

Towards the Total Synthesis of a Dolabellane Diterpenoid, and Studies in Synthetic Organic Electrochemistry

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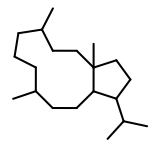
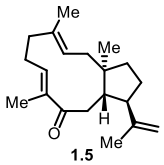
Abstract

Chapter one begins with an introduction on the dolabellane diterpenoid natural product family, followed by a summary of the most recent total and formal syntheses of dolabellane diterpenoids. Previous work carried out in the Burton group towards the target natural product (**1.5**), a member of the dolabellane family, will also be discussed.

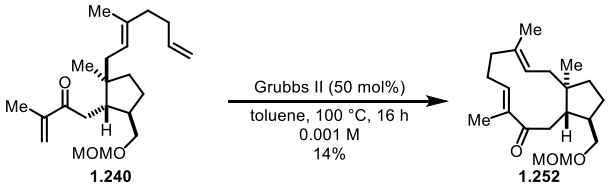


1.1
dolabellane skeleton



1.5
target dolabellane diterpenoid

We then discuss our own work towards the natural product target **1.5**. Significant progress towards the racemic natural product target has been achieved, and we have isolated the product **1.252** that derives from the key ring-closing metathesis reaction of **1.240**.



1.240 **1.252**

We have also achieved multi-gram syntheses of both enantiomers of an advanced intermediate in the natural product synthesis, and this work is detailed at the end of Chapter one. The synthesis of both enantiomers of the target natural product will be crucial in confirming the absolute configuration of the target natural product, **1.5**.

Chapter two is focused on the field of synthetic organic electrochemistry, and the work that we have done using this synthetic tool. Although we were ultimately unsuccessful in our stated aim of replacing the manganese(III) based oxidant in the radical cyclisation of substrates containing a dicarbonyl functional group, several observations were made which we expect will guide future research in this area.

Declaration

The work described in the thesis is entirely the work of the author except where specifically indicated and does not include any collaborative work.

This thesis has not been previously submitted for a degree, diploma, or any other qualification at the University of Oxford or elsewhere.

Joseph Mason

September 2018

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Finally I would like to express my love and appreciation for my family: you have been a never-ending source of support and encouragement.

Abbreviations

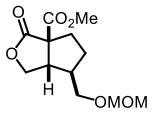
AAA	Asymmetric allylic alkylation	DMF	Dimethylformamide
Ac	Acetyl	DMP	Dess-Martin periodinane
Aq.	Aqueous	DMSO	Dimethylsulfoxide
Ar	Aryl	d.r.	Diastereomeric ratio
Bn	Benzyl	EDTA	Ethylenediaminetetraacetic acid
Bu	*n*-Butyl	e.e.	Enantiomeric excess
Bz	Benzoyl	ESI^+	Electrospray ionisation
b.p.	Boiling point	Et	Ethyl
Cat.	Catalyst	Eq.	Equivalents
Conc.	Concentrated	FI	Field ionisation
COSY	Correlation spectroscopy	Grubbs I	1st Generation Grubbs catalyst
Cp	Cyclopentyl	Grubbs II	2nd generation Grubbs catalyst
CSA	(±)-Camphor-10-sulfonic acid	h	Hour
Cy	Cyclohexyl	HG-II	Hoveyda-Grubbs 2nd generation
dba	dibenzylideneacetone		catalyst
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	HMBC	Heteronuclear Multiple Bond
DCC	*N,N'*-dicyclohexylcarbodiimide		Coherence
DCM	Dichloromethane	HMDS	Hexamethyldisilazane
DCE	Dichloroethane	HSQC	Heteronuclear single quantum
DIBAL-H	Diisobutylaluminium hydride		coherence
DMAP	4-(Dimethylamino)pyridine	HWE	Horner-Wadsworth-Emmons
DME	Dimethoxyethane	Hz	Hertz

i	Iso	NOESY	Nuclear Overhauser effect
IBX	2-iodoxybenzoic acid		spectroscopy
Im	Imidazole	OPP	pyrophosphate
IR	Infra-red	Ph	Phenyl
J	Coupling constant	PMB	Para-Methoxy benzyl
Lit.	Literature	ppm	Parts per million
LDA	Lithium diisopropyl amide	PPTS	Pyridinium *para*-toluenesulfonate
M	Molar	Pr	Propyl
mmol	millimoles	py	Pyridine
m-CPBA	Meta-Chloroperbenzoic acid	R	Generic group
Me	Methyl	R_f	Retention factor
m.p.	Melting point	rt	Room temperature
MOM	Methoxymethyl	RCM	Ring closing metathesis
MS	Molecular Sieves	RVC	Reticulated vitreous carbon
Ms	Methanesulfonyl	s	Second(s)
MTBE	Methyl *tert*-butyl ether	sal	N,N'-bis(salicylidene)ethylenediamine
m/z	Mass / charge ratio	Sat.	Saturated
Nap	2-Napthyl	SET	Single electron transfer
NHK	Nozaki-Hiyama-Kishi	SM	Starting material
Nic	Nicotinoyl	t	tert
NMO	N-Methylmorpholine N-oxide	TBAF	Tetrabutylammonium fluoride
NMR	Nuclear Magnetic Resonance	TBS	*tert*-Butyldimethylsilyl
nOe	Nuclear Overhauser effect	TBDPS	*tert*-Butyldiphenylsilyl

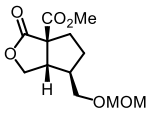
TES	Triethylsilyl	TMS	Trimethylsilyl
Tf	Trifluoromethanesulfonyl	Ts	*Para*-toluenesulfonyl
THF	tetrahydrofuran	TS	Transition state
TMEDA	Tetramethylethylenediamine	UV	Ultraviolet

Note on Convention

Throughout this text, wedged bonds are used to denote a specific enantiomer, while straight bonds are used to denote that the compound is racemic.[1]



Racemic



Enantioenriched

[1] Maehr, H. *Journal of Chemical Education* **1985**, 62, 114-120.

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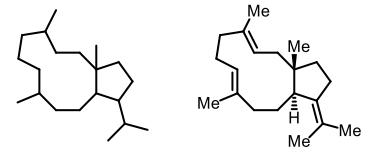
1 Towards the Total Synthesis of a Dolabellane Diterpenoid

1.1 Introduction

The following introduction serves to familiarise the reader with the history and relevant background on the Dolabellane family, and will also discuss previous attempts within the Burton Group to synthesise the target natural product.

1.1.1 Background

The dolabellane diterpenoid family has been the subject of a number of synthetic and biological studies since the discovery of the first, β-araneosene **1.2** (Figure 1.1, right), by Borschberg in 1975 from the mould *Sordaria araneosa*.[1] The structure of **1.2** was not published in mainstream literature however until much later,[2] by which time the skeleton **1.1** had been renamed "dolabellane" by Ireland, Faulkner, Finer and Clardy after minor constituents bearing the same structure were found in the sea hare *Dolabella californica*.[3]



1.1 dolabellane skeleton

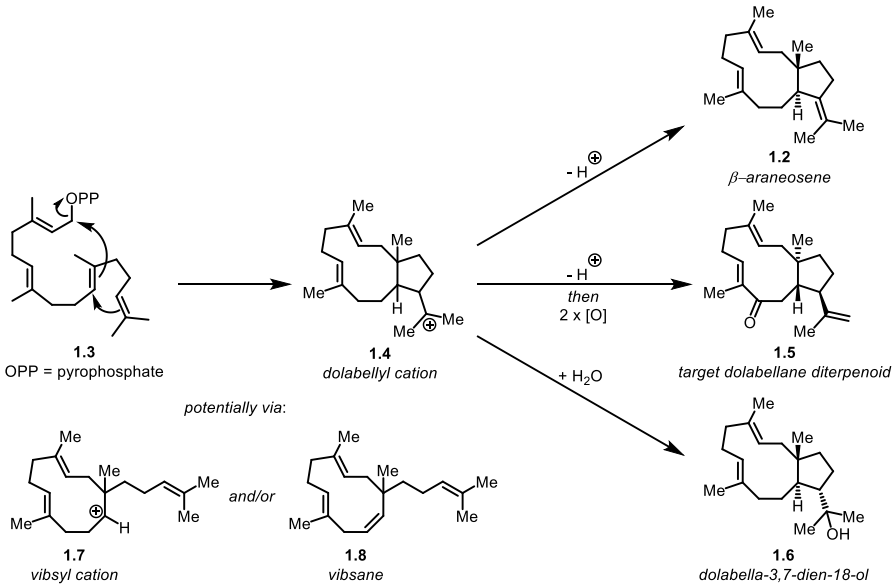
1.2 β-araneosene

Figure 1.1. The dolabellane skeleton **1.1** (left), and β-araneosene **1.2** (right).

Dolabellanes have been isolated from both marine and terrestrial organisms, and a number of reports have demonstrated a diverse range of pharmacologically important effects, such as cytotoxic, antibacterial and phytotoxic activity.[4] This, in combination with their interesting structural challenges, has attracted many synthetic chemists to this class of natural products over the years (see Section 1.1.3 onwards).

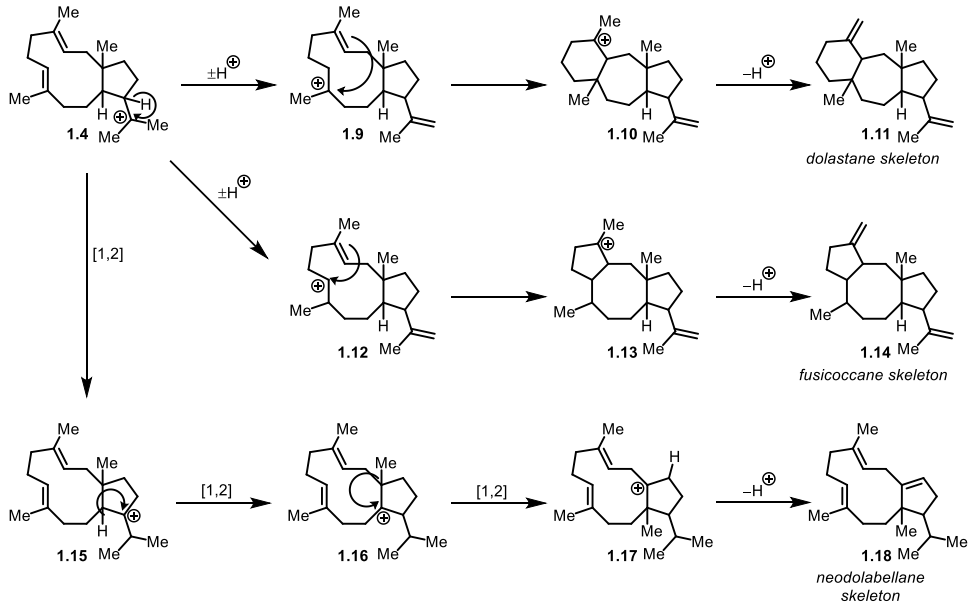
1.1.2 Biosynthetic Route

There is a high degree of structural diversity within this family, with alkene isomerisation and varying degrees of oxygenation accounting for most of the variation in structure. Each natural product is proposed to come from a common intermediate, geranylgeranyl pyrophosphate **1.3**.[4] A cascade cyclisation gives the dolabellyl cation **1.4**; from here rearrangements, proton transfers, or the addition of nucleophiles may occur to give a range of natural products, of which three are shown below (Scheme 1.1). Further complexity may be added by enzymatic oxidation of the alkenes present, or of the C-H bonds.[4,5] The precise orientation of the geranylgeranyl chain in the transition state of cyclisation is controlled enzymatically; thus the absolute configuration may vary from one natural product to the next as the active site in the enzyme changes from one organism to another. Although a detailed study of the cyclases that would be required for such a cascade has not yet been reported, natural products containing the vibsane skeleton **1.8** have been isolated along with dolabellanes from the liverwort *Odontoschisma denudantum*.[6–9] This circumstantial evidence indicates that the vibsane and dolabellane families may share a common chemical precursor.



Scheme 1.1. Proposed biosynthesis of the dolabellyl cation **1.4**, and subsequent reactions to give three natural products.[2,4,10,11]

It has been speculated that the dolabellyl cation **1.4** may also serve as the biosynthetic precursor for other natural product families, such as the dolastanes **1.11**, fusicoccanes **1.14**, and neodolabellanes **1.18** (Scheme 1.2).[4] Whilst this speculation is based only on structural analogy, it does come from sensible chemical transformations and thus may be borne out in reality. For example, the dolastane **1.11** and fusicoccane **1.14** skeletons could come from an acid catalysed transannular cyclisation of the dolabellane scaffold, while a series of [1,2]-hydride and methanide shifts could give the neodolabellane skeleton **1.18**.

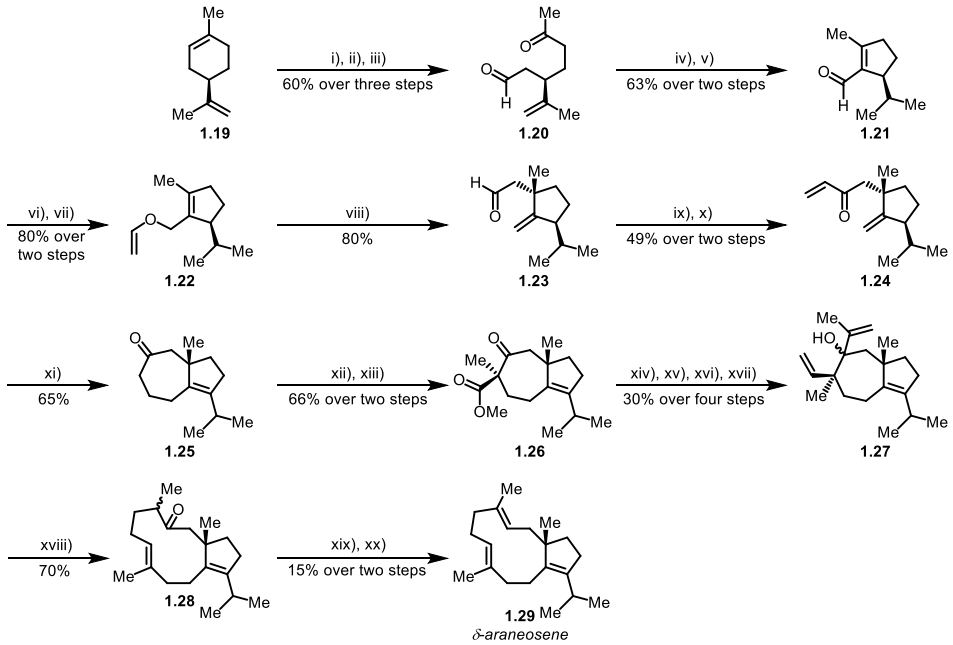


Scheme 1.2. Proposed biosynthetic sequences to give other natural product families.[4]

1.1.3 Previous Syntheses of the Dolabellane Family

The first enantioselective total synthesis of a member of the dolabellane diterpenoid was reported by Mehta, who synthesised (-)-δ-araneosene **1.29** (Scheme 1.3).[12] *R*-(+)-limonene **1.19** was used as the entry point into a natural product synthesis that was completed in 20 steps. The route began with an oxidative cleavage of the most electron rich alkene in **1.19** to give **1.20**. This was followed by hydrogenation of the remaining alkene and an acidic cyclisation to give the cyclopentene **1.21**. A Luche reduction then treatment with ethyl vinyl ether and mercury(II) acetate gave the vinyl ether **1.22**. This was used in the first key step, a facially selective Claisen rearrangement in which the vinyl ether approaches the least hindered face of the cyclopentene, to install the all carbon quaternary stereocentre. The resulting aldehyde **1.23** was elaborated with a Barbier coupling and oxidation to give enone **1.24**, whereupon treatment with a Brønsted acid catalyst yielded cycloheptanone **1.25**. A regioselective carbomethoxylation and methylation gave **1.26** as the major diastereomer

(although a separation of diastereomers was considered unnecessary). A four step sequence of reduction, selective oxidation, Wittig olefination and Grignard addition gave allylic alcohol **1.27**. An elegantly designed oxy-Cope rearrangement was performed to facilitate the ring expansion of **1.27** to give the required 11-membered ring. Finally, reduction of ketone **1.28** followed by elimination gave the desired natural product **1.29** in a poor yield. The author reported that transannularly cyclised products were also observed, but did not report the yield or exact identity of these products.



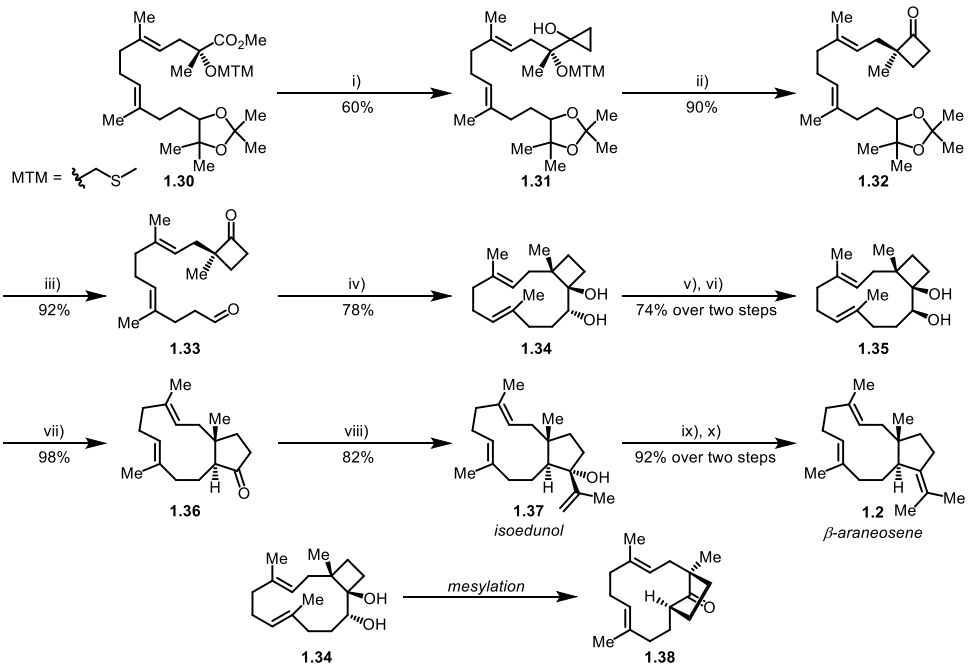
Scheme 1.3. Enantioselective total synthesis of δ-araneosene (**1.29**), reported by Mehta (1990).[12] *Reagents and conditions*: i) *m*-CPBA, $CHCl_3$, 0 °C, 10 h; ii) 1% H_2SO_4, THF, rt, 1 h; iii) $NaIO_4$, THF, H_2O, 25 °C; iv) H_2 (20 psi), PtO_2, EtOAc, 1 h; v) piperidine, AcOH, benzene, reflux, 1 h; vi) $NaBH_4$, $CeCl_3 \bullet 6H_2O$, MeOH, 0 °C, 30 min; vii) ethyl vinyl ether, $Hg(OAc)_2$, rt, 20 h; viii) sealed tube, 200 °C, 1 h; ix) vinyl bromide, Mg, THF, rt, 30 min; x) PCC, CH_2Cl_2, 4 Å molecular sieves, rt, 1 h; xi) $HClO_4$ (cat.), Ac_2O, EtOAc, rt, 25 min; xii) NaH, $(MeO)_2CO$, reflux, 6 h; xiii) K_2CO_3, MeI, acetone, reflux, 24 h; xiv) $LiAlH_4$, Et_2O, rt, 1 h; xv) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -60 °C; xvi) methyl triphenylphosphonium bromide, sodium *tert*-amyloxide, rt, 10 min; xvii) isopropenyl magnesium bromide, THF, reflux, 30 min; xviii) sealed tube, 170 °C, 1 h; xix) $LiAlH_4$, Et_2O, rt, 1 h; xx) MsCl, pyridine, CH_2Cl_2, 20 h.

Since this first total synthesis, a number of complete, formal, and partial total syntheses have been reported, which are summarised in the review by Hiersemann in 2005.[5] The remainder of this introduction will discuss syntheses published since 2005, and work within

the Burton group towards the total synthesis of our target natural product. For this discussion, particular emphasis has been placed on the key steps and the methods in which the 5 and 11-membered rings have been formed.

1.1.4 Enantioselective Total Syntheses by Corey and Co-Workers

Corey's syntheses of isoedunol (**1.37**) and β-araneosene (**1.2**) feature an unusual Sm(II) mediated pinacol coupling to install the 11-membered ring (Scheme 1.4).[13] The dicarbonyl precursor for this comes from the protected hydroxyl ester **1.30**, in which the quaternary stereocentre has been installed using the method published by Seebach.[14] A Kulinkovich reaction gave cyclopropanol **1.31**, which undergoes a ring expansion in the presence of trimethylaluminium to give **1.32**; deprotection of the acetonide **1.32** and periodate cleavage resulted in the formation of **1.33**. Following the pinacol coupling, an oxidation and reduction gives the *cis* diol **1.35**: mesylation of the 2° alcohol gives a leaving group capable of an *in situ* pinacol rearrangement. The authors reported that while the *trans* diol **1.34** could also undergo a pinacol rearrangement, it was the exocyclic sigma bond which migrated to give the bridged structure **1.38**. An X-ray crystal structure of *trans* diol **1.34** showed that the 12-membered ring enforced a conformation in which the exocyclic cyclobutane bond was antiperiplanar to the 2° alcohol, resulting in a stereoelecronic preference for the migration of the less substituted carbon atom. In contrast, the X-ray structure of the *cis* diol **1.35** situated the endocyclic cyclobutane bond antiperiplanar to the 2° alcohol: activation of this *cis* diol gave a near quantitative yield of the desired bicyclic product **1.36**. A further three steps gave isoedunol **1.37** and β-araneosene **1.2** in excellent yield.

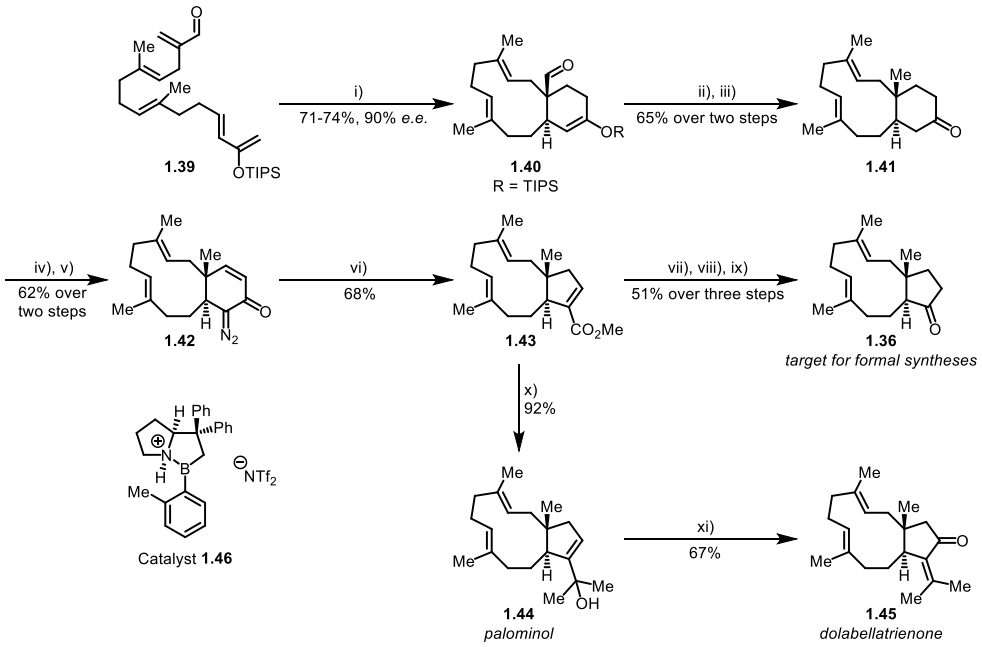


Scheme 1.4. Syntheses of isoedunol **1.37** and β-araneosene **1.2**, reported by Corey and co-workers (2005).[13] *Reagents and conditions*: i) $ClTi(O\textit{i}\text{-}Pr)_3$ (2.5 eq.), EtMgBr (5 eq.), THF, 0 °C – rt, 48 h; ii) $AlMe_3$ (1 eq.), CH_2Cl_2, -10 to 4 °C, 72 h; iii) 4:1 $AcOH/H_2O$, 55 °C, 3 h *then* $NaIO_4$ (3 eq.), 23 °C, 30 min; iv) SmI_2 (10 eq.), THF, 70 °C, 2.5 h; v) DMSO (3.4 eq.), $(COCl)_2$ (2.8 eq.), Et_3N (10.1 eq.), CH_2Cl_2, -78 to 4 °C, 24 h; vi) $LiAlH_4$ (10 eq.), THF, 70 °C, 5 min; vii) MsCl (1.1 eq.), Et_3N (4.2 eq.), CH_2Cl_2, -30 to 23 °C, 73 h; viii) 2-lithiopropene (3 eq.), Et_2O, -10 °C, 30 min; ix) chloromethyl methyl ether (6 eq.), $\textit{i}\text{-}Pr_2NEt$ (6 eq.), Bu_4NI (1 eq.), THF, 67 °C, 6 h; x) Li (160 eq.), 7:1 THF/NH_3, -78 to -60 °C, 3 h.

Further to this work, Corey and co-workers published a second paper reporting the formal syntheses of isoedunol **1.37** and syntheses of isoedunol **1.37** and β-araneosene **1.2**, as well as the enantioselective total syntheses of dolabellatrienone **1.45** syntheses of dolabellatrienone **1.45** and palominol **1.44** (

Scheme 1.5~~Scheme 1.5~~).[15] The first key step was an enantioselective Diels-Alder of enone **1.39**. This rapidly gave an advanced intermediate **1.40** with the 11-membered ring installed with the correct diastereomer of each alkene. Reduction of the aldehyde functional group of **1.40** was achieved by formation of the corresponding dithiane and treatment with deactivated Raney Ni. The TIPS protecting group was subsequently removed with TBAF to give the ketone **1.41**. Oxidation with IBX and diazo transfer gave **1.42**, which could be photoirradiated in MeOH to perform a Wolff rearrangement. In this manner a ring contraction was achieved to give ester **1.43** in good yield. From here ketone **1.36** could be

synthesised via a conjugate reduction using L-Selectride®, then α-oxygenation, reduction to give a diol and finally periodate cleavage completed the formal synthesis of isoedunol **1.37** and β-araneosene **1.2**.



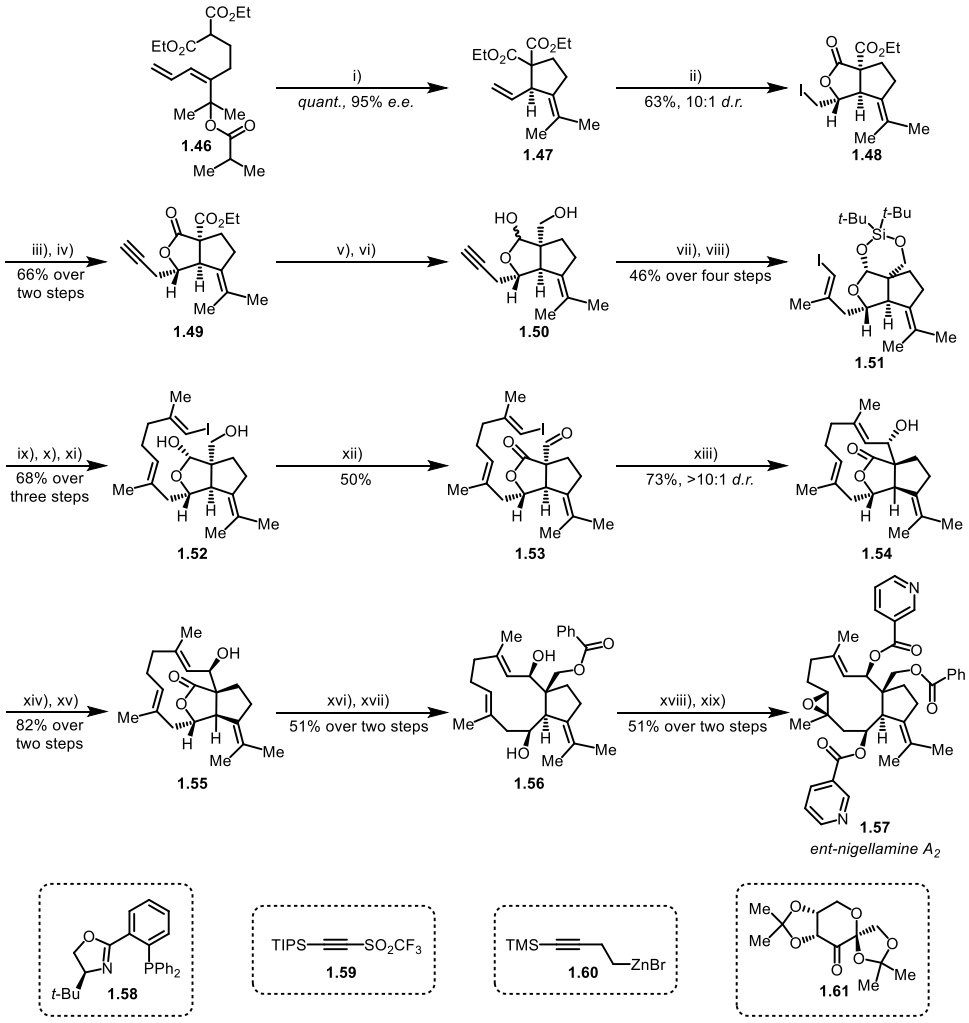
Scheme 1.5. Enantioselective total syntheses of palominol **1.44**, dolabellatrienone **1.45**, and formal syntheses of isoedunol **1.37** and β-araneosene **1.2**, reported by Corey and co-workers (2006).[15] *Reagents and conditions*: i) catalyst **1.46** (0.2 eq.), toluene, -93 to -78 °C, 13 h; ii) $(Me_2AlSCH_2)_2$ (3 eq.), 1,2-dichloroethane, 60 °C, 12 h *then* TBAF (1.5 eq.), THF, 25 °C, 5 min; iii) "hydrogen free" Raney® (excess), THF, 25 °C, 10 h; iv) NaHMDS (3 eq.), TMSCl (1.5 eq.), -78 to 0 °C, 1 h *then* IBX.MPO (1:1 IBX/4-methoxypyridine *N*-oxide hydrate, 3 eq.), 1:5 CH_2Cl_2/DMSO, 25 °C, 6 h; v) 2,4,6-triisopropylbenzenesulfonyl azide (12 eq.), benzyltriethylammonium chloride (0.5 eq.), 18-crown-6 (catalytic), 1:1 benzene/66% aqueous KOH, 40 – 45 °C, 48 h; vi) 450 W Hanovia UV lamp, 1:120 Et_3N/MeOH, 25 °C, 3 h *then* DBU, 115 °C, 18 h; vii) L-Selectride (4 eq.), THF, -30 to 0 °C, 1.5 h; viii) LDA (1 eq.), O_2 (balloon), PEt_3 (2 drops), THF, 0 °C, 40 min; ix) $LiAlH_4$ (3 eq.), THF, 25 °C, 10 min *then* $NaIO_4$ (excess), silica gel, CH_2Cl_2, 25 °C, 15 min; x) MeLi (6 eq.), THF, -20 °C, 1 h; xi) PDC (2 eq.), 4 Å molecular sieves, CH_2Cl_2, 25 °C, 5 h.

Palominol **1.44** was synthesised by the addition of an excess of MeLi to ester **1.43**; dolabellatrienone **1.45** was obtained by an oxidative rearrangement of **1.44** using pyridinium dichromate (PDC).

1.1.5 Enantioselective Total Syntheses of Nigellamine A_2 by Ready and Co-Workers

Ready and co-workers envisaged that the 5-membered ring core of the dolabellane natural product nigellamine A_2 could be synthesised via an intramolecular addition of a substituted

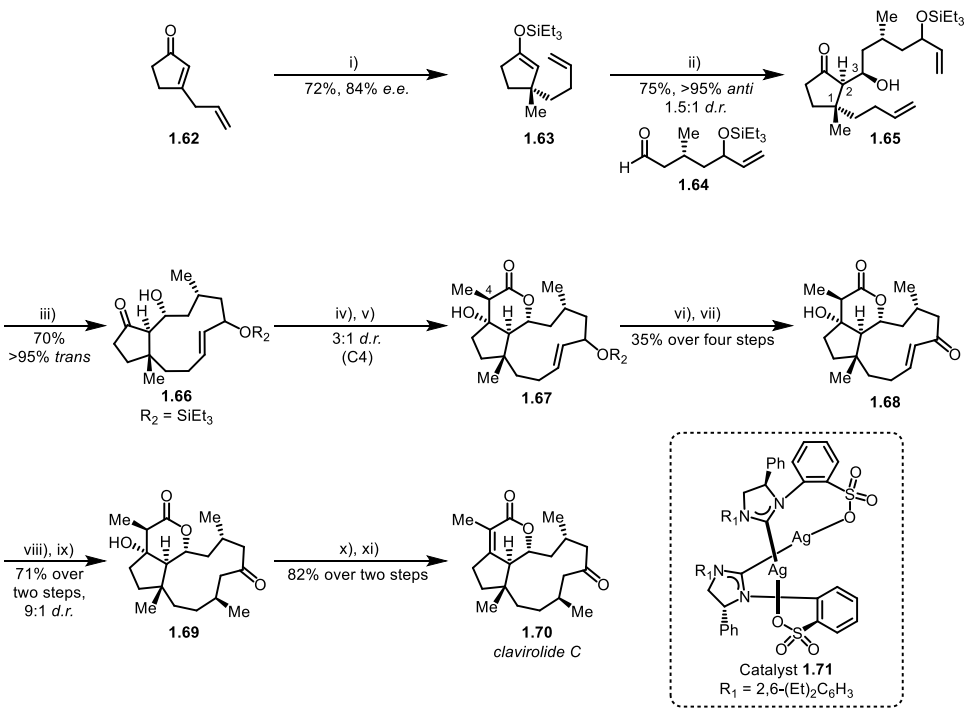
malonate onto a metal π-allyl intermediate (Scheme 1.6).[17] Treating malonate **1.46** with $Pd_2(dba)_3$ and ligand **1.58** gave a quantitative yield of **1.47** with excellent enantioselectivity. An iodolactonisation gave the bicyclic lactone **1.48** in good diastereoselectivity; Fuchs' radical alkynylation using triflate **1.59** followed by removal of the TIPS protecting group gave **1.49**. Reduction of the lactone and ester functional groups in **1.49** gave lactol **1.50**. A Negishi methyliodination using the Wipf modification installed the vinyl iodide moiety, and protection with $(t\text{-Bu})_2Si(OTf)_2$ gave **1.51**. The vinyl iodide **1.51** was subsequently used in a cross coupling with the alkyl zinc reagent **1.60**, whereupon deprotection and methyliodination gave **1.52**. An oxidation gave **1.53**, followed by a high yielding Nozaki-Hiyama-Kishi cyclisation that went with complete diastereoselectivity, albeit the incorrect one. An oxidation and reduction sequence reset the stereochemistry of the alcohol **1.54** to give **1.55**. From here a sequence of reduction, multiple acetylations, and a Shi epoxidation gave the *ent*-Nigellamine A_2 (**1.57**). The absolute configuration reported by the isolation chemists (Yoshikawa and co-workers)[16] was confirmed by synthesising the other enantiomer using the same methodology.



Scheme 1.6. Enantioselective total syntheses of nigellamine A_2 (**1.57**), reported by Ready and co-workers (2006).[17] *Reagents and conditions*: i) $Pd_2(dba)_3$ (1.25 mol%), ligand **1.58** (7.5 mol%), LiHMDS (1 eq.), DMSO, rt, 12 h; ii) I_2 (3 eq.), CH_2Cl_2, 0 °C, 12 h; iii) *hv* (300 nm) alkyne **1.59** (1.4 eq.), $(Bu_3Sn)_2$ (0.6 eq.), benzene, rt, 10 h; iv) TBAF (2 eq.), THF, 0 °C, 1 h; v) DIBAL-H (5.9 eq.), CH_2Cl_2, -78 to 5 °C, 1.5 h; vi) $NaBH_4$ (2.9 eq.), MeOH, 0 °C, 1 h; vii) Me_3Al (20 eq.), Cp_2ZrCl_2 (6.7 eq.), H_2O (6.7 eq.), I_2 (8.9 eq.), CH_2Cl_2, -20 to 0 °C, 50 h; viii) di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (1.5 eq.), 2,6-lutidine (3 eq.), -78 °C – rt; ix) alkylzinc bromide **1.60** (2.5 eq.), $PdCl_2(dppf)$ (4 mol%), DMF, dark, rt, 16 h; x) TBAF (2.5 eq.), THF, 0 °C, 2 h; xi) Me_3Al (15 eq.), Cp_2ZrCl_2 (5 eq.), H_2O (5 eq.), I_2 (10 eq.), CH_2Cl_2, -20 to 0 °C, 4 h; xii) PCC (4 eq.), 4 Å molecular sieves, celite, CH_2Cl_2, 0 °C – rt, 16 h; xiii) $CrCl_2$ (20 eq.), $Ni(acac)_2$ (0.8 eq.), DMSO, rt – 80 °C, 22 h; xiv) DMP (2 eq.), CH_2Cl_2, 0 – 4 °C, 2 h; xv) $LiAlH(i\text{-}Bu)_2t\text{-}Bu$ (4 eq.), THF, -78 °C, 30 min; xvi) $LiAlH_4$ (20 eq.), THF, 55 °C. 24 h; xvii) BzCl (1.5 eq.), DMAP (0.4 eq.), Et_3N (4.6 eq.), CH_2Cl_2, -20 °C, 1 h; xviii) ketone **1.61** (0.6 eq.), Oxone, $Na_2B_4O_7 \bullet 10H_2O$ (0.05 M solution in 4 x 10^{-4} M aqueous $Na_2(EDTA)$), K_2CO_3, acetonitrile-DMM, 0 °C; xix) nicotinic acid (6 eq.), DMAP (6 eq.), DCC (6 eq.), DMF, 60 °C, 36 h.

1.1.6 Enantioselective Total Synthesis of Clavirolide C by Hoveyda and Co-Workers

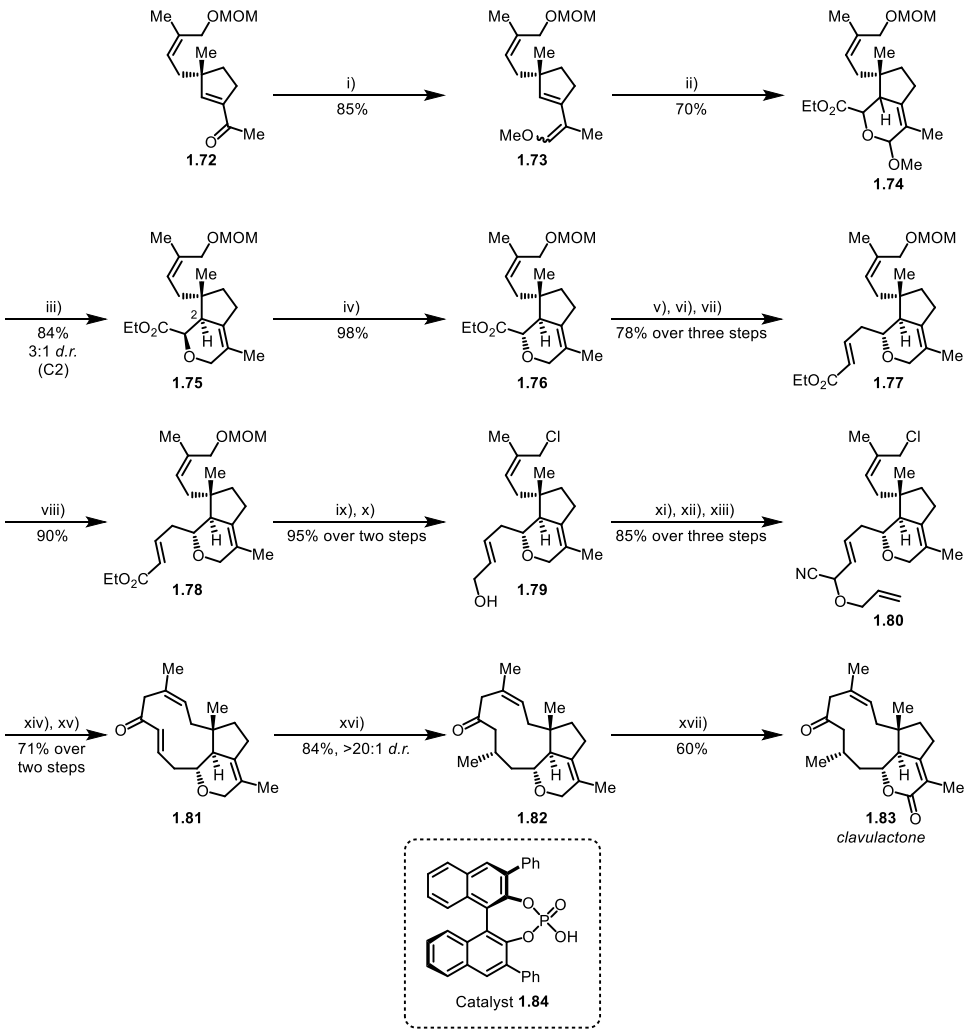
The synthesis of clavirolide C (**1.70**) published by Hoveyda and co-workers began with an asymmetric copper-catalysed conjugate addition of **1.62** to give the silyl enol ether **1.63** in 86% yield and >98% *e.e* (Scheme 1.7).[18] Aldehyde **1.64** was synthesised in seven steps, a sequence which also began with an asymmetric conjugate addition. Addition of *n*-BuLi to the silyl enol ether **1.63** generated the lithium enolate, which was treated with BEt_3 to give the corresponding boron enolate. Together with aldehyde **1.64,** this boron enolate gave the β-hydroxyketone **1.65** with >95% *anti*-aldol selectivity. Facial selectivity on the cyclopentene however was only 1.5:1, due to the poor steric differentiation between the methyl and butenyl groups. A macrocyclic ring closing metathesis with the Hoveyda-Grubbs 2nd generation catalyst gave a single diastereomer of alkene **1.66**. The alcohol functional group of **1.66** was esterified and subjected to a Reformatsky reaction to give the lactone **1.67**, as a mixture of diastereomers at the C4 position. This mixture of diastereomers was taken without purification as it was inconsequential to the total synthesis; a deprotection step and oxidation gave enone **1.68**. Conjugate addition of $Me_2CuLi{\bullet}LiCl$ in the presence of TMSCl installed the methyl group in 71% yield with 9:1 diastereoselectivity. Activation of the alcohol **1.69** and elimination of the newly formed mesylate gave the desired natural product, clavirolide C (**1.70**).



Scheme 1.7. Enantioselective total synthesis of clavirolide C (**1.70**), reported by Hoveyda and co-workers (2008).[18] *Reagents and conditions:* i) Catalyst **1.71** (3.75 mol%), $Cu(OTf)_2$ (7.5 mol%), Me_3Al (3 eq.), THF, -78 °C, 36 h *then* Et_3SiOTf (4 eq.), -78 °C, 4 h; ii) *n*-BuLi (1 eq.), aldehyde **1.64** (1.6 eq.), BEt_3 (3 eq.), THF, -78 °C, 1.5 h; iii) Hoveyda-Grubbs catalyst (5 mol%), DCE, reflux, 6 h; iv) 2-bromopropionyl bromide (6 eq.), DMAP (0.4 eq.), pyridine (12 eq.), CH_2Cl_2, -78 to 22 °C, 1 h; v) SmI_2 (2.2 eq.), THF, 0 °C; vi) (+)-CSA (sub-stoichiometric quantity), MeOH, 0 °C, 15 min; vii) MnO_2 (excess), Et_2O, rt, 1 h; viii) MeLi (8 eq.), CuI (4 eq.), TMSCl (4 eq.), THF, -78 °C, 15 min; ix) HF·pyridine (excess), THF, 0 °C, 5 min; x) MsCl (10.2 eq.), Et_3N (10.2 eq.), CH_2Cl_2, 0 °C, 30 min; xi) DBU (5.1 eq.), MeOH, 55 °C, 2 h.

1.1.7 Enantioselective Total Synthesis of Clavulactone by Yao and Co-Workers

Yao and co-workers targeted clavulactone (**1.83**) for their synthetic efforts, a natural product that had been isolated from samples of the Pacific soft coral Clavularia viridis (Scheme 1.8).[19] Their first key step: a hetero-Diels-Alder between diene **1.73** (synthesised from **1.72**) and ethyl glyoxylate. The mixture of products (**1.74**) obtained was immediately reduced with triethylsilane to give the 2,5-dihydropyran **1.75** as a 3:1 mixture of diastereomers. Reconfiguration of the α-centre to the ester functionality of **1.75** was achieved with NaHMDS.

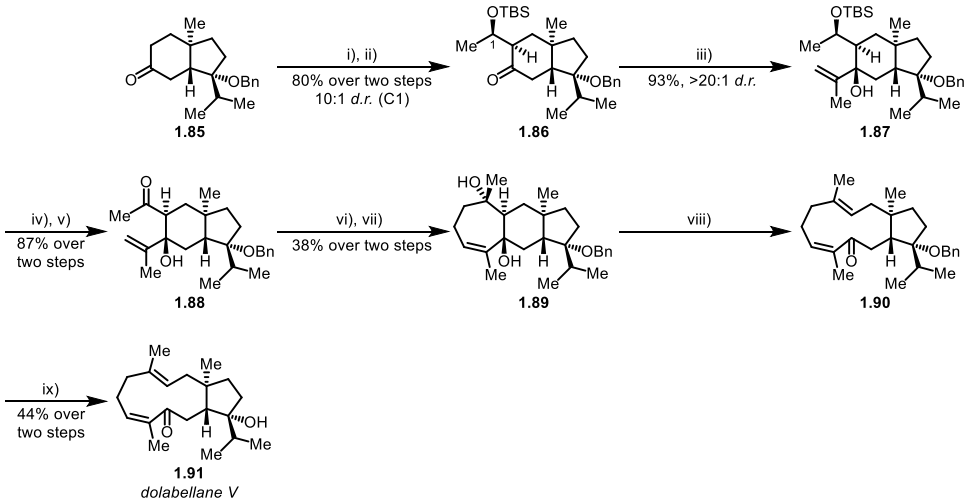


Scheme 1.8 Enantioselective total synthesis of clavulactone (**1.83**), reported by Yao and co-workers (2012).[19] *Reagents and conditions*: i) methoxymethyltriphenylphosphonium chloride (1.5 eq.), *t*-BuOK (1.5 eq.), THF, -20 °C, 1 h; ii) Catalyst **1.84** (0.1 eq.), ethyl glyoxalate (4 eq.), 4 Å MS, toluene, rt, 24 h; iii) Et_3SiH (5 eq.), BF_3•Et_2O (1 eq.), CH_2Cl_2, -78 °C, 20 min; iv) NaHMDS (2 eq.), THF, -78 to 0 °C, 30 min; v) DIBAL-H (1 eq.), CH_2Cl_2, -78 °C, 30 min; vi) methoxymethyltriphenylphosphonium chloride (2 eq.), NaHMDS (2 eq.), THF, -78 to 0 °C, 1 h *then* *p*-toluenesulfonic acid (0.2 eq.), 10:1 acetone/H_2O, rt, 1 h; vii) $(EtO)_2P(O)CH_2CO_2Et$ (2 eq.), NaHMDS (2 eq.), THF, -78 to 0 °C, 1 h; viii) 1:1 6 M $HCl_{(aq)}$/THF, 0 °C, 5 h; ix) MsCl (2 eq.), Et_3N (3 eq.), LiCl (3 eq.), 2.5:1 DMF/CH_2Cl_2, 0 °C – rt, 1 h; x) DIBAL-H (2.5 eq.), CH_2Cl_2, 0 °C, 30 min; xi) DMP (1.9 eq.), $NaHCO_3$ (6.1 eq.), CH_2Cl_2, rt, 2 h; xii) KCN (substoichiometric quantity), 18-crown-6 (catalytic quantity), TMSCN (3.2 eq.), CH_2Cl_2, rt, 5 h; xiii) PPTS (0.2 eq.), vinyl ethyl ether (10 eq.), CH_2Cl_2, rt, 8 h; xiv) NaHMDS (10 eq.), THF, 40 °C, 5 h; xv) PPTS (0.1 eq.), 5:1 MeOH/H_2O, rt, 2 h *then* 2% $NaOH_{(aq.)}$, Et_2O, 0 °C, 2 h; xvi) MeLi (3 eq.), CuCN (1.5 eq.), THF, 0 – 15 °C, 35 min; xvii) PCC (10 eq.), 4 Å MS, benzene, 80 °C, 30 min.

From **1.76** a six step sequence gave alcohol **1.79**, from which the protected cyanohydrin **1.80** could be synthesised. This was treated with NaHMDS under very dilute conditions to effect a cyclisation reaction, and the ketone functionality was revealed to give enone **1.81** in high yield. Conjugate addition of $Me_2CuLi•LiCN$ to the enone **1.81** gave **1.82** in >20:1 *d.r.*, which was oxidised to give clavulactone (**1.83**) in a 1.9% overall yield.

1.1.8 Enantioselective Total Synthesis of (+)-Dolabellane V by Magauer and Co-Workers

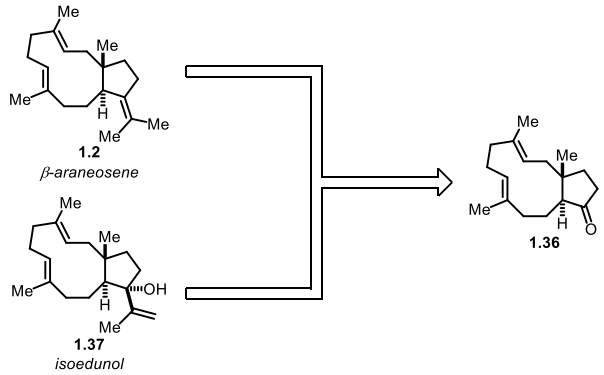
Most recently, a synthetic undertaking was reported in 2016 by Magauer and co-workers for the enantioselective total synthesis of (+)-dolabellane V (**1.91**).[20] Admirably, a full report detailing the unsuccessful routes was published, but the successful route began with ketone **1.85** (Scheme 1.9), which had been synthesised in eight steps via a procedure first reported by Grainger and co-workers.[21] An aldol reaction of the lithium enolate of **1.85**, followed by protection, gave **1.86** in an excellent yield. Installation of the isopropenyl group gave **1.87**, which was followed by deprotection and oxidation to give ketone **1.88**. Addition of a butenyl group gave the precursor for a ring closing metathesis, which was carried out using the Stewart-Grubbs catalyst at high dilution with 20 mol% of 2,6-dichloro-1,4-benzoquinone to give **1.89**. Activation of the 3° alcohol of **1.89** with triflic anhydride led to the desired Grob fragmentation, the product (**1.90**) of which was deprotected to give the desired natural product **1.91**.



Scheme 1.9. Enantioselective total synthesis of (+)-Dolabellane V (**1.92**), reported by Magauer and co-workers (2016).[20] *Reagents and conditions*: i) LDA (1.1 eq.), acetaldehyde (1.2 eq.), THF, -78 °C, 1.25 h; ii) *tert*-butyldimethylchlorosilane (1.4 eq.), imidazole (3.2 eq.), DMAP (0.1 eq.), DMF, 0 – 23 °C, 13 h; iii) $LaCl_3$•2LiCl (1 eq.), isopropenylmagnesium bromide (3 eq.), THF, 0 °C, 30 min; iv) TBAF (1.5 eq.), THF, 0 – 23 °C, 2 h; v) TPAP (0.07 eq.), NMO (1.5 eq.), 4 Å MS, CH_2Cl_2, 23 °C, 45 min; vi) $LaCl_3$·2LiCl (1 eq.), 3-butenylmagnesium bromide (3 eq.), THF, 0 °C, 30 min; vii) Stewert-Grubbs catalyst (0.2 eq.), 2,6-dichloro-1-4-benzoquinone (0.2 eq.), toluene, 111 °C, 40 h; viii) Tf_2O (5 eq.), 2,6-lutidine (20 eq.), CH_2Cl_2, -78 °C, 1.5 h; ix) DDQ (5 eq.), 10:1 DCE/pH 7 aqueous buffer solution, 40 °C, 1 h.

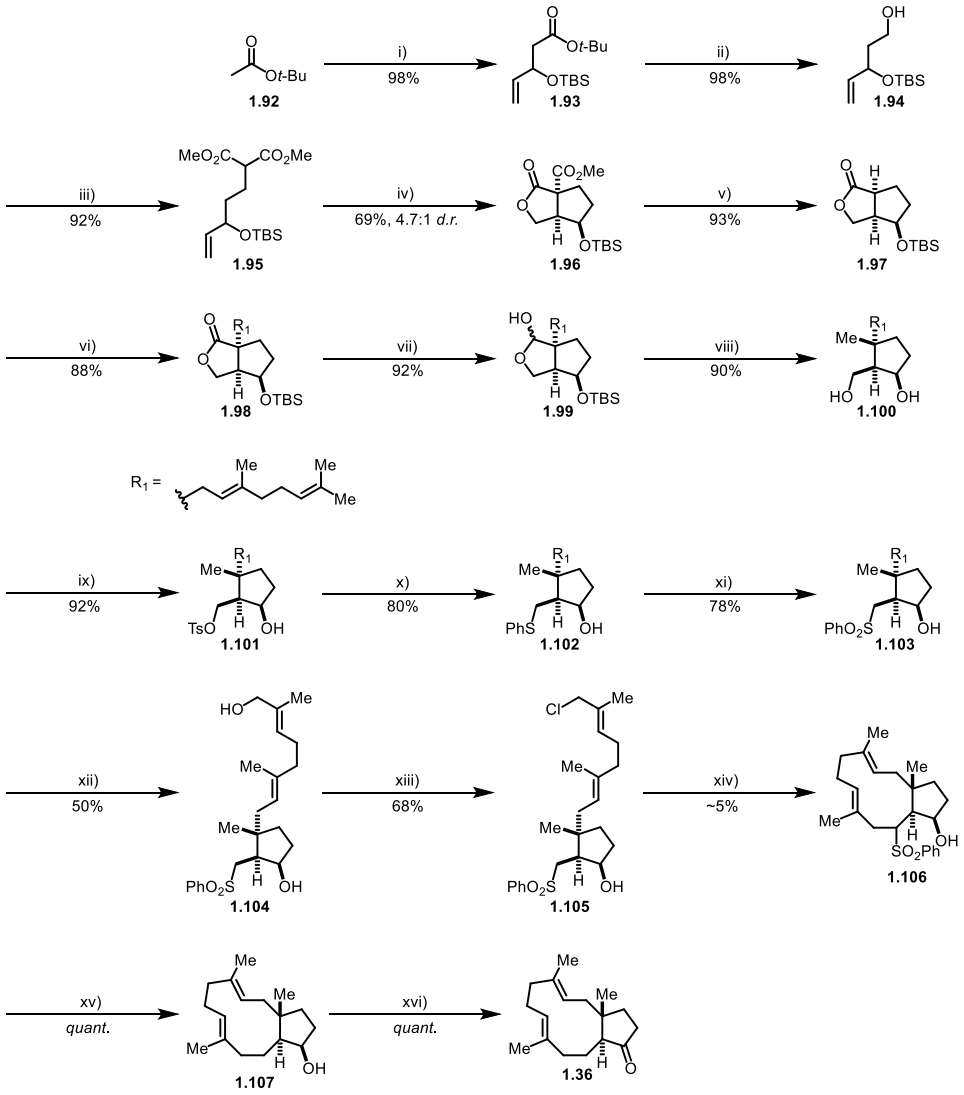
1.1.9 Formal Syntheses of β-Araneosene and Isoedunol by the Burton Group

In 2011 Hallside reported the formal synthesis of β-araneosene (**1.2**) and isoedunol (**1.37**),[22] via the synthesis of ketone **1.36** (Scheme 1.10), a strategy previously reported by Corey and co-workers.[13]



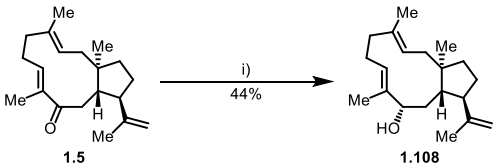
Scheme 1.10. The strategy for the formal synthesis of β-araneosene (**1.2**) and isoedunol (**1.37**) from ketone **1.36**.[13]

The forward synthesis by Hallside (Scheme 1.11) began with an aldol reaction of **1.92** and subsequent alcohol protection to give **1.93.** A reduction with DIBAL-H, activation then displacement with sodium dimethyl malonate followed to give malonate **1.95**. The oxidative cyclisation using manganese(III) acetate and copper(II) triflate gave the desired bicyclic lactone **1.96** in good yield and moderate diastereoselectivity. A Krapcho decarboxylation and subsequent alkylation of **1.97** using geranyl bromide gave lactone **1.98** in excellent yield. A two-step reduction protocol followed, involving a DIBAL-H reduction to give lactol **1.99** then a Wolff-Kishner reaction to give the deprotected diol **1.100** in excellent yield. Installation of the sulfone moiety over three steps worked well, and Hallside was able to achieve a 50% yield of **1.104** after two cycles of the Sharpless allylic oxidation. Unfortunately the key cyclisation to form the 11-membered ring was poorly yielding; the bromide and tosylate analogues to chloride **1.105** gave only a trace of the desired product **1.106**, and protecting the alcohol moiety with a *tert*-butyldimethylsilyl group did not improve the yield of **1.106** either. The formal synthesis was completed however, by reduction of sulfone **1.106** and oxidation of the alcohol functionality, to give **1.36**.



Scheme 1.11. Formal synthesis of β-araneosene (**1.2**) and isoedunol (**1.37**), reported by Hallside (2011).[22] *Reagents and conditions*: i) LDA (1.2 eq.), acrolein (1.2 eq.), THF, -78 °C, 1 h *then tert*-butyldimethylchlorosilane (1.2 eq.), imidazole (2.5 eq.), CH_2Cl_2, 0 °C – rt, 5 h; ii) DIBAL-H (2 eq.), THF, -35 °C, 1.5 h; iii) MsCl (1.1 eq.), Et_3N (1.2 eq.), CH_2Cl_2, 0 °C – rt, 3 h *then* NaH (2.9 eq.), dimethyl malonate (2.9 eq.), KI (0.3 eq.), 1:3 DMF/THF, 0 – 80 °C, 16 h; iv) $Mn(OAc)_3 \bullet 2H_2O$ (2.1 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 80 °C, 3.5 h; v) LiCl (3.5 eq.), 1:50 H_2O/DMSO, 160 °C, 2.5 h; vi) LiHMDS (2 eq.), geranyl bromide (2 eq.), THF, -60 °C – rt, 7 h; vii) DIBAL-H (1.2 eq.), CH_2Cl_2, -70 to -60 °C, 30 mins; viii) KOH (8 eq.), $N_2H_4 \bullet H_2O$ (10 eq.), diethylene glycol, 170 °C, 3 h; ix) TsCl (3 eq.), DMAP (0.5 eq.), pyridine, 60 °C, 2.5 h; x) PhSH (1.3 eq.), PhSNa (1 spatula) KO*t*-Bu (1.1 eq.), DMSO, rt – 30 °C, 20 h; xi) ammonium molybdate (0.4 eq.), H_2O_2 (20 eq.), EtOH, 0 – 5 °C, 3 h; xii) SeO_2 (7 mol%), salicylic acid (11 mol%), *t*-BuOOH (2.8 eq.), CH_2Cl_2, rt, 3 h, 2 cycles; xiii) MsCl (2 eq.), LiCl (3.1 eq.), 2,6-lutidine (3.1 eq.), DMF, 0 °C, 3 h; xiv) LiHMDS (2.7 eq.), THF, 80 °C, 27 h; xv) Mg, MeOH, 50 °C, 3 h; xvi) DMP (3500 eq.), CH_2Cl_2, rt, 16 h.

1.1.10 Our Target Structure



1.5
isolated natural product

1.108

Scheme 1.12. The target natural product (**1.5**), a dolabellane diterpenoid (left), and the product **1.108** of the Luche reduction on which Mosher ester analysis was performed, reported by Palermo and co-workers.[10] *Reagents and conditions*: i) $NaBH_4$ (2.7 eq.), $CeCl_3$ (1 eq.), MeOH, 0 °C, 1 h.

The target natural product, dolabellane **1.5** (Scheme 1.12), was isolated by Palermo and co-workers from the gorgonian *Convexella magelhaenica* in 2010.[10] The structure was determined by NMR analysis, including ^{1}H, ^{13}C, COSY, HSQC, HMBC and ROESY. The absolute configuration was determined using **1.108**, which was synthesised by carrying out a Luche reduction on **1.5** to give a single diastereoisomer of the alcohol **1.108**. This alcohol was then analysed using the modified Mosher's method, and Δδ values were consistent with the structure shown above (Scheme 1.12). Rationale for the highly stereoselective nature of the transformation, where neither face of the ketone is obviously blocked to nucleophillic attack, and a chelated transition state does not seem possible, was not provided by the authors. As such, the absolute configuration of the target natural product is a question that has not yet been satisfactorily answered. The effect of this compound was assayed on two different cell lines, with IC_{50} values obtained for each assay: 2.5 μM against PANC1 (human ductal pancreatic carcinoma) and 39.8 μM against LM3 (murine lung adenocarcinoma cells).

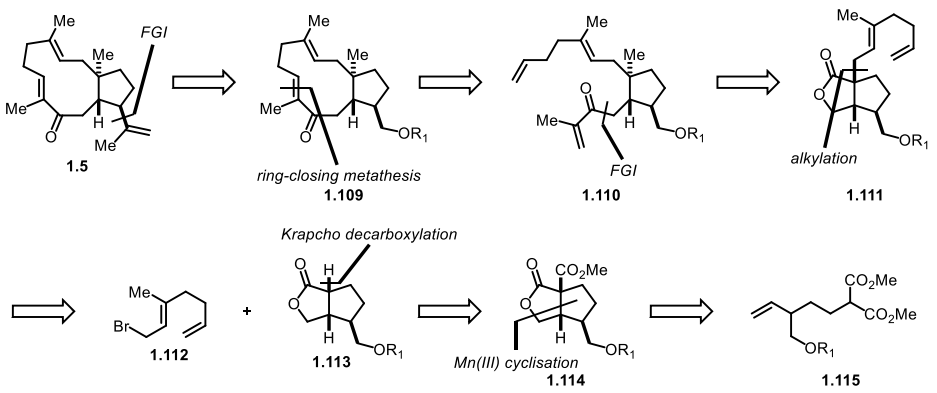
In light of this report, synthetic efforts in the Burton group commenced, for the purpose of confirming the absolute structure of this natural product and for the determination of any future medicinal benefit.

1.2 Previous Synthetic Studies in the Burton Group

The target natural product **1.5** has been an ongoing challenge within the Burton group over the past 7 years. Each new student researcher came with a fresh perspective and an alternative idea on how to solve the problem. The following will discuss the positive and negative aspects of each route, with a view to circumvent the critical failures that each predecessor encountered. Each researcher used a key Mn(III) mediated oxidative cyclisation to build the cyclopentane core, a research area that has been summarised in Chapter 2 (see section 2.1.2).

1.2.1 Synthetic Efforts by James Lua

Work on the target natural product began in the Burton group in 2012 with Part II undergraduate chemist James Lua,[23] who selected the following retrosynthesis (Scheme 1.13).

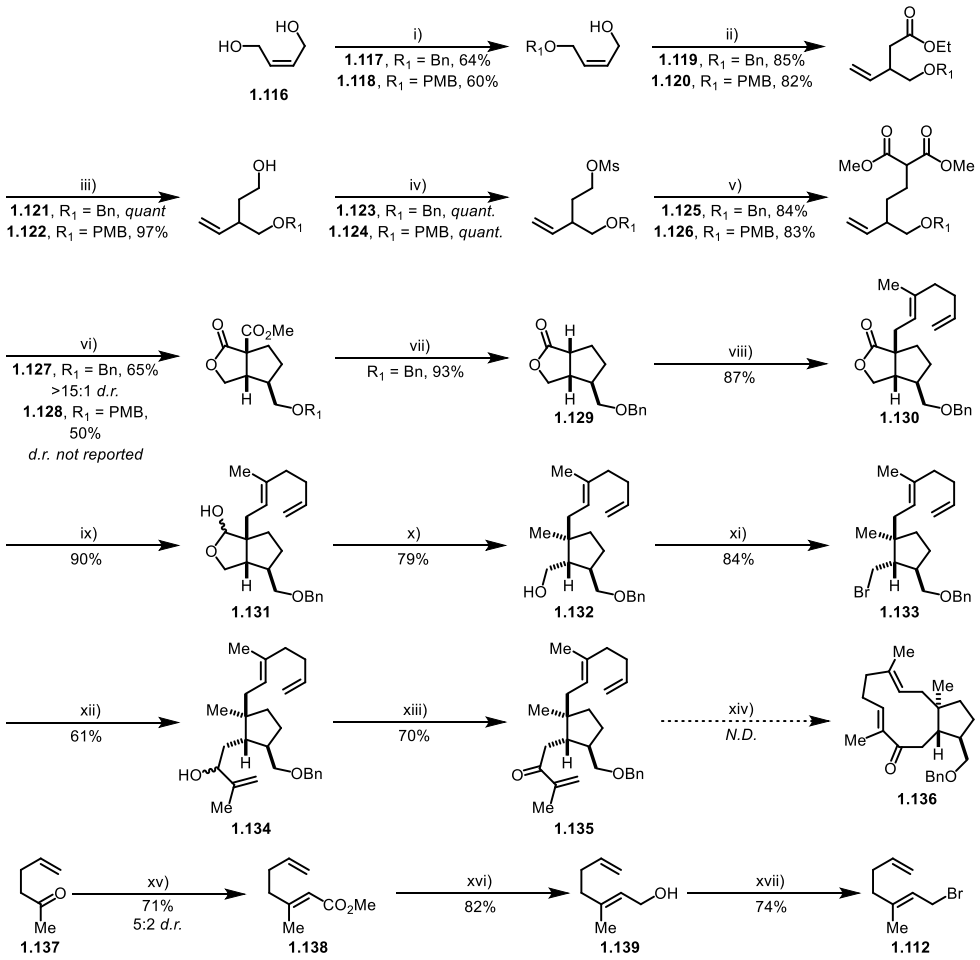


Scheme 1.13. The retrosynthetic disconnection developed by Lua.[23]

Two alcohol protecting groups, Bn and PMB, were used with a view to studying their tolerance to the oxidative cyclisation, as well as their suitability for this particular synthesis. Starting from commercially available diol **1.116**, mono protection gave **1.117** and **1.118** in acceptable yield (Scheme 1.14). A Johnson-Claisen rearrangement gave **1.119**/**1.120**, which

was followed by a $LiAlH_4$ reduction. Mesylation and substitution yielded the malonates **1.125** and **1.126**. For the key diastereoselective oxidative cyclisation, it was discouraging to see that a poorer-than-average yield had been reported (*c.f.* Chapter 2, section 2.1.4). Lua speculated that oxidation of the benzylic positions of **1.125** and **1.126** had occurred, with subsequent loss of the protecting group, based upon a visual analysis of the crude ^{1}H NMR spectrum. Whilst the benzyl protected substrate **1.125** only gave a modest improvement over the PMB one (**1.126**), it was sufficient to continue with the synthesis. However, future synthetic campaigns would ideally use an alternative protecting group, one more stable to oxidation. A Krapcho decarboxylation followed by alkylation gave **1.130** in high yield. However the route to access the required bromide **1.112** was, whilst simple on paper, more challenging in reality. The poor diastereoselectivity of a Horner-Wadsworth-Emmons reaction on ketone **1.137,** coupled with similar R_f values for the (*E*) and (*Z*) isomers of **1.138** resulted in a moderate yield of isolated product. This was therefore an area that we highlighted for further investigation when we came to our own synthetic attempt. The DIBAL-H reduction and deoxybromination reactions to give **1.139** and **1.112** respectively were high yielding however.

Continuing with Lua's synthesis (Scheme 1.14), a DIBAL-H and subsequent Wolff-Kishner reduction led to **1.132**, which could be deoxybrominated to give **1.133**. Lithium-halogen exchange followed by treatment with two equivalents of methacrolein gave the macrocyclic precursor **1.135**. Whilst Lua was able to attempt the ring closing metathesis, he did not have sufficient time to complete its purification and characterisation. A ^{1}H NMR spectrum of the crude material and LRMS gave preliminary evidence for the formation of macrocycle **1.136**, but further evidence would be required to be confident of the analysis.

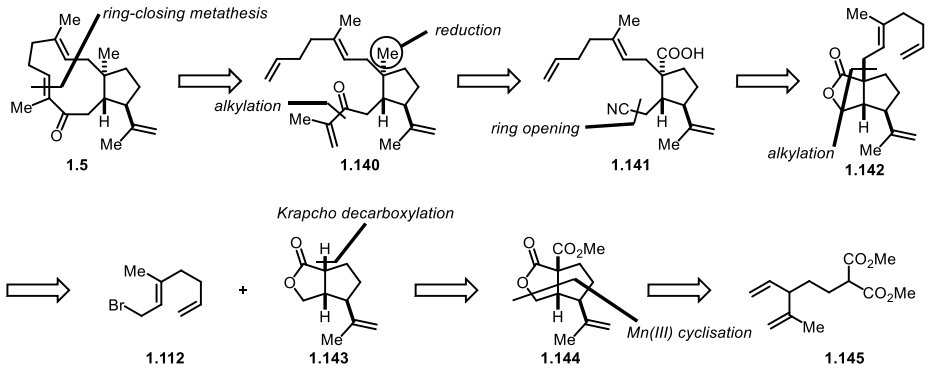


Scheme 1.14. Attempted synthesis of the target natural product **1.5**, reported by Lua.[23] *Reagents and conditions*: Condition set a: R_1 = Bn, Condition set b: R_1 = PMB; i) a) NaH (1 eq.), benzyl bromide (1 eq.), Bu_4NI (0.5 eq.), DMF, rt, 1.5 h; b) NaH (1 eq.), 4-methoxybenzyl chloride (1 eq.), DMF, rt, 1.5 h; ii) a) triethyl orthoacetate (5 eq.), propionic acid (5 mol%), *p*-xylene, 180 °C, 4 h; b) triethyl orthoacetate (5 eq.), propionic acid (5 mol%), *p*-xylene, 180 °C, 4 h; iii) a) and b) $LiAlH_4$ (1 eq.), Et_2O, 0 °C – rt, 1 h; iv) a) and b) MsCl (1.2 eq.), Et_3N (1.5 eq.), CH_2Cl_2, 0 °C – rt, 1.5 h; v) a) and b) NaH (3 eq.), dimethylmalonate (3 eq.), KI (0.5 eq.), 1:1 DMF/THF, 0 – 80 °C, 21 h; vi) a) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 80 °C, 2.5 h; b) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 60 °C, 2.5 h; vii) LiCl (2 eq.), H_2O (2 eq.), DMF, 150 °C, 2 h; viii) LiHMDS (2 eq.), bromide **1.112** (2 eq.), THF, -60 to -20 °C, 2.25 h; ix) DIBAL-H (1.2 eq.), CH_2Cl_2, -60 °C, 3 h; x) KOH (8 eq.), $N_2H_4.H_2O$ (10 eq.), diethylene glycol, 160 to 180 °C, 8 h; xi) MsCl (3 eq.), Et_3N (4.5 eq.), THF, 0 °C, 2 h, *then* LiBr (7 eq.), 0 °C, 1 h; xii) *t*-BuLi (2.2 eq.), methacrolein (2 eq.), THF, -78 °C, 2.5 h; xiii) IBX (3 eq.), DMSO, dark, rt, 5 h; xiv) Grubbs catalyst (2nd gen., 1 eq.), toluene, 100 °C, 0.5 h; xv) NaH (1.5 eq.), trimethylphosphonoacetate (1.5 eq.), THF, 0 – 70 °C, 16 h; xvi) DIBAL-H (2.2 eq.), hexane, -35 to 0 °C, 3 h; xvii) MsCl (1.4 eq.), Et_3N (2.1 eq.), THF, 0 °C, 2 h *then* LiBr (5.1 eq.), THF, 0 °C, 1 h.

1.2.2 Synthetic Efforts by Steven Ferrara

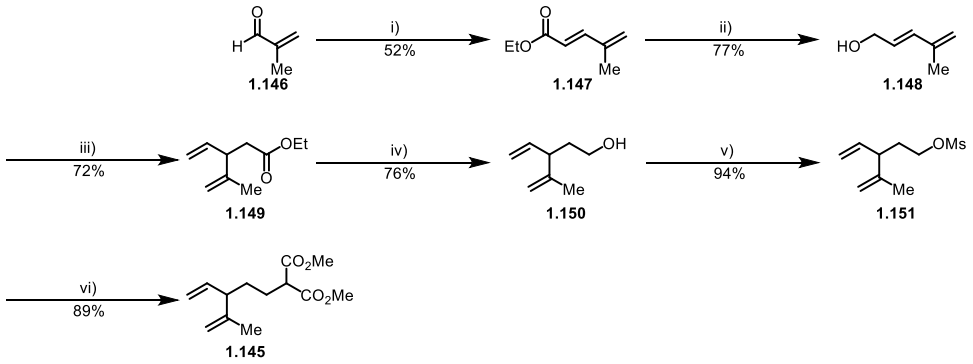
D.Phil. student Steven Ferrara opted for an alternative retrosynthetic strategy (Scheme 1.15), one in which the 1,1-disubstituted alkene was in place from the very beginning of the

synthesis.[24] Ferrara also proposed that the α,β-unsaturated ketone **1.140** required for the ring closing metathesis could come from the alkylation of the nitrile **1.141**, which in turn would come from opening the lactone **1.142** with a cyanide anion.



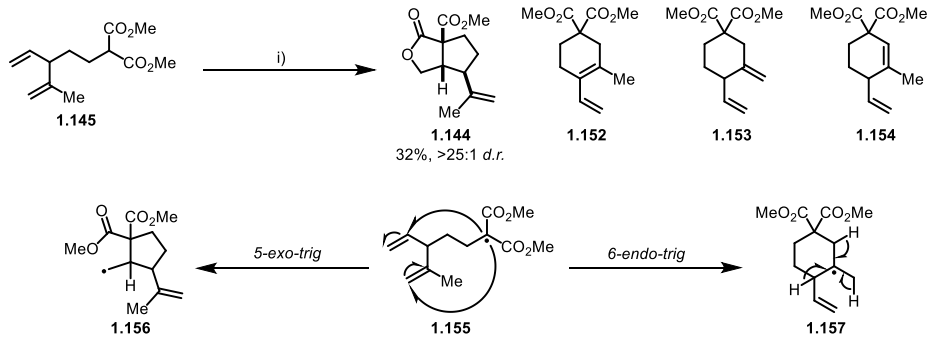
Scheme 1.15. The retrosynthetic disconnection developed by Ferrara.[24]

Ferrara's synthesis began with a Wittig reaction on aldehyde **1.146**, followed by reduction, Johnson-Claisen rearrangement and a second reduction to give alcohol **1.148** in good yield (Scheme 1.16). Mesylation and displacement of this leaving group with sodium dimethylmalonate (prepared *in situ*) provided the desired malonate **1.145** in excellent yield.



Scheme 1.16. *Reagents and conditions*: i) (carbethoxymethylene)triphenylphosphorane (1 eq.), CH_2Cl_2, 60 °C, 2 h; ii) $LiAlH_4$ (1 eq.), Et_2O, 0 °C, 30 min; iii) triethyl orthoacetate (7 eq.), propionic acid (0.06 eq.), 138 °C, 4 h, *under distillation conditions*; iv) $LiAlH_4$ (1 eq.), Et_2O, 0 °C, 30 min; v) Et_3N (1.5 eq.), MsCl (1.2 eq.), 0 °C – rt, 1.5 h; vi) NaH (3 eq.), dimethyl malonate (3 eq.), KI (0.5 eq.), 1:1 THF/DMF, 0 – 80 °C, 2 h.

Unfortunately the oxidative cyclisation suffered from a lack of selectivity with products from both a *5-exo-trig* radical cyclisation onto the terminal alkene and *6-endo-trig* cyclisation onto the 1,1-disubstituted alkene observed (Scheme 1.17). The three cyclohexene products (**1.152**, **1.153**, and **1.154**) all come from the same *6-endo-trig* cyclisation, with subsequent oxidation and proton loss giving rise to each product. Unfortunately a complicated purification meant that a yield could only be obtained for the desired bicyclic lactone **1.144**, but after having screened a variety of temperatures and concentrations it was clear that this method would be unsuitable for the total synthesis.

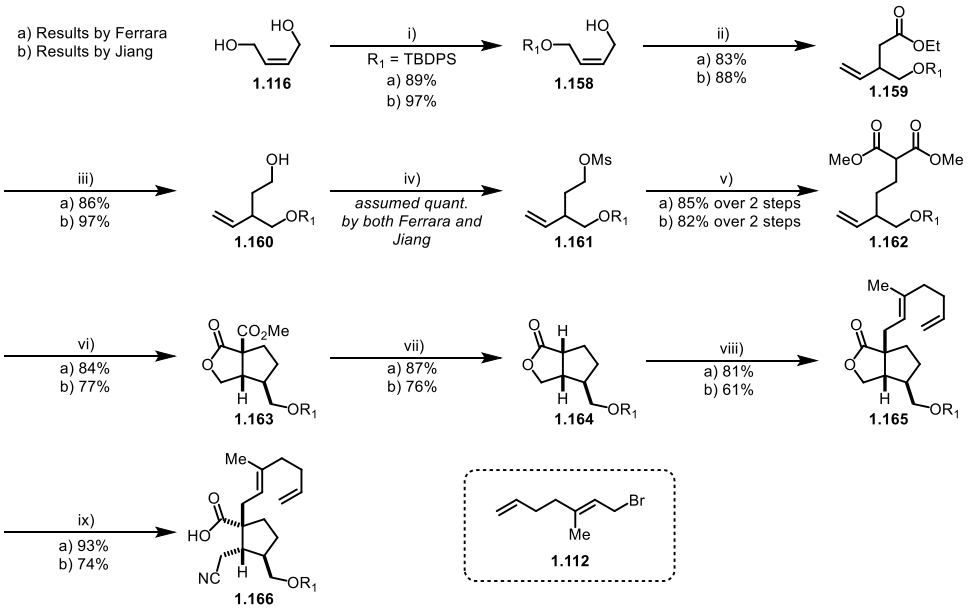


Scheme 1.17. *Reagents and conditions*: i) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 80 °C, 4 h.

1.2.3 Use of TBDPS Protecting Group by Ferrara and Jiang

In light of this unfavorable result, Ferrara switched to a TBDPS-protected alcohol in place of the 1,1-disubstituted alkene, which would not suffer the same selectivity issue in the oxidative cyclisation. The alcohol, once deprotected, could serve as a handle for the introduction of the alkene moiety at a later stage. This disconnection was also later used by Lingfan Jiang in her efforts towards the synthesis of the same target dolabellane diterpenoid. Since the work by the two researchers closely overlaps they will be discussed in parallel from here on.

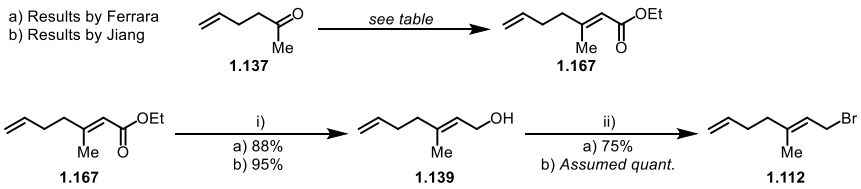
The required lactone was synthesised by both Ferrara and Jiang using the same synthetic route (Scheme 1.18),[24,25] with only minor modifications when it came to reaction conditions. Starting from the commercially available diol **1.116**, mono protection with *tert*-butyldiphenylsilyl chloride provided access to the alcohol **1.158** in excellent yield. A Johnson-Claisen reaction followed, then reduction, mesylation and displacement to give malonate **1.162**. The oxidative cyclisation to give the bicyclic lactone **1.163** proceeded well in the hands of both researchers, as did the Krapcho decarboxylation and alkylation with the electrophile **1.112**. Lactone ring opening was achieved by heating to 185 °C in the presence of potassium cyanide in DMSO to give the carboxylic acid **1.166** in 74-93% yield.

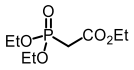
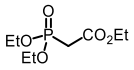
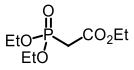
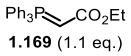


Scheme 1.18. *Reagents and conditions*: i) a) *i*-Pr_2NEt (10 eq.), TBDPSCl (1.05 eq.), DMF, rt, 1 h; b) NaH (1.05 eq.), TBDPSCl (1 eq.), THF, rt, 2 h; ii) a) triethyl orthoacetate (7 eq.), propionic acid (0.06 eq.), 138 °C, 18 h; b) triethyl orthoacetate (7 eq.), propionic acid (0.06 eq.), 138 °C, 22 h; iii) a) $LiAlH_4$ (1 eq.), Et_2O, 0 °C, 30 min; b) DIBAL-H (2.3 eq.), THF, -78 to 0 °C, 1 h; iv) a) Et_3N (1.5 eq.), MsCl (1.2 eq.), CH_2Cl_2, 0 °C - rt, 1.5 h; b) Et_3N (1.2 eq.), MsCl (1.2 eq.), CH_2Cl_2, rt, 1.5 h; v) a) NaH (3 eq.), dimethyl malonate (3 eq.), KI (0.5 eq.), 1:1 THF/DMF, 80 °C, 1.5 h; b) NaH (2.4 eq.), dimethyl malonate (2.5 eq.), KI (0.5 eq.), THF, 80 °C, 9 h; vi) a) $Mn(OAc)_3•2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 80 °C, 3 h; b) $Mn(OAc)_3•2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 80 °C, 5.5 h; vii) a) and b) LiCl (2 eq), H_2O (2 eq.), DMF, 150 °C, 2 h; viii) a) bromide **1.112** (2 eq.), LiHMDS (2 eq.), THF, -78 °C, 2.5 h; b) bromide **1.112** (2 eq.), LiHMDS (2 eq.), THF, -78 °C, 4 h; ix) a) and b) KCN (5 eq.), DMSO, 185 °C, 1.5 h.

The bromide **1.112** was synthesised by both Ferrara and Jiang using the same disconnection as Lua: a Horner-Wadsworth-Emmons reaction on **1.137**.[23–25] Moderate levels of diastereoselectivity were obtained by Ferrara (Table 1.1, entry 1), while poorer selectivity was obtained at room temperature by Jiang (entry 2). Changing the base to NaH had a moderate effect on the selectivity (entry 3), while the preformed ylide **1.169** gave no conversion (entry 4). These results once again highlighted to us that an alternative approach was required for our own synthetic campaign. Following separation of the two isomers by column chromatography, a reduction of **1.167** then deoxybromination gave bromide **1.112** (Table 1.1).

Table 1.1. Synthesis of Electrophile **1.112** [a]



Entry	Reagent	Base	Conditions	Yield[d]	d.r.
1[b]	 **1.168** (1 eq.)	*n*-BuLi (1.2 eq.)	THF, -78 °C – rt, 22 h	80%	6.1:1
2[c]	 **1.168** (1 eq.)	*n*-BuLi (1.2 eq.)	THF, rt, 22 h	74%	3:1
3[c]	 **1.168** (1 eq.)	NaH (1.2 eq.)	THF, rt, 22 h	N.D.	2:1
4[c]	 **1.169** (1.1 eq.)	None	THF, rt, 22 h	0%	N.A.

[a] *Reagents and conditions*: i) a) DIBAL-H (2.2 eq.), THF, -78 to 0°C, 2.5 h; b) DIBAL-H (2.3 eq.), THF, -78 to 0°C, 1 h; ii) a) and b) MsCl (1.4 eq.), Et_3N (2.1 eq.), THF, 0 °C, 2 h *then* LiBr (5 eq.), THF, 0 °C, 1.5 h; [b] Methodology carried out by Ferrara; [c] Methodology carried out by Jiang. [d] A combined yield of the mixture of both diastereomers.

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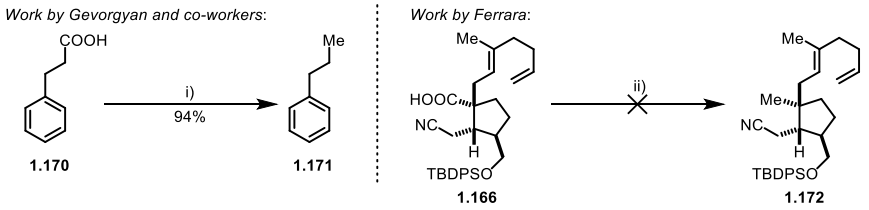
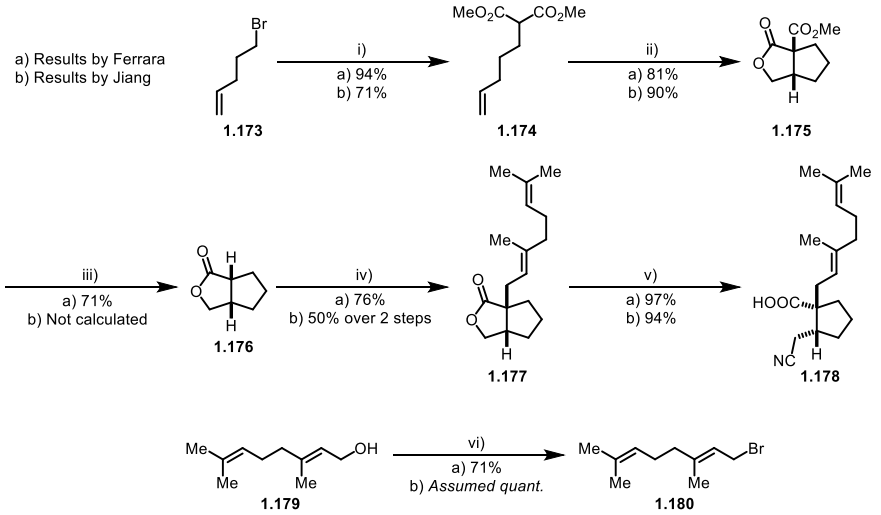
1.2.4 Optimisations Carried Out for the Reduction of the Carboxylic Acid 1.166

Methods for the direct, complete reduction of a carboxylic acid to a methyl group have been reported in the literature, and Ferrara attempted one method that utilised $HSiEt_3$ with $B(C_6F_5)_3$. This had been shown to work well by Gevorgyan and co-workers,[26] but unfortunately no reaction took place (Scheme 1.19) when applied to **1.166**.



Scheme 1.19. *Reagents and conditions*: i) $B(C_6F_5)_3$ (5 mol%), $HSiEt_3$ (6 eq.), CH_2Cl_2, rt, 20 h; ii) $B(C_6F_5)_3$ (5 mol%), $HSiEt_3$ (3 eq.), CH_2Cl_2, rt, 20 h.

It was this result that prompted Ferrara to synthesise a model substrate that could be used to optimise this difficult reduction, while Jiang came directly to this conclusion. The lactone **1.177** was synthesised in just six steps and was opened in the same manner as previous using potassium cyanide, to give the carboxylic acid **1.178** (Scheme 1.20).

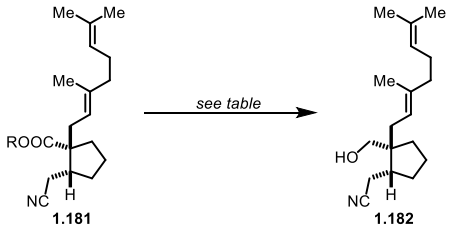


Scheme 1.20. *Reagents and conditions*: i) a) NaH (3 eq.), dimethyl malonate (3 eq.), 1:1 THF/DMF, 80 °C, 1.5 h; b) NaH (3 eq.), dimethyl malonate (3 eq.), 1:1 THF/DMF, 80 °C, 2 h; ii) a) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 80 °C, 8 h; b) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 80 °C, 22 h; iii) a) LiCl (2 eq.), H_2O (2 eq.), DMF, 150 °C, 2 h; b) LiCl (2 eq.), H_2O (2 eq.), DMF, 150 °C, 6 h, yield not reported due to volatility; iv) a) LiHMDS (2 eq.), bromide **1.180** (2 eq.), THF, -78 °C, 2 h; b) LiHMDS (2 eq.), bromide **1.180** (2 eq.), THF, -78 °C, 3 h; v) a) KCN (5 eq.), DMSO, 185 °C, 3 h; b) KCN (4 eq.), DMSO, 185 °C, 2.5 h vi) a) PBr_3 (0.4 eq.), pyridine (0.1 eq.), 1:3 hexane/Et_2O, 0 °C, 1.5 h; b) PBr_3 (0.4 eq.), pyridine (0.1 eq.), Et_2O, 0 °C, 1 h.

From here Ferrara carried out a number of different direct reduction methods with minimal success. Borane (Table 1.2, entry 1) was found to reduce the alkenes present; other methods trialled suffered from a lack of reactivity (entries 2 – 7). As such, Ferrara switched to an alternative tactic using a set of Wolff-Kishner like methodologies (see Section 1.2.5 below).

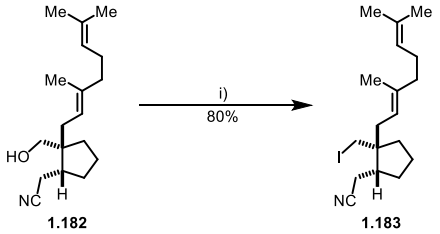
Jiang however, after some optimisation of conditions (Table 1.2, entries 8 - 10), was able to successfully synthesise alcohol **1.182** by treatment of carboxylic acid **1.178** with ethyl chloroformate to give the mixed anhydride, followed by reduction with $NaBH_4$ in the same pot. From here, the corresponding iodide **1.183** could be synthesised with an Appel reaction in 80% yield (Scheme 1.21). With a better leaving group in place it was supposed that the final reduction would be easier.

Table 1.2. Screening of Conditions for the Reduction of Carboxylic Acid **1.178**, reported by Ferrara and Jiang.[24,25]



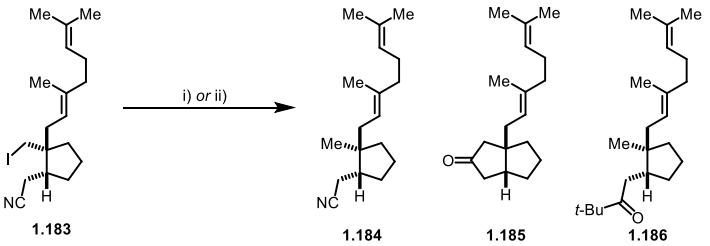
Entry	R	Conditions [c]	Yield
1 [a]	H	BH_3•SMe_2, THF, 65 °C, 1 h	0
2 [a]	H	$LiBH_4$, EtOH, rt, 24 h	N.R.
3 [a]	Me	$LiBH_4$, EtOH, rt, 24 h	trace [d]
4 [a]	Me	$LiBH_4$, EtOH, 50 °C, 24 h	trace [d]
5 [a]	Me	$LiBH_4$, THF, 50 °C, 24 h	N.R.
6 [a]	H	MeO_2CCl, NEt_3, THF *then* $NaBH_4$	N.R.
7 [a]	H	MeO_2CCl, NEt_3, THF *then* $LiBH_4$	N.R.
8 [b]	H	Oxalyl chloride (3 eq.), DMF (2 eq.), THF, rt, 6 h *then* $NaBH_4$ (2 eq.), DMF, rt, 22 h	53
9 [b]	H	Oxalyl chloride (3 eq.), DMF (2 eq.), THF, rt, 22 h *then* $NaBH_4$ (2 eq.), DMF, rt, 22 h	70
10 [b]	H	EtO_2CCl (1.1 eq.), *N*-methyl morpholine (1.1 eq.), THF, 0 °C, 6 h *then* $NaBH_4$ (3 eq.), THF/MeOH, rt, 6.5 h	94

[a] Methodology carried out by Ferrara; [b] Methodology carried out by Jiang; [c] Information on the number of equivalents of reagents was not available in the case of Ferrara's experiments; [d] Product detected only by LRMS [*m/z* 276 $(M+H)^+$].



Scheme 1.21. *Reagents and conditions*: i) I_2 (1.5 eq.), PPh_3 (2 eq.), imidazole (2 eq.), THF, rt, 6 h.

Treatment of the iodide with zinc and acetic acid gave a mixture of the desired product **1.184** in conjunction with ketone **1.185** (Scheme 1.22). It is likely that the ketone was formed as a result of the addition of an intermediate alkylzinc species onto the nitrile functional group, followed by hydrolysis during the aqueous workup. Dehalogenation using *t*BuLi in MeOH gave a mixture of starting material, ketone **1.185** and ketone **1.186**. From these observations it was concluded that the formation of nucleophilic carbon species should be avoided in order to maintain the integrity of the nitrile.

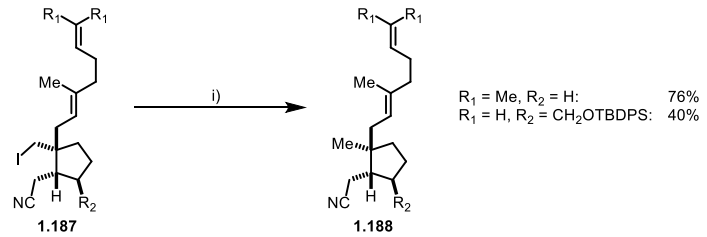


1.183 **1.184** **1.185** **1.186**

	1.184	**1.185**	**1.186**
i)	30%	65%	0%
ii)	0%	44%	8%

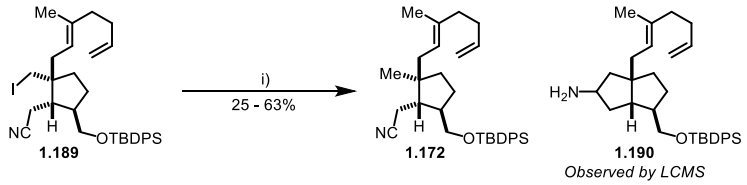
Scheme 1.22. *Reagents and conditions*: i) Zinc (10 eq.), AcOH (2 eq.), 1:1 Et_2O/MeOH, rt, 4 h; ii) *t*-BuLi (2 eq.), MeOH (2 eq.), 3:2 pentane/Et_2O, -78 °C, 1.5 h.

Jiang next treated iodide **1.183** with $NaBH_4$ in sulfolane, a method reported by Hutchins and co-workers.[27] After some optimisation a yield of 76% of **1.184** was obtained (Scheme 1.23, R_1 = Me, R_2 = H). Unfortunately when it came to the real system a low yield of 40% was obtained (Scheme 1.23, R_1 = H, R_2 = $CH_2OTBDPS$), with the remainder of the mass suspected to be derived from the silyl protecting group, which implied that it was unstable to the reaction conditions.



Scheme 1.23. *Reagents and conditions*: i) $NaBH_4$ (12 eq.), sulfolane, 60 °C, 6 h.

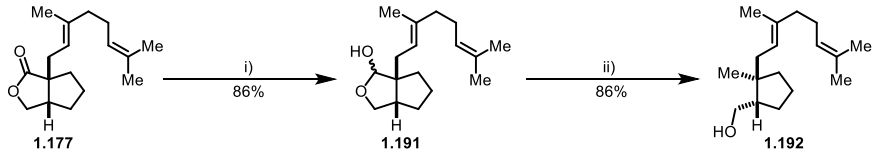
A radical reduction was next examined by Jiang using a combination of $NaBH_4$ and $InCl_3$ according to the procedure reported by Baba *et al*. Moderate yields of the desired product **1.172** were obtained with poor reproducibility (Scheme 1.24), and the molecular weight [*m/z* 502.4 $(M+H)^+$] of the side product **1.190** was observed in the LRMS. Jiang was unfortunately unable to carry out further investigation due to time constraints.



Scheme 1.24. *Reagents and conditions*: i) $InCl_3$ (1 eq.), $NaBH_4$ (3 eq.), MeCN, 0 °C, 1.5 h.

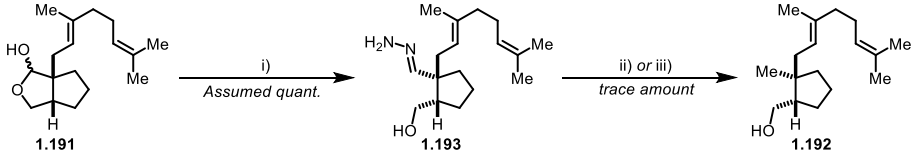
1.2.5 Optimisations Carried Out by Ferrara for the Reduction of Lactone 1.176

In his final attempt Ferrara elected to optimise a Wolff-Kishner type methodology on the model substrate **1.191**, synthesised from **1.177** (Scheme 1.25). Whilst the traditional methodology using hydrazine monohydrate and potassium hydroxide at 180 °C was successful, it was known from the work by Hallside that the TBDPS protecting group was labile in these strong conditions (see Scheme 1.11, conditions VIII).[22] As such a milder variant of the Wolff-Kishner reduction was required.



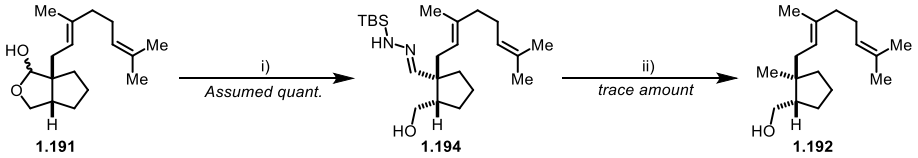
Scheme 1.25. *Reagents and conditions*: i) DIBAL-H (1.1 eq.), CH_2Cl_2, -78 °C, 1.5 h; ii) $N_2H_4 \bullet H_2O$ (25 eq.), KOH (1 eq.), diethylene glycol, 130 – 180 °C, 4.5 h.

The Cram and Scott modifications were attempted,[28,29] which both require preformation of the hydrazone **1.193** followed by treatment with KO*t*-Bu in either DMSO or toluene. Unfortunately only traces of the desired alcohol **1.192** were ever observed (Scheme 1.26).



Scheme 1.26. *Reagents and conditions*: i) $N_2H_4 \bullet H_2O$, EtOH, 100 °C, 16 h; ii) KO*t*-Bu, DMSO, rt, 24 h; iii) KO*t*-Bu, toluene, 110 °C, 24 h.

Finally the Myers modification was attempted: it appeared that the hydrazone **1.194** had been synthesised as required (Scheme 1.27), but once again only a trace of the alcohol **1.192** was observed in the crude reaction mixture and time constraints prevented any further investigation.[30]

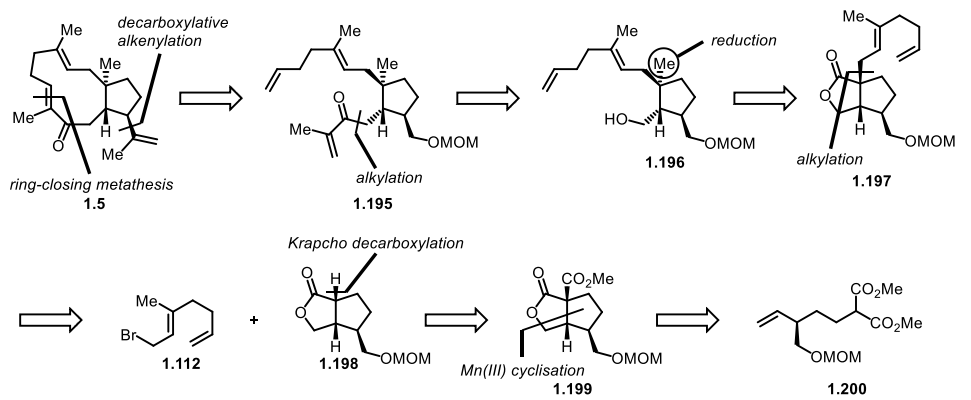


Scheme 1.27. *Reagents and conditions*: i) 1,2-bis(*tert*-butyldimethylsilyl)hydrazine, $Sc(OTf)_3$, *neat*, 0 - 23 °C; ii) KO*t*-Bu, HO*t*-Bu, DMSO, rt, 24 h.

1.3 Areas of the Route Selected for Potential Improvement

We wished to learn from the results of the previous studies, whilst also taking advantage of the most recently published methodologies. Our first disconnection (Scheme 1.28) was to take the 1,1-disubstituted alkene back to a protected alcohol, like our predecessors. Unlike

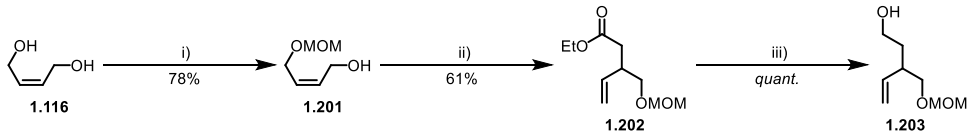
them, we could take advantage of a recently published decarboxylative alkenylation methodology, published in 2017 by Baran and co-workers.[31] A ring closing metathesis would be used to close the 11-membered ring, which the report by Hoveyda and co-workers (see Scheme 1.7) on clavirolide C (**1.70**),[18] and preliminary work by Lua (Scheme 1.14),[23] suggested could be successful. A functional group interconversion would strip back the enone moiety to a simpler alcohol **1.196**. It was clear that the best chance of success for completing the difficult reduction, which had been so heavily worked upon by previous researchers, would be to use the Wolff-Kishner reduction. Although this reaction requires harsh conditions, an appropriately chosen protecting group would be stable. The Mn(III) promoted diastereoselective oxidative cyclisation would relay the stereochemical information from one sp^3 stereocentre to the remaining two. However, since we wished to synthesise a single enantiomer of the natural product, it was clear that we would need to develop a method for the enantiopure synthesis of malonate **1.200**. A judicious choice of protecting group may allow for a more facile synthesis and productive optimisation. To that end, the methoxy methyl (MOM) protecting group was selected since it should survive the range of basic and nucleophilic reagents encountered in the proposed route, while its removal would require treatment with just a mild acid. Finally the poor diastereoselectivity obtained by Lua, Ferrara and Jiang in the synthesis of bromide **1.112** (see Scheme 1.14 and Table 1.1) offered an excellent opportunity for improvement.



Scheme 1.28. Our retrosynthesis, guided by the reports of Lua, Ferrara and Jiang.[23–25]

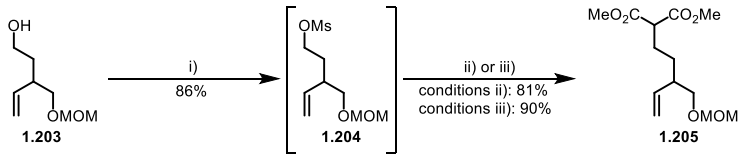
1.4 Synthetic Studies Using Racemic Material

We decided to test the viability of the new route using cheaper and more readily available racemic material **1.203**, the synthesis of which is shown below (Scheme 1.29)



Scheme 1.29. *Reagents and conditions*: i) NaH (1 eq.), MOMCl (1 eq.), THF, 0 °C, 6 h; ii) $MeC(OEt)_3$ (5 eq.), propionic acid (10 mol%), toluene, reflux, 24 h; iii) $LiAlH_4$ (1 eq.), Et_2O, 0 °C, 1.5 h.

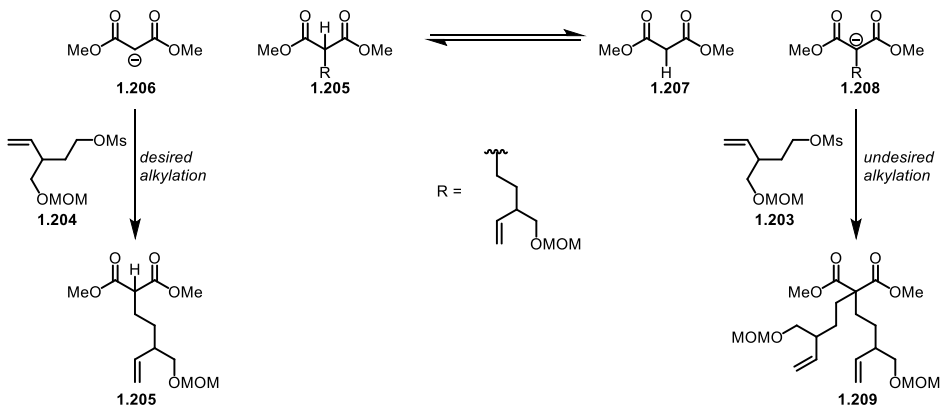
This synthesis began with an excellent yield for the mono protection of *cis*-2-butene-1,4-diol **1.116** using chloromethyl methyl ether (Scheme 1.29).[32] A Johnson-Claisen rearrangement was then performed to give ester **1.202** in 61% in good yield,[23] followed by a quantitative $LiAlH_4$ reduction to give alcohol **1.203**. This three step route gave access to multi-gram quantities of **1.203**, which was expected to be sufficient to test the forthcoming steps. The malonate portion of **1.205** was installed by converting the alcohol **1.203** into the mesylate **1.204**, followed by treatment with sodium dimethylmalonate (Scheme 1.30).



Scheme 1.30. *Reagents and conditions*: i) MsCl (1.2 eq.), Et_3N (1.5 eq.), CH_2Cl_2, 0 °C – rt, 1.5 h; ii) NaH (3 eq.), dimethyl malonate (3 eq.), KI (0.5 eq.), 1:1 THF/DMF, 80 °C, 22 h; iii) NaH (2 eq.), dimethyl malonate (3 eq.), KI (0.5 eq.), 1:2 THF/DMF, 80 °C, 3 h.

The standard conditions used within our group and the wider chemistry community are to employ an excess of dimethylmalonate, with an equimolar quantity of strong base like sodium hydride. These conditions are to ensure that there is always an excess of sodium dimethylmalonate, to facilitate full conversion of the alkylating partner, as well as to prevent over alkylation. We had indeed observed this double alkylation in synthesising a simpler substrate using a similar set of conditions (see Chapter 2, Scheme 2.31). While the yield was good using these conditions (Scheme 1.30, conditions II), the crude ^{1}H NMR spectrum and TLC suggested that over alkylation had indeed occurred.

We hypothesised that an equilibrium might be set up between the anion of the product (**1.208**), and the anion of the dimethylmalonate **1.206**, since we would not expect a large pKa difference between these two conjugate acids (Scheme 1.31). The anion of the product (**1.208**) could lead to the undesired side-product **1.209**, and thus its concentration should be minimised. If one were to reduce the quantity of sodium hydride added from three equivalents to two, while keeping to three equivalents of dimethyl malonate, it should in principle push the equilibrium shown below (Scheme 1.31) across to the left hand side and minimise the amount of dialkylated product **1.209** formed in the reaction. In effect, the reaction would be buffered with dimethyl malonate.



Scheme 1.31 The potential equilibrium between anions **1.205** and **1.207**, and the effect this would have on the product distribution.

In addition to this, we observed during our first alkylation reaction that the sodium dimethylmalonate was poorly soluble in DMF and was prone to precipitating out. This led to the formation of a thick white foam which could not be stirred using a magnetic stirrer bar. We were concerned that without proper stirring we could not be certain that the NaH added had fully reacted, presenting both an issue of reproducibility but also safety. Since stirring only recommenced once the sodium dimethylmalonate re-dissolved (after the reaction had been heated to approximately 60 °C), there was the potential for hydrogen gas to be released suddenly at high temperature when the NaH came into contact with the rest of the solution.

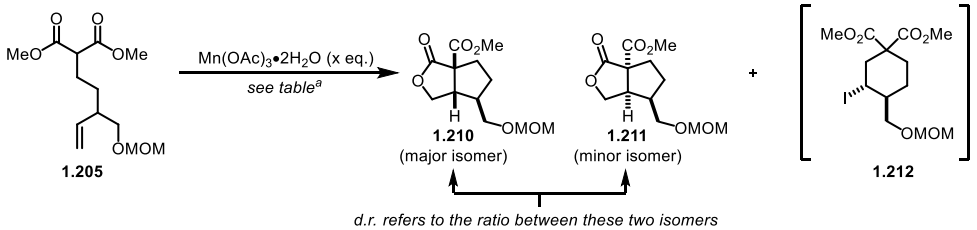
With both our hypothesis on the potential for a disadvantageous equilibrium to be set up, as well as the safety issues involved with using too little DMF, our next reaction attempt changed both variables at once. The freely stirring mixture of sodium dimethylmalonate in an increased volume of DMF alleviated safety concerns, and we found no trace of the dialkylated product **1.209**. The purification was therefore quicker and simpler, and the yield was improved to 90% (Scheme 1.30, conditions III). It is plausible that the improvement in the purity and yield was due to the reduction in the amount of sodium hydride used, but we

cannot rule out that it could also be due to the change in solvent and correspondingly, the concentration. However, there can be no doubt that the reaction was safer and more successful using the new set of conditions. A suitable control experiment that could be run in the future would be to carry out the reaction with increased volume of DMF, using three equivalents of NaH, and compare the results.

Our first extensive optimisation however came with the manganese(III) oxidative cyclisation. Treatment of **1.205** under the standard conditions used by Ferrara and Jiang (see Scheme 1.18, condition set VI, and Table 1.3, entry 1) gave a suboptimal yield of 68% of the lactones **1.210** and **1.211**. Since this was an early step in our synthetic route, an improved yield was highly desirable for ensuring that sufficient material remained to complete the synthesis. A number of conditions were screened, using ^{1}H NMR with a known quantity of dimethyl terephthalate to determine the yield and diastereoselectivity in each case. An extended relaxation delay of 10 s was used in each experiment to ensure that all resonances had fully relaxed, allowing for quantitative integration. The yields reported are for the major diastereomer in the case of NMR yields, and for the mixture of diastereomers in the case of isolated yields. Reducing the temperature (entries 1-3) only had the effect of increasing the reaction time. Running the reaction at substrate concentrations of 0.1 or 0.4 M (entries 4 and 5) gave a similar yield of product **1.210**, but a concentration of 0.02 M proved deleterious (entry 6). Using 1.5 eq. of $Cu(OTf)_2$ only worsened matters (entry 7). We were fortunate that a new set of conditions were discovered by Ainsua Martinez (a D.Phil. student in the Burton group),[33,34] who found that a Mn(III)/I^- system gave excellent yields of bis-lactones. In our hands, the methodology gave a much improved isolated yield of 76% of **1.210** (entry 8), which was sufficient to continue with the synthesis. With the Mn(III)/I^- set

of conditions we were also able to isolate the side product **1.212**, which we suspect comes from a competing *6-endo-trig* radical cyclisation (discussed in more detail below).

Table 1.3. Screening of Conditions for the Oxidative Cyclisation of Malonate **1.205**



Entry	Equiv. of $Mn(OAc)_3•2H_2O$	Additive	Conc. /M	Temp. /°C	Time /h	Yield[b]	d.r.
1	2	$Cu(OTf)_2$ (1 eq.)	0.2	80	2.5	68 (64%)	11:1
2	2	$Cu(OTf)_2$ (1 eq.)	0.2	60	24	69	12:1
3	2	$Cu(OTf)_2$ (1 eq.)	0.2	40	48	68	12:1
4	2	$Cu(OTf)_2$ (1 eq.)	0.1	80	3	66	12:1
5	2	$Cu(OTf)_2$ (1 eq.)	0.4	80	3	65	11:1
6	2	$Cu(OTf)_2$ (1 eq.)	0.02	80	5.5	41	12:1
7	2	$Cu(OTf)_2$ (1.5 eq.)	0.2	80	3	61	12:1
8	3	KI (0.5 eq.)	0.15	80	8	78 (76)[c]	9:1
9	3	KI (0.5 eq.)	0.15	60	48	76	10:1
10	3	KI (0.5 eq.)	0.15	40	48	46	9:1
11[d]	3	KI (0.5 eq.)	0.15	80	8	(73)	9:1
12[e]	3	KI (0.5 eq.)	0.15	80	8	(79)	9:1

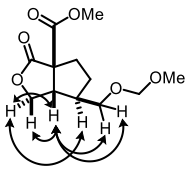
[a] *Reagents and conditions*: $Mn(OAc)_3•2H_2O$, additive, MeCN. The amount of Mn(III) added, the nature of the additive, the temperature, the concentration of the malonate **1.205** and the time are as described in the table. [b] The yield was determined from the crude ^1H NMR spectrum by employing an extended relaxation time (D1) of 10 seconds, and comparing the integrals with a known quantity of dimethyl teraphthalate. Yields in parentheses are isolated yields. [c] 5% of iodide **1.212** was also isolated. [d] Reaction performed on an 18.2 mmol scale. [e] Reaction performed using $Mn(OAc)_3•2H_2O$ that had been placed on the high vacuum line overnight, using 24 mmol of substrate.

Reactions run at a temperature to 60 °C or 40 °C (entries 9 and 10) required much longer to go to completion, and gave little or no improvement to the yield and diastereoselectivity. On a larger scale (18.2 mmol, entry 11), an isolated yield of 73% of **1.210** and **1.211** was obtained. Finally, using $Mn(OAc)_3•2H_2O$ that had been placed under high vacuum overnight

to remove traces of acetic acid brought this isolated yield back up to 79% on a 24 mmol scale (entry 12).

Unfortunately we were unable to separate the two diastereomers **1.210** and **1.211** at this stage, so we carried out the next steps on the mixture. For simplicity only the major diastereomer **1.210** has been depicted in the coming steps (*vide infra*). We made every attempt to separate the diastereomers after each new transformation, with the expectation that their physical properties may have diverged, but it was not until a late stage cyanide displacement that these diastereomers were finally separated (see Scheme 1.44).

The major diastereomer was assigned the configuration shown above on the basis of the ^{1}H NOESY data collected (Figure 1.2), and the correlations that were observed are in keeping with the structure that was expected from previous reports in the Burton group. Although we were unable to unambiguously assign a *cis*-fused ring junction at this stage, we deemed that the high energy *trans*-fused 5,5-bicycle was a highly unlikely alternative.

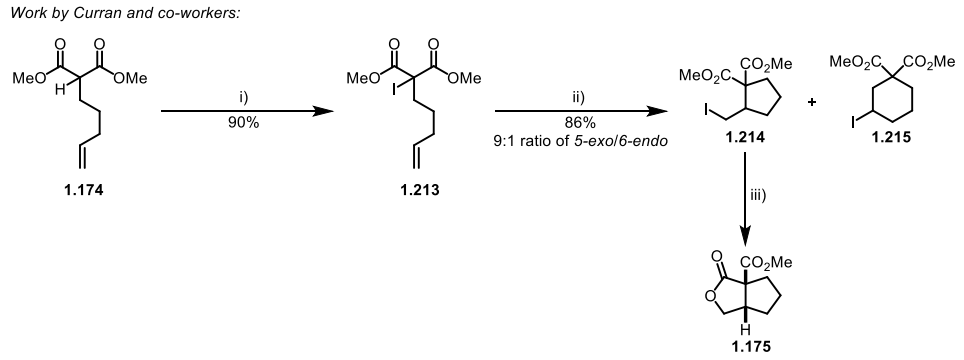


1.210

Figure 1.2. Selected nOe correlations, obtained from a ^{1}H NOESY spectrum (see Experimental section, chapter 3).

With regard to the side product iodide **1.212**, we hypothesise that it comes from a competing *6-endo-trig* radical cyclisation (see Chapter two, section 2.1.2 for a full discussion of mechanism of Mn(III) promoted oxidative cyclisations). Relevant to this observation, Curran and co-workers were able to isolate the analogous iodocyclohexane product **1.215** during their research on the atom-transfer cyclisations of iodomalonates (Scheme 1.32).[35]

Ainusa-Martinez proposed that the Mn(III)/I^- methodology performs the same series of transformations as Curran and co-workers, but in a single pot as opposed to three.[33]



Scheme 1.32. Work by Curran and co-workers on the atom transfer cyclisations of iodo malonate. *Reagents and conditions*: i) KH, NIS, THF, -78 °C; ii) $(Me_3Sn)_2$ (10 mol%), *hv* (275 W, sunlamp), benzene, 40 – 80 °C, 10 min; iii) 110 °C, 2 h.

With regard to the iodide **1.212**, the correlations that were observed in the ^{1}H NOESY were in keeping with the stereochemistry of **1.212** depicted in Table 1.3 and Figure 1.3, with a *trans* relationship between the iodide functional group and the CH_2OCH_2OMe group. Furthermore, a ^3J coupling of 11.0 Hz was observed between protons H_a and H_b (see Figure 1.3), which is indicative of a *trans*-diaxial relationship between these protons. This observation is further evidence in favour of the assigned relative stereochemistry of **1.212**.

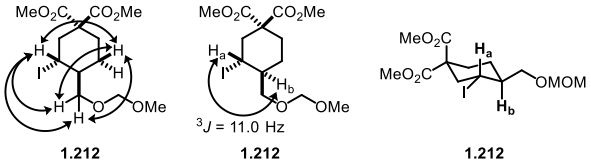
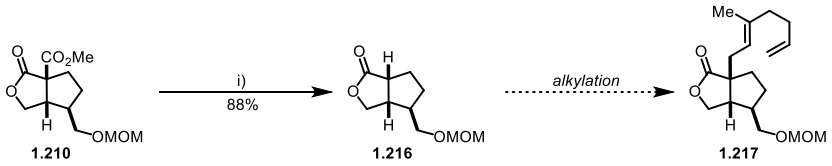


Figure 1.3. Selected nOe correlations (left), obtained from a ^{1}H NOESY spectrum (see Experimental Section). Illustrations of the vicinal (^3J) coupling between H_a and H_b (middle), and the presumed chair conformation with the iodine and CH_2OMOM placed in the equatorial positions, which forces H_a and H_b to occupy the axial positions.

The conditions previously reported by Lua for the Krapcho decarboxylation of **1.127** (Scheme 1.14) were found to give an excellent yield when applied to **1.210** on a multigram scale (Scheme 1.33),[23] to provide **1.216** ready for alkylation. Mapping the nOe correlations of **1.216** obtained from a ^{1}H NOESY confirmed the *cis*-fusion of the bicyclic ring system

(Figure 1.4). To do this the required electrophile must first be synthesised, and this is discussed in the following section.



Scheme 1.33. *Reagents and conditions*: i) LiCl (2 eq.), H_2O (2 eq.), DMF, 150 °C, 3 h.

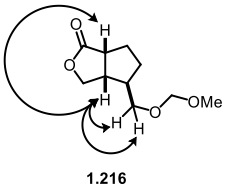
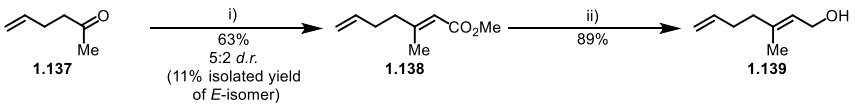


Figure 1.4. Selected nOe correlations, obtained from a ^{1}H NOESY spectrum (see Experimental section, chapter 3).

1.4.1 Synthesis of Alcohol 1.139

In all previous attempts in the synthesis of the target dolabellane diterpenoid (**1.5**) by Lua, Ferrara and Jiang, each used a Horner-Wadsworth-Emmons reaction to install the desired (*E*)-alkene stereochemistry in **1.138**.[23–25] Unfortunately on each occasion the diastereoselectivity was poor; the separation of each diastereomer by column chromatography worse. Using this method an isolated yield of just 11% was obtained for diastereomerically pure **1.138** after two rounds of flash chromatography (Scheme 1.34). It was apparent to us that this method would quickly become time-consuming, tedious, and delay our synthetic endeavours. A new method was sought, one which would deliver a single diastereomer of **1.139**.



Scheme 1.34. *Reagents and conditions*: i) trimethyl phosphonoacetate (1.1 eq.), *n*-BuLi (1.2 eq.), THF, -78 °C – rt, 24 h; ii) DIBAL-H (2.3 eq.), THF, -78 to 0 °C, 2 h.

The configuration of the tertiary alkene of both **1.138** and **1.139** was confirmed by comparison of the ^{1}H and ^{13}C NMR peaks obtained by us with those reported by Lua in the case of ester **1.138**, and by Lua, Ferrara and Jiang in the case of alcohol **1.139**.[23–25] It is worth noting that in the case of ester **1.138** these peaks specifically did not match those reported by Lua for the opposite (undesired) (*Z*)-diastereomer. Our strongest evidence however came from obtaining a ^{1}H NOESY spectrum for both the ester **1.138** and alcohol **1.139**, whose nOe correlations (Figure 1.5) are in keeping with the proposed structure for these compounds.

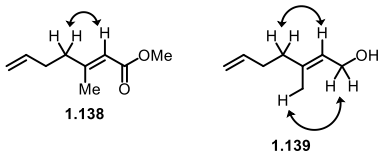
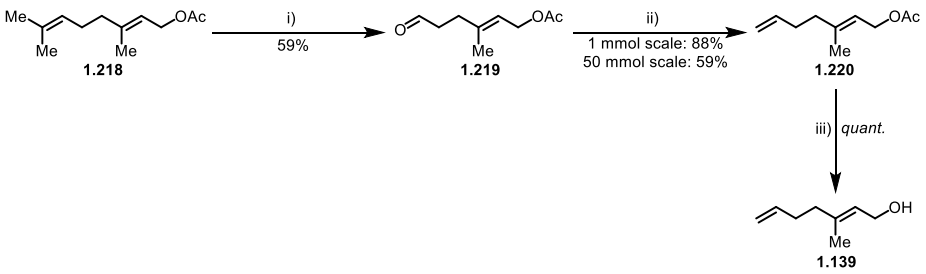


Figure 1.5. Selected nOe correlations, obtained from a ^{1}H NOESY spectrum (see Experimental section, chapter 3).

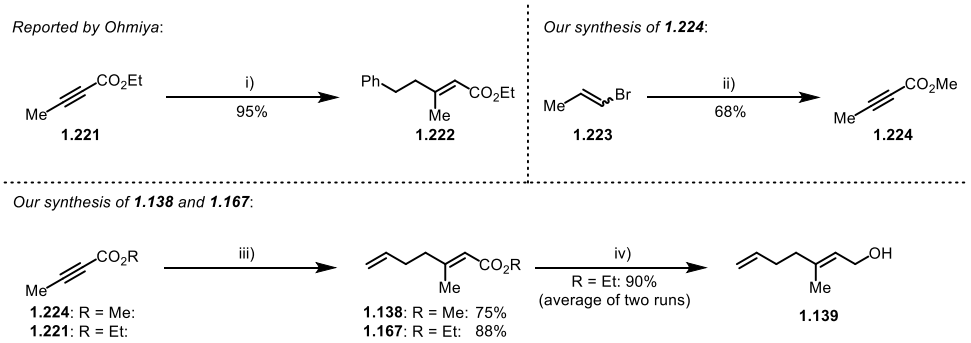
A literature search revealed a method for the synthesis of **1.139** that began with commercially available geranyl acetate **1.218**: epoxidation and ring opening to form a diol, followed by *in situ* oxidative cleavage to give **1.219** (Scheme 1.35); a Wittig reaction would reform the alkene to give **1.220**. Whilst homologations such as these are synthetically cumbersome, it did have the potential to be operationally simple and crucially, deliver a single diastereomer of the product. In practice, following the procedure by Leighton and co-workers for the selective cleavage of geranyl acetate **1.218** gave a moderate yield of aldehyde **1.219** (Scheme 1.35).[36] The Wittig reaction worked very well on a small scale, but unfortunately the yield of **1.220** was poorer on a large scale. This reduction in yield was attributed to the increased time required for addition of reagents during which the aldehyde may decompose, and the slower rate of heat transfer out of the reaction vessel (due to the larger volume:surface area ratio). A lithium aluminium hydride reduction of **1.220** gave **1.139** in a quantitative yield.



Scheme 1.35. *Reagents and conditions*: i) *m*-CPBA (1 eq.), CH_2Cl_2, -10 °C – rt, 4 h, *then* H_5IO_6 (1 eq.), 1:2.5 Et_2O/THF, 0 °C, 30 min; ii) LiHMDS (1 eq.), methyltriphenylphosphonium bromide (1 eq.), THF, 0 °C, 1 h; iii) $LiAlH_4$ (1 eq.), Et_2O, 0 °C – rt, 1 h.

Whilst the overall yield of **1.139** on large scale for this route was acceptable and none of the (*Z*)-isomer had been observed, this result was not ideal, since this route was one step longer than the route reported by Lua, Jiang and Ferrara.[23–25] As such, we continued to search for an alternative method.

A further search of the literature for the synthesis of **1.139** revealed a method for the alkylcupration of alkynyl esters, to give a single diastereomer of alkene after quenching with a proton source. Ohmiya and co-workers reported a substrate highly similar to our own, shown below (Scheme 1.36).[37] In our own studies, we used both the methyl and ethyl but-2-ynoates (**1.224** and **1.221**). Both starting materials were commercially available, but the methyl ester **1.224** was considerably more expensive, so this was synthesised in a single step using the procedure reported by Dixon and co-workers (Scheme 1.36).[38]



Scheme 1.36. *Reagents and conditions*: i) 2-phenylethylmagnesium bromide (1.2 eq.), CuI (1.2 eq.), TMEDA (3 eq.), -40 to -78 °C, 2.5 h; ii) *n*-BuLi (2.1 eq.), THF, -78 °C, 1.5 h, *then* methyl chloroformate (1.3 eq.), -78 °C – rt, 3.5 h; iii) 3-butenylmagnesium bromide (1.2 eq.), CuI (1.2 eq.), TMEDA (3 eq.), THF, -40 to -78 °C, 2.5 h; iv) DIBAL-H (2.3 eq.), THF, -78 to 0 °C, 2 h.

Carbocupration of the esters **1.224** and **1.221**, then carefully quenching with methanol, gave excellent yields of the corresponding α,β-unsaturated esters **1.138** and **1.167** (Scheme 1.36). Importantly, none of the undesired (*Z*)-alkene was observed, which greatly simplified the purification process. It was observed that far fewer organic extractions during the workup were required for the ethyl ester **1.167**, probably due to a higher $Et_2O/NH_4Cl_{(sat.\ aq.)}$ partition coefficient. A more efficient workup means that less of the ethyl ester **1.167** was lost during the isolation process, as compared to the methyl ester **1.138**, and went some way to explain the difference between the yields of the two products. Confirmation that the (*E*)-diastereomer had been synthesised was made by comparison of the ^{1}H NMR data to the authentic sample prepared earlier in the case of methyl ester **1.138**, and by comparison of the ^{1}H NMR data to that reported by Jiang in the case of ethyl ester **1.167**.[25] We also obtained nOe data in the case of the latter, which was in keeping with the expected structure (Figure 1.6). Reduction of both esters could be achieved using DIBAL-H to give an excellent yield of alcohol **1.139** (Scheme 1.34 and Scheme 1.36).

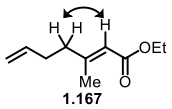
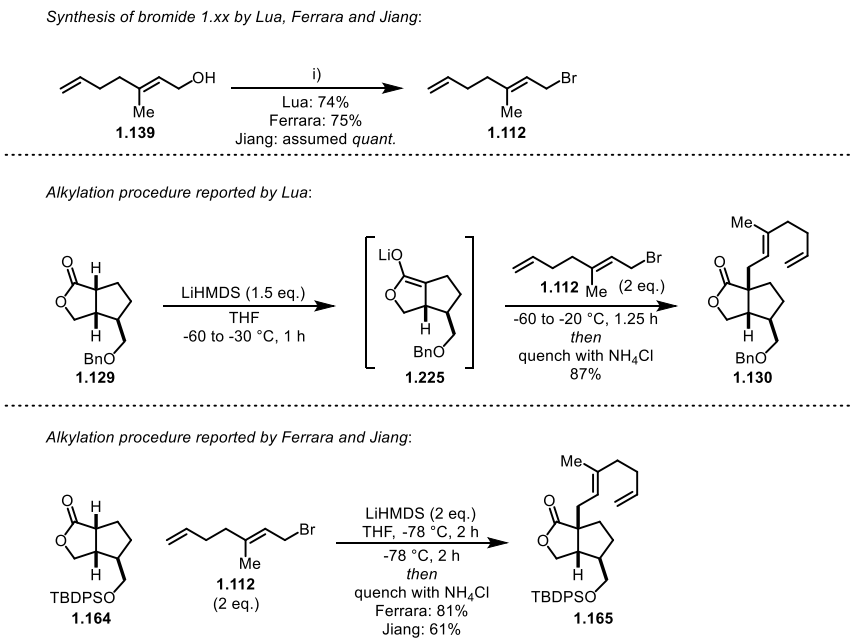


Figure 1.6. Selected nOe correlations, obtained from ^{1}H nOe spectra (see Experimental section, chapter 3).

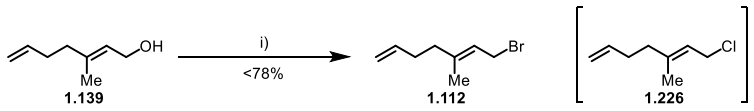
1.4.2 The Alkylation of Lactone 1.216

We planned to use the conditions reported by Jiang, Lua and Ferrara for the enolate alkylation of **1.216**,[23–25] since they had been shown to work extremely well. Lua had treated alcohol **1.139** with methanesulfonyl chloride to give the corresponding mesylate, which could be displaced with lithium bromide to give **1.112** (Scheme 1.37, top). From there, Lua added LiHMDS to a cooled solution of lactone **1.129**, then added the allylic bromide **1.112**, allowed the reaction to warm to -20 °C, and quenched (Scheme 1.37, middle). Ferrara and Jiang added LiHMDS to a solution containing both lactone **1.164** and bromide **1.112**, stirred at -78 °C for 2 h, then quenched to give **1.165** (Scheme 1.37, bottom).



Scheme 1.37. The synthesis of bromide **1.212**, and a summary of the different methods with which the alkylation product was obtained. *Reagents and conditions*: i) MsCl (1.4 eq.), Et_3N (2.1 eq.), THF, 0 °C, 2 h *then* LiBr (5 eq.), 0 °C, 1 h.

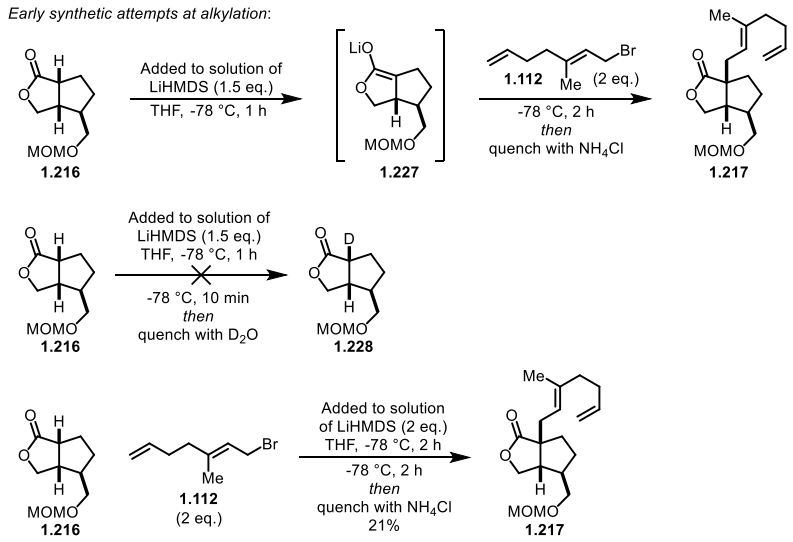
In our hands the bromide **1.112** was not obtained as cleanly as had been reported by Jiang, Lua and Ferrara (Scheme 1.38).[23–25] Although we were unable to separate the side-product, we tentatively assigned it as the corresponding chloride **1.226**. This we felt was a sensible prediction since the peaks for the side product in the ^{1}H NMR spectrum did not correspond to our authentic sample of the alcohol **1.139**, nor that of an intermediate mesylate. Unfortunately the bromide **1.112** decomposed on silica, and we were unable to remove the side product using a Kugelrohr distillation. It is not clear whether Jiang, Lua or Ferrara also observed the same side product and did not report the observation, or were simply able to avoid forming the chloride **1.226** in the reaction mixture.



Scheme 1.38. *Reagents and conditions*: i) MsCl (1.4 eq.), Et_3N (2 eq.), THF, 0 °C, 2 h, *then* LiBr (5 eq.), 0 °C, 1.5 h.

Nevertheless, we used this batch of contaminated bromide **1.112** in our early trials for the alkylation. We recognised that this was not ideal, but we felt that a small percentage (<20%) of the chloride **1.226** would not significantly impact the outcome of the reaction, particularly given that two equivalents of alkylating agent **1.112** would be used. This decision was also made in light of our failed attempts at purification. We thought that the optimum way to generate the lithium enolate **1.227** would be to add a solution of lactone **1.216** dropwise over 1 h to a solution of LiHMDS that had been cooled to -78 °C. This would ensure that the concentration of lactone **1.216** would remain low in the presence of the enolate **1.227**, to minimise the potential for a Claisen condensation. Once the enolate **1.227** was generated, a solution of the electrophile **1.112** would be added. In practice however, no product could be isolated from the complex mixture that was obtained (Scheme 1.39, top). We planned to determine whether the enolate **1.227** was being formed by attempting to

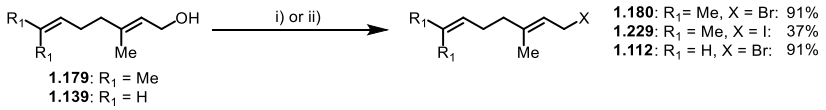
deuterate the α-position. Using the same procedure to generate the enolate **1.227**, then quenching with D_2O however gave only an intractable mixture of products (Scheme 1.39, middle). Using the reverse addition procedure, whereby a solution of lactone **1.216** and bromide **1.112** was added dropwise to a cooled solution of the base (reported by Jiang and Ferrara),[24,25] gave a 21% yield of the desired product **1.217**. It was clear however that substantial optimisation was required before we could progress further with the synthesis.



Scheme 1.39. Early attempts at the synthesis of alkylated lactone **1.217**.

To optimise the reactivity towards substitution rather than competing decomposition pathways, we used a model reaction that employed allyl bromide as the electrophile. The commercial availability of allyl bromide, and facile purification (via a base wash and distillation) of this electrophile, made it a suitable starting point. Our first reaction was performed by adding the base to a solution of lactone **1.216** and allyl bromide that had been precooled to -78 °C over 2 h followed by quenching with NH_4Cl gave a 33% yield of the desired alkylated lactone **1.217** (Table 1.4**,** entry 1). In addition, 14% of the dimer **1.230** was isolated, which presumably comes from the addition of enolate **1.227** to the starting

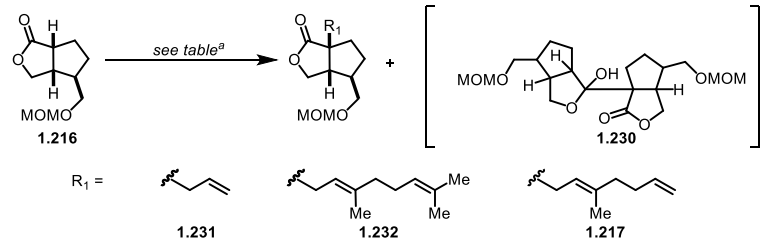
material **1.216**. Undesired reactivity was avoided by switching the order of addition (entry 2), and by optimising the base (entries 2-7), which gave an excellent yield of **1.231** (entry 4). Next, we tested a model electrophile (**1.180**) that more closely resembled the correct electrophile. This was synthesised by treating geraniol with phosphorus tribromide to give bromide **1.180** in a yield of 91% (Scheme 1.40, R_1 = Me, X = Br).



Scheme 1.40. *Reagents and conditions*: i) X = Br, PBr_3 (0.4 eq.), pyridine (0.1 eq.), Et_2O, 0 °C, 1.5 h; ii) X = I, I_2 (1.03 eq.), PPh_3 (1.03 eq.), imidazole (1.03 eq.), 2:3 MeCN/Et_2O, 0 °C, 2 h.

Using this material, we were pleased to obtain an excellent yield of the alkylated product **1.232** reproducibly (Table 1.4, entries 8 and 9). Furthermore, these yields were on a par with that obtained when using allyl bromide as the electrophile (compare with entry 4). We thought that an upper limit to the yield might have been reached as a result of using bromide as a leaving group. An attempt was made to synthesise the corresponding iodide electrophile **1.229**, but this was poorly yielding (Scheme 1.40, R_1 = Me, X = I). Furthermore, we found that it had begun to decompose overnight, despite being stored at -78 °C. Unsurprisingly, this iodide **1.229** was found to perform much more poorly than the bromide **1.180** in the alkylation reaction (Table 1.4, entry 10), with only a complex mixture of products obtained. Confident that using a bromide leaving group was the correct choice, we continued our optimisation using **1.112**.

Table 1.4. Optimisation of the Alkylation of Lactone **1.216**



Entry [a]	Electrophile	Base [b]	Added…	To…	Yield [c]
1	Allyl bromide	LiHMDS (1 M in THF)	Base	Lactone + E^+	33 [d]
2	Allyl bromide	LiHMDS (1 M in THF)	Lactone + E^+	Base	57
3	Allyl bromide	LiHMDS (1 M in toluene)	Lactone + E^+	Base	60
4	Allyl bromide	NaHMDS (0.6 M in toluene)	Lactone + E^+	Base	78
5	Allyl bromide	KHMDS (0.5 M in toluene)	Lactone + E^+	Base	57
6	Allyl bromide	LDA	Lactone + E^+	Base	<5
7	Allyl bromide	NaHMDS (0.6 M in toluene)	Lactone + E^+	Base + TMEDA (5 eq.)	76
8	**Bromide 1.180**	NaHMDS (0.6 M in toluene)	Lactone + E^+	Base	75
9	**Bromide 1.180**	NaHMDS (0.6 M in toluene)	Lactone + E^+	Base	76
10	**Iodide 1.219**	NaHMDS (0.6 M in toluene)	Lactone + E^+	Base	0 [e]
11	**Bromide 1.112**	NaHMDS (0.6 M in toluene)	Lactone + E^+	Base	65 [f]
12	**Bromide 1.112**	NaHMDS (0.6 M in toluene)	Lactone + E^+	Base	36 [f]
13	**Bromide 1.112**	NaHMDS (0.6 M in toluene)	Lactone + E^+	Base	75 [g]
14	**Bromide 1.112**	NaHMDS (0.6 M in toluene)	Lactone + E^+	Base	85 [g,h]

[a] *Reagents and conditions*: Base (2 eq.), electrophile (2 eq.), THF, -78 °C, 2 h. The identity of the base and electrophile are as described in the table. Reactions performed using 0.25 mmol of lactone unless otherwise noted. [b] The solvent and concentration that each base was provided in is given in paratheses. [c] Isolated yield. [d] 14% of the dimer **1.230** was also isolated. The reaction was conducted using racemic starting material **1.216** and the relative configuration of **1.230** was not determined. [e] The partially decomposed electrophile iodide **1.229** was used, and the crude material after the alkylation was poor, and so isolation of the product was not attempted. [f] Bromide **1.112** synthesised using the mesylation procedure was used, and was therefore contaminated with the suspected chloride **1.226**. [g] Bromide **1.112** was synthesised using the PBr_3 procedure. [h] Average of three runs. Yields for each run are as follows: 86% when using 1.57 mmol of lactone; 86% when using 2 mmol of lactone; 84% when using 4.5 mmol of lactone.

However the material synthesised was contaminated with what we judged to be the analogous chloride **1.226** (see Scheme 1.38), and use of this mixture of electrophiles resulted in yields of **1.217** that lacked reproducibility (Table 1.4, entries 11 and 12). Furthermore, both of these yields were much poorer than what we expected on the basis of comparison with our model electrophiles. Cognisant that no such analogous chloride was observed when phosphorus tribromide was used to synthesise the electrophile **1.180**, we trialled the same method to synthesise **1.112** (Scheme 1.40). This method gave a 91% yield of bromide **1.112** (Scheme 1.40, R_1 = H, X = Br) which was isolated in high purity (by ^{1}H and ^{13}C NMR). Using this material in the alkylation of **1.216** on a 0.25 mmol scale gave a much improved 75% yield of **1.217** (Table 1.4, entry 13). Further trials conducted later in the synthetic campaign demonstrated that this reaction improved on larger scales, and was now highly reproducible, with yields of 86%, 86%, and 84% obtained on 1.57 mmol, 2 mmol and 4.5 mmol scales respectively (entry 14).

With regard to the stereochemistry of each of the compounds synthesised above, the ^{1}H NMR and ^{13}C NMR data were in keeping with that reported by Jiang and Ferrara.[24,25] Furthermore, data relating to the nuclear Overhauser effect was collected for bromides **1.180** and **1.112**, and were found to be in keeping with the structure depicted in Scheme 1.40. In addition, we were pleased to see that the nOe correlations for the alkylated products **1.232** and **1.217** indicated that the *cis*-fusion of the bicyclic ring was intact, *i.e*. alkylation occurred on the same face as the CH_2OMOM substituent as expected (Figure 1.7).

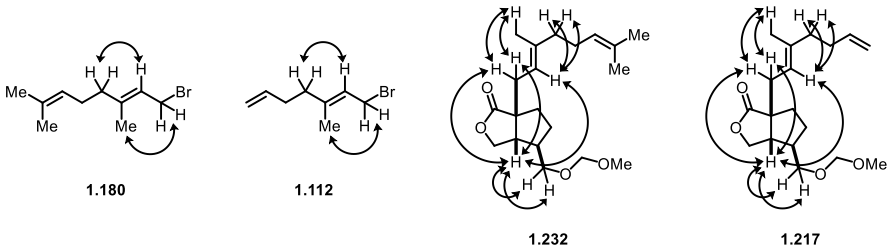
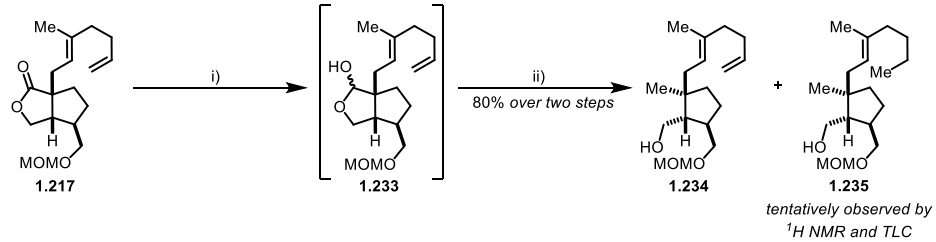


Figure 1.7. Selected nOe correlations, obtained from ^{1}H nOe and ^{1}H NOESY spectra (see Experimental section, chapter 3).

1.4.3 Reduction of Lactone 1.217 to Alcohol 1.234

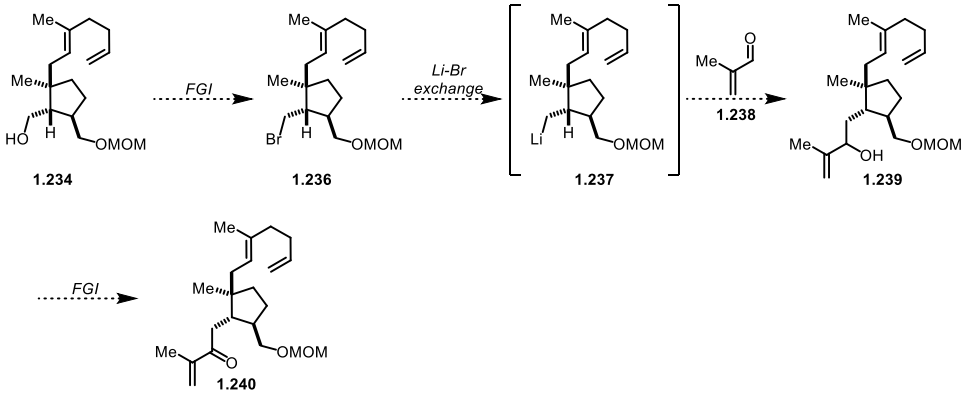
With conditions in hand to form the challenging all carbon quaternary centre of **1.217**, we focused on the upcoming steps. A DIBAL-H reduction of **1.217** gave **1.233** as a 1:1 ratio of diastereomers and a subsequent Wolff-Kishner reduction gave an 80% yield of **1.234** on a 3 mmol scale (Scheme 1.41). In early attempts we tentatively observed that the side-product **1.235** was also formed in this reaction. Although we were unable to isolate it, we observed a second spot at a slightly higher R_f on the TLC plate, and the integration of the signals in the crude ^{1}H NMR spectrum that corresponded to terminal alkene protons was slightly smaller than expected. We made a tentative assignment that reduction of the terminal alkene had occurred, which may occur if diimide is present, which could come from the oxidation of hydrazine in air. By using a freshly purchased bottle of hydrazine monohydrate and removing oxygen from the solvent with the freeze-pump-thaw technique, no such side product was observed.



Scheme 1.41. *Reagents and conditions*: i) DIBAL-H (1.2 eq.), CH_2Cl_2, -78 to -60 °C, 1 h; ii) $N_2H_4 \bullet H_2O$ (10 eq.), KOH (8 eq.), diethylene glycol, 160 – 180 °C, 8 h.

1.4.4 Functional Group Interconversion to Enone 1.240

The next transformation to optimise was to take alcohol **1.234** and convert it to the enone **1.240**, which would be capable of undergoing a ring-closing metathesis to form the 11-membered ring present in the natural product **1.5**. This transformation would prove to be far more challenging than originally anticipated.



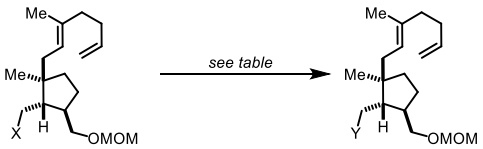
Scheme 1.42. Desired synthetic sequence to convert alcohol **1.234** into enone **1.240**.

Our first synthetic sequence was to convert the alcohol **1.234** into the corresponding bromide **1.236** (Scheme 1.42); this could undergo a lithium-halogen exchange to give a potent nucleophilic species **1.237**, and we expected that treating this with methacrolein **1.238** would give alcohol **1.239** *via* a 1,2-addition. Oxidation of the allylic alcohol **1.239** would give enone **1.240**.

In practice, direct deoxybromination/deoxyiodination (Table 1.5, entries 1, 2 and 3) resulted only in decomposition of material, judged on the basis of crude ^{1}H NMR spectrum. Although we were able to synthesise the mesylate **1.241** in a quantitative yield (entry 4), we were disappointed to find that the conditions used by Lua (entry 5) were not suitable to convert this to the bromide **1.236**.[23] This was surprising, since Lua had obtained an excellent yield of 84% for his substrate **1.132** bearing a benzyl protecting group instead of methoxy methyl

group (Scheme 1.14, conditions XI). Treating the mesylate **1.241** with LiBr at 25 °C gave no conversion (judged by TLC), and steadily warming this solution resulted in decomposition (entry 6). We screened alternative counterions that might display different reactivity, in solvents capable of dissolving the salt, but to no avail. Tetrabutylammonium bromide in toluene (entry 7) and NaBr in DMSO (entry 8) gave low conversions after extended reaction times, although the reaction did seem to be cleaner than previous attempts. Taking the best of these salts and switching the solvent to acetone gave only decomposition (entry 9).

Table 1.5. Screening of Conditions to Convert Alcohol **1.234** to Bromide **1.236**



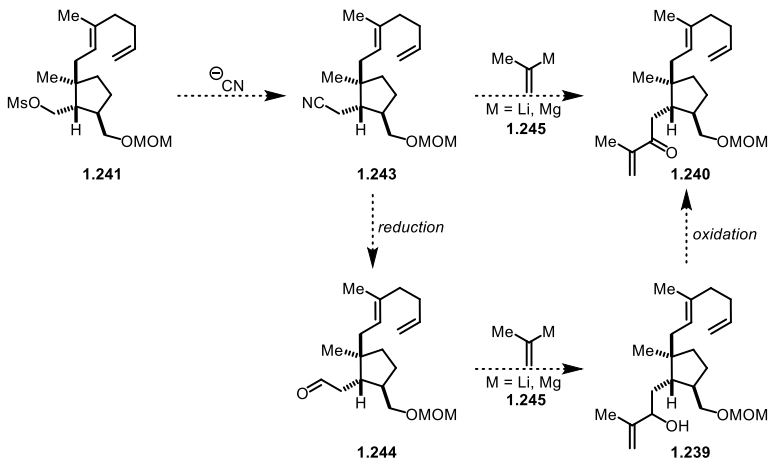
1.234: X = OH
1.241: X = OMs

1.242: Y = I
1.236: Y = Br
1.241: Y = OMs

Entry	X	Conditions	Y	Observations
1	OH	I_2 (1.2 eq.), PPh_3 (1.2 eq.), imidazole (1.5 eq.), 2:3 MeCN/Et_2O, 0 °C, 1 h	I	Decomposition.
2	OH	PBr_3 (2.4 eq.), pyridine (9.2 eq.), Et_2O, 0 °C, 3 h	Br	Decomposition, with partial loss of MOM protecting group
3	OH	PPh_3 (1.5 eq.), CBr_4 (1.5 eq.), MeCN, rt, 1 h	Br	Decomposition.
4	OH	MsCl (3 eq.), Et_3N (4.5 eq.), THF, 0 °C, 2 h	OMs	*Quant.* yield.
5	OMs	LiBr (7 eq.), THF, 0 °C, 1 h	Br	0% conversion
6	OMs	LiBr (10 eq.), THF, rt – 40 °C, 16 h	Br	Decomposition.
7	OMs	Bu_4NBr (10 eq.), toluene, rt – 35 °C, 72 h	Br	~39% conversion
8	OMs	NaBr (10 eq.), DMSO, rt – 35 °C, 72 h	Br	~21% conversion
9	OMs	Bu_4NBr (10 eq.), acetone, 35 °C, 96 h	Br	Decomposition.

From the results obtained it was clear to us that the bromide **1.236** was too unstable to be reproducibly synthesised and we would need an alternative method to synthesise the enone

1.240. Our successful synthesis of the mesylate **1.241** however prompted us to search for carbonyl umpolung synthons that would be capable of reacting with this electrophile. A source of cyanide could fulfil this role, and the alternative route is outlined below (Scheme 1.43).

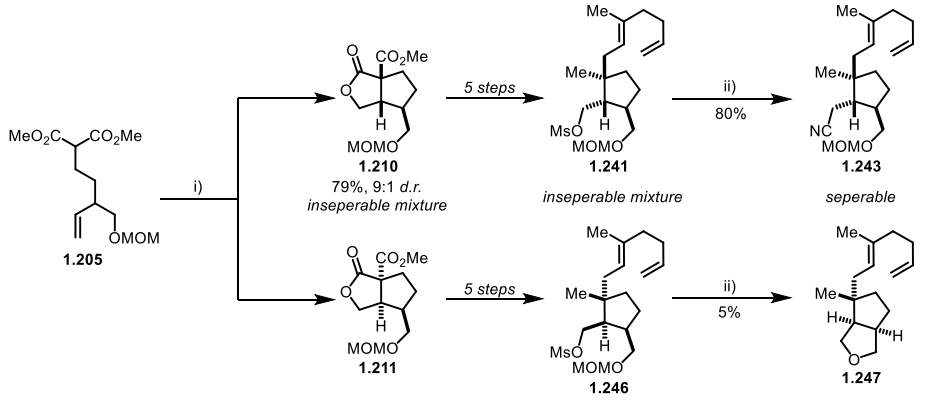


Scheme 1.43. Alternative route to enone **1.240**.

After displacement of the mesylate leaving group with cyanide, the ideal next step would be to treat **1.243** directly with an organometallic reagent to give the enone **1.240** (Scheme 1.43). We were cognisant however that there were relatively few reports of the direct addition of organometallic nucleophiles to nitriles, and comparatively more reports that went via an additional reduction and oxidation.

In practice, we found that displacement with cyanide was extremely effective, and an 80% yield of the desired product **1.243** was obtained (Scheme 1.44). There was also an unexpected benefit to this reaction. The undesired diastereomer **1.211** that had resulted from the manganese promoted oxidative cyclisation had not yet been removed due to poor, if any, separation on silica, and was still present in up to 10% by mass (Scheme 1.44). After

mesylation, the two diastereomers behaved very differently: the desired diastereomer **1.241** underwent displacement with cyanide to give **1.243** in high yield; the undesired diastereomer **1.246** underwent an intramolecular cyclisation to give the fused bicyclic tetrahydrofuran **1.247** in a 5% isolated yield (Scheme 1.44). These two products **1.243** and **1.247** had substantially different levels of retention on silica, and separation was achieved.

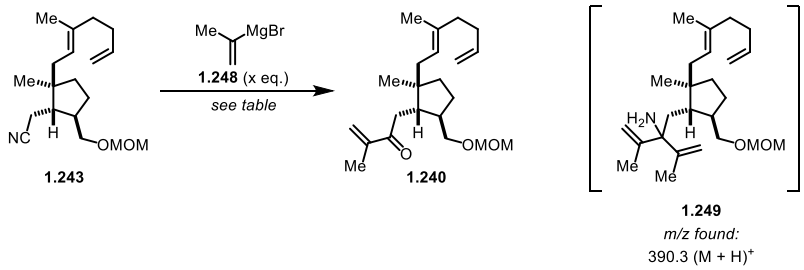


Scheme 1.44. Schematic for the synthesis of the two diastereomers of bicyclic lactone, **1.210** and **1.211**, subsequent transformations, and treament with cyanide that finally allowed for their separation. *Reagents and conditions*: i) $Mn(OAc)_3 \bullet 2H_2O$ (3 eq.), KI (0.5 eq.), MeCN, 80 °C, 8 h; ii) NaCN (5 eq.), NaI (1 eq.), DMSO, 90 °C, 6 h.

With the nitrile **1.243** in hand we attempted to add the Grignard reagent **1.248** to directly reach the desired enone **1.240**. We screened a number of different conditions, following the progress of each reaction by TLC, and quenching the reaction when deemed appropriate (Table 1.6). Unfortunately we were unable to achieve conversion, even after adding a large excess of Grignard reagent and heating the reaction mixture to reflux (entry 1). A report by Weiberth and Hall demonstrated that the addition of Grignard reagents to nitriles could be catalysed using substoichiometric quantities of CuI.[39] Unfortunately we did not observe any conversion for our substrate using this additive (entry 2). A large excess of Grignard reagent in conjunction with CuI led to a complex mixture of products (entry 3). We did observe a peak from a mass spectrometry (ESI^+) trace from this reaction, with a *m/z* that corresponded to amine **1.249** $(M + H)^+$, but such was the complexity of the TLC and crude ^1H

NMR spectrum that isolation was not attempted. We hypothesised that we could achieve alternative reactivity by switching the solvent to Et_2O, but this too displayed poor reactivity (entries 4 and 5). Under more forcing conditions the desired product was isolated in 10% yield (entry 6), using preparative TLC to purify a complicated mixture of products, but were unable to identify any of the side products nor the desired product **1.240**. The addition of CuI to this set of conditions only gave us starting material back.

Table 1.6. Attempted Optimisation for Addition of a Grignard Reagent to Nitrile **1.243**

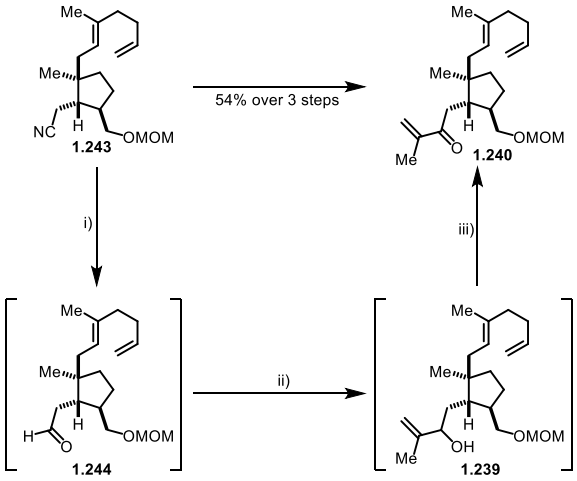


Entry	Equiv. of Grignard	Additives	Solvent	Temp.	Time /h	Yield
1	2 + 5	-	THF	rt – reflux	48	No conversion
2	1.1 + 2.2	CuI (0.05 eq.)	THF	reflux	48	No conversion
3	5	CuI (0.2 eq.)	THF	reflux	17	Complex mixture[a]
4	1.5	-	Et_2O	0 °C - rt	24	No conversion
5	1.5	-	Et_2O	rt	6	No conversion
6	1.5	-	Et_2O	reflux	16	10%
7	1.5 + 1.5	CuI (0.1 eq.)	Et_2O	rt – reflux	48	No conversion

[a] A peak was observed in the mass spectrometry trace (ESI^+) of the crude material, whose *m/z* corresponded to the amine **1.249**.

It was clear that the direct addition of the Grignard reagent **1.248** to nitrile **1.243** was not feasible and so we instead pursued our alternative route, detailed in Scheme 1.43. This was to reduce the nitrile **1.243** to a far more reactive aldehyde (**1.244**, after quench); addition of the Grignard reagent **1.248** would give an allylic alcohol (**1.239**), which could be oxidised to

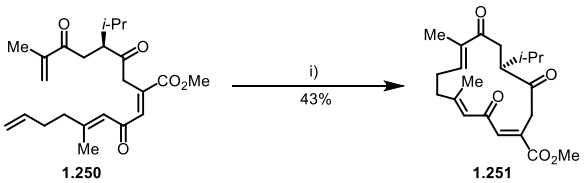
the enone **1.240**. This route was far more successful and a 54% yield of enone **1.240** was achieved after a three step transformation (Scheme 1.45).



Scheme 1.45. *Reagents and conditions*: i) DIBAL-H (1.2 eq.), CH_2Cl_2, 0 °C, 1.5 h; ii) isopropenylmagnesium bromide (1.5 eq.), THF, -78 °C – rt, 2 h; iii) IBX (3 eq.), 1:3 DMSO/THF, rt, 2 h, dark.

1.4.5 Ring Closing Metathesis of 1.240

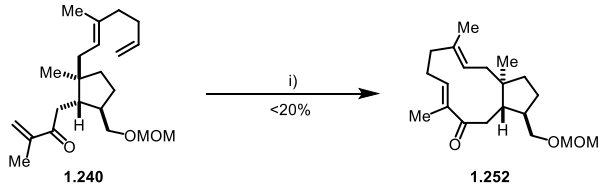
Our next goal was to optimise the ring closing metathesis, a reaction that we expected would be difficult. The entropic cost to making the required 11-membered ring means that intermolecular metatheses and polymerisation reactions can often dominate.[40] To our knowledge the closest example, in terms of stereoelectronic factors, is that of the synthesis of methyl sarcoate **1.251** reported by Nakata and co-workers (Scheme 1.46).[41,42]



Scheme 1.46. Ring closing metathesis reaction to synthesise methyl sarcoate **1.251**, reported by Nakata and co-workers.[41,42] *Reagents and conditions*: i) Grubbs 2nd gen. (1 eq.), toluene (0.001 M), 100 °C, 0.5 h.

Although the reaction used a stoichiometric amount of the expensive Grubbs 2nd generation catalyst, and gave a moderate yield of product, we were attracted to these conditions as it gave the desired (*E*)-stereochemistry of the newly formed alkene.

Using these conditions with just 3.4 mg of enone **1.240**, we were able to isolate the desired product **1.252** using preparative TLC (Scheme 1.47). Mapping the correlations on the ^{1}H NOESY spectrum (Figure 1.8) provided strong evidence that we had obtained the (*E*)-configured enone as well as retaining the rest of the stereochemical information. Analysis of the crude ^{1}H NMR spectrum showed that this was not the only product however (we were unable to isolate the side products for characterisation), and we endeavoured to find conditions that would give just the desired product.



Scheme 1.47. *Reagents and conditions*: i) Grubbs II (1 eq.), toluene (0.001 M), 100 °C, 1 h.

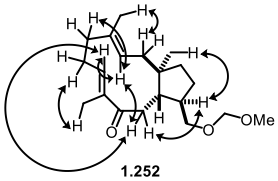
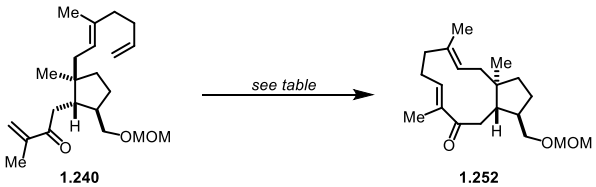


Figure 1.8. Selected nOe correlations, obtained from a ^{1}H NOESY spectrum (see Experimental section, chapter 3).

With a limited supply of enone **1.240** available, we decided to test each set of conditions using just 5 mg of starting material, and compare the crude TLC and ^{1}H NMR spectrum obtained to the data from our positive result (Scheme 1.47, and Table 1.7, entry 1). In this manner we could quickly eliminate any conditions that gave either no conversion or polymerisation, without wasting precious material. In this manner, we found that reducing

the catalyst loading to 50 mol% (Table 1.7, entry 2) gave similar results to using 100 mol%, but further reduction to 20 mol% (entry 3) gave incomplete conversion. This was true even after leaving the reaction considerably longer (entry 4), indicating that catalyst deactivation might be the limiting factor. Running the reaction at the lower temperature of 50 °C (entry 5) to avoid decomposition of the catalyst, and compensating by running the reaction for longer, simply gave an increased number of unknown side products. Likewise, running the reaction at 100 °C but stopping after just 30 minutes (entry 6) also gave an increased number of side products. Conditions used by Hoveyda and co-workers for the synthesis of clavirolide C (section 1.1.6) gave complete conversion,[18] but no trace of the desired product (entry 7). Finally, increasing the concentration to 0.01 M (entry 8), or changing the solvent to CH_2Cl_2 (entry 9) gave poorer results than those originally obtained in entries 1 and 2. Since an improved set of conditions were not forthcoming we decided to scale the reaction up to use 30 mg of starting material **1.240** so that we could obtain a meaningful yield (entry 10). Unsurprisingly, based on the TLC and ^{1}H NMR data that we had collected so far, the product **1.252** could only be isolated in 14% yield.

Table 1.7. Attempted Optimisation of the Ring-Closing Metathesis of **1.240**



1.240 **1.252**

Entry [a]	Catalyst	Loading /mol%	Solvent	Temp /°C	Conc. /M	Time	Results
1	Grubbs II	100	Toluene	100	0.001	1	Product obtained
2	Grubbs II	50	Toluene	100	0.001	1	Product obtained
3	Grubbs II	20	Toluene	100	0.001	2	Poor conversion
4	Grubbs II	20	Toluene	100	0.001	16	Poor conversion
5	Grubbs II	50	Toluene	50	0.001	88	Increased side product
6	Grubbs II	50	Toluene	100	0.001	0.5	Increased side products
7	HG-II	20	DCE	86	0.001	72	0%
8	Grubbs II	50	Toluene	100	0.01	0.5	Increased side products
9	Grubbs II	50	CH_2Cl_2	40	0.001	0.5	Increased side products
10 [a]	Grubbs II	50	Toluene	100	0.001	16	14%

[a] Reactions conducted on a 14.3 µmol scale unless otherwise noted. [b] Reaction conducted on an 86.1 µmol scale.

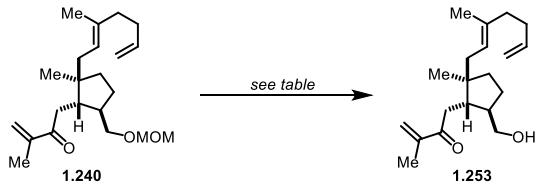
1.4.6 Removal of the Protecting Group

In parallel to screening conditions for the ring closing metathesis, we screened a variety of conditions for the deprotection of the primary alcohol. The reason for this was two-fold: first, the deprotected alcohol **1.253** could perform more favourably in the ring-closing metathesis; second, the deprotection of enone **1.240** would serve as a useful litmus test for the deprotection of the ring closed product **1.252**.

Our initial conditions for the deprotection of **1.240** were scandium(III) triflate at room temperature in dichloromethane.[43] Unfortunately no conversion was observed in either anhydrous CH_2Cl_2 (Table 1.8, entry 1), nor when water was added and the reaction heated to

40 °C (entry 2). Deprotection conditions reported by Raju and co-workers gave poor conversion after 1 h (entry 3),[44] and multiple side products (from which isolation of the desired product was not attempted) when the reaction was driven to completion (entry 4). Treatment of **1.240** with 2 M $HCl_{(aq.)}$ in MeOH (entry 5) was equally discouraging. Conditions reported by Fürstner (entry 6),[45] Fuwa (entry 7),[46] and Covey (entry 8),[47] and their respective co-workers were all unsuccessful, giving a number of different products (as determined by TLC and crude ^{1}H NMR spectrum, from which isolation of the desired product was not attempted).

Table 1.8. Attempted Optimisation for the Deprotection of Enone **1.240**.

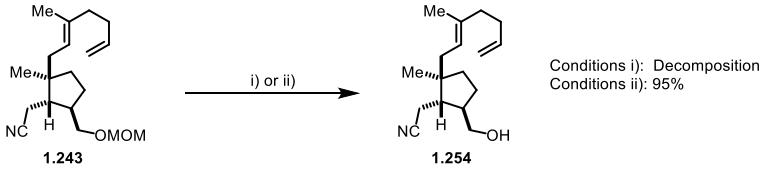


1.240 **1.253**

Entry	Reagents and solvent	Temp. /°C	Time /h	Results
1	$Sc(OTf)_3$ (1 eq.), CH_2Cl_2	25	1	No conversion
2	$Sc(OTf)_3$ (1 eq.) + H_2O (1 drop), CH_2Cl_2	40	2	No conversion
3	$Zn(OTf)_2$ (0.1 eq.), IPA	85	1	Poor conversion
4	$Zn(OTf)_2$ (1.3 eq.), IPA	85	16	Multiple side products
5	1:15 2 M $HCl_{(aq.)}$/MeOH	65	24	Multiple side products
6	Me_3SiCl (20 eq.), Bu_4NBr (20 eq.), CH_2Cl_2	0	4	Multiple side products
7	$LiBF_4$ (10 eq.), 1:25 H_2O/MeCN	72	16	Multiple side products
8	1.8:7:2 conc. HCl/MeOH/CH_2Cl_2	25	24	Multiple side products

The results obtained so far for both the alcohol deprotection and ring closing metathesis were highly discouraging, and we were especially concerned that even if we were able to optimise the ring closing of **1.240**, we might not be able to remove the protecting group

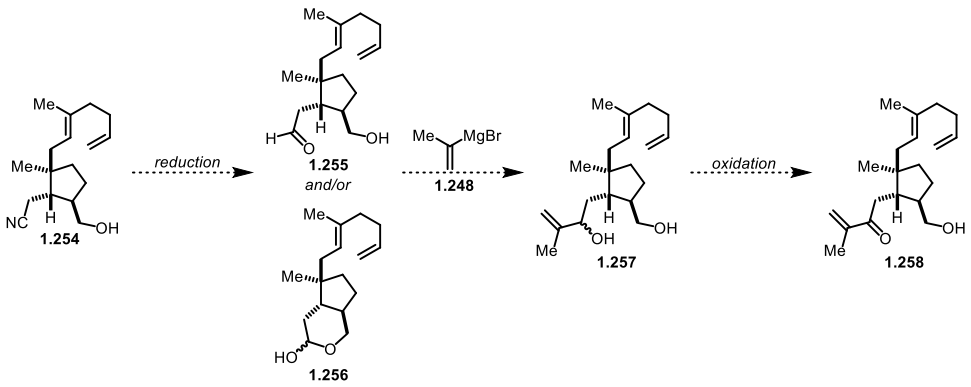
from **1.252**. A change in tactic was needed, and we decided to remove the protecting group at an earlier point in the synthesis, namely, from the nitrile **1.243**. Treatment with $Sc(OTf)_3$ gave the familiar pattern of decomposition, but alternative conditions using a 1.8:7:2 ratio of concentrated HCl (37%) to MeOH to CH_2Cl_2 gave an exceptionally clean crude ^1H NMR spectrum,[47] and we obtained **1.254** in an isolated yield of 95% (Scheme 1.48).



Scheme 1.48. *Reagents and conditions*: i) $Sc(OTf)_3$ (1 eq.), CH_2Cl_2, 0 °C – rt, 5 h, 0%; ii) 1.8:7:2 conc. HCl (37%)/MeOH/CH_2Cl_2, rt, 27 h, 95%.

1.4.7 Functional Group Interconversion to Allylic Alcohol 1.257

The excellent yield for the deprotection of **1.243** to give **1.254** was a boon to the synthetic campaign. We were keen to keep it in the synthesis, despite the obvious functional group incompatibilities in the upcoming steps: DIBAL-H reduction, Grignard addition, and oxidation of the 2° allylic alcohol moiety, all in the presence of a primary alcohol (Scheme 1.49). We reasoned that the first two problems could be solved by using an excess of reagent, whilst the oxidation could be performed with a judicious choice of reagent, such as manganese dioxide.



Scheme 1.49. Upcoming transformations on the nitrile **1.254**.

In practice, the DIBAL reduction of nitrile **1.254** appeared to cleanly provide access to the lactol **1.256** (Scheme 1.50~~Scheme 1.50~~). However, the mass spectrum provided some evidence that hemiaminals **1.259**, **1.260**, and **1.261** were also present. This mixture of lactol **1.256** and the hemiaminals **1.259** – **1.261** would come from incomplete hydrolysis after the reduction of the nitrile **1.254**. This was somewhat surprising however since we had expected that the aqueous workup and column chromatography on silica (a substance generally presumed to be mildly acidic) would give complete hydrolysis. Treating this mixture of with isopropenyl magnesium bromide gave just a moderate yield of the allylic alcohol **1.257**.

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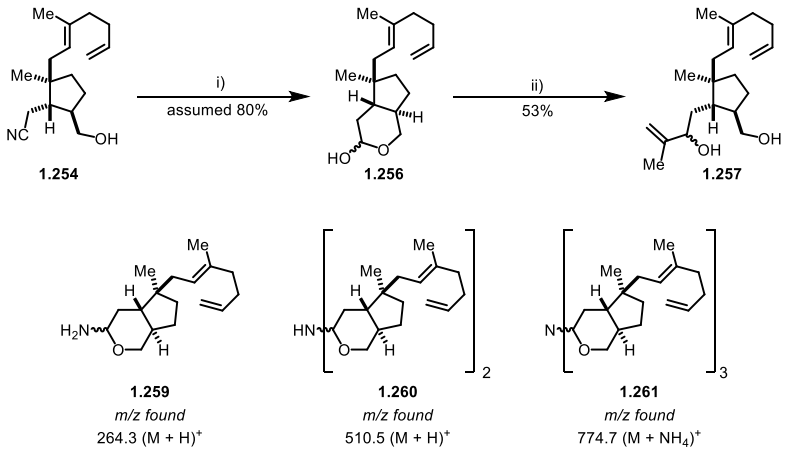
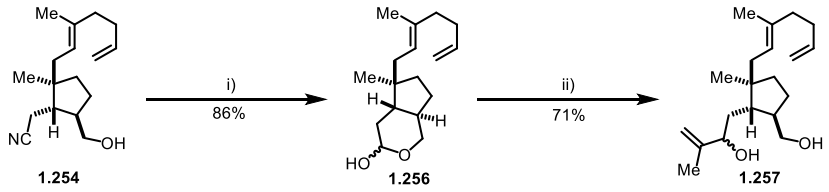


Scheme 1.50. *Reagents and conditions*: i) DIBAL-H (2.2 eq.), CH_2Cl_2, -78 to 0 °C, 1.5 h; ii) isopropenylmagnesium bromide (5 eq.), THF, -78 °C to rt, 16 h, *quench and then* isopropenylmagnesium bromide (5 eq.), THF, 0 °C to rt, 3 h.

This problem was quickly rectified however by stirring the mixture of lactol **1.256** and hemiaminals **1.259** – **1.261** overnight in a 1:1 mixture of 2 M $HCl_{(aq.)}$/THF at room temperature (Scheme 1.51~~Scheme 1.51~~). The removal of some of the peaks in the ^{1}H NMR spectrum was noted (Figure 1.9), with corresponding increases in intensity in the remaining peaks. Whilst we did not isolate any of the suspected hemiaminals and thus cannot be certain that the peaks removed belonged them, this is extremely likely to be the case. The diol **1.257** was then isolated in an improved yield after subjecting the pure lactol **1.256** to two rounds of Grignard reagent addition.



Scheme 1.51. *Reagents and conditions*: i) DIBAL-H (2.2 eq.), CH_2Cl_2, -78 to 0 °C, 1.5 h, *stir overnight with Rochelle's salt, purify by column chromatography, then* stir overnight in 1:1 2 M HCl/THF; ii) isopropenylmagnesium bromide (3.75 eq.), THF, 0 °C – rt, 3 h, *quench and then* isopropenylmagnesium bromide (5 eq.), THF, 0 °C – rt, 3 h.

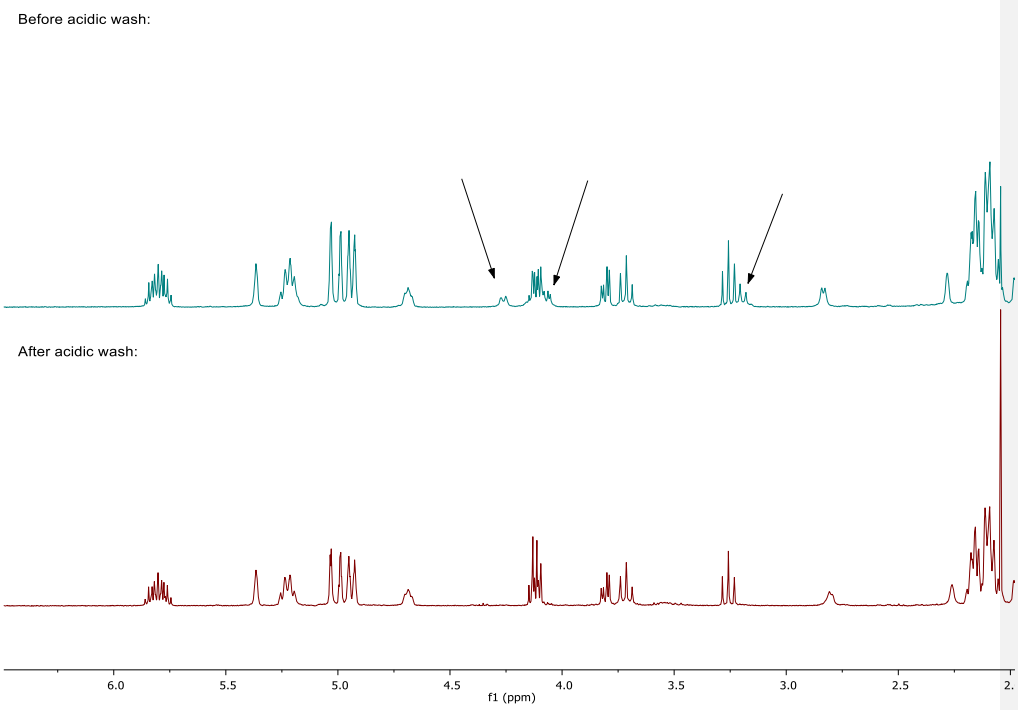
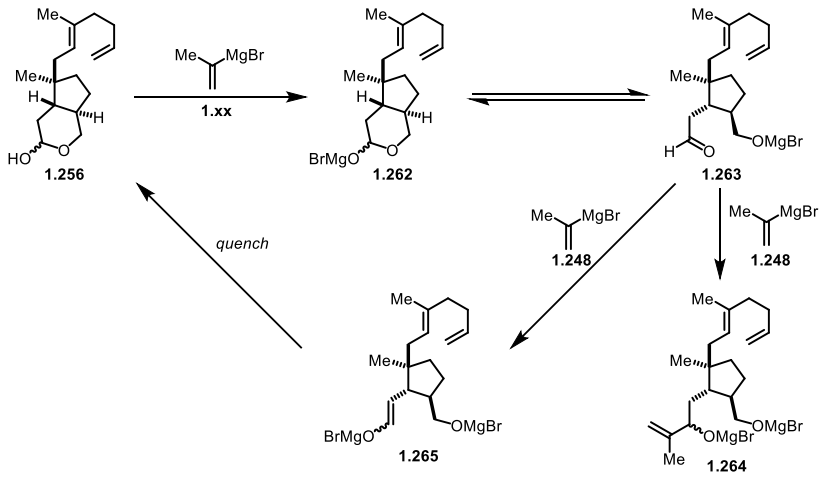


Figure 1.9. Comparison of the ^{1}H NMR spectra obtained before and after stirring the lactol **1.256** in acidic media overnight. Arrows have been drawn in to indicate the peaks that were no longer present after stirring.

A single round of Grignard reagent addition resulted in incomplete conversion, despite using extended reaction times and an excess of the Grignard reagent, but quenching and subjecting the crude material to further Grignard reagent gave good conversion (Scheme 1.51). We suspect that deprotonation of the lactol **1.256** gives an equilibrium mixture of aldehyde **1.263** and hemiacetoxide **1.262** (Scheme 1.52); a second deprotonation of the former would give the enolate **1.265**, which is unreactive to Grignard addition. Quenching this enolate would give back the starting material, which can be resubmitted to the reaction to give higher conversion.



Scheme 1.52. Proposed reaction mechanism upon treatment of lactol **1.256** with Grignard reagent **1.248**.

1.4.8 Ring Closing Metathesis of Allylic Alcohol 1.257

A sufficient quantity of diol **1.257** had now been synthesised to allow for the optimisation of the ring-closing metathesis reaction. We expected that the more electron rich allylic alcohol **1.257** (as compared to enone **1.240**, see Table 1.7) would be much more reactive to ring closing metathesis. Hoye and Zhao first published this effect as a list of similar allylic alcohols and allylic methyl ethers, each with their relative reactivity (Figure 1.10).[48] A review by Lin and Davis suggested that of the various explanations put forth for such an effect,[49] hydrogen bonding of the alcohol to the chloride ligand of catalyst **1.271** was the most likely.

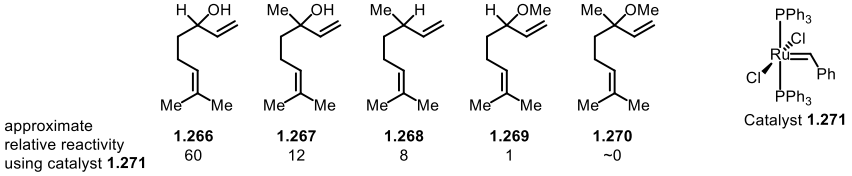
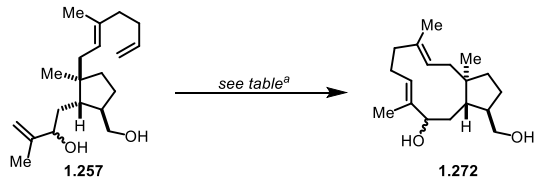


Figure 1.10. The approximate relative reactivity of differentially substituted dienes, as reported by Hoye and Zhao.[48]

We began by testing the best conditions for the ring closing metathesis of enone **1.240** on alcohol **1.257**, but the data from the ^{1}H NMR spectrum and TLC suggested that complete polymerisation had taken place, since there were now no discrete peaks/spots in either

(Table 1.9, entry 1). Fortunately we had elected to once again to perform each set of conditions on a 5 mg scale, and only scale up the reactions which looked promising. For this screening we used freeze-pump-thaw degassing to remove dissolved oxygen, as oxygen has been reported to be detrimental to ring-closing metatheses.[40] We aimed to reduce the reactivity of the system by switching to a less active catalyst (entries 2 and 3), reducing the reaction time (entry 3, as compared to 2) or reducing the temperature (entry 5). We also added 2,6-dichlorobenzoquinone, which has been reported to remove undesired ruthenium hydride species capable of alkene isomerisation (entry 4),[50] but unfortunately this had no effect. It was only by a combination of reducing the catalyst loading, reaction temperature and reaction time that the reactivity was sufficiently modulated to enable us to at least distinguish different species in the crude ^{1}H NMR spectrum and TLC (entry 6).

Table 1.9. Attempted Optimisation of the Ring Closing Metathesis of Alcohol **1.257**

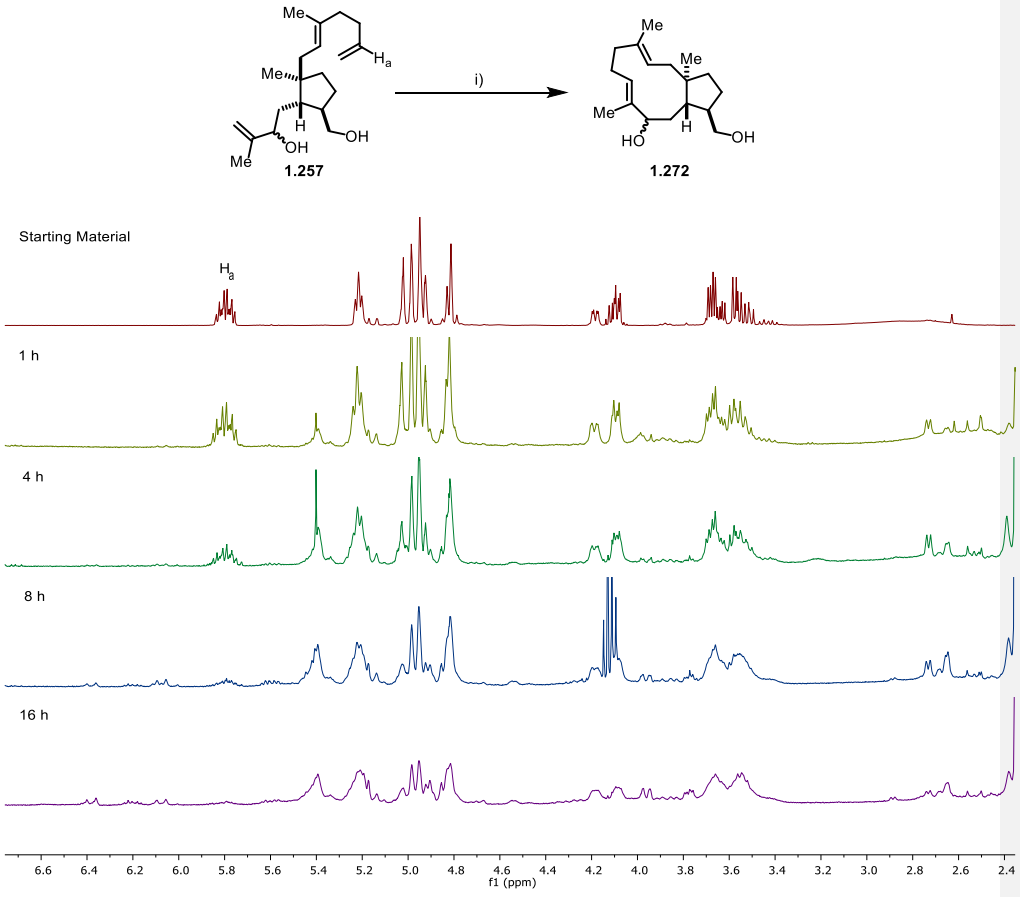


1.257 **1.272**

Entry [a]	Catalyst	Loading	Temp. /°C	Time	Results
1	Grubbs II	50	100	1	Polymerisation
2 [b]	Grubbs I	50	100	17.5	Polymerisation
3	Grubbs I	50	100	2	Polymerisation
4 [c]	Grubbs I	50	100	2	Polymerisation
5	Grubbs II	50	25	16	Polymerisation
6	Grubbs II	10	25	16	Distinguishable products

[a] *Reagents and conditions*: 0.001 M concentration of **1.257**, toluene (degassed using the freeze-pump-thaw technique). Catalyst, loading, temperature and time are as described in the table. After the allotted time, each reaction was reduced *in vacuo* to give the crude product, which was taken in $CDCl_3$ for a ^{1}H NMR. [b] Reaction quenched with 100 eq. of ethyl vinyl ether, stirred for 10 minutes, then reduced *in vacuo* to give the crude product. [c] 2,6-dichlorobenzoquinone (1 eq.) was added to the reaction.

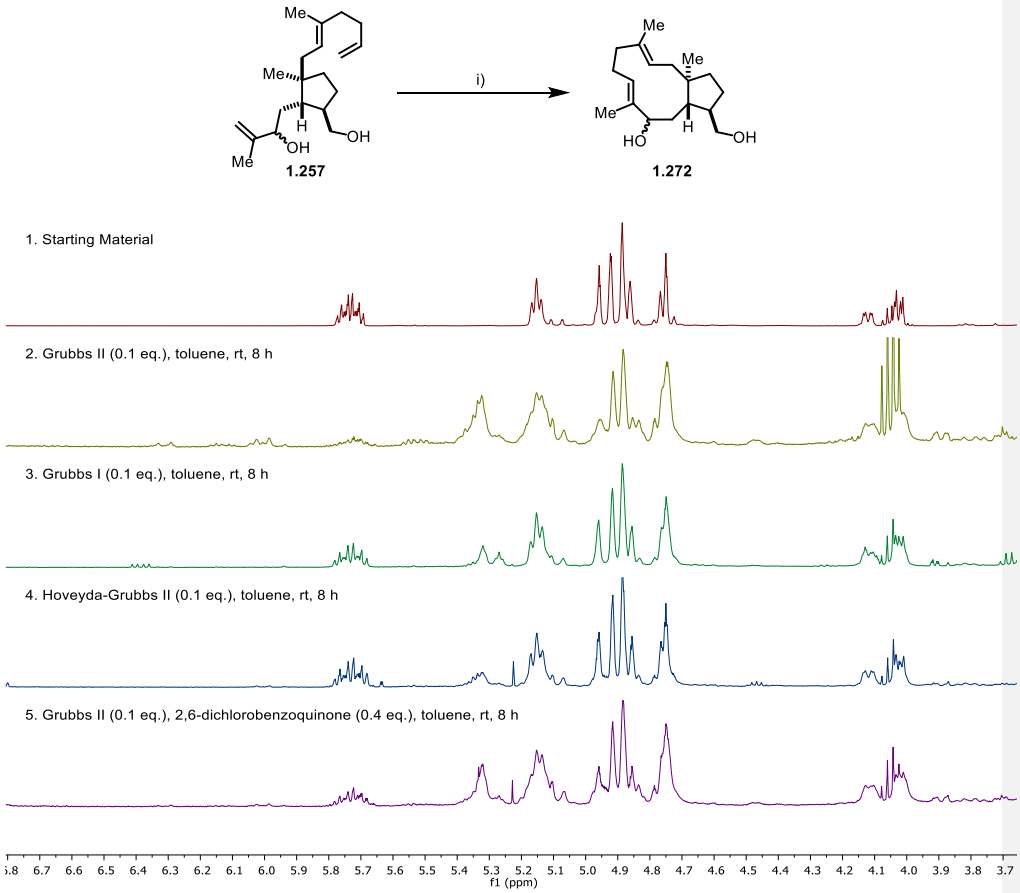
With a more sensible starting point in reactivity in hand, we wished to find the optimum time to stop the reaction. Since the reaction was too dilute to reliably use TLC, we elected to perform several reactions in parallel, quenching each at defined time points, and comparing their conversion by ^{1}H NMR spectrum. The peak at 5.80 ppm in the ^{1}H NMR spectrum that corresponds to the vinylic $H_2C{=}C\mathbf{H_a}$-R in the starting material **1.257** was a sensible choice to monitor conversion since it was in an isolated region of the spectrum and would not be present in the desired product **1.272**.



Scheme 1.53. Time study of the ring-closing metathesis reaction of allylic alcohol **1.257**. *Reagents and conditions*: i) Grubbs II (10 mol%), toluene (freeze-pump-thaw degassed, 0.001 M), rt, time as indicated for each crude ^{1}H NMR spectrum.

It can be seen from Scheme 1.53 that of the four time points that were trialled, the optimum reaction time is eight hours. We therefore elected to use this reaction time for the further screening of conditions.

Next, we compared the conversion of starting material to product for the following catalysts: Grubbs I, Grubbs II, Hoveyda-Grubbs II, and Grubbs II with 2,6-dichlorobenzoquinone as an additive (Scheme 1.54).

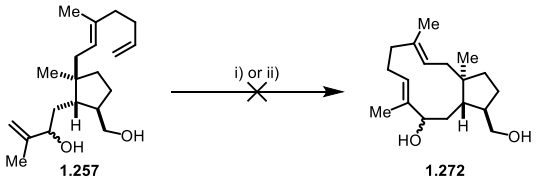


Scheme 1.54. Comparison of the different levels of conversion that are obtained with different ring closing metathesis catalysts.

Neither Grubbs I nor Hoveyda-Grubbs II (Scheme 1.54, spectra 3 and 4) were able to achieve levels of conversion comparable to Grubbs II (spectrum 2). Since we had used ^{1}H NMR

spectra to determine the conversion, we could once again estimate the purity of the crude material. We determined from a visual analysis of spectra 2 and 5 that the addition of 2,6-dichlorobenzoquinone minimised the formation of side products, presumably by minimising alkene isomerisation.[50]

We decided that sufficient optimisation had been performed to justify moving to a larger scale (30 mg of **1.257**) reaction. Our most promising conditions so far had been using Grubbs II as the catalyst with 2,6-dichlorobenzoquinone as an additive. Unfortunately we were unable to isolate any product when using 0.1 eq. of catalyst and 0.4 eq. of additive (Scheme 1.55, conditions I). Recognising that the reaction conversion was not complete under these conditions, we increased the loading of catalyst and additive to 0.5 and 2 equivalents respectively (conditions II), but were still unable to isolate the desired product. Further optimisation of this reaction could not be completed due to time constraints.

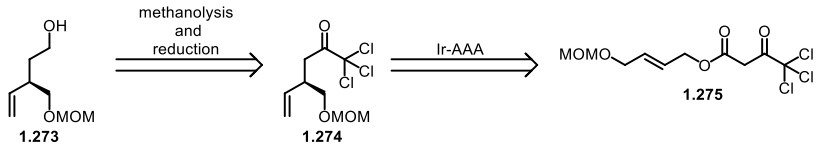


Scheme 1.55. *Reagents and conditions*: i) Grubbs II (0.1 eq.), 2,6-dichlorobenzoquinone (0.4 eq.), toluene, rt, 8 h; ii) Grubbs II (0.5 eq.), 2,6-dichlorobenzoquinone (2 eq.), toluene, rt, 8 h.

Although we were unable to complete the total synthesis using racemic material in the time available to us, we were able to develop in parallel a method that would synthesise enantiopure material which could intercept the racemic route developed so far. Future work in the area will be able to take advantage of this optimised route, and the material synthesised from it. The different routes that were trialled, along with the route that was ultimately successful, are detailed below (section 1.5).

1.5 Synthesis of Enantioenriched Alcohol 1.273

To synthesise the required single enantiomer of alcohol **1.273** from our disconnection (Scheme 1.28), we proposed that an iridium catalysed asymmetric allylic alkylation (Ir-AAA) to form trichloroketone **1.274** from **1.275** could be used to install the stereocentre (Scheme 1.56). The trichloroketone functional group is extremely versatile, and can be subjected to hydrolysis or alcolysis to give the corresponding acid or ester, which can be reduced to give an alcohol.[51–53]



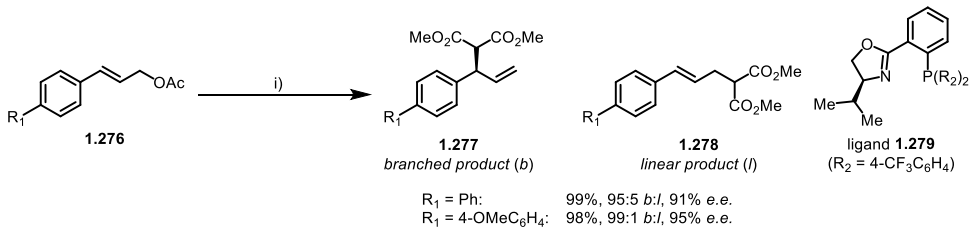
Scheme 1.56. An outline of the strategy proposed for the preparation of alcohol **1.273**

This new methodology would expand upon previous work within the Burton group achieved by Jiang.[25] The following is a summary of their work, along with key findings reported in the literature relevant to this methodology.

1.5.1 Iridium Catalysed Asymmetric Allylic Alkylation (AAA)

A short introduction to this field will now be presented to give the necessary context and background information to the reader.

Helmchen and co-workers reported the first asymmetric allylic alkylation, whereby aryl allylic acetates reacted with sodium dimethylmalonate to give selectively the branched product in excellent yields and enantioselectivities (Scheme 1.57).[54] Note that the ratio of the branched product to linear product will henceforth be abbreviated to "*b*:*l*".



Scheme 1.57. The first iridium catalysed asymmetric allylic alkylation, reported by Helmchen and co-workers.[54] *Reagents and conditions*: i) $[Ir(COD)Cl]_2$ (4 mol%), ligand **1.279** (8 mol%), sodium dimethylmalonate (3 eq.), THF, reflux, 24 h.

Later reports have typically used phosphoramidite ligands such as the ones shown below in Figure 1.11. These ligands have been found to be particularly efficient at giving good branched to linear ratios and high enantiomeric excesses.[55]

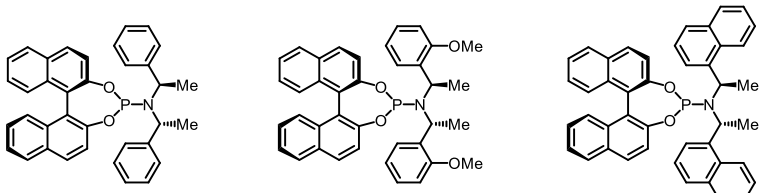
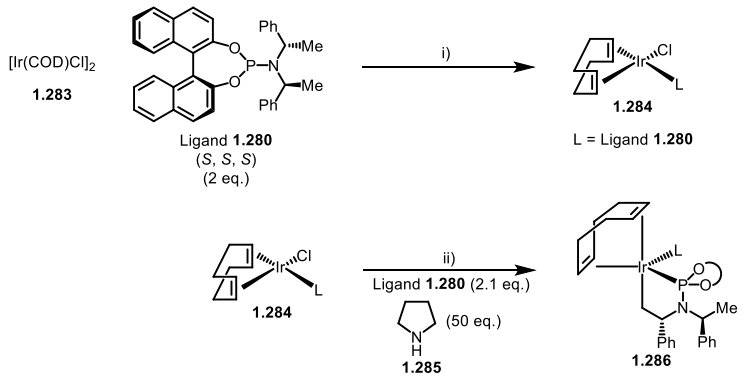


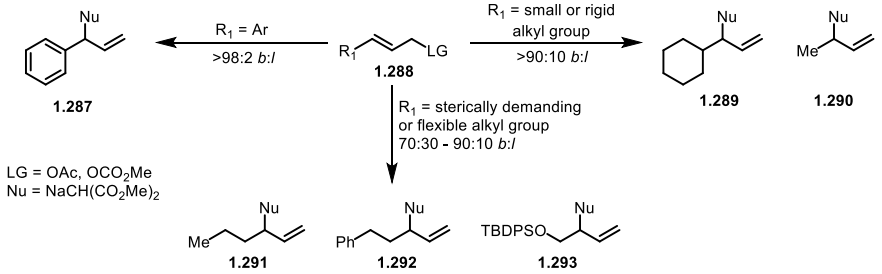
Figure 1.11. Commonly used phosphoramidite ligands for iridium catalysed asymmetric allylic alkylations.

In 2003 Hartwig and co-workers reported the identification of the Ir-metallocycle **1.286** which they proposed to be the active catalyst in iridium catalysed AAA reactions which used a phosphoramidite ligand (Scheme 1.58).[56] Taking the precatalyst $[Ir(COD)Cl]_2$ with the ligand **1.280** formed the square planar complex **1.284**, but this was found to be incompetent as a catalyst. Treatment of this with pyrrolidine however gave a new species, which was determined to be **1.286.** Reactions catalysed by this metallocycle **1.286** were much faster and did not begin with an induction period, which meant that lower catalyst loadings were now possible. However it was noted by Tosatti and co-workers in their review that the active catalyst **1.286** that is formed from $[Ir(COD)Cl]_2$ is oxygen and moisture sensitive,[55] a limitation of this methodology.



Scheme 1.58. Synthesis of the active catalyst **1.286**, reported by Hartwig and co-workers.[56] *Reagents and conditions*: i) THF, rt, 10 mins; ii) THF, rt, o/n.

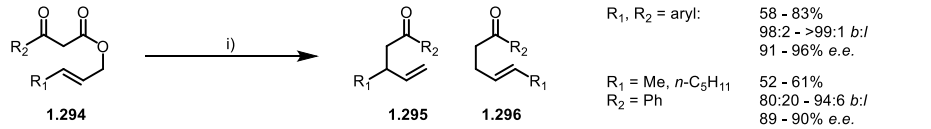
Much of the reports related to the iridium catalysed AAA are concerned with the use of stabilised carbon nucleophiles, in particular malonates,[54,57,58] but also aliphatic nitro compounds,[59] malononitriles,[60,61] α,β-unsaturated malonates (which react at the γ-position),[62] and β-ketoesters.[63] The vast majority of the allylic substrates used have been styrenyl in nature (Scheme 1.59), since these often give a far better ratio of branched to linear products (>98:2 *b*:*l*). In cases where the authors have placed aliphatic substituents on the alkene, the regioselectivity can drop to 90:10 for small substituents such as Me, and even 70:30 for sterically demanding substituents such as *n*-Pr, *n*-octyl or *i*-Pr.[64]



Scheme 1.59. Typical branched to linear ratios that can be expected for different allylic substituents.[64]

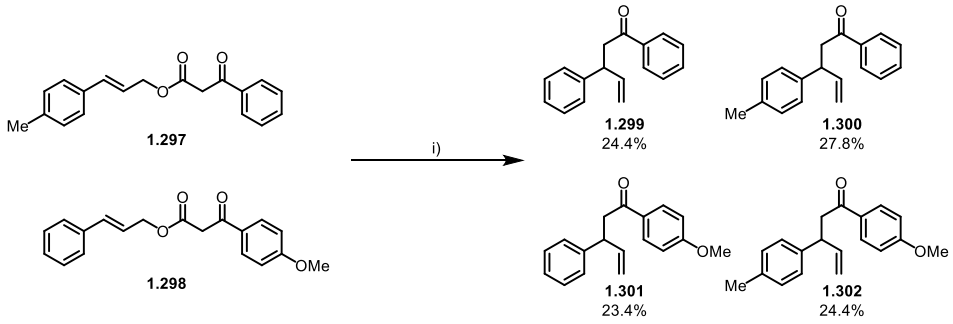
Nucleophiles based on a heteroatom such as nitrogen or oxygen have also been widely reported and reviewed,[55,64–66] but are beyond the scope of this short introduction.

This short introduction concludes by summarising the work of You and co-workers,[67] who reported a decarboxylative iridium catalysed AAA where the nucleophile is "built-in" to the substrate (Scheme 1.60). Excellent yields, branched to linear ratios, and enantiomeric excesses were obtained in the cases were R_1 and R_2 are aromatic, but poorer performance was observed when R_1 was aliphatic. No substrates were reported where R_2 was not aromatic.



Scheme 1.60. Enantioselective iridium catalysed decarboxylative allylic alkylation reported by You and co-workers.[67] *Reagents and conditions*: i) $[Ir(COD)Cl]_2$ (2 mol%), ligand **1.280** (4 mol%), DBU (200 mol%), CH_2Cl_2, reflux, 3 – 22 h.

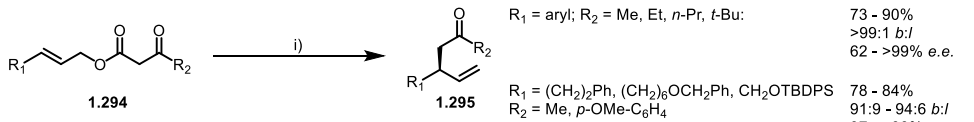
This reaction may formally be classed as a Carroll rearrangement, but a crossover experiment performed by the authors showed that since all four possible products were generated in approximately equal yields (determined by GC), the reaction cannot proceed via an intramolecular or cage-ion pair process (Scheme 1.61).



Scheme 1.61. Crossover experiment reported by You and co-workers.[67] *Reagents and conditions*: i) $[Ir(COD)Cl]_2$ (2 mol%), ligand **1.280** (4 mol%), DBU (200 mol%), CH_2Cl_2, reflux.

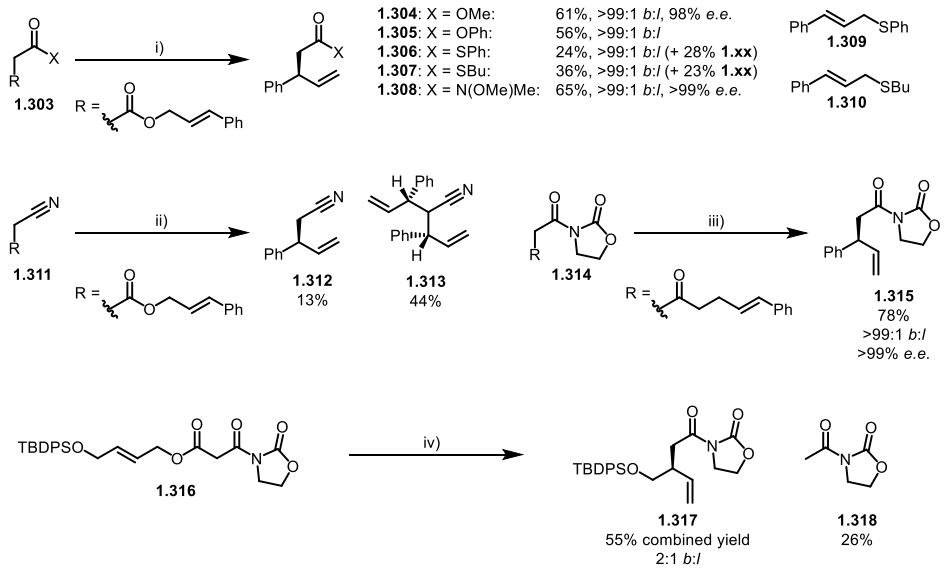
1.5.2 Relevant Work in the Burton Group

Inspired by the work of You and co-workers,[67] Jiang extended the methodology to include alkyl β-ketoesters and demonstrated an impressive substrate scope with high yields and enantiomeric excessed throughout (Scheme 1.62).[25]



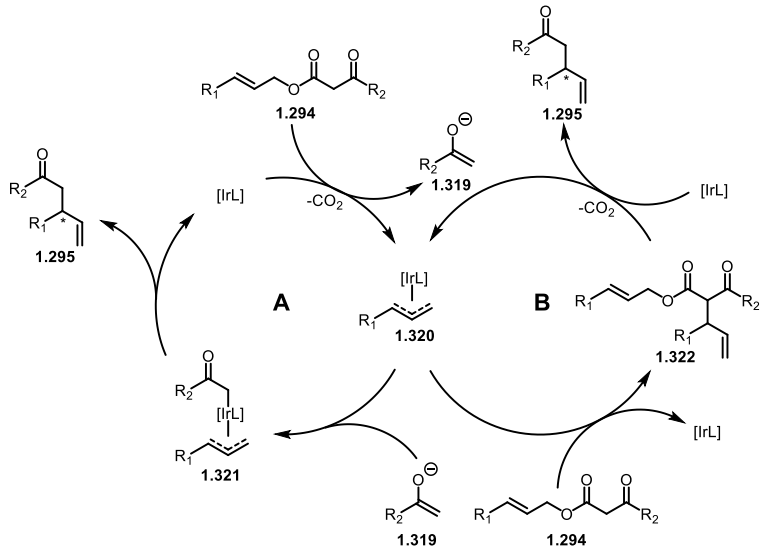
Scheme 1.62 Methodology reported by Jiang for the decarboxylative allylic alkylation of β-ketoesters. *Reagents and conditions*: i) $[Ir(COD)Cl]_2$ (4 mol%), ligand **1.280** (8 mol%), TBD (16 mol%), THF, rt, 1.5 – 4 h.

Jiang also aimed to optimise the reaction for substrates which contained an additional or alternative heteroatom, including malonates, mono thiomalonates, β-imidoesters, β-amidoesters, and α-cyanoesters (Scheme 1.63). The malonate class (X = OMe, OPh) gave only moderate yields of **1.304**/**1.305** and required very high loadings of catalyst. The monothiomalonates gave very poor yields of the desired products **1.306**/**1.307** in addition to the sulphanes **1.309** and **1.310**. The Weinreb amide **1.308** was synthesised in a moderate yield, but a very high catalyst loading was still required. The α-cyanoesters gave a poor yield of **1.312**, with 44% of the over alkylated product **1.313**. Switching to the β-imidoester **1.314** was much more successful for the styrene class, but unfortunately when the alkene possessed only alkyl substituents (**1.316**), the branched to linear ratio was much poorer and acetyloxazolidinone **1.318** was isolated as a side product. Since the optimisation for the model substrate in each class was not as successful as desired, and often required very high catalyst loadings, a substrate scope was not attempted.



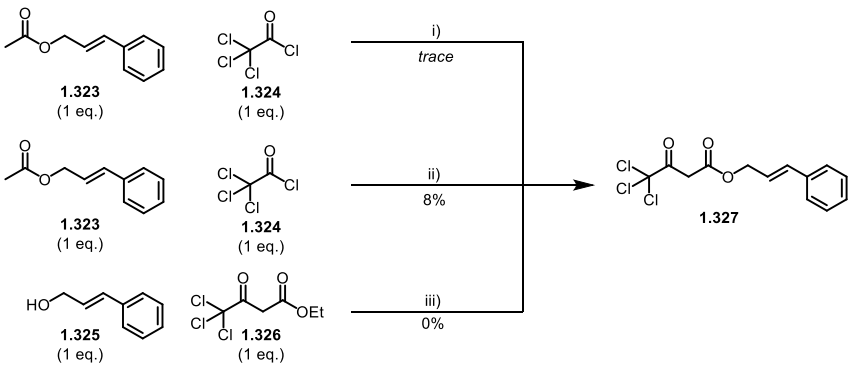
Scheme 1.63. Alternative substrates trialled by Jiang.[25] *Reagents and conditions*: Standard conditions: $[Ir(COD)Cl]_2$ (y mol%), ligand **1.281** (2y mol%), TBD (4y mol%), THF; i) X = OMe: y = 12, 60 °C, 22 h; X = OPh: y = 12, 50 °C, 3 h; X = SPh: y = 4, rt, 5 h; X = SBu: y = 12, 50 °C, 7 h; X = N(OMe)Me: y = 12, 50 °C, 6 h; ii) y = 12, 40 °C, 3 h; iii) y = 4, rt, 22 h; iv) y = 4, 40 °C, 6 h.

Jiang proposed the following mechanism to account for the side-products that had been isolated (Scheme 1.64).[25] At the beginning of the reaction when the concentration of ester **1.294** is high, it seems likely that the cycle B predominates, to give the intermediate **1.322**. This intermediate can then undergo decarboxylation to give the product **1.295** and the alkyliridium complex **1.320**. Towards the end of the reaction when the concentration of ester **1.294** is low, the ketone enolate **1.319** competes for the alkyliridium complex **1.320**, to give **1.321** (Scheme 1.64, cycle A). Reductive elimination of this complex gives the product **1.295** and the iridium catalyst.



Scheme 1.64. Mechanism proposed by Jiang for the decarboxylative alkylation.[25]

Although Jiang did not formally report her attempts to use trichloro β-ketoesters in her doctoral thesis, her weekly reports would suggest that she attempted their synthesis via the reactions shown below (Scheme 1.65), but was unsuccessful in obtaining a clean sample of **1.327** in useful quantities.



Scheme 1.65. Attempted synthesis of β-trichloroketoesters by Jiang. *Reagents and conditions*: i) LDA (1 eq.), THF, -78 °C; ii) LiHMDS (1.5 eq.), THF, -78 °C; iii) DMAP (1 eq.), 4 Å MS, toluene, rt – 130 °C.

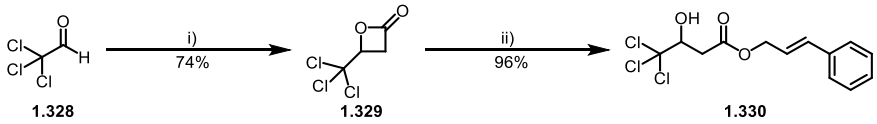
It was this analysis of the work by Jiang that prompted us to choose the trichloro β-ketoester substrate class for testing, since Jiang had already showed that the other

substrate classes were unsuitable for the Ir-AAA. Furthermore the versatility of the trichloroketone functional group that would be present in the product was attractive to us.

1.5.3 The Synthesis and Iridium Catalysed AAA of Trichloro-β-Ketoester 1.327

The optimisation process began by attempting the synthesis and Ir-AAA of substrate **1.327**; since cinnamyl alcohol is commercially available we expected the synthesis to be straightforward. Furthermore literature precedents (briefly surveyed above) suggested we could expect high branched:linear ratios for the substrate to initially simplify the problem (see Scheme 1.59).

We envisaged that the starting material **1.327** could come from a lactone ring opening and oxidation sequence (Scheme 1.66, Table 1.10). This lactone **1.329**, also known as Wynberg's lactone,[68] has been used as a single enantiomer on a number of occasions in the pursuit of total synthesis.[69,70] In our case the chiral centre would be rendered achiral by oxidation later in the synthesis which means that an achiral amine would make a suitable catalyst for the synthesis of **1.329**.

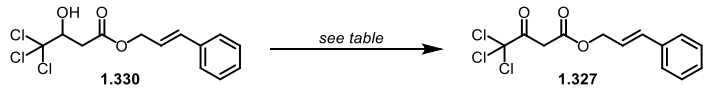


1.328 **1.329** **1.330**

Scheme 1.66. *Reagents and conditions*: i) acetyl chloride (2 eq.), Et_3N (2 eq.), Et_2O, 0 °C, 2 h; ii) cinnamyl alcohol (1.05 eq.), LDA (1.1 eq.), THF, 0 °C, 1 h.

Chloral **1.328** (obtained from chloral hydrate by distillation from a mixture containing concentrated sulfuric acid and phosphorus pentoxide) was treated with acetyl chloride and triethylamine in Et_2O to give lactone **1.329** in 74% yield after distillation (Scheme 1.66). From here the lactone could be rapidly opened with the appropriate alkoxide to give the trichloroalcohol **1.330**.

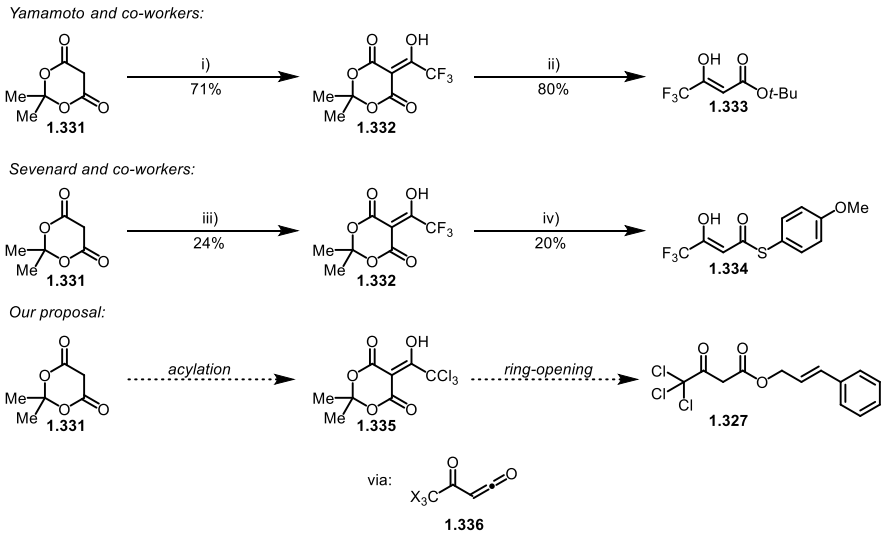
Table 1.10. Screening of Conditions for the Oxidation of **1.330**



Entry	Conditions	Yield	Notes
1	$(COCl)_2$ (1.1 eq.), DMSO (2.2 eq.), Et_3N (5 eq.), CH_2Cl_2, -78 to -50 °C, 2 h	30%	Incomplete conversion
2	$(COCl)_2$ (2 eq.), DMSO (4 eq.), Et_3N (5 eq.), CH_2Cl_2, -78 to -50 °C, 3 h	N.D.	Increased decomposition compared to entry 1
3	DMP (1.3 eq.), CH_2Cl_2, 0 °C, 4 h	25%	
3	DMP (2.2 eq.), CH_2Cl_2, 0 °C, 4 h	0%	Extensive decomposition of product
4	DMP (1.05 eq.), $NaHCO_3$ (3 eq.), CH_2Cl_2, 0 °C, 5 h	0%	No conversion
5	PCC (2 eq.), NaOAc (4 eq.), silica gel, CH_2Cl_2, rt, 6 days	0%	No conversion
6	CrO_3 (1.1 eq.), 1:25 H_2SO_4/AcOH, rt, 1.25 h	0%	No conversion

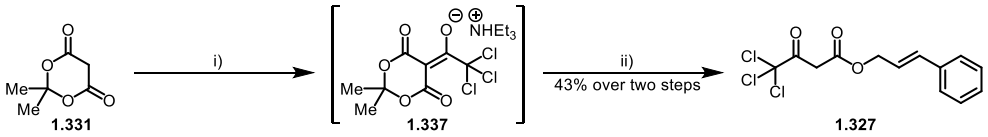
Unfortunately the oxidation of **1.330** proved more challenging than expected. We screened a number of oxidants but most conditions would either not oxidise this electron poor alcohol or gave the product **1.327** along with varying levels of decomposition (Table 1.10, entries 1-6). A Swern oxidation (entry 1) and DMP oxidation (entry 3) gave a 25-30% yield of the product **1.327**, but these yields were not sufficient to begin optimisation of this methodology, and certainly not for a total synthesis.

In searching for an alternative solution to our problem we were inspired by the work published by Yamamoto and co-workers,[71] and later by Sevenard and co-workers.[72] These authors detailed the acylation of Meldrum's acid **1.331** with *N*-trifluoroacetylimidazole to give **1.332** (Scheme 1.67), which was found to be prone to formation of the ketal **1.336**. Trapping **1.336** with a variety of nucleophiles gave a range of products in typically good yield: suitable examples are provided below (Scheme 1.67).



Scheme 1.67. *Reagents and conditions*: i) *N*-trifluoroacetylimidazole (1.1 eq.), imidazole (1 eq.), $CHCl_3$, rt, 35 min; ii) *t*-BuOH (1.1 eq.), $CHCl_3$, rt, 3 days; iii) *N*-trifluoroacetylimidazole (1 eq.), imidazole (1 eq.), $CHCl_3$, rt, 30 min *then* 1:3 $CHCl_3$/half saturated solution of HCl in Et_2O, -30 °C, 15 min; iv) 4-(methoxy)thiophenol (1 eq.), CH_2Cl_2, rt, 4 days.

In a forward sense, we used commercially available trichloroacetyl chloride to generate **1.337**, and adapted the ring opening conditions that had been reported by Hansen and co-workers in their synthesis of Sitagliptin (Scheme 1.68).[73] An acceptable yield of the desired trichloro β-ketoester **1.327** was achieved, enabling us to begin optimisation of the Ir-AAA. It was noted in the ^1H and ^{13}C NMR spectra ($CDCl_3$) that **1.327** exists in equilibrium with the two diasteromeric enol tautomers.

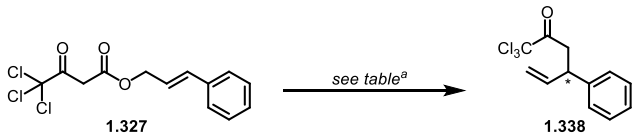


Scheme 1.68. *Reagents and conditions*: i) trichloroacetyl chloride (1 eq.), Et_3N (2 eq.), CH_2Cl_2, -40 °C, 2 h; ii) cinamyl chloride (1 eq.), TFA (1 eq.), CH_2Cl_2, 40 °C, 18 h.

Unfortunately the conditions trialled for the iridium catalysed AAA failed to give any of the desired product **1.338** (Table 1.11), with either the complete recovery or complete decomposition of starting material **1.327** in each case. This was surprising to us, since a range of β-ketoesters had all performed well in the studies by Jiang (Scheme 1.62), results

which we were able to replicate. Tosatti and co-workers had reported the sensitivity of the active catalyst **1.286** (see Scheme 1.58) to acids,[74] and we postulated that the increased acidity of our substrate compared to Jiang's (see Scheme 1.62) was causing the catalyst **1.286** to decompose. Cesium carbonate was added in an attempt to neutralised this acid (entries 3 and 4), selected for its use in published Ir-AAA methodologies,[55,67] but no conversion to the product was observed. We also tried heating the reaction to 50 °C (Table 1.11, entry 5) and although this resulted in complete consumption of starting material **1.327**, none of the desired product **1.338** was isolated.

Table 1.11. Screening of Conditions for the Ir-AAA of β-Ketoester **1.326**



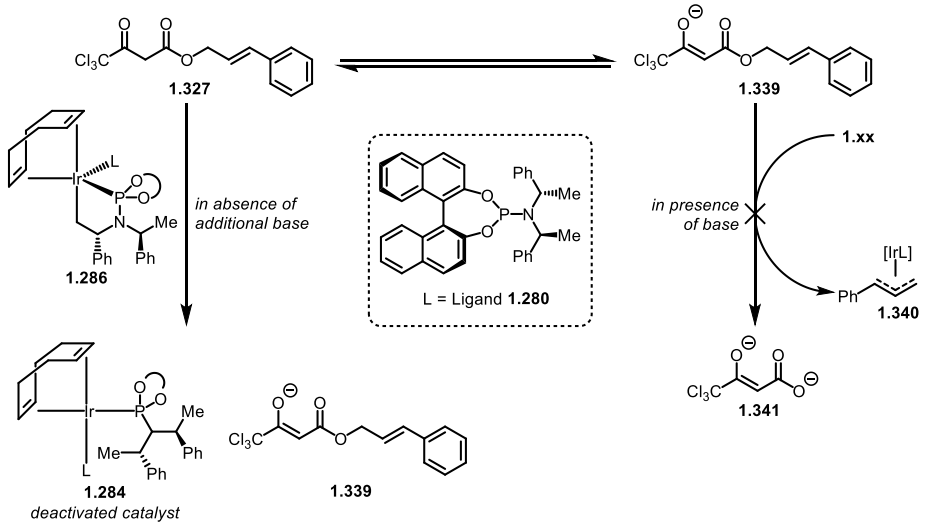
1.327 **1.338**

Entry	Base	Temp. /°C	Time /h	Yield (Conversion by crude ^{1}H NMR)
1	None	25	5	0 (0)
2	None	65	24	0 (0)
3	Cs_2CO_3 (0.3 eq.)	25	17	0 (0)
4	Cs_2CO_3 (1.2 eq.)	25	24	0 (0)
5	Cs_2CO_3 (1.2 eq.)	25 – 50	18.5	0 (*complete*)
6	Cs_2CO_3 (1.2 eq., pre-stirred with ester)	25 - 50	21	0 (*complete*)

[a] *Reagents and Conditions*: $[Ir(COD)Cl]_2$ (4 mol%), phosphoramidite ligand **1.280** (*S*,*S*,*S*-enantiomer, 8 mol%), TBD (16 mol%), THF. The identity and number of equivalents of base added, temperature and time as described in the table.

Our final set of conditions involved the pre-stirring ester **1.327** with cesium carbonate (Table 1.11, entry 6). Unfortunately this set of conditions gave no conversion either, at which point optimisation was ceased. Our hypothesis for the poor results is that there are two competing problems when using a substrate with a lower pK_a than a typical β-keto ester (Scheme 1.69). On the one hand, the protons generated by **1.327** may react with the active

catalyst **1.286**, rendering it inert, as described by Tosatti and co-workers.[55] On the other hand, the first step in the catalytic cycle was described by Jiang to be formation of the iridium π-allyl complex **1.320**, ejecting a carboxylate anion (which decarboxylates to give **1.319**, see Scheme 1.64). This is unlikely to proceed when the substrate **1.327** exists as its corresponding enolate **1.339**, since the formation of dianion **1.341** could only come from an extremely high energy transition state.



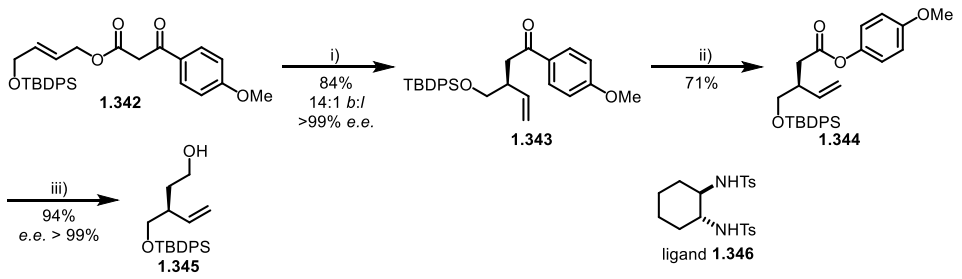
Scheme 1.69. Proposed explanation for the poor reactivity of β-ketoester **1.326** in both the presence and absence of base.

With a poorly yielding route to make starting material **1.327**, and no promising results, we decided to switch to a substrate that had been shown to be more successful by Jiang.

1.5.4 Synthesis of Enantioenriched Alcohol Via an Iridium Catalysed AAA of 1.351

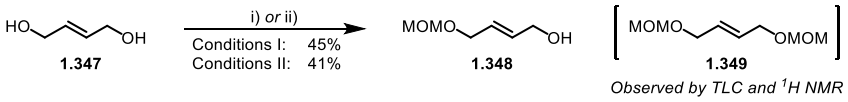
As discussed in Section 1.5.2, Jiang had found success in the iridium catalysed decarboxylative AAA of β-ketoesters. To couple this success with her objective to synthesise a single enantiomer of the target Dolabellane diterpenoid **1.5**, she sought a method to convert the enantioenriched ketone **1.343** into alcohol **1.345** (Scheme 1.70). With optimisation of the conditions reported by Shibasaki and co-workers,[75] Jiang was able to

perform a Baeyer-Villiger oxidation on **1.343** to give the corresponding ester **1.344**,[25] which has a good leaving group in place to enable reduction all the way down to the alcohol **1.345**. We envisaged that we could repeat this methodology on scale large enough to be suitable for our efforts towards the natural product **1.5**, using a MOM protecting group rather than a TBDPS one.



Scheme 1.70. Conversion of β-ketoester **1.342** to alcohol **1.345**, as reported by Jiang.[25] *Reagents and conditions*: i) $[Ir(COD)Cl]_2$ (4 mol%), ligand **1.281** (8 mol%), TBD (16 mol%), THF, rt, 3 h; ii) bis(trimethylsilyl)peroxide (1.1 eq.), $SnCl_4$ (0.5 eq.), ligand **1.346** (0.5 eq.), K_2CO_3 (1.5 eq.), 4 Å MS, CH_2Cl_2, 0 °C, 1 h; iii) DIBAL-H (2.3 eq.), THF, 0 °C, 1 h.

The route began with a mono protection of the commercially available diol **1.347** (Scheme 1.71). Unfortunately conditions reported by McDougal and coworkers (conditions I),[32] and by Forsyth and co-workers (conditions II),[76] both gave a mixture of product **1.348**, starting material **1.347**, and doubly protected alcohol **1.349**. Since this was the first step from commercially available starting materials, we accepted this limitation without further attempts at optimisation and moved onto the next step, a transesterification reaction.

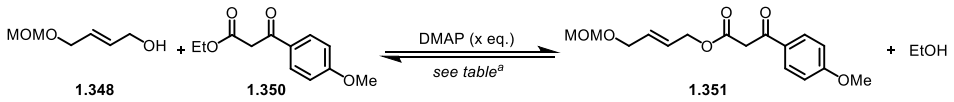


Scheme 1.71. *Reagents and conditions*: i) NaH (1 eq.), chloromethylmethyl ether (1 eq.), THF, 0 °C to rt, 24 h; ii) chloromethylmethyl ether(1.2 eq.), *i*-Pr_2NEt (3.9 eq.), CH_2Cl_2, 0 °C to rt, 5 h;

Under the thermal conditions that were analogous to those used by Jiang for such a transesterification, a poor yield was achieved (Table 1.12, entries 1 and 2), and so we elected to use a microwave reactor instead. The "microwave effect" has been repeatedly

reported to decrease the time required for a reaction to reach completion,[77] and we postulated that it could offer us an improvement in terms of time required and yield. Just one hour of microwave heating (entry 3) gave the same yield as 16 h of microwave heating (entry 2). It was clear that in the case of microwave heating, a lack of conversion was the reason for the poor yield. Heating the reaction for 5 hours at 120 °C (entry 4) gave a much improved yield, but heating the reaction to 140 °C (entry 5) gave a poorer yield and a number of side products. Using two equivalents of the ester **1.350** (entry 6) improved the yield of **1.351** to 65%. Combining this with multiple cycles of heating, reduction *in vacuo*, and re-addition of solvent (entry 7) gave a satisfactory yield of 76% of **1.351**, with 12% of the starting material **1.348** re-isolated. We hypothesise that this complicated procedure is required to continuously remove the ethanol that is produced as a by-product, which pushes the equilibrium over to the right hand side.

Table 1.12. Synthesis of β-Ketoester **1.351**



1.348 **1.350** (x eq.) **1.351**

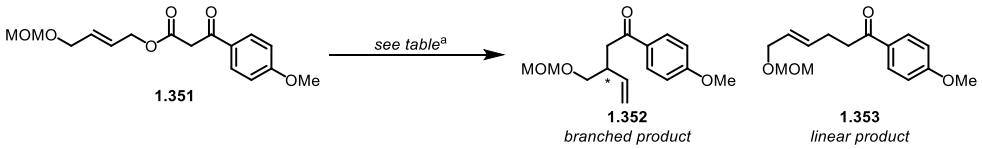
Entry	Heating Method	Equiv. of DMAP/ester (x)	Temperature / °C	Time /h	Yield
1[b]	Conventional	1	120	16	46
2[c]	Conventional	1	120	16	36
3	Microwave	1	120	1	35
4	Microwave	1	120	5	60
5	Microwave	1	140	5	37
6	Microwave	2	120	5	65
7	Microwave	2	120	5 x 1[d]	76 (86 b.r.s.m)

[a] *Reagents and conditions*: i) ethyl 3-(4-methoxyphenyl)-3-oxopropanoate, DMAP, toluene. The method of heating, equivalents of reagents, temperature and time of heating as specified in the table. [b] 1.5 g/(mmol of alcohol **1.348**) of 4 Å molecular sieves added to reaction. [c] 5 g/(mmol of alcohol **1.348**) of 4 Å molecular sieves added to reaction. [d] After 1 h of microwave heating, the reaction was reduced *in vacuo* at 50 °C to remove as much toluene and ethanol as was able. The reaction was then refilled with toluene, sealed, and resubmitted to microwave heating. The cycle was repeated until a total time of 5 h of microwave heating had occurred.

According to the procedure reported by Jiang, and our own correspondence with her, the iridum catalysed asymmetric alkylation reaction of β-ketoesters was highly robust. The iridium precatalyst, ligand, and TBD were all weighed out on the bench and transferred to a vial that had been dried with a heat gun. Recognising that the active catalyst had been described as oxygen and moisture sensitive,[55] we decided to go a step further and weigh out the hygroscopic TBD under a nitrogen atmosphere whilst flame drying our glassware. Our initial attempt (Table 1.13, entry 1) at the desired AAA of β-ketoester **1.351** proved extremely successful: our results were very much in line to those Jiang had reported. Subsequent attempts to improve the reaction (entries 3 and 4) whilst on a rotation at

Syngenta[1] gave poorer results, and simply trying reproduce our initial result was also unsuccessful (entry 5).

Table 1.13. Attempted optimisation of the Ir-AAA of β-ketoester **1.351**



Entry	Temp. /°C	Time /h	Yield (%)	Branched:linear ratio (1.352:1.353)	*e.e* of 1.352
1	20	3	78	14:1	>99%
2[b]	28	3	59	6:1	-99%
3	10[c]	6	63	8:1	-
4	0 – 20[c,d]	16	53	4:1	-
5	20[c]	4	51	5:1	-
6	20	4	N.D.	5:1	-
7	20	3.5	N.D.	6:1	-
8	20	3.5	N.D.	5:1	-

[a] *Reagents and conditions*: [Ir(COD)Cl_2 (4 mol%), ligand **1.281** (*R,R,R* enantiomer, 8 mol%), TBD (16 mol%), THF. Iridium pre-catalyst and ligand were weighed out in air, while a new bottle of TBD used, opened only under a nitrogen atmosphere. TBD was weighed out under a nitrogen atmosphere. [b] (*S,S,S*) enantiomer of ligand **1.281** used. [c] Older, preopened bottle of TBD was used. Water contamination possible. [d] No conversion was observed at 0 °C, so the reaction was allowed to warm to 20 °C.

We considered that the pre-opened bottle of TBD located at Syngenta may have acquired some moisture, but switching back to the original bottle of TBD that had previously given excellent results gave no improvement (entries 6, 7 and 8). The levels of enantioenrichment were not measured for entries 3-8 since it was clear that these reactions would not be suitable for the total synthesis on the basis of the yield and branched-to-linear ratio alone. At this point we are unable to explain the discrepancy between the results reported by Jiang, our initial result (Table 1.13, entry 1), and our subsequent results (entries 2-8). It is

[1] Jealott's Hill International Research Centre, Bracknell, Berkshire, UK

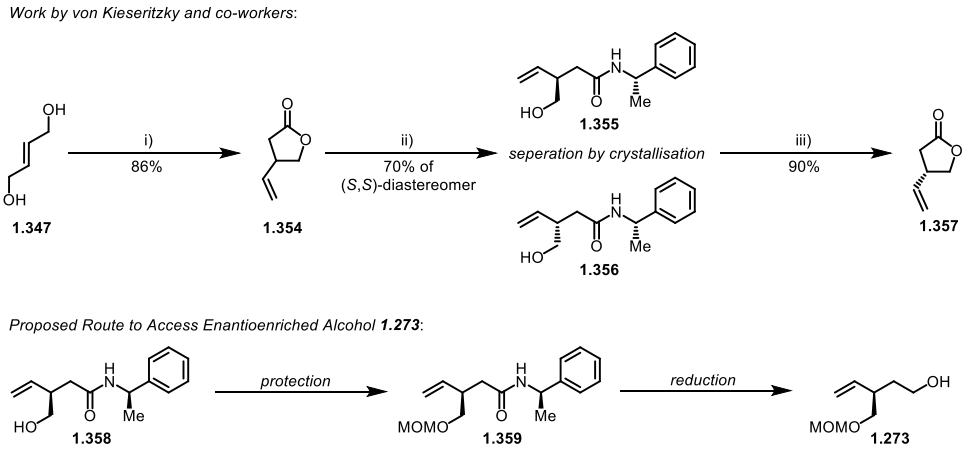
plausible that some human error occurred in the case of entries 1 and 2, to give erroneously good results. However given the similarity in yield, branched to linear ratio, and enantioselectivity between entry 1 and the reports by Jiang,[25] we consider this unlikely.

It had become clear to us that this route was in fact not sufficiently robust to be used to synthesise the multigram quantities of material required to complete the total synthesis. Additionally, the expense and high loadings of the ligand **1.281** was sufficient to prompt us to explore alternative avenues.

1.5.5 Synthesis of Enantioenriched Alcohol Via a Resolution of Taniguchi's Lactone

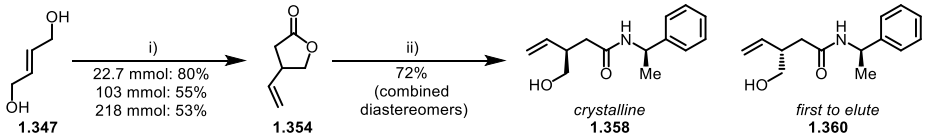
An earlier literature search had revealed a report detailing the synthesis of 8.4 kg of (*S*)-Taniguchi lactone **1.357** (Scheme 1.72, top) by von Kieseritzky and co-workers.[78] This report offered itself as an improvement on the original method by Taniguchi and co-workers,[79,80] a method which has been taken up by the synthetic community to synthesise a number of natural products.[80–83] Whilst we were engaged in the optimisation of an iridium catalysed asymmetric allylic alkylation (see section 1.5.4), we thought that this report would allow us to determine the absolute configuration of the carbon stereocentre by comparison of the optical rotation values. In our re-examination of the report however, we noticed that the authors synthesised amides **1.355** and **1.356** on their way to the lactone **1.357** (Scheme 1.72, top). In principle one could take the analogous enantioenriched amide **1.358**, protect the alcohol functionality and reduce the amide moiety to deliver alcohol **1.273** (Scheme 1.72, bottom). Furthermore this resolution could in principle provide access to both enantiomers of alcohol **1.273**, and ultimately both enantiomers of the desired dolabellane natural product **1.5**. As we had previously highlighted the potential for uncertainty in the

reported absolute configuration of this natural product (see section 1.1.10),[10] the synthesis of both enantiomers of this natural product was prudent.



Scheme 1.72. Top: synthesis of (*S*)-Taniguchi lactone **1.357** reported by von Kieseritzky and co-workers.[78] Bottom: Our proposed route to access enantioenriched alcohol **1.273** from the amide **1.358**. *Reagents and conditions*: i) triethyl orthoacetate (1.44 eq.), hydroquinone (0.21 eq.), 120 – 150 °C. 48 h; ii) (*S*)-1-benzylmethylamine (1 eq.), Ti(O*i*-Pr)$_4$ (1.55 eq.), THF, 75 °C, 12 h; iii) 1:2.6:4.8 conc. H_2SO_4/1,4-dioxane/H_2O, 80 °C, 12 h.

Following the procedure detailed by von Kieseritzky and co-workers we began with a Johnson-Claisen rearrangement on diol **1.347** (Scheme 1.73). Whilst the yield of **1.354** was excellent on a small scale (80%, 22.7 mmol), we only achieved 55% on a 103 mmol scale, and a 53% yield when on a 218 mmol scale, for which we were unable to identify a reason. Nevertheless, sufficient material was obtained, and we could progress to the key resolution via a lactone ring opening with (*R*)-(+)-α-methylbenzylamine, which gave a yield of 72% for the combined diastereomers **1.358** and **1.360**.



Scheme 1.73. *Reagents and conditions*: i) triethylorthoacetate (1.44 eq.), hydroquinone (0.21 eq.), *neat*, 120 - 150 °C, 48 h; ii) (*R*)-1-benzylmethylamine (1 eq.), Ti(*i*-PrO)$_4$ (1.55 eq.), THF, 75 °C, 16 h.

The resolution reaction was repeated twice more on larger scales to give sufficient material to progress with the total synthesis. Cognisant of the adage that crystalisations tend to be

more successful on larger scales, we combined the material from all the ring opening reactions that had been performed. Whilst we could not replicate the facile crystallisation on the crude material reported by von Kieseritzky and co-workers,[78] we were able to partially separate the two diastereoisomers by column chromatography (0 - 95% EtOAc in isohexane). As (*R*,*S*)-**1.360** eluted first, we could isolate a number of fractions in >95:5 *d.r.* before coelution of (*R*,*R*)-**1.358** began. The remainder of the fractions were concentrated *in vacuo*, and this mixture of diastereomers could be recrystallised from a minimum quantity of boiling methyl tert-butyl ether to give (*R*,*R*)-**1.358** in >95:5 *d.r.* We found that extremely slow cooling over several hours was the key to forming the desired crystals as opposed to an amorphous solid material. After three rounds of column chromatography and crystallisation, we were able to recover almost the entirety of material as two separated, pure diastereomers. The purity of each diastereomer was confirmed by ^{1}H and ^{13}C NMR (see experimental section, chapter 3, pages 281-285). To confirm the relative configuration of amide **1.358**, an X-ray crystal structure was obtained, the results of which were in keeping with the expected structure (Figure 1.12). Furthermore the optical rotation was approximately equal in magnitude and opposite in sign to that reported by von Kieseritzky and co-workers for the (*S*,*S*)-enantiomer amide **1.356** (our results: $[\alpha]_D$ (25 °C) +82.5° (c = 1.0, $CHCl_3$); lit: $[\alpha]_D$ (25 °C) -75.50° (c = 1.0, $CHCl_3$)).[78] The optical rotation of the enantiopure (*R*)-(+)-α-methylbenzylamine in our bottle was also in keeping with literature values (our results: $[\alpha]_D$ (25 °C) +32.5° (c = 1.0, $CHCl_3$); lit: $[\alpha]_D$ (25 °C) +28.8° (c = 1.0, $CHCl_3$)).[84]

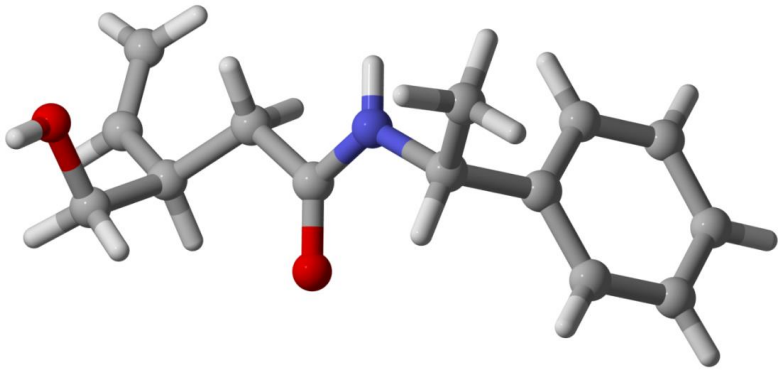
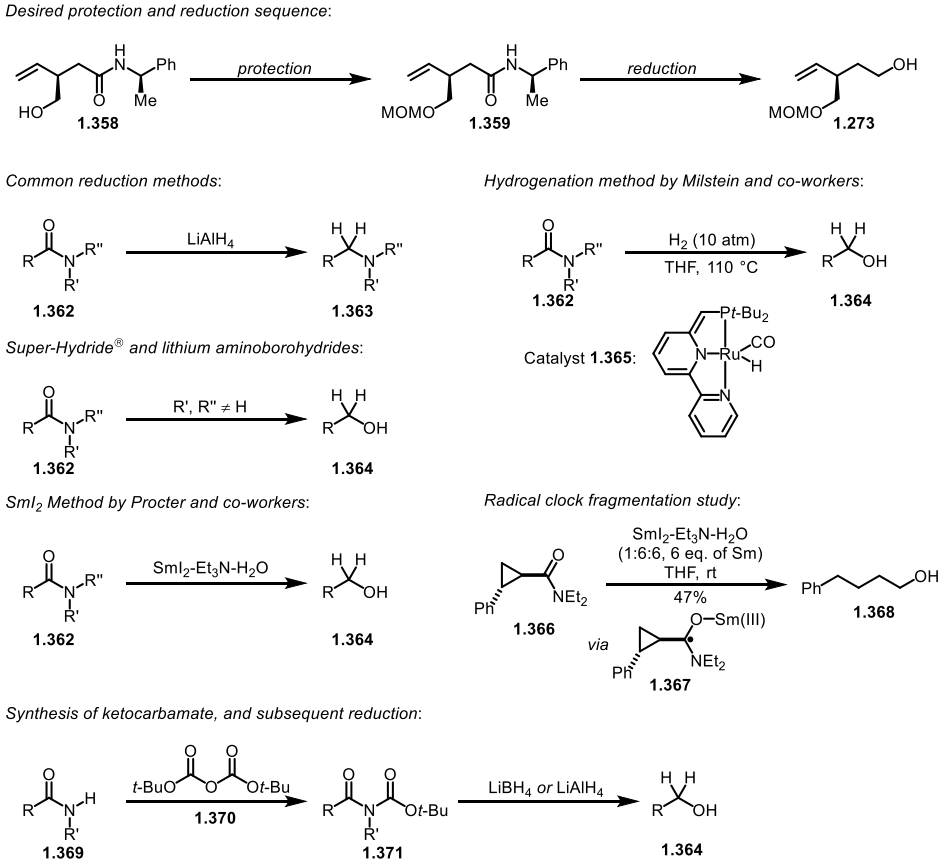


Figure 1.12. X-ray single crystal structure of amide **1.358**. Raw data may be found in the experimental section, chapter 3.

Amide **1.360** was assumed to possess (*R*,*S*) stereochemistry since the alternative (*R*,*R*) configuration had already been separately isolated and characterised.

We were now able to, in principle, take both diastereomers through the synthetic route to ultimately synthesise both enantiomers of the natural product **1.5**. For this we required a reductive method that would convert the amide **1.358** into the desired alcohol **1.273**; our own knowledge of synthetic chemistry and a literature search suggested that a competing C-O cleavage is often observed to give an undesired amine. Finding new methods to give selective C-N bond cleavage is an active research area (Scheme 1.74): older examples include the use of $LiBHEt_3$ (AKA Super-Hydride®),[85] and lithium aminoboranes,[86–88] but these typically only work for tertiary amides, not primary and secondary; newer methods have utilised Ru-pincer complexes or molybdenum catalysts to achieve selectivity,[89,90] but these typically require elevated temperatures and hydrogen pressures, or suffer from a limited substrate scope. One promising report was that of Procter and co-workers,[91] who used samarium diiodide in conjunction with an amine and water, to effect the chemoselective reduction of amides.

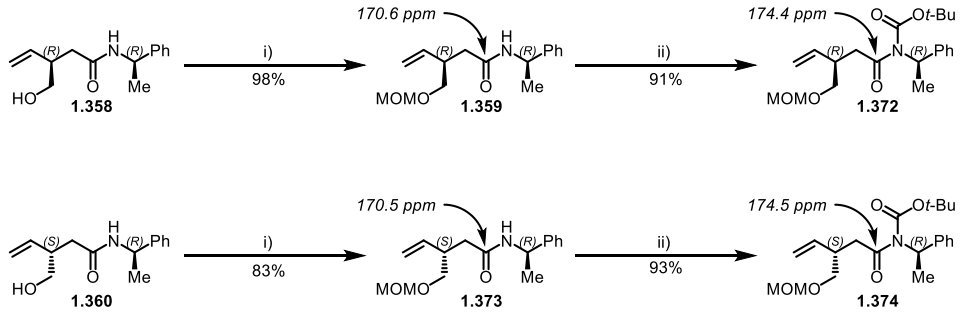


Scheme 1.74. A short survey of literature methods for the chemoselective reduction of an amide to an alcohol.

The substrate scope was promising since it included 1°, 2° and 3° amides, and was not limited to aromatic amides or amides that were sterically unhindered. Furthermore the experimental method did not require the use of specialised equipment like a glovebox. Unfortunately for us, a radical clock fragmentation study indicated that a single electron transfer mechanism was at work to give radical **1.367**. Since our substrate contains a terminal alkene, the possibility of a radical polymerisation dissuaded us from this otherwise excellent piece of chemistry. In light of this, we felt that the method with the highest chance of success would be to first convert the amide **1.369** into the ketocarbamate **1.371**, which would improve the selectivity of reduction towards the desired alcohol. This transformation

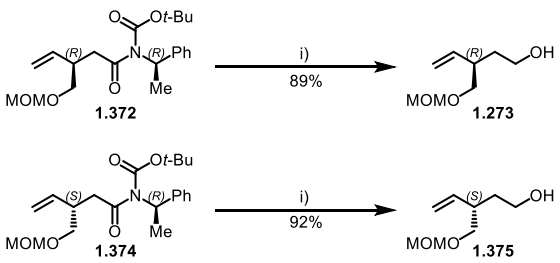
has been well used within the synthetic community,[92] and draws parallels with the use and subsequent removal of the Evan's auxillery.[93]

We began with a high yielding MOM protection of the alcohol functional group in **1.358** (Scheme 1.75), where it was noted that an almost quantitative yield of **1.359** could be achieved when the Hünig's base was stirred over calcium hydride overnight, distilled, then used immediately. Activation of the amide moiety was achieved using an excess of di-*tert*-butyl dicarbonate, which proceeded in a reliably high yield to give **1.372** and **1.374** from **1.359** and **1.373** respectively.



Scheme 1.75. *Reagents and conditions*: i) MOMCl (3 eq.), *i*-Pr_2NEt (4 eq.), CH_2Cl_2, 0 °C, 7 h; In the case of (*R,R*) amide **1.358**, Hünig's base was distilled from CaH_2 immediately before use, whereas for (*S,R*)-amide **1.360** the Hünig's base had been stored for no longer than 1 month in a sealed flask under an argon atmosphere, after having been distilled from CaH_2. ii) Di-*tert*-butyl dicarbonate (3 eq.), DMAP (0.5 eq.), THF, 75 °C, 6 h; iii) $LiAlH_4$ (2 eq.), Et_2O, 0 °C, 2 h.

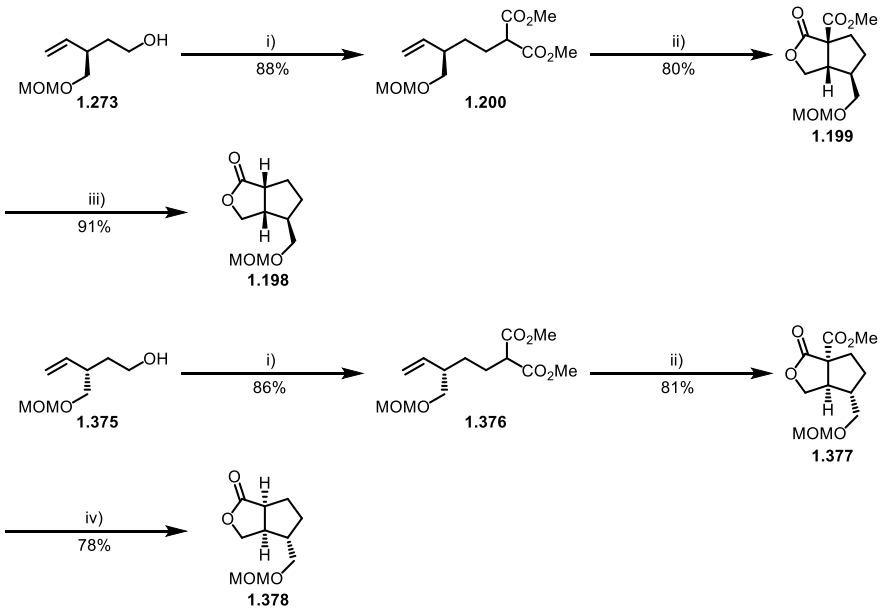
We noted that by attaching a second carbonyl group to amide **1.359**, the ^{13}C chemical shift for the peak that corresponds to the indicated carbonyl (Scheme 1.75) moved from 170.6 to 174.4 ppm. This increase in chemical shift indicates that there is reduced electron density at the carbonyl-carbon atom, which we expected to correspond with increased reactivity when treated with a nucleophile. A similar effect was noted for the diastereomer **1.374**. Confident that selectivity would be high, a lithium aluminium hydride reduction in Et_2O at 0 °C was trialled and we isolated an 89-91% yield for the two enantiomers of the desired alcohol, **1.273** and **1.375** (Scheme 1.76).



Scheme 1.76. *Reagents and conditions*: i) $LiAlH_4$ (2 eq.), Et_2O, 0 °C, 2 h.

1.6 Towards the Total Syntheses of Both (+) and (-) Dolabellane

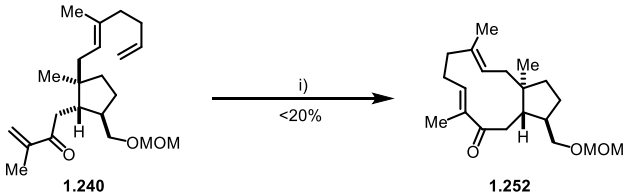
Although we did not have sufficient time to push enantiopure material through all of the steps which had been optimised using racemic material, we were able to reach the bicyclic lactones **1.198** and **1.378**. As expected, the yields of all reactions were high for both enantiomers (Scheme 1.77), with the exception of the decarboxylation of lactone **1.377** (derived from the (*S*)-configured alcohol **1.375**). Unfortunately the reactivity of the bicyclic lactones to typical TLC stains ($KMnO_4$, vanillin, H_2SO_4) is very poor, and we stopped the reaction in the mistaken belief that the reaction had finished. Furthermore, separation of the starting material **1.377** from the product **1.378** was also poor, and so the isolated yield was lower than expected. Eager to not repeat the same mistake, we used four equivalents of water rather than three when it came to the decarboxylation of **1.199**, and heated for 6 hours rather than 4 to ensure the reaction went to completion. We were relieved to note that this was the case, and were able to isolate a much better yield of **1.198**. Despite these difficulties, we nevertheless were able to synthesise lactones **1.198** and **1.378** in high yield.



Scheme 1.77. *Reagents and conditions*: i) MsCl (1.2 eq.), Et_3N (1.5 eq.), CH_2Cl_2, 0 °C to rt, 1.5 h, *then* NaH (2 eq.), dimethylmalonate (3 eq.), 1:2 THF/DMF, 80 °C, 2.5 h, dark; ii) $Mn(OAc)_3 \bullet 2H_2O$ (3 eq.), KI (0.5 eq.), MeCN, 80 °C, 8 h, dark; iii) LiCl (2 eq.), H_2O (3 eq.), DMF, 150 – 155 °C, 4 h; iv) LiCl (2 eq.), H_2O (4 eq.), DMF, 150 °C, 6 h.

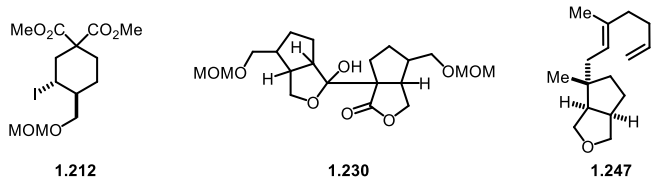
1.7 Conclusions and Future Work

During the course of our studies towards the total synthesis of the target natural product **1.5**, a dolabellane diterpenoid, we were able to optimise almost every step to a reliable yield of 70% or more. In this optimisation we were able to synthesise the ring closed product **1.252** and confirm by analysis of the ^{1}H NOESY spectrum obtained that the correct diastereomer of enone had been obtained (Scheme 1.78).



Scheme 1.78. *Reagents and conditions*: i) Grubbs II (1 eq.), toluene (0.001 M), 100 °C, 1 h.

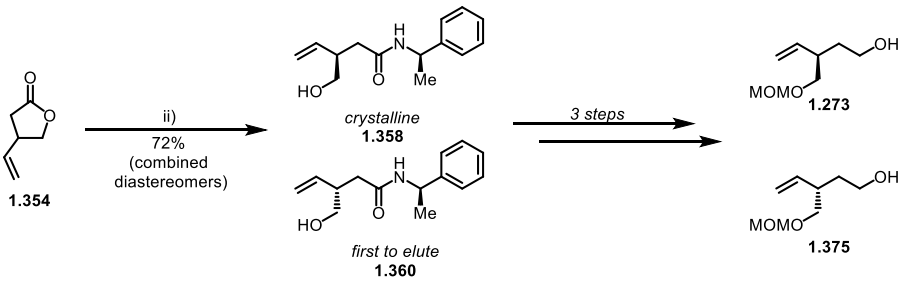
Furthermore we have been able to isolate and fully characterise side products like **1.212**, **1.230**, and **1.247**, contributing to our understanding of the reaction that yielded them in each case (Scheme 1.79).



1.212 **1.230** **1.247**

Scheme 1.79. Side products that have been isolated and fully characterised in the course of this project.

Finally, we sought out and found a reliable method for the synthesis of gram quantities of both enantiomers of the intermediate alcohols **1.273** and **1.375** via the resolution of the Taniguchi lactone **1.354** (Scheme 1.80).



1.354

Scheme 1.80. Overview of the synthesis of both enantiomers of the intermediate alcohol (**1.273** and **1.375**) via a resolution of the Taniguchi lactone (**1.354**).

It is our belief that each of these achievements should aid future synthetic efforts in this area. Future work will focus on the optimisation of the remaining steps using racemic material. Once a reliable set of conditions is found we will use our supply of the enantioenriched lactones to complete the total synthesis of both the (+) and (-) enantiomers of the dolabellane diterpenoid natural product **1.5**.

2 Radical Cyclisations of Dicarbonyl Compounds

2.1 Introduction

The following chapter begins with a discussion on the early and most recent work in the fields of manganese promoted oxidative cyclisations and synthetic organic electrochemistry. The introduction to the former also constitutes part of the background reading to Chapter I, since the methodology underpins each of the Dolabellane synthetic campaigns within the Burton group. The introduction to the latter will include some key principles of electrochemistry that may be of use to the reader. The chapter continues with an analysis of our own work on the topic, specifically towards the oxidative radical cyclisation of compounds containing a dicarbonyl functional group.

2.1.1 Manganese Triacetate Dihydrate

A subject of much discussion in this thesis is manganese triacetate, $Mn(OAc)_3$, but this simple formula structure conceals the true structural complexity of this oxidant. In the solid state it exists as an oxo-centred trimer, with bridging acetate ligands (Figure 2.1).[94] The solution state structure is unknown, but is typically depicted as an oxo-centred trimer of Mn(III) metal ions. For synthetic procedures, the bench stable, commercially available dihydrate $Mn(OAc)_3 \bullet 2H_2O$ is typically used without further purification.

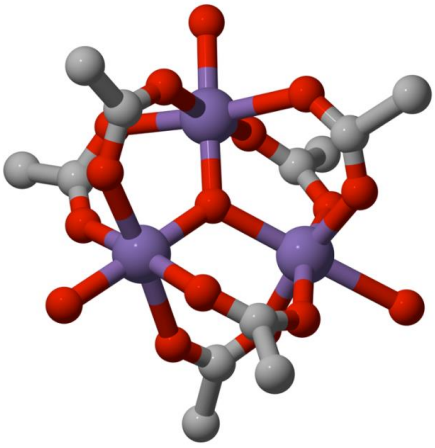
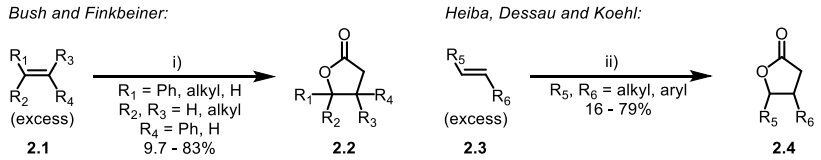


Figure 2.1. The crystal structure of manganese(III) acetate, reported by Hessel and Romers.[94]

2.1.2 Manganese Promoted Oxidative Cyclisations

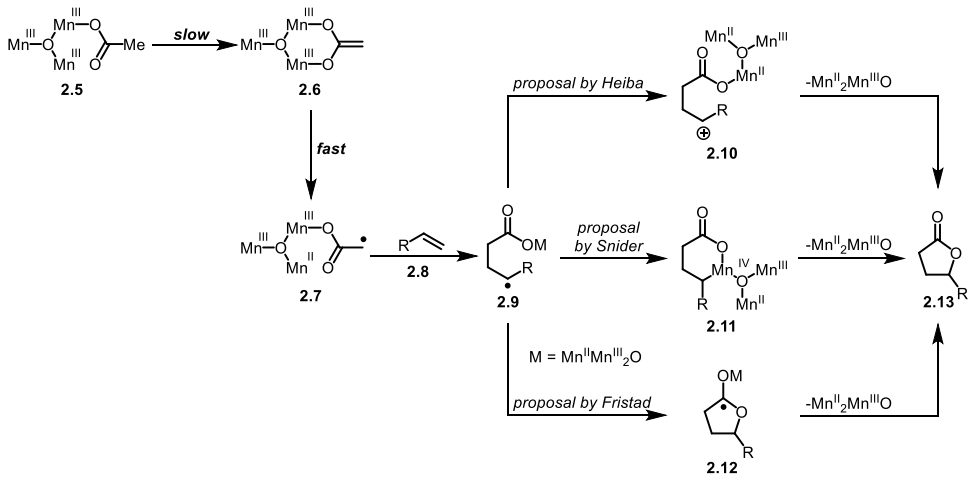
The use of manganese(III) to promote an oxidative cyclisation was first reported independently by the groups of Bush and Heiba in 1968.[95,96] In their papers, each author reports the formation of γ-lactones from the treatment of styrenes with two equivalents of $Mn(OAc)_3 \bullet 2H_2O$ in acetic acid (Scheme 2.1). In each case the yields are based on the amount of $Mn(OAc)_3 \bullet 2H_2O$ consumed.



Scheme 2.1. The oxidative cyclisation of simple alkenes, reported by Bush and Finkbeiner (left)[95] and Heiba, Dessau and Koehl (right).[96] *Reagents and conditions*: i) $Mn(OAc)_3 \bullet 2H_2O$ (1 eq.), olefin (20 eq.), 1:4 Ac_2O/AcOH, reflux, 1 h; ii) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), KOAc, AcOH, 135 °C, 1 h.

The mechanism for this reaction has since been proposed to be the following (Scheme 2.2): coordination of Mn(III) to acetic acid gives **2.5**; formation of enol **2.6** is followed by an inner sphere single electron transfer to give the carbon centred radical **2.7**; this reacts with the alkene **2.8** at the least substituted position to give radical **2.9**. Three mechanisms have been put forth to explain the second oxidation: Heiba and co-workers suggested the formation of

an isolated carbocation **2.10**;[97] Fristad and co-workers suggested a *5-endo-trig* radical cyclisation onto the nearby carbonyl group and oxidation of **2.12**;[98] Snider and co-workers suggested the formation of a Mn(IV) metallocycle **2.11** which can undergo reductive elimination to give the product **2.13**.[99] The proposal by Heiba and co-workers has since been discredited since Mn(III) does oxidises isolated primary and secondary carbon centred radicals too slowly,[99] and Fristad and co-workers showed in their studies that an isolated carbocation was unlikely.[98] In the absence of a nearby carboxylate group (required in both Snider's and Fristad's proposals), or co-oxidant, the typical pathway for termination of primary and secondary radicals is hydrogen atom abstraction (see Scheme 2.4, bottom).

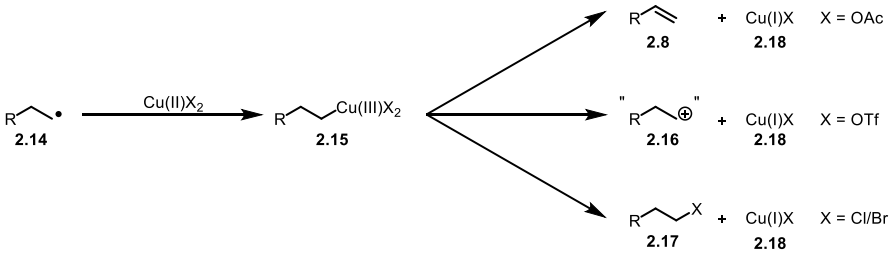


Scheme 2.2. Mechanistic pathways proposed by Heiba,[97] Snider,[99] and Fristad (and associated co-workers).[100]

Since then, a range of dicarbonyl oxidations using $Mn(OAc)_3$ have been reported and this topic has been reviewed elsewhere.[99,101,102] The following section will however discuss the specific modes of termination that are typically observed, and how the addition of co-oxidants and the choice of solvent can influence this.

2.1.3 Modes of Termination

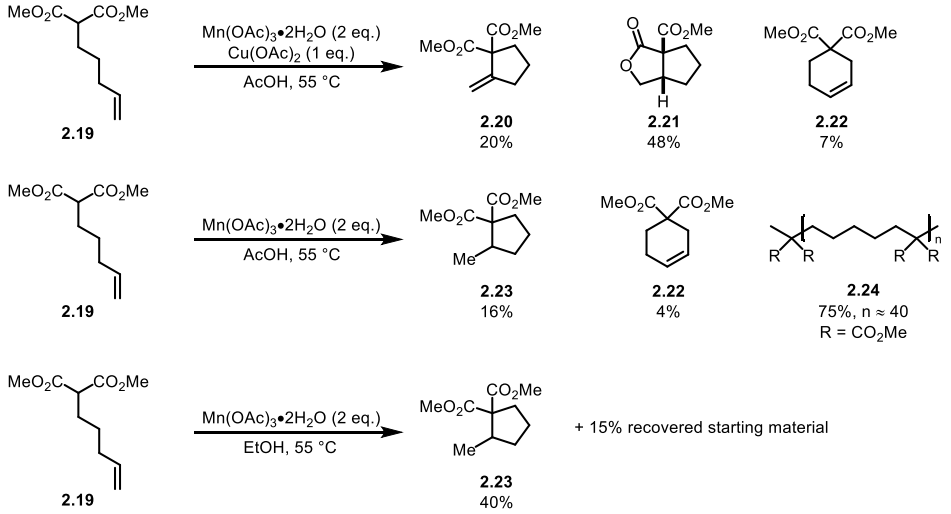
As discussed above, Mn(III) oxidises isolated primary and secondary carbon centred radicals only slowly. For substrates that lack a nearby carboxylate group or other facilitating group, hydrogen atom abstraction is the typical mode of termination (Scheme 2.4, bottom). In cases where one wishes to terminate the reaction via oxidation of a primary or secondary radical, a source of Cu(II) can be used as a co-oxidant. This is based on the work by Kochi and co-workers who demonstrated that copper(II) oxidises alkyl radicals with a rate constant of approximately 10^6 mol^{-1} s^{-1},[103,104] to give alkylcopper(III) intermediates **2.15** (Scheme 2.3).[99] This is followed by either a β-H elimination to give **2.8** (where acetate ligands are used), oxidation to give a species (**2.16**) that possesses the reactivity of a carbocation (where triflate ligands are used), or reductive elimination to give an alkyl halide (**2.17**, where chloride or bromide ligands are used). Heiba and Dessau later showed that the use of $Cu(OAc)_2$ was compatible with $Mn(OAc)_3$, and that the former oxidised secondary radicals 350 times faster than the latter.[97] The Cu(I) that is produced is oxidised back to Cu(II) by Mn(III), so that only a substoichiometric quantity of $Cu(OAc)_2$ is required in cases where at least two equivalents of $Mn(OAc)_3$ have been added.[99]



Scheme 2.3. Schematic for the co-oxidation of primary carbon centred radicals **2.14** with Cu(II).[99] The major product obtained is dependent on the ligand on the copper.

In 1991, Snider studied the radical cyclisation of malonate **2.19** using $Mn(OAc)_3 \bullet 2H_2O$ and $Cu(OAc)_2 \bullet H_2O$, and was able to isolate the following products: *exo*-alkene **2.20**, bicyclic

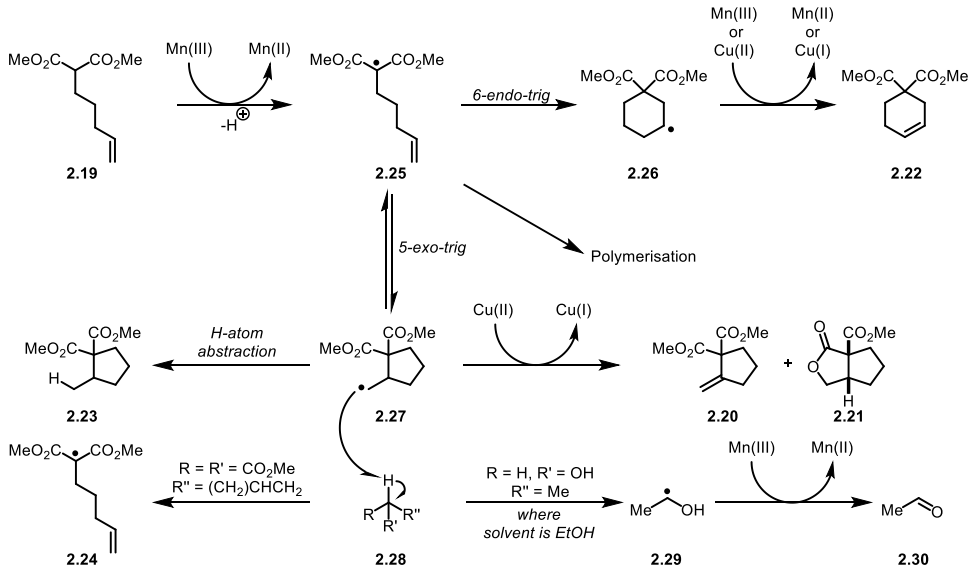
lactone **2.21**, and cyclohexene **2.22** (Scheme 2.4, top).[105] In the absence of Cu(II), the major product was polymer **2.24**, in addition to a small quantity of cyclopentane **2.23**, and cyclohexene **2.22** (Scheme 2.4, middle). Finally, Snider found that taking malonate **2.19** with two equivalents of $Mn(OAc)_3 \bullet 2H_2O$ in EtOH (a good hydrogen atom donor) gives the saturated methyl cyclopentane **2.23** in 40% yield (Scheme 2.4, bottom).



Scheme 2.4. Oxidative cyclisation of malonate **2.19**, reported by Snider and co-workers.[105]

Snider proposed the following mechanistic pathways to explain the observations (Scheme 2.5).[106] Starting with malonate **2.19**, loss of a proton and oxidation gives the radical **2.25**. This can undergo a *5-exo-trig* cyclisation to give **2.27**, or a *6-endo-trig* cyclisation to give **2.26**, or react with another molecule of starting material to begin a polymerisation sequence. When Cu(II) is present, termination occurs via oxidation to give the *exo*-alkene **2.20** and/or the bicyclic lactone **2.21**. In cases where Cu(II) is not present, and the solvent is a good hydrogen atom donor like EtOH, a hydrogen atom abstraction pathway dominates to give the saturated cyclopentane **2.23**. This hydrogen may come from another molecule of starting material, to regenerate **2.25**, or from EtOH to give α-hydroxyradical **2.29** which is

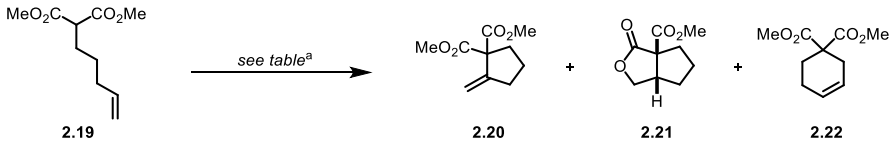
then oxidised by Mn(III) to give acetaldehyde **2.30**. Finally, in cases where neither oxidation nor hydrogen atom abstraction processes are efficient, the cyclisation can reverse (due to the high stability of an α-malono radical) to give **2.25**, which can polymerise. In most cases the predominant product is one which comes from a *5-exo-trig* cyclisation, but a small amount of cyclohexene **2.22** is often observed. Only cases in which the termination process is slow does one observe polymerisation.



Scheme 2.5. Mechanistic pathways available to radical **2.25**, proposed by Snider and co-workers.

The nature of the product isolated as a result of this second oxidation by Cu(II) is dependent on the solvent used, as well as the ligands that are coordinated to the copper (see Scheme 2.3). Snider and co-workers studied the effect of different solvents on the ratio of lactone to *exo*-alkene products.[105,106] The two most profound differences in product ratio are found for the following solvents (Table 2.1). Acetonitrile (entry 6) is found to preferentially give lactone **2.21**, contrary to the results for most other solvents, and is much more selective than acetic acid (entry 1). Dimethyl sulfoxide was found to be exceptionally selective for the exo-alkene **2.20** (entry 5), and gives the greatest combined yield.

Table 2.1. The Effect of Solvent on the Ratio of Products from an Oxidative Cyclisation, Reported by Snider and Co-workers.[106]

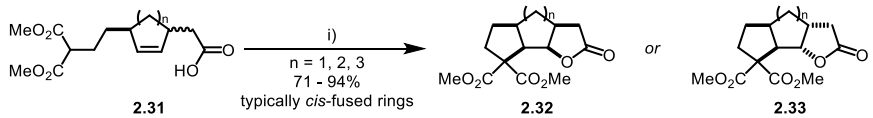


2.19 **2.20** **2.21** **2.22**

Entry	Solvent	Time /h	Temp. /°C	2.20	2.21	2.22	2.20 : 2.21
1	AcOH	28	55	20	48	7	1 : 2.4
2	EtOH	156	60	22	14	4	1.6 : 1
3	MeOH	68	70	35	17	5	2.1 : 1
4	DMF	67	75	32	17	5	1.9 : 1
5	DMSO	68	75	53	5	2	10.6 : 1
6	CH_3CN	11	55	8	38	3	1 : 4.8

[a] *Reagents and conditions*: $Mn(OAc)_3$ (2 eq.), $Cu(OAc)_2$ (1 eq.); temperature, solvent and time as described in table.

Building on the reports by Snider and co-workers, Burton and co-workers optimised the use of sources of Cu(II) with weakly coordinated anions, such as $Cu(OTf)_2$ or $Cu(BF_4)_2$, to promote the formation of tricyclic γ-lactones **2.32**/**2.33** (Scheme 2.6).[107] The use of a weakly coordinating anion favours oxidative substitution to give the γ-lactone product, instead of the oxidative β-hydride elimination that was typically observed by Snider (see Table 2.1). Although Snider also reported a preference for the analogous lactone product when the solvent was acetonitrile, the selectively obtained by Burton with a weakly coordinating anion was complete.

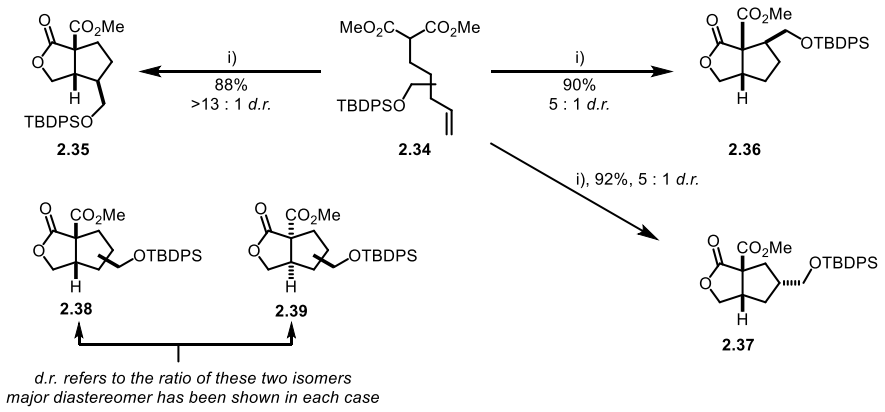


2.31 **2.32** **2.33**

Scheme 2.6. Synthesis of tricyclic γ-lactones reported by Burton and co-workers.[107] *Reagents and conditions*: i) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), $Cu(OTf)_2$ or $Cu(BF_4)_2$ (1 eq.), MeCN, reflux.

2.1.4 Use of Oxidative Cyclisations Within the Burton Group

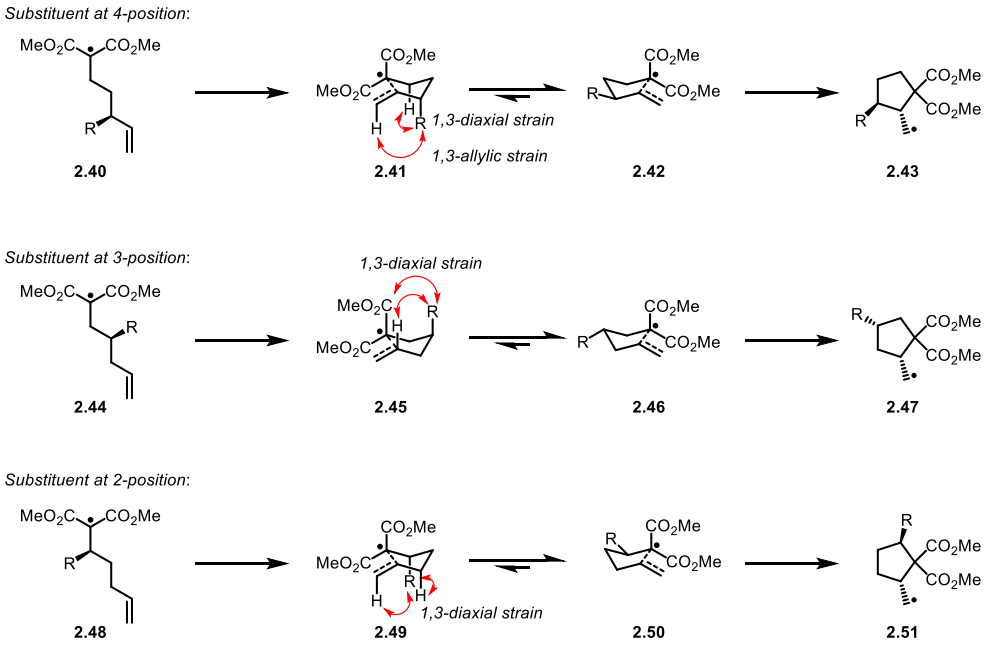
Following their initial report on the use of $Cu(OTf)_2$,[108] Burton and co-workers have extended the methodology to a range of bicycles with varying substitution patterns (Scheme 2.7).[109] The yields for this reaction are typically excellent, and the high diastereoselectivity is especially useful. Note that all the products obtained with this methodology are *cis*-fused at the ring junction, and the diastereoselectivity that is reported throughout this thesis refers to the ratio between **2.39** (where the lactone ring is on the same face as the substituent) and **2.38** (where the opposite is true).



Scheme 2.7. A demonstration of the diastereoselectivity at each position of the cyclopentane ring, reported by Burton and co-workers. *Reagents and conditions*: i) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 80 °C, 24 h.

The high diastereoselectivity (>13:1, Scheme 2.7) observed for the cyclisation of substrates substituted at the 4-position (e.g. **2.40**) may be rationalised by considering a Beckwith-Houk model.[110,111] This model (Scheme 2.8, top) assumes a "loose" chair-like pre-transition state conformation (**2.42**) which places the allylic substituent and the terminal alkene in the pseudo-equatorial positions. This is done to minimise the 1,3-allylic strain between the vinylogous proton and the alkyl substituent (R), and to minimise the 1,3-diaxial strain with the equatorial sp^3 proton. Poorer diastereoselectivity is observed for substrates that are substituted at the 2- and 3- positions (Scheme 2.8, middle and bottom), as the transition

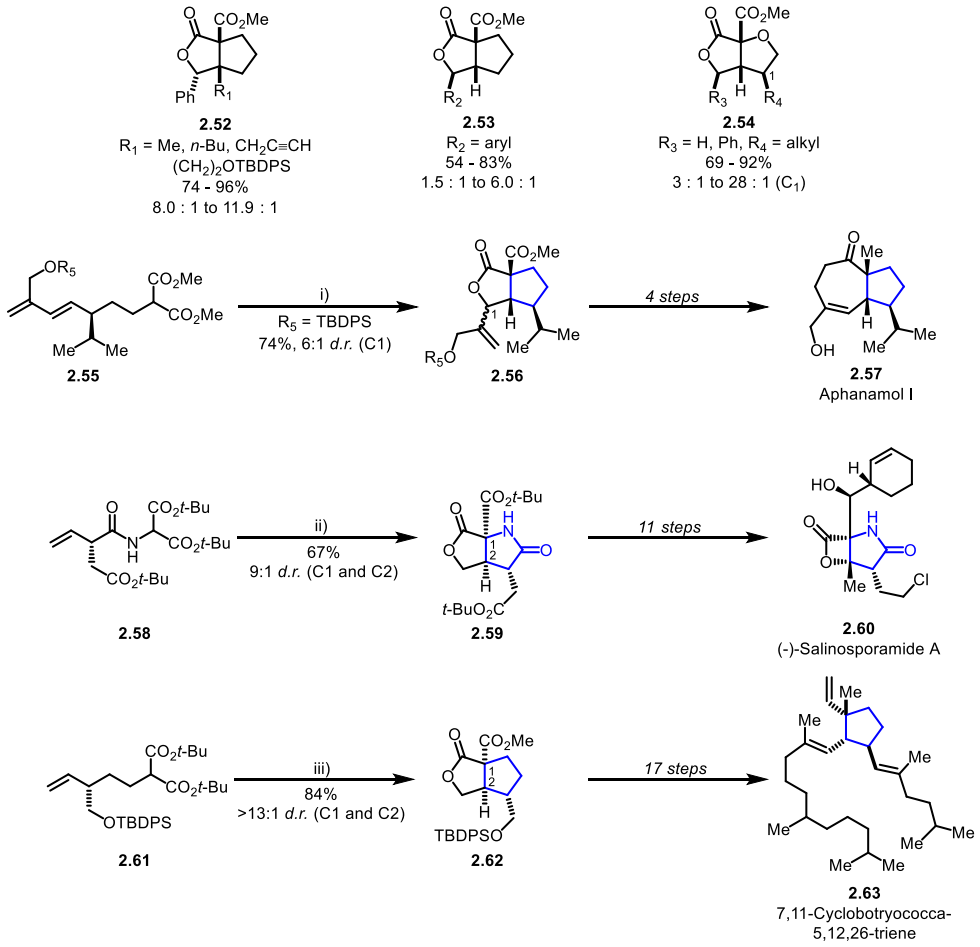
states (**2.45** and **2.49**) that give rise to the minor diastereomer do not suffer from the same increase in 1,3-allylic strain when the substituent (R) is placed in the pseudo-axial position.



Scheme 2.8. A model proposed by Burton and co-workers, based on the Beckwith-Houk model,[110,111] to explain the observed diastereoselectivity for substituents at the 2-, 3-, and 4-positions.

Burton and co-workers have published a range of substrates, to include highly substituted cyclopentanes,[109,112] bicyclic tetrahydrofurans,[113] and γ-lactam-γ-lactone bicycles.[114] The utility of this methodology has been further emphasised within the Burton group by the total syntheses of a range of natural products (Scheme 2.9).[114–116]

The ability to form a radical at the α-position of malonates, and have them engage in *5-exo-trig* cyclisations has been clearly demonstrated to be a useful one. The next logical step to improve the methodology is to eliminate the super-stoichiometric quantity of metal waste that is produced as a by-product. With this goal in mind, we turn to the concepts of electrochemistry and the advantages that it has to offer.



Scheme 2.9. Scope of the Mn(III)/Cu(II) methodology for the synthesis of complex bicycles (top) and their use in the total and formal syntheses of different natural products (middle and bottom).[114–116] *Reagents and conditions*: i) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, reflux, 0.5 h; ii) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 25 °C, 1 h; iii) $Mn(OAc)_3 \bullet 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN, 80 °C, 2 h.

2.2 Introduction to Electrochemistry

Electrochemistry is experiencing a "renaissance" within the synthetic community: while chemists in the past have been content with the operational simplicity of a chemical oxidant, reports are now emerging that suggests a push towards harnessing the advantages that electrochemistry has to offer.[117,118] Among these advantages are the ability to oxidise or reduce a functional group with far greater selectivity than the equivalent chemical reagents, the reduction in chemical waste, and the opportunities for scalability. A short

description of the key terminology, typical electrochemical setups, and pertinent examples of application to organic synthesis will now be provided.

2.2.1 Setup

An electrochemical setup consists of two electrodes an anode and a cathode, placed in an electrolyte (a combination of a solvent and supporting electrolyte), which are connected to a source of electrical energy such as a battery, galvanostat or potentiostat. At the anode electrons flow from the solution to the power supply, while at the cathode electrons flow from the power supply to the solution. The electrode at which the substrate is either oxidised or reduced is termed the "working electrode", while either a reduction or oxidation respectively at the "counter electrode" completes the electrical circuit. The reactions we shall concern ourselves with in this introduction are anodic oxidations, where the substrate is oxidised to give the product, and either solvent, a proton source, or another species is reduced cathodically.

The simplest setup uses an undivided cell, where the anode and cathode are contained within the same chamber, and the substrate may interact with both the anode and the cathode (Figure 2.2, left). This simplicity comes at a cost however, as the oxidised substrate may be prematurely reduced at the cathode, to make for a non-productive sequence of electron transfers. The alternative setup is a divided cell (Figure 2.2, right), where the anode and cathode are separated by a semi-permeable membrane. This membrane allows the passage of monatomic or small ions, to preserve the overall neutrality of each cell half, but not more complicated species like the substrate. Whilst the reaction setup is more complicated, the substrate, intermediates and the product are now prevented from interacting with the cathode.

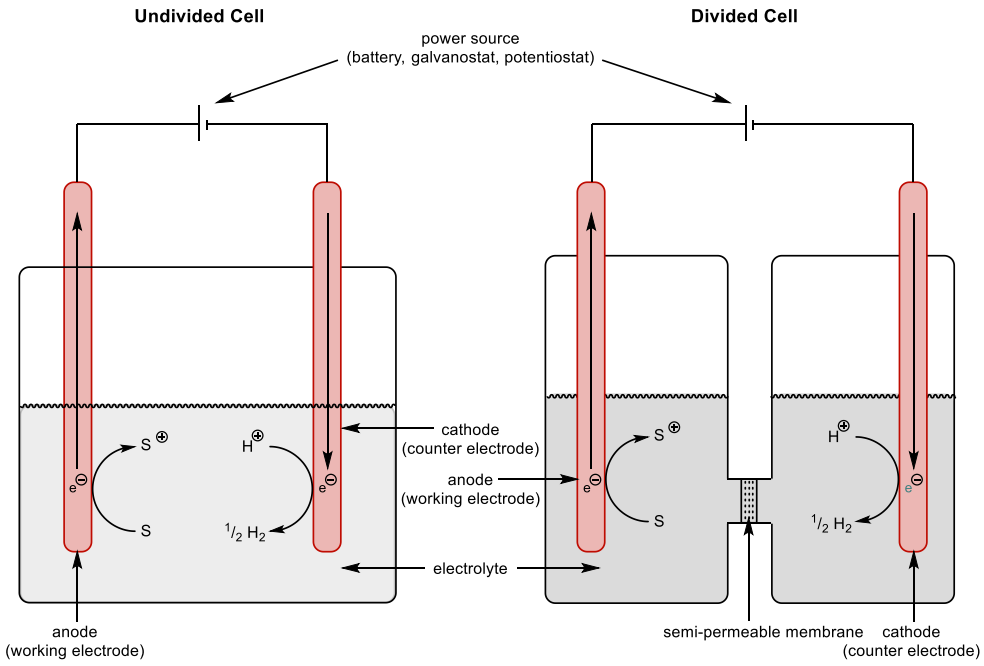


Figure 2.2. Schematic for an undivided cell (left) and a divided cell (right). Note that a third electrode may be added in each case for an electrolysis that is run under constant potential conditions.

In parallel to these two types of setup, an electrolysis can either be conducted using a constant current, or at a constant potential. The former uses a galvanostat, which changes the applied potential difference between the electrodes to ensure that a constant, preset current flows for the duration of the reaction. The latter process uses a potentiostat, which makes use of a third, reference electrode to monitor the potential difference between the working electrode and the solution. The advantage of a constant potential is that the selectivity of oxidation is maintained for the length of the reaction. However as the concentration of substrate decreases, the current will also decrease and with it the rate of the reaction. As a result it can be extremely time consuming to drive the electrolysis to completion. An electrolysis performed under constant current conditions can reach completion in a determinable length of time, depending on the current set, scale and the number of oxidations required per molecule of substrate. However, as the concentration of

substrate decreases, the potential at the working electrode must increase to maintain the set current. Selectivity therefore decreases as the reaction progresses. We can alternatively formulate these two statements by relation to Ohm's Law (Equation 2.1):[119]

$$V = iR$$

Equation 2.1

where *V* is the potential of the electrochemical cell, *i* is the current through the cell and *R* is the resistance of the cell.

The resistance of the cell is directly related to the number of electrolytically active species in solution: as the reaction progresses and the number of these species drops, the resistance will increase. Under constant current conditions, the potential must increase to compensate; under constant potential, the current must decrease to compensate.

2.2.2 The Electrolyte

The electrolyte is a combination of a solvent, and a supporting electrolyte, added to increase the conductivity of the solution. The supporting electrolyte is usually an ionic salt such as lithium perchlorate, tetrabutylammonium tetrafluoroborate or tetrabutylammonium tosylate.[120] Important properties of the electrolyte should be that it is readily separable from the product, a good conductor, dissolve the substrate, and the potential at which decomposition occurs should be greater than 200 mV more anodic than the oxidation potential of the substrate.[121]

Since electrolysis is always composed of both an oxidation and reduction, one must consider what happens at both electrodes. A common bi-product of oxidation at the anode is the generation of protons; thus to preserve the initial pH of the reaction an alcoholic solvent (e.g. methanol) is often chosen. Reduction of this solvent at the cathode gives hydrogen gas

and the corresponding alkoxide, which neutralises the acid formed at the anode (Figure 2.3). Solvents other than methanol have been reported however, such as acetic acid, acetonitrile, dichloromethane, tetrahydrofuran, and combinations thereof.[120]

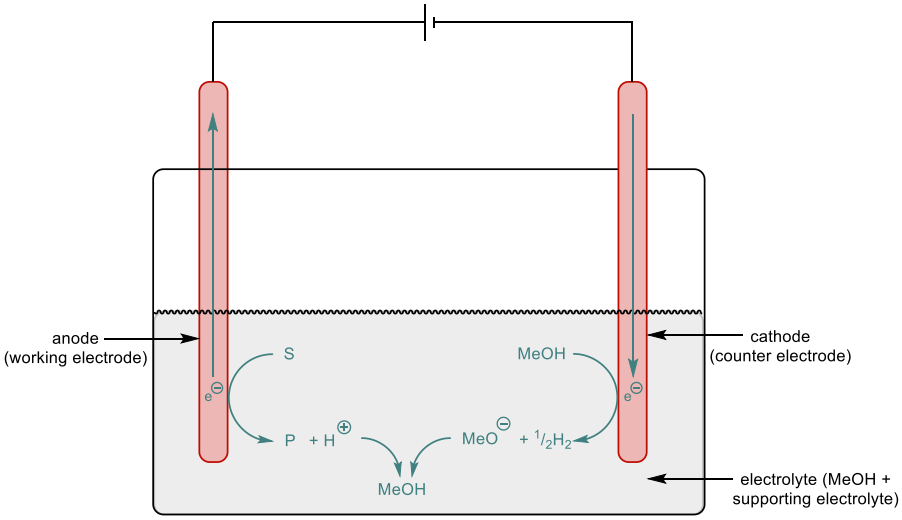


Figure 2.3. Schematic for the advantages of using an alcoholic solvent such as methanol for electrolysis. Reduction of methanol at the cathode liberates hydrogen and a methoxide anion, which can quench the acid released as a by-product of oxidation at the anode.

2.2.3 The Electrode

The electrode is not as innocent a spectator as we have implied so far. Its composition and surface area can have serious implications for the success of the reaction. Unlike chemical oxidants, the oxidation does not take place in bulk solution, but rather on the surface of the electrode inside the double layer (see section 2.2.4). As such the surface of the electrode must be inert to any reactive species generated by oxidation of the substrate, else the success of the transformation will be diminished.

Whilst electrodes can in principle be built from any conductive material that is stable to the reaction conditions, the most common are: platinium, glassy carbon rods, magnesium,

stainless steel, or reticulated vitreous carbon (RVC) foam. The latter is particularly attractive as it is cheap, commercially available, chemically resistant, and has a very high surface area (Figure 2.4). In addition to these choices, sacrificial electrodes made of metals such as lead and zinc may be employed, which are consumed as the reaction progresses.

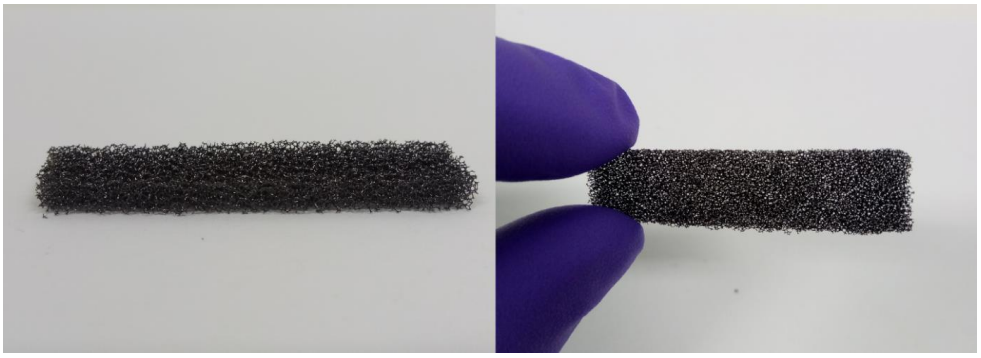


Figure 2.4. Reticulated vitreous carbon foam, illustrating the extremely high surface area (left) and porosity (right) of the material.

2.2.4 The Electric Double Layer

Application of a potential difference across the two electrodes causes the formation of an electric double layer at each electrode. If we take the anode as an example, this positively charged electrode will attract a high concentration of negatively charged anions to its surface. This forms the innermost “compact layer” of the electric double layer. The high concentration of negatively charged anions at the electrode surface attract a layer of greater-than-bulk concentration of positively charged cations, which in turn attract more anions, and the process continues until the potential is identical to the bulk solution. These multiple secondary layers constitute the “diffuse layer”, and it is the compact and diffuse layers which make up the electric double layer. This effect is important to the synthetic organic chemist because redox events will occur at the surface of the electrode, inside the compact layer. Many organic transformations, but in particular radical cyclisations, are sufficiently fast to be able to outcompete diffusion through the compact layer. It is for this

reason that highly reactive intermediates can be generated in the presence of nucleophilic solvents and protons.

2.2.5 Undertaking an Electrochemical Reaction

Electrochemical reactions are unique in that the time required for the reaction to go to completion can, for an ideal reaction under constant current conditions, be precisely predicted using Faraday's Law (Equation 2.2).

$$Q = nNF$$

Equation 2.2

where Q is the charge consumed, measured in Coulombs (C), n is the number of moles of substrate to be oxidised, and F is the Faraday constant, equal to 96485 C mol^{-1}. The Faraday constant can be viewed as a molar equivalent of electrons and relates the stoichiometry of the reaction to the amount of charge that is required to pass.

Since Equation 2.3 relates the charge consumed to the applied current and time, we can solve the equation to find the time required to perform the required number of redox events, and drive the reaction to completion.

$$Q = it$$

Equation 2.3

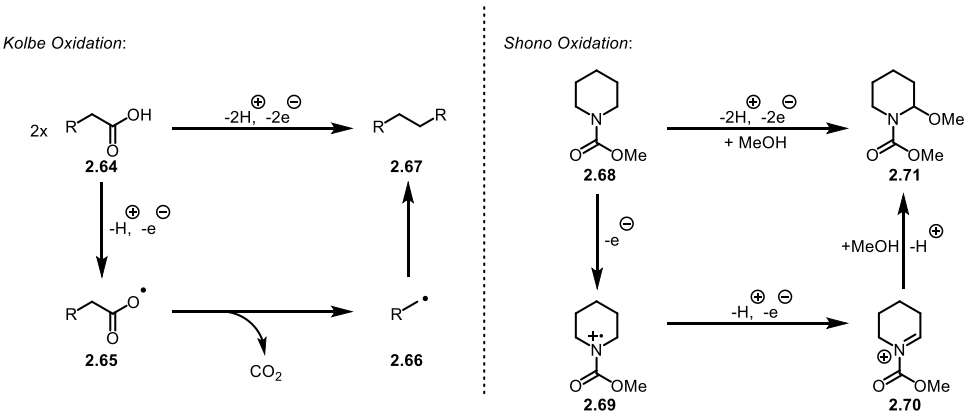
where Q is the charge consumed, i is the current, and t is time.

A similar process can be applied to a reaction performed under constant potential conditions, but this involves measuring how the current changes with respect to time, and integrating to find the charge consumed.

2.2.6 Selected Examples of Synthetically Useful Electrochemistry

The earliest example of a synthetically useful electrolysis is that reported by Kolbe,[122] work that gave rise to the eponymously named reaction (Scheme 2.10, left). Building on the report by Faraday who electrolysed an acetate solution and obtained ethane,[123] the reaction oxidises a carboxylic acid **2.64** to give a carboxylate radical **2.65**, which loses CO_2 to give the radical **2.66**. A pair of radicals then dimerise to give the product **2.67**.

The Shono oxidation (Scheme 2.10, right) is another example of a powerful methodology which has been taken up by the electrosynthetic community,[124,125] either to repeat the reaction on a new substrate,[126] for the synthesis of a natural product,[127] or to modify the reaction for a previously undiscovered purpose (*c.f.* the "cation-pool" method by Yoshida and co-workers).[128]

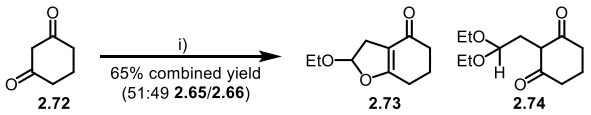


Scheme 2.10. The Kolbe oxidation (left),[122] and the Shono oxidation (right).[124]

In the intermediate years between the discovery of these two reactions, and in the past four decades since Shono's initial report, there has been a great deal of discovery in the field of synthetic organic electrochemistry. A full discussion of the work in the field of synthetic organic electrochemistry will not be provided here, but we will note the variety of reviews

on the topic to demonstrate the increasing uptake in the field.[117,119–121,123,129–131] Instead we will focus on the reports that are relevant to our own results and discussion.

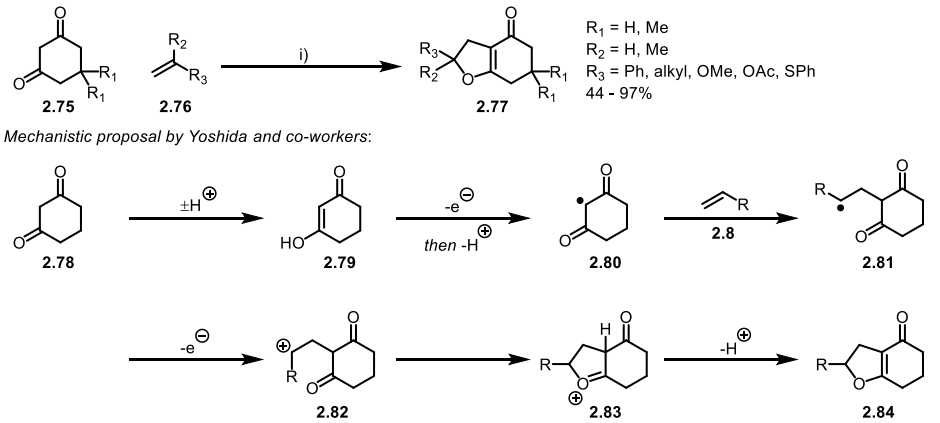
Torii and co-workers developed a method for the electrosynthesis of **2.73** and **2.74** from the cyclic diketone **2.72** (Scheme 2.11).[132] Although their report was brief and contained just a single substrate, their method gave the desired products in good yield. These products were treated with $(NH_4)_2CO_3$ in MeOH for the synthesis of 4-hydroxyindole, their ultimate goal for the report.



2.72 **2.73** **2.74**

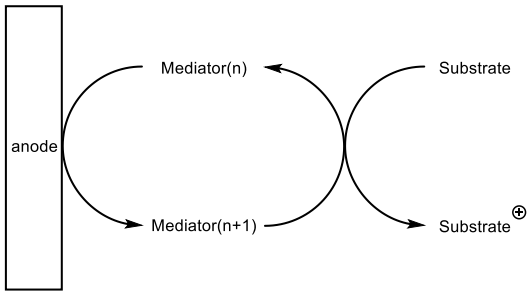
Scheme 2.11. Work by Torii and co-workers.[132] *Reagents and conditions*: i) NaOEt (0.5 eq.), ethyl vinyl ether (2 eq.), EtOH, rt, Pt foil anode/cathode (4x3 cm^2), constant current (14 mA/cm^2), 1.5 F/mol. Note: the yield was calculated to be 83% based on recovered diketone **2.72**.

Yoshida and co-workers took the oxidation of cyclic diketones **2.75** a step further in their initial letter,[133] and later full paper on the topic (Scheme 2.12), by using a range of alkenes.[134] Typically good yields were obtained for products **2.77** bearing a variety of different substituents. Yoshida and co-workers rationalised this reaction with the following mechanistic proposal, illustrated in Scheme 2.12. The cyclic diketone **2.78** tautomerises to the enol form **2.79**: subsequent oxidation gives the radical **2.80** which adds to the least hindered end of an alkene to give radical **2.81**. This radical is then oxidised to the carbocation **2.82**, which intramolecularly cyclises and loses a proton to give the product **2.84**.



Scheme 2.12. Work by Yoshida and co-workers.[133,134] *Reagents and conditions*: i) alkene **2.76** (1.5 – 20 eq.), Et_4NOTs (0.2 M), MeCN, carbon rod anode, platinum plate cathode, 10 mA, 3.0 F mol^{-1}, undivided cell.

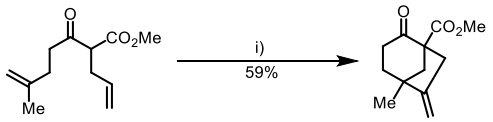
An alternative to the oxidation of a substrate directly at the anode is to use an electrochemical mediator. The mediator is oxidised at the anode and it is this oxidised form of the mediator which removes an electron from the substrate (Scheme 2.13).



Scheme 2.13. A schematic for the general principle of an electrochemical mediator.

An ideal mediator is able to be oxidised and reduced continuously without degradation, acting as a catalyst with only a sub-stoichiometric amount added to the reaction. This concept is not new, having been used for example by Torri and co-workers for the *N*-oxoammonium/bromide doubly mediated oxidation of alcohols to aldehydes,[135] the iodide mediated synthesis of aziridines by Little and co-workers,[136] and more recently by Baran and co-workers for the *N*-hydroxyphthalimide mediated allylic C—H oxidation.[137]

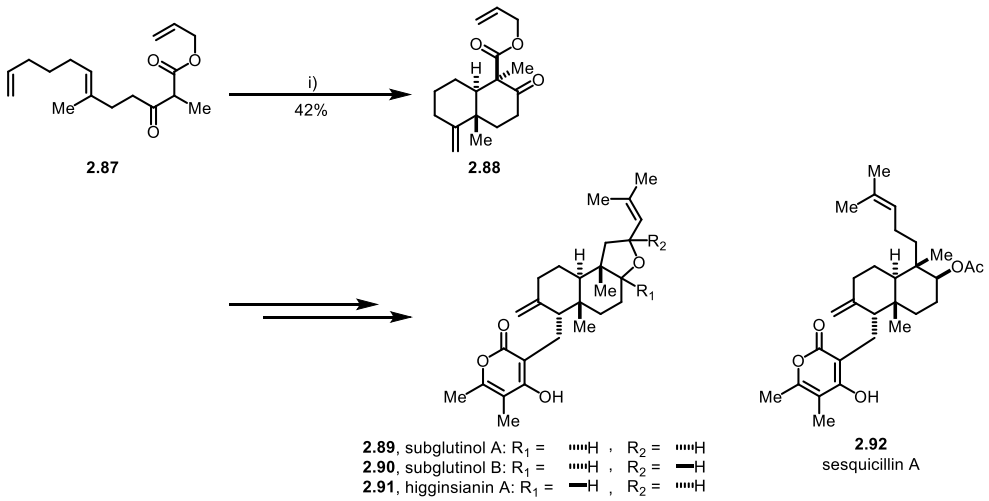
Snider and co-workers published work on the Mn(II)/Cu(II) mediated electrochemical oxidation of **2.85** to give the bicyclic structure **2.86** (Scheme 2.14).[138] A divided cell was used, presumably to prevent the Mn(III) that is produced at the anode from getting prematurely reduced at the cathode. A good yield was obtained for **2.86**, but unfortunately all other substrates used were far less successful.



2.85 **2.86**

Scheme 2.14. Work by Snider and co-workers.[138] *Reagents and conditions*: i) $Mn(OAc)_2$ (0.2 eq.), $Cu(OAc)_2$ (0.1 eq.), NaOAc (0.75 M), 4:1 AcOH/EtOH (containing 2% water), 60 °C, 80 mA, 8.1 F mol^{-1}, divided cell, $^1/_4$ inch graphite rods anode/cathode.

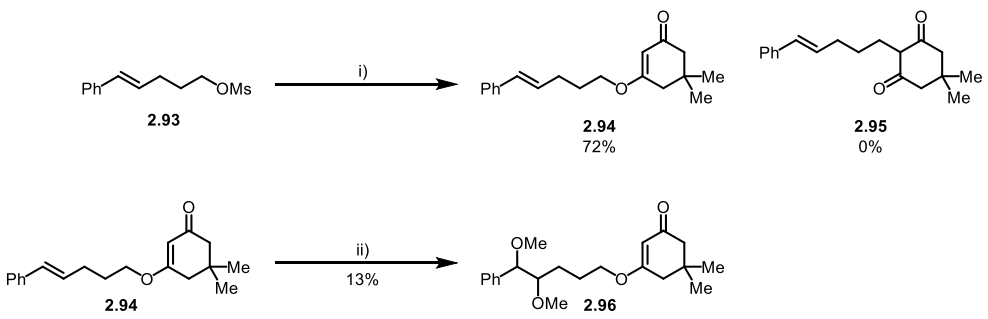
Most recently Baran and co-workers published their work on the formal syntheses of subglutinols A and B (**2.89**/**2.90**), and total syntheses of higginsianin A (**2.91**) and sesquicillin A (**2.92**).[139] The synthetic route for all four of the natural products took advantage of an optimised Mn(II)/Cu(II) mediated oxidative cyclisation (Scheme 2.15), with the anode responsible for the formation and turnover of the active Mn(III)/Cu(II) species. A moderate yield of product **2.88** was achieved when considering the complexity of the cyclisation, on a scale sufficient (>800 mg of product **2.88**) to complete the syntheses. It should be noted here that this work was published in the literature approximately three and a half years after this author first began an electrosynthesis project, and nearly two years after we switched our focus to the total synthesis of a Dolabellane diterpenoid natural project (see Chapter 1).



Scheme 2.15. Mn(II) and Cu(II) mediated electrolysis of β-ketoester **2.87** for the formal syntheses of subglutinol A and B, and the total syntheses of higginsianin A and sesquicillin A, reported by Baran and co-workers.[139] *Reagents and conditions*: i) carbon cloth electrodes, 20 mA, 2.2 F mol^{-1}, $Mn(OAc)_2$ (50 mol%), $Cu(sal)_2$ (2 mol%), KOAc (20 eq.), 1:3:14 Ac_2O/EtOAc/AcOH, rt, 22 h.

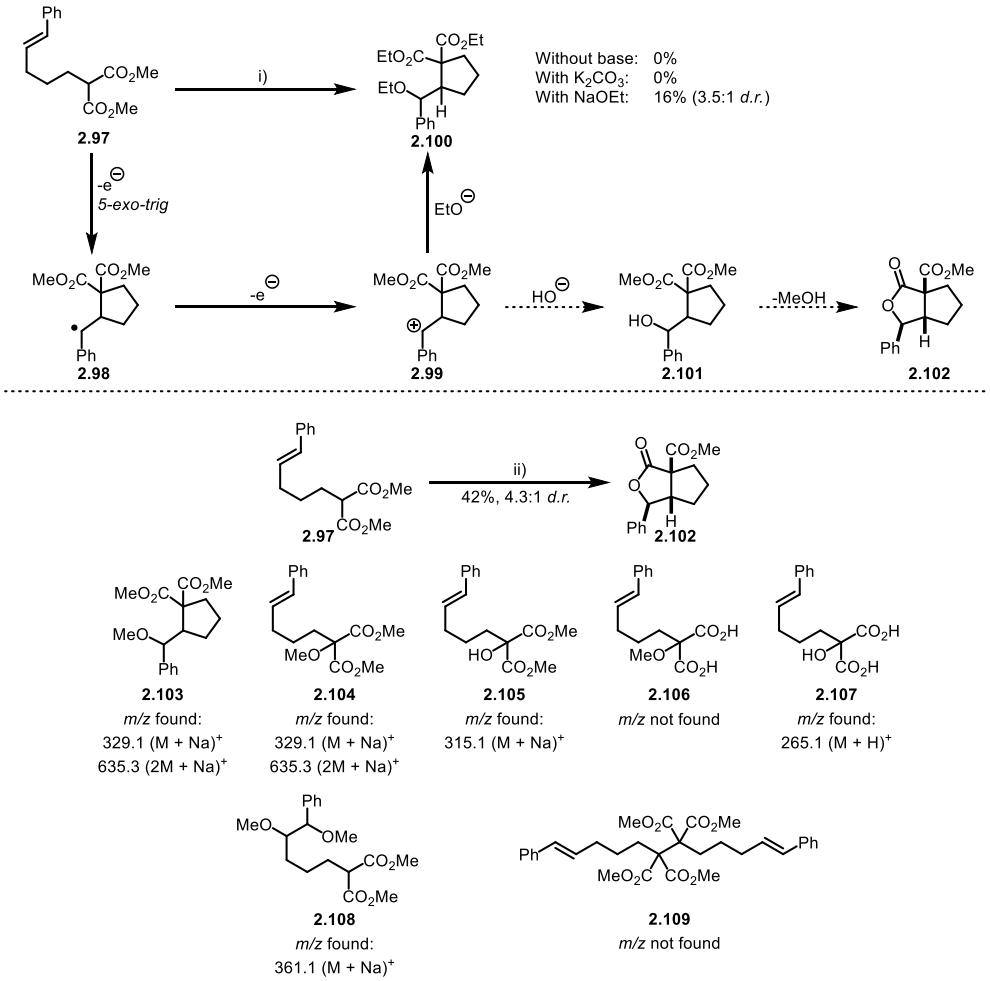
2.2.7 Previous Electrochemical Work in the Burton Group

D.Phil. student Ainsua Martinez reported in 2017 her work towards the goal of a manganese free methodology for the synthesis of bicyclic γ-lactones (Scheme 2.16).[33] This work began with an attempt to extend the work of Yoshida and co-workers by using an intramolecular substrate.[134] Unfortunately the desired starting material **2.95** could not synthesised, as **2.93** instead alkylated on oxygen to give **2.94**. Electrolysis of this material gave a poor yield of **2.96** where oxidation occurred at the styryl moiety rather than the enol ether functionality.



Scheme 2.16. Oxidation of styrene **2.94** reported by Ainsua Martinez.[33] *Reagents and conditions*: i) Graphite rod for anode/cathode, 10 mA, 3.0 F mol^{-1}, Et_4NOTs (0.2 M), MeOH, rt.

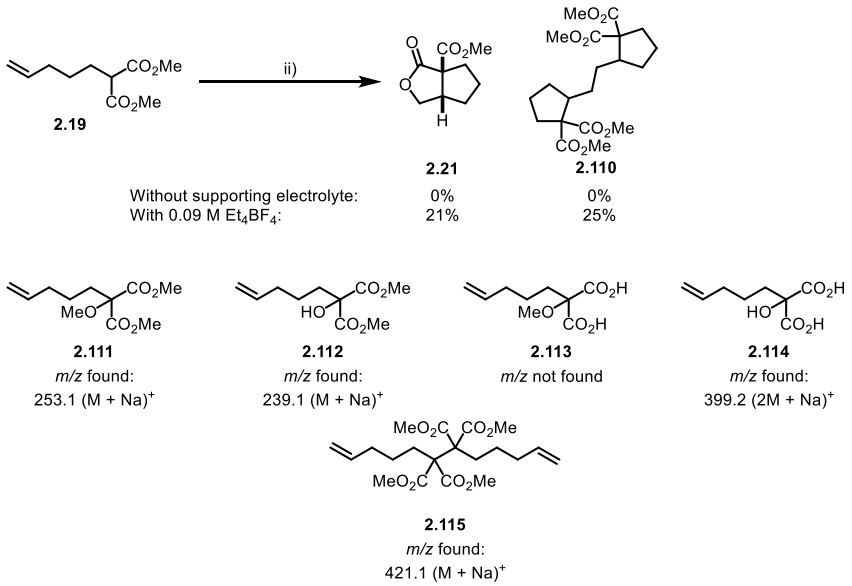
Considering the multitude of reports concerning the generation of a malonyl radicals for the synthesis of bicyclic lactones (sections 2.1.2 to 2.1.4), Ainsua Martinez next electrolysed malonate **2.97** (Scheme 2.17). In the absence of base or presence of K_2CO_3, no conversion was observed. Sodium ethoxide in ethanol however gave the cyclised malonate **2.100** in 16% yield. It was hypothesised that **2.100** arose by nucleophilic attack of the benzylic cation **2.99** by the solvent, and that switching to a source of hydroxide would give alcohol **2.101**, which could lactonise *in situ* to give the desired bicyclic lactone **2.102**. Although this hypothesis proved to be correct, and a 42% yield of **2.102** was obtained with moderate diastereoselectivity (Scheme 2.17, bottom), the results were not ideal.



Scheme 2.17. Electrolysis of **2.97** with mechanistic hypotheses (top), and electrolysis of **2.97** with other products observed by mass spectrometry (bottom), reported by Ainsua Martinez.[33] *Reagents and conditions*: i) Graphite rod for anode/cathode, 10 mA, 2.0 F mol^{-1}, NaOEt (1.4 eq.), EtOH, rt; ii) Graphite rod for anode/cathode, 10 mA, 2.0 F mol^{-1}, NaOH (1.4 - 1.6 eq.), MeOH, 40 °C.

A number of inseparable side products were observed by ESI mass spectrometry including the cyclopentane **2.103**, acylic ethers **2.104** and **2.108**, and acyclic alcohols **2.105** and **2.107**. Ainsua Martinez further speculated that the ether **2.106** and the dimer **2.109** are probably formed under these conditions. Further attempts at optimisation by changing the solvent, the concentration of substrate, the electrolyte, and its concentration resulted only in poorer yields than that already obtained.

Ainsua Martinez also electrolysed the terminal alkene **2.19** to study the effects the phenyl group might play on stabilising the putative carbocation **2.99**. As expected, without this stabilisation offered by the phenyl group, the yield of the lactone **2.21** was much poorer (Scheme 2.18). In the absence of supporting electrolyte (as per the conditions used earlier) no product was obtained. Recognising that increasing the ionic strength would help to stabilise a primary carbocation, Et_4NBF_4 was added, and a 21% of **2.21** was obtained in conjunction with 25% of **2.110**.



Scheme 2.18. Electrolysis of malonate **2.19** bearing a terminal alkene, reported by Ainsua Martinez.[33] *Reagents and conditions*: i) graphite rod for anode/cathode, 10 mA, NaOH (1.2 eq.), MeOH, rt. Without supporting electrolyte: 2 F mol^{-1}; with supporting electrolyte (0.09 M Et_4BF_4): 5 F mol^{-1}.

The results of Ainsua Martinez demonstrate a severe dependence on the ability of the substrate to stabilise a carbocation, thus limiting the potential substrate scope were a methodology to be optimised. Ultimately they moved back to a non-metal chemical oxidant (NIS) to obtain the desired bicyclic γ-lactones, to achieve their aim of replacing the manganese based methodology.

2.2.8 Project Proposal

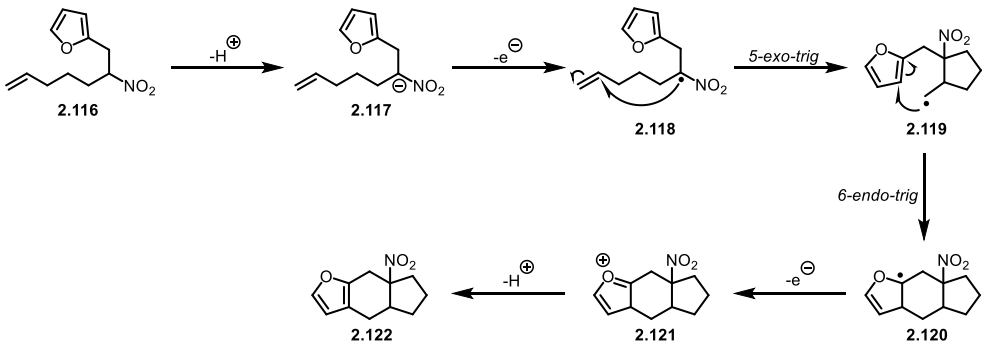
Whilst Snider and Baran (and their respective co-workers) have clearly demonstrated the use of manganese and copper based oxidants as catalysts enabled by electrochemistry (see section 2.2.6), we believed that further improvements could be made, where the metal oxidants were replaced entirely. This would reduce the toxicity profile, and is a worthy goal in line with the first principle of green chemistry.[140,141] The work of Ainsua Martinez demonstrated that such a goal could be reached, so long as a facile second oxidation was possible.[33] As such we decided to focus on cyclisations in which the terminating second oxidation step would restore aromaticity to an appropriate functional group, which we believed would have a sufficiently low oxidation potential that it would be a favoured process over alternative termination pathways.

2.3 Nitroalkene Substrate Class

2.3.1 Rationale for Design

This author began working in electrochemistry for a rotation project within the Burton group in the first year of D.Phil. studies. For this project we decided upon an ambitious substrate which if successful, would give the interesting tricyclic structure **2.122** (Scheme 2.19), which contains a number of different chemical groups for downstream functionalisation. Since the pK_a of a secondary nitroalkane (16.9 in DMSO)[142] is quite similar to that of dimethylmalonate (15.9 in DMSO),[143] we believed that the nitro functional group would serve as a useful proxy for a malonate. We envisaged that deprotonation of our substrate (**2.116**) would give the nitronate anion **2.117**; oxidation would give the corresponding radical **2.118**. A *5-exo-trig* radical cyclisation would form one of the new rings, and a subsequent *6-endo-trig* cyclisation would form the remaining ring. A second

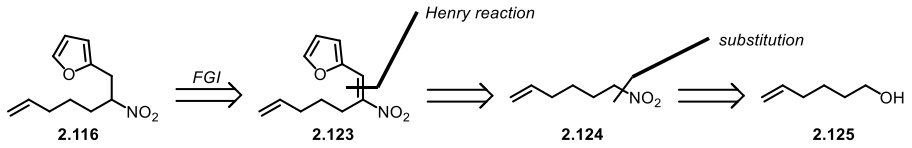
oxidation and removal of a proton would restore aromaticity to give the desired product **2.122**.



Scheme 2.19. Proposed substrate **2.116**, which could in principle undergo the desired set of oxidations and radical cyclisations to give the functionally interesting tricycle **2.122**.

2.3.2 Synthesis of Starting Material

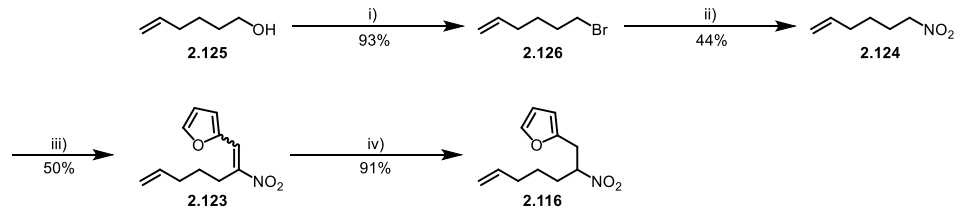
We began by outlining a retrosynthesis (Scheme 2.20) that we believed would furnish the desired starting material in a quantity that would be sufficient to screen a range of different conditions (i.e. > 1 g). In the forward sense, we could begin with commercially available alcohol **2.125**, activate it by transformation into the corresponding halide, then perform a chemoselective substitution with a source of nitrite to reach **2.124**. A Henry reaction would install the furan group, and conjugate reduction would give the desired nitro alkene **2.116**.



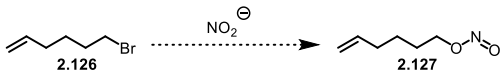
Scheme 2.20. Outlined retrosynthesis for nitroalkene **2.106**.

Alcohol **2.125** was subjected to a deoxybromination reaction using PBr_3 and a 93% yield of the corresponding bromide **2.126** was obtained (Scheme 2.21, top). A substitution reaction using sodium nitrite followed, but unfortunately a poor yield of the desired product **2.124** was obtained.

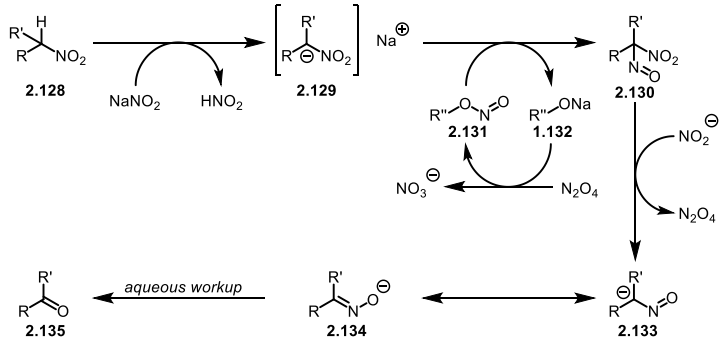
*Our synthesis of furan **2.116***:



Potential side reaction in our system:



Work by Kornblum and co-workers, on the reactions between nitro compounds and nitrite esters:



Scheme 2.21. Synthesis of furan **2.116** (top). *Reagents and conditions*: i) PBr_3 (0.5 eq.), Et_2O, 0 °C to rt, 18 h; ii) $NaNO_2$, DMF, rt, 3 h; iii) *n*-$BuNH_2$ (0.4 eq.), furfural (1.1 eq.), AcOH, 80 °C, 3 h; iv) $NaBH_4$ (2.4 eq.), 3:1 1,4-dioxane/EtOH, 0 °C, 1.5 h. A schematic to describe a potential side reaction which could give the nitrite ester **2.127** (middle). A summary of the report by Kornblum and co-workers on the further reactions that can occur between nitroalkanes and nitrite esters when in the presence of a base such as sodium nitrite.[144]

Although we were unable to isolate and characterise any side products, it is plausible that this ambident nucleophile might also react to give the undesired nitrite ester **2.127** (Scheme 2.21, middle). We later discovered two reports by Kornblum and co-workers that support this, and furthermore detail an additional side reaction (Scheme 2.21, bottom).[144,145] They found that sodium nitrate could act as a base to give the nitronate anion **2.129**, which could react with a nitrite ester (**2.131**) to give alkoxide **2.132** and the nitrosated nitro compound **2.130**. The latter would break down to give the oxime **2.134**, and ketone **2.135** upon aqueous workup. Finally, the authors noted that only a substoichiometric quantity of nitrite ester is required to fully decompose the nitro compound, *i.e*. the nitrite ester **2.131** is a

catalyst. This was explained by noting that the alkoxide **2.132** and N_2O_4 may react together to regenerate the nitrite ester **2.131**. Whilst we did not attempt isolation of any of the side-products noted above, it is likely the decomposition mechanisms reported by Kornblum and co-workers were active in our case.

The Henry reaction was also only moderately yielding, and although a consistently incomplete conversion complicated the purification of the product **2.123**, it could be isolated cleanly (Scheme 2.21, top). Finally, conjugate reduction using sodium borohydride gave an excellent yield of the nitroalkene **2.116**.

2.3.3 Cyclic Voltammetry Studies

Since the synthesis of the starting material had not been high yielding, it was deemed prudent to conduct cyclic voltammetry studies that could be done using model substrates and very small quantities of **2.116**. This would allow us to gain insight into the electrochemical behavior of nitro groups and their nitronates.

The following conditions were selected for our studies: sodium hydroxide would be used as a base, for its simplicity of use and appropriate pKa (32 in DMSO); nitromethane (pKa of 17.2 in DMSO), nitropropane (pKa of 16.9 in DMSO) and 2-methylfuran as model substrates; and methanol as a solvent.[142]

Comparison of the traces obtained between a control run (Figure 2.5, trace a) and from a solution containing just nitromethane (trace b) showed that the nitro group could not be oxidised in the range we measured (0 to +1.6 V vs Leakless Ag/AgCl reference). When NaOH was added however (trace c), a peak occurred at +1.11 V, which we attributed to oxidation of the nitromethane anion. The cyclic voltammogram of a MeOH solution containing only

NaOH and the supporting electrolyte (trace e) featured only a single peak at the much higher potential of +1.47 V. Finally, the trace obtained from 2-methyl furan displayed a single sharp peak at +1.41 V (trace d). These results indicate that the only the nitronate of a nitroalkane is capable of being oxidised, and that this oxidation occurs at a much lower potential than 2-methyl furan. This was important since our desired reaction (Scheme 2.19) required oxidation of the nitronate, not the furan group, to give a radical capable of a *5-exo-trig* cyclisation.

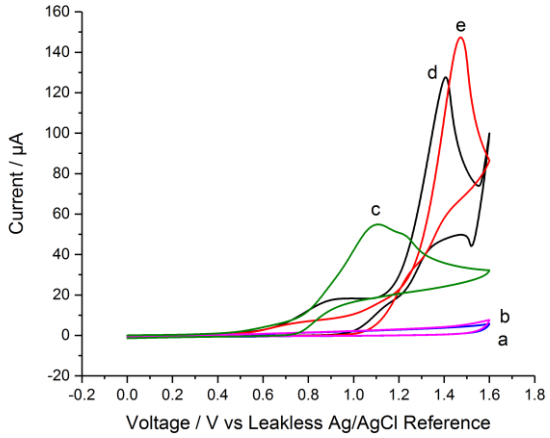


Figure 2.5. Cyclic voltammograms in MeOH (from standard Winchester, containing O_2) of (a) 0.1 M Et_4NOTs; b) 0.1 M Et_4NOTs, 10 mM nitromethane; (c) 0.1 M Et_4NOTs, 10 mM nitromethane, 10 mM NaOH; (d) 0.1 M Et_4NOTs, 10 mM 2-methylfuran; (e) 0.1 M Et_4NOTs, 10 mM NaOH.

It can be seen from Figure 2.6 that traces of dissolved oxygen in the solution can have a profound effect on the voltammogram obtained for both nitropropane (traces a and b) and nitromethane (traces c and d). The removal of oxygen has no effect on the potential at which the first oxidation occurs, but it does give rise to a second peak at a higher potential. This suggested to us that either the starting material, or an intermediate produced upon electron transfer, could react with oxygen.

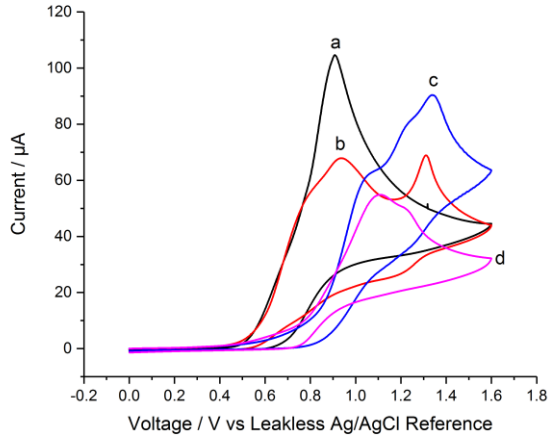


Figure 2.6. Cyclic voltammograms of solutions containing MeOH, 0.1 M Et_4NOTs, 10 mM NaOH and the following: (a) 10 mM 2-nitropropane; (b) 10 mM 2-nitropropane using degassed MeOH; (c) 10 mM nitromethane using degassed MeOH; (d) 10 mM nitromethane. The removal of dissolved oxygen from the solution was achieved by bubbling N_2 gas through it for 15 min.

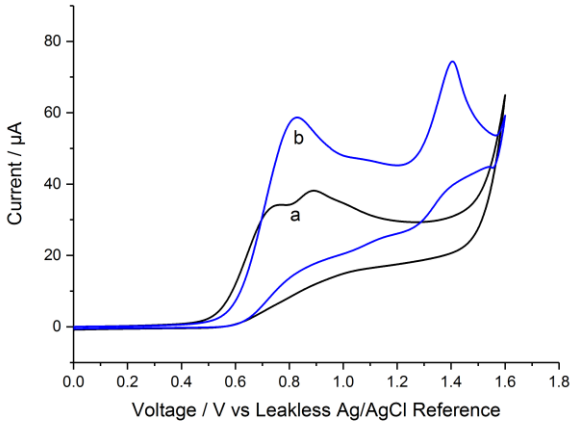
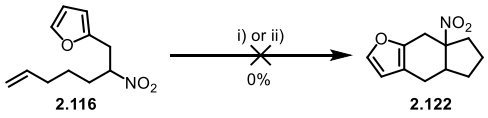


Figure 2.7. Cyclic voltammograms of solutions containing MeOH, 0.1 M Et_4NOTs, 10 mM NaOH and the following: (a) 10 mM nitroalkene **2.106**; (b) 10 mM nitroalkene **2.106** using degassed MeOH. The removal of dissolved oxygen from the solution was achieved by bubbling N_2 gas through it for 15 min.

We observed a similar effect when comparing the cyclic voltammograms of nitrofuran **2.116** (Figure 2.7) and thus decided that all synthetic studies would be conducted using solvent that had been sparged with an inert gas. With the information collected so far, the next logical step was to conduct the reaction using a galvanostat, on a scale large enough for the

purification and analysis of any products. Our initial attempts at the electrochemical cyclisation of **2.116** were wholly unsuccessful: in both cases there was extensive decomposition on the basis of the crude ^{1}H NMR spectra and TLC and a poor quantity of starting material was recovered (Scheme 2.22). At this point we were unsure whether it was the electrochemical oxidation that required tuning, or the subsequent chemical steps that needed optimisation. Given our lack of success, and limited time remaining to complete this rotation project, we decided to turn our attention towards a simpler substrate that had been proven to work with chemical methods.

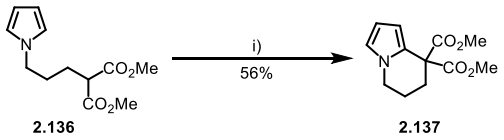


Scheme 2.22. *Reagents and conditions*: i) NaOH (1 eq.), Et_4NOTs (0.1 M), MeOH, 25 °C, carbon rod anode/cathode, 10 mA, 2.2 F mol^{-1}, 5.7 mA cm^{-2}; ii) as per i), but at 65 °C. 32% starting material **2.116** was recovered in each case.

2.4 Malonate Substrate Class

We chose the malonate substrate class because of the extensive research that had been conducted within the Burton group on both the synthesis of substituted malonates, and their subsequent oxidative cyclisation reactions. A publication by Magolan and Kerr on the Mn(III) promoted oxidative cyclisation of pyrrole **2.136** suggested that a similar substrate would make an excellent starting point for our methodological studies (Scheme 2.23).[146]

Work by Magolan and Kerr:



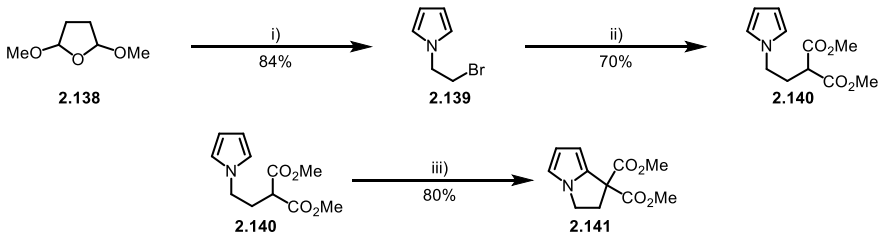
Scheme 2.23. Work by Magolan and Kerr.[146] *Reagents and Conditions*: i) $Mn(OAc)_3 \bullet 2H_2O$ (3 eq.), MeOH, reflux, 16-24 h.

In addition, a short and high yielding synthesis of a similar substrate, **2.140**, had been described by a previous member of the Burton group.[147] Malonate **2.140** (see Scheme 2.24)

would therefore be a suitable test substrate to optimise our electrochemical technique, conditions, and setup. From these optimised conditions, we envisaged that it might be possible to subject a range of aromatic and alkenyl derivatives to a successful electrochemical oxidative cyclisation.

2.4.1 Synthesis of Starting Material

Forming the pyrrole **2.139** from the masked 1,4-dialdehyde **2.138** could be achieved on a multigram scale (Scheme 2.24), and a good yield of the malonate **2.140** was obtained in the subsequent substitution reaction. Although the large excess of dimethyl malonate necessitated a vacuum distillation to remove this starting material, followed by purification by column chromatography, we were rewarded with multigram quantities of **2.140** in sufficiently high purity. Submission of **2.140** to a Mn(III) promoted oxidative cyclisation using the conditions reported by Magolan and Kerr gave a 80% isolated yield of the desired product **2.141**.[146]



Scheme 2.24. *Reagents and conditions*: i) 2-bromoethylamine hydrobromide (1 eq.), NaOAc (1 eq.), 1:3:3 AcOH/H_2O/DCE, 80 to 90 °C, 1.5 h; ii) NaH (4.85 eq.), dimethyl malonate (4.85 eq.), KI (0.8 eq.), DMF, 0 °C to rt, 24 h; iii) $Mn(OAc)_3 \bullet 2H_2O$ (3 eq.), MeOH, 65 °C, 3.5 h.

2.4.2 Design of the Electrochemical Reactor

An electrochemical setup of our own design is depicted in Figure 2.8, and was used to study the electrochemical cyclisation of malonate **2.140.** We designed the reactor with the principle purpose of being simple to setup, and therefore reproducible for each experiment. Furthermore the use of Quickfit® glassware would allow for the rigorous exclusion of water

and oxygen, should this prove necessary. A three-necked round bottomed flask was used, equipped with a stirrer bar to provide adequate mixing. Glassy carbon rods serve as the anode and cathode, which are pushed through thermometer adapters to provide an airtight seal, which are fitted to the two side arms of the round bottomed flask. A Suba-Seal® was fitted to the centre adapter, through which reagents could be added, and an argon balloon attached to maintain an inert atmosphere. The final advantage to this setup was that because of our use of a round-bottomed flask, we could easily and evenly heat our reactions using DrySyn® adapters. This setup was used for all of the optimisation reactions we performed using malonate **2.140**.

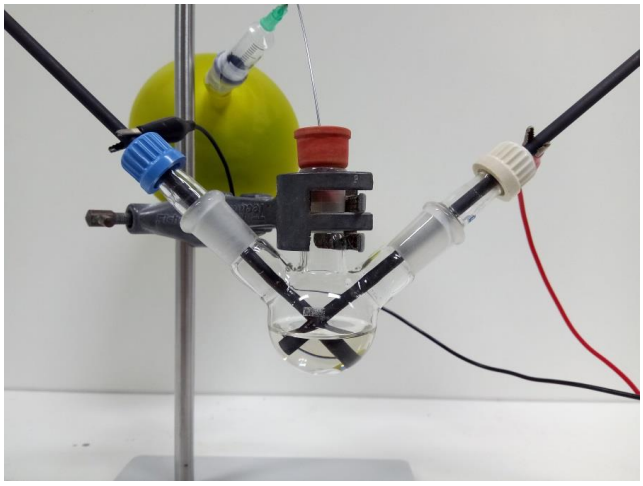


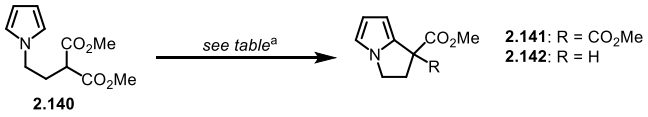
Figure 2.8. The initial electrochemical setup used for the electrochemical studies on the malonate substrate **2.140**.

2.4.3 Optimisation of conditions

Our optimisation began by screening a variety of bases and different temperatures (Table 2.2): neither NaOH nor K_2CO_3 were especially effective at 25 °C (entries 1-3) but we were pleased to achieve a positive result when the temperature was increased to 65 °C (entry 4). The desired product **2.141** was obtained in an isolated yield of 26%, along with a 22% yield

of the decarboxylated product **2.142**. Unfortunately LiOMe (entry 5) gave a poorer combined yield of cyclised products, and an increased ratio of decarboxylation product **2.142** too.

Table 2.2. Screening of Conditions for the Cyclisation of Malonate **2.140**



2.140

Entry	Base	Base equiv.	Temp. /°C	Charge /Fmol^{-1}	Yield of 2.141 (%)	Yield of 2.142 (%)
1	NaOH	1.1	25	3.0	0	0
2	K_2CO_3	1.1	25	2.2	Trace	Trace
3	K_2CO_3	2.0	25	2.2	0	0
4	K_2CO_3	1.1	65	2.2	26	22
5	LiOMe	1.1	65	2.2	13	27
6	K_2CO_3	1.1	65	0	0	0
7	none	N/A	65	2.2	0	0

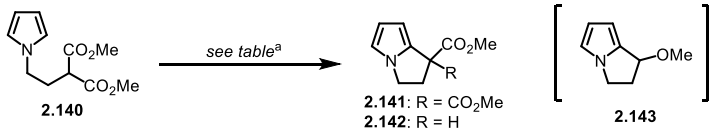
[a]*Reagents and conditions*: Glassy carbon rods were used as the anode and cathode with a surface area in solution of 1.7 cm^2, at a current of 10 mA. Et_4NOTs (0.1 M) was used as a supporting electrolyte, and the concentration of substrate **2.140** was 0.074 M in MeOH. The base, and equivalents of base, temperature and charge are as described in the table.

Two control experiments were completed, which demonstrated that the application of an electric potential was required to obtain product (Table 2.2, entry 6), and that a base was indeed required (entry 7), to presumably generate the malonate enolate. In the absence of either of these, the crude ^{1}H NMR spectra indicated a complicated mixture of products that could not be separated, and no remaining starting material. Clearly base and electrolysis induced decomposition were problems to which solutions were sorely needed.

From this starting point (Table 2.2, entry 4), we performed a more thorough screen of the following parameters: the current, the temperature, and the number of equivalents of base used (Table 2.3). These parameters were screened in parallel, and the results were then

analysed. From this screening it was clear that there was a subtle balance between the two cyclised products **2.141**/**2.142**, and decomposition. For example, a longer reaction time that comes as a consequence of a smaller current (Table 2.3, entry 1) gives a greater amount of the monoester **2.142** than diester **2.141**, whereas in all other cases there is an equal or greater amount of diester **2.141**. The best result came from using a sub-stoichiometric amount of base (entry 6), which gave the highest quantity of the desired product, and a minimal quantity of decomposition. Two equivalents of base gave none of the desired product but we did isolate a side product, which was tentatively characterised as **2.143** on the basis of the ^{1}H NMR spectrum that was obtained before the sample decomposed.

Table 2.3. Screening of Conditions for the Cyclisation of Malonate **2.140**.



2.140

2.141: R = CO_2Me
2.142: R = H

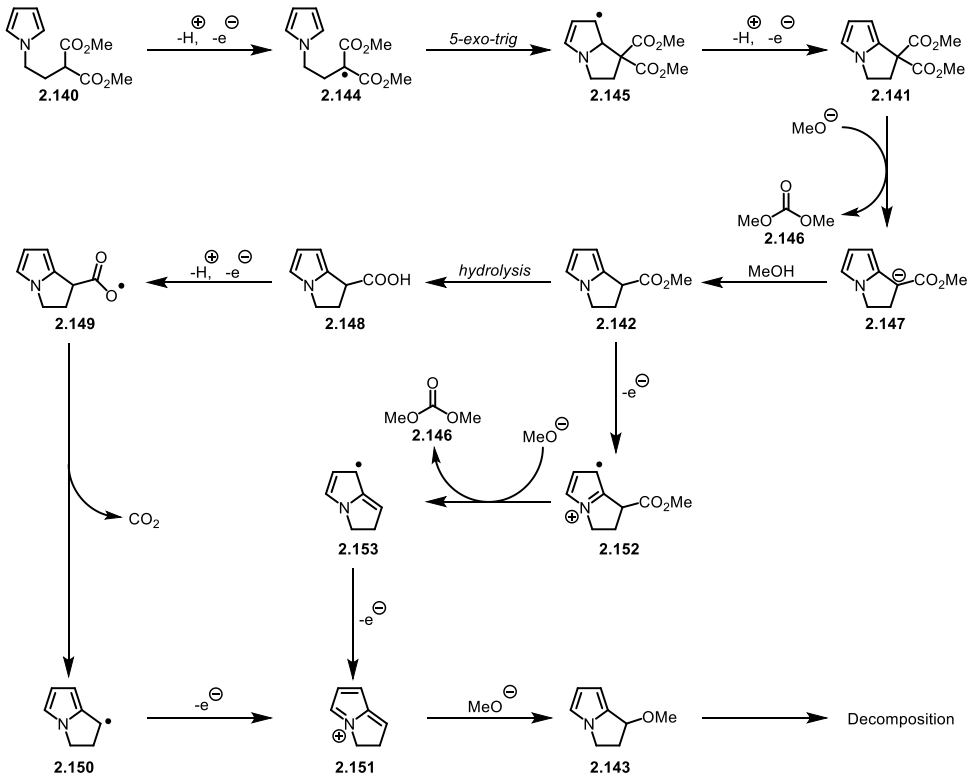
2.143

Entry	Current /mA	Base equiv.	Temp. /°C	Yield of 2.141 (%)	Yield of 2.142 (%)	Recovered 2.140 (%)
1	5	1.1	40	7	15	0
2	10	1.1	40	35	20	0
3	20	1.1	40	0	0	25
4	10	1.1	50	20	23	0
5	10	1.1	65	26	22	0
6	10	0.5	65	45	0	31
7	10	2.0	65	0	0	0[b]

[a] *Reagents and conditions*: Glassy carbon rods were used as the anode and cathode with a surface area in solution of 1.7 cm^2, at a current of 10 mA for a total charge passed of 2.2 F mol^{-1}. K_2CO_3 was used as a base and Et_4NOTs (0.1 M) as the supporting electrolyte, and the concentration of substrate **2.140** was 0.074 M in MeOH. The equivalents of base, temperature and current are as described in the table. [b] An 8% yield of a side-product was obtained which was tentatively characterised as **2.143**.

We proposed a plausible mechanistic scheme using known literature transformations to explain the range of products that we had isolated from this screening (Scheme 2.25).

Removal of a proton (by the base) and an electron (at the anode) from **2.140** gives a radical capable of undergoing a *5-exo-trig* cyclisation to give **2.145**. A second oxidation and removal of a proton gives the desired product **2.141**.



Scheme 2.25. Proposed mechanistic pathways to explain the formation of the observed products.

From here an undesired sequence of events can take place, beginning with a base initiated *retro*-Claisen condensation to give the anion **2.147**. This can take a proton from the solvent to give the other major product, **2.142**. Two possible pathways were identified that could give the product **2.143**: the first began with a hydrolysis; the second began with an oxidation. Hydrolysis of **2.142** would give the carboxylic acid **2.148**, which could undergo a Kolbe-like oxidation and loss of CO_2 to give radical **2.150**, whose oxidation would give the cation **2.151**. The second pathway would intercept at this cation, but would come about via an oxidation of **2.142** to give **2.152**, a base induced decarboxylation to give **2.153**, and a

second oxidation reaction to give cation **2.151**. In each pathway, the carbocation **2.151** would be quenched by methoxide to give the observed product **2.143**.

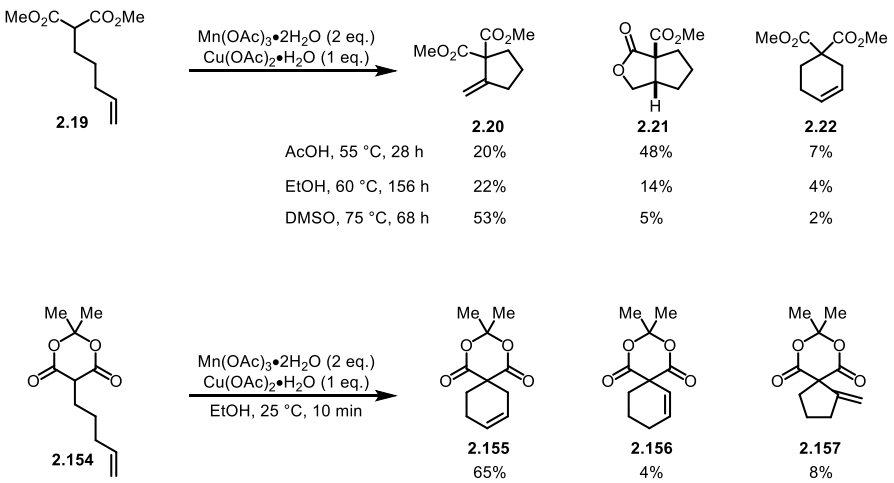
2.4.4 Discussion of Results

The results that had been obtained so far seemed extremely promising, but decomposition of the product **2.141** was certainly an issue. Our results suggested that using a less basic medium might improve the yield of the desired product (Table 2.3, entry 6, versus entry 7). For this a correspondingly more acidic dicarbonyl that would still be able to form the oxidisable enolate would be required. We hypothesised that a Meldrum's acid derivative, in place of the malonate functionality, could be suitable. Since these derivatives typically have a much lower pK_a than the equivalent malonate, a much weaker base, or no base at all, would be required to generate the enolate that seemed necessary.

2.5 Meldrum's Acid Substrate Class

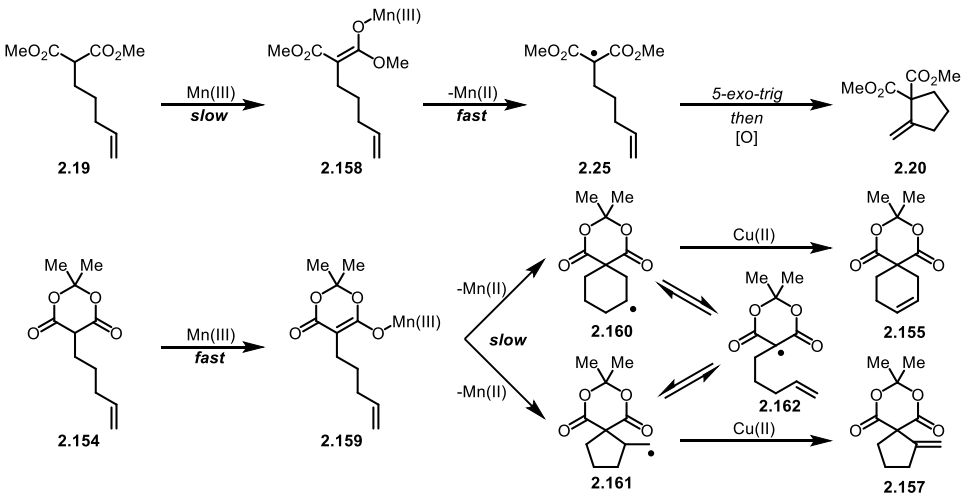
2.5.1 Introduction

The key difference between Meldrum's acid and dimethyl malonate is that the former has a pK_a of 7.32 whilst the latter has a pK_a of 15.87 (measured in DMSO at 25 °C).[143] This difference in pK_a leads to some fundamental differences in reactivity, beyond the ease of forming the corresponding enolate of each. This is exemplified in the report by Snider and co-workers on the oxidation by Mn(III) and Cu(II) of alkenyl derivatives of Meldrum's acid (Scheme 2.26).[148]



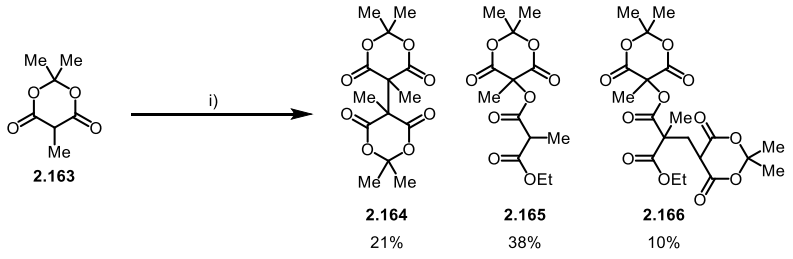
Scheme 2.26. The cyclisation of malonate **2.19**, compared with the cyclisation of acid **2.144**, as reported by Snider and co-workers.[148]

Other alkene substitution patterns were also cyclised, with all except the most hindered showing a preference for the *6-endo-trig* cyclisation. By studying the difference in rates between substrates with different alkene substitution patterns Snider determined that the alkene must be involved in the rate determining step, unlike the malonate substrate class. Snider therefore proposed the following mechanistic pathway for each substrate class (Scheme 2.27).



Scheme 2.27. Differences in the rate determining step between malonates and Meldrum's acid derivates, reported by Snider and co-workers.[148]

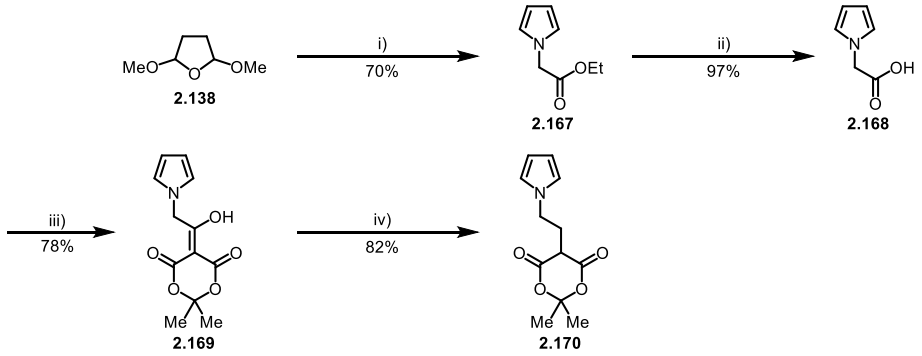
A final point of interest in the report by Snider and co-workers is the fact that for the substrates that were slowest to cyclise, products that appeared to be dimers were observed. The authors conducted a more thorough investigation into this dimerisation using methyl Meldrum's acid **2.163** (Scheme 2.28), and were able to isolate the following products, C–C dimer **2.164**, C–O dimer **2.165**, and the trimer **2.166** that may result from addition of **2.163** to methylene Meldrum's acid, which comes from the oxidation of starting material **2.163**. These observations became relevant to our own studies and will be discussed further in the next section.



Scheme 2.28. Dimerisation study of methyl Meldrum's acid, conducted by Snider and co-workers.[148]

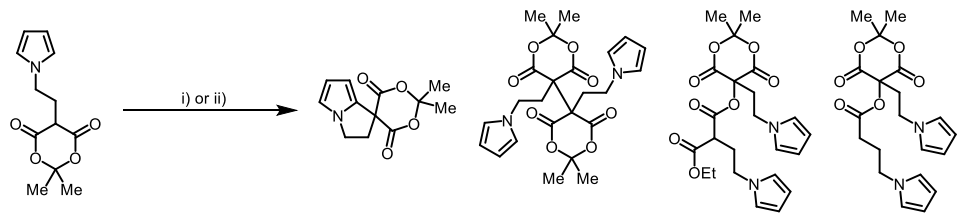
2.5.2 Synthesis of Starting Material 2.170

The synthesis of the required Meldrum's acid was high yielding and took just four steps (Scheme 2.29). The procedure reported by Taylor and co-workers was used to synthesise pyrrole **2.167**.[149] Hydrolysis of this ester gave an almost quantitative yield, which provided the carboxylic acid **2.168** required to acylate Meldrum's acid to give **2.169**, using a procedure adapted from that patented by Song and co-inventors.[150] Finally reduction using $NaBH_4$ gave **2.170** in an excellent yield.[151]



Scheme 2.29. Synthesis of pyrrole **2.170**. *Reagents and conditions*: i) glycine ethyl ester hydrochloride (1 eq.), NaOAc (1.7 eq.), 1:2 H_2O/AcOH, reflux, 4 h; ii) NaOH (5 eq.), 1:1 THF/H_2O, 0 °C, 1 h; iii) Meldrum's acid (1.1 eq.), DMAP (0.1 eq.), *i*-Pr_2NEt (2.2 eq.), Piv-Cl (1 eq.), MeCN, 0 to 50 °C, 4 h; iv) $NaBH_4$ (4 eq.), 1:6 AcOH/CH_2Cl_2, 0 °C, 1 h.

Submission of the Meldrum's acid derivative **2.170** to both chemical and electrochemical oxidations gave a diverse set of products (Scheme 2.30). The collection of products is very much in keeping with the results that Snider and co-workers obtained (Scheme 2.27 and Scheme 2.28), but unfortunately the isolated yields of each product were extremely poor. Nevertheless we believed that the results could be improved by modifying the conditions to select for the desired product **2.171** in preference to the dimers **2.172**, **2.173** and **2.174**. We shall first briefly discuss the modifications made to the electrochemical setup however, since these modifications were made in anticipation of optimising the reaction (section 2.5.3).



2.170	Conditions	2.171	2.172	2.173	2.174
0% recovered	Chemical (i)	14%	15%	12%	0%
8% recovered	Electrochemical (ii)	8%	8%	0%	2%

Scheme 2.30. *Reagents and conditions*: i) $Mn(OAc)_3 \bullet 2H_2O$ (3 eq.), EtOH, rt, 1 h; ii) 2,6-lutidine (0.5 eq.), $LiClO_4$ (0.1 M), MeCN, 40 °C, RVC anode/cathode, 10 mA, 2.2 F mol^{-1}.

2.5.3 Improvements Made on the Experimental Setup

The setup used for the electrolysis of pyrrolomalonate **2.140** was suitable for our initial foray into electrochemistry, but we wished to take what we had learnt and build an improved setup that could be used for the substantive D.Phil. project. Firstly, we wished to switch out the carbon rod electrodes in favour of RVC foam, as we postulated that the higher surface area of the latter would favour intramolecular reactions as opposed to intermolecular reactions. A higher surface area of electrode would result in a lower current density and it was expected that this would lead to a smaller concentration of reactive radical intermediates at the electrode surface. More practically, care was required to ensure the carbon rods did not short circuit in the setup shown in Figure 2.8, and the rods needed to be thoroughly cleaned to ensure fouling would not impact subsequent reactions. By comparison RVC electrodes are sufficiently cheap such that they can be used disposably, ensuring that each reaction is exposed to a fresh electrode surface, which should improve reproducibility.

With the above considerations in mind, we took note of the publication by Baran and co-workers on electrochemical C–H allylic oxidation, who provided detailed instructions on how to build their electrochemical cell in the supplementary information.[137] The key feature of

their design was a pair of RVC electrodes, which sandwich a glass slide, placed inside a test tube equipped with a stirrer bar. This setup was reproduced for our work, as shown in Figure 2.9. A key modification that we made was to mount conducting metal slices onto the glass slide, which the electrodes could be pushed onto to secure them in place. We found that this was substantially quicker than soldering to the RVC foam and the electrodes remained securely connected to the galvanostat throughout the reaction.

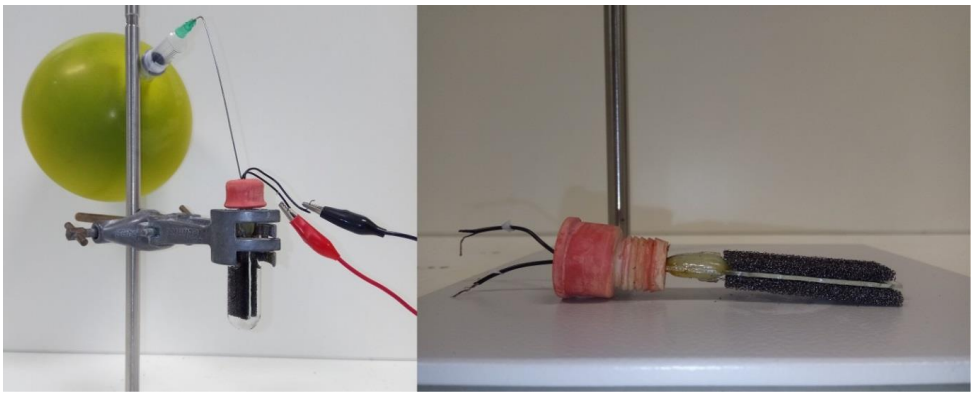


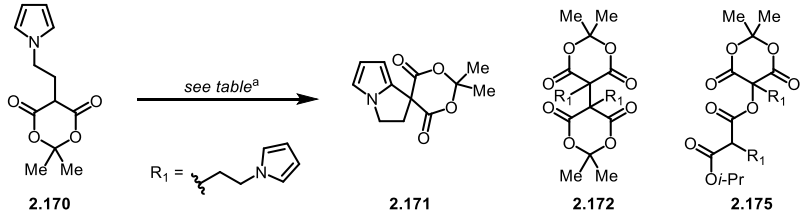
Figure 2.9. Left: new electrochemical setup, based closely on the design reported by Baran and co-workers.[137] Right: a view of the electrode from the side to show the glass slide sandwiched by the two electrodes.

2.5.4 Optimisation of conditions

For the optimisation of this reaction, we selected the following parameters: the number of equivalents of base (2,6-lutidine), the amount of charge passed (a parameter equivalent to the number of equivalents of a hypothetical one-electron oxidant added), solvent, temperature, the concentration of the substrate and supporting electrolyte, current, and additives. The yields were determined by comparison of the peak integrals of the product in the crude proton NMR spectrum with that of a known quantity of 1,2,4,5-tetrachloro-2-nitrobenzene added to the crude material. An extended relaxation delay of 30 seconds was used in each experiment to ensure that all resonances had fully relaxed, allowing for quantitative integration.

We began with the equivalents of base used and the charge passed (Table 2.4). It was noted that in absence of base no product was isolated (entry 1), but otherwise this parameter had minimal effect upon the yield of the desired product **2.171** (entries 2, 3 and 4). With regard to the two isolated side products **2.172**/**2.175**, increasing the quantity of base to a full equivalent (entry 3), and two equivalents (entry 4), changed the product distribution slightly. We tried reducing the amount of charge passed to the theoretical minimum for this two-electron oxidation (entry 5), but the yield of pyrrole **2.171** was unchanged, and the change to the product distribution was minor.

Table 2.4. Screening of Base Equivalents and Charge for the Cyclisation of **2.170**.



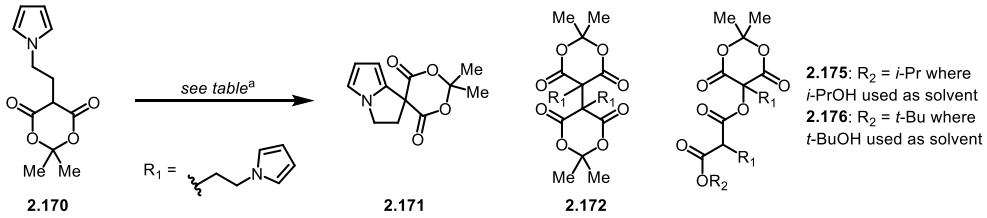
Entry	Equiv. of Base	Charge /F mol^{-1}	Yield (%)[b]			
			2.171	**2.172**	**2.175**	**2.170**
1	0	2.2	0	0	0	<20%
2	0.5	2.2	20	16	22	0
3	1	2.2	21	9	28	0
4	2	2.2	21	10	25	0
5	0.5	2	22	8	26	0

[a] *Reagents and conditions*: Reticulated vitreous carbon foam was used as the anode and cathode, in a setup according to the procedure described above in section 2.5.3 (*vide supra*) and in the experimental section. A current of 10 mA was used, with 2,6-lutidine as a base, and $LiClO_4$ (0.1 M) was used as the supporting electrolyte. The reactions were conducted at 40 °C in 1:4 *i*-PrOH/MeCN, with the concentration of substrate equal to 66 mM. The equivalents of base used and amount of charge passed are as described in the table. [b] The yield was determined from the crude ^{1}H NMR spectrum by employing an extended relaxation time (D1) of 30 seconds, and comparing the integrals with a known quantity of 1,2,4,5-tetrachloro-3-nitrobenzene.

Nevertheless the reaction appeared to be cleaner after studying the crude ^{1}H NMR spectrum and so we continued our screen using 0.5 equivalents of base and 2 F mol^{-1} of charge.

The next two parameters that were screened were the solvent and the temperature (Table 2.5).

Table 2.5. Screening of Solvents and Temperatures for the Cyclisation of **2.170**.



2.170 **2.171** **2.172**

Entry	Solvent	Temp. /°C	Yield (%) [b]			
			2.171	**2.172**	**2.175/2.176**	**2.170**
1 [c]	MeCN	40	14	8	N/A	19
2	1:4 *i*-PrOH/MeCN	40	22	8	26	0
3 [c]	2:3 *i*-PrOH/MeCN	40	21	8	22	0
4	1:4 *i*-PrOH/MeCN	25	21	8	27	0%
5	1:4 *t*-BuOH/MeCN	25	20	8	23 [d]	0%
6	1:4 *i*-PrOH/MeCN	0	20	<5	37	0%
7	1:4 *t*-BuOH/MeCN	0	20	9	30 [d]	0%
8	1:4 acetone/MeCN	0	13	~16 [e]	N/A	~5% [e]

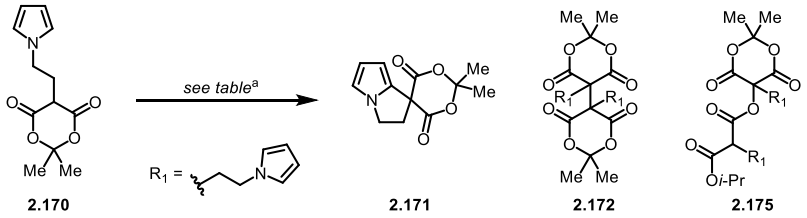
[a] *Reagents and conditions*: Reticulated vitreous carbon foam was used as the anode and cathode, in a setup according to the procedure described above in section 2.5.3 (*vide supra*) and in the experimental section. A current of 10 mA was used with a total amount of charge passed was 2.0 F, with 2,6-lutidine (0.5 eq.) as a base, and $LiClO_4$ (0.1 M) was used as the supporting electrolyte. The concentration of substrate was equal to 66 mM. The solvent and the temperature are as described in the table. [b] The yield was determined from the crude ^{1}H NMR spectrum by employing an extended relaxation time (D1) of 30 seconds, and comparing the integrals with a known quantity of 1,2,4,5-tetrachloro-3-nitrobenzene. [c] The total amount of charge passed was 2.2 F mol^{-1}. [d] The *t*-Bu ester analogue **2.175** was assigned by analogy to the ethyl- and *iso*-propyl analogues **2.173** and **2.175** that had been fully characterised. [e] Approximate yields, since the peaks in the ^{1}H NMR spectrum overlapped with those of other impurities.

Increasing the quantity of *i*-PrOH (Table 2.5, entry 3, compared to entry 2) or switching to *t*-BuOH (entries 5 and 7, compared to entries 4 and 6) did not drastically change the yield of

the desired product, nor the product distribution, with the exception of giving the *t*-Bu analogue **2.176** (this was characterised by analogy to the ethyl and iso-propyl analogues **2.173** and **2.175**, where full characterisations were made). A decrease in the yield of the malonate dimer **2.176** when using *t*-BuOH was noted (entry 5), but the greatest improvement in the combined yield was found when the reaction was conducted at 0 °C using *i*-PrOH (entry 6).

Reducing the concentration of the substrate to 33 mM (Table 2.6, entry 2) from 66 mM (entry 1) gave an improvement in the yield of the desired product **2.171**.

Table 2.6. The Effect of Substrate Concentration on the Cyclisation of **2.170**.



2.170 **2.171** **2.172** **2.175**

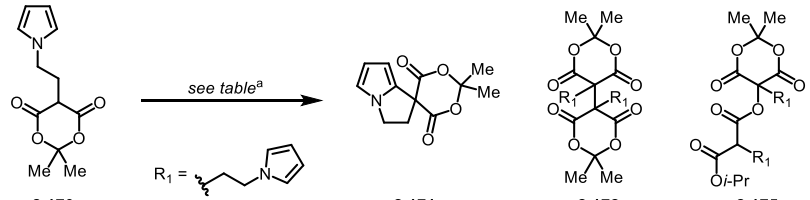
Entry	Concentration	Yield (%)[b]			
	/mM	**2.171**	**2.172**	**2.175**	**2.170**
1	66	20	<5	37	0
2	33	25	<5	39	0
3	8	12	<5	25	0

[a] *Reagents and conditions*: Reticulated vitreous carbon foam was used as the anode and cathode, in a setup according to the procedure described above in section 2.5.3 (*vide supra*) and in the experimental section. A current of 10 mA was used with a total amount of charge passed was 2.0 F mol^{-1}, with 2,6-lutidine (0.5 eq.) as a base, and $LiClO_4$ (0.1 M) was used as the supporting electrolyte in 1:4 *i*-PrOH/MeCN at 0 °C. Concentration of substrate as described in the table. [b] The yield was determined from the crude ^1H NMR spectrum by employing an extended relaxation time (D1) of 30 seconds, and comparing the integrals with a known quantity of 1,2,4,5-tetrachloro-3-nitrobenzene.

A sensible hypothesis is that the reduction in concentration reduces the rate of an unwanted dimerisation process, allowing the desired *5-exo-trig* reaction to occur. A further reduction to 8 mM (entry 3) however gave a drastic drop in the yield of all products.

Reducing the current to 5 mA had no effect (Table 2.7, entry 1), but increasing the current to 20 (entry 3) and 50 mA (entry 4) had a deleterious effect on the yield of all products. At a higher current we would expect the electrode potential to increase (see section 2.2.1, Equation 2.1) and a corresponding reduction in selectivity of oxidation. This would seem to be the case in our system, where a poor selectivity of oxidation could lead to oxidation of the pyrrole motif in the products **2.171** and **2.175**.

Table 2.7. The Effect of Current on the Cyclisation of **2.170**.



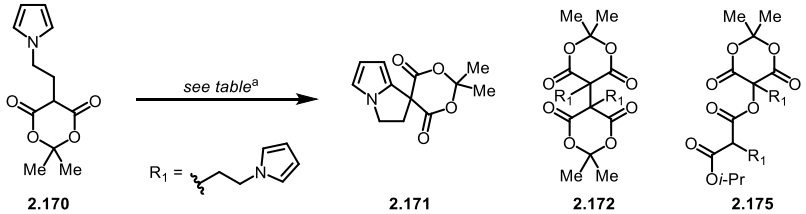
Entry	Current /mA	Yield (%) [b]			
		2.171	**2.172**	**2.175**	**2.170**
1	5	25	<5	38	0
2	10	25	<5	39	0
3	20	18	<5	35	<5
4	50	5	<5	11	28

[a] *Reagents and conditions*: Reticulated vitreous carbon foam was used as the anode and cathode, in a setup according to the procedure described above in section 2.5.3 (*vide supra*) and in the experimental section. The total amount of charge passed was 2.0 F, with 2,6-lutidine (0.5 eq.) as a base, and $LiClO_4$ (0.1 M) was used as the supporting electrolyte in 1:4 *i*-PrOH/MeCN at 0 °C. The concentration of substrate was equal to 33 mM. Current as described in the table. [b] The yield was determined from the crude ^{1}H NMR spectrum by employing an extended relaxation time (D1) of 30 seconds, and comparing the integrals with a known quantity of 1,2,4,5-tetrachloro-3-nitrobenzene.

In a final attempt to improve the yield we increased the concentration of supporting electrolyte (Table 2.8, entry 2), and added one equivalent $Cu(OAc)_2 \bullet H_2O$ (entry 3). We had hypothesised that if the second oxidation was slow, and the desired *5-exo-trig* cyclisation reversible, increasing the rate of the second oxidation could improve the yield of product **2.171**. Copper(II) has been shown on a number of occasions (see section 2.1.3) to improve

the yield of desired product due to its ability to rapidly oxidise radicals. An increased concentration of supporting electrolyte had been shown by Moeller and co-workers to improve the rate of second oxidation and thus yield of product.[152] Unfortunately we found that both sets of conditions led to a reduction in the yield of **2.171**, and so further optimisation of this reaction was terminated.

Table 2.8. Screening of Concentration of the Supporting Electrolyte and the Effect of Additives on the Cyclisation of **2.170**.



Entry	$LiClO_4$ Conc. /M	Additives	Yield (%)[b]			
			2.171	**2.172**	**2.175**	**2.170**
1	0.1	None	25	<5	39	0
2	1.0	None	16	<5	22	7
3	0.1	$Cu(OAc)_2 \bullet H_2O$ (1 eq.)	12	6	14	20

[a] *Reagents and conditions*: Reticulated vitreous carbon foam was used as the anode and cathode, in a setup according to the procedure described above in section 2.5.3 (*vide supra*) and in the experimental section. A current of 10 mA was used, and the total amount of charge passed was 2.0 F, with 2,6-lutidine (0.5 eq.) as a base, and $LiClO_4$ was used as the supporting electrolyte in 1:4 *i*-PrOH/MeCN at 0 °C. The concentration of substrate was equal to 33 mM. Concentration of the supporting electrolyte and the addition of any additives are as described in the table. [b] The yield was determined from the crude ^{1}H NMR spectrum by employing an extended relaxation time (D1) of 30 seconds, and comparing the integrals with a known quantity of 1,2,4,5-tetrachloro-3-nitrobenzene.

2.5.5 Discussion of Results

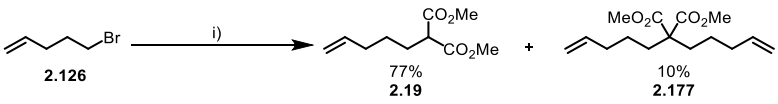
As a result of the screening we had found conditions that allowed us to isolate and characterise over 60% of material that had undergone a single electron transfer event, as opposed to decomposition products. This suggested to us that the single electron transfer step was likely functioning as desired. However whilst the results of this electrochemical study were interesting, they were clearly not synthetically useful. As such, we decided that an alternative substrate should be the subject of any future studies. We would be able to

take the information garnered from our studies on the nitroalkene (**2.116**) and pyrrole (**2.140**/**2.170**) substrates, and apply this to increase the likelihood of future success.

2.6 Non-Pyrrole Substrate

We decided to subject a variety of malonate derivatives to the optimised electrochemical setup and conditions. This decision was taken for two reasons: one, the radical obtained from oxidation of the Meldrum's acid derivative **2.170** was unselective in its chemistry; two, the radicals obtained from the oxidation of malonates **2.140** and **2.170** were more selective in their respective cyclisations, but the products **2.141** and **2.171** were unstable. With this in mind, a sensible alteration was to remove the pyrrole moiety, and replace it with an alkene or aryl group that would be less susceptible to over-oxidation or base mediated decomposition (see Scheme 2.25). We synthesised two different substrates and tested each under the electrochemical conditions that had been used in earlier experiments.

The terminal alkene **2.19** was synthesised in a single step, in conjunction with the double alkylation product **2.177** (Scheme 2.31).

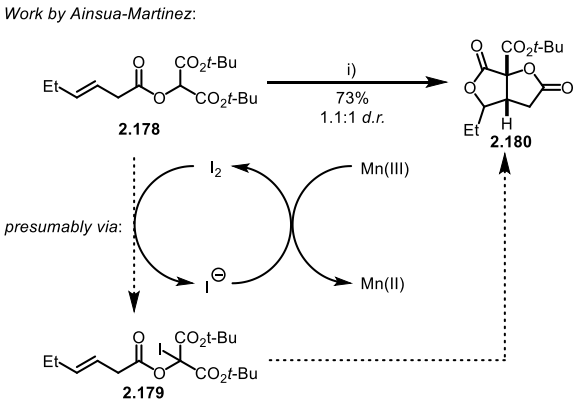


2.126 — 77% **2.19** + 10% **2.177**

Scheme 2.31. Synthesis of malonates **2.19** and **2.177**. *Reagents and conditions*: i) NaH (3 eq.), dimethyl malonate (3 eq.), KI (0.5 eq.), 1:1 THF/DMF, 80 °C, 18 h.

Our strategy for the electrochemical oxidation of **2.19** was based upon a separate piece of work by Ainsua Martinez,[33,34] who reported a Cu(II) free alternative to the classic conditions used within the Burton group (see section 2.1.4) for the synthesis of bicyclic lactone **2.180** (Scheme 2.32). This methodology was also used in our synthetic campaign towards a Dolabellane diterpenoid (see Chapter 1). Ainsua Martinez proposed that this reaction

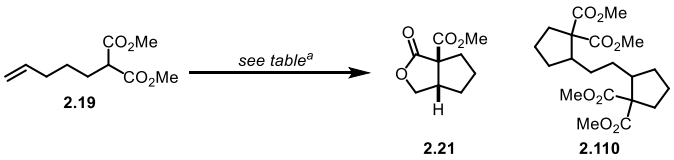
passed through the iodomalonate **2.179**: we hypothesised that a plausible mechanism for the synthesis of **2.179** would be an iodination of the malonate **2.178** with iodine, which could in principle be generated by oxidation of the potassium iodide with Mn(III) (Scheme 2.32). If this is the case, it should be possible to replace the Mn(III) with anodic oxidation to generate the required iodine. This would constitute an example of iodide acting as an electrochemical mediator (see section 2.2.6), which has been previously reported by Little and co-workers.[136]



Scheme 2.32. Work reported by Ainsua Martinez,[33,34] a reaction which was postulated to go via **2.179**, which we propose occurs by reaction of **2.178** with iodine. *Reagents and conditions*: i) $Mn(OAc)_3 \bullet 2H_2O$ (3 eq.), KI (0.5 eq.), MeCN, 80 °C, 19 h.

We were disappointed to not obtain any of the desired product **2.21** (Table 2.9, entry 1), but were able to isolate the cyclised dimer **2.110**. Reducing the amount of charge passed (entry 2) or changing the source of iodide (entry 3) had minimal effect, but we were surprised to find that removal of the iodide entirely gave an improvement in the yield of the dimer **2.110** (entry 4) while removal of the strong base gave no conversion at all (entries 5 and 6).

Table 2.9. Screening of Conditions for the Cyclisation of Malonate **2.19.**

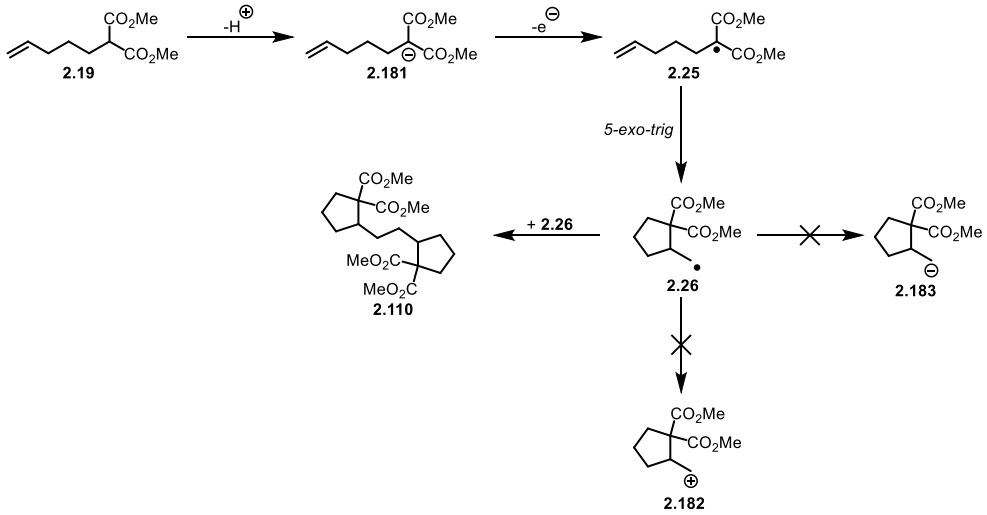


Entry	Base	Additive	F mol^{-1}	Conversion (%)	Yield of 2.21 (%)	Yield of 2.110 (%)
1	NaOMe (2 eq.)	KI (2 eq.)	3.9	>95	0	53
2	NaOMe (2 eq.)	KI (2 eq.)	2.2	>95	0	61
3	NaOMe (2 eq.)	Bu_4NI (2 eq.)	2.2	>95	0	55
4	NaOMe (2 eq.)	None	2.2	>95	0	71
5	None	Bu_4NI (2 eq.)	2.2	0%	-	-
6	2,6-lutidine (2 eq.)	Bu_4NI (2 eq.)	2.2	0%	-	-

[a] *Reagents and conditions*: i) $LiClO_4$ (0.1 M), MeOH, rt, RVC anode/cathode, 8 mA; the base and additives added, and the amount of charged passed, are as described in the table. [b] Subjecting **2.19** to the following conditions, $Mn(OAc)_3 \bullet 2H_2O$ (3 eq.), KI (0.5 eq.), MeCN, 80 °C, 6.5 h, gave **2.21** in a yield of 91%.

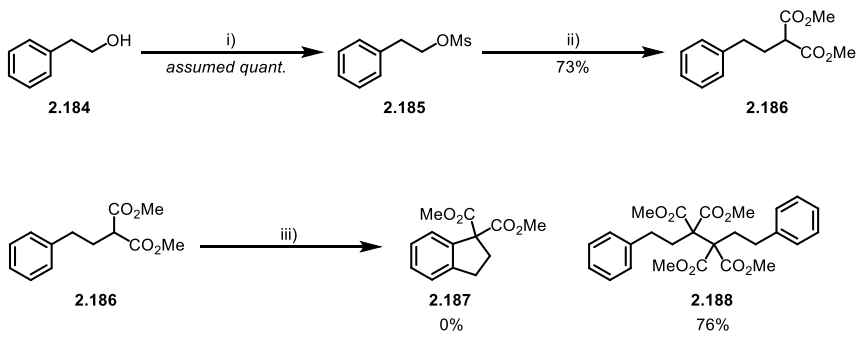
Clearly the electrochemical oxidation of **2.19** is not a mediated one, and we propose that the product is formed via the following mechanism (Scheme 2.33). Oxidation of the anion **2.181** at the anode gives the corresponding radical **2.25**; a *5-exo-trig* radical cyclisation follows, then dimerisation with another molecule of **2.26**. This was somewhat unsurprising since we did not expect another radical species to be present, and neither reduction to give anion **2.183**, nor oxidation to give cation **2.182** would be a facile transformation.

Nonetheless this result was encouraging, not least because the yield of product **2.110** was far higher than any previous result obtained, but also because these conditions could give an excellent yield of a cyclised non-dimerised product, if only the right class of substrates was found.



Scheme 2.33. Proposed mechanistic pathway to give dimer **2.110**.

Our final substrate was **2.186**, where the alkene moiety had been replaced by a phenyl group. It was also reminiscent of the earlier substrate **2.140** bearing the pyrrole group, but with the key difference that the expected product **2.187** should not be oxidised further. Whilst the synthesis of **2.186** was relatively simple and gave an excellent yield, the electrochemical cyclisation was less promising (Scheme 2.34). Oxidation of **2.174** gave solely the dimer **2.188**, albeit in an excellent yield of 76%. We were disappointed that the desired cyclisation had not taken place, but pleased that oxidation of the presumed enolate of malonate **2.186** had taken place so smoothly.

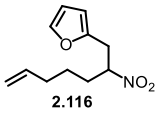


Scheme 2.34. *Reagents and conditions*: i) Ms-Cl (1.2 eq.), Et_3N (1.5 eq.), CH_2Cl_2, 0 °C – rt, 1.5 h; ii) NaH (2 eq.), dimethyl malonate (3 eq.), KI (0.5 eq.), 1:2 THF/DMF, 80 °C, 3 h; iii) NaOMe (0.5 eq.), $LiClO_4$ (0.1 M), MeOH, rt, RVC anode/cathode, 10 mA, 2.2 F mol^{-1}.

Unfortunately we were unable to continue any further optimisation due to time constraints, but were pleased to improve upon the yields that Ainsua Martinez obtained for the cyclisation of similar malonate substrates (see section 2.2.7). Future work in this area may be able to tune the conditions and electrochemical setup that we have optimised, to obtain cyclised products equal to or greater in complexity than those that have been obtained using the Mn(III)/Cu(II) and Mn(III)/I^- oxidative systems.

2.7 Conclusions and Future Work

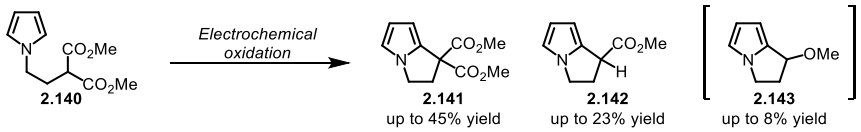
Our efforts began using cyclic voltammetry to study the nitrofuran **2.116** (Scheme 2.35), where we found that only the corresponding nitronate anion could be oxidised, and that oxygen could interfere with this process. Unfortunately we were unable to translate this knowledge into successful synthetic yields, and so moved on to an alternative substrate.



Scheme 2.35. Nitrofuran **2.116**, whose oxidative behavior was studied using cyclic voltammetry.

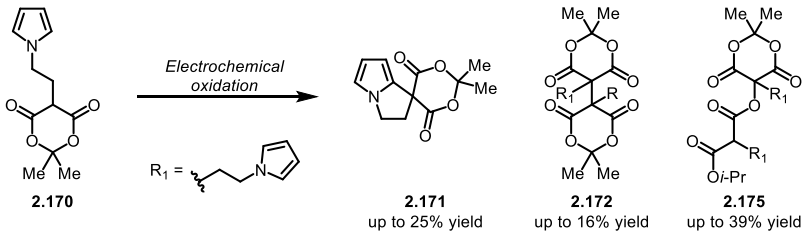
This simpler substrate took the form of malonate **2.140**, and we were able to obtain some moderate yields of the desired cyclised product **2.141**, in addition to **2.142** and **2.143**

(Scheme 2.36). Not only did this show that an electrochemical oxidation of a malonate was possible in the presence of base, but also that the resulting radical was capable of a radical cyclisation and second oxidation to give the desired product. The products that were obtained allowed us to propose a plausible mechanism, which suggested that conducting the reaction in a less strongly basic medium might be more successful. For this a correspondingly more acidic substrate was required.



Scheme 2.36. A summary of the results obtained for the electrochemical oxidation of malonate **2.140**.

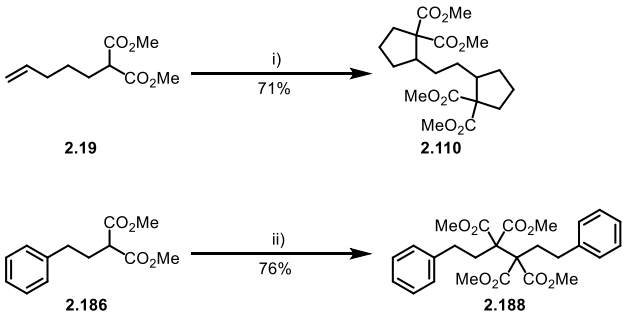
Our investigations therefore turned to the Meldrum's acid derivative **2.170**. A more thorough screening was performed, using ^{1}H NMR spectrum to determine the yield for each set of conditions. Our best set of conditions gave a combined yield of over 60%, but we were unfortunately unable to tune the selectivity in favor of the desired cyclised monomer and obtained dimerisation products **2.172** and **2.175** instead (Scheme 2.37).



Scheme 2.37. A summary of the results obtained for the electrochemical oxidation of Meldrum's acid derivative **2.170**.

With the time that remained we decided to return to substrates more similar to those studied by Ainsua Martinez.[33] We were pleased to find that using our optimised set of conditions and electrochemical setup, we obtained much improved yields for the oxidation products of both **2.19** and **2.186** (Scheme 2.38). Both substrates demonstrated that

oxidation of the α-position of a malonate functional group was possible, without resorting to a metal-based mediator like $Mn(OAc)_2$.[138,139] Furthermore the resulting radical could undergo a radical cyclisation onto a tethered alkene, to give a product like **2.110**.



Scheme 2.38. *Reagents and conditions*: i) NaOMe (2 eq.), $LiClO_4$ (0.1 M), MeOH, rt, RVC anode/cathode, 8 mA, 2.2 F mol^{-1}; ii) NaOMe (0.5 eq.), $LiClO_4$ (0.1 M), MeOH, rt, RVC anode/cathode, 10 mA, 2.2 F mol^{-1}.

Our work on the electrochemical oxidation of malonates in the presence of base represents the first step in what we hope will become a methodology to rival that of the Mn(III) based systems. Future work in this area will focus on finding a method to efficiently terminate the radical processes that avoid unwanted dimerisations. With such a method in hand we fully expect that the electrochemical setup and set of conditions should be suitable for optimising the methodology.

3. Experimental

3.1 General Experimental

All reactions were carried out under a nitrogen or argon atmosphere, unless specified otherwise, using standard vacuum line techniques and glassware that was oven or flame dried and cooled under argon before use. Solvents were dried according to the procedure outlined by Williams and Lawton,[153] or by stirring overnight on CaH_2, then distilling the solvent onto activated 4 Å molecular sieves, and stored in the dark. Water was purified by an Elix® UV-10 system. All other reagents were used as supplied (analytical or HPLC grade) without prior purification, unless otherwise specified.

Chromatographic techniques:

Thin layer chromatography (TLC) was performed on aluminium plates coated with 60 F254 silica. Plates were visualised using UV light (254 nm), an acidic vanillin dip, or basic potassium permanganate. Retention factors (R_f) are reported with the solvent system used in parentheses. Extractions during a reaction workup were performed with the specified solvent, monitored by TLC, and repeated until none of the product(s) were observed to be present in the most recent extraction. Flash column chromatography was performed on Kieselgel 60 silica, and the solvent system used is recorded in parentheses. HPLC analysis was performed on an Agilent 1200 series.

NMR Analysis:

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on Bruker AVIII 700 (with inverse TCI 1H/13C/15N cryoprobe, 700/176 MHz), Bruker AV500 (with ^{13}C cryoprobe, 500/125 MHz) or Bruker AV400 (400/100 MHz) spectrometer in a solution of deuterated chloroform

unless stated otherwise. The field was locked by external referencing to the relevant deuteron resonance. Proton and carbon chemical shifts (δ) are reported in ppm, referenced to tetramethylsilane (δ = 0 ppm) and observed coupling constants *J* in Hz. Resonances are described as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), dt (doublet of triplets) *etc*. Unless otherwise specified, coupling constants have been rounded to nearest 0.5 Hz. NMR assignments were made on the basis of coupling constants, chemical shifts, COSY, HSQC, HMBC, nOe and NOESY data, and by comparison to literature where possible. H' and H'' refer to diastereotopic protons attached to the same carbon atom and imply no particular stereochemistry.

The numbering of atoms in each structure has been done to allow the assignment of ^{1}H and ^{13}C NMR resonances to specific atoms, and is not consistent with the IUPAC guidelines.

In some cases the assignment was not clear, and so each of the different possibilities has been listed, separated by a forward slash, e.g. 13/15.

Mass Spectrometry:

Low resolution mass spectra were recorded on either a VG MassLab 20-250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on a Bruker MicroTOF by the mass spectrometry service at the Chemistry Research Laboratory, University of Oxford.

Other Analytical Techniques:

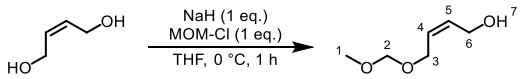
Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Melting points were determined for compounds that existed as a solid at room temperature (20 – 25 °C), and were purified by recrystallisation.

IR spectra were recorded on a Bruker Tensor 27 FT–IR spectrometer with a diamond ATR module. Absorption maxima (ν_{max}) are reported in cm^{-1}, and are described as strong (s), medium (m), weak (w) or broad (br).

Optical rotations were measured using a Perkin-Elmer 241 polarimeter in a cell of 1 dm path length (l). Specific rotations are denoted as $[\alpha]_D$ (T) (T = temperature in °C, D refers to the D line of a sodium lamp, where the wavelength of light is 589 nm) and are calculated according to the following equation, where α is the observed rotation and c is the concentration in g/100 mL. The solvent used to dissolve the sample is recorded in parentheses.

$$[\alpha]_D\ (\mathrm{T}) = \frac{100\alpha}{\mathrm{lc}}$$

(*Z*)-4-(Methoxymethoxy)but-2-en-1-ol, 1.201



According to the procedure reported by Díez and co-workers.[154] cis-2-Butene-1,4-diol (10 mL, 122 mmol, 1 eq.) was dissolved in THF (1200 mL) under an argon atmosphere, and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 4.88 g, 122 mmol, 1 eq.) was carefully added portionwise, and the resulting suspension was stirred for 10 mins. Chloromethyl methylether (9.5 mL, 122 mmol, 1 eq.) was added, and the reaction was stirred for 1 h. Upon completion, the reaction was quenched with water, and the solution was extracted with EtOAc three times. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and reduced *in vacuo*. Purification by column chromatography (70% EtOAc in petroleum ether [40 – 60 °C]) afforded the title compound as a clear oil (12.6 g, 78%).

R_f: 0.6 (EtOAc).

ν_{max} (cm^{-1}) 3405 (br. w), 2361 (w), 2342 (w), 1034 (s).

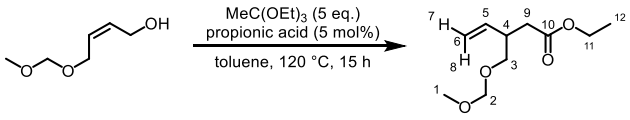
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 – 5.81 (m, 1H, 5), 5.68 (dtt, *J* = 11.0, 7.0, 1.5 Hz, 1H, 4), 4.63 (s, 2H, 2), 4.22 – 4.17 (m, 2H, 6), 4.15 (ddt, *J* = 6.5, 1.5, 0.5 Hz, 2H, 3), 3.37 (s, 3H, 1), 2.15 (t, *J* = 5.5 Hz, 1H, 7).

^{13}C NMR (126 MHz, $CDCl_3$) δ 132.8 (5), 127.9 (4), 95.5 (2), 62.6 (3), 58.5 (6), 55.5 (1).

HRMS (ESI^+) $C_6H_{13}O_3^+$ [$(M + H)^+$] requires 133.0859, found 133.0859.

Data in accordance with that reported by Griengl and co-workers.[155]

Ethyl 3-((methoxymethoxy)methyl)pent-4-enoate, 1.202



According to the procedure reported by Prasad and co-workers, with modifications.[156] The alcohol **1.201** (12.6 g, 95.3 mmol, 1 eq.), triethylorthoacetate (90 mL, 477 mmol, 5 eq.) and propionic acid (0.36 mL, 4.77 mmol, 0.05 eq.) was dissolved in toluene (600 mL). A short Vigreux column was attached, and was equipped with a thermometer and condenser, which was connected to a 500 mL round-bottomed flask. The reaction mixture was heated to reflux at 140 °C for 16 h, and volatiles were distilled off for the duration of this time. Propionic acid (0.36 mL, 4.77 mmol, 0.05 eq.) was added, and the reaction mixture was heated for a further 8 h. The reaction mixture was allowed to cool, and then reduced *in vacuo*. Purification by column chromatography (10:90 EtOAc in petroleum ether [40 – 60 °C]) afforded the title compound (11.8 g, 61%).

R_f: 0.4 (12:88 EtOAc/petroleum ether [40-60 °C]).

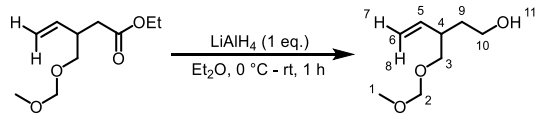
ν_{max} (cm^{-1}) 2932 (w), 2360 (w), 2342 (w), 1733 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1H, 5), 5.13 (dt, *J* = 17.5, 1.5 Hz, 1H, 8), 5.09 (dt, *J* = 10.5, 1.5 Hz, 1H, 7), 4.61 (d, *J* = 6.5 Hz, 1H, 2'), 4.59 (d, *J* = 6.5 Hz, 1H, 2''), 4.12 (q, *J* = 7.0 Hz, 2H, 11), 3.54 (dd, *J* = 9.5, 6.0 Hz, 1H, 3'), 3.46 (dd, *J* = 9.5, 6.5 Hz, 1H, 3''), 3.34 (s, 3H, 1), 2.92 – 2.81 (m, 1H, 4), 2.54 (dd, *J* = 15.5, 6.0 Hz, 1H, 9'), 2.35 (dd, *J* = 15.5, 8.0 Hz, 1H, 9''), 1.24 (t, *J* = 7.0 Hz, 3H, 12).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4 (10), 138.1 (5), 116.4 (6), 96.6 (2), 70.2 (3), 60.5 (11), 55.4 (1), 40.4 (4), 36.6 (9), 14.4 (12).

HRMS (ESI$^+$) $C_{10}H_{18}O_4Na^+$ [(M + Na)$^+$] requires 225.1097, found 225.1099.

3-((Methoxymethoxy)methyl)pent-4-en-1-ol, 1.203



According to the procedure reported by Lua, with modifications.[23] To a stirred solution of $LiAlH_4$ (2.2 g, 57.8 mmol, 1 eq.) in Et_2O (80 mL) at 0 °C was added dropwise a solution of ester **1.202** (11.7 g, 57.8 mmol, 1 eq.) in Et_2O (20 mL). The reaction was allowed to warm to room temperature, and was stirred for 1 h. Following completion by TLC (10:90 EtOAc/petroleum ether [40-60 °]), the reaction was cooled to 0 °C, and 2.2 mL H_2O was added, followed by 2.2 mL NaOH (aq. 1 M). The resulting mixture was stirred for 5 minutes, then 6.6 mL H_2O was added. The mixture was stirred for a further 15 minutes, then dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the title compound, which was used without further purification (9.4 g, *quant.*).

R_f: 0.1 (30:70 EtOAc/petroleum ether [40-60 °C]).

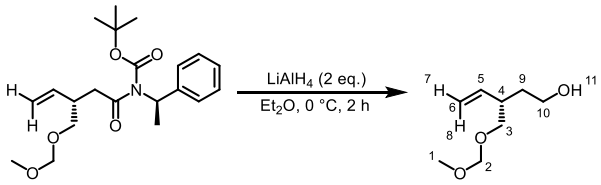
ν_{max} (cm^{-1}) 3405 (br. w), 2929 (w), 2361 (w), 1038 (s).

^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddd, *J* = 17.5, 10.5, 8.5 Hz, 1H, 5), 5.16 – 5.05 (m, 2H, 7, 8), 4.62 (s, 2H, 2), 3.71 (dq, *J* = 11.5, 6.0 Hz, 1H, 10'), 3.64 (ddt, *J* = 11.5, 7.0, 5.5 Hz, 1H, 10''), 3.49 (dd, *J* = 9.5, 6.0 Hz, 1H, 3'), 3.46 (dd, *J* = 9.5, 6.5 Hz, 1H, 3''), 3.35 (s, 3H, 1), 2.54 – 2.43 (m, 1H, 4), 1.88 (dd, *J* = 6.0, 5.5 Hz, 1H, 11), 1.81 – 1.71 (m, 1H, 9'), 1.59 (ddt, *J* = 14.5, 8.5, 6.0 Hz, 1H, 9'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6 (5), 116.3 (6), 96.6 (2), 71.4 (3), 61.0 (10), 55.4 (1), 41.4 (4), 34.7 (9).

HRMS (ESI^+) $C_8H_{17}O_3^+$ [$(M + H)^+$] requires 161.1172, found 161.1176.

(*S*)-3-((methoxymethoxy)methyl)pent-4-en-1-ol, 1.375



According to the procedure reported by Lua, with modifications.[23] To a suspension of $LiAlH_4$ (850 mg, 22.4 mmol, 2 eq.) in Et_2O (50 mL), cooled to 0 °C, was added a solution of ketocarbamate **1.374** (4.22 g, 11.2 mmol, 1 eq.) in Et_2O (20 mL) dropwise. The reaction was stirred at 0 °C for 2 h, then quenched by the addition of 0.85 mL H_2O. An addition of 0.85 mL NaOH (1M, aq.) followed, and the resulting mixture was stirred for a 5 mins, then 2.5 mL H_2O was added. The mixture was stirred for a further 15 minutes, then dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude material. Purification by column chromatography (70 – 100% Et_2O in pentane) afforded the title compound (1.59 g, 89%).

R_f: 0.3 (Et_2O).

$[\alpha]_D$ (25 °C) +27.6 (c = 1.0, $CHCl_3$)

ν_{max} (cm^{-1}) 3408 (br. w), 2930 (w), 2360 (w), 1039 (s).

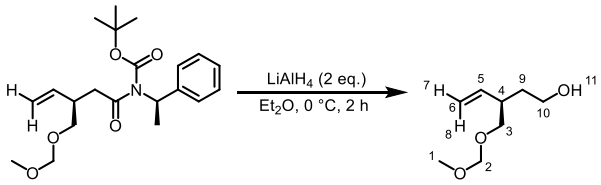
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (ddd, *J* = 17.5, 10.5, 8.5 Hz, 1H, 5), 5.17 – 5.06 (m, 2H, 7, 8), 4.63 (s, 2H, 2), 3.72 (dt, *J* = 11.5, 6.0 Hz, 1H, 10'), 3.66 (dt, *J* = 11.5, 6.5 Hz, 1H, 10''), 3.51 (dd, *J* = 9.5, 6.0 Hz, 1H, 3'), 3.49 (dd, *J* = 9.5, 6.5 Hz, 1H, 3''), 3.36 (s, 3H, 1), 2.55 – 2.44 (m, 1H, 4), 1.83 – 1.72 (m, 2H, 9', 11), 1.61 (ddt, *J* = 14.5, 8.5, 6.0 Hz, 1H, 9'').

^{3}*J* coupling to the alcoholic proton (H11) was not observed.

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6 (5), 116.3 (6), 96.7 (2), 71.4 (3), 61.1 (10), 55.5 (1), 41.4 (4), 34.7 (9).

HRMS (ESI^+) $C_8H_{17}O_3^+$ [$(M + H)^+$] requires 161.1172, found 161.1177.

(*R*)-3-((methoxymethoxy)methyl)pent-4-en-1-ol, 1.273



An analogous procedure to that used above for the synthesis of **1.375** was used, requiring ketocarbamate **1.372** (6.95 g, 18.4 mmol, 1 eq.), $LiAlH_4$ (1.40 g, 36.8 mmol, 2 eq.) in a total of 115 mL of Et_2O, to give the title compound (2.72 g, 92%) after purification.

R_f: 0.3 (Et_2O).

$[\alpha]_D$ (25 °C) -26.9 (c = 1.0, $CHCl_3$)

ν_{max} (cm^{-1}) 3412 (br. w), 2931 (w), 2360 (w), 1043 (s).

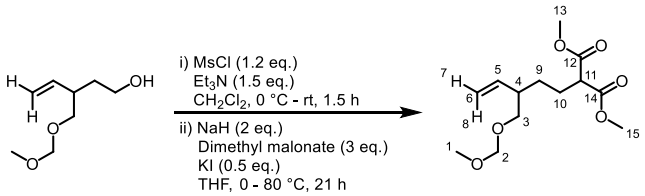
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (ddd, *J* = 17.5, 10.5, 8.5 Hz, 1H, 5), 5.17 – 5.06 (m, 2H, 7, 8), 4.62 (s, 2H, 2), 3.72 (dt, *J* = 11.5, 6.0 Hz, 1H, 10'), 3.66 (dt, *J* = 11.5, 6.5 Hz, 1H, 10''), 3.51 (dd, *J* = 9.5, 6.0 Hz, 1H, 3'), 3.48 (dd, *J* = 9.5, 6.5 Hz, 1H, 3''), 3.36 (s, 3H, 1), 2.55 – 2.44 (m, 1H, 4), 1.82 – 1.72 (m, 2H, 9', 11), 1.61 (ddt, *J* = 14.5, 8.5, 6.0 Hz, 1H, 9'').

^{3}*J* coupling to the alcoholic proton (H11) was not observed.

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6 (5), 116.3 (6), 96.7 (2), 71.4 (3), 61.1 (10), 55.5 (1), 41.4 (4), 34.7 (9).

HRMS (ESI^+) $C_8H_{17}O_3^+$ [$(M + H)^+$] requires 161.1172, found 161.1177.

Dimethyl 2-(3-((methoxymethoxy)methyl)pent-4-en-1-yl)malonate, 1.205



According to the procedure reported by Lua, with modifications.[23] A solution of alcohol **1.203** (4.28 g, 26.7 mmol, 1 eq.) and triethylamine (5.6 mL, 40.1 mmol, 1.5 eq.) in CH_2Cl_2 was cooled to 0 °C, then methanesulfonyl chloride (2.5 mL, 32.0 mmol, 1.2 eq.) was added dropwise. The reaction was then allowed to warm to room temperature, and stirred for 1.75 h. The reaction was quenched with 1 M HCl (aq.), and the organic layer was separated off. The aqueous layer was extracted five times with CH_2Cl_2, and the combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo*. The residue was then redissolved in THF (65 mL) for further use.

To a suspension of NaH (2.14 g, 53.4 mmol, 2 eq., 60% in mineral oil) in DMF (130 mL) cooled to 0 °C was added dimethylmalonate (9.25 mL, 80.1 mmol, 3 eq.) dropwise, and the resulting slurry was allowed to warm to rt. The solution of the intermediate in THF previously prepared was cooled to 0 °C, and added *via* cannula to the solution in DMF. Potassium iodide (2.22 g, 13.4 mmol, 0.5 eq.) was added, and the reaction mixture was heated to 80 °C. The reaction was stirred at this temperature for 3 h, then allowed to cool, and quenched with sat. aq. NH_4Cl. The reaction mixture was extracted with EtOAc, and the combined organics were washed three times with H_2O, once with brine, then dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (20 – 40% EtOAc in petroleum ether [40-60 °C]) yielded the title compound as a clear oil (6.59 g, 90%).

R_f: 0.3 (3:97 EtOAc in CH_2Cl_2).

ν_{max} (cm^{-1}) 2953 (w), 2361 (m), 2342 (m), 1734 (s).

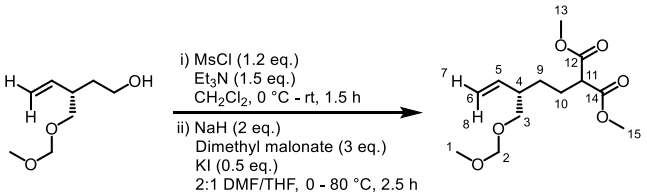
^1H NMR (500 MHz, $CDCl_3$) δ 5.63 (ddd, *J* = 18.0, 10.0, 8.5 Hz, 1H, 5), 5.14 – 5.05 (m, 2H, 7, 8), 4.59 (s, 2H, 2), 3.73 (s, 3H, 13/15), 3.72 (s, 3H, 13/15), 3.47 – 3.40 (m, 2H, 3), 3.34 (dd, *J* = 8.0, 7.5 Hz, 1H, 11), 3.34 (s, 3H, 1), 2.36 – 2.25 (m, 1H, 4), 1.97 (dddd, *J* = 13.5, 11.5, 8.0, 5.0 Hz, 1H, 10'), 1.84 (dddd, *J* = 13.5, 11.5, 7.5, 5.0 Hz, 1H, 10''), 1.52 (ddt, *J* = 13.5, 11.5, 5.0 Hz, 1H, 9'), 1.29 (dddd, *J* = 13.5, 11.5, 9.0, 5.0 Hz, 1H, 9'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9 (12/14), 169.9 (12/14), 139.2 (5), 116.7 (6), 96.6 (2), 71.1 (3), 55.3 (1), 52.6 (13/15), 52.6 (13/15), 51.8 (11), 44.0 (4), 28.9 (9), 26.6 (10).

m/z (ESI^+) 297.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{13}H_{22}O_6Na^+$ [$(M + Na)^+$] requires 297.1309, found 297.1304.

Dimethyl (*S*)-2-(3-((methoxymethoxy)methyl)pent-4-en-1-yl)malonate, 1.375



An analogous procedure to that used above for the synthesis of **1.205** was used, requiring alcohol **1.375** (1.57 g, 9.80 mmol, 1 eq.) to give the title compound (2.30 g, 86%).

R_f: 0.4 (40% EtOAc in petroleum ether [40 – 60 °C]).

$[\alpha]_D$ (25 °C) +8.4 (c = 1.0, $CHCl_3$).

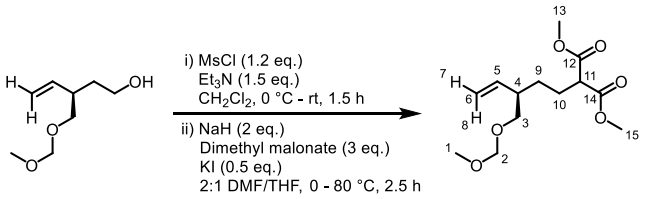
ν_{max} (cm^{-1}) 2954 (w), 2360 (w), 1735 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (ddd, *J* = 18.0, 10.0, 8.5 Hz, 1H, 5), 5.14 – 5.06 (m, 2H, 7, 8), 4.60 (s, 2H, 2), 3.73 (s, 3H, 13/15), 3.73 (s, 3H, 13/15), 3.47 – 3.41 (m, 2H, 3), 3.35 (dd, *J* = 8.0, 7.5 Hz, 1H, 11), 3.34 (s, 3H, 1), 2.36 – 2.25 (m, 1H, 4), 1.97 (dddd, *J* = 13.5, 11.5, 7.5, 4.5 Hz, 1H, 10'), 1.85 (dddd, *J* = 13.5, 11.5, 7.5, 5.0 Hz, 1H, 10''), 1.53 (dddd, *J* = 13.5, 11.5, 5.5, 4.5 Hz, 1H, 9'), 1.30 (dddd, *J* = 13.5, 11.5, 9.0, 5.0 Hz, 1H, 9'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9 (12/14), 169.9 (12/14), 139.2 (5), 116.7 (6), 96.7 (2), 71.1 (3), 55.4 (1), 52.6 (13/15), 52.6 (13/15), 51.8 (11), 44.1 (4), 28.9 (9), 26.6 (10).

HRMS (ESI^+) $C_{13}H_{22}O_6Na^+$ [$(M + Na)^+$] requires 297.1309, found 297.1309.

Dimethyl (*R*)-2-(3-((methoxymethoxy)methyl)pent-4-en-1-yl)malonate, 1.200



An analogous procedure to that used above for the synthesis of **1.205** was used, requiring alcohol **1.273** (2.68 g, 16.7 mmol, 1 eq.) to give the title compound (4.05 g, 88%).

R_f: 0.4 (40% EtOAc in petroleum ether [40 – 60 °C]).

$[\alpha]_D$ (25 °C) -8.0 (c = 1.0, $CHCl_3$).

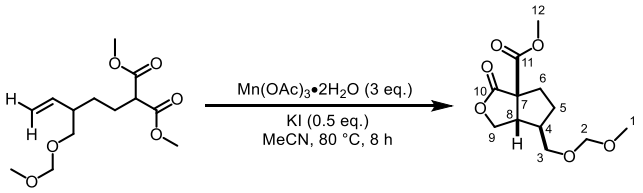
ν_{max} (cm^{-1}) 2954 (w), 2360 (w), 1735 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (ddd, *J* = 18.0, 10.0, 8.5 Hz, 1H, 5), 5.14 – 5.06 (m, 2H, 7, 8), 4.60 (s, 2H, 2), 3.73 (s, 3H, 13/15), 3.73 (s, 3H, 13/15), 3.48 – 3.41 (m, 2H, 3), 3.35 (dd, *J* = 8.0, 7.5 Hz, 1H, 11), 3.34 (s, 3H, 1), 2.36 – 2.25 (m, 1H, 4), 1.97 (dddd, *J* = 13.5, 11.5, 8.0, 5.0 Hz, 1H, 10'), 1.85 (dddd, *J* = 13.5, 11.5, 7.5, 5.0 Hz, 1H, 10''), 1.53 (dddd, *J* = 13.5, 11.5, 5.0, 5.0 Hz, 1H, 9'), 1.30 (dddd, *J* = 13.5, 11.5, 9.5, 5.0 Hz, 1H, 9'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9 (12/14), 169.9 (12/14), 139.2 (5), 116.7 (6), 96.7 (2), 71.1 (3), 55.4 (1), 52.6 (13/15), 52.6 (13/15), 51.8 (11), 44.1 (4), 28.9 (9), 26.6 (10).

HRMS (ESI^+) $C_{13}H_{22}O_6Na^+$ [$(M + Na)^+$] requires 297.1309, found 297.1308.

Methyl (3a*R,6*R**,6a*S**)-6-((methoxymethoxy)methyl)-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate, 1.210**



According to the procedure reported by Burton and co-workers, with modifications.[33,34] To a round bottomed flask equipped with a stirrer bar under an atmosphere of argon, containing $Mn(OAc)_3•2H_2O$ (19.3 g, 72.0 mmol, 3 eq.) and potassium iodide (1.99 g, 12.0 mmol, 0.5 eq.), was added a solution of malonate **1.205** (6.59 g, 24.0 mmol, 1 eq.) in MeCN (160 mL). A reflux condenser was attached, and the reaction mixture was heated to 80 °C for 8 h. The reaction mixture was allowed to cool to room temperature, then quenched with sat. aq. $Na_2S_2O_3$ solution (160 mL). The organic layer was separated off, and the aqueous layer extracted five times with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (20 – 50% EtOAc in petroleum ether [40-60 °C]) afforded the title compound (4.92 g, 79%).

[Purification yielded a 9:1 mixture of the two diastereomers; the NMR resonances reported below correspond to the major diastereomer.]

R_f: 0.3 (0.1:4:96 IPA/EtOAc/CH_2Cl_2).

ν_{max} (cm^{-1}) 2953 (w), 1771 (s), 1739 (s), 1040 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (s, 2H, 2), 4.53 (dd, *J* = 9.5, 7.0 Hz, 1H, 9'), 4.25 (dd, *J* = 9.5, 1.5 Hz, 1H, 9''), 3.76 (s, 3H, 12), 3.55 (dd, *J* = 9.5, 5.5 Hz, 1H, 3'), 3.41 (dd, *J* = 9.5, 8.0 Hz, 1H, 3''), 3.32 (s, 3H, 1), 2.87 (td, *J* = 7.0, 1.5 Hz, 1H, 8), 2.56 (ddd, *J* = 14.0, 8.0, 6.5 Hz, 1H, 6'),

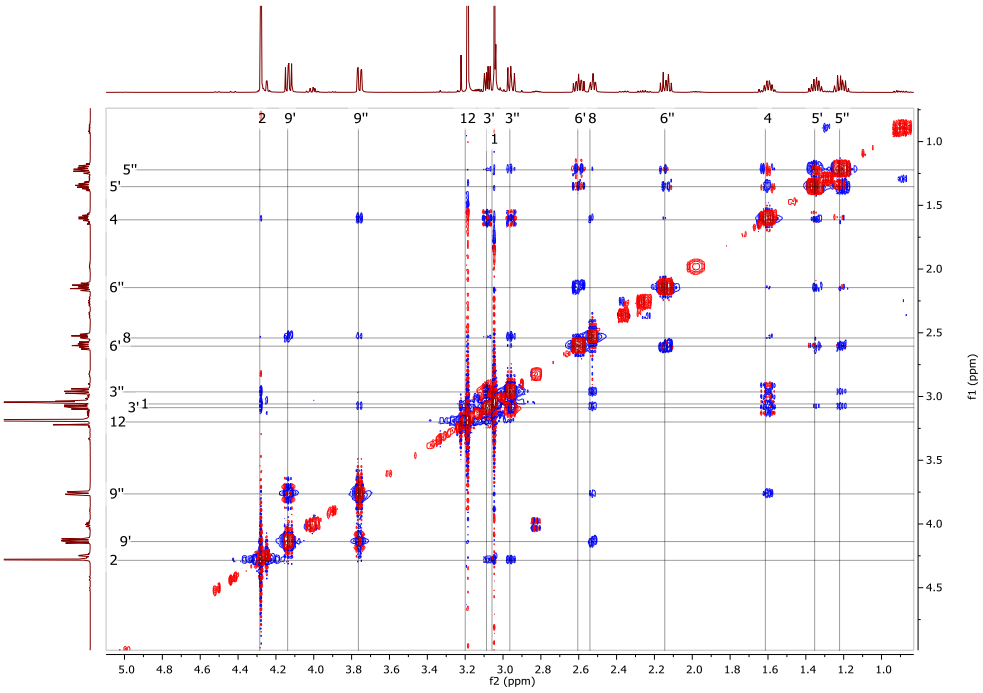
2.23 – 2.12 (m, 2H, 4, 6''), 1.84 (dtd, *J* = 13.0, 7.0, 6.5 Hz, 1H, 5'), 1.61 (dq, *J* = 13.0, 8.0 Hz, 1H, 5'').

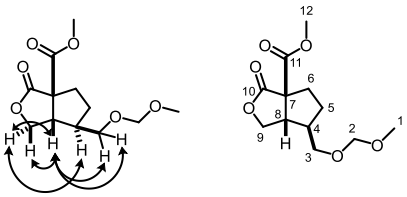
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5 (10), 170.4 (11), 96.6 (2), 72.0 (9), 69.7 (3), 61.5 (7), 55.4 (1), 53.3 (12), 50.4 (8), 47.3 (4), 32.8 (6), 29.5 (5).

m/z (ESI^+) 281.1 $[(M + Na)^+]$.

HRMS (ESI^+) $C_{12}H_{18}O_6Na^+$ $[(M + Na)^+]$ requires 281.0996, found 281.0993.

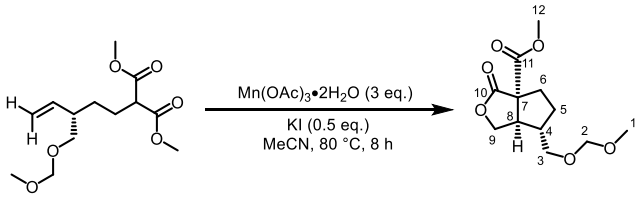
^{1}H NOESY (Benzene-d_6):





NOESY experiments were carried out on the racemic and both enantiopure samples in both deuterated chloroform and deuterated benzene, and all showed the same correlation data. The spectrum that was obtained using benzene as the solvent clearly separated all of the resonances and it is therefore this spectrum which has been presented above.

Methyl (3a*S*,6*S*,6a*R*)-6-((methoxymethoxy)methyl)-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate, 1.377



An analogous procedure to that used above for the synthesis of **1.210** was used, requiring malonate **1.376** (2.26 g, 8.24 mmol, 1 eq.) to give the title compound (1.72 g, 81%).

R_f: 0.3 (50% EtOAc in petroleum ether [40 – 60 °C]).

$[\alpha]_D$ (25 °C) +56.9 (c = 1.0, $CHCl_3$).

ν_{max} (cm^{-1}) 2954 (w), 1771 (s), 1740 (s), 1043 (s).

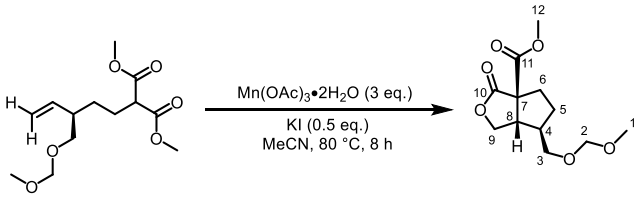
^{1}H NMR (500 MHz, C_6D_6) δ 4.29 (s, 2H, 2), 4.14 (dd, *J* = 9.0, 7.0 Hz, 1H, 9'), 3.76 (dd, *J* = 9.0, 2.0 Hz, 1H, 9''), 3.19 (s, 3H, 12), 3.09 (dd, *J* = 9.5, 5.5 Hz, 1H, 3'), 3.05 (s, 3H, 1), 2.96 (dd, *J* = 9.5, 7.5 Hz, 1H, 3''), 2.60 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1H, 6''), 2.53 (ddd, *J* = 7.0, 7.0, 2.0 Hz, 1H, 8), 2.15 (ddd, *J* = 14.0, 8.0, 7.5 Hz, 1H, 6'), 1.61 (ddddd, *J* = 8.0, 7.5, 7.5, 7.0, 5.5 Hz, 1H, 4), 1.36 (dddd, *J* = 13.0, 7.5, 7.5, 6.0 Hz, 1H, 5'), 1.22 (dddd, *J* = 13.0, 8.0, 8.0, 8.0 Hz, 1H, 5'').

^{13}C NMR (126 MHz, C_6D_6) δ 175.8 (10), 170.5 (11), 96.5 (2), 71.4 (9), 69.5 (3), 61.6 (7), 54.9 (1), 52.5 (12), 50.5 (8), 47.1 (4), 32.8 (6), 29.4 (5).

m/z (ESI^+) 281.0 [$(M + Na)^+$].

HRMS (ESI^+) $C_{12}H_{18}O_6Na^+$ [$(M + Na)^+$] requires 281.0996, found 281.0995.

Methyl (3a*R*,6*R*,6a*S*)-6-((methoxymethoxy)methyl)-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate, 1.199



An analogous procedure to that used above for the synthesis of **1.210** was used, requiring malonate **1.200** (4.03 g, 14.7 mmol, 1 eq.) to give the title compound (3.05 g, 80%).

R_f: 0.3 (50% EtOAc in petroleum ether [40 – 60 °C]).

$[\alpha]_D$ (25 °C) -61.0 (c = 1.0, $CHCl_3$).

ν_{max} (cm^{-1}) 2953 (w), 1772 (s), 1740 (s), 1043 (s).

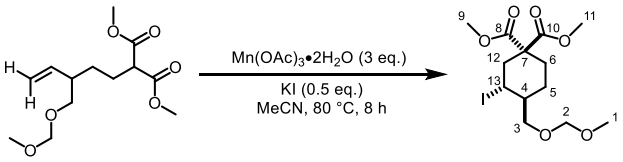
^{1}H NMR (500 MHz, C_6D_6) δ 4.28 (s, 2H, 2), 4.13 (dd, *J* = 9.0, 7.0 Hz, 1H, 9'), 3.76 (dd, *J* = 9.0, 2.0 Hz, 1H, 9''), 3.19 (s, 3H, 12), 3.08 (dd, *J* = 9.5, 5.5 Hz, 1H, 3'), 3.05 (s, 3H, 1), 2.96 (dd, *J* = 9.5, 7.5 Hz, 1H, 3''), 2.61 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1H, 6''), 2.53 (ddd, *J* = 7.0, 7.0, 2.0 Hz, 1H, 8), 2.15 (ddd, *J* = 14.0, 8.0, 7.5 Hz, 1H, 6'), 1.60 (ddddd, *J* = 8.0, 7.5, 7.5, 7.0, 5.5 Hz, 1H, 4), 1.35 (dddd, *J* = 13.0, 7.5, 7.5, 6.0 Hz, 1H, 5'), 1.22 (dddd, *J* = 13.0, 8.0, 8.0, 8.0 Hz, 1H, 5'').

^{13}C NMR (126 MHz, C_6D_6) δ 175.8 (10), 170.5 (11), 96.5 (2), 71.4 (9), 69.5 (3), 61.6 (7), 54.9 (1), 52.5 (12), 50.5 (8), 47.1 (4), 32.8 (6), 29.4 (5).

m/z (ESI^+) 281.0 [$(M + Na)^+$].

HRMS (ESI^+) $C_{12}H_{18}O_6Na^+$ [$(M + Na)^+$] requires 281.0996, found 281.0998.

Dimethyl (3*R,4*S**)-3-iodo-4-((methoxymethoxy)methyl)cyclohexane-1,1-dicarboxylate, 1.212**



The title compound was isolated as a side product (see chapter 1, table 1.3) from the above reaction (18 mg, 5%). An analogous procedure to that used above for the synthesis of **1.210** was used, requiring malonate **1.205** (250 mg, 0.91 mmol, 1 eq.), but where the $Mn(OAc)_3•2H_2O$ had not been placed under high vacuum overnight, and so likely contained traces of AcOH.

R_f: 0.5 (20:80 EtOAc/petroleum ether [40-60 °C]).

ν_{max} (cm^{-1}) 2952 (w), 2361 (w), 1730 (s).

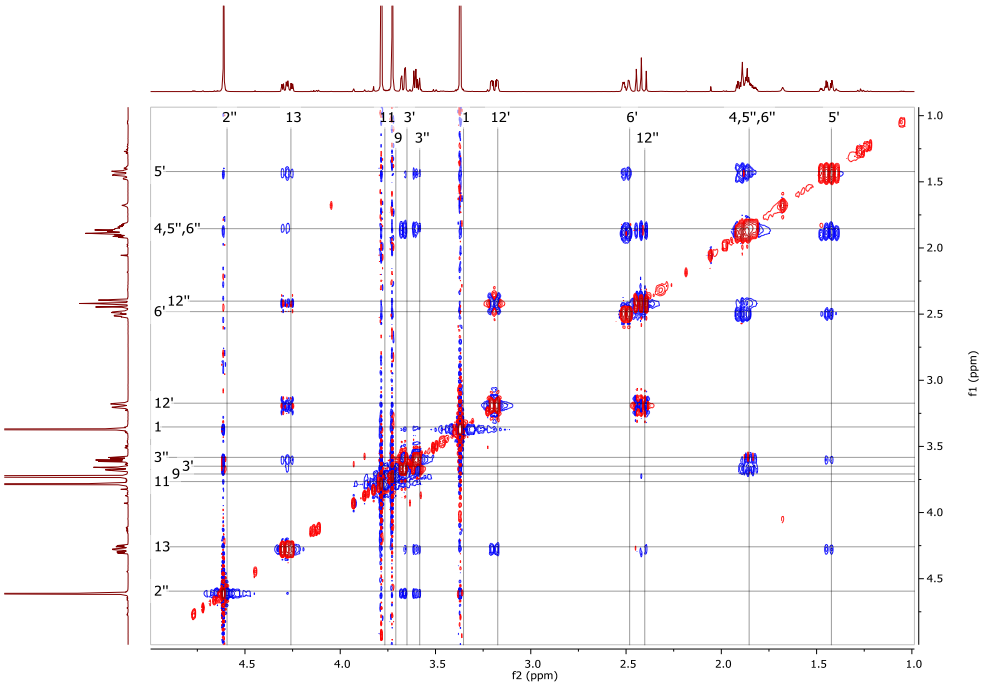
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (s, 2H, 2), 4.26 (ddd, *J* = 13.0, 11.0, 4.0 Hz, 1H, 13), 3.77 (s, 3H, 9/11), 3.71 (s, 3H, 9/11), 3.65 (dd, *J* = 9.5, 2.5 Hz, 1H, 3'), 3.58 (dd, *J* = 9.5, 5.5 Hz, 1H, 3''), 3.35 (s, 3H, 1), 3.17 (ddd, *J* = 13.5, 4.0, 2.5 Hz, 1H, 12'), 2.48 (dddd, *J* = 13.5, 3.0, 3.0, 2.5 Hz, 1H, 6'), 2.40 (dd, *J* = 13.5, 13.0 Hz, 1H, 12''), 1.92 – 1.78 (m, 3H, 4, 5'', 6''), 1.48 – 1.35 (m, 1H, 5').

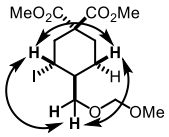
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8 (8/10), 170.7 (8/10), 96.8 (2), 73.1 (3), 57.6 (7), 55.5 (1), 53.1 (9/11), 52.9 (9/11), 46.3 (4), 44.8 (12), 30.8 (6), 29.4 (13), 26.4 (5).

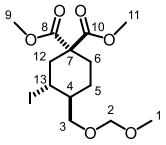
m/z (ESI^+) 423.0 [$(M + Na)^+$].

HRMS (ESI^+) $C_{13}H_{21}O_6INa^+$ [$(M + Na)^+$] requires 423.0275 found 423.0270.

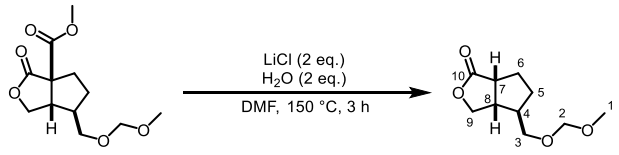
^{1}H NOESY ($CDCl_3$):







(3a*S,4*R**,6a*R**)-4-((methoxymethoxy)methyl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one, 1.216**



According to the procedure reported by Lua, with modifications.[23] To a solution of ester **1.210** (3.45 g, 13.4 mmol, 1 eq.) in dry DMF (65 mL), was added anhydrous LiCl (1.12 g, 26.8 mmol, 2 eq.) and H_2O (0.48 mL, 26.8 mmol, 2 eq.). The reaction was heated to 150 °C for 3 h, then allowed to cool to room temperature. A solution of sat. aq. NH_4Cl (65 mL) was added, and the mixture was extracted with EtOAc. The combined organics were washed with water and brine, then dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (30% EtOAc in petroleum ether [30-40 °C]) afforded the title compound (2.37 g, 88%).

R_f: 0.2 (30% EtOAc in petroleum ether [30-40 °C]).

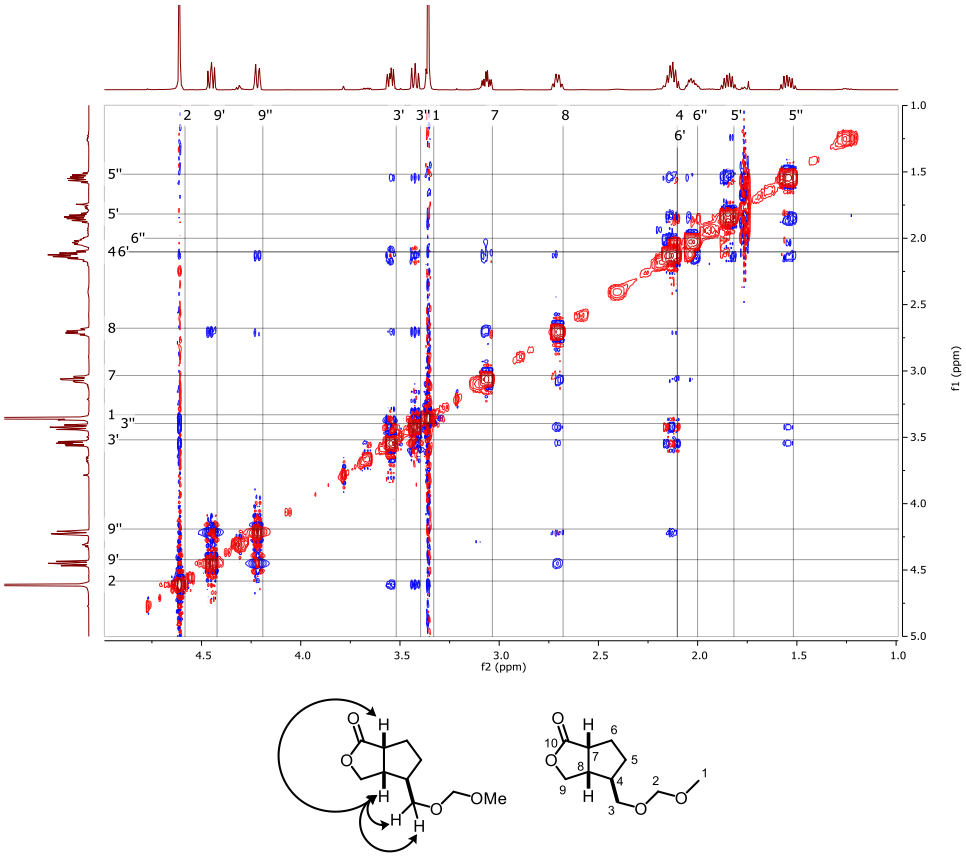
ν_{max} (cm^{-1}) 2951 (w), 1757 (s), 1041 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (s, 2H, 2), 4.42 (dd, *J* = 9.5, 7.0 Hz, 1H, 9'), 4.19 (dd, *J* = 9.5, 2.5 Hz, 1H, 9''), 3.52 (dd, *J* = 9.5, 6.0 Hz, 1H, 3'), 3.40 (dd, *J* = 9.5, 7.5 Hz, 1H, 3''), 3.33 (s, 3H, 1), 3.04 (ddd, *J* = 9.5, 9.5, 4.0 Hz, 1H, 7), 2.68 (dddd, *J* = 9.5, 7.0, 7.0, 2.5 Hz, 1H, 8), 2.10 (m, 2H, 4, 6'), 2.00 (dddd, *J* = 13.5, 7.0, 7.0, 4.0 Hz, 1H, 6''), 1.82 (dddd, *J* = 13.5, 7.0, 7.0, 7.0 Hz, 1H, 5'), 1.52 (dddd, *J* = 13.5, 8.0, 8.0, 7.0 Hz, 1H, 5'').

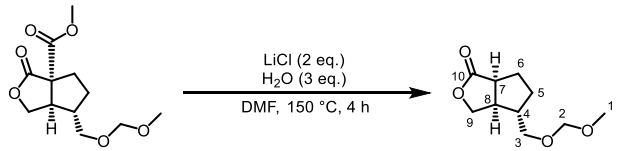
^{13}C NMR (126 MHz, $CDCl_3$) δ 180.9 (10), 96.6 (2), 72.4 (9), 70.1 (3), 55.4 (1), 46.7 (4), 44.6 (7), 44.0 (8), 29.6 (5), 28.6 (6).

HRMS (ESI^+) $C_{10}H_{17}O_4^+$ [$(M + H)^+$] requires 201.1121, found 201.1123.

^{1}H NOESY ($CDCl_3$):



(3a*R*,4*S*,6a*S*)-4-((Methoxymethoxy)methyl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one, 1.378



An analogous procedure to that used above for the synthesis of **1.216** was used, requiring ester **1.377** (1.64 g, 6.36 mmol, 1 eq.) to give the title compound (1.00 g, 78%).

R_f: 0.4 (75% EtOAc in petroleum ether [40 – 60 °C]).

$[\alpha]_D$ (25 °C) +69.2 (c = 1.0, $CHCl_3$)

ν_{max} (cm^{-1}) 2945 (w), 1762 (s), 1041 (s).

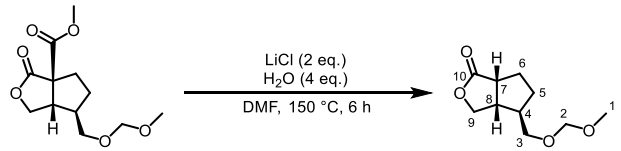
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (s, 2H, 2), 4.44 (dd, *J* = 9.5, 7.0 Hz, 1H, 9'), 4.21 (dd, *J* = 9.5, 2.5 Hz, 1H, 9''), 3.54 (dd, *J* = 9.5, 6.0 Hz, 1H, 3'), 3.41 (dd, *J* = 9.5, 7.5 Hz, 1H, 3''), 3.35 (s, 3H, 1), 3.05 (ddd, *J* = 9.5, 9.5, 4.0 Hz, 1H, 7), 2.69 (dddd, *J* = 9.5, 7.0, 7.0, 2.5 Hz, 1H, 8), 2.17 – 2.08 (m, 2H, 4, 6'), 2.03 (dddd, *J* = 13.5, 7.0, 7.0, 4.0 Hz, 1H, 6''), 1.84 (dddd, *J* = 13.5, 7.0, 7.0, 7.0 Hz, 1H, 5'), 1.54 (dddd, *J* = 13.5, 8.0, 8.0, 7.0 Hz, 1H, 5'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 181.0 (10), 96.7 (2), 72.5 (9), 70.1 (3), 55.4 (1), 46.7 (4), 44.7 (7), 44.0 (8), 29.6 (5), 28.7 (6).

m/z (ESI^+) 223.0 [$(M + Na)^+$].

HRMS (ESI^+) $C_{10}H_{16}O_4Na^+$ [$(M + Na)^+$] requires 223.0941 found 223.0943.

(3a*S*,4*R*,6a*R*)-4-((Methoxymethoxy)methyl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one, 1.198



An analogous procedure to that used above for the synthesis of **1.216** was used, requiring ester **1.199** (3.01 g, 11.6 mmol, 1 eq.) to give the title compound (2.11 g, 91%).

R_f: 0.4 (75% EtOAc in petroleum ether [40 – 60 °C]).

$[\alpha]_D$ (25 °C) -69.1 (c = 1.0, $CHCl_3$).

ν_{max} (cm^{-1}) 2946 (w), 1763 (s), 1042 (s).

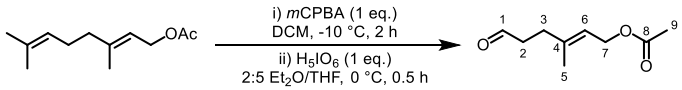
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (s, 2H, 2), 4.44 (dd, *J* = 9.5, 7.0 Hz, 1H, 9'), 4.21 (dd, *J* = 9.5, 2.5 Hz, 1H, 9''), 3.53 (dd, *J* = 9.5, 6.0 Hz, 1H, 3'), 3.41 (dd, *J* = 9.5, 7.5 Hz, 1H, 3''), 3.35 (s, 3H, 1), 3.05 (td, *J* = 9.5, 9.5, 4.0 Hz, 1H, 7), 2.69 (dddd, *J* = 9.5, 7.0, 7.0, 2.5 Hz, 1H, 8), 2.15 – 2.07 (m, 2H, 4, 6'), 2.02 (dddd, *J* = 13.5, 7.0, 7.0, 4.0 Hz, 1H, 6''), 1.83 (dddd, *J* = 13.5, 7.0, 7.0, 7.0 Hz, 1H, 5'), 1.53 (dddd, *J* = 13.5, 8.0, 8.0, 7.0 Hz, 1H, 5'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 181.0 (10), 96.7 (2), 72.5 (9), 70.1 (3), 55.4 (1), 46.7 (4), 44.7 (7), 44.0 (8), 29.6 (5), 28.6 (6).

m/z (ESI^+) 223.0 [$(M + Na)^+$].

HRMS (ESI^+) $C_{10}H_{16}O_4Na^+$ [$(M + Na)^+$] requires 223.0941 found 223.0941.

(*E*)-3-Methyl-6-oxohex-2-en-1-yl acetate, 1.219



According to the procedure reported by Leighton and co-workers.[36] A solution of geranyl acetate (1 mL, 4.67 mmol, 1 eq.) in CH_2Cl_2 (25 mL) was cooled to -10 °C, and a solution of *m*-CPBA (50-55%, 1.55 g, 4.67 mmol, 1 eq.) in CH_2Cl_2 (9 mL) was added dropwise to it. The reaction mixture was allowed to warm to room temperature, stirred for 2 h, then poured into aqueous NaOH (2 M, 25 mL). The organic layer was separated off, and the aqueous was extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo.* The residue was dissolved in Et_2O (1 mL), and added dropwise to a solution of H_5IO_6 (1.06 g, 4.67 mmol, 1 eq.) in THF (2.5 mL) at 0 °C. The reaction was stirred for 30 minutes, then poured into sat. aq. $NaHCO_3$. The organic layer was separated off, and the aqueous extracted with Et_2O. The combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (20:80 Et_2O/pentane) afforded the title compound (469 mg, 59%).

[Careful removal of solvent was carried out using a rotary evaporator equipped with a water bath that was kept below 25 °C to avoid losing product due to volatility.]

R_f: 0.1 (20:80 Et_2O/pentane).

ν_{max} (cm^{-1}) 2936 (w), 1732 (s), 1229 (s).

^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.5 Hz, 1H, 1), 5.35 (tq, *J* = 7.0, 1.5 Hz, 1H, 6), 4.57 (d, *J* = 7.0 Hz, 2H, 7), 2.57 (td, *J* = 7.5, 1.5 Hz, 2H, 2), 2.37 (t, *J* = 7.5 Hz, 2H, 3), 2.05 (s, 3H, 9), 1.72 (d, *J* = 1.5 Hz, 3H, 5).

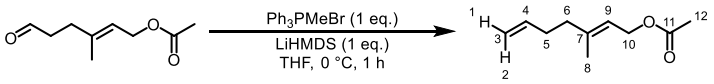
^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8 (1), 171.2 (8), 140.1 (4), 119.4 (6), 61.2 (7), 41.9 (2), 31.6 (3), 21.2 (9), 16.7 (5)

m/z (ESI^+) 193.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_9H_{14}O_3Na^+$ [$(M + Na)^+$] requires 193.0835, found 193.0837.

Data is in accordance with that reported in the literature.[36]

(*E*)-3-Methylhepta-2,6-dien-1-yl acetate, 1.220



According to the procedure reported by Leighton and co-workers.[36] To a mixture of methyltriphenylphosphonium bromide (MTPPB, 422 mg, 1.18 mmol, 1 eq.) in THF (11 mL) cooled to 0 °C was added LiHMDS (1 M in toluene, 1.2 mL, 1.2 mmol, 1 eq.) dropwise to give an orange solution. This was stirred for 30 minutes at 0 °C, then a solution of aldehyde **1.219** (200 mg, 1.18 mmol, 1 eq.) in THF (0.25 mL) was added dropwise at 0 °C. The resulting white mixture was stirred at 0 °C for a further 30 minutes, before being poured into water. The mixture was extracted three times with Et_2O, then washed with brine, and dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (2:98 Et_2O/pentane) afforded the title compound (176 mg, 88%).

[Careful removal of solvent was carried out using a rotavap equipped with a water bath that was kept below 25 °C to avoid losing product due to volatility.]

R_f: 0.4 (4:96 Et_2O/pentane).

ν_{max} (cm^{-1}) 2934 (w), 1738 (s), 1228 (s).

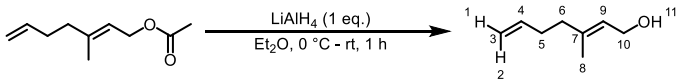
^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 4), 5.35 (tq, *J* = 7.0, 1.5 Hz, 1H, 9), 5.02 (dq, *J* = 17.0, 1.5 Hz, 1H, 2), 4.96 (d, *J* = 10.5 Hz, 1H, 1), 4.58 (d, *J* = 7.0 Hz, 2H, 10), 2.23 – 2.15 (m, 2H, 5), 2.15 – 2.09 (m, 2H, 6), 2.05 (s, 3H, 12), 1.70 (d, *J* = 1.5 Hz, 3H, 8).

^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (11), 141.8 (7), 138.2 (4), 118.7 (9), 114.8 (3), 61.5 (10), 38.9 (6), 32.0 (5), 21.2 (12), 16.6 (8).

HRMS (ESI^+) $C_{10}H_{16}O_2Na^+$ [$(M + Na)^+$] requires 191.1043, found 191.1045.

Data is in accordance with that reported in the literature.[36]

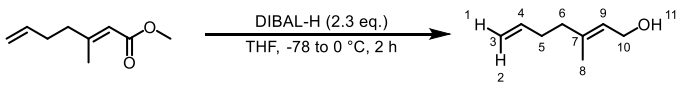
(*E*)-3-Methylhepta-2,6-dien-1-ol, 1.139



According to the procedure reported by Lua, with modifications.[23] To a stirred mixture of $LiAlH_4$ (214 mg, 5.63 mmol, 1 eq.) in Et_2O (8 mL), cooled to 0 °C, was added a solution of ester **1.220** (947 mg, 5.63 mmol, 1 eq.) in Et_2O (2 mL) dropwise. The resulting mixture was allowed to warm to rt and stirred for 1 h. The reaction was then quenched dropwise with 0.21 mL H_2O, then 0.21 mL 2 M $NaOH_{(aq.)}$ and stirred for 5 minutes. Three additional mass equivalents of H_2O (0.63 mL) were then added, and the reaction stirred until a white precipitate was observed. The reaction was dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the title compound, which was used in the next step without further purification.

[Careful removal of solvent was carried out using a rotavap equipped with a water bath that was kept below 25 °C to avoid losing product due to volatility.]

The title compound was also obtained via the following procedure, and it was this procedure that was used to synthesise the majority of alcohol **1.139**. This reduction using DIBAL-H was also used for the ethyl ester analogue **1.167** (see Scheme 1.36).



According to the procedure reported by Jiang.[25] A solution of ester **1.138** (2.00 g, 13.0 mmol, 1 eq.) in THF (46 mL) was cooled to -78 °C, whereupon DIBAL-H (1 M in hexanes, 30 mL, 30.0 mmol, 2.3 eq.) was added dropwise. The resulting solution was stirred at -78 °C for 1 h, then 0 °C for 1 h. The reaction was then quenched with a solution of sat. aq. Rochelle's salt, and stirred overnight. The reaction mixture was then extracted with Et_2O, and the combined organics were dried (Na_2SO_4), filtered and reduced *in vacuo* to give the

crude product. Purification by column chromatography (30% Et_2O in pentane) afforded the title compound (1.46 g, 89%).

R_f: 0.3 (40:60 Et_2O/pentane).

ν_{max} (cm^{-1}) 3321 (br. m), 2931 (m), 1669 (m), 993 (s).

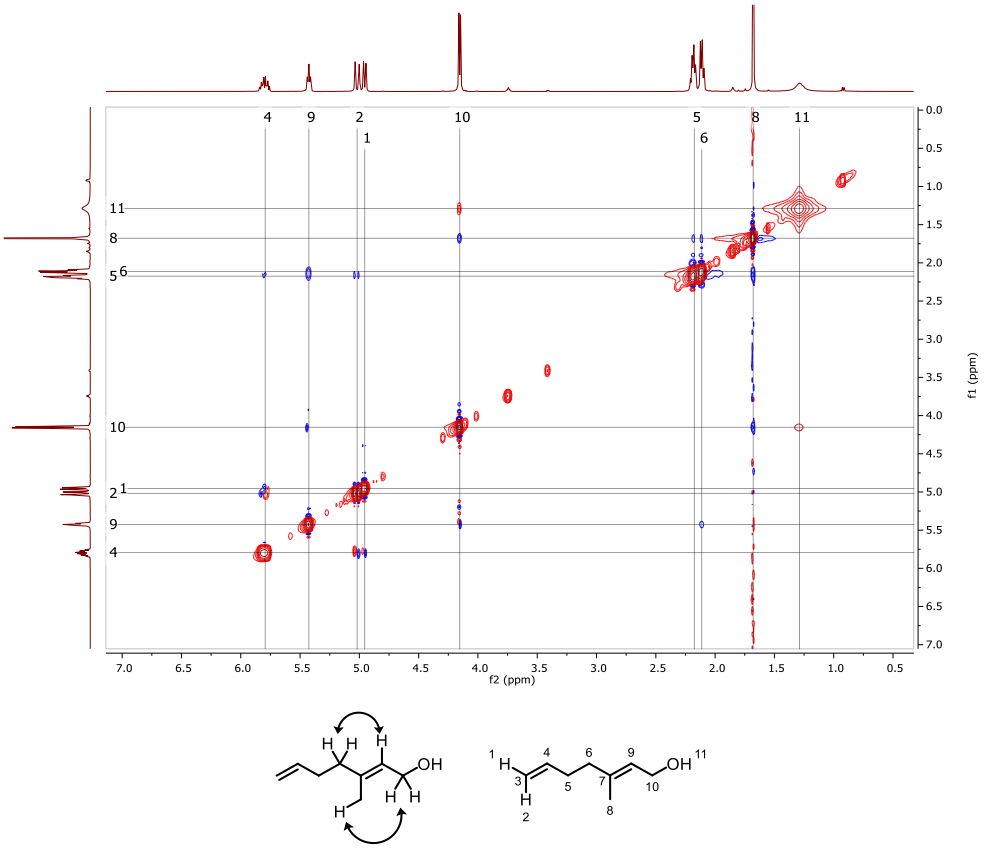
^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, 4), 5.42 (tq, *J* = 7.0, 1.5 Hz, 1H, 9), 5.02 (dq, *J* = 17.0, 1.5 Hz, 1H, 2), 4.95 (d, *J* = 10.5 Hz, 1H, 1), 4.15 (d, *J* = 7.0 Hz, 2H, 10), 2.23 – 2.15 (m, 2H, 5), 2.15 – 2.07 (m, 2H, 6), 1.67 (s, 3H, 8), 1.31 (br. s, 1H, 11).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3 (7), 138.4 (4), 123.8 (9), 114.8 (3), 59.5 (10), 38.9 (6), 32.1 (5), 16.4 (8).

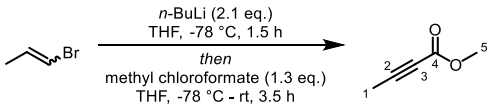
HRMS (ESI^+) $C_8H_{15}O^+$ [$(M + H)^+$] requires 127.1117, found 127.1119.

Data is in accordance with that reported in the literature.[25,157]

^{1}H NOESY:



Methyl but-2-ynoate, 1.224



According to the procedure reported by Dixon and co-workers. [38] A three-necked flask equipped with a stirrer bar and internal thermometer was placed under nitrogen, and charged with 1-bromo-1-propene (mixture of *cis* and *trans*, 5 mL, 58.4 mmol, 1 eq.). Anhydrous THF was added (60 mL), and the solution was cooled to -78 °C. *n*-BuLi (2.35 M, 52 mL, 123 mmol, 2.1 eq.) was added dropwise, at a rate that ensured the internal temperature was no greater than -60 °C. The reaction was stirred at -78 °C for 1.5 h, then methyl chloroformate (6 mL, 75.9 mmol, 1.3 eq.) was added dropwise, at a rate that ensured the internal temperature was between -70 and -60 °C. Upon completion of addition, the reaction was stirred at -78 °C for 2 h, then allowed to gradually warm to room temperature over 1.5 h. The reaction was then quenched with 30 mL of water, and extracted with Et_2O. The combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo* to obtain the crude product. Purification by distillation (62 °C, 50 mbar) afforded the title compound as a slightly yellow oil (3.92 g, 68%). Note: Collection flasks were cooled to -78 °C during distillation to minimise loss of product due to volatility.

b.p. 62 °C, 50 mbar.

ν_{max} (cm^{-1}) 2958 (m), 2359 (s), 2340 (s), 1745 (w).

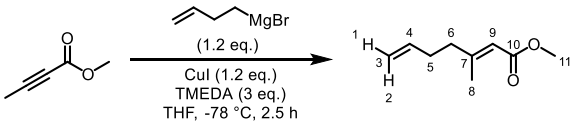
^1H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H, 5), 1.97 (s, 3H, 1).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.3 (4), 85.8 (2), 72.2 (3), 52.7 (5), 3.8 (1).

HRMS (ESI^+) $C_5H_7O_2^+$ [$(M + H)^+$] requires 99.0441, found 99.0440.

Data in accordance with that reported by Dixon and co-workers. [38]

Methyl (*E*)-3-methylhepta-2,6-dienoate, 1.138



According to the procedure reported by Ohmiya and co-workers, with modifications.[37]

To prepare the Grignard reagent:

To a flame dried, three-necked round-bottomed flask equipped with magnesium turnings (744 mg, 30.6 mmol, 1.25 eq.), stirrer bar and a reflux condenser was added THF (30 mL). The mixture was heated to reflux for 2 mins, then allowed to cool to rt. Approximately two crystals of iodine were added, and the solution was heated to reflux for 1 minute. A solution of 4-bromo-1-butene (2.5 mL, 24.5 mmol, 1 eq.) in THF (17.5 mL) was then added dropwise, using a heat gun to initiate the reaction, without stirring the reaction. The initiation was evidenced by a colour change from light brown to grey. Once initiation had taken place, the remainder of the 4-bromo-1-butene was added with moderate stirring, and the reaction was stirred at room temperature for at least 1 h before use.

To effect the conjugate addition to the alkyne:

To a mixture of CuI (2.32 g, 12.2 mmol, 1.2 eq.) in THF (1.3 mL) was added TMEDA (4.6 mL, 30.6 mmol, 3 eq.). The resulting solution was cooled to -40 °C, and the solution of Grignard reagent was added (25 mL, 12.2 mmol, 1.2 eq.) dropwise down the side of the flask. The reaction was stirred at -40 °C for 30 mins, then cooled to -78 °C. A solution of methyl 2-butynoate (1 g, 10.2 mmol, 1 eq.) in THF (10 mL) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then quenched with MeOH that had been pre-cooled to -78 °C, via a cannula that was cooled with dry ice pellets. The reaction was allowed to warm to rt over

1 h, then a sat. aq. solution of NH_4Cl (30 mL) was added. The reaction was extracted with Et_2O, and the combined organics were dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (2% Et_2O in pentane) afforded the title compound (2.36 g, 75%).

R_f: 0.5 (2% Et_2O in pentane).

ν_{max} (cm^{-1}): 2948 (w), 1717 (s), 1648 (m), 1147 (s).

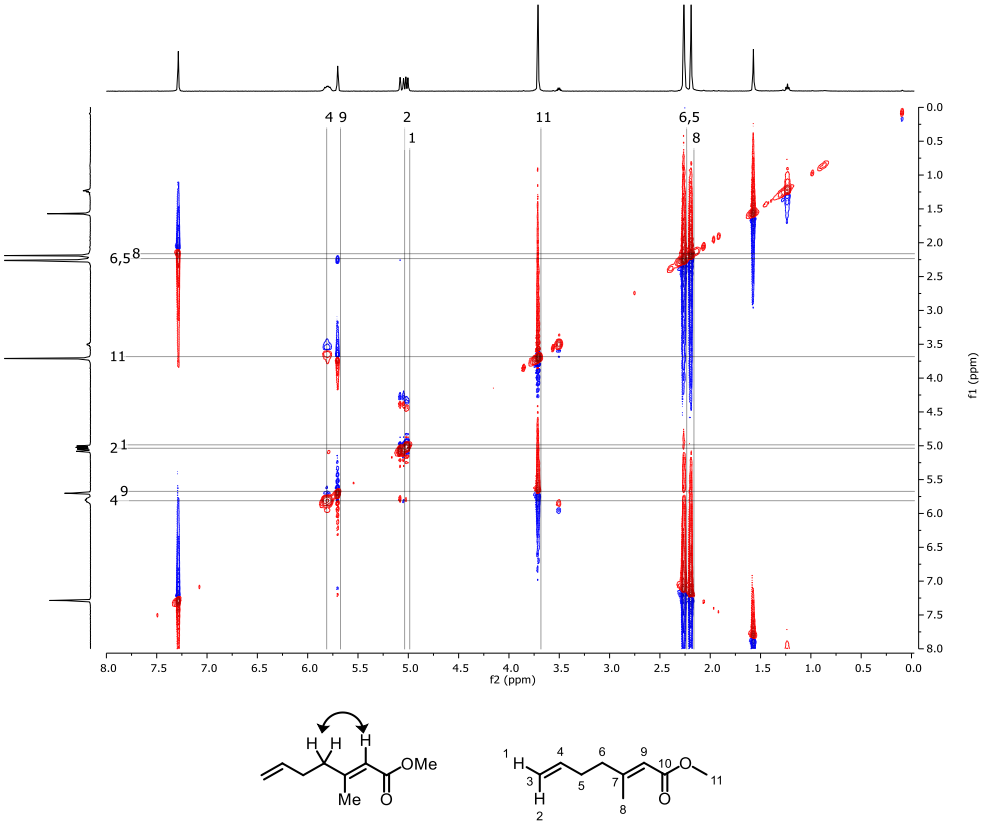
^1H NMR (500 MHz, $CDCl_3$) δ 5.84 – 5.71 (m, 1H, 4), 5.67 (dt, *J* = 1.5, 1.0 Hz, 1H, 9), 5.04 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1H, 2), 5.00 – 4.97 (dd, *J* = 10.0, 2.0, 1H, 1), 3.68 (s, 3H, 11), 2.27 – 2.21 (m, 4H, 5, 6), 2.16 (d, *J* = 1.5 Hz, 3H, 8).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3 (10), 159.6 (7), 137.4 (4), 115.6 (3/9), 115.5 (3/9), 51.0 (11), 40.3 (6), 31.6 (5), 18.9 (8).

HRMS (ESI^+) $C_9H_{15}O_2^+$ [$(M + H)^+$] requires 155.1067, found 155.1067.

Data is in accordance with that reported by Lua.[23]

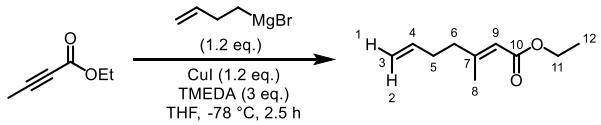
^{1}H NOESY:


4 9
2
1
11
6,5
8
6,5 8
11
2 1
4 9
f2 (ppm)
f1 (ppm)

H
H
H
OMe
Me
O

1
H
4
6
9
10
O
11
3
H
2
5
7
8
O

Ethyl (*E*)-3-methylhepta-2,6-dienoate, 1.167



According to the procedure reported by Ohmiya and co-workers, with modifications.[37]

To prepare the Grignard reagent:

To a flame dried, three-necked round-bottomed flask equipped with magnesium turnings (992 mg, 40.8 mmol, 1.7 eq.), stirrer bar and a reflux condenser was added THF (30 mL). The mixture was heated to reflux for 2 mins, then allowed to cool to rt. Approximately two crystals of iodine were added, and the solution was heated to reflux for 1 minute. A solution of 4-bromo-1-butene (2.5 mL, 24.5 mmol, 1 eq.) in THF (7.5 mL) was then added dropwise, using a heat gun to initiate the reaction, without stirring the reaction. The initiation was evidenced by a colour change from light brown to grey. Once initiation had taken place, the remainder of the 4-bromo-1-butene was added with moderate stirring, and the reaction was heated to reflux for 1 h before use.

To effect the conjugate addition to the alkyne:

To a mixture of CuI (4.67 g, 24.5 mmol, 1.2 eq.) in THF (2.6 mL) was added TMEDA (9.25 mL, 61.2 mmol, 3 eq.). The resulting solution was cooled to -40 °C, and the solution of Grignard reagent was added (25 mL, 12.2 mmol, 1.2 eq.) dropwise down the side of the flask. The reaction was stirred at -40 °C for 30 mins, then cooled to -78 °C. A solution of ethyl 2-butynoate (2.35 mL, 20.4 mmol, 1 eq.) in THF (20 mL) was added dropwise, and the reaction was stirred at -78 °C for 2 h, then quenched with MeOH that had been pre-cooled to -78 °C, via a cannula that was cooled with dry ice pellets. The reaction was allowed to warm to rt

over 1 h, then a sat. aq. solution of NH_4Cl (60 mL) was added. The reaction was extracted with Et_2O, and the combined organics were washed with sat. aq. NH_4Cl and brine, then dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (4% Et_2O in pentane) afforded the title compound (2.36 g, 75%).

R_f: 0.4 (4% Et_2O in pentane).

ν_{max} (cm^{-1}): 2981 (w), 1714 (s), 1648 (m), 1145 (s).

^1H NMR (500 MHz, $CDCl_3$) δ 5.85 – 5.72 (m, 1H, 4), 5.67 (q, *J* = 1.5 Hz, 1H, 9), 5.04 (d, *J* = 17.0 Hz, 1H, 2), 4.98 (d, *J* = 10.0 Hz, 1H, 1), 4.14 (q, *J* = 7.0 Hz, 2H, 11), 2.28 – 2.21 (m, 4H, 5, 6), 2.16 (d, *J* = 1.5 Hz, 3H, 8), 1.27 (t, *J* = 7.0 Hz, 3H, 12).

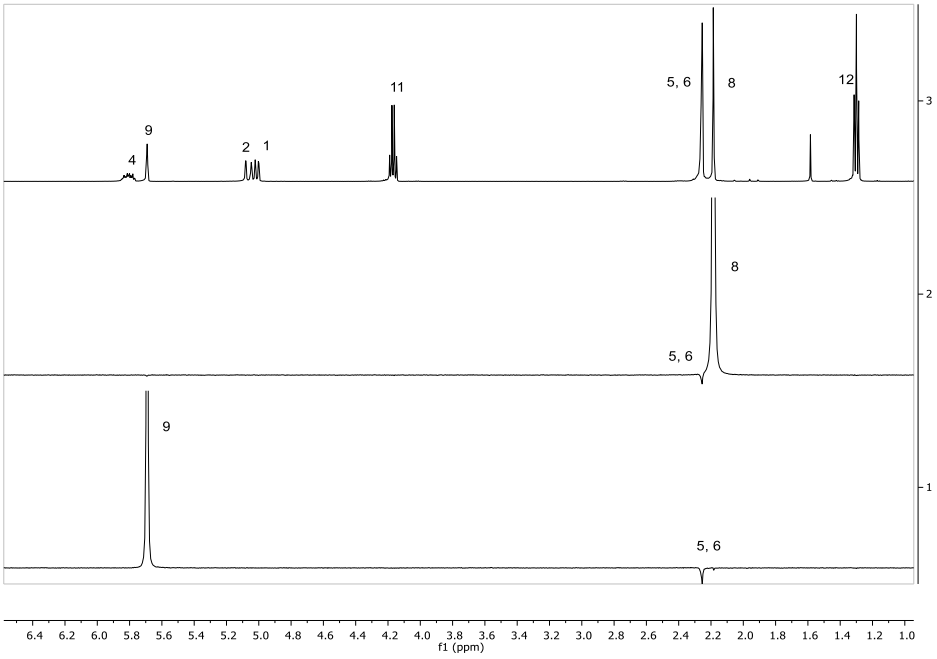
^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9 (10), 159.2 (7), 137.4 (4), 116.0 (9), 115.4 (3), 59.7 (11), 40.3 (5/6), 31.7 (5/6), 18.9 (8), 14.5 (12).

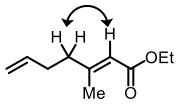
m/z (ESI^+) 169.2 [$(M + H)^+$].

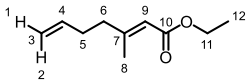
HRMS (ESI^+) $C_{10}H_{17}O_2^+$ [$(M + H)^+$] requires 169.1223, found 169.1225.

Data in accordance with that reported by Jiang.[25]

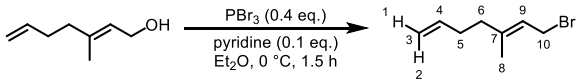
^{1}H nOe enhancements:







(*E*)-7-Bromo-5-methylhepta-1,5-diene, 1.112



According to the procedure reported by Jiang.[25] All the following steps, including removal of solvent, were rigorously carried out in the dark. To a stirred solution of alcohol **1.139** (400 mg, 3.17 mmol, 1 eq.) in Et_2O (4 mL) was added pyridine (0.03 mL, 0.32 mmol, 0.1 eq.) at room temperature. The reaction was then cooled to 0 °C, and phosphorus tribromide (0.12 mL, 1.27 mmol, 0.4 eq.) was added dropwise over 30 minutes. The reaction was stirred at 0 °C for a further 1 h, then quenched with H_2O. The mixture was extracted with pentane twice, and the combined organics were washed with sat. aq. $NaHCO_3$, then dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the title compound (544 mg, 91%). Removal of solvent was done with a 20 °C water bath, and the pressure was not reduced below 200 mbar. The compound was then stored at -20 °C, where it was observed to be stable for at least 1 week.

R_f: Not obtained, due to instability of product on silica.

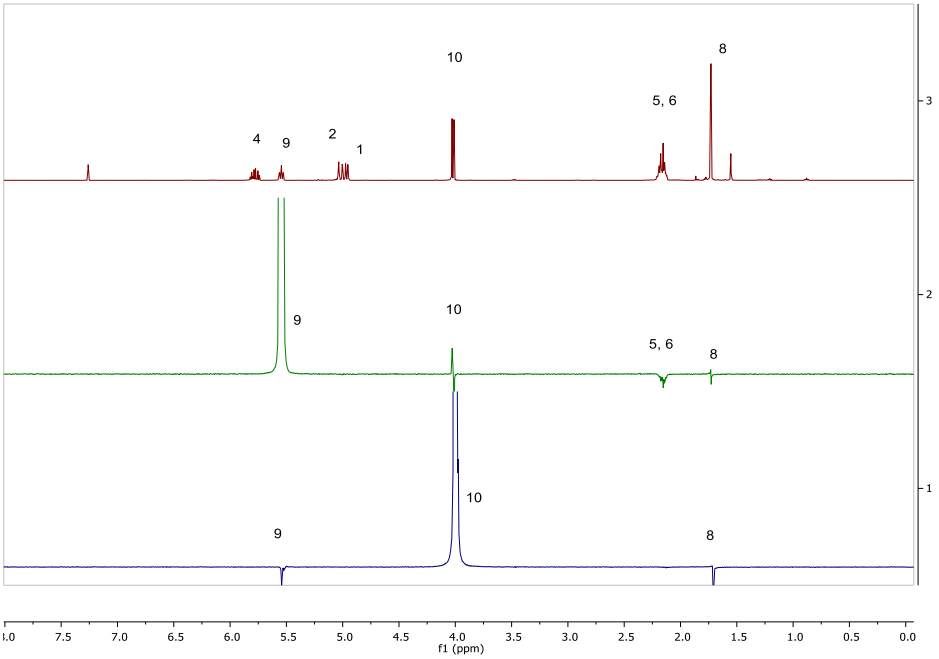
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 4), 5.54 (tq, *J* = 8.5, 1.5 Hz, 1H, 9), 5.02 (dq, *J* = 17.0, 1.5 Hz, 1H, 2), 4.96 (ddt, *J* = 10.0, 2.0, 1.0 Hz, 1H, 1), 4.02 (d, *J* = 8.5 Hz, 2H, 10), 2.24 – 2.10 (m, 4H, 5, 6), 1.73 (d, *J* = 1.5 Hz, 3H, 8).

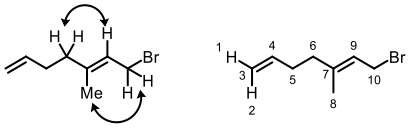
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.1 (7), 138.0 (4), 121.0 (9), 115.0 (3), 38.9 (6), 31.9 (5), 29.6 (10), 16.1 (8).

Mass spectrometry data could not be obtained for this compound.

Data in accordance with that reported by Jiang.[25]

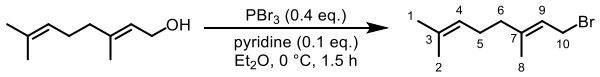
nOe spectra:





Note: the apparent enhancement of resonances 8 and 10 after irradiation of resonance 9 is the result of a *J*-coupling artefact.

(*E*)-1-Bromo-3,7-dimethylocta-2,6-diene, 1.180



According to the procedure reported by Jiang.[25] All the following steps, including removal of solvent, were rigorously carried out in the dark. To a stirred solution of geraniol (5 mL, 28.5 mmol, 1 eq.) in Et_2O (35 mL) was added pyridine (0.23 mL, 2.85 mmol, 0.1 eq.) at room temperature. The reaction was then cooled to 0 °C, and phosphorus tribromide (1.1 mL, 11.4 mmol, 0.4 eq.) was added dropwise over 30 minutes. The reaction was stirred at 0 °C for a further 1 h, then quenched with H_2O. The mixture was extracted with pentane twice, and the combined organics were washed with sat. aq. $NaHCO_3$, then dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the title compound (5.83 g, 94%). Removal of solvent was done with a 20 °C water bath, and the pressure was not reduced below 200 mbar. The compound was then stored at -20 °C, where it was observed to be stable for at least 1 week.

R_f: Not obtained, due to instability of product on silica.

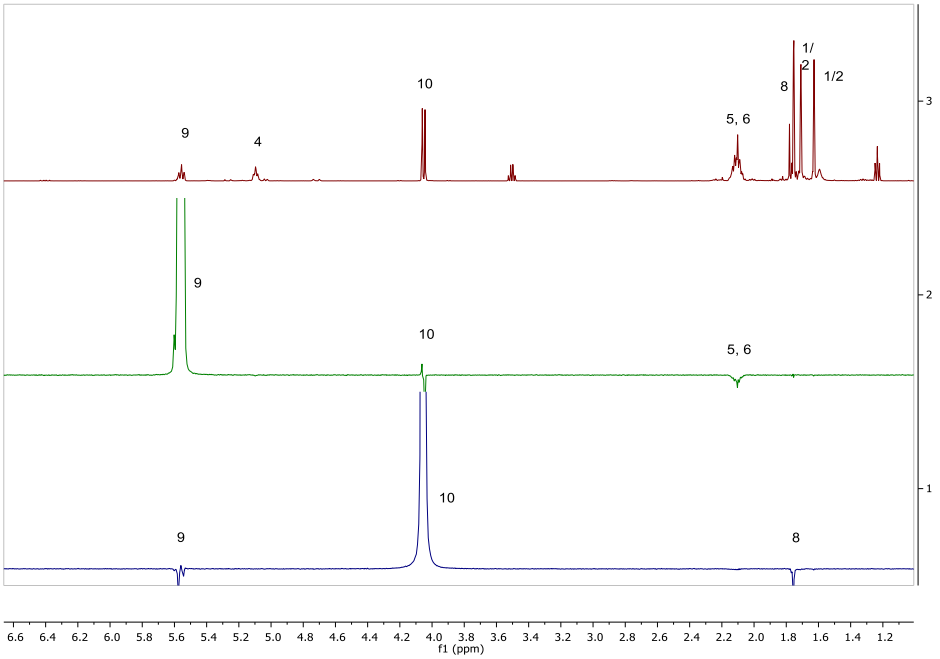
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (tq, *J* = 8.5, 1.5 Hz, 1H, 9), 5.11 – 4.98 (m, 1H, 4), 4.03 (d, *J* = 8.5 Hz, 2H, 10), 2.15 – 1.95 (m, 4H, 5, 6), 1.73 (d, *J* = 1.5 Hz, 3H, 8), 1.68 (d, *J* = 1.5 Hz, 3H, 1/2), 1.60 (d, *J* = 1.5 Hz, 3H, 1/2).

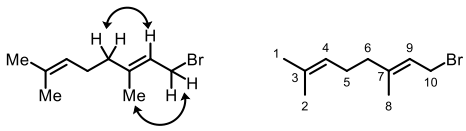
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.8 (7), 132.2 (3), 123.7 (4), 120.7 (9), 39.7 (6), 29.9 (10), 26.3 (5), 25.8 (1/2), 17.9 (1/2), 16.1 (8).

Mass spectrometry data could not be obtained due to instability and volatility of the compound.

Data in accordance with that reported by Jiang.[25]

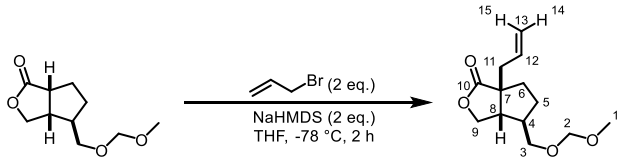
nOe spectra:


9
4
10
5, 6
8
1/
2
1/2
9
10
5, 6
10
9
8
f1 (ppm)


H
H
H
Me
Me
Me
Br
H
H

1
2
3
4
5
6
7
8
9
10
Br

(3a*S,4*R**,6a*S**)-6a-Allyl-4-((methoxymethoxy)methyl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one, 1.231**



To a solution of NaHMDS (0.83 mL, 0.50 mmol, 2 eq., 0.6 M in toluene) in THF (3.7 mL), cooled to -78 °C, was added a solution of allyl bromide (43 µL, 0.50 mmol, 2 eq.) and lactone **1.216** (50 mg, 0.25 mmol, 1 eq.) in THF (1 mL) dropwise over 2 h using a syringe pump. Upon completion of the addition, the reaction was stirred for a further 10 minutes at -78 °C then quenched rapidly with sat. aq. NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organics were washed with brine, then dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography afforded the title compound (47 mg, 78%).

R_f: 0.4 (36% EtOAc in petroleum ether [30-40 °C]).

ν_{max} (cm^{-1}): 2934 (w), 1761 (s), 1041 (s).

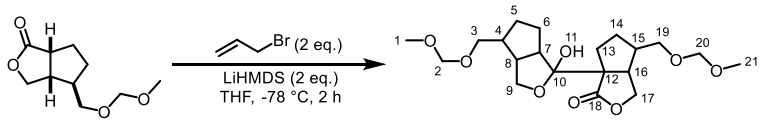
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dddd, *J* = 17.0, 10.0, 8.0, 7.0 Hz, 1H, 12), 5.20 – 5.10 (m, 2H, 14, 15), 4.60 (s, 2H, 2), 4.32 (dd, *J* = 9.5, 8.0 Hz, 1H, 9'), 4.13 (dd, *J* = 9.5, 2.0 Hz, 1H, 9''), 3.51 (dd, *J* = 9.5, 6.0 Hz, 1H, 3'), 3.41 (dd, *J* = 9.5, 7.5 Hz, 1H, 3''), 3.34 (s, 3H, 1), 2.54 (ddt, *J* = 13.5, 7.0, 1.5 Hz, 1H, 11'), 2.41 (ddd, *J* = 8.0, 6.0, 2.0 Hz, 1H, 8), 2.29 (dd, *J* = 13.5, 8.0 Hz, 1H, 11''), 2.21 – 2.12 (m, 1H, 4), 2.12 – 2.04 (m, 1H, 6''), 1.87 – 1.73 (m, 2H, 5'', 6'), 1.57 – 1.46 (m, 1H, 5').

^{13}C NMR (126 MHz, $CDCl_3$) δ 182.5 (10), 133.0 (12), 119.5 (13), 96.7 (2), 72.0 (9), 70.2 (3), 55.5 (7), 55.4 (1), 48.0 (4), 47.7 (8), 40.9 (11), 35.6 (6), 29.0 (5).

m/z (ESI^+) 263.1 [$(M + Na)^+$].

HRMS (ESI^+) $C_{13}H_{20}O_4Na^+$ [$(M + Na)^+$] requires 263.1254 found 263.1260.

1-Hydroxy-4,6'-bis((methoxymethoxy)methyl)decahydro-1*H*,1'*H*,3'*H*-[1,3'a-bi(cyclopenta[*c*]furan)]-3'-one, 1.230



The title compound was obtained during optimisation of the alkylation reaction of lactone **1.216** (see chapter one, Table 1.4).

To a solution of lactone **1.216** (50 mg, 0.25 mmol, 1 eq.) and allyl bromide (43 µL, 0.50 mmol, 2 eq.) in THF (5 mL), cooled to -78 °C, was added LiHMDS (1 M in THF, 0.5 mL, 0.5 mmol, 2 eq.) dropwise over 2 h. The reaction was stirred for a further 10 min at -78 °C, then quenched by pouring over a solution of sat. aq. NH_4Cl. The resulting mixture was extracted with EtOAc, and the combined organics were washed with brine, then dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (36% EtOAc in petroleum ether [30 – 40 °C]) afforded the title compound (7 mg, 14%).

R_f: 0.1 (40% EtOAc in petroleum ether [40-60 °C]).

ν_{max} (cm^{-1}): 3468 (w, br.), 2950 (m), 2360 (w), 1740 (s).

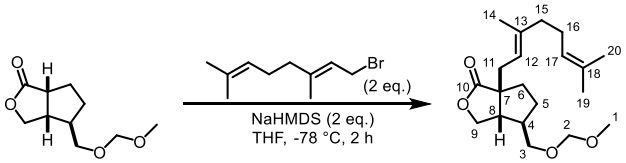
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (s, 2H, 2/20), 4.60 (s, 2H, 2/20), 4.43 (dd, *J* = 9.0, 7.0 Hz, 1H, 17'), 4.21 – 4.12 (m, 2H, 11, 17''), 4.00 (t, *J* = 8.5 Hz, 1H, 9'), 3.61 (dd, *J* = 8.5, 8.0 Hz, 1H, 9''), 3.56 (dd, *J* = 9.5, 6.0 Hz, 1H, 19'), 3.50 – 3.39 (m, 2H, 3', 19''), 3.36 (s, 3H, 1/21), 3.35 (s, 3H, 1/21), 3.34 – 3.31 (m, 1H, 3''), 2.68 (tdd, *J* = 9.0, 4.5, 1.5 Hz, 1H, 7), 2.59 – 2.48 (m, 2H, 8, 16), 2.19 (m, 1H, 15), 2.15 – 2.08 (m, 1H, 4), 2.08 – 1.95 (m, 4H, 5', 6'', 13', 13''), 1.78 (dq, *J* = 14.0, 7.0 Hz, 1H, 14'), 1.71 – 1.60 (m, 1H, 6'), 1.58 – 1.46 (m, 2H, 5'', 14'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 182.6 (18), 107.2 (10), 96.8 (2/20), 96.6 (2/20), 73.9 (17), 71.1 (9), 70.7 (3), 70.0 (19), 62.5 (12), 55.5 (1/21), 55.3 (1/21), 50.0 (7), 49.5 (8), 48.4 (15), 46.6 (16), 44.4 (4), 32.8 (13), 32.1 (5), 29.5 (14), 26.0 (6).

m/z (ESI^+) 423.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{20}H_{32}O_8Na^+$ [$(M + Na)^+$] requires 423.1989 found 423.1985.

(3a*S,4*R**,6a*S**)-6a-((*E*)-3,7-Dimethylocta-2,6-dien-1-yl)-4-((methoxymethoxy)methyl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one, 1.232**



To a solution of NaHMDS (0.83 mL, 0.50 mmol, 2 eq., 0.6 M in toluene) in THF (3.7 mL), cooled to -78 °C, was added a solution of bromide **1.180** (112 mg, 0.50 mmol, 2 eq.) and lactone **1.216** (50 mg, 0.25 mmol, 1 eq.) in THF (1 mL) dropwise over 2 h using a syringe pump. Upon completion of the addition, the reaction was stirred for a further 15 minutes at -78 °C then quenched rapidly with sat. aq. NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organics were washed with brine, then dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (12% EtOAc in pentane) afforded the title compound (63 mg, 76%, average of two runs).

R_f: 0.3 (10% EtOAc in pentane).

ν_{max} (cm^{-1}): 2934 (m), 2360 (w), 1761 (s).

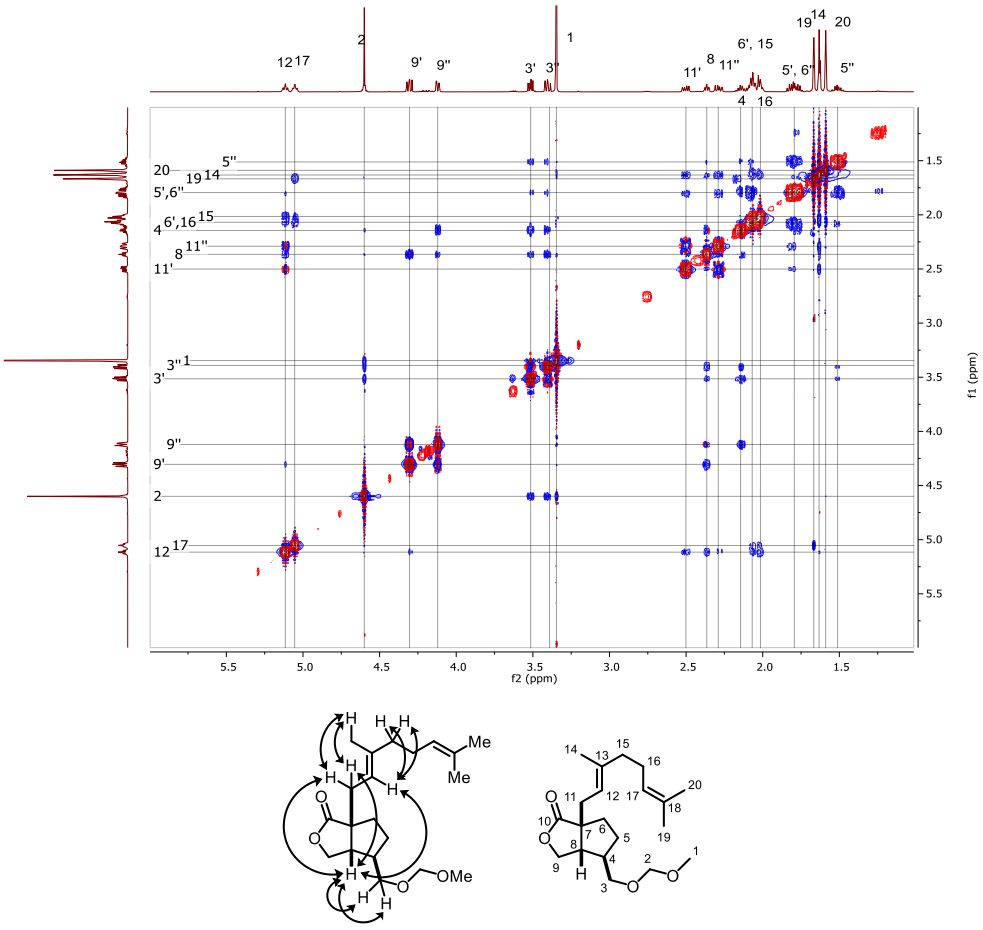
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.12 (dddd, *J* = 8.5, 7.0, 2.6, 1.3 Hz, 1H, 12), 5.05 (ddt, *J* = 7.0, 5.5, 1.5 Hz, 1H, 17), 4.60 (s, 2H, 2), 4.31 (dd, *J* = 9.5, 7.5 Hz, 1H, 9'), 4.12 (dd, *J* = 9.5, 2.0 Hz, 1H, 9''), 3.52 (dd, *J* = 9.5, 6.0 Hz, 1H, 3'), 3.40 (dd, *J* = 9.5, 7.5 Hz, 1H, 3''), 3.35 (s, 3H, 1), 2.50 (dd, *J* = 14.0, 7.0 Hz, 1H, 11'), 2.37 (ddd, *J* = 7.5, 6.0, 2.0 Hz, 1H, 8), 2.29 (dd, *J* = 14.0, 8.5 Hz, 1H, 11''), 2.21 – 2.11 (m, 1H, 4), 2.11 – 2.04 (m, 3H, 6'', 16), 2.04 – 1.99 (m, 2H, 15), 1.86 – 1.73 (m, 2H, 5'', 6'), 1.67 (d, *J* = 1.5 Hz, 3H, 19), 1.63 (d, *J* = 1.5 Hz, 3H, 14), 1.59 (d, *J* = 1.5 Hz, 3H, 20), 1.57 – 1.46 (m, 1H, 5').

^{13}C NMR (126 MHz, $CDCl_3$) δ 183.0 (10), 139.7 (13), 131.8 (18), 124.0 (17), 118.5 (12), 96.7 (2), 72.1 (9), 70.4 (3), 56.1 (7), 55.4 (1), 48.1 (4), 47.7 (8), 40.0 (15), 35.7 (6), 34.9 (11), 29.1 (5), 26.6 (16), 25.8 (19), 17.8 (20), 16.4 (14).

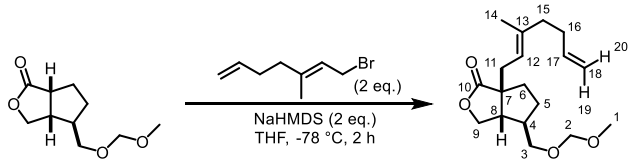
m/z (ESI$^+$) 359.2 [(M + Na)$^+$].

HRMS (ESI$^+$) $C_{20}H_{32}O_4Na^+$ [(M + Na)$^+$] requires 359.2193, found 359.2199.

^{1}H NOESY:



(3a*R,4*S**,6a*R**)-4-((Methoxymethoxy)methyl)-6a-((*E*)-3-methylhepta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one, 1.217**



To a solution of NaHMDS (0.83 mL, 0.50 mmol, 2 eq., 0.6 M in toluene) in THF (3.7 mL), cooled to -78 °C, was added a solution of bromide **1.112** (112 mg, 0.50 mmol, 2 eq.) and lactone **1.216** (50 mg, 0.25 mmol, 1 eq.) in THF (1 mL) dropwise over 2 h using a syringe pump. Upon completion of the addition, the reaction was stirred for a further 15 minutes at -78 °C then quenched rapidly with sat. aq. NH_4Cl. The reaction mixture was extracted with EtOAc and the combined organics were washed with brine, then dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (5-25% EtOAc in petroleum ether [40-60 °C]) afforded the title compound (63 mg, 76%, average of two runs).

R_f: 0.3 (25% EtOAc in petroleum ether [40-60 °C])

ν_{max} (cm^{-1}): 2930 (w), 2360 (w), 1763 (s), 1044 (s).

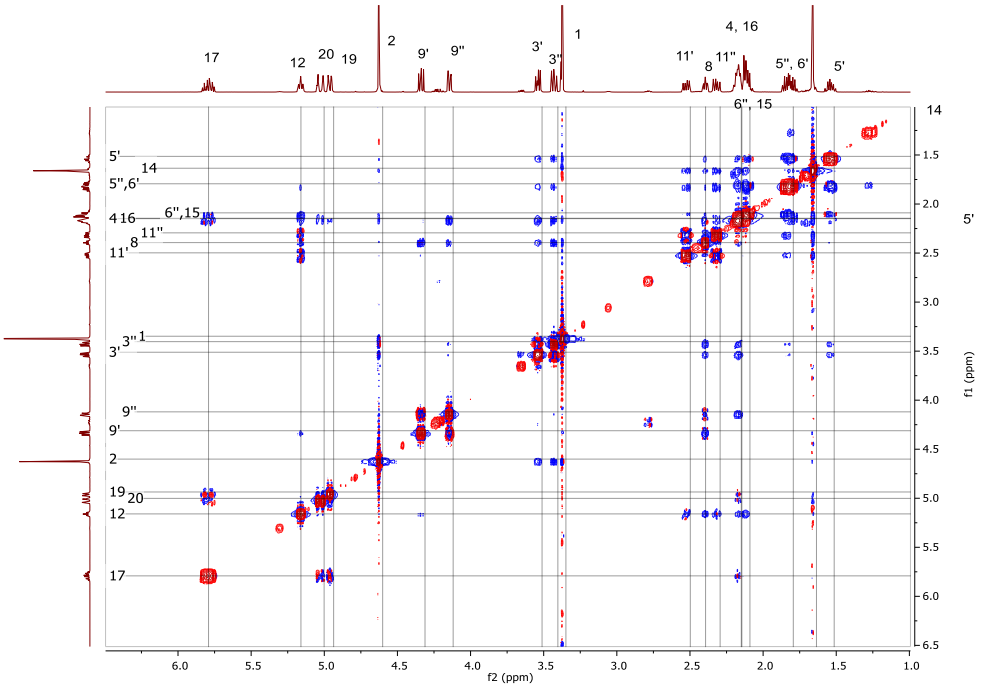
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, 17), 5.13 (ddq, *J* = 8.0, 7.0, 1.5 Hz, 1H, 12), 5.00 (dq, *J* = 17.0, 1.5 Hz, 1H, 20), 4.94 (ddt, *J* = 10.5, 2.5, 1.0 Hz, 1H, 19), 4.60 (s, 2H, 2), 4.31 (dd, *J* = 9.5, 7.5 Hz, 1H, 9'), 4.12 (dd, *J* = 9.5, 2.0 Hz, 1H, 9''), 3.51 (dd, *J* = 9.5, 6.0 Hz, 1H, 3'), 3.40 (dd, *J* = 9.5, 7.5 Hz, 1H, 3''), 3.35 (s, 3H, 1), 2.50 (dd, *J* = 14.0, 7.0 Hz, 1H, 11'), 2.37 (ddd, *J* = 7.5, 6.0, 2.0 Hz, 1H, 8), 2.29 (dd, *J* = 14.0, 8.0 Hz, 1H, 11''), 2.18 – 2.12 (m, 3H, 4, 16), 2.11 – 2.06 (m, 3H, 6'', 15), 1.86 – 1.72 (m, 2H, 5'', 6'), 1.63 (d, *J* = 1.5 Hz, 3H, 14), 1.57 – 1.46 (m, 1H, 5').

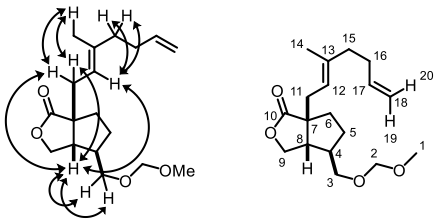
^{13}C NMR (126 MHz, $CDCl_3$) δ 182.9 (10), 139.2 (13), 138.4 (17), 118.8 (12), 114.8 (18), 96.7 (2), 72.1 (9), 70.3 (3), 56.0 (7), 55.4 (1), 48.1 (4), 47.7 (8), 39.3 (15), 35.7 (6), 34.8 (11), 32.3 (16), 29.1 (5), 16.4 (14).

m/z (ESI^+) 331.2 $[(M + Na)^+]$.

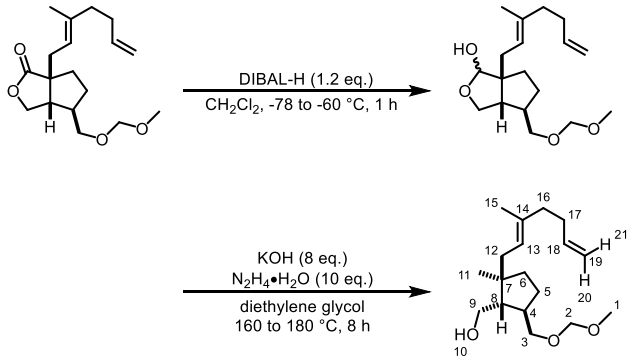
HRMS (ESI^+) $C_{18}H_{28}O_4Na^+$ $[(M + Na)^+]$ requires 331.1880 found 331.1879.

^{1}H NOESY:





((1*R,2*S**,5*S**)-5-((Methoxymethoxy)methyl)-2-methyl-2-((*E*)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)methanol, 1.234**



According to the procedure reported by Lua,[23] with modifications.

To prepare the lactol:

A solution of lactone **1.217** (1.17 g, 3.79 mmol, 1 eq.) in CH_2Cl_2 (40 mL) was cooled to -78 °C and DIBAL-H (4.5 mL, 1 M in hexanes, 4.5 mmol, 1.2 eq.) was added dropwise. The solution was warmed to -60 °C and the reaction was stirred at this temperature for 1 h. The reaction was then cooled back down to -78 °C, and quenched with 10 mL MeOH that was precooled to -78 °C and delivered via a cannula that was cooled with pellets of dry ice. The reaction was allowed to warm to rt, and then 40 mL of sat. aq. Rochelle's salt was added and stirred rapidly overnight. The mixture was extracted with CH_2Cl_2, then dried, filtered, and reduced *in vacuo* to give the crude product. This was taken on directly to the next step.

To reduce the lactol:

To a solution of the lactol **1.233** (assumed 3.79 mmol, 1 eq.) prepared above in diethylene glycol (19 mL, deoxygenated via freeze-pump-thaw techniques) was added KOH (72 mg, 1.29 mmol, 8 eq.). The mixture was stirred, then freeze-pump-thawed once more. Hydrazine monohydrate (0.08 mL, 1.61 mmol, 10 eq.) was measured out and transferred to the

reaction in a nitrogen atmosphere. The reaction was then heated to 160 °C for 4 h, then 180 °C for a further 4 h, with the reaction setup protected by a blast shield for the entirety of heating. The reaction was allowed to cool to room temperature, then quenched with sat. aq. NH_4Cl, before diluting with H_2O and EtOAc. The mixture was extracted with EtOAc, then dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (30% EtOAc in petroleum ether [40-60 °C]) afforded the title compound (895 mg, 80% over two steps).

R_f: 0.3 (30% EtOAc in petroleum ether [40-60 °C]).

ν_{max} (cm^{-1}) 3448 (w, br.), 2928 (m), 2360 (w), 1038 (s).

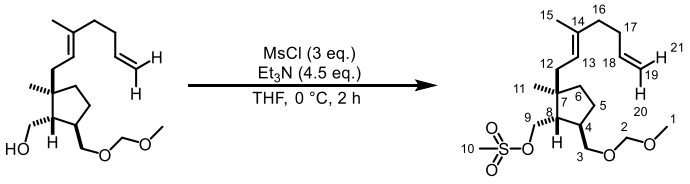
^1H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 18), 5.21 (ddq, *J* = 8.5, 7.0, 1.5 Hz, 1H, 13), 5.00 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1H, 21), 4.93 (ddt, *J* = 10.0, 2.0, 1.0 Hz, 1H, 20), 4.66 (d, *J* = 6.5 Hz, 1H, 2'), 4.65 (d, *J* = 6.5 Hz, 1H, 2''), 3.68 (ddd, *J* = 10.5, 9.0, 3.5 Hz, 1H, 9'), 3.63 (dd, *J* = 9.0, 4.5 Hz, 1H, 3'), 3.58 (dd, *J* = 9.0, 2.0 Hz, 1H, 10), 3.45 – 3.38 (m, 1H, 9''), 3.37 (s, 3H, 1), 3.32 (dd, *J* = 10.5, 9.0 Hz, 1H, 3''), 2.20 – 2.05 (m, 6H, 4, 12', 16, 17), 1.95 (dd, *J* = 14.0, 7.0 Hz, 1H, 12''), 1.86 (dtd, *J* = 13.0, 9.5, 8.0 Hz, 1H, 5'), 1.60 (s, 3H, 15), 1.54 – 1.45 (m, 2H, 6'', 8), 1.34 (ddd, *J* = 12.5, 8.0, 3.5 Hz, 1H, 6'), 1.22 (dddd, *J* = 13.0, 9.5, 6.0, 3.5 Hz, 1H, 5''), 0.77 (s, 3H, 11).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8 (18), 136.5 (14), 121.5 (13), 114.5 (19), 96.5 (2), 72.7 (3), 64.1 (9), 56.0 (8), 55.8 (1), 46.3 (7), 44.3 (4), 39.5 (16), 39.4 (12), 37.9 (6), 32.5 (17), 26.2 (5), 20.7 (11), 16.3 (15).

m/z (ESI^+) 319.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{18}H_{32}O_3Na^+$ [$(M + Na)^+$] requires 319.2244 found 319.2243.

((1*R,2*S**,5*S**)-5-((Methoxymethoxy)methyl)-2-methyl-2-((*E*)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)methyl methanesulfonate, 1.241**



According to the procedure reported by Jiang, with modifications.[25] A solution of alcohol **1.234** (895 mg, 3.02 mmol, 1 eq.) in THF (4.1 mL) was cooled to 0 °C, to which triethylamine (1.9 mL, 13.6 mmol, 4.5 eq.) was added. Methanesulfonyl chloride (0.7 mL, 9.06 mmol, 3 eq.) was then added dropwise, and the resulting solution was stirred for 2 h at 0 °C. The reaction was then diluted with pentane, and quenched with H_2O. The mixture was extracted with EtOAc, and the combined organics were washed with $NaHCO_3$, then dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product, which was used in the next step without further purification.

R_f: 0.4 (40% EtOAc in petroleum ether [40-60 °C]).

ν_{max} (cm^{-1}) 2932 (m), 2361 (w), 1175 (s).

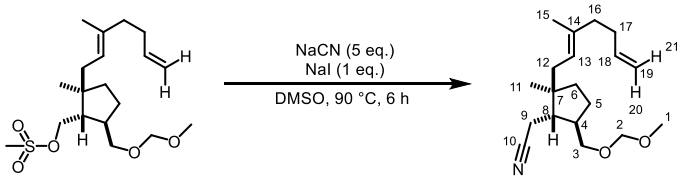
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 18), 5.20 (ddt, *J* = 8.5, 7.5, 1.5 Hz, 1H, 13), 5.01 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1H, 21), 4.94 (ddt, *J* = 10.0, 2.0, 1.0 Hz, 1H, 20), 4.61 (d, *J* = 6.5 Hz, 1H, 2'), 4.61 (d, *J* = 6.5 Hz, 1H, 2''), 4.28 (d, *J* = 6.5 Hz, 2H, 9), 3.51 (dd, J = 9.5, 6.0 Hz, 1H, 3'), 3.45 (dd, *J* = 9.5, 7.0 Hz, 1H, 3''), 3.36 (s, 3H, 1), 3.00 (s, 3H, 10), 2.29 – 2.13 (m, 3H, 12', 17), 2.13 – 2.03 (m, 3H, 4, 16), 1.98 (dd, *J* = 14.0, 7.5 Hz, 1H, 12''), 1.84 (dtd, *J* = 12.5, 9.0, 7.5 Hz, 1H, 5'), 1.77 (dt, *J* = 9.0, 6.5 Hz, 1H, 8), 1.72 – 1.54 (m, 4H, 6', 15), 1.48 – 1.42 (m, 1H, 5''), 1.41 – 1.32 (m, 1H, 6''), 0.90 (s, 3H, 11).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8 (18), 136.8 (14), 121.2 (13), 114.6 (19), 96.7 (2), 71.8 (3), 71.1 (9), 55.4 (1), 49.3 (8), 45.7 (7), 41.9 (4), 39.8 (12), 39.5 (16), 38.3 (6), 37.4 (10), 32.5 (17), 26.7 (5), 20.9 (11), 16.4 (15).

m/z (ESI^+) 397.2 $[(M + Na)^+]$.

HRMS (ESI^+) $C_{19}H_{34}O_5SNa^+$ $[(M + Na)^+]$ requires 397.2019 found 397.2018.

2-((1*S,2*R**,5*R**)-5-((Methoxymethoxy)methyl)-2-methyl-2-((*E*)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)acetonitrile, 1.243**



According to the procedure reported by Yli-Kauhaluoma and co-workers, with modifications.[158] The mesylate **1.241** (1.13 g, 3.02 mmol, 1 eq.) was dissolved in anhydrous DMSO (30 mL). NaCN (740 mg, 15.1 mmol, 5 eq.) and NaI (453 mg, 3.02 mmol, 1 eq.) were added and the reaction was heated to 90 °C for 6 h in the dark. The reaction was cooled to 0 °C and quenched with sat. aq. $NaHCO_3$, then extracted with EtOAc. The combined organics were washed with sat. aq. $NaHCO_3$ and brine, then dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (15% EtOAc in petroleum ether [40 – 60 °C]) afforded the title compound (749 mg, 81%).

R_f: 0.4 (15% EtOAc in petroleum ether [40 – 60 °C]).

ν_{max} (cm^{-1}): 2929 (m), 2360 (w), 1044 (s).

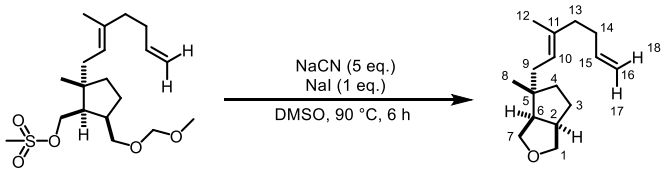
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 18), 5.19 (ddq, *J* = 8.5, 7.0, 1.5 Hz, 1H, 13), 5.01 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1H, 21), 4.95 (ddt, *J* = 10.0, 2.0, 1.0 Hz, 1H, 20), 4.62 (s, 2H, 2), 3.55 (dd, *J* = 7.0, 3.5 Hz, 1H, 3'), 3.53 (dd, *J* = 7.0, 3.8 Hz, 1H, 3''), 3.37 (s, 3H, 1), 2.42 (dd, *J* = 17.0, 6.5 Hz, 1H, 9'), 2.40 (dd, *J* = 17.0, 7.0 Hz, 1H, 9''), 2.21 (dd, *J* = 14.0, 8.5 Hz, 1H, 12'), 2.19 – 2.14 (m, 2H, 17), 2.13 – 2.02 (m, 3H, 4, 16), 1.97 (dd, *J* = 14.0, 7.0 Hz, 1H, 12''), 1.89 – 1.75 (m, 1H, 5'), 1.68 (ddd, *J* = 9.5, 7.0, 6.5 Hz, 1H, 8), 1.61 (s, 3H, 15), 1.60 – 1.52 (m, 1H, 6'), 1.47 – 1.33 (m, 2H, 5'', 6''), 0.89 (s, 3H, 11).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6 (18), 136.9 (14), 120.7 (13), 119.9 (10), 114.5 (19), 96.6 (2), 71.3 (3), 55.3 (1), 46.8 (8), 45.8 (7), 44.0 (4), 39.4 (16), 39.1 (12), 37.5 (6), 32.3 (17), 26.0 (5), 20.7 (11), 17.5 (9), 16.3 (15).

m/z (ESI^+) 328.2 $[(M + Na)^+]$.

HRMS (ESI^+) $C_{19}H_{31}O_2NNa^+$ $[(M + Na)^+]$ requires 328.2247 found 328.2247.

(3a*R,4*S**,6a*R**)-4-methyl-4-((*E*)-3-methylhepta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*c*]furan, 1.247**



The title compound was isolated as a side product from the above reaction. Note that the sample of mesylate **1.241** was a 9:1 mixture of diastereomers. The minor diastereomer reacts to give the title compound (6.5 mg, 5%).

R_f: 0.4 (15% EtOAc in petroleum ether [40-60 °C]).

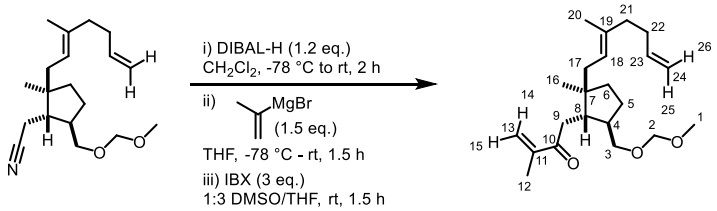
ν_{max} (cm^{-1}): 2932 (s), 2845 (m), 1451 (w).

1H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H, 15), 5.19 (tq, J = 7.5, 1.5 Hz, 1H, 10), 5.01 (d, J = 17.0, 1H, 18), 4.94 (d, J = 10.0 Hz, 1H, 17), 3.83 (dd, J = 9.0, 7.5 Hz, 1H, 1'), 3.69 – 3.53 (m, 2H, 7), 3.46 (dd, J = 9.0, 4.0 Hz, 1H, 1''), 2.79 – 2.63 (m, 1H, 2), 2.30 (ddd, J = 9.0, 7.5, 5.5 Hz, 1H, 6), 2.16 (m, 2H, 14), 2.10 (m, 2H, 13), 1.98 – 1.94 (m, 2H, 9), 1.90 (dtd, J = 13.0, 9.0, 7.5 Hz, 1H, 3'), 1.60 (s, 3H, 12), 1.50 – 1.45 (m, 2H, 4), 1.43 – 1.36 (m, 1H, 3''), 0.93 (s, 3H, 8).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8 (15), 136.4 (11), 121.7 (10), 114.5 (16), 76.0 (1), 70.3 (7), 53.7 (6), 45.0 (5), 44.2 (2), 39.7 (9), 39.6 (13), 38.4 (4), 32.6 (14), 30.6 (3), 21.4 (8), 16.4 (12).

HRMS (ESI^+) $C_{16}H_{27}O^+$ [$(M + H)^+$] requires 235.2056 found 235.2058.

1-((1*S,2*R**,5*R**)-5-((Methoxymethoxy)methyl)-2-methyl-2-((*E*)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)-3-methylbut-3-en-2-one, 1.240**



To reduce the nitrile:

A solution of nitrile **1.243** (300 mg, 0.983 mg, 1 eq.) in CH_2Cl_2 (10 mL) was cooled to -78 °C, and DIBAL-H (1.2 mL, 1 M in hexanes, 1.2 mmol, 1.2 eq.) was added dropwise. The reaction was allowed to warm slowly to 0 °C over the course of 1 h and was stirred at this temperature for a further 30 minutes. The reaction was then cooled to -78 °C and quenched with MeOH (10 mL). The reaction was allowed to warm to rt, and sat. aq. Rochelle's salt was added and the mixture was stirred rapidly overnight. The reaction was then extracted with CH_2Cl_2, and the combined organics were washed with 1 M $HCl_{(aq)}$ and sat. aq. $NaHCO_3$, then dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. This was taken directly onto the next step without further purification.

To add the Grignard:

To a solution of the aldehyde **1.244** (assumed 0.982 mmol, 1 eq.) prepared above in THF (20 mL), cooled to -78 °C, was added isopropenyl magnesium bromide (0.5 M in THF, 3 mL, 1.5 eq.) dropwise. The reaction was stirred at -78 °C for 1 h, allowed to warm to rt over 30 mins, and stirred for a further 30 mins at rt. The reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo*. This material was taken directly onto the next step without further purification.

To oxidise the allylic alcohol (mixture of diastereomers):

According to the procedure reported by Lua, with modifications.[23] To a solution of the allylic alcohol **1.239** (assumed 0.982 mmol, 1 eq.) prepared above in 1:3 DMSO/THF (8 mL) was added IBX (856 mg, 2.95 mmol, 3 eq.) in the dark. The reaction was stirred at rt for 2 h, then quenched with a 1:1 ratio of sat. aq. $Na_2S_2O_3$ and $NaHCO_3$. The mixture was extracted with EtOAc, then the combined organics were washed with brine, dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (12% EtOAc in petroleum ether [40 – 60 °C]) afforded the title compound (195 mg, 57%).

R_f: 0.3 (12:88 EtOAc/petroleum ether [40-60 °C]).

ν_{max} (cm^{-1}) 2927 (m), 1673 (s), 1046 (s).

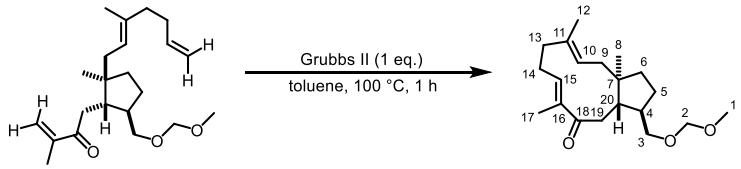
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (s, 1H, 14/15), 5.87 – 5.71 (m, 2H, 14/15, 23), 5.20 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, 18), 5.00 (ddt, *J* = 17.0, 2.0, 1.5 Hz, 1H, 26), 4.93 (ddt, *J* = 10.0, 2.0, 1.0 Hz, 1H, 25), 4.54 (d, *J* = 6.5 Hz, 1H, 2'), 4.53 (d, *J* = 6.5 Hz, 1H, 2''), 3.40 – 3.29 (m, 5H, 1, 3), 2.75 – 2.62 (m, 2H, 9), 2.25 – 2.11 (m, 2H, 22), 2.11 – 2.01 (m, 3H, 17', 21), 1.97 – 1.91 (m, 2H, 4, 8), 1.88 (s, 3H, 12), 1.86 – 1.77 (m, 2H, 5', 17''), 1.58 (d, *J* = 1.5 Hz, 3H, 20), 1.51 (m, 1H, 6'), 1.44 – 1.33 (m, 2H, 5'', 6''), 0.81 (s, 3H, 16).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.5 (10), 145.0 (11), 138.9 (23), 136.2 (19), 124.5 (13), 121.6 (18), 114.5 (24), 96.7 (2), 72.1 (3), 55.3 (1), 47.0 (4/8), 45.9 (7), 44.8 (4/8), 39.6 (21), 39.2 (17), 38.8 (9), 37.4 (6), 32.5 (22), 26.7 (5), 20.8 (16), 18.0 (12), 16.3 (20).

m/z (ESI^+) 371.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{22}H_{36}O_3Na^+$ [$(M + Na)^+$] requires 371.2557 found 371.2558.

(3*R,3a*S**,6*E*,10*E*,12a*R**)-3-((Methoxymethoxy)methyl)-6,10,12a-trimethyl-2,3,3a,4,8,9,12,12a-octahydrocyclopenta[11]annulen-5(1*H*)-one, 1.252**



According to the procedure reported by Nakata and co-workers.[41,42] The enone **1.240** (3.4 mg, 0.01 mmol, 1 eq.) was dissolved in toluene (sparged for 1 h), and the Grubbs 2nd gen ruthenium based catalyst (8.5 mg, 0.01 mmol, 1 eq.) was added to the resulting solution. The reaction was sparged with argon for a further 15 mins, then a reflux condenser was added with an argon balloon and outlet needle fitted to ensure a continual flow of argon in order to displace any volatiles produced in the reaction. The reaction was heated to 100 °C for 1 h, then cooled to rt. The solution was reduced *in vacuo* at 20 °C to give the crude product. Purification by prep TLC (12% EtOAc in CH_2Cl_2) afforded the title compound (0.7 mg, <20%).

R_f: 0.4 (12% EtOAc in CH_2Cl_2).

ν_{max} (cm^{-1}) 2926 (s), 1673 (s), 1044 (s).

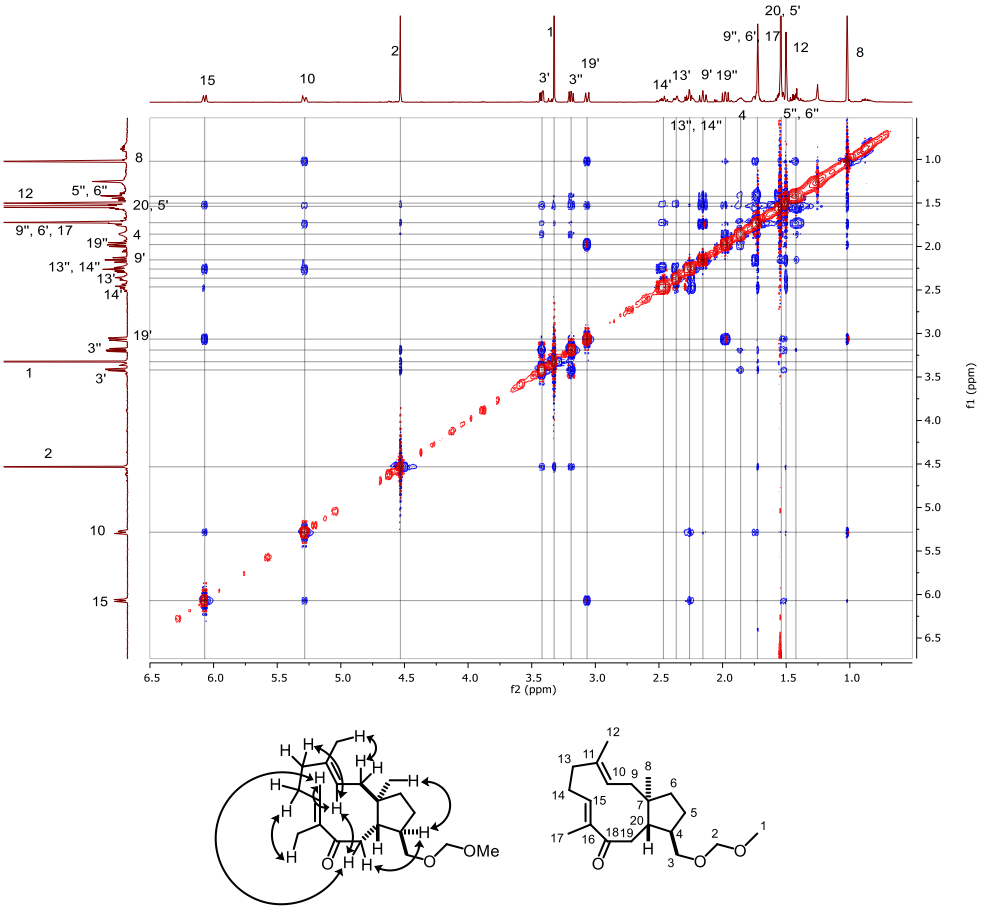
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 – 5.99 (m, 1H, 15), 5.38 – 5.24 (m, 1H, 10), 4.53 (s, 2H, 2), 3.42 (dd, *J* = 9.5, 4.5 Hz, 1H, 3'), 3.32 (s, 3H, 1), 3.19 (dd, *J* = 9.5, 7.0 Hz, 1H, 3''), 3.06 (dd, *J* = 13.0, 2.5 Hz, 1H, 19'), 2.51 – 2.42 (m, 1H, 14'), 2.40 – 2.33 (m, 1H, 13'), 2.31 – 2.22 (m, 2H, 13'', 14''), 2.15 (dd, *J* = 13.0, 12.5 Hz, 1H, 9'), 1.98 (dd, *J* = 13.0, 9.5 Hz, 1H, 19''), 1.90 – 1.81 (m, 1H, 4), 1.77 – 1.69 (m, 5H, 6', 9'', 17), 1.58 – 1.51 (m, 2H, 5', 20), 1.50 (s, 3H, 12), 1.48 – 1.35 (m, 2H, 5'', 6''), 1.02 (s, 3H, 8).

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.3 (18), 142.0 (15), 135.8 (11), 134.7 (16), 124.9 (10), 96.7 (2), 70.4 (3), 55.3 (1), 50.0 (4), 46.1 (7), 45.3 (19), 44.5 (20), 42.8 (5), 42.5 (9), 39.7 (13), 28.3 (6), 24.3 (14), 23.5 (8), 15.2 (12), 12.4 (17).

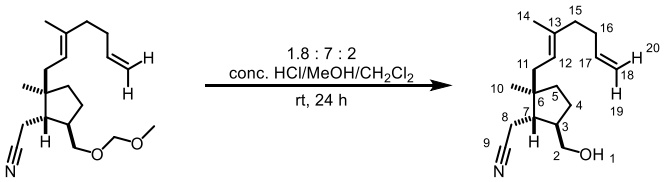
m/z (ESI^+) 343.2 $[(M + Na)^+]$.

HRMS (ESI^+) $C_{20}H_{32}O_3Na^+$ $[(M + Na)^+]$ requires 343.2244 found 343.2243.

^{1}H NOESY:



2-((1*S,2*R**,5*R**)-5-(Hydroxymethyl)-2-methyl-2-((*E*)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)acetonitrile, 1.254**



According to the procedure reported by Covey and co-workers, with modifications.[47] The protected alcohol **1.243** (749 mg, 2.45 mmol, 1 eq.) was dissolved in MeOH (106 mL) and CH_2Cl_2 (30 mL). Concentrated HCl (37%, 27 mL) was added carefully, and the reaction was stirred at rt for 24 h. The reaction was then quenched slowly with sat. aq. $NaHCO_3$, then extracted with EtOAc. The combined organics were washed with brine, then dried (Na_2SO_4), filtered and reduced *in vacuo* to yield the crude product. Purification by column chromatography (40% EtOAc in petroleum ether [40 – 60 °C]) afforded the title compound (611 mg, 95%).

R_f: 0.3 (40% EtOAc in petroleum ether [40 – 60 °C]).

ν_{max} (cm^{-1}): 3435 (w, br.), 2925 m), 2361 (w), 2247 (w), 909 (s).

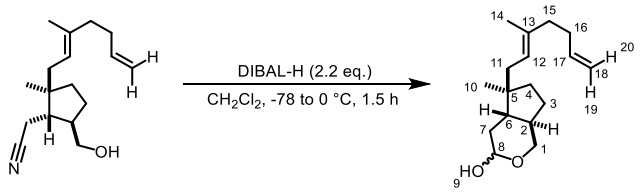
^{1}H NMR (700 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 17), 5.19 (t, *J* = 7.5 Hz, 1H, 12), 5.01 (d, *J* = 17.0 Hz, 1H, 20), 4.94 (d, *J* = 10.0 Hz, 1H, 19), 3.70 (dd, *J* = 10.5, 6.0 Hz, 1H, 2'), 3.67 (dd, *J* = 10.5, 6.0 Hz, 1H, 2''), 2.43 (dd, *J* = 17.0, 6.5 Hz, 1H, 8'), 2.37 (dd, *J* = 17.0, 6.5 Hz, 1H, 8''), 2.22 – 2.14 (m, 3H, 11', 16), 2.10 (t, *J* = 7.5 Hz, 2H, 15), 2.02 (dddd, *J* = 15.5, 9.5, 6.0, 6.0 Hz, 1H, 3), 1.96 (dd, *J* = 14.5, 7.5 Hz, 1H, 11''), 1.87 – 1.80 (m, 1H, 4'), 1.68 (ddd, *J* = 9.5, 6.5, 6.5 Hz, 1H, 7), 1.61 (s, 3H, 14), 1.58 – 1.51 (m, 1H, 5'), 1.50 (s, 1H, 1), 1.42 (m, 2H, 4'', 5''), 0.88 (s, 3H, 10).

^{13}C NMR (176 MHz, $CDCl_3$) δ 138.7 (17), 137.1 (13), 120.8 (12), 120.2 (9), 114.6 (18), 66.3 (2), 46.4 (3), 46.3 (7), 45.9 (6), 39.5 (15), 39.2 (11), 37.6 (5), 32.4 (16), 25.8 (4), 20.8 (10), 17.8 (8), 16.4 (14).

m/z (ESI^+) 284.2 $[(M + Na)^+]$.

HRMS (ESI^+) $C_{17}H_{27}ONNa^+$ $[(M + Na)^+]$ requires 284.1985 found 284.1984.

(4a*S,5*R**,7a*R**)-5-Methyl-5-((*E*)-3-methylhepta-2,6-dien-1-yl)octahydrocyclopenta[*c*]pyran-3-ol, 1.255**



A solution of nitrile **1.254** (611 mg, 2.34 mmol, 1 eq.) in CH_2Cl_2 (47 mL) was cooled to -78 °C, to which DIBAL-H (1M in hexanes, 5.2 mL, 5.20 mmol, 2.2 eq.) was added dropwise. The reaction was allowed to warm to 0 °C over 1 h, and stirred for a further 30 mins at this temperature. The reaction was then cooled to -78 °C, and quenched with MeOH. The resulting solution was allowed to warm to rt, then a saturated aqueous solution of Rochelle's salt was added, and stirred overnight. The reaction was then extracted with CH_2Cl_2, and the combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Column chromatography was performed (25% EtOAc in petroleum ether [40 – 60 °C]), and the isolated product was redissolved in 1:1 mixture of THF/2 M $HCl_{(aq.)}$ and stirred overnight. The mixture was then extracted with EtOAc, and the combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the title compound (530 mg, 86%).

R_f: 0.3 (30% EtOAc in petroleum ether [40 – 60 °C]).

ν_{max} (cm^{-1}): 3386 (s, br.), 2931 (s), 2361 (w), 1640 (m).

In the following assignment, the two diastereomers were arbitrarily assigned the labels A and B. In many cases two peaks at different chemical shifts were determined to be the equivalent nucleus on each diastereomer: these have been assigned to either diastereomer A or diastereomer B where possible, and this labelling is consistent. i.e. one carbon atom

labelled “B” will be part of the same diastereomer as another atom labelled “B”. In some cases we were confident of our assignment of which proton or carbon atom a peak belonged to, but it was not clear whether this peak belonged to A or B, and so these have been labelled, for example, 1 A/B.

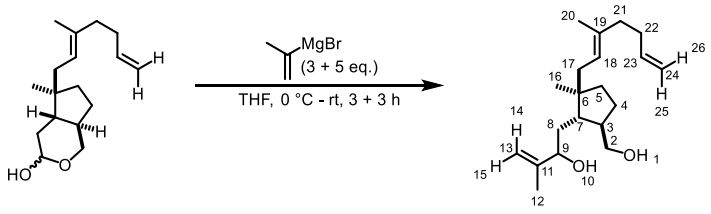
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.73 (m, 2H, 17A, 17B), 5.41 – 5.34 (m, 1H, 8B), 5.27 – 5.17 (m, 2H, 12A, 12B), 5.01 (dt, *J* = 17.0, 2.0 Hz, 2H, 20A, 20B), 4.94 (d, *J* = 10.5 Hz, 2H, 19A, 19B), 4.74 – 4.66 (m, 1H, 8A), 4.11 (dd, *J* = 10.5, 4.5 Hz, 1H, 1A'), 3.80 (dd, *J* = 10.5, 4.0 Hz, 1H, 1B'), 3.72 (t, *J* = 10.5 Hz, 1H, 1B''), 3.26 (t, *J* = 10.5 Hz, 1H, 1A''), 2.21 – 2.13 (m, 4H), 2.12 – 2.05 (m, 6H), 2.00 – 1.86 (m, 3H), 1.82 – 1.62 (m, 7H), 1.60 (s, 6H, 14A, 14B), 1.56 – 0.85 (m, 10H), 0.83 (s, 3H, 10A/B), 0.78 (s, 3H, 10A/B).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0 (17 A/B), 138.8 (17 A/B), 136.3 (13 A/B), 136.1 (13 A/B), 122.1 (12 A/B), 121.8 (12 A/B), 114.6 (18 A/B), 114.4 (18 A/B), 97.2 (8 A), 91.4 (8 B), 71.0 (1 A), 66.5 (1 B), 51.8, 44.9, 43.1 (5 A/B), 42.6 (5 A/B), 41.5, 41.5, 40.1, 39.8, 39.6, 39.6, 38.1, 37.0, 35.2, 32.5, 32.5, 32.3, 26.1, 25.3, 23.4 (10 A/B), 22.7 (10 A/B), 16.3 (14 A, 14 B).

m/z (ESI^+) 303.2 $[(M + K)^+]$, 287.2 $[(M + Na)^+]$.

HRMS (ESI^+) $C_{17}H_{28}O_2Na^+$ $[(M + Na)^+]$ requires 287.1982 found 287.1983.

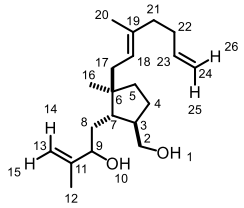
1-((1*S,2*R**,5*R**)-5-(Hydroxymethyl)-2-methyl-2-((*E*)-3-methylhepta-2,6-dien-1-yl)cyclopentyl)-3-methylbut-3-en-2-ol, 1.257**



A solution of isopropenylmagnesium bromide (0.5 M in THF, 15 mL, 7.5 mmol, 3.75 eq.) was cooled to 0 °C, whereupon a solution of lactol **1.256** (530 mg, 2.00 mmol, 1 eq.) in THF (10 mL) was added dropwise. The reaction was allowed to warm to rt, and stirred for 3 h. The reaction was then quenched with a solution of sat. aq. NH_4Cl, and extracted with EtOAc. The combined organics were washed with brine, then dried (Na_2SO_4), filtered and reduced *in vacuo*. Analysis of the ^{1}H NMR spectrum of the crude material revealed that the reaction had not gone to completion, and so the crude material was resubmitted to the reaction, using the same conditions as above, with the exception that 5 equivalents of the Grignard reagent were used. Purification by column chromatography (25-40% EtOAc in petroleum ether [40 – 60 °C]) afforded the title compound (434 mg, 71%).

Although the mixture of diastereomers was taken forward in the next step, a small sample (ca. 15 mg) was carefully purified by preparative TLC (45% EtOAc in petroleum ether [40-60 °C]) to obtain a sample of each diastereomer. ^{1}H and ^{13}C NMR, infrared, and mass spectrometry data were obtained for each diastereomer, as well as the mixture that was obtained from the first round of purification. The assignment of signals in the NMR spectra was carried out on the pure diastereomers, and may be found below with the rest of the characterisation data. The two diastereomers were arbitrarily assigned the labels “A” and “B”, and a determination of the absolute configuration at the allylic alcohol stereocentre (carbon 9) was not carried out.

***Diastereomer A*:**



R_f: 0.4 (50% EtOAc in petroleum ether [40 – 60 °C]).

v_{max} (cm^{-1}): 3304 (br), 2981 (s), 2360 (m), 1381 (m).

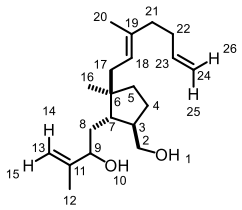
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H, 23), 5.22 (dd, *J* = 7.5, 7.0 Hz, 1H, 18), 5.01 (dq, *J* = 17.0, 2.0 Hz, 1H, 26), 4.98 – 4.91 (m, 2H, 14/15, 25), 4.82 (t, *J* = 1.5 Hz, 1H, 14/15), 4.10 (dd, *J* = 9.5, 3.5 Hz, 1H, 9), 3.68 (dd, *J* = 11.0, 5.0 Hz, 1H, 2'), 3.58 (dd, *J* = 11.0, 7.5 Hz, 1H, 2''), 2.68 (s, 2H, 1, 10), 2.19 – 2.12 (m, 2H, 22), 2.12 – 2.06 (m, 3H, 17'', 21), 2.06 – 1.93 (m, 1H, 3), 1.88 (dd, *J* = 14.0, 7.0 Hz, 1H, 17'), 1.83 – 1.71 (m, 4H, 4'', 12), 1.67 (dt, *J* = 14.0, 3.5 Hz, 1H, 8'), 1.60 (s, 3H, 20), 1.53 – 1.31 (m, 3H, 5, 7, 8''), 1.31 – 1.21 (m, 1H, 4'), 0.79 (s, 3H, 16).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5 (11), 138.9 (23), 136.0 (19), 121.7 (18), 114.5 (24), 110.9 (13), 77.5 (9), 67.5 (2), 49.0 (7), 47.1 (3), 46.9 (6), 39.6 (17), 39.3 (21), 37.3 (5), 35.5 (8), 32.6 (22), 25.9 (4), 20.6 (16), 17.9 (12), 16.4 (20).

m/z (ESI^+) 329.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{20}H_{34}O_2Na^+$ [$(M + Na)^+$] requires 329.2451 found 329.2453.

***Diastereomer B*:**



R_f: 0.5 (50% EtOAc in petroleum ether [40 – 60 °C]).

ν_{max} (cm^{-1}): 3322 (br.), 2932 (s), 2360 (w), 1450 (m).

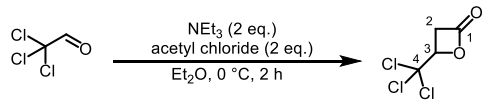
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 23), 5.22 (t, *J* = 7.5 Hz, 1H, 18), 5.10 – 4.97 (m, 2H, 14/15, 26), 4.94 (d, *J* = 9.5 Hz, 1H, 25), 4.84 (s, 1H, 14/15), 4.19 (dd, *J* = 10.0, 3.0 Hz, 1H, 9), 3.64 (dd, *J* = 10.5, 5.5 Hz, 1H, 2'), 3.53 (dd, *J* = 10.5, 8.0 Hz, 1H, 2''), 2.50 (s, 2H, 1, 10), 2.19 – 2.13 (m, 2H, 22), 2.09 (m, 3H, 17', 21), 2.05 – 1.94 (m, 1H, 3), 1.90 (dd, *J* = 14.0, 7.0 Hz, 1H, 17''), 1.84 – 1.72 (m, 1H, 4'), 1.76 (s, 3H, 12), 1.60 (m, 5H, 7, 8', 20), 1.50 – 1.42 (m, 1H, 5'), 1.37 (m, 2H, 5'', 8''), 1.33 – 1.26 (m, 1H, 4''), 0.79 (s, 3H, 16).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6 (11), 138.9 (23), 136.1 (19), 121.9 (18), 114.4 (24), 110.1 (13), 73.5 (9), 68.1 (2), 46.5 (6), 45.8 (3), 45.6 (7), 39.6 (17/21), 39.6 (17/21), 37.8 (5), 36.7 (8), 32.6 (22), 26.9 (4), 21.1 (16), 18.7 (12), 16.4 (20).

m/z (ESI^+) 329.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{20}H_{34}O_2Na^+$ [$(M + Na)^+$] requires 329.2451 found 329.2454.

4-(Trichloromethyl)oxetan-2-one, 1.329



Chloral (anhydrous, 3.5 g, 35.9 mmol, 1 eq.) was added to a flame-dried round bottomed flask and dissolved in Et_2O (35 mL). The resulting solution was cooled to 0 °C, and then acetyl chloride (5.1 mL, 71.7 mmol, 2 eq.) was added. An addition funnel was charged with a solution of Et_3N (10 mL, 72 mmol, 2 eq.) in Et_2O (15 mL), and this solution was added in a dropwise fashion over 1.5 h. An internal temperature probe ensured that the temperature of the solution in the round bottomed flask did not exceed 5 °C. The reaction was stirred for a further 30 minutes, then quenched with pH 2 buffer, and diluted with petroleum ether (40-60 °C). The organic layer was separated off, dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by vacuum distillation (42 °C @ 0.2 mbar) afforded the title compound (5.04 g, 74%).

[Chloral hydrate (50 g, 302 mmol, 1 eq.) was purchased from Sigma-Aldrich, and was added to P_2O_5 (15 g, 106 mmol, 0.35 eq.). Sulfuric acid (16 mL, 302 mmol, 1 eq.) was added in one portion to give a biphasic mixture. Atmospheric distillation (95 °C) with rapid stirring afforded the desired anhydrous chloral. Acetyl chloride and triethylamine were purified by atmospheric distillation prior to use.]

b.p. 42 °C @ 0.2 mbar.

ν_{max} (cm^{-1}) 2979 (w), 1853 (s), 1407 (m).

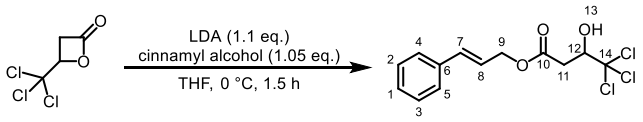
^1H NMR (500 MHz, $CDCl_3$) δ 5.00 (dd, *J* = 5.5, 4.0 Hz, 1H, 3), 3.73 (dd, *J* = 17.0, 5.5 Hz, 1H, 2'), 3.59 (dd, *J* = 17.0, 4.0 Hz, 1H, 2'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.1 (1), 96.8 (4), 76.2 (3), 42.7 (2).

HRMS (ESI^+) $C_4H_4O_2Cl_3^+$ [$(M + H)^+$] requires [188.9271, 189.9305, 190.9242, 191.9275, 192.9212], found [188.9267, 189.9261, 190.9236, 191.9267, 192.9208].

Data is in accordance with that reported in the literature.[159]

Cinnamyl 4,4,4-trichloro-3-hydroxybutanoate, 1.330



According to the procedure reported by Hashimoto *et al*.[160] Diisopropylamine (1.7 mL, 11.7 mmol, 1.1 eq.) was dissolved in THF (30 mL), and the resulting solution was cooled to 0 °C. *n*-BuLi (1.6 M in hexane, 7.5 mL, 11.7 mmol, 1.1 eq.) was added dropwise over 15 minutes, and reaction was stirred at 0 °C for 15 minutes. A solution of cinnamyl alcohol (1.5 mL, 11.1 mmol, 1.05 eq.) in THF (10 mL) was then added dropwise over 25 minutes. The solution was stirred for a further 5 minutes at 0 °C, then a solution of lactone **1.329** (2.0 g, 10.6 mmol, 1 eq.) was added dropwise over 20 minutes at 0 °C. The solution was stirred for a further 15 minutes, then quenched with sat. aq. NH_4Cl. The reaction mixture was allowed to warm to room temperature, and the organic layer was separated off. The aqueous layer was extracted three times with Et_2O, and then the combined organics were washed with aq. 2 M HCl, dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (14:86 EtOAc/petroleum ether [40-60 °C]) afforded the title compound (3.29 g, 96%).

R_f: 0.3 (14:86 EtOAc/petroleum ether [40-60 °C]).

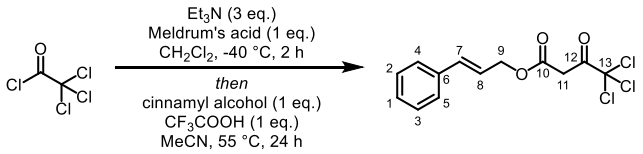
ν_{max} (cm^{-1}) 3415 (br. m), 2361 (m), 1716 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2H, 4, 5), 7.37 – 7.30 (m, 2H, 2, 3), 7.30 – 7.25 (m, 1H, 1), 6.69 (dt, *J* = 16.0, 1.5 Hz, 1H, 7), 6.29 (dt, *J* = 16.0, 6.5 Hz, 1H, 8), 4.83 (dd, *J* = 6.5, 1.5 Hz, 2H, 9), 4.66 (ddd, *J* = 9.5, 5.0, 2.5 Hz, 1H, 12), 3.62 (dd, *J* = 5.0, 1.0 Hz, 1H, 13), 3.13 (ddd, *J* = 16.5, 2.5, 1.0 Hz, 1H, 11'), 2.83 (dd, *J* = 16.5, 9.5 Hz, 1H, 11'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (10), 136.1 (6), 135.1 (7), 128.8 (2, 3), 128.4 (1), 126.8 (4, 5), 122.5 (8), 102.2 (14), 79.5 (12), 66.1 (9), 37.3 (11).

HRMS (ESI^+) $C_{13}H_{13}O_3Cl_3Na^+$ [$(M + Na)^+$] requires [344.9823, 345.9856, 346.9793, 347.9827, 348.9764], found [344.9823, 345.9856, 346.9793, 347.9827, 348.9763].

Cinnamyl 4,4,4-trichloro-3-oxobutanoate, 1.327



According to the procedure reported by Hansen and co-workers, with modifications.[73] To a stirred solution of Meldrum's acid (1.83 g, 12.7 mmol, 1 eq.) and Et_3N (3.5 mL, 25.4 mmol, 2 eq.) in CH_2Cl_2 (60 mL), cooled to -40 °C, was added trichloroacetyl chloride (1.4 mL, 12.7 mmol, 1 eq.) dropwise over 1 h. The reaction was stirred for a further 1.5 h at -40 °C, then allowed to warm to rt and stirred for a further 10 minutes. Cinnamyl alcohol (1.6 mL, 12.7 mmol, 1 eq.) was then added dropwise, followed by a dropwise addition of trifluoroacetic acid (0.97 mL, 12.7 mmol, 1 eq.). The reaction was stirred at rt for 1 h, then stirred at 40 °C for 18.5 h. The reaction was quenched with water, and extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo*. Purification by column chromatography (50% CH_2Cl_2 in petroleum ether [40 – 60 °C]) afforded the title compound (1.77 g, 43%).

R_f: 0.4 (1:1 CH_2Cl_2/petroleum ether [40-60 °C]).

ν_{max} (cm^{-1}) 3028 (w), 1764 (s), 1737 (s), 965 (s).

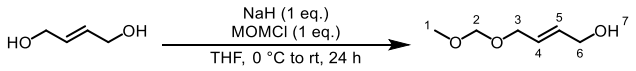
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H, 4, 5), 7.37 – 7.30 (m, 2H, 2, 3), 7.30 – 7.24 (m, 1H, 1), 6.69 (dt, *J* = 16.0, 1.5 Hz, 1H, 7), 6.28 (dt, *J* = 16.0, 6.5 Hz, 1H, 8), 4.85 (dd, *J* = 6.5, 1.5 Hz, 2H, 9), 4.07 (s, 2H, 11).

^{13}C NMR (126 MHz, $CDCl_3$) δ 182.8 (12), 165.2 (10), 136.0 (6), 135.3 (7), 128.8 (2, 3), 128.4 (1), 126.8 (4, 5), 122.1 (8), 95.6 (13), 66.8 (9), 41.0 (11).

m/z (ESI^-) [318.9, 320.9] [$(M - H)^-$].

HRMS (ESI^-) $C_{13}H_{10}O_3Cl_3^-$ [$(M - H)^-$] requires [318.9701, 320.9672, 322.9642], found [318.9702, 320.9672, 322.9641].

(*E*)-4-(Methoxymethoxy)but-2-en-1-ol, 1.348



According to the procedure reported by Forsyth.[76] A solution of (2E)-2-butene-1,4-diol (3.0 mL, 38.9 mmol, 1 eq.) in CH_2Cl_2 was cooled to 0 °C, to which *i*-Pr_2NEt (26 mL, 152 mmol, 3.9 eq.) was added. Chloromethyl methyl ether (3.5 mL, 46.7 mmol, 1.2 eq.) was then added dropwise, and the reaction was allowed to warm to rt. After stirring for 5 h at this temperature, the reaction was quenched with sat. aq. $NaHCO_3$, and extracted with CH_2Cl_2. The combined organics were washed with brine, then dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (0 – 50% EtOAc in *iso*-hexane) afforded the title compound (2.12 g, 41%).

R_f: 0.4 (30% Et_2O in pentane).

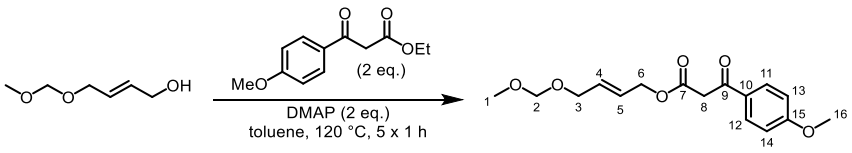
ν_{max} (cm^{-1}): 3402 (m, br.), 2887 (m), 1033 (s).

^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (dtt, *J* = 15.5, 5.0, 1.5 Hz, 1H, 5), 5.82 (dtt, *J* = 15.5, 6.0, 1.5 Hz, 1H, 4), 4.64 (s, 2H, 2), 4.19 – 4.14 (m, 2H, 6), 4.07 (dq, *J* = 6.0, 1.5 Hz, 2H, 3), 3.37 (s, 3H, 1), 1.63 – 1.57 (m, 1H, 7).

^{13}C NMR (126 MHz, $CDCl_3$) δ 132.4 (5), 127.6 (4), 95.8 (2), 67.3 (3), 63.1 (6), 55.4 (1).

No molecular ion could be found for this compound.

(*E*)-4-(Methoxymethoxy)but-2-en-1-yl 3-(4-methoxyphenyl)-3-oxopropanoate, 1.351



Alcohol **1.348** (1.58 g, 12.0 mmol, 1 eq.), ethyl 3-(4-methoxyphenyl)-3-oxopropanoate (4.6 mL, 24.0 mmol, 2 eq.) and DMAP (2.93 g, 24.0 mmol, 2 eq.) were dissolved in toluene (10 mL) in a microwave vial equipped with a stirrer bar. The vial was sealed, and heated to 120 °C with microwave radiation for 1 h. The volatiles were then removed *in vacuo* (50 °C, minimum pressure reached was 40 mbar). An additional 10 mL of toluene was then added, the vial resealed, and reheated. This was repeated 3 more times for a total microwave heating time of 5 h. The reaction was reduced *in vacuo* one final time to yield the crude product. Purification by column chromatography (0 – 40% EtOAc in isohexane) afforded the title compound (2.82 g, 76%).

R_f: 0.3 (20% EtOAc in pentane).

ν_{max} (cm^{-1}): 2939 (w), 1738 (s), 1676 (s), 1600 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H, 11, 12), 6.97 – 6.91 (m, 2H, 13, 14), 5.85 – 5.81 (m, 2H, 4, 5), 4.66 (m, 2H, 6), 4.62 (s, 2H, 2), 4.06 – 4.03 (m, 2H, 3), 3.96 (s, 2H, 8), 3.87 (s, 3H, 16), 3.35 (s, 3H, 1).

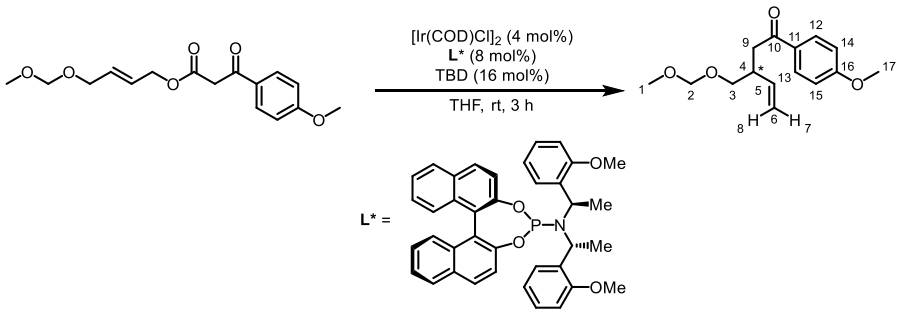
^{13}C NMR (126 MHz, $CDCl_3$) δ 190.8 (9), 167.5 (7), 164.2 (15), 131.1 (5), 131.0 (11, 12), 129.2 (10), 126.2 (4), 114.1 (13, 14), 95.9 (2), 66.9 (3), 65.2 (6), 55.7 (16), 55.4 (1), 45.8 (8).

Low intensity peaks relating to the enol tautomers were also observed, but have not been reported.

m/z (ESI^-) 307 [$(M - H)^-$].

HRMS (ESI^+) $C_{16}H_{21}O_6^+$ [$(M + H)^+$] requires 309.1333, found 309.1330.

3-((Methoxymethoxy)methyl)-1-(4-methoxyphenyl)pent-4-en-1-one, 1.352



According to the procedure reported by Jiang, with modifications.[25] To a sealed vial containing $[Ir(COD)Cl]_2$ (6 mg, 0.009 mmol, 0.04 eq.) and (11b*R*)-N,N-bis((*R*)-1-(2-methoxyphenyl)ethyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-amine **1.281** (11 mg, 0.019 mmol, 0.08 eq.) was added 0.1 mL THF, and the resulting solution was stirred at 20 °C for 10 mins. A solution of triazabicyclodecene (5 mg, 0.037 mmol, 0.16 eq.) in THF (0.2 mL) was added, and the reaction was stirred for precisely 5 minutes before a solution of ketone **1.351** (69 mg, 0.225 mmol, 1 eq.) in THF (0.4 mL) was added. The reaction was allowed to stir for 3 h at 20 °C, then transferred to a round bottomed flask (using EtOAc to wash the vial repeatedly), and reduced *in vacuo* to give the crude product. Purification by column chromatography (10% EtOAc in pentane) afforded the title compound (46 mg, 78%).

R_f: 0.4 (10% EtOAc in pentane).

ν_{max} (cm^{-1}): 2934 (w), 2362 (w), 1674 (s), 1641 (s).

^1H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 2H, 12, 13), 6.97 – 6.89 (m, 2H, 14, 15), 5.84 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1H, 5), 5.11 (dt, *J* = 17.5, 1.5 Hz, 1H, 8), 5.07 (dt, *J* = 10.5, 1.5 Hz, 1H, 7), 4.61 (s, 2H, 2), 3.87 (s, 3H, 17), 3.60 (dd, *J* = 9.5, 5.5 Hz, 1H, 3'), 3.55 (dd, *J* = 9.5, 6.0 Hz, 1H, 3''), 3.33 (s, 3H, 1), 3.17 (dd, *J* = 16.0, 6.0 Hz, 1H, 9'), 3.10 (ddddd, *J* = 7.5, 7.0, 6.0, 6.0, 5.5 Hz, 1H, 4), 2.97 (dd, *J* = 16.0, 7.0 Hz, 1H, 9'').

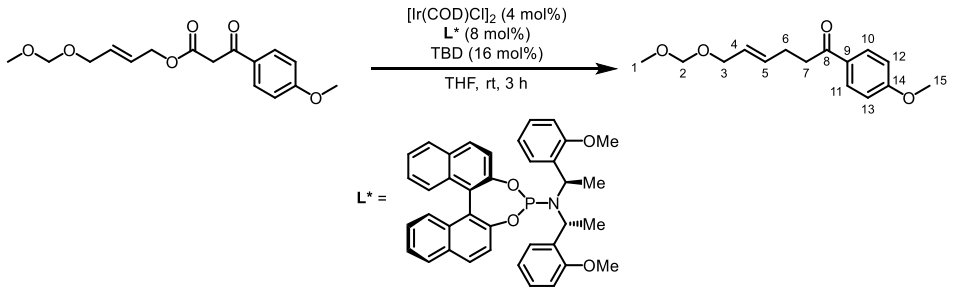
^{13}C NMR (126 MHz, $CDCl_3$) δ 197.6 (10), 163.5 (16), 138.8 (5), 130.5 (12, 13), 130.5 (11), 116.0 (6), 113.8 (14, 15), 96.7 (2), 70.5 (3), 55.6 (17), 55.4 (1), 39.9 (9), 39.6 (4).

m/z (ESI^+) 287.1 [$(M + Na)^+$].

HRMS (ESI^+) $C_{15}H_{20}O_4Na^+$ [$(M + Na)^+$] requires 287.1254, found 287.1254.

ee: >99% [Chiralcel® OB column (4.6 mm x 250 mm), 2% 2-propanol in *n*-hexane, flow rate 1 mL min^{-1}, detection wavelength = 250 nm; t_R(*R*) = 27.68 min; t_S(*S*) = 38.46 min.

(*E*)-6-(Methoxymethoxy)-1-(4-methoxyphenyl)hex-4-en-1-one, 1.353



The title compound was obtained as a side product from the above reaction, and was isolated during the above purification (3 mg, 5%).

R_f: 0.2 (10% EtOAc in pentane).

ν_{max} (cm^{-1}): 2935 (m), 2361 (w), 1676 (s), 1600 (s).

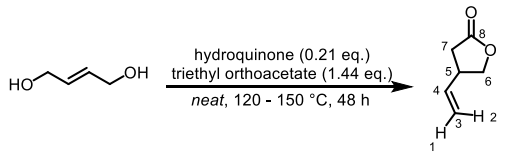
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.89 (m, 2H, 10, 11), 6.98 – 6.88 (m, 2H, 12, 13), 5.82 (m, 1H, 5), 5.65 (dtt, *J* = 15.5, 6.5, 1.5 Hz, 1H, 4), 4.63 (s, 2H, 2), 4.01 (dd, *J* = 6.5, 1.0 Hz, 2H, 3), 3.87 (s, 3H, 15), 3.36 (s, 3H, 1), 3.03 (t, *J* = 7.5 Hz, 2H, 7), 2.49 (tdd, *J* = 7.5, 6.5, 1.5 Hz, 2H, 6).

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0 (8), 163.6 (14), 133.5 (5), 130.4 (10, 11), 130.1 (9), 126.9 (4), 113.9 (12, 13), 95.7 (2), 68.0 (3), 55.6 (15), 55.4 (1), 37.7 (7), 27.1 (6).

m/z (ESI^+) 287.0 [$(M + Na)^+$].

HRMS (ESI^+) $C_{15}H_{20}O_4Na^+$ [$(M + Na)^+$] requires 287.1254, found 287.1255.

4-Vinyldihydrofuran-2(3*H*)-one, 1.354



According to the procedure reported by von Kieseritzky *et al*.[78] 2-Butene-1,4-diol (2 g, 22.7 mmol, 1 eq.), triethyl orthoacetate (6 mL, 32.7 mmol, 1.44 eq.) and hydroquinone (525 mg, 4.77 mmol, 0.21 eq.) were taken in a round bottom flask, equipped with a 5 cm Vigreux column that was connected to a thermometer, condenser, and collection flask. The reaction was placed under a nitrogen atmosphere, and heated to 120 °C. During this time, EtOH was observed to distil across from the reaction vessel to the collection flask (temperature recorded by thermometer was 78 °C; a ^{1}H NMR of the contents of the collection flask was found to contain EtOH along with a small quantity of triethyl orthoacetate). Once distillation of EtOH ceased, the distillation apparatus was exchanged for a reflux condenser, and the reaction was heated to 150 °C for 48 h. The reaction was then allowed to cool to room temperature, and reduced *in vacuo* to give the crude product. Purification by column chromatography (0 – 25% EtOAc in iso-hexane) afforded the title compound (2.02 g, 80%).

R_f: 0.2 (25% EtOAc in petroleum ether [40 – 60 °C]).

ν_{max} (cm^{-1}) 2986 (w), 1775 (s), 1168 (s).

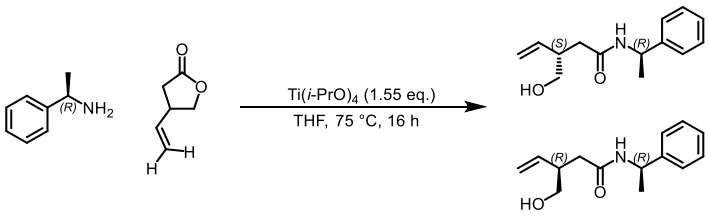
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 17.0, 10.5, 7.5 Hz, 1H, 4), 5.21 – 5.13 (m, 2H, 1, 2), 4.42 (dd, *J* = 9.0, 7.5 Hz, 1H, 6'), 4.00 (dd, *J* = 9.0, 7.5 Hz, 1H, 6''), 3.26 – 3.16 (m, 1H, 5), 2.65 (dd, *J* = 17.5, 8.5 Hz, 1H, 7'), 2.37 (dd, *J* = 17.5, 8.5 Hz, 1H, 7'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.6 (8), 135.9 (4), 117.6 (3), 72.3 (6), 39.9 (5), 34.2 (7).

HRMS (ESI$^+$) $C_6H_9O_2^+$ [(M + H)$^+$] requires 113.0597, found 113.0595.

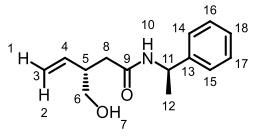
Data in accordance with that reported by Hammerschmidt and co-workers.[161]

(*S*)-3-(Hydroxymethyl)-*N*-((*R*)-1-phenylethyl)pent-4-enamide, 1.360
and (*R*)-3-(Hydroxymethyl)-*N*-((*R*)-1-phenylethyl)pent-4-enamide, 1.358



According to the procedure reported by von Kieseritzky *et al*.[78] A solution of lactone **1.354** (1.75 g, 15.6 mmol, 1 eq.), (*R*)-1-α-benzylmethylamine (2.0 mL, 15.6 mmol, 1 eq.) and titanium (IV) isopropoxide (7.25 mL, 24.2 mmol, 1.55 eq.) in THF (3.5 mL) was placed under a nitrogen atmosphere, and heated to 75 °C for 16 h. The reaction mixture was then allowed to cool to room temperature, and quenched with 2 M $HCl_{(aq)}$. The resulting mixture was stirred at room temperature for 1 h, then transferred to a separating funnel and extracted with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo*. A combination of two rounds of column chromatography was sufficient to yield (*R,S*) in purity >95:5 *d.r.*, and the other (*R,R*) diastereomer could be recrystallized from the enriched mixture that resulted from the two rounds of chromatography using hot TBME and cooling slowly over 4 h. The two compounds were characterised separately, detailed below.

(S)-3-(Hydroxymethyl)-N-((R)-1-phenylethyl)pent-4-enamide, 1.360



R_f: 0.15 (EtOAc).

$[\alpha]_D$ (25 °C) +88.6 (c = 1.0, $CHCl_3$)

ν_{max} (cm^{-1}) 3283 (br. m.), 1638 (s), 1542 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 4H, 14, 15, 16, 17), 7.27 – 7.22 (m, 1H, 18), 6.13 (d, *J* = 8.0 Hz, 1H, 10), 5.78 – 5.67 (m, 1H, 4), 5.16 – 5.05 (m, 3H, 1, 2, 11), 3.58 (dd, *J* = 11.0, 5.5 Hz, 1H, 6'), 3.53 (dd, *J* = 11.0, 6.5 Hz, 1H, 6''), 2.95 (s, 1H, 7), 2.71 (ddddd, *J* = 7.5, 7.0, 6.5, 6.5, 5.5 Hz, 1H, 5), 2.37 (dd, *J* = 14.5, 7.0 Hz, 1H, 8'), 2.29 (dd, *J* = 14.5, 6.5 Hz, 1H, 8''), 1.46 (d, *J* = 7.0 Hz, 3H, 12).

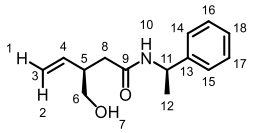
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (9), 143.1 (13), 138.2 (4), 128.8 (16, 17), 127.5 (18), 126.3 (14, 15), 116.8 (3), 65.5 (6), 49.0 (11), 43.0 (5), 39.0 (8), 21.9 (12).

m/z (ESI^+) 256.1 [$(M + Na)^+$].

HRMS (ESI^+) $C_{14}H_{19}O_2NNa^+$ [$(M + Na)^+$] requires 256.1308, found 256.1306.

Data in accordance to that reported in the literature.[161]

(R)-3-(Hydroxymethyl)-N-((R)-1-phenylethyl)pent-4-enamide, 1.358



R_f: 0.20 (EtOAc).

m.p. 98.0 – 101.6 °C

$[\alpha]_D$ (25 °C) +82.5 (c = 1.0, $CHCl_3$)

ν_{max} (cm^{-1}) 3308 (br. s), 2360 (w), 1639 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 4H, 14, 15, 16, 17), 7.27 – 7.22 (m, 1H, 18), 6.19 (d, *J* = 8.0 Hz, 1H, 10), 5.72 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H, 4), 5.14 – 5.02 (m, 3H, 1, 2, 11), 3.61 (dd, *J* = 11.0, 5.5 Hz, 1H, 6'), 3.55 (dd, *J* = 11.0, 6.5 Hz, 1H, 6''), 3.09 (s, 1H, 7), 2.70

(ddddd, *J* = 7.5, 7.5, 6.5, 6.0, 5.5 Hz, 1H, 5), 2.38 (dd, *J* = 14.5, 7.5 Hz, 1H, 8'), 2.28 (dd, *J* = 14.5, 6.0 Hz, 1H, 8''), 1.46 (d, *J* = 7.0 Hz, 3H, 12).

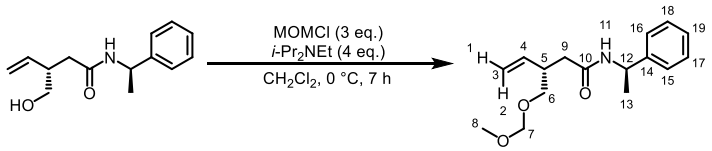
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4 (9), 143.1 (13), 138.2 (4), 128.7 (16, 17), 127.5 (18), 126.3 (14, 15), 116.8 (3), 65.4 (6), 49.0 (11), 42.9 (5), 38.9 (8), 21.8 (12).

m/z (ESI^+) 256.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{14}H_{19}O_2NNa^+$ [$(M + Na)^+$] requires 256.1308, found 256.1305.

Data in accordance to that reported in the literature.[161]

(*S*)-3-((Methoxymethoxy)methyl)-*N*-((*R*)-1-phenylethyl)pent-4-enamide, 1.373



According to the procedure reported by Forsyth and co-workers, with modifications.[76] A solution of alcohol **1.360** (3.48 g, 14.9 mmol, 1 eq.) in CH_2Cl_2 (32 mL) was cooled to 0 °C. Diisopropylethylamine (10 mL, 59.6 mmol, 4 eq.) was then added, followed by chloromethyl methyl ether (2.25 mL, 29.8 mmol, 2 eq.). The reaction was stirred for 4 h at 0 °C, then an additional quantity of chloromethyl methyl ether (1.1 mL, 14.9 mmol, 1 eq.) was added, and the reaction stirred for a further 3 h at 0 °C. The reaction was allowed to warm to room temperature, and quenched with sat. aq. $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2, and the combined organics dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (0 – 25% EtOAc in petroleum ether [40-60 °C]) afforded the title compound (3.44 g, 83%).

R_f: 0.1 (40% EtOAc in petroleum ether [40 – 60 °C]).

$[\alpha]_D$ (25 °C) +80.1 (c = 1.0, $CHCl_3$)

ν_{max} (cm^{-1}) 3286 (br. w), 2930 (w), 2360 (w), 1638 (s).

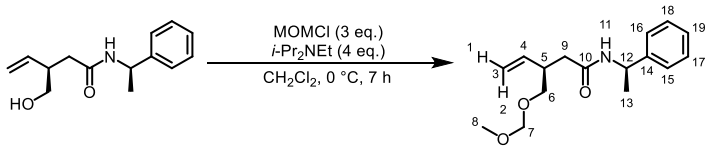
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 4H, 15, 16, 17, 18), 7.30 – 7.21 (m, 1H, 19), 5.91 (d, *J* = 8.0 Hz, 1H, 11), 5.77 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1H, 4), 5.18 – 5.06 (m, 3H, 1, 2, 12), 4.53 (d, *J* = 6.5 Hz, 1H, 7'), 4.52 (d, *J* = 6.5 Hz, 1H, 7''), 3.53 – 3.44 (m, 2H, 6), 3.29 (s, 3H, 8), 2.90 – 2.79 (m, 1H, 5), 2.40 (dd, *J* = 14.0, 6.5 Hz, 1H, 9'), 2.22 (dd, *J* = 14.0, 8.0 Hz, 1H, 9''), 1.46 (d, *J* = 7.0 Hz, 3H, 13).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5 (10), 143.3 (14), 138.5 (4), 128.7 (17, 18), 127.5 (19), 126.3 (15, 16), 116.4 (3), 96.6 (7), 70.3 (6), 55.4 (8), 48.8 (12), 40.8 (5), 38.9 (9), 21.8 (13).

m/z (ESI^+) 300.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{16}H_{24}O_3N^+$ [$(M + H)^+$] requires 278.1751, found 278.1749.

(*R*)-3-((Methoxymethoxy)methyl)-*N*-((R)-1-phenylethyl)pent-4-enamide, 1.359



According to the procedure reported by Forsyth and co-workers, with modifications.[76] A solution of alcohol **1.358** (5 g, 21.4 mmol, 1 eq.) in CH_2Cl_2 (47 mL) was cooled to 0 °C. Diisopropylethylamine (15 mL, 86 mmol, 4 eq.) was then added, followed by chloromethyl methyl ether (3.5 mL, 42.8 mmol, 2 eq.). The reaction was stirred for 4 h at 0 °C, then an additional quantity of chloromethyl methyl ether (1.8 mL, 21.4 mmol, 1 eq.) was added, and the reaction stirred for a further 3 h at 0 °C. The reaction was allowed to warm to room temperature, and quenched with sat. aq. $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2, and the combined organics dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (0 – 25% EtOAc in petroleum ether [40-60 °C]) afforded the title compound (5.84 g, 98%).

R_f: 0.1 (40% EtOAc in petroleum ether [40 – 60 °C]).

$[\alpha]_D$ (25 °C) +72.2 (c = 1.0, $CHCl_3$)

ν_{max} (cm^{-1}) 3285 (br. w), 2930 (w), 1638 (s), 1542 (s).

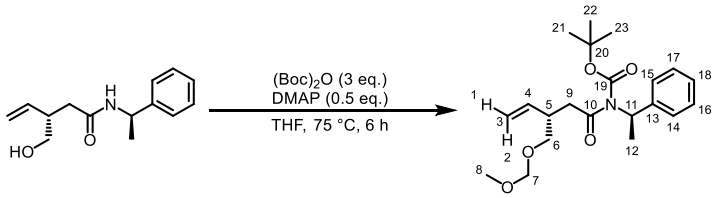
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 4H, 15, 16, 17, 18), 7.27 – 7.22 (m, 1H, 19), 5.94 (d, *J* = 8.0 Hz, 1H, 11), 5.76 (ddd, *J* = 17.5, 10.5, 8.0 Hz, 1H, 4), 5.17 – 5.03 (m, 3H, 1, 2, 12), 4.59 (d, *J* = 6.5 Hz, 1H, 7'), 4.58 (d, *J* = 6.5 Hz, 1H, 7''), 3.54 (dd, *J* = 9.5, 5.5 Hz, 1H, 6'), 3.49 (dd, *J* = 9.5, 6.0 Hz, 1H, 6''), 3.33 (s, 3H, 8), 2.84 (ddddd, *J* = 8.0, 7.5, 6.5, 6.0, 5.5, 1H, 5), 2.41 (dd, *J* = 14.5, 6.5 Hz, 1H, 9'), 2.22 (dd, *J* = 14.5, 7.5 Hz, 1H, 9''), 1.47 (d, *J* = 7.0 Hz, 3H, 13).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6 (10), 143.2 (14), 138.4 (4), 128.7 (17, 18), 127.4 (19), 126.3 (15, 16), 116.5 (3), 96.7 (7), 70.4 (6), 55.4 (8), 48.7 (12), 40.8 (5), 38.9 (9), 21.7 (13).

m/z (ESI^+) 300.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{16}H_{23}O_3NNa^+$ [$(M + Na)^+$] requires 300.1570, found 300.1573.

***tert*-Butyl ((*S*)-3-((methoxymethoxy)methyl)pent-4-enoyl)((*R*)-1-phenylethyl)carbamate, 1.374**



According to the procedure reported by Gin and co-workers, with modifications.[162] To a solution of the amide **1.373** (871 mg, 3.14 mmol, 1 eq.) in THF (30 mL) was added di-tert-butyl dicarbonate (2.05 g, 9.42 mmol, 3 eq.) and dimethylaminopyridine (192 mg, 1.57 mmol, 0.5 eq.). The resulting solution was heated to 75 °C for 6 h, before the reation was allowed to cool to room temperature, and reduced *in vacuo* to give the crude product. Purification by column chromatography (20% EtOAc in petroleum ether [40-60 °C]), followed by reduction *in vacuo* (25 °C, 0.5 mbar, to remove remaining unreacted di-tert-butyl dicarbonate) afforded the title compound (1.108 g, 93%).

R_f: 0.5 (20% EtOAc in petroleum ether [40 – 60 °C]).

$[\alpha]_D$ (25 °C) +76.0 (c = 1.0, $CHCl_3$)

ν_{max} (cm^{-1}) 2979 (w), 2361 (w), 1729 (s), 1687 (s).

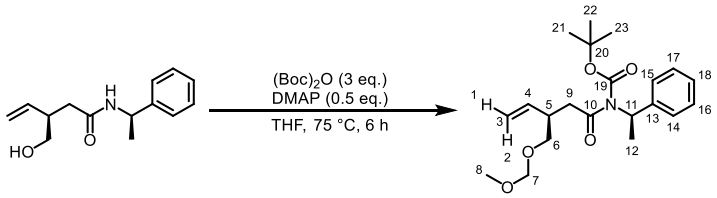
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H, 16, 17), 7.27 – 7.23 (m, 2H, 14, 15), 7.23 – 7.19 (m, 1H, 18), 6.02 (q, *J* = 7.0 Hz, 1H, 11), 5.80 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1H, 4), 5.14 (dt, *J* = 17.5, 1.5 Hz, 1H, 2), 5.09 (ddd, *J* = 10.5, 1.5, 1.0 Hz, 1H, 1), 4.62 (s, 2H, 7), 3.58 (dd, *J* = 9.5, 6.0 Hz, 1H, 6'), 3.53 (dd, *J* = 9.5, 6.5 Hz, 1H, 6''), 3.36 (s, 3H, 8), 3.14 – 2.99 (m, 2H, 5, 9'), 2.91 (dd, *J* = 15.5, 8.0 Hz, 1H, 9''), 1.64 (d, *J* = 7.0 Hz, 3H, 12), 1.15 (s, 9H, 21, 22, 23).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5 (10), 153.5 (19), 141.9 (13), 138.8 (4), 128.2 (16, 17), 126.8 (18), 126.5 (14, 15), 116.1 (3), 96.6 (7), 83.1 (20), 70.6 (6), 55.4 (8), 51.3 (11), 40.7 (5), 39.9 (9), 27.6 (21, 22, 23), 17.3 (12).

m/z (ESI^+) 400.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{21}H_{31}O_5NNa^+$ [$(M + Na)^+$] requires 400.2094, found 400.2091.

***tert*-Butyl ((*R*)-3-((methoxymethoxy)methyl)pent-4-enoyl)((*R*)-1-phenylethyl)carbamate, 1.372**



An analogous procedure to that used above for the synthesis of **1.374** was used, requiring amide **1.359** (5.79 g, 20.9 mmol, 1 eq.) to give **1.372** (7.19 g, 91%).

R_f: 0.4 (20% EtOAc in petroleum ether [40 – 60 °C]).

$[\alpha]_D$ (25 °C) +78.8 (c = 1.0, $CHCl_3$)

ν_{max} (cm^{-1}): 2979 (w), 2360 (w), 1729 (s), 1687 (s).

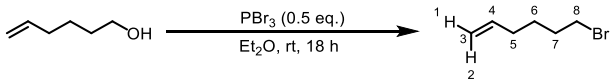
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H, 16, 17), 7.26 – 7.17 (m, 3H, 14, 15, 18), 6.00 (q, *J* = 7.0 Hz, 1H, 11), 5.84 (ddd, *J* = 17.5, 10.5, 7.5 Hz, 1H, 4), 5.17 (d, *J* = 17.5 Hz, 1H, 2), 5.11 (dd, *J* = 10.5, 1.5 Hz, 1H, 1), 4.62 (d, *J* = 7.0 Hz, 1H, 7'), 4.60 (d, *J* = 7.0 Hz, 1H, 7''), 3.57 (dd, *J* = 9.5, 5.5 Hz, 1H, 6'), 3.50 (dd, *J* = 9.5, 6.0 Hz, 1H, 6''), 3.35 (s, 3H, 8), 3.11 – 2.94 (m, 3H, 5, 9), 1.64 (d, *J* = 7.0 Hz, 3H, 12), 1.15 (s, 9H, 21, 22, 23).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4 (10), 153.5 (19), 141.9 (13), 138.9 (4), 128.2 (16, 17), 126.7 (18), 126.5 (14, 15), 116.1 (3), 96.6 (7), 83.0 (20), 70.5 (6), 55.3 (8), 51.3 (11), 40.5 (5), 39.8 (9), 27.6 (21, 22, 23), 17.2 (12).

m/z (ESI^+) 400.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{21}H_{31}O_5NNa^+$ [$(M + Na)^+$] requires 400.2094, found 400.2093.

6-Bromohex-1-ene, 2.126



According to the procedure reported by Murphy and co-workers.[163] Hex-5-en-1-ol (2.40 mL, 20 mmol, 1 eq.) was dissolved in dry Et_2O (20 mL) and cooled to 0 °C, whereupon PBr_3 (0.94 mL, 10 mmol, 0.5 eq.) was added dropwise, while maintaining the temperature below 0 °C. The reaction was allowed to warm to room temperature, and was stirred for 18 h, by which time a colour change to orange was observed. The reaction mixture was quenched slowly with ice water, extracted with Et_2O, washed with H_2O and brine; drying over Na_2SO_4, filtration and concentration *in vacuo* yielded the crude product. Flash chromatography with petroleum ether (30-40 °C) yielded the title compound (1.54 g, 47 %).

R_f 0.6 (petroleum ether [30-40 °C]).

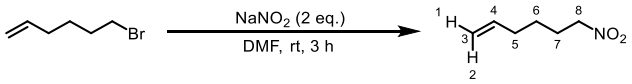
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 4), 5.02 (dq, *J* = 17.0, 1.5 Hz, 1H, 2), 4.97 (dq, *J* = 10.0, 1.5 Hz, 1H, 1), 3.41 (t, *J* = 7.0 Hz, 2H, 8), 2.16 – 2.01 (m, 2H, 5), 1.97 – 1.81 (m, 2H, 7), 1.60 – 1.47 (m, 2H, 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (4), 115.1 (3), 33.9 (8), 32.9 (5), 32.3 (7), 27.5 (6).

m/z (FI) 162.0043 (M), 164.0043 (M).

Data in accordance with that found in the literature.[164]

6-Nitrohex-1-ene, 2.124



According to the procedure reported by Parsons and co-workers.[165] To a stirred solution of sodium nitrite (0.93 g, 13.5 mmol, 2 eq.) in DMF (1.6 mL) was added **2.126** (1.10 g, 6.75 mmol, 1 eq.) and the reaction was stirred at room temperature for 3 h. The reaction mixture was quenched with acidic ice water (pH = 2), and extracted with Et_2O; the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* at 25 °C to yield the crude product. Purification was achieved by column chromatography (5% Et_2O in petroleum ether [40-60 °C]) to afford the title compound (0.380 g, 44%).

R_f 0.4 (5% Et_2O in petroleum ether [30-40 °C]).

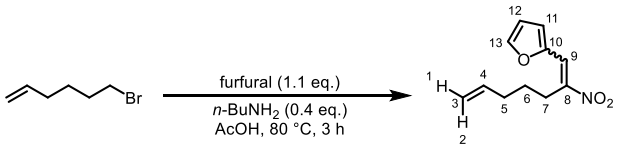
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H, 4), 5.02 (m, 2H, 1, 2), 4.39 (t, *J* = 7.0 Hz, 2H, 8), 2.11 (qt, *J* = 7.0, 1.0 Hz, 2H, 5), 2.02 (m, 2H, 7), 1.49 (m, 2H, 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5 (4), 115.7 (3), 75.7 (8), 33.0 (5), 26.9 (7), 25.5 (6).

m/z (FI) 129.0790 (M).

Data in accordance with that found in the literature. [165]

2-(2-Nitrohepta-1,6-dien-1-yl)furan, 2.123



According to the procedure reported by Rezende and co-workers, with modifications.[166] A solution of **2.124** (350 mg, 2.71 mmol, 1 eq.), *n*-butylamine (0.11 mL, 1.08 mmol, 0.4 eq.) and furfural (0.25 mL, 2.98 mmol, 1.1 eq.) in AcOH (0.5 mL) under N_2 was heated at 80 °C for 3 h. The reaction mixture was allowed to cool, then quenched with H_2O; this was extracted with EtOAc, washed with brine, then dried over Na_2SO_4, filtered and reduced *in vacuo* to yield the crude product. Purification by column chromatography (2% Et_2O in pentane) afforded the title compound (280 mg, 50%).

R_f 0.3 (2% Et_2O in pentane).

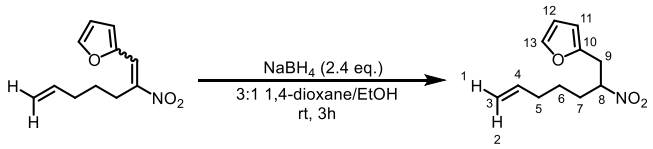
ν_{max} (cm^{-1}) 1646 (m), 1508 (s), 1302 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H, 9), 7.63 (d, *J* = 2.0 Hz, 1H, 13), 6.82 (d, *J* = 3.5 Hz, 1H, 11), 6.58 (dd, *J* = 3.5, 2.0 Hz, 1H, 12), 5.84 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 4), 5.05 (dq, *J* = 17.0, 1.5 Hz, 1H, 2), 5.00 (dq, *J* = 10.0, 1.5 Hz, 1H, 1), 3.05 (t, *J* = 7.5 Hz, 2H, 7), 2.18 (tdt, *J* = 7.5, 6.5, 1.5 Hz, 2H, 5), 1.71 (p, *J* = 7.5 Hz, 2H, 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7 (8), 148.0 (10), 146.4 (13), 138.0 (4), 120.7 (9), 119.5 (11), 115.3 (3), 113.1 (12), 33.5 (5), 27.2 (7), 27.2 (6).

m/z (FI) 207.0893 (M).

2-(2-Nitrohept-6-en-1-yl)furan, 2.116



According to the procedure reported by Wang and co-workers, with modifications.[167] An oven-dried round bottomed flask was charged with $NaBH_4$ (110 mg, 2.90 mmol, 2.4 eq.), 1,4-dioxane (7.5 mL) and EtOH (2.5 mL), and cooled to 0 °C. A solution of **2.123** (250 mg, 1.21 mmol, 1 eq.) in 1,4-dioxane (2.5 mL) was then added dropwise over 20 min at 0 °C. The reaction was then stirred at this temperature for a further 1 h. The reaction mixture was quenched with NH_4Cl (sat. aq.) and allowed to warm to rt; this was extracted with EtOAc, and the combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude compound. Purification by column chromatography (2% Et_2O in pentane) yielded the title compound (230 mg, 91%).

R_f 0.6 (4% Et_2O in pentane).

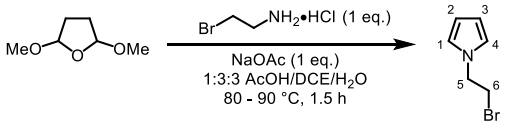
ν_{max} (cm^{-1}) 1549 (s), 1365 (w), 1147 (w).

^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 2.0, 1.0 Hz, 1H, 13), 6.29 (dd, *J* = 3.0, 2.0 Hz, 1H, 12), 6.11 (dd, *J* = 3.0, 1.0 Hz, 1H, 11), 5.73 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 4), 5.06 – 4.94 (m, 2H, 1, 2), 4.77 (dddd, *J* = 10.0, 8.5, 5.5, 4.5 Hz, 1H, 8), 3.33 (dd, *J* = 15.5, 8.5 Hz, 1H, 9'), 3.07 (dd, *J* = 15.5, 5.5 Hz, 1H, 9''), 2.16 – 1.94 (m, 3H, 5, 7'), 1.86 – 1.72 (m, 1H, 7''), 1.45 (p, *J* = 7.5 Hz, 2H, 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5 (10), 142.4 (13), 137.4 (4), 115.7 (3), 110.6 (12), 108.0 (11), 87.1 (8), 32.9 (5), 32.8 (7), 32.5 (9), 24.9 (6).

m/z (FI) 209.1052 (M).

1-(2-Bromoethyl)-1*H*-pyrrole, 2.139



According to the procedure reported by Rodin.[147] 2-bromoethylamine hydrochloride (5 g, 24.4 mmol, 1 eq.), NaOAc (2g, 24.4 mmol, 1 eq.), H_2O (30 mL), AcOH (10 mL) and CH_2Cl_2 (30 mL) were added to a round bottomed flask with a reflux condensor attached. The reaction mixture was heated to 80 °C and 2,5-dimethoxytetrahydrofuran (3.22 g, 24.4 mmol, 1 eq.) was added; the temperature was then increased to 90 °C and stirred for 1.5 h. The reaction mixture was allowed to cool, and was extracted with CH_2Cl_2; the combined organics were dried (Na_2SO_4), filtered and reduced in vacuo to yield the crude product. Purification by column chromatography (10% Et_2O in petroleum ether [30-40 °C]) afforded the title compound (3.54g, 84%).

R_f 0.5 (10% Et_2O in petroleum ether [30-40 °C]).

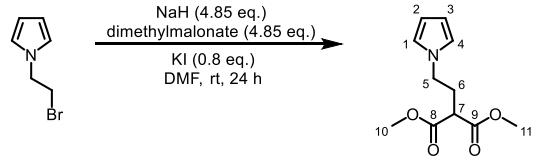
ν_{max} (cm^{-1}) 1497 (m), 1282 (m), 1089 (m), 720 (s).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (t, *J* = 2.0 Hz, 2H, 1, 4), 6.19 (t, *J* = 2.0 Hz, 2H, 2, 3), 4.28 (t, *J* = 7.0 Hz, 2H, 5), 3.59 (t, *J* = 7.0 Hz, 2H, 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 120.8 (1, 4), 108.9 (2, 3), 51.1 (5), 31.2 (6).

m/z (FI) 172.9838 (M), 174.9816 (M).

Dimethyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 2.140



According to the procedure reported by Rodin.[147] NaH (60% dispersion in oil, 3.79 g, 94.8 mmol, 4.85 eq.) was dissolved in DMF (80 mL) and the solution was cooled to 0 °C. Dimethyl malonate (10.8 mL, 94.8 mmol, 4.85 eq.) was added dropwise with stirring, followed by **2.139** (3.4 g, 19.5 mmol, 1eq.). Potassium iodide (2.62 g, 15.8 mmol, 0.8 eq.) was added, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched slowly with NH_4Cl (sat. aq.) and extracted with EtOAc; the combined organics were washed with brine, dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Vacuum distillation was used to remove the excess dimethylmalonate (38 °C, 0.5 mmHg), and the remaining liquid was purified from remaining impurities by column chromatography (10% acetone in pentane) to afford the title compound (3.08 g, 70%).

R_f 0.3 (28% Et_2O in petroleum ether [30-40 °C]).

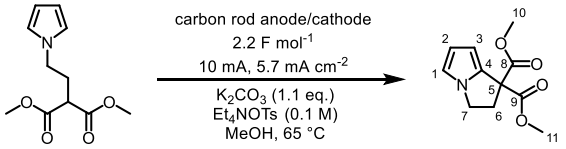
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (t, *J* = 2.0 Hz, 2H, 1, 4), 6.15 (t, *J* = 2.0 Hz, 2H, 2, 3), 3.97 (t, *J* = 7.0 Hz, 2H, 5), 3.74 (s, 6H, 10, 11), 3.28 (t, *J* = 7.5 Hz, 1H, 7), 2.35 (dt, *J* = 7.5, 7.0 Hz, 2H, 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (8, 9), 120.7 (1, 4), 108.6 (2, 3), 52.8 (10, 11), 48.7 (7), 46.9 (5), 30.8 (6).

m/z (ESI^+) 264.1 [$(M + K)^+$], 248.1 [$(M + Na)^+$], 226.1 [$(M + H)^+$].

HRMS (ESI^+) $C_{11}H_{15}NO_4Na$ [$(M + Na)^+$] requires 248.0893, found 248.0893.

Dimethyl 2,3-dihydro-1*H*-pyrrolizine-1,1-dicarboxylate, 2.141



An oven-dried three-necked round bottomed flask was sealed, evacuated and backfilled with N_2 three times, then placed under an atmosphere of argon. Potassium carbonate (135 mg, 0.977 mmol, 1.1 eq.), Et_4NOTs (362 mg), **2.140** (200 mg, 0.888 mmol, 1 eq.) and dry MeOH (12 mL) were added, a reflux condenser was attached, and Ar was bubbled through the reaction mixture for 10 min. Carbon rod electrodes attached to a power supply (Keithley 2200-72-1 Programmable Power Supply) were immersed into the reaction mixture, to a depth of 1 cm for the anode and 2 cm for the cathode. The reaction mixture was heated to 65 °C, and current was passed at 10 mA for 314 min to give a total amount of charge passed equal to 2.2 F/mol. The reaction mixture was allowed to cool to room temperature, and reduced *in vacuo.* The resulting solid was re-dissolved in H_2O, and this solution was extracted with Et_2O; the combined organics were washed with brine, then reduced *in vacuo* to give the crude product. Purification by column chromatography (30% Et_2O in petroleum ether [30-40 °C]) afforded the title compound (52 mg, 26%).

This compound was also synthesised using the following method:

To a solution of malonate **2.140** (50 mg, 0.222 mmol, 1 eq.) in MeOH (1 mL) was added $Mn(OAc)_3 \bullet 2H_2O$ (178 mg, 0.666 mmol, 3 eq.). The resulting mixture was heated to 65 °C for 3.5 h. The solvent was then removed *in vacuo*, and then partitioned between brine and EtOAc. The organic layer was separated off, and the aqueous layer repeatedly extracted with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo* to

give the crude product. Purification by column chromatography afforded the title compound (40 mg, 80%).

R_f 0.3 (30% Et_2O in petroleum ether [30-40 °C]).

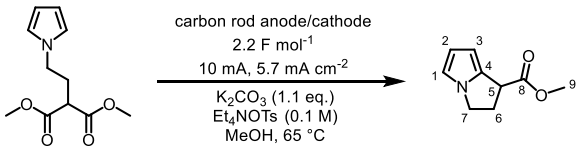
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (dd, *J* = 2.5, 1.5 Hz, 1H, 1), 6.26 (dd, *J* = 3.5, 2.5 Hz, 1H, 2), 6.15 (dd, *J* = 3.5, 1.5 Hz, 1H, 3), 4.08 (t, *J* = 7.0 Hz, 2H, 7), 3.77 (s, 6H, 10, 11), 3.06 (t, *J* = 7.0 Hz, 2H, 6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1 (8, 9), 132.2 (4), 115.3 (1), 113.2 (2), 103.1 (3), 58.6 (5), 53.3 (10, 11), 45.0 (7), 37.1 (6).

m/z (ESI^+) 469.2 [$(2M + Na)^+$], 246.1 [$(M + Na)^+$], 224.1 [$(M + H)^+$].

HRMS (ESI^+) $C_{11}H_{13}NO_4Na$ [$(M + Na)^+$] requires 246.0737, found 246.0736.

Methyl 2,3-dihydro-1*H*-pyrrolizine-1-carboxylate, 2.141



Title compound isolated as a side product in the above electrochemical reaction (see chapter 2, table 2.3, 32 mg, 22%).

R_f 0.5 (30% Et_2O in petroleum ether [30-40 °C]).

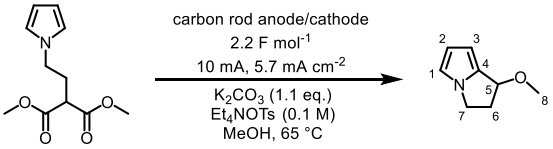
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (dd, *J* = 2.5, 1.5 Hz, 1H, 1), 6.23 (dd, *J* = 3.5, 2.5 Hz, 1H, 2), 5.97 (ddd, *J* = 3.5, 1.5, 0.5 Hz, 1H, 3), 4.12 (ddd, *J* = 10.0, 8.0, 6.0 Hz, 1H, 7''), 4.02 (ddd, *J* = 8.5, 5.0, 0.5 Hz, 1H, 5), 3.96 (ddd, *J* = 10.0, 8.5, 5.5 Hz, 1H, 7'), 2.87 (dddd, *J* = 13.0, 8.0, 5.5, 5.0 Hz, 1H, 6'), 2.72 (dddd, *J* = 13.0, 8.5, 8.5, 6.0 Hz, 1H, 6'').

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9 (8), 133.8 (4), 114.7 (1), 112.8 (2), 100.8 (3), 52.4 (9), 45.6 (7), 42.3 (5), 31.6 (6).

m/z (ESI^+) 204.1 [$(M + K)^+$], 188.1 [$(M + Na)^+$], 166.1 [$(M + H)^+$].

HRMS (ESI^+) $C_9H_{11}NO_2Na$ [$(M + Na)^+$] requires 188.0682, found 188.0682.

1-Methoxy-2,3-dihydro-1*H*-pyrrolizine, 2.143



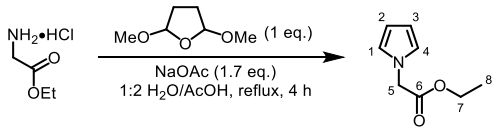
Title compound isolated as a side product in the above reaction (see chapter 2, table 2.3, 16 mg, 8%).

R_f 0.5 (30% Et_2O in petroleum ether [30-40 °C]).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (dd, *J* = 2.5, 1.0 Hz, 1H, 1), 6.25 (dd, *J* = 3.5, 2.5 Hz, 1H, 2), 6.10 (dd, *J* = 3.5, 1.0 Hz, 1H, 3), 4.68 (dd, *J* = 6.5, 1.5 Hz, 1H, 5), 4.14 (ddd, *J* = 10.5, 8.0, 7.0 Hz, 1H, 7'), 3.92 (ddd, *J* = 10.5, 9.0, 2.5 Hz, 1H, 7''), 3.35 (s, 3H, 8), 2.76 (dtd, *J* = 13.5, 9.0, 8.0, 6.5 Hz, 1H, 6'), 2.51 (ddt, *J* = 13.5, 7.0, 2.5, 1.5 Hz, 1H, 6'').

Further characterisation was prohibited due to rapid compound degradation.

Ethyl 2-(1*H*-pyrrol-1-yl)acetate, 2.167



According to the procedure reported by Taylor and co-workers.[149] Glycine ethyl ester hydrochloride (9.07 g, 65 mmol, 1 eq.) and sodium acetate (9.02 g, 110 mmol, 1.7 eq.) were dissolved in solution of H_2O (40 mL) and AcOH (80 mL). 2,5-Dimethoxytetrahydrofuran (8.25 mL, 65 mmol, 1 eq.) was added to the reaction mixture, which was heated to reflux for 4 h with stirring. The reaction mixture was allowed to cool, then poured onto H_2O. The solution was extracted with EtOAc, then neutralised with solid Na_2CO_3, then extracted once more with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (25:75 EtOAc/petroleum ether [40-60 °C]) afforded the title compound as a yellow oil (7.03 g, 70%).

R_f: 0.6 (25:75 EtOAc/petroleum ether [40-60 °C]).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (t, *J* = 2.0 Hz, 2H, 2, 3), 6.27 – 6.20 (m, 2H, 1, 4), 4.64 (s, 2H, 5), 4.25 (q, *J* = 7.0 Hz, 2H, 7), 1.32 (t, *J* = 7.0 Hz, 3H, 8).

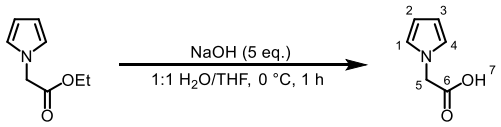
^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8 (6), 121.8 (2, 3), 109.0 (1, 4), 61.6 (7), 50.8 (5), 14.1 (8).

m/z (ESI$^+$) 176.1 [(M + Na)$^+$], 154.1 [(M + H)$^+$].

HRMS (ESI$^+$) $C_8H_{12}O_2N^+$ [(M + H)$^+$] requires 154.0863, found 154.0862.

Data in accordance with that reported in the literature.[149]

2-(1*H*-Pyrrol-1-yl)acetic acid, 2.168



According to the procedure by Taylor and co-workers.[149] Ester **2.167** (4.12 g, 26.9 mmol, 1 eq.) was dissolved in a 1:1 mixture of THF/H_2O (total volume: 160 mL), and the mixture was cooled to 0 °C. NaOH (5.4 g, 135 mmol, 5 eq., pellets) was crushed using a pestle and mortar, and added to the reaction in one portion, and the reaction was stirred at 0 °C for 1 h. The reaction was acidified using 2 M $HCl_{(aq.)}$, and the resulting solution extracted five times with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered and reduced *in vacuo* to give the title compound (3.28 g, 97%), which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (t, *J* = 2.0 Hz, 2H, 1, 4), 6.23 (t, *J* = 2.0 Hz, 2H, 2, 3), 4.70 (s, 2H, 5). Proton 7 was not observed.

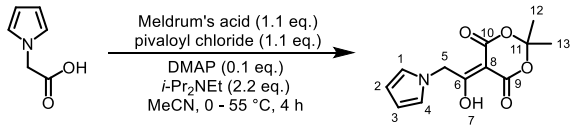
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (6), 121.9 (1, 4), 109.5 (2, 3), 50.4 (5).

m/z (ESI^-) 124.1 [$(M - H)^-$].

HRMS (ESI^-) $C_6H_6O_2N^-$ [$(M - H)^-$] requires 124.0404, found 124.0403.

Data in accordance with that reported in the literature. [149]

5-(1-Hydroxy-2-(1*H*-pyrrol-1-yl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione, 2.169



According to the procedure by Song *et al*.[150] Carboxylic acid **2.168** (1g, 7.99 mmol, 1 eq.), Meldrum's acid (1.27 g, 8.79 mmol, 1.1 eq.) and dimethylaminopyridine (DMAP, 98 mg, 0.799 mmol, 0.1 eq.) were added to a flame-dried round-bottomed flask, which was placed under an argon atmosphere. MeCN (6 mL) was then added, and rapidly stirred to dissolve the solid reagents. Diisopropylethylamine (3.1 mL, 17.6 mmol, 2.2 eq.) was then added in one portion, and the reaction was cooled to 0 °C. Pivaloyl chloride (1.08 mL, 8.79 mmol, 1 eq.) was then added dropwise over 90 minutes between 0 – 5 °C. The reaction was then heated to 50 °C for 2.5 hr, and then allowed to cool to room temperature. 8 mL of 17.7% phosphoric acid was added, which led to immediate precipitation of the crude product. This was filtered, and washed three times with MeCN/H_2O (3:2), and precipitate collected. 2 M $HCl_{(aq.)}$ was added to the mother liquor to induce further precipitation; the precipitate was filtered off, washed three times with MeCN/H_2O (3:2), and collected. The combined precipitates were dried under vacuum for 6 hours with the aid of phosphorus pentoxide drying agent, to give the title compound (1.57 g, 78%).

mp: decomposed at 120 °C.

ν_{max} (cm^{-1}) 3001 (w), 2359 (w), 1783 (m), 1738 (s).

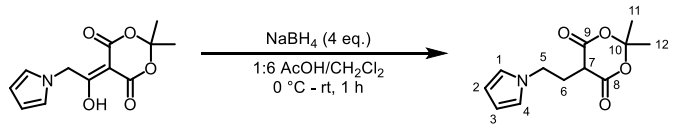
^1H NMR (500 MHz, $CDCl_3$) δ 15.56 (s, 1H, 7), 6.73 (t, *J* = 2.0 Hz, 2H, 1, 4), 6.23 (t, *J* = 2.0 Hz, 2H, 2, 3), 5.47 (s, 2H, 5), 1.77 (s, 6H, 12, 13).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.7 (6), 170.5 (9/10), 160.2 (9/10), 122.3 (1, 4), 109.4 (2, 3), 106.1 (11), 91.0 (8), 51.7 (5), 27.1 (12, 13).

m/z (ESI^-) 250.1 [$(M - H)^-$].

HRMS (ESI^-) $C_{12}H_{12}O_5N^-$ [$(M - H)^-$] requires 250.0721, found 250.0719.

5-(2-(1*H*-Pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, 2.170



According to the procedure by Wong and co-workers.[151] Enol **2.169** (4.30 g, 17.1 mmol, 1 eq.) and AcOH (11 mL) were dissolved in CH_2Cl_2 (65 mL), and the resulting solution was cooled to 0 °C and placed under an argon atmosphere. $NaBH_4$ (2.59 g, 68.4 mmol, 4 eq.) was added portionwise over 1 hr, then carefully quenched with 2M $HCl_{(aq.)}$. The mixture was allowed to warm to room temperature then extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (40:60 EtOAc/petroleum ether [40-60 °C]) afforded the title compound (3.34 g, 82%).

R_f: 0.3 (40:60 EtOAc/petroleum ether [40-60 °C]).

mp: 103.8 – 106.6 °C.

ν_{max} (cm^{-1}) 3002 (w), 1783 (m), 1742 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (t, *J* = 2.0 Hz, 2H, 1, 4), 6.16 (t, *J* = 2.0 Hz, 2H, 2, 3), 4.24 (t, *J* = 7.0 Hz, 2H, 5), 3.04 (t, *J* = 6.0 Hz, 1H, 7), 2.49 (td, *J* = 7.0, 6.0 Hz, 2H, 6), 1.74 (s, 3H, 11/12), 1.66 (s, 3H, 11/12).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2 (8, 9), 120.9 (1, 4), 109.1 (2, 3), 105.4 (10), 46.3 (5), 42.6 (7), 28.6 (11/12), 28.0 (6), 26.1 (11/12).

m/z (ESI^-) 236.1 [$(M - H)^-$].

HRMS (ESI^-) $C_{12}H_{14}O_4N^-$ [$(M - H)^-$] requires 236.0928, found 236.0929.

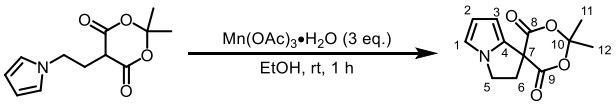
General Procedure A for the Electrochemical Cyclisation of 2.170

Dicarbonyl **2.170** and $LiClO_4$ (64 mg, 0.1 M) were added to a flame dried vial equipped with a stirrer bar, and place under an argon atmosphere. The solvent (sparged with argon for 15 min) was added, followed by the correct quantity of 2,6-lutidine. Reticulated Vitreous Carbon (RVC) foam was cut (Goodfellow, 24 pores/cm, 45x13x3.2 mm, 30x13x3.2 mm submersed in solution) and fitted to the electrode assembly, which was lowered into the reaction vial. The reaction was heated to the desired temperature, and the leads to the anode and cathode were connected to the power supply (Keithley 2200-72-1 Programmable Power Supply). The desired current was passed until the appropriate amount of charge had been transferred. The vial and electrode assembly were washed repeatedly with EtOAc into a conical flask. This included refilling the vial with EtOAc, and left to stand for 10 min, followed by 1 min of sonication to wash the remaining product from the electrode assembly. Brine (50 mL) was added, and the aqueous layer was extracted five times with EtOAc. The combined organics were dried (Na_2SO_4), filtered and reduced *in vacuo* (CAUTION: do not allow temperature of water bath for rotary evaporator to exceed 25 °C; removal of solvent should be carried out in a fume hood, behind a blast shield).

Determination of Yields Using ^1H NMR:

To the sample in question, free of solvent, 1,2,4,5-tetrachloro-3-nitrobenzene (51.5 mg) was added. Deuterated chloroform (2 mL) was added, and the sample was sonicated until it had fully dissolved. 0.5 mL of this solution was taken into a clean and dry NMR tube, and a ^1H NMR was run, with the following modifications to the normal procedure: 64 scans, D1 = 30 seconds.

2',2'-Dimethyl-2,3-dihydrospiro[pyrrolizine-1,5'-[1,3]dioxane]-4',6'-dione, 2.171



Dicarbonyl **2.170** (200 mg, 0.84 mmol, 1 eq.) was dissolved in EtOH (10 mL), and $Mn(OAc)_3 \bullet 2H_2O$ (676 mg, 2.52 mmol, 3 eq.) was added in one portion. The reaction was stirred at room temperature for 1 h, and then quenched with brine. The subsequent mixture was extracted five times with EtOAc, and the combined organic layers were dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (28:72 EtOAc/petroleum ether [40-60 °C]) afforded the title compound (27 mg, 14%). This purification was attempted a number of times on a number of samples from different reactions, unfortunately >95% purity (by analysis of ^{1}H NMR integrals) was the highest purity that was achieved. However, this level of purity was sufficient for us to be confident that the structure of **2.171** is in keeping with the data. Two impurities exist in the sample used for characterisation (>95% purity): the dimer **2.172** and the isopropyl ester **2.175**.

This compound was also synthesised a number of times using electrochemistry, detailed in general procedure A. The best yield using these conditions (calculated by quantitative ^{1}H NMR) was 25%.

R_f: 0.3 (28:72 EtOAc/petroleum ether [40-60 °C]).

ν_{max} (cm^{-1}): 2922 (w), 2361 (w), 1773 (m), 1741 (s).

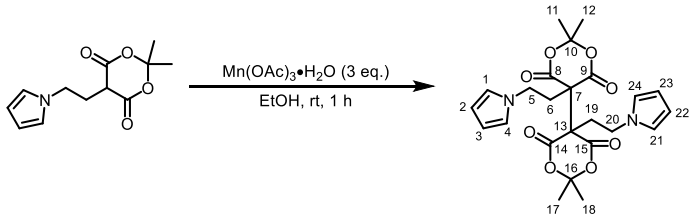
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, *J* = 2.5, 1.0 Hz, 1H, 1), 6.23 (dd, *J* = 4.0, 2.5 Hz, 1H, 2), 5.93 (dd, *J* = 4.0, 1.0 Hz, 1H, 3), 4.32 (t, *J* = 6.5 Hz, 2H, 5), 3.21 (t, *J* = 6.5 Hz, 2H, 6), 1.95 (s, 3H, 11/12), 1.81 (s, 3H, 11/12).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (8, 9), 132.2 (4), 116.4 (1), 113.5 (2), 105.8 (10), 101.3 (3), 52.7 (7), 45.9 (5), 41.7 (6), 29.3 (11/12), 29.2 (11/12).

m/z (ESI^+) 258.1 [$(M + Na)^+$].

HRMS (ESI^+) $C_{12}H_{14}O_4N^+$ [$(M + H)^+$] requires 236.0917, found 236.0919.

5,5'-Bis(2-(1*H*-pyrrol-1-yl)ethyl)-2,2,2',2'-tetramethyl-[5,5'-bi(1,3-dioxane)]-4,4',6,6'-tetraone, 2.172



The title compound was obtained as a side product in the above reaction, but unfortunately could not be separated from the cyclised monomer **2.171**. The sample that we used for characterisation existed as a 1:4 ratio of dimer **2.172** to monomer **2.171**. However, we are nonetheless confident that the data obtained is in keeping with the structure proposed for **2.172**.

This compound was also synthesised a number of times using electrochemistry, detailed in general procedure A. The best yield using these conditions (calculated by ^{1}H NMR) was 16%.

R_f: 0.3 (28:72 EtOAc/petroleum ether [40-60 °C]).

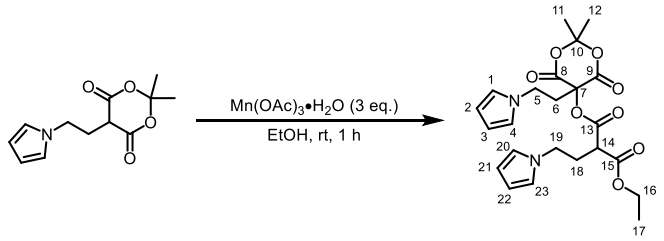
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (t, *J* = 2.0 Hz, 4H, 1, 4, 21, 24), 6.14 (t, *J* = 2.0 Hz, 4H, 2, 3, 22, 23), 3.88 – 3.81 (m, 4H, 5, 20), 3.00 – 2.92 (m, 4H, 6, 19), 1.80 (s, 6H, 11/12/17/18), 1.74 (s, 6H, 11/12/17/18).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3 (8, 9, 14, 15), 120.6 (1, 4, 21, 24), 109.2 (2, 3, 22, 23), 108.2 (10, 16), 56.6 (7, 13), 45.9 (5, 20), 36.7 (6, 19), 30.3 (11/12/17/18), 28.9 (11/12/17/18).

m/z (ESI^{+}) 495.2 [(M + Na)$^{+}$].

HRMS (ESI^{+}) $C_{24}H_{29}O_8N_2^{+}$ [(M + H)$^{+}$] requires 473.1918, found 473.1917.

1-(5-(2-(1*H*-Pyrrol-1-yl)ethyl)-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl) 3-ethyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 2.173



Dicarbonyl **2.170** (200 mg, 0.84 mmol, 1 eq.) was dissolved in EtOH (10 mL), and $Mn(OAc)_3•2H_2O$ (676 mg, 2.52 mmol, 3 eq.) was added in one portion. The reaction was stirred at room temperature for 1 h, and then quenched with brine. The subsequent mixture was extracted five times with EtOAc, and the combined organic layers were dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. Purification by column chromatography (28:72 EtOAc/petroleum ether [40-60 °C]) afforded the title compound (23 mg, 12%).

R_f: 0.3 (28:72 EtOAc/petroleum ether [40-60 °C]).

ν_{max} (cm^{-1}): 2940 (w), 1793 (m), 1754 (s), 1735 (s).

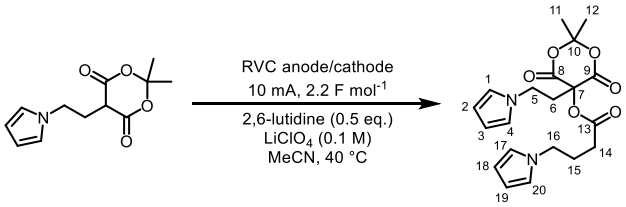
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (t, *J* = 2.0 Hz, 2H, 20, 23), 6.63 (t, *J* = 2.0 Hz, 2H, 1, 4), 6.17 (t, *J* = 2.0 Hz, 2H, 21, 22), 6.16 (t, *J* = 2.0 Hz, 2H, 2, 3), 4.29 – 4.19 (m, 2H, 16), 4.15 – 4.09 (m, 2H, 5), 4.06 (ddd, *J* = 14.5, 6.5, 5.5 Hz, 1H, 19'), 3.94 (ddd, *J* = 14.5, 8.5, 6.0 Hz, 1H, 19''), 3.36 (dd, *J* = 9.0, 6.5 Hz, 1H, 14), 2.57 – 2.49 (m, 2H, 6), 2.43 (ddt, *J* = 14.5, 8.5, 6.5 Hz, 1H, 18''), 2.35 (dddd, *J* = 14.5, 9.0, 6.0, 5.5 Hz, 1H, 18'), 1.94 (s, 3H, 11/12), 1.82 (s, 3H, 11/12), 1.31 (t, *J* = 7.0 Hz, 3H, 17).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4 (13), 167.1 (15), 163.4 (8/9), 163.0 (8/9), 120.8 (20, 23), 120.6 (1, 4), 109.2 (2, 3), 108.8 (21, 22), 108.7 (10), 75.0 (7), 62.5 (16), 47.8 (14), 46.2 (19), 43.6 (5), 38.0 (6), 30.7 (18), 28.7 (11/12), 28.7 (11/12), 14.1 (17).

m/z (ESI^+) 461.2 [$(M + H)^+$].

HRMS (ESI^+) $C_{23}H_{29}O_8N_2^+$ [$(M + H)^+$] requires 461.1918, found 461.1917.

5-(2-(1*H*-Pyrrol-1-yl)ethyl)-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl 4-(1*H*-pyrrol-1-yl)butanoate, 2.174



Dicarbonyl **2.170** (94 mg, 0.395 mmol, 1 eq.) and $LiClO_4$ (64 mg, 0.1 M) were added to a flame dried vial equipped with a stirrer bar, and place under an argon atmosphere. MeCN (6 mL, sparged with argon for 15 min) was added, followed by 2,6-lutidine (0.023 mL, 0.198 mmol, 0.5 eq.). Reticulated Vitreous Carbon (RVC) foam was cut and fitted to the electrode assembly, which was lowered into the reaction vial. The reaction was heated to 40 °C, and the leads to the anode and cathode were connected to the power supply (Keithley 2200-72-1 Programmable Power Supply). A current of 10 mA was passed until a total charge equal to 2.2 F mol^{-1} had been transferred. The vial and electrode assembly were washed repeatedly with EtOAc into a conical flask. This included refilling the vial with EtOAc, and left to stand for 10 min, followed by 1 min of sonication to wash the remaining product from the electrode assembly. Brine (50 mL) was added, and the aqueous layer was extracted five times with EtOAc. The combined organics were dried (Na_2SO_4), filtered and reduced *in vacuo* (CAUTION: do not allow temperature of water bath for rotary evaporator to exceed 25 °C; removal of solvent should be carried out in a fume hood, behind a blast shield). Purification by column chromatography (32:68 EtOAc/petroleum ether [40-60 °C]) yielded the title compound (1.2 mg, 2%).

R_f: 0.6 (32:68 EtOAc/petroleum ether [40-60 °C]).

ν_{max} (cm^{-1}): 2956 (w), 2923 (m), 1791 (w), 1752 (s).

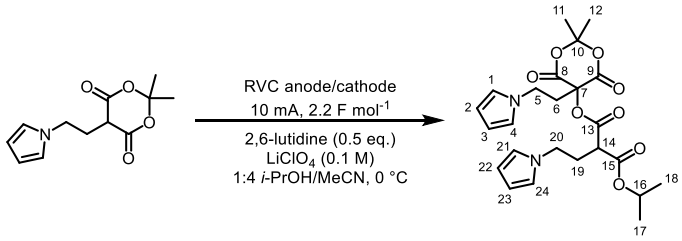
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (t, *J* = 2.0 Hz, 2H, 17, 20), 6.63 (t, *J* = 2.0 Hz, 2H, 1, 4), 6.16 (t, *J* = 2.0 Hz, 2H, 18, 19), 6.15 (t, *J* = 2.0 Hz, 2H, 2, 3), 4.15 – 4.08 (m, 2H, 5), 3.95 (t, *J* = 6.5 Hz, 2H, 16), 2.54 – 2.47 (m, 2H, 6), 2.42 (t, *J* = 7.0 Hz, 2H, 14), 2.10 (p, *J* = 7.0 Hz, 2H, 15), 1.94 (s, 3H, 11/12), 1.81 (s, 3H, 11/12).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2 (13), 163.8 (8, 9), 120.8 (17, 20), 120.6 (1, 4), 109.1 (2, 3), 108.6 (10), 108.6 (18, 19), 74.5 (7), 47.9 (16), 43.8 (5), 37.9 (6), 29.8 (14), 28.8 (11/12), 28.7 (11/12), 26.5 (15).

HRMS (FI^+) $C_{20}H_{24}O_6N_2^+$ [M^+] requires 388.1634, found 388.1638.

HRMS (ESI^+) $C_{20}H_{25}O_6N_2^+$ [$(M + H)^+$] requires 389.1707, found 389.1707.

1-(5-(2-(1*H*-Pyrrol-1-yl)ethyl)-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl) 3-isopropyl 2-(2-(1*H*-pyrrol-1-yl)ethyl)malonate, 2.175



According to General Procedure A, dicarbonyl **2.170** (94 mg, 0.395 mmol) with 2,6-lutidine (0.5 eq.) in a solution comprised of 1:4 *i*PrOH/MeCN gave the title compound. From an exhaustive screening of conditions, the best yield (determined using ^{1}H NMR) was found to be 39%.

R_f: 0.4 (22:78 EtOAc/petroleum ether [40-60 °C]).

ν_{max} (cm^{-1}): 2984 (w), 2360 (w), 1794 (m), 1756 (s), 1733 (s).

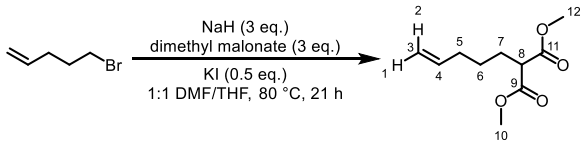
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (t, *J* = 2.0 Hz, 2H, 21, 24), 6.63 (t, *J* = 2.0 Hz, 2H, 1, 4), 6.17 (t, *J* = 2.0 Hz, 2H, 22, 23), 6.16 (t, *J* = 2.0 Hz, 2H, 2, 3), 5.06 (h, *J* = 6.5 Hz, 1H, 16), 4.15 – 4.09 (m, 2H, 5), 4.05 (ddd, *J* = 14.5, 6.5, 5.5 Hz, 1H, 20'), 3.93 (ddd, *J* = 14.5, 8.5, 6.0 Hz, 1H, 20''), 3.33 (dd, *J* = 9.0, 6.0 Hz, 1H, 14), 2.57 – 2.48 (m, 2H, 6), 2.48 – 2.26 (m, 2H, 19), 1.94 (s, 3H, 11/12), 1.82 (s, 3H, 11/12), 1.30 (d, *J* = 6.5 Hz, 3H, 17/18), 1.28 (d, *J* = 6.5 Hz, 3H, 17/18).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5 (13), 166.6 (15), 163.4 (8/9), 163.0 (8/9), 120.8 (21, 24), 120.6 (1, 4), 109.2 (2, 3), 108.7 (22, 23), 108.7 (10), 75.0 (7), 70.5 (16), 48.0 (14), 46.2 (20), 43.6 (5), 38.0 (6), 30.7 (19), 28.7 (11/12), 28.7 (11/12), 21.7 (17/18), 21.6 (17/18).

m/z (ESI^+) 497.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{24}H_{30}O_8N_2Na^+$ [$(M + Na)^+$] requires 497.1894, found 497.1887.

Dimethyl 2-(pent-4-en-1-yl)malonate, 2.19



Sodium hydride (60% in mineral oil, 1.8 g, 45 mmol, 3 eq.) was added to DMF (40 mL) in a flame-dried flask, and the resulting suspension was cooled to 0 °C. Dimethyl malonate (5.0 mL, 45 mmol, 3 eq.) was added dropwise, followed by a solution of 1-bromopent-4-ene (1.8 mL, 15 mmol, 1 eq.) in THF (40 mL). Potassium iodide (1.26 g, 7.60 mmol, 0.5 eq.) was added, a reflux condenser attached, and the reaction mixture was heated to 80 °C for 21 h. The reaction was allowed to cool, and was then poured over sat. aq. NH_4Cl. The organic layer was separated off, and the aqueous layer was extracted three times with EtOAc. The combined organics were washed three times with water, once with brine, then dried (Na_2SO_4), filtered, and reduced *in vacuo* to give the crude product. Purification by column chromatography (0 – 15% EtOAc in isohexane) afforded the title compound as a clear oil (2.35 g, 77%).

R_f: 0.4 (70:28:2 petroleum ether [30-40 °C]/CH_2Cl_2/EtOAc).

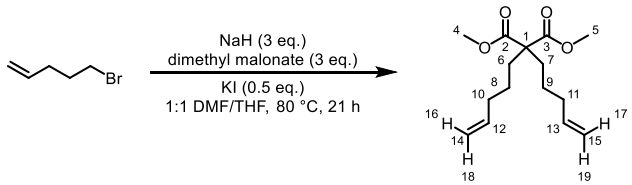
ν_{max} (cm^{-1}): 2955 (w), 1734 (s), 1435 (m).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, 4), 5.01 (dq, *J* = 17.0, 1.5 Hz, 1H, 2), 4.96 (dq, *J* = 10.0, 1.5 Hz, 1H, 1), 3.73 (s, 6H, 10, 12), 3.36 (t, *J* = 7.5 Hz, 1H, 8), 2.07 (m, 2H, 5), 1.95 – 1.86 (m, 2H, 7), 1.46 – 1.36 (m, 2H, 6).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0 (9, 11), 138.0 (4), 115.2 (3), 52.6 (10, 12), 51.7 (8), 33.4 (5), 28.4 (7), 26.7 (6).

HRMS (ESI$^+$) $C_{10}H_{16}O_4Na^+$ [(M + Na)$^+$] requires 223.0941, found 223.0941.

Dimethyl 2,2-di(pent-4-en-1-yl)malonate, 2.177



The title compound was isolated as a bi-product from the above reaction (199 mg, 10%).

R_f: 0.3 (10% EtOAc in petroleum ether [40 – 60 °C]).

ν_{max} (cm^{-1}): 2953 (w), 2360 (w), 1731 (s).

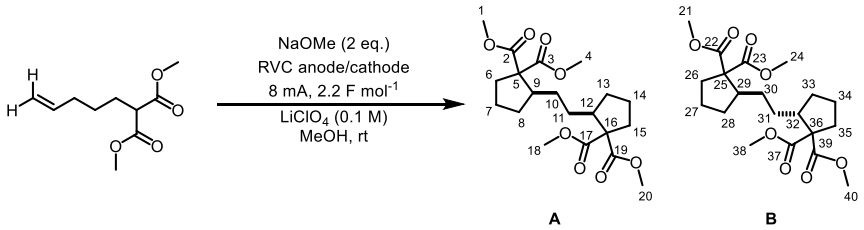
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 2H, 12, 13), 5.01 (dq, *J* = 17.0, 1.5 Hz, 2H, 16, 17), 4.96 (d, *J* = 10.0 Hz, 2H, 18, 19), 3.71 (s, 6H, 4, 5), 2.12 – 1.99 (m, 4H, 10, 11), 1.95 – 1.80 (m, 4H, 6, 7), 1.32 – 1.18 (m, 4H, 8, 9).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4 (2, 3), 138.2 (12, 13), 115.1 (14, 15), 57.7 (1), 52.5 (4, 5), 33.9 (11, 10), 32.2 (6, 7), 23.6 (8, 9).

m/z (ESI^+) 291.2 [$(M + Na)^+$].

HRMS (ESI^+) $C_{15}H_{24}O_4Na^+$ [$(M + Na)^+$] requires 291.1567, found 291.1566.

Tetramethyl 2,2'-(ethane-1,2-diyl)bis(cyclopentane-1,1-dicarboxylate), 2.110



To a solution of malonate **2.19** (100 mg, 0.5 mmol, 1 eq.) in MeOH (6 mL, sparged with argon for 30 min) was added $LiClO_4$ (64 mg, 0.1 M) and NaOMe (25% wt. in MeOH, 0.23 mL, 1.0 mmol, 2 eq.). Reticulated vitreous carbon electrodes were used as the anode and cathode to pass a current of 8 mA through the solution for a time of 3 h and 41 mins, to give a total charge passed equal to 2.2 F mol^{-1}. The reaction was then poured onto sat. aq. NH_4Cl, and the reaction vessel and electrodes were thoroughly washed with EtOAc. The aqueous phase was extracted with EtOAc, and the combined organics were dried (Na_2SO_4), filtered and reduced *in vacuo* to yield the crude product. Purification by column chromatography (16% EtOAc in petroleum ether [40 – 60 °C]) afforded the title compound (71 mg, 71%).

R_f: 0.2 (16% EtOAc in petroleum ether [40 – 60 °C]).

ν_{max} (cm^{-1}): 2953 (w), 2360 (w), 1725 (s).

A 1:1 mixture of the two diastereomers was obtained, and we were unable to separate them using chromatography. As such the mixture was assigned, with the two diastereomers labelled A and B arbitrarily. *We do not claim to have assigned specific NMR signals to either the cis or trans diastereomer, however they have been labelled as such to assist the reader, as we were able to assign separate signals as corresponding to the same diastereomer, unaware as to which one this may be*.

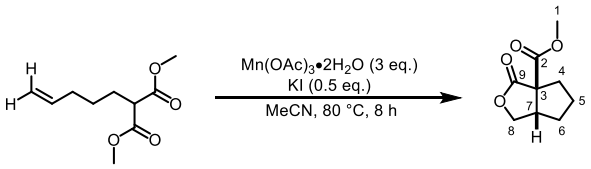
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 6H, C(O)OC**H$_3$** protons), 3.73 (s, 6H, C(O)OC**H$_3$** protons), 3.72 (s, 12H, C(O)OC**H$_3$** protons), 2.56 (m, 2H, 9, 12), 2.50 – 2.36 (m, 6H, 29, 32, alicyclic protons), 2.09 – 1.91 (m, 8H, 8', 13', 28', 33', alicyclic protons), 1.85 (m, 4H, alicyclic protons), 1.66 (m, 2H, 30'', 31''), 1.62 – 1.50 (m, 6H, 10'', 11'', alicyclic protons), 1.46 – 1.30 (m, 4H, 28'', 33'', 8'', 13''), 1.16 – 1.07 (m, 2H, 10', 11'), 1.07 – 0.97 (m, 2H, 30', 31').

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2 (**C**=O), 173.2 (**C**=O), 172.2 (**C**=O), 172.1 (**C**=O), 63.6 (5, 16, 25, 36), 52.5 (C(O)O**C**H_3), 52.1 (C(O)O**C**H_3), 47.1 (29, 32), 45.8 (9, 12), 34.7, 34.6, 31.0, 30.7, 30.5, 29.8 (10, 11), 23.1.

m/z (ESI$^+$) 421.2 [$(M + Na)^+$].

HRMS (ESI$^+$) $C_{20}H_{30}O_8Na^+$ [$(M + Na)^+$] requires 421.1833, found 421.1833.

Methyl (3a*R,6a*S**)-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3H)-carboxylate, 2.21**



According to the procedure reported by Burton and co-workers, with modifications.[34] $Mn(OAc)_3•2H_2O$ (3.81 g, 14.2 mmol, 3 eq.) and KI (393 mg, 2.37 mmol, 0.5 eq.) were taken in a flask equipped with a reflux condenser, and heated to 80 °C. A solution of malonate **2.19** (949 mg, 4.74 mmol, 1 eq.) in acetonitrile (30 mL, sparged with argon for 30 mins) was added, and the resulting suspension was heated to 80 °C for 6.5 h. The reaction mixture was allowed to cool to rt, then quenched with a sat. aq. solution of sodium thiosulfate. The reaction was extracted with EtOAc, and the combined organics were washed with sat. aq. $NaHCO_3$ and brine, then dried (Na_2SO_4), filtered and reduced *in vacuo* to yield the crude product. Purification by column chromatography (20% EtOAc in petroleum ether [40 – 60 °C]) afforded the title compound (795 mg, 91%).

R_f: 0.3 (20% EtOAc in petroleum ether [40 – 60 °C]).

ν_{max} (cm^{-1}): 2957 (w), 1768 (s), 1739 (s).

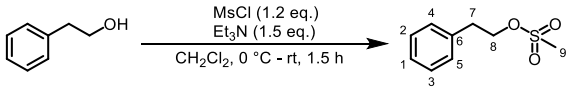
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (dd, *J* = 9.0, 7.5 Hz, 1H, 8'), 4.06 (dd, *J* = 9.0, 2.5 Hz, 1H, 8''), 3.76 (s, 3H, 1), 3.14 – 3.05 (m, 1H, 7), 2.37 (ddd, *J* = 13.5, 9.5, 7.0 Hz, 1H, 4'), 2.30 – 2.21 (m, 1H, 4''), 2.11 – 1.99 (m, 1H, 6'), 1.87 – 1.76 (m, 1H, 5'), 1.71 – 1.56 (m, 2H, 5'', 6'').

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5 (9), 170.6 (2), 73.1 (8), 61.7 (3), 53.2 (1), 45.7 (7), 34.8 (4), 34.2 (6), 26.0 (5).

m/z (ESI^+) 391.2 [$(2M + Na)^+$].

HRMS (ESI^+) $C_9H_{12}O_4Na^+$ [$(M + Na)^+$] requires 207.0628, found 207.0630.

Phenethyl methanesulfonate, 2.185



According to the procedure reported by Lua, with modifications.[23] A solution of 2-phenylethanol (1 mL, 8.35 mmol, 1 eq.) in CH_2Cl_2 (30 mL) was cooled to 0 °C, and Et_3N (1.75 mL, 12.5 mmol, 1.5 eq.) was added, followed by methanesulfonyl chloride (0.77 mL, 10.0 mmol, 1.2 eq.) dropwise. The reaction was allowed to warm to rt and stirred for 1.5 h. The reaction was then quenched with 1 M $HCl_{(aq)}$ and extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered and reduced *in vacuo* to give the crude product. A sample of this was fully characterised, and the rest was taken on to the next step without further purification.

R_f: 0.4 (2% EtOAc in CH_2Cl_2).

ν_{max} (cm^{-1}): 3030 (w), 1348 (s), 1169 (s).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H, 2, 3), 7.29 – 7.26 (m, 1H, 1), 7.26 – 7.18 (m, 2H, 4, 5), 4.43 (t, *J* = 7.0 Hz, 2H, 8), 3.06 (t, *J* = 7.0 Hz, 2H, 7), 2.84 (s, 3H, 9).

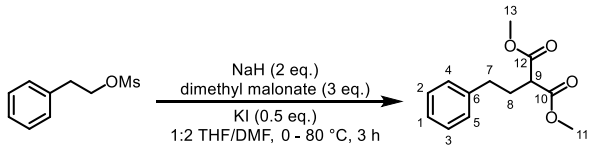
^{13}C NMR (126 MHz, $CDCl_3$) δ 136.5 (6), 129.1 (4, 5), 128.9 (2, 3), 127.2 (1), 70.5 (8), 37.5 (9), 35.8 (7).

m/z (ESI^+) 223.1 [$(M + Na)^+$].

HRMS (ESI^+) $C_9H_{12}O_3SNa^+$ [$(M + Na)^+$] requires 223.0399, found 223.0402.

Data in accordance with that reported by Morita *et al*.[168]

Dimethyl 2-phenethylmalonate, 2.186



According to the procedure reported by Lua, with modifications.[23] NaH (60% in mineral oil, 668 mg, 16.7 mmol, 2 eq.) was suspended in DMF (40 mL) and this suspension was cooled to 0 °C. Dimethyl malonate (2.9 mL, 25.1 mmol, 3 eq.) was then added dropwise, and the reaction was allowed to warm to rt. A solution of mesylate **1.2.185** (assumed 8.35 mmol, 1 eq.) prepared above in THF (20 mL) was added, followed by KI (694 mg, 4.18 mmol, 0.5 eq.). The reaction mixture was heated to 80 °C for 3 h, then allowed to cool to rt, and quenched with sat. aq. NH_4Cl. This mixture was extracted with EtOAc, and the combined organics were washed three times with H_2O and once with brine, then dried (Na_2SO_4), filtered and reduced *in vacuo* to yield the crude product. Purification by column chromatography (CH_2Cl_2) and removal of any remaining dimethyl malonate *in vacuo* afforded the title compound (1.44 g, 73%).

R_f: 0.6 (CH_2Cl_2).

ν_{max} (cm^{-1}): 2954 (w), 1732 (s), 1435 (m).

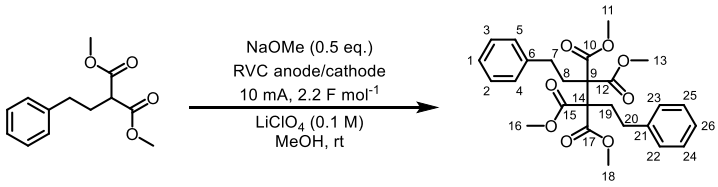
^1H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H, 2, 3), 7.23 – 7.16 (m, 3H, 1, 4, 5), 3.74 (s, 6H, 11, 13), 3.39 (t, *J* = 7.5 Hz, 1H, 9), 2.66 (t, *J* = 8.5 Hz, 2H, 7), 2.30 – 2.18 (m, 2H, 8).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8 (10, 12), 140.6 (6), 128.6 ([2 and 3] or [4 and 5]), 128.6 ([2 and 3] or [4 and 5]), 126.4 (1), 52.6 (11, 13), 51.0 (9), 33.4 (7), 30.5 (8).

m/z (ESI^+) 259.1 [$(M + Na)^+$].

HRMS (ESI$^+$) $C_{13}H_{16}O_4Na^+$ [(M + Na)$^+$] requires 259.0941, found 259.0948.

Tetramethyl 1,6-diphenylhexane-3,3,4,4-tetracarboxylate, 2.188



To a solution of malonate **2.186** (118 mg, 0.5 mmol, 1 eq.) in MeOH (6 mL, sparged with argon for 30 mins) was added $LiClO_4$ (64 mg, 0.1 M) and NaOMe (0.06 mL, 0.25 mmol, 0.5 eq.). Reticulated vitreous carbon electrodes were used as the anode and cathode, to pass a current of 10 mA through the solution for a time of 2 h and 57 mins, to give a total charge passed equal to 2.2 F mol^{-1}. The reaction was then poured onto sat. aq. NH_4Cl, and the reaction vessel and electrodes were thoroughly washed with EtOAc. The aqueous phase was extracted with EtOAc, and the combined organics were dried (Na_2SO_4), filtered and reduced *in vacuo* to yield the crude product. Purification by column chromatography (2% EtOAc in CH_2Cl_2) afforded the title compound (89 mg, 76%).

R_f: 0.4 (2% EtOAc in CH_2Cl_2).

ν_{max} (cm^{-1}): 2952 (w), 1728 (s), 1434 (m).

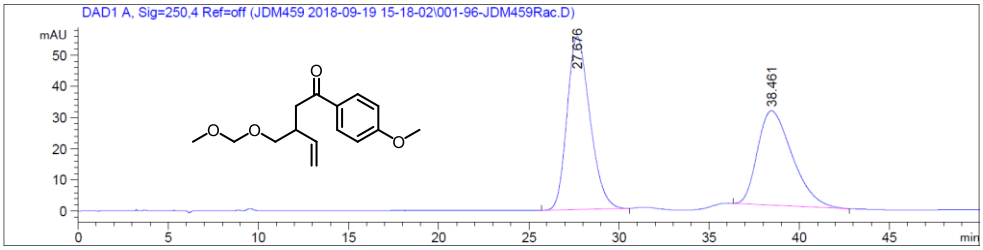
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 4H, 2, 3, 24, 25), 7.23 – 7.15 (m, 6H, 1, 4, 5, 22, 23, 26), 3.82 (s, 12H, 11, 13, 16, 18), 2.72 – 2.64 (m, 4H, 7, 20), 2.36 – 2.29 (m, 4H, 8, 19).

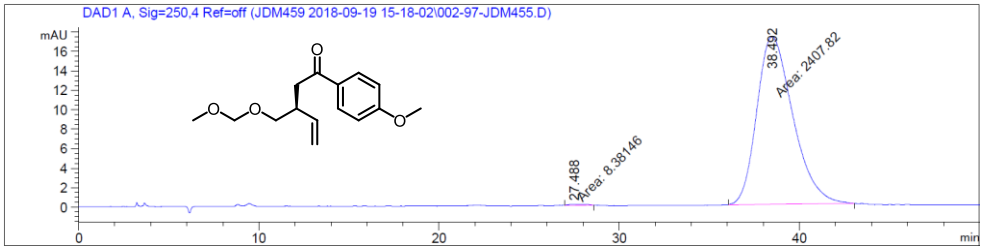
^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3 (10, 12, 15, 17), 141.8 (6, 21), 128.7 (4, 5, 22, 23), 128.6 (2, 3, 24, 25), 126.2 (1, 26), 63.5 (9, 14), 52.9 (11, 13, 16, 18), 33.7 (8, 19), 32.2 (7, 20).

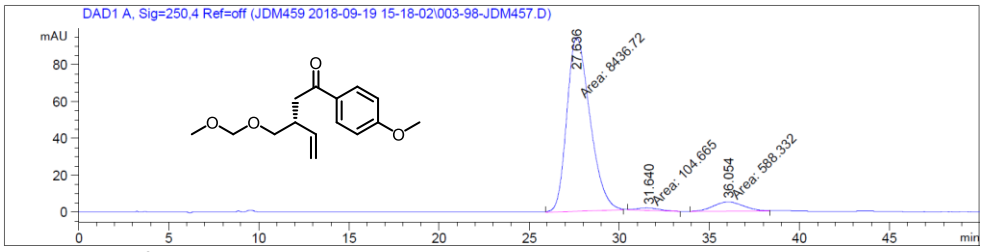
m/z (ESI$^+$) 493.2 [(M + Na)$^+$].

HRMS (ESI$^+$) $C_{26}H_{30}O_8Na^+$ [(M + Na)$^+$] requires 493.1833, found 493.1830.

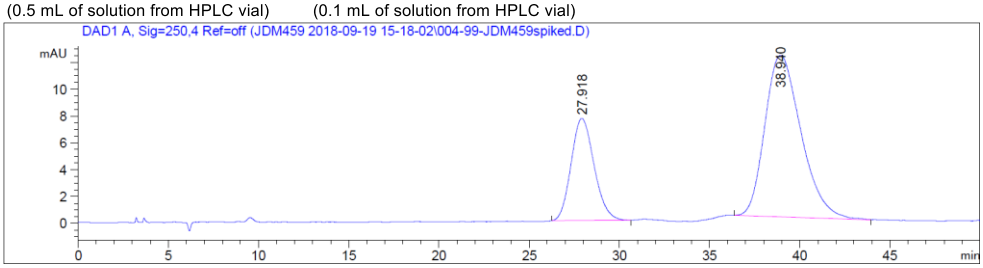
3.2 HPLC Traces for 1.352







(0.5 mL of solution from HPLC vial) (0.1 mL of solution from HPLC vial)



The racemic sample (top) was obtained by combining 1.1 mg of (*R*)-**1.352** and 1.1 mg of (*S*)-**1.352** in a vial. This was dissolved in a solution of 1:20 IPA/hexane. Enantioenriched samples (middle) were also taken into solution using a 1:20 ratio of IPA/hexane. To ensure

that the peaks observed were authentic, 0.5 mL of the solution from the HPLC vial of (*S*)-**1.352** was taken in a separate vial, and combined with 0.1mL of the solution from the HPLC vial of (*R*)-**1.352**. This solution was made up to the neck of the HPLC vial with an additional quantity of 1:20 IPA/hexane, and analysed by HPLC. The trace obtained is provided above (bottom). 10 µL aliquots were used for each HPLC run. The absolute configuration that has been tentatively assigned to the structures overlaying the HPLC traces is by analogy to that reported by Jiang using the same methodology on highly similar substrates.[25]

Racemic:

Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.676	BB	1.3067	4874.01221	55.38625	54.6762
2	38.461	BB	1.8099	4040.30249	30.21879	45.3238

Enantioenriched (*S*):

Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.488	MM	1.1606	8.38146	1.20359e-1	0.3469
2	38.492	MM	2.3214	2407.82471	17.28735	99.6531

Enantioenriched (*R*):

Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.636	MM	1.4891	8436.72266	94.42866	92.4094
2	31.640	MM	1.3499	104.66453	1.29226	1.1464

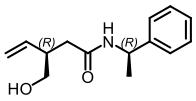
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
3	36.054	MM	1.9557	588.33234	5.01377	6.4441

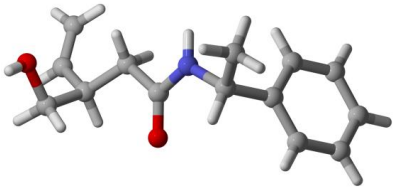
1.352 (*S*) spiked with 1.352 (*R*):

Signal 1: DAD1 A, Sig=250,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.918	BB	1.0624	673.55377	7.61164	28.6648
2	38.940	BB	1.6435	1676.20898	12.05995	71.3352

3.3 X-ray Data for 1.358





a = 15.7654(5) Å	α= 90°.
b = 15.7654(5) Å	β= 90°.
c = 5.0925(2) Å	γ = 90°.

Table 1. Crystal data and structure refinement for **1.358**.

Empirical formula	C14 H19 N O2	Formula weight	233.31
Temperature	150 K	Wavelength	1.54184 Å
Crystal system	Tetragonal	Space group	P 41
Volume	1265.73(9) $Å^3$	Z	4
Density (calculated)	1.224 Mg/m^3	Absorption coefficient	0.648 mm^{-1}
F(000)	504	Crystal size	0.350 x 0.020 x 0.010 mm^3
Theta range	3.965 to 76.551°.	Index ranges	-19<=h<=18 -8<=k<=19 -6<=l<=6
Reflections collected	6970	Independent reflections	2500 [R(int) = 0.067]
Completeness to theta = 73.047°	99.0 %	Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.99 and 0.61	Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2500 / 1 / 155	Goodness-of-fit on F^2	1.0137
Final R indices [I>2sigma(I)]	R1 = 0.0629 wR2 = 0.1700	R indices (all data)	R1 = 0.0659 wR2 = 0.1755
Absolute structure parameter	-0.2(2)	Largest diff. peak and hole	0.44 and -0.25 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **1.358**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Label	x	y	z	U(eq)
C(1)	4359(2)	8645(2)	3629(5)	23
N(2)	3469(1)	8419(1)	3235(4)	24
C(3)	2959(2)	8190(2)	5238(5)	21

C(4)	2087(2)	7883(2)	4406(5)	25
C(5)	1431(2)	7886(2)	6592(5)	24
C(6)	1206(2)	8769(2)	7594(6)	30
O(7)	874(1)	9278(1)	5523(5)	35
C(11)	4930(2)	7866(2)	3639(5)	23
C(12)	4843(2)	7238(2)	1738(5)	28
C(13)	5369(2)	6530(2)	1759(6)	33
C(14)	5988(2)	6444(2)	3672(6)	33
C(15)	6086(2)	7072(2)	5560(6)	35
C(16)	5564(2)	7781(2)	5538(5)	29
C(21)	4627(2)	9282(2)	1531(5)	27
O(31)	3190(1)	8225(1)	7546(4)	27
C(41)	640(2)	7403(2)	5896(6)	28
C(42)	457(2)	7040(2)	3647(7)	38
H(11)	4412	8930	5345	27
H(41)	1893	8219	2952	31
H(42)	2169	7301	3839	30
H(51)	1694	7598	8087	29
H(61)	1717	9043	8340	36
H(62)	748	8769	8889	36
H(121)	4415	7289	475	33
H(131)	5300	6104	514	40
H(141)	6342	5970	3704	40
H(151)	6521	7020	6785	42
H(161)	5638	8212	6764	35
H(212)	5211	9416	1802	40
H(211)	4290	9786	1646	40
H(213)	4558	9022	-178	42
H(411)	226	7382	7198	33
H(422)	869	7011	2317	45
H(421)	-75	6804	3364	44
H(21)	3284	8341	1664	29
H(71)	840	9783	6007	51

Table 3. Bond lengths [Å] for **1.358**

C(1)-N(2)	1.461(3)	C(11)-C(16)	1.398(4)
C(1)-C(11)	1.523(3)	C(12)-C(13)	1.391(4)
C(1)-C(21)	1.526(3)	C(12)-H(121)	0.936
C(1)-H(11)	0.987	C(13)-C(14)	1.385(4)
N(2)-C(3)	1.348(3)	C(13)-H(131)	0.93
N(2)-H(21)	0.86	C(14)-C(15)	1.389(5)

C(3)-C(4)	1.517(3)	C(14)-H(141)	0.933
C(3)-O(31)	1.232(3)	C(15)-C(16)	1.388(4)
C(4)-C(5)	1.520(4)	C(15)-H(151)	0.93
C(4)-H(41)	0.961	C(16)-H(161)	0.93
C(4)-H(42)	0.97	C(21)-H(212)	0.956
C(5)-C(6)	1.524(4)	C(21)-H(211)	0.958
C(5)-C(41)	1.502(3)	C(21)-H(213)	0.968
C(5)-H(51)	0.979	C(41)-C(42)	1.313(4)
C(6)-O(7)	1.425(4)	C(41)-H(411)	0.932
C(6)-H(61)	0.991	C(42)-H(422)	0.939
C(6)-H(62)	0.977	C(42)-H(421)	0.928
O(7)-H(71)	0.836	C(11)-C(12)	1.392(4)

Table 4. Bond angles [°] for **1.358**

N(2)-C(1)-C(11)	111.8(2)	C(6)-O(7)-H(71)	110
N(2)-C(1)-C(21)	109.3(2)	C(1)-C(11)-C(12)	120.9(2)
C(11)-C(1)-C(21)	111.7(2)	C(1)-C(11)-C(16)	120.2(2)
N(2)-C(1)-H(11)	108.3	C(12)-C(11)-C(16)	118.9(2)
C(11)-C(1)-H(11)	108.3	C(11)-C(12)-C(13)	120.4(3)
C(21)-C(1)-H(11)	107.3	C(11)-C(12)-H(121)	119.1
C(1)-N(2)-C(3)	122.3(2)	C(13)-C(12)-H(121)	120.4
C(1)-N(2)-H(21)	119.2	C(12)-C(13)-C(14)	120.3(3)
C(3)-N(2)-H(21)	117.6	C(12)-C(13)-H(131)	120.2
N(2)-C(3)-C(4)	114.5(2)	C(14)-C(13)-H(131)	119.5
N(2)-C(3)-O(31)	122.2(2)	C(13)-C(14)-C(15)	119.7(3)
C(4)-C(3)-O(31)	123.3(2)	C(13)-C(14)-H(141)	120.8
C(3)-C(4)-C(5)	114.2(2)	C(15)-C(14)-H(141)	119.5
C(3)-C(4)-H(41)	109.2	C(14)-C(15)-C(16)	120.2(3)
C(5)-C(4)-H(41)	110.2	C(14)-C(15)-H(151)	118.9
C(3)-C(4)-H(42)	105.4	C(16)-C(15)-H(151)	120.9
C(5)-C(4)-H(42)	108.2	C(11)-C(16)-C(15)	120.5(3)
H(41)-C(4)-H(42)	109.5	C(11)-C(16)-H(161)	119
C(4)-C(5)-C(6)	114.0(2)	C(15)-C(16)-H(161)	120.6
C(4)-C(5)-C(41)	113.0(2)	C(1)-C(21)-H(212)	108.2
C(6)-C(5)-C(41)	110.4(2)	C(1)-C(21)-H(211)	110.5
C(4)-C(5)-H(51)	106.2	H(212)-C(21)-H(211)	109.9
C(6)-C(5)-H(51)	105.2	C(1)-C(21)-H(213)	108.7
C(41)-C(5)-H(51)	107.4	H(212)-C(21)-H(213)	109.4
C(5)-C(6)-O(7)	110.6(2)	H(211)-C(21)-H(213)	110.1
C(5)-C(6)-H(61)	109.7	C(5)-C(41)-C(42)	127.6(3)
O(7)-C(6)-H(61)	109.7	C(5)-C(41)-H(411)	115.6

C(5)-C(6)-H(62)	113.4	C(42)-C(41)-H(411)	116.7
O(7)-C(6)-H(62)	103.2	C(41)-C(42)-H(422)	119.8
H(61)-C(6)-H(62)	110	C(41)-C(42)-H(421)	120.6
H(422)-C(42)-H(421)	119.6		

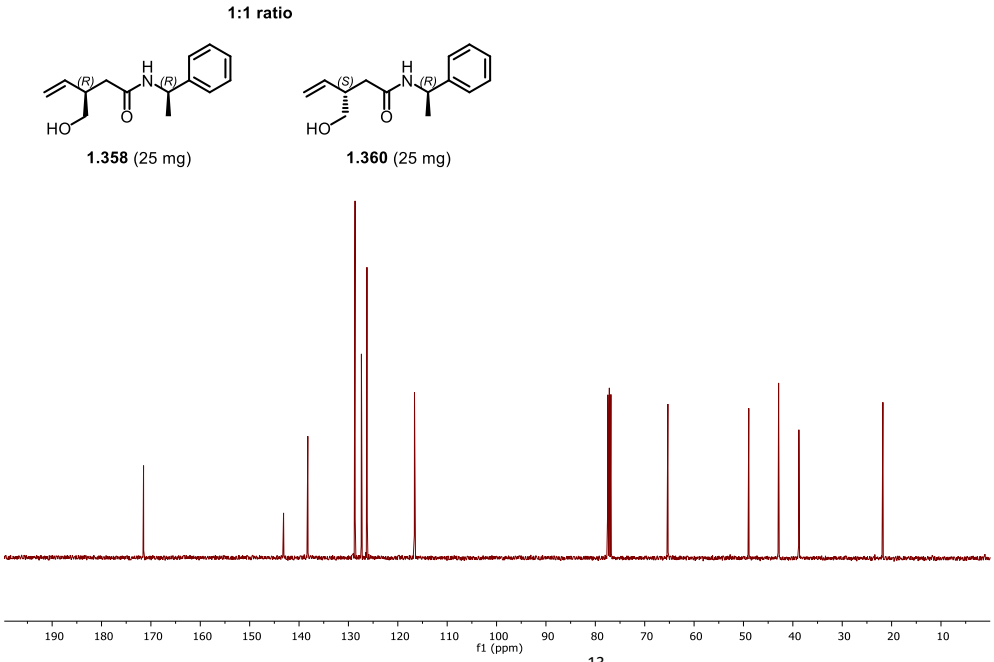
Table 5. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **1.358**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

Label	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	22(1)	26(1)	19(1)	-5(1)	0(1)	-3(1)
N(2)	22(1)	33(1)	17(1)	-1(1)	0(1)	0(1)
C(3)	23(1)	21(1)	19(1)	0(1)	3(1)	0(1)
C(4)	24(1)	27(1)	24(1)	-1(1)	0(1)	-2(1)
C(5)	23(1)	25(1)	25(1)	2(1)	-3(1)	0(1)
C(6)	25(1)	30(1)	36(1)	-3(1)	-1(1)	0(1)
O(7)	34(1)	27(1)	42(1)	-2(1)	-7(1)	2(1)
C(11)	21(1)	26(1)	21(1)	0(1)	3(1)	-2(1)
C(12)	29(1)	30(1)	25(1)	-4(1)	-1(1)	-1(1)
C(13)	36(1)	32(1)	32(1)	-5(1)	8(1)	2(1)
C(14)	31(1)	33(1)	37(1)	5(1)	6(1)	7(1)
C(15)	27(1)	47(2)	31(1)	5(1)	0(1)	4(1)
C(16)	26(1)	38(1)	24(1)	-1(1)	1(1)	1(1)
C(21)	29(1)	28(1)	24(1)	1(1)	1(1)	-5(1)
O(31)	26(1)	37(1)	18(1)	1(1)	-2(1)	-5(1)
C(41)	23(1)	24(1)	36(1)	6(1)	4(1)	1(1)
C(42)	24(1)	37(2)	52(2)	-5(1)	-6(1)	-7(1)

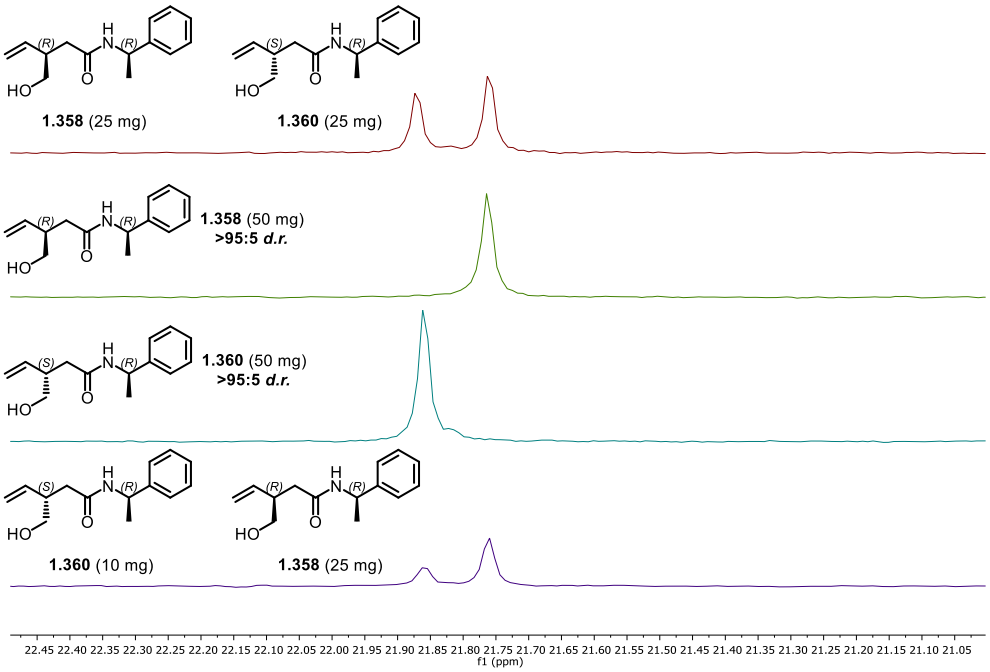
Table 6. Hydrogen bonds for **1.358** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(21)...O(31)#1	0.86	2.11	2.946(4)	164
O(7)-H(71)...O(7)#2	0.84	2.01	2.830(4)	166

3.4 Determination of Diastereomeric Purity of 1.358 and 1.360 by ^{13}C NMR.



Expanding the region 21.0 to 22.5 ppm, and overlaying ^{13}C NMR spectra:



4. References

1 Borschberg, H.-J., ETH Zürich Ph.D. Thesis, **1975**.

2 Jenny, L.; Borschberg, H.-J., *Helv. Chim. Acta*, **1995**, *78*, 715–731.

3 Ireland, C.; Faulkner, D. J.; Finer, J.; Clardy, J., *J. Am. Chem. Soc.*, **1976**, *98*, 4664–4665.

4 Rodríguez, A. D.; González, E.; Ramírez, C., *Tetrahedron*, **1998**, *54*, 11683–11729.

5 Hiersemann, M.; Helmboldt, H., *Top. Curr. Chem.*, **2005**, *243*, 73–136.

6 Hashimoto, T.; Toyota, M.; Koyama, H.; Kikkawa, A.; Yoshida, M.; Tanaka, M.; Takaoka, S.; Asakawa, Y., *Tetrahedron Lett.*, **1998**, *39*, 579–582.

7 Fukuyama, Y.; Minami, H.; Takeuchi, K.; Kodama, M.; Kawazu, K., *Tetrahedron Lett.*, **1996**, *37*, 6767–6770.

8 Fukuyama, Y.; Minami, H.; Kagawa, M.; Kodama, M.; Kawazu, K., *J. Nat. Prod.*, **1999**, *62*, 337–339.

9 Sono, M.; Hanaoaka, M.; Hashimoto, T.; Asakawa, Y.; Tori, M., *Synlett*, **2009**, *2009*, 469–471.

10 Rojo de Almeida, M. T.; Siless, G. E.; Perez, C. D.; Veloso, M. J.; Schejter, L.; Puricelli, L.; Palermo, J. A., *J. Nat. Prod.*, **2010**, *73*, 1714–1717.

11 Amico, V.; Currenti, R.; Oriente, G.; Piattelli, M.; Tringali, C., *Phytochemistry*, **1981**, *20*, 848–849.

12 Mehta, G., *Pure Appl. Chem*, **1990**, *62*, 1263–1268.

13 Kingsbury, J. S.; Corey, E. J., *J. Am. Chem. Soc.*, **2005**, *127*, 13813–13815.

14 Seebach, D.; Naef, R., *Helv. Chim. Acta*, **1981**, *64*, 2704–2708.

15 Snyder, S. A.; Corey, E. J., *J. Am. Chem. Soc.*, **2006**, *128*, 740–742.

16 Morikawa, T.; Xu, F.; Kashima, Y.; Matsuda, H.; Ninomiya, K.; Yoshikawa, M., *Org. Lett.*, **2004**, *6*, 869–872.

17 Bian, J.; Van Wingerden, M.; Ready, J. M., *J. Am. Chem. Soc.*, **2006**, *128*, 7428–7429.

18 Brown, M. K.; Hoveyda, A. H., *J. Am. Chem. Soc.*, **2008**, *130*, 12904–12906.

19 Yang, Z.-Y.; Liao, H.-Z.; Sheng, K.; Chen, Y.-F.; Yao, Z.-J., *Angew. Chem. Int. Ed.*, **2012**, *51*, 6484–6487.

20 Hugelshofer, C. L.; Magauer, T., *Chem. Eur. J.*, **2016**, *22*, 15125–15136.

21 Defaut, B.; Parsons, T. B.; Spencer, N.; Male, L.; Kariuki, B. M.; Grainger, R. S., *Org. Biomol. Chem.*, **2012**, *10*, 4926.

22 Hallside, M. S., University of Oxford D.Phil. Thesis, **2011**.

23 Lua, J. S. J., University of Oxford Part II Thesis, **2012**.

24 Ferrara, S. J., University of Oxford D.Phil. Thesis, **2013**.

25 Jiang, L., University of Oxford D.Phil. Thesis, **2016**.

26 Gevorgyan, V.; Rubin, M.; Liu, J.-X.; Yamamoto, Y., *J. Org. Chem.*, **2001**, *66*, 1672–1675.

27 Hutchins, R. O.; Kandasamy, D.; Dux, F.; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J., *J. Org. Chem.*, **1978**, *43*, 2259–2267.

28 Cram, D. J.; Sahyun, M. R. V., *J. Am. Chem. Soc.*, **1962**, *84*, 1734–1735.

29 Grundon, M. F.; Henbest, H. B.; Scott, M. D., *J. Chem. Soc.*, **1963**, 1855–1858.

30 Furrow, M. E.; Myers, A. G., *J. Am. Chem. Soc.*, **2004**, *126*, 5436–5445.

31 Edwards, J. T.; Merchant, R. R.; McClymont, K. S.; Knouse, K. W.; Qin, T.; Malins, L. R.; Vokits, B.; Shaw, S. A.; Bao, D.-H.; Wei, F.-L.; Zhou, T.; Eastgate, M. D.; Baran, P. S., *Nature*, **2017**, *545*, 213–218.

32 McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D., *J. Org. Chem.*, **1986**, *51*, 3388–3390.

33 Ainsua Martinez, S., University of Oxford D.Phil. Thesis, **2017**.

34 Ainsua Martinez, S.; Gillard, M.; Chany, A.-C.; Burton, J. W., *Tetrahedron*, **2018**, *74*, 5012–5021.

35 Curran, D. P.; Chang, C. T., *J. Org. Chem.*, **1989**, *54*, 3140–3157.

36 Plummer, C. W.; Soheili, A.; Leighton, J. L., *Org. Lett.*, **2012**, *14*, 2462–2464.

37 Ohmiya, H.; Zhang, H.; Shibata, S.; Harada, A.; Sawamura, M., *Angew. Chem. Int. Ed.*, **2016**, *55*, 4777–4780.

38 Darses, B.; Michaelides, I. N.; Dixon, D. J., *Org. Chem. Front.*, **2014**, *1*, 117.

39 Weiberth, F. J.; Hall, S. S., *J. Org. Chem.*, **1987**, *52*, 3901–3904.

40 Gradillas, A.; Pérez-Castells, J., *Angew. Chem. Int. Ed.*, **2006**, *45*, 6086–6101.

41 Ichige, T.; Kamimura, S.; Mayumi, K.; Sakamoto, Y.; Terashita, S.; Ohteki, E.; Kanoh, N.; Nakata, M., *Tetrahedron Lett.*, **2005**, *46*, 1263–1267.

42 Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M., *J. Org. Chem.*, **2009**, *74*, 230–243.

43 Chandler, C. L.; Phillips, A. J., *Org. Lett.*, **2005**, *7*, 3493–3495.

44 T. Reddy, K.; Sreenivasulu, R.; Hatti, I.; Anitha, K.; R. Raju, R., *Curr. Org. Synth.*, **2015**, *12*, 67–70.

45 Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A., *J. Am. Chem. Soc.*, **2003**, *125*, 15512–15520.

46 Fuwa, H.; Yamaguchi, H.; Sasaki, M., *Org. Lett.*, **2010**, *12*, 1848–1851.

47 Scaglione, J. B.; Manion, B. D.; Benz, A.; Taylor, A.; DeKoster, G. T.; Rath, N. P.; Evers, A. S.; Zorumski, C. F.; Mennerick, S.; Covey, D. F., *J. Med. Chem.*, **2006**, *49*, 4595–4605.

48 Hoye, T. R.; Zhao, H., *Org. Lett.*, **1999**, *1*, 1123–1125.

49 Lin, Y. A.; Davis, B. G., *Beilstein J. Org. Chem.*, **2010**, *6*, 1219–1228.

50 Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H., *J. Am. Chem. Soc.*, **2005**, *127*, 17160–17161.

51 Ram, R. N.; Soni, V. K.; Gupta, D. K., *Tetrahedron*, **2012**, *68*, 9068–9075.

52 Temme, L.; Frehland, B.; Schepmann, D.; Robaa, D.; Sippl, W.; Wünsch, B., *Eur. J. Med. Chem.*, **2018**, *144*, 672–681.

53 Xu, Z.; Li, Y.; Xiang, Q.; Pei, Z.; Liu, X.; Lu, B.; Chen, L.; Wang, G.; Pang, J.; Lin, Y., *J. Med. Chem.*, **2010**, *53*, 4642–4653.

54 Janssen, J. P.; Helmchen, G., *Tetrahedron Lett.*, **1997**, *38*, 8025–8026.

55 Tosatti, P.; Nelson, A.; Marsden, S. P., *Org. Biomol. Chem.*, **2012**, *10*, 3147.

56 Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F., *J. Am. Chem. Soc.*, **2003**, *125*, 14272–14273.

57 Gnamm, C.; Förster, S.; Miller, N.; Brödner, K.; Helmchen, G., *Synlett*, **2007**, *2007*, 0790–0794.

58 Bartels, B.; García-Yebra, C.; Helmchen, G., *European J. Org. Chem.*, **2003**, *2003*, 1097–1103.

59 Dahnz, A.; Helmchen, G., *Synlett*, **2006**, 0697–0700.

60 Förster, S.; Tverskoy, O.; Helmchen, G., *Synlett*, **2008**, *2008*, 2803–2806.

61 Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M., *Org. Lett.*, **2017**, *19*, 1527–1529.

62 Liu, W.-B.; Okamoto, N.; Alexy, E. J.; Hong, A. Y.; Tran, K.; Stoltz, B. M., *J. Am. Chem. Soc.*, **2016**, *138*, 5234–5237.

63 Liu, W.-B.; Reeves, C. M.; Stoltz, B. M., *J. Am. Chem. Soc.*, **2013**, *135*, 17298–17301.

64 Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R., *Chem. Commun.*, **2007**, 675–691.

65 Hartwig, J. F.; Stanley, L. M., *Acc. Chem. Res.*, **2010**, *43*, 1461–1475.

66 Takeuchi, R.; Kezuka, S., *Synthesis*, **2006**, *2006*, 3349–3366.

67 He, H.; Zheng, X. J.; Li, Y.; Dai, L. X.; You, S. L., *Org. Lett.*, **2007**, *9*, 4339–4341.

68 Wynberg, H.; Staring, E. G. J., *J. Am. Chem. Soc.*, **1982**, *104*, 166–168.

69 Liu, G.; Romo, D., *Org. Lett.*, **2009**, *11*, 1143–1146.

70 Li, J.; Cisar, J. S.; Zhou, C.-Y.; Vera, B.; Williams, H.; Rodríguez, A. D.; Cravatt, B. F.; Romo, D., *Nat. Chem.*, **2013**, *5*, 510–517.

71 Morita, Y.; Kamakura, R.; Takeda, M.; Yamamoto, Y., *Chem. Commun.*, **1997**, 359–360.

72 Sevenard, D. V.; Didenko, A. V.; Lorenz, D.; Vorobiev, M.; Stelten, J.; Dülcks, T.; Sosnovskikh, V. Y., *Tetrahedron*, **2017**, *73*, 1495–1502.

73 Hansen, K. B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E. J. J.; Armstrong III, J. D., *J. Am. Chem. Soc.*, **2009**, *131*, 8798–8804.

74 Tosatti, P.; Nelson, A.; Marsden, S. P., *Org. Biomol. Chem.*, **2012**, *10*, 3147.

75 Göttlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M., *Synlett*, **1997**, *1997*, 971–973.

76 Wang, C.; Forsyth, C. J., *Org. Lett.*, **2006**, *8*, 2997–3000.

77 de la Hoz, A.; Díaz-Ortiz, Á.; Moreno, A., *Chem. Soc. Rev.*, **2005**, *34*, 164–178.

78 von Kieseritzky, F.; Wang, Y.; Axelson, M., *Org. Process Res. Dev.*, **2014**, *18*, 643–645.

79 Ishibashi, F.; Taniguchi, E., *Chem. Lett.*, **1986**, 1771–1774.

80 Ishibashi, F.; Taniguchi, E., *Bull. Chem. Soc. Jpn.*, **1988**, *61*, 4361–4366.

81 Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R., *J. Am. Chem. Soc.*, **2001**, *123*, 3239–3242.

82 Miyaoka, H.; Hara, Y.; Shinohara, I.; Kurokawa, T.; Yamada, Y., *Tetrahedron Lett.*, **2005**, *46*, 7945–7949.

83 Ota, K.; Sugata, N.; Ohshiro, Y.; Kawashima, E.; Miyaoka, H., *Chem. Eur. J.*, **2012**, *18*, 13531–13537.

84 Wu, M. J.; Pridgen, L. N., *J. Org. Chem.*, **1991**, *56*, 1340–1344.

85 Brown, H. C.; Kim, S. C., *Synthesis*, **1977**, *1977*, 635–636.

86 Hutchins, R. O.; Learn, K.; El-Telbany, F.; Stercho, Y. P., *J. Org. Chem.*, **1984**, *49*, 2438–2443.

87 Myers, A. G.; Yang, B. H.; David, K. J., *Tetrahedron Lett.*, **1996**, *37*, 3623–3626.

88 Pasumansky, L.; Goralski, C. T.; Singaram, B., *Org. Process Res. Dev.*, **2006**, *10*, 959–970.

89 Krackl, S.; Someya, C. I.; Enthaler, S., *Chem. Eur. J.*, **2012**, *18*, 15267–15271.

90 Dub, P. A.; Ikariya, T., *ACS Catal.*, **2012**, *2*, 1718–1741.

91 Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J., *J. Am. Chem. Soc.*, **2014**, *136*, 2268–2271.

92 Zimmermann, G.; Papke, B.; Ismail, S.; Vartak, N.; Chandra, A.; Hoffmann, M.; Hahn, S. A.; Triola, G.; Wittinghofer, A.; Bastiaens, P. I. H.; Waldmann, H., *Nature*, **2013**, *497*, 638–642.

93 Evans, D. A.; Ennis, M. D.; Mathre, D. J., *J. Am. Chem. Soc.*, **1982**, *104*, 1737–1739.

94 Hessel, L. W.; Romers, C., *Recl. des Trav. Chim. des Pays-Bas*, **2010**, *88*, 545–552.

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

96 Heiba, E. I.; Dessau, R. M.; Koehl, W. J., *J. Am. Chem. Soc.*, **1968**, *90*, 5905–5906.

97 Heiba, E. I.; Dessau, R. M., *J. Am. Chem. Soc.*, **1971**, *93*, 524–527.

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

99 Snider, B. B., *Chem. Rev.*, **1996**, *96*, 339–363.

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

101 Jasperse, C. P.; Curran, D. P.; Fevig, T. L., *Chem. Rev.*, **1991**, *91*, 1237–1286.

102 Mondal, M.; Bora, U., *RSC Adv.*, **2013**, *3*, 18716.

103 Jenkins, C. L.; Kochi, J. K., *J. Am. Chem. Soc.*, **1972**, *94*, 843–855.

104 Kochi, J. K.; Bemis, A.; Jenkins, C. L., *J. Am. Chem. Soc.*, **1968**, *90*, 4616–4625.

105 Snider, B. B.; Merritt, J. E.; Dombroski, M. A.; Buckman, B. O., *J. Org. Chem.*, **1991**, *56*, 5544–5553.

106 Snider, B. B.; Mccarthy, B. A., *J. Org. Chem*, **1993**, *58*, 6217–6223.

107 Hulcoop, D. G.; Burton, J. W., *Chem. Commun.*, **2005**, 4687–4689.

108 Hulcoop, D. G.; Burton, J. W., *Chem. Commun.*, **2005**, 4687.

109 Powell, L. H.; Docherty, P. H.; Hulcoop, D. G.; Kemmitt, P. D.; Burton, J. W., *Chem. Commun.*, **2008**, 2559–2561.

110 Beckwith, A. L. J., *Tetrahedron*, **1981**, *37*, 3073–3100.

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

112 Logan, A. W. J.; Parker, J. S.; Hallside, M. S.; Burton, J. W., *Org. Lett.*, **2012**, *14*, 2940–2943.

113 Chany, A.-C.; Marx, L. B.; Burton, J. W., *Org. Biomol. Chem*, **2015**, *13*, 9190–9193.

114 Logan, A. W. J.; Sprague, S. J.; Foster, R. W.; Marx, L. B. L. B.; Garzya, V.; Hallside, M. S.; Thompson, A. L.; Burton, J. W., *Org. Lett.*, **2014**, *16*, 4078–4081.

115 Ferrara, S. J.; Burton, J. W., *Chem. Eur. J.*, **2016**, *22*, 11597–11600.

116 Davies, J. J.; Krulle, T. M.; Burton, J. W., *Org. Lett.*, **2010**, *12*, 2738–2741.

117 Yan, M.; Kawamata, Y.; Baran, P. S., *Chem. Rev.*, **2017**, *117*, 13230–13319.

118 Waldvogel, S. R.; Janza, B., *Angew. Chem. Int. Ed.*, **2014**, *53*, 7122–7123.

119 Sperry, J. B.; Wright, D. L., *Chem. Soc. Rev.*, **2006**, *35*, 605–621.

120 Moeller, K. D., *Tetrahedron*, **2000**, *56*, 9527–9554.

121 Schäfer, H. J., *Angew. Chem. Int. Ed.* , **1981**, *20*, 911–934.

122 Kolbe, H., *Ann. der Chemie und Pharm.*, **1849**, *69*, 257–294.

123 Lund, H., *J. Electrochem. Soc.*, **2002**, *149*, S21.

124 Shono, T.; Hamaguchi, H.; Matsumura, Y., *J. Am. Chem. Soc.*, **1975**, *97*, 4264–4268.

125 Jones, A. M.; Banks, C. E., *Beilstein J. Org. Chem.*, **2014**, *10*, 3056–3072.

126 Alfonso-Súarez, P.; Kolliopoulos, A. V.; Smith, J. P.; Banks, C. E.; Jones, A. M., *Tetrahedron Lett.*, **2015**, *56*, 6863–6867.

127 Wong, P. L.; Moeller, K. D., *J. Am. Chem. Soc.*, **1993**, *115*, 11434–11445.

128 Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K., *J. Am. Chem. Soc.*, **1999**, *121*, 9546–9549.

129 Horn, E. J.; Rosen, B. R.; Baran, P. S., *ACS Cent. Sci.*, **2016**, *2*, 302–308.

130 Schäfer, H.-J., in *Electrochemistry IV*, Springer-Verlag, Berlin/Heidelberg, pp. 91–151.

131 Feng, R.; Smith, J. A.; Moeller, K. D., *Acc. Chem. Res.*, **2017**, *50*, 2346–2352.

132 Torii, S.; Uneyama, K.; Onishi, T.; Fujita, Y.; Ishiguro, M.; Nishida, T., *Chem. Lett.*, **1980**, *9*, 1603–1604.

133 Yoshida, J.; Sakaguchi, K.; Isoe, S., *Tetrahedron Lett.*, **1986**, *27*, 6075–6078.

134 Yoshida, J. J.; Sakaguchi, K.; Isoe, S., *J. Org. Chem.*, **1988**, *53*, 2525–2533.

135 Inokuchi, T.; Matsumoto, S.; Torii, S., *J. Org. Chem.*, **1991**, *56*, 2416–2421.

136 Chen, J.; Yan, W.-Q.; Lam, C. M.; Zeng, C.-C.; Hu, L.-M.; Little, R. D., *Org. Lett.*, **2015**, *17*, 986–989.

137 Horn, E. J.; Rosen, B. R.; Chen, Y.; Tang, J.; Chen, K.; Eastgate, M. D.; Baran, P. S., *Nature*, **2016**, *533*, 77–81.

138 Snider, B. B.; McCarthy, B. A., in *ACS Symposium Series*, American Chemical Society, **1994**, vol. 577, pp. 84–97.

139 Merchant, R. R.; Oberg, K. M.; Lin, Y.; Novak, A. J. E.; Felding, J.; Baran, P. S., *J. Am. Chem. Soc.*, **2018**, *140*, 7462–7465.

140 Anastas, P.; Warner, J., *Green Chemistry: Theory and Practice*, Oxford University Press, New York, **1998**.

141 Linthorst, J. A., *Found. Chem.*, **2010**, *12*, 55–68.

142 Ripin, D. H.; Evans, D. A., Evan's pKa Table, http://www.chem.wisc.edu/areas/reich/pkatable/index.htm, (accessed 8 August 2018).

143 Arnett, E. M.; Harrelson, J. A., *J. Am. Chem. Soc.*, **1987**, *109*, 809–812.

144 Kornblum, N.; Blackwood, R. K.; Mooberry, D. D., *J. Am. Chem. Soc.*, **1956**, *78*, 1501–1504.

145 Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E., *J. Am. Chem. Soc.*, **1956**, *78*, 1497–1501.

146 Magolan, J.; Kerr, M. A., *Org. Lett.*, **2006**, *8*, 4561–4564.

147 Rodin, J., University of Oxford Part II Thesis, **2008**.

148 Snider, B. B.; Smith, R. B., *Tetrahedron*, **2002**, *58*, 25–34.

149 Unsworth, W. P.; Coulthard, G.; Kitsiou, C.; Taylor, R. J. K., *J. Org. Chem.*, **2014**, *79*, 1368–1376.

150 WO 2006/104997 A2, **2006**.

151 Winkler, M.; Maynadier, M.; Wein, S.; Lespinasse, M.-A.; Boumis, G.; Miele, A. E.; Vial, H.; Wong, Y.-S., *Org. Biomol. Chem.*, **2015**, *13*, 2064–2077.

152 Smith, J. A.; Moeller, K. D., *Org. Lett.*, **2013**, *15*, 5818–5821.

153 Williams, D. B. G.; Lawton, M., *J. Org. Chem.*, **2010**, *75*, 8351–8354.

154 Peña, J.; Antón, A. B.; Moro, R. F.; Marcos, I. S.; Garrido, N. M.; Díez, D., *Tetrahedron*, **2011**, *67*, 8331–8337.

155 Avi, M.; Gaisberger, R.; Feichtenhofer, S.; Griengl, H., *Tetrahedron*, **2009**, *65*, 5418–5426.

156 Nidhiry, J. E.; Prasad, K. R., *Tetrahedron*, **2013**, *69*, 5525–5536.

157 Yildizhan, S.; van Loon, J.; Sramkova, A.; Ayasse, M.; Arsene, C.; ten Broeke, C.; Schulz, S., *ChemBioChem*, **2009**, *10*, 1666–1677.

158 Bichlmaier, I.; Kurkela, M.; Joshi, T.; Siiskonen, A.; Rüffer, T.; Lang, H.; Suchanová, B.; Vahermo, M.; Finel, M.; Yli-Kauhaluoma, J., *J. Med. Chem.*, **2007**, *50*, 2655–2664.

159 Ganta, A.; Shamshina, J. L.; Cafiero, L. R.; Snowden, T. S., *Tetrahedron*, **2012**, *68*, 5396–5405.

160 Hashimoto, K.; Kitaguchi, J.-I.; Mizuno, Y.; Kobayashi, T.; Shirahama, H.; Oh, O. H. N. M., *Tetrahedron Lett.*, **1996**, *37*, 2275–2278.

161 Malová Križková, P.; Lindner, W.; Hammerschmidt, F., *Synthesis*, **2018**, *50*, 651–657.

162 Bultman, M. S.; Ma, J.; Gin, D. Y., *Angew. Chem. Int. Ed.*, **2008**, *47*, 6821–6824.

163 Murphy, J. A.; Schoenebeck, F.; Findlay, N. J.; Thomson, D. W.; Zhou, S.; Garnier, J., *J. Am. Chem. Soc.*, **2009**, *131*, 6475–6479.

164 Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K., *Org. Lett.*, **2007**, *9*, 1565–1567.

165 Marsh, G. P.; Parsons, P. J.; McCarthy, C.; Cornique, X. G., *Org. Lett.*, **2007**, *9*, 2613–2616.

166 Vallejos, G.; Fierro, A.; Rezende, M. C.; Sepúlveda-Boza, S.; Reyes-Parada, M., *Bioorganic Med. Chem.*, **2005**, *13*, 4450–4457.

167 Cai, S.; Zhang, S.; Zhao, Y.; Wang, D. Z., *Org. Lett.*, **2013**, *15*, 2660–2663.

168 Morita, J.-I.; Nakatsuji, H.; Misaki, T.; Tanabe, Y., *Green Chem.*, **2005**, *7*, 711.