next step.

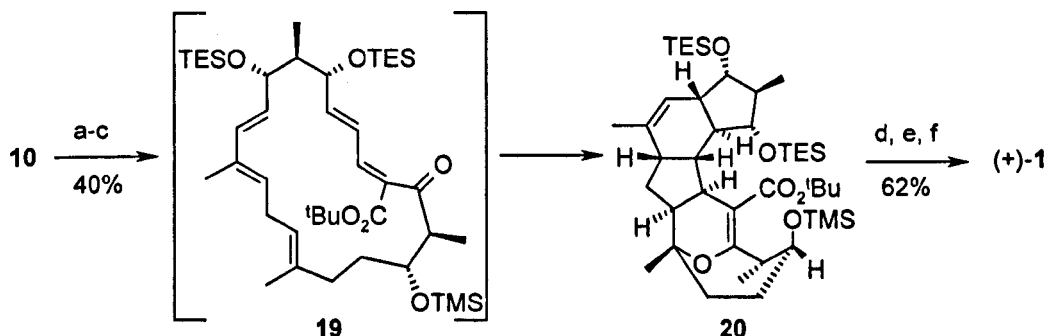


Scheme 4

Reagents and conditions: (a) $t\text{Bu}_2\text{BOTf}$, Et_3N , DCM (b) Me_3Al , $\text{MeONHMe}\cdot\text{HCl}$, THF (c) TMSCl , im, DMAP, DCM (d) $\text{LiCH}_2\text{P}(\text{O})(\text{OMe})_2$, THF (e) $\text{Ba}(\text{OH})_2$, THF then (*E*)- β -iodomethacrolein, THF/ H_2O (f) PPTS, MeOH (g) Et_2BOMe , NaBH_4 , THF, MeOH (h) TESCl , im, DMAP, DCM (i) $\text{Me}_3\text{SnSnMe}_3$, $\text{Pd}(\text{PPh}_3)_4$, $i\text{Pr}_2\text{NEt}$, PhH (j) Pd_2dba_3 , LiCl , $i\text{Pr}_2\text{NEt}$, NMP (k) LDA , $t\text{BuOAc}$, THF (l) TBAF , THF (m) MeOCOC , py, DCM (n) TMSCl , im, DCM (o) Pd_2dba_3 , THF (5 mM)

The stage was now set to test Sorensen's hypothesis; a selenium-mediated oxidation of **10** gave unsaturated macrocycle **19** (Scheme 5) that spontaneously underwent two tandem intramolecular Diels-Alder reactions to give the desired pentacycle **20** in 36% yield from **10**. This remarkable transformation displays the power and selectivity of intramolecular Diels-Alder reactions to generate complicated polycyclic structures with excellent stereocontrol. The excellent stereoselectivity observed in this key

transformation is discussed in section 1.4.2. Note that a low yield (36%) was obtained because the selenium-mediated oxidation generates a mixture of *Z* and *E* geometrical isomers. The tandem Diels-Alder reactions, therefore, are believed to proceed in excellent yield and stereocontrol. Global deprotection and EDC-mediated lactonisation then gave (+)-1 in 62% yield.



Scheme 5

Reagents and conditions: (a) KHMDS, PhSeBr, THF (b) *m*CPBA, DCM (c) NaHCO₃ (d) PPTS, MeOH (e) TFA/DCM (f) EDC, DMAP, DCM

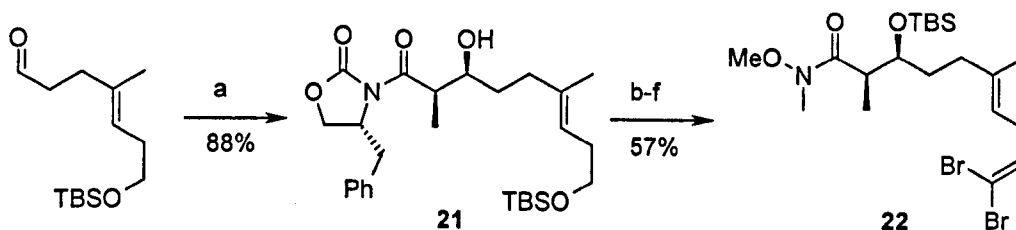
More recently Sorensen has published a full account of this work,⁸ in which he also detailed a total synthesis of the natural enantiomer (-)-1 and an optimisation of the route for large-scale synthesis. This optimisation led to an improvement to the weakest synthetic step in the sequence, the selenium-mediated oxidation, although this step still proceeded in modest yield and selectivity. Impressively, multigram quantities of the hydroxy-acid precursor to (-)-1 have been synthesised, stored as the precursor rather than as the natural product because of the precursor's greater stability. Sorensen has proposed that the efficiency and selectivity of the tandem Diels-Alder reactions suggest that this route may mimic a biosynthetic pathway to the natural product, although this hypothesis has not yet been tested.

1.4.2 Evans' total synthesis

Evans also published a total synthesis of 1 in 2002,⁷ shortly after Sorensen's total synthesis was published. The strategy employed is very similar, using two intramolecular Diels-Alder reactions to fold up a 19-membered macrocycle into a lactonisation precursor of the natural product. Evans used different disconnections to form the macrocycle, although there are strong similarities between the two approaches,

especially in the use of asymmetric aldol chemistry to establish the absolute and relative stereochemistry of the substituents on the macrocycle.

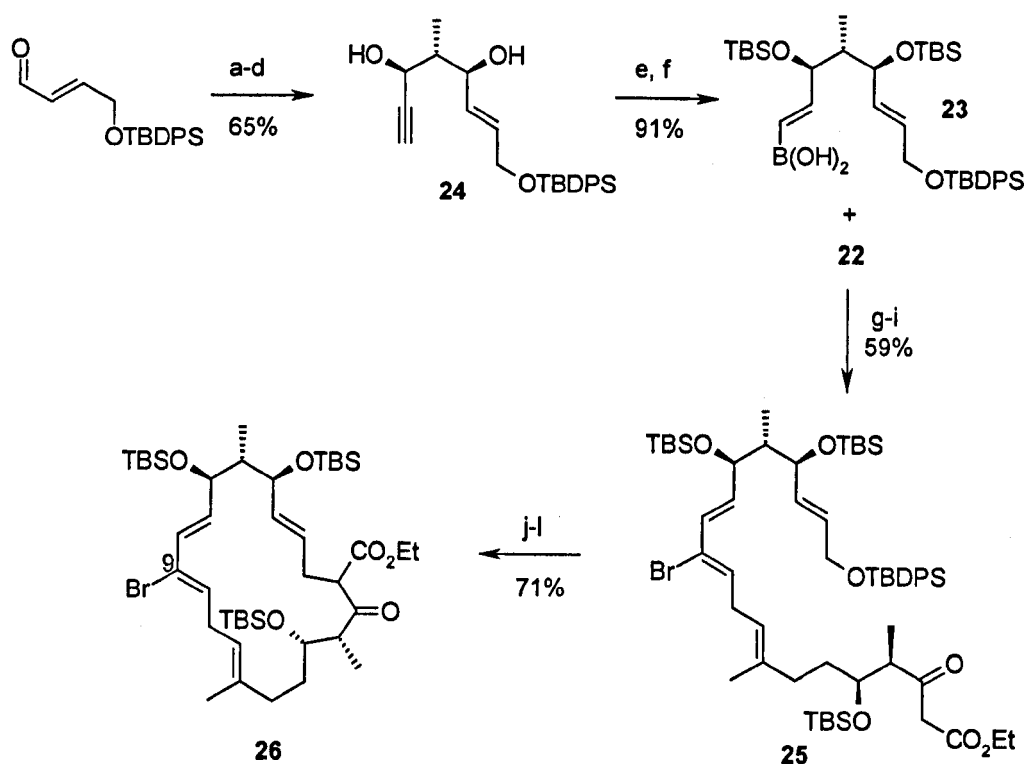
Thus, similar oxazolidinone-based aldol chemistry formed **21**, which was converted to fragment **22** *via* Weinreb amidation, TBS protection, selective primary TBS deprotection, oxidation and a Corey-Fuchs olefination (Scheme 6).



Scheme 6

Reagents and conditions: (a) (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone, Bu₂BOTf, NEt₃ (b) MeNHOMe.HCl, Me₃Al, THF (c) TBSCl, im (d) TsOH, ^tBu₄NHSO₄, MeOH (e) DMP (f) CBr₄, PPh₃

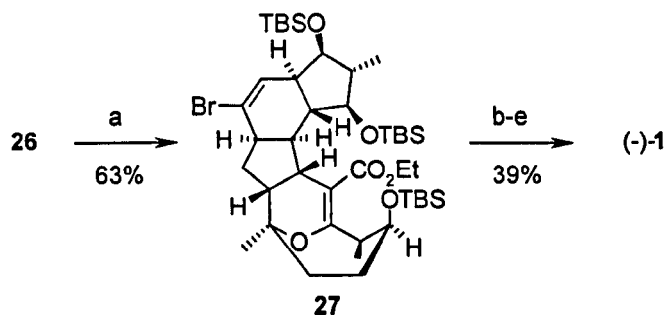
The synthesis of fragment **23** (Scheme 7) commenced with similar aldol chemistry, followed by Weinreb amidation, alkynone formation and a diastereoselective DIBAL reduction to give **24**. TBS protection and hydroboration gave **23**, which was then coupled with fragment **22** in a Suzuki reaction in excellent yield. The resulting Weinreb amide was reduced to the aldehyde and homologated with ethyl diazoacetate to give the ketoester **25**. Selective removal of the TBDPS group and iodination of the resulting alcohol gave an allylic iodide which cyclised in good yield with Cs₂CO₃ to form the desired macrocycle **26**. Once again note the similarity with the approach taken by Sorensen. The same bond is being formed by the macrocyclisation, but with an alkylation of an allylic iodide rather than with a Trost-Tsuji reaction on an allylic carbonate. Note that **26** was deliberately designed with a bromide at C9 to provide flexibility; if the subsequent Diels-Alder reaction proceeded *via* an endo transition state **26** could furnish FR182877 as planned, but if it proceeded *via* an exo transition state **26** could supply hexacyclenic acid instead.



Scheme 7

Reagents and conditions: (a) (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone, Bu₂BOTf, NEt₃ (b) MeNHOMe.HCl, Me₃Al, THF (c) HCCMgBr, THF (d) DIBAL, THF (e) TBSCl, im (f) cat. Cy₂BH, catecholborane then 1N NaOH (g) Pd(PPh₃)₄, Ti₂CO₃ (h) DIBAL, THF (i) ethyl diazoacetate, cat. SnCl₂ (j) TBAF, AcOH (k) I₂, PPh₃ (l) Cs₂CO₃

The desired unsaturation was once again introduced with a selenium reagent, this time with benzeneseleninic anhydride (Scheme 8). With this procedure Evans isolated a 63% yield of the desired pentacycle **27**, a slight improvement on the yield Sorensen obtained although it should be noted that the substrate is not the same. Global deprotection, Suzuki methylation, saponification of the ester and lactonisation with Mukaiyama's reagent then yielded (-)-**1**.



Scheme 8

Reagents and conditions: (a) $\text{Ph}_2\text{Se}_2\text{O}_3$, SO_3/py , NEt_3 , THF (b) $\text{HF}/\text{CH}_3\text{CN}$ (c) trimethylboroxine, Cs_2CO_3 , $[\text{Pd}(\text{dppf})\text{Cl}_2]$, DMF (d) TMSOK, THF (e) 1-methyl-2-chloropyridinium iodide, NaHCO_3

Evans' total synthesis is an elegant approach, although it is very similar to that of Sorensen, and represented the first total synthesis of the correct enantiomer of the natural product.

More recently Evans has published a full account of this synthesis.¹⁰ Interestingly, he used this account to discuss the stereochemical outcome of the tandem Diels-Alder reactions, thereby rationalising why the cyclisations proceed as desired. Molecular modelling was used to attempt to rationalise the observed stereochemical outcome. To achieve this he needed to be able to predict which Diels-Alder cyclisation occurs first. This was achieved by modelling a simplified macrocycle **28** (Figure 5) and analysing the frontier molecular orbitals. The conclusion of this work was that the best HOMO-LUMO orbital overlap leads to the C2-C10 and C3-C7 bonds that are formed in the Diels-Alder reaction that forms the B ring. For all the modelling reported in this section, Evans performed geometry optimisations at the PM3 level, and obtained single point energies of the optimised geometries with *ab initio* methods at the STO-3G level.

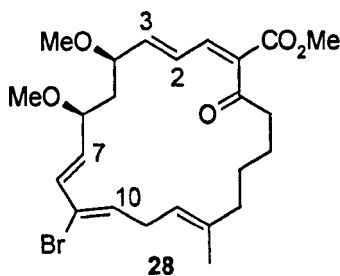


Figure 5

Having concluded that the B-ring cyclisation occurs first, the observed stereochemical outcome of this cyclisation was then analysed. To achieve this the two possible *endo* conformations, *endo*-1 and *endo*-2 (Figure 6), were modelled at different constrained C2-C10 and C3-C7 distances, to produce energy curves that represent the increasing energy penalty of approaching the transition state. The conclusion was that the macrocycle prefers the *endo*-1 transition state by 4.9-9.4 kcalmol⁻¹, which gave the same stereochemical outcome as was observed in the laboratory. Interestingly, it appears that the stereoselectivity is a direct consequence of the substituents at C16 and C17, as confirmed by Evans when similar calculations were applied to a variety of macrocycles with alternative stereochemistry at C16 and C17.

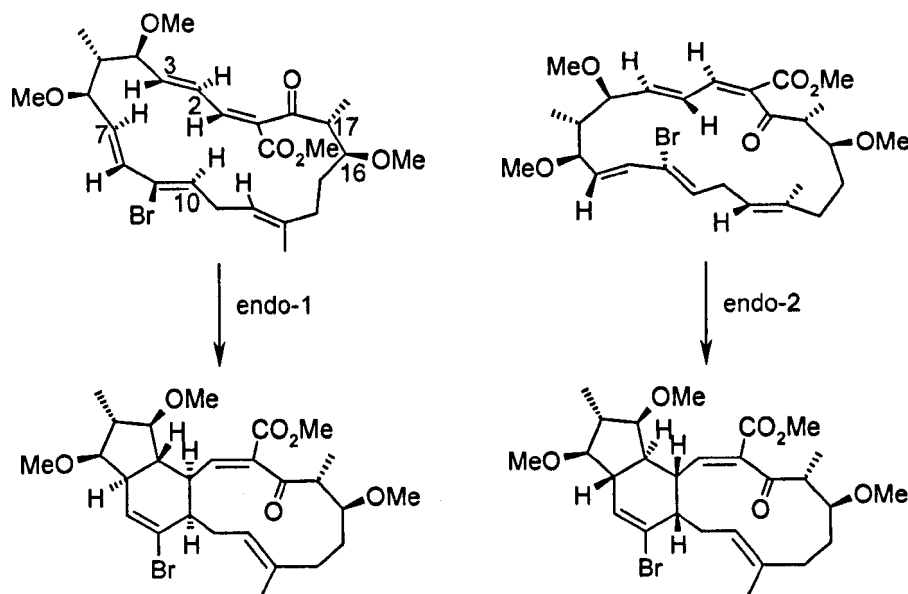


Figure 6: The two possible *endo* modes of cyclisation for the first Diels-Alder reaction

Evans also rationalised the stereochemical outcome of the second cycloaddition. Again the two possible transition states, TS1 and TS2 (Figure 7), were modelled by constraining the C12-C1 and C13-O distances. The modelling suggested that TS1 is the lower energy pathway, again giving the same stereochemical outcome as was observed in the laboratory.

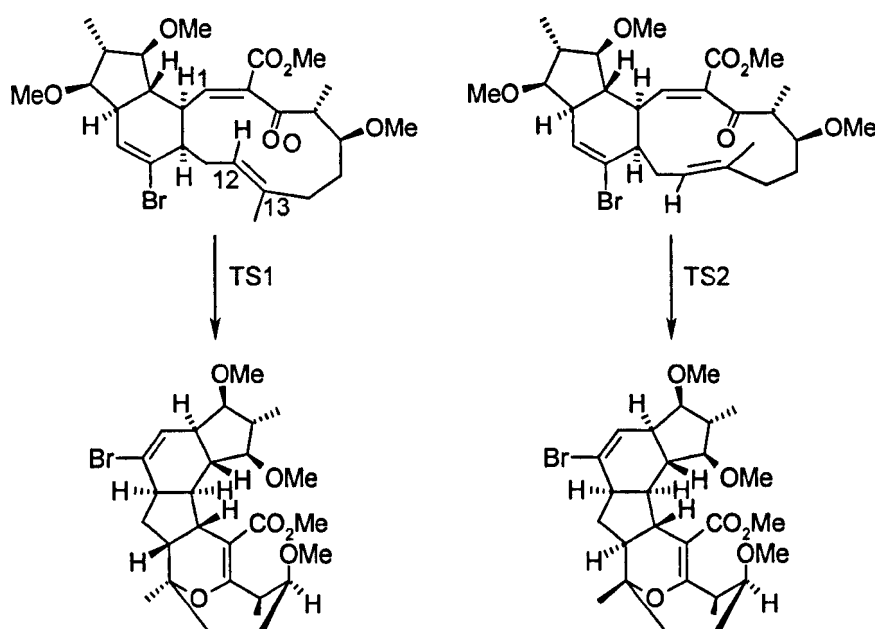
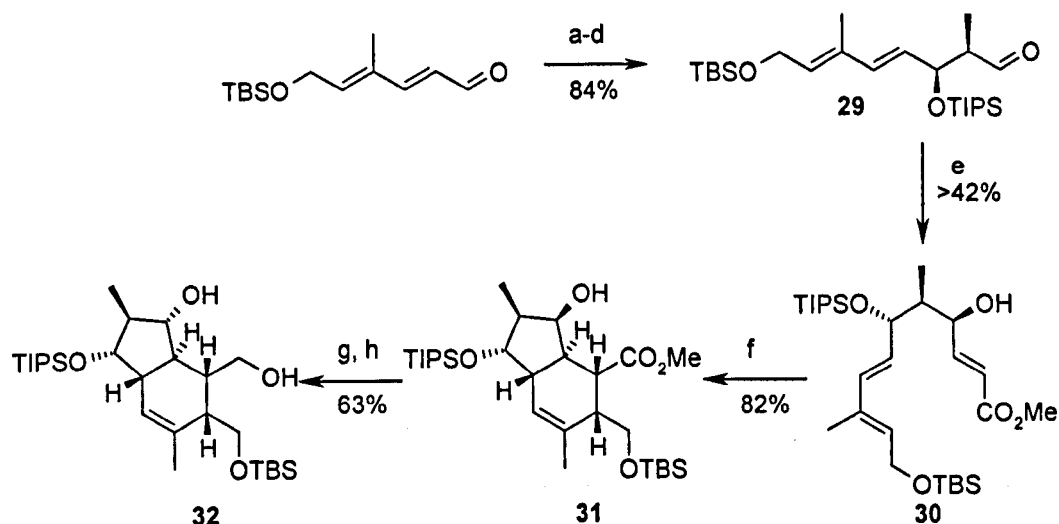


Figure 7: The two possible modes of cyclisation for the hetero Diels-Alder reaction

1.4.3 Nakada's model studies

Nakada has published²² a model study that uses a Diels-Alder reaction to form the AB ring system. This work is summarised below in Scheme 9; first an asymmetric aldol reaction, Weinreb amidation, hydroxyl protection and DIBAL reduction formed **29**. This aldehyde underwent a Nozaki-Hiyama-Kishi coupling with methyl (*E*)-2-iodoacrylate, to give **30** after a separation-oxidation-reduction cycle to separate and recycle the other diastereoisomer. Although **30** does not possess the correct relative stereochemistry for a synthesis of **1**, it was found that it underwent the desired Diels-Alder reaction to form **31**, which could be converted to **32** (which possesses the desired relative stereochemistry) by an oxidation-reduction cycle. This model study demonstrated further the validity of the Diels-Alder reaction to form the AB ring system.

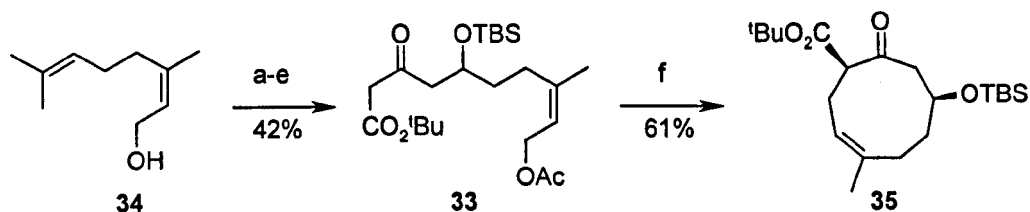


Scheme 9

Reagents and conditions: (a) (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone, Bu₂BOTf, NEt₃, DCM (b) MeONHMe.HCl, Me₃Al, THF (c) TIPSOt₃, NEt₃, DCM (d) DIBAL, THF (e) methyl (*E*)-2-iodoacrylate, NiCl₂, CrCl₂, NaHCO₃, THF (f) BHT, PhMe (g) DMP, NaHCO₃, DCM (h) DIBAL, DCM

1.4.4 Clarke's model studies

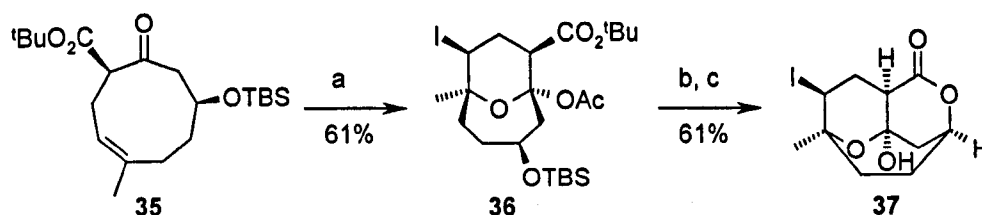
Clarke has published two model studies relating to FR182877. In the first²³ he revealed that he is exploring a Diels-Alder approach to form the B ring. However the purpose of the communication was to report a competing [3,3]-sigmatropic rearrangement, and so will not be discussed further. The second model study that he has reported²⁴ concerned the synthesis of the DEF ring system of hexacyclinic acid, and could also be applicable to a synthesis of FR182877. The key disconnections of the tricyclic ring system rely upon an intramolecular Pd(0) π -allyl substitution reaction and a transannular iodocyclisation. The desired cyclisation precursor **33** was synthesised from nerol **34** (Scheme 10) in 5 steps. **33** then furnished the desired 9-membered macrocycle **35** in an optimised yield of 61%, with the two substituents in a *cis* relationship.



Scheme 10

Reagents and conditions: (a) Ac_2O , py, DMAP (b) *m*CPBA, DCM (c) HIO_4 , THF, H_2O (d) $^t\text{BuOC}(\text{OTMS})=\text{CHC}(\text{OTMS})=\text{CH}_2$, TiCl_4 , DCM (e) TBSOTf, py (f) NaH, $\text{Pd}(\text{PPh}_3)_4$, dppe, THF

The desired bicyclic ring system was formed by iodocyclisation of the ketone oxygen of **35** onto the iodonium, with the solvent (acetic acid) trapping the intermediate oxonium ion to yield **36** (Scheme 11). HF effected concomitant deprotection of the TBS and acetate groups, and finally a TFA-mediated lactonisation yielded the desired tricyclic model system **37**.



Scheme 11

Reagents and conditions: (a) AcOI, AcOH (b) 40% aq. HF, MeCN (c) TFA, DCM

It is interesting to note that Clarke found that **35** exists in a chair-boat conformation in solution (Figure 8), whereas it appears from the observed stereochemistry of **36** that the iodonium that forms **36** is derived from a boat-boat conformation of **35** (Figure 8). Only in the boat-boat conformation can the ketone oxygen approach the iodonium ion sufficiently closely to react. As iodonium ion formation is reversible it follows that a boat-boat derived iodonium will be formed on the reaction pathway.

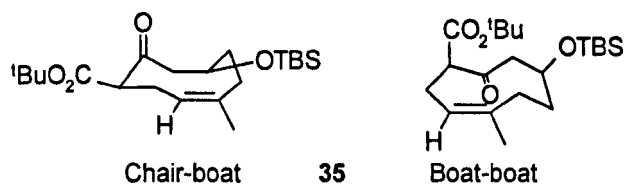
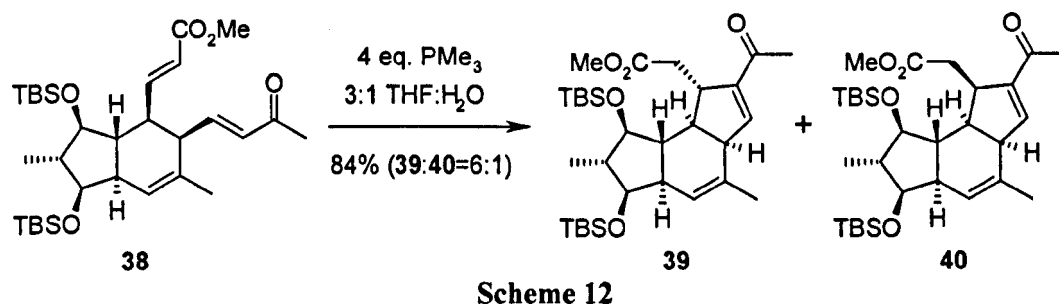


Figure 8: Chair-boat and boat-boat conformations of 35

In addition to **37** being a model of the DEF rings of hexacyclinic acid, it should be noted that if dehydration could be achieved then **37** could provide a model of the tricyclic bridgehead olefin system found in FR182877.

1.4.5 Roush's model studies

Roush has published a model study²⁵ where he forms the C ring with an intramolecular vinylogous Morita-Baylis-Hillman cyclisation.²⁶ By treating enone-enoate **38** with 4 eq. PMe₃ in 3:1 THF:water an 84% yield of the desired cyclopentene was isolated, with a dr of 6:1 in favour of the desired diastereoisomer **39** (Scheme 12). An excess of phosphine was required, and the choice of solvent was also important as other solvents gave lower yields and lower diastereoselectivities. This communication does not present the synthesis of **38**. This approach represents an interesting alternative to the tandem Diels-Alder reactions used by Sorensen and Evans, and this model study is promising for Roush's planned synthesis of FR182877.



1.5 Project aims

The DEF ring system represents the most synthetically interesting and structurally challenging feature of **1**. The principal aim of this project was therefore to explore novel synthetic strategies to form this key tricyclic ring system. At the outset of this project Sorensen had already published his initial communication,³ detailing his first approach to the molecule. We were therefore especially interested in developing alternative approaches that differed markedly from the hetero Diels-Alder/lactonisation approach that he takes to form the DEF ring system.

As was noted in section 1.1, the bridgehead olefin is sufficiently strained to undergo epoxidation in air. Interestingly, the resulting epoxide has no biological activity,⁴ suggesting that this strained part of the natural product is of prime importance to the biological action of **1**. It was one of our intentions, therefore, to test simple structures that were synthesised during the course of the project for microtubule-stabilising activity and cytotoxicity.

Chapter 2: Results and discussion

2.1 Overview of synthetic strategy

As discussed in section 1.5, the principal aim of this project was to explore novel ways to synthesise the tricyclic portion of FR182877. Firstly, we investigated methods for synthesising the bicyclic tetrahydropyranopyranone unit **41** (Figure 9). This work is presented in section 2.2.

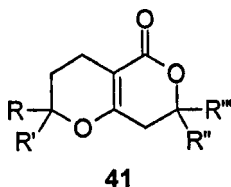
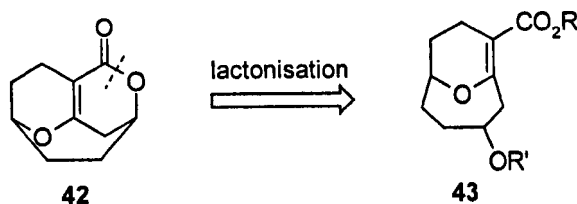


Figure 9: The bicyclic tetrahydropyranopyranone unit

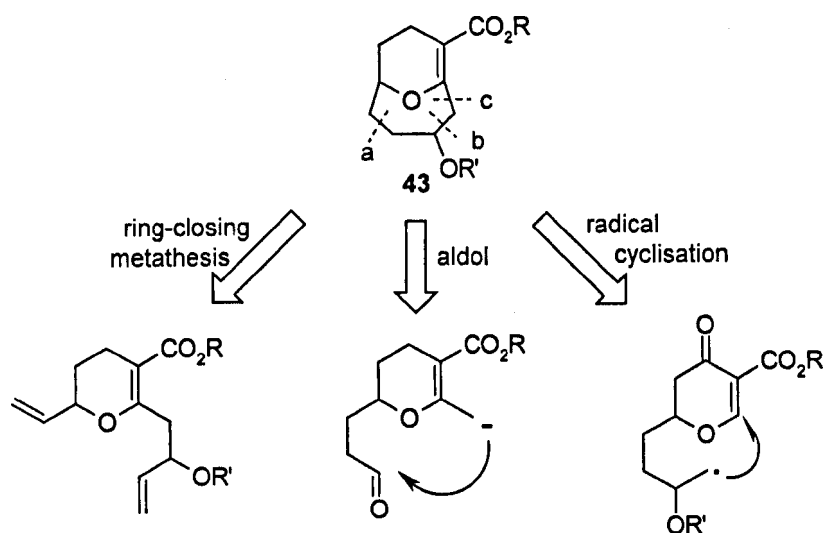
We then examined methods to form the desired tricyclic model compound **42**. It was envisaged that **42** could be formed from a lactonisation of a suitably functionalised bicyclic compound **43** (Scheme 13). There are many powerful ways in the literature to form strained lactones from hydroxy acids,²⁷ and since the inception of this project two total syntheses of FR182877 have used a lactonisation as their final step (see section 1.4).



Scheme 13

This gave us the task of synthesising compound **43**, which still contains a degree of ring strain by virtue of its bridgehead olefin. Strategically, different disconnections have been explored based on disconnecting the 7-membered ring. These disconnections are shown in Scheme 14. Disconnection (a) with ring-closing metathesis (RCM) is discussed in section 2.4, and is revisited in section 2.6. This disconnection relies upon the tetrahydropyranopyranone methodology expounded in section 2.2. Disconnection (b) depends upon an intramolecular aldol reaction and is discussed in section 2.3.

Finally, disconnection (c) relies upon an intramolecular radical cyclisation and is discussed in section 2.5.

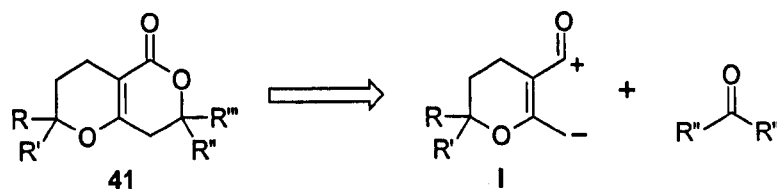


Scheme 14

2.2 Synthesis of tetrahydropyranopyranones

2.2.1 Introduction

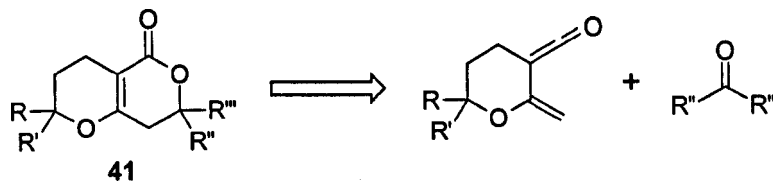
Initial studies focused on the synthesis of the bicyclic tetrahydropyranopyranone unit **41**. At the outset of this project, Sorensen had published his strategy to forming FR182877 (see section 1.4.1), and we were therefore interested in developing a different strategy to form this subunit. Strategically we decided to disconnect the bicycle into synthon **I** and a carbonyl compound (Scheme 15). Different approaches to forming synthon **I** were investigated, and are discussed below.



Scheme 15

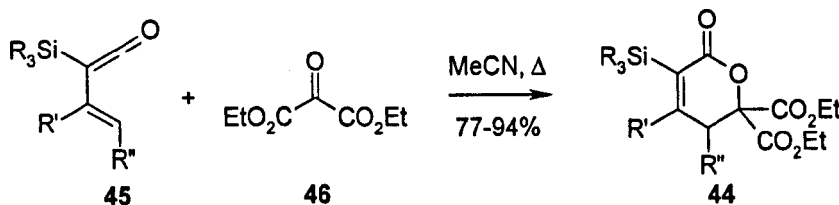
2.2.2 Vinylketene cycloadditions

One possible representation of synthon **I** is a vinylketene. This disconnection is shown in Scheme 16. In a forward sense this disconnection is a formal [4+2] cycloaddition (whether stepwise or concerted).



Scheme 16

This cyclisation has precedent in a paper by Danheiser²⁸ where 5,6-dihydro-pyran-2-ones **44** were formed from a cyclisation between silyl vinylketenes **45** and diethyl ketomalonate **46** (Scheme 17). Danheiser proposed that this reaction proceeds *via* a concerted cycloaddition rather than a stepwise process, although no direct experimental evidence was provided to support this hypothesis. The silyl group is known to stabilise vinylketenes,²⁹ so in its absence it was envisaged that ketene formation and cyclisation would have to be done in a one-pot reaction. In addition, R' and R'' (Scheme 17) in **45** were alkyl groups, phenyl groups or hydrogen, whereas in our case we require oxygenation in the R' position from the dihydropyran ring. This oxygenation would be expected to make the vinylketene more electron rich, and therefore more reactive. The Danheiser paper reported that ordinary aliphatic aldehydes did not participate in this reaction whereas diethyl ketomalonate did, so diethyl ketomalonate was chosen as the carbonyl compound for our test reaction.

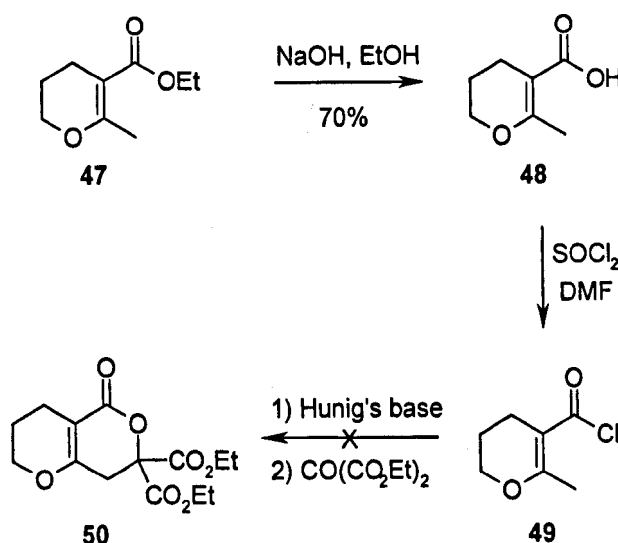


Scheme 17: Literature precedent for a [4+2] cycloaddition of a silyl vinylketene with diethyl ketomalonate²⁸

Our strategy is outlined in Scheme 18. The dihydropyran **47** that was required for this approach was synthesised as in the literature³⁰ from 1,3-dibromopropane and ethyl acetoacetate in 41% yield, and corresponded with literature data.³¹ The ester in **47** was

then hydrolysed in ethanol/aq. NaOH to give the corresponding acid³² **48**. Treating the acid **48** with thionyl chloride and catalytic quantities of DMF yielded the corresponding acid chloride **49**. The acid chloride **49** was not isolated as it was expected to be unstable, but its formation could be monitored by TLC by derivatising samples in methanol and monitoring formation of the methyl ester.³³ In addition, it was found that by quenching the reaction mixture with methanol the expected methyl ester could be isolated on work-up.

The acid chloride **49** was then treated sequentially with diethyl ketomalonate and Hünig's base, with the aim of forming a vinylketene *in situ* that could undergo an intramolecular cyclisation with the diethyl ketomalonate. However, this reaction proved unsuccessful, despite trying a range of conditions, solvents and Lewis acids. In all cases a complicated mixture of products was obtained, from which we failed to isolate any desired product **50**. As the presence of vinylketene in the reaction mixture was never proven, it is unclear whether the reaction failed because the vinylketene was not formed, or because the vinylketene did not participate in the required cyclisation.

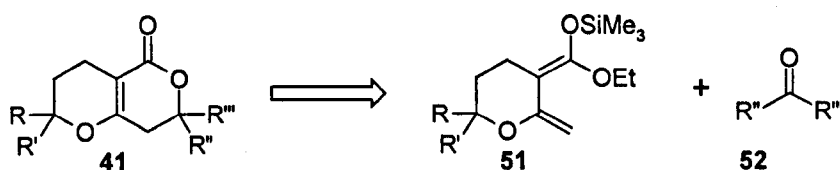


Scheme 18

2.2.3 Brassard's diene approach

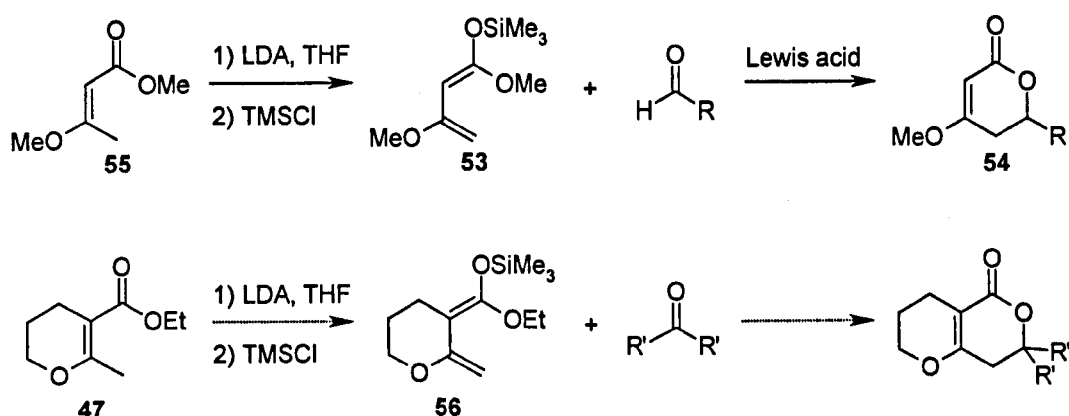
It was thought that the above approach failed due to either difficulty in forming the vinylketene or to inherent instability of the vinylketene. We therefore wanted to investigate similar cycloadditions using an alternative 4π component. One such

alternative could be a vinyl silyl ketene acetal. Thus, **41** could be disconnected to **51** and **52** (Scheme 19).



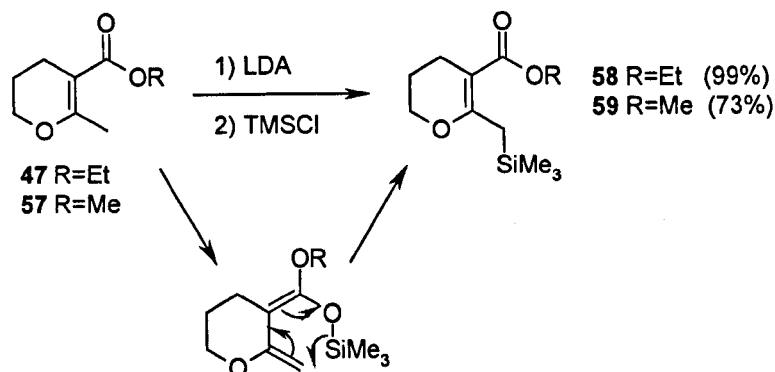
Scheme 19

This approach is well precedented, as the cycloaddition between 'Brassard's diene' **53** and aldehydes to give 5,6-dihydro-pyran-2-ones **54** has been well documented (Scheme 20).^{34,35} We were therefore encouraged to try this approach to form the bicyclic unit. Brassard's diene has been synthesised by quenching the enolate of **55** with TMSCl.³⁴ It was therefore envisaged that the required silyl ketene acetal **56** could be formed from **47** in an analogous fashion.



Scheme 20

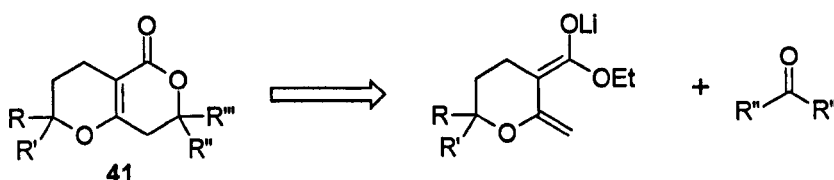
However, when either **47** or **57**³³ were treated sequentially with LDA and TMSCl the C-silylated products **58** and **59** (Scheme 21) were isolated rather than the desired O-silylated product. The C-silylated product may be the result of a [1,5] sigmatropic shift that moves the TMS group from the oxygen to the carbon, as shown. A similar transformation has been reported for Brassard's diene,³⁵ which undergoes the shift on heating. It should be noted that our system has the 4π system constrained as *s-cis* as is required for the [1,5] sigmatropic shift and so might be expected to rearrange more readily than Brassard's diene itself.



Scheme 21

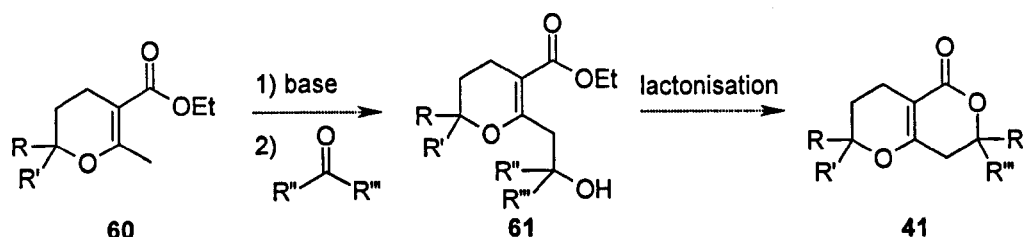
2.2.4 γ -Deprotonation and subsequent aldol reaction.

Given the failure to isolate the required vinyl silyl ketene acetal, we decided to investigate a simpler approach involving a direct reaction of an enolate with a carbonyl compound (Scheme 22), *i.e.* an aldol disconnection.



Scheme 22

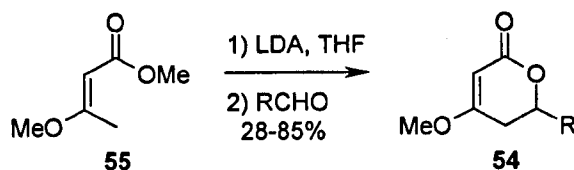
In the forward sense, this requires deprotonation of 60 (Scheme 23) and trapping of the resulting enolate with a carbonyl compound to give the corresponding aldol product 61. Lactonisation of 61 could then furnish the desired bicyclic unit 41.



Scheme 23

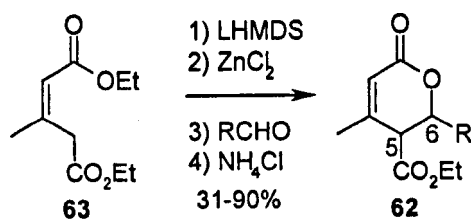
This approach has precedent in a paper by Heathcock³⁶ where 5,6-dihydro-pyran-2-ones 54 are formed from an aldol reaction between 55 and a range of aldehydes (Scheme 24). A separate lactonisation step was not necessary, as the alkoxides that were formed from

the aldol reaction spontaneously reacted with the ester under the reaction conditions to give the corresponding lactones **54**.



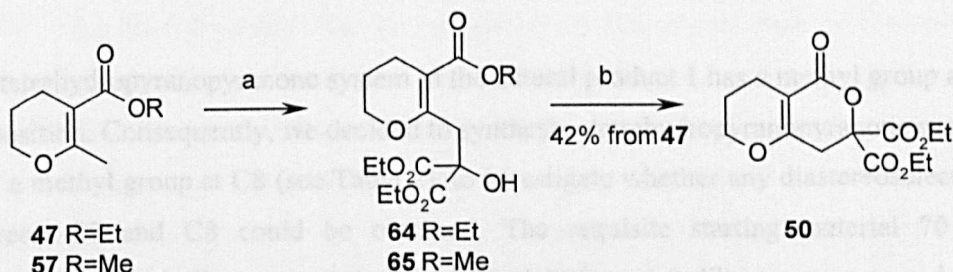
Scheme 24

This chemistry is revisited in a paper by Audin³⁷ where 5,6-dihydro-pyran-2-ones **62** are synthesised from dimethyl-3-methylglutaconate **63** and a range of aldehydes (Scheme 25). Interestingly, the observed diastereoselectivity between C5 and C6 was found to vary widely depending on the nature of R, from complete *syn* diastereoselectivity for R=Bn to complete *anti* diastereoselectivity for R=^tBu, Ph.



Scheme 25³⁷

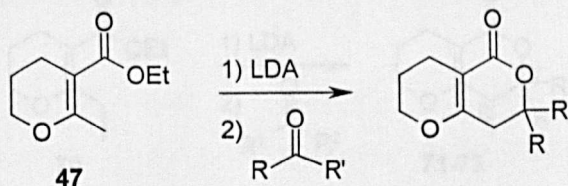
We proceeded to investigate whether this approach could be applied to the synthesis of tetrahydropyranopyranones. By deprotonation of dihydropyran **47** or **57** and subsequent trapping with diethyl ketomalonate in the presence of DMPU, the resulting adduct was isolated in 51% yield for the ethyl ester **64** and 56% yield for the methyl ester **65** (Scheme 26). It was later found that these adducts could be made to lactonise to the required tetrahydropyranopyranone **50** by heating at reflux with (±)-CSA in toluene in the presence of 5Å molecular sieves. It should be noted that no lactonisation was observed with aq. HCl, TsOH or (±)-CSA in THF.



Scheme 26

Reagents and conditions: (a) LDA, DMPU, THF; $\text{CO}(\text{CO}_2\text{Et})_2$ (b) $(\pm)$ -CSA, PhMe, 5Å molecular sieves

When alternative carbonyl compounds were used instead of diethyl ketomalonate then the tetrahydropyranopyranone product was isolated directly in one step, *i.e.* the aldol reaction and lactonisation occurred under the same conditions. By experimenting with the reaction conditions for the test case with benzaldehyde, it was found that yields were improved by omission of DMPU, and by performing the reaction at -22°C overnight. This reaction proved to be amenable to a variety of carbonyl compounds, and was high yielding in the cases of cyclohexanone, benzaldehyde and propionaldehyde (Table 1).³⁸ X-ray structures for **66** and **68** were obtained and are shown in Figure 10.



Entry	Product	R	R'	Yield
1	66	Ph	H	81
2	67	^nPr	H	83
3	68	$-(\text{CH}_2)_5-$		82
4	50	CO_2Et	CO_2Et	42
5	69	$\text{CH}=\text{CH}_2$	H	63

Table 1

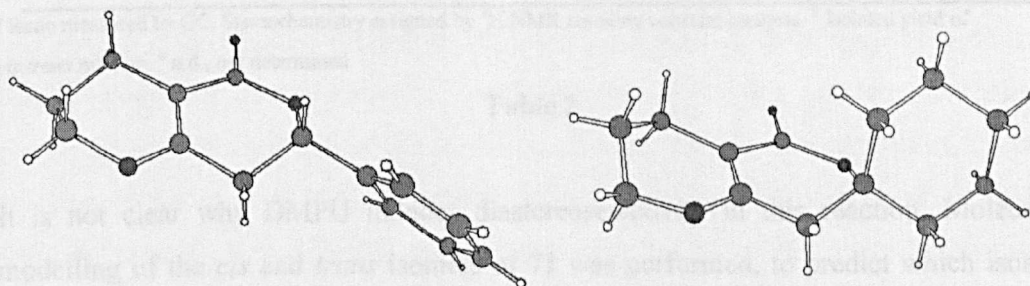
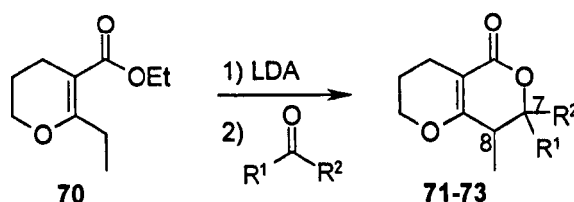


Figure 10: X-ray crystal structures of 66 (left) and 68 (right)

The tetrahydropyranopyranone system in the natural product **1** has a methyl group at the C8 position. Consequently, we decided to synthesise tetrahydropyranopyranone systems with a methyl group at C8 (see Table 2), to investigate whether any diastereoselectivity between C7 and C8 could be obtained. The requisite starting material **70** was synthesised in a similar manner to **47** in 49% yield from 1,3-dibromopropane and ethyl propionylacetate. Deprotonation of **70** with LDA as before followed by trapping with a carbonyl compound gave the desired bicyclic material. It was found that modest *trans* diastereoselectivity between C7 and C8 could be obtained with benzaldehyde by using DMPU (up to 78:22 by GC, Table 2, entries 1-4). The diastereoisomers of **71** were separable by careful column chromatography, and by analysis of the coupling constant between 7-H and 8-H the two diastereoisomers could be identified as *cis* ($J=3.5$ Hz) or *trans* ($J=10.1$ Hz). Once the diastereoisomers had been identified, the diastereoisomeric ratio was then obtained by GC analysis of the crude mixture. No significant diastereoselectivity was observed without DMPU for benzaldehyde or propionaldehyde (entries 1 and 5).



Entry	Product	R ¹	R ²	DMPU eq.	Cis:trans ^a	Yield ^b
1	71	Ph	H	0	55:45	82
2	71	Ph	H	0.5	43:57	n.d. ^c
3	71	Ph	H	2.0	30:70	n.d. ^c
4	71	Ph	H	8.0	22:78	n.d. ^c
5	72	Et	H	0	50:50	77
6	73	- (CH ₂) ₅ -		0	-	39

^a Ratio measured by GC. Stereochemistry assigned by ¹H NMR coupling constant analysis. ^b Isolated yield of *cis:trans* mixture. ^c n.d., not determined

Table 2

It is not clear why DMPU induces diastereoselectivity in this reaction. Molecular modelling of the *cis* and *trans* isomers of **71** was performed, to predict which isomer was the thermodynamic product. The molecular modelling (for each isomer) used a

MMFF forcefield to select the lowest energy conformation with a Monte-Carlo conformation search as implemented by SpartanTM, then the semi-empirical method PM3 was used to minimise the geometry of this conformation. The single point energy of this minimised conformation was then calculated using HF/6-31G*. However, the modelling predicted that the *cis* and *trans* isomers were essentially equal in energy (<0.1 kcal mol⁻¹ difference). This small difference in energy, along with the small observed diastereoselectivities, made it difficult for us to conclude whether the *trans* diastereoselectivity that we observed is a kinetic or a thermodynamic effect, as a small error in the molecular modelling calculations would have greatly affected this analysis.

In section 1.5 we stated that it was our intention to test simple compounds that were synthesised in the course of the project for biological activity. Thus, compounds **50**, **66**, **67**, **68**, **69** and **71** were tested for effect on tubulin polymerisation and cell growth inhibition *in vitro* (testing performed by Novartis). In all cases, however, no biological activity was detected. This result was not surprising, given that these compounds do not closely resemble the natural product and do not possess the strained olefin that is believed to be of prime importance for the biological activity of FR182877.

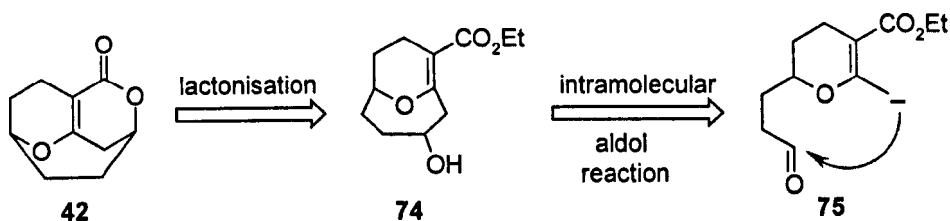
This approach successfully used an intermolecular aldol reaction between a dihydropyran and a carbonyl compound to furnish the desired bicyclic unit. In the following sections, our efforts to form the tricyclic unit are discussed, commencing with our efforts to use similar aldol chemistry in an *intramolecular* sense.

2.3 Intramolecular aldol approach to tricyclic system

2.3.1 Introduction

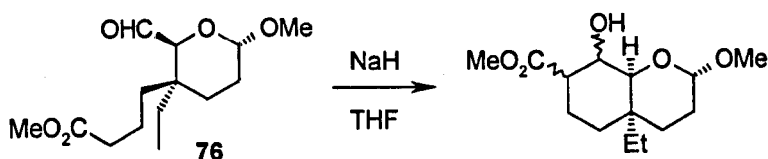
We wanted to investigate whether an intramolecular aldol reaction could provide, after lactonisation, the desired tricyclic motif (Scheme 27). There are two problems to overcome for this chemistry to be successful. Firstly, because the product of the aldol reaction **74** would be expected to contain strain by virtue of the bridgehead olefin, and the aldol reaction is in principle reversible, the position of equilibrium may favour the starting material **75**. Secondly, the aldol reaction would require a deprotonation of the

α,β -unsaturated ester in **75** in the presence of the aldehyde, when the γ -proton to the ester might be expected to be considerably less acidic than the α -proton to the aldehyde.



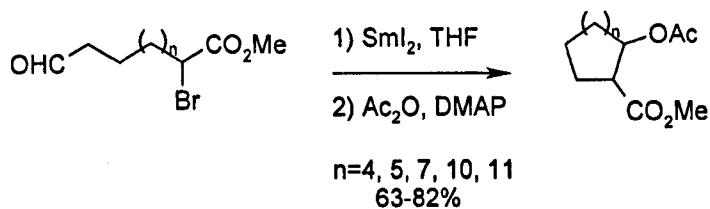
Scheme 27

However, strategies have been reported in the literature to effect intramolecular aldol cyclisations where an aldehyde is acting as the electrophile. In the example given below (Scheme 28) an intramolecular aldol reaction has been effected between an ester and an aldehyde (yield not reported).³⁹ However, the observed chemoselectivity in this example may have been due to the steric congestion around the α proton to the aldehyde in **76**, so kinetic deprotonation may have led to α -deprotonation of the ester group instead.



Scheme 28

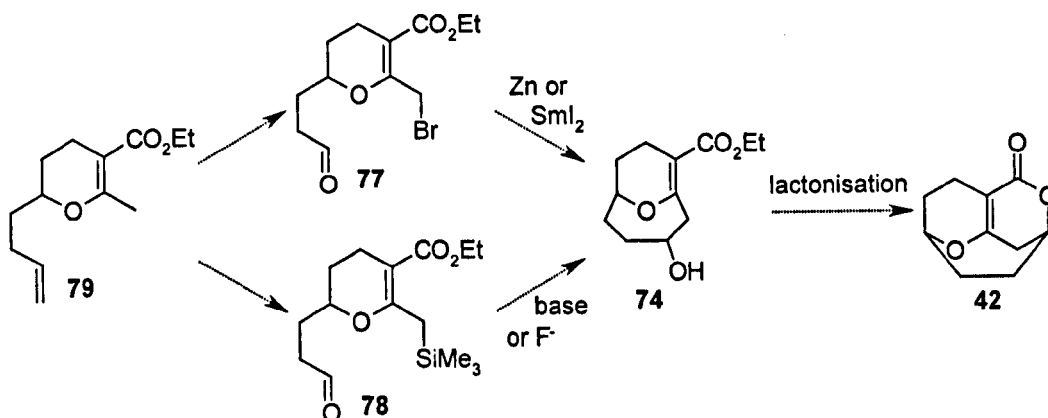
Intramolecular aldol reactions between an ester and an aldehyde in the literature have more commonly employed a Reformatsky reaction between an α -halo ester and an aldehyde.^{40,41} In the example given (Scheme 29) a range of medium and large-sized rings have been formed from a SmI_2 -mediated intramolecular Reformatsky reaction between an α -bromo ester and an aldehyde.⁴²



Scheme 29

We conceived that similar Reformatsky chemistry could be utilised on a bromide such as **77** (Scheme 30). An alternative solution would be to attempt the cyclisation on a

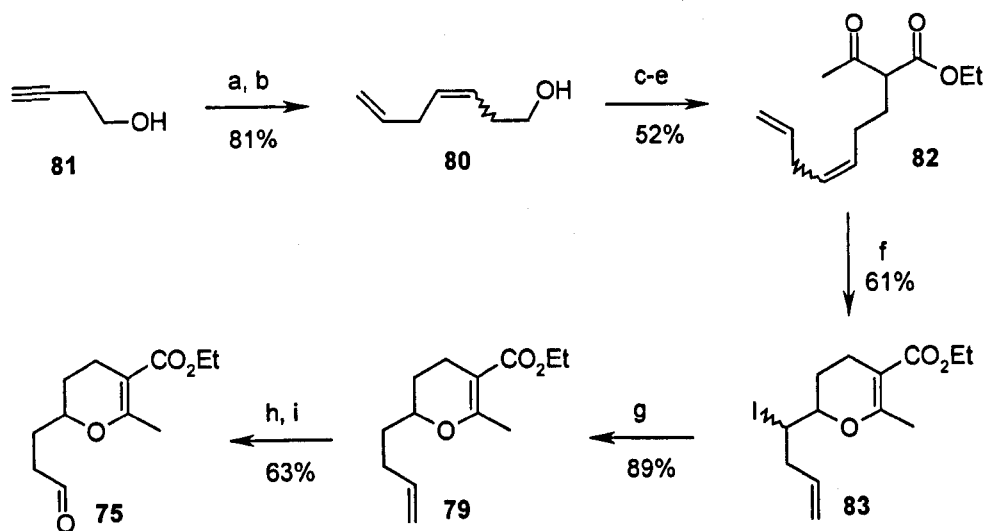
silane such as **78** with base (*i.e.* a Peterson reaction) or with fluoride, although this approach is not well precedented. We anticipated that **77** and **78** could be accessed from **79**, and thus **79** became our initial target.



Scheme 30

2.3.2 Synthesis of intramolecular aldol substrates

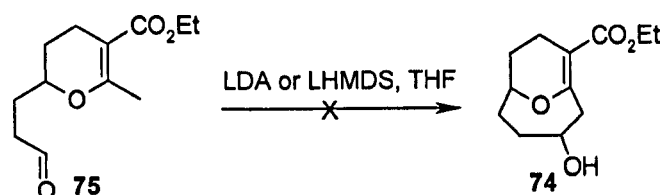
A synthetic route to **79** was found (Scheme 31) which relied upon an iodine-mediated cyclisation of a keto-ester onto an olefin.⁴³ Alcohol **80** was synthesised as reported in the literature⁴⁴ from 3-butyne-1-ol **81** *via* allylation and a reduction of the alkyne to the alkene with $\text{PdCl}_2/\text{NaBH}_4$. This route provided us with large quantities of **80** in high yield, although it should be noted that the $\text{PdCl}_2/\text{NaBH}_4$ reduction step⁴⁵ was found to be unreliable; on occasions significant quantities of unreacted starting material and over-reduced product (where the terminal alkene was hydrogenated) were observed in the crude mixture, and extensive purification by chromatography was needed to isolate the desired diene. Compound **80** was then converted to the corresponding iodide *via* the tosylate according to literature procedure,⁴⁶ and subsequent alkylation of the iodide with ethyl acetoacetate furnished **82**. Iodine-mediated cyclisation to give **83** and subsequent $\text{Bu}_3\text{SnH}/\text{AIBN}$ deiodination then furnished the desired dihydropyran **79**. The alkene **79** was then subjected to an OsO_4 catalysed dihydroxylation followed by NaIO_4 cleavage to give the corresponding aldehyde **75**.



Scheme 31

Reagents and conditions: (a) $\text{CH}_2=\text{CHCH}_2\text{Br}$, CuCl , K_2CO_3 , $n\text{Bu}_4\text{NCl}$, DMF (b) PdCl_2 , NaBH_4 , DCM/PEG200 (c) TsCl , NEt_3 , DMAP , DCM (d) NaI , acetone (e) $\text{CH}_3\text{CONaCHCO}_2\text{Et}$, THF (f) I_2 , NaHCO_3 , MeCN (g) Bu_3SnH , AIBN , PhMe (h) $\text{K}_2\text{OsO}_2(\text{OH})_4$, NMO , quinuclidine, acetone/water (i) NaIO_4 , $\text{MeOH/H}_2\text{O}$

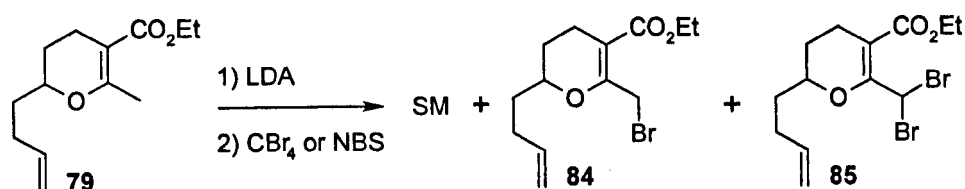
With **75** in hand, we then attempted to perform an intramolecular aldol cyclisation directly (Scheme 32). Unfortunately, attempts to effect the base-mediated aldol cyclisation of **75** only gave recovered starting material.



Scheme 32

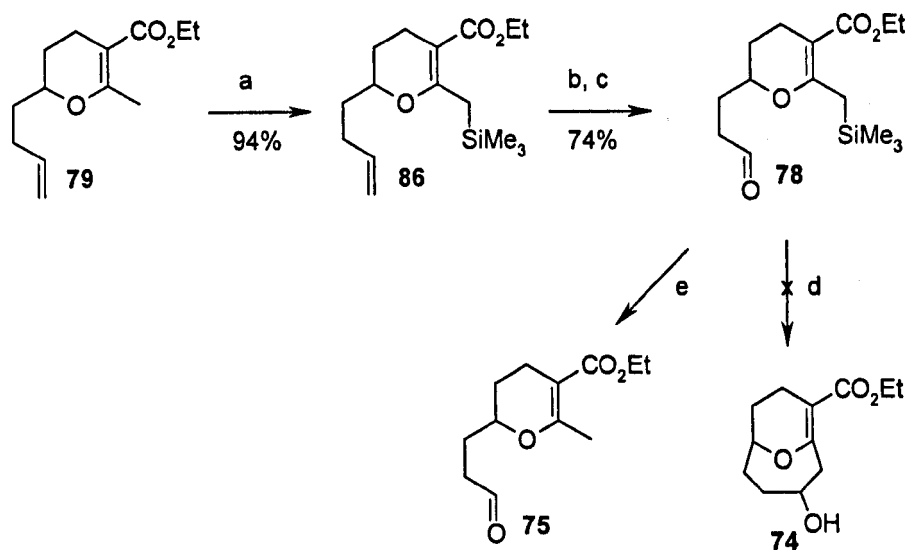
Given the failure of this direct approach, we then investigated the synthesis of the brominated and silylated substrates required (**77** and **78**, Scheme 30). Unfortunately all attempts to perform the bromination of **79** to form **84** failed to give the desired bromide. Radical (NBS, AIBN) and acidic (NBS, AcOH) conditions led to complicated mixtures of products, from which no desired product could be isolated. Basic conditions gave higher yields of the desired product **84**, but MS showed that **84** was contaminated with starting material **79** and dibromide **85** (Scheme 33). *Bis*-bromination is a common problem with base-mediated brominations, as the pK_a of the monobromide is lower than the pK_a of the starting material. Unfortunately, it was not possible to isolate **84**

from this mixture by chromatography, as the R_f values of **79**, **84** and **85** were found to be very similar.



Scheme 33

As efforts to isolate the desired bromide failed, we decided to concentrate on synthesising the corresponding silylated compound **78**. Thus **79** could be silylated with LDA/TMSCl to give **86** and the alkene of **86** could then be oxidatively cleaved as before to furnish **78** (Scheme 34). It was thought that the presence of the silyl group might favour a direct aldol cyclisation, by making the proton γ to the ester group in **78** more acidic. Thus aldol cyclisations of **78** were attempted with LDA, LHMDS, KHMDS and NaHMDS, but in all cases complicated mixtures of products were obtained from which no desired product **74** could be obtained. We then moved onto examining fluoride-mediated cyclisations of **78**. However, treatment of **78** with either TBAF or dry CsF gave the desilylated product **75**, with no desired cyclisation.



Scheme 34

Reagents and conditions: (a) LDA, THF; TMSCl (b) $\text{K}_2\text{OsO}_2(\text{OH})_4$, NMO, quinuclidine, acetone/water (c) NaIO_4 , $\text{MeOH}/\text{H}_2\text{O}$ (d) LDA or LHMDS or KHMDS or NaHMDS, THF (e) CsF or TBAF, THF

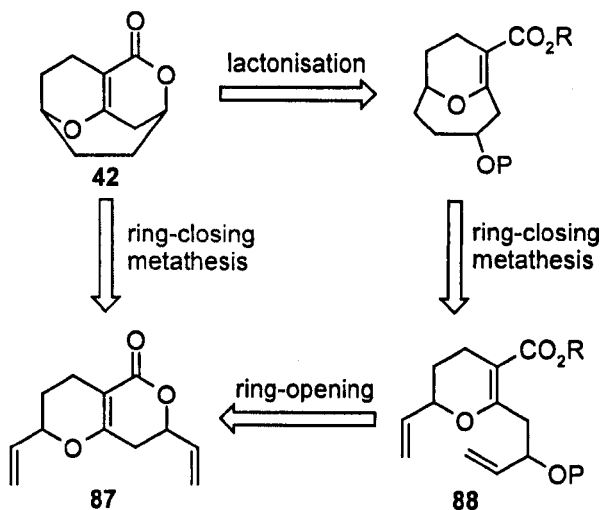
At this juncture, alternative solutions to synthesising the tricyclic motif were sought. In the next section, we return to using an intermolecular aldol reaction, focusing on a ring-closing metathesis reaction to form the 7-membered ring.

2.4 Direct metathesis approach to tricyclic system

2.4.1 Introduction

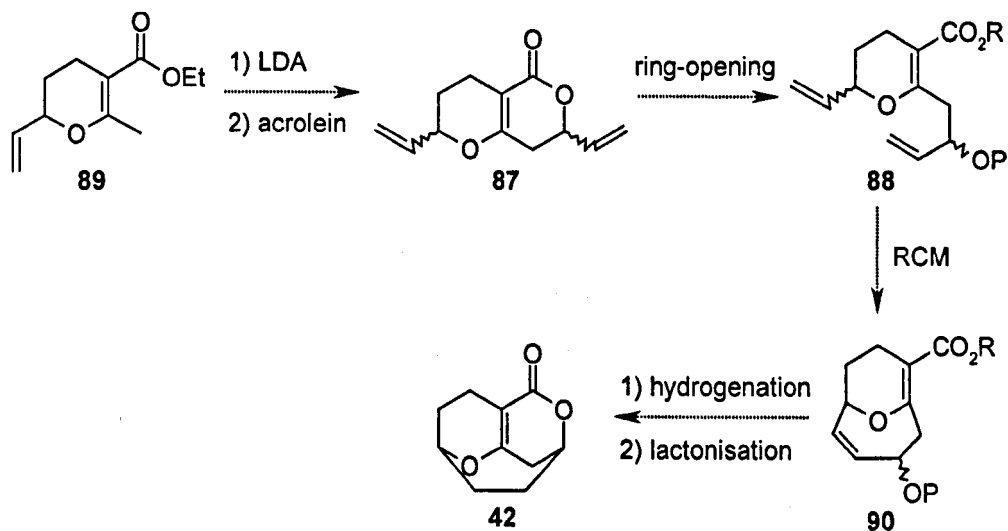
The previous two sections have demonstrated that, although intermolecular aldol reactions have been successful at forming bicyclic tetrahydropyranopyranones, efforts to extend this methodology to an intramolecular aldol reaction have not been successful. As an alternative, we were interested in an approach that used an intermolecular aldol reaction, followed by a ring-closing metathesis (RCM) reaction to furnish the desired tricyclic motif. Although ring-closing metathesis has been used extensively in recent years to synthesise a wide variety of ring sizes, very little work has been performed on RCM to synthesise strained ring systems, and we were therefore intrigued by the possibility that RCM could be applied to our problem.

This disconnection is shown in Scheme 35. A direct RCM disconnection (shown in red) would disconnect the desired tricyclic motif **42** to give **87**, which could in turn be synthesised by using the chemistry developed in section 2.2.4. This is a very challenging ring-closing metathesis reaction, as we are synthesising a highly strained product. A less challenging RCM disconnection is shown in black, where the RCM reaction is performed on the ring-opened compound **88**.



Scheme 35

In the forward sense, it was envisaged that treatment of **89** with LDA and acrolein would provide **87**. Ring-opening of the lactone to give **88** and subsequent ring-closing metathesis could then provide **90**. It was envisaged that **87** would be synthesised as a mixture of diastereoisomers, and therefore **90** would also be formed as a mixture of diastereoisomers. Only one diastereoisomer would have the correct stereochemistry to form **42** with a lactonisation, although it was thought that the other diastereoisomer could still furnish **42** *via* a Mitsunobu reaction.



Scheme 36

In recent years ring-closing metathesis has proved to be a remarkably successful route towards medium and large-sized rings,^{47,48} including 7-membered oxacycles as required

for our disconnection. The ruthenium-based RCM catalysts developed by Grubbs (Figure 11) have been found to be especially useful for natural product synthesis, due to their stability, ease of use and functional group tolerance.

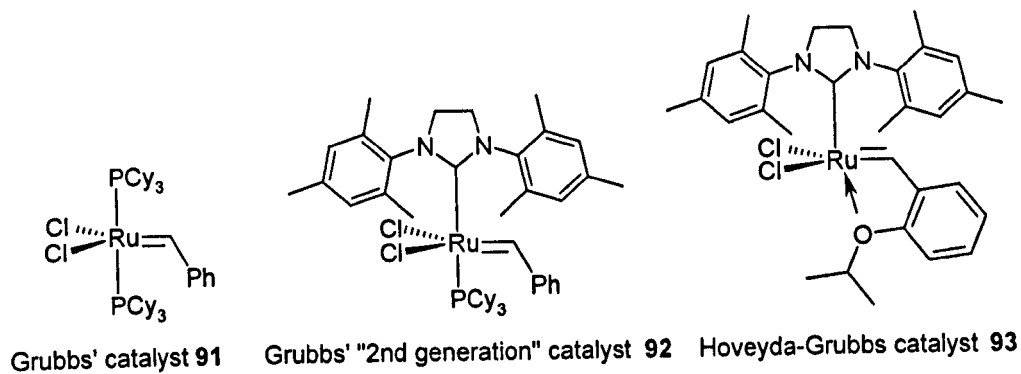


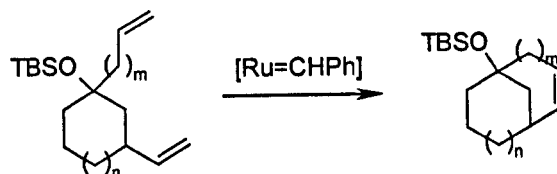
Figure 11

However, to our knowledge there are no examples of RCM being utilised to synthesise bridged rings with a bridgehead olefin, as we require. RCM is not generally a successful method to form strained ring systems, as the product that is formed may be a substrate for the catalyst, so making the reaction reversible. Even at high dilution, therefore, for strained ring systems oligomerisation is more likely to be observed than ring-closure. For this reason, before embarking on the synthetic work required to synthesise the RCM substrates we wanted to apply computational techniques to investigate whether **89** (Scheme 36) was a realistic class of substrate for a ring-closing metathesis reaction.

2.4.2 Can metathesis form strained ring systems? Computational studies

Although there are no examples in the literature of RCM being used to form strained bridgehead olefin compounds, Grubbs has published a communication where he attempted to quantify how much strain could be successfully introduced in a RCM reaction.⁴⁹ In this report, he calculated theoretical enthalpies of ring-closure (using the MM2 forcefield) for various bridged bicycloalkenes and then correlated these values to the experimental observations as to whether they underwent ring-closing metathesis or oligomerisation. These results are summarised in Table 3, and led Grubbs to propose that for this series of bicycloalkenes there was a good correlation between a low enthalpy of ring-closure and a successful cyclisation. Furthermore, he proposed that for RCM reactions to be successful, the enthalpy of ring-closure should be of the order of

10 kcal mol⁻¹ or less. However, as this approach only considered reaction enthalpies, the kinetics of the reaction were not taken into account. Clearly, a RCM reaction will fail if it is not kinetically feasible, regardless of how low the enthalpy of ring-closure is.



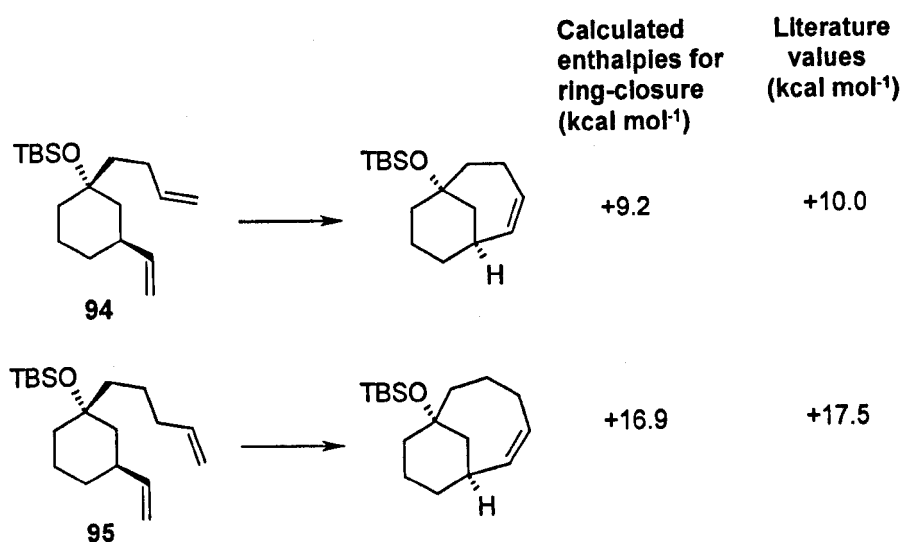
Entry	n	m	[Ru] (mol%)	T	Yield (%)	ΔH^a / kcal mol ⁻¹
1 ^b	0	1	5	RT	87	1.2
2 ^c	0	2	5	RT	(>95 Conv.) ^d	6.9
3 ^c	1	2	10	reflux	96	10.0
4 ^c	0	3	10	reflux	0	13.1
5 ^c	1	0	10	reflux	84	13.3
6 ^c	1	3	10	reflux	0	17.5

^a MM2 calculations. ^b Concentration in DCM=0.05M. ^c Concentration in DCM=0.005M. ^d Conversion by NMR spectroscopy.

Table 3: The theoretical enthalpies of ring-closure and the experimental RCM observations of a series of bicycloalkenes as reported by Grubbs⁴⁹

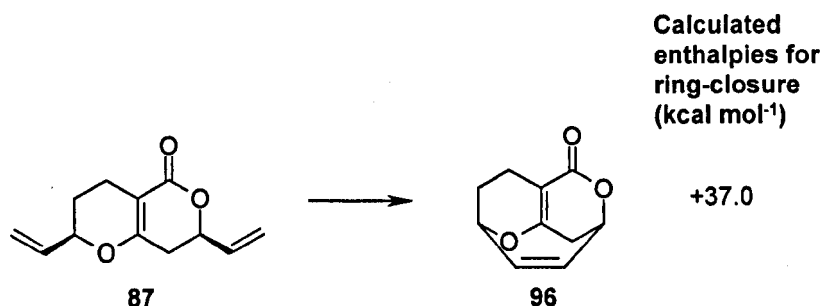
Following on from Grubbs' work, we wanted to calculate the enthalpy of ring-closure for our proposed cyclisations, by calculating the single point energies for the ring-closed and ring-opened forms. Although Grubbs used a MM2 forcefield to calculate the enthalpies of ring-closure, molecular mechanics is only considered to be an accurate method for obtaining molecular geometries and comparing conformations, and not a suitable method for obtaining relative energies of different molecules. We therefore decided to calculate the single point energies using *ab initio* techniques with the Hartree-Fock approximation. For all the energies obtained in this section, we used an MMFF forcefield to select the lowest energy conformation with a Monte-Carlo conformation search as implemented by SpartanTM, then the semi-empirical method PM3 to minimise the geometry of this conformation. The single point energy of this minimised conformation was then calculated using HF/6-31G*. The enthalpy of ring-closure was then defined as (single point energy of ring-closed form) + (single point energy of ethylene) – (single point energy of ring-opened form).

This method was used first to calculate the enthalpies of ring-closure for two of the examples that Grubbs has reported. Compound **94** (Scheme 37) was reported to undergo ring-closing metathesis (but only at high dilutions) whereas **95** was reported to undergo only oligomerisation. Our results (9.2 kcal mol⁻¹ for **94** and 16.9 kcal mol⁻¹ for **95**) were in excellent agreement with those reported by Grubbs using the MM2 forcefield (10.0 kcal mol⁻¹ for **94** and 17.5 kcal mol⁻¹ for **95**). Indeed, it is surprising that our results correlate with Grubbs' results so well, given that different calculation methods were used. These results suggest, therefore, that a molecular mechanics approach to these enthalpies may be acceptable, although as our method was still quick to compute we decided to continue to use HF/6-31G* to obtain our enthalpies of ring-closure. It should also be noted that we were concerned that molecular mechanics would be an especially poor method to model bridgehead olefins.



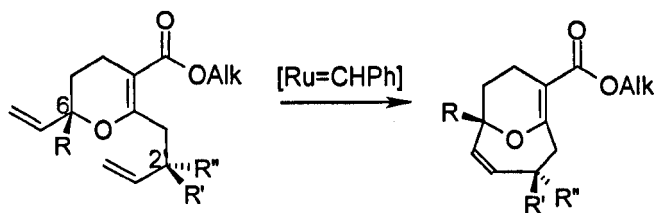
Scheme 37: Calculated theoretical enthalpies of ring-closure, as calculated by us and by Grubbs⁴⁹

We then went on to apply this method to the ring-closures that we require for our synthesis. Firstly, we examined the 'direct' RCM of the *cis* diastereoisomer of **87** to give **96** (Scheme 38). The calculated enthalpy of ring-closure obtained was +37.0 kcal mol⁻¹, a very high value that suggests that this cyclisation would be unlikely to be successful in the laboratory.



Scheme 38

We then investigated alternative ring-closures (Table 4), to assess whether these cyclisations were likely to be successful in the laboratory. Not surprisingly the enthalpy of ring-closure decreased substantially when the lactone was opened, *i.e.* the substrates listed in Table 4 all have a significantly lower enthalpy of ring-closure than 37.0 kcal mol⁻¹. Where R'=R''=H (entries 1 and 4), the calculated enthalpies were in the range that Grubbs suggested for successful cyclisations, *i.e.* less than 10 kcal mol⁻¹. With the additional oxygen functionality at C2' (entries 2, 3, 5 and 6), the enthalpies of ring-closure are higher, but are still in the range where Grubbs reports successful cyclisations. It is worth commenting that the enthalpies were not found to depend greatly on stereochemistry, *i.e.* entries 2 and 3 gave similar enthalpies of ring-closure, as did entries 5 and 6. Benzyloxy (OBn) groups were used in the modelling so that, if the RCM were successful, concomitant hydrogenation of the double bond of the product and of the benzyl group could be achieved. Similarly, the alkyl groups on the ester were chosen according to the planned synthetic route (see sections 2.4.3 and 2.4.4).



Entry	R	R'	R''	Alk	Calculated enthalpy of ring-closure (kcal mol ⁻¹)
1	H	H	H	Et	9.3
2	H	OBn	H	Me	12.2
3	H	H	OBn	Me	13.5
4	Me	H	H	Et	5.8
5	Me	OBn	H	Me	11.5
6	Me	H	OBn	Me	11.2

Table 4

Interestingly, where R=Me (as in the natural product) the calculated enthalpies were lower than where R=H (compare entries 1-3 to entries 4-6), and in the case of entry 4 (with no oxygenation at C2') markedly lower. This reduction in theoretical enthalpy of ring-closure for the substrates that possessed a methyl group at C6 cannot be ascribed to the *gem*-dialkyl effect. The *gem*-dialkyl effect is the observed rate enhancement of cyclisation when alkyl groups are placed on the acyclic chain that connects the two reacting centres. This observed effect is believed to be principally the result of a higher population of reactive *syn* rotamers (the "reactive rotamer effect"), with a smaller contribution coming from the reduction in internal angles in the acyclic chain (the "Thorpe-Ingold effect").^{50,51} However, both these effects only affect the free energy of activation, *i.e.* the *gem*-dialkyl effect is purely a rate enhancement, and does not affect relative free energies (or relative enthalpies) of starting material and product. As the enthalpy of ring-closure refers to relative energies between starting material and product, it follows that we cannot explain the above results in terms of the *gem*-dialkyl effect. It is unclear, therefore, why the methylated substrates have a lower enthalpy of ring-closure.

To conclude, these molecular modelling results suggested that ring-closing metathesis might be a viable approach if RCM is performed prior to lactonisation. They also

suggested that an extra methyl group at C6 might facilitate the cyclisation, and that a lack of oxygenation at C2' might also lead to a more facile cyclisation. These results, therefore, suggested four targets for synthesis (**97-100**, Figure 12). The syntheses of the unmethylated substrates **97** and **98** are presented in section 2.4.3, and the syntheses of the methylated substrates **99** and **100** are presented in section 2.4.4. The RCM reactions of both classes of substrates are discussed in section 2.4.5.

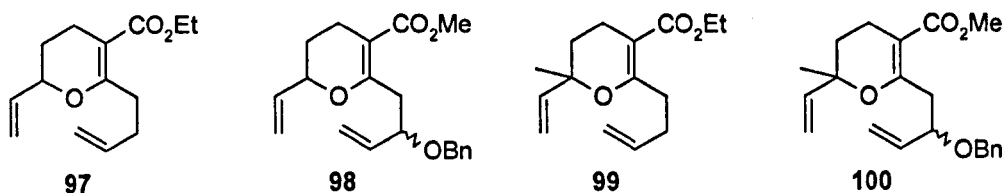
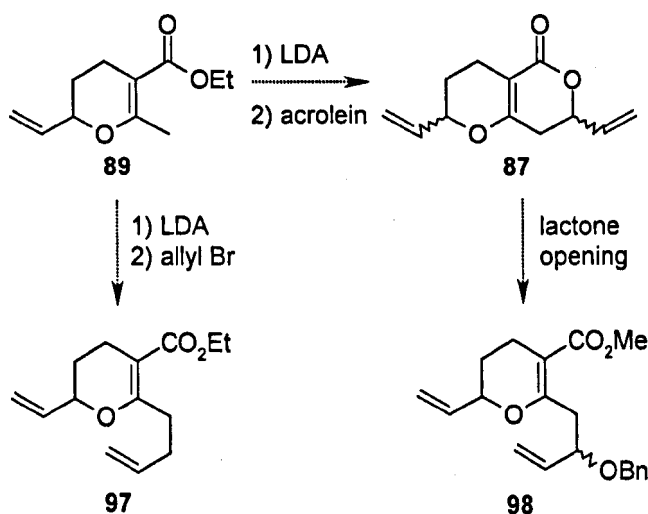


Figure 12

2.4.3 Syntheses of unmethylated RCM substrates

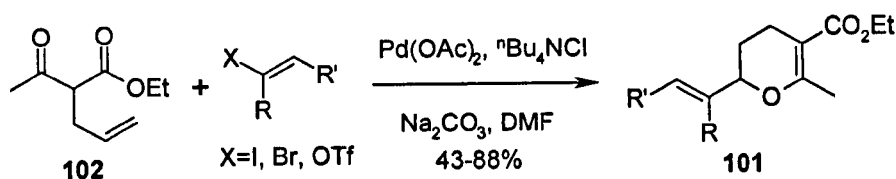
It was envisaged that **97** could be synthesised from an allylation of the enolate derived from **89** (Scheme 39), and that **98** could be synthesised from a ring-opening of **87**, which in turn could be synthesised from an intermolecular aldol reaction between **89** and acrolein.



Scheme 39

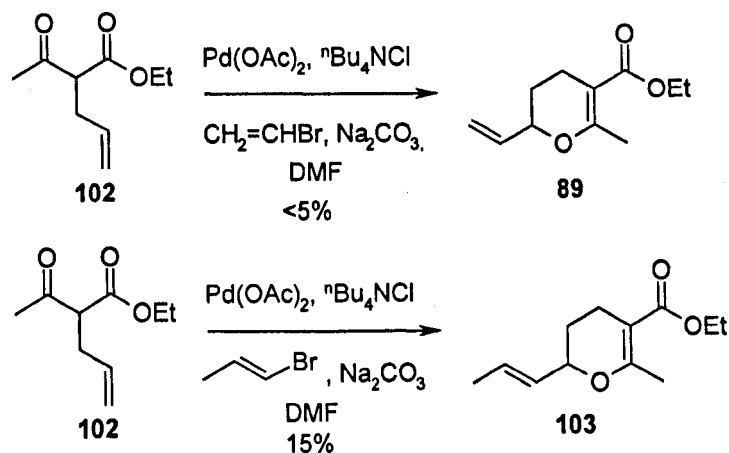
We therefore required an efficient synthesis of **89**. To achieve this goal, we were initially attracted to some work done by Cacchi,⁵² who showed that the desired

dihydropyran derivatives **101** could be synthesised from an allylated ketoester **102** and vinylic halides or triflates (Scheme 40).



Scheme 40: Literature precedent for the formation of vinyldihydropyrans⁵²

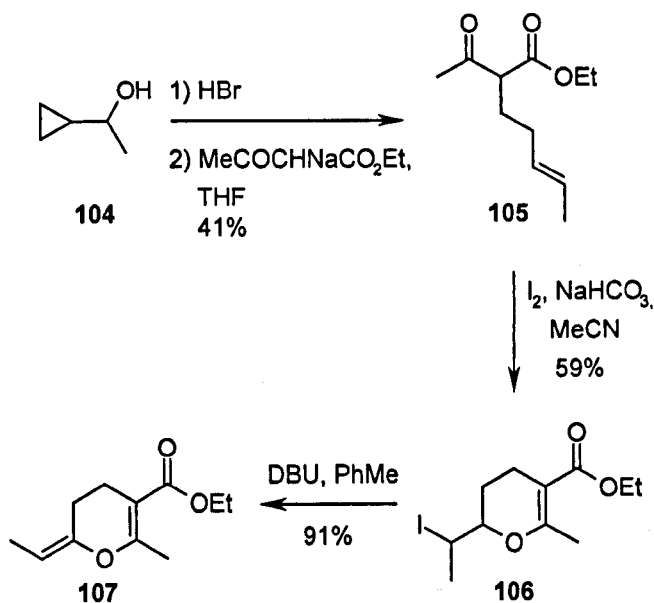
The starting material **102** for the palladium reaction was synthesised from allyl bromide and ethyl acetoacetate in 50% yield to give a sample that corresponded with literature data⁵³ (Scheme 41). Unfortunately, when **102** was treated with vinyl bromide, palladium (II) acetate, sodium carbonate and tetrabutylammonium chloride according to literature procedure,⁵² only trace amounts (<5%) of the desired product **89** was obtained. Note that this method has only been proven to work for sterically bulky vinylic halides, although it is not really clear why such poor yields are obtained with less bulky substrates. This reaction was also attempted with 1-bromo-1-propene instead of vinyl bromide, as a test for the methodology, and the corresponding product **103** was obtained in 15% yield. Given these disappointing results, we decided to investigate alternative solutions for the synthesis of **89**.



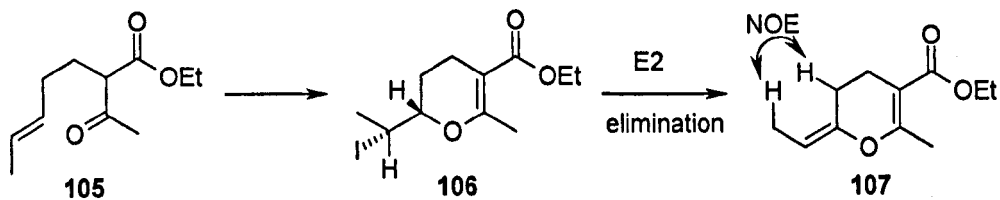
Scheme 41

An alternative solution was found using an iodine-mediated cyclisation (Scheme 42) as in section 2.3.2. Treating 1-cyclopropylethanol **104** with 48% HBr as reported in the literature⁵⁴ gave 5-bromo-2-pentene, which corresponded with literature data.⁵⁵ This was then coupled to ethyl acetoacetate to give **105** which corresponded with literature

data⁵⁶ in 41% overall yield from **104**. This material **105** was then cyclised with iodine to give the required dihydropyran **106** in 59% yield. Unfortunately, treatment of **106** with DBU, Dabco™ or ^tBuOK/^tBuOH gave the trisubstituted alkene **107** as the sole product, rather than the desired terminal alkene.

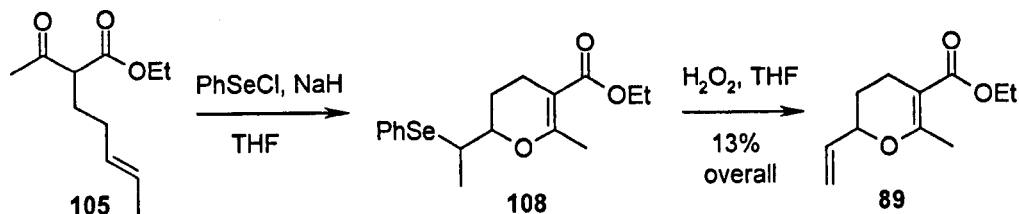


For this synthesis the stereochemistry of **106** was not important, as we intended to form the terminal alkene **89** that could be formed from either diastereoisomer of **106**. However, it is worth commenting that **107** was formed as the *E* isomer as shown, as shown by NOE studies. This was the expected result, as from literature precedent⁵⁴ the 5-bromo-2-pentene formed in this way should have been predominantly *E*, which would then be expected to give the *E* isomer of **107** by a stereospecific cyclisation and an antiperiplanar E2 elimination as shown in Scheme 43.



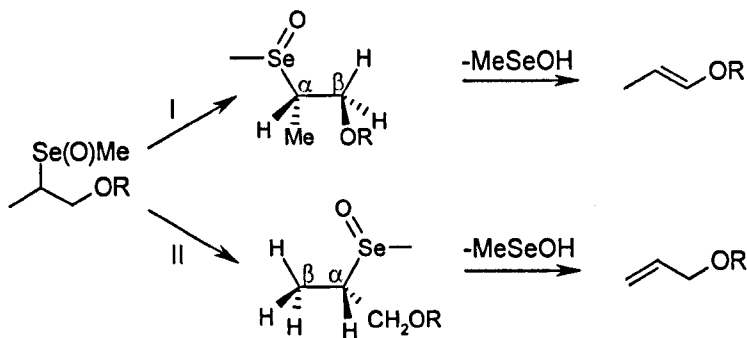
In order to form the desired terminal alkene, the cyclisation of **105** was effected with phenylselenenyl chloride and sodium hydride⁵⁷ to give the corresponding selenide **108** (Scheme 44). On treatment with H₂O₂, the resulting selenoxide underwent elimination

to give the desired terminal alkene **89**. However, the overall yield was very low (13%) due to the inefficiency of the cyclisation step.



Scheme 44

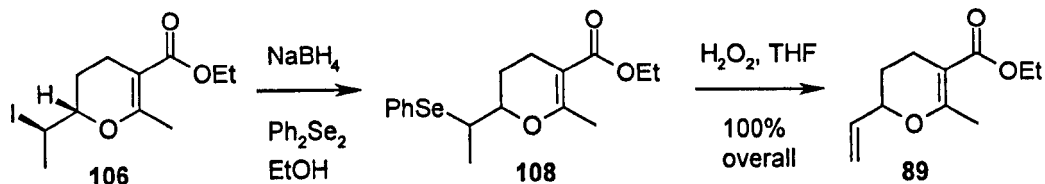
The regioselectivity of this elimination was expected as it is well documented in the literature⁵⁸ that selenoxides eliminate away from a nearby oxygen. One possible explanation for this observation is that there are more eclipsing interactions in the transition state that leads to the allylic product (*i.e.* the external alkene) than in the transition state that leads to the vinylic product (*i.e.* the internal alkene). Molecular modelling studies by Fujimoto *et al.*⁵⁸ have supported this theory, by demonstrating that for a simplified system these eclipsing interactions are worse in the transition state that leads to the internal double bond. Thus in pathway I (Scheme 45), which leads to the internal double bond, there are more unfavourable eclipsing interactions between the α and β substituents than in pathway II.



Scheme 45: Formation of the internal double bond (top) is disfavoured due to more unfavourable eclipsing interactions⁵⁸

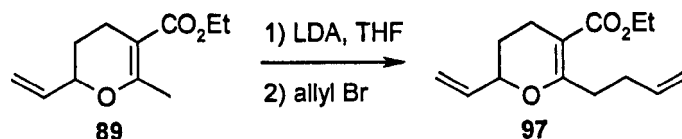
However, the cyclisation with PhSeCl/NaH was found to afford irreproducible results and low yields, and no cyclised product was obtained with NPSP/SnCl₄.⁵⁹ Consequently, the preferred method was to form the dihydropyran **106** with iodine then to displace iodine with a nucleophilic source of selenium⁶⁰ (generated from diphenyl diselenide and sodium borohydride) to give the selenide **108** (Scheme 46). The desired

product **89** could then be formed from the selenide **108** as before. The selenide formation and elimination steps could be performed in one pot, in overall quantitative yield (74% + 25% from recycling of recovered selenide with hydrogen peroxide).



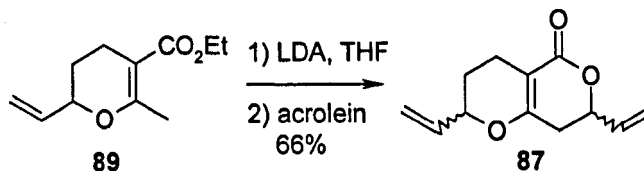
Scheme 46

With an efficient synthesis of **89** in hand, we then investigated the synthesis of the desired RCM substrates **97** and **98**. The non-oxygenated compound **97** was synthesised from **89** by trapping the enolate with allyl bromide (Scheme 47). Unfortunately, **97** was contaminated with starting material that could not be separated by chromatography, but a sample of pure **97** for characterisation purposes was isolated at a later date from a failed RCM reaction.



Scheme 47

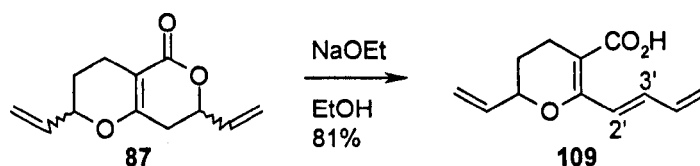
On treatment of **89** with LDA and subsequent reaction with acrolein³⁸ the desired bicyclic compound **87** (Scheme 48), formed as a 1:1 mixture of diastereoisomers, could be synthesised in 66% yield if the reaction mixture was maintained at -78°C for 24 hours before warming to -22°C overnight.



Scheme 48

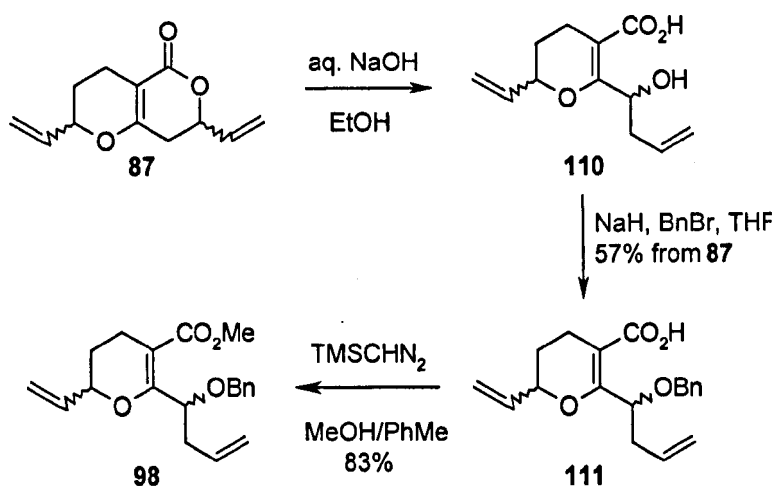
A direct approach where the lactone was opened with sodium ethoxide was then attempted, but the product that was isolated from this reaction had characteristic ¹H NMR signals for a diene. Full characterisation of the compound then revealed that it

was the elimination product **109** as shown in Scheme 49, assigned as the *E* isomer from the coupling constant observed between 2'-H and 3'-H of 15.2 Hz.



Scheme 49

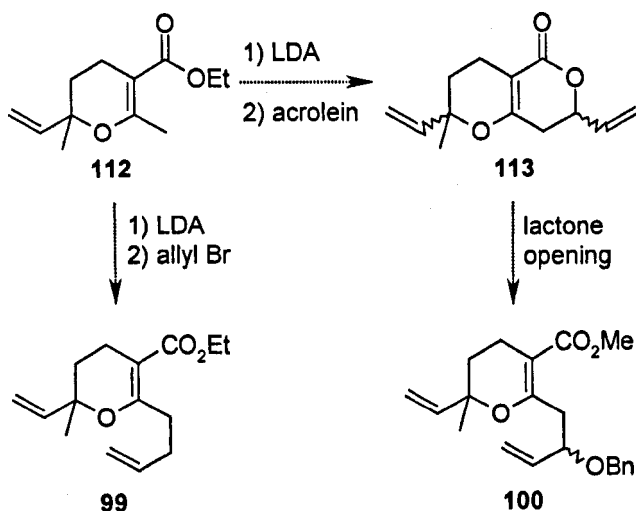
Instead of a direct ring-opening, therefore, we decided to saponify **87** to give the corresponding hydroxy acid **110**. Benzylation of **110** to give **111** and subsequent esterification of **111** then gave the desired RCM substrate **98** (Scheme 50).



Scheme 50

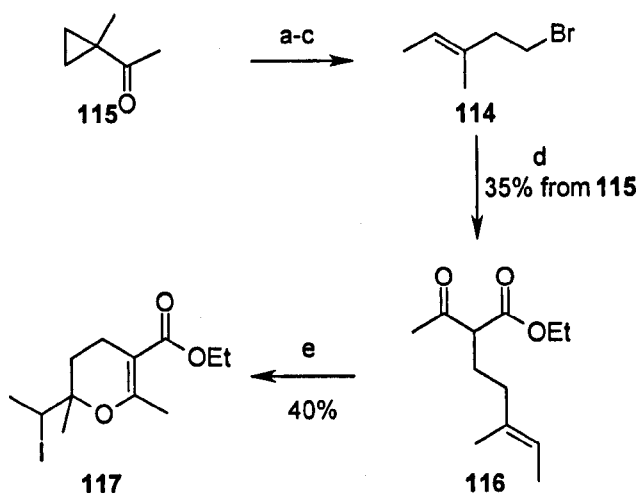
2.4.4 Syntheses of methylated RCM substrates

With **97** and **98** in hand, we then moved on to examine the synthesis of the methylated RCM substrates **99** and **100**. We planned to use similar chemistry to that used for the unmethylated series, *i.e.* it was thought that **99** and **100** could be accessed from **112** and **113** (Scheme 51).



Scheme 51

The synthesis of **112** utilised similar methodology as for **89**. Thus **114** was synthesised according to literature procedure^{61,62} from methyl 1-methylcyclopropyl ketone **115** (Scheme 52). This was coupled to the Na salt of ethyl acetoacetate to give **116**, which could then be cyclised with iodine in moderate yield to give **117**.

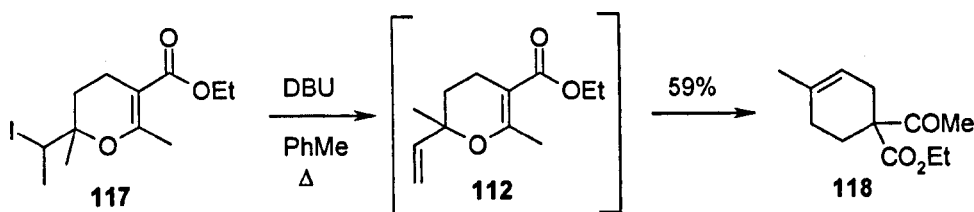


Scheme 52

Reagents and conditions: (a) LAH, Et₂O (b) PBr₃, LiBr, 2,4,6-collidine, Et₂O (c) ZnBr₂, Et₂O (d) Na salt of ethyl acetoacetate, ⁿBu₄NI, THF (e) I₂, NaHCO₃, MeCN

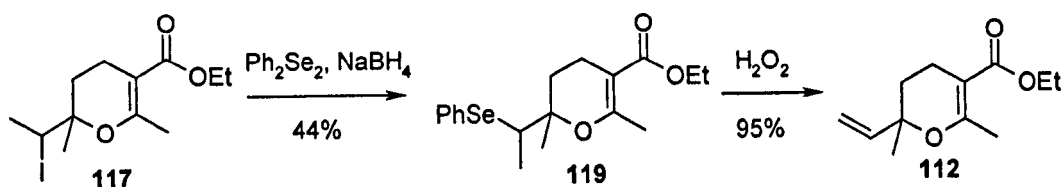
It was anticipated that base-mediated elimination of HI from **117** would give **112** directly (Scheme 53). However, under the forcing conditions required for elimination (DBU, refluxing toluene) the isolated product only possessed one alkene signal in the ¹H NMR spectrum, and ¹³C NMR spectroscopy showed that the product had a ketone

group. Full characterisation then confirmed that the product was **118**, which was the result of the desired product **112** undergoing a Claisen rearrangement.



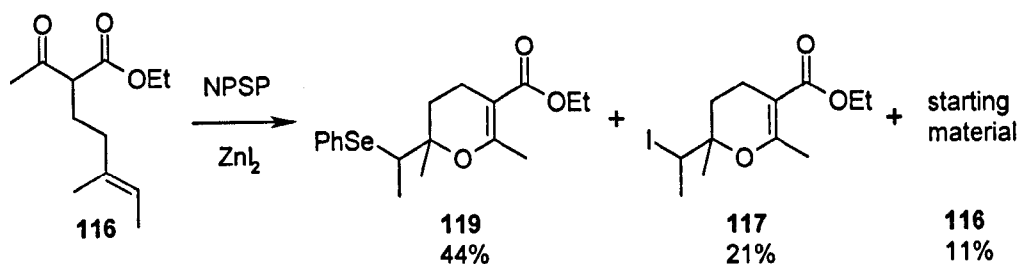
Scheme 53

To avoid this problem **117** could be converted to the corresponding selenide **119** (Scheme 54) with $\text{Se}_2\text{Ph}_2/\text{NaBH}_4$ as in section 2.4.3, but this reaction was slow and gave a poor yield (47%), presumably due to the steric encumbrance of having a quaternary centre adjacent to the carbon undergoing $\text{S}_\text{N}2$ attack. The selenide **119** could then be oxidised with H_2O_2 to give **112**. However, the low yields of both the iodine-mediated cyclisation and the subsequent selenylation prompted us to investigate other routes to the desired selenide **119**.



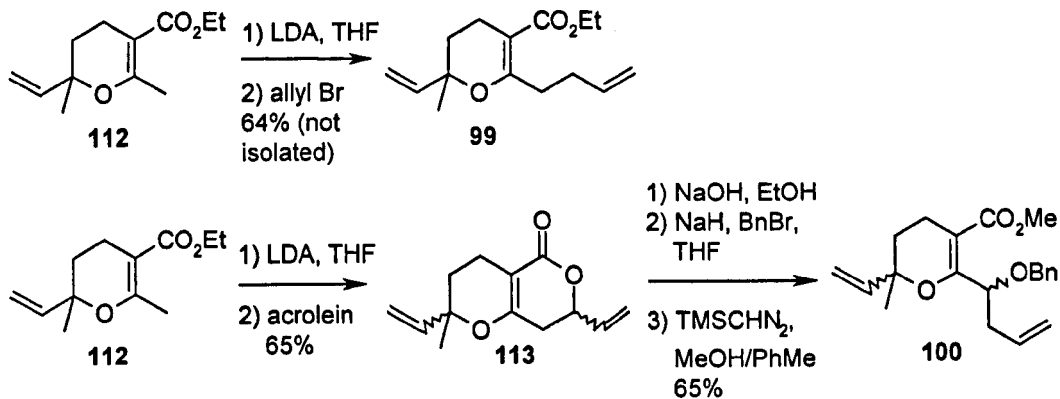
Scheme 54

A more efficient process was found where **116** was cyclised with NPSP/ ZnI_2 ⁵⁹ to give a 44% yield of the desired selenide **119**, along with 21% of the corresponding iodide **117** and 11% of recovered starting material **116** (Scheme 55). Both **116** and **117** were then recycled to synthesise more selenide. This approach gave a significantly higher overall yield of selenide so was the preferred route to synthesise **112**.



Scheme 55

With **112** in hand, we then synthesised the desired RCM substrates **99** and **100**, using the same chemistry as reported in section 2.4.3. Thus, **99** was synthesised from **112** with LDA and allyl bromide (Scheme 56). Once again the product (formed in 64% yield) was contaminated with starting material (89% pure by LCMS) but extensive chromatography gave 20% yield of pure product. The oxygenated RCM substrate **100** was then synthesised from **112** via the tetrahydropyranopyranone **113** as in the previous section.

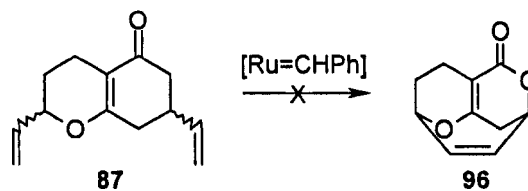


Scheme 56

With the four desired RCM substrates in hand (**97-100**), we were then in a position to examine the RCM reactions of these substrates.

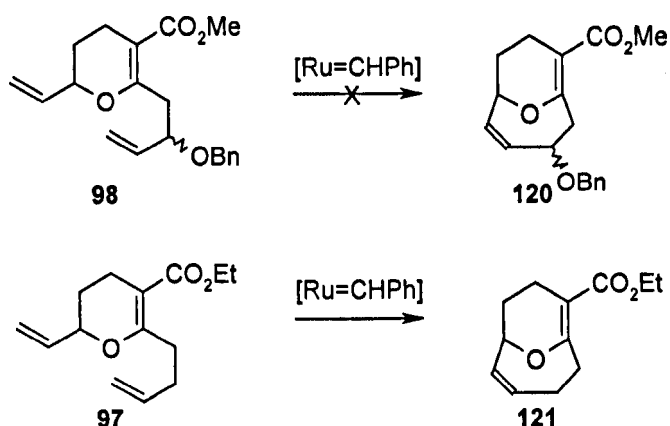
2.4.5 Ring-closing metathesis reactions

The first RCM reaction that we investigated was the 'direct' RCM of **87** (Scheme 57). From the calculations that had been made on this system (see section 2.4.2) we did not expect this RCM to be successful, but we wished to confirm this in the laboratory. Also, clearly only the *cis* diastereoisomer of **87** can cyclise, but **87** was formed as a 1:1 mixture of *cis:trans* diastereoisomers. Not surprisingly, the RCM of **87** with either 1st generation **91** or 2nd generation Grubbs' catalysts **92**⁶³ (see Figure 11 for catalyst structures) gave a complicated mixture of products from which we failed to isolate any desired product **96**, even when the reaction was performed at high dilution (<0.01M). As discussed previously, the product of this reaction would be highly strained, and therefore prone to ring-opening to form oligomers and polymers.



Scheme 57

We then investigated the RCM reactions of substrates **97** and **98**. Attempts to effect RCM on **98** with Grubbs' 2nd generation catalyst afforded complicated mixtures, with no identifiable desired product **120** (Scheme 58). Treatment of **97** with Grubbs' 1st generation catalyst gave no reaction. However, treatment of **97** with 2nd generation catalyst gave a complicated mixture that contained dimer and desired product **121** (according to MS). However, the desired product could not be isolated from this mixture by chromatography.



Scheme 58

One concern we had with this class of substrates was the degree of oxidation in these compounds. Although Grubbs' catalyst is tolerant of oxygen functionality in the substrate, in some cases RCM reactions can be severely hindered by stable chelate structures between the metal carbene and a nearby oxygen. One possible chelate structure for **97** when bound to the catalyst is shown in Figure 13. Where chelation occurs, Fürstner has suggested⁶⁴ that addition of $\text{Ti}(\text{O}^i\text{Pr})_4$ can break up these stable chelate structures and thereby improve the yield of the RCM reaction. Interestingly, addition of $\text{Ti}(\text{O}^i\text{Pr})_4$ appeared to speed up the reaction and gave a slightly cleaner reaction. However, the desired product **121** could still not be isolated by chromatography.

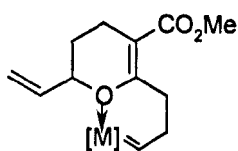
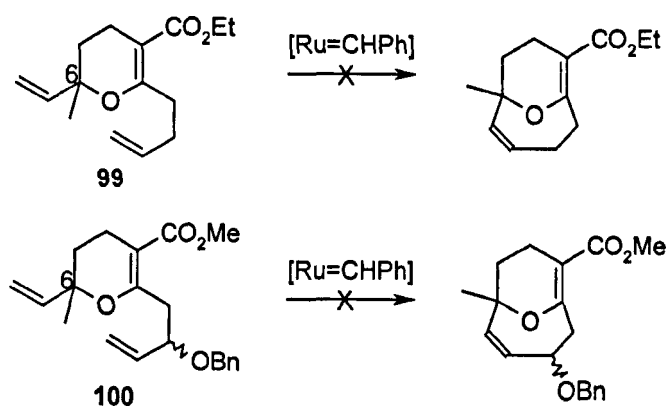


Figure 13

Given the failure to isolate the desired product, we then investigated RCM reactions of **99** and **100** (Scheme 59). However, on treatment of either **99** or **100** with either Grubbs' 2nd generation catalyst **92** or the Hoveyda-Grubbs catalyst⁶⁵ **93** (see Figure 11 for catalyst structures) only slow decomposition of the starting material was observed. The low reactivity of these substrates to RCM catalysts may be a consequence of the quaternary centre at C6. Thus, even if the enthalpy of ring-closure is very low, a proximal quaternary centre may stop the catalyst initiating the reaction.



Scheme 59

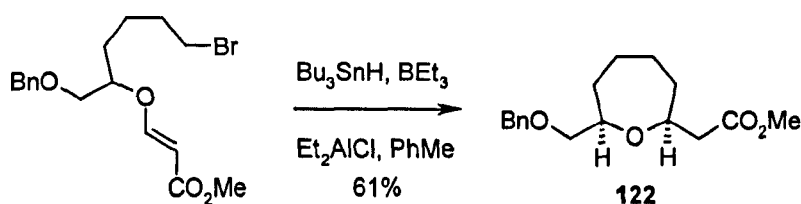
This disappointing result led us to consider alternatives to ring-closing metathesis. In section 2.5 our efforts to effect radical cyclisations are reported. In section 2.6, however, a more successful RCM approach is reported, based on an alternative class of substrates.

2.5 Radical cyclisation approach to tricyclic system

2.5.1 Introduction

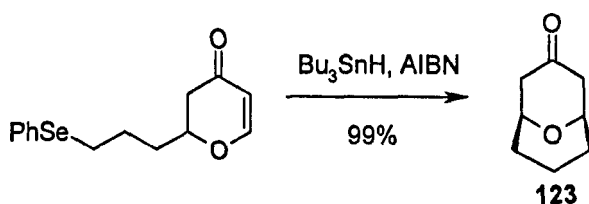
Radical cyclisations are a commonly used strategy in the literature to form a variety of ring sizes. In particular, the formation of 5-membered rings *via* 5-*exo-trig* cyclisations of a carbon-centred radical onto an alkene has proved to be very successful. There are

also, however, a number of examples of 7-membered rings, including 7-membered oxacycles, that have been synthesised *via* 7-*exo-trig* cyclisations of a carbon-centred radical onto an alkene.⁶⁶ These cyclisations are considerably less facile than the 5-*exo-trig* cyclisations, but can still occur in high yield if the alkene is activated, for example by conjugation. In the example shown (Scheme 60), a 7-membered oxacycle **122** has been synthesised from a cyclisation of a carbon-centred radical onto an alkoxyacrylate.⁶⁷



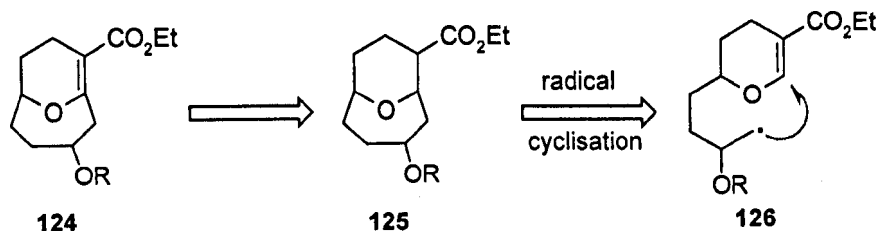
Scheme 60⁶⁷

There are also numerous examples of intramolecular radical cyclisations being used to form oxabicycles in the literature.⁶⁸ In the example shown (Scheme 61) a 9-oxa-bicyclo[3.3.1]nonane **123** has been synthesised in quantitative yield from a cyclisation of a carbon-centred radical onto a dihydropyranone.⁶⁹



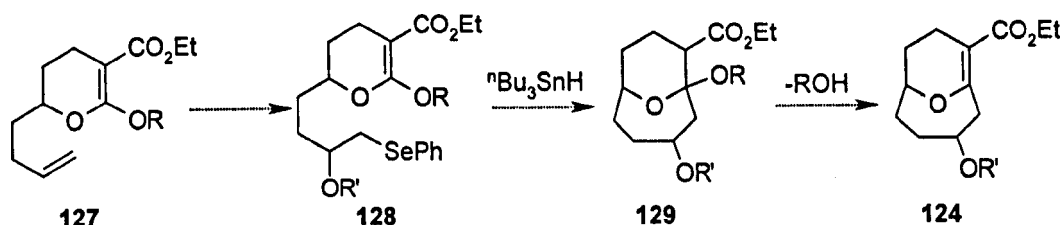
Scheme 61⁶⁹

However, to our knowledge there are no examples in the literature of a radical cyclisation being used to form a 7-membered bridged ring, as we require. We were therefore interested to investigate whether this methodology could be adapted to our ring system. One possible disconnection is shown in Scheme 62. It was envisaged that the bridgehead olefin compound **124** could be accessed from the saturated compound **125**, which in turn could be synthesised from **126** *via* a radical cyclisation of a carbon-centred radical onto an α,β -unsaturated ester.



Scheme 62

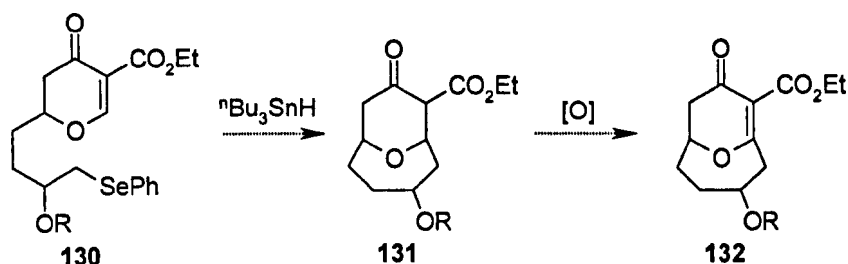
The conversion of the saturated compound **125** to the bridgehead olefin **124** is not a trivial transformation. To achieve this goal we developed two different strategies. The first strategy relied upon an elimination to install the bridgehead olefin, as shown in Scheme 63. It was thought that a dihydropyran such as **127** could be functionalised by *e.g.* an oxyselenylation to give **128**, which possesses the desired oxygenation and a radical precursor (SePh in this example). On treatment of **128** with a tin hydride source and an initiator, it was thought that the resulting radical might cyclise onto the α,β -unsaturated ester to give **129**. The desired bridgehead olefin could then be installed with an elimination (of ROH) to give **124**. Lactonisation of **124** would then furnish the desired tricyclic motif. Our efforts to realise this goal are reported in section 2.5.2.



Scheme 63

This strategy required a synthesis of the starting material **127**. As this synthesis was not well precedented in the literature, we also developed an alternative strategy that relied upon an oxidation to install the bridgehead olefin (Scheme 64). It was thought that this strategy would require a dihydropyranone such as **130** (with the extra ketone at C4) instead of a dihydropyran, to ensure that the oxidation proceeded with the correct regiochemistry and to simplify the synthesis of the starting material. Thus, a similar intramolecular radical cyclisation could convert **130** to **131** and an oxidation could then yield the desired bridgehead olefin compound **132**. It is worth commenting that if this route were applied to a total synthesis of FR182877, then the ketone in the

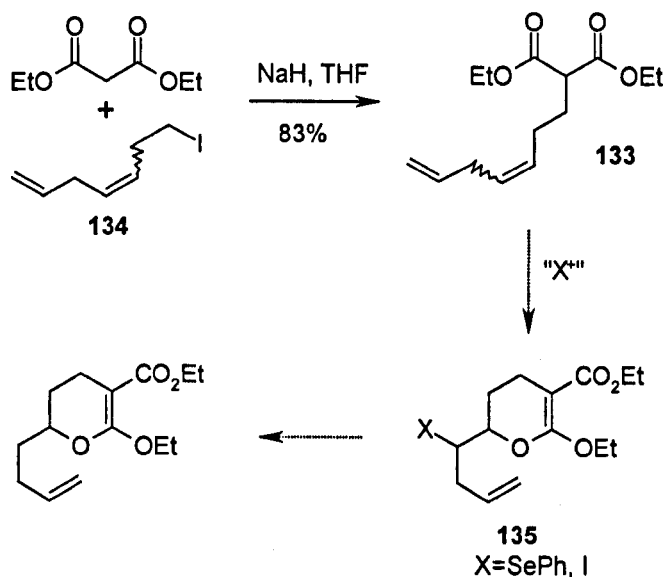
dihydropyranone could be used to introduce the A-C rings. Our efforts to realise this goal are reported in section 2.5.3.



Scheme 64

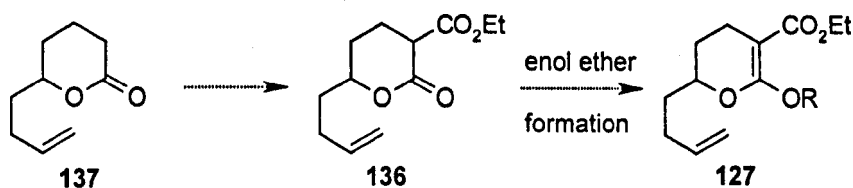
2.5.2 Dihydropyran model system

For this approach, we required a synthesis of **127** (Scheme 63). A conceptually simple approach to **127** relies upon an intramolecular cyclisation of a malonate group onto an alkene, as shown (Scheme 65). Thus **133** was synthesised in high yield from diethyl malonate and **134** (see section 2.3.2, Scheme 31 for synthesis of **134**). Unfortunately all efforts to effect cyclisation of **133** with various electrophilic sources of iodine and selenium failed to give the desired product **135**. This failure contrasts with the successful cyclisation of the ketoester of **82** onto the same sidechain as reported in section 2.3.2. It appears that the malonate group cyclisation is considerably less facile than the ketoester cyclisation, possibly due to the lower proportion of enol present in the malonate system. Although no products were successfully isolated from these reactions, it was clear from ^1H NMR spectroscopy analysis of the crude mixtures that the main reaction occurring was addition of the reagent across the terminal alkene (*e.g.* addition of PhSe and Cl when PhSeCl was used).



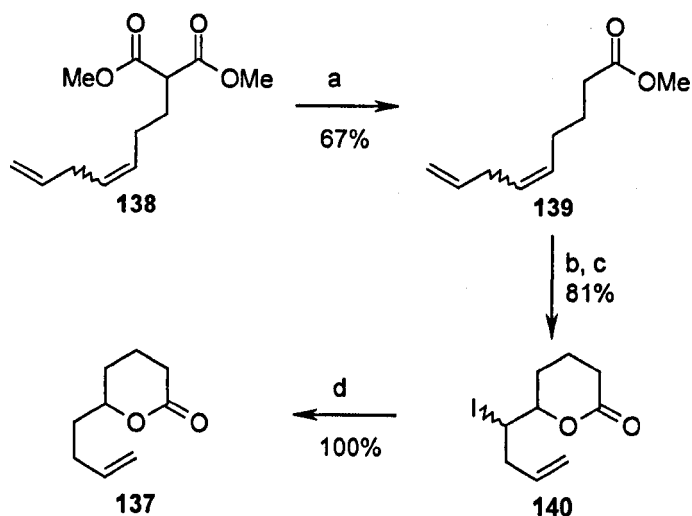
Scheme 65

As an alternative, it was thought that **127** could be synthesised from **136** *via* enol ether formation (Scheme 66). It was envisaged that **136** could in turn be synthesised from **137**.



Scheme 66

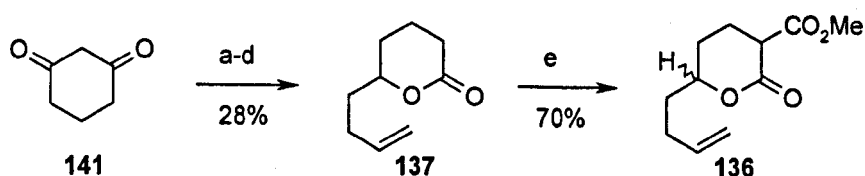
The lactone **137** required for this approach was synthesised from **138** (Scheme 67). Thus Krapcho decarboxylation of **138** furnished **139**, then saponification of the ester and iodolactonisation of the resulting carboxylic acid gave **140**, and subsequent tin-mediated deiodination furnished **137**, which corresponded with literature data.⁷⁰



Scheme 67

Reagents and conditions: (a) NaCl, DMSO/H₂O (b) NaOH, EtOH (c) I₂, NaHCO₃, MeCN (d) Bu₃SnH, AIBN, PhMe

This route was chosen initially, as quantities of **138** had already been synthesised for another route. However, when larger quantities of **137** were required it was more convenient to synthesise **137** according to the literature route from cyclohexanedione **141**, *via* allylation, Ba(OH)₂ cleavage, NaBH₄ reduction and an acid-catalysed lactonisation (Scheme 68).⁷¹ Treatment of **137** with LHMDS and Me₂CO₃ then furnished **136** as a 1:1 mixture of diastereoisomers.

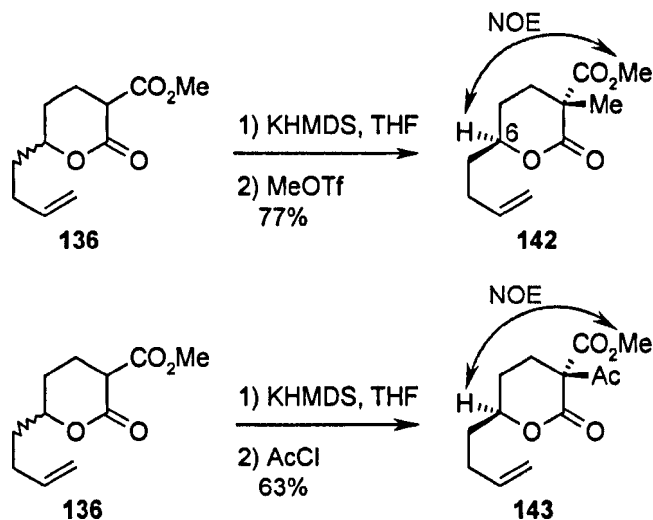


Scheme 68

Reagents and conditions: (a) allyl Br, KOH, Cu, H₂O (b) aq. Ba(OH)₂ (c) NaBH₄, aq. NaOH (d) HCl (e) LHMDS, THF, Me₂CO₃

With **136** in hand, we then attempted to form the corresponding enol ether. However, all efforts to form the enol ether, enol triflate or enol acetate of **136** failed with NaH/BF₄OEt₃, EtⁱPr₂N/BF₄OMe₃, NaH/BF₄OMe₃, NaH/Me₂SO₄, TMSCHN₂/MeOH, KHMDS/PhNTf₂, KHMDS/BF₄OMe₃, KHMDS/BF₄OEt₃ or AcCl/py. In most cases starting material was recovered, although when **136** was treated sequentially with KHMDS and MeOTf clean C-methylation was observed to give **142** (Scheme 69) as a single diastereoisomer. A NOE was observed between the methyl ester and 6-H,

suggesting that the isolated diastereoisomer was *trans* as drawn. Similarly when **136** was treated sequentially with KHMDS and AcCl then clean C-acetylation was observed to give **143**, again as a single diastereoisomer shown by NOE data to be the *trans* diastereoisomer. The observed stereochemistry of the product in both cases is the expected result of axial attack of the electrophile onto the enolate. It is unclear why the enolate derived from **136** cannot be induced to react on oxygen, even when 'hard' electrophiles and potassium enolates are used.

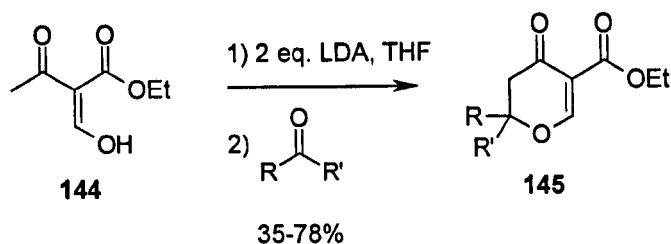


Scheme 69

With the failure of this approach to form the required starting material, we decided to turn our attention to the dihydropyranone system.

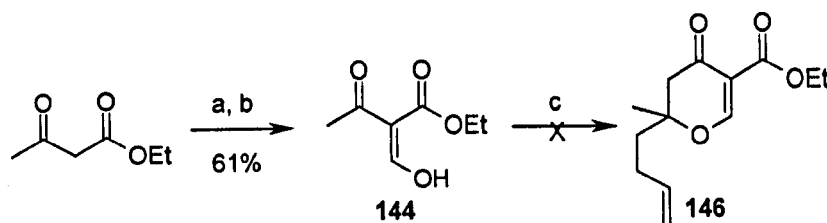
2.5.3 Dihydropyranone model system

To synthesise the dihydropyranone that we required for this approach, we were attracted initially to some chemistry developed by Totah, where the dianion of **144** was formed and reacted with ketones to give the corresponding dihydropyranones **145** (Scheme 70).⁷²



Scheme 70⁷²

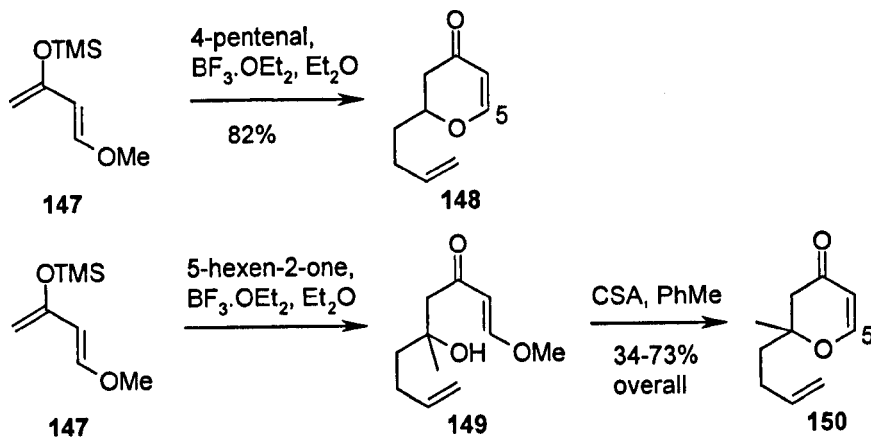
If 5-hexen-2-one was used as the ketone in this reaction, it was anticipated that the desired product **146** would be isolated (Scheme 71). The required starting material **144** was synthesised according to literature procedure in 2 steps from ethyl acetoacetate,⁷² and was fully characterised to ensure that it corresponded with the literature data. However, on subsequent reaction with 2 eq. LDA and 5-hexen-2-one no desired product was obtained, despite repeated attempts to recreate the published procedure exactly. Also, an attempt was made to repeat a literature example using acetone as the ketone (for which Totah reported a 78% yield) but only traces of the desired material was obtained. It is unclear why we failed to repeat the literature in this case.



Scheme 71

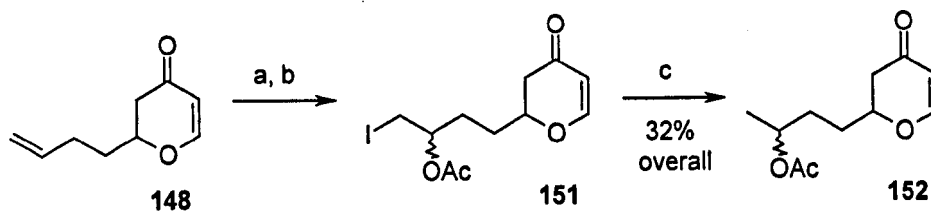
Reagents and conditions: (a) DMF dimethyl acetal, TsOH cat. (b) 10% aq. HCl, THF (c) 2 eq. LDA then 5-hexen-2-one

As an alternative, it was found that Danishefsky's diene **147** reacted smoothly with 4-butenal in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ ⁷³ to give the desired adduct **148** (Scheme 72). Similarly, 5-hexen-2-one reacted with Danishefsky's diene to give the Mukaiyama aldol product **149**, which could be isolated if desired but in low yield. However, it was found that the crude mixture of **149** could be cyclised to the required Diels-Alder product **150** with TFA/THF (as reported by Danishefsky)⁷⁴ or more efficiently with CSA/PhMe, albeit in variable yield (34-73% over 2 steps).



Scheme 72

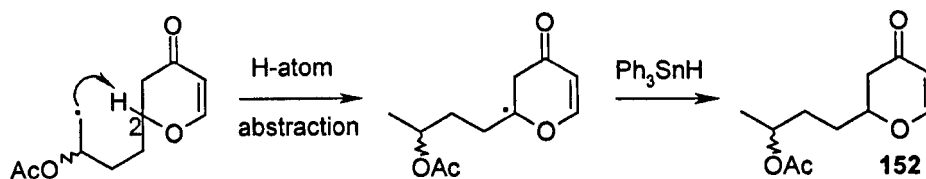
Although substrates **148** and **150** lack the ester functionality at C5, we proceeded to test them to see if we could form a bicyclic compound with a radical cyclisation. Thus treatment of **148** with $\text{I}_2/\text{BTI}^{75}$ gave the iodohydrin which was then acetylated to give **151** (Scheme 73), although **151** was found to be unstable and difficult to purify. Solutions of Ph_3SnH and AIBN were then slowly added *via* a syringe pump to a solution of **151** that was heated at reflux. However, the only isolated product from this reaction was the reduced uncyclised product **152**. It seems that even with slow addition of the Ph_3SnH the radical that was generated from **151** was reduced before cyclisation took place.



Scheme 73

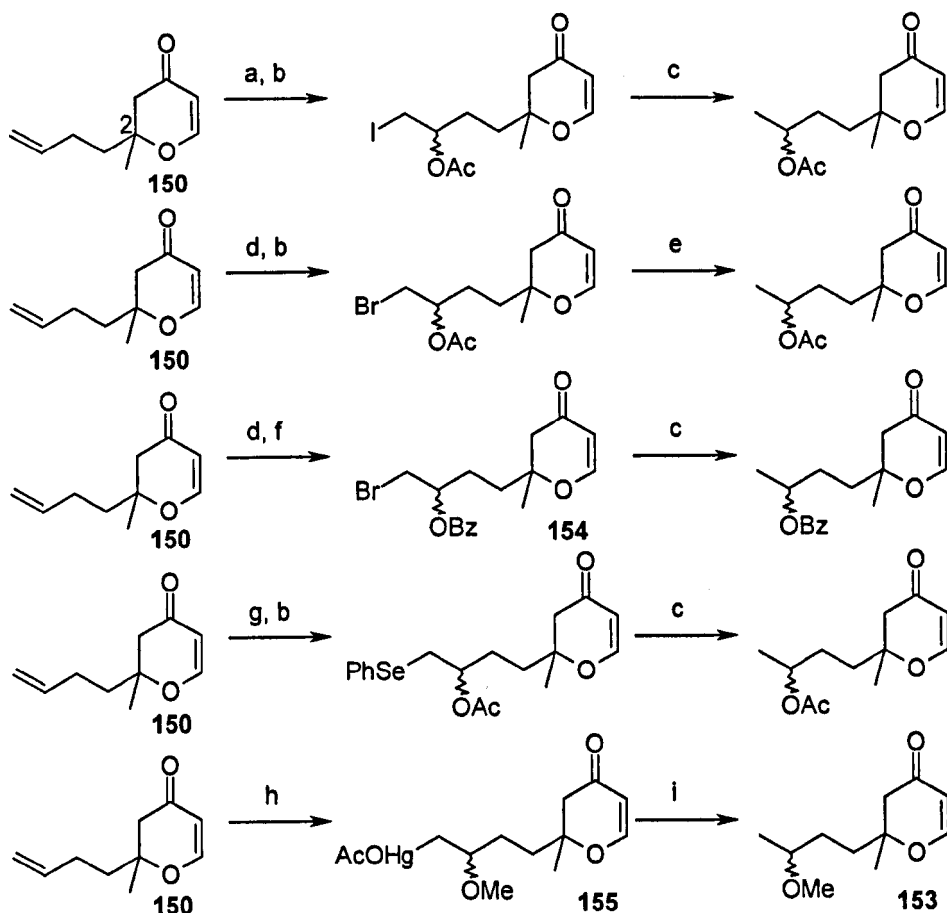
Reagents and conditions: (a) I_2 , BTI, $\text{MeCN}/\text{H}_2\text{O}$ (b) py, Ac_2O (c) Ph_3SnH , AIBN, PhH

It is unclear whether the radical generated from **151** is being reduced directly by Ph_3SnH or by competing 1,5-hydrogen abstraction from the hydrogen on C2 (Scheme 74). There is also the possibility of 1,5-hydrogen abstraction from the hydrogen on the acetate group, although this was considered unlikely as it requires the ester group to be in an unfavourable *s-trans* conformation.



Scheme 74

To avoid the possibility of 1,5-hydrogen abstraction, we decided to concentrate on applying the same chemistry to **150**, which clearly cannot undergo the above 1,5-hydrogen abstraction as it has a methyl group at C2. A range of potential radical precursors were synthesised from **150** (Scheme 75), utilising bromohydrin formations,⁷⁶ hydroxyselenylations⁷⁷ and methoxymercurations.^{78,79} However, in all cases only uncyclised reduced products were observed on treatment with either $\text{Bu}_3\text{SnH/AIBN}$ or $\text{Ph}_3\text{SnH/AIBN}$, although due to difficulties with purifying the products only **153** was successfully isolated and characterised.



Scheme 75

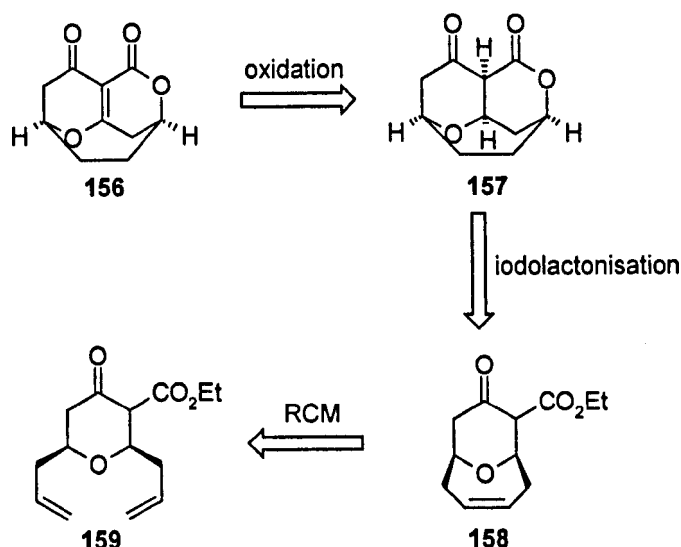
Reagents and conditions: (a) I_2 , BTL, MeCN/ H_2O (b) py, Ac_2O (c) Ph_3SnH , AIBN, PhH (d) NBS, H_2O (e) Bu_3SnH , AIBN, PhH (f) BzCl, py, DMAP, DCM (g) PhSeCl, MeCN/ H_2O (h) $Hg(OAc)_2/HgO/MeOH$ (i) $NaBH(OMe)_3$, DCM

These substrates all lack a hydrogen at C2, and **154** and **155** also do not possess an acetate group (with the concomitant 1,5-hydrogen) so these substrates cannot undergo a competing hydrogen-abstraction. The failure of these substrates to cyclise seems to indicate that the inherent rate of cyclisation of the generated primary radical onto the enone is significantly smaller than the rate of reduction by the tin hydride. This approach was therefore not pursued any further, although the basic strategy of making an unstrained bicyclic system and then introducing the bridgehead olefin with an oxidation will be re-examined in section 2.6.

2.6 Alternative ring-closing metathesis approach to tricyclic system

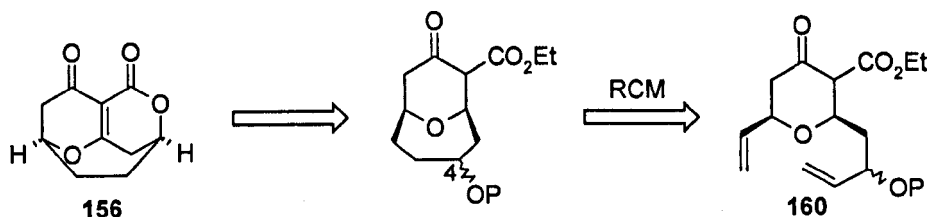
2.6.1 Introduction

In the previous section, we investigated an approach where we envisaged that an unstrained bicyclic ring system could provide a bridgehead olefin ring system with an oxidation. Although the key radical cyclisation step failed, we wanted to investigate whether a similar approach could be taken, but using a ring-closing metathesis reaction instead of a radical cyclisation. One possible disconnection is shown in Scheme 76, where the desired compound **156** is formed from a relatively unstrained system **157**. This in turn could be synthesised from **158** via an iodolactonisation. It was envisaged that **158** could be synthesised with a RCM on a *cis* substituted pyranone **159**. Our efforts to pursue this strategy are presented in 2.6.3.



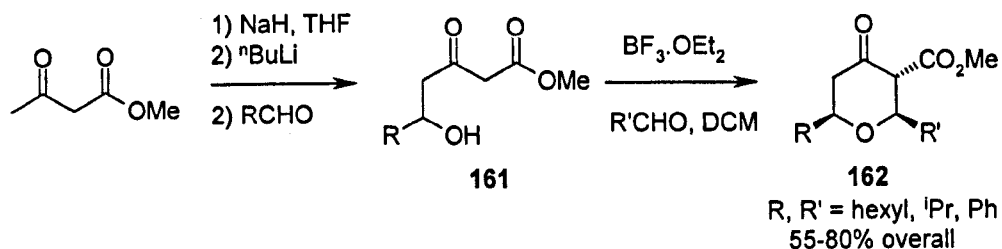
Scheme 76

The approach detailed above relies upon a challenging oxidation as the last step to install the bridgehead olefin. Consequently, we developed an alternative strategy that utilises an alternative RCM disconnection, with the oxygen functionality at C4 already in place (Scheme 77). Our efforts to pursue this approach are presented in section 2.6.4.



Scheme 77

Both of our proposed routes require the synthesis of a tetrahydropyranone with two pendant vinyl groups (as for **159** and **160**). In addition, for RCM the vinyl groups must be *cis* on the tetrahydropyranone ring. To solve this problem we utilised chemistry that has recently been reported by Clarke (Scheme 78).⁸⁰ This approach used an aldol reaction between the dianion of methyl acetoacetate and an aldehyde to form **161**,⁸¹ then a tandem Knoevenagel condensation/intramolecular Michael addition with a different aldehyde to obtain the desired tetrahydropyranone **162**. This approach was found to be diastereoselective, giving the diastereoisomer shown, as a consequence of the reaction being under thermodynamic control. Note that in some cases **162** is formed as a mixture of keto and enol forms, which were found to be separable by chromatography.



Scheme 78⁸⁰

Once the tetrahydropyranone ring has been formed, both of our proposed routes then rely upon a ring-closing metathesis reaction to form the bridged oxabicyclic system. There are several examples in the literature of RCM being used to synthesise bridged oxabicyclic structures.⁸²⁻⁸⁵ In the example shown (Scheme 79), an 8-oxa-bicyclo[4.3.1]decane **163** was synthesised in excellent yield using Grubbs' 1st generation catalyst **91**.⁸²



2.6.2 Molecular modelling of tetrahydropyranones

We then calculated the enthalpy of ring-closure for the proposed substrates for both of the approaches that were discussed in the previous section. These results are summarised in Table 5. The enthalpy of ring-closure for entry 1 (the substrate required for the iodolactonisation strategy) was calculated to be 13.2 kcal mol⁻¹, which is just in the range that Grubbs reported possible (see section 2.4.2). The enthalpy of ring-closure for the substrate for the alternative strategy (entries 2 and 3 for the 2 diastereoisomers) revealed an interesting dependence on stereochemistry, as the enthalpy of ring-closure for entry 2 was significantly lower than the enthalpy of ring-closure for entry 3. At a

later date problems arose with the RCM of these ketoesters (see section 2.6.5), so we also examined a series of ketal substrates (entries 4-7). The same dependence on stereochemistry was apparent, entries 4 and 6 having significantly lower enthalpies of ring-closure than entries 5 and 7. These results were promising for our approach, as entries 2, 4 and 6 possess the correct stereochemistry for a direct lactonisation as the final step to form the tricyclic motif. Moreover, these results suggested that it might be possible to effect RCM on a mixture of diastereoisomers and isolate only the desired diastereoisomer of cyclised product, thereby solving the problem of separation of the diastereoisomers.

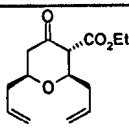
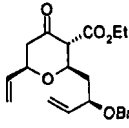
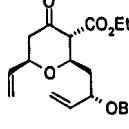
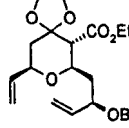
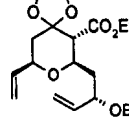
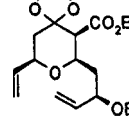
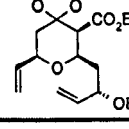
Entry	Structure	Theoretical enthalpy of ring-closure (kcalmol ⁻¹)
1		13.2
2		6.0
3		11.2
4		7.5
5		14.7
6		9.3
7		15.0

Table 5

Examination of the modelling results suggested that the dependence on stereochemistry of the enthalpies of ring-closure was principally the result of differences in product energies, rather than substrate energies. The minimised structures of these products suggested that these differences in energies might be due to a steric clash present in the RCM products of entries 3, 5 and 7. Comparison of the minimised conformations of **164** and **165** (Figure 14, ester groups removed for clarity) revealed that in both cases the 7-membered ring adopts a conformation where the OBn group is pseudo-equatorial. In the case of **164**, this conformation places H-4 in a pseudo-axial position, where it clashes with the tetrahydropyranone ring. For **165**, H-4 is also in a pseudo-axial position, although now there is no steric clash.

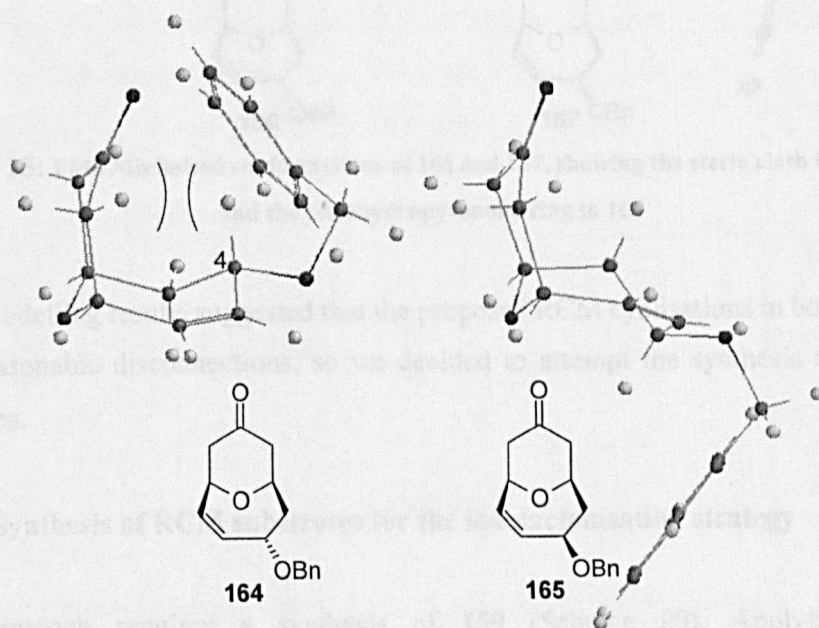


Figure 14: PM3 Minimised conformations of **164** and **165**, showing the steric clash between 4-H and the tetrahydropyranone ring in **164**

For the ketal series, a similar analysis was made. Again, the 7-membered rings of **166** and **167** (Figure 15, ester groups removed for clarity) adopt conformations where the OBn group is pseudo-equatorial, leading (for **166**) to a steric clash between H-4 and the tetrahydropyranone ring. In this case, this steric clash may be enhanced by the presence of the ketal.

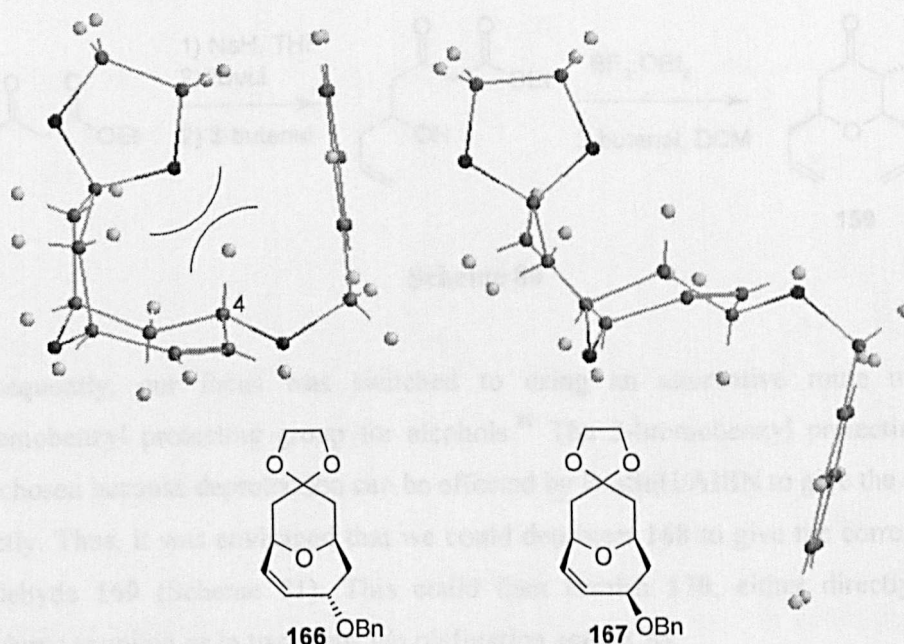
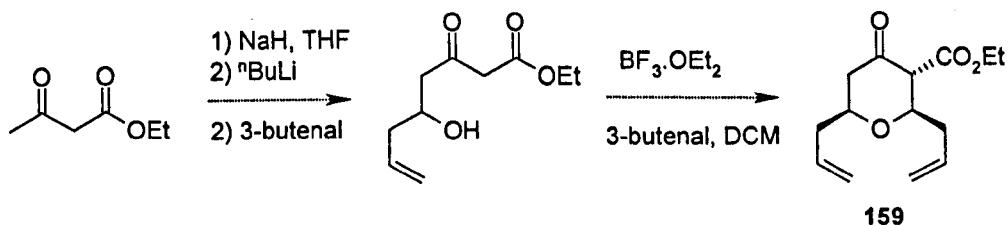


Figure 15: PM3 Minimised conformations of 166 and 167, showing the steric clash between 4-H and the tetrahydropyranone ring in 166

These modelling results suggested that the proposed RCM cyclisations in both strategies were reasonable disconnections, so we decided to attempt the synthesis of the RCM substrates.

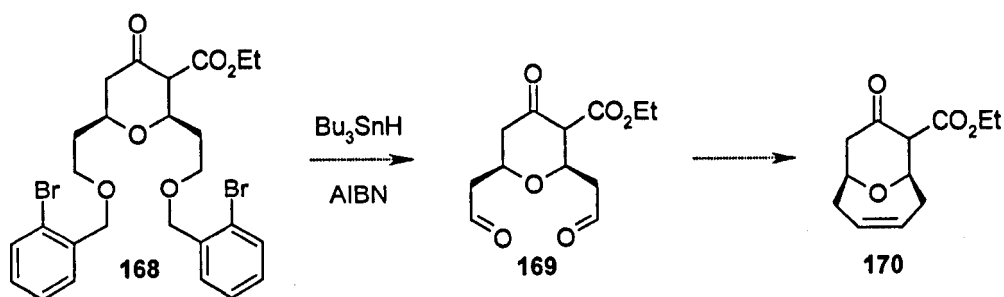
2.6.3 Synthesis of RCM substrates for the iodolactonisation strategy

This approach required a synthesis of **159** (Scheme 80). Applying Clarke's methodology to synthesise **159** would require a double condensation of two units of 3-butenal with ethyl acetoacetate (Scheme 80). However, attempts to isolate 3-butenal from allyl Grignard additions to DMF⁸⁶ led to mixtures of 3-butenal and the isomerised product 2-butenal. Other synthetic routes to 3-butenal have been reported^{87,88} but given the propensity for 3-butenal to isomerise under neutral conditions it was considered unlikely that 3-butenal would be compatible with the acidic conditions required for the tandem Knoevenagel condensation/Michael addition.



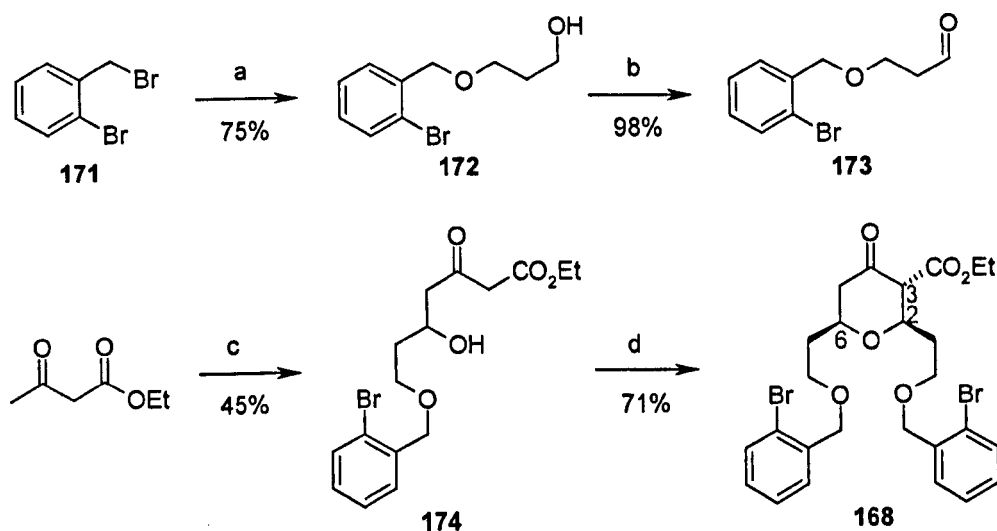
Scheme 80

Consequently, our focus was switched to using an alternative route using the 2-bromobenzyl protecting group for alcohols.⁸⁹ The 2-bromobenzyl protecting group was chosen because deprotection can be effected by $\text{Bu}_3\text{SnH/AIBN}$ to give the aldehyde directly. Thus, it was envisaged that we could deprotect **168** to give the corresponding dialdehyde **169** (Scheme 81). This could then furnish **170**, either directly with a McMurry coupling or in two steps *via* olefination and RCM.



Scheme 81

Our approach to synthesise **168** is given in Scheme 82. 2-Bromobenzyl bromide **171** was combined with an excess of 1,3-propanediol and NaH in DMF to give the corresponding alcohol **172** in 75% yield. Oxidation of **172** with Dess-Martin periodinane then gave aldehyde **173** in 98% yield. This aldehyde had been reported in the literature but was synthesised *via* a less convenient three step sequence from 2-bromobenzyl alcohol.⁹⁰ The aldehyde **173** was then combined with the dianion of ethyl acetoacetate, and then combined again with the resulting product **174** and $\text{BF}_3\cdot\text{OEt}_2$ to give the desired tetrahydropyranone, in a mixture of keto and enol forms in 92% yield. The keto form **168** could be separated from this mixture by careful chromatography in 71% yield, as a single diastereoisomer. The stereochemistry of **168** was assigned as shown, on the basis of a strong NOE between 2-H and 6-H (indicating a *cis* relationship between 2-H and 6-H) and a large coupling constant of 10.6 Hz between 2-H and 3-H (indicating a *trans* diaxial relationship between 2-H and 3-H).



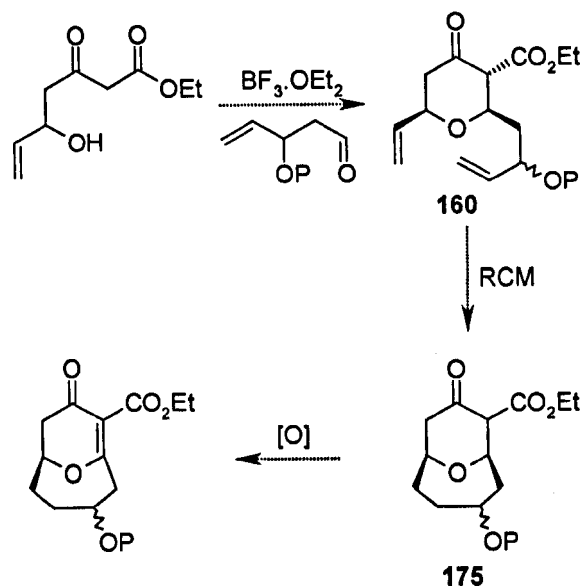
Scheme 82

Reagents and conditions: (a) 1,3-propanediol, NaH, DMF (b) DMP, DCM (c) i. NaH, THF ii. ^tBuLi iii. **173** (d) BF₃·OEt₂, **173**, DCM

However, when the deprotection of **168** was attempted with Bu₃SnH/AIBN a complicated mixture of products was obtained, with no significant quantities of desired product. The hydrogenation of **168** was also attempted, in an effort to isolate the diol, but again gave complicated mixtures of products. As the alternative RCM disconnection approach was progressing more efficiently (see section 2.6.4), we decided to concentrate primarily on that route instead. This approach does, however, remain a promising route to the desired tricyclic motif.

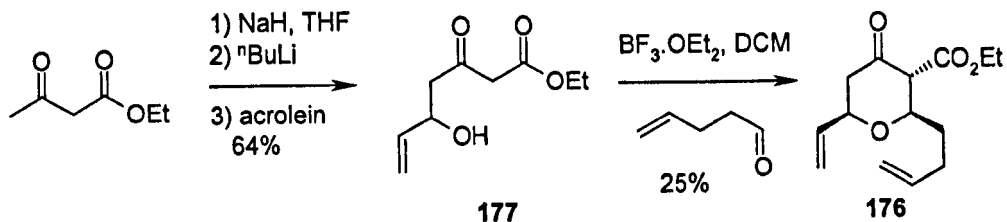
2.6.4 Synthesis of oxygenated RCM substrates

This strategy is outlined in Scheme 83. It was envisaged that tetrahydropyranone **160** could be synthesised as a mixture of diastereoisomers by using similar chemistry as employed in the previous section. A ring-closing metathesis reaction and subsequent hydrogenation could then provide **175** as desired.



Scheme 83

Before embarking on a synthesis of **160**, we synthesised **176** (Scheme 84) as a test for the methodology and because a more thorough analysis of the NMR spectroscopy data could be made (as **176** was synthesised as a single diastereoisomer). Thus the dianion of ethyl acetoacetate was reacted with acrolein to give **177**, which was then combined with 4-penten-2-ol and $\text{BF}_3 \cdot \text{OEt}_2$ to give **176**, albeit in poor yield.



Scheme 84

Analysis of the NOE and coupling constant data of **176** confirmed that **176** was formed as a single diastereoisomer as shown. Large coupling constants (*ca.* 11 Hz) were observed for **176** between 2-H and 3-H and between 5-H and 6-H, consistent with diaxial couplings in a chair conformation (Figure 16, E=CO₂Me). NOEs were observed between 2-H and 6-H and between 3-H and 5-H, as expected. The NOE difference between 2-H and 6-H was larger than the NOE difference between 3-H and 5-H, as would be expected as the C-O bonds in the ring would be expected to be shorter than the C-C bonds in the ring, bringing 2-H and 6-H closer together.

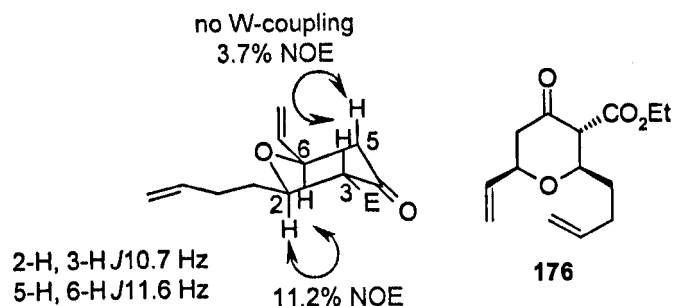


Figure 16: NOE and coupling constant data for 176

We then compared our data to the data recorded by Clarke, for a closely related series of compounds (Figure 17).⁸⁰ The NOE and coupling constant data matched very closely. However, Clarke observed a small (0.8 Hz) W-coupling between 3-H and 5-H, which we did not observe. Clarke has argued that his data, specifically the NOE data and W-coupling that he observed, showed that the tetrahydropyranones he synthesised adopt a twist-boat conformation, stabilised by donation of the lone pair from the ring oxygen into the π^* of the ketone. However, in our opinion his data, particularly the large coupling constants observed between 2-H and 3-H and between 5-H and 6-H, are more consistent with a chair conformation. Indeed, in a recent private communication Dr. Clarke informed us that he now also believes that these tetrahydropyranones adopt chair conformations.

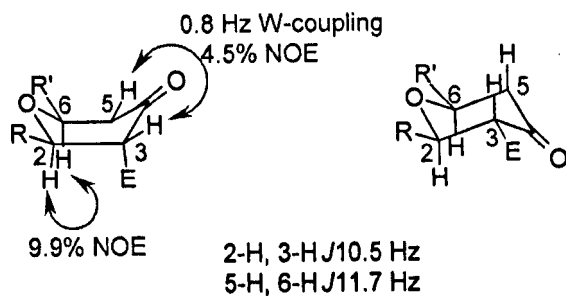
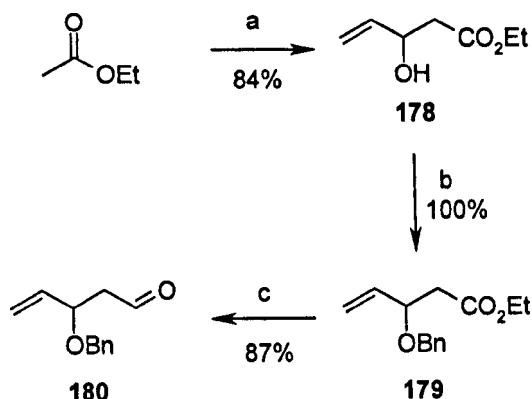


Figure 17: Chair and boat conformations of the class of tetrahydropyranones synthesised by Clarke.^{13f} J values given for R="Pr, R'=Ph, NOE data given for R="Pr, R'="Hexyl. E=CO₂Me

We then investigated the synthesis of the tetrahydropyranones with the oxygen functionality in place. A benzyl-protected aldehyde was synthesised first for this approach (Scheme 85). Thus, an aldol reaction between ethyl acetate and acrolein gave 178 in good yield, with either LDA or LHMDS, which corresponded with literature data.⁹¹ Benzylation of 178 using standard basic conditions (NaH/BnBr) gave mainly

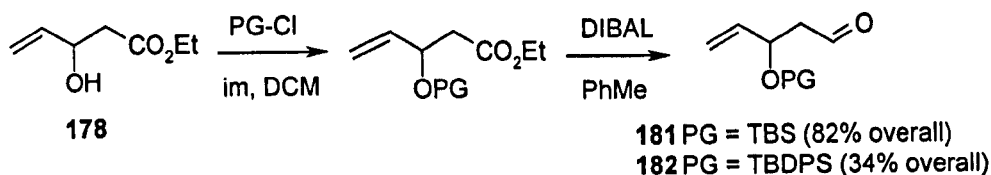
undesired elimination products, but under acidic conditions (benzyl 2,2,2-trichloroacetimidate, triflic acid)⁹² the desired benzylated material **179** was obtained. DIBAL reduction then gave the corresponding aldehyde **180**.



Scheme 85

Reagents and conditions: (a) LDA, THF; acrolein (b) Benzyl 2,2,2-trichloroacetimidate, triflic acid, Et₂O (c) DIBAL, PhMe

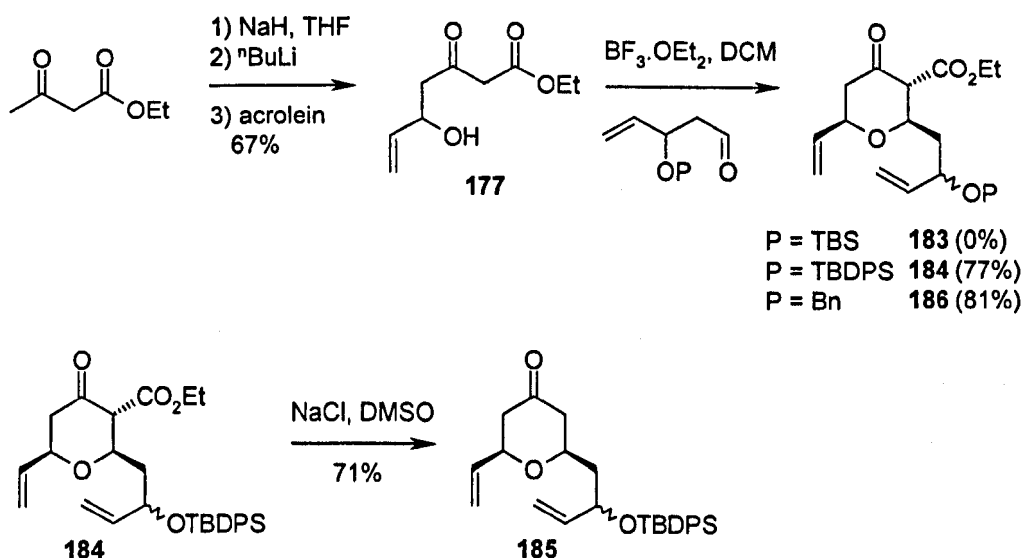
The analogous TBS and TBDPS protected aldehydes were also synthesised (Scheme 86), for synthetic flexibility later on in the sequence. Thus **181** and **182** were synthesised in two steps from **178**, and **181** corresponded with literature data.⁹³



Scheme 86

Attempts were then made to convert the aldehydes into the corresponding tetrahydropyranones (Scheme 87). The TBS-protected aldehyde **181** decomposed under the reaction conditions (BF₃·OEt₂, DCM), and gave no desired product **183**. However, the TBDPS-protected aldehyde **178** gave a 77% yield of the desired product **184**, a consequence of the greater acid-stability of the TBDPS group.⁹⁴ Note that **184** was isolated as a 2:1 mixture of diastereoisomers, and as an inseparable mixture of keto and enol forms. Due to the complexity of the NMR spectroscopy data of **184**, a sample was subjected to Krapcho decarboxylation conditions and characterised as the decarboxylated form **185**. Treatment of **177** with the benzyl-protected aldehyde **180** and BF₃·OEt₂ again gave the desired tetrahydropyranone, as a 1:1 mixture of

diastereoisomers. This time it was possible to separate the keto and enol tautomers by chromatography to give 64% yield of keto **186** and 17% yield of enol.



Scheme 87

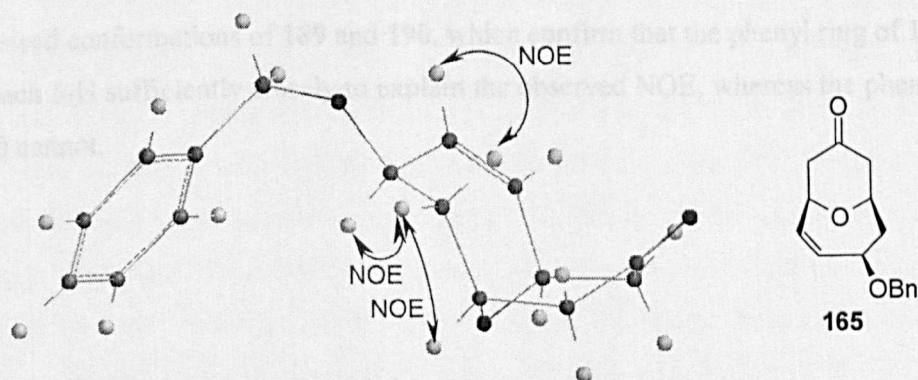
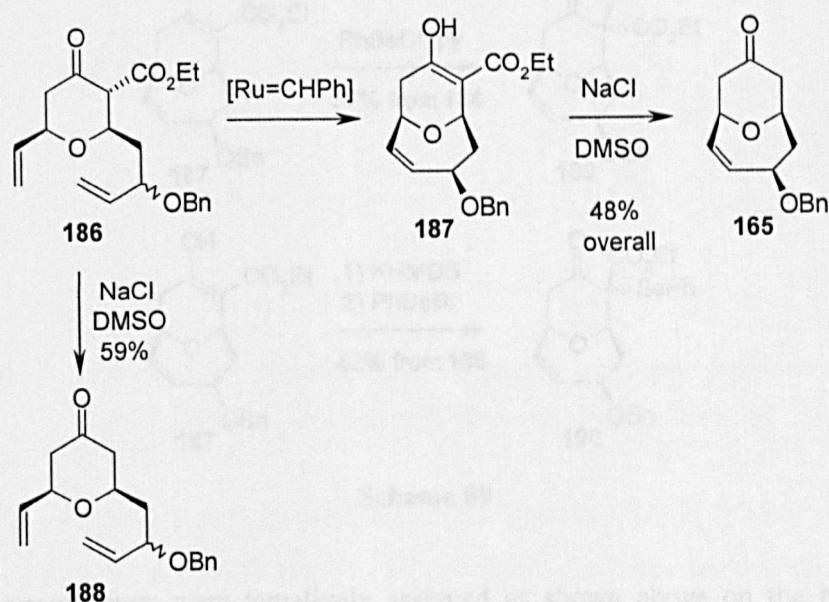
With **184** and **186** in hand, we then investigated the ring-closing metathesis reactions of these substrates.

2.6.5 RCM of ketoester substrates

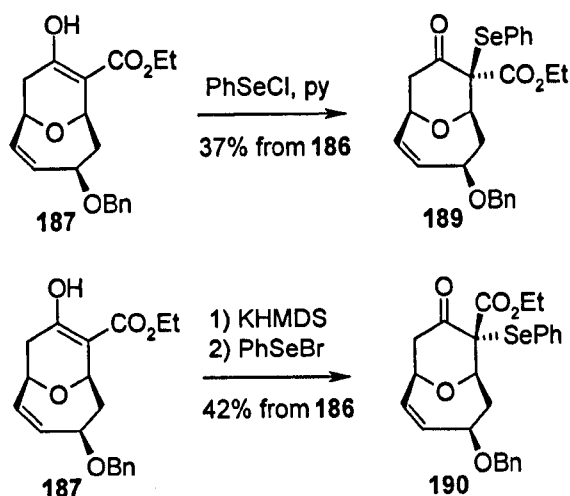
Submitting the TBDPS-protected material **184** to 20 mol% Grubbs' 2nd generation catalyst **92** gave a complicated mixture that contained the desired product as a mixture of diastereoisomers, some starting material and other unidentified products. Unfortunately the desired product could not be isolated from this mixture, and attempts to derivatise it by hydrogenation and selenylation to a product that could be characterised failed. We therefore concentrated on the RCM of the benzylated material **186**.

Submitting **186** to the same conditions gave the desired product **187** as a single diastereoisomer (Scheme 88). Again, the product could not be separated from the starting material due to the similar R_f values of **186** and **187**, but upon decarboxylation the decarboxylated product **165** could be isolated and characterised. NOE data confirmed that the stereochemistry of **165** was as shown (Figure 18). This

diastereoisomer has the desired stereochemistry for the lactonisation that was planned to form the tricyclic motif. Extra confirmation that the starting material **186** was a 1:1 mixture of diastereoisomers was obtained by decarboxylating the starting material and then fully characterising the decarboxylated product **188**. These results demonstrated that one diastereoisomer of the starting material undergoes RCM, whereas the other diastereoisomer polymerises or remains unreacted. The yield over the two steps was 44%, *i.e.* 88% yield of the isolated diastereoisomer, though it should be noted that the yield was recorded on a small scale. Pleasingly, these results were in accordance with the molecular modelling results (see section 2.6.2), as the modelling predicted that the diastereoisomer of **186** that gives **187** on cyclisation should cyclise more easily than the other diastereoisomer (compare entries 2 and 3, Table 5, page 73).



We then investigated the oxidation of **187**, in an attempt to install the bridgehead olefin. It was found that semi-purified **187** could be selenylated to give the corresponding selenide, which could be isolated and characterised. Interestingly, the diastereoselectivity of the selenylation was completely reversed depending on the reaction conditions; KHMDS/PhSeBr gave one diastereoisomer **189** whereas py/PhSeCl gave the other diastereoisomer **190** (Scheme 89). It is unclear why such a complete switch in diastereoselectivity is observed on changing the reaction conditions. Once again note that the yields (42% and 37% over 2 steps from the monocyclic precursor **186**) represent excellent yields (84% and 74%) with respect to the isolated diastereoisomer.



Scheme 89

The diastereoisomers were tentatively assigned as shown above on the basis of an observed NOE (for **189**) between the SePh protons and 5-H (an NOE between the SePh protons and 6-H was observed for both diastereoisomers). Figure 19 shows the minimised conformations of **189** and **190**, which confirm that the phenyl ring of **189** can approach 5-H sufficiently closely to explain the observed NOE, whereas the phenyl ring in **190** cannot.

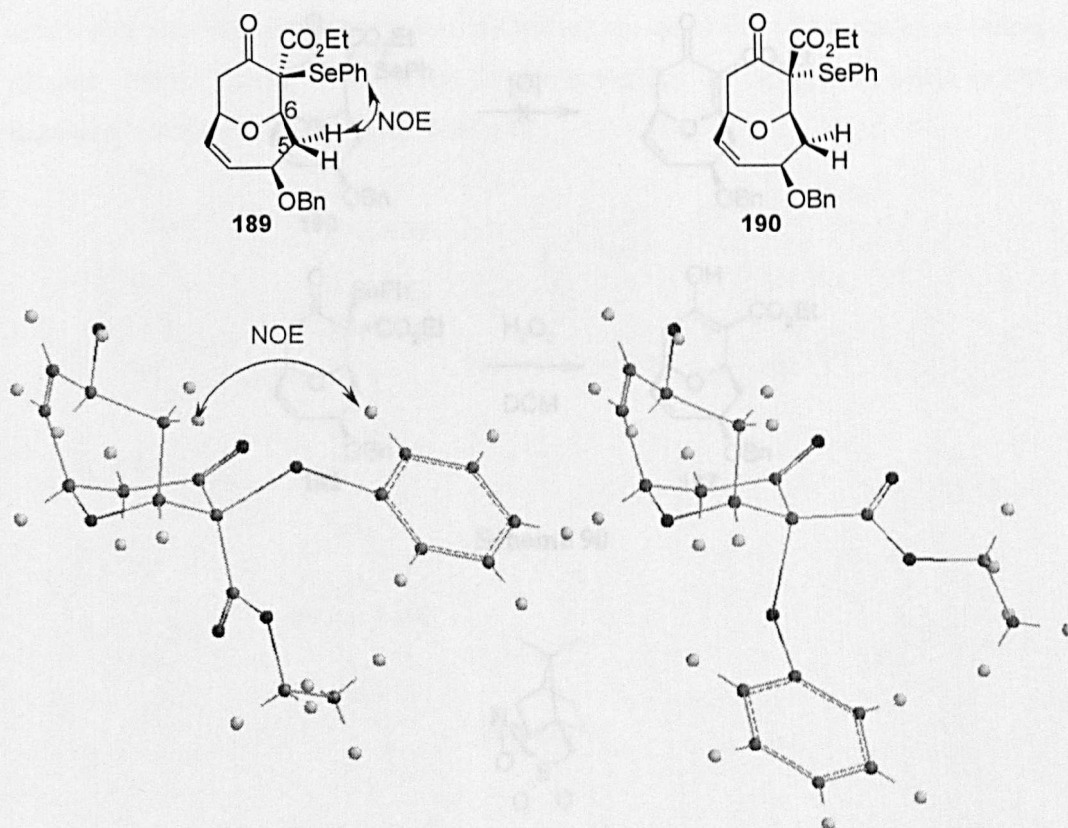
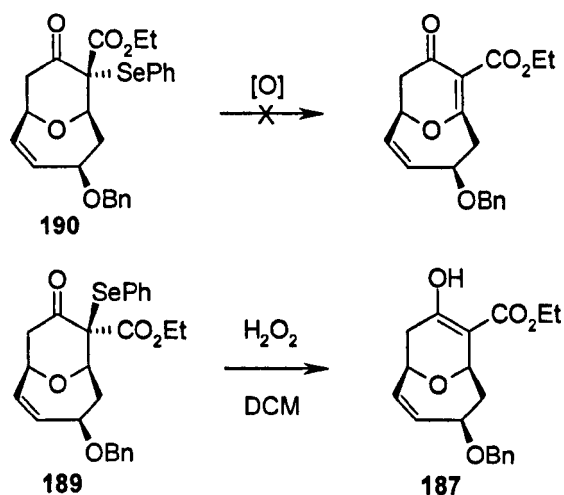


Figure 19: PM3 minimised conformations of **189** and **190**, with benzyl groups removed for clarity, showing the observed NOE between 5-H and SePh for **189**

We then investigated oxidation reactions of the selenides, in an attempt to form the bridgehead olefin. It should be noted that only **190** can undergo the desired selenoxide elimination, as **189** would give a highly strained *trans* double bond on *syn* selenoxide elimination. However, initially we had not assigned the stereochemistry of **189** and **190**, and so we attempted to effect the oxidation of both diastereoisomers. Unfortunately, treatment of **190** with Davis' camphor-derived oxaziridine⁹⁵ (Figure 20) or with H₂O₂ gave complicated mixtures with no desired product. Surprisingly, treatment of **189** with H₂O₂ gave a clean conversion to the ketoester **187** (Scheme 90). Presumably this unusual transformation proceeds *via* nucleophilic attack on the selenium centre by hydrogen peroxide, although we are unaware of any examples in the literature where hydrogen peroxide has effected this transformation. Although these results were not promising for our approach, they did permit the isolation and characterisation of **187**.



Scheme 90

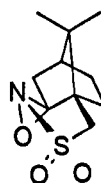
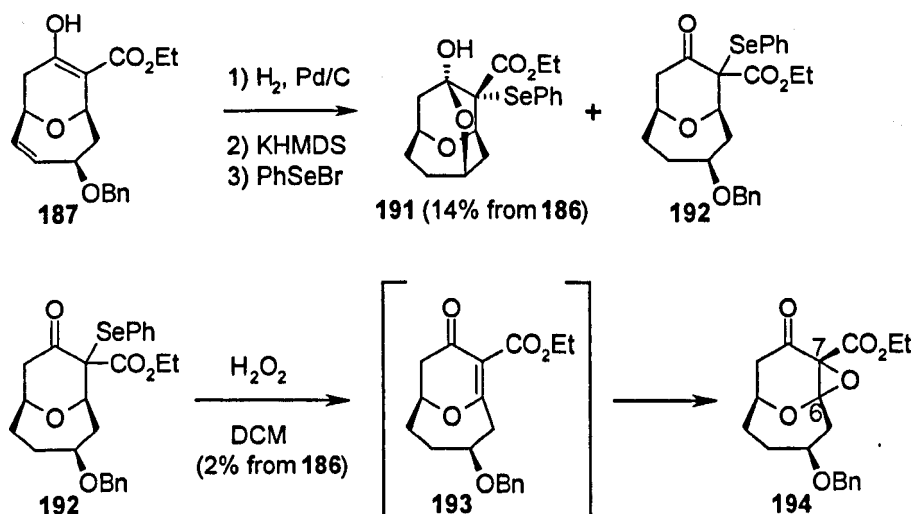


Figure 20: Structure of (-)-(10-camphorsulfonyl)oxaziridine (Davis' oxaziridine)⁹⁵

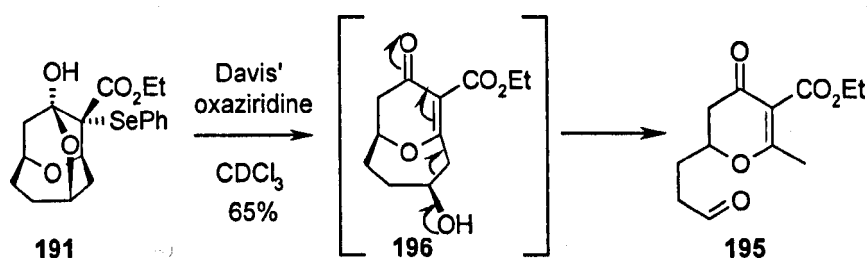
As the oxidation reactions of **189** and **190** were unsuccessful, it was decided to investigate the hydrogenation of **187** instead, with a view to installing the bridgehead olefin at a later stage in the synthesis. Hydrogenation of **187** gave a mixture of inseparable products, which could be selenylated to give **191** (Scheme 91), albeit in low overall yield (14% over 3 steps, *i.e.* 28% with respect to the isolated diastereoisomer). This structurally interesting cage structure was the result of the deprotected hydroxyl cyclising onto the ketone to form a lactol. In addition to **191**, a small quantity of impure benzylated material **192** was isolated. Treatment of crude **192** with H_2O_2 furnished, along with other unidentified products, a low yield of a product that was initially assigned as the desired bridgehead olefin **193**, on the basis of the ^1H NMR data. However MS and ^{13}C NMR data, specifically the ^{13}C NMR shifts of C6 and C7 of 77.2 and 84.6 ppm, suggested that this product was actually the epoxide **194** derived from the desired bridgehead olefin compound. This result was encouraging, in that it suggested that we were transiently producing the desired product. However, the ease with which the bridgehead olefin was epoxidised suggests that for this approach to be successful we may have to avoid the use of oxidants that epoxidise electrophilic

alkenes. It is worth commenting that H_2O_2 does not generally effect the epoxidation of alkenes without a base, so this result demonstrated that the bridgehead olefin in **193** is unusually reactive to nucleophilic oxidants.



Scheme 91

Attempted oxidation of **191** with Davis' oxaziridine gave a promising crude mixture by ^1H NMR spectroscopy, but the only product obtained after chromatography was **195** (Scheme 92), presumably the result of a retro-aldol ring-opening of the desired product **196**. Once again this result suggested that we were transiently producing the desired product. However, the ease with which the retro-aldol reaction occurred when the bridgehead alkene was installed suggests that we should avoid substrates and conditions where the retro-aldol reaction is likely to be problematic.

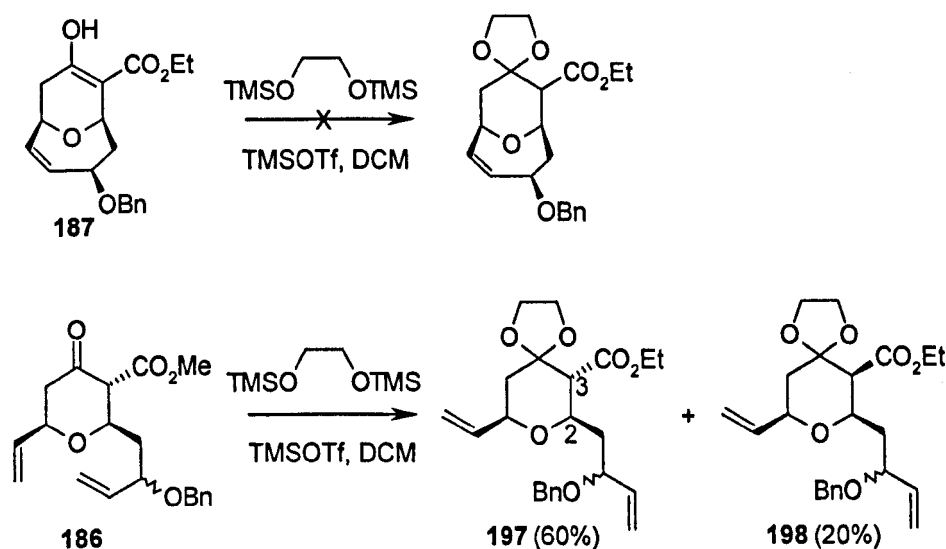


Scheme 92

2.6.6 Synthesis and RCM of ketal substrates

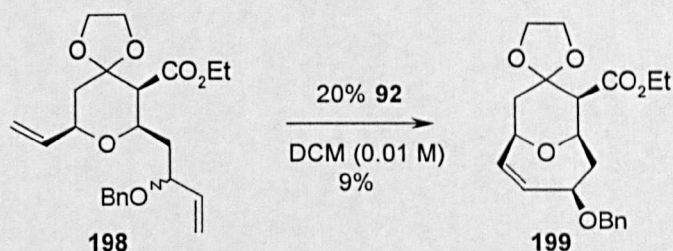
To avoid the retro-aldol problem that we encountered with the ketoesters, it was decided to investigate the use of the ketal protecting group to protect the ketone. It was hoped that by masking the ketone the retro-aldol reaction would be less facile. It was also hoped that it would be possible to purify and isolate the ketals after RCM, and that after hydrogenation the presence of the ketal would stop the liberated hydroxyl cyclising onto the ketone (see Scheme 91).

Attempts were therefore made to form the ketals of **186** and **187**. Efforts to effect the ketalisation of **187** led to complicated mixtures of products, but ketalisation of **186** with Noyori conditions⁹⁶ proceeded efficiently to give the corresponding ketal as a mixture of diastereoisomers (Scheme 93). Extensive chromatography achieved the separation of **197** (60% yield) and **198** (20% yield). Ketals **197** and **198** were identified as the mixture of diastereoisomers as shown by analysis of the coupling constants between 2-H and 3-H.



Scheme 93

With **197** and **198** in hand, we then investigated the RCM reactions of these ketals. RCM of the minor isomer **198** gave a small yield (9%) of the desired product **199** (Scheme 94), again shown by NOE studies (Figure 21) to be a single diastereoisomer as drawn.



Scheme 94

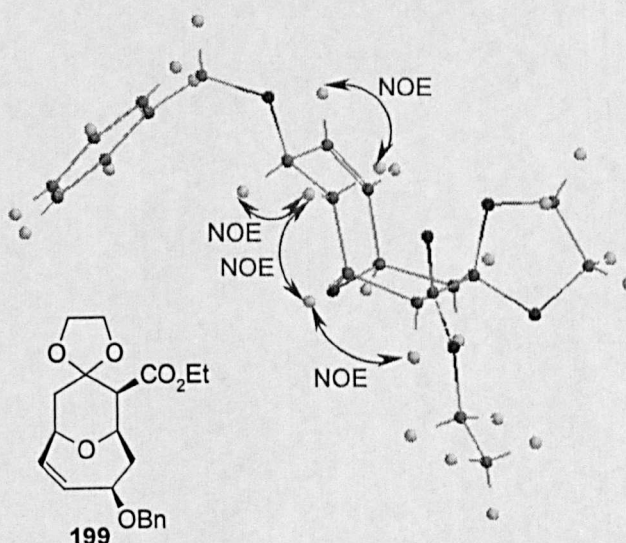
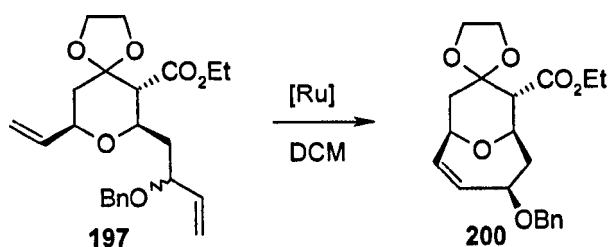


Figure 21: NOE data for **199**, proving that the stereochemistry is as shown

RCM of the major isomer **197** also gave the desired product **200** (Table 6) as a single diastereoisomer, as shown by NOE studies (Figure 22). Both **199** and **200** could be separated by chromatography from the starting material, in contrast to the ketoester series (see section 2.6.5). Pleasingly, the isolated diastereoisomers of **199** and **200** again corresponded to the RCM substrates that were predicted to have a lower enthalpy of ring-closure (see section 2.6.2). For the RCM of **197** we examined a variety of conditions in an attempt to optimise the yield. 1st generation Grubbs' catalyst **91** gave a low yield of product (Table 6, entry 1). However, good yields could be achieved by using Grubbs' 2nd generation catalyst **92** or the Hoveyda-Grubbs catalyst **93** (Table 6, entries 2-5). The best conditions that were tried (10% **92**, 0.005 M in DCM, entry 4) gave a 41% yield (*i.e.* 82% with respect to the isolated diastereoisomer), so these conditions were used for a large scale reaction (entry 6) but disappointingly only gave a 30% yield on the bigger scale. Alternatively, it was found that the reaction could be effected much more quickly at 60°C in a microwave reactor (entry 7), giving a higher yield than observed with traditional heating at the same concentration (compare entries

2 and 7). Unfortunately, the small size of the reactor that was available meant that the use of high dilution (which was required for a high yield) for the microwave reaction was not practical.



Entry	Catalyst used	Reaction scale (mmol)	Conc ⁿ (M)	% [Ru]	T (°C)	Time (h)	Yield ^a
1	91	0.25	0.005	20	reflux	40	7
2	92	0.5	0.02	10	reflux	16	18
3	92	0.25	0.01	5	reflux	20	29
4	92	0.25	0.005	10	reflux	12	41
5	93	0.5	0.005	20	reflux	24	35
6	92	5	0.005	10	reflux	16	30
7	92	0.1	0.02	10	60 ^b	2	30

^a Isolated yield of single diastereoisomer, *i.e.* compares to a maximum possible yield of 50%. ^b Reaction performed in a sealed tube in a microwave reactor.

Table 6

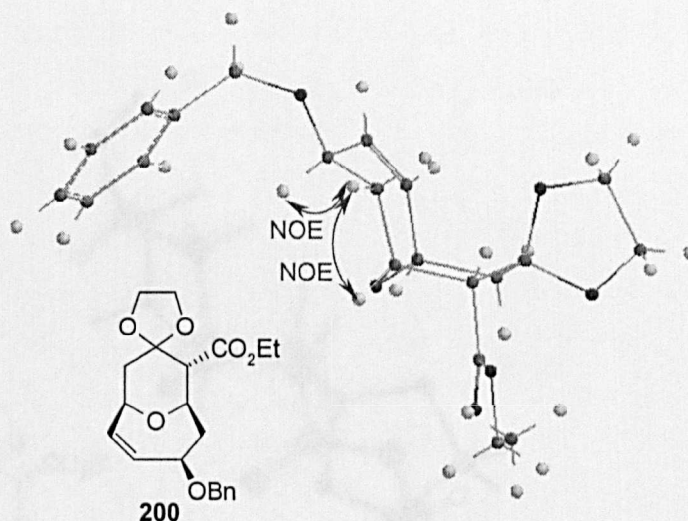
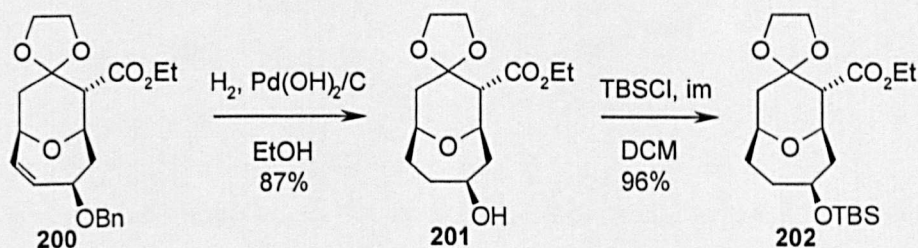


Figure 22: NOE data for **200**, proving that the stereochemistry is as shown

Concomitant hydrogenation of the alkene and benzyl group of **200** proceeded efficiently to give the corresponding alcohol **201** (Scheme 95). This reaction highlighted one advantage of the ketal group over the ketone series (see section 2.6.5) as the ketal prevented the deprotected hydroxyl cyclising onto the ketone, and **201** could be isolated in high yield. The alcohol **201** was crystalline, and the X-ray crystal structure confirmed the stereochemistry (Figure 23) and showed that **201** adopts in a twist-boat conformation. This result contrasts with the modelling results that are presented in 2.6.2, which suggested that the RCM ring-closed products adopt chair conformations, although as **201** does not have the C2-C3 alkene that the ring-closed products possess it may be expected to adopt a different conformation. Protection of the alcohol in **201** as a TBS ether then gave **202**. The TBS protecting group was chosen as we wanted to be able to remove the protecting group at a later stage, after the installation of the bridgehead olefin, without affecting the bridgehead olefin.



Scheme 95

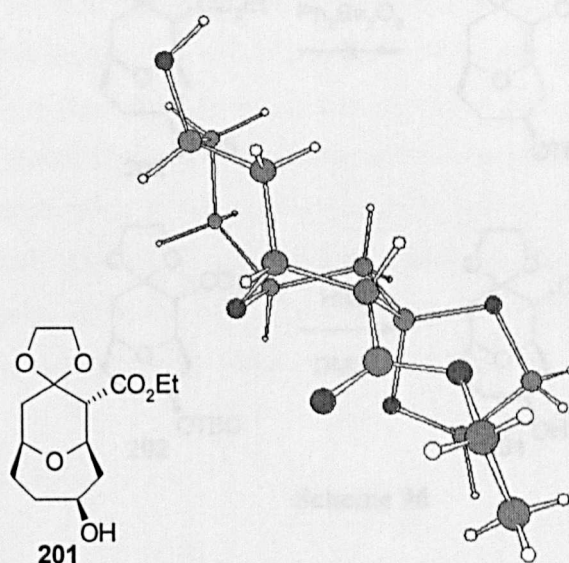
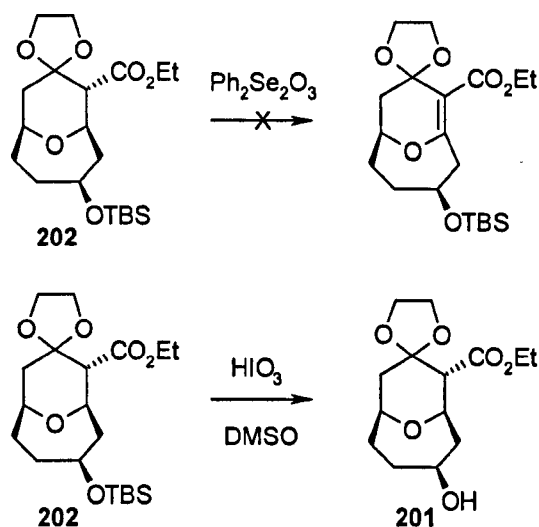


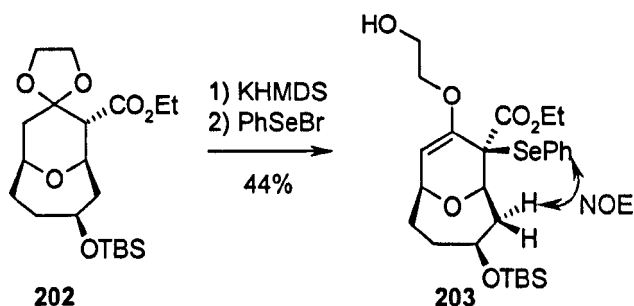
Figure 23: X-ray structure of **201**, showing that the tetrahydropyranone ring (in the centre of the structure) is in a twist-boat conformation

We then investigated the oxidation of **202** to install the bridgehead olefin. A direct oxidation with benzeneseleninic anhydride⁹⁷ was attempted, but no reaction was observed (Scheme 96) even after extensive heating in a microwave reactor. This result was not unexpected, as benzeneseleninic anhydride has only been shown to oxidise ketones to enones, rather than esters to α,β -unsaturated esters as we require. A direct oxidation with HIO_3 .DMSO as reported by Nicolaou⁹⁸ was also attempted but after only 5 minutes had given clean TBS deprotection to give **201**, and in any case this method has also not been used to oxidise esters to α,β -unsaturated esters in the literature.



Scheme 96

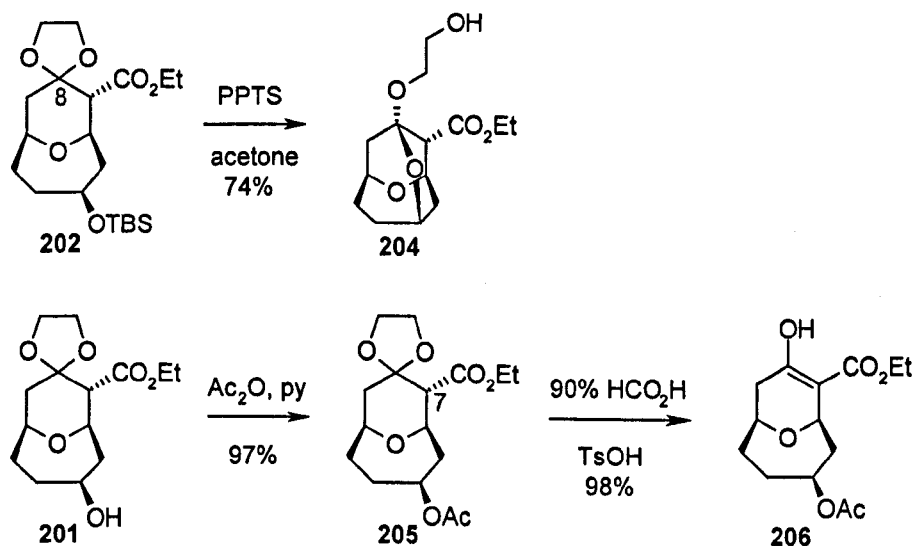
We then investigated a two step oxidation of **202** *via* the selenide. Unfortunately, treatment of **202** with KHMDS and PhSeBr gave **203** (Scheme 97) and recovered starting material, rather than the desired selenide. This result suggested that having the ketal in place prevents selenylation at the proximal centre, presumably due to the steric congestion involved with having two contiguous quaternary centres. The selenide **203** was isolated as a single diastereoisomer, tentatively assigned as the diastereoisomer drawn as previously (see Figure 19) on the basis of a NOE between the phenyl protons and H-5.



Scheme 97

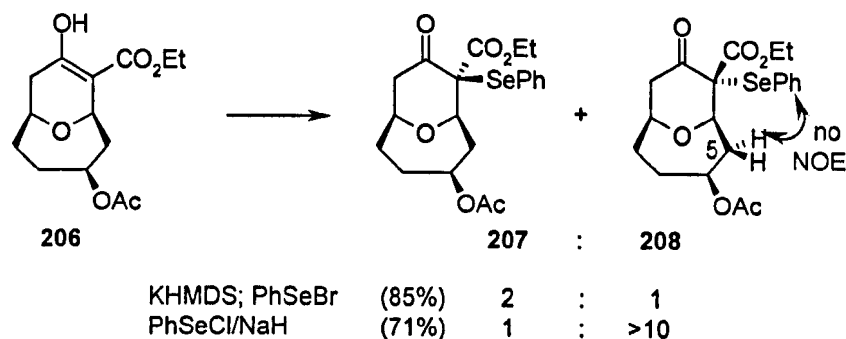
To summarise, incorporation of the ketal group allowed us to purify and isolate the RCM products, and stopped the liberated hydroxyl cyclising onto the ketone. However, it also prevented the selenylation due, we believe, to steric hindrance. We decided, therefore, to deprotect the ketal after the RCM and hydroxyl protection, and to attempt selenylation on the resulting ketone. Attempts to deprotect the ketal of **202** led to

concomitant TBS deprotection and cyclisation of the hydroxyl onto C8 to give **204** (Scheme 98). We therefore protected the alcohol in **201** as an acetate to give **205**, as it was thought that the acetate would be stable to the ketal deprotection conditions. An acetate group was also considered a suitable protecting group for later manipulations, as at some stage before lactonisation the ester at C7 would have to be saponified, thereby giving us the opportunity to remove the acetate protecting group and saponify the ester at C7 in the same step. Ketal deprotections of **205** with HCl/THF or $\text{BF}_3 \cdot \text{OEt}_2$ /acetone were unsuccessful, but it was found that treatment of **205** with TsOH in 90% aq. formic acid⁹⁹ gave a quantitative yield of the desired enol **206**.



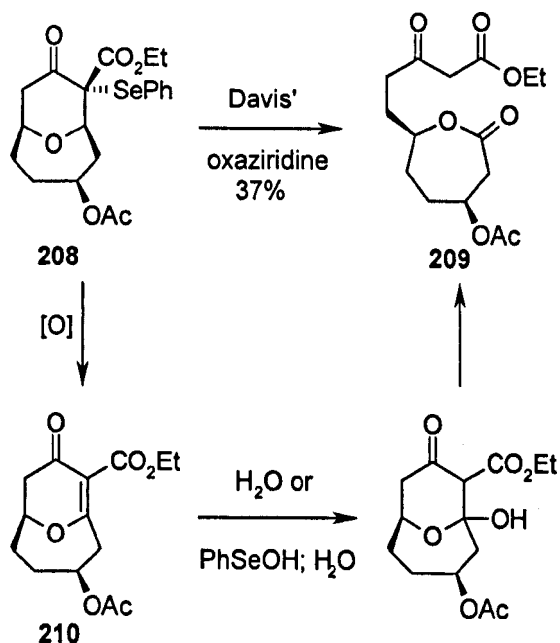
Scheme 98

Selenylation of **206** with $\text{KHMDs}/\text{PhSeBr}$ then gave the desired selenide, but with poor diastereoselectivity by ^1H NMR spectroscopy (Scheme 99), and the diastereoisomers **207** and **208** were not separable by chromatography. However, it was found that by using PhSeCl/NaH the selenide **208** was obtained in greater than 10:1 diastereoselectivity by ^1H NMR spectroscopy, which permitted the characterisation of **208**. As previously, the selenides were tentatively assigned as shown as no NOE was observed between the phenyl hydrogens and the H-5 proton of **208**.



Scheme 99

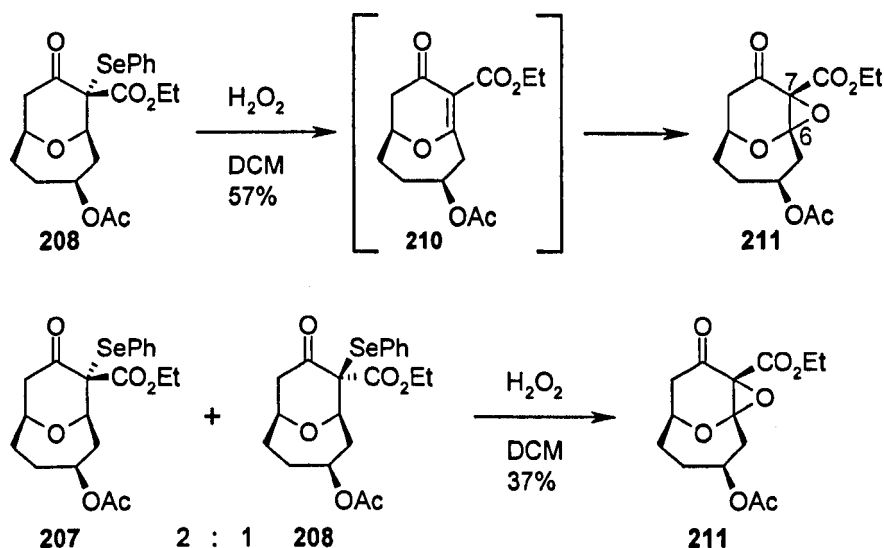
However, attempts to oxidise **208** with Davis' oxaziridine led to a hydrolysis product (as indicated by MS) as the only isolated product, which NMR data identified as being the ring-opened product **209** (Scheme 100). A plausible mechanism for this transformation proceeds *via* the desired bridgehead olefin compound **210** (Scheme 100). Direct hydrolysis of **210** with water would give the observed product **209**, or alternatively the addition of PhSeOH followed by hydrolysis of the Se-O bond would also lead to **209**.



Scheme 100

If this hydrolysis was occurring due to addition of PhSeOH in the reaction mixture, then it should be possible to minimise this side reaction by having an excess of oxidant (so that the PhSeOH formed in the elimination is further oxidised before it can react with

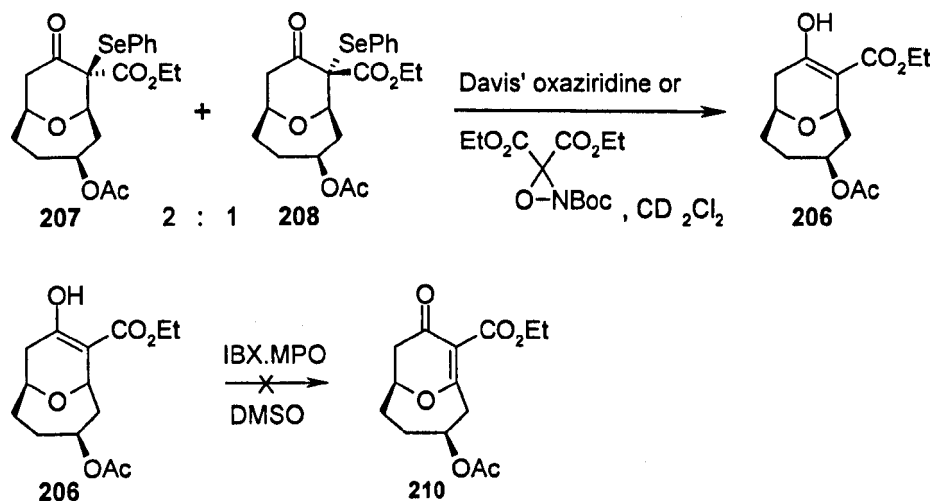
the bridgehead olefin) and by using short reaction times. Thus, **208** was rapidly exposed to a large excess of H_2O_2 , and was worked up as soon as TLC indicated a complete reaction (10 minutes at 0°C). The product obtained, in 57% yield, had lost the hydrogen signal at 6-H in the ^1H NMR data, as would be expected for the desired bridgehead olefin **210**. However, MS and the ^{13}C NMR shifts of C6 and C7 of 77.2 and 84.4 ppm suggested that the product was actually an epoxide **211** derived from the bridgehead olefin (Scheme 101). Similarly, treatment of a mixture of diastereoisomers **207** and **208** with H_2O_2 furnished the epoxide **211** in 37% yield. These results were not unexpected, given that the formation of the benzylated epoxide **194** was observed from similar reaction conditions (see Scheme 91).



Scheme 101

As a consequence of this result, we examined alternative oxidants for the oxidation of selenide **208**, in the hope that they would oxidise the selenide but wouldn't epoxidise the bridgehead olefin. Specifically, we examined the oxidation of a mixture of **207** and **208** with Davis' oxaziridine (as before but this time in excess) and with a ketomalonate-derived oxaziridine that has been reported by our group.¹⁰⁰ However, in both cases NMR spectroscopy of the crude mixture showed that the C-Se bond had been cleaved to give **206** (Scheme 102). It is unclear how mechanistically the C-Se bond has been cleaved in this case, as unlike the hydrogen peroxide reaction discussed in section 2.6.5 (see Scheme 90) there are no good nucleophiles in this reaction to attack the selenium centre. Finally, an attempt was made to effect the direct oxidation of **206** to

give **210** with IBX.MPO as reported by Nicolaou,¹⁰¹ using the method reported by Santagostino¹⁰² to synthesise the IBX, but no reaction was observed.



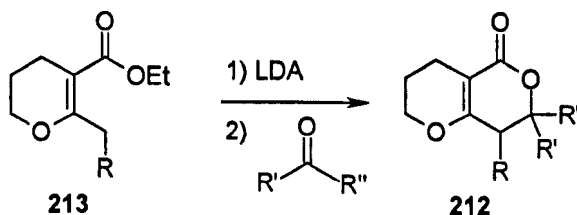
Scheme 102

These disappointing results forced us to re-examine our strategy to these strained ring systems. In chapter 3 we review the findings of this project and discuss avenues for future research.

Chapter 3: Synopsis of results to date and future work

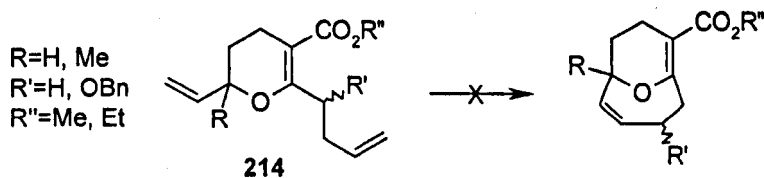
3.1 Synopsis of results to date

To summarise, a general route to the bicyclic tetrahydropyranone unit **212** was found (Scheme 103) that used an intermolecular aldol reaction between a dihydropyran **213** and a range of carbonyl compounds (see section 2.2.4).³⁸



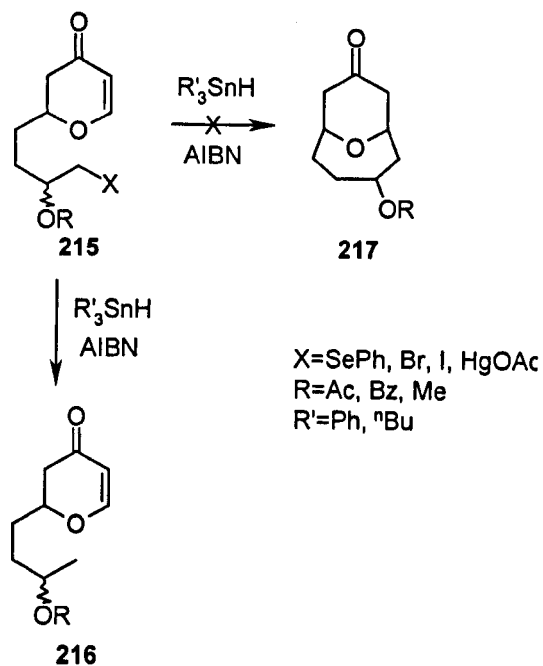
Scheme 103

Unfortunately, attempts to extend this approach to form the desired tricyclic motif by utilising an *intramolecular* aldol failed (see section 2.3). However, by using intermolecular aldol reactions a range of ring-closing metathesis (RCM) substrates **214** was synthesised (Scheme 104). However, attempts to effect the RCM of these substrates failed, although in one case some degree of desired cyclisation was observed by MS (see section 2.4).



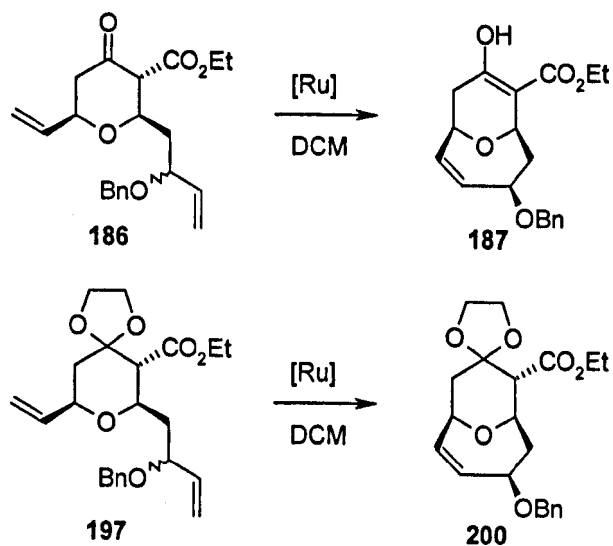
Scheme 104

An alternative approach to form the desired motif relied upon an intramolecular radical cyclisation of a carbon-centred radical onto an enone **215** (Scheme 105). However, only reduction products **216** were observed, with no evidence of the desired cyclised product **217** (see section 2.5.3).



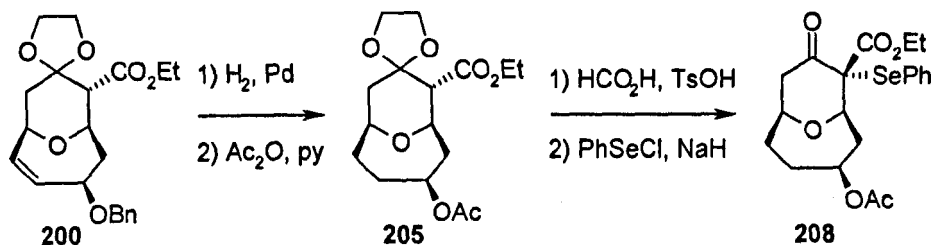
Scheme 105

Finally, we investigated an alternative RCM approach, where the bridgehead carbons were saturated (Scheme 106). This approach was successful with either the ketone or ketal substrates, although in both cases only one of the diastereoisomers underwent cyclisation (see sections 2.6.5 and 2.6.6). These interesting results were correlated to a lower theoretical enthalpy of ring-closure for the diastereoisomer that underwent cyclisation (see section 2.6.2).



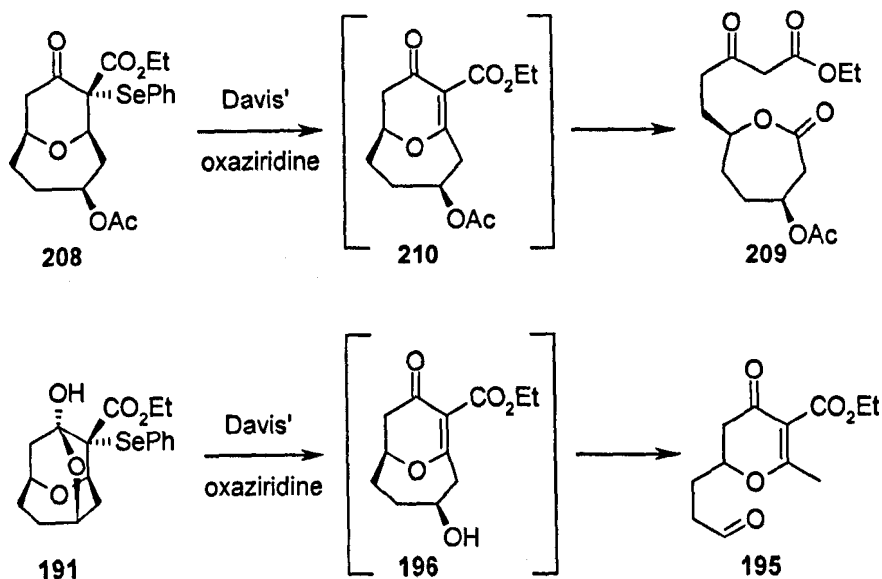
Scheme 106

The ketal series was preferred, as the ring-closed products could be directly characterised and subsequent hydrogenation gave the desired hydroxy compound efficiently (Scheme 107). However, the ketal group stopped selenylation due to steric congestion, so it was necessary to remove the ketal group before selenylation to form **208**.



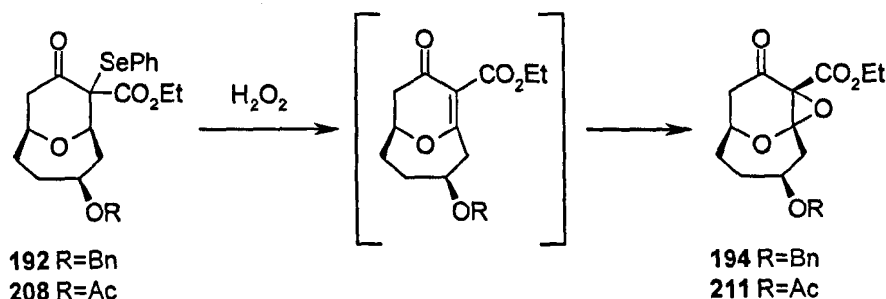
Scheme 107

However, attempts to effect the oxidation/elimination of **208** to give the bridgehead olefin **210** failed due to hydrolysis of the resulting bridgehead olefin (Scheme 108). Similarly, oxidation of **191** gave **195** via a retro-aldol ring-opening of the desired bridgehead olefin compound.



Scheme 108

Another problem that we encountered was that the bridgehead olefin was reactive to nucleophilic oxidants, so under certain reaction conditions the corresponding epoxides were isolated (Scheme 109).

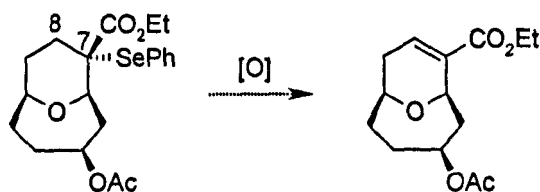


Scheme 109

It is our belief that the presence of the ketone group facilitated both the ring-opening and the epoxidation reactions of the desired bridgehead olefin. Future models, therefore, should avoid the use of the ketone group.

3.2 Future research

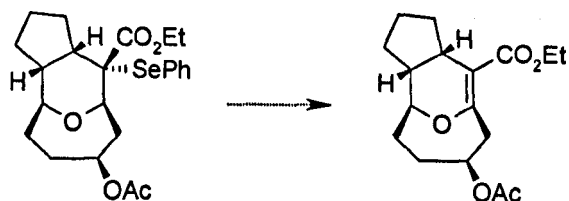
We have demonstrated that ring-closing metathesis is a viable route to *saturated* [4.3.1]-oxabicyclic ring systems. However, oxidation of these saturated bicycles to form bridgehead olefins led to ring-opened or epoxidised products. It is our belief that the ketone group is facilitating these reactions, and therefore a successful model should not have this ketone in place when oxidation is attempted. However, we have shown that masking of the ketone group as a ketal stops the selenylation (see section 2.6.6), due to the steric demand of having two contiguous quaternary centres, and if C8 is unsubstituted the oxidation may furnish the undesired C7-C8 unsaturated product (e.g. as in Scheme 110).



Scheme 110

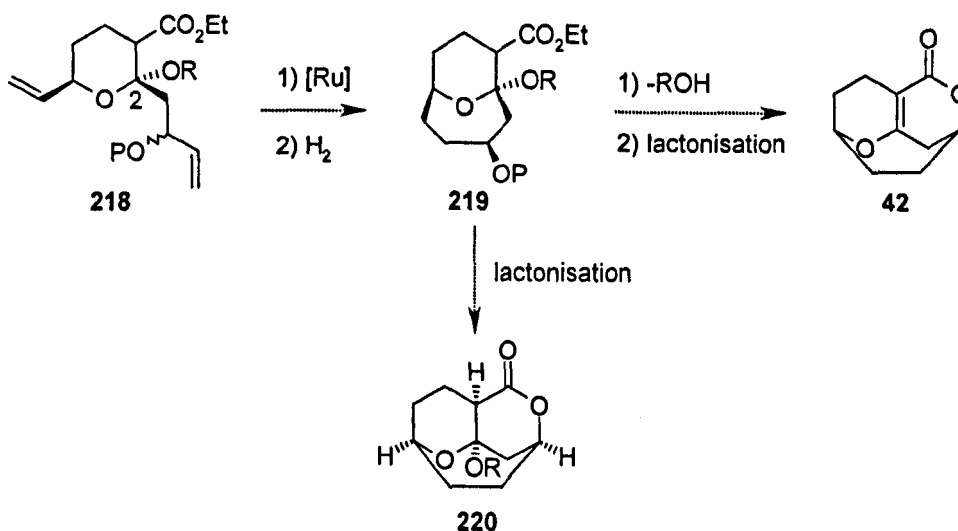
Nevertheless, it should be noted that the bridgehead olefin in the natural product does not isomerise into the alternative C7-C8 position as above. An interesting model study

to perform, therefore, would be to have the cyclopentane in position as in the natural product and to then try to effect the oxidation/elimination (Scheme 111).



Scheme 111

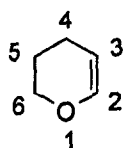
Another interesting approach to try would be to attempt the RCM on a substrate with extra oxygenation at C2 such as **218** (Scheme 112). The extra substituent should facilitate the ring-closure, and provide a substrate **219** that could be directly lactonised to give **220**, which is a model of the hexacyclinic acid tricyclic motif, or if elimination of ROH could be effected **219** could provide a model of the FR182877 tricyclic motif **42**.



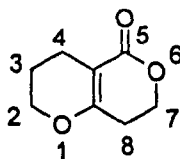
Scheme 112

Chapter 4: Experimental

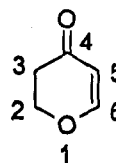
Throughout this chapter, the following numbering systems have been used:



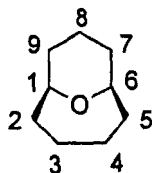
Dihydropyrans



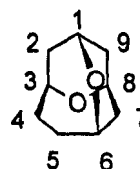
Tetrahydropyranopyranones



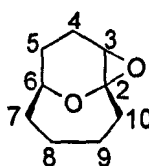
2,3-Dihydro-pyran-4-ones



10-Oxa-bicyclo[4.3.1]decanes



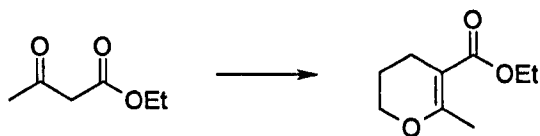
2,7-Dioxa-tricyclo[4.3.1.1^{3,8}]undecanes



2,11-Dioxa-tricyclo[4.4.1.0^{1,3}]undecanes

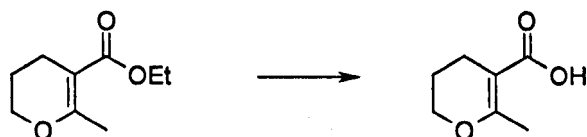
All reactions were carried out under a positive pressure of nitrogen unless otherwise stated. Solvents were freshly distilled before use unless supplied specially dried (1,2-dichloroethane, ethanol, DMF) or unless otherwise stated. Solutions of ⁿBuLi were titrated against diphenylacetic acid prior to use. NMR spectroscopy analyses were performed on Bruker 250, 300, 400 or 500 MHz instruments; chemical shifts are quoted in ppm relative to TMS (as referenced to chloroform), with coupling constants quoted in Hz. GC and IR analyses (in cm⁻¹) were recorded on an Agilent 4890D chromatograph and a Mattson Satellite FTIR spectrometer respectively. Mass spectrometry was carried out by CI using ammonia.

2-Methyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester³¹ 47



Ethyl acetoacetate (1.30 g, 10 mmol) was dissolved in abs. ethanol (35 ml) and stirred at room temperature under nitrogen. Sodium ethoxide (3.24 g, 21% w/w in EtOH, 10 mmol) was added portionwise and the reaction mixture was stirred for 20 minutes. 1,3-dibromopropane was added dropwise and the reaction mixture was stirred at room temperature overnight, then was heated at reflux for 4 hours. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (4 x 70 ml). The organic layers were washed with water and dried over magnesium sulfate, filtered, then concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 1:9 ethyl acetate:petrol, to obtain the *title compound* (0.69 g, 41%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1623, 1705; δ_{H} (300 MHz, CDCl_3) 4.15 (2H, q, J 7.1, OCH_2CH_3), 4.01 (2H, t, J 5.2, 6-H), 2.30 (2H, td, J 6.3, 1.5, 4-H), 2.22 (3H, t, J 1.5, CCH_3), 1.87-1.79 (2H, m, 5-H), 1.28 (3H, t, J 7.1, OCH_2CH_3); δ_{C} (100 MHz, CDCl_3) 168.5 (C), 164.7 (C), 101.2 (C), 66.5 (CH_2), 59.4 (CH_2), 21.5 (CH_2), 21.2 (CH_2), 20.1 (CH_3), 14.3 (CH_3); Found: $[\text{M}+\text{H}]^+$, 171.1023. $\text{C}_9\text{H}_{14}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 171.1021. IR and ^1H NMR data corresponded with literature data.³¹

2-Methyl-5,6-dihydro-4H-pyran-3-carboxylic acid³² 48

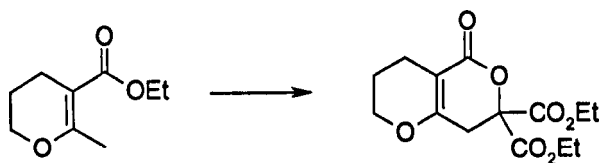


Starting material (4.75 g, 27.9 mmol), NaOH (46.5 ml, 3 M aq. sol., 140 mmol) and abs. ethanol (50 ml) were combined and heated to reflux overnight. HCl (80 ml, 2 M aq. sol., 160 mmol) was added and the reaction mixture was stirred for 20 mins. The product was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water (100 ml) and dried over magnesium sulfate, filtered, then concentrated *in vacuo* to obtain the *title compound* (2.78 g, 70%) as a white solid, m.p. 112°C; $\nu_{\max}$ / cm^{-1} 1604, 1678; δ_{H} (300 MHz, CDCl_3) 4.07 (2H, t, J 5.2, 6-H), 2.34 (2H, td, J 6.4, 1.2, 4-H), 2.27 (3H, t, J 1.2, CCH_3), 1.90-1.83 (2H, m, 5-H); δ_{C} (100 MHz,

CDCl₃) 174.7 (C), 167.6 (C), 100.6 (C), 66.9 (CH₂), 21.5 (CH₂), 21.1 (CH₂), 20.7 (CH₃); Found: [M+H]⁺, 143.0707. C₇H₁₀O₃+H⁺ requires: [M+H]⁺, 143.0708.

5-Oxo-3,4,5,8-tetrahydro-2H-pyrano[4,3-b]pyran-7,7-dicarboxylic acid diethyl ester

50



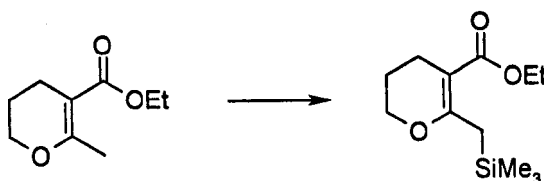
A solution of ⁿBuLi in hexanes (0.492 ml, 2.54 M, 1.25 mmol) was added to ⁱPr₂NH (0.185 ml, 1.3 mmol) in THF (2 ml) under nitrogen at 0°C. The reaction mixture was stirred for 30 minutes, then was cooled to -78°C and a solution of starting material (170 mg, 1 mmol) in THF (0.5 ml) was added dropwise. The reaction mixture was stirred at -78°C for 35 minutes, then diethyl ketomalonate (0.228 ml, 1.31 mmol) was added dropwise and the reaction mixture was stirred for 90 minutes at -78°C, then the reaction flask was sealed up and placed in the freezer (at -22°C) overnight. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (2 x 10 ml). The organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude mixture was combined with (±)-camphor-10-sulfonic acid (220 mg, 0.947 mmol) and toluene (10 ml) at room temperature under N₂ with 5Å sieves. The reaction mixture was heated at reflux for 14 hours, and then cooled. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (2 x 10 ml). The organic layers were washed with sat. brine and dried over magnesium sulfate, filtered, then concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 20:80-25:75 ethyl acetate:petrol, to obtain the *title compound* (125 mg, 42%) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1649, 1729, 1747; δ_{H} (300 MHz, CDCl₃) 4.31 (4H, q, *J*7.1, CO₂CH₂CH₃), 4.15 (2H, t, *J*5.2, 2-H), 3.10 (2H, t, *J*1.8, 8-H), 2.29 (2H, t, *J*6.3, 4-H), 1.92 (2H, m, 3-H), 1.29 (6H, t, *J*7.1, CH₂CH₃); δ_{C} (75 MHz, CDCl₃) 166.1 (C), 164.1 (C), 162.7 (C), 100.6 (C), 81.2 (C), 67.9 (CH₂), 63.1 (CH₂), 31.8 (CH₂), 21.4 (CH₂), 18.4 (CH₂), 14.0 (CH₃); Found: [M+H]⁺, 299.1141. C₁₄H₁₈O₇+H⁺ requires: [M+H]⁺, 299.1131.

2-Methyl-5,6-dihydro-4H-pyran-3-carboxylic acid methyl ester³³ 57



Sodium (1.15 g, 50 mmol) was added in slices to methanol (30 ml) under nitrogen at 0°C. When all the sodium had reacted methyl acetoacetate (5.81 g, 50 mmol) was added and the reaction mixture was stirred for 75 mins at 0°C. 1,3-Dibromopropane (10.10 g, 50 mmol) was added and the reaction mixture was heated at reflux for 6 hours. The reaction mixture was filtered to remove precipitated NaBr and extracted with ether (3 x 50 ml). The combined organic layers were washed with sat. NaHCO₃, then with sat. brine, then dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 5:95 ethyl acetate:petrol, to obtain the *title compound* (3.27 g, 42%) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1625, 1708; δ_{H} (300 MHz, CDCl₃) 4.03 (2H, t, *J*5.2, 6-H), 3.70 (3H, s, OCH₃), 2.30 (2H, t, *J*6.4, 4-H), 2.23 (3H, t, *J*1.3, CCH₃), 1.88-1.80 (2H, m, 5-H); δ_{C} (62.5 MHz, CDCl₃) 168.8 (C), 165.1 (C), 100.9 (C), 66.6 (CH₂), 50.8 (CH₃), 21.5 (CH₂), 21.3 (CH₂), 20.1 (CH₃); Found: [M+H]⁺, 157.0860. C₈H₁₂O₃+H⁺ requires: [M+H]⁺, 157.0865.

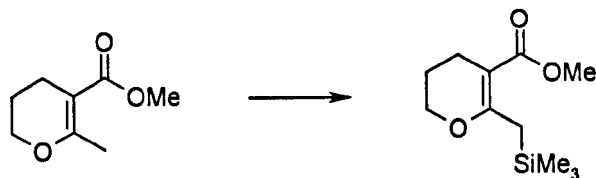
2-Trimethylsilanylmethyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 58



A solution of ⁿBuLi in hexanes (0.506 ml, 2.47 M, 1.25 mmol) was added to ⁱPr₂NH (0.185 ml, 1.31 mmol) in THF (2 ml) under nitrogen at 0°C. The reaction mixture was stirred for 30 minutes, then cooled to -78°C, then a solution of starting material (170 mg, 1 mmol) in THF (1 ml) was added dropwise. The reaction mixture was stirred at -78°C for 35 minutes, then TMSCl (0.22 ml, 1.73 mmol) was added dropwise and the reaction mixture stirred for 3.5 hours at -78°C, then the reaction mixture was allowed to warm to room temperature. The reaction mixture was taken up in diethyl ether and sat. NaHCO₃ solution, then the organic layer was dried over sodium sulfate, filtered, and

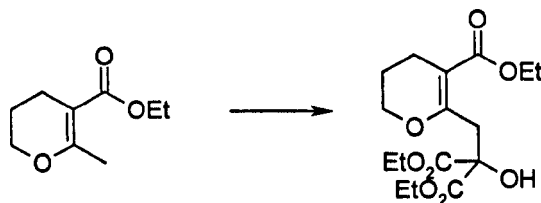
concentrated *in vacuo* to obtain the desired product (240 mg, 99%) as a colourless oil; $\nu_{\max} / \text{cm}^{-1}$ 1604, 1699; δ_{H} (300 MHz, CDCl_3) 4.14 (2H, q, J 7.1, CH_2CH_3), 4.00 (2H, t, J 5.2, 6-H), 2.39 (2H, s, CH_2SiMe_3), 2.33 (2H, t, J 6.5, 4-H), 1.82 (2H, m, 5-H), 1.28 (3H, t, J 7.1, CH_2CH_3), 0.06 (9H, s, SiMe_3); δ_{C} (75 MHz, CDCl_3) 168.9 (C), 168.4 (C), 98.4 (C), 66.4 (CH_2), 59.3 (CH_2), 24.8 (CH_2), 22.0 (CH_2), 21.6 (CH_2), 14.5 (CH_3), -1.0 (CH_3); Found: $[\text{M}+\text{H}]^+$, 243.1414. $\text{C}_{12}\text{H}_{22}\text{O}_3\text{Si}+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 243.1416.

2-Trimethylsilylmethyl-5,6-dihydro-4H-pyran-3-carboxylic acid methyl ester 59



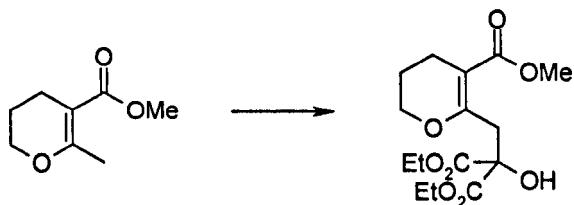
A solution of $n\text{BuLi}$ in hexanes (0.54 ml, 2.33 M, 1.25 mmol) was added to $i\text{Pr}_2\text{NH}$ (0.185 ml, 1.31 mmol) in THF (2 ml) under nitrogen at 0°C . The reaction mixture was stirred for 30 minutes, then cooled to -78°C , then a solution of starting material (156 mg, 1 mmol) in THF (1 ml) was added dropwise. The reaction mixture was stirred at -78°C for 40 minutes, then TMSCl (0.22 ml, 1.73 mmol) was added dropwise and the reaction mixture was stirred for 35 minutes at -78°C , then the reaction mixture was allowed to warm to room temperature. The reaction mixture was taken up in diethyl ether and sat. NaHCO_3 solution, then the organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to obtain the *title compound* (167 mg, 73%) as a colourless oil; $\nu_{\max} / \text{cm}^{-1}$ 1602, 1703; δ_{H} (300 MHz, CDCl_3) 4.00 (2H, t, J 5.2, 6-H), 3.68 (3H, s, OMe), 2.38 (2H, s, CH_2SiMe_3), 2.32 (2H, t, J 6.5, 4-H), 1.83 (2H, tt, J 6.5, 5.2, 5-H), 0.05 (9H, s, SiMe_3); δ_{C} (75 MHz, CDCl_3) 169.3 (C), 168.8 (C), 98.2 (C), 66.5 (CH_2), 50.8 (CH_3), 24.8 (CH_2), 22.0 (CH_2), 21.6 (CH_2), -1.0 (CH_3); Found: $[\text{M}+\text{H}]^+$, 229.1253. $\text{C}_{11}\text{H}_{20}\text{O}_3\text{Si}+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 229.1247.

**2-(3'-Ethoxycarbonyl-5',6'-dihydro-4H-pyran-2'-ylmethyl)-2-hydroxy-malonic acid
diethyl ester 64**



A solution of $n\text{BuLi}$ in hexanes (0.517 ml, 2.42 M, 1.25 mmol) was added to $i\text{Pr}_2\text{NH}$ (0.185 ml, 1.31 mmol) in THF (2 ml) under nitrogen at 0°C . The reaction mixture was stirred for 30 minutes, then was cooled to -78°C and a solution of starting material (170 mg, 1 mmol) in THF (1 ml) was added dropwise. The reaction mixture was stirred at -78°C for 35 minutes, then diethyl ketomalonate (0.182 ml, 1.2 mmol) was added dropwise, followed by addition of DMPU (0.157 ml, 1.3 mmol). The reaction mixture was stirred for 2 hours at -78°C , then was allowed to warm to room temperature overnight. The reaction mixture was taken up in DCM and water, and extracted with DCM (2 x 10 ml). The organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:7 ethyl acetate:petrol, to obtain the *title compound* (174 mg, 51%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1625, 1673, 1703, 1740; δ_{H} (250 MHz, CDCl_3) 5.34 (1H, s, OH), 4.23 (2H, q, J 7.0, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.22 (2H, q, J 7.0, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.15 (2H, q, J 7.0, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.91 (2H, t, J 4.1, 6-H), 3.46 (2H, s, CH_2COH), 2.30 (2H, t, J 5.9, 4-H), 1.80 (2H, m, 5-H), 1.26 (6H, t, J 7.0, CH_2CH_3), 1.25 (3H, t, J 7.0, CH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 169.9 (C), 169.9 (C), 161.7 (C), 105.8 (C), 77.8 (C), 66.5 (CH_2), 61.9 (CH_2), 60.6 (CH_2), 38.2 (CH_2), 38.1 (CH_2), 21.2 (CH_2), 14.2 (CH_3), 14.0 (CH_3); Found: $[\text{M}+\text{H}]^+$, 345.1554. $\text{C}_{16}\text{H}_{24}\text{O}_8+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 345.1549.

2-(3'-Methoxycarbonyl-5',6'-dihydro-4H-pyran-2'-ylmethyl)-2-hydroxy-malonic acid diethyl ester 65



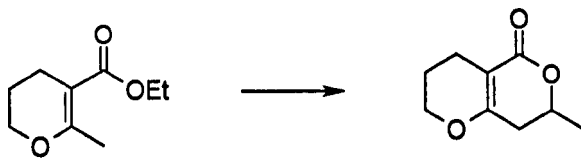
A solution of n BuLi in hexanes (0.517 ml, 2.42 M, 1.25 mmol) was added to i Pr₂NH (0.185 ml, 1.31 mmol) in THF (2 ml) under nitrogen at 0°C. The reaction mixture was stirred for 30 minutes, then cooled to -78°C, then a solution of starting material (156 mg, 1 mmol) in THF (0.5 ml) was added dropwise. The reaction mixture was stirred at -78°C for 35 minutes, then diethyl ketomalonate (0.261 ml, 1.5 mmol) was added dropwise, followed by addition of DMPU (0.157 ml, 1.3 mmol) and the reaction mixture was stirred for 5 hours at -78°C. The reaction mixture was allowed to warm to room temperature and stirred for 15 mins. The reaction mixture was then taken up in DCM and water, and extracted with DCM (2 x 10 ml). The organic layers were washed with sat. NaHCO₃ solution and dried over magnesium sulfate, filtered, then concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 5:95-50:50 ethyl acetate:petrol, to obtain the *title compound* (183 mg, 55%) as a yellow oil; ν_{max} / cm⁻¹ 1625, 1680, 1708, 1740; δ_{H} (250 MHz, CDCl₃) 5.16 (1H, s, OH), 4.25 (2H, q, *J*7.1, CO₂CH₂CH₃), 4.25 (2H, q, *J*7.2, CO₂CH₂CH₃), 3.94 (2H, t, *J*5.1, 6-H), 3.71 (3H, s, CO₂CH₃), 3.51 (2H, s, CH₂COH), 2.32 (2H, t, *J*6.4, 4-H), 1.82 (2H, tt, *J*6.4, 5.1, 5-H), 1.29 (6H, t, *J*7.1, CO₂CH₂CH₃); δ_{C} (62.5 MHz, CDCl₃) 170.0 (C), 169.9 (C), 161.9 (C), 105.5 (C), 77.8 (C), 66.5 (CH₂), 62.0 (CH₂), 51.7 (CH₃), 38.0 (CH₂), 21.3 (CH₂), 21.1 (CH₂), 13.9 (CH₃); Found: [M+H]⁺, 331.1389. C₁₅H₂₂O₈+H⁺ requires: [M+H]⁺, 331.1393.

7-Phenyl-3,4,7,8-tetrahydro-2H-pyrano[4,3-b]pyran-5-one 66



A solution of $n\text{BuLi}$ in hexanes (0.293 ml, 2.51 M, 0.735 mmol) was added to $i\text{Pr}_2\text{NH}$ (0.109 ml, 0.772 mmol) in THF (1.5 ml) under nitrogen at 0°C . The reaction mixture was stirred for 30 minutes, then cooled to -78°C , then a solution of starting material (100 mg, 0.588 mmol) in THF (0.5 ml) was added dropwise. The reaction mixture was stirred at -78°C for 45 minutes, then benzaldehyde (0.090 ml, 0.882 mmol) was added dropwise. The reaction mixture was then stirred for 90 minutes at -78°C , then the reaction flask was sealed up and placed in the freezer (at -22°C) overnight. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (2 x 10 ml). The organic layers were washed with sat. brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:7 ethyl acetate:petrol, to obtain the *title compound* (109 mg, 81%) as a white solid, m.p. $116\text{--}118^\circ\text{C}$; ν_{max} / cm^{-1} 1648, 1689; δ_{H} (300 MHz, CDCl_3) 7.45–7.30 (5H, m, Ph), 5.41 (1H, dd, $J_{12.4}$, 4.0, 7-H), 4.28–4.06 (2H, m, 2-H), 2.87–2.28 (4H, m, 4-H and 8-H), 1.98 (2H, m, 3-H); δ_{C} (75 MHz, CDCl_3) 167.3 (C), 165.2 (C), 138.9 (C), 128.6 (CH), 128.5 (CH), 126.0 (CH), 100.6 (C), 76.6 (CH), 67.7 (CH₂), 34.6 (CH₂), 21.6 (CH₂), 18.6 (CH₂); Found: $[\text{M}+\text{H}]^+$, 231.1010. $\text{C}_{14}\text{H}_{14}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 231.1021. The structure was also confirmed by X-ray crystallography.

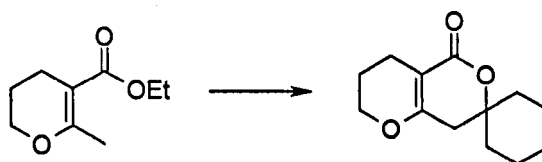
7-Ethyl-3,4,7,8-tetrahydro-2H-pyrano[4,3-b]pyran-5-one 67



A solution of $n\text{BuLi}$ in hexanes (0.234 ml, 2.51 M, 0.588 mmol) was added to $i\text{Pr}_2\text{NH}$ (0.091 ml, 0.647 mmol) in THF (1.5 ml) under nitrogen at 0°C . The reaction mixture was stirred for 30 minutes, then cooled to -78°C , then a solution of starting material (100 mg, 0.588 mmol) in THF (0.5 ml) was added dropwise. The reaction mixture was

stirred at -78°C for 35 minutes, then propionaldehyde (0.057 ml, 0.882 mmol) was added dropwise. The reaction mixture was stirred for 90 minutes at -78°C , then the reaction flask was sealed up and placed in the freezer (at -22°C) overnight. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (2 x 10 ml). The organic layers were washed with sat. brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:7 ethyl acetate:petrol, to obtain the *title compound* (89 mg, 83% yield) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1649, 1700; δ_{H} (250 MHz, CDCl_3) 4.22-4.14 (1H, m, 7-H), 4.12-3.93 (2H, m, 2-H), 2.39-2.04 (4H, m, 4-H and 8-H), 1.85-1.79 (2H, m, 3-H), 1.73-1.52 (2H, m, CHCH_2CH_3), 0.90 (3H, t, J 7.5); δ_{C} (75 MHz, CDCl_3) 167.9 (C), 165.3 (C), 100.2 (C), 76.4 (CH), 67.5 (CH_2), 32.1 (CH_2), 27.7 (CH_2), 21.6 (CH_2), 18.5 (CH_2), 9.2 (CH_3); Found: $[\text{M}+\text{H}]^+$, 183.1028. $\text{C}_{10}\text{H}_{14}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 183.1021.

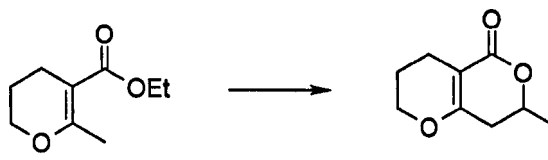
***Spiro[cyclohexane-1,7'-3',4',7',8'-tetrahydro-2H-pyrano[4',3'-b]pyran-5'-one]* 68**



A solution of $^n\text{BuLi}$ in hexanes (0.234 ml, 2.51 M, 0.588 mmol) was added to $i\text{Pr}_2\text{NH}$ (0.091 ml, 0.647 mmol) in THF (1.5 ml) under nitrogen at 0°C . The reaction mixture was stirred for 30 minutes, then cooled to -78°C , then a solution of starting material (100 mg, 0.588 mmol) in THF (0.5 ml) was added dropwise. The reaction mixture was stirred at -78°C for 35 minutes, then cyclohexanone (0.091 ml, 0.882 mmol) was added dropwise. The reaction mixture was stirred for 90 minutes at -78°C , then the reaction flask was sealed up and placed in the freezer (at -22°C) overnight. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (2 x 10 ml). The organic layers were washed with sat. brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:7 ethyl acetate:petrol, to obtain the *title compound* (107 mg, 82%) as a white solid, m.p. $83-84^{\circ}\text{C}$; $\nu_{\text{max}} / \text{cm}^{-1}$ 1656, 1695; δ_{H} (300 MHz, CDCl_3) 4.07 (2H, t, J 5.2, 2'-H), 2.35 (2H, t, J 1.8, 8'-H), 2.22 (2H, t, J 6.2, 4'-H), 1.91-1.83 (4H,

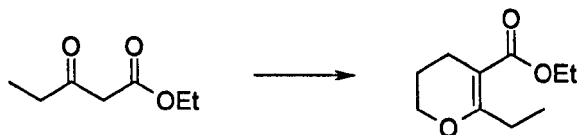
m, 3-H and 2H of 2-H) 1.76-1.20 (8H, m, 2H of 2-H, 3-H and 4-H); δ_C (75 MHz, $CDCl_3$) 167.0 (C), 163.7 (C), 99.6 (C), 78.4 (C), 67.4 (CH_2), 37.3 (CH_2), 36.3 (CH_2), 25.3 (CH_2), 21.7 (CH_2), 21.6 (CH_2), 18.4 (CH_2); Found: $[M+H]^+$, 223.1326. $C_{13}H_{18}O_3+H^+$ requires: $[M+H]^+$, 223.1334. The structure was also confirmed by X-ray crystallography.

7-Vinyl-3,4,7,8-tetrahydro-2H-pyrano[4,3-b]pyran-5-one 69



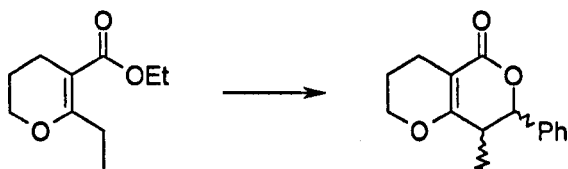
A solution of $nBuLi$ in hexanes (0.258 ml, 2.51 M, 0.647 mmol) was added to iPr_2NH (0.099 ml, 0.706 mmol) in THF (1.5 ml) under nitrogen at $0^\circ C$. The reaction mixture was stirred for 30 minutes, then cooled to $-78^\circ C$, then a solution of starting material (100 mg, 0.588 mmol) in THF (0.5 ml) was added dropwise. The reaction mixture was stirred at $-78^\circ C$ for 35 minutes, then acrolein (0.079 ml, 1.18 mmol) was added dropwise. The reaction mixture was stirred for 90 minutes at $-78^\circ C$, then the reaction flask was sealed up and placed in the freezer (at $-22^\circ C$) overnight. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (2 x 10 ml). The organic layers were washed with sat. brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:7 ethyl acetate:petrol, to obtain the *title compound* (67 mg, 63%); ν_{max} / cm^{-1} 1649, 1702; δ_H (250 MHz, $CDCl_3$) 5.93 (1H, ddd, J 17.3, 10.6, 5.7, $\underline{CH}=\underline{CH_2}$), 5.38 (1H, dt, J 17.3, 1.2, $CH=\underline{CH_2}$), 5.26 (1H, dt, J 10.6, 1.1, $CH=\underline{CH_2}$), 4.89-4.79 (1H, m, 7-H), 4.23-4.03 (2H, m, 2-H), 2.61-2.15 (4H, m, 4-H and 8-H), 1.98-1.88 (2H, m, 3-H); δ_C (62.5 MHz, $CDCl_3$) 167.1 (C), 164.7 (CH), 135.0 (CH_2), 117.7 (C), 100.5 (C), 76.5 (CH), 67.6 (CH_2), 32.4 (CH_2), 21.6 (CH_2), 18.5 (CH_2); Found: $[M+H]^+$, 181.0858. $C_{10}H_{12}O_3+H^+$ requires: $[M+H]^+$, 181.0865.

2-Ethyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 70



Ethyl propionylacetate (2.88 g, 20 mmol) was dissolved in abs. EtOH (15 ml) under nitrogen. NaOEt (6.51 g, 21% w/w in EtOH, 21 mmol) was added dropwise and the reaction mixture stirred for 30 mins. 1,3-Dibromopropane (4.24 g, 21 mmol) was added dropwise and the reaction mixture was heated at reflux for 19 hours. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with dilute aq. NH_4Cl , then with brine and dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 5:95 ethyl acetate:petrol, to obtain the *title compound* (1.81 g, 49%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1619, 1704; δ_{H} (250 MHz, CDCl_3) 4.15 (2H, q, J 7.1, OCH_2CH_3), 3.99 (2H, t, J 5.2, 6-H), 2.62 (2H, q, J 6.5, CCH_2CH_3), 2.29 (2H, t, J 6.5, 4-H), 1.85-1.76 (2H, m, 5-H), 1.26 (3H, t, J 7.1, OCH_2CH_3), 1.09 (3H, t, J 7.5, CCH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 169.6 (C), 168.2 (C), 100.4 (C), 66.5 (CH_2), 59.4 (CH_2), 26.6 (CH_2), 21.6 (CH_2), 21.4 (CH_2), 14.2 (CH_3), 11.9 (CH_3); Found: $[\text{M}+\text{H}]^+$, 185.1177. $\text{C}_{10}\text{H}_{16}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 185.1178.

8-Methyl-7-phenyl-3,4,7,8-tetrahydro-2H-pyrano[4,3-b]pyran-5-one 71

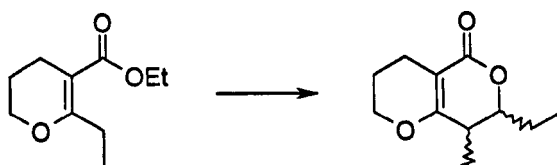


A solution of $n\text{BuLi}$ in hexanes (0.244 ml, 2.56 M, 0.625 mmol) was added to $i\text{Pr}_2\text{NH}$ (0.093 ml, 0.657 mmol) in THF (1.5 ml) under nitrogen at 0°C . The reaction mixture was stirred for 30 minutes, then cooled to -78°C , then a solution of starting material (93 mg, 0.5 mmol) in THF (0.5 ml) was added dropwise. The reaction mixture was stirred at -78°C for 35 minutes, then benzaldehyde (0.076 ml, 0.75 mmol) was added dropwise. The reaction mixture was stirred for 3 hours at -78°C , then the reaction flask was sealed up and placed in the freezer (at -22°C) overnight. The reaction mixture was taken up in

diethyl ether and water, and extracted with diethyl ether (2 x 10 ml). The organic layers were washed with sat. brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:7 ethyl acetate:petrol, to obtain the *title compound* (100 mg, 82%) as a colourless oil, shown by GC and ^1H NMR spectroscopy to be a 55:45 mixture of *cis:trans* diastereoisomers; $\nu_{\text{max}} / \text{cm}^{-1}$ 1643, 1705; δ_{H} (300 MHz, CDCl_3) 7.33-7.23 (5H, m, Ph for both isomers), 5.49 (0.5H, d, J 3.5, 7-H for *cis* isomer), 4.89 (0.5H, d, J 10.1, 7-H for *trans* isomer), 4.22-4.01 (2H, m, 2-H for both isomers), 2.81 (0.5H, m, 8-H for *trans* isomer), 2.49-2.13 (2.5H, m, 8-H for *cis* isomer and 4-H for both isomers), 1.94-1.84 (2H, m, 3-H for both isomers), 0.97 (1.5H, d, J 7.0, Me for *trans* isomer), 0.82 (1.5H, d, J 7.1, Me for *cis* isomer); δ_{C} (75 MHz, CDCl_3) 171.2 (C, *cis*), 167.9 (C, *trans*), 167.5 (C, *cis*), 167.0 (C, *trans*), 137.8 (C, *trans*), 136.9 (C, *cis*), 128.7 (CH, *trans*), 128.5 (CH, *cis*), 128.5 (CH, *trans*), 127.9 (CH, *cis*), 127.4 (CH, *trans*), 125.7 (CH, *cis*), 99.9 (C, *trans*), 99.3 (C, *cis*), 83.2 (CH, *trans*), 77.5 (CH, *cis*), 67.9 (CH_2 , *cis*), 67.7 (CH_2 , *trans*), 38.1 (CH, *cis*), 37.7 (CH, *trans*), 21.7 (CH_2 , *cis*), 21.5 (CH_2 , *trans*), 18.9 (CH_2 , *trans*), 18.7 (CH_2 , *cis*), 12.6 (CH_3 , *trans*), 11.3 (CH_3 , *cis*); Found: $[\text{M}+\text{NH}_4]^+$, 262.1447. $\text{C}_{15}\text{H}_{16}\text{O}_3+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 262.1443.

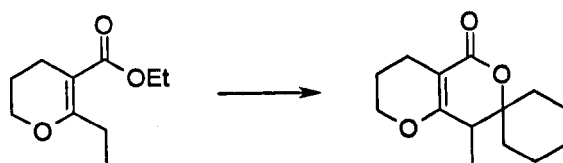
A portion of the above mixture was purified by flash column chromatography, eluting with 3:7 ethyl acetate:petrol, to obtain a sample of *trans* isomer as a white solid, m.p. 106-107°C shown by GC to contain less than 5% *cis* diastereoisomer; $\nu_{\text{max}} / \text{cm}^{-1}$ 1638, 1705; δ_{H} (300 MHz, CDCl_3) 7.33-7.23 (5H, m, Ph), 4.89 (1H, d, J 10.1, 7-H), 4.22-4.01 (2H, m, 2-H), 2.81 (1H, m, 8-H), 2.49-2.13 (2H, m, 4-H), 1.94-1.84 (2H, m, 3-H), 0.97 (3H, d, J 7.0, Me); δ_{C} (75 MHz, CDCl_3) 167.9 (C), 167.0 (C), 137.8 (C), 128.7 (CH), 128.5 (CH), 127.4 (CH), 99.9 (C), 83.2 (CH), 67.7 (CH_2), 37.7 (CH), 21.5 (CH_2), 18.9 (CH_2), 12.6 (CH_3); Found: $[\text{M}+\text{NH}_4]^+$, 262.1449. $\text{C}_{15}\text{H}_{16}\text{O}_3+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 262.1443.

7-Ethyl-8-methyl-3,4,7,8-tetrahydro-2H-pyrano[4,3-b]pyran-5-one 72



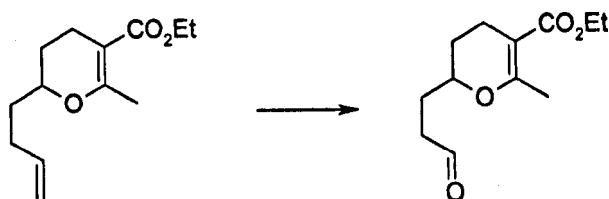
A solution of n BuLi in hexanes (0.205 ml, 2.44 M, 0.5 mmol) was added to i Pr₂NH (0.078 ml, 0.55 mmol) in THF (1.5 ml) under nitrogen at 0°C. The reaction mixture was stirred for 30 minutes, then cooled to -78°C, then a solution of starting material (92 mg, 0.5 mmol) in THF (0.5 ml) was added dropwise. The reaction mixture was stirred at -78°C for 35 minutes, then propionaldehyde (0.055 ml, 0.75 mmol) was added dropwise. The reaction mixture was stirred for 75 mins at -78°C, then the reaction flask was sealed up and placed in the freezer (at -22°C) overnight. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (2 x 10 ml). The organic layers were washed with sat. brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:7 ethyl acetate:petrol, to obtain the *title compound* (76 mg, 77%) as a colourless oil, shown by GC and ^1H NMR spectroscopy to be a 1:1 mixture of *cis:trans* diastereoisomers; ν_{max} / cm^{-1} 1644, 1701; δ_{H} (300 MHz, CDCl_3) 4.24-3.90 (3H, m, 2-H and 7-H), 2.50-2.08 (3H, m, 4-H and 8-H), 1.88 (2H, m, 3-H), 1.46-1.83 (2H, m, CH_2CH_3), 1.11 (1.5H, d, J 7.0, CHCH_3 of one diastereoisomer), 1.05 (1.5H, d, J 7.1, CHCH_3 of one diastereoisomer), 0.99 (1.5H, t, J 8.1, CH_2CH_3 of one diastereoisomer), 0.96 (1.5H, t, J 8.1, CH_2CH_3 of one diastereoisomer); δ_{C} (62.5 MHz, CDCl_3); 171.1 (C), 168.1 (C), 167.9 (C), 167.2 (C), 99.4 (C), 99.1 (C), 81.9 (CH), 79.3 (CH), 67.7 (CH_2), 67.5 (CH_2), 35.3 (CH), 35.3 (CH), 25.7 (CH_2), 24.1 (CH_2), 21.6 (CH_2), 21.5 (CH_2), 18.7 (CH_2), 18.5 (CH_2), 13.6 (CH_3), 18.4 (CH_3), 9.6 (CH_3), 9.3 (CH_3); Found: $[\text{M}+\text{H}]^+$, 197.1178. $\text{C}_{11}\text{H}_{16}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 197.1178.

Spiro[cyclohexane-1,7'-8'-methyl-3',4',7',8'-tetrahydro-2H-pyrano[4',3'-b]pyran-5'-one] 73



A solution of $n\text{BuLi}$ in hexanes (0.432 ml, 2.54 M, 1.1 mmol) was added to $i\text{Pr}_2\text{NH}$ (0.155 ml, 1.1 mmol) in THF (2 ml) under nitrogen at 0°C . The reaction mixture was stirred for 30 minutes, then cooled to -78°C , then a solution of starting material (184 mg, 1 mmol) in THF (0.5 ml) was added dropwise. The reaction mixture was stirred at -78°C for 35 minutes, then cyclohexanone (0.156 ml, 1.5 mmol) was added dropwise. The reaction mixture was stirred for 3 hours at -78°C , then the reaction flask was sealed up and placed in the freezer (at -22°C) overnight. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (2 x 10 ml). The organic layers were washed with sat. brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:7 ethyl acetate:petrol, to obtain the *title compound* (91 mg, 39%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1651, 1695; δ_{H} (300 MHz, CDCl_3) 4.16-4.00 (2H, m, 2'-H), 2.34-2.12 (3H, m, 4'-H and 8'-H), 2.00-1.80 (4H, m, 3'-H and 2-H), 1.76-1.36 (7H, m, 2-H, 3-H and 4-H), 1.32-1.22 (1H, m, 4-H), 1.08 (3H, d, J 7.1); δ_{C} (100 MHz, CDCl_3) 169.2 (C), 166.7 (C), 98.4 (C), 80.4 (C), 67.6 (CH_2), 39.6 (CH), 34.8 (CH_2), 32.6 (CH_2), 25.3 (CH_2), 22.0 (CH_2), 21.6 (CH_2), 21.2 (CH_2), 18.4 (CH_2), 13.0 (CH_3); Found: $[\text{M}+\text{H}]^+$, 237.1494. $\text{C}_{14}\text{H}_{20}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 237.1491.

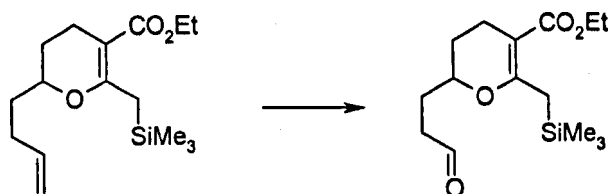
2-Methyl-6-(3'-oxo-propyl)-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 75



NMO (32 mg, 0.275 mmol) was added in batches to $\text{K}_2\text{OsO}_2(\text{OH})_4$ (1 mg, 0.003 mmol), starting material (31 mg, 0.138 mmol), acetone (0.9 ml) and water (0.09 ml). The reaction mixture was then stirred at room temperature overnight, then sat. sodium sulfite

solution was added and the reaction mixture was stirred for one hour. The resulting mixture was then extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a colourless oil (20 mg). A portion of this crude product (17.6 mg) was dissolved in methanol (1.83 ml) and water (0.37 ml), and sodium periodate (29 mg, 0.136 mmol) was added in portions. The reaction mixture was then stirred for 3.5 hours and diluted with ethyl acetate (3 ml). The resulting mixture was filtered through celite and washed with sat. NaHCO₃ solution, then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to obtain the *title compound* (17 mg, 63%) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1621, 1703, 1724; δ_{H} (250 MHz, CDCl₃) 9.81 (1H, t, *J*1.4, CHO), 4.14 (2H, q, *J*7.1, OCH₂CH₃), 3.89-3.79 (1H, m, 6-H), 2.63 (2H, tdd, *J*7.3, 2.3, 1.4, CHOCH₂), 2.56-1.43 (6H, m, 4-H, 5-H and OCHCH₂), 2.19 (3H, t, *J*1.4, CCH₃), 1.27 (3H, t, *J*7.1, OCH₂CH₃); δ_{C} (62.5 MHz, CDCl₃) 201.7 (C), 175.4 (C), 164.2 (C), 101.3 (C), 75.2 (CH), 59.6 (CH₂), 39.8 (CH₂), 27.2 (CH₂), 26.8 (CH₂), 21.4 (CH₂), 20.2 (CH₃), 14.4 (CH₃); Found: [M+H]⁺, 227.1277. C₁₂H₁₈O₄+H⁺ requires: [M+H]⁺, 227.1283.

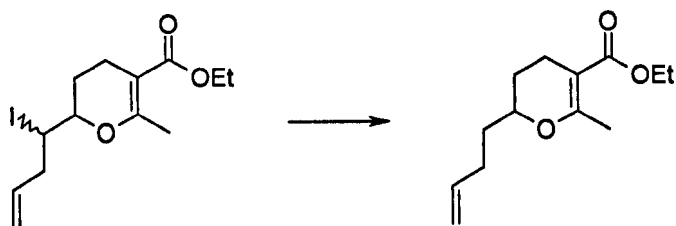
**6-(3-Oxo'-propyl)-2-trimethylsilylmethyl-5,6-dihydro-4H-pyran-3-carboxylic acid
ethyl ester 78**



NMO (62 mg, 0.533 mmol) was added in batches to K₂OsO₂(OH)₄ (2.0 mg, 0.005 mmol), starting material (79 mg, 0.267 mmol), acetone (1.8 ml) and water (0.18 ml). The reaction mixture was then stirred at room temperature for 3.5 hours, then sat. aq. sodium sulfite was added and the reaction mixture was stirred for 30 minutes, then extracted with ethyl acetate (6 x 10 ml). The combined organic layers were washed with sat. aq. NH₄Cl, then with sat. brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a colourless oil. This oil was dissolved in methanol (5.3 ml) and water (1.1 ml), and sodium periodate (84 mg, 0.393 mmol) was added in portions. The reaction mixture was then stirred for 3 hours and diluted with ethyl acetate (5 ml). The

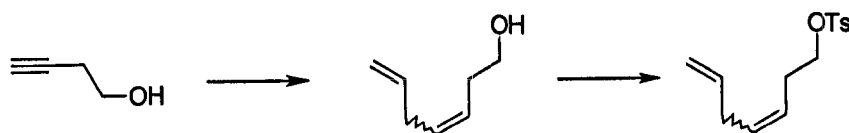
resulting mixture was filtered through celite and washed with sat. aq. NaHCO₃, sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to obtain the *title compound* (59 mg, 74%) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1600, 1698, 1727; δ_{H} (250 MHz, CDCl₃) 9.80 (1H, t, *J*1.2, CHO), 4.10 (2H, q, *J*7.1, OCH₂), 3.83-3.73 (1H, m, 6-H), 2.65-1.38 (10H, m, 4-H, 5-H, CHCH₂, CHCH₂CH₂ and CH₂-TMS), 1.24 (3H, t, *J*7.1, OCH₂CH₃), 0.01 (9H, s, SiMe₃); δ_{C} (62.5 MHz, CDCl₃) 201.6 (CH), 168.8 (C), 167.6 (C), 98.3 (C), 75.1 (CH), 59.3 (CH₂), 39.8 (CH₂), 27.5 (CH₂), 27.3 (CH₂), 24.6 (CH₂), 21.7 (CH₂), 14.5 (CH₃), -1.0 (CH₃); Found: [M+H]⁺, 299.1676. C₁₅H₂₆O₄Si+H⁺ requires: [M+H]⁺, 299.1679.

6-But-3'-enyl-2-methyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 79



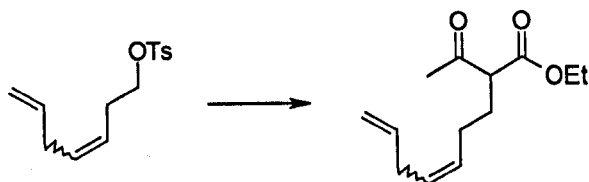
AIBN (23 mg, 0.14 mmol) and starting material (350 mg, 1 mmol) in toluene (90 ml) were combined under nitrogen, and the solvent was degassed by passing nitrogen through the reaction mixture for one hour. Bu₃SnH (0.909 ml, 3.43 mmol) was added and the reaction mixture was heated at reflux for 5 hours, then stirred at room temperature overnight. NEt₃ was added and the resulting reaction mixture concentrated *in vacuo* and purified by flash column chromatography, eluting with 2:1:97 ethyl acetate:NEt₃:petrol, to obtain the *title compound* (200 mg, 89% yield) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1621, 1706; δ_{H} (250 MHz, CDCl₃) 5.82 (1H, ddt, *J*16.9, 10.3, 6.7, 3'-H), 5.08-4.95 (2H, m, 4'-H), 4.14 (2H, q, *J*7.1, OCH₂), 3.89-3.78 (1H, m, 6-H), 2.44-1.42 (8H, m, 4-H, 5-H, 1'-H and 2'-H), 2.21 (3H, s, CCH₃), 1.27 (3H, t, *J*7.1, OCH₂CH₃); δ_{C} (75 MHz, CDCl₃) 168.8 (C), 164.7 (C), 137.9 (CH), 115.0 (CH₂), 101.0 (C), 75.7 (CH), 59.5 (CH₂), 33.9 (CH₂), 29.4 (CH₂), 26.7 (CH₂), 21.4 (CH₂), 20.4 (CH₃), 14.4 (CH₃); Found: [M+H]⁺, 225.1485. C₁₃H₂₀O₃+H⁺ requires: [M+H]⁺, 225.1491.

*Toluene-4-sulfonic acid hepta-3,6-dienyl ester*⁴⁶



CuCl (83 mg, 0.84 mmol), K₂CO₃ (3.50 g, 25.3 mmol) and ⁿBu₄NCl (468 mg, 1.69 mmol) were added to a solution of 3-butyn-1-ol (1.22 g, 16.9 mmol) in DMF (3 ml) with rapid stirring. The resulting reaction mixture was stirred for 15 minutes, then allyl bromide (1.43 ml, 16.9 mmol) was added dropwise and the resulting reaction mixture was stirred for 22 hours. The reaction mixture was filtered through celite, then was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to give crude hept-6-en-3-yn-1-ol. Sodium borohydride (5.10 g, 134.8 mmol) was added in portions to a mixture of PdCl₂ (239 mg, 1.35 mmol), PEG200 (300 ml) and DCM (190 ml). The resulting reaction mixture was cooled in a salt/ice bath, then a solution of the crude hept-6-en-3-yn-1-ol in DCM (8 ml) was added in one portion. The reaction mixture was allowed to warm to room temperature over one hour, then was stirred at room temperature for 4.5 hours. The reaction mixture was then poured into water (600 ml) and extracted with DCM (3 x 200 ml). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*, and the resulting crude was purified by flash column chromatography, eluting with 30:70 ethyl acetate:petrol to give hept-3,6-dien-1-ol (1.53 g, 81%). Triethylamine (2.14 ml, 15.4 mmol) was added to a solution of a portion of this material (1.01 g, 9.02 mmol) in DCM (20 ml) at 0°C. TsCl (1.97 g, 10.3 mmol) and DMAP (5 mg) was added to the resulting mixture, and the reaction mixture was allowed to warm slowly to room temperature overnight. The reaction mixture was taken up in DCM and water, and was extracted with DCM (3 x 20 ml). The combined organic extracts were washed with sat. NaHCO₃, dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude mixture was purified by flash column chromatography, eluting with 3:97 ethyl acetate:petrol to give the *title compound* (2.45 g, 73% overall) as a colourless oil; δ_H (250 MHz, CDCl₃) 7.81-7.76 (2H, m, Ph), 7.36-7.32 (2H, m, Ph), 5.74 (1H, ddt, *J* 17.1, 10.1, 6.2, 6-H), 5.57-5.27 (2H, m, 3-H and 4-H), 5.03-4.92 (2H, m, 7-H), 4.01 (2H, t, *J* 7.0, 1-H), 2.76-2.69 (2H, m, 5-H), 2.44 (3H, s, Me), 2.44-2.35 (2H, m, 2-H). ¹H NMR data corresponded with literature data.⁴⁶

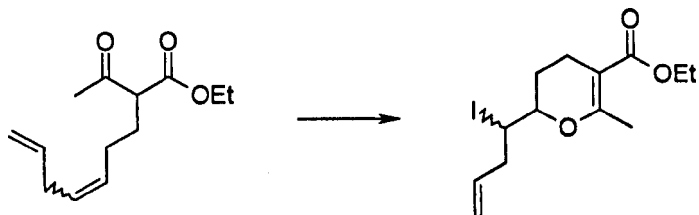
2-Acetyl-nona-5,8-dienoic acid ethyl ester 82



Sodium iodide (2.59 g, 17.3 mmol) was added to a solution of starting material (1.72 g, 6.47 mmol) in acetone (19 ml), and the resulting reaction mixture was stirred at room temperature for 40 hours. The reaction mixture was then taken up in diethyl ether and water and extracted with diethyl ether (2 x 50 ml). The combined organic fractions were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give crude 7-iodo-hepta-1,4-diene. Ethyl acetoacetate (0.59 ml, 6.49 mmol) was added dropwise to a suspension of sodium hydride (275 mg, 60% w/w, 6.88 mmol) in THF (15 ml) under nitrogen at 0°C. The reaction mixture was stirred for one hour, then a solution of crude 7-iodo-hepta-1,4-diene (all of the material synthesised above) in THF (30 ml) was added over 30 minutes. The reaction mixture was stirred at 0°C for one hour, then heated at reflux overnight. The reaction mixture was then taken up in diethyl ether and water, extracted with diethyl ether (2 x 50 ml), then the combined organic fractions were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:97 ethyl acetate:petrol, to obtain the *title product* (823 mg, 57% over two steps) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1640, 1711, 1731; δ_{H} (250 MHz, CDCl_3) 5.73 (1H, ddt, J 17.1, 10.1, 6.2, 8-H), 5.43-5.31 (2H, m, 5-H and 6-H), 4.96 (1H, dq, J 17.1, 1.8, 9-H), 4.91 (1H, dq, J 10.1, 1.6, 9-H), 4.13 (2H, q, J 7.1, OCH_2CH_3), 3.37 (1H, t, J 7.1, 2-H), 2.73-2.66 (2H, m, 7-H), 2.16 (3H, s, COCH_3), 2.08-1.79 (4H, m, 3-H and 4-H), 1.21 (3H, J 7.1, OCH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 203.0 (C), 169.7 (C), 136.7 (CH), 129.0 (CH), 128.4 (CH), 114.8 (CH_2), 61.3 (CH_2), 59.0 (CH), 31.4 (CH_2), 28.9 (CH_3), 27.8 (CH_2), 24.8 (CH_2), 14.1 (CH_3); Found: $[\text{M}+\text{H}]^+$, 225.1487. $\text{C}_{13}\text{H}_{20}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 225.1491.

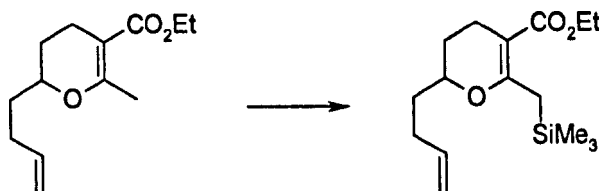
6-(1'-Iodo-but-3'-enyl)-2-methyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester

83



Iodine (1.07 g, 4.22 mmol) and sodium hydrogen carbonate (199 mg, 2.36 mmol) were added to a solution of starting material (473 mg, 2.11 mmol) in acetonitrile (25 ml) and the reaction mixture was stirred for 2 days at room temperature under nitrogen. The reaction mixture was then taken up in diethyl ether and sufficient sodium thiosulfate solution to effect the solution colourless, then extracted with diethyl ether (2 x 50 ml). The combined organic layers were washed with water, then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:97-5:95 ethyl acetate:petrol, to obtain the *title compound* (453 mg, 61%) as a white solid, m.p. 55°C; $\nu_{\max}$ / cm^{-1} 1625, 1705; δ_{H} (250 MHz, CDCl_3) 5.80 (1H, ddt, J 15.8, 11.3, 6.8, 3'-H), 5.18-5.10 (2H, m, 4'-H), 4.19-4.10 (1H, m, OCH), 4.15 (2H, q, J 7.1, OCH_2CH_3), 3.47 (1H, dt, J 10.6, 2.8, 1'-H), 2.74 (2H, t, J 6.8, 2'-H), 2.25 (3H, s, CCH_3), 2.54-1.66 (4H, m, 4-H and 5-H), 1.27 (3H, t, J 7.1, OCH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 168.3 (C), 164.2 (C), 136.0 (CH), 118.0 (CH_2), 101.7 (C), 77.5 (CH), 59.7 (CH_2), 40.7 (CH_2), 36.3 (CH), 26.7 (CH_2), 21.4 (CH_2), 20.0 (CH_3), 14.4 (CH_3); Found: $[\text{M}+\text{H}]^+$, 351.0438. $\text{C}_{13}\text{H}_{19}\text{IO}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 351.0457.

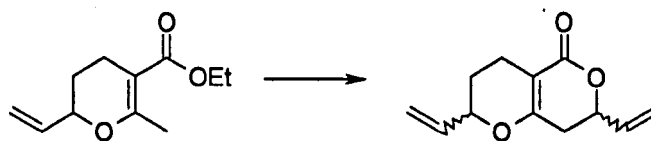
2-But-3'-enyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 86



A solution of $^n\text{BuLi}$ in hexanes (0.652 ml, 1.54 M, 1.00 mmol) was added to $^i\text{Pr}_2\text{NH}$ (0.148 ml, 1.05 mmol) in THF (2 ml) under nitrogen at 0°C. The reaction mixture was stirred for 30 minutes, then cooled to -78°C, then a solution of starting material (180

mg, 0.803 mmol) in THF (1 ml) was added dropwise. The reaction mixture was stirred at -78°C for 40 minutes, then TMSCl (0.176 ml, 1.39 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. Sat. aq. NaHCO_3 was added, then the mixture was extracted with diethyl ether (3 x 10 ml). The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain the *title compound* (224 mg, 94%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1600, 1642, 1699; δ_{H} (250 MHz, CDCl_3) 5.76 (1H, ddt, J 17.1, 10.1, 6.4, $\text{CH}_2=\text{CH}$), 5.02-4.88 (2H, m, $\text{CH}_2=\text{CH}$), 4.06 (2H, q, J 7.1, OCH_2CH_3), 3.78-3.68 (1H, m, 6-H), 2.33 (2H, s, SiCH_2), 2.41-1.33 (8H, m, 4-H, 5-H, CHCH_2 and CHCH_2CH_2), 1.20 (3H, t, J 7.1, OCH_2CH_3), -0.01 (9H, s, SiMe_3); δ_{C} (62.5 MHz, CDCl_3) 168.8 (C), 168.1 (C), 137.9 (CH), 114.9 (CH_2), 98.0 (C), 75.5 (CH), 59.1 (CH_2), 34.4 (CH_2), 29.4 (CH_2), 27.2 (CH_2), 24.6 (CH_2), 21.7 (CH_2), 14.5 (CH_3), -1.1 (CH_3); Found: $[\text{M}+\text{H}]^+$, 297.1881. $\text{C}_{16}\text{H}_{28}\text{O}_3\text{Si}+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 297.1886.

2,7-Divinyl-3,4,7,8-tetrahydro-2H-pyrano[4,3-b]pyran-5-one 87



A solution of $n\text{BuLi}$ in hexanes (1.06 ml, 2.47 M, 2.63 mmol) was added to $i\text{Pr}_2\text{NH}$ (0.386 ml, 2.75 mmol) in THF (20 ml) under nitrogen at 0°C . The reaction mixture was stirred for 30 minutes, then cooled to -78°C , then a solution of starting material (494 mg, 2.5 mmol) in THF (5 ml) was added dropwise. The reaction mixture was stirred at -78°C for 40 minutes, then acrolein (0.501 ml, 7.5 mmol) was added dropwise. The reaction mixture was stirred for 24 hours at -78°C , then the reaction flask was sealed up and placed in the freezer (at -22°C) overnight. The reaction mixture was taken up in diethyl ether and water, and extracted with diethyl ether (2 x 100 ml). The organic layers were washed with sat. brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 25:75 ethyl acetate:petrol, to obtain the *title compound* (345 mg, 66%) as a colourless oil as a 1:1 mixture of diastereoisomers; $\nu_{\text{max}} / \text{cm}^{-1}$ 1651, 1706; δ_{H} (400 MHz, CDCl_3) 5.98-5.82 (2H, m, $\text{CH}_2=\text{CH}$), 5.42-5.24 (4H, m, $\text{CH}_2=\text{CH}$), 4.91-4.83 (1H, m, 7-H), 4.60-4.56 (0.5 H, m, 2-H for one diastereoisomer), 4.49-4.44

(0.5H, m, 2-H for one diastereoisomer), 2.63-1.69 (6H, m, 3-H, 4-H and 8-H); δ_C (62.5 MHz, $CDCl_3$) 167.2 (C), 166.9 (C), 164.2 (C), 164.0 (C), 135.8 (CH), 135.6 (CH), 135.1 (CH), 135.0 (CH), 117.7 (CH₂), 117.1 (CH₂), 100.6 (CH), 100.3 (CH), 77.8 (CH), 77.5 (CH), 75.3 (CH), 75.2 (CH), 32.5 (CH₂), 32.4 (CH₂), 27.1 (CH₂), 26.5 (CH₂), 18.4 (CH₂), 17.5 (CH₂); Found: $[M+H]^+$, 207.1021. $C_{12}H_{14}O_3+H^+$ requires: $[M+H]^+$, 207.1021.

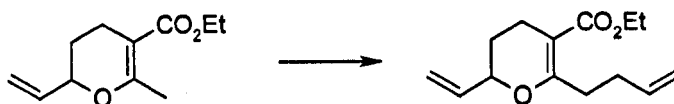
2-Methyl-6-vinyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 89



Sodium borohydride (80 mg, 2.12 mmol) was added in portions to a solution of diphenyl diselenide (326 mg, 1.04 mmol) in ethanol (10 ml) under nitrogen and the reaction mixture was stirred at room temperature for 5 minutes (solution went yellow to colourless). A solution of starting material (601 mg, 1.85 mmol) in ethanol (5 ml) was added dropwise, and the resulting reaction mixture was heated at reflux overnight. The reaction mixture was allowed to cool to room temperature, THF (8 ml) was added, then H_2O_2 (2.34 ml of 27% aqueous solution, ~18.5 mmol) was added dropwise, while cooling the reaction mixture to 0°C. The reaction mixture was then stirred at room temperature for 6 hours. The reaction mixture was taken up in diethyl ether and water, extracted with diethyl ether (2 x 30 ml) then the combined organic fractions were washed thoroughly with sodium hydrogen sulfite solution. The organic layers were washed with water, then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:97 ethyl acetate:petrol, to obtain the *title compound* (268 mg, 74%) as a colourless oil and recovered selenide. The recovered selenide was dissolved in THF (4.5 ml) and treated with H_2O_2 (0.70 ml of 27% aqueous solution), followed by workup as above to give additional *title compound* (95 mg, 26%) thereby achieving quantitative yield overall; ν_{max} / cm^{-1} 1622, 1706; δ_H (300 MHz, $CDCl_3$) 5.88 (1H, ddd, J 17.3, 10.6, 5.7, $CH_2=CH$), 5.29 (1H, dt, J 17.3, 1.4, $CH_2=CH$), 5.20 (1H, dt, J 10.6, 1.3, $CH_2=CH$), 4.40-4.34 (1H, m, 6-H), 4.15 (2H, q, J 7.1, OCH_2CH_3), 2.38-1.59 (4H, m, 4-H and 5-H), 2.26 (3H, t, J 1.4, CCH_3), 1.28 (3H, t, J 7.1, OCH_2CH_3); δ_C (75

MHz, CDCl₃) 168.6 (C), 164.1 (C), 136.8 (CH), 116.2 (CH₂), 101.2 (C), 76.5 (CH), 59.6 (CH₂), 26.8 (CH₂), 20.8 (CH₂), 20.3 (CH₃), 14.4 (CH₃); Found: [M+H]⁺, 197.1173. C₁₁H₁₆O₃+H⁺ requires: [M+H]⁺, 197.1178.

2-But-3'-enyl-6-vinyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 97



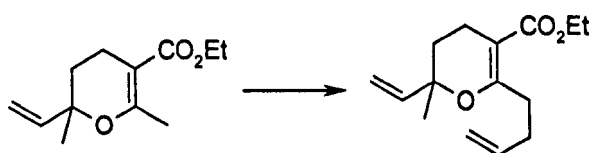
A solution of ⁿBuLi in hexanes (0.517 ml, 2.42 M, 1.25 mmol) was added to ⁱPr₂NH (0.185 ml, 1.313 mmol) in THF (3 ml) under nitrogen at 0°C. The reaction mixture was stirred for 30 minutes, then cooled to -78°C, then a solution of starting material (196 mg, 1 mmol) in THF (1 ml) was added dropwise. The reaction mixture was stirred at -78°C for 40 minutes, then allyl bromide (0.487 ml, 1.73 mmol) was added dropwise and the reaction mixture was stirred at -78°C for 4 hours, then was stirred at -30°C overnight before allowing the reaction mixture to warm to room temperature. The reaction mixture was then taken up in diethyl ether and water, and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:97 ethyl acetate, to obtain the *title compound*, contaminated with starting material which could not be separated by chromatography, (184 mg, <78%) as a colourless oil. Spectroscopic data was obtained from a purer sample of the *title compound* that was recovered from a failed ring-closing metathesis reaction; $\nu_{\max}$ / cm⁻¹ 1619, 1728; δ_{H} (250 MHz, CDCl₃) 5.95-5.77 (2H, m, CH₂=CH), 5.34-5.18 (2H, m, CH₂=CH), 5.08-4.92 (2H, m, CH₂=CH), 4.39-4.32 (1H, m, 6-H), 4.16 (2H, q, *J* 7.1, OCH₂CH₃), 2.86-2.68 (2H, m, OCCH₂), 2.46-1.53 (6H, m, 4-H, 5-H and CH₂=CHCH₂), 1.28 (3H, t, *J* 7.1, OCH₂CH₃); δ_{C} (62.5 MHz, CDCl₃) 168.3 (C), 166.8 (C), 138.1 (CH), 136.9 (CH), 116.1 (CH₂), 114.6 (CH₂), 101.4 (C), 76.4 (CH), 59.6 (CH₂), 32.6 (CH₂), 31.8 (CH₂), 26.8 (CH₂), 20.9 (CH₂), 14.3 (CH₃); Found: [M+H]⁺, 237.1489. C₁₄H₂₀O₃+H⁺ requires: [M+H]⁺, 237.1491.

(1'-Benzyloxy-but-3'-enyl)-6-vinyl-5,6-dihydro-4H-pyran-3-carboxylic acid methyl ester 98



Starting material (47 mg, 0.150 mmol) was taken up in benzene (1.6 ml) and methanol (0.4 ml), and (trimethylsilyl)diazomethane was added dropwise (0.160 ml, 2 M solution in hexanes, 0.32 mmol). The reaction mixture was stirred for one hour at room temperature, then concentrated *in vacuo* and purified by flash column chromatography, eluting with 5:95 ethyl acetate:petrol, to give the *title compound* (41 mg, 83%) as a colourless oil as a 1:1 mixture of diastereoisomers; $\nu_{\max}$ / cm^{-1} 1617, 1706; δ_{H} (250 MHz, CDCl_3) 7.33-7.24 (5H, m, Ph), 5.92-5.74 (2H, m, $\text{CH}_2=\text{CH}$), 5.31-5.15 (4H, m, $\text{CH}_2=\text{CH}$), 4.61 (1H, d, J 12.0, CH_2Ph), 4.38 (1H, d, J 12.0, CH_2Ph), 4.36-4.09 (2H, m, 6-H and CHOBN), 3.67 (3H, s, OMe), 3.22-3.08 (1H, m, CCH_2), 2.99-2.86 (1H, m, CCH_2), 2.47-2.20 (2H, m, 4-H), 1.97-1.86 (1H, m, 5-H), 1.70-1.51 (1H, m, 5-H); δ_{C} (62.5 MHz, CDCl_3) 168.5 (C), 164.0 (C), 138.8 (C), 138.4 (CH), 136.7 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 117.0 (CH_2), 116.2 (CH_2), 102.5 (C), 78.9 (CH), 76.4 (CH), 70.1 (CH_2), 51.0 (CH_3), 39.1 (CH_2), 26.7 (CH_2), 21.1 (CH_2); Found: $[\text{M}+\text{H}]^+$, 329.1749. $\text{C}_{20}\text{H}_{24}\text{O}_4+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 329.1753.

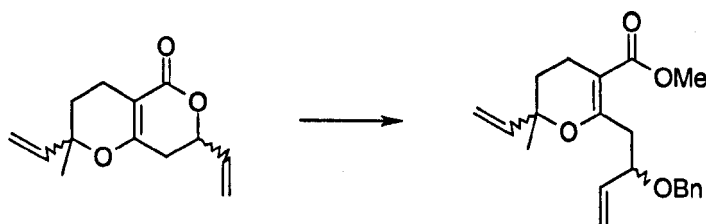
2-But-3'-enyl-6-methyl-6-vinyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 99



A solution of $^n\text{BuLi}$ in hexanes (0.236 ml, 2.38 M, 0.625 mmol) was added to $^i\text{Pr}_2\text{NH}$ (0.092 ml, 0.657 mmol) in THF (1.5 ml) under argon at 0°C . The reaction mixture was stirred for 30 minutes, then cooled to -78°C , then a solution of starting material (105 mg, 0.5 mmol) in THF (1 ml) was added dropwise. The reaction mixture was stirred at -78°C for 40 minutes, then allyl bromide (0.075 ml, 0.865 mmol) was added dropwise. The reaction mixture was stirred at -78°C for one hour, then allowed to warm to room

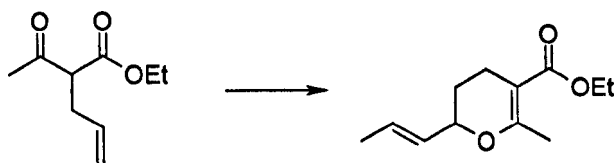
temperature slowly overnight. The resulting mixture was then quenched with sat. aq. NH_4Cl , taken up in diethyl ether and water, and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was partially purified by flash column chromatography, eluting with 1:99 ethyl acetate:*iso*-hexane to obtain impure *title compound* (90 mg, 89% pure by LCMS, 64%) as a colourless oil. To obtain a pure sample for characterisation and further testing a portion of this product was purified by further flash column chromatography, eluting with 1:199 ethyl acetate:*iso*-hexane to give pure *title compound* (25 mg, 20%); $\nu_{\text{max}} / \text{cm}^{-1}$ 1617, 1702; δ_{H} (500 MHz, CDCl_3) 5.80 (1H, ddt, J 17.0, 10.2, 6.6, $\text{CH}_2=\text{CHCH}_2$), 5.72 (1H, dd, J 17.4, 10.9, $\text{CH}_2=\text{CHC}$), 5.06 (1H, d, J 17.4, $\text{CH}_2=\text{CHC}$), 5.02-4.88 (3H, m, $\text{CH}_2=\text{CHC}$ and $\text{CH}_2=\text{CHCH}_2$), 4.07 (2H, q, J 7.1, OCH_2), 2.77-2.65 (2H, m, $\text{CH}_2=\text{CHCH}_2\text{CH}_2$), 2.29-2.23 (2H, m, $\text{CH}_2=\text{CHCH}_2$), 2.16-2.10 (2H, m, 4-H), 1.70-1.51 (2H, m, 5-H), 1.25 (3H, s, CCH_3), 1.20 (3H, t, J 7.1, OCH_2CH_3); δ_{C} (125 MHz, CDCl_3) 168.3 (C), 166.0 (C), 141.1 (CH), 138.1 (CH), 114.6 (CH_2), 113.2 (CH_2), 100.4 (C), 77.5 (C), 59.6 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 31.2 (CH_2), 26.0 (CH_3), 19.3 (CH_2), 14.3 (CH_3); Found: $[\text{M}+\text{H}]^+$, 251.1639. $\text{C}_{15}\text{H}_{22}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 251.1647.

2-(2'-Benzyloxy-but-3'-enyl)-6-methyl-6-vinyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 100

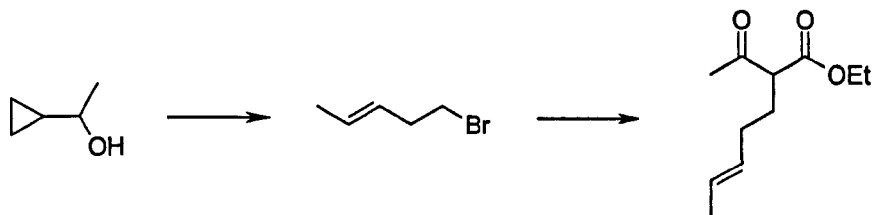


NaOH (11.4 ml, 1 M aq., 11.4 mmol) was added to a solution of starting material (501 mg, 2.27 mmol) in ethanol (11.4 ml). The reaction mixture was stirred for 6 hours at room temperature, then was acidified with 1 M aq. HCl . The resulting mixture was then extracted with diethyl ether (3 x 30 ml), and the combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude hydroxy acid was then added as a solution in THF (2 ml) to a mixture of NaH (227 mg, 60% w/w in mineral oil, 5.69 mmol) and THF (18 ml) at 0°C under argon. The mixture was stirred at 0°C for one hour, then warmed to room temperature.

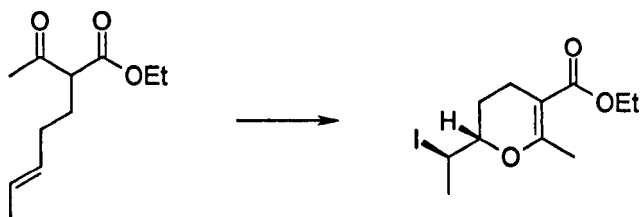
Benzyl bromide (0.810 ml, 6.82 mmol) was added dropwise, and the reaction mixture was stirred for 6 hours. Additional NaH (100 mg, 60% in mineral oil, 2.5 mmol) was then added and the reaction mixture was stirred overnight. The reaction mixture was then quenched with sat. aq. NH_4Cl , taken up in diethyl ether and water, and extracted with diethyl ether (3 x 30 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was then taken up in toluene (10 ml) and methanol (2.5 ml), and trimethylsilyl diazomethane (1.14 ml, 2 M sol. in hexanes, 2.27 mmol) was added dropwise. The resulting reaction mixture was stirred at room temperature under argon for 45 minutes, then was concentrated *in vacuo* and purified by flash column chromatography, eluting with 2:98 ethyl acetate:*iso*-hexane to obtain the *title compound* (491 mg, 63%) as a colourless oil as a 1:1 mixture of diastereoisomers; ν_{max} / cm^{-1} 1613, 1704; δ_{H} (400 MHz, CDCl_3) 7.26-7.15 (5H, m, Ph), 5.80-5.65 (2H, m, $\text{CH}_2=\text{CHC}$ and $\text{CH}_2=\text{CHCH}$), 5.20-4.96 (4H, m, $\text{CH}_2=\text{CHC}$ and $\text{CH}_2=\text{CHCH}$), 4.52 (0.5H, d, $J_{12.0}$, CH_2Ph), 4.52 (0.5H, d, $J_{12.0}$, CH_2Ph), 4.33 (0.5H, d, $J_{12.0}$, CH_2Ph), 4.31 (0.5H, d, $J_{12.0}$, CH_2Ph), 4.12-4.06 (1H, m, $\text{CH}_2=\text{CHCH}$), 3.58 (3H, s, OMe), 3.20 (0.5H, dd, $J_{13.5}$, 7.5, $\text{CH}_2=\text{CHCHCH}_2$), 3.06 (0.5H, dd, $J_{13.5}$, 6.4, $\text{CH}_2=\text{CHCHCH}_2$), 2.94 (0.5H, dd, $J_{13.5}$, 7.5, $\text{CH}_2=\text{CHCHCH}_2$), 2.76 (0.5H, dd, $J_{13.5}$, 6.4, $\text{CH}_2=\text{CHCHCH}_2$), 2.30-2.08 (2H, m, 4-H), 1.68-1.47 (2H, m, 5-H), 1.23 (1.5H, s, OCCH_3), 1.20 (1.5H, s, OCCH_3); δ_{C} (100 MHz, CDCl_3) 169.0 (C), 168.9 (C), 163.7 (C), 163.6 (C), 141.4 (CH), 141.4 (CH), 139.3 (C), 139.2 (C), 138.8 (CH), 138.7 (CH), 128.6 (CH), 128.6 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 117.6 (CH_2), 113.8 (CH_2), 113.7 (CH_2), 102.0 (C), 101.9 (C), 79.7 (CH), 79.4 (CH), 78.3 (C), 78.3 (C), 70.5 (CH_2), 70.5 (CH_2), 51.4 (CH_3), 39.6 (CH_2), 39.5 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 26.3 (CH_3), 26.3 (CH_3), 19.9 (CH_2), 19.8 (CH_2); Found: $[\text{M}+\text{H}]^+$, 343.1904. $\text{C}_{21}\text{H}_{26}\text{O}_4+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 343.1909.



DMF (2 ml), palladium(II) acetate (6.6 mg, 0.029 mmol), tetrabutylammonium chloride (180 mg, 0.646 mmol), sodium carbonate (218 mg, 2.06 mmol) and starting material (100 mg, 0.588 mmol) were combined under nitrogen. (*E*)-1-Bromo-1-propene (0.061 ml, 0.706 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then heated (oil bath set to 60°C) for 20 hours, then additional palladium(II) acetate (8 mg) and (*E*)-1-bromo-1-propene (0.050 ml) was added and the reaction mixture was heated (oil bath set to 60°C) for 4 hours. The reaction mixture was cooled to room temperature and filtered through celite. The resulting organic layer was washed with water, sat. NH_4Cl solution, sat. brine and dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:97-10:90 ethyl acetate:petrol, to obtain the *title compound* (18 mg, 15%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1621, 1706; δ_{H} (300 MHz, CDCl_3) 5.79 (1H, dqd, J 15.4, 6.7, 0.7, $\text{CH}_3\text{CH}=\text{CH}$), 5.56 (1H, ddd, J 15.4, 6.8, 1.4, $\text{CH}_3\text{CH}=\text{CH}$), 4.34-4.27 (1H, m, 6-H), 4.17 (2H, q, J 7.1, OCH_2CH_3), 2.45-2.19 (2H, m, 4-H and 5-H), 2.26 (3H, s, CCH_3), 1.95-1.55 (2H, m, 4-H and 5-H), 1.75 (3H, d, J 6.7, $\text{CH}_3\text{CH}=\text{CH}$), 1.29 (3H, t, J 7.1, OCH_2CH_3); δ_{C} (75 MHz, CDCl_3) 168.7 (C), 164.4 (C), 129.9 (CH), 128.8 (CH), 101.1 (C), 72.3 (CH), 59.6 (CH_2), 27.3 (CH_2), 21.1 (CH_2), 20.4 (CH_3), 17.8 (CH_3), 14.4 (CH_3); Found: $[\text{M}+\text{H}]^+$, 211.1336. $\text{C}_{12}\text{H}_{18}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 211.1334.

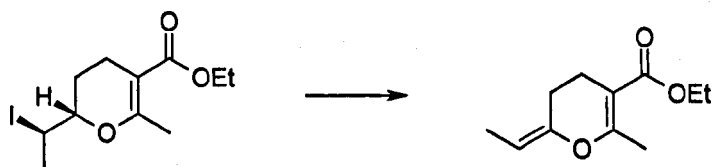


Starting material (6 ml, 61.5 mmol) was added dropwise over 2 hours to 48% aq. HBr (50 ml) at 0°C, and the resulting reaction mixture was stirred at 0°C for 1.5 hours. The reaction mixture was taken up in water and pentane and extracted with pentane (2 x 100 ml). The combined organic extracts were washed with sat. aq. NaHCO₃ and brine, then dried over magnesium sulfate and concentrated *in vacuo* to give crude 5-bromo-pent-2-ene. Ethyl acetoacetate (12.3 ml, 97.0 mmol) was added dropwise over 30 minutes to a suspension of NaH (2.91 g, 60% str. in oil, 72.8 mmol) in DMF (45 ml) at 0°C, and the resulting reaction mixture was stirred for 30 minutes. The crude 5-bromo-pent-2-ene and ⁿBu₄NI (895 mg, 2.42 mmol) were added, and the resulting reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. The reaction mixture was then taken up in diethyl ether and aq. NH₄Cl, then extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with water, then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 5:95 ethyl acetate:petrol, to obtain the *title compound* (5.00 g, 41%) as a colourless oil; δ_{H} (250 MHz, CDCl₃) 5.46-5.21 (2H, m, 5-H and 6-H), 4.15 (2H, q, *J*7.1, CH₂CH₃), 3.37 (1H, t, *J*7.0, 2-H), 2.18 (3H, s, Ac), 1.98-1.81 (4H, m, 3-H and 4-H), 1.60 (3H, br d, *J*5.8, 7-H), 1.23 (3H, t, *J*7.1, CH₂CH₃). ¹H NMR data corresponded with literature data.¹⁰³



Iodine (527 mg, 2.08 mmol) and sodium hydrogen carbonate (95 mg, 1.13 mmol) were added to a solution of starting material (200 mg, 1.01 mmol) in acetonitrile (1 ml) and the reaction mixture was stirred overnight at room temperature under nitrogen. Additional acetonitrile (1 ml) was then added and the reaction mixture was stirred for 3 hours. The reaction mixture was then taken up in diethyl ether and sufficient sodium thiosulfate solution to effect the solution colourless, then extracted with diethyl ether (2 x 10 ml). The combined organic layers were washed with water, then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 5:95 ethyl acetate:petrol, to obtain the *title compound* (194 mg, 59%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1626, 1705; δ_{H} (250 MHz, CDCl_3) 4.22 (1H, dq, J 7.0, 6.2, CHI), 4.11 (2H, q, J 7.1, OCH_2CH_3), 3.55 (1H, ddd, J 9.5, 6.2, 2.5, 6-H), 2.46-1.59 (4H, m, 4-H and 5-H), 2.20 (3H, t, J 1.4, CCH_3), 1.90 (3H, d, J 7.0, CH_3CHI), 1.23 (3H, t, J 7.1, OCH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 168.1 (C), 163.8 (C), 101.6 (C), 79.8 (CH), 59.6 (CH_2), 28.4 (CH), 25.6 (CH_2), 23.9 (CH_3), 20.8 (CH_2), 20.0 (CH_3), 14.4 (CH_3); Found: $[\text{M}+\text{H}]^+$, 325.0288. $\text{C}_{11}\text{H}_{17}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 325.0301.

(*E*)-6-Ethylidene-2-methyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 107



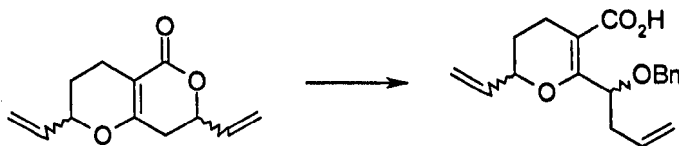
DBU (0.105 ml, 0.699 mmol) was added to a solution of starting material (180 mg, 0.555 mmol) in toluene (3 ml) under nitrogen and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then heated (oil bath at 90°C) for six hours, then allowed to cool to room temperature. The reaction mixture was then

taken up in diethyl ether and water, and extracted with diethyl ether (2 x 10 ml). The combined organic layers were washed with water, then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:97 ethyl acetate:petrol, to obtain the *title product* (99 mg, 91%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1630, 1694, 1710; δ_{H} (300 MHz, CDCl_3) 5.08 (1H, q, J 7.1, $\text{CH}=\text{C}$), 4.13 (2H, q, J 7.1, OCH_2CH_3), 2.37 (4H, s, 5-H and 4-H), 2.25 (3H, s, CCH_3), 1.56 (3H, d, J 7.1, $\text{CH}_3\text{CH}=\text{C}$), 1.25 (3H, t, J 7.1, OCH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 167.9 (C), 162.3 (C), 148.7 (C), 102.0 (C), 101.1 (CH), 59.7 (CH_2), 21.2 (CH_2), 20.2 (CH_2), 19.6 (CH_3), 14.3 (CH_3), 10.4 (CH_3); Found: $[\text{M}+\text{H}]^+$, 197.1180. $\text{C}_{11}\text{H}_{16}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 197.1178.

2-((*E*)-Buta-1',3'-dienyl)-6-vinyl-5,6-dihydro-4H-pyran-3-carboxylic acid 109

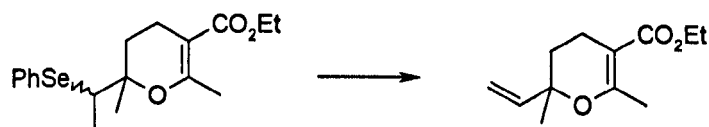


Sodium (36 mg, 1.57 mmol) was dissolved in ethanol (11 ml) under nitrogen and stirred for one hour. A solution of starting material (269 mg, 1.31 mmol) in ethanol (1 ml) was added, then the reaction mixture was stirred at room temperature for 4 hours before heating at reflux for 3 hours, then was allowed to cool to room temperature. The reaction mixture was acidified with 2 M HCl, then the mixture was stirred with diethyl ether for 30 minutes and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the *title compound* (219 mg, 81%) as an off-white solid, m.p. not determined as decomposed 140-150°C; $\nu_{\max}$ / cm^{-1} 1573, 1650, 1672, 1730; δ_{H} (250 MHz, CDCl_3) 7.44 (1H, d, J 15.2, CCH), 6.93 (1H, d, J 15.2, 10.8, CCH=CH), 6.52 (1H, dt, J 16.8, 10.8, CH=CHCH=CH₂), 5.94 (1H, ddd, J 17.3, 10.6, 5.4, OCHCH), 5.46-5.22 (4H, m, $\text{CH}_2=\text{CH}$), 4.51-4.44 (1H, m, 6-H), 2.60-1.61 (4H, m, 4-H and 5-H); δ_{C} (75 MHz, CDCl_3) 174.0 (C), 161.1 (C), 136.9 (CH), 136.5 (CH), 135.2 (CH), 125.7 (CH), 121.3 (CH_2), 116.4 (CH_2), 103.3 (C), 76.4 (CH), 26.6 (CH_2), 21.7 (CH_2); Found: $[\text{M}+\text{H}]^+$, 207.1019. $\text{C}_{12}\text{H}_{14}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 207.1021.



3 M NaOH solution (3.33 ml, 10 mmol) was added to a solution of starting material (412 mg, 2 mmol) in ethanol (3.33 ml), and stirred at room temperature for 4.5 hours. The reaction mixture was then acidified with 2 M HCl solution, and the mixture was stirred with diethyl ether for 40 minutes. The mixture was extracted with diethyl ether (3 x 20 ml), then the combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the intermediate hydroxy acid (391 mg). A portion of this hydroxy acid (86 mg) was then added to NaH (38 mg, 60% w/w in mineral oil, 0.958 mmol) in THF (1.8 ml) at 0°C under nitrogen. The reaction mixture was then stirred for one hour, allowed to warm to room temperature and benzyl bromide (0.137 ml, 1.15 mmol) was added dropwise. The reaction mixture was stirred for 5 hours, then quenched with sat. aq. NH₄Cl and extracted with diethyl ether (3 x 10 ml). The combined organic extracts were then washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was then purified by flash column chromatography, eluting with 3:7 ethyl acetate:petrol, to obtain the *title compound* (77 mg, 57%) as a colourless oil shown by ¹H NMR spectroscopy to be a 1:1 mixture of diastereoisomers; ν_{max} / cm⁻¹ 1594, 1675; δ_{H} (250 MHz, CDCl₃) 7.33-7.26 (5H, m, Ph), 5.93-5.76 (2H, m, CH₂=CH), 5.33-5.17 (4H, m, CH₂=CH), 4.63 (1H, dd, *J*12.2, 3.8, CH₂Ph), 4.40 (1H, d, *J*12.2, CH₂Ph), 4.42-4.13 (2H, m, 6-H and CHOBn), 3.23-3.12 (1H, m, CCH₂), 3.03-2.86 (1H, m, CCH₂), 2.51-2.24 (2H, m, 4-H), 1.99-1.89 (1H, m, 5-H), 1.68-1.52 (1H, m, 5-H); δ_{C} (62.5 MHz, CDCl₃) 173.7 (C), 173.4 (C), 165.9 (C), 165.3 (C), 138.6 (C), 138.4 (C), 138.2 (CH), 138.0 (CH), 136.5 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 117.3 (CH₂), 117.3 (CH₂), 116.4 (CH₂), 102.7 (C), 102.4 (C), 79.0 (CH), 78.7 (CH), 76.9 (CH), 76.8 (CH), 70.2 (CH₂), 39.4 (CH₂), 26.7 (CH₂), 21.1 (CH₂), 20.9 (CH₂); Found: [M+H]⁺, 315.1606. C₁₉H₂₂O₄+H⁺ requires: [M+H]⁺, 315.1596.

2,6-Dimethyl-6-vinyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 112



Hydrogen peroxide (9.27 ml, 27% aq. solution) was added dropwise to a solution of starting material (2.70 g, 7.35 mmol) in THF (100 ml) at 0°C. The reaction mixture was then stirred at room temperature for 3.5 hours, then *ca.* 50 ml of solvent was removed from the reaction mixture under reduced pressure. The resulting mixture was then taken up in diethyl ether and water, and extracted with diethyl ether (3 x 200 ml). The combined organic layers were washed with aq. sodium sulfite, then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 1:99 ethyl acetate:petrol, to obtain the *title compound* (1.47 g, 95%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1623, 1705; δ_{H} (250 MHz, CDCl_3) 5.74 (1H, dd, J 17.1, 10.5, $\text{CH}_2=\text{CH}$), 5.07 (1H, dd, J 17.1, 0.9, $\text{CH}_2=\text{CH}$), 5.05 (1H, dd, J 10.5, 0.9, $\text{CH}_2=\text{CH}$), 4.11 (2H, q, J 7.1, OCH_2), 2.37-2.05 (2H, m, 4-H), 2.26 (3H, t, J 1.4, $\text{C}=\text{CCH}_3$), 1.80-1.54 (2H, m, 5-H), 1.31 (3H, s, CHCCH_3), 1.25 (3H, t, J 7.1, CH_2CH_3); δ_{C} (75 MHz, CDCl_3) 168.6 (C), 163.3 (C), 140.7 (CH), 113.3 (CH_2), 100.4 (C), 77.8 (C), 59.5 (CH_2), 31.2 (CH_2), 26.3 (CH_3), 20.4 (CH_3), 19.3 (CH_2), 14.4 (CH_3); Found: $[\text{M}+\text{H}]^+$, 211.1341. $\text{C}_{12}\text{H}_{18}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 211.1334.

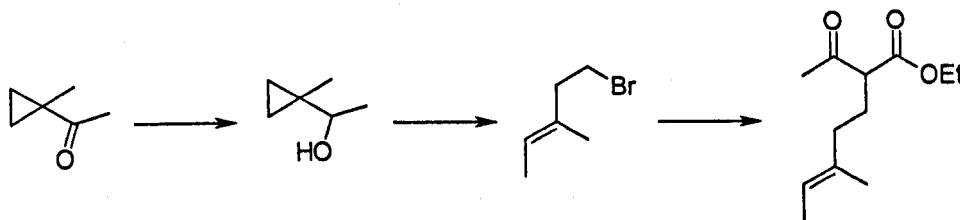
2-Methyl-2,7-divinyl-3,4,7,8-tetrahydro-2H-pyrano [4,3-b] pyran-5-one 113



A solution of $^n\text{BuLi}$ in hexanes (1.79 ml, 2.34 M, 4.2 mmol) was added to $^i\text{Pr}_2\text{NH}$ (0.618 ml, 4.4 mmol) in THF (8 ml) under argon at 0°C. The reaction mixture was stirred for 30 minutes, then cooled to -78°C, then a solution of starting material (841 mg, 4 mmol) in THF (2 ml) was added dropwise. The reaction mixture was stirred at -78°C for 40 minutes, then acrolein (0.802 ml, 12 mmol) was added dropwise. The reaction mixture was stirred at -78°C overnight, then allowed to warm to -20°C for 4

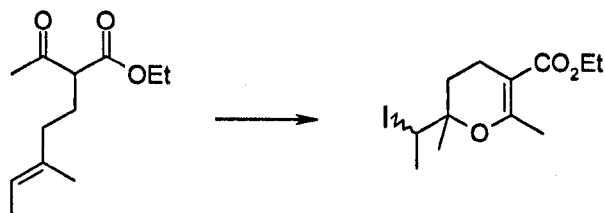
hours, then allowed to warm to room temperature. The resulting mixture was then quenched with sat. aq. NH_4Cl , taken up in diethyl ether and water, and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 15:85-20:80 ethyl acetate:iso-hexane to obtain the *title compound* (572 mg, 65%) as a colourless oil as a 1:1 mixture of diastereoisomers; $\nu_{\text{max}} / \text{cm}^{-1}$ 1647, 1702; δ_{H} (400 MHz, CDCl_3) 5.89 (1H, ddd, J 17.3, 10.6, 5.6, $\text{CHCH}=\text{CH}_2$), 5.76 (0.5H, dd, J 17.3, 10.9, $\text{CCH}=\text{CH}_2$), 5.67 (0.5H, dd, J 17.3, 10.9, $\text{CCH}=\text{CH}_2$), 5.33 (1H, d, J 17.3, $\text{CHCH}=\text{CH}_2$), 5.21 (1H, d, J 10.6, $\text{CHCH}=\text{CH}_2$), 5.09 (0.5H, d, J 17.3, $\text{CCH}=\text{CH}_2$), 5.08 (0.5H, d, J 10.9, $\text{CCH}=\text{CH}_2$), 5.05 (0.5H, d, J 10.9, $\text{CCH}=\text{CH}_2$), 4.99 (0.5H, d, J 17.3, $\text{CCH}=\text{CH}_2$), 4.84-4.78 (1H, m, 7-H), 2.60-2.03 (4H, m, 3-H and 8-H), 1.86-1.62 (2H, m, 4-H), 1.34 (1.5H, s, CCH_3), 1.30 (1.5H, s, CCH_3); δ_{C} (100 MHz, CDCl_3) 167.1 (C), 167.0 (C), 163.4 (C), 163.3 (C), 140.2 (CH), 139.4 (CH), 135.0 (CH), 134.9 (CH), 117.6 (CH_2), 117.6 (CH_2), 113.9 (CH_2), 113.7 (CH_2), 99.8 (C), 99.4 (C), 79.6 (C), 79.5 (C), 75.2 (CH), 75.2 (CH), 32.5 (CH_3), 31.4 (CH_2), 31.2 (CH_2), 26.6 (CH_2), 25.2 (CH_2), 16.7 (CH_2), 16.5 (CH_2); Found: $[\text{M}+\text{H}]^+$, 221.1151. $\text{C}_{13}\text{H}_{16}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 221.1178.

2-Acetyl-5-methyl-hept-5-enoic acid ethyl ester 116



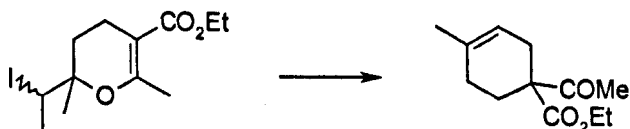
A solution of starting material (25 g, 255 mmol) in diethyl ether (150 ml) was added dropwise to LiAlH_4 (9.87 g, 260 mmol) in diethyl ether (350 ml) at 0°C under nitrogen, and stirred for two hours at 0°C . The reaction mixture was then quenched carefully with sat. aq. Na_2SO_4 (33.4 ml). The resulting mixture was then filtered through celite, and washed through with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated *in vacuo* to give the crude alcohol (22.3 g). A portion of the resulting crude (9.01g) was then combined with diethyl ether (250 ml), 2,4,6-collidine (5.72 ml, 43.2 mmol) and lithium bromide (9.38 g, 108 mmol) under

nitrogen. Maintaining the reaction temperature under -40°C PBr_3 (6.26 ml, 66.6 mmol) was added dropwise, and the resulting reaction mixture was stirred for two hours keeping the reaction temperature below 0°C . Additional 2,4,6-collidine (9.83 ml, 74.3 mmol) was added, and the mixture was taken up in pentane and water and extracted with pentane (3 x 100 ml). The combined organic layers were washed with sat. aq. NaHCO_3 , sat. brine and water then dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude mixture was then taken up in diethyl ether (15 ml) and added dropwise to a suspension of zinc bromide (16.7 g, 74.3 mmol) in diethyl ether (35 ml) over 30 minutes, maintaining the reaction temperature below -40°C . The reaction mixture was then stirred for 3 hours, maintaining the reaction temperature below 0°C , then taken up in pentane and water and extracted with pentane (3 x 100 ml). The combined organic layers were washed with sat. aq. NaHCO_3 , sat. brine and three times with water then dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude mixture was then taken up in THF (100 ml) and added dropwise over one hour to a suspension of the sodium salt of ethyl acetoacetate (18.17 g, 120 mmol) and tetrabutylammonium iodide (2.21 g, 5.97 mmol) in THF (260 ml) at 0°C under nitrogen. The reaction mixture was then heated at reflux for 40 hours, cooled to room temperature then partially concentrated *in vacuo*. The resulting mixture was then taken up in diethyl ether and water and extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:97 ethyl acetate:petrol, to obtain the *title compound* (7.71 g, 35%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1642, 1716, 1742; δ_{H} (250 MHz, CDCl_3) 5.22-5.12 (1H, m, $\text{C}=\underline{\text{CH}}$), 4.16 (2H, q, J 7.1, OCH_2), 3.39-3.33 (1H, m, 2-H), 2.19 (3H, s, COCH_3), 1.97-1.90 (4H, m, 3-H and 4-H), 1.57-1.51 (6H, m, $\text{CH}=\text{C}\underline{\text{CH}_3}$ and 7-H), 1.28-1.21 (3H, t, J 7.1, $\text{CH}_2\underline{\text{CH}_3}$); δ_{C} (62.5 MHz, CDCl_3) 203.2 (C), 169.8 (C), 134.2 (C), 120.0 (CH), 61.2 (CH_2), 59.0 (CH), 37.2 (CH_2), 28.9 (CH_3), 26.2 (CH_2), 15.2 (CH_3), 14.1 (CH_3), 13.3 (CH_3); Found: $[\text{M}+\text{H}]^+$, 213.1496. $\text{C}_{12}\text{H}_{20}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 213.1491.



Iodine (2.54 g, 10 mmol) and sodium hydrogen carbonate (471 mg, 5.61 mmol) were added to a solution of starting material (1.06 g, 5 mmol) in acetonitrile (60 ml) under nitrogen. The reaction mixture was stirred at room temperature for 5 hours, then was taken up in diethyl ether and sufficient sodium thiosulfate solution to effect the solution colourless and extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 2:98 ethyl acetate:petrol, to obtain the *title compound* (815 mg, 48%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1623, 1707; δ_{H} (250 MHz, CDCl_3) 4.28 (1H, q, J 7.0, CHI), 4.15 (2H, q, J 7.1, OCH_2), 2.32-1.71 (4H, m, 4-H and 5-H), 2.23 (3H, t, J 1.5, $\text{C}=\text{CCH}_3$), 1.91 (3H, d, J 7.0, CHICH_3), 1.37 (3H, s, CHICCH_3), 1.28 (3H, t, J 7.1, CH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 168.3 (C), 162.7 (C), 100.7 (C), 78.7 (C), 59.7 (CH_2), 32.8 (CH), 30.9 (CH_2), 22.7 (CH_3), 20.3 (CH_3), 20.3 (CH_3), 18.5 (CH_2), 14.4 (CH_3); Found: $[\text{M}+\text{H}]^+$, 339.0449. $\text{C}_{12}\text{H}_{19}\text{O}_3\text{I}+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 339.0457.

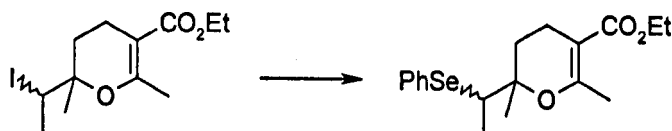
1-Acetyl-4-methyl-cyclohex-3-enecarboxylic acid ethyl ester 118



DBU (0.055 ml, 0.369 mmol) was added to a solution of starting material (96 mg, 0.284 mmol) in toluene (5 ml) under nitrogen, and the resulting reaction mixture was heated at reflux overnight. After cooling to room temperature, the mixture was extracted with diethyl ether (3 x 10 ml), and the combined organic layers were washed with 2 M aq. HCl, then with sat. aq. NaHCO_3 , then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. DBU (0.1 ml, 0.671 mmol) was then added to a solution of the resulting crude mixture in toluene (2 ml) and heated at reflux for 4 days.

After cooling to room temperature, the mixture was extracted with diethyl ether (3 x 10 ml), and the combined organic layers were washed with 2 M aq. HCl, then with sat. aq. NaHCO₃, then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 10:90 ethyl acetate:petrol, to obtain the *title compound* (35 mg, 59%) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1713, 1758; δ_{H} (250 MHz, CDCl₃) 5.33-5.28 (1H, m, 3-H), 4.18-4.06 (2H, m, OCH₂), 2.50-2.30 (2H, m, 2-H), 2.11 (3H, s, COCH₃), 2.15-1.85 (4H, m, 5-H and 6-H), 1.55 (3H, s, CCH₃), 1.18 (3H, t, *J*7.1, CH₂CH₃); δ_{C} (62.5 MHz, CDCl₃) 205.2 (C), 172.2 (C), 133.5 (C), 117.9 (CH), 61.3 (CH₂), 58.9 (C), 30.0 (CH₂), 27.1 (CH₂), 27.1 (CH₂), 25.8 (CH₃), 23.2 (CH₃), 14.0 (CH₃); Found: [M+H]⁺, 211.1334. C₁₂H₁₈O₃+H⁺ requires: [M+H]⁺, 211.1334.

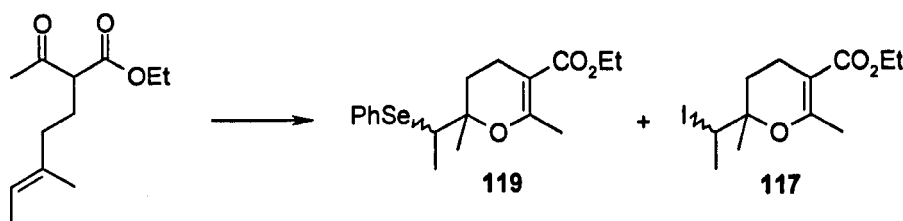
**2,6-Dimethyl-6-(1'-phenylselanyl-ethyl)-5,6-dihydro-4H-pyran-3-carboxylic acid
ethyl ester 119**



Sodium borohydride (70 mg, 1.84 mmol) was added in portions to a solution of diphenyl diselenide (283 mg, 0.908 mmol) in ethanol (10 ml) under nitrogen and the reaction mixture was stirred at room temperature for 5 minutes (solution went yellow to colourless). A solution of starting material (545 mg, 1.61 mmol) in ethanol (10 ml) was added dropwise, and the resulting reaction mixture was heated at reflux for 8 days and then quenched with sat. aq. NaHCO₃. After cooling to room temperature the mixture was extracted with diethyl ether (3 x 30 ml), then the combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 2:98 ethyl acetate:petrol, to obtain the *title compound* (258 mg, 44%) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1621, 1706; δ_{H} (250 MHz, CDCl₃) 7.59-7.55 (2H, m, Ph), 7.30-7.23 (3H, m, Ph), 4.15 (2H, q, *J*7.1, OCH₂), 3.50 (1H, q, *J*7.1, CHSePh), 2.45-2.15 (2H, m, 4-H), 2.12 (3H, t, *J*1.4, C=CCH₃), 1.92-1.68 (2H, m, 5-H), 1.42 (3H, d, *J*7.1, CHSePhCH₃), 1.33 (3H, s, CHSePhCCH₃), 1.28 (3H, t, *J*7.1, CH₂CH₃); δ_{C} (75 MHz, CDCl₃) 168.5 (C), 163.4 (C), 134.8 (CH), 130.0 (C), 129.0 (CH), 127.5 (CH), 100.0 (C), 79.9 (C),

59.6 (CH₂), 48.5 (CH), 28.4 (CH₂), 21.5 (CH₃), 20.4 (CH₃), 19.1 (CH₂), 17.7 (CH₃), 14.5 (CH₃); Found: [M+H]⁺, 367.0983, 369.0971. C₁₈H₂₄O₃⁷⁸Se+H⁺ requires: [M+H]⁺, 367.0977. C₁₈H₂₄O₃⁸⁰Se+H⁺ requires: [M+H]⁺, 369.0969.

2,6-Dimethyl-6-(1'-phenylselanyl-ethyl)-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 119 and 6-(1'-Iodo-ethyl)-2,6-dimethyl-5,6-dihydro-4H-pyran-3-carboxylic acid ethyl ester 117



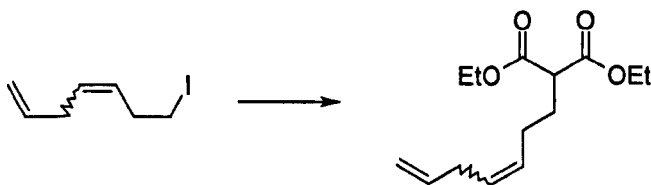
N-(Phenylseleno)phthalimide (831 mg, 2.75 mmol) was added to a solution of starting material (531 mg, 2.5 mmol) in DCM (25 ml) under nitrogen. Zinc iodide (798 mg, 2.5 mmol) was added in batches to the reaction mixture and the resultant mixture was stirred at room temperature for 3 days. Triethylamine and sat. aq. NaHCO₃ were added and the resulting mixture was extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 1:99-2:98 ethyl acetate:petrol, to obtain the *title selenide* (400 mg, 44%) and *title iodide* (181 mg, 21%) as colourless oils.

Data for **119**; $\nu_{\max}$ / cm⁻¹ 1621, 1704; δ_{H} (250 MHz, CDCl₃) 7.62-7.54 (2H, m, Ph), 7.30-7.24 (3H, m, Ph), 4.14 (2H, q, *J*7.1, OCH₂), 3.44 (1H, q, *J*7.0, CHSePh), 2.31-2.23 (2H, m, 4-H), 2.17 (3H, t, *J*1.4, C=CCH₃), 2.13-1.71 (2H, m, 5-H), 1.46 (3H, d, *J*7.0, CHSePhCH₃), 1.30 (3H, s, CHSePhCCH₃), 1.27 (3H, t, *J*7.1, CH₂CH₃); δ_{C} (75 MHz, CDCl₃) 168.6 (C), 163.0 (C), 135.0 (CH), 129.7 (C), 129.1 (CH), 127.7 (CH), 100.3 (C), 79.9 (C), 59.6 (CH₂), 47.0 (CH), 29.5 (CH₂), 21.2 (CH₃), 20.4 (CH₃), 18.9 (CH₂), 17.3 (CH₃), 14.5 (CH₃); Found: [M+H]⁺, 367.0970, 369.0961. C₁₈H₂₄O₃⁷⁸Se+H⁺ requires: [M+H]⁺, 367.0977. C₁₈H₂₄O₃⁸⁰Se+H⁺ requires: [M+H]⁺, 369.0969.

Data for **117**; $\nu_{\max}$ / cm⁻¹ 1621, 1706; δ_{H} (250 MHz, CDCl₃) 4.27 (1H, q, *J*7.0, CHI), 4.14 (2H, q, *J*7.1, OCH₂), 2.31-2.20 (2H, m, 4-H), 2.21 (3H, t, *J*1.4, C=CCH₃), 2.13-

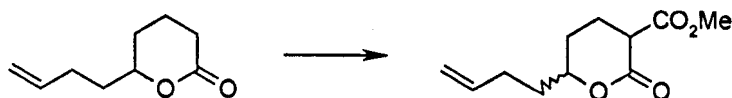
1.70 (2H, m, 5-H), 1.90 (3H, d, J 7.0, CH₃CH), 1.36 (3H, s, CH₃CH), 1.27 (3H, t, J 7.1, CH₂CH₃); δ_c (62.5 MHz, CDCl₃) 168.3 (C), 162.7 (C), 100.7 (C), 78.4 (C), 59.7 (CH₂), 32.8 (CH), 30.9 (CH₂), 22.7 (CH₃), 20.3 (CH₃), 20.3 (CH₃), 18.4 (CH₂), 14.4 (CH₃); Found: $[M+H]^+$, 339.0459. C₁₂H₁₉O₃I+H⁺ requires: $[M+H]^+$, 339.0457.

2-(2-Ethoxy-acetyl)-nona-5,8-dienoic acid ethyl ester 133



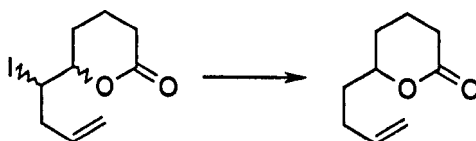
Diethyl malonate (0.152 ml, 1 mmol) was added dropwise to a suspension of sodium hydride (32 mg, 60% w/w in mineral oil, 0.8 mmol) in THF (1 ml) at 0°C under argon, and stirred for 15 minutes. The reaction mixture was allowed to warm to room temperature, and a solution of the iodide starting material (111 mg, 0.5 mmol, synthesised from the tosylate as described for the synthesis of 82) in THF (1.5 ml) was added dropwise. The reaction mixture was stirred at room temperature overnight, quenched with sat. aq. NH₄Cl, taken up in diethyl ether and water and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 1:39 ethyl acetate:iso-hexane, to obtain the *title compound* (105 mg, 83%) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1639, 1731, 1747; δ_H (400 MHz, CDCl₃) 5.72 (1H, ddt, J 17.0, 10.3, 6.5, 8-H), 5.43-5.32 (2H, m, 5-H and 6-H), 4.96 (1H, dq, J 17.0, 1.7, 9-H), 4.91 (1H, dq, J 10.3, 1.6, 9-H), 4.18-4.08 (4H, m, OCH₂), 3.27 (1H, t, J 7.4, 2-H), 2.70 (2H, t, J 6.5, 7-H), 2.07-1.87 (4H, m, 3-H and 4-H), 1.20 (6H, t, J 7.1, CH₃); δ_c (100 MHz, CDCl₃) 169.8 (C), 137.1 (CH), 129.3 (CH), 128.8 (CH), 115.2 (CH₂), 61.7 (CH₂), 51.7 (CH), 31.8 (CH₂), 28.9 (CH₂), 25.2 (CH₂), 14.5 (CH₃); Found: $[M+H]^+$, 255.1587. C₁₄H₂₂O₄+H⁺ requires: $[M+H]^+$, 255.1596.

6-But-3'-enyl-2-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester 136



A solution of starting material (89 mg, 0.577 mmol) in THF (1.5 ml) was added to LHMDs (1.15 ml, 1 M sol. in THF, 1.15 mmol) in THF (0.5 ml) at -78°C under argon. The reaction mixture was stirred for 10 minutes and then dimethyl carbonate (0.49 ml, 5.77 mmol) was added quickly. The reaction mixture was stirred at -78°C for 8 hours, then at -22°C overnight, then allowed to warm to room temperature and stirred at room temperature for 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl , taken up in diethyl ether and water and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with DCM, to obtain the *title compound* (86 mg, 70%) as a colourless oil shown by ^1H NMR spectroscopy to be a 1:1 mixture of diastereoisomers; $\nu_{\text{max}} / \text{cm}^{-1}$ 1642, 1739; δ_{H} (400 MHz, CDCl_3) 5.78-5.67 (1H, m, $\text{CH}=\text{CH}_2$), 4.99 (1H, dt, J 17.1, 1.5, $\text{CH}=\text{CH}_2$), 4.93 (1H, d, J 10.3, $\text{CH}=\text{CH}_2$), 4.33-4.24 (1H, m, 6-H), 3.71 (3H, t, J 2.2, OMe), 3.52 (0.5H, t, J 7.7, 3-H of one diastereoisomer), 3.45-3.41 (0.5H, m, 3-H of other diastereoisomer), 2.24-1.48 (8H, m, 4-H, 5-H, $\text{CH}_2=\text{CHCH}_2$ and $\text{CH}_2=\text{CHCH}_2\text{CH}_2$); δ_{C} (100 MHz, CDCl_3) 179.6 (C), 169.4 (C), 168.0 (C), 166.9 (C), 137.0 (CH), 115.4 (CH_2), 80.2 (CH), 79.4 (CH), 52.7 (CH_3), 52.6 (CH_3), 47.6 (CH), 45.7 (CH), 34.7 (CH_2), 34.3 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 26.9 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 21.4 (CH_2); Found: $[\text{M}+\text{NH}_4]^+$, 230.1396. $\text{C}_{11}\text{H}_{16}\text{O}_4+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 230.1392.

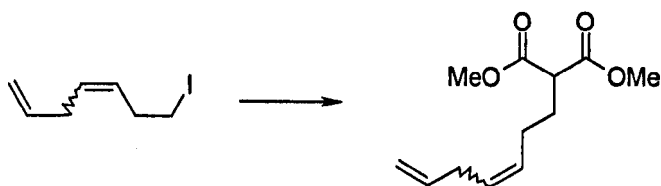
6-But-3'-enyl-tetrahydro-pyran-2-one⁷⁰ 137



AIBN (39 mg, 0.24 mmol) and starting material (476 mg, 1.70 mmol) in toluene (140 ml) were combined under argon, and the solvent degassed by passing argon through the reaction mixture for 10 minutes. Bu_3SnH (1.55 ml, 5.83 mmol) was added and the

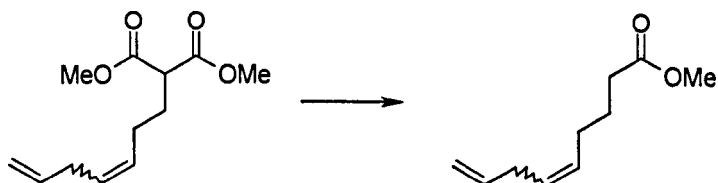
reaction mixture was heated at reflux for 6 hours, then allowed to cool to room temperature. NEt_3 was added and the resulting reaction mixture was concentrated *in vacuo* and purified by flash column chromatography, eluting with DCM, to obtain the *title compound* (262 mg, 100% yield) as a colourless oil; δ_{H} (400 MHz, CDCl_3) 5.80 (1H, ddt, J 17.2, 10.1, 6.6, 3'-H), 5.05 (1H, dq, J 17.2, 1.5, 4'-H), 5.01-4.98 (1H, m, 4'-H), 4.33-4.26 (1H, m, 6-H), 2.62-2.40 (2H, m, 3-H), 2.32-1.30 (8H, m, 4-H, 5-H, 1'-H and 2'-H). ^1H NMR data corresponded with literature data.⁷⁰

2-(2-Methoxy-acetyl)-nona-5,8-dienoic acid methyl ester 138



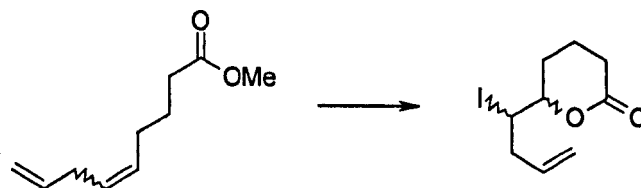
Dimethyl malonate (0.638 ml, 5.58 mmol) and a solution of starting material (620 mg, 2.79 mmol, synthesised from the tosylate as described for the synthesis of 82) in THF (5 ml) were added to a suspension of sodium hydride (179 mg, 60% w/w in mineral oil, 4.47 mmol) in THF (10 ml) at 0°C under argon, and the resulting reaction mixture was stirred for 60 hours at room temperature. The mixture was then quenched with sat. aq. NH_4Cl , taken up in diethyl ether and water and extracted with diethyl ether (3 x 30 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:97 ethyl acetate:*iso*-hexane, to obtain the *title compound* (526 mg, 83%) as a colourless oil; ν_{max} / cm^{-1} 1639, 1735; δ_{H} (400 MHz, CDCl_3) 5.62 (1H, ddt, J 17.1, 10.1, 6.3, 8-H), 5.33-5.20 (2H, m, 5-H and 6-H), 4.86 (1H, dq, J 17.1, 1.7, 9-H), 4.81 (1H, dq, J 10.1, 1.5, 9-H), 3.57 (6H, s, OMe), 3.22 (1H, t, J 7.4, 2-H), 2.60 (2H, t, J 6.3, 7-H), 1.96-1.78 (4H, m, 3-H and 4-H); δ_{C} (100 MHz, CDCl_3) 169.8 (C), 136.6 (CH), 128.7 (CH), 128.6 (CH), 114.8 (CH_2), 52.4 (CH_3), 50.9 (CH), 31.4 (CH_2), 28.6 (CH_2), 24.8 (CH_2); Found: $[\text{M}+\text{H}]^+$, 227.1293. $\text{C}_{12}\text{H}_{18}\text{O}_4+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 227.1283.

Nona-5,8-dienoic acid methyl ester 139



Dimethyl sulfoxide (15.5 ml), water (2.5 ml) and sodium chloride (301 mg, 5.15 mmol) were added to starting material (1.06 g, 4.69 mmol). The reaction mixture was then heated in an oil bath at 140°C overnight, then in an oil bath at 160°C for 2 days. After cooling to room temperature the reaction mixture was then taken up in diethyl ether and water and extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 3:97 ethyl acetate:*iso*-hexane, to obtain the *title compound* (528 mg, 67%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1639, 1740; δ_{H} (400 MHz, CDCl_3) 5.73 (1H, ddt, J 17.1, 10.1, 6.2, 8-H), 5.41-5.32 (2H, m, 5-H and 6-H), 4.96 (1H, dq, J 17.1, 1.7, 9-H), 4.90 (1H, dq, J 10.1, 1.7, 9-H), 3.60 (3H, s, OMe), 2.73-2.70 (1.8H, m, 7-H of major geometrical isomer), 2.68-2.65 (0.2H, m, 7-H of minor geometrical isomer), 2.24 (1.8H, t, J 7.4, 2-H of major geometrical isomer), 2.24 (0.2H, t, J 7.4, 2-H of minor geometrical isomer), 2.05-1.95 (2H, m, 4-H), 1.63 (2H, qn, J 7.4, 3-H); δ_{C} (100 MHz, CDCl_3) 174.0 (C), 136.8 (CH), 129.6 (CH), 127.8 (CH), 114.6 (CH_2), 51.4 (CH_3), 33.4 (CH_2), 31.4 (CH_2), 26.4 (CH_2), 24.7 (CH_2); Found: $[\text{M}+\text{NH}_4]^+$, 186.1491. $\text{C}_{10}\text{H}_{16}\text{O}_2+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 186.1494.

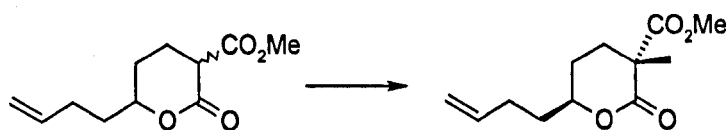
6-(1'-Iodo-but-3'-enyl)-tetrahydropyran-2-one 140



NaOH (10.7 ml, 1 M aq., 10.7 mmol) was added to a solution of starting material (360 mg, 2.14 mmol) in ethanol (11 ml). The reaction mixture was stirred at room temperature for 3 hours and then acidified with 1 M aq. HCl. The resulting mixture was extracted with diethyl ether (3 x 30 ml). The combined organic layers were washed with

sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Sodium hydrogen carbonate (192 mg, 2.29 mmol) and iodine (1034 mg, 4.09 mmol) was then added to a solution of the resulting crude in MeCN (25 ml) under argon at 0°C. The reaction mixture was allowed to warm to room temperature, and stirred for 20 hours, then was taken up in diethyl ether and sufficient sodium thiosulfate solution to effect the solution colourless. The resulting mixture was extracted with diethyl ether (3 x 50 ml) and the combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with DCM, to obtain the *title compound* (483 mg, 81%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1641, 1732; δ_{H} (400 MHz, CDCl_3) 5.77-5.67 (1H, m, $\text{CH}=\text{CH}_2$), 5.13-5.09 (2H, m, $\text{CH}=\text{CH}_2$), 4.17-3.91 (2H, m, 6-H and CH), 2.78-1.58 (8H, m, CHICH_2 , 3-H, 4-H and 5-H); δ_{C} (100 MHz, CDCl_3) 170.4 (C), 135.6 (CH), 118.4 (CH_2), 80.9 (CH), 40.4 (CH_2), 36.2 (CH), 29.5 (CH_2), 27.7 (CH_2), 18.2 (CH_2); Found: $[\text{M}+\text{NH}_4]^+$, 298.0306. $\text{C}_9\text{H}_{13}\text{IO}_2+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 298.0304.

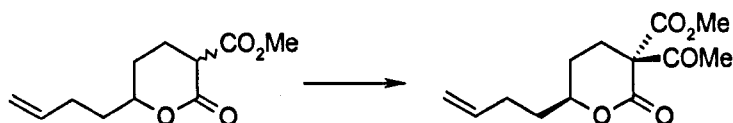
(3*R, 6*S**)-6-But-3'-enyl-3-methyl-2-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester 142**



A solution of KHMDS in toluene (0.632 ml, 0.38 M, 0.24 mmol) was added to a solution of starting material (42 mg, 0.2 mmol) in THF (2 ml) at -78°C under nitrogen. The reaction mixture was stirred at -78°C for 15 minutes, and then methyl trifluoromethanesulfonate (0.034 ml, 0.3 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature slowly overnight, then quenched with water, taken up in diethyl ether and water, and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. aq. NaHCO_3 solution, then with sat. aq. NH_4Cl solution, then with sat. brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 10:90 ethyl acetate:petrol to obtain the *title compound* (35 mg, 77%) as a colourless oil, a single diastereoisomer as shown; $\nu_{\max}$ / cm^{-1} 1641, 1735; δ_{H} (250 MHz, CDCl_3) 5.76 (1H, ddt, J 17.1, 10.1, 6.7, $\text{CH}_2=\text{CH}$), 5.08-4.96 (2H, m,

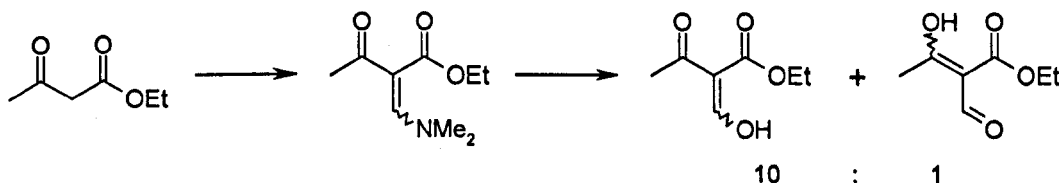
$\underline{\text{CH}_2=\text{CH}}$), 4.27-4.15 (1H, m, 6-H), 3.75 (3H, s, OMe), 2.53-2.39 (1H, m, 4-H), 2.32-2.08 (2H, m, $\text{CH}_2=\text{CH}\underline{\text{CH}_2}$), 2.00-1.87 (1H, m, 4-H), 1.84-1.53 (4H, m, 5-H and $\text{CH}_2=\text{CHCH}_2\underline{\text{CH}_2}$), 1.49 (3H, s, CCH_3); δ_{C} (75 MHz, CDCl_3) 172.6 (C), 171.6 (C), 137.1 (CH), 115.6 (CH_2), 78.3 (CH), 53.0 (CH_3), 49.6 (C), 34.5 (CH_2), 29.7 (CH_2), 28.9 (CH_2), 25.6 (CH_2), 23.0 (CH_3); Found: $[\text{M}+\text{H}]^+$, 227.1280. $\text{C}_{12}\text{H}_{18}\text{O}_4+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 227.1283.

(3*S, 6*S**)-3-Acetyl-6-but-3'-enyl-2-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester 143**



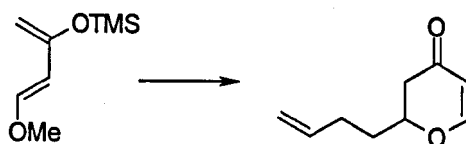
A solution of KHMDS in toluene (0.526 ml, 0.38 M, 0.2 mmol) was added to a solution of starting material (42 mg, 0.2 mmol) in THF (2 ml) at -78°C under nitrogen. The reaction mixture was stirred at -78°C for 30 minutes and then acetyl chloride (0.028 ml, 0.4 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature slowly overnight, then stirred at room temperature for a further 24 hours. The resulting mixture was then quenched with water, taken up in diethyl ether and water, and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 20:80 ethyl acetate:petrol, then repurified, eluting with 15:85 ethyl acetate:petrol, to obtain the *title compound* (32 mg, 63%) as a colourless oil, a single diastereoisomer as shown; ν_{max} / cm^{-1} 1642, 1721; δ_{H} (250 MHz, CDCl_3) 5.76 (1H, ddt, J 17.1, 10.1, 6.7, $\text{CH}_2=\underline{\text{CH}}$), 5.09-4.96 (2H, m, $\underline{\text{CH}_2}=\text{CH}$), 4.36-4.25 (1H, m, 6-H), 3.82 (3H, s, OMe), 2.63-2.49 (1H, m, 4-H), 2.37 (3H, s, COMe), 2.40-2.08 (3H, m, 4-H and $\text{CH}_2=\text{CH}\underline{\text{CH}_2}$), 1.97-1.48 (4H, m, 5-H and $\text{CH}_2=\text{CHCH}_2\underline{\text{CH}_2}$); δ_{C} (75 MHz, CDCl_3) 198.6 (C), 168.4 (C), 166.4 (C), 137.0 (CH), 115.8 (CH_2), 80.3 (CH), 67.0 (C), 53.6 (CH_3), 34.7 (CH_2), 29.7 (CH_2), 28.8 (CH_2), 27.8 (CH_3), 25.5 (CH_2); Found: $[\text{M}+\text{H}]^+$, 255.1238. $\text{C}_{13}\text{H}_{18}\text{O}_5+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 255.1232.

2-Acetyl-3-hydroxy-acrylic acid ethyl ester¹⁰⁴ 144



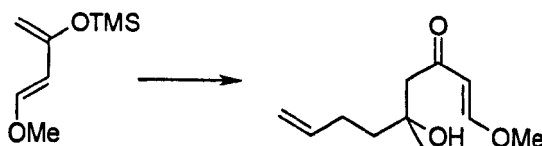
TsOH.H₂O (20 mg, 0.10 mmol) was added to a mixture of ethyl acetoacetate (5.89 ml, 46.4 mmol) and N,N-dimethylformamide dimethyl acetal (9.24 ml, 69.5 mmol), and the resulting reaction mixture was heated in an oil bath set to 100°C for 3 hours, then was stirred at room temperature overnight. The resulting reaction mixture was concentrated *in vacuo* then was vacuum distilled (85°C, pressure not recorded) to give crude 2-acetyl-3-dimethylamino-acrylic acid ethyl ester (6.75 g). 10% aq. HCl (26.2 ml) was added to a solution of this crude material (5.93 g) in THF (73 ml). The resulting reaction mixture was stirred at room temperature for 3 hours, then taken up in diethyl ether and water, and extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was partially purified by vacuum distillation, then purified by flash column chromatography, eluting with 5:95 ethyl acetate:petrol to obtain the *title compound* (3.95 g, 61%); $\nu_{\max}$ / cm⁻¹ 1580, 1641, 1720; δ_{H} (250 MHz, CDCl₃) 17.03 (0.9 H, d, *J*6.0, OH of major tautomer), 14.54 (0.1H, s, OH of minor tautomer), 9.96 (0.1H, s, CHO of minor tautomer), 9.12 (0.9H, d, *J*6.0, CH of major tautomer), 4.32 (0.2H, q, *J*7.1, OCH₂ of minor tautomer), 4.19 (1.8 H, q, *J*7.2, OCH₂ of major tautomer), 2.48 (2.7 H, s, COCH₃ of major tautomer), 2.45 (0.3H, s, COCH₃ of minor tautomer), 1.32 (0.3H, t, *J*7.1, CH₂CH₃ of minor tautomer), 1.26 (2.7H, t, *J*7.2, CH₂CH₃ of major tautomer) ; δ_{C} of major tautomer (62.5 MHz, CDCl₃) 199.4 (C), 187.2 (CH), 164.9 (C), 107.9 (C), 60.2 (CH₂), 26.2 (CH₃), 14.2 (CH₃); Found: [M+H]⁺, 159.0653. C₇H₁₀O₄+H⁺ requires: [M+H]⁺, 159.0657. ¹H NMR data corresponded with literature data.¹⁰⁴

2-But-3'-enyl-2,3-dihydro-pyran-4-one 148



$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.23 ml, 10 mmol) was added to a solution of 4-pentenal (1.48 ml, 15 mmol) and 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (1.94 ml, 10 mmol) in diethyl ether (40 ml) at -78°C under nitrogen. The reaction mixture was stirred at -78°C overnight, then was quenched with solid NaHCO_3 and sat. aq. NaHCO_3 . The resulting mixture was allowed to warm to room temperature, then taken up in diethyl ether and water, and extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 20:80 ethyl acetate:petrol, to obtain the *title compound* (1.25 g, 82%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1596, 1643, 1680; δ_{H} (250 MHz, CDCl_3) 7.30 (1H, d, J 5.8, 6-H), 5.74 (1H, ddt, J 17.1, 10.1, 6.4, $\text{CH}=\text{CH}_2$), 5.33 (1H, dt, 5.8, 0.9, 5-H), 5.04-4.92 (2H, m, $\text{CH}=\text{CH}_2$), 4.42-4.30 (1H, m, 2-H), 2.53-2.31 (2H, m, 3-H), 2.25-2.05 (2H, m, $\text{CH}_2=\text{CHCH}_2$), 1.95-1.61 (2H, m, $\text{CH}_2=\text{CHCH}_2\text{CH}_2$); δ_{C} (62.5 MHz, CDCl_3) 192.4 (C), 163.2 (CH), 136.9 (CH), 115.7 (CH_2), 106.9 (CH), 78.7 (CH), 41.7 (CH_2), 33.4 (CH_2), 28.8 (CH_2); Found: $[\text{M}+\text{H}]^+$, 153.0912. $\text{C}_9\text{H}_{12}\text{O}_2+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 153.0916.

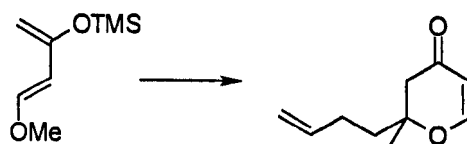
5-Hydroxy-1-methoxy-5-methyl-nona-1,8-dien-3-one 149



$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.123 ml, 1 mmol) was added dropwise to a solution of 5-hexen-2-one (0.174 ml, 1.5 mmol) and 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (0.194 ml, 1 mmol) in diethyl ether (4 ml) at -78°C under nitrogen. The reaction mixture was stirred at -78°C for three hours, then was quenched with solid NaHCO_3 and sat. aq. NaHCO_3 . The resulting mixture was allowed to warm to room temperature, then taken up in diethyl ether and water, and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column

chromatography, eluting with 20:80 ethyl acetate:petrol, to obtain the *title compound* (50 mg, 25%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1589, 1620, 1639, 1670; δ_{H} (250 MHz, CDCl_3) 7.61 (1H, d, J 12.5, 1-H), 5.79 (1H, ddt, J 17.1, 10.4, 6.7, 8-H), 5.57 (1H, d, J 12.6, 2-H), 4.99 (1H, dq, J 17.1, 1.5, 9-H), 4.94-4.88 (1H, m, 9-H), 4.38 (1H, s, OH), 3.71 (3H, s, OMe), 2.61 (1H, d, J 16.5, 4-H), 2.57 (1H, d, J 16.5, 4-H), 2.17-2.04 (2H, m, 7-H), 1.67-1.45 (2H, m, 6-H), 1.20 (3H, s, CCH_3); δ_{C} (62.5 MHz, CDCl_3) 201.0 (C), 163.8 (CH), 138.8 (CH), 114.3 (CH_2), 106.6 (CH), 71.8 (C), 57.7 (CH_3), 49.5 (CH_2), 41.2 (CH_2), 28.3 (CH_2), 26.9 (CH_3); Found: $[\text{M}+\text{H}]^+$, 199.1326. $\text{C}_{11}\text{H}_{18}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 199.1334.

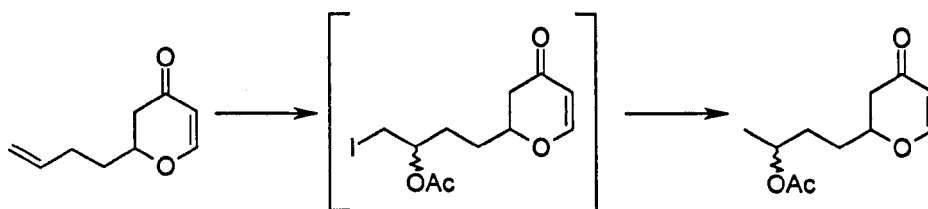
2-But-3'-enyl-2-methyl-2,3-dihydro-pyran-4-one 150



$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.23 ml, 10 mmol) was added dropwise over 15 minutes to a solution of 5-hexen-2-one (2.32 ml, 20 mmol) and 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (1.94 ml, 10 mmol) in diethyl ether (40 ml) at -78°C under nitrogen. The reaction mixture was stirred at -78°C for 30 minutes, then was quenched with solid NaHCO_3 and sat. aq. NaHCO_3 . The resulting mixture was allowed to warm to room temperature, then taken up in diethyl ether and water, and extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. ($\pm$)-CSA (2.32 g, 10 mmol) was added to a solution of the resulting crude in toluene (60 ml) under nitrogen and the resulting reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was taken up in sat. aq. NaHCO_3 solution and diethyl ether, and extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 0:100-1:99 methanol: DCM to obtain the *title compound* (569 mg, 34%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1598, 1643, 1677; δ_{H} (250 MHz, CDCl_3) 7.20 (1H, d, J 6.1, 6-H), 5.79 (1H, ddt, J 17.1, 10.1, 6.4, $\text{CH}=\text{CH}_2$), 5.36 (1H, d, J 6.1, 5-H), 5.08-4.95 (2H, m, $\text{CH}=\text{CH}_2$), 2.61 (1H, d, J 16.5, 3-H), 2.41 (1H, d, J 16.5, 3-H), 2.23-2.06 (2H, m, $\text{CH}_2=\text{CHCH}_2$), 1.93-1.64 (2H, m, $\text{CH}_2=\text{CHCH}_2$),

1.39 (3H, s, CH₃); δ_c (62.5 MHz, CDCl₃) 192.2 (C), 161.2 (CH), 137.5 (CH), 115.1 (CH₂), 105.5 (CH), 83.2 (C), 46.5 (CH₂), 38.3 (CH₂), 27.7 (CH₂), 23.1 (CH₃); Found: [M+NH₄]⁺, 184.1331. C₁₀H₁₄O₂+NH₄⁺ requires: [M+NH₄]⁺, 184.1338.

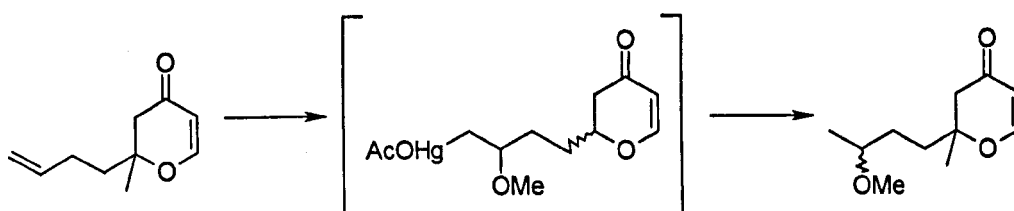
2-But-3'-acetoxy-2,3-dihydro-pyran-4-one 152



Iodine (46 mg, 0.181 mmol) was added to a solution of starting material (46 mg, 0.302 mmol) in acetonitrile (2 ml) and water (0.5 ml) under nitrogen at -15°C. BTI (130 mg, 0.302 mmol) was added and the reaction mixture was allowed to warm to room temperature over 1.5 hours. The resulting mixture was taken up in diethyl ether and water and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. aq. sodium thiosulfate, water and brine, before being dried over magnesium sulfate, filtered and concentrated *in vacuo*. Pyridine (0.67 ml) was then added to a solution of the resulting crude in acetic anhydride (1.67 ml) under nitrogen at 0°C. The reaction mixture was stirred overnight at room temperature, then was concentrated *in vacuo*. The resulting residue was taken up in diethyl ether and water, and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was partially purified by flash column chromatography, eluting with 30:70 ethyl acetate:petrol to obtain an impure sample of the iodoacetate intermediate (34 mg). A portion of this intermediate (20 mg) was then dissolved in benzene (8 ml) and degassed by passing nitrogen through the solution for 10 minutes. The resulting solution was heated to reflux, and then separate degassed solutions of Ph₃SnH (42 mg, 0.118 mmol) in benzene (3.5 ml) and AIBN (3 mg, 0.018 mmol) in benzene (3.5 ml) were added via syringe pump over 7 hours. The resulting reaction mixture was heated at reflux overnight, then allowed to cool to room temperature, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography, eluting with 30:70 ethyl acetate:petrol to obtain the *title compound* (12 mg, 32%) as a colourless oil as a

mixture of diastereoisomers; $\nu_{\max}$ / cm^{-1} 1595, 1675, 1733; δ_{H} (250 MHz, CDCl_3) 7.34 (1H, d, J 6.1, 6-H), 5.40 (1H, dd, J 6.1, 0.9, 5-H), 5.01-4.86 (1H, m, 3'-H), 4.46-4.33 (1H, m, 2-H), 2.52 (1H, dd, J 16.8, 12.8, 3-H), 2.42 (1H, ddd, J 16.8, 4.3, 0.9, 3-H), 2.04 (3H, s, Ac), 1.92-1.63 (4H, m, 1'-H and 2'-H), 1.24 (3H, d, J 6.1, 4'-H); δ_{C} (62.5 MHz, CDCl_3) 192.3 (C), 170.7 (C), 163.0 (CH), 107.1 (CH), 79.3 (CH), 78.9 (CH), 70.4 (CH), 70.1 (CH), 41.8 (CH_2), 31.3 (CH_2), 31.0 (CH_2), 30.4 (CH_2), 30.2 (CH_2), 21.3 (CH_3), 20.0 (CH_3); Found: $[\text{M}+\text{NH}_4]^+$, 230.1395. $\text{C}_{11}\text{H}_{16}\text{O}_4+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 230.1392.

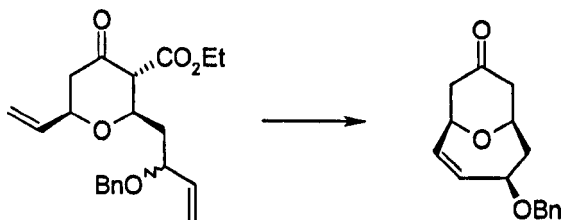
2-(3'-Methoxy-butyl)-2-methyl-2,3-dihydro-pyran-4-one 153



A solution of starting material (166 mg, 1 mmol) in methanol (2 ml) was added to red mercury(II) oxide (108 mg, 0.5 mmol) and mercury(II) acetate (159 mg, 0.5 mmol) under nitrogen. The resulting reaction mixture was stirred at room temperature for 24 hours, and then the reaction mixture was concentrated by passing a stream of nitrogen over the reaction mixture overnight. DCM (2 ml) was added to the resulting mixture, the reaction mixture was cooled to -10°C then sodium trimethoxyborohydride (153 mg, 1.2 mmol) was added. The reaction mixture was allowed to warm to room temperature overnight, and then filtered through celite, washing the celite residues with DCM. The combined organic layers were concentrated *in vacuo*, and the resulting residue was purified by flash column chromatography, eluting with 20:80 ethyl acetate:petrol to obtain the *title compound* (100 mg, 51%) as a colourless oil, shown by ^1H NMR spectroscopy to be a 1:1 mixture of diastereoisomers; $\nu_{\max}$ / cm^{-1} 1597, 1676; δ_{H} (250 MHz, CDCl_3) 7.18 (1H, d, J 6.1, 6-H), 5.32 (1H, d, J 6.1, 5-H), 3.32-3.20 (1H, m, 3'-H), 3.27 (3H, s, OMe), 2.57 (0.5H, d, J 16.5, 1 diastereoisomer of 3-H), 2.56 (0.5H, d, J 16.5, 1 diastereoisomer of 3-H), 2.39 (0.5H, d, J 16.5, 1 diastereoisomer of 3-H), 2.37 (0.5H, d, J 16.5, 1 diastereoisomer of 3-H), 1.99-1.45 (4H, m, 1'-H and 2'-H), 1.35 (3H, s, CCH_3), 1.10 (3H, d, J 6.1, 4'-H); δ_{C} (62.5 MHz, CDCl_3) 192.4 (C), 161.3 (CH), 105.4

(CH), 83.3 (C), 76.3 (CH), 56.0 (CH₃), 46.6 (CH₂), 46.3 (CH₂), 34.8 (CH₂), 30.1 (CH₂), 23.1 (CH₃), 22.9 (CH₃), 18.9 (CH₃); Found: [M+H]⁺, 199.1334. C₁₁H₁₈O₃+H⁺ requires: [M+H]⁺, 199.1334.

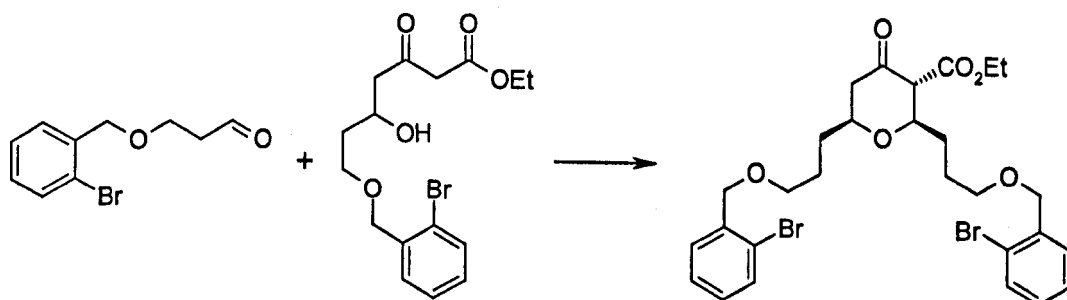
(1R*, 4R*, 6R*)-4-Benzoyloxy-10-oxa-bicyclo[4,3,1]dec-2-en-8-one 165



Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (324 mg, 0.382 mmol) was added to a degassed solution of starting material (685 mg, 1.91 mmol) in DCM (400 ml) and the resulting reaction mixture was heated at reflux for 40 hours. The reaction mixture was allowed to cool to room temperature, tris(hydroxymethyl)phosphine (1.07 g, 8.66 mmol) was added and the reaction mixture was stirred for 30 minutes. Water (200 ml) was added and the resulting mixture was stirred for 1 hour, then the organic phase was separated, washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was partially purified by flash column chromatography, eluting with 8:92 ethyl acetate:petrol to obtain an impure sample of ring-closed product (554 mg). NaCl (12 mg, 0.2 mmol) was added to a portion of the resulting crude (33 mg) in DMSO (1.5 ml) and water (0.04 ml), and the resulting reaction mixture was heated in an oil bath set to 140°C for three hours, then in an oil bath set to 150°C for 40 hours. The reaction mixture was cooled to room temperature, then taken up in diethyl ether and water and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with water then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 30:70 ethyl acetate:petrol to obtain the *title compound* (14 mg, 48%) as a colourless oil, a single diastereoisomer as shown; ν_{max} / cm⁻¹ 1717; δ_{H} (400 MHz, CDCl₃) 7.38-7.27 (5H, m, Ph), 5.93 (1H, dq, *J*11.6, 1.8, 3-H), 5.40 (1H, ddd, *J*11.6, 3.8, 2.4, 2-H), 5.11-5.08 (1H, m, 1-H), 4.69-4.64 (1H, m, 6-H), 4.59-4.54 (1H, m, 4-H), 4.58 (1H, d, *J*10.9, CH₂Ph), 4.55 (1H, d, *J*10.9, CH₂Ph), 2.87-2.81 (2H, m, 7-H and 9-H), 2.42 (1H, dt, *J*13.8, 0.8, 9-H), 2.38 (1H, ddt, *J*13.5, 8.4, 1.8, 5-H), 2.30 (1H,

dt, J 13.9, 1.6, 7-H), 1.87 (1H, dt, J 13.5, 10.5, 5-H); δ_c (75 MHz, $CDCl_3$) 205.3 (C), 138.2 (C), 135.7 (CH), 130.1 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 75.7 (CH), 72.7 (CH), 71.2 (CH), 70.7 (CH_2), 47.2 (CH_2), 45.0 (CH_2), 42.5 (CH_2); Found: $[M+H]^+$, 259.1341. $C_{16}H_{18}O_3+H^+$ requires: $[M+H]^+$, 259.1334.

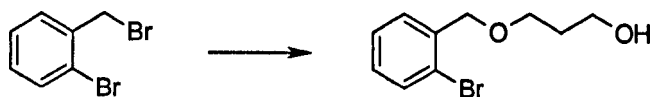
(2*R, 3*R**, 6*S**)-2,6-Bis-[3-(2'-bromo-benzyloxy)-propyl]-4-oxo-tetrahydro-pyran-3-carboxylic acid ethyl ester 168**



$BF_3 \cdot OEt_2$ (0.062 ml, 0.508 mmol) was added to a solution of aldehyde starting material (122 mg, 0.5 mmol) and alcohol starting material (158 mg, 0.423 mmol) in DCM (5 ml) at $-45^\circ C$ under nitrogen. The reaction mixture was stirred overnight at $-45^\circ C$, then was allowed to warm to room temperature. The reaction mixture was taken up in diethyl ether and aq. $NaHCO_3$, and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 75:25 DCM:petrol to obtain the keto *title compound* (181 mg, 71%) as a colourless oil and additional material (52 mg, 21%) as a mixture of keto and enol forms. Data for keto form; ν_{max} / cm^{-1} 1569, 1594, 1620, 1651, 1718, 1740; δ_H (400 MHz, $CDCl_3$) 7.52 (1H, dd, J 8.0, 1.0, 3'-H), 7.51 (1H, dd, J 8.0, 1.0, 3'-H), 7.45 (1H, dd, J 7.6, 1.5, 6'-H), 7.40 (1H, dd, J 7.6, 1.5, 6'-H), 7.29 (2H, td, J 7.6, 1.0, 5'-H), 7.15-7.10 (2H, m, 4'-H), 4.57-4.49 (4H, m, $\underline{CH_2}Ar$), 4.28-4.16 (2H, m, $\underline{CH_2}CH_3$), 4.11 (1H, ddd, J 10.6, 8.4, 3.1, 2-H), 3.96-3.90 (1H, m, 6-H), 3.73-3.60 (4H, m, $O\underline{CH_2}CH_3$), 3.33 (1H, d, J 10.6, 3-H), 2.51 (1H, dd, J 14.3, 2.5, 5-H), 2.32 (1H, dd, J 14.3, 11.7, 5-H), 2.00-1.83 (4H, m, $OCH_2\underline{CH_2}$), 1.27 (3H, t, J 7.1, Me); δ_c (75 MHz, $CDCl_3$) 202.0 (C), 168.0 (C), 137.7 (C), 137.5 (C), 132.6 (CH), 132.4 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 127.4 (CH), 127.4 (CH), 122.8 (C), 122.5 (C), 75.6 (CH), 74.0 (CH), 72.4 (CH_2), 72.2 (CH_2), 66.6 (CH_2), 66.5 (CH_2), 63.0 (CH), 61.2 (CH_2), 47.2

(CH₂), 36.4 (CH₂), 35.0 (CH₂), 14.2 (CH₃); Found: [M+NH₄]⁺, 618.0726. C₂₆H₃₀O₆⁸¹Br₂+NH₄⁺ requires: [M+NH₄]⁺, 618.0712. Found: [M+NH₄]⁺, 616.0741. C₂₆H₃₀O₆⁷⁹Br⁸¹Br+NH₄⁺ requires: [M+NH₄]⁺, 616.0732. Found: [M+NH₄]⁺, 614.0744. C₂₆H₃₀O₆⁷⁹Br₂+NH₄⁺ requires: [M+NH₄]⁺, 614.0753.

3-(2'-Bromo-benzyloxy)-propan-1-ol 172



1,3-Propanediol (4.86 g, 63.9 mmol) was added to a solution of 2-bromobenzyl bromide (5.32 g, 21.3 mmol) in DMF (120 ml) at 0°C under nitrogen. NaH (1.06 g, 60% w/w, 26.6 mmol) was added in portions, and the resulting reaction mixture was allowed to warm to room temperature with stirring overnight. The reaction mixture was then neutralised with 2 M HCl, and the resulting mixture was taken up in diethyl ether and water and extracted diethyl ether (3 x 200 ml). The combined organic layers were washed with twice with water then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 25:75 ethyl acetate:petrol to obtain the *title compound* (3.91 g, 75%) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1569, 1593, 1634, 3321; δ_{H} (250 MHz, CDCl₃) 7.53 (1H, br d, *J*7.6, 3'-H), 7.42 (1H, br d, *J*7.6, 6'-H), 7.30 (1H, br td, *J*7.6, 0.9, 5'-H), 7.14 (1H, br t, *J*7.6, 4'-H), 4.57 (2H, s, CH₂Ar), 3.80-3.69 (4H, m, 1-H and 3-H), 2.47 (1H, s br, OH), 1.89 (2H, qn, *J*5.8, 2-H); δ_{C} (75 MHz, CDCl₃) 137.4 (C), 132.6 (CH), 129.2 (CH), 129.1 (CH), 127.5 (CH), 122.9 (C), 72.6 (CH₂), 69.6 (CH₂), 61.5 (CH₂), 32.2 (CH₂); Found: [M+H]⁺, 247.0157. C₁₀H₁₃O₂⁸¹Br+H⁺ requires: [M+H]⁺, 247.0157. Found: [M+H]⁺, 245.0179. C₁₀H₁₃O₂⁷⁹Br+H⁺ requires: [M+H]⁺, 245.0177.

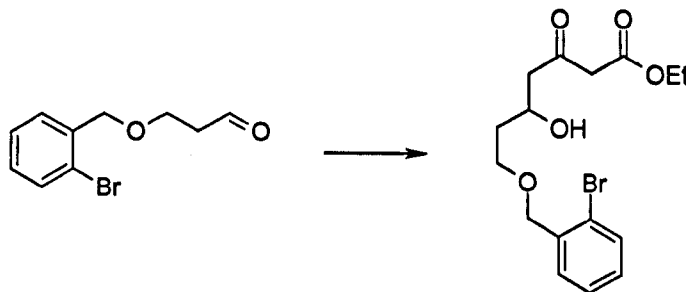
3-(2'-Bromo-benzyloxy)-propionaldehyde 173



A solution of starting material (265 mg, 1.08 mmol) in wet DCM (2 ml) was added to a solution of Dess-Martin periodinane (688 mg, 1.62 mmol) in wet DCM (3 ml) and the resulting mixture was stirred overnight. Additional Dess-Martin periodinane (200 mg,

0.472 mmol) was added and the resulting reaction mixture was stirred for 4 hours, then diethyl ether and sat. aq. NaHCO₃ was added and the mixture was stirred for 10 minutes and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with aq. Na thiosulfate, sat. aq. NaHCO₃ and with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to obtain the *title compound* (256 mg, 98%) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1569, 1593, 1629, 1725; δ_{H} (250 MHz, CDCl₃) 9.82 (1H, m, 1-H), 7.52 (1H, d, *J*7.6, 3'-H), 7.42 (1H, d, *J*7.6, 6'-H), 7.29 (1H, t, *J*7.6, 5'-H), 7.13 (1H, t, *J*7.6, 4'-H), 4.57 (2H, s, CH₂Ar), 3.88 (2H, td, *J*6.1, 1.5, 3-H), 2.75-2.68 (2H, m, 2-H); δ_{C} (62.5 MHz, CDCl₃) 201.0 (CH), 136.9 (C), 132.3 (CH), 128.9 (CH), 127.2 (CH), 122.5 (C), 72.2 (CH₂), 64.2 (CH₂), 43.6 (CH₂), one CH missing; Found: [M+NH₄]⁺, 262.0273. C₁₀H₁₁O₂⁸¹Br+NH₄⁺ requires: [M+NH₄]⁺, 262.0266. Found: [M+NH₄]⁺, 260.0293. C₁₀H₁₁O₂⁷⁹Br+NH₄⁺ requires: [M+NH₄]⁺, 260.0286.

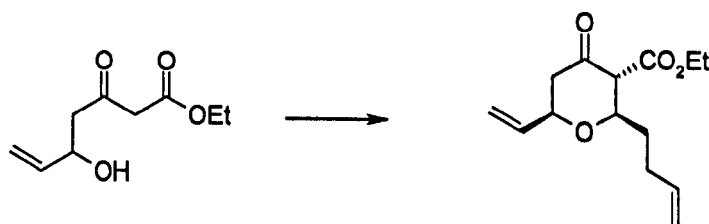
7-(2'-Bromo-benzyloxy)-5-hydroxy-3-oxo-heptanoic acid ethyl ester 174



A solution of ⁿBuLi in hexanes (0.571 ml, 2.10 M, 1.2 mmol) was added dropwise to a suspension of the sodium salt of ethyl acetoacetate (198 mg, 1.3 mmol) in THF (4 ml) under nitrogen at -10°C. The reaction mixture was stirred for 15 minutes, then cooled to -70°C. A solution of starting material (243 mg, 1 mmol) in THF (1 ml) was added dropwise and the reaction mixture was allowed to warm slowly to room temperature overnight. The resulting mixture was then quenched with sat. aq. NH₄Cl, taken up in diethyl ether and water, and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 25:75 ethyl acetate:petrol to obtain the *title compound* (169 mg, 45%) as a colourless oil; $\nu_{\max}$ / cm⁻¹ 1569, 1645, 1706, 1729, 1739, 3405; δ_{H} (250 MHz, CDCl₃) 7.53 (1H, dd, *J*7.6, 1.0, 3'-H), 7.41 (1H, dd, *J*7.6, 1.6, 6'-H), 7.29

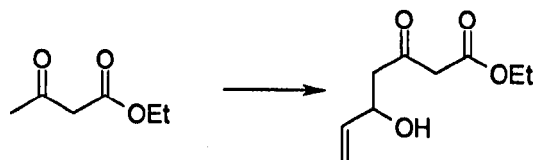
(1H, td, J 7.6, 1.0, 5'-H), 7.14 (1H, td, J 7.6, 1.6, 4'-H), 4.55 (2H, s, CH_2Ar), 4.36-4.25 (1H, m, 5-H), 4.17 (2H, q, J 7.1, CH_2CH_3), 3.78-3.65 (2H, m, 7-H), 3.47 (2H, s, 2-H), 3.28 (1H, br s, OH), 2.73 (2H, d, J 6.1, 4-H), 1.87-1.76 (2H, m, 6-H), 1.26 (3H, t, J 7.1, Me); δ_{C} (75 MHz, CDCl_3) 202.8 (C), 166.8 (C), 137.1 (C), 132.3 (CH), 129.0 (CH), 128.9 (CH), 127.2 (CH), 122.6 (C), 72.3 (CH_2), 68.0 (CH_2), 66.1 (CH), 61.2 (CH_2), 49.7 (CH_2), 49.6 (CH_2), 35.9 (CH_2), 13.9 (CH_3); Found: $[\text{M}+\text{NH}_4]^+$, 392.0898. $\text{C}_{16}\text{H}_{21}\text{O}_5^{81}\text{Br}+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 392.0896. Found: $[\text{M}+\text{NH}_4]^+$, 390.0914. $\text{C}_{16}\text{H}_{21}\text{O}_5^{79}\text{Br}+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 390.0916.

(2*R, 3*R**, 6*R**)-2-But-3'-enyl-4-oxo-6-vinyl-tetrahydro-pyran-3-carboxylic acid ethyl ester 176**



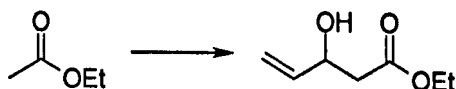
$\text{BF}_3 \cdot \text{OEt}_2$ (0.092 ml, 0.75 mmol) was added to a solution of starting material (93 mg, 0.5 mmol) and 4-pentenal (0.060 ml, 0.61 mmol) in DCM (5 ml) at -40°C under nitrogen. The reaction mixture was allowed to warm to room temperature slowly over 2.5 hours, then taken up in diethyl ether and water, and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 1:5:94 triethylamine:ethyl acetate:petrol to obtain the *title compound* (31 mg, 25%) as a colourless oil, a single diastereoisomer as shown; $\nu_{\text{max}} / \text{cm}^{-1}$ 1607, 1642, 1718, 1744; δ_{H} (250 MHz, CDCl_3) 5.98-5.70 (2H, m, $\text{CH}=\text{CH}_2$), 5.36-5.20 (2H, m, $\text{CHCH}=\text{CH}_2$), 5.08-4.95 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 4.33-4.14 (3H, m, OCH_2 and 6-H), 3.95 (1H, ddd, J 10.7, 7.9, 3.4, 2-H), 3.26 (1H, d, J 10.7, 3-H), 2.53 (1H, dd, J 14.3, 2.7, 5-H), 2.37 (1H, dd, J 14.3, 11.6, 5-H), 2.36-2.10 (2H, m, $\text{CH}_2\text{CH}=\text{CH}_2$), 1.80-1.59 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}=\text{CH}_2$), 1.29 (3H, t, J 7.1, CH_3); δ_{C} (75 MHz, CDCl_3) 201.8 (C), 168.0 (C), 137.6 (CH), 136.6 (CH), 116.5 (CH_2), 115.3 (CH_2), 77.0 (CH), 77.6 (CH), 63.0 (CH), 61.3 (CH_2), 46.7 (CH_2), 34.1 (CH_2), 29.4 (CH_2), 14.2 (CH_3); Found: $[\text{M}+\text{H}]^+$, 253.1442. $\text{C}_{14}\text{H}_{20}\text{O}_4+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 253.1440.

5-Hydroxy-3-oxo-hept-6-enoic acid ethyl ester 177



A solution of $n\text{BuLi}$ in hexanes (4 ml, 2.50 M, 10 mmol) was added dropwise to a suspension of the sodium salt of ethyl acetoacetate (1.52 g, 10 mmol) in THF (50 ml) under nitrogen at 0°C . The reaction mixture was stirred for 20 minutes, and then acrolein (0.535 ml, 8 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 3 hours. The resulting mixture was then quenched with sat. aq. NH_4Cl , taken up in diethyl ether and water, and extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 20:80-25:75 ethyl acetate:petrol to obtain the *title compound* (954 mg, 64%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1646, 1713, 1740; δ_{H} (250 MHz, CDCl_3) 5.86 (1H, ddd, J 17.1, 10.4, 5.5, 6-H), 5.30 (1H, dt, J 17.1, 1.4, 5-H), 5.14 (1H, dt, J 10.4, 1.5, 5-H), 4.65-4.55 (1H, m, 5-H), 4.19 (2H, q, J 7.1, OCH_2), 3.48 (2H, s, 2-H), 2.83-2.76 (3H, m, 4-H and OH), 1.27 (3H, t, J 7.1, CH_3); δ_{C} (62.5 MHz, CDCl_3) 202.7 (C), 167.0 (C), 138.8 (CH), 115.2 (CH_2), 68.4 (CH), 61.5 (CH_2), 49.9 (CH_2), 49.3 (CH_2), 14.0 (CH_3); Found: $[\text{M}+\text{H}]^+$, 187.0970. $\text{C}_9\text{H}_{14}\text{O}_4+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 187.0970.

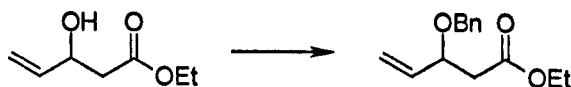
3-Hydroxy-pent-4-enoic acid ethyl ester⁹¹ 178



A solution of $n\text{BuLi}$ in hexanes (112 ml, 2.46 M, 275 mmol) was added to $i\text{Pr}_2\text{NH}$ (40.4 ml, 288 mmol) in THF (300 ml) under nitrogen at 0°C . The reaction mixture was stirred for 30 minutes, then cooled to -78°C , then a solution of ethyl acetate (24.5 ml, 250 mmol) in THF (24.5 ml) was added dropwise over 30 minutes. The reaction mixture was stirred at -78°C for 45 minutes, and then acrolein (18.4 ml, 275 mmol) was added dropwise over 30 minutes. The reaction mixture was stirred at -78°C for 30 minutes, and then the resulting mixture was quenched slowly with sat. aq. NH_4Cl and allowed to

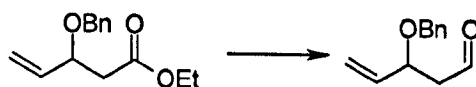
warm to room temperature. The resulting mixture was taken up in diethyl ether and water, and extracted with diethyl ether (3 x 500 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with DCM to obtain the *title compound* (30.3 g, 84%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1644, 1735; δ_{H} (250 MHz, CDCl_3) 5.88 (1H, ddd, J 17.1, 10.4, 5.5, 4-H), 5.31 (1H, dt, J 17.1, 1.5, 5-H), 5.15 (1H, dt, J 10.4, 1.5, 5-H), 4.58-4.48 (1H, m, 3-H), 4.17 (2H, q, J 7.1, OCH_2), 3.04 (1H, d, J 4.6, OH), 2.57 (1H, dd, J 16.2, 4.6, 2-H), 2.50 (1H, dd, J 16.2, 7.9, 2-H), 1.26 (3H, t, J 7.1, CH_3); δ_{C} (62.5 MHz, CDCl_3) 172.1 (C), 138.9 (CH), 115.2 (CH_2), 68.9 (CH), 60.7 (CH_2), 41.2 (CH_2), 14.1 (CH_3); Found: $[\text{M}+\text{H}]^+$, 145.0863. $\text{C}_7\text{H}_{12}\text{O}_3+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 145.0865. ^1H NMR data corresponded with literature data.⁹¹

3-Benzoyloxy-pent-4-enoic acid ethyl ester 179



Benzyl 2,2,2-trichloroacetimidate (30 g, 119 mmol) was added to a solution of starting material (12.2 g, 84.9 mmol) in diethyl ether (600 ml) under nitrogen. The reaction mixture was cooled to 0°C and a solution of trifluoromethanesulfonic acid (0.85 ml, 9.67 mmol) in diethyl ether (6.6 ml) was added. The reaction mixture was allowed to warm to room temperature and stirred for 40 hours. The resulting mixture was then taken up in diethyl ether and washed with sat. aq. NaHCO_3 , sat. aq. NH_4Cl then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 4:96 ethyl acetate:petrol to obtain the *title compound* (19.8 g, 100%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1595, 1738; δ_{H} (250 MHz, CDCl_3) 7.33-7.26 (5H, m, Ph), 5.79 (1H, ddd, J 17.4, 10.1, 7.3, 4-H), 5.37-5.25 (2H, m, 5-H), 4.59 (1H, d, J 11.8, CH_2Ph), 4.40 (1H, d, J 11.8, CH_2Ph), 4.34-4.24 (1H, m, 3-H), 4.21-4.08 (2H, m, OCH_2), 2.68 (1H, dd, J 15.0, 8.2, 2-H), 2.51 (1H, dd, J 15.0, 5.5, 2-H), 1.25 (3H, t, J 7.1, CH_3); δ_{C} (62.5 MHz, CDCl_3) 170.8 (C), 138.3 (C), 137.3 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 118.0 (CH_2), 77.0 (CH), 72.1 (CH_2), 60.5 (CH_2), 41.2 (CH_2), 14.2 (CH_3); Found: $[\text{M}+\text{NH}_4]^+$, 252.1593. $\text{C}_{14}\text{H}_{18}\text{O}_3+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 252.1600.

3-Benzoyloxy-pent-4-enal 180



DIBAL (60 ml, 1M in hexanes, 60 mmol) was added dropwise over 40 minutes to a solution of starting material (11.72 g, 50 mmol) in toluene (200 ml) under nitrogen at -78°C , and the reaction mixture was stirred for 1 hour. Methanol (12.2 ml, 300 mmol) was added dropwise over 15 minutes, the reaction mixture was stirred for 15 minutes, then was allowed to warm to room temperature before pouring into aq. Rochelle's salt solution. The resulting mixture was stirred for 30 minutes, and then extracted with diethyl ether (3 x 200 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was partially purified by flash column chromatography, eluting with 50:50-100:0 DCM:petrol to obtain the *title compound* (8.29 g, 87%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1601, 1727; δ_{H} (250 MHz, CDCl_3) 9.76 (1H, t, $J_{2,1}$, 1-H), 7.39-7.26 (5H, m, Ph), 5.82 (1H, ddd, $J_{17,4}$, 10.1, 7.3, 4-H), 5.39-5.30 (2H, m, 5-H), 4.63 (1H, d, $J_{11,6}$, CH_2Ph), 4.41 (1H, d, $J_{11,6}$, CH_2Ph), 4.38-4.30 (1H, m, 3-H), 2.76 (1H, ddd, $J_{16,5}$, 8.2, 2.1, 2-H), 2.56 (1H, ddd, $J_{16,5}$, 4.6, 2.1, 2-H); δ_{C} (75 MHz, CDCl_3) 200.8 (CH), 138.0 (C), 137.0 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 118.4 (CH_2), 75.4 (CH), 70.4 (CH_2), 49.2 (CH_2); Found: $[\text{M}+\text{NH}_4]^+$, 208.1334. $\text{C}_{12}\text{H}_{14}\text{O}_2+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 208.1338.

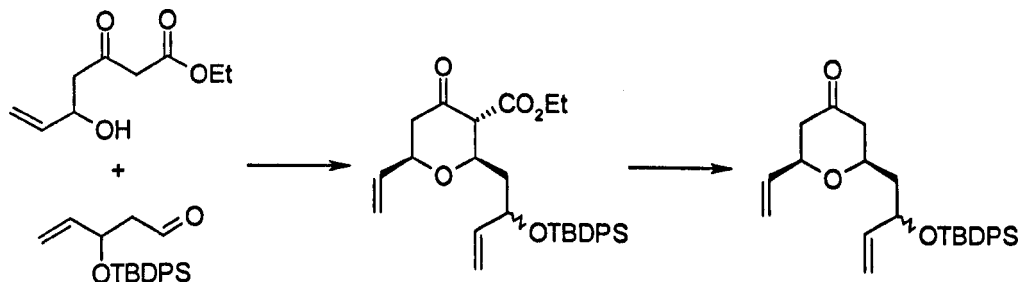
3-(*tert*-Butyl-diphenyl-silanyloxy)-pent-4-enal 182



Imidazole (408 mg, 3 mmol) and TBDPSCl (0.92 ml, 3.6 mmol) were added to a solution of starting material (433 mg, 3 mmol) in DCM (15 ml) under nitrogen at 0°C , and the resulting reaction mixture was allowed to warm to room temperature with stirring overnight. The reaction mixture was taken up in DCM and water, and the organic layer was washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was partially purified by flash column chromatography, eluting with 3:97 ethyl acetate:petrol to obtain crude 3-(*tert*-butyl-diphenyl-silanyloxy)-pent-4-enoic acid ethyl ester (900 mg) which contained TBDPSCl

as an impurity. DIBAL (2.06 ml, 1M in hexanes, 2.06 mmol) was added dropwise over 30 minutes to a solution of a portion of this crude (716 mg) in toluene (10 ml) under nitrogen at -78°C, and the reaction mixture was stirred for 40 minutes. Methanol (0.5 ml) was added, the reaction mixture was stirred for 15 minutes, then was allowed to warm to room temperature before pouring into aq. Rochelle's salt solution. The resulting mixture was stirred for 20 minutes, then extracted three times with diethyl ether. The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 2:98 ethyl acetate:petrol to obtain the *title compound* (279 mg, 35%) as a colourless oil; ν_{max} / cm^{-1} 1644, 1727; δ_{H} (250 MHz, CDCl_3) 9.69 (1H, t, J 2.4, 1-H), 7.69-7.63 (4H, m, Ph), 7.48-7.33 (6H, m, Ph), 5.89 (1H, ddd, J 17.1, 10.4, 5.8, 4-H), 5.14 (1H, dt, J 17.1, 1.2, 5-H), 5.06 (1H, dt, J 10.4, 1.2, 5-H), 4.64 (1H, qt, J 5.8, 1.2, 3-H), 2.57-2.40 (2H, m, 2-H), 1.06 (9H, s, ^tBu); δ_{C} (62.5 MHz, CDCl_3) 201.6 (CH), 139.1 (CH), 135.9 (CH), 133.4 (C), 129.9 (CH), 129.8 (CH), 127.7 (CH), 127.5 (CH), 115.5 (CH_2), 70.2 (CH), 50.7 (CH_2), 26.9 (CH_3), 19.3 (C); Found: $[\text{M}+\text{H}]^+$, 339.1789. $\text{C}_{21}\text{H}_{26}\text{O}_2\text{Si}+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 339.1780.

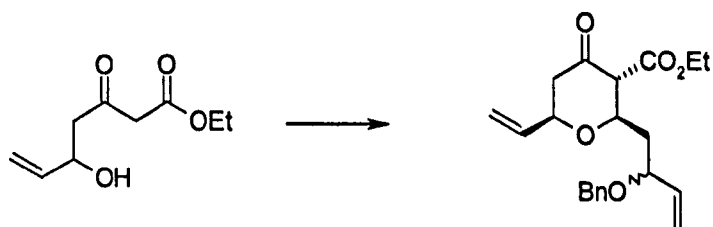
(2*R, 6*R**, 2'*R*/*S*'*)-2-[2'-(*tert*-Butyl-diphenyl-silanyloxy)-but-3-enyl]-6-vinyl-tetrahydro-pyran-4-one 185**



$\text{BF}_3 \cdot \text{OEt}_2$ (0.123 ml, 1 mmol) was added to a solution of aldehyde starting material (260 mg, 0.768 mmol) and alcohol starting material (205 mg, 1.1 mmol) in DCM (6 ml) at -45°C under nitrogen. The reaction mixture was stirred at -45°C for 3 days, then was quenched with pyridine and allowed to warm to room temperature. The reaction mixture was taken up in diethyl ether and aq. NaHCO_3 , and extracted with diethyl ether (3 x 30 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash

column chromatography, eluting with 5:95 ethyl acetate:petrol to obtain the carboxylated tetrahydropyranone as a mixture of keto and enol tautomers (299 mg, 77%). Due to the complexity of the spectroscopic data for this compound, it was characterised as the decarboxylated material; NaCl (12 mg, 0.2 mmol) and water (0.04 ml) was added to a portion of the carboxylated material (46 mg, 0.091 mmol) in DMSO (1.5 ml) and the resulting mixture was heated in an oil bath set to 150°C overnight, then was heated in an oil bath set to 160°C for 24 hours. The reaction mixture was taken up in diethyl ether and water, and extracted three times with diethyl ether. The combined organic layers were washed with water then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 5:95 ethyl acetate:petrol to obtain the *title compound* (28 mg, 71% for this step, 55% overall) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1590, 1713; δ_{H} (400 MHz, CDCl_3) 7.74-7.64 (4H, m, Ph), 7.45-7.33 (6H, m, Ph), 5.86-5.72 (2H, m, $\text{CH}=\text{CH}_2$), 5.22-4.83 (4H, m, $\text{CH}=\text{CH}_2$), 4.46-4.38 (1H, m, 6-H), 3.96-3.63 (2H, m, 2-H and 2'-H), 2.39-1.60 (6H, m, 3-H, 5-H and 1'-H), 1.08 (6H, s, 'Bu of major diastereoisomer), 1.04 (3H, s, 'Bu of minor diastereoisomer); δ_{C} (100 MHz, CDCl_3) 206.8 (C), 140.6 (CH), 140.0 (CH), 137.1 (CH), 136.0 (CH), 135.9 (CH), 135.2 (C), 134.8 (CH), 133.9 (C), 129.6 (CH), 129.5 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.4 (CH), 115.9 (CH_2), 115.5 (CH_2), 115.1 (CH_2), 114.9 (CH_2), 76.8 (CH), 73.5 (CH), 73.1 (CH), 71.9 (CH), 71.3 (CH), 47.8 (CH_2), 47.2 (CH_2), 47.1 (CH_2), 44.9 (CH_2), 43.9 (CH_2), 27.0 (CH_3), 26.5 (CH_3), 19.4 (C), 19.0 (C); Found: $[\text{M}+\text{H}]^+$, 435.2356. $\text{C}_{27}\text{H}_{34}\text{O}_3\text{Si}+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 435.2355.

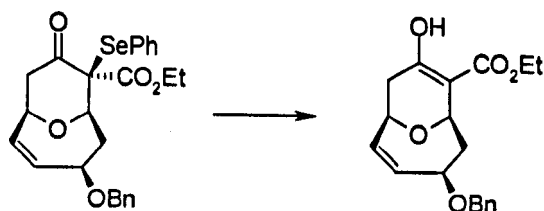
(2*R, 3*R**, 6*R**, 2'*R*/*S**)-2-(2'-Benzyloxy-but-3'-enyl)-oxo-6-vinyl-tetrahydro-pyran-3-carboxylic acid ethyl ester 186**



$\text{BF}_3 \cdot \text{OEt}_2$ (0.76 ml, 6.18 mmol) was added to a solution of starting material (767 mg, 4.12 mmol) and 3-benzyloxy-pent-4-enal (940 mg, 4.94 mmol) in DCM (40 ml) at

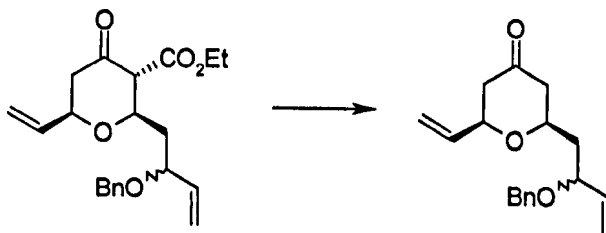
-60°C under nitrogen. The reaction mixture was stirred at -60°C for 40 hours, then allowed to warm to room temperature over 6 hours, then taken up in diethyl ether and water and extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 1:2:97 triethylamine:ethyl acetate:toluene to obtain the *title compound* (1.20 g, 81%) as a mixture of keto and enol tautomers. This mixture was then purified by flash column chromatography, eluting with 5:95 ethyl acetate:petrol to obtain the major keto tautomer (947 mg, 64%) as a colourless oil, shown by ¹H NMR spectroscopy to be a 1:1 mixture of diastereoisomers; $\nu_{\text{max}} / \text{cm}^{-1}$ 1611, 1649, 1718, 1743; δ_{H} (400 MHz, CDCl₃) 7.36-7.10 (5H, m, Ph), 5.90-5.68 (2H, m, CH=CH₂), 5.32-5.15 (4H, m, CH=CH₂), 4.63 (0.5H, d, *J*12.1, one diastereoisomer of CH₂Ph), 4.58 (0.5H, d, *J*11.6, one diastereoisomer of CH₂Ph), 4.37 (0.5H, d, *J*11.6, one diastereoisomer of CH₂Ph), 4.33 (0.5H, d, *J*12.1, one diastereoisomer of CH₂Ph), 4.33-3.95 (5H, m, 2-H, 6-H, CHOBn and CH₂CH₃), 3.39 (0.5H, d, *J*10.7, one diastereoisomer of 3-H), 3.21 (0.5H, d, *J*10.8, one diastereoisomer of 3-H), 2.52 (0.5H, dd, *J*14.6, 6.2, one diastereoisomer of 5-H), 2.51 (0.5H, dd, *J*14.6, 6.2, one diastereoisomer of 5-H), 2.35 (0.5H, d, *J*14.6, one diastereoisomer of 5-H), 2.33 (0.5H, d, *J*14.6, one diastereoisomer of 5-H), 2.14-1.71 (2H, m, CH₂CHOBn), 1.28 (1.5H, t, *J*7.2, one diastereoisomer of Me), 1.26 (1.5H, t, *J*7.2, one diastereoisomer of Me); δ_{C} (62.5 MHz, CDCl₃) 201.6 (C), 167.7 (C), 138.7 (C), 138.4 (CH), 137.9 (CH), 136.5 (CH), 128.3 (CH), 127.7 (CH), 127.4 (CH), 118.6 (CH₂), 117.1 (CH₂), 116.3 (CH₂), 76.7 (CH), 75.4 (CH), 74.7 (CH), 70.1 (CH₂), 70.0 (CH₂), 63.1 (CH), 62.7 (CH), 61.2 (CH₂), 46.7 (CH₂), 46.4 (CH₂), 41.2 (CH₂), 39.8 (CH₂), 14.1 (CH₃); Found: [M+H]⁺, 359.1861. C₂₁H₂₆O₅+H⁺ requires: [M+H]⁺, 359.1858.

(1R*, 4R*, 6R*)-4-Benzoyloxy-8-hydroxy-10-oxa-bicyclo[4.3.1]deca-2,7-diene-7-carboxylic acid ethyl ester 187



H₂O₂ (0.013 ml, 27% w/w aq. solution) was added to a solution of starting material (13 mg, 0.027 mmol) in DCM (2 ml) under nitrogen at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 4.5 hours, then taken up in diethyl ether and aq. NaHCO₃ and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 10:90 ethyl acetate:petrol to obtain the *title compound* (5.8 mg, 66%) as a colourless oil; ν_{max} / cm⁻¹ 1627, 1661, 1722, 3427; δ_{H} (250 MHz, CDCl₃) 12.06 (1H, s, OH), 7.38-7.25 (5H, m, Ph), 5.85 (1H, dt, *J*11.9, 2.6, 3-H), 5.37 (1H, ddd, *J*11.9, 2.7, 1.8, 2-H), 4.93-4.89 (1H, m, 4-H), 4.81 (1H, ddd, *J*7.9, 4.6, 1.2, 6-H), 4.71-4.61 (1H, m, 1-H), 4.57 (1H, d, *J*11.9, CH₂Ph), 4.51 (1H, d, *J*11.9, CH₂Ph), 4.19 (2H, q, *J*7.1, CH₂CH₃), 2.74 (1H, ddd, *J*17.7, 7.9, 1.5, 5-H), 2.55 (1H, ddd, *J*13.4, 8.2, 4.0, 9-H), 2.21-2.10 (2H, m, 5-H and 9-H), 1.28 (3H, t, *J*7.1, CH₂CH₃); δ_{C} (125 MHz, CDCl₃) 170.2 (C), 165.9 (C), 138.6 (C), 133.8 (CH), 129.7 (CH), 128.4 (CH), 127.5 (CH), 102.2 (C), 73.5 (CH), 71.8 (CH), 70.8 (CH₂), 66.1 (CH), 60.5 (CH₂), 42.0 (CH₂), 32.3 (CH₂), 14.2 (CH₃), one CH missing; Found: [M+NH₄]⁺, 348.1813. C₁₉H₂₂O₅+NH₄⁺ requires: [M+NH₄]⁺, 348.1811.

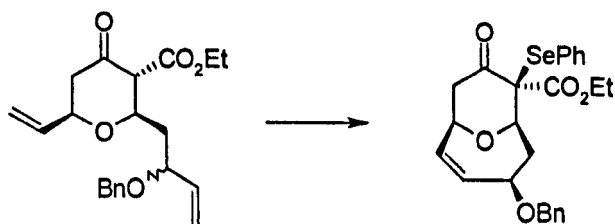
(2R*, 6R*, 2'R/S*)-2-(2'-Benzoyloxy-but-3'-enyl)-6-vinyl-tetrahydro-pyran-4-one 188



NaCl (12 mg, 0.2 mmol) was added to a solution of starting material (36 mg, 0.1 mmol) in DMSO (1.5 ml) and water (0.04 ml), and the resulting reaction mixture was heated in

an oil bath set to 150°C for four days. The reaction mixture was cooled to room temperature, then taken up in diethyl ether and water and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with water then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 10:90 ethyl acetate:petrol then was repurified by flash column chromatography, eluting with DCM to obtain the *title compound* (16.9 mg, 59%) as a colourless oil, shown by ¹H NMR spectroscopy to be a 1:1 mixture of diastereoisomers; $\nu_{\max}$ / cm⁻¹ 1647, 1721; δ_{H} (250 MHz, CDCl₃) 7.38-7.23 (5H, m, Ph), 5.96-5.67 (2H, m, CH=CH₂), 5.32-5.15 (4H, m, CH=CH₂), 4.61 (0.5H, d, J11.9, CH₂Ph), 4.59 (0.5H, d, J11.6, CH₂Ph), 4.34 (0.5H, d, J11.6, CH₂Ph), 4.33 (0.5H, d, J11.9, CH₂Ph), 4.14-3.71 (3H, m, 2-H, 6-H and CHOBn), 2.46-2.11 (4H, m, 3-H and 5-H), 1.86-1.65 (2H, m, CH₂CHOBn); δ_{C} (75 MHz, CDCl₃) 206.6 (C), 206.5 (C), 138.5 (CH), 138.4 (C), 138.2 (CH), 137.2 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 118.2 (CH₂), 117.2 (CH₂), 115.9 (CH₂), 77.3 (CH), 77.2 (CH), 76.9 (CH), 75.9 (CH), 73.7 (CH), 73.2 (CH), 70.4 (CH₂), 70.2 (CH₂), 48.0 (CH₂), 47.6 (CH₂), 47.3 (CH₂), 47.2 (CH₂), 42.7 (CH₂), 41.7 (CH₂); Found: [M+H]⁺, 287.1656. C₁₈H₂₂O₃+H⁺ requires: [M+H]⁺, 287.1647.

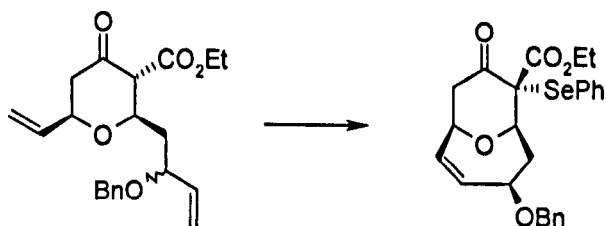
(1R*, 4R*, 6R*, 7S*)- 4-Benzoyloxy-8-oxo-7-phenylselanyl-10-oxa-bicyclo[4.3.1]dec-2-ene-7-carboxylic acid ethyl ester 189



Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (324 mg, 0.382 mmol) was added to a degassed solution of starting material (685 mg, 1.91 mmol) in DCM (400 ml) and the resulting reaction mixture was heated at reflux for 40 hours. The reaction mixture was allowed to cool to room temperature, tris(hydroxymethyl)phosphine (1.07 g, 8.66 mmol) was added and the reaction mixture was stirred for 30 minutes. Water (200 ml) was added and the resulting mixture was stirred for 1 hour, then the organic phase was separated, washed with water, dried over magnesium sulfate, filtered and concentrated

in vacuo. The resulting crude was partially purified by flash column chromatography, eluting with 8:92 ethyl acetate:petrol to obtain an impure sample of ring-closed product (554 mg). A solution of the resulting crude (66 mg) in DCM (1 ml) was then added to a solution of phenylselenenyl chloride (48 mg, 0.251 mmol) and pyridine (0.022 ml, 0.26 mmol) in DCM (2 ml) at 0°C under nitrogen, then the reaction mixture was allowed to warm to room temperature and stirred at room temperature for 2 days. The reaction mixture was taken up in diethyl ether and water and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with 10% aq. HCl and with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 15:85 ethyl acetate:petrol to obtain the *title compound* (41 mg, 37%) as a colourless oil, a single diastereoisomer tentatively assigned as shown on the basis of NOE studies; $\nu_{\max}$ / cm^{-1} 1713, 1736; δ_{H} (400 MHz, CDCl_3) 7.60-7.57 (2H, m, SePh), 7.44-7.29 (8H, m, SePh and CH_2Ph), 5.94 (1H, dq, J 11.5, 2.1, 3-H), 5.36 (1H, ddd, J 11.5, 4.1, 2.1, 2-H), 5.06-5.02 (1H, m, 1-H), 4.77 (1H, dd, J 11.2, 8.1, 6-H), 4.58 (1H, d, J 11.9, CH_2Ph), 4.54 (1H, d, J 11.9, CH_2Ph), 4.50 (1H, dqn, J 11.2, 2.1, 4-H), 4.13-4.05 (2H, m, CH_2CH_3), 3.15 (1H, dd, J 15.0, 10.3, 9-H), 2.64 (1H, ddt, J 13.9, 8.1, 2.1, 5-H), 2.60 (1H, d, J 15.0, 9-H), 2.02 (1H, dt, J 13.9, 11.2, 5-H), 1.15 (3H, t, J 7.1, Me); δ_{C} (62.5 MHz, CDCl_3) 199.1 (C), 167.7 (C), 138.1 (C), 137.7 (CH), 136.0 (CH), 129.7 (CH), 129.7 (CH), 129.0 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 124.7 (C), 75.7 (CH), 75.5 (CH), 72.8 (CH), 70.7 (CH_2), 67.7 (C), 62.1 (CH_2), 43.8 (CH_2), 39.5 (CH_2), 13.8 (CH_3); Found: $[\text{M}+\text{H}]^+$, 487.1027. $\text{C}_{25}\text{H}_{26}\text{O}_5$ $^{80}\text{Se}+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 487.1024. Found: $[\text{M}+\text{H}]^+$, 485.1034. $\text{C}_{25}\text{H}_{26}\text{O}_5$ $^{78}\text{Se}+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 485.1032.

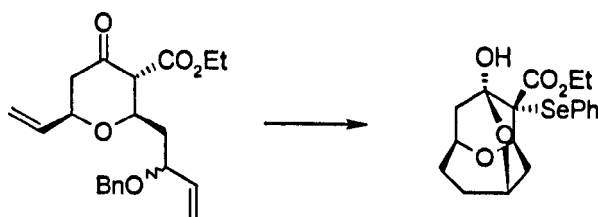
(1*R, 4*R**, 6*R**, 7*R**)-4-Benzoyloxy-8-oxo-7-phenylselenanyl-10-oxa-bicyclo[4.3.1]dec-2-ene-7-carboxylic acid ethyl ester 190**



Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (324 mg, 0.382 mmol) was added to a

degassed solution of starting material (685 mg, 1.91 mmol) in DCM (400 ml) and the resulting reaction mixture was heated at reflux for 40 hours. The reaction mixture was allowed to cool to room temperature, then tris(hydroxymethyl)phosphine (1.07 g, 8.66 mmol) was added and the reaction mixture was stirred for 30 minutes. Water (200 ml) was added and the resulting mixture was stirred for 1 hour, then the organic phase was separated, washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was partially purified by flash column chromatography, eluting with 8:92 ethyl acetate:petrol to obtain an impure sample of ring-closed product (554 mg). KHMDS (0.22 ml, 0.5 M in toluene, 0.11 mmol) was added to a portion of the resulting crude (33 mg) in THF (1 ml) at -78°C under nitrogen, and the reaction mixture was stirred for 10 minutes. A solution of PhSeBr (28 mg, 0.12 mmol) in THF (1 ml) was then added and the reaction mixture was stirred at -78°C for 40 minutes, then at -20°C overnight. The reaction mixture was allowed to warm to room temperature then was taken up in diethyl ether and sat. NH₄Cl solution and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 20:80 ethyl acetate:petrol to obtain the *title compound* (23 mg, 42%) as a colourless oil, a single diastereoisomer tentatively assigned on the basis of NOE studies as shown; ν_{max} / cm⁻¹ 1660, 1713, 1748; δ_{H} (400 MHz, CDCl₃) 7.60-7.58 (2H, m, SePh), 7.44-7.27 (8H, m, SePh and CH₂Ph), 5.92 (1H, dq, *J*11.5, 1.7, 3-H), 5.49 (1H, ddd, *J*11.5, 4.4, 2.4, 2-H), 5.09-5.05 (1H, m, 1-H), 4.75 (1H, dd, *J*10.9, 7.5, 6-H), 4.54 (2H, s, CH₂Ph), 4.52 (1H, dqn, *J*10.9, 2.0, 4-H), 4.01 (1H, dq, *J*10.8, 7.1, CH₂CH₃), 3.87 (1H, dq, *J*10.8, 7.1, CH₂CH₃), 3.75 (1H, dd, *J*16.2, 10.3, 9-H), 2.58 (1H, ddt, *J*13.8, 7.5, 1.9, 5-H), 2.46 (1H, dd, *J*16.2, 2.1, 9-H), 1.84 (1H, dt, *J*13.8, 10.9, 5-H), 1.09 (3H, t, *J*7.1, Me); δ_{C} (62.5 MHz, CDCl₃) 196.8 (C), 174.6 (C), 138.0 (C), 137.4 (CH), 135.0 (CH), 131.0 (CH), 130.0 (CH), 129.1 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 126.6 (C), 75.5 (CH), 74.1 (CH), 72.8 (CH), 70.7 (CH₂), 62.0 (C), 61.5 (CH₂), 40.8 (CH₂), 40.3 (CH₂), 13.8 (CH₃); Found: [M+NH₄]⁺, 504.1281. C₂₅H₂₆O₅⁸⁰Se+NH₄⁺ requires: [M+NH₄]⁺, 504.1289. Found: [M+NH₄]⁺, 502.1309. C₂₅H₂₆O₅⁷⁸Se+NH₄⁺ requires: [M+NH₄]⁺, 502.1297.

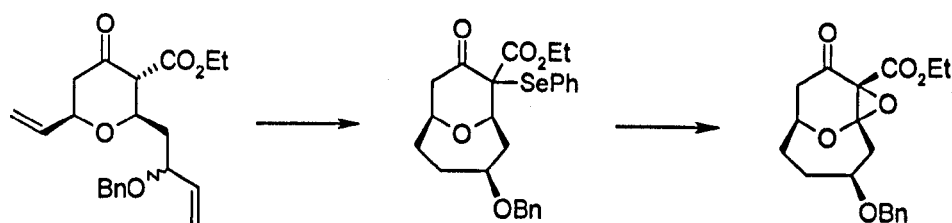
(1*R, 3*S**, 6*S**, 7*R**, 8*R**)- 1-Hydroxy-9-phenylselanyl-2,7-dioxatricyclo[4.3.1.1^{3,8}]undecane-9-carboxylic acid ethyl ester 191**



Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (324 mg, 0.382 mmol) was added to a degassed solution of starting material (685 mg, 1.91 mmol) in DCM (400 ml) and the resulting reaction mixture was heated at reflux for 40 hours. The reaction mixture was allowed to cool to room temperature, tris(hydroxymethyl)phosphine (1.07 g, 8.66 mmol) was added and the reaction mixture was stirred for 30 minutes. Water (200 ml) was added and the resulting mixture was stirred for 1 hour, then the organic phase was separated, washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was partially purified by flash column chromatography, eluting with 8:92 ethyl acetate:petrol to obtain an impure sample of ring-closed product (554 mg). A solution of the resulting crude (140 mg) in EtOAc (3 ml) was then added to a suspension of Pd/C (150 mg, 10%) in EtOAc (1 ml) under nitrogen. The flask was flushed with hydrogen, and the reaction mixture was stirred under hydrogen for 6 days. The reaction mixture was then filtered through celite and concentrated *in vacuo*. KHMDS (0.848 ml, 0.5M in toluene, 0.424 mmol) was then added to a solution of the resulting crude in THF (2 ml) at -78°C under nitrogen, and the reaction mixture was stirred for 10 minutes. A solution of PhSeBr (110 mg, 0.466 mmol) in THF (1 ml) was added and the reaction mixture was stirred at -78°C for 15 minutes, then at -20°C overnight. The reaction mixture was allowed to warm to room temperature and then was taken up in diethyl ether and sat. NH₄Cl solution and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 10:90-15:85 ethyl acetate:petrol to obtain the *title compound* (24 mg, 14%) as a colourless oil, a single diastereoisomer tentatively assigned as shown on the basis of NOE studies; ν_{max} / cm⁻¹ 1722; δ_{H} (400 MHz, CDCl₃) 7.74-7.71 (2H, m, SePh), 7.43-7.39 (1H, m, SePh), 7.34-7.30 (2H, m, SePh), 5.93 (1H, s, OH), 4.54-4.51 (1H, m, 3-H), 4.43-4.39 (2H, m, 6-H and 8-H), 4.04 (1H, dq, J10.8,

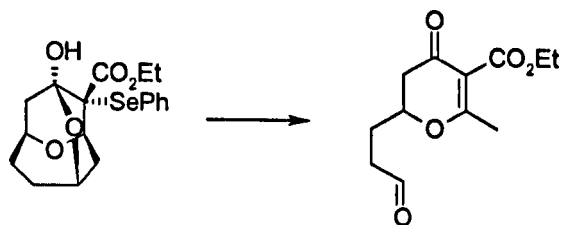
7.2, OCH₂), 3.90 (1H, dq, *J*10.8, 7.2, OCH₂), 3.15 (1H, dd, *J*14.1, 8.5, 2-H), 2.29-1.80 (6H, m, 4-H, 5-H and 7-H), 1.92 (1H, d, *J*14.1, 2-H), 1.15 (3H, t, *J*7.2, Me); δ_c (62.5 MHz, CDCl₃) 170.8 (C), 138.7 (CH), 129.6 (CH), 128.7 (CH), 126.2 (C), 96.0 (C), 72.7 (CH), 72.2 (CH), 71.8 (CH), 61.4 (CH₂), 35.6 (CH₂), 33.2 (CH₂), 32.4 (CH₂), 31.7 (CH₂), 29.7 (C), 13.8 (CH₃); Found: [M+H]⁺, 399.0707. C₁₈H₂₂O₅⁸⁰Se+H⁺ requires: [M+H]⁺, 399.0711. Found: [M+H]⁺, 397.0717. C₁₈H₂₂O₅⁷⁸Se+H⁺ requires: [M+H]⁺, 397.0719.

(2*S, 3*S**, 6*S**, 9*S**)-9-Benzoyloxy-4-oxo-2,11-dioxo-tricyclo[4.4.1.0^{1,3}]undecane-3-carboxylic acid ethyl ester 194**



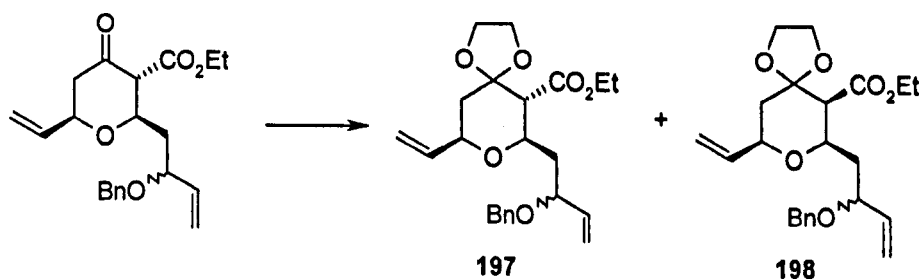
Tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (340 mg, 0.4 mmol) was added to a degassed solution of starting material (717 mg, 2 mmol) in DCM (400 ml) and the resulting reaction mixture was heated at reflux for 2 days. The reaction mixture was allowed to cool to room temperature, triethylamine (0.11 ml, 0.8 mmol) and tris(hydroxymethyl)phosphine (840 mg, 6.77 mmol) were added and the resulting mixture was stirred for 30 minutes. Water (150 ml) was added and the resulting mixture was stirred for 1 hour, then the organic phase was separated, washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was partially purified by flash column chromatography, eluting with 8:92 ethyl acetate:petrol to obtain an impure sample of ring-closed product (402 mg). A solution of the resulting crude (284 mg) in EtOH (10 ml) was then added to Pd(OH)₂/C (40 mg, 20% dry wt. Pd) under nitrogen. The flask was flushed with hydrogen, and the reaction mixture was stirred under hydrogen for 6 hours. The reaction mixture was then filtered through celite and concentrated *in vacuo*. KHMDS (1.72 ml, 0.5M in toluene, 0.86 mmol) was then added to a solution of the resulting crude in THF (3 ml) at -78°C under nitrogen, and the reaction mixture was stirred for 10 minutes. A solution of PhSeBr (213 mg, 0.903 mmol) in THF (1 ml) was added and the reaction mixture was stirred at

-78°C for 15 minutes, then at -20°C overnight. The reaction mixture was allowed to warm to room temperature and then was taken up in diethyl ether and sat. NH₄Cl solution and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 30:70 ethyl acetate:petrol to obtain an impure sample of the selenide (74 mg). H₂O₂ (0.022 ml, 27% aq. solⁿ w/w) was then added to a solution of a portion of the resulting crude (28 mg) in DCM (2 ml), and the resulting mixture was stirred for 2 days. The reaction mixture was taken up in diethyl ether and water and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 21:79 ethyl acetate:petrol to obtain the *title product* (3.6 mg, 2% overall) as a white solid, m.p. 94-96°C; ν_{max} / cm⁻¹ 1722, 1747; δ_{H} (500 MHz, DCM) 7.35-7.25 (5H, m, Ph), 4.41 (1H, d, *J*12.1, CH₂Ph), 4.38 (1H, d, *J*12.1, CH₂Ph), 4.25 (1H, dt, *J*11.7, 6.4, 9-H), 3.97 (1H, dq, *J*10.9, 7.1, CH₂CH₃), 3.84 (1H, tt, *J*4.9, 1.7, 6-H), 3.64 (1H, dq, *J*10.9, 7.1, CH₂CH₃), 2.81 (1H, dd, *J*19.2, 6.4, 10-H), 2.49 (1H, dd, *J*14.3, 5.3, 5-H), 2.39 (1H, d, *J*19.2, 10-H), 2.37-2.28 (1H, m, 7-H or 8-H), 2.20-2.10 (1H, m, 7-H or 8-H), 2.12 (1H, dt, *J*14.3, 1.8, 5-H), 1.90-1.83 (2H, m, 7-H or 8-H), 1.06 (3H, t, *J*7.1, CH₃); δ_{C} (62.5 MHz, CDCl₃) 198.5 (C), 164.6 (C), 138.0 (C), 128.4 (CH), 127.7 (CH), 127.7 (CH), 84.6 (C), 77.2 (C), 72.3 (CH), 71.7 (CH), 70.4 (CH₂), 62.1 (CH₂), 42.6 (CH₂), 35.1 (CH₂), 27.0 (CH₂), 26.5 (CH₂), 13.8 (CH₃); Found: [M+NH₄]⁺, 347.1503. C₁₉H₂₂O₆+H⁺ requires: [M+NH₄]⁺, 347.1495.



(-)-(10-Camphorsulfonyl)oxaziridine (3.5 mg, 0.0151 mmol) was added to a solution of starting material (4.6 mg, 0.0116 mmol) in CDCl_3 (2 ml), and the resulting reaction mixture was stirred for 24 hours. The resulting reaction mixture was then concentrated *in vacuo* and the resulting crude was purified by flash column chromatography, eluting with 75:25-100:0 ethyl acetate:DCM to obtain the *title compound* (1.8 mg, 65%) as a colourless oil; δ_{H} (250 MHz, CDCl_3) 9.83 (1H, t, J 0.9, 3'-H), 4.53-4.41 (1H, m, 6-H), 4.28 (2H, q, J 7.1, CH_2CH_3), 2.73-2.49 (4H, m, 5-H and 2'-H), 2.20 (3H, s, CClH_3), 2.12-2.04 (2H, m, 1'-H), 1.32 (3H, t, J 7.1, CH_2CH_3); Found: $[\text{M}+\text{H}]^+$, 241.1070. $\text{C}_{12}\text{H}_{16}\text{O}_5+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 241.1076. Sample decomposed before IR and ^{13}C NMR data could be recorded.

(2*R**, 3*R**, 6*R**, 2'*R/S**)-Spiro[2-(2'-benzyloxy-but-3'-enyl)-6-vinyl-tetrahydro-pyran-3-carboxylic acid ethyl ester-4,2''-1'',3''-dioxolane] 197 and (2*R**, 3*S**, 6*R**, 2'*R/S**)-Spiro[2-(2'-benzyloxy-but-3'-enyl)-6-vinyl-tetrahydro-pyran-3-carboxylic acid ethyl ester-4,2''-1'',3''-dioxolane] 198



1,2-Bis(trimethylsiloxy)ethane (0.3 ml, 2.04 mmol) was added to a solution of TMSOTf (2 drops) in DCM (8 ml) at -78°C under nitrogen, then a solution of starting material (609 mg, 1.70 mmol) in DCM (2 ml) was added and the reaction mixture was stirred at -78°C overnight. The reaction mixture was then allowed to warm to room temperature and stirred at room temperature for 2 hours, then was poured into aq. NaHCO_3 and

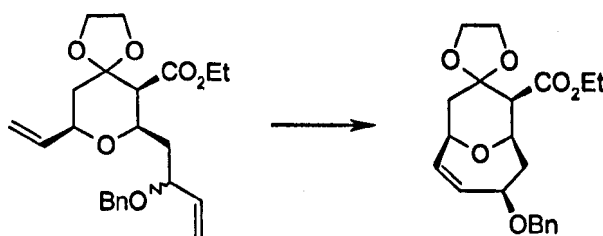
extracted with diethyl ether (3 x 30 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 20:80 ethyl acetate:petrol to obtain the *title compound* as two isomers, **197** (409 mg, 60%) and **198** (138 mg, 20%) as colourless oils, both shown by ^1H NMR spectroscopy to be a 1:1 mixture of diastereoisomers.

Data for **197**; ν_{max} / cm^{-1} 1607, 1645, 1731; δ_{H} (400 MHz, CDCl_3) 7.35-7.23 (5H, m, Ph), 5.86-5.68 (2H, m, $\text{CH}=\text{CH}_2$), 5.32-5.08 (4H, m, $\text{CH}=\text{CH}_2$), 4.60 (0.5H, d, J 12.3, one diastereoisomer of CH_2Ph), 4.55 (0.5H, d, J 11.6, one diastereoisomer of CH_2Ph), 4.37 (0.5H, d, J 12.3, one diastereoisomer of CH_2Ph), 4.36 (0.5H, d, J 11.6, one diastereoisomer of CH_2Ph), 4.22-3.83 (9H, m, 2-H, 6-H, 4''-H, 5''-H, CHOBn and CH_2CH_3), 2.67 (0.5H, d, J 10.7, one diastereoisomer of 3-H), 2.58 (0.5H, d, J 10.8, one diastereoisomer of 3-H), 1.98 (0.5H, ddd, J 13.5, 10.2, 4.8, one diastereoisomer of CH_2CHOBn), 1.82-1.47 (3.5H, m, 5-H and one diastereoisomer of CH_2CHOBn), 1.27 (1.5H, t, J 7.0, one diastereoisomer of Me), 1.25 (1.5H, t, J 7.0, one diastereoisomer of Me); δ_{C} (100 MHz, CDCl_3) 169.8 (C), 169.8 (C), 138.9 (CH), 138.6 (C), 138.0 (CH), 137.7 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.4 (CH), 127.2 (CH), 118.7 (CH_2), 116.8 (CH_2), 115.2 (CH_2), 115.2 (CH_2), 107.6 (C), 107.6 (C), 78.0 (CH), 75.5 (CH), 75.0 (CH), 74.8 (CH), 73.2 (CH), 72.5 (CH), 70.1 (CH_2), 69.9 (CH_2), 65.3 (CH_2), 64.8 (CH_2), 60.7 (CH_2), 60.7 (CH_2), 55.9 (CH), 55.5 (CH), 41.3 (CH_2), 41.2 (CH_2), 40.6 (CH_2), 39.3 (CH_2), 14.2 (CH_3); Found: $[\text{M}+\text{NH}_4]^+$, 420.2377. $\text{C}_{23}\text{H}_{30}\text{O}_6+\text{NH}_4^+$ requires: $[\text{M}+\text{H}^+]$, 420.2386.

Data for **198**; ν_{max} / cm^{-1} 1606, 1739; δ_{H} (400 MHz, CDCl_3) 7.36-7.24 (5H, m, Ph), 5.90 (0.5H, ddd, J 17.6, 10.6, 5.7, one diastereoisomer of $\text{CHOBnCH}=\text{CH}_2$), 5.85 (0.5H, ddd, J 17.6, 10.6, 5.7, one diastereoisomer of $\text{CHOBnCH}=\text{CH}_2$), 5.77-5.68 (1H, m, $\text{CHOCHCH}=\text{CH}_2$), 5.30-5.18 (3H, m, $\text{CH}=\text{CH}_2$), 5.13 (0.5H, dt, J 10.6, 1.3, one diastereoisomer of $\text{CHOBnCH}=\text{CH}_2$), 5.12 (0.5H, dt, J 10.6, 1.3, one diastereoisomer of $\text{CHOBnCH}=\text{CH}_2$), 4.60 (0.5H, d, J 12.0, one diastereoisomer of CH_2Ph), 4.57 (0.5H, d, J 11.5, one diastereoisomer of CH_2Ph), 4.35 (0.5H, d, J 12.0, one diastereoisomer of CH_2Ph), 4.35 (0.5H, d, J 11.5, one diastereoisomer of CH_2Ph), 4.22-3.92 (8.5H, m, one diastereoisomer of 2-H, 6-H, 4''-H, 5''-H, CHOBn and CH_2CH_3), 3.87 (0.5H, ddd,

7.8, 5.4, 3.1, one diastereoisomer of 2-H), 2.55-2.53 (1H, m, 3-H), 2.44-2.37 (1H, m, 5-H), 2.07-2.00 (0.5H, m, one diastereoisomer of CH_2CHOBN), 1.75-1.57 (2.5H, m, 5-H and CH_2CHOBN), 1.25 (1.5H, t, J 7.1, one diastereoisomer of Me), 1.24 (1.5H, t, J 7.1, one diastereoisomer of Me); δ_{C} (100 MHz, CDCl_3) 169.6 (C), 169.4 (C), 138.5 (CH), 138.2 (CH), 138.0 (CH), 138.0 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 127.5 (CH), 118.4 (CH_2), 117.0 (CH_2), 115.7 (CH_2), 115.5 (CH_2), 107.0 (C), 77.8 (CH), 76.2 (CH), 75.9 (CH), 75.9 (CH), 72.6 (CH), 71.8 (CH), 70.4 (CH_2), 70.2 (CH_2), 64.6 (CH_2), 64.6 (CH_2), 64.5 (CH_2), 64.5 (CH_2), 60.4 (CH_2), 60.4 (CH_2), 53.2 (CH), 52.7 (CH), 39.5 (CH_2), 38.7 (CH_2), 37.3 (CH_2), 37.2 (CH_2), 14.3 (CH_3), one C missing; Found: $[\text{M}+\text{H}]^+$, 403.2115. $\text{C}_{23}\text{H}_{30}\text{O}_6+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 403.2121.

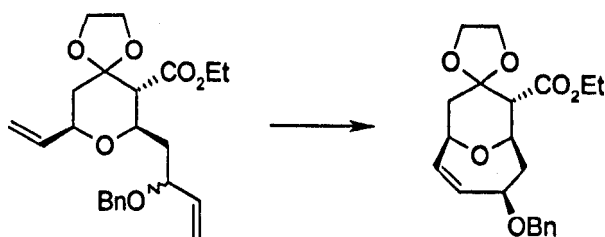
(1R*, 4R*, 6R*, 7S*)-Spiro[4-benzyloxy-10-oxa-bicyclo[4.3.1]dec-2-ene-7-carboxylic acid ethyl ester-8,2'-1',3'-dioxolane] 199



A degassed solution of tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (64 mg, 0.075 mmol) in DCM (10 ml) was added to a degassed solution of starting material (101 mg, 0.25 mmol) in DCM (15 ml) and the resulting reaction mixture was heated at reflux for 40 hours. The reaction mixture was concentrated *in vacuo*, and the resulting crude was purified by flash column chromatography, eluting with 20:80 ethyl acetate:petrol to obtain the *title compound* (8 mg, 9%) as a colourless oil; ν_{max} / cm^{-1} 1743; δ_{H} (400 MHz, CDCl_3) 7.37-7.26 (5H, m, Ph), 5.85 (1H, dq, J 11.7, 1.9, 3-H), 5.35 (1H, ddd, J 11.7, 3.4, 2.5, 2-H), 4.77-4.64 (3H, m, 1-H, 4-H and 6-H), 4.58 (1H, d, J 11.9, CH_2Ph), 4.54 (1H, d, J 11.9, CH_2Ph), 4.23-3.90 (4H, m, 4'-H and 5'-H), 4.13 (2H, q, J 7.1, CH_2CH_3), 3.12 (1H, d, J 5.6, 7-H), 2.93 (1H, ddd, J 13.0, 11.7, 9.2, 5-H), 2.22-2.14 (1H, m, 5-H), 1.93 (1H, dd, J 13.7, 7.4, 9-H), 1.85 (1H, dd, J 13.7, 1.6, 9-H), 1.25 (3H, t, J 7.1, CH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 168.4 (C), 138.6 (C), 133.6 (CH), 130.1 (CH), 128.4 (CH), 127.6

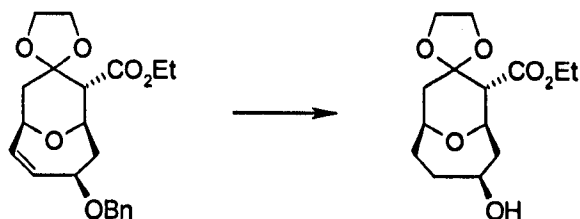
(CH), 127.4 (CH), 105.8 (C), 74.6 (CH), 73.3 (CH), 70.7 (CH₂), 70.1 (CH), 66.1 (CH₂), 64.0 (CH₂), 60.4 (CH₂), 51.5 (CH), 38.9 (CH₂), 37.0 (CH₂), 14.2 (CH₃); Found: [M+H]⁺, 375.1807. C₂₁H₂₆O₆+H⁺ requires: [M+H]⁺, 375.1808.

(1*R, 4*R**, 6*R**, 7*R**)-Spiro[4-benzyloxy-10-oxa-bicyclo[4.3.1]dec-2-ene-7-carboxylic acid ethyl ester-8,2'-1',3'-dioxolane] 200**



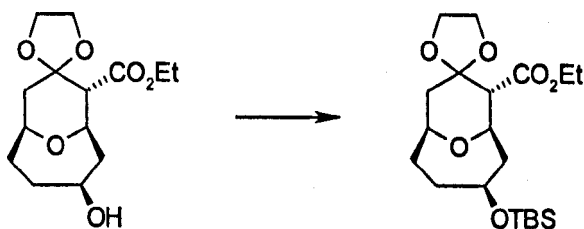
A degassed solution of tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium (IV) dichloride (425 mg, 0.5 mmol) in DCM (100 ml) was added to a degassed solution of starting material (2.01 g, 5 mmol) in DCM (900 ml) and the resulting reaction mixture was heated at reflux overnight. The reaction mixture was concentrated *in vacuo*, and the resulting crude was purified by flash column chromatography, eluting with 25:75 ethyl acetate:petrol to obtain the *title compound* (554 mg, 30%) as a colourless oil; ν_{max} / cm⁻¹ 1738; δ_{H} (400 MHz, CDCl₃) 7.35-7.26 (5H, m, Ph), 5.86 (1H, dd, *J*11.6, 1.7, 3-H), 5.45 (1H, ddd, *J*11.6, 3.4, 2.5, 2-H), 4.85-4.80 (1H, m, 1-H), 4.64 (1H, dqn, *J*11.4, 2.3, 4-H), 4.58 (1H, d, *J*11.8, CH₂Ph), 4.54 (1H, d, *J*11.8, CH₂Ph), 4.53 (1H, t, *J*9.2, 6-H), 4.18 (2H, q, *J*7.1, CH₂CH₃), 4.07-3.89 (4H, m, 4'-H and 5'-H), 2.71-2.63 (3H, m, 5-H, 7-H and 9-H), 2.30 (1H, ddt, *J*12.9, 9.2, 1.9, 5-H), 1.73 (1H, dt, *J*13.8, 1.7, 9-H), 1.28 (3H, t, *J*7.1, CH₂CH₃); δ_{C} (75 MHz, CDCl₃) 170.6 (C), 138.4 (C), 133.5 (CH), 131.3 (CH), 128.4 (CH), 127.6 (CH), 127.5 (CH), 105.3 (C), 73.7 (CH), 73.5 (CH), 70.8 (CH₂), 70.1 (CH), 64.6 (CH₂), 63.8 (CH₂), 60.7 (CH₂), 51.9 (CH), 40.6 (CH₂), 35.1 (CH₂), 14.1 (CH₃); Found: [M+H]⁺, 375.1813. C₂₁H₂₆O₆+H⁺ requires: [M+H]⁺, 375.1808.

(1*S, 4*S**, 6*R**, 7*R**)-Spiro[4-hydroxy-10-oxa-bicyclo[4.3.1]decane-7-carboxylic acid ethyl ester-8,2'-1',3'-dioxolane] 201**



A solution of starting material (321 mg, 0.857 mmol) in EtOAc (2 ml) was added to a suspension of Pd(OH)₂/C (80 mg, 20% dry wt. Pd) in EtOAc (8 ml) under nitrogen. The flask was flushed with hydrogen, and the reaction mixture was stirred under hydrogen overnight. The reaction mixture was then filtered through celite and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with ethyl acetate to obtain the *title compound* (214 mg, 87%) as a white solid, m.p. 119-120°C; ν_{max} / cm⁻¹ 1641, 1732; δ_{H} (400 MHz, CDCl₃) 4.52 (1H, td, *J* 9.2, 1.7, 6-H), 4.26-4.13 (4H, m, 1-H, 4-H and 6-H), 4.08-3.92 (4H, m, 4'-H and 5'-H), 2.80 (1H, d, *J* 1.7, 7-H), 2.19-1.64 (8H, m, 2-H, 3-H, 5-H and 9-H), 1.41 (1H, br s, OH), 1.28 (3H, t, *J* 7.1, CH₂CH₃); δ_{C} (62.5 MHz, CDCl₃) 170.8 (C), 106.9 (C), 70.8 (CH), 68.8 (CH), 68.4 (CH), 64.6 (CH₂), 60.7 (CH₂), 53.6 (CH), 43.5 (CH₂), 34.3 (CH₂), 34.3 (CH₂), 28.7 (CH₂), 14.2 (CH₃), one CH₂ missing; Found: [M+H]⁺, 287.1489. C₁₄H₂₂O₆+H⁺ requires: [M+H]⁺, 287.1495. The structure was also confirmed by X-ray crystallography.

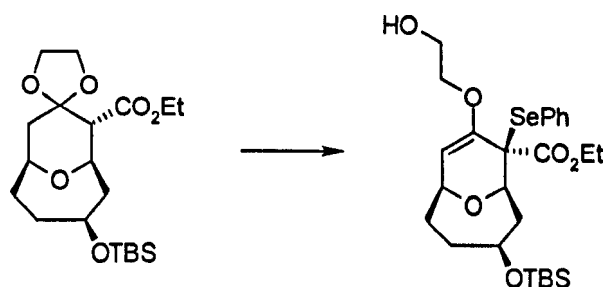
(1*S, 4*S**, 6*R**, 7*R**)-Spiro[4-(*tert*-butyl-dimethyl-silanyloxy)-10-oxa-bicyclo[4.3.1]decane-7-carboxylic acid ethyl ester-8,2'-1',3'-dioxolane] 202**



Imidazole (178 mg, 2.62 mmol) and TBSCl (263 mg, 1.75 mmol) were added to a solution of starting material (250 mg, 0.873 mmol) in DCM (10 ml) under nitrogen at 0°C. The resulting reaction mixture was allowed to warm to room temperature then was stirred at room temperature for 2 days. The reaction mixture was then taken up in diethyl ether and aq. NH₄Cl, and extracted with diethyl ether (3 x 50 ml). The combined

organic layers were washed with sat. aq. NH_4Cl then with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 15:85 ethyl acetate:petrol to obtain the *title compound* (335 mg, 96%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1733; δ_{H} (250 MHz, CDCl_3) 4.50 (1H, td, J 7.6, 3.9, 6-H), 4.28-4.07 (4H, m, 1-H, 4-H and CH_2CH_3), 4.01-3.89 (4H, m, 4'-H and 5'-H), 3.01 (1H, d, J 3.9, 7-H), 2.19 (1H, dd, J 13.9, 7.6, 9-H), 2.11-1.62 (7H, m, 2-H, 3-H, 5-H, and 9-H), 1.27 (3H, t, J 7.2, CH_2CH_3), 0.88 (9H, s, ^tBu), 0.05 (3H, s, SiMe), 0.04 (3H, s, SiMe); δ_{C} (75 MHz, CDCl_3) 171.0 (C), 107.3 (C), 70.6 (CH), 69.7 (CH), 69.3 (CH), 64.6 (CH_2), 64.6 (CH_2), 60.7 (CH_2), 52.7 (CH), 43.2 (CH_2), 36.3 (CH_2), 33.9 (CH_2), 29.4 (CH_2), 25.9 (CH_3), 18.2 (C), 14.3 (CH_3), -4.8 (CH_3), -4.9 (CH_3); Found: $[\text{M}+\text{H}]^+$, 401.2355. $\text{C}_{20}\text{H}_{36}\text{O}_6\text{Si}+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 401.2359.

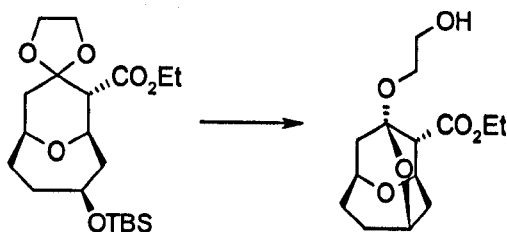
(1*S, 4*S**, 6*R**, 7*S**)-4-(tert-Butyl-dimethyl-silanyloxy)-8-(2'-hydroxy-ethoxy)-7-phenylselanyl-10-oxa-bicyclo[4.3.1]dec-8-ene-7-carboxylic acid ethyl ester 203**



KHMDS (0.539 ml, 0.5 M in toluene, 0.270 mmol) was added to a solution of starting material (54 mg, 0.135 mmol) in THF (1 ml) at -78°C under nitrogen, and the reaction mixture was stirred for 20 minutes. A solution of PhSeBr (95 mg, 0.404 mmol) in THF (1 ml) was then added and the reaction mixture was stirred at -78°C for 2 hours, then was allowed to warm to room temperature slowly overnight. The reaction mixture was then taken up in diethyl ether and sat. aq. NH_4Cl and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 20:80-30:70 ethyl acetate:petrol to obtain the *title compound* (33 mg, 44%) as a colourless oil; $\nu_{\text{max}} / \text{cm}^{-1}$ 1658, 1726; δ_{H} (400 MHz, CDCl_3) 7.70-7.67 (2H, m, Ph), 7.39-7.25 (3H, m, Ph), 4.78 (1H, d, J 2.7, 9-H), 4.53-4.49

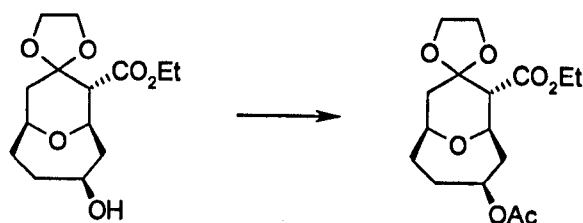
(2H, m, 1-H and 6-H), 4.05-3.96 (4H, m, 1'-H and $\underline{\text{CH}_2\text{CH}_3}$), 3.94-3.76 (3H, m, 4-H and 2'-H), 2.28-2.23 (1H, m, 5-H), 2.06 (1H, ddd, J 13.6, 10.7, 9.4, 5-H), 1.81-1.72 (3H, m, 2-H and 3-H), 1.53-1.50 (1H, m, 2-H), 1.13 (3H, t, J 7.1, $\underline{\text{CH}_2\text{CH}_3}$), 0.87 (9H, s, ^tBu), 0.02 (3H, s, SiMe), 0.02 (3H, s, SiMe), OH missing; δ_{C} (62.5 MHz, CDCl_3) 170.5 (C), 150.0 (C), 137.5 (CH), 129.4 (CH), 128.7 (CH), 126.3 (C), 99.7 (CH), 71.0 (CH), 70.3 (CH), 69.6 (CH), 69.4 (CH_2), 61.9 (CH_2), 60.5 (CH_2), 56.6 (C), 43.0 (CH_2), 37.1 (CH_2), 30.8 (CH_2), 25.8 (CH_3), 18.2 (C), 13.8 (CH_3), -4.8 (CH_3), -4.9 (CH_3); Found: $[\text{M}+\text{NH}_4]^+$, 574.2112. $\text{C}_{26}\text{H}_{40}\text{O}_6\text{Si}^{80}\text{Se}+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 574.2103. Found: $[\text{M}+\text{NH}_4]^+$, 572.2112. $\text{C}_{26}\text{H}_{40}\text{O}_6\text{Si}^{78}\text{Se}+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 572.2111.

(1*R, 3*S**, 6*S**, 8*R**, 9*R**)-1-(2'-Hydroxy-ethoxy)-2,7-dioxatricyclo[4.3.1.1^{3,8}]undecane-9-carboxylic acid ethyl ester 204**



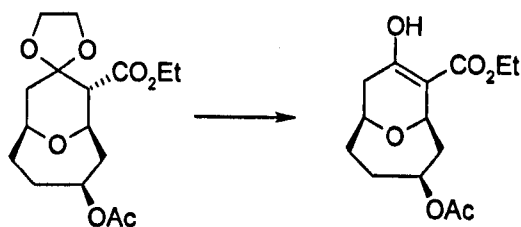
PPTS (9 mg, 0.035 mmol) was added to a solution of starting material (47 mg, 0.117 mmol) in acetone (2 ml) and the resulting reaction mixture was heated at reflux overnight. Additional PPTS (20 mg, 0.080 mmol) was added and the resulting reaction mixture was stirred for 24 hours then was concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 80:20 ethyl acetate:petrol to obtain the *title compound* (25 mg, 74%) as a colourless oil; ν_{max} / cm^{-1} 1645, 1739; δ_{H} (250 MHz, CDCl_3) 4.68-4.65 (1H, m, 8-H), 4.50-4.45 (1H, m, 6-H), 4.42-4.36 (1H, m, 3-H), 4.17 (2H, q, J 7.1, $\underline{\text{CH}_2\text{CH}_3}$), 3.78-3.63 (4H, m, 1'-H and 2'-H), 2.87 (1H, dd, J 13.4, 8.5, 2-H), 2.84 (1H, br s, OH), 2.68 (1H, s, 9-H), 2.20-1.81 (7H, m, 2-H, 4-H, 5-H and 7-H), 1.26 (3H, t, J 7.1, $\underline{\text{CH}_2\text{CH}_3}$); δ_{C} (75 MHz, CDCl_3) 169.9 (C), 95.3 (C), 72.7 (CH), 71.1 (CH), 70.8 (CH), 62.7 (CH_2), 61.8 (CH_2), 60.7 (CH_2), 49.2 (CH), 34.2 (CH_2), 33.8 (CH_2), 33.2 (CH_2), 32.6 (CH_2), 14.1 (CH_3); Found: $[\text{M}+\text{H}]^+$, 287.1494. $\text{C}_{14}\text{H}_{22}\text{O}_6+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 287.1495.

(1*S, 4*S**, 6*R**, 7*R**)-Spiro[4-acetoxy-10-oxa-bicyclo[4.3.1]decane-7-carboxylic acid ethyl ester-8,2'-1',3'-dioxolane] 205**



Pyridine (0.5 ml) was added to a solution of starting material (57 mg, 0.2 mmol) in acetic anhydride (1 ml) at 0°C under nitrogen. The reaction mixture was allowed to warm to room temperature, then was stirred at room temperature for 4 hours. The reaction mixture was partially concentrated *in vacuo*, and the resulting crude was purified by flash column chromatography, eluting with 30:70 ethyl acetate:petrol to obtain the *title compound* (64 mg, 97%) as a colourless oil; $\nu_{\max}$ / cm^{-1} 1733; δ_{H} (400 MHz, CDCl_3) 5.18 (1H, dtd, J 10.2, 5.1, 3.3, 4-H), 4.48 (1H, ddd, J 9.1, 7.8, 2.7, 6-H), 4.24-4.17 (1H, m, 1-H), 4.18 (2H, q, J 7.1, CH_2CH_3), 4.06-3.91 (4H, m, 4'-H and 5'-H), 2.81 (1H, d, J 2.7, 7-H), 2.36-2.25 (2H, m, 5-H and 9-H), 2.20-2.08 (2H, m, 2-H and 3-H), 2.03 (1H, ddd, J 10.6, 7.8, 3.3, 5-H), 2.02 (3H, s, Ac), 1.81-1.67 (3H, m, 2-H, 3-H and 9-H), 1.27 (3H, t, J 7.1, CH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 170.5 (C), 170.2 (C), 106.6 (C), 71.3 (CH), 70.7 (CH), 69.4 (CH), 64.7 (CH_2), 64.2 (CH_2), 60.7 (CH_2), 52.4 (CH), 38.0 (CH_2), 35.3 (CH_2), 30.2 (CH_2), 28.9 (CH_2), 21.4 (CH_3), 14.2 (CH_3); Found: $[\text{M}+\text{H}]^+$, 329.1606. $\text{C}_{16}\text{H}_{24}\text{O}_7+\text{H}^+$ requires: $[\text{M}+\text{H}]^+$, 329.1600.

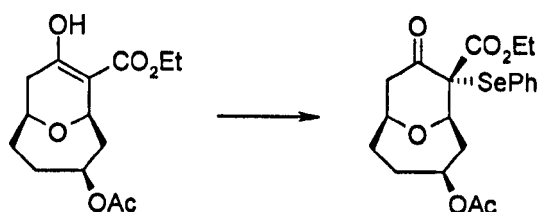
(1*S, 4*S**, 6*R**)-4-Acetoxy-8-hydroxy-10-oxa-bicyclo[4.3.1]dec-7-ene-7-carboxylic acid ethyl ester 206**



$\text{TsOH}\cdot\text{H}_2\text{O}$ (100 mg) was added to a solution of starting material (290 mg, 0.883 mmol) in 90% aq. formic acid (15 ml). The resulting reaction mixture was stirred at room temperature overnight, then was poured cautiously into aq. NaHCO_3 . The resulting mixture was quenched with solid NaHCO_3 , then was extracted with diethyl ether (3 x 20

ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 20:80 ethyl acetate:petrol to obtain the *title compound* (245 mg, 98%) as a white solid, m.p. 54-55°C; $\nu_{\max}$ / cm^{-1} 1623, 1657, 1736; δ_{H} (250 MHz, CDCl_3) 12.24 (1H, s, OH), 5.29-5.20 (1H, m, 4-H), 4.69 (1H, td, J 5.2, 1.5, 6-H), 4.29 (1H, q, J 7.0, 1-H), 4.28-4.15 (2H, m, CH_2CH_3), 2.76 (1H, ddd, J 17.4, 6.4, 1.8, 9-H), 2.36 (1H, dt, J 15.3, 5.2, 5-H), 2.20-1.69 (6H, m, 2-H, 3-H, 5-H and 9-H), 1.95 (3H, s, Ac), 1.29 (3H, t, J 7.1, CH_2CH_3); δ_{C} (75 MHz, CDCl_3) 170.4 (C), 170.2 (C), 168.5 (C), 101.0 (C), 72.0 (CH), 69.7 (CH), 67.1 (CH), 60.5 (CH_2), 38.6 (CH_2), 33.4 (CH_2), 30.1 (CH_2), 28.2 (CH_2), 21.2 (CH_3), 14.2 (CH_3); Found: $[\text{M}+\text{NH}_4]^+$, 302.1605. $\text{C}_{14}\text{H}_{20}\text{O}_6+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 302.1604.

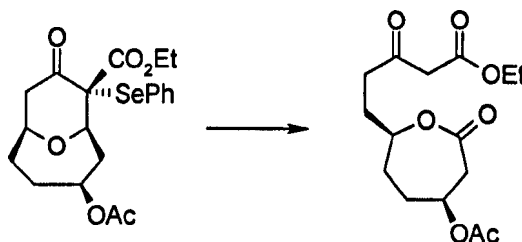
(1*S, 4*S**, 6*R**, 7*R**)-4-Acetoxy-8-oxo-7-phenylselanyl-10-oxa-bicyclo[4.3.1]decane-7-carboxylic acid ethyl ester 208**



Sodium hydride (12 mg, 60% w/w in mineral oil, 0.310 mmol) was added to a solution of starting material (44 mg, 0.155 mmol) in THF (2 ml) at 0°C under nitrogen, and the resulting reaction mixture was stirred for 15 minutes. Phenylselenenyl chloride (59 mg, 0.310 mmol) was added, and the resulting reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was taken up in sat. aq. NH_4Cl and diethyl ether, and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 25:75 ethyl acetate:petrol to obtain the *title compound* (48 mg, 71%) as a colourless oil as a mixture of diastereoisomers, with the major isomer (>10:1 by ^1H NMR spectroscopy) tentatively assigned as shown on the basis of NOE studies; $\nu_{\max}$ / cm^{-1} 1579, 1717, 1738; δ_{H} (250 MHz, CDCl_3) 7.63-7.55 (2H, m, Ph), 7.44-7.26 (3H, m, Ph), 5.17-5.06 (1H, m, 4-H), 4.59 (1H, dd, J 10.4, 8.2, 6-H), 4.57-4.47 (1H, m, 1-H), 4.11-3.90 (2H, m, CH_2CH_3), 3.08 (1H, dd, J 17.5, 8.5, 9-H), 2.61 (1H, dd, J 17.5, 6.7, 9-H),

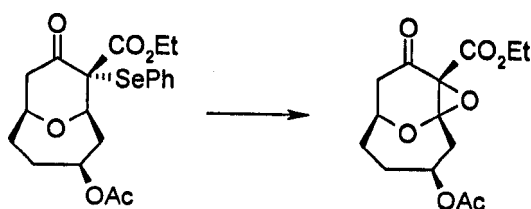
2.37-2.26 (1H, m, 5-H), 2.17-1.56 (5H, m, 2-H, 3-H and 5-H), 1.99 (3H, s, Ac), 1.12 (3H, t, J 7.1, CH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 197.1 (C), 169.9 (C), 166.5 (C), 137.7 (CH), 129.9 (CH), 128.9 (CH), 126.5 (C), 72.7 (CH), 71.4 (CH), 70.3 (CH), 61.7 (CH_2), 39.6 (CH_2), 39.1 (CH_2), 30.8 (CH_2), 30.2 (CH_2), 21.3 (CH_3), 13.8 (CH_3), one C missing; Found: $[\text{M}+\text{NH}_4]^+$, 458.1079. $\text{C}_{20}\text{H}_{24}\text{O}_6^{80}\text{Se}+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 458.1082. Found: $[\text{M}+\text{NH}_4]^+$, 456.1093. $\text{C}_{20}\text{H}_{24}\text{O}_6^{78}\text{Se}+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 456.1090.

(2'S*, 5'S*)-5-(5'-Acetoxy-7'-oxo-oxepan-2'-yl)-3-oxo-pentanoic acid ethyl ester 209



(-)-(10-Camphorsulfonyl)oxaziridine (35 mg, 0.155 mmol) was added to a solution of starting material (34 mg, 0.077 mmol) in CDCl_3 (2 ml) and the resulting reaction mixture was stirred at room temperature overnight, then was stirred in an oil bath set to 50°C for 24 hours. The reaction mixture was concentrated *in vacuo* and the resulting crude was purified by flash column chromatography, eluting with 40:60 ethyl acetate:petrol to obtain the *title compound* (9.0 mg, 37%) as a colourless oil; ν_{max} / cm^{-1} 1645, 1733; δ_{H} (400 MHz, CDCl_3) 5.24-5.20 (1H, m, 2'-H), 4.84 (1H, dt, J 9.3, 6.2, 5-H), 4.20 (2H, q, J 7.1, CH_2CH_3), 3.51 (1H, d, J 15.7, 2-H), 3.46 (1H, d, J 15.7, 2-H), 3.11 (1H, dd, J 17.6, 6.8, 6'-H), 3.12-3.07 (1H, m, 4-H), 2.94 (1H, d, J 14.2, 4-H), 2.83 (1H, dd, J 17.6, 6.2, 6-H), 2.17-1.80 (4H, m, 3-H and 4-H), 2.06 (3H, s, Ac), 1.29 (3H, t, J 7.1, CH_2CH_3); δ_{C} (62.5 MHz, CDCl_3) 199.7 (C), 170.3 (C), 169.9 (C), 166.7 (C), 75.4 (CH), 65.6 (CH), 61.6 (CH_2), 49.8 (CH_2), 48.5 (CH_2), 38.5 (CH_2), 32.2 (CH_2), 29.1 (CH_2), 20.9 (CH_3), 14.1 (CH_3); Found: $[\text{M}+\text{NH}_4]^+$, 318.1559. $\text{C}_{14}\text{H}_{20}\text{O}_7+\text{NH}_4^+$ requires: $[\text{M}+\text{NH}_4]^+$, 318.1553.

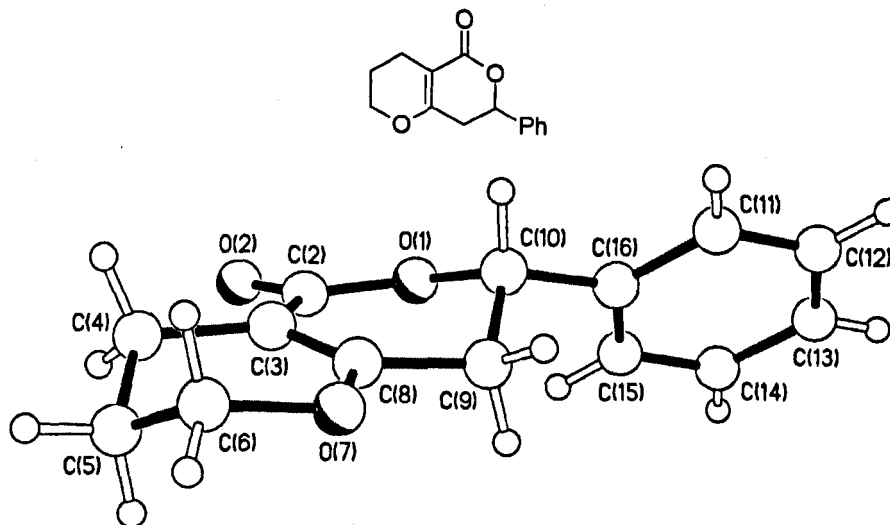
(2*S, 3*S**, 6*S**, 9*S**)-9-Acetoxy-4-oxo-2,11-dioxo-tricyclo[4.4.1.0^{1,3}]undecane-3-carboxylic acid ethyl ester 211**



H₂O₂ (0.5 ml, 27% aq. solⁿ w/w) was added to a solution of starting material (23.9 mg, 0.0544 mmol) in DCM (2 ml) at 0°C under nitrogen, and the resulting reaction mixture was stirred for one hour at 0°C. The reaction mixture was taken up in water and diethyl ether, and extracted with diethyl ether (3 x 10 ml). The combined organic layers were washed with sat. brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude was purified by flash column chromatography, eluting with 20:80 ethyl acetate:petrol to obtain the *title compound* (9.2 mg, 57%) as a white solid, m.p. 104-106°C; ν_{max} / cm⁻¹ 1643, 1741; δ_{H} (250 MHz, CDCl₃) 5.29-5.24 (1H, m, 9-H), 4.39-4.20 (3H, m, 6-H and CH₂CH₃), 2.89 (1H, dd, *J*19.1, 6.1, 5-H), 2.71 (1H, dd, *J*15.0, 5.5, 10-H), 2.44 (1H, d, *J*19.1, 5-H), 2.28-1.83 (5H, m, 5-H, 7-H and 8-H), 2.02 (3H, s, Ac), 1.33 (3H, t, *J*7.1, CH₂CH₃); δ_{C} (125 MHz, CDCl₃) 198.0 (C), 169.7 (C), 164.7 (C), 84.4 (C), 77.2 (C), 72.4 (CH), 68.0 (CH), 62.2 (CH₂), 42.5 (CH₂), 35.6 (CH₂), 27.4 (CH₂), 26.9 (CH₂), 21.2 (CH₃), 14.1 (CH₃); Found: [M+NH₄]⁺, 316.1392. C₁₄H₁₈O₇+NH₄⁺ requires: [M+NH₄]⁺, 316.1396.

Appendix: X-ray crystallographic data

7-Phenyl-3,4,7,8-tetrahydro-2H-pyrano[4,3-b]pyran-5-one 66



Crystal data and structure refinement for 66

Identification code	AA0102
Empirical formula	C ₁₄ H ₁₄ O ₃
Formula weight	230.25
Temperature	293(2) K
Diffractometer, wavelength	Siemens P4, 1.54178 Å
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 6.2083(5) Å alpha = 90 deg. b = 8.3250(7) Å beta = 98.967(7) deg. c = 11.436(2) Å gamma = 90 deg.
Volume, Z	583.86(11) Å ³ , 2
Calculated density	1.310 Mg/m ³
Absorption coefficient	0.747 mm ⁻¹
F(000)	244
Crystal colour/morphology	Colourless blocks
Crystal size	0.33 x 0.30 x 0.27 mm
Theta range for data collection	3.91 to 59.94 deg.
Index ranges	-5 ≤ h ≤ 6, -7 ≤ k ≤ 9, -9 ≤ l ≤ 12
Reflns collected / unique	1029 / 987 [R(int) = 0.0137]

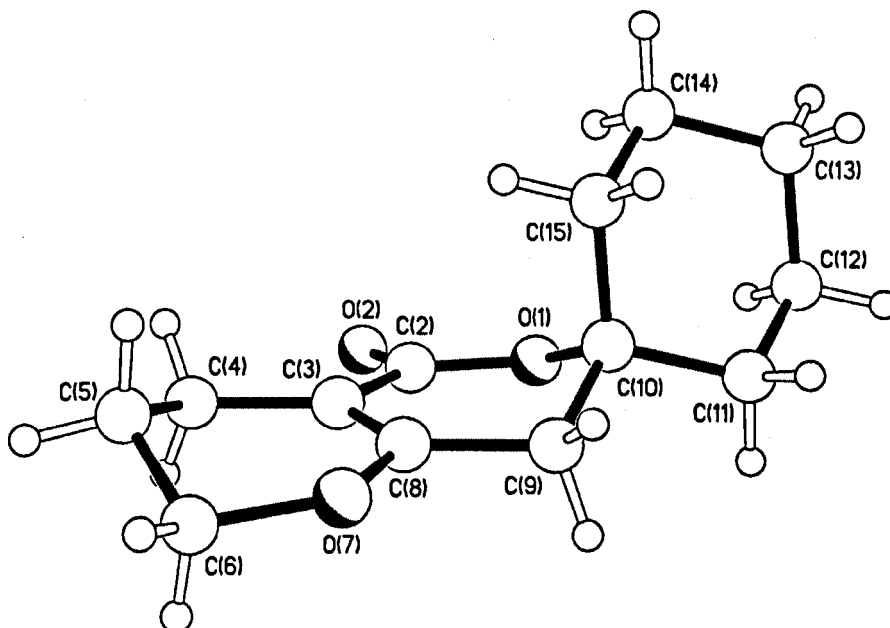
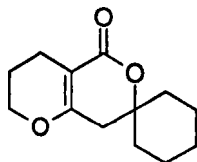
Reflns observed [$F > 4\sigma(F)$]	924
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	975 / 11 / 151
Goodness-of-fit on F^2	1.052
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0361$, $wR2 = 0.0976$
R indices (all data)	$R1 = 0.0393$, $wR2 = 0.1034$
Absolute structure parameter	-0.1(4)
Extinction coefficient	0.005(2)
Largest diff. peak and hole	0.118 and -0.157 e. $\text{\AA}^{-3}$
Mean and maximum shift/error	0.000 and 0.001

Bond lengths [$\text{\AA}$] and angles [deg] for 66

O(1)-C(2)	1.363(3)
O(1)-C(10)	1.455(3)
C(2)-O(2)	1.213(4)
C(2)-C(3)	1.449(4)
C(3)-C(8)	1.338(4)
C(3)-C(4)	1.503(4)
C(4)-C(5')	1.510(8)
C(4)-C(5)	1.517(6)
C(5)-C(6)	1.489(7)
C(6)-O(7)	1.455(5)
C(5')-C(6')	1.461(10)
C(6')-O(7)	1.463(9)
O(7)-C(8)	1.339(3)
C(8)-C(9)	1.495(4)
C(9)-C(10)	1.506(4)
C(10)-C(16)	1.516(3)
C(11)-C(12)	1.39
C(11)-C(16)	1.39
C(12)-C(13)	1.39
C(13)-C(14)	1.39
C(14)-C(15)	1.39

C(15)-C(16)	1.39
C(2)-O(1)-C(10)	118.6(2)
O(2)-C(2)-O(1)	116.5(3)
O(2)-C(2)-C(3)	123.8(3)
O(1)-C(2)-C(3)	119.7(3)
C(8)-C(3)-C(2)	119.3(3)
C(8)-C(3)-C(4)	122.5(3)
C(2)-C(3)-C(4)	117.8(3)
C(3)-C(4)-C(5')	109.9(5)
C(3)-C(4)-C(5)	107.6(3)
C(6)-C(5)-C(4)	111.4(4)
O(7)-C(6)-C(5)	111.7(5)
C(6')-C(5')-C(4)	112.5(10)
C(5')-C(6')-O(7)	113.4(10)
C(8)-O(7)-C(6)	116.1(3)
C(8)-O(7)-C(6')	113.7(7)
C(3)-C(8)-O(7)	125.0(3)
C(3)-C(8)-C(9)	121.6(3)
O(7)-C(8)-C(9)	113.3(3)
C(8)-C(9)-C(10)	110.0(3)
O(1)-C(10)-C(9)	111.0(2)
O(1)-C(10)-C(16)	107.0(2)
C(9)-C(10)-C(16)	112.3(2)
C(12)-C(11)-C(16)	120.0
C(13)-C(12)-C(11)	120.0
C(12)-C(13)-C(14)	120.0
C(15)-C(14)-C(13)	120.0
C(16)-C(15)-C(14)	120.0
C(15)-C(16)-C(11)	120.0
C(15)-C(16)-C(10)	120.7(2)
C(11)-C(16)-C(10)	119.2(2)

Spiro[cyclohexane-1,7'-3',4',7',8'-tetrahydro-2H-pyrano[4',3'-b]pyran-5'-one] 68



Crystal data and structure refinement for 68

Identification code	AA0101
Empirical formula	C ₁₃ H ₁₈ O ₃
Formula weight	222.27
Temperature	293(2) K
Diffractometer, wavelength	Siemens P4, 1.54178 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 7.4771(3) Å alpha = 106.302(4) deg. b = 9.2733(6) Å beta = 105.735(4) deg. c = 9.4601(4) Å gamma = 98.607(4) deg.
Volume, Z	587.60(5) Å ³ , 2
Calculated density	1.256 Mg/m ³
Absorption coefficient	0.712 mm ⁻¹
F(000)	240
Crystal colour/morphology	Colourless blocks
Crystal size	0.40 x 0.30 x 0.27 mm

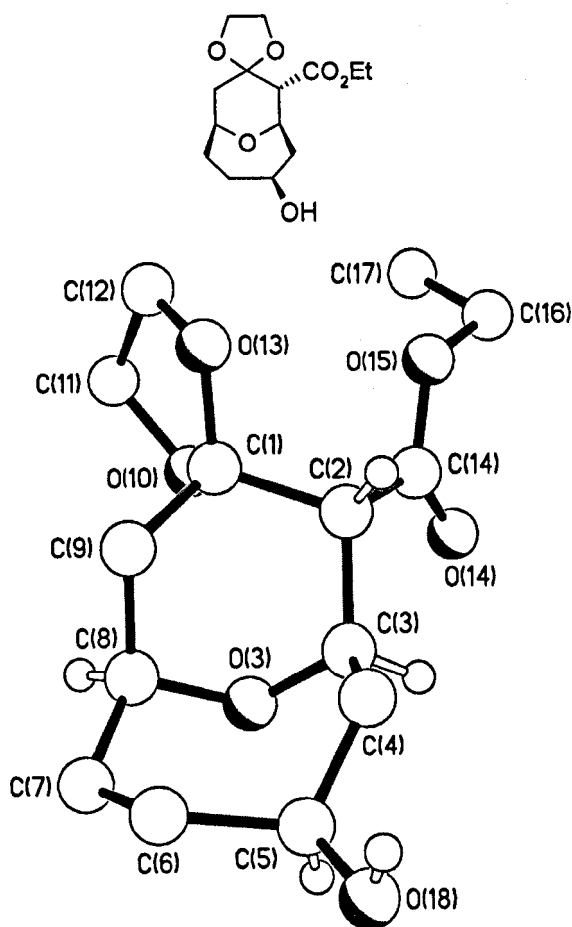
Theta range for data collection	5.12 to 59.98 deg.
Index ranges	-8<=h<=2, -9<=k<=9, -10<=l<=10
Reflns collected / unique	1868 / 1717 [R(int) = 0.0108]
Reflns observed [F>4sigma(F)]	1531
Absorption correction	None
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	1651 / 0 / 146
Goodness-of-fit on F ²	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0510, wR2 = 0.1364
R indices (all data)	R1 = 0.0727, wR2 = 0.1670
Extinction coefficient	0.035(7)
Largest diff. peak and hole	0.504 and -0.185 e.A ⁻³
Mean and maximum shift/error	0.000 and 0.000

Bond lengths [Å] and angles [deg] for 68

O(1)-C(2)	1.351(2)
O(1)-C(10)	1.472(2)
C(2)-O(2)	1.212(2)
C(2)-C(3)	1.457(3)
C(3)-C(8)	1.334(3)
C(3)-C(4)	1.503(3)
C(4)-C(5)	1.513(4)
C(5)-C(6)	1.453(4)
C(6)-O(7)	1.446(3)
O(7)-C(8)	1.351(3)
C(8)-C(9)	1.490(3)
C(9)-C(10)	1.517(3)
C(10)-C(15)	1.523(3)
C(10)-C(11)	1.523(3)
C(11)-C(12)	1.518(3)
C(12)-C(13)	1.518(4)
C(13)-C(14)	1.528(4)
C(14)-C(15)	1.513(3)
C(2)-O(1)-C(10)	119.55(15)

O(2)-C(2)-O(1)	117.7(2)
O(2)-C(2)-C(3)	122.8(2)
O(1)-C(2)-C(3)	119.4(2)
C(8)-C(3)-C(2)	118.8(2)
C(8)-C(3)-C(4)	122.0(2)
C(2)-C(3)-C(4)	119.0(2)
C(3)-C(4)-C(5)	108.8(2)
C(6)-C(5)-C(4)	111.8(2)
O(7)-C(6)-C(5)	113.3(2)
C(8)-O(7)-C(6)	115.5(2)
C(3)-C(8)-O(7)	124.6(2)
C(3)-C(8)-C(9)	122.5(2)
O(7)-C(8)-C(9)	112.9(2)
C(8)-C(9)-C(10)	111.5(2)
O(1)-C(10)-C(9)	109.1(2)
O(1)-C(10)-C(15)	108.3(2)
C(9)-C(10)-C(15)	112.9(2)
O(1)-C(10)-C(11)	105.0(2)
C(9)-C(10)-C(11)	111.1(2)
C(15)-C(10)-C(11)	110.0(2)
C(12)-C(11)-C(10)	113.0(2)
C(13)-C(12)-C(11)	111.6(2)
C(12)-C(13)-C(14)	111.1(2)
C(15)-C(14)-C(13)	111.0(2)
C(14)-C(15)-C(10)	112.7(2)

(1*S, 4*S**, 6*R**, 7*R**)-Spiro[4-hydroxy-10-oxa-bicyclo[4.3.1]decane-7-carboxylic acid
ethyl ester-8,2'-1',3'-dioxolane] 201**



Crystal data and structure refinement for 201

Identification code	AA0306
Empirical formula	C ₁₄ H ₂₂ O ₆
Formula weight	286.32
Temperature	293(2) K
Diffractometer, wavelength	Bruker P4, 1.54178 Å
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	$a = 5.6423(8) \text{ Å}$ $\alpha = 90^\circ$ $b = 13.1408(10) \text{ Å}$ $\beta = 93.662(8)^\circ$ $c = 19.0725(12) \text{ Å}$ $\gamma = 90^\circ$
Volume, Z	1411.2(2) Å ³ , 4
Density (calculated)	1.348 Mg/m ³

Absorption coefficient	0.878 mm ⁻¹
F(000)	616
Crystal colour / morphology	Colourless platy needles
Crystal size	1.00 x 0.13 x 0.01 mm ³
□ range for data collection	4.09 to 59.99°
Index ranges	-6 ≤ h ≤ 0, -14 ≤ k ≤ 0, -21 ≤ l ≤ 21
Reflns collected / unique	2327 / 2090 [R(int) = 0.0778]
Reflns observed [F > 4σ(F)]	1204
Absorption correction	None
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	2090 / 1 / 186
Goodness-of-fit on F ²	1.001
Final R indices [F > 4σ(F)]	R1 = 0.0655, wR2 = 0.1522
R indices (all data)	R1 = 0.1251, wR2 = 0.1743
Extinction coefficient	0.0074(9)
Largest diff. peak, hole	0.244, -0.202 eÅ ⁻³
Mean and maximum shift/error	0.000 and 0.000

Bond lengths [Å] and angles [deg] for 201

C(1)-O(10)	1.404(5)
C(1)-O(13)	1.430(5)
C(1)-C(9)	1.522(7)
C(1)-C(2)	1.568(6)
C(2)-C(14)	1.502(7)
C(2)-C(3)	1.537(6)
C(3)-O(3)	1.438(5)
C(3)-C(4)	1.512(6)
O(3)-C(8)	1.468(5)
C(4)-C(5)	1.508(7)
C(5)-O(18)	1.440(6)
C(5)-C(6)	1.546(7)
C(6)-C(7)	1.511(7)
C(7)-C(8)	1.518(7)

C(8)-C(9)	1.516(7)
O(10)-C(11)	1.441(6)
C(11)-C(12)	1.480(8)
C(12)-O(13)	1.425(6)
C(14)-O(14)	1.202(6)
C(14)-O(15)	1.337(6)
O(15)-C(16)	1.456(6)
C(16)-C(17)	1.462(9)
O(10)-C(1)-O(13)	107.3(4)
O(10)-C(1)-C(9)	112.2(4)
O(13)-C(1)-C(9)	109.9(4)
O(10)-C(1)-C(2)	108.4(4)
O(13)-C(1)-C(2)	109.7(4)
C(9)-C(1)-C(2)	109.3(4)
C(14)-C(2)-C(3)	113.8(4)
C(14)-C(2)-C(1)	110.4(4)
C(3)-C(2)-C(1)	109.8(4)
O(3)-C(3)-C(4)	114.0(4)
O(3)-C(3)-C(2)	110.8(4)
C(4)-C(3)-C(2)	114.1(4)
C(3)-O(3)-C(8)	114.2(3)
C(5)-C(4)-C(3)	115.7(4)
O(18)-C(5)-C(4)	111.2(4)
O(18)-C(5)-C(6)	108.5(4)
C(4)-C(5)-C(6)	112.1(4)
C(7)-C(6)-C(5)	115.0(4)
C(6)-C(7)-C(8)	116.8(4)
O(3)-C(8)-C(9)	110.7(4)
O(3)-C(8)-C(7)	109.4(4)
C(9)-C(8)-C(7)	116.0(4)
C(8)-C(9)-C(1)	110.4(4)
C(1)-O(10)-C(11)	106.1(3)
O(10)-C(11)-C(12)	102.8(4)
O(13)-C(12)-C(11)	106.6(4)

C(12)-O(13)-C(1)	106.9(4)
O(14)-C(14)-O(15)	123.8(5)
O(14)-C(14)-C(2)	125.3(5)
O(15)-C(14)-C(2)	110.9(4)
C(14)-O(15)-C(16)	118.1(4)
O(15)-C(16)-C(17)	112.0(5)

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