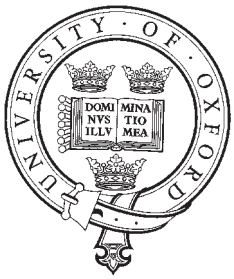

Synthesis of Complex γ-Lactones Mediated By Manganese(III)

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Abstract

This thesis details the development of manganese(III) acetate-mediated oxidative radical cyclisation methodology. In particular, the use of radicals to form complex, highly sterically congested and strained carbo- and heterocycles in a stereocontrolled manner is described.

Chapter 1 gives a summary of the literature regarding three key areas relevant to this work. Radical reaction mechanisms are introduced, including the use of transition metals and lanthanides in *C*-centred radical cyclisations. The formation of highly sterically congested vicinal all-carbon quaternary stereocentres is also discussed. Finally, the use of radical cyclisation methodology for the synthesis of complex cyclic structures and applications in natural product total synthesis is examined.

Chapter 2 gives an account of the manganese(III) acetate-mediated cyclisation of 5-pentenyl malonates bearing a terminal aryl group. The effects of the aryl group are tested with a range of electronically varied substituents. The formation of bi- and tricyclic cyclopentane-lactones bearing adjacent quaternary-quaternary-tertiary stereocentres is demonstrated.

Chapter 3 demonstrates the synthesis of highly strained tricyclic *bis*-lactones. The metal complexes manganese(III) acetate and cerium(IV) ammonium nitrate are shown to give complementary stereoselectivity across a range of cyclisation substrates. Possible synthetic applications of tricyclic *bis*-lactones are also investigated.

Chapter 4 details an asymmetric formal synthesis of the proteasome inhibitor salinosporamide A. An oxidative radical cyclisation forms the key heterocycle in Danishefsky's synthesis of this biologically important molecule, and showcases the use of the radical chemistry in natural product synthesis.

Full experimental details, selected NMR spectra, and X-ray crystallographic data are also provided.

Declaration

The work described in this 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.

Angus W.J. Logan

September 2012

Contents

Selected Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Ar	aryl
aq	aqueous
atm	atmosphere(s)
BHT	2,6-di-*tert*-butyl-4-methylphenol
bmim	1-butyl-3-methylamidazolium
Bn	benzyl
b.p.	boiling point
d	day(s)
cat.	catalytic
Cp	cyclopentadienyl
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEM	diethyl malonate
DiBAl-H	diisobutylaluminium hydride
DIC	diisopropylcarbodiimide
DiPA	diisopropylamine
DMAP	*N,N*-dimethylpyridin-4-amine
DMF	dimethyl formamide
DMM	dimethyl malonate
DMS	dimethyl sulfide

DMSO	dimethylsulfoxide
d	day(s)
d.e.	diastereomeric excess
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
FI	field ionisation
FID (NMR)	free induction decay
FID (GC)	flame ionisation detector
ESI	electrospray ionisation
GC	gas chromatography
h	hour(s)
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
IPA	isopropyl alcohol
m-CPBA	*meta*-chloroperbenzoic acid
min	minute(s)
m.p.	melting point
Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
NMP	*N*-methyl-2-pyrollidinone
NMR	nuclear magnetic resonance
PE	petroleum ether b.p. 40–60 °C
Pg	a protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
Piv	pivaloyl
py	pyridine
RT	room temperature
sat	saturated

SET	single electron transfer
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
Ts	4-methylbenzenesulfonyl

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To the CRL service staff: Drs Barbara Odell and Tim Claridge in NMR ran many nOe experiments at rather short notice and were always helpful. I would like to thank Dr Amber Thompson for running a number of crystal structures and help with processing. The mass spectrometry service were also invaluable.

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parents, Crawford and Christine, for all the love and support that they have unfailingly given me; I couldn't ask for better.

1 Introduction

This thesis focuses on the synthesis of bi- and tricyclic γ-lactones and tricyclic *bis*-lactones using oxidative radical cyclisation reactions. In particular, the formation of compact, highly oxidised, and sterically congested molecules will be discussed. The electronic effect of substituents will also be examined. This Chapter gives a summary of literature precedent in the fields of (oxidative) radical cyclisations, the use of transition metals and lanthanides to mediate these reactions, the stereocontrolled synthesis of vicinal quaternary stereocentres, and the synthesis of strained cyclopentane-lactones.

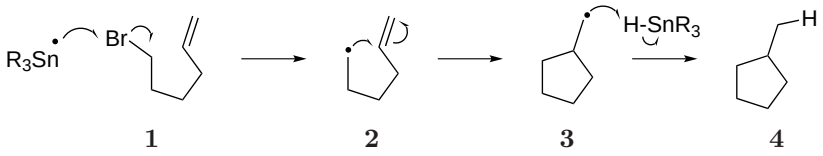
1.1 Radical Cyclisation Reactions

Free radical cyclisations are a frequently used reaction for the synthesis of carbo- and heterocyclic systems.[1,2] Under mild conditions, complex structures may be formed from relatively simple precursors. Prime motivations for the use of radical reactions include the inherently high reactivity of carbon radic-

als, low susceptibility to steric incumberance, generally predictable kinetic reactivity, and operationally simple reaction procedures.

1.1.1 Reductive Radical Cyclisation Mechanisms

The classical radical cyclisation involves the reduction of a C-X bond (**Scheme 1.1**), where X is typically a halogen *e.g.* **1**, by a trialkyl stannane radical generated *in situ* from stoichiometric hydride with an initiator such as AIBN, peroxides, or UV light.[3] Other reagents, most notably silicon hydrides[4–6] may also be employed, although their use is not as widespread as tin due to the latter's well-proven reactivity. The radical thus generated, **2**, may then undergo 5-*exo*-trig cyclisation, generally according to Baldwin's rules,[7] to give radical **3**. The radical chain is then propagated by hydrogen atom abstraction from another R_3SnH molecule, which gives the reduced product, methylcyclopentane **4**. Whilst radical reactions have been used to synthesise rings of many sizes, this Chapter will focus only on five and six membered rings.



Scheme 1.1: Trialkyltin hydride mediated 5-hexenyl radical cyclisation.

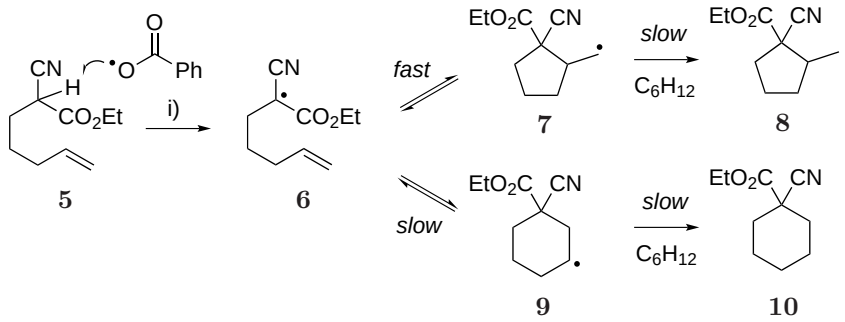
Aside from the toxicity issues involved in handling organotin species, this reductive approach has two significant drawbacks. Firstly a heavy halide has been replaced by a hydrogen and the halide lost as R_3Sn-X. Modern organic chemistry is focused on reducing waste and this is an archetypal "atom uneconomical" reaction: the major waste stream is R_3Sn-X, which is not incorporated in the product.[8] Secondly, the oxidation level of the product has been reduced relative to the starting material. Baran and Hoffmann have formalised the concept of "redox economy",[9] and reductive radical cyclisations do not meet these criteria either: reactivity has been traded for structural complexity.

Nevertheless, a number of excellent synthetic methodologies and total syntheses have been developed using the tributyl tin radical. Other metals have been used in highly selective reductive radical reactions, most notably samarium(II).[10,11]

1.1.2 Oxidative Radical Cyclisation Reactions

In contrast to the overall two electron reduction in a reductive radical cyclisation, oxidative radical cyclisation reactions result in a two electron oxidation of the substrate. A distinction should be drawn

between oxidative *initiation* and oxidative *termination*. A classic example of oxidative initiation is the cyclisation of β-nitrile **5** by Julia (**Scheme 1.2**).[12] Oxidative initiation commences with abstraction of a hydrogen atom from β-nitrile ester **5** by the benzoyloxy radical, which gives radical **6**. In this case, the oxidant is the benzoyloxyl radical, which is itself reduced to benzoic acid. Thus, radical **6** has been generated *oxidatively*.



Reagents & Conditions: i) $(PhCO_2)_2$, C_6H_{12}, 80 °C.

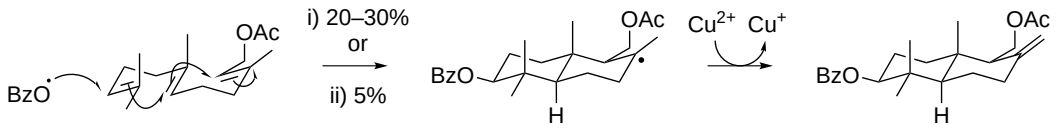
Scheme 1.2: Julia's demonstration of oxidative radical initiation.[12]

In this reaction however, there is no corresponding oxidant for radicals **7** and **9**. Thus the *termination* in this case is *reductive*. Overall, there is no change in oxidation level. Huang and co-workers showed that the first cyclisation (**6**→**7** or **9**) can be reversible for malonyl systems such as **5**.[13] Hydrogen abstraction from the solvent (cyclohexane) is slow for both radicals **7** and **9**, and as the cyclohexyl radical **9** is more stable, cyclohexane **10** is therefore exclusively formed as the thermodynamic product.

Benzoyloxyl radicals are useful, but not general, oxidative radical initiators but do not normally act as oxidative terminators. Oxidative termination is most often achieved with a transition metal. One of the earliest examples was Breslow and co-workers' farnesyl acetate cascade cyclisation (**Scheme 1.3**) using $Cu(OBz)_2$ as the terminal oxidant (*vide infra* **Section 1.2.2**).[14,15] Treatment of farnesyl acetate **11** with benzoyloxyl radical generated by thermal decomposition or photolysis of benzoyl peroxide gave decalin **12** in up to 30% and 5% yield respectively. The intermediate tertiary radical **13** underwent oxidative elimination, mediated by $Cu(OBz)_2$, which gave *exo*-alkene **12** in an overall $2e^-$ oxidation from diene **11**.

1.1.3 Relative Radical Cyclisation Reaction Rates

In the case of an unsubstituted 5-hexenyl substrate such as **14** (**Scheme 1.4**), it is not immediately clear whether the 5-*exo* (**14**→**15**) or 6-*endo* (**14**→**16**) cyclisation mode would be preferred. It should

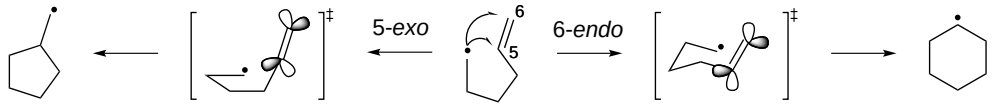


11 **13** **12**

Reagents & Conditions: i) $(BzO)_2$, $Cu(OBz)_2$, CuCl, MeCN, 80 °C; ii) $(BzO)_2$, $Cu(OBz)_2$, fluorescein, hν, MeCN, RT.

Scheme 1.3: Breslow's oxidative farnesyl cascade radical cyclisation.[15]

be noted that both reactions are irreversible (*cf.* **Section 1.2.1**).[16] Experimentally, it was shown that the reaction of 5-hexenyl radical **14** gives a 98:2 ratio of **15**:**16**, which implies that $\frac{k_{1,5}}{k_{1,6}} \approx 50$ (at 333 K). However, the cyclohexyl radical **16** is thermodynamically more stable than the methylcyclopentyl radical **15**.



15 **17** **14** **18** **16**

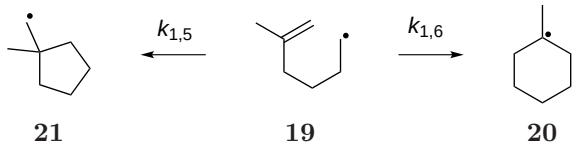
Scheme 1.4: Transition states for 5-*exo* and 6-*endo* cyclisation of 5-hexenyl radical **14**.

By considering the overlap of the $2p$ singly occupied molecular orbital (SOMO) with the π/π^* orbital of the alkene in the transition state, the apparent contradiction was resolved with the radical attacking *vertically* relative to the nodal plane of the π system.[17] Thus, the preferred 5-*exo* mode of reaction (transition state **17**) is a consequence of stereoelectronic effects, rather than thermodynamics.[7,18] The extra strain required to attain the necessary arrangement of reactive centres in the 6-*endo* transition state **18** outweighs the thermodynamic factors that would otherwise favour formation of **16**.

This hypothesis was strengthed by thermodynamic data regarding the activation energies, which suggest that $\Delta H^{\ddagger}_{1,6} - \Delta H^{\ddagger}_{1,5} = 7.0$ kJmol^{-1} and $\Delta S^{\ddagger}_{1,6} - \Delta S^{\ddagger}_{1,5} = -11.7$ Jmol^{-1}.[19–21] Clearly, the enthalpic term dominates the activation energy at common laboratory temperatures <250 °C and the reaction leading to the less thermodynamically favoured product **15** has a correspondingly lower $\Delta H^{\ddagger}$.

This conclusion has also gained significant computational support. In independent studies Beckwith[22] and later Houk[23] calculated the transition state energies using MM2 force field models, with fixed and flexible reactants respectively. These calculations showed that the 5-*exo* transition state **17** was 7.1 kJ mol^{-1} (Beckwith) or 10.0 kJ mol^{-1} (Houk) more favourable than 6-*endo* transition state **18**, with the latter figure closer to experimental values at 283 K, probably due to the more advanced model used by Houk and Spellmeyer.

The rate of cyclisation of 5-substituted substrate **19**, and other substituted substrates, was studied by Beckwith and co-workers (**Scheme 1.5**).[24] It was found experimentally that $\frac{k_{1,5}}{k_{1,6}} = 0.62$ showing that the substituent at C-5 biases the reaction toward the 6-*endo* mode. It would be tempting to ascribe this to the enhanced stability, by hyperconjugation, of tertiary radical **20** over primary radical **21**, *i.e.* a thermodynamic argument.



Scheme 1.5: Radical cyclisation of 5-substituted substrate **19**.

Detailed kinetic studies showed that the substituent only slightly increases the relative rate of the 6-*endo* cyclisation, but dramatically decreases the rate of the 5-*exo* cyclisation.[25] This has been attributed to steric effects.

1.2 Single Electron Oxidants for Oxidative Radical Reactions

Due to their ability to easily change oxidation state, a number of transition metals and lanthanides have been used as single electron oxidants in organic synthesis. In particular, this Section will focus on manganese(III) acetate and ammonium cerium(IV) nitrate, with a brief look at other relevant metals.[26]

1.2.1 Manganese(III) Acetate

Manganese(III) acetate was first used in organic synthesis in the 1960s.[27] Manganese displays rich redox chemistry, with oxidation states +2,+3,+4,+6, and +7 all accessible under the slightly acidic conditions typical of manganese(III) acetate radical reactions.[28] Of interest in this case are the electrode potentials for the redox reactions given in **Equations 1.1** and **1.2**. It can be seen that the reduction of Mn^{3+} to Mn^{2+} is a favourable process, and so Mn^{3+} is a strong oxidant. Manganese(III) is however prone to disproportionation to Mn^{2+} and Mn^{4+}.

$$Mn^{3+} + e^- \rightarrow Mn^{2+} = +1.50\text{V} \tag{1.1}$$

$$Mn^{3+} \rightarrow Mn^{4+} + e^- = -1.06\text{V} \tag{1.2}$$

Anhydrous manganese(III) acetate has been reported as an *oxo*-centred trimer $Mn_3O(OAc)_6$ (**Figure**

1.1), with analogous iron and chromium compounds also characterised.[29–31] More commonly used as the dihydrate in synthesis, it has not been ascertained whether the trimeric form persists in solution, however based on mechanistic understanding this seems likely (see **Section 1.2.1.1**). For the purposes of this thesis, manganese(III) acetate will be represented as the monomeric $Mn(OAc)_3{\cdot}2H_2O$ species, and will be abbreviated as MAN.

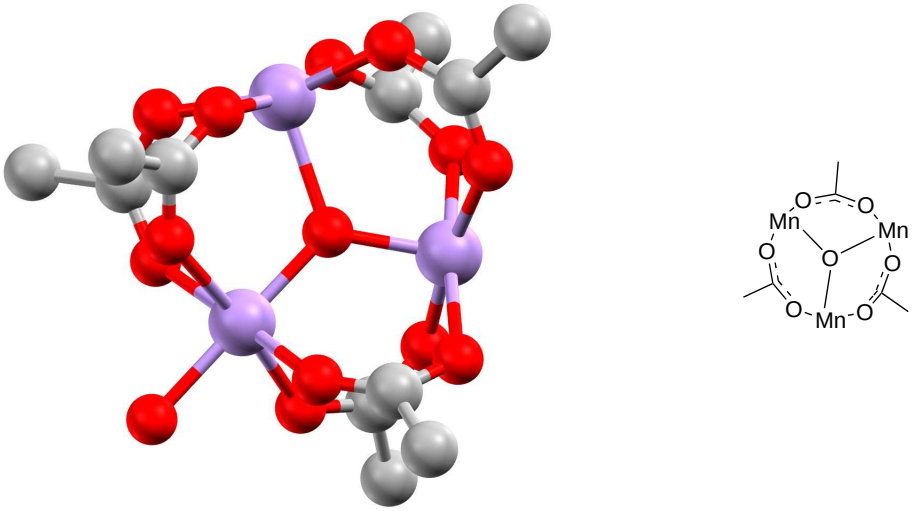
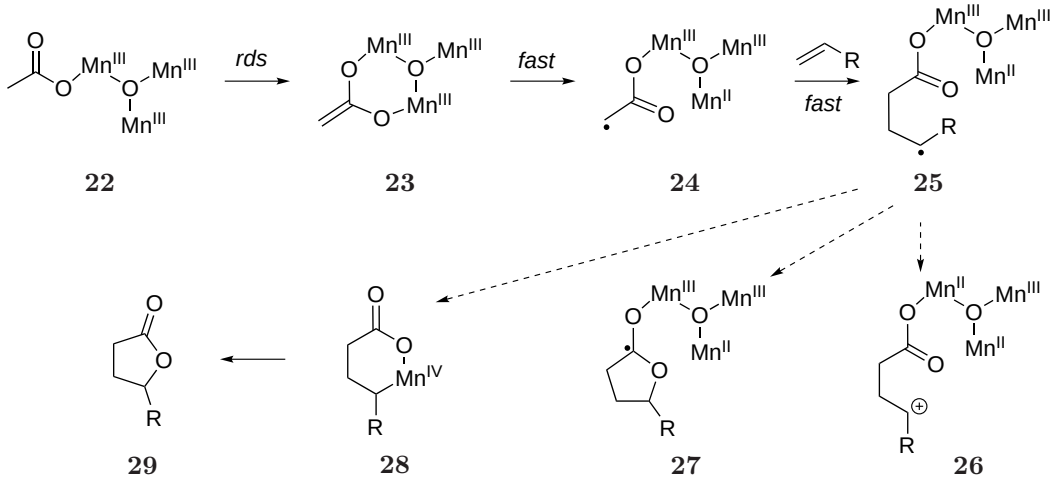


Figure 1.1: Single crystal X-ray diffraction structure of $Mn_3(\mu_3\text{-O})(\mu\text{-OAc})_6$ showing the bridging acetates. Adapted from Hessel and Romers.[29] Three acetates are omitted from the drawn structure for clarity.

1.2.1.1 Synthesis of γ-Lactones From Alkenes

An early use of MAN was in the intermolecular oxidative addition of acetic acid to alkenes to give γ-lactones.[32,33] Fristad and Peterson studied this reaction in depth, and proposed a mechanism (**Scheme 1.6**) based on their observations of reaction stoichiometry, enolisation rates, and alkene concentration rate dependence.[34]

After the initial coordination of trimeric MAN to acetic acid, **22**, Fristad and Peterson showed that the rate determining step was the irreversible formation of manganese enolate **23**. This was shown by monitoring the reaction in HOAc/DOAc-d_4: formation of lactone **29** exceeded the rate of H/D exchange, which implied that every manganese enolate formed reacted with an alkene.[35] Additionally, it was shown that the rate of reaction, relative to acetic acid, was $\log(k_{rel}) = 0.344\ \Delta pK_a$ ($\Delta pK_a =$



Scheme 1.6: Proposed mechanism for the formation of γ-lactones by addition of acetic acid to alkenes.

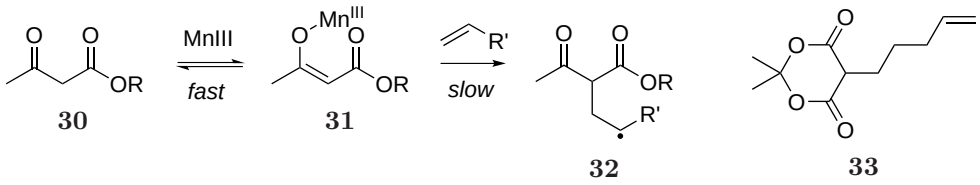
pK_a(acetic acid)−pK_a(substituted acid)) over a pK_a range of 16 for acetic acid derivatives with electron withdrawing groups (NC-, $PhSO_2$-, MeO_2C-, HO_2C-, Cl-).[34] As electron withdrawing groups enhance the rate of reaction, β-keto esters and malonates have also been widely used and studied (see **Section 1.3.2**).

Enolate **23** is then oxidised by single electron transfer to give *electrophilic* radical **24**, which then rapidly adds to the least hindered end of an alkene to give adduct radical **25** with the trimeric MAN complex believed to be still coordinated. From this point, there are a number of plausible mechanisms which would give lactone **29**: a) formation of cation **26** by further oxidation and then trapping with the carboxylate, b) attack of radical **25** on to the carbonyl oxygen to give **27**, which is then oxidised with loss of Mn^{II}, and c) formation of the six-membered organometallic **28**, followed by reductive elimination.[36] Formation of cation **26** is unlikely, unless R is a strong cation stabilising group *e.g.* phenyl. Accordingly, the reaction of norbornene with MAN in acetic acid did not give any rearrangement products corresponding to formation of the 2-norbornyl cation.[34] Computational studies have shown that the 5-*endo*-trig cyclisation on to a carbonyl oxygen is disfavoured,[37] and so it is unlikely that the pathway through radical **27** is in operation. It will be assumed that **28** is the major reaction pathway, although there is still no definitive proof as to exactly which mechanism is in operation.

1.2.1.2 Reactions of Acetic Acid Derivatives

For highly acidic acetic derivatives (p$K_a \leq 12$), such as β-keto ester **30**, the mechanism changes (**Scheme 1.7**). The enolisation is now fast (**30**→**31**) due to the low pK_a, and so addition to the alkene is the rate

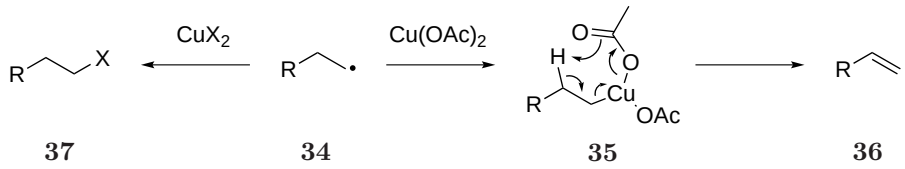
determining step (**31**→**32**).[38] Evidence suggests that the isolated β-keto ester radical is not formed, and in fact simultaneous oxidation/addition to the alkene gives radical **32**. The same mechanism is also in operation when alkenyl-substituted Meldrum's acid derivatives **33** are used.[39]



Scheme 1.7: Mechanism of oxidative addition with highly C-H acidic ($pK_a \leq 12$) substrates.

1.2.2 Use of Copper(II) as Co-Oxidant

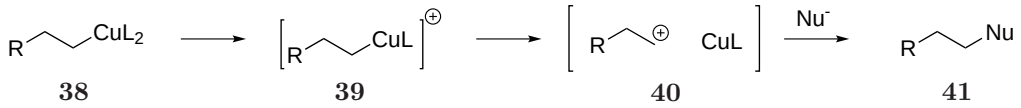
In 1971, Heiba and Dessau investigated copper(II) acetate as a co-oxidant in MAN reactions, with copper(II) being ≈350× faster at oxidising alkyl radicals than MAN.[40] This followed from extensive studies by Kochi and co-workers on the oxidation of radicals with transition metal salts, in particular copper(II), which reacts with alkyl radicals with a rate constant of $\approx 10^6$ $M^{-1}s^{-1}$.[41,42] Alkyl radicals such as **34** may be trapped by copper(II) salts and go on to more elaborate products (**Scheme 1.8**). When copper(II) acetate is used the organocuprate **35** may then undergo elimination potentially *via* a pericyclic-like reaction to give alkene **36** with loss of copper(I).[43] Secondary radicals have been shown to give moderate levels of *E*-selectivity and favour the less substituted Hofmann elimination product.[44] When copper(II) halides are used, products such as alkyl halide **37** are formed by either ligand transfer or reductive elimination.



Scheme 1.8: Oxidation pathways mediated by copper(II) salts.

The predominant pathway is determined by the choice of copper ligand. With ligands that have a high affinity for the copper(III) cation, *e.g.* RCO_2^-, alkene **36** is the major product formed by elimination of copper(I). However, in organocuprates **38** with highly stabilised ligands, *e.g.* TfO^- and $[BF_4]^-$, substitution rather than elimination is the dominant pathway. It was proposed by Kochi that this was due to ligand dissociation giving highly electron deficient species **39** (**Scheme 1.9**), which may then

dissociate further to give the formal cation **40**, which may then react with a nucleophile to give **41**.[45] The use of such ligands is discussed further in **Section 1.2.3**.



38 **39** **40** **41**

Scheme 1.9: Ligand dissociation from organocuprate **38** to give an alkyl cation.

During the course of the reaction, copper(I) is formed and may be oxidised by manganese(III) to regenerate the required copper(II) species, as the oxidation potential is low (**Equation 1.3**). In principle, this means that cyclisation reactions may be catalytic in copper(II) salts. The low oxidation potential shows that although copper(II) is a less powerful oxidant than manganese(III) the high rate of reaction with alkyl radicals means it is a more effective oxidant than manganese(III).

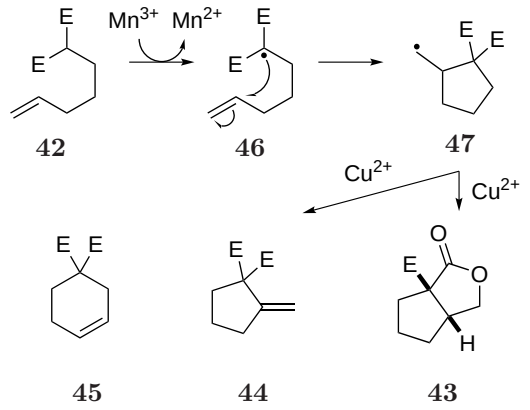
$$Cu^{+} \rightarrow Cu^{2+} + e^{-} = -0.16 \text{ V} \tag{1.3}$$

1.2.3 Cyclopentane-Lactones by Oxidative Radical Cyclisation

In 1991, Snider and co-workers reported the reaction of 4-pentenyl malonate **42** with MAN and $Cu(OAc)_2$ in acetic acid, which gave the cyclopentane products **43** and **44**, and the cyclohexene **45**. A plausible mechanism is shown in **Scheme 1.10**. Malonate **42** was oxidised by MAN to give radical **46**. The radical underwent a 5-*exo*-trig cyclisation to give adduct radical **47**, which then reacted with copper(II). Bicyclic γ-lactone **43** was formed by displacement of copper(I) by the proximal ester, which subsequently underwent hydrolysis. Alkene **44** was maybe formed by elimination of copper(I). Cyclohexene **45** was the product of a 6-*endo* cyclisation, followed by oxidation and elimination of copper(I).[46] It should be noted that in contrast to the radicals discussed in **Section 1.1.3**, formation of radical **47** can be reversible. In the absence of $Cu(OAc)_2$ as an oxidant, polymeric material was obtained.

It was clear that solvent also had a significant influence on both yield and selectivity.[47] Of particular interest are **Scheme 1.10 Entries 4** and **5**. The use of the polar aprotic solvent DMSO resulted in 10:1 selectivity for *exo*-alkene **44** over γ-lactone **43**, while the opposite is observed when MeCN is used instead. The authors did not propose an explanation for this selectivity.

The poor yield for the reaction carried out in EtOH was due to a reductive reaction also in operation (**Scheme 1.11**). Instead of radical **47** being slowly oxidised by Mn^{3+} it may abstract a hydrogen atom from a solvent molecule, **47**→**48**+**49**. Radical **49** can then be oxidised to acetaldehyde **50**, thus

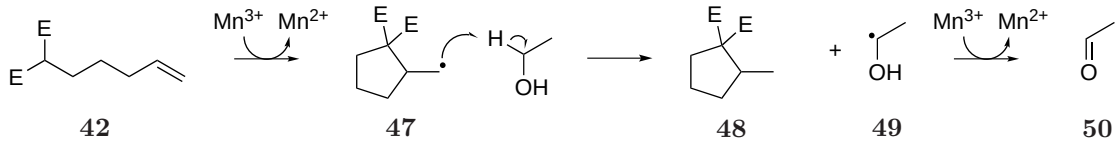


Entry	Solvent	T / °C	Yield / %		
			43	**44**	**45**
1	AcOH	55	48	20	7
2	EtOH[a]	60	14	22	4
3	DMF	75	17	32	5
4	DMSO	75	5	53	2
5	MeCN	55	38	8	3

[a]No copper(II) additive.

Scheme 1.10: Snider's synthesis of bicyclic γ-lactones.[46] All reactions were carried out with 2 eq. $Mn(OAc)_3{\cdot}2H_2O$ and 1 eq. of $Cu(OAc)_2$. E = CO_2Me.

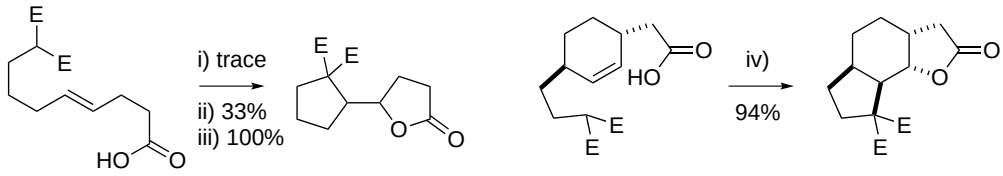
completing the radical chain. This is equivalent to the case illustrated in **Scheme 1.2**, where no net oxidation or reduction of the substrate has taken place.



Scheme 1.11: Formation of cyclopentane **48** by hydrogen abstraction. E = CO_2Me.

As discussed in **Section 1.2.2**, strongly dissociated ligands on Cu^{2+}, *e.g.* TfO^- or $[BF_4]^-$, should promote oxidative substitution over β-hydride elimination. This was demonstrated in the Burton group with the cyclisation of malonate **51**, which gave lactone **52** in excellent yield as a mixture of diastereomers (**Scheme 1.12**). With no copper(II) additive, only a trace amount of lactone **52** was detected. With copper(II) acetate, lactone **52** was obtained in 33% yield and finally with copper(II) triflate, a quantitative yield of **52** was obtained.[48] It was also shown that carboxylates were better nucleophiles for the oxidative displacement than hydroxyl, with malonate **53** cyclising to give tricyclic γ-lactone **54** in 94% yield.[49]

Following on from these results, the cyclisation of 4-pentenyl malonate **42** and substituted compounds was investigated further. It was reasoned that the choice of copper(II) salt, solvent, and concentration should effectively control the product distribution. Thus, low substrate concentration in alcohol should favour the formation of methylcyclopentane **48**, as the effective concentration of alcohol is high so hydrogen abstraction is likely. Conversely, high concentration in non-alcoholic solvents should favour oxidation reactions. To select between alkene **44** and γ-lactone **43**, ligand and solvent were considered. Based on Snider[46] and Kochi's[45] data, the use of the tightly coordinated $Cu(OAc)_2$ in DMSO should



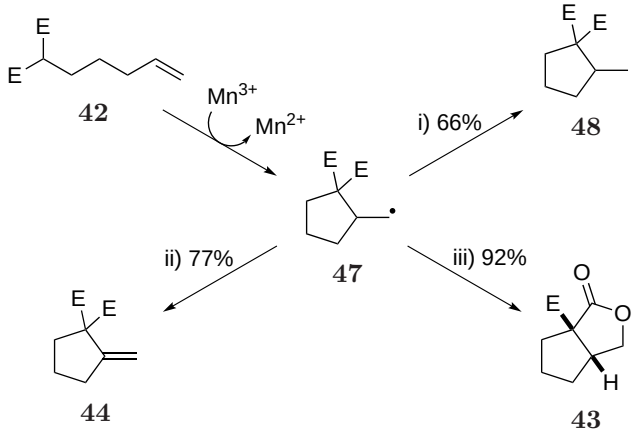
51 **52** **53** **54**

Reagents & Conditions: All reactions were carried out with 2 eq. $Mn(OAc)_3{\cdot}2H_2O$ in MeCN at 80 °C. Additive: i) none; ii) 1 eq. $Cu(OAc)_2$; iii, iv) 1 eq. $Cu(OTf)_2$.

Scheme 1.12: Burton's syntheses of THFs and lactones by oxidative radical cyclisation with $Cu(OTf)_2$ as co-oxidant. E = CO_2Me.[48,49]

favour alkene **44** formation by β-hydride elimination. Similarly, $Cu(OTf)_2$ in MeCN should favour lactonisation as the ligands are more dissociated and so substitution is more likely.

This was indeed the case (**Scheme 1.13**).[50] Treatment of malonate **42** with MAN in ethanol (0.02 M) gave methylcyclopentane **48** in 66% yield. With MAN and $Cu(OAc)_2$ in DMSO (0.20 M), alkene **44** was formed in 77% yield, with a small amount (7%) of γ-lactone **43**. Finally, MAN and $Cu(OTf)_2$ in MeCN (0.20 M) gave γ-lactone **43** in 92% yield. For oxidative reactions, it was found that the use of deoxygenated solvent was essential, as residual oxygen may react with radical intermediates.



Reagents & Conditions: All reactions were carried out with 2 eq. $Mn(OAc)_3{\cdot}2H_2O$ at 80 °C. i) EtOH (0.02 M); ii) 1 eq. $Cu(OAc)_2$, DMSO (0.20 M); iii) 1 eq. $Cu(OTf)_2$, MeCN (0.20 M).

Scheme 1.13: Selective synthesis of compounds **43**, **44**, and **48**. E = CO_2Me.[50]

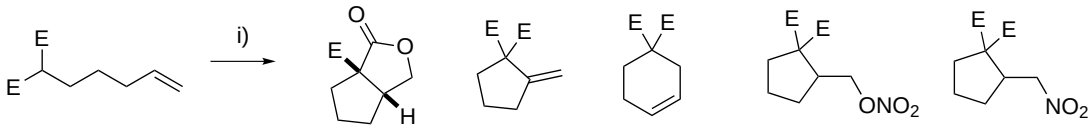
1.2.4 Ammonium Cerium(IV) Nitrate

Similarly to MAN, ammonium cerium(IV) nitrate (CAN) has also been identified as an effective single electron oxidant.[40] CAN is a bright orange solid, which in solution exists as the 12 coordinate $[Ce(NO_3)_6]^{2-}$ anion with each nitrate coordinated through two oxygen atoms.[51] The reduction potential (**Equation**

1.4) is similar to that of MAN (**Equation 1.1**). Cerium is unique amongst the lanthanides in that the +4 oxidation state is stable, with an electron arrangement of [Xe], unlike the remaining lanthanides in which the +3 oxidation state is predominant.

$$Ce^{4+} + e^- \rightarrow Ce^{3+} = +1.44 \text{ V} \tag{1.4}$$

Baciocchi and Ruzziconi studied the reaction of CAN with pentenyl malonate **42** in the presence and absence of copper(II) salts.[52] In the absence of copper(II), a complex mixture of products was obtained (**Scheme 1.14**). Cyclopentanes **55** and **56** were probably formed as a result of ligand transfer from CAN and direct reaction with NO_2 formed under the reaction conditions respectively. In the presence of 1 eq. $Cu(OAc)_2{\cdot}H_2O$ however, γ-lactone **43** was obtained in 55% yield with smaller amounts of alkene **44** (3%) and cyclohexene **45** (4%) also isolated.



42 **43** **44** **45** **55** **56**

Reagents & Conditions: i) 2 eq. CAN, 1 eq. $Cu(OAc)_2$, AcOH.

Scheme 1.14: Baciocchi and Ruzziconi's studies of oxidative radical cyclisations mediated by CAN.[52] E = CO_2Me.

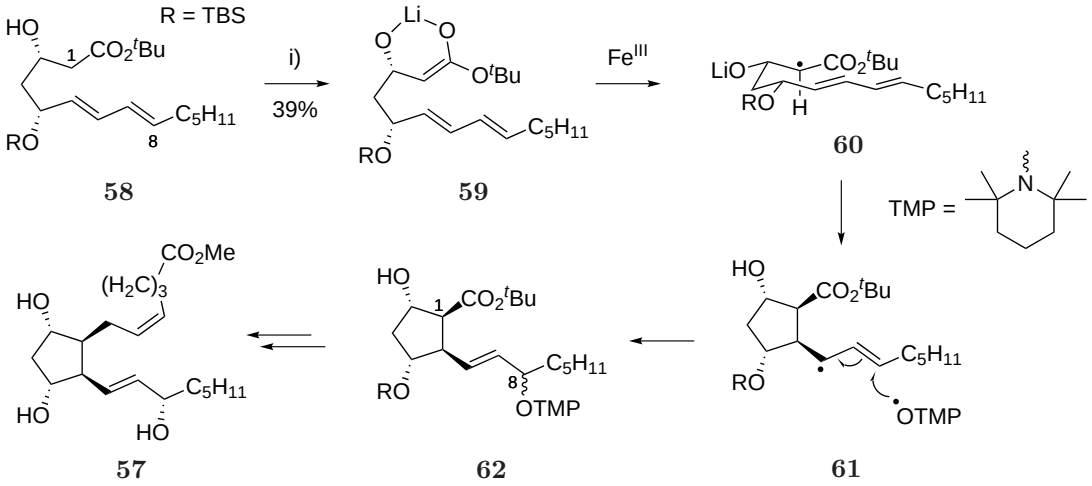
It has been shown that CAN is a better oxidant of alkyl radicals than MAN by an order of magnitude.[40] Despite this apparent advantage, the use of CAN is not as widespread as MAN for oxidative radical cyclisation reactions. A possible reason for this is the frequent formation of products corresponding to ligand transfer reactions. However, the overall reactivity is similar to that of MAN, and CAN should find further utility due to its widespread availability and ease of handling.[53,54]

1.2.5 Other Transition Metals for Oxidative Radical Cyclisations

Despite MAN and CAN being the most utilised and studied single electron transition metal oxidants, other metals have also been identified as competent oxidants. Most studies have been on the radical addition to phenols, in which the termination step is not critical as the reaction is strongly driven by the facile oxidation of the resultant cyclohexadienyl radical.

Iron(III) salts in particular have also been used for the cyclisation of pentenyl esters and malonates. Jahn and co-workers have introduced ferrocenium hexafluorophosphate $[FeCp_2][PF_6]$ for oxidising lithium

enolates to radicals.[55,56] A distinct advantage of this methodology is there is no necessity for a strongly C-H acidic malonate, as LDA is used as a strong base for the initial enolisation. This was utilised in their total synthesis of prostaglandin analogue 15-F_{2t}-isoprostane **57**; a proposed mechanism is shown in **Scheme 1.15**.[57]



Scheme 1.15: Oxidative radical cyclisation in Jahn and Dinca's synthesis of 15-F_{2t}-isoprostane **57**.[57]

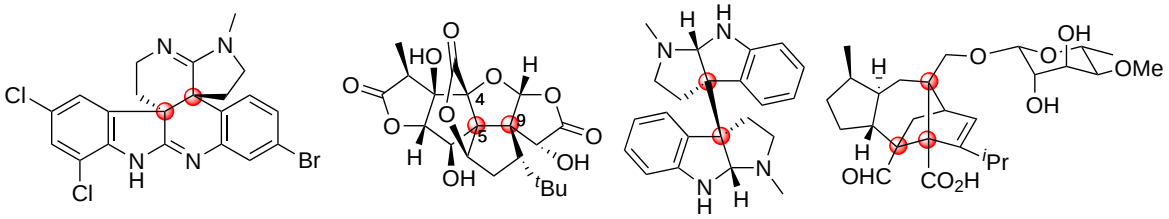
Treatment of ester **58** with 2 eq. of LDA gave lithium enolate **59**, which was then oxidised by stoichiometric $[FeCp_2][PF_6]$ to give radical **60**. Radical **60** then underwent a 5-*exo*-trig cyclisation to give allylic radical **61**, which was trapped by TEMPO at the distal position from the initial cyclisation to give cyclopentane **62** as a separable 2:1 mixture of C-8 epimers. The C-1 diastereoselectivity was moderate, with 23% of the C-1 epimer also isolated, representing a dr of 1.7:1. This selectivity could be reversed to favour the C-1 epimer using ^{t}BuMgCl as an additive, which coordinates to the ester and free alcohol and results in a ring-flip of transition state **60**.

1.3 Complexity Driven Synthesis

The ability to construct highly complex structures in a regio- and stereocontrolled manner is one of the major accomplishments of synthetic organic chemistry. This Section will give an overview of two contemporary research topics: the synthesis of all-carbon quaternary stereocentres (**Section 1.3.1**) and the synthesis of complex cyclic structures by oxidative radical cyclisation methods (**Section 1.3.2**).

1.3.1 Stereocontrolled Synthesis of Vicinal All-Carbon Quaternary Centres

Vicinal all-carbon quaternary centres are present in many natural products. Due to the sterically congested nature of such centres and the inherent paucity of attached heteroatoms, their formation is often a formidable challenge, and many approaches have been developed to tackle this problem.[58,59] Some of these approaches will be shown in the total syntheses of the natural products perophoramidine **63**, ginkgolide B **64**, chimonanthine **65**, and sordarin **66** (**Figure 1.2**)



63 **64** **65** **66**

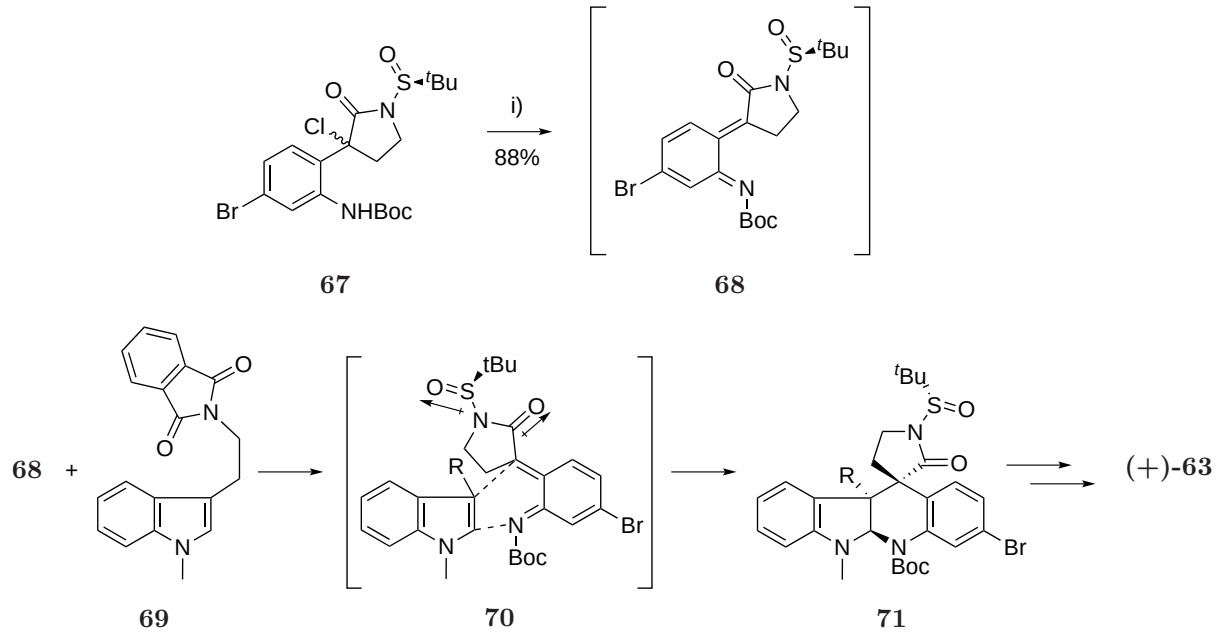
Figure 1.2: Some examples of natural products containing vicinal all-carbon stereocentres.

1.3.1.1 Thermal Pericyclic Reactions

Pericyclic reactions have long been used as "lynch pin" reactions in the synthesis of complex molecules.[60] The reactions are well understood theoretically and experimentally. An archetypal complexity generating reaction is the Diels-Alder [4+2] cycloaddition, in which the reaction of a diene with a dienophile gives a cyclohexene with two new σ-bonds and control of up to four stereocentres. The driving force is the formation of two σ-bonds in place of the two π-bonds in the parent diene. As the two reactants are both flat at their reactive centres, the effects of steric interaction are minimised as far as possible, thus allowing highly substituted structures to be formed. The stereoselectivity is generally predictable from easily understood models. These factors have allowed rational development of the reaction and its use in total synthesis.[60]

The power of the Diels-Alder reaction was shown in the recent synthesis of (+)-perophoramidine **63**. A diastereoselective intermolecular hetero Diels-Alder reaction was the key bond forming step in Qin and co-worker's 2010 total synthesis (**Scheme 1.16**).[61] In the presence of 4.5 eq. of $AgClO_4$, pyrrolidine **67** forms orthoazaquinonemethide **68**. The *trans-trans* configuration of the newly formed double bonds avoids interaction between the pyrrolidine carbonyl and the imine nitrogen lone pair.

Orthoazaquinonemethide **68** then underwent a reverse electron demand Diels-Alder reaction with the electron rich alkene in phthalate protected tryptamine **69**. The reaction proceeded through *exo*



Reagents & Conditions: i) 3:1 **67**:**69**, 4.5 eq. $AgClO_4$, toluene, –78 °C.

Scheme 1.16: Hetero Diels-Alder reaction in Qin's 2010 synthesis of (+)-perophoramidine.[61]

transition state **70**. The absolute stereochemistry is controlled by the chiral-at-sulfur auxiliary on the pyrrolidone moiety, with the sulfinamide and pyrrolidone carbonyl dipoles opposed in TS‡ **70**. The reaction yielded a separable 11:1 mixture of diastereomers, and the major diastereomer was transformed into enantioenriched (+)-perophoramidine **63**.

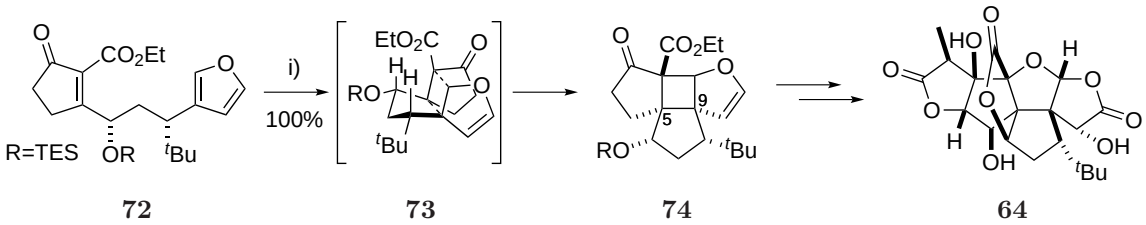
1.3.1.2 [2+2] Cycloaddition Reactions

The thermal dimerisation of alkenes, formally a [2+2] cycloaddition, is symmetry disallowed under the Woodward-Hoffmann rules, as the interaction would be a $[_{\pi}2_s +_{\pi} 2_s]$ arrangement. There are two cases in which this reaction is allowed: photochemical excitement, and in the reaction of ketenes with alkenes.[62] Both examples have been used in the synthesis of ginkgolide B **64**. To date there have only been two syntheses of racemic ginkgolide B **64**.[63,64]

Due to their unique reactivity, radicals generated by exposure to UV light are often used in the construction of strained systems that are not accessible by thermal methods. This strain may then be exploited in further synthetic transformations. The photochemical promotion of an electron from $\pi \rightarrow \pi^*$ generates the correct orbital symmetry $[_{\pi}2_s +_{\pi} 2_s]$ for the reaction to occur.

In their 1999 synthesis of ginkgolide B **64**, Crimmins and co-workers utilised a photochemically activated reaction to construct the highly substituted carbon core of the natural product (**Scheme**

1.17).[63] The electron rich furan moiety in substrate **72** underwent a [2+2] cycloaddition with the electron poor α,β-unsaturated malonate through transition state **73**. This minimised $A^{1,3}$ strain in the newly forming cyclopentane: the two bulky substituents are placed in *pseudo*-equatorial positions, with the two protons *pseudo*-axial. This transformation gave cyclobutane **74** as a single diastereomer in 100% yield with adjacent all-carbon quaternary stereocentres and allowed the total synthesis of ginkgolide B **64**.

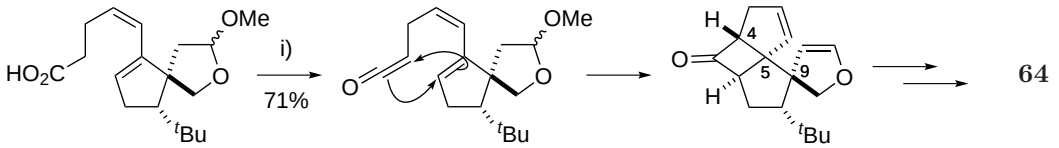


72 **73** **74** **64**

Reagents & Conditions: i) hν > 350 nm, hexanes, RT.

Scheme 1.17: Synthesis of the carbon core of ginkgolide B **64** by Crimmins and co-workers.[63]

Corey and co-workers opted to use a [2+2] cycloaddition of an alkene to a ketene to set the vicinal all-quaternary stereocentres C-5 and C-9 in their 1988 total synthesis of ginkgolide B **64** (**Scheme 1.18**).[64] Treatment of acid **75** with oxalyl chloride gave an intermediate acid chloride that when heated with NBu_3 in toluene formed ketene **76**, which reacted with the adjacent alkene to give cyclobutane **77** in 71% yield. Under the mildly acidic conditions ($HNBu_3Cl$ formed during the ketene formation), elimination of methanol also occurred to give the corresponding enol ether.



75 **76** **77**

Reagents & Conditions: $(COCl)_2$, benzene, RT, then NEt_3, toluene, 110 °C.

Scheme 1.18: Ketene-alkene [2+2] cycloaddition in Corey's synthesis of ginkgolide B **64**.[64]

The stereochemistry at the ring junctions is a consequence of the mechanism of the cycloaddition (**Figure 1.3**). One explanation for the allowed [2+2] cycloaddition of ketenes with alkenes has the ketene approach at 90° to the alkene, with the interaction now a $[_\pi 2_s +_\pi 2_a]$ process. The ketene then rotates as the bond is made to give cyclobutanone (**Figure 1.3**). The alkyl tether sits on the least hindered side, *i.e.* adjacent to the alkene proton.

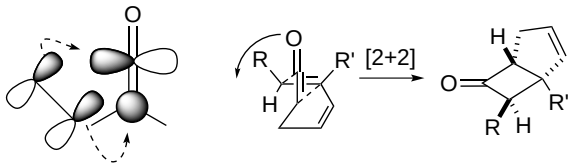
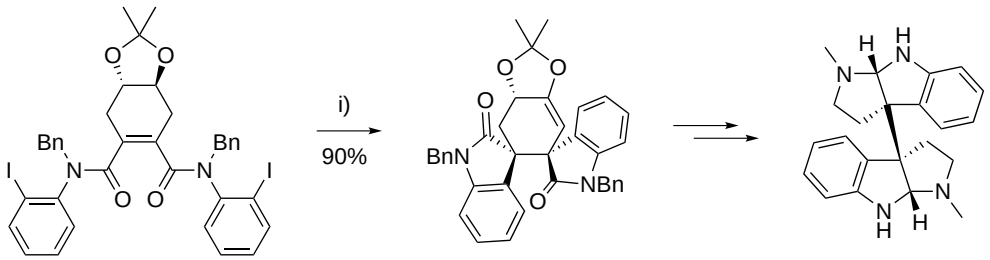


Figure 1.3: Stereoselectivity in the intramolecular [2+2] cycloaddition of ketene **76**.

1.3.1.3 Transition Metal Catalysed Alkylation

Palladium catalysed coupling reactions are now a standard tool for C-C bond formation. The mechanisms of these reactions are generally well understood, including their chemo-, regio-, and stereoselectivity. These reactions (Suzuki, Stille, Sonogashira, Heck etc.) have been extensively used in natural product synthesis, and this area has been well reviewed.[65]

Of particular note in this area is the synthesis of (–)-chimonanthine (–)-**65** by Overman and co-workers, who utilised an intramolecular double Heck reaction to install the vicinal all-carbon stereocentres (**Scheme 1.19**).[66] Treatment of diiodide **78** under standard Heck conditions gave the asymmetric cyclohexene **79**. With the acetonide protecting group in diiodide **78** replaced by two TBDPS groups, *meso*-**65** could also be accessed.[67]

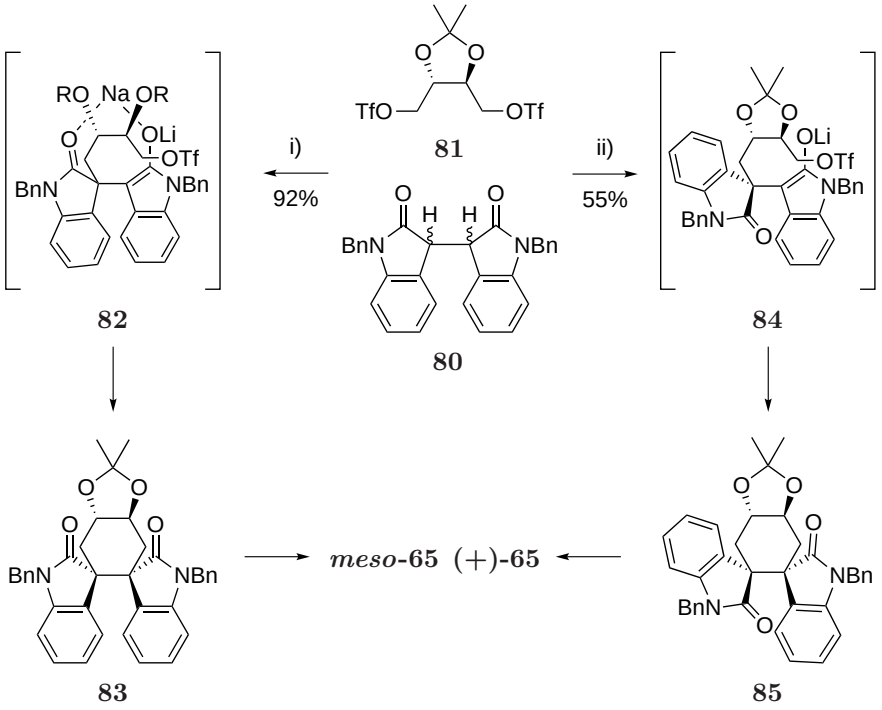


78 **79** **(–)-65**

Reagents & Conditions: i) 10 mol% $PdCl_2(PPh_3)_2$, Et_3N, DMA, 100 °C.

Scheme 1.19: Double Heck reaction in Overman's synthesis of (–)-chimonanthine **65**.[66]

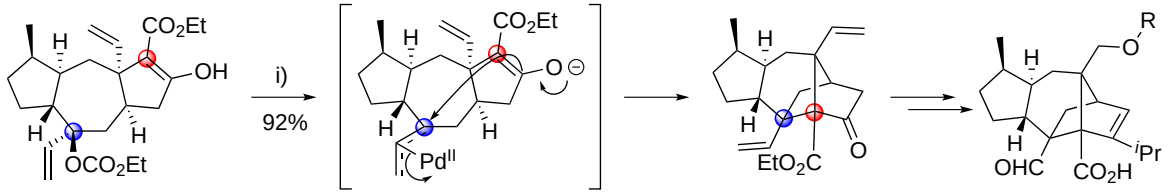
Overman and co-workers also disclosed a double alkylation approach to chimonanthine **65** through an intermediate lacking the alkene in **79** (**Scheme 1.20**).[68] Treatment of dihydroisoindigo **80** with NaHMDS in THF with ditriflate **81** gave *via* chelated transition state **82** the *cis bis*-spirooxindole **83**, which was taken forward to *meso*-chimonanthine **65**. Conversely, treatment of **80** and **81** with LiHMDS in THF/DMPU gave *via* transition state **84** the C_2-symmetric *bis*-spirooxindole **85**, which was elaborated to (+)-chimonanthine **65** These syntheses are notable for the fact they involve the *intermolecular* formation of vicinal all-carbon quaternary stereocentres.



Reagents & Conditions: i) 2.1 eq. NaHMDS, THF, –78 °C; ii) 2.1 eq. LiHMDS, THF/DMPU, –78 °C.

Scheme 1.20: Double enolate alkylation approach by Overman and co-workers for the synthesis of *meso*-chimonanthine **65** and (+)-chimonanthine **65**

Narasaka and co-workers took advantage of the Tsuji-Trost allylic alkylation reaction to construct the bicyclic [2.2.1]-heptane core of sordarin **66**, and install the vicinal quaternary all-carbon stereocentres shown in red and blue (**Scheme 1.21**).[69] Treatment of allyl carbonate **86** with 10 mol% $Pd(PPh_3)_4$ gave π-allyl species **87**. This was then attacked intramolecularly by the transannular acetoacetate to form the key C-C bond in 92% yield, with 5% of β-hydride elimination product. It was found that sodium hydride, not normally used in this reaction, was essential to minimise β-hydride elimination as this increased the nucleophilicity of the enolised acetoacetate.



Reagents & Conditions: i) 10 mol% $Pd(PPh_3)_4$, 1.1 eq. NaH, 1,4-dioxane, 80 °C.

Scheme 1.21: Installation of vicinal quaternary stereocentres in Narasaka's synthesis of (–)-sordarin **66**.[69]

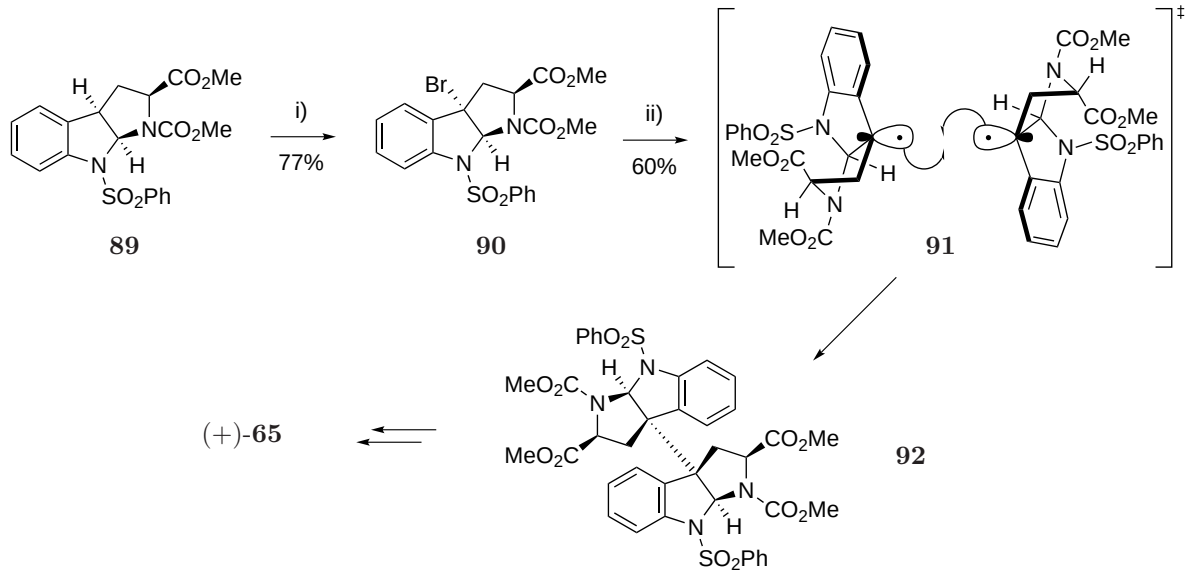
Despite these two notable examples, there remains few examples of transition metal catalysed/mediated

formation of vicinal all-carbon stereocentres. This to an extent may be due to the large steric demands of palladium when ligands are coordinated and additionally the solvation of charged metal species.

1.3.1.4 Radical Reactions

As discussed in **Section 1.1**, radicals are also excellent candidates for forming heavily sterically congested C-C bonds. As by definition there are only a maximum of three substituents on the carbon, radical reactions have reduced steric requirements as there are generally no metals and associated ligands carried with the reactive carbon. As the reactions are under kinetic control, the regio- and stereoselectivity may be anticipated.

This high reactivity was demonstrated in Movassaghi and Schmidt's synthesis of (+)-chimonanthine **65**. Exploiting the symmetry of the natural product, an elegant radical dimerisation was developed. The synthesis has two consecutive radical reactions: a radical bromination, followed by a radical dimerisation to form the key C-C bond (**Scheme 1.22**).[70]



Reagents & Conditions: i) dibromohydantoin, AIBN, CCl_4, 80 °C; ii) $[CoCl(PPh_3)_3]$, acetone, RT.

Scheme 1.22: Movassaghi and Schmidt's radical dimerisation for the total synthesis of (+)-chimonanthine (+)-**65**. Transition state adapted from Movassaghi and Schmidt.[70]

Tryptophan derivative **89** was converted to the corresponding bromide **90**. The benzylic position was oxidised to a radical with AIBN, which then abstracted bromine from dibromohydantoin. The C-2 ester was found to be essential for stabilising the intermediates, as in its absence it was not possible to retain optical purity in the benzylic bromination.

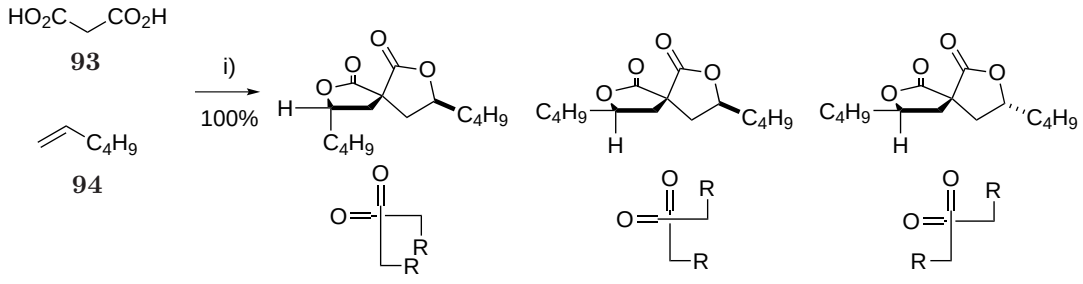
After unsuccessfully attempting to perform the coupling with tributyltin radical or $[Mn_2(CO)_{10}]$, stoichiometric $[CoCl(PPh_3)_3]$ was found to give 60% yield of the desired dimer on a 6.0 mmol scale with complete retention of stereochemistry at the newly formed C-C bond. A further four steps were required to complete the synthesis of (+)-chimonanthine (+)-**65**. This represented a rapid synthesis, with the natural product completed in only 8 steps.

1.3.2 Quaternary Stereocentres by Oxidative Radical Cyclisations

Radical cyclisation reactions have been used in the synthesis of complex, strained polycyclic structures. This Section describes the intermolecular synthesis of spirocyclic *bis*-lactones, and the intramolecular synthesis of tricyclic *bis*-lactones from simple precursors.

1.3.2.1 Spirocyclic *bis*-Lactones

The reaction of malonic acid **93** with two equivalents of an alkene under oxidative radical conditions was first reported by Kurosawa and co-workers.[71] In 1985 Fristad and Hershberger studied this reaction further and gave a rigorous determination of by-products and stereochemistry.[72] In the presence of 4 eq. of MAN, malonic acid **93** was treated with hexene **94** and other alkenes (**Scheme 1.23**). The reaction followed the usual mechanism for the addition of acetic acid across an alkene, but as a second equivalent of alkene was also present spirocyclic compounds **95**, **96**, and **97** were formed in 100% yield, in a ratio of 1:5:5.



Reagents & Conditions: i) $Mn(OAc)_3$, AcOH, 70 °C.

Scheme 1.23: Synthesis of spirocyclic *bis*-lactones from hexene. Scheme adapted from Fristad and Hershberger.[72]

None of the intermediate mono-alkylated lactone-acid was isolated, even with a 10-fold excess of malonic acid **93**. The first addition/oxidation forms a lactone-acid rather than malonic acid, and the remaining malonate proton is now more acidic. Based on the mechanism discussed in **Section 1.2.1.1**,

this makes the second cyclisation faster, and so no monoalkylated product was obtained. In contrast, the use of monomethylmalonic acid gave the mono-lactone in 76% yield (based on oxidant used). This further illustrates that free carboxylic acids are more effective than esters in the final oxidative substitution step (*cf.* **Scheme 1.12**).

The stereochemistry was determined by the use of NMR and a novel IR method (**Figure 1.4**). Spirolactones **95** and **97** are C_2 symmetric, and so have half the number of ^{13}C NMR signals as unsymmetrical **96**. Considering δ_H for the lactone proton, spirolactone **95** has a higher shift than spirolactone **97** (4.67 *vs.* 4.20), due to deshielding by the carbonyl of the other lactone. As the spirocyclic systems are rigid, the carbonyl groups act as a coupled oscillator with the anti-symmetric stretch lying at higher frequency. The relative intensity of the two IR stretches was used to determine the carbonyl dihedral angle using vector addition. For *syn*-isomer **95**, the dihedral angle is acute to avoid steric interaction between the alkyl chains, so the symmetric IR mode gives a more intense signal than the anti-symmetric mode. For *anti*-isomer **97**, the dihedral angle is obtuse so the anti-symmetric IR mode is more intense. This technique was employed when spiro *bis*-lactones without lactone protons were synthesised.

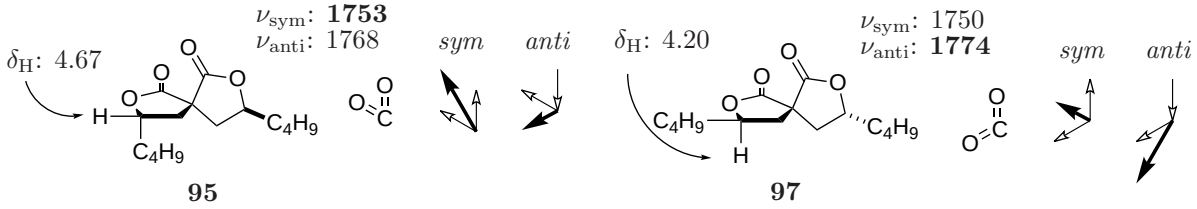
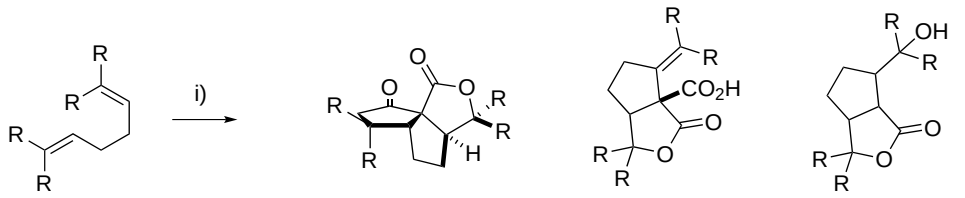


Figure 1.4: Determination of lactone stereochemistry by spectroscopic methods.[72]

The reaction of 1,5-dienes with malonic acid was also studied (**Scheme 1.24**). Upon exposure of dienes **98** (R = Me) and **99** (R = Ph) to malonic acid and MAN, spiro *bis*-lactones **100** and **101** respectively were obtained, along with monolactone products **102**, **103**, **104**, and **105**. The monolactones arose from oxidation of the adduct tertiary radical to a formal cation, followed by either elimination or decarboxylation. The stereochemistry of the monolactones was not rigorously proven.

The reaction of methyl substituted diene **98** gave spiro *bis*-lactone in 40% yield with small amounts of monolactones **102** and **104** (8% each). For the cyclisation of **99**, however, spiro *bis*-lactone **101** was obtained in only 12% yield, with the major products being alkene **103** (42%) and alcohol **105** (23%). As the radical obtained from the first cyclisation is doubly benzylic the oxidation to a carbenium is facile, and so these pathways dominate.



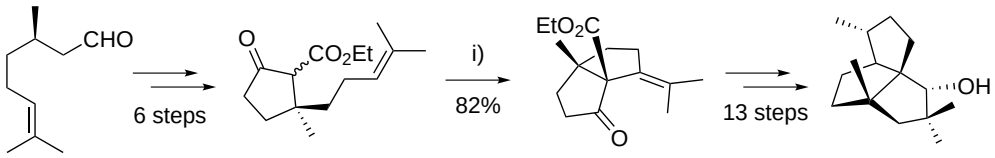
98 R = Me **100** R = Me **102** R = Me **104** R = Me
99 R = Ph **101** R = Ph **103** R = Ph **105** R = Ph

Reagents & Conditions: i) $Mn(OAc)_3{\cdot}2H_2O$, AcOH, 70 °C.

Scheme 1.24: Spirodilactonisation of 1,5 dienes.[72]

1.3.2.2 The Total Synthesis of (–)-Cameroonan-7α-ol

Recently Taber and Nelson completed the total synthesis of (–)-cameroonan-7α-ol **106** in 20 steps with a MAN-mediated oxidative radical cyclisation as a key step (**Scheme 1.25**).[73] Cameroonan **106** is a sesquiterpene with three *cis*-fused cyclopentane rings and five contiguous sterocentres, with vicinal all-carbon quaternary stereocentres.



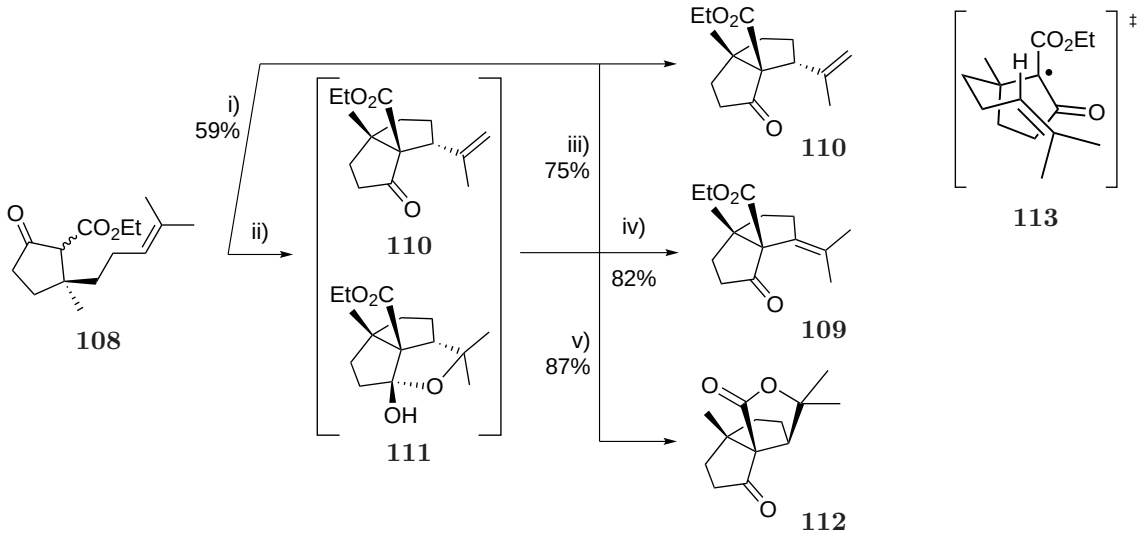
(+)-107 **108** **109** **106**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OAc)_2{\cdot}H_2O$, AcOH, 80 °C, then 5 mol% *p*-TsOH·H_2O, PhMe, 110 °C.

Scheme 1.25: Intermediates in Taber and Nelson's synthesis of (–)-cameroonan-7α-ol **106**.

The cyclisation precursor **108** was synthesised in 6 steps from (*R*)-citronellal (+)-**107**, with a rhodium(II) catalysed C-H insertion into a diazo precursor as a key step. The β-keto ester **108** was then treated with MAN and $Cu(OAc)_2$ (**Scheme 1.26**). The use of MeCN as solvent gave *exo*-alkene **110** as the major product in 59% with isomers accounting for another 30%. Conducting the reaction in AcOH at reflux gave a complex mixture of isomers (not shown) that when hydrolysed gave ketone **110** and lactol **111**. Acid-mediated rearrangement selectively gave ketones **109**, **110**, or **112** depending on the equivalents of acid or the time of reaction. Ketone **109** was taken forward to (–)-cameroonan-7α-ol in 13 further steps.

This reaction is notable for the stereoselective formation of ketone **110**. The reaction proceeds through TS‡ **113**, which minimises 1,5-diaxial interactions by placing the proton in the axial position. This has the consequence of putting the vinyl substituent inside the bowl of the 5,5-*cis* fused structure.



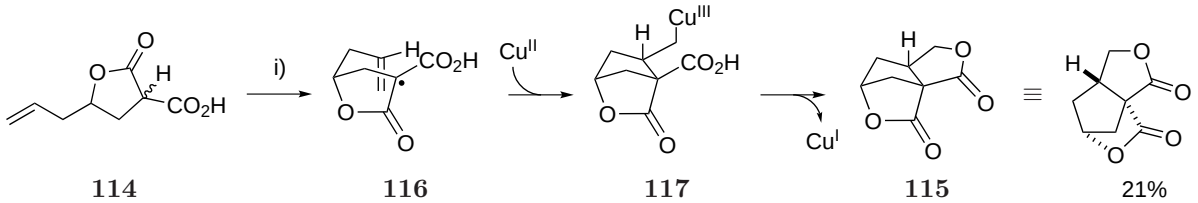
Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OAc)_2$, MeCN, RT, 14 h; ii) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OAc)_2$, AcOH, 80 °C, 2 h, then H_2O; iii) 5 mol% *p*-TsOH, PhMe, 110 °C, 1 h; iv) 5 mol% *p*-TsOH, PhMe, 110 °C, 4 h; v) 105 mol% *p*-TsOH, PhMe, 110 °C, 4 h.

Scheme 1.26: Selective synthesis of bi- and tricyclic ketones **109**, **110**, and **112**.

Vicinal all-carbon quaternary centres are also formed in this reaction. Although one of the centres is not directly involved in the reaction, this still represents a high level of reactivity whilst creating a highly congested ring junction.

1.3.2.3 Proposed Work & Initial Studies

Brief studies on the oxidative radical cyclisation of unsaturated γ-lactones have previously been conducted in the group. For example, treatment of lactone-acid **114** with MAN and $Cu(OTf)_2$ gave tricyclic *bis*-lactone **115** (**Scheme 1.27**).[74]



Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C.

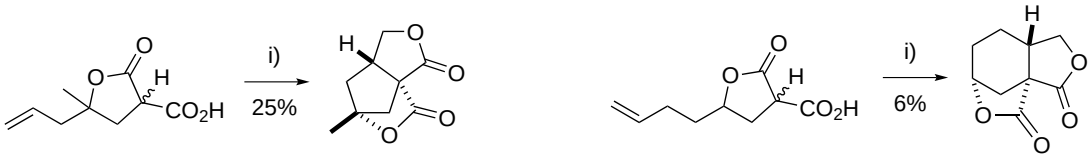
Scheme 1.27: Synthesis of tricyclic *bis*-lactone **115**.[74]

Similar to the oxidative radical reactions previously discussed, the reaction commences with the formation of a manganese enolate followed by single electron oxidation, which gives radical **116**. After the initial cyclisation, the radical is oxidised by Cu^{2+} to give copper(III) intermediate **117**, which finally

loses Cu^+ by substitution by the pendant carboxylate.

Unusually, the highly strained *trans*-fused lactone **115** was the major product, with a *trans*-*cis* ratio of 5:1, which suggests the alkene must adopt the more hindered *pseudo*-axial position in radical **116**. The stereochemistry was unambiguously determined by X-ray crystal structures of both *trans* and *cis* isomers, and also by nOe experiments. Cyclohexene products from the competing 6-*endo* cyclisation mode were also isolated, with an apparent 5-*exo*:6-*endo* ratio of 2:1. This reflects the higher level of strain in the transition state for these reactions.

Other substrates were also submitted to the radical cyclisation conditions: methyl substituted lactone **118** and hexenyl lactone **119** (**Scheme 1.28**). Lactone **118** cyclised under the same conditions as **114** giving tricyclic *bis*-lactone **120** as a 7:1 mixture of diastereomers in 25% combined yield. The *trans*-fused diastereomer was the major product. Oxidative radical cyclisation of lactone **119** gave the 6-*exo* product as a single diastereomer; again the *trans* diastereomer.

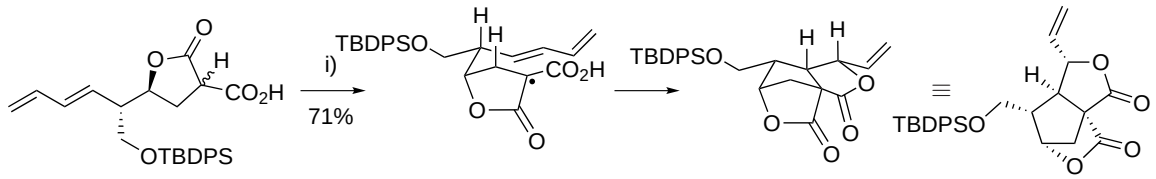


118 **120** **119** **121**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C.

Scheme 1.28: Formation of other tricyclic *bis*-lactones under oxidative radical cyclisation conditions.

During studies on the total synthesis of prostaglandin, another tricyclic *bis*-lactone was also synthesised (**Scheme 1.29**). In contrast to the previously described examples, the cyclisation of diene **122** *via* radical **123** gave exclusively the *cis*-fused product **124**. It should be noted that the adduct radical from the first cyclisation is allylic, and hence somewhat stabilised. The alkene could be elaborated by cross metathesis.



122 **123** **124**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C.

Scheme 1.29: Synthesis of tricyclic *bis*-lactone towards the total synthesis of prostaglandin.[50]

The stereochemistry was assigned by nOe experiments. The exclusive *cis*-fused product is a con-

sequence of transition state **123** in which the two protons shown in the *pseudo*-axial position, which minimises 1,3-diaxial strain, with the bulky -CH_2OTBDPS placed into the *pseudo*-equatorial position. Houk and Beckwith calculated that such cyclisations proceed through a *pseudo*-chair, and this result is in accord with these predictions.[18, 23, 75]

1.4 Project Aims

The formation of tricyclic *bis*-lactones represents a particularly useful complexity generating reaction. The aim of the project was broadly to increase the applications of oxidative radical methodology for the synthesis of functionalised γ-lactones, already developed by the Burton group, to the formation of both bi- and tricyclic γ-lactones. In particular, the effect of radical stabilising groups on the alkene were to be investigated, with the proposal that such stabilisation of the adduct radical would improve the yield and selectivity of these reactions.

2

Cyclisations of Linear γ-Styryl Malonates

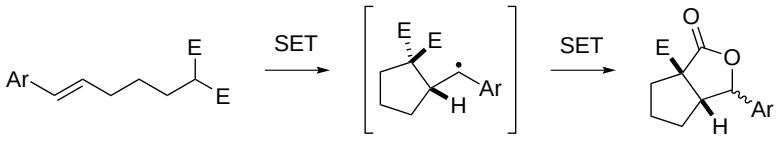
This Chapter discusses investigations into the MAN-mediated radical cyclisation of linear γ-styryl malonates to form cyclopentane-lactones with a variety of aryl groups and substituents. A new carbon-carbon bond, a new carbon-oxygen bond, and up to three new contiguous stereocentres are formed in the reaction.[76]

2.1 Background & Motivation

The MAN-mediated radical cyclisation of γ-unsaturated malonates **42** has been a long standing research topic within the Burton group. As discussed in **Chapter 1**, the reaction conditions may be tuned to give a variety of products in the presence of copper(II) salts as *C*-centred radical single electron oxidising agents.

In order to investigate the electronic effects of a radical stabilising group on the adduct radical formed

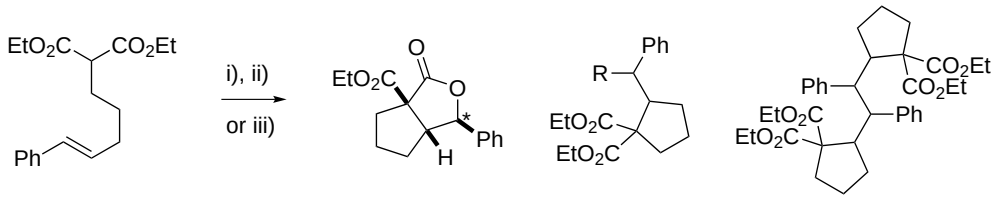
after the inital 5-*exo*-trig cyclisation, it was proposed that a range of aryl-substituted substrates **125** bearing a terminal aryl group would be synthesised (**Scheme 2.1**). These would also yield an additional benzylic stereocentre after cyclisation. After the initial cyclisation to form the cyclopentane, the adduct radical **126** is benzylic. The electronic properties of the aryl group will influence the stability and lifetime of the radical. After the radical is oxidised by a suitable metal, *e.g.* Mn^{3+} or Cu^{2+}, the formal cation is then trapped by the proximal ester, which gives lactone **127** with an additional benzylic stereocentre.



125 **126** **127**

Scheme 2.1: Proposed cyclisation of γ-styryl malonates. E = CO_2-Alkyl.

The groups of Citterio and Jahn have previously synthesised similar lactones with an ethyl ester (**Scheme 2.2**). Treatment of malonate **128** with MAN at low concentration (0.05 M) in acetic acid gave 65% isolated yield of lactone **129** with 10:1 dr at the benzylic stereocentre, and 35% of benzylic oxidation products **130a,b** (2.5:1).[77] Exposure of the lithium enolate of malonate **128** to ferrocenium hexafluorophosphate $[FeCp_2][PF_6]$ gave lactone **129** in up to 28% yield with 10:1 dr, as well as 48% of dimer **131**.[55] The use of $CuCl_2$ as the oxidant gave lactone **129** in 15% yield with 9:1 dr, cyclopentane **130c** in 21% yield by ligand transfer from copper, and 47% of dimer **131**.[56]



128 **129** **130** **131**

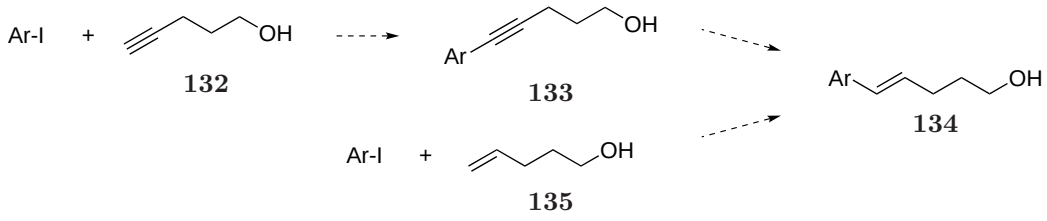
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, AcOH, 60 °C; ii) LDA, –78 °C, then 1.75 eq. $[FeCp_2][PF_6]$, 7.00 eq. HMPA, DME, 0 °C; iii) LDA, –78 °C, then $CuCl_2$, DME, 0 °C.

Scheme 2.2: Literature precedence for the synthesis of aryl-substituted cyclopentane-lactones. **130a**, R = OAc; **130b**, R = (=O); **130c**, R = Cl.

While the precedence for the reaction is good, the range of by-products obtained is not ideal and it was proposed that in a similar manner to the cyclisation of 4-pentenyl malonates **42** the selectivity of the reaction could be improved. The use of more concentrated conditions and less toxic solvents would also be desirable.

2.2 Substrate Synthesis

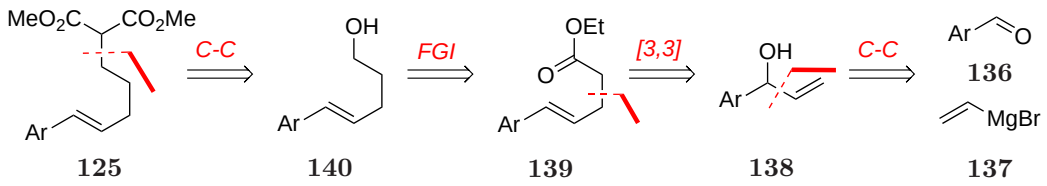
In order to investigate the cyclisation of malonates such as **125** an effective substrate synthesis was required. Two approaches, one from benzaldehydes (**Section 2.2.1**) and one from pentenyl malonate **42** (**Section 2.2.2**), were used for the synthesis of electronically diverse malonates **125**. Other routes, such as Heck or Sonogashira coupling, were also considered but were not pursued (**Scheme 2.3**). Sonogashira coupling of alkyne **132** with aryl iodides would give alkyne **133**, which could be reduced to give alkene **134**. The range of aryl iodides is not as extensive as the range of benzaldehydes available. The Heck reaction is notoriously substrate specific,[78] and would also require the use of aryl halides coupled to alkene **135**. Early installation of the malonate was also thought to be undesirable due to the high acidity of the malonate proton ($pK_a \approx 13$).



Scheme 2.3: Routes considered for substrate synthesis

2.2.1 Synthesis from Benzaldehydes

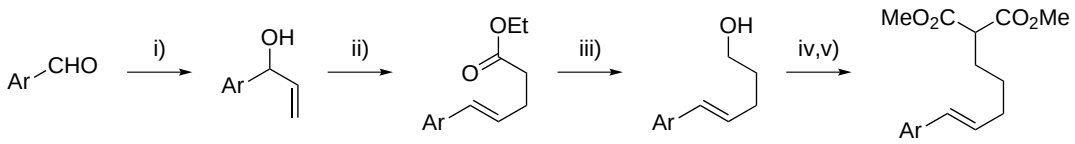
A retrosynthesis of the desired malonates **125** commencing from benzaldehydes **136** is presented in **Scheme 2.4**. Addition of vinylmagnesium bromide **137** to benzaldehydes **136** would give allylic alcohols **138**. A Johnson-Claisen rearrangement[79] would give γ-unsaturated esters **139**, which have the functionalisation pattern required. After reduction of esters **139** to alcohols **140**, transformation of the resultant hydroxyl to a leaving group followed by displacement with a malonate anion would give the desired cyclisation substrates **125**.



Scheme 2.4: Retrosynthesis of γ-styryl malonate substrates.

Vinylmagnesium bromide was added to benzaldehydes **136** in THF in uniformly excellent yields, and

the products were generally used without purification (**Table 2.1**). All reactions were carried out at 0 °C, except for benzaldehydes bearing nitro substituents. These were carried out at –78 °C to prevent addition into the nitro group, which is the starting point for the Bartoli indole synthesis.[80] No indole products were detected by MS or ^{1}H NMR spectroscopy, suggesting the aldehyde is more reactive than the nitro group.



Reagents & Conditions: i) vinylmagnesium bromide, THF, 0 °C; ii) $MeC(OEt)_3$, cat. CH_3COOH, 140 °C; iii) $LiAlH_4$, Et_2O, 0 °C; iv) MsCl, NEt_3, DCM, 0 °C; v) DMM, NaH, KI, DMF/THF, 80 °C

Entry	Ar	i) / (%)	ii) / (%)	iii) / (%)	iv, v) / (%)	$^3J_{HC=CH}$ / Hz
1	Ph	**141** (99)	**142** (57)	**143** (89)	**144** (81)	15.8
2	4-FC_6H_4	**145** (95)	**146** (53)	**147** (75)	**148** (49)	15.8
3	2-FC_6H_4	**149** (77)	**150** (89)	**151** (74)	**152** (70)	15.9
4	4-BrC_6H_4	**153** (99)	**154** (55)	**155** (85)	**156** (51)	15.9
5	4-MeC_6H_4	**157** (100)	**158** (21)	**159** (88)	**160** (66)	15.8
6	2-MeC_6H_4	**161** (95)	**162** (63)	**163** (75)	**164** (86)	15.7
7	3-$OMeC_6H_4$	**165** (63)	**166** (57)	**167** (62)	**168** (70)	15.8
8	4-$OMeC_6H_4$	**169** (98)	**170** (20)	**171** (52)	**172** (62)	15.8
9	3-$NO_2C_6H_4$	**173** (100)	**174** (78)	**175** (68)	**176** (72)	15.9
10	4-$NO_2C_6H_4$	**177** (93)	**178** (80)	**179** (77)	**180** (69)	n/a
11	2-naphthyl	**181** (98)	**182** (35)	**183** (90)	**184** (72)	15.8

Table 2.1: Synthesis of γ-styryl malonate radical cyclisation substrates.

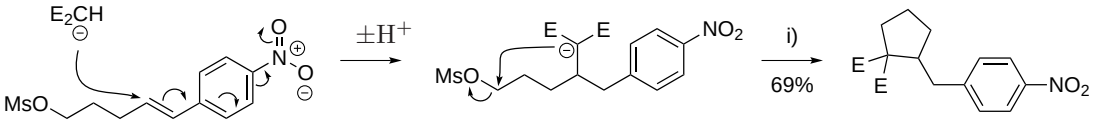
The resulting allyl alcohols **138** were then subjected to a Johnson-Claisen reaction[79] which gave γ-unsaturated esters **139** in moderate to good yields with excellent selectivity for the *E*-isomer, as determined by ^{1}H NMR spectroscopy. In particular, with more electron rich allylic alcohols (4-Me **157**, 4-OMe **169**, naphthyl **181**) low yields were obtained. The yields quoted refer to the isolated *E*-isomer, and the $^3J_{HC=CH}$ coupling constant for the malonates is shown in **Table 2.1**.

Reduction of esters **139** with $LiAlH_4$ gave alcohols **140**. As it is known that $LiAlH_4$ may reduce aryl nitro groups to azo-compounds,[81] esters **174** and **178** were reduced with DiBAl-H at –78 °C. In most cases, this reaction was clean enough to use the resultant alcohols without purification, however flash column chromatography was usually performed to remove any impurities from the Johnson-Claisen rearrangement due to the increased polarity of the alcohol products over the ester products.

Alcohols **140** were then mesylated in excellent yield and alkylated with the sodium anion of dimethyl malonate (DMM), which gave the desired γ-styryl malonates **125**. In order to increase the rate of reaction, potassium iodide was used to displace the mesylate and give the more reactive iodide *in situ*; in principle this is substoichiometric in iodide, however a stoichiometric amount of potassium iodide was

used.[82]

When attempting to synthesise the *para*-nitro substituted cyclisation substrate **180** (**Table 2.1**, **Entry 10**) Michael addition of the malonate anion to the electron deficient unsaturated system in mesylate **185** followed by proton transfer and displacement of the mesylate gave cyclopentane **180** *via* anion **186** in 69% yield (**Scheme 2.5**). It is probable that the Michael addition is faster than displacement of the mesylate, rather than alkylation followed by another deprotonation and cyclisation.



185 **186** **180**

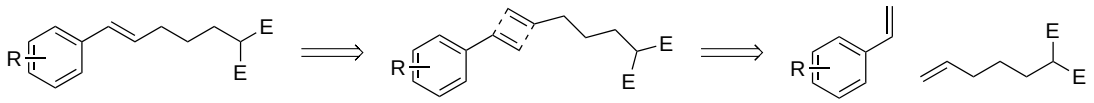
Reagents & Conditions: i) DMM, NaH, KI, DMF/THF, 80 °C.

Scheme 2.5: Carbocyclisation of mesylate **185** under alkylation conditions. E = CO_2Me.

This route delivered a range of electronically diverse malonates **125**. This demonstrated the generality of the procedures, despite the lower yields and stereoselectivity for electron rich substrates. Nitro groups and halides were tolerated.

2.2.2 Use of Olefin Cross Metathesis

The synthetic route outlined in **Section 2.2.1** proved able to deliver significant quantities of the desired malonates. However, the route was not convergent with each cyclisation substrate requiring at least five steps to synthesise. A route with a later divergence point was desired and an obvious choice was the use of olefin cross metathesis between a styrene and an appropriate terminal alkene (**Scheme 2.6**).



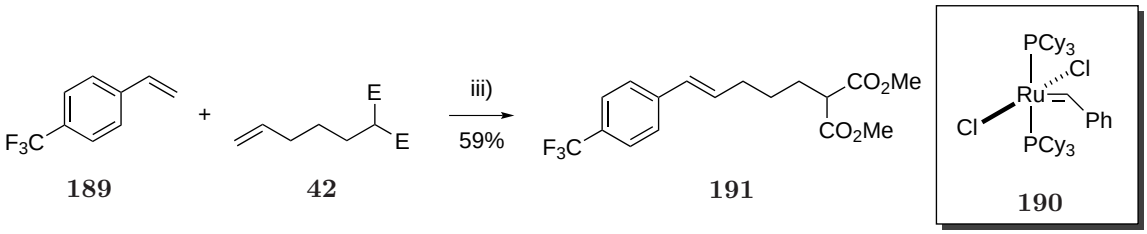
125 **187** **188** **42**

Scheme 2.6: An olefin cross metathesis approach to substituted styrenes **125**. E = CO_2-Alkyl.

From previous work within the group, large quantities of alkene **42** were available.* A cross metathesis reaction between *para*-trifluoromethylstyrene **189** and alkene **42** in the presence of Grubbs 1st generation catalyst **190** gave substituted styrene **191** in moderate yield (**Scheme 2.7**). The colour of the sample clearly showed however that significant amounts of ruthenium had co-eluted with the product. An attempt to remove the Ru using the oxidative procedure of Knight and co-workers[83] unfortunately led

*Malonate **42** was synthesised by P. Ross Walker.

to decomposition of the styrene. As this substrate bearing a *para*-CF_3 was highly electron deficient, this procedure was also unlikely to be suitable for more electron rich substrates as oxidation would be easier.



189 **42** **191** **190**

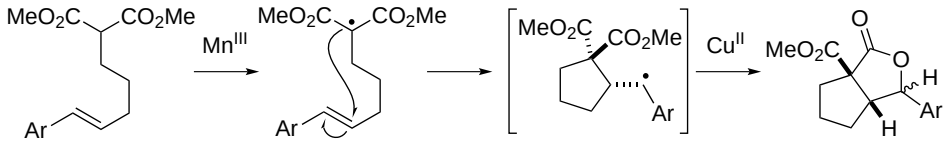
Reagents & Conditions: i) 5 mol% Grubbs 1st generation catalyst **190**, DCM, 40 °C.

Scheme 2.7: Synthesis of *para*-CF_3 substituted substrate **191** by olefin cross metathesis. E = CO_2Me.

Given the difficulties in removing the ruthenium residues, the high cost of the catalyst, and additionally the high cost and instability of styrene coupling partners, it was felt this route was not effective in delivering sufficient amounts of the cyclisation substrates. Whilst this must be balanced against the time and material savings compared to the original route, a large number of benzaldehydes are commercially available and a scalable synthesis from benzaldehydes had already been developed.

2.3 Oxidative Radical Cyclisation Optimisation

With the required malonates **125** in hand, attention was now turned to the MAN-mediated radical cyclisation reaction. Previous work within the group had shown that MeCN was the most effective for these reactions. It is highly polar, but only weakly coordinating unlike DMSO, which has been shown to favour alkene formation over substitution.[50] The effects of concentration, temperature, and copper(II) loading were investigated. The proposed reaction mechanism is shown in **Scheme 2.8**.



125 **192** **126** **127**

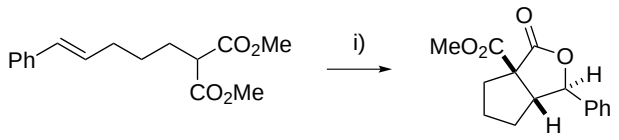
Scheme 2.8: Optimisation of the oxidative radical cyclisation reaction.

2.3.1 Optimisation of Reaction Conditions

Optimisation of the reaction conditions was carried out with phenyl substituted substrate (*E*)-**144**. All reactions were run at 80 °C with 2 eq. MAN and 1 eq. copper(II) triflate and on ≈0.25 mmol

scale. It was found that the concentration had a major impact both on the isolated yield and on the diastereoselectivity. The results are outlined in **Table 2.2**. The isolated yield reached a maximum when the concentration was 0.40 M (**Entry 3**). The diastereoselectivity reached a maximum when the concentration was 0.60 M (**Entry 4**). Thus, 0.40 M was chosen as the optimum concentration. In all cases, the metal salts were pre-heated under vacuum and then malonate **144** was added as a solution in MeCN at the desired concentration and stirred under N_2 overnight.

The ^{1}H NMR data were consistent with the results of Citterio and Jahn. The $\boldsymbol{\delta_H}$ of the benzylic proton for the major epimer of lactone **193** was 5.06 ppm, which was consistent with Citterio and Jahn's values of 5.05 and 5.00 ppm respectively.[56,77] For the minor epimer, $\boldsymbol{\delta_H}$ for the benzylic proton was 5.89 ppm, consistent with Jahn's value of 5.80 ppm; Citterio did not give data for this compound. The IR data also provided evidence that cyclisation had taken place. The single absorbance in malonate **144** at 1735 cm^{-1} was replaced with two absorptions in cyclopentane-lactone **193** at 1740 and 1774 cm^{-1} corresponding to the ester and lactone respectively.



144 **193**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C.

Entry	[**144**] / M	Yield / %	dr
1	0.1	79	2.8:1
2	0.2	71	3.4:1
3	0.4	84	4.5:1
4	0.6	67	5.7:1
5	0.8	62	5.2:1
6	1.0	55	3.8:1

Table 2.2: Optimisation of reaction conditions for the radical cyclisation of malonate **144**.

The crude mass recovery in all cases was good, and the yields refer to isolated product. These data suggested that as the concentration increased more polymerisation occurred, which would explain the reduced yields as the concentration was increased. Polymerisation may occur by addition of the malonyl radical to another substrate molecule followed by a 1,5-hydrogen atom shift to regenerate the malonyl radical.[46] The dr was measured by integration of the diastereomeric benzylic protons in the crude ^{1}H NMR spectra. The relative stereochemistry shown was determined by ^{1}H NMR nOe experiments and single crystal X-ray crystallography, which is discussed in **Section 2.3.4**.

It was found that substoichiometric quantities of copper(II) triflate also gave good yields in the cyclisation reaction (**Table 2.3**). This is not unexpected as manganese(III) reoxidises copper(I) back to

copper(II) (*vide supra* **Section 1.2.2**). However, the dr was not as high as with stoichiometric copper(II) triflate. In all cases, the reaction was run at 0.40 M in MeCN at 80 °C with 2 eq. MAN.

Entry	mol% $Cu(OTf)_2$	Yield / %	dr
1	100	84	4.5:1
2	50	72	4.4:1
3	25	79	3.7:1
4	10	77	3.8:1

Table 2.3: Investigation of the use of substoichiometric amounts of copper(II) triflate. Reactions conducted with 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 0.40 M MeCN, 80 °C.

The use of substoichiometric copper did give good results, with both yield and dr being retained even at 10 mol% copper(II) loading. The best result was still obtained with stoichiometric copper(II) however, and so this was chosen as the optimum condition. The residual copper is easily removed during work-up and flash column chromatography, and so there is little advantage to using substiochiometric amounts of copper(II).

In stereoselective reactions, temperature is frequently a factor due to the difference in transition state entropies. The effect of temperature on the oxidative radical cyclisation reaction was investigated (**Table 2.4**). Lowering the temperature gave an increase in dr, but with a concomitant decrease in yield. Taking into account the yield of the major diastereomer, the best result was still found to be 80 °C.

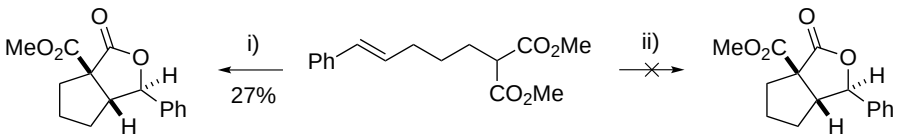
Entry	T / °C	Yield / %	dr
1	80	84	4.4:1
2	60	70	6.0:1
3	40	74	7.4:1

Table 2.4: Effect of temperature on the oxidative radical cyclisation of malonate **144**. Reactions conducted with 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, 0.40 M MeCN, 80 °C.

2.3.2 Control Reactions

Two factors had to be considered in the above discussion. Firstly, was there a requirement to use both MAN *and* copper(II) triflate, or was one or the other sufficient? Secondly, was the product formed under kinetic or thermodynamic control?

It was readily shown that the combination of both metals was, in fact, crucial (**Scheme 2.9**). Submitting malonate **144** to the standard reaction conditions with only 2 eq. of MAN gave cyclised product **193** in 28% isolated yield (57% based on recovered starting material). If only 2 eq. of copper(II) triflate was used with no MAN present the starting material decomposed and no cyclised product was isolated.

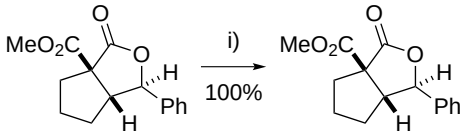


193 **(*E*)-144** **193**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 0.40 M MeCN, 80 °C; ii) 2 eq. $Cu(OTf)_2$, 0.40 M MeCN, 80 °C

Scheme 2.9: Control reaction with only MAN or copper(II) triflate.

The two epimers formed in the radical cyclisation were readily separable by semi-preparative HPLC. When diastereomerically pure cyclised product **193** was resubmitted to the same reaction conditions, none of the other diastereomer was formed (**Scheme 2.10**). This confirmed the radical cyclisation is under kinetic rather than thermodynamic control, as if it were under thermodynamic control the reaction would have equilibrated back to give a mixture of product diastereomers.



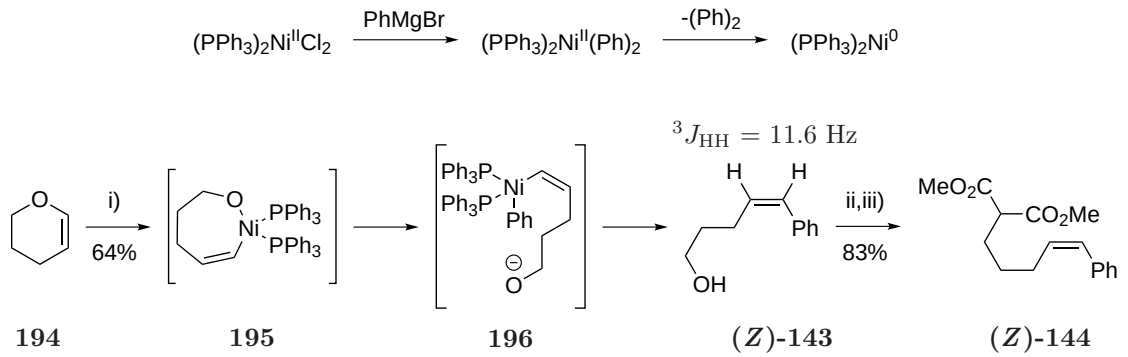
193 **193**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, 0.40 M MeCN, 80 °C

Scheme 2.10: Resubmission of diastereomerically pure cyclisation product to the reaction conditions.

The alkene geometry was not expected to affect the outcome of the reaction, based on the proposed mechanism. In order to investigate this pentenyl malonate (*Z*)-**144** was synthesised. Rather than rely on a moderately *Z*-selective olefination reaction, such as addition of an unstabilised ylid to an aldehyde, a highly stereoselective synthesis involving low-valent nickel was used (**Scheme 2.11**).[84] Wenkert and co-workers studied the reaction of enol ethers with nickel(0) catalysts, formed *in situ* by reduction of nickel(II) precursors. The reaction of dihydropyran **194** with $(PPh_3)_2NiCl_2$ and PhMgBr gave exclusively (*Z*)-alkene (*Z*)-**143**. In the proposed mechanism, the nickel(II) precursor was reduced to nickel(0) by displacement of the chloride ligands with a Grignard reagent, followed by reductive elimininationation of biphenyl. The nickel(0) species then inserted into the sp^2 C-O bond to give nickelocycle **195**, and was then attacked by PhMgBr with retention of the *cis*-configuration to give nickel complex **196**. If the phosphine ligand was PPh_3, complete retention was obtained, whereas with dppp some inversion to the *trans*-configuration resulted.

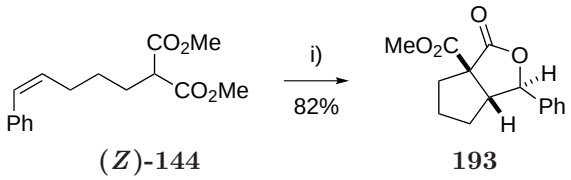
Following the procedure of Stahl and Liu,[85] dihydropyran **194** was reacted with PhMgBr and 10 mol% $(PPh_3)_2NiCl_2$, which gave alcohol (*Z*)-**143** in 64% yield. The alkene configuration was determined by



Reagents & Conditions: i) $(PPh_3)_2NiCl_2$, PhMgBr, PhMe, 115 °C; ii) MsCl, NEt_3, DCM, RT; iii) DMM, NaH, KI, DMF/THF, 80 °C.

Scheme 2.11: Synthesis of cyclisation substrate *Z*-**144**.

coupling constant analysis [$^3J_{HH}$ = 11.6 Hz]. A small amount of alkene (*E*)-**143** was also formed [$^3J_{HH}$ = 15.8 Hz], with an overall *Z*:*E* ratio of 20:1. Treatment of the alcohol under the same conditions as for the (*E*)-series (MsCl then DMM anion) gave malonate (*Z*)-**144** in 53% yield from dihydropyran **194**. Malonate (*Z*)-**144** was reacted with MAN and $Cu(OTf)_2$ in MeCN, which gave cyclopentane-lactone **193** in 82% yield with 4.2:1 dr (**Scheme 2.12**). This result showed that there is no requirement for the alkene to be geometrically pure as the result is consistent with the cyclisation of (*E*)-**144**.



Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, 0.40 M, 80 °C.

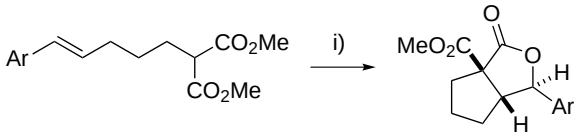
Scheme 2.12: Cyclisation of (*Z*)-**193** to investigate affect of alkene geometry.

This was an important result in terms of the applicability of the methodology as alkene geometry is often hard to control. Common olefination methods such as Wittig reactions, cross metathesis, and the Julia reaction are all stereoselective rather than stereospecific. With no requirement for strict control of alkene geometry the oxidative radical cyclisation methodology may be more widely applied.

2.3.3 Cyclisations of Other Substrates

The conditions optimised for phenyl substituted substrate **144** were then applied to other aryl substituted substrates. The results are summarised in **Table 2.5**. Most reactions proceeded in around 75% yield, with substrates bearing electron withdrawing substituents in the *ortho* (**Entry 3**) and *meta* (**Entry**

9) positions giving the corresponding cyclopentane-lactones in slightly reduced yields. It can also be seen that electron rich substrates (**Entries 5**, **6**, and **10**) had lower levels of diastereoselectivity. In the extreme case of the 4-OMe substituted substrate (**Entry 8**), none of the desired cyclopentane-lactone was isolated and it was only detected by MS [HRMS found 313.1045, $C_{16}H_{18}NaO_5$ requires 313.1046] as part of an intractable mixture. Naphthyl substituted substrate **184** cyclised in 83% yield (**Entry 10**), which is consistent with the cyclisation of phenyl substituted substrate **144**. The dr was lower than for substrate **144** (1.9:1 *vs.* 4.1:1), which reflected the higher electron density of the naphthyl group compared to a phenyl.



125 **197**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_2{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, 0.40 M MeCN, 80 °C.

Entry	Ar	Yield (%)	dr	δ_H / ppm major	δ_H / ppm minor
1	Ph	**193** (84)	4.5:1	5.06	5.89
2	4-FC_6H_4	**198** (72)	4.1:1	5.03	5.90
3	2-FC_6H_4	**199** (54)	4.8:1	5.40	6.07
4	4-BrC_6H_4	**200** (74)	4.2:1	5.01	6.08
5	4-MeC_6H_4	**201** (58)	1.5:1	5.00	5.85
6	2-MeC_6H_4	**202** (72)	1.3:1	5.31	5.95
7	3-$MeOC_6H_4$	**203** (73)	6.0:1	5.01	5.85
8	4-$MeOC_6H_4$	n/a	n/a	n/a	n/a
9	3-$NO_2C_6H_4$	**204** (66)	3.4:1	5.16	5.95
10	2-naphthyl	**205** (83)	1.9:1	5.22	6.05

Table 2.5: Oxidative radical cyclisation reaction of aryl substituted pentenyl malonates.

The same trend in $\boldsymbol{\delta_H}$ for the benzylic protons was observed for aryl-substituted cyclopentane-lactones as for phenyl cyclopentane-lactone **193**. The major diastereomer consistently had a higher $\boldsymbol{\delta_H}$ for the benzylic proton than for the minor diastereomer, despite the installation of strongly electron withdrawing/donating groups. This suggested that the structure of the cyclopentane-lactones had a larger influence of the proton environment than the electronic effects of the adjacent aryl ring. This was alluded to by Fristad and Hershberger in their intermolecular synthesis of malonic spirocyclices (*vide supra* **Section 1.3.2.1**).[72] The higher $\boldsymbol{\delta_H}$ of the benzylic proton in the minor diastereomer suggested it was on the same face as the ester carbonyl. The range of $\boldsymbol{\delta_H}$ was 5.00–5.40 and 5.80–6.10 ppm for the major and minor isomers respectively.

2.3.4 Stereochemistry

The stereochemistry of the cyclised products **193** was assigned by ^{1}H NMR nOe experiments on diastereomerically pure samples of both epimers. Due to the steric contraints of the bowl-shaped bicycle, it was expected that the all *cis*-isomer would be prevalent. The initial radical cyclisation would give the *cis*-ring junction based on the prediction of the Beckwith-Houk transition state model,[18, 23, 75] while the lactonisation would be controlled by minimising steric interactions between the phenyl ring and the cyclopentane.

The key ^{1}H NMR nOe correlations are shown in **Figure 2.1**. This clearly showed that in the major *cis*-isomer **193** irradiation of the benzylic proton gave an enhancement of the cyclopentane protons. In the minor *trans*-isomer *epi*-**193**, irradiation of the benzylic proton adjacent did not enhance the cyclopentane methylene protons as it was now outside the bowl and thus too far away, however enhancement of the ester was observed. The diastereomers of cyclopentane-lactones **198** and **204** were separable by semi-preparative HPLC. The stereochemistry was assigned by ^{1}H NMR nOe experiments on all four compounds, with the results consistent with those obtained for cyclopentane-lactone **193**.

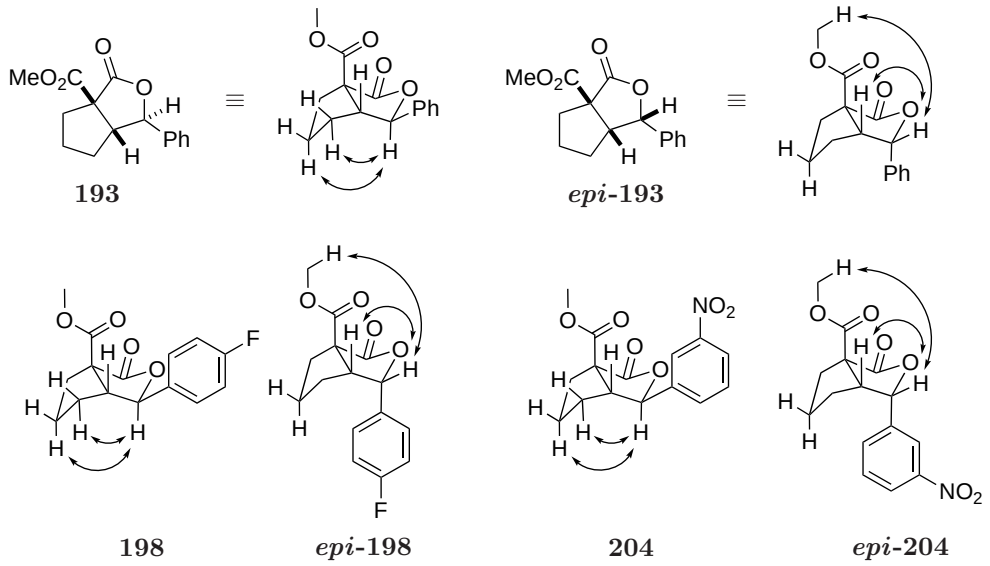
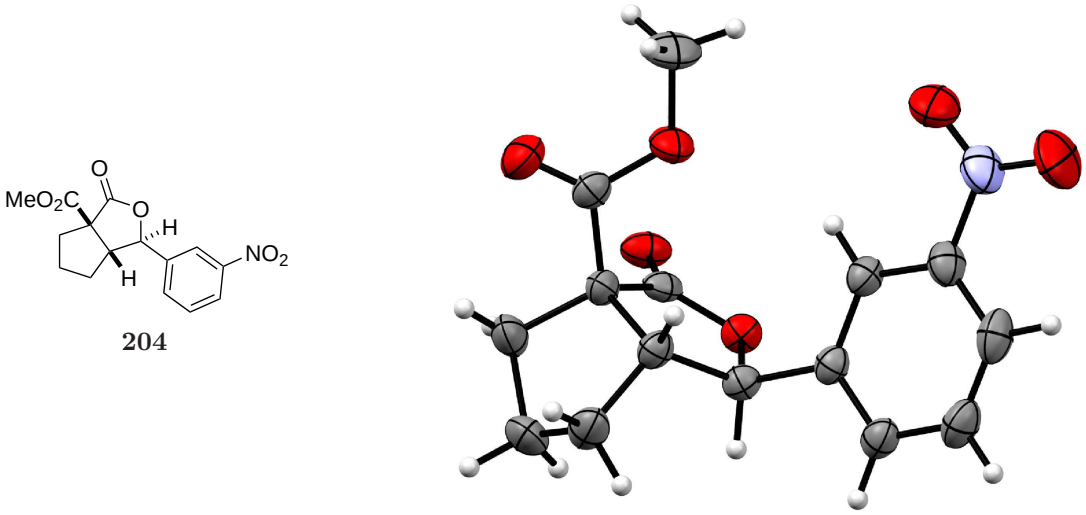


Figure 2.1: Key ^{1}H NMR nOe correlations for the major and minor epimers of cyclopentane-lactones **193**, **198**, and **204**.

Interestingly, $\boldsymbol{\delta_H}$ for the epimeric benzylic protons was very different. For the major *cis*-isomer **193** $\boldsymbol{\delta_H} = 5.06$, and for the minor *trans*-isomer *epi*-**193** $\boldsymbol{\delta_H} = 5.89$. Their separation in a clean section of the ^{1}H NMR spectrum also allowed these peaks to be used to determine the dr of the crude products. This

difference was consistent with the shifts from the other cyclised products (*vide supra* **Section 2.3.3**) and allowed the stereochemistry of other products to established by analogy.

The ^{1}H NMR nOe data were corroborated by a single X-ray diffraction structure of the major diastereomer of 3-nitro substituted lactone **204**.† The X-ray structure clearly shows the all *cis*-arrangement of the substituents (**Figure 2.2**).



204

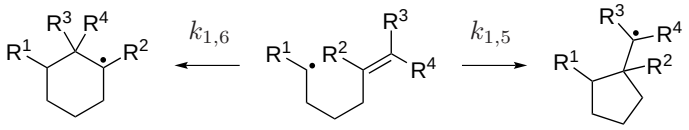
Figure 2.2: X-ray crystal structure of cyclopentane-lactone **204**. Ellipses are shown at 50% probability.

2.4 Cyclisation of Trisubstituted γ-Styryl Malonates

As discussed in **Section 1.1.3**, the rate of intramolecular radical cyclisation on to 2,2-disubstituted alkenes is slower than for monosubstituted alkenes. Beckwith and co-workers studied the relative rates of radical cyclisation with substituted 5-hexenyl radicals (**Table 2.6**).[24,75] When R^1 is methyl, the rate of 5-*exo* is increased by 40%, while the rate of 6-*endo* reaction is unchanged. In contrast, when R^2 is methyl (**Entry 3**) the rate of 5-*exo* cyclisation drops by 98%, but the rate of 6-*endo* is doubled. The 5-*exo* mode is sterically disfavoured while the 6-*endo* mode is electronically favoured, which led to selectivity for the 6-*endo* product. This hypothesis is strengthed by the fact that the rate of 5-*exo* cyclisation when R^2 is *i*-Pr (**Entry 4**) is the same as when R^2 is Me. When R^2 and R^3 are both substituted, the

†Full crystallographic data are given in **Appendix B**. The original data were inverted to correspond to the structures shown in the text.

rate of both 5-*exo* and 6-*endo* reactions are slowed relative to the unsubstituted substrate, but there is some selectivity now for the 5-*exo* cyclisation mode. Disubstitution at both R^3 and R^4 slows the rate of 6-*endo* cyclisation (**Entry 6**), while increasing the rate of 5-*exo* cyclisation due to stabilisation of the adduct radical. Cyclisation on to an internal alkene in a cyclopentene is slow (**Entry 7**), with moderate selectivity for the 5-*exo* product.

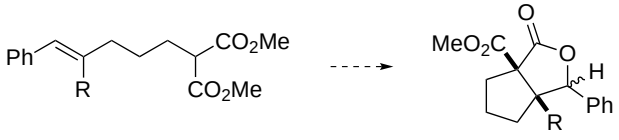


208 **206** **207**

Entry	R^1	R^2	R^3	R^4	$k_{1,5}$ (rel)	$k_{1,6}$ (rel)	$k_{1,5}/k_{1,6}$
1	H	H	H	H	1.0	0.02	48
2	Me	H	H	H	1.4	0.02	74
3	H	Me	H	H	0.022	0.04	0.62
4	H	^{i}Pr	H	H	0.022	0.07	0.31
5	H	Me	Me	H	0.11	0.02	5.4
6	H	H	Me	Me	2.3	<0.011	>200
7	H	-$(CH_2)_3$-		H	0.11	0.03	4.2

Table 2.6: Beckwith and co-worker's data for the rate of substituted 5-hexenyl radical cyclisation. All rate constants are relative to $k_{1,5}$ with R^1=R^2=R^3=R^4=H.

It was proposed that the oxidative radical methodology developed previously could be extended to the reaction of 1,2,2-trisubstituted alkenes **209** to give γ-lactones **209** (**Scheme 2.13**). While the rate of reaction of 2,2-disubstituted alkenes has been shown to be significantly less than for monosubstituted alkenes, it was proposed that the extra stability conferred on the adduct radical by the terminal aryl group would facilitate this reaction. This proposal was strengthened by the fact that substitution at R^2 and R^3 with a methyl group (**Table 2.6 Entry 5**) leads to selectivity for the 5-*exo* cyclised product **209**. This reaction would generate contiguous quaternary-quaternary-tertiary stereocentres, with the two quaternary stereocentres being all-carbon. As discussed in **Section 1.3.1**, this is a highly desirable reaction as the formation of vicinal all-carbon quaternary stereocentres is still challenging.

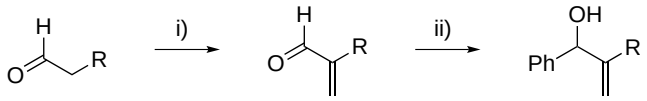


209 **210**

Scheme 2.13: Proposed synthesis of bicyclic γ-lactones containing vicinal all-carbon quaternary stereocentres.

2.4.1 Substrate Synthesis

The synthesis of the cyclisation precursors followed the same route as for the disubstituted substrates in **Section 2.2**. Methacrolein **211** was alkylated with PhMgBr, which gave allylic alcohol **212** in quantitative yield (**Table 2.7**). Few α,β-unsaturated starting aldehydes were commercially available and are also only moderately stable, and so other substrates were synthesised from the corresponding aldehydes by a Mannich reaction.[86] The reaction of hexanal **213** and isovaleraldehyde **214** with formaldehyde and diethylamine hydrochloride in water gave α,β-unsaturated aldehydes **215** and **216** in 83% and 63% yield respectively after distillation.

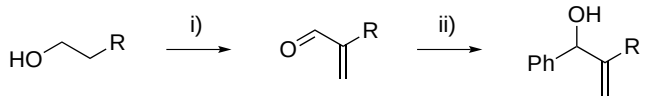


Reagents & Conditions: i) 37% aq. CH_2O, $Et_2NH{\cdot}HCl$, H_2O, 70 °C; ii) PhMgBr, THF, 0 °C.

Entry	R	i) / Yield (%)	ii) / Yield (%)
1	Me	**211** (n/a)	**212** (100)
2	C_5H_{11} (**213**)	**215** (83)	**217** (89)
3	$CH(CH_3)_2$ (**214**)	**216** (63)	**218** (97)

Table 2.7: Synthesis of starting α,β-aldehydes from aldehydes followed by Grignard addition.

Other α,β-unsaturated aldehydes were synthesised from alcohols by a one-pot Parikh-Doering oxidation[87] and methylenation.[88] The Parikh-Doering oxidation has a number of advantages over the commonly used Swern reaction.[89] In particular, there is no requirement for rigorous temperature control and $SO_3{\cdot}py$ is a stable solid. The use of Böhme's salt ($H_2C{=}NMe_2{\cdot}Cl$)[90] as a methylenating agent also simplified the reaction as it is a solid, and there was no need to use toxic formaldehyde solution. The yield for these reactions was not particularly high, with pent-4-ynol **219** giving 24% of alcohol **220** (**Table 2.8**), however it did deliver sufficient amounts of the required materials. The intermediate aldehyde **221** was not isolated or purified due to its low stability and low boiling point. The TBDPS-protected alcohol **222** gave α,β-unsaturated aldehyde **223** in 42% isolated yield. Aldehyde **223** was then alkylated with PhMgBr, which gave alcohol **224** in 94% yield.

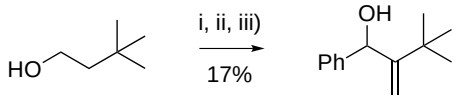


Reagents & Conditions: i) $SO_3{\cdot}py$, DMSO, NEt_3 then $Me_2N{=}CH_2{\cdot}Cl$, DCM, RT; ii) PhMgBr, THF, 0 °C.

Entry	R	i) / Yield (%)	ii) / Yield (%)
1	$CH_2C{\equiv}CH$ (**219**)	[**225**] (n/a)	**220** (24)
2	$(CH_2)_2OTBDPS$ (**222**)	**223** (42)	**224** (94)

Table 2.8: One-pot Parikh-Doering oxidation and methylenalation followed by Grignard addition.

The final substrate pursued was the *tert*-butyl substituted alkene **226**, which started with the oxidation of alcohol **227** (**Scheme 2.14**). Various oxidation methods were screened, including Swern, Parikh-Doering, and TEMPO but only PCC gave clean oxidation to the aldehyde. An aqueous Mannich reaction then installed the *exo*-methylene, followed by alkylation with PhMgBr, which gave α,β-unsaturated aldehyde **228** in a low yield of 17% over three steps.



227 **228**

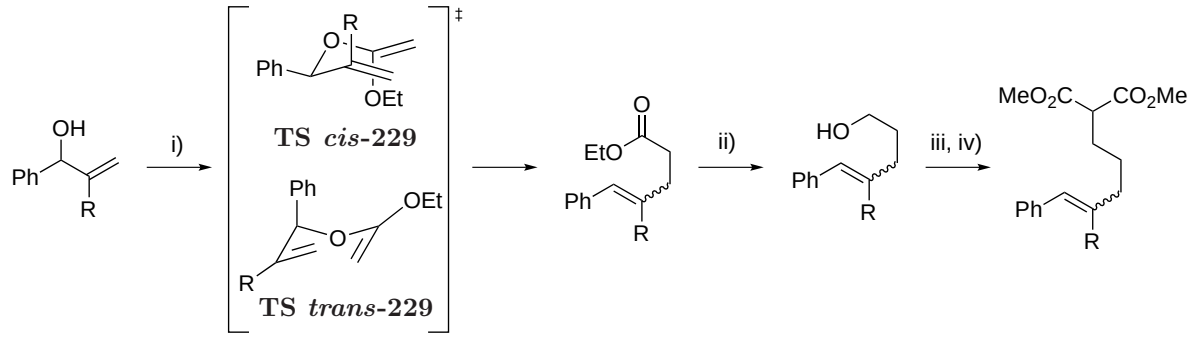
Reagents & Conditions: i) PCC, DCM, RT; ii) aq. CH_2O, 10 mol% pyrrolidine, 10 mol% propionic acid, IPA, 45 °C; iii) PhMgBr, THF, 0 °C.

Scheme 2.14: Oxidation, methylenalation, and alkylation of 3,3-dimethylbutanol **227**.

In a similar manner to the 1,2-disubstituted substrate synthesis shown in **Section 2.2.1**, the allylic alcohols were then converted to the desired pentenyl malonates by a Johnson-Claisen rearrangement, reduction of the resultant ester, mesylation, and finally alkylation with DMM (**Table 2.9**). The Johnson-Claisen rearrangement was not completely stereoselective with double bond isomers visible in the ^{1}H NMR spectra. With a second substituent on the alkene, there is little difference between transition states ***cis*-229** and ***trans*-229** (**Table 2.9**). It should be noted that for **Entries 1** and **2** the (*E*)-isomer has the phenyl and R groups on the same side of the alkene, and for **Entries 3–6** the (*Z*)-isomer has the phenyl and R groups on the same side due to the CIP priorities.

The alkene geometry was determined by ^{1}H NMR nOe experiments (**Figure 2.3**). Irradiation of the allylic protons in ester **230** and alcohol **243** showed correlation to the alkene proton. In the case of alcohol **246**, no enhancement was shown with the alkene proton, only to the methyl groups on the *tert*-butyl substituent indicating that alcohol **246** had the *E*-configuration shown. Although it had been shown that the alkene geometry did not have an effect on the reaction outcome (**Section 2.3.2**), this was required for rigorous characterisation. Most rearrangements proceeded through transition state ***cis*-229**, which gave the geometric isomer with the phenyl and R groups on the same side. As expected, allylic alcohols bearing larger substituents gave increasing amounts of product obtained from transition state ***trans*-229**, *e.g.* alkene **243**, as there is a steric interaction between the R group and the phenyl group. Alcohol **228** gave the (*E*)-isomer as the major product, reflecting the large steric bulk of the *tert*-butyl group compared to the *iso*-propyl group. Considering A-values for the *tert*-butyl and *iso*-propyl substituents, ($A_{^t\mathrm{Bu}} - A_{^i\mathrm{Pr}}$) is 8.4 kJmol^{-1},[91] rationalises the experimental results.

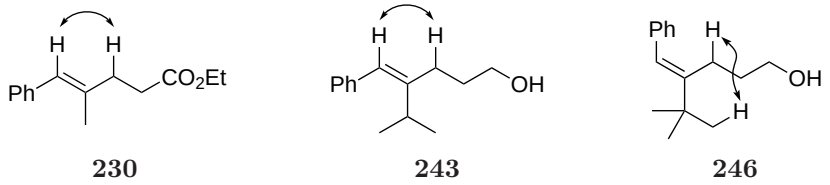
The trisubstituted malonates were less stable than the disubstituted malonates in **Section 2.2.1**.



Reagents & Conditions: i) $MeC(OEt)_3$, 7 mol% propionic acid, 145 °C; ii) $LiAlH_4$, Et_2O, 0 °C; iii) MsCl, NEt_3, DCM, 0 °C; iv) DMM, NaH, KI, DMF/THF, 80 °C.

Entry	R	i) / (%) (*E*:*Z*)			ii) / (%)		iii) / (%)	
1	Me	**230**	(67)	(>20:1)	**231**	(76)	**232**	(84)
2	*n*-Bu	**233**	(80)	(>20:1)	**234**	(99)	**235**	(72)
3	$CH_2C{\equiv}CH$	**236**	(79)	(1:14)	**237**	(79)	**238**	(87)
4	$(CH_2)_2OTBDPS$	**239**	(83)	(1:14)	**240**	(73)	**241**	(62)
5	*i*-Pr	**242**	(81)	(1:5)	**243**	(88)	**244**	(85)
6	*t*-Bu	**245**	(72)	(10:1)	**246**	(75)	**226**	(92)

Table 2.9: Summary of the synthesis of trisubstituted pentenyl malonate cyclisation substrates.



230 **243** **246**

Figure 2.3: Alkene geometry determination by ^{1}H NMR nOe experiments.

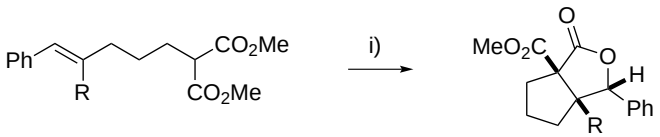
This is probably due to slight distortion in the alkene due to the bulk of the substituents, so the alkene is no longer as stable. Alkyne **238** was especially unstable, with the freshly purified compound rapidly decomposing even under an inert atmosphere.

2.4.2 Oxidative Radical Cyclisation Reactions

2.4.2.1 Primary and Secondary Substituted Substrates

The trisubsituted malonates synthesised were subjected to the same cyclisation conditions as those developed for the di-substituted malonates (*vide supra* **Section 2.3**). Despite the increased steric hindrance at the reactive carbon, the yields and diastereoselectivity were better than those for the 1,2-disubstituted compounds (**Table 2.10**).

The reactions were uniformly clean, with the dr being conveniently determined by integration of the singlet benzylic proton in the product lactones. The $\mathbf{\Delta\delta_H}$ for the diastereomeric protons was >0.15 ppm



Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, 0.40 M MeCN, 80 °C.

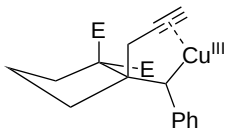
Entry	R	Yield (%)	dr	δ_H / ppm major	δ_H / ppm minor
1	Me	**247** (83)	8.0:1	5.45	5.25
2	*n*-Bu	**248** (91)	10.7:1	5.51	5.19
3	$CH_2C{\equiv}CH$	**249** (74)	11.9:1	5.89	5.31
4	$(CH_2)_2OTBDPS$	**250** (96)	10.2:1	5.46	5.30

Table 2.10: Cyclisation of trisubstituted pentenyl malonates.

in all cases. The crude spectra were virtually indistinguishable from the purified product, with flash column chromatography serving only to remove trace impurities and metal salts.

This reaction is notable for being a stereoselective synthesis of highly functionalised molecules bearing vicinal all-carbon quaternary centres (*vide supra* **Section 1.3.1**). These reactions resulted in the formation of quaternary-quaternary-tertiary stereocentres, with both quaternary centres being all-carbon. In addition, the products are highly oxidised, which will allow further synthetic transformations. Given the high level of steric hindrance, the yields and levels of stereocontrol are very high.

Alkyne substituted pentenyl malonate **238** gave the highest dr despite the alkyne being significantly smaller than the alkyl chain in malonate **235**. This suggested that the copper may remain coordinated to the alkyne,[92] which holds intermediate **251** rigid giving rise to the high dr (**Figure 2.4**).



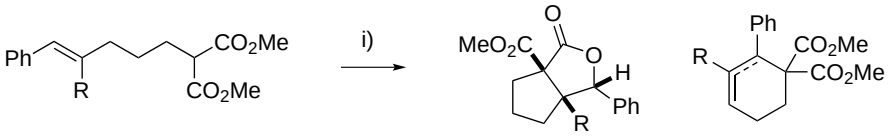
251

Figure 2.4: Copper coordination to an alkyne in oxidative radical cyclisation. E = CO_2Me.

Silyl-protected substrate **241** may have been expected to give higher dr, but the bulky TBDPS is fairly far away from the reactive centre, and also the long O-Si bond places the Si further away still so it is more like *n*-butyl substrate **235**. Methyl substrate **232** did give a slightly lower dr, but considering the A-value of a methyl group and an ethyl group, the difference ($A_{ethyl} - A_{methyl}$) is only 210 $Jmol^{-1}$,[91] which rationalised the observed data.

2.4.2.2 Tertiary and Quaternary Substrates

In order to investigate the limits of steric hindrance the reaction would tolerate, *iso*-propyl substituted substrate **244** and *tert*-butyl substituted substrate **226** were reacted under the same conditions as for the primary and secondary substituted substrates (**Table 2.11**).



5-*exo* 6-*endo*

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, 0.40 M MeCN, 80 °C.

Entry	R	5-*exo* / Yield (%)	6-*endo* / Yield (%)
1	*i*-Pr	**252** (39)	**253** (48)
2	*t*-Bu	**254** (0)	**255** (23)

Table 2.11: Cyclisation of more sterically hindered substrates.

The *iso*-propyl substituted malonate **244** underwent cyclisation in good overall yield. A 1:1.2 mixture of 5-*exo*:6-*endo* cyclised products was obtained, which showed that for the first time the 6-*endo* mode is more favoured than the 5-*exo* mode due to the steric bulk of the alkene substituent. The 5-*exo* product **252** was obtained as a single diastereomer. The 6-*endo* product **253** was shown by both ^{1}H and ^{13}C NMR spectroscopy to be an inseparable mixture of alkene regioisomers.

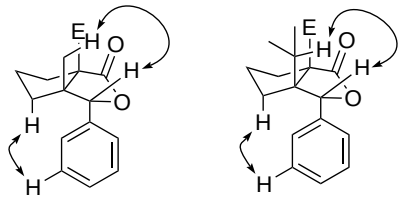
Attempts to cyclise *tert*-butyl substituted substrate **226** gave 6-*endo* cyclised compound **255** as a single regioisomer in 23% yield. Trace amounts of 5-*exo* product **254** were observed by MS [HRMS: Found 339.1171, $C_{19}H_{24}NaO_4$ requires 339.1567] and 5% of dimer **256** was isolated. No other products were isolated and this suggested that polymerisation was occurring.

2.4.3 Stereochemistry

The stereochemistry of the cyclised products was established by analysis of the $\boldsymbol{\delta_H}$ of the benzylic proton, ^{1}H NMR nOe experiments, and finally single crystal X-ray diffraction. In all cases $\boldsymbol{\delta_H}$ for the major diastereomer was higher than that for the minor. This was opposite to the situation observed for the disubstituted substrates (*vide supra* **Section 2.3.4**). This suggested that the major diastereomer had the benzylic proton on the convex face of the bowl-shaped 5,5-*cis* fused ring system with the phenyl ring in the usually more hindered concave face.

This hypothesis was strengthened by ^{1}H NMR nOe analysis of cyclopentane-lactones **247** and **252** (**Figure 2.5**). Irradiation of the benzylic proton showed no enhancement of the cyclopentane protons,

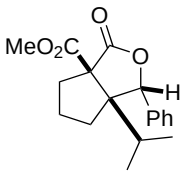
but showed enhancement of the substituent. Conversely, irradiation of the cyclopentane protons showed enhancement of the aromatic protons. This also implies that the phenyl ring is inside the bowl, with the benzylic proton on the outside face.



247 **252**

Figure 2.5: Selected ^{1}H NMR nOe enhancements for determination of stereochemistry. E = CO_2Me.

Cyclopentane-lactone **252** was obtained as a single crystal suitable for X-ray diffraction, which allowed unambiguous determination of the stereochemistry (**Figure 2.6**).‡ The single crystal X-ray diffraction structure clearly showed the reason for the inversion of the expected stereochemistry. This inversion was initially surprising, but it is likely that it avoids steric interactions between the phenyl group and the bridgehead substituents. The inside position of the bowl is less hindered than the outside, due to the bridgehead substituent and so the phenyl group is preferentially orientated into that position.



252

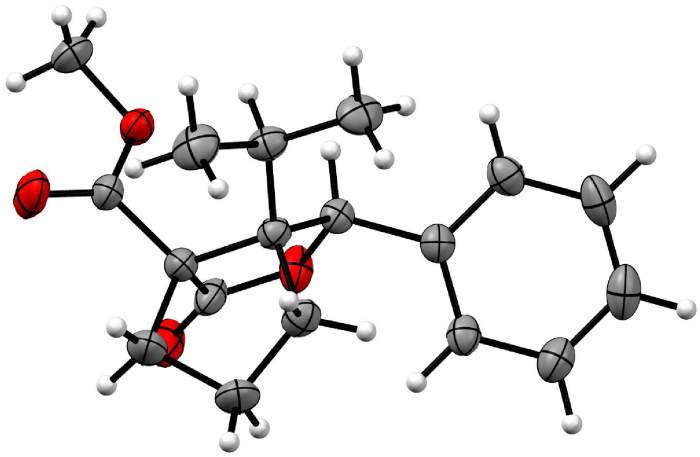


Figure 2.6: X-ray crystal structure of cyclopentane-lactone **252**. Ellipses are shown at 50% probability.

‡Full crystallographic data are given in **Appendix B**. The original data were inverted to correspond to the structures shown in the text.

2.5 Cyclisation of Tetrasubstituted γ-Styryl Malonates

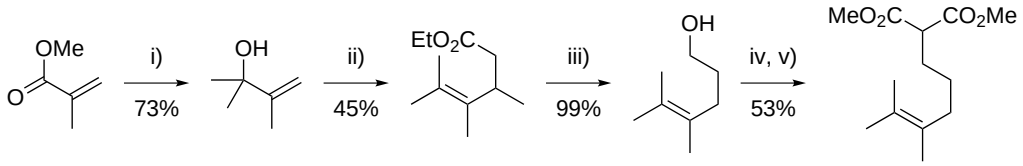
Encouraged by the success of the trisubstituted substrates, we sought to extend the methodology further to tetrasubstituted alkenes. Cyclisation of this class of substrate would give access to three contiguous quaternary centres two of which would be all-carbon.

2.5.1 Tetra-alkyl Substituted Substrate

All the preceeding substrates had the adduct radical from the initial cyclisation stabilised by an aryl group. Trisubstituted radicals are also well stabilised by hyperconjugation, rather than mesomeric effects. Importantly this would also expand the utility of the developed methodology as an adjacent aromatic ring would not be required.

2.5.1.1 Substrate Synthesis

The synthesis of the required malonate was acheived in the same manner as previous substrates (**Scheme 2.15**). Methyl methacrylate **257** was treated with excess MeMgI, which gave tertiary allylic alcohol **258**. Subsequent Johnson-Claisen reaction gave ester **259**, which was then reduced with $LiAlH_4$, which gave alcohol **260** in quantitative yield. Mesylation and substitution with DMM gave malonate **261** in 53% yield. All the compounds in this sequence were volatile, and it was difficult to bring through large quantities without loss of material.



257 **258** **259** **260** **261**

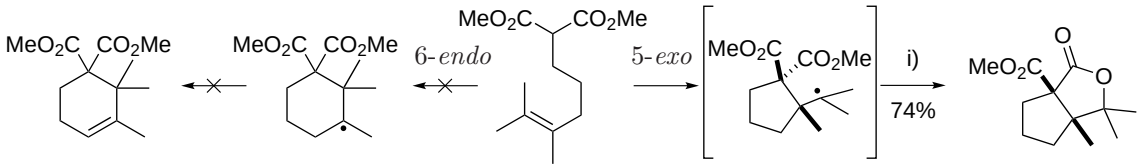
Reagents & Conditions: i) MeI, Mg, THF, then methyl methacrylate **257**, 70 °C; ii) $MeC(OEt)_3$, 7 mol% propionic acid, 145 °C; iii) $LiAlH_4$, Et_2O, 0 °C; iv) MsCl, NEt_3, DCM, 0 °C→RT; v) DMM, NaH, KI, THF/DMF, 80 °C.

Scheme 2.15: Synthesis of trialkyl substituted malonate **261**.

2.5.1.2 Oxidative Radical Cyclisation

Under the previously developed conditions (**Section 2.3**), malonate **261** underwent 5-*exo*-trig cyclisation to give adduct radical **262**, which was then oxidised to give cyclopentane-lactone **263** in 74% yield (**Scheme 2.16**). This cyclisation was not as clean as the phenyl substituted substrates with some extra

methyl ester signals visible in the crude ^{1}H NMR spectrum, however no other products were isolated after flash column chromatography.



264 **265** **261** **262** **263**

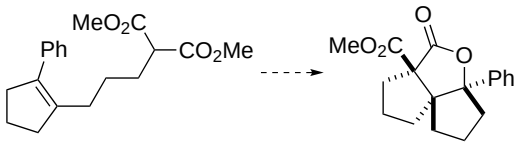
Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, 0.40 M MeCN, 80 °C.

Scheme 2.16: Oxidative radical cyclisation of tetra-alkyl substituted alkenyl malonate **261**.

No cyclohexene **264** corresponding to the 6-*endo* reaction was detected by MS or ^{1}H NMR spectroscopy. Despite both ends of the alkene having similar reactivity, as both of the possible adduct radicals **262** and **265** are tertiary, the 5-*exo* pathway dominated. Based on the Beckwith and co-worker's data (*vide supra* **Table 2.6 Entry 6**), this was not unexpected as disubstitution at the 1 position leads to a 40% increase in the rate of 5-*exo* cyclisation.

2.5.2 Cyclic Substrates Bearing an Internal Alkene

Cyclisation of cyclic substrate **266** bearing an internal alkene was pursued next (**Figure 2.7**). This would give access to tricyclic cyclopentane-lactone **267** with a spiro junction and three contiguous quaternary stereocentres, of which two are all-carbon.



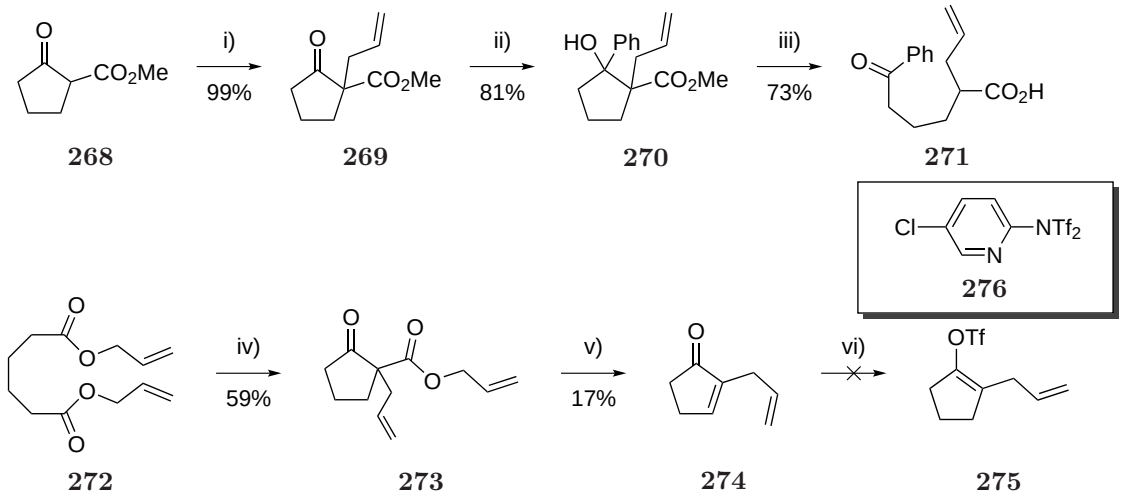
266 **267**

Figure 2.7: Cyclic substrate with an internal alkene to give a tricyclic cyclopentane-lactone.

2.5.2.1 Substrate Synthesis

Synthesis of the desired cyclisation substrate proved difficult. Two routes were initially explored (**Scheme 2.17**). Alkylation of malonate **268** with allyl bromide quantitatively gave alkene **269**, which was then selectively alkylated with PhMgBr at low temperature, which gave alcohol **270** in 81% yield. Attempts to hydrolyse the ester to the corresponding carboxylic acid failed as the substrate underwent a retro-aldol reaction to give acid **271**.

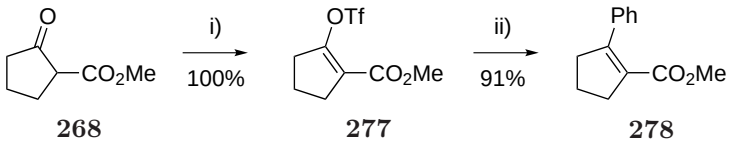
The second route involved Dieckmann condensation of diallyl adipate **272**, with the intermediate anion quenched with allyl bromide to give **273** in a moderate 59% yield.[93] Palladium catalysed decarboxylation gave enone **274**. It was proposed that conjugate reduction of the enone with L-Selectride, followed by quenching the oxyanion with a triflate source would give triflate **275**.[94] The use of triflic anhyride and Comin's reagent **276** both proved unsuccessful, and the high volatility of the products prevented optimisation of this reaction.



Reagents & Conditions: i) allyl bromide, NaH, THF, 0 °C; ii) PhMgBr, THF, –78 °C→RT; iii) KOH, MeOH/H_2O, RT; iv) allyl alcohol, NaH, then allyl bromide, PhMe, 90 °C; v) $Pd(OAc)_2$, PPh_3, MeCN, 80 °C; vi) L-Selectride, then Comin's reagent **276**, THF, –78 °C.

Scheme 2.17: Failed routes towards internal alkene **266**.

Eventually, an early stage introduction of the internal double bond followed by installation of the phenyl group proved to be the solution (**Scheme 2.18**). Treatment of β-keto ester **268** with Hünig's base and Tf_2O, quantitatively gave triflate **277** with simultaneous regioselective formation of the alkene.[95] A Suzuki coupling of triflate **277** with phenylboronic acid gave the desired tetrasubstitued alkene **278** in 91% yield.

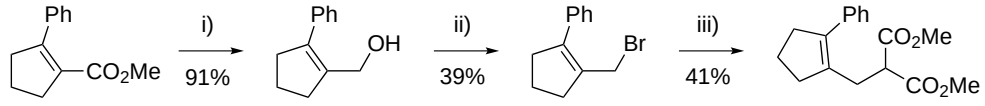


Reagents & Conditions: i) Tf_2O, Hünig's base, –78 °C→RT, DCM; ii) $PhB(OH)_2$, 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, Na_2CO_3, 3:1 benzene/EtOH, 75 °C.

Scheme 2.18: Early introduction of phenyl ring and internal alkene.

A one-carbon homologation was required to set the correct oxidation pattern. Ester **278** was reduced to allylic alcohol **279** with $LiAlH_4$ (**Scheme 2.19**). Treatment of alcohol **279** with PBr_3 gave bromide

280 in a low yield of 39%, with a number of impurities apparent by TLC analysis. A number of polar impurities co-eluted with the product during flash column chromatography. In addition, the silica turned a dark red colour, although the eluent was colourless. It is possible the allylic bromide decomposed on silica, as a stable cation could be formed adjacent to the phenyl ring. Allylic bromide **280** was then alkylated with DMM in the presence of K_2CO_3, which gave malonate **281** in 41% yield. The low yield was due to the impurities carried through from the previous step.

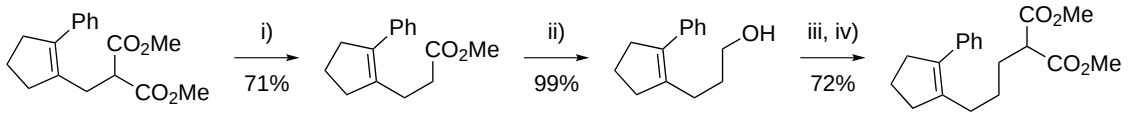


278 **279** **280** **281**

Reagents & Conditions: i) $LiAlH_4$, Et_2O, 0 °C; ii) PBr_3, 10 mol% pyridine, 7:2 Et_2O/hexane, 0 °C; iii) DMM, K_2CO_3, acetone, 60 °C.

Scheme 2.19: One carbon homologation of alkene **278**.

Malonate **281** was then decarboxylated under modified Krapcho conditions[96] to give ester **282** in 71% yield (**Scheme 2.20**). Ester **282** was then reduced with $LiAlH_4$, the resulting alcohol **283** was mesylated and the mesylate was displaced with DMM anion, which gave the cyclisation substrate **266** in 71% yield over three steps from ester **282**.



281 **282** **283** **266**

Reagents & Conditions: i) NaCl, H_2O, DMSO, 170 °C; ii) $LiAlH_4$, Et_2O, 0 °C; iii) MsCl, NEt_3, DCM, 0 °C→RT; iv) DMM, NaH, KI, THF/DMF, 80 °C.

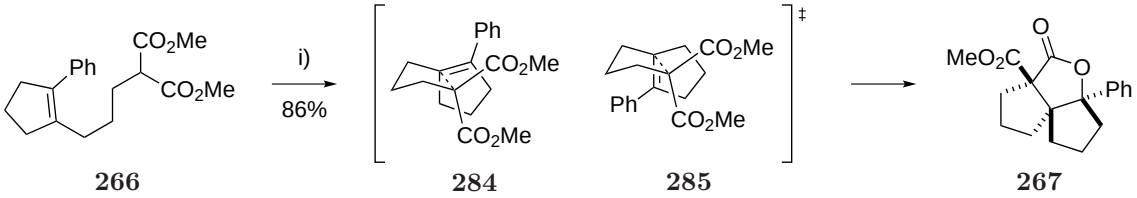
Scheme 2.20: Synthesis of cyclisation substrate **266** bearing an internal alkene.

While this route delivered the desired cyclisation substrate, it did have a number of flaws. In particular, the high step count (9 steps from malonate **268**) was mainly due to the one-carbon homologation. The low yield for displacement of the allylic bromide (**280**→**281**) was due to the low purity of bromide **280**. The problematic bromination reaction (**279**→**280**) could potentially be improved by using MsCl and LiBr rather than PBr_3, with this reagent combination frequently used for allylic brominations.[97]

2.5.2.2 Oxidative Radical Cyclisation

With malonate **266** in hand, its reactivity in the oxidative cyclisation reaction was investigated. Submission of malonate **266** to the optimised conditions gave tricyclic lactone **267** in 2 hours (TLC analysis) in

86% isolated yield as a single diastereomer (**Scheme 2.21**). Both of the plausible chair-like transition states **284** and **285** give the same product. Unfortunately lactone **267** was not crystalline, and so structure and stereochemistry determination relied on two-dimensional NMR experiments and ^{1}H NMR nOe correlations.

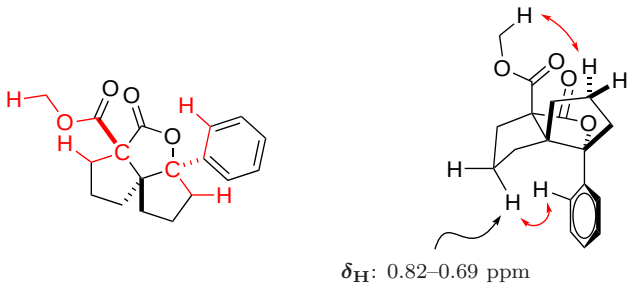


266 **284** **285** **267**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, 0.40 M MeCN, 80 °C.

Scheme 2.21: Formation of tricyclic lactone **267** by oxidative radical cyclisation.

Multiple bond C-H correlations (HMBC) were used to fully assign the C-C connectivity, especially the quaternary centres (**Figure 2.8**). The carbon attached to the ester was identified by a correlation with the methyl ester protons. This in turn showed a strong coupling to the left hand (as drawn) cyclopentane ring, with the remainder of this isolated spin system determined by COSY and HSQC. The high $\boldsymbol{\delta_C}$ [97.9 ppm] of the benzylic carbon allowed identification of the second right hand cyclopentane ring by HMBC, and the again the remainder of this spin system was determined by COSY and HSQC.



$\boldsymbol{\delta_H}$: 0.82–0.69 ppm

Figure 2.8: Structural and stereochemical assignment of tricyclic cyclopentane-lactone **267**.

The stereochemistry was assigned on the basis of ^{1}H nOe experiments. Strong enhancements were seen from the methyl ester protons with the right hand cyclopentane, and from the aromatic protons and the left hand cyclopentane. The ring junctions were determined to be all *cis* by consideration of the ^{1}H NMR nOe result, the proposed transition state, and the higher energy of a 5,5-*trans* system. Also of note was the low $\boldsymbol{\delta_H}$ [0.82–0.69 (1H, m)] of the proton facing into the 5,5-*cis* fused bowl. This was due to shielding caused by the aromatic ring current,[98] which shows that the face of the aromatic ring is in close proximity to the proton. The protons in this cyclopentane spin system were more widely dispersed

as well, also indicative of the influence of the aromatic ring.

2.6 Conclusions

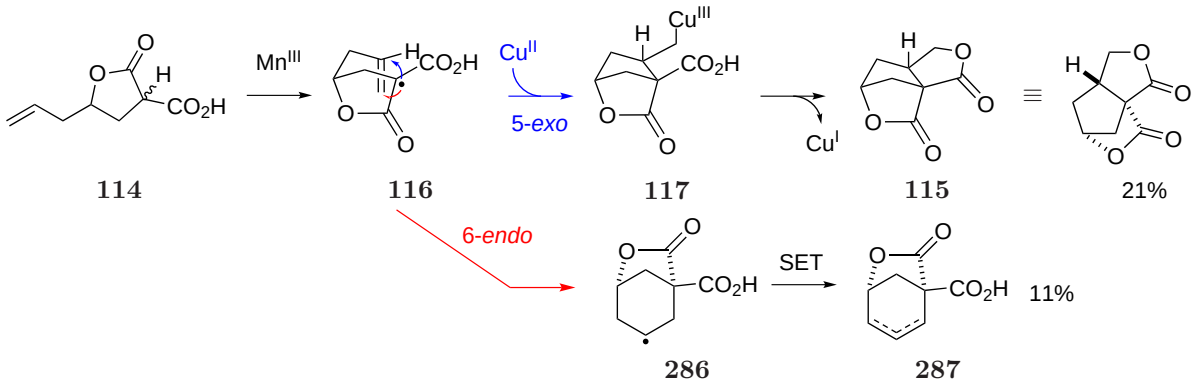
Robust methodology for the synthesis of highly sterically congested cyclopentane-lactones has been developed.[76] Investigation of the effect of adduct radical stabilisation by aryl groups with varied electronic properties showed that the cyclisation is most effective with electronically neutral substituents. Highly electron donating substituents are not well tolerated. Halides are tolerated, allowing the prospect of further functionalisation by cross-coupling reactions.

The methodology was extended to the synthesis of vicinal quaternary all-carbon sterocentres. A range of products with contiguous quaternary-quaternary-tertiary, and quaternary-quaternary-quaternary stereocentres were obtained. These complex products were formed in excellent yields with high levels of diastereoselectivity. This reactivity showcases the use of oxidative radical cyclisations to form highly substituted systems under mild conditions with readily accessible starting materials. Fragile functionality such as alkynes and silyl protection groups was preserved, which should allow the widespread use of this methodology.

3

Synthesis of Tricyclic *bis*-Lactones

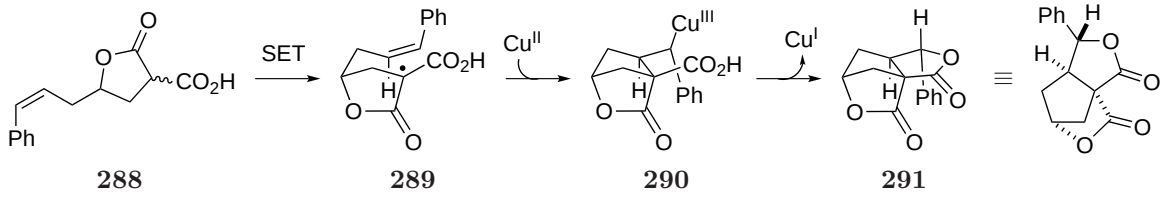
Previous work in the group had shown that tricyclic *bis*-lactones were accessible from allyl lactones (**Section 1.3.2.3** and **Scheme 3.1**). The reaction was, however, low yielding and non-selective with significant amounts of the 6-*endo* product also isolated. This product arises from 6-*endo* radical cyclisation onto the less hindered terminus of the alkene to give adduct radical **286**, which is then oxidised by either manganese(III) or copper(II) to give regioisomeric cyclohexenes **287**. To circumvent these problems, it was postulated that cyclisation onto a terminal styryl group would allow benzylic stabilisation of the adduct radical. This Chapter describes the synthesis of the cyclisation substrates and the MAN and CAN mediated oxidative radical cyclisations of both styryl and terminal olefin substrates, which gave tricyclic *bis*-lactones in improved yields. Chemoselective transformations of the resulting *bis*-lactones are also explored.



Scheme 3.1: Previous synthesis of tricyclic *bis*-lactones showing the competing 6-*endo* cyclisation pathway.

3.1 Oxidative Radical Cyclisations of Lactone-Acids

Previous work in the group had shown that esters were unsuitable substrates for oxidative radical cyclisations to form *bis*-lactones, and this was confirmed by the author (*vide infra* **Section 3.1.2**). Thus, the cyclisation of lactone-acid **288** was to be investigated. The proposed mechanism is shown in **Scheme 3.2**. In the proposed mechanism the manganese enolate of lactone **288** is oxidised by SET to give radical **289**. It is possible that the manganese remains coordinated as the carboxylate complex during the cyclisation. Radical **289** then undergoes a 5-*exo*-trig cyclisation, with the adduct radical being oxidised by copper(II) to give copper(III) intermediate **290**. The adduct radical could also be oxidised by manganese(III). The copper(III) is then displaced by the free carboxylic acid, which gives tricyclic *bis*-lactone **291**; potentially this could also occur *via* a benzylic cation.



Scheme 3.2: Proposed mechanism for the stereoselective synthesis of tricyclic *bis*-lactone **291**.

The stereochemistry would be controlled by the minimisation of 1,3-diaxial strain in the reactive chair-like conformation **289**. The reactive alkene is placed in the *pseudo*-equatorial position to minimise steric interactions according to the Beckwith-Houk model. To form the lactone, the phenyl is placed *cis* to the adjacent proton to minimise 1,3-diaxial interactions. This leads to the all-*cis* tricyclic *bis*-lactone **291**.

3.1.1 Synthesis of the Terminal Aryl Substrate

In order to investigate the oxidative radical cyclisation, lactone-acid **288** was desired, and a retrosynthesis is presented in **Figure 3.1**. Under basic conditions, epoxide **292** could be opened by a malonate anion, with the γ-lactone spontaneously forming upon acidic work up. Epoxide **292** would be obtained from alkyne **293** *via* Lindlar semi-hydrogenation. The (*Z*)-alkene geometry was not likely to affect the reaction (*vide supra* **Section 2.3.2**). The alkyne **293** would be available from chlorohydrin **294**, which would be the product of the alkylation of phenylacetylene **295** with epichlorohydrin **296** in the presence of boron trifluoride.[99] Both enantiomers of epichlorohydrin **296** are commercially available, allowing synthesis of **288** as a single enantiomer if desired.

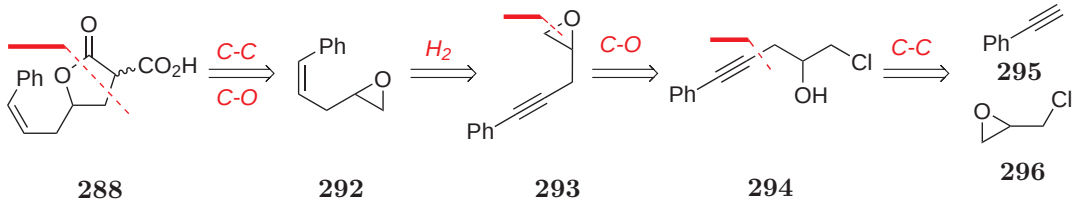
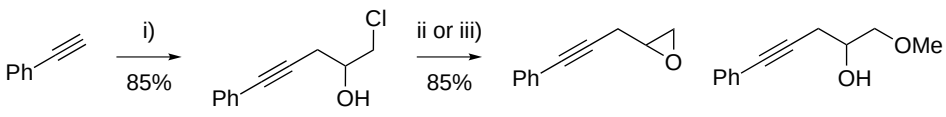


Figure 3.1: Proposed retrosynthesis of lactone-malonic acid **288**.

Following a modified version of Yamaguchi and Hirao's procedure, phenylacetylene, **295** was deprotonated with ^{n}BuLi, transmetallated with $BF_3{\cdot}OEt_2$, and finally treated with epichlorohydrin, **296**, which gave chlorohydrin **294** in good yield (**Scheme 3.3**).[99] It was found to be imperative that fresh $BF_3{\cdot}OEt_2$ was used. Use of old (ca. two months) $BF_3{\cdot}OEt_2$ led to an intractable polymeric mixture. The use of $BF_3{\cdot}$THF was reported by Evans and Knight to be superior to $BF_3{\cdot}Et_2O$ for this reaction.[100] Following this procedure, which also used a slight excess of epichlorohydrin **296** rather than alkyne **295**, gave only a 53% yield of chlorohydrin **294** on the same scale (50.0 mmol) and so the original Yamaguchi procedure was used.



Reagents & Conditions: i) ^{n}BuLi, $BF_3{\cdot}OEt_2$ then epichlorohydrin **296**, THF, –78 °C; ii) K_2CO_3, 20 mol% TBAI, MeOH, RT, 82%; iii) KO^{t}Bu, ^{t}BuOH, 35 °C.

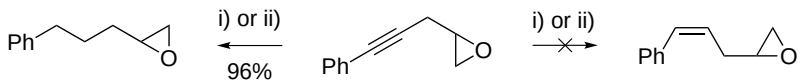
Scheme 3.3: Synthesis of epoxide **293**.

Re-epoxidation of chlorohydrin **294** also proved straightforward, closing readily in methanol in the presence of K_2CO_3. It was noticed that as the reaction time increased, a significant (and increasing)

amount of a polar impurity formed and this was suggested to be methyl ether **297**. In order to minimise its formation, a catalytic amount of TBAI was added to speed up the epoxidation with epoxide **293** isolated in 82% yield with small amounts of ether **297** removed by flash column chromatography. Performing the reaction in ^{t}BuOH with KO^{t}Bu as the base suppressed formation of the ether by-product and gave epoxide **293** in 85% yield. Epoxide **293** was, as expected, highly sensitive to acid and 1 M aqueous HCl workup led to complete decomposition of the product, so a water wash was used instead.

On the basis of literature precedent, it was anticipated that the Lindlar semi-hydrogenation of alkyne **293** would be straightforward, as under standard Lindlar reductions conditions other β-epoxy alkynes had been shown to give (*Z*)-alkenes.[101–103] However, this proved not to be the case. Treatment of epoxide **293** with 20 wt% Lindlar catalyst (5 wt% on $CaSO_4$ poisoned with Pb, Strem Chemicals Inc. or Sigma-Aldrich) in toluene for 5 h under H_2 gave alkane **298** in near quantitative yield (**Scheme 3.4**). Quenching the reaction after 1 h showed there was similar amounts of alkane **298** and the desired alkene **292** present. However, the rate of reaction was not reproducible with ratios of alkyne **293**, alkene **292**, and alkane **292** found to vary between reactions, perhaps due to the hetereogenous nature of the reaction.

Another frequently employed reducing agent is P-2 nickel boride with ethylenediamine as a catalyst poison.[104,105] The catalyst was readily prepared by treatment of $Ni(OAc)_2$ with $NaBH_4$ in ethanol.[106] Exposure of alkyne **293** to P-2 NiB and ethylenediamine gave exclusively the over-reduced alkane **298** in quantitative yield, so this set of reagents was not pursued further.



298 **293** **292**

Reagents & Conditions: i) 15 wt% Lindlar catalyst, 1 atm H_2, PhMe, RT, ii) 10 mol% P-2 NiB, 1 atm. H_2, PhMe, RT.

Scheme 3.4: Over reduction of alkyne **293** with Lindlar's catalyst and P-2 NiB.

The three reaction components had similar R_f values in a variety of TLC solvent systems; consequently the reaction was best monitored by GC, which gave clear separation of the respective peaks. The flame ionisation detector (FID) in the GC gave signal areas proportional to the number of carbons in the analyte, so quantitative responses were obtained without recourse to individual calibration for each component. All the components also had the same oxygenation, so no effects due to incomplete flame ionisation would be encountered.[107]

The hydrogenation of alkenes is thermodynamically more favourable than the reduction of alkynes, so the selectivity of the reduction relies on the preferential binding of alkynes over alkenes. As a hetero-

geneous catalyst, the exact configuration of the active site and the disposition of the reactive atoms is not known despite much effort, hence predicting which catalyst and poison to use is difficult.[108]

In order to understand the Lindlar reduction better, a time series comparing the ratio of products over the course of an hour was run and the results are shown in **Figure 3.2**. Alkyne **293** was consumed smoothly, with concomitant formation of alkene **292** and a small, but steadily increasing, amount of alkane **298**. When alkyne **293** was almost completely consumed, alkene **292** was then rapidly reduced to give the undesired alkane **298**. This showed that the reaction would have to be stopped within a very narrow window, and given the variable rate of the reaction this was clearly not experimentally practical.

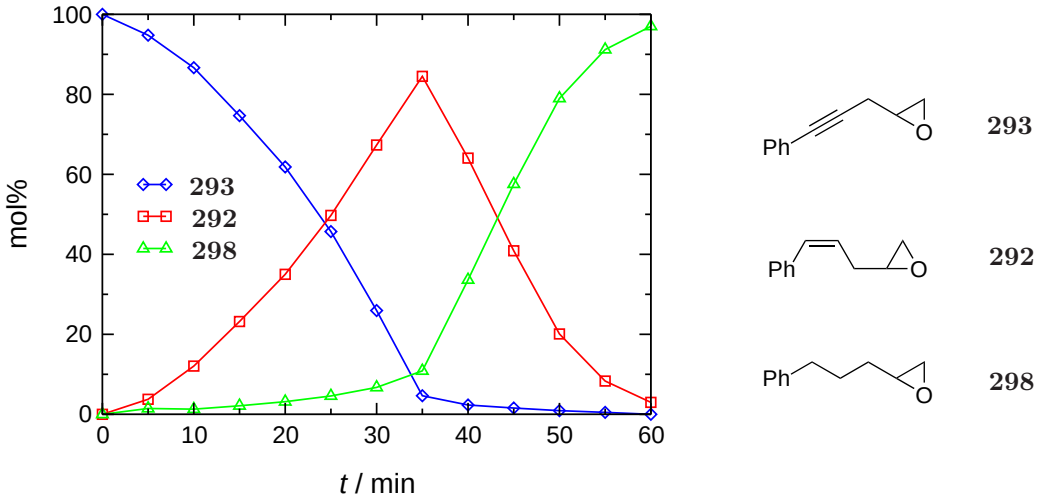
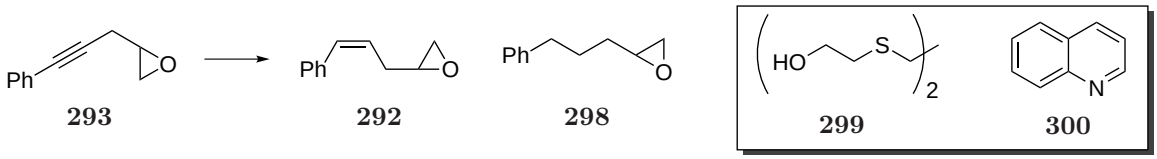


Figure 3.2: Time course of the semi-hydrogenation of alkyne **293** with Lindlar's catalyst. Aliquots were removed every 5 min, filtered through cotton wool to remove heterogeneous catalyst and injected directly into the GC.

In an attempt to solve the problems with the Lindlar reduction additives and solvents were screened and the results are shown in **Table 3.1**. It was proposed that reducing the rate of reaction would give a longer time in which **292** was the dominant product. To that end sulfide **299**, which is known as a useful catalyst activity modifier in Lindlar reductions,[109] was added to the reaction, but this completely poisoned the catalyst and even after 48 h, there was only 15% conversion (**Entry 2**). Increasing the loading of Lindlar catalyst with respect to sulfide **299** did not increase the conversion. Quinoline is a well known surface modifier for Lindlar catalysts, and is thought to homogenise the active palladium catalytic sites.[110] With high catalyst loading quinoline did not prevent over reduction in either EtOAc or EtOH as the solvent (**Entries 3** and **4**), however at 2% catalyst loading (**Entry 5**), some selectivity for the desired alkene **292** was shown.

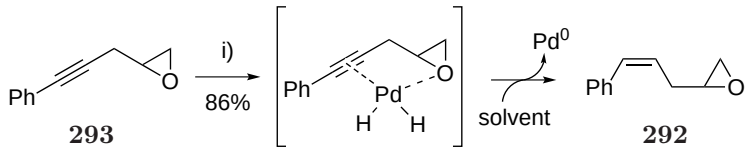


293 **292** **298** **299** **300**

Entry	Additive	Solvent	Lindlar / wt%	t / h	mol% (**293**:**292**:**298**)
1	–	PhMe	20	5	0:0:100
2	2.5% **299**	EtOAc	20	24	85:15:0
3	7.5% **300**	EtOAc	20	1	2:38:60
4	100% **300**	EtOH	20	1	0:0:100
5	100% **300**	EtOH	2	25	20:78:2
6	100% **300**	octene	15	3	13:84:3
7	100% **300**	octene/EtOH	15	1	2:94:4
8	100% **300**	allyl alcohol	15	3	3:96:1

Table 3.1: Conditions screened for the semi-hydrogenation of alkyne **293**.

It was proposed that a solvent containing a primary alkene would act as a sacrificial reduction substrate. Previous work by, for example, Ho, Jacobsen, and Evans[111–113] had shown that terminal alkenes are useful additives in alkyne hydrogenations as they are selectively hydrogenated in the presence of the semi-reduced alkyne. 1-Octene was chosen in this case, and this gave a considerable improvement (**Table 3.1, Entry 6**). However, when the reaction was run in 1:1 octene:ethanol, for the first time the reaction contained >90 mol% of alkene **292** (**Table 3.1, Entry 7**). This suggested that the substrate may remain coordinated through the epoxide oxygen to the palladium after the first reduction, leading to over reduction (**Scheme 3.5**). We posited that ethanol acted to displace alkene **292** from the catalyst surface. In order to combine these two effects, a reaction was run in allyl alcohol, which led to complete conversion to alkene **292** (24:1 Z:E) with only a trace (<1%) of the over reduced product (**Table 3.1, Entry 8**).



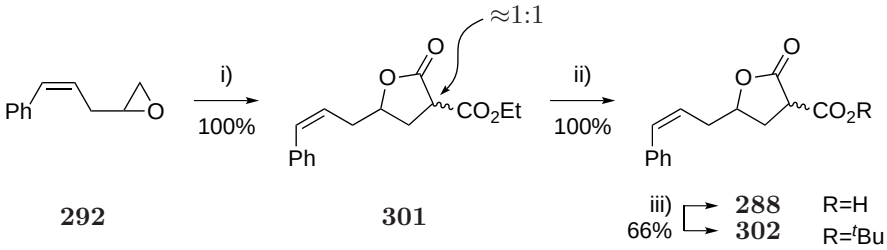
293 **292**

Reagents & Conditions: i) 15 wt% Lindlar catalyst, 1 atm H_2, 1.0 eq. quinoline, allyl alcohol, RT.

Scheme 3.5: Successful semi-hydrogenation of alkyne **293** to alkene **292**.

The semi-reduction could be stirred with minimal monitoring without the formation of alkane **292** and reactions were typically complete in 3 hours. In the absence of GC, the reaction was best monitored by developing TLC plates in acidic vanillin: the alkyne stained bright red, while the alkene stained deep purple. This reaction was successfully carried out on 30.0 mmol scale.

Epoxide **292** was transformed to lactone-ester **301** by alkylation with diethyl malonate (DEM) with freshly prepared NaOEt as the base in EtOH. It was found that the reaction gave the best yield when run almost neat in EtOH, with the base added slowly to a solution of DEM and epoxide **292**. The lactone formed upon acidic workup, which gave lactone-ester **301** in quantitative yield, as an inconsequential ≈1:1 mixture of epimers at the malonate carbon. The ester was then hydrolysed with KOH in EtOH/H_2O, which gave the desired cyclisation substrate **288** in 5 steps and 70% overall yield from epichlorohydrin **296**. The corresponding *tert*-butyl ester **302** was synthesised by DCC-mediated coupling of acid **288** with ^{t}BuOH.



292 **301**

Reagents & Conditions: i) 3 eq. DEM, 3 eq. NaOEt (2 M in EtOH), 0 °C→RT, 16 h; ii) KOH, ethanol/H_2O, 0 °C; iii) DCC, ^{t}BuOH, DCM, 0 °C.

Scheme 3.6: Synthesis of lactone-acid **288** by lactonisation and ester hydrolysis.

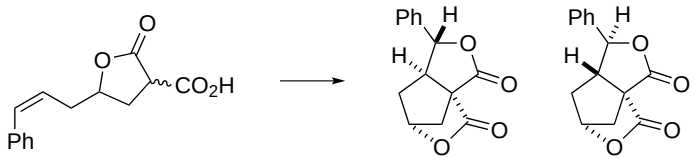
A practical synthesis of lactone-acid **288** had been developed. The key step was a solvent controlled semi-reduction of a sensitive β-oxygenated aryl alkyne with Lindlar's catalyst. The oxidative radical cyclisation reactions of lactone-ester **301** and lactone-acid **288** were now investigated.

3.1.2 MAN-Mediated Oxidative Radical Cyclisations

Attempts to cyclise ethyl ester **301** under the conditions developed in **Chapter 2** proved unsuccessful, with an inseparable mixture of products obtained. No mass corresponding to the desired tricyclic *bis*-lactone **291** was detected by MS analysis. Additionally, TLC analysis showed a large number of products. Similarly, the reaction of *tert*-butyl ester **302** gave an intractable mixture, with none of the desired product isolated or detected by MS. This confirmed previous results on the attempted cyclisation of lactone esters.

Lactone-acid **288** was exposed to the same conditions as for the linear substrates (2 eq. MAN, 1 eq. $Cu(OTf)_2$, 0.40 M in MeCN, 80 °C), but no product was isolated. The crude ^{1}H NMR spectrum showed complete consumption of starting material as the alkene protons were absent with only broad peaks visible. As the the mass recovery was also good this suggested that polymerisation was occurring.

The reactions also stayed a dark brown colour with substantial amounts of salts complicating workup. In comparison, reactions of the linear substrates turned a pale blue colour when completed and the workup was homogeneous. The reaction was then run at lower concentration (0.08 M) in an attempt to minimise polymerisation. A mixture of diastereomers **291** and **303** was obtained in 18% yield and 1:2.5 dr. Increasing the dilution to 10 mM gave 50–65% isolated yield as a 1:5.7 mixture of diastereomers **291**:**303** (**Table 3.2 Entry 3**). Further dilution did not improve the yield. Diastereomeric ratios as high as 1:12 were obtained, but were not reproducible, with the value quoted being representative of the ratio obtained after a number of repeats. The conditions shown in **Entry 3** were the most reliable, and the reaction generally gave reproducible yield and dr, so this set of conditions was used as a benchmark for optimisation. The tricyclic *bis*-lactones were difficult to purify by flash column chromatography due to their high polarity and their lack of functionality to stain on TLC. The stereochemistry was determined by ^{1}H NMR nOe experiments and X-ray crystal diffraction, and this is discussed in **Section 3.1.4**.



288 **291** **303**

Entry	Conc / mM	T / °C	Yield / %	**291**:**303**
1	40	80	0	n.d.
2	80	80	18	1:2.5
3	10	80	50–65	1:5.7
4[a]	25	80	35	1:1.9
5[b]	10	80	47	1:3.2
6[c]	10	80	59	1:1.9

[a]A 0.05 M solution of acid **288** in MeCN was added by syringe pump over 2 hr to a 1.0 M solution of MAN and $Cu(OTf)_2$ and stirred for a further 2 h. [b]2 eq. K_2CO_3 added. [c]2 eq. $TsOH{\cdot}H_2O$ added.

Table 3.2: Optimisation of the MAN-mediated oxidative radical cyclisation of lactone-acid **288**.

It was proposed that keeping the amount of free lactone-acid **288** present low would minimise polymerisation. Lactone-acid **288** was added dropwise to the reaction mixture over 2 h to this end (**Table 3.2 Entry 4**), however this gave only a 35% yield of the *bis*-lactones with 1:1.9 dr. As the rate determining step is the formation of a manganese enolate (*vide infra* **Section 1.2.1.1**), it was proposed that additives that promoted the enolisation would enhance the reaction. In order to test this, two equivalents of K_2CO_3 (**Table 3.2 Entry 5**) and *p*-TsOH (**Table 3.2 Entry 6**) were added to the reaction. Neither additive gave any improvement over the standard manganese conditions.

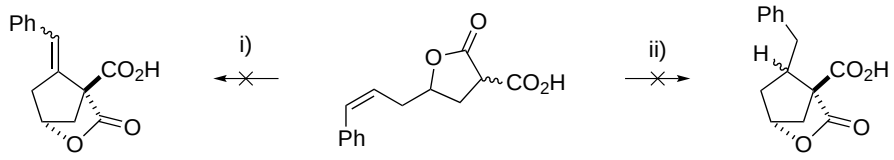
In contrast to the cyclisation reactions described in **Chapter 2** these reactions were not particularly

clean, and it was not possible to measure dr by simple integration of the crude ^{1}H NMR spectra. This also precluded attempts to perform design-of-experiment (multivariate analysis) optimisation.[114,115] As there were no signals available for reliable integration, the yield (calculated against an internal standard) was not reproducible from the crude reaction.

Analysis by HPLC proved more effective, with peaks corresponding to the two diastereomers easily resolvable. This was used to screen different copper(II) salts ($Cu(OAc)_2$, $Cu(BF_4)_2{\cdot}H_2O$, $Cu(acac)_2$, $CuSO_4{\cdot}2H_2O$).[27] In an effort to promote the enolisation of acid **288**, various Lewis acids were screened ($Yb(OTf)_3 \cdot xH_2O$, $Zn(OTf)_2$, $FeCl_3$). Finally, alternative polar solvents were screened (AcOH, 10% HMPA in MeCN, toluene, DMF, THF).[27] No improvement was found for any additive or solvent over the conditions identified previously.

Ionic liquids have been reported to be effective solvents for oxidative radical reactions.[116] Treatment of lactone-acid **288** with 2 eq. MAN, 1 eq. $Cu(OTf)_2$ in 5:1 DCM:[bmim][BF_4] gave tricyclic *bis*-lactones **291** and **303** in ca. 50% yield and 1:2.2 dr. The product was not pure; even after repeated flash column chromatography a brown tinge remained and numerous extra peaks were visible in the ^{1}H NMR spectroscopy.

Previous work in the Burton group had demonstrated that it was possible to choose the product of the radical cyclisation reaction by the choice of solvent and concentration (*vide supra* **Section 1.2.3**). However treatment of lactone-acid **288** with MAN and $Cu(OAc)_2$ in DMSO did not give any cyclised product, with an intractable mixture of products obtained (**Scheme 3.7**). Similarly, exposure of acid **288** to MAN in EtOH also gave a complex mixture of products. Both crude products were treated with $TMSCHN_2$ in MeOH/PhMe to methylate the acid[117] in an effort to provide a more easily purified mixture, but nothing corresponding to alkene **304** or cyclopentane **305** was isolated.



304 **288** **305**

Reagents & Conditions: i) 2 eq. MAN, 1 eq. $Cu(OAc)_2$, 20 mM DMSO, 80 °C; ii) 2 eq. MAN, 10 mM EtOH, 70 °C.

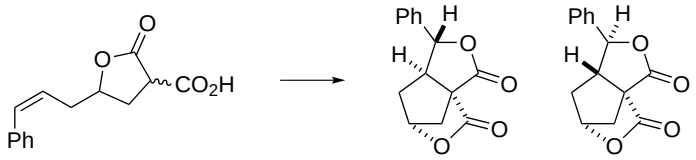
Scheme 3.7: Failed synthesis of *exo*-alkene **304** and cyclopentane **305**.

Overall, the cyclisation reactions of **288** proved difficult to optimise with concentration, temperature, copper loading, and various additives proving to be relatively ineffective in improving the yield and/or dr. It was not possible to prevent polymerisation, which may account for the low isolated yields despite

the high mass recovery.

3.1.3 CAN-Mediated Oxidative Radical Cyclisations

As discussed in **Section 1.2.4**, ceric ammonium nitrate (CAN) is also capable of mediating oxidative radical cyclisation reactions. While the use of CAN has not been as widespread as MAN, it was proposed that it might allow the synthesis of tricyclic *bis*-lactones. Similarly to MAN, CAN has been shown to be compatible with copper(II) salts. Attempts were made to optimise the CAN-mediated oxidative radical cyclisation of lactone-acid **288**; the results are summarised in **Table 3.3**.



288 **291** **303**

Entry	Solvent	Conc. / mM	T / °C	Yield / %	**291**:**303**
1	MeCN	10	25	63	1.3:1
2	MeCN	10	80	43	1:0
3	MeCN	5.0	25	19	1:0
4[a]	MeCN	50	25	38	3.8:1
5[a]	MeCN	10	25	51	1.6:1
6	MeCN	100	0	13	1.5:1
7	MeCN	100	25	39	2.8:1
8	MeCN	100	80	24	1:0
9[b]	MeCN	100	25	22	1.4:1

All reactions were carried out with 2 equivalents of CAN and were complete (all starting material consumed) within 3 h. [a]A 1.0 M solution of acid **288** in MeCN was added by syringe pump over 2 h to a 1.0 M solution of CAN and $Cu(OTf)_2$ and stirred for a further 30 min; [b]Reaction conducted without $Cu(OTf)_2$.

Table 3.3: Formation of tricyclic *bis*-lactone **291** mediated by CAN.

Temperature seemed to have a large influence on the diastereoselectivity. At a concentration of 10 mM changing the temperature from RT to 80 °C gave a dramatic improvement in stereoselectivity (**Table 3.3 Entries 1** and **2**). Similarly, at 100 mM increasing the temperature from 0→80 °C gave a change in stereoselectivity from ≈1:1 to 1:0 in favour of the *cis*-isomer **291** but at the expense of reduced yield (**Table 3.3 Entries 6**–**8**).

As alternative solvents MeOH, AcOH, and DME were screened. No *bis*-lactone products were obtained from these reactions, which demonstrated that MeCN was the preferred solvent for this substrate. The use of the ionic liquid [bmim][BF_4] was also investigated, but only gave 32% yield with 1:1.7 dr.

In order to investigate the use of CAN further, the reaction was conducted without $Cu(OTf)_2$ (**Table**

3.3 Entry 9). Tricyclic *bis*-lactones **291** and **303** were obtained in 22% yield and 1.4:1 dr. This was comparable to when stoichiometric $Cu(OTf)_2$ was used with CAN, however both the yield and dr were slightly diminished. Despite extensive attempts at optimisation, the initial conditions proved the most effective. It is intriguing that using CAN resulted in a change in the product distribution with respect to the use of MAN. As discussed in XXX, it is thought that trimeric MAN is carried on the carboxylic acid moiety after oxidation. In the case of CAN, this is less likely as the nitrate ligands are much more tightly bound than acetates. The additional steric bulk of the coordinated MAN may induce the change in stereochemistry, however detailed modelling would be required to investigate this further.

3.1.4 Stereochemistry

The stereochemistry of the tricyclic *bis*-lactone **303** was assigned by ^{1}H NMR nOe correlations, shown in **Figure 3.3**. In contrast to bicyclic lactones, ^{1}H NMR nOe experiments did not got give an unambiguous assignment. The fact that key proton H-4 bisects H-3/H-3' and H-5/H-5' and did not give a strong correlation to H-2 thereby prevented definitive proof of the C-4 stereochemistry. This was the case in both $CDCl_3$ and benzene-d_6, in which the proton resonances were more dispersed.

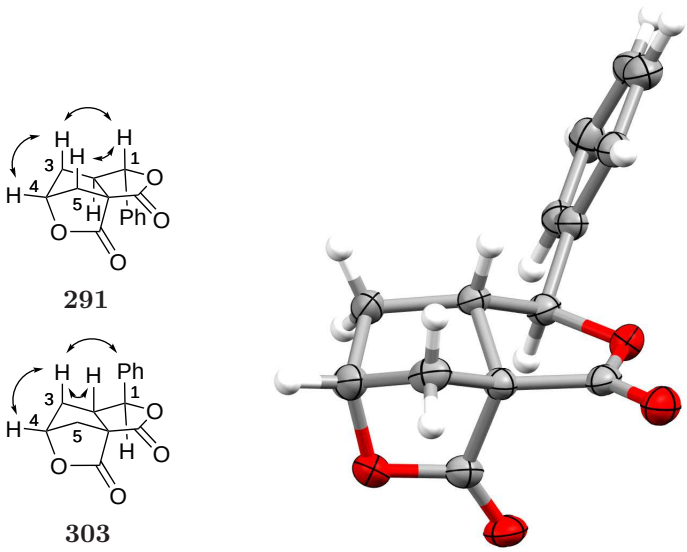


Figure 3.3: Stereochemical assignment by ^{1}H NMR nOe correlations and single crystal X-ray diffraction structure of *bis*-lactone **303**.

The stereochemistry of the *trans*-isomer **303** was firmly established by single crystal X-ray diffraction.* An X-ray diffraction quality crystal was grown from DCM/hexane, which clearly showed the

*The single crystal X-ray structure was obtained by Nicholas G. White.

H-1↔H-2 *trans* relationship and the H-2↔H-4 *cis* relationship. Unfortunately the *cis*-isomer **291** was not crystalline and so structure determination was based on ^{1}H NMR nOe correlations and comparison with the major diastereomer **303**.

It is worth noting the large difference in the IR stretching frequencies of *bis*-lactones **303** and **291** compared to an unstrained γ-lactone: γ-butyrolactone has $\nu_{C=O}$ = 1768 cm^{-1}, whereas **291** has $\nu_{C=O}$ = 1799 cm^{-1}, which is half way between the value for β-lactones ($\nu_{C=O} \approx$ 1840 cm^{-1}) and an isolated γ-lactone.[118] The diastereomer **303** has an IR frequency of $\nu_{C=O}$ = 1782 cm^{-1}, which is closer to that for an isolated γ-lactone. The two carbonyl groups did not appear to act as a coupled oscillator, unlike the *bis*-lactones described in **Section 1.3.2.1**. While the γ-lactone IR band did show a slight shoulder, it was not possible to resolve the frequency of the symmetric and anti-symmetric stretches. Additionally, the dihedral angle between the two carbonyl groups is acute for both **303** and **291**; 75° and 48° respectively† so no difference would be expected in the symmetric and anti-symmetric stretch between the diastereomers.

The unusual 5,5-*trans* stereochemistry was consistent with the products obtained from the oxidative radical cyclisations described in **Section 1.3.2.3**. Further precedence for similar stereochemical arrangements came from Taber and co-worker's synthesis of (–)-cameroonan-7α-ol **106**,[73] as shown in **Section 1.3.2.2**.

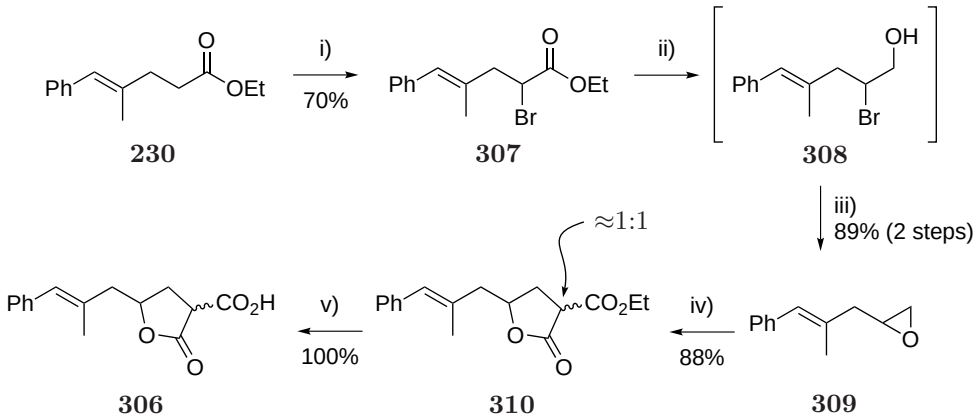
3.1.5 Cyclisations of More Substituted Substrates

3.1.5.1 Substrate Syntheses

Following the success of the radical cyclisations onto pentenyl malonates with tri- and tetrasubstitued alkenes (*vide supra* **Section 2.4**), the analogous trisubstituted lactone-acid **306** was synthesised from ester **230** (**Scheme 3.8**). The enolate of ester **230** was formed with LDA, and was trapped with TMSCl to prevent self-condensation,[119] and then quenched with NBS, which gave α-bromoester **307** in 70% yield. On small scale (0.50 mmol), yields of up to 97% were obtained and a yield of 70% was obtained on 6.0 mmol scale.

Ester **307** was cleanly reduced to bromohydrin **308** with DiBAl-H in DCM at –40 °C to avoid any reduction of the C-Br bond. Bromohydrin **308** was carried forward without purification and treatment with KO^{t}Bu in ^{t}BuOH gave epoxide **309**. Under conditions developed previously, treatment with DEM and NaOEt gave lactone-ester **310** in 88% yield as a 1:1 mixture of diastereomers. Lactone-ester **310**

†These values were obtained by MMFF94 calculations, ChemBioDraw 3D.

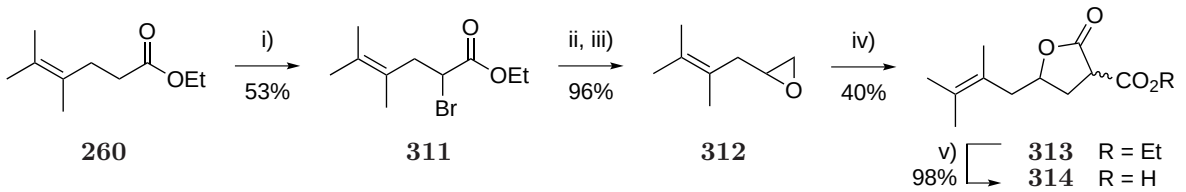


Reagents & Conditions: i) LDA, TMSCl, THF, –78 °C, then NBS, –40 °C; ii) DiBAl-H, DCM, –40 °C; iii) KO^{t}Bu, ^{t}BuOH, 35 °C; iv) DEM, NaOEt, 0 °C→RT; v) KOH, EtOH/H_2O, 0 °C.

Scheme 3.8: Synthesis of trisubstituted lactone-acid **306**.

was then hydrolysed with aqueous KOH, which gave lactone-acid **306** in quantitative yield. This route is convergent with that for the synthesis of the linear substrates described in **Chapter 2**. The common intermediates are the γ,δ-unsaturated esters, such as ester **230**, which were available by a Johnson-Claisen rearrangement of appropriately substituted allylic alcohols.

In order to synthesise a cyclisation substrate containing a tetrasubstituted alkene, ester **260** was treated with NBS, which gave α-bromo ester **311** in 53% yield (**Scheme 3.9**). Bromoester **311** was reduced with DiBAl-H, and the crude halohydrin was treated with KO^{t}Bu, which gave epoxide **312** in 96% yield. Under the previously developed lactonisation conditions, epoxide **312** was treated with DEM, which gave ester **313** that was subsequently saponified with aqueous KOH to give cyclisation substrate **314**.

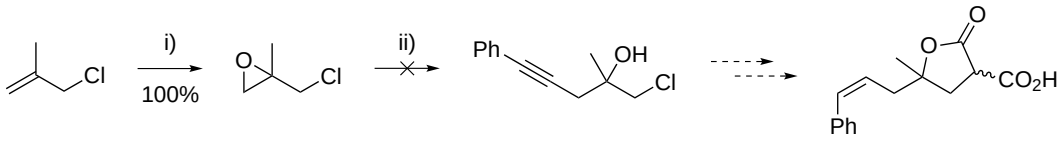


Reagents & Conditions: i) LDA, TMSCl, then NBS, THF –78 °C→RT; ii) DiBAl-H, DCM, –40 °C; iii) KO^{t}Bu, HO^{t}Bu, 35 °C; iv) DEM, NaOEt, EtOH, 0 °C→RT; v) KOH, EtOH/H_2O, 0 °C.

Scheme 3.9: Synthesis of tetrasubstituted cyclisation substrate **314**.

In order to provide comparison with previously studied substrates lacking a stabilising phenyl group, lactone-acid **315** was required (**Scheme 3.10**). It was proposed that a similar route to lactone-acid would be used. Epoxide **316** was synthesised by *m*-CPBA oxidation of allylic chloride **317**. Attempts to alkylate epoxide **316** with phenylacetylene anion under Yamaguchi's conditions[99] to give chlorohydrin

318 failed.

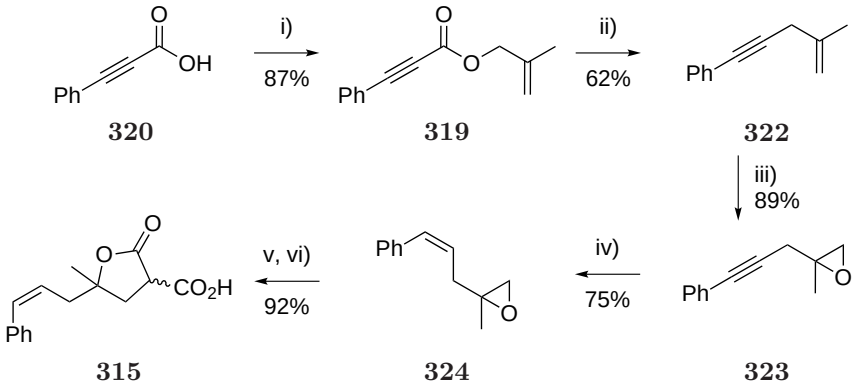


317 **316** **318** **315**

Reagents & Conditions: i) *m*-CPBA, DCM, RT; ii) phenylacetylene **295**, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, –78 °C.

Scheme 3.10: Originally proposed route to cyclisation substrate **315**.

A synthesis was developed that avoided the problem of alkylating sterically hindered epoxide **316** (**Scheme 3.11**). Tunge and co-workers developed a Pd-catalysed decarboxylative sp–sp^3 C-C coupling in which CO_2 was extruded from allylic alkynoates, such as alkyne **319**, with formation of a C-C bond.[120] Thus alkyne **319**, synthesised by esterification of phenylpropiolic acid **320** with 2-methylallyl alcohol **321**, was treated with 10 mol% of $Pd(PPh_3)_4$, which gave enyne **322** in 62% yield. The reaction took 48 hours to reach completion, in line with Tunge's data, which showed that π-allyl formation is not the rate determining step. Subsequently, epoxidation of alkene **322** with *m*-CPBA gave epoxide **323** in 89% yield. Under the previously developed alkyne hydrogenation conditions (*vide supra* **Section 3.1.1**) enyne **322** was treated with H_2 and Lindlar's catalyst in allyl alcohol, which gave alkene **324** in 75% yield. Under the previously developed conditions, epoxide **324** was treated with DEM, which gave the corresponding lactone-ester, which was hydrolysed with KOH to give lactone-acid **315** in 92% yield from epoxide **324**.



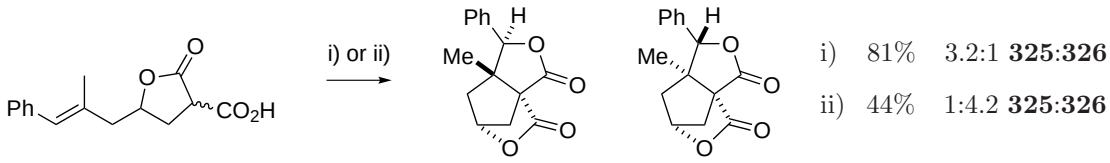
320 **319** **322** **323** **324** **315**

Reagents & Conditions: i) 2-methylallyl alcohol **321**, DIC, DMAP, DCM, RT; ii) 10 mol% $Pd(OAc)_2$, 40 mol% PPh_3, PhMe, 75%; iii) *m*-CPBA, DCM, 0 °C; iv) 15 wt% Lindlar catalyst, 1. eq quinoline, H_2, allyl alcohol, RT; v) DEM, NaOEt, EtOH, 92%; vi) KOH, $EtOH/H_2O$, 100%.

Scheme 3.11: Successful synthesis of lactone-acid **315**.

3.1.5.2 Oxidative Radical Cyclisations

With a range of substrates in hand, their reactivity in the oxidative radical cyclisation reaction was investigated. Under the optimised conditions developed for the cyclisation reaction (*vide supra* **Sections 3.1.2** and **3.1.3**) lactone-acid **306** underwent cyclisation in the presence of MAN and $Cu(OTf)_2$, which gave diastereomeric tricyclic *bis*-lactones **325** and **326** in 81% yield as a 3.2:1 mixture of diastereomers (**Scheme 3.12**). In a similar fashion to the reaction of lactone-acid **288**, using CAN in place of MAN for the cyclisation of lactone-acid **288** gave an inversion in the diastereoselectivity. Treatment of lactone-acid **306** with CAN gave a 1:4.2 mixture of **325** and **326** in 44% overall yield. While the yield was not as good as with MAN, the inversion of stereochemistry is remarkable, and allows moderately selective access to both diastereomers. This reaction yields a tricyclic [5.2.1.$0^{1,5}$] *bis*-lactone with stereocontrol containing vicinal all-carbon quaternary stereocentres.



306 **325** **326**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C; ii) 2 eq. CAN, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C.

Scheme 3.12: Oxidative radical cyclisation of lactone-acid **306**.

The stereochemistry of lactones **325** and **326** was established by ^{1}H NMR nOe experiments and single crystal X-ray diffraction (**Figure 3.4**). As for lactones **303** and **291**, the ^{1}H NMR nOe correlations were not conclusive, with the H-4 proton bisecting the cyclopentane protons and the lack of a proton at the ring junction, which further complicated the analysis. Both diastereomers were crystalline, and single crystal X-ray diffraction quality crystals were grown from DCM/hexane.

The improved yield obtained with 2,2-disubstituted substrate **306** was in line with the results discussed in **Section 2.4**. When compared to the cyclisation of lactone-acid **288**, the cyclisation of lactone-acid **306** gave better and more consistent yields. The purity of the crude product was also higher, with crude ^{1}H NMR showing less evidence of by-products and polymerisation.

Tetraalkyl substituted lactone-acid **314** was also a viable oxidative radical cyclisation substrate (**Scheme 3.13**). In the presence of MAN and $Cu(OTf)_2$, lactone-acid **314** underwent oxidative radical cyclisation, which gave tricyclic *bis*-lactone **327** as a single diastereomer in a low yield of 24% despite excellent mass recovery from the reaction. The same reaction with CAN in place of MAN gave the same

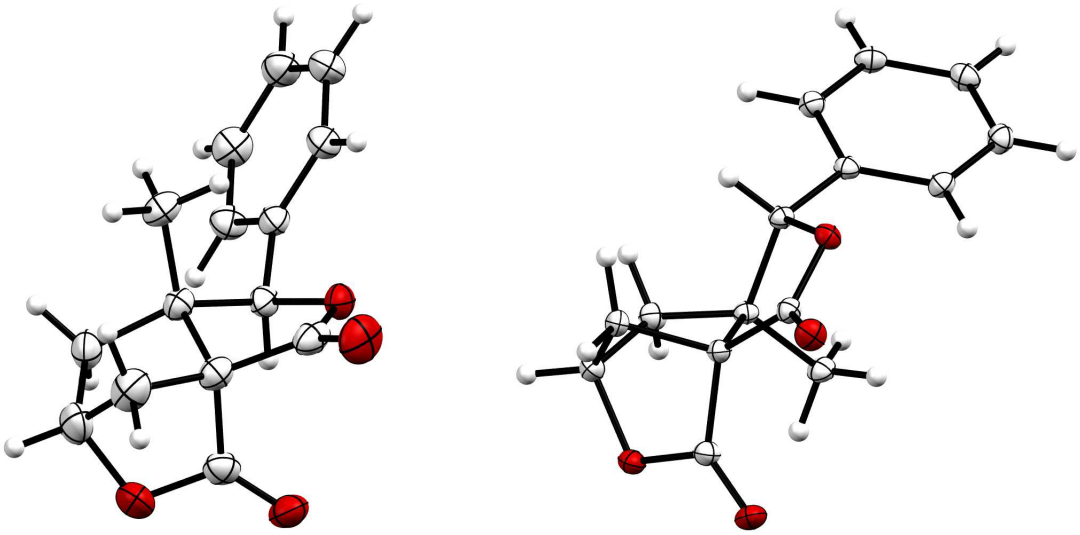
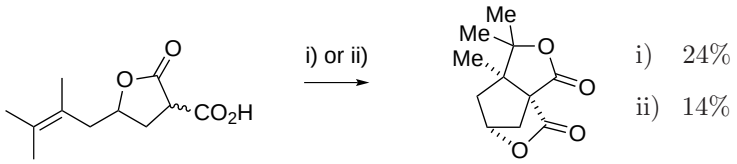


Figure 3.4: Single crystal X-ray diffraction structures of tricyclic *bis*-lactones **325** and **326**. Ellipses are shown at 50% probability.

single diastereomer in 14% yield. It was not possible to unambiguously establish the stereochemistry by ^{1}H NMR nOe experiments as the H-4 proton was too far away from the ring junction methyl group. The stereochemistry shown was tentatively assigned on the basis of MMFF94 calculations,[121] which showed that the diastereomer shown is 54 kJmol^{-1} lower in energy than the other possible diastereomer.



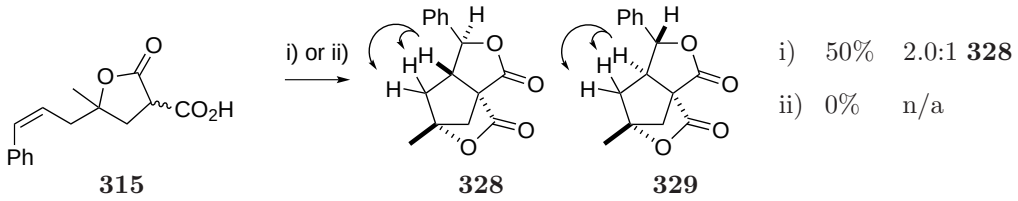
314 **327**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C; ii) 2 eq. CAN, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C.

Scheme 3.13: Oxidative radical cyclisation of tetraalkyl substituted lactone-acid **314**.

The reaction also tolerated substitution on the starting lactone (**Scheme 3.14**). Treatment of lactone-acid **315** with MAN and $Cu(OTf)_2$ gave tricyclic *bis*-lactones **328** and **329** in 50% yield with 2.0:1 dr determined from the crude ^{1}H NMR spectrum. With CAN in place of MAN, no product was obtained and no resonances corresponding to the product lactones were present in the crude ^{1}H NMR spectrum. It was not possible to unambiguously determine the relative stereochemistry of diastereomers **328** and **329** as the protons on the methyl group are too far away from the ring junction proton to show ^{1}H NMR nOe correlations to the ring junction proton in either diastereomer. Neither diastereomer was crystalline,

which precluded structure determination by single crystal X-ray diffraction.



315 **328** **329**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C; ii) 2 eq. CAN, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C.

Scheme 3.14: Oxidative radical cyclisation of methyl-substituted lactone-acid **315**.

Attempts to scale up the cyclisation reactions were not successful, and decreased yields were observed when moving beyond 150 μmol scale. The large solvent volumes required also made scale up troublesome, as the acetonitrile had to be removed due to its miscibility with water. Aqueous work-up was complicated by the presence of significant amounts of heterogeneous manganese salts, which were a consequence of the background polymerisation, which meant that not all the manganese was consumed in the reaction.

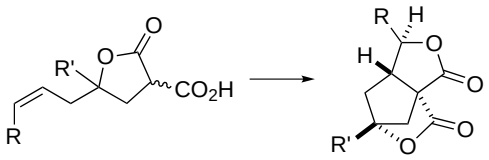
3.2 Comparison with Terminal Alkene Substrates

The cyclisation of lactone-acids **288** and **315** allowed direct comparison with the analogous reaction of lactone-acids **114** and **118** (**Table 3.4**). Previous work in the group had shown that these substrates underwent oxidative radical cyclisation to give the corresponding tricyclic *bis*-lactones **115** and **120** in 21% and 25% yield respectively. Under the newly developed conditions, the phenyl substituted substrates **288** and **315** gave tricyclic *bis*-lactones **303** and **328** in 65% and 50% yield respectively. This showed that the phenyl substitution improved the reaction by stabilisation of the adduct radical. The terminal alkene substrate **114** previously synthesised by Smith[74] was treated with MAN under the optimised conditions (10 μmol in MeCN, 80 °C), which led to an improvement in yield with 41% isolated, but at the expense of diastereoselectivity, which dropped to 1.2:1 from 5.0:1.

3.3 Synthetic Applications

The two lactones contained in cyclopentane *bis*-lactone **303** were differentiated, as shown by the large difference in IR stretching frequency ($\nu_{C=O} = 1782$ cm^{-1} *vs.* 1756 cm^{-1}). It was proposed that the more strained lactone would preferentially undergo nucleophilic attack.

It had previously been shown in the group that *bis*-lactone **115** opened in methanol at 65 °C, with



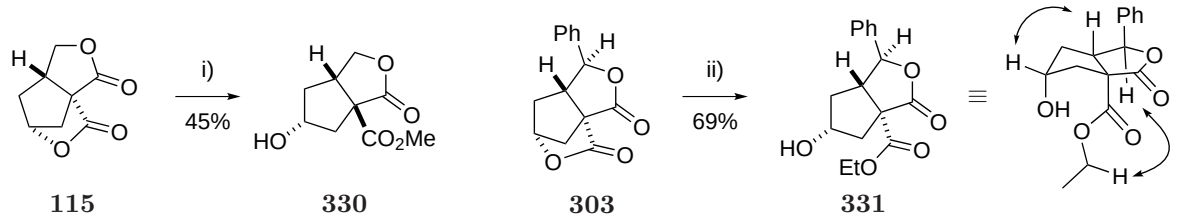
All reactions were conducted in MeCN at 80 °C with 2 eq. $Mn(OAc)_2{\cdot}H_2O$ and 1 eq. $Cu(OTf)_2$.

Entry	Substrate	R, R'	Concentration / M	Yield / %	dr
1	**114**[a]	H, H	0.20	**115** 21	5.0:1
2	**114**	H, H	10 m	**115** 41	1.2:1
3	**288**	Ph, H	10 m	**303** 65	5.7:1
4	**118**[a]	H, Me	0.20	**120** 25	7.0:1
5	**315**	Ph, Me	10 m	**328** 50	2.0:1

Reaction results by A. K. Smith (Part II Thesis, University of Oxford, 2008).[74]

Table 3.4: Comparison of terminal alkene and terminal phenyl alkene oxidative radical cyclisations.

isomerisation of the ring junction from *trans* to *cis* to give methyl ester **330** (**Scheme 3.15**).[74] Treatment of *bis*-lactone **303** with ethanol gave only recovered starting material, however the addition of 10 mol% of K_2CO_3 gave a clean transformation to the selectively ring opened ester **331** with no trace of the doubly opened product.



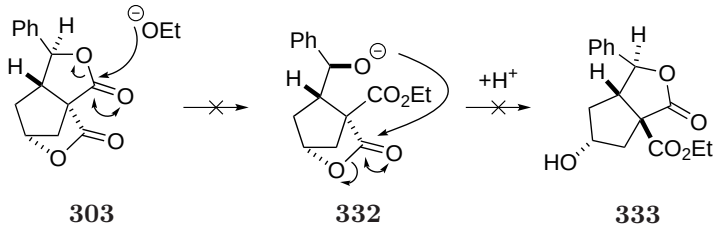
115 **330** **303** **331**

Reagents & Conditions: i) MeOH, 65 °C; ii) 10 mol% K_2CO_3, EtOH, RT.

Scheme 3.15: Opening of *bis*-lactone **303** with basic ethanol, with key ^{1}H NMR nOe correlations shown.

With precedence for the inversion of the ring junction (lactone **115** → ester **330**), it was possible that ethoxide could open the less strained lactone (**Scheme 3.16**). Alkoxide **332** thus formed could then re-lactonise to give the *cis*-fused lactone **333**. In order to rule out this possibility, ^{1}H NMR nOe data consistent with the stereochemistry shown were obtained for alcohol **331**, which showed that only the more strained lactone had reacted. With the bridging lactone now open, the structure is less rigid and there was a strong ^{1}H NMR nOe enhancement from the junction proton to the proton adjacent to the alcohol. Additionally, there was an enhancement from the benzylic proton to the alkyl group of the ester.

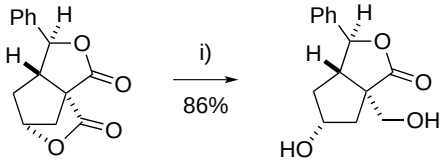
These results showed that nucleophiles preferentially attack the more strained lactone. In order to further exploit this, selective reduction with sodium borohydride was undertaken. This gave the highly polar diol **334** (**Scheme 3.17**). A number of other products were visible by TLC analysis, but good



303 **332** **333**

Scheme 3.16: Alternative lactone opening by ethoxide and subsequent relactonisation to give *epi*-**331**.

separation was achieved with DCM and methanol.

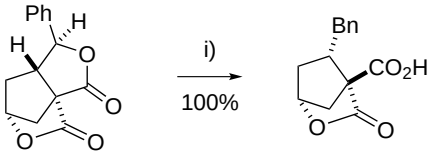


303 **334**

Reagents & Conditions: i) 2 eq. $NaBH_4$, 1:1 MeOH/THF, RT.

Scheme 3.17: Chemoselective reduction of the more strained lactone in *bis*-lactone **303**.

In addition to nucleophilic attack, cyclopentane *bis*-lactone also contained benzyloxy functionality. Exposure to H_2 in the presence of palladium on charcoal in EtOAc gave the hydrogenated product, carboxylic acid **305**, in quantitative yield after filtering through Celite® (**Scheme 3.18**).



303 **305**

Reagents & Conditions: i) Pd/C, H_2, EtOAc, RT.

Scheme 3.18: Hydrogenation of the benzyloxy functionality of *bis*-lactone **303**.

It has been shown that the tricyclic *bis*-lactones are potentially useful synthetic building blocks. The reactivity relies on the difference in reactivity between the two differentiated lactones, with the bridged lactone reacting preferentially with nucleophiles. The benzyloxy functionality was reactive toward catalytic hydrogenation.

3.4 Conclusions

The synthesis of tricyclic *bis*-lactones from simple γ-lactone starting materials under oxidative radical cyclisation conditions has been demonstrated. The efficiency of these reactions was generally lower than for the synthesis of the related bicyclic lactones described in **Chapter 2**. The use of 1,2,2-trisubstituted substrates was again shown to be effective and led to improved yields relative to 1,2-disubstituted substrates. The highly functionalised tricyclic *bis*-lactones underwent a range of chemoselective transformations. The potential use of such products in synthesis will be discussed in **Chapter 5**.

4

A Formal Synthesis of (–)-Salinosporamide A

This Chapter describes a formal total synthesis of the proteasome inhibitor (–)-salinosporamide A. This synthesis builds on work undertaken in the Burton group by S.J. Sprague (DPhil, University of Oxford, 2007–2010) and R.W. Foster (Part II, University of Oxford, 2010–2011) in which oxidative radical cyclisation of *N*-protected amidomalonates gave substituted pyrrolidinone-lactones with high levels of diastereocontrol.

4.1 Salinosporamide A

Isolated in 2003 from the obligate marine bacterium *Salinospora tropica*,[122] salinosporamide A **335** has attracted widespread attention, both for its activity as a specific 20S proteasome inhibitor and as a challenging synthetic target. Its key structural feature is a reactive β-lactone, which forms the pharmacologically active site. This motif is shared with omuralide **336**, although salinosporamide A is

≈35× more potent in parallel assays. This significant increase in activity is due to the unique mode of reaction in which THF **337** is formed by displacement of the pendant chloride after the β-lactone is opened (**335**→**338**) by the Thr1O$^{\gamma}$ residue in the target proteasome.[123] Salinosporamide A **335** is currently undergoing clinical trials under the names *marizomib* and *NPI-0052*.

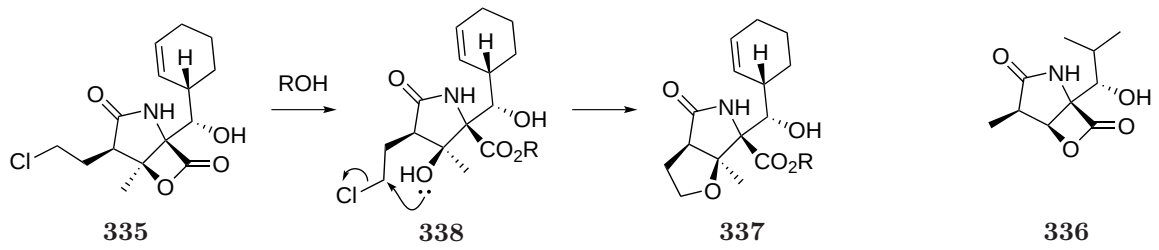
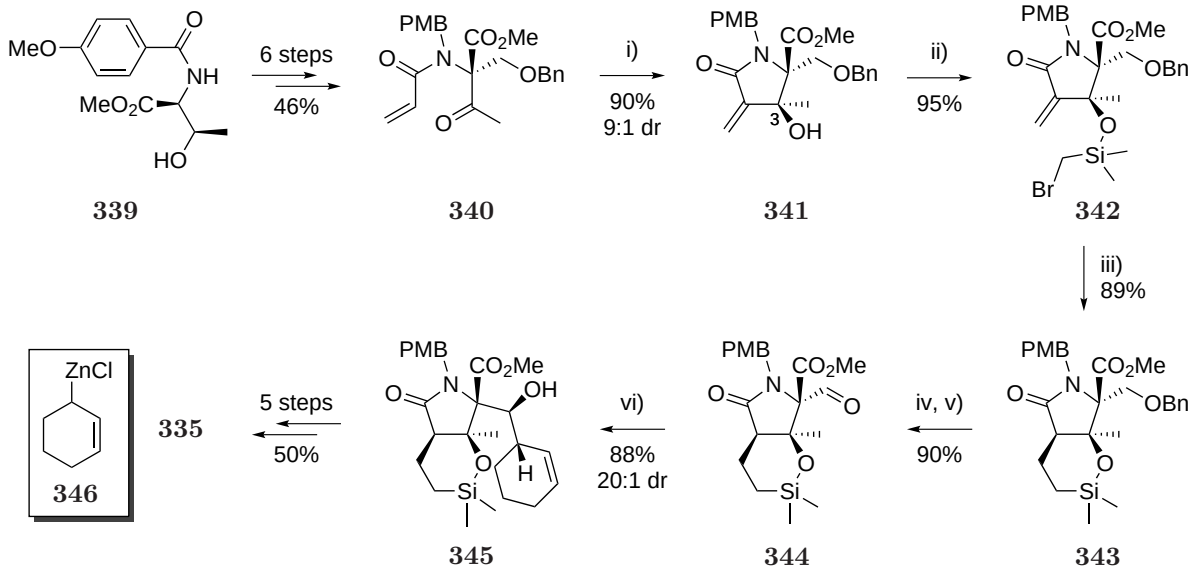


Figure 4.1: β-Lactone proteasome inhibitors salinosporamide A (**335**) and omuralide (**336**). R = Thr1O$^{\gamma}$.

4.1.1 Corey and Danishefsky's Total Syntheses

Corey and Reddy developed the first synthesis of salinosporamide A **335** from (*S*)-threonine in 2004 (**Scheme 4.1**).[124] Protected (*S*)-threonine **339** was converted in six steps to acrylamide **340** in 46% yield. Acrylamide **340** then underwent a Baylis-Hillman reaction mediated by quinuclidine, which gave *exo*-alkene **341** as an inseparable 9:1 mixture of C-3 epimers. The alcohol was then silylated to give silyl ether **342**, which also allowed separation of the C-3 epimers.



Reagents & Conditions: i) quinuclidine, DME, 0 °C, 7 d; ii) $BrCH_2SiMe_2Cl$, Et_3N, DMAP, DCM, 0 °C; iii) Bu_3SnH, AIBN, PhH, 80 °C; iv) Pd/C, H_2, EtOH, RT; v) Dess-Martin periodinane, DCM, 0 °C; vi) **346**, THF, –78 °C.

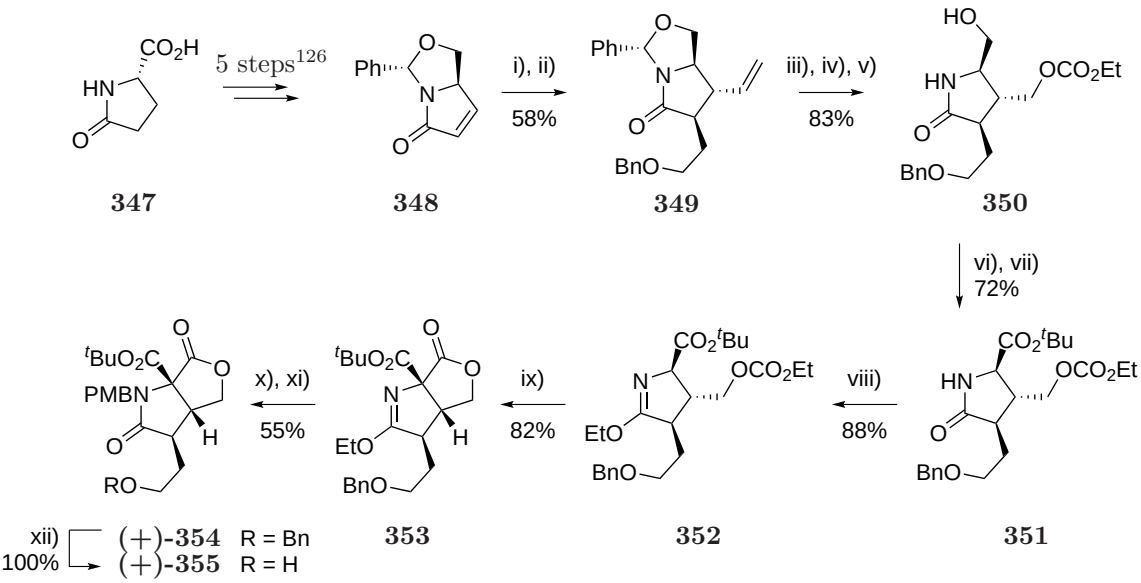
Scheme 4.1: Key steps in Corey and Reddy's synthesis of (–)-salinosporamide **335**.

An interesting radical 6-*endo* cyclisation gave bicycle **343**. The product from a 5-*exo* cyclisation was not detected, which is probably due to the long O–Si bond compared to a C–C bond, which favours a 6-*endo* cyclisation over a 5-*exo* cyclisation due to the reduced steric hindrance. The benzyl protecting group was removed by catalytic hydrogenation, and the free alcohol was oxidised with Dess-Martin periodinane, which gave aldehyde **344**. The aldehyde was alkylated with organozinc **346**, which gave homoallylic alcohol **345** in 88% yield and >20:1 dr. This highly diastereoselective transformation has been used in nearly all total syntheses of salinosporamide A **335**, and alcohol **345** was readily transformed to (+)-salinosporamide A **335**.

Shortly afterwards, Danishefsky and Endo disclosed their synthesis of **335** (**Scheme 4.2**).[125] Pyroglutamic acid **347** was converted to the conjugated dihydropyrrolone **348**,[126] which was converted to the conjugate adduct with vinylmagnesium bromide in the presence of catalytic copper(I) iodide, followed by electrophilic alkylation with $I(CH_2)_2OBn$. The stereochemistry was controlled by the oxazolone moiety. This gave substituted pyrrolidinone **349** in 58% yield from **348** with 14:1 dr at C-1. Ozonolysis with reductive workup, followed by acylation of the resulting alcohol and acidic removal of the hemiaminal gave alcohol **350** in 83% yield from alkene **348**. Alcohol **350** was oxidised with Jones reagent, and the corresponding carboxylic acid was converted to *tert*-butyl ester **351** with the *tert*-butyl acetal of DMF in 72% yield over two steps.

In order to install the γ-lactone a modified Claisen ester condensation was used. Lactam **351** was coverted to imidate **352** with Meerwein's salt and K_2CO_3 in 88% yield. Treatment of imidate **352** with LiHMDS gave γ-lactone **353** in 82% yield with no epimerisation at C-1. Subsequently, imidate **353** was hydrolysed with HCl, and the amide was protected with a PMB group to give lactone **(+)-354**. The benzyl group was then removed to give alcohol **(+)-355**.

A further 16 steps was required to complete the synthesis of (–)-salinosporamide A **335**. Thus, **335** was synthesised in 33 steps from pyroglutamic acid **347**, with an overall yield of 1.8%. Given the size of salinosporamide A **335**, a number of steps and functional group interconversions and protection/deprotection steps were required. A particular problem was the construction of the quaternary centre adjacent to nitrogen, with the introduction of the γ-lactone taking five steps. Inspired by the work of Danishefsky and Endo, we aimed to prepare the benzyl ether intermediate (+)-**354** by a manganese(III) acetate-mediated cyclisation reaction.

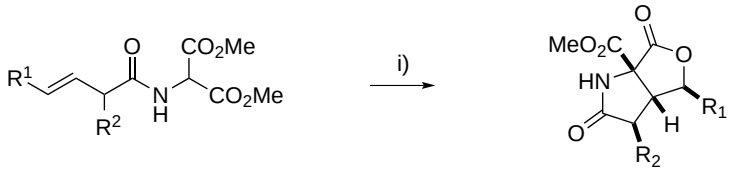


Reagents & Conditions: i) $H_2C{=}CHMgBr$, TMSCl, CuI, THF, –78 °C, 75%; ii) $I(CH_2)_2OBn$, LDA, THF, RT, 77% 14:1 dr; iii) O_3, 3:1 DCM:MeOH, –78 °C, then $NaBH_4$, 0 °C, 86%; iv) $ClCO_2Et$, pyridine, RT, 96%; v) TfOH, 9:1 THF:H_2O, RT, 100%; vi) Jones reagent, acetone, RT; vii) $MeNCH(O^tBu)_2$, PhMe, 110 °C, 72% over 2 steps; viii) $[Et_3O][BF_4]$, K_2CO_3, DCM, RT, 88%; ix) LiHMDS, THF, –20 °C, 82%; x) 1 M aq. HCl, THF, 0 °C, 90%; xi) PMBCl, NaH, DMF, RT, 61%; xii) $Pd(OH)_2/C$, H_2, EtOH, RT, 100%.

Scheme 4.2: Intermediate pyrrolidinone-lactones in Danishefsky and Endo's synthesis of salinosporamide A **335**.

4.2 Pyrrolidinone-Lactones by Oxidative Radical Cyclisation

Pyrrolidinones are common in natural products and drugs, and the Burton group has developed reliable oxidative radical cyclisation methodology for the synthesis of a variety of substituted pyrrolidinone-lactones (**Scheme 4.3**).[127] For example, S. Sprague showed that exposure of amidomalonate **356** to MAN and $Cu(OTf)_2$ gave pyrrolidinone-lactone **357** in 71% yield as a single diastereomer although the yield for this reaction was found to be reduced on larger scales.

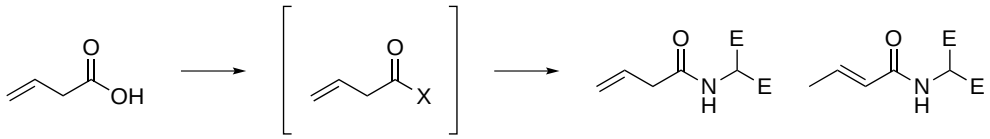


356	R^1 = H	R^2 = H	**357**	71%
358	R^1 = H	R^2 = $(CH_2)_2OBn$	**361**	0%
359	R^1 = Ph	R^2 = Bn	**362**	62%
360	R^1 = Ph	R^2 = $(CH_2)_2OBn$	**363**	55%

Scheme 4.3: Diastereoselective synthesis of *N*-unsubstituted pyrrolidinone-lactones.

Attempts to extend the cyclisation reaction to allow access to methyl ester **361**, a close analogue to Danishefsky's intermediate benzyl ether **354**, did not prove successful. Under the previously developed conditions, substituted amidomalonate **358** failed to undergo cyclisation, with an intractable mixture of products obtained; numerous attempts at optimisation proved unsuccessful.[127]

Problems were also encountered with substrate synthesis due to the difficulty in coupling β,γ-unsaturated acids **364** with the relatively non-nucleophilic α-amino malonates. Strongly activated acids **365** were required, which frequently led to the double bond skipping into conjugation to give **366** (**Scheme 4.4**).



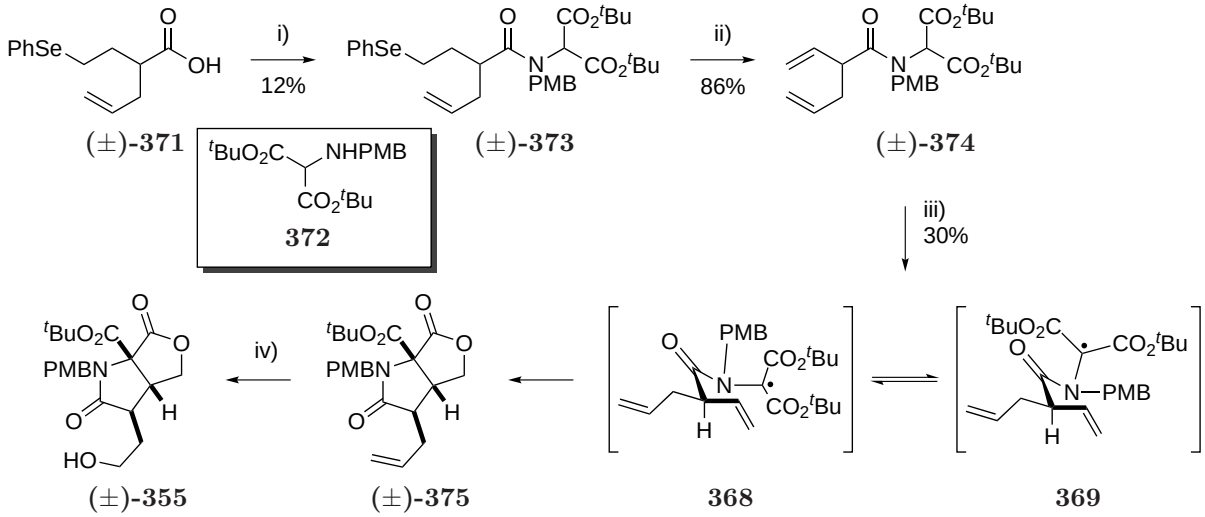
364 **365** **356** **366**

Scheme 4.4: Problematic amidation due to unwanted conjugation. E = CO_2Me.

The use of a phenyl group to stabilise the adduct radical (*cf.* **Chapter 2**) simplified the synthesis of the cyclisation precursor as alkene isomerisation was minimised, and the reaction of phenyl-substituted amidomalonate **359** gave pyrrolidinone-lactone **362** in 62% yield, with a dr of 5:1 at the benzylic stereocentre. Encouraged by these results, under the same conditions S. Sprague showed that the cyclisation of the -$(CH_2)_2$OBn substituted substrate **360** gave pyrrolidinone-lactone **363** as a single diastereomer in 55% yield. However, methods to convert the phenyl-substituted lactone **363** into H-substituted lactone **361** would involve multiple synthetic transformations.

In order to circumvent both of these problems, a route to Danishefsky's intermediate alcohol (±)-**355** involving selenium as a latent alkene was developed by Robert Foster during his Part II work (**Scheme 4.5**).[128] This synthesis was different in two key ways. Firstly, the alkene was introduced by elimination of the selenoxide under mild conditions *after* formation of the amidomalonate. This avoided problems with the alkene skipping into conjugation with the acid or amide. Secondly, a *para*-methoxybenzyl group was installed on the amide nitrogen, which prevented oxidation of the substrate during the oxidative radical cyclisation and was also proposed to bias the substrate into the reactive *s-cis* conformation **367**. The *s-trans* conformation is unreactive as the alkene is too far away to undergo the desired 5-*exo*-trig cyclisation. The substrate may adopt either *s-cis* **368** or *trans* **369** conformations, and with no *N*-substitution the *trans* conformation **370** is likely to be preferred to minimise steric interactions.

Foster prepared acid (±)-**371** by allylation of γ-butyrolactone, followed by ring-opening with phenyl

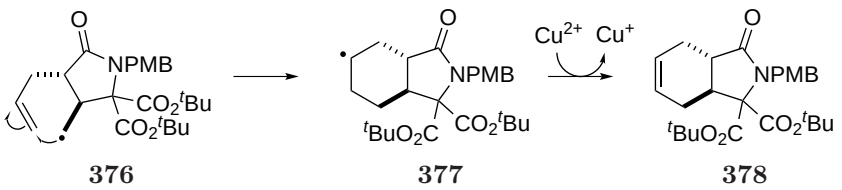


Reagents & Conditions: i) $(COCl)_2$, cat. DMF, DCM, then **372**, sat. aq. $NaHCO_3$/DCM; ii) *m*-CPBA, DCM, –15°C, then DMS, DiPA, 40 °C; iii) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, MeCN, 40 °C; iv) O_3/O_2, DCM/MeOH, –78 °C, then $NaBH_4$, 0 °C.

Scheme 4.5: Foster's synthesis of racemic Danishefsky's intermediate (±)-**355**.

selenide anion.[129] Amidation with secondary amine **372**[130] gave malonate (±)-**373** in a low yield of 12%. One-pot oxidation and selenoxide elimination gave cyclisation precursor (±)-**374**. Reaction of alkene (±)-**374** under optimised conditions gave pyrrolidinone-lactone (±)-**375** in 30% yield. The *N*-PMB was proposed to bias the substrate in to the reactive *s-cis* conformation **368**. Alkene (±)-**375** was then ozonolysed with a reductive $NaBH_4$ workup, which gave racemic alcohol (±)-**355**, previously synthesised by Danishefsky in asymmetric form.

The synthesis clearly had some drawbacks. The yields in the amide coupling (**371**→**373**) and the MAN radical cyclisation reaction (**374**→**375**) were low. In the cyclisation reaction, an unusual 5,6-*trans* fused structure was also isolated in 23% yield (**Scheme 4.6**). After the initial cyclisation, radical **376** then underwent a 6-*endo* cyclisation to give radical **377**, which was then oxidised by Cu^{2+} to finally give cyclohexene **378**.



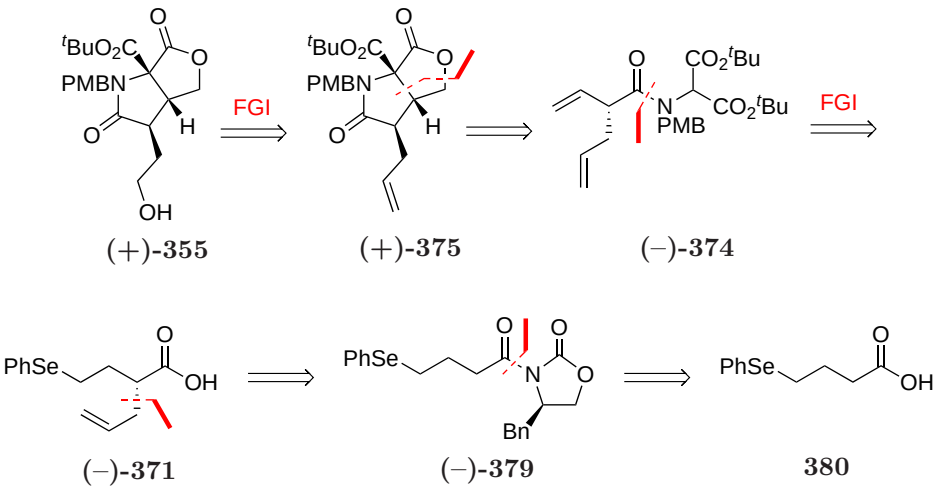
Scheme 4.6: Formation of 5,6-*trans* fused tetrahydroisoindole **378**.

4.3 Asymmetric Synthesis of Danishefsky's Intermediate

Based on Foster's results described in **Section 4.2**, an asymmetric preparation of alcohol (+)-**355** was devised. Efforts were taken to improve the yield and selectivity in the problematic amidation and cyclisation reactions, and a complete synthesis with comparison to literature data is presented.

4.3.1 Retrosynthesis

The retrosynthetic plan toward the intermediate in Danishefsky's synthesis, alcohol (+)-(**355**), is outlined in **Scheme 4.7**. Alcohol (+)-**355** would come from the ozonolysis of alkene (+)-**375** with *in situ* reduction of the ozonide. Pyrrolidinone-lactone (+)-**375** would be prepared by an oxidative radical cyclisation of alkene (–)-**374**, analogous to the synthetic route shown in **Section 4.2**. Alkene (–)-**374** would come from oxidation and elimination of the selenium present in acid (–)-**371** after coupling with *N*-PMB protected aminomalonate. The allyl group present in acid (–)-**371** would be introduced by Evans' asymmetric alkylation of imide (–)-**379**,[131] with Evans' auxiliary coupled to known acid **380**.

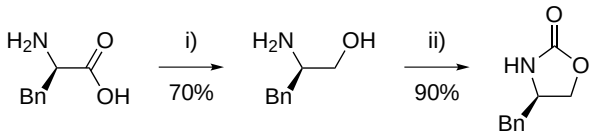


Scheme 4.7: Proposed retrosynthesis of alcohol (+)-**355**, an intermediate in Danishefsky's synthesis.

4.3.2 Forward Synthesis

The synthesis commenced with the opening of γ-butyrolactone (**381**) with sodium phenylselenoate, generated from reduction of diphenyl diselenide with sodium borohydride, which gave carboxylic acid **380** in 97% yield (**Scheme 4.9**).[129] The crystals obtained from this were initially bright yellow, but could be purified to colourless by repeated washings with water and recrystallisation from hexane and

Et_2O. Acid **380** was then coupled with Evans' auxiliary (*R*)-**382** using Ho and Mathre's protocol *via* the pivalic mixed anhydride in the presence of LiCl,[132] which gave imide (–)-**379**. Evans auxiliary (*R*)-**382** was synthesised from D-phenylalanine **383** (**Scheme 4.8**). Treatment of carboxylic acid **383** with $LiAlH_4$ in THF gave amino alcohol **384** in 70% yield.[133] Condensation with diethyl carbonate in the presence of catalytic K_2CO_3 gave Evans auxiliary (*R*)-**382** in 90% yield, with all data in accordance with literature values.[134]

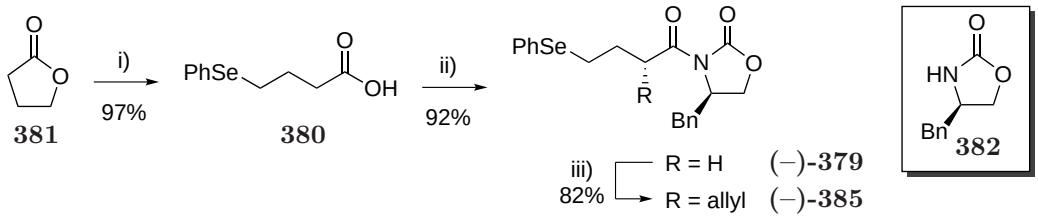


383 **384** **(+)-382**

Reagents & Conditions: i) $LiAlH_4$, THF, 60→75 °C; ii) $CO(OEt)_2$, 10 mol% K_2CO_3, 135 °C.

Scheme 4.8: Synthesis of Evans auxiliary by literature protocols.[133,134]

Alkylation of imide (–)-**379** with allyl iodide, freshly filtered through neutral alumina, gave allylated imide (–)-**385** in 82% yield on 8.6 mmol scale. It was found that control of the temperature was crucial to obtain good yields and stereoselectivity: during the addition of both the base and allyl iodide the internal temperature was kept below –70 °C. The minor epimer was not visible by crude ^{1}H NMR spectroscopy, which implied a dr >20:1. A slightly more polar spot was observed by TLC analysis, which could be partially removed by flash column chromatography. The ee of subsequent compounds was determined by chiral HPLC.



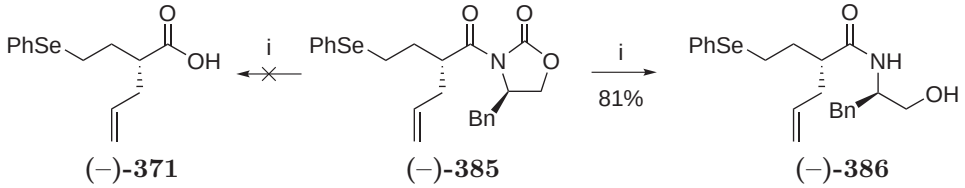
381 **380**

Reagents & Conditions: i) $(PhSe)_2$, $NaBH_4$, DMF, 120 °C; ii) PivCl, TEA, THF, –10 °C, then (*R*)–Evans' auxiliary **382**, LiCl, –10 °C→RT; iii) LiHMDS, then allyl iodide, THF, –78 °C.

Scheme 4.9: Diastereoselective allylation of selenium acid (–)-**380**.

Efforts were then directed toward the cleavage of the auxiliary to give acid (–)-**371**. The conditions commonly employed for this transformation, namely lithium hydroperoxide in THF/water,[135] are very similar to the conditions used for oxidising a selenide to the corresponding selenoxide. To avoid this, lithium hydroxide alone was employed. This gave exclusively the *endo*-cyclic cleave product (–)-**386**, indicating that the *exo*-cyclic carbonyl reactivity is inhibited by steric hinderance (**Scheme 4.10**).

Various equivalents of LiOH and concentrations of THF/water were also screened, but acid (–)-**371** was not formed under any conditions.



(–)-371 **(–)-385** **(–)-386**

Reagents & Conditions: i) 4 eq. LiOH, 4:1 THF/water.

Scheme 4.10: *Endo*-cyclic cleavage of imide (–)-**385**.

As the use of LiOH did not prove successful, lithium hydroperoxide (LiO_2H) was next investigated (**Table 4.1**). Initial reactions gave low yields of acid **371** in low purity. The use of a 1:1 mixture of H_2O_2 and LiOH gave the best mass recovery, although the purity was still low.

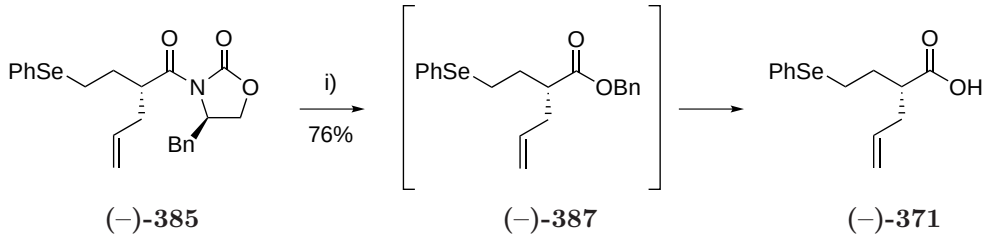
Entry	Conditions	Mass Yield / % of impure acid **371**
1	4 eq. H_2O_2, 2 eq. LiOH	16
2	2 eq. H_2O_2, 4 eq. LiOH	24
3	1 eq. H_2O_2, 2 eq. LiOH	55
4	2 eq. H_2O_2, 2 eq. LiOH	69

Table 4.1: Summary of attempts to cleave Evans' auxiliary from imide (–)-**385** with LiO_2H. All reactions were carried out at 0.10 M in 4:1 THF:H_2O.

For some very hindered substrates, Evans and co-workers discovered that LiOBn was "the only reagent that prove[d] successful" in removing the auxiliary,[136] although they did not speculate on the reason for this reactivity. Thus, under conditions developed by Léo Marx (DPhil, University of Oxford, 2011–2014) for a related system, transesterification of (–)-**385** with LiOBn gave ester **387** (**Scheme 4.11**). Addition of 5 equivalents of aqueous 1 M LiOH gave a small amount of acid (–)-**371**, but the reaction was very sluggish. Using a 0.5 M LiOH solution in 1:1 water:MeOH gave rapid conversion, with acid (–)-**371** isolated in 76% yield with excellent purity. Residual benzyl alcohol was hard to remove by flash column chromatography as acid (–)-**371** streaked on silica. Removal was best acheived by successive azeotropic distillation with 1:1 H_2O/MeOH (5×) then once with toluene after acid/base extraction.

With sufficient quantities of material in hand, the coupling between *N*-PMB aminomalonate **372*** and acid (–)-**371** was then investigated (**Scheme 4.12**). Conversion of acid (–)-**371** to the corresponding acid chloride was achieved by the reaction of oxalyl chloride in DCM with catalytic DMF. The acid chloride was used without characterisation or purification and reacted immediately under Schotten–Baumann

*Aminomalonate **372** was prepared by R.W. Foster.

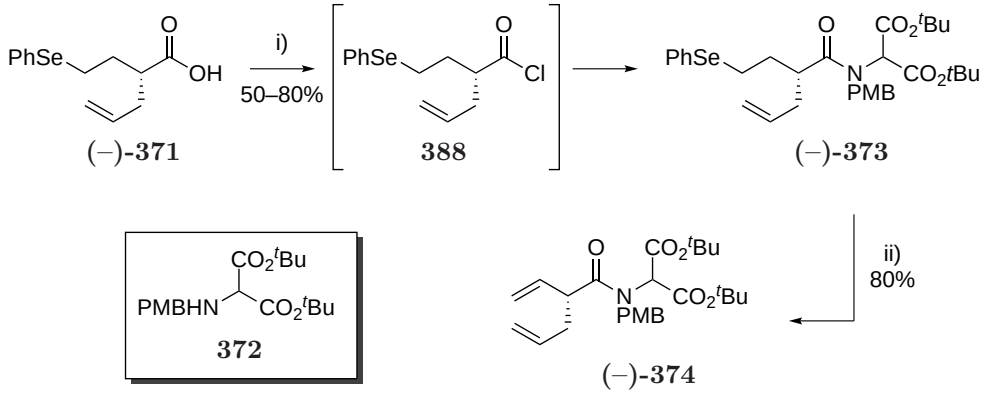


(–)-385 **(–)-387** **(–)-371**

Reagents & Conditions: i) LiOBn, THF, then LiOH, MeOH, 0 °C.

Scheme 4.11: Successful one-pot cleavage of Evans' auxiliary with LiOBn and LiOH.

conditions[137,138] with amine **372**. This reaction proved to be capricious with yields varying from 50–80% and was highly dependent on the mixing acheived in the biphasic amidation. The reaction was more reliable on larger scale and good quantities of amide (–)-**373** were obtained. This suggests that residual moisture in the flask on small scale affected the formation of the acid chloride. Additionally, a small excess of enantioenriched acid (–)-**371** was required as the aminomalonate **372** is sterically hindered and electronically deactivated. After oxidation of the selenide to the selenoxide with *m*-CPBA, elimination in the presence of DiPA[139] gave cyclisation substrate alkene (–)-**374**.



(–)-371 **388** **(–)-373**

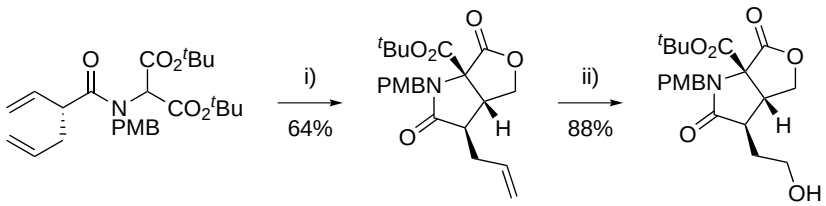
(–)-374

Reagents & Conditions: i) oxalyl chloride, cat. DMF, DCM, 1 h then **372**, 1:1 DCM/sat. aq. $NaHCO_3$, 16 h; ii) *m*-CPBA –15→0 °C, 30 min, then DMS, DiPA, 45 °C, DCM.

Scheme 4.12: Synthesis of oxidative radical cyclisation substrate (–)-**374** by amidation and selenoxide elimination.

Previous work in the group had shown that when treated with manganese(III) acetate and 1 eq. copper(II) triflate alkene (±)-**374** gave γ-lactone **375** in low yield accompanied by cyclohexene **378** as a major side product (**Section 4.2**). Formation of γ-lactone **375** is most likely mediated by copper(II) triflate. In light of this, the reaction was conducted with 2 eq. copper(II) triflate to ensure the primary radical was oxidised rather than undergoing further cyclisation. The reaction time was also reduced to two hours. Under these conditions, cyclised pyrrolidinone-lactone (+)-**375** was obtained as a single

diastereomer in 64% yield, which was a significant improvement over the previously developed conditions (**Scheme 4.13**). Attempts to run the reaction at 80 °C led to poor mass recovery suggesting either polymerisation or removal of the *tert*-butyl group(s), which would be possible under the acidic reaction conditions. Alkene (+)-**375** was then subjected to ozonolysis with a reductive workup ($NaBH_4$ in MeOH), which gave alcohol (+)-**355** in 88% yield.

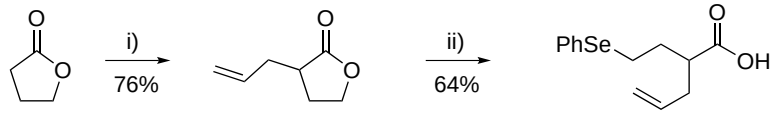


(–)-374 **(+)-375** **(+)-355**

Reagents & Conditions: i) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 2 eq. $Cu(OTf)_2$, 0.40 M MeCN, 40 °C; ii) O_3/O_2, DCM/MeOH, –78 °C, then $NaBH_4$, 0 °C.

Scheme 4.13: Oxidative radical cyclisation and ozonolysis to give Danishefsky's intermediate alcohol (+)-**355**.

In order to obtain ee values by HPLC analysis, a synthesis of (±)-**355** was also pursued. The required racemic acid (±)-**371** was obtained by opening allyl γ-butyrolactone **389**, obtained by allylation of γ-butyrolactone **381**, with sodium phenylselenide (**Scheme 4.14**). The following steps were the same as those for the asymmetric synthesis, with all data in agreement with the asymmetric route.



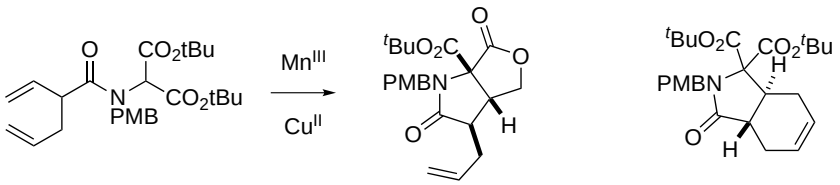
381 **389** **(±)-371**

Reagents & Conditions: i) DiPA, ^{n}BuLi, then allyl bromide, THF, –78 °C; ii) diphenyl diselenide, $NaBH_4$, DMF, 100→120 °C.

Scheme 4.14: Synthesis of ±-**371** from butyrolactone **381**.

Initial optimisation of the oxidative radical cyclisation was conducted with racemic (±)-**374**. During these studies, cyclohexene **390** was isolated and single crystals suitable for X-ray diffraction were obtained by slow diffusion of hexane into DCM. The X-ray structure unambigously showed the *trans* arrangement at the ring junction (**Figure 4.2**). While the *trans* geometry had been suggested by NMR coupling constant analysis [$^3J_{HH} = 13.2$ Hz], the X-ray crystal structure provided definitive proof.[†] This reaction is remarkable as it is equivalent to a Diels-Alder reaction with a α,β-unsaturated pyrrolidinone containing an internal *trans*-alkene.

[†]Full crystallographic data are given in **Appendix B**



(±)-374 **(±)-375** **378**

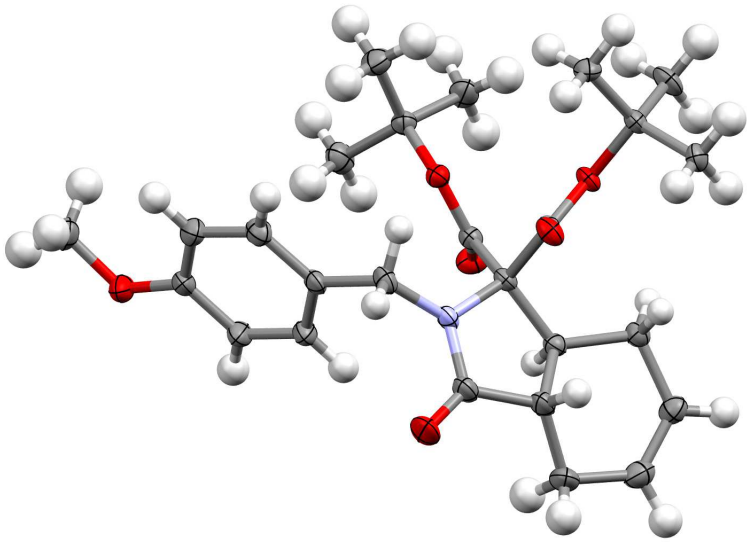


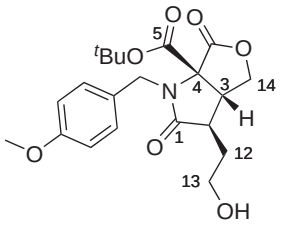
Figure 4.2: Single crystal X-ray diffraction structure of *trans*-5,6-fused cyclohexene **378**.

4.3.3 Comparison with Literature Data

With the asymmetric synthesis of alcohol (+)-**355** accomplished, the data obtained were compared to Danishefsky's data.[125,‡] The 500 MHz ^{1}H NMR data are presented in **Table 4.2**, and the 125 MHz ^{13}C NMR data are presented in **Table 4.3**. The numbering of the pyrrolidinone core is derived from the original isolation paper,[122] and is shown in **Figure 4.3**. The PMB and *tert*-butyl groups are labeled separately from this numbering.

While the ^{1}H NMR spectrum showed good correspondance with Danishefsky's published data apart from the OH resonance, the ^{13}C NMR spectrum showed some differences. In particular the signals corresponding to C-13 and C-3 (**Table 4.3**, **Entries 11** and **15**) had $\boldsymbol{\Delta\delta_C}$ >0.2 ppm. It was clear from the supplied spectrum (**Appendix A**) that the concentration of Danishefsky's sample was higher than our own, but changing the concentration (4.0 mg to 15.0 mg in 500 μL $CDCl_3$) did not alter the C-13

‡Professor Danishefsky kindly provided the original ^{1}H NMR and ^{13}C NMR spectra for comparison.



355

Figure 4.3: Numbering scheme used for assignment of alcohol (+)-**355**.

Entry	Assignment	Synthetic $\boldsymbol{\delta_H}$ / ppm (500 MHz, $CDCl_3$)	Lit. $\boldsymbol{\delta_H}$ [a] / ppm (400 MHz, $CDCl_3$)	$\lvert\boldsymbol{\Delta\delta_H}\rvert$ / ppm
1	$CH_2C(CHCH)_2$	7.28, 2H, d	7.29, 2H, d	0.01
2	$MeOC(CHCH)_2$	6.82, 2H, d	6.80, 2H, d	0.02
3	CHHAr	4.77, 1H, d	4.79, 1H, d	0.02
4	14	4.64, 1H, dd	4.65, 1H, dd	0.01
5	CHHAr	4.48, 1H, d	4.49, 1H, d	0.01
6	14'	4.08, 1H, dd	4.08, 1H, d	0.00
7	13	3.87–3.77, 2H, m	3.87–3.79, 2H, m	n/a
8	OCH_3	3.77, 3H, s	3.78, 3H, s	0.01
9	3	3.14, 1H, ddd	3.15,[b] 1H, m	0.01
10	2	2.61, 1H, ddd	2.60, 1H, m	0.01
11	OH	2.54, 1H, t	2.38, 1H, br	0.16
12	12	1.99, 1H, dddd	1.99, 1H, m	0.00
13	12'	1.78, 1H, dddd	1.77, 1H, m	0.01
14	$C(CH_3)_3$	1.46, 9H, s	1.47, 9H, s	0.01

Table 4.2: Comparison of synthetic alcohol (+)-**355** and literature ^{1}H NMR data.

[a] All literature data have been corrected by +0.07 ppm as the original spectrum was referenced with the $CHCl_3$ solvent residual at 7.20 ppm rather than 7.27 ppm.

[b] Reported in the Supporting Information as 3.26 ppm (after correction). The value here is based on measurement of the original spectra.

or C-15 shifts. As there was a free alcohol in **355**, it was also possible that the acidity of the $CDCl_3$ was having an effect; using $CDCl_3$ filtered through basic alumina did not cause any change in the spectra.

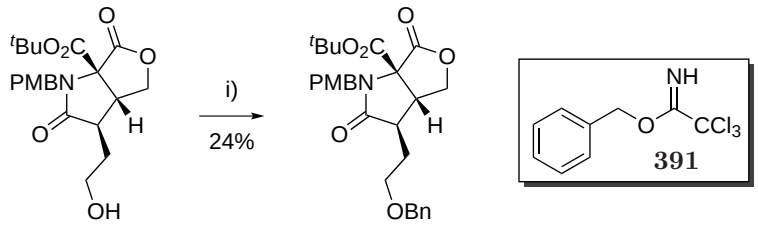
In addition to this, the $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ value obtained was significantly different (+22.3 (0.54 in $CHCl_3$) *vs.* lit. +67.3 (0.54 in $CHCl_3$)). This discrepancy was attributed to the fact that Danishefsky's sample contained some impurity. Analysis by chiral HPLC (ChiralPak AD-H, 10% IPA in hexane) against (±)-**355** showed that the synthetic alcohol (+)-**355** was enantioenriched, with an ee >95% (**Appendix A**). Chiral HPLC analysis (ChiralPak AD-H, 10% IPA in hexane) was also carried out the ozonolysis substrate, alkene (+)-**375**, which also showed ee >95% and with no plausible mechanism of racemisation this also implies an ee >95% for alcohol (+)-**355**.

Benzylation of alcohol **355** gave benzyl ether **354**, which itself is also an intermediate in Danishefsky's synthesis (**Scheme 4.15**). To avoid basic epimerisation of C-2, the normal Williamson synthesis

Entry	Assignment	Synthetic δ_C / ppm (125 MHz, $CDCl_3$)	Lit. δ_H / ppm (100 MHz, $CDCl_3$)	$\lvert\Delta\delta_C\rvert$ / ppm
1	1	176.6	176.6	0.0
2	15	170.7	170.7	0.0
3	5	167.2	167.2	0.0
4	$H_3CO\mathit{C}(CHCH)_2$	159.4	159.3	0.1
5	$CH_2C(\mathit{C}HCH)_2$	130.5	130.3	0.2
6	$CH_2\mathit{C}(CHCH)_2$	129.0	128.9	0.1
7	$CH_2C(CH\mathit{C}H)_2$	114.2	114.1	0.1
8	$\mathit{C}(CH_3)_3$	85.6	85.5	0.1
9	4	71.7	71.7	0.0
10	14	71.3	71.3	0.0
11	13	61.4	60.9	0.5
12	$O\mathit{C}H_3$	55.7	55.6	0.1
13	2	46.7	46.5	0.2
14	$\mathit{C}H_2Ar$	46.3	46.1	0.2
15	3	45.4	45.0	0.4
16	12	34.1	34.0	0.1
17	$C(\mathit{C}H_3)_3$	28.3	28.1	0.2

Table 4.3: Comparison of synthetic alcohol (+)-**355** and literature ^{13}C NMR data.

of benzylic ethers (strong base with benzylic bromide) was not used. Instead, the use of benzyl trichloroimidate **391** allowed the use of acidic conditions to install the benzyl ether. The use of 5 mol% triflic acid or 5 mol% PPTS did not give any conversion to ether (+)-**354**. Using 20 mol% TMSOTf and 2 eq. of imidate **391** gave a small amount of conversion [MS (ESI+) 518 $[M+Na]^+$]; addition of another 2 eq. of imidate **391** and 100 mol% TMSOTf finally gave complete reaction of the starting material. Unfortunately the yield for this reaction was very low, probably due to the lability of the *tert*-butyl ester under the strongly Lewis acidic conditions and so no reliable $[\alpha]_D^{25}$ value was obtained for benzyl ether (+)-**354**. The ^1H NMR and ^{13}C NMR values were in excellent agreement and are shown in **Appendix A**, which confirmed that our synthetic alcohol (+)-**355** was indeed the correct compound.



(+)-**355** (+)-**354**

Reagents & Conditions: i) 4.0 eq. benzyl trichloroimidate **391**, 100 mol% TMSOTf, DCM.

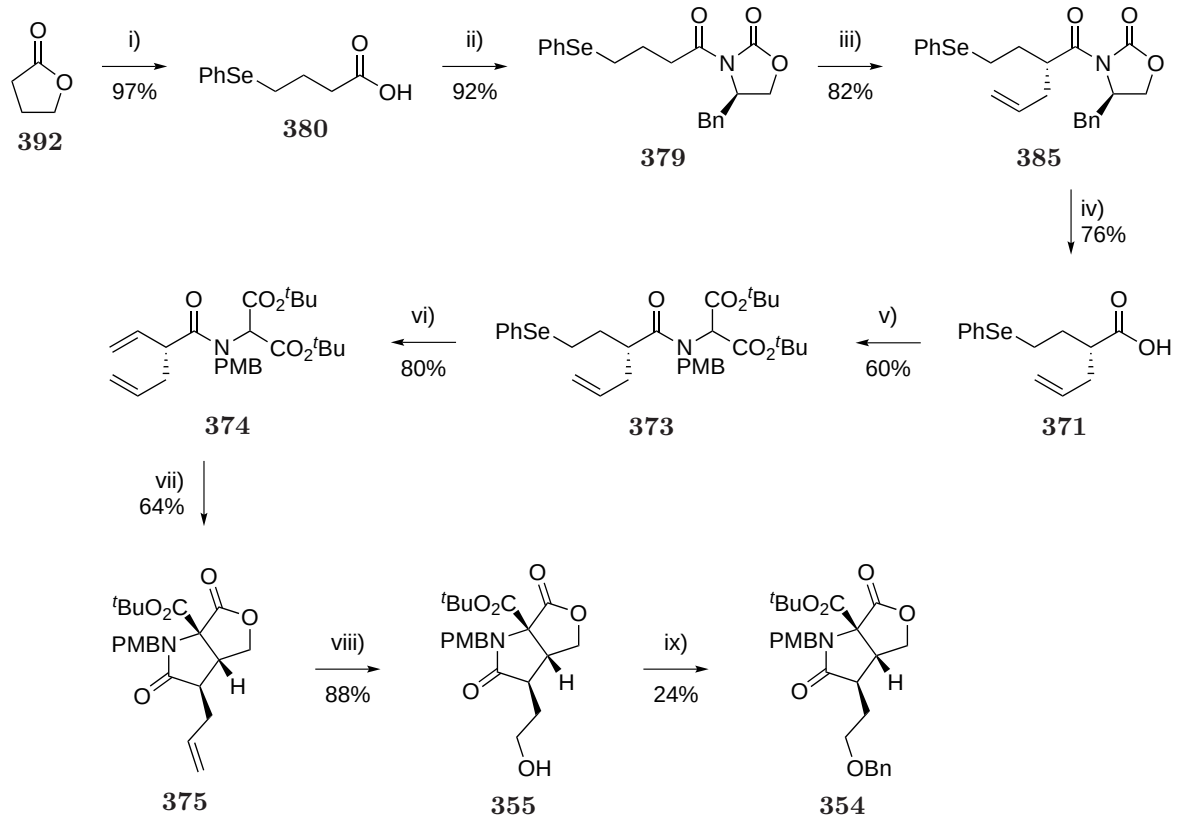
Scheme 4.15: Benzylation of alcohol (+)-**355** under Lewis acidic conditions.

4.4 Conclusions

An asymmetric formal synthesis of (–)-salinosporamide A **335** has been achieved. The intermediate in Danishefsky's synthesis, alcohol (+)-**355**, was prepared in 8 steps from cheap commercially available γ-butyrolactone **381** in 19% overall yield. This represents a considerable increase in efficiency over the original synthesis in which (+)-**355** was prepared in 17 steps from pyroglutamic acid. The use of oxidative radical reactions to give densely functionalised hetereocycles with high levels of diastereoselectivity has been demonstrated in natural product total synthesis. The full synthetic scheme is given in **Section 4.5** and the ^{1}H and ^{13}C NMR spectra of alcohol (+)-**355** and benzyl ether (+)-**354** and HPLC traces of acid **371** and alcohol **355** are given in **Appendix A**.

Omuralide **336** is a proteasome inhibitor sharing the same fused pyrrolidinone-β lactone pharmacophore as salinosporamide A **335**. The key structural differences are the truncated side chain, the lack of pendant chloride, and the simpler secondary alcohol moiety. In addition, omuralide **336** lacks the quaternary stereocentre present in salinosporamide A **335**. The same general approach as for salinosporamide A **335** could be utilised to develop of a total synthesis of omuralide **336**. Significant progress was made towards this target by Mareike Wiedmann (Part II, University of Oxford, 2011–2012).[140]

4.5 Complete Synthetic Scheme



Reagents & Conditions: i) $(PhSe)_2$, $NaBH_4$, DMF, 110 °C; ii) PivCl, NEt_2, THF, –20 °C, then LiCl, (*R*)-**382**, 0 °C; iii) NaHMDS, allyl iodide, THF, –78 °C; iv) LiOBn, THF, 0 °C, then LiOH, MeOH, RT; v) $(COCl)_2$, DCM, RT, then **372**, aq. $NaHCO_3$; vi) *m*-CPBA, DCM, –15→0 °C, then DMS, DiPA, 45 °C; vii) 2 eq. $Mn(OAc)_3{\cdot}2H_2O$, 2 eq. $Cu(OTf)_2$, 0.40 M MeCN, 40 °C; viii) O_3/O_2, MeOH/DCM, –78 °C, then $NaBH_4$, 0 °C; ix) **391**, TMSOTf, DCM, RT.

Scheme 4.16: Complete synthetic scheme for the synthesis of Danishefsky's intermediates alcohol **355** and benzyl ether **354**.

5

Future Work & Conclusions

This Chapter outlines possible future work based on the results presented in previous Chapters. A proposal for the development of intermolecular tricyclic *bis*-lactone formation is presented in **Section 5.2**, which would result in a significant increase in molecular complexity. Secondly, the possible use of oxidative radical cyclisation methodology for use in the total synthesis of a natural product is shown in **Section 5.1**. Finally, conclusions on the project outcomes are described in **Section 5.3**.

5.1 The Total Synthesis of (+)-Brefeldin A

The macrolactone (+)-brefeldin A **393** was isolated in 1958 by Singleton and co-workers from a culture of *Penicillium decumbens* (**Figure 5.1**).[141] Originally used as an antibiotic, it is now frequently used for the study of protein transport within cells and as a protein-protein interaction inhibitor.[142,143] It has been the subject of a number of total syntheses to date, with Corey's synthesis in 1976 being the first.[61,144,145]

The main synthetic challenges are the allylic C-4 stereocentre and the isolated C-7 stereocentre , which has little functionality close by to enable functionalisation and stereocontrol.

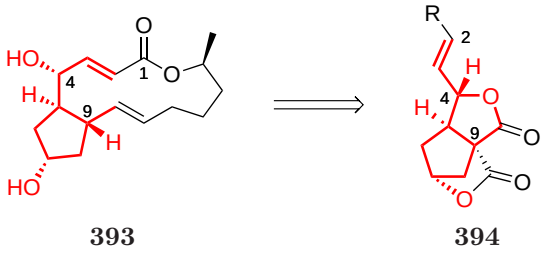
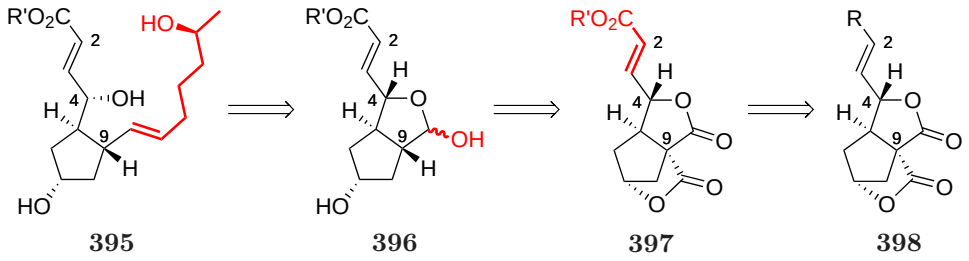


Figure 5.1: (+)-Brefeldin A **393** and its potential tricyclic *bis*-lactone precursor.

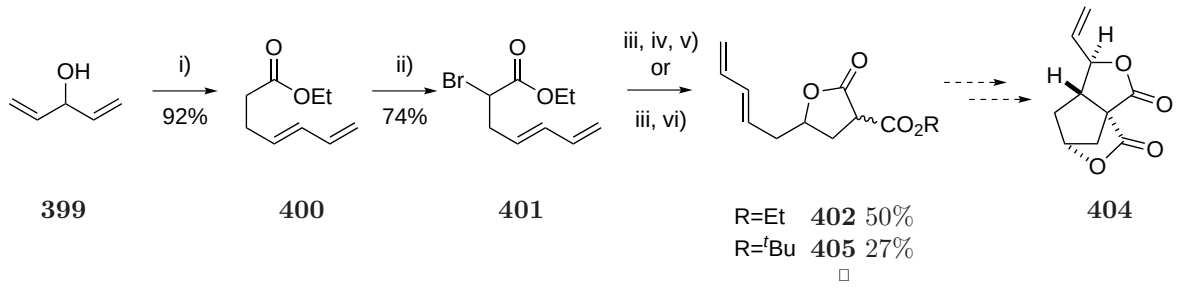
It was proposed that the tricyclic *bis*-lactones such as **394** could be transformed to give (+)-brefeldin A **393** (**Scheme 5.1**). The correct substitution and oxygenation patterns are present in the cyclised structure **394** as highlighted. The bottom half of the macrolactone **395** could be introduced by an olefination reaction on the corresponding lactol **396**. The lactone ester **397** could be introduced on the pendant alkene **398** by either cross metathesis (R=H) or by an olefination reaction on the corresponding aldehyde (R≠H).



Scheme 5.1: Proposed retrosynthesis of (+)-brefeldin A **393** *via* a oxidative radical cyclisation.

The first route toward tricyclic *bis*-lactone **398** (R=H) commenced from divinyl carbinol **399** (**Scheme 5.2**). A Johnson-Claisen reaction gave diene **400**. Bromination with NBS gave α-bromo ester **401**, was carried over three steps (reduction, epoxidation, lactonisation) without extensive purification due to the high volatility of the intermediates. Thus, treatment of ester **401** with DiBAl-H, KO^{t}Bu, and DEM gave lactone-ester **402** in 50% yield over three steps. All attempts to hydrolyse esters **403** failed, with poor mass recovery and no evidence of the desired acid by MS, ^{1}H NMR, or IR.

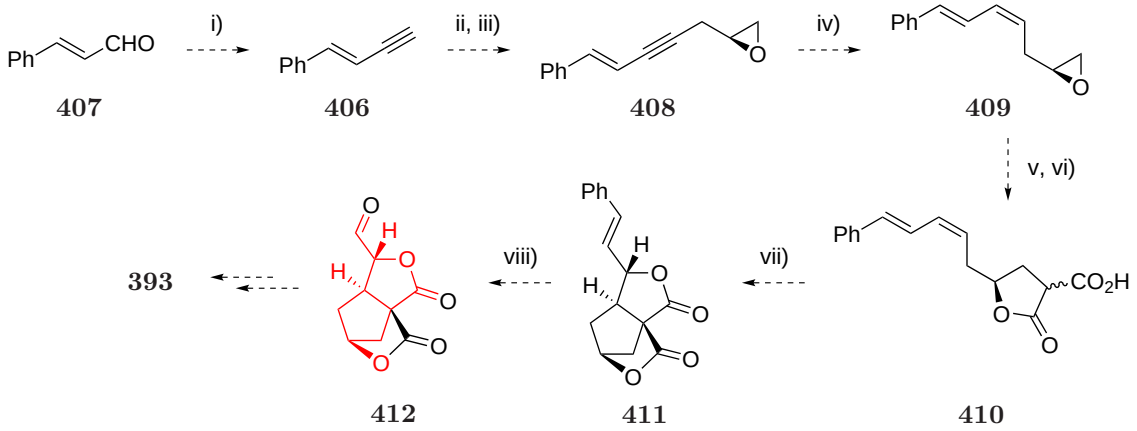
The inability to hydrolyse the esters under acidic or basic conditions precluded further progress on this route. This was possibly due to the sensitivity of the terminal diene moiety, and so a route with a terminal phenyl group, more in line with the substrates in **Chapter 3**, is proposed (**Scheme 5.3**). Enyne



Reagents & Conditions: i) $MeC(OEt)_3$, 7 mol% propionic acid, 145 °C; ii) LDA, TMSCl, NBS, THF, –78→–40 °C; iii) DiBAl-H, DCM, –40 °C; iv) KO^{t}Bu, HO^{t}Bu, 35 °C; v) NaOEt, DEM, 0 °C→RT; vi) KO^{t}Bu, HO^{t}Bu, 35 °C, then di-*tert*-butyl malonate.

Scheme 5.2: Attempted route to the core of brefeldin A **393**.

406 would be available from a Colvin rearrangement of cinnamaldehyde **407** with TMS-diazomethane.[146] Epoxide **408** would be available by alkylation of the anion of enyne **406** with epichlorohydrin **296** under Yamaguchi's conditions,[99] followed by basic epoxidation. Semi-hydrogenation of the enyne under the conditions developed in **Section 3.1.1** would give *E,Z*-diene **409**. Lactonisation followed by saponification would give cyclisation substrate **410**. Treatment of acid **410** would give tricyclic *bis*-lactone **411**. Ozonolysis of the pendant styrene would give aldehyde **412**, which could be transformed to (+)-brefeldin A **393**.



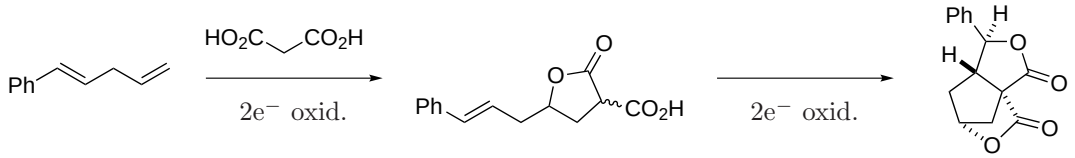
Reagents & Conditions: i) LDA, $TMSCHN_2$, THF, –78 °C; ii) ^{n}BuLi, $BF_3{\cdot}Et_2O$, *S*-**296**, THF, –78 °C; iii) KO^{t}Bu, HO^{t}Bu, 35 °C; iv) H_2, Lindlar catalyst, quinoline, allyl alcohol, RT; v) NaOEt, DEM, 0 °C; vi) KOH, EtOH/H_2O, 0 °C; vii) $Mn(OAc)_3{\cdot}2H_2O$, $Cu(OTf)_2$, MeCN, 80 °C; viii) O_3/O_2, then PPh_3, DCM, –78 °C.

Scheme 5.3: Proposed 2nd generation route to (+)-brefeldin A **393**.

This route would allow access to both enantiomers of brefeldin A **393** as both enantiomers of epichlorhydrin **413** are readily available. Addition of the phenyl group should also reduce the volatility of the intermediates.

5.2 Intermolecular Tricylic bis-Lactone Synthesis

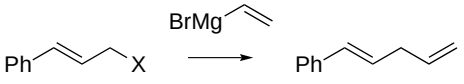
As shown in **Chapter 3**, highly strained tricyclic *bis*-lactones were accessible by transition metal mediated oxidative radical cyclisation reactions. However, an early use of MAN was the lactonisation of alkenes (*vide supra* **Section 1.1**). It was proposed that exposure of 1,4-skipped diene **414** to malonic acid would initially give lactone-ester (*E*)-**288** directly, followed a second oxidative radical cyclisation to give tricyclic *bis*-lactone **303** (**Scheme 5.4**). As two γ-lactones are formed, there is an overall $4e^-$ oxidation and so four equivalents of a suitable transition single electron metal oxidant would be required.



414 (*E*)-**288** **303**

Scheme 5.4: Proposed reaction of malonic acid with a 1,4-skipped diene.

Skipped 1,4-diene **414** was synthesised by a copper(I) catalysed allylic displacement of cinnamyl derivates with vinylmagnesium bromide (**Table 5.1**). Cinnamyl bromide **415** and cinnamyl pivalate **416** were treated with vinylmagnesium bromide in the presence of a copper(I) catalyst. In the presence of copper iodide, pivalate **416** reacted with vinymagnesium bromide, which gave diene **414** (**Entries 1–3**). No evidence of S_N2' reactivity was observed by ^{1}H NMR spectroscopy.[147,148] However, the yields were only moderate even with stoichiometric copper(I). Use of the more soluble $Li_2[CuCl_4]$ (Kochi's catalyst) was investigated with cinnamyl bromide **415** (**Entries 4** and **5**).[149] Reverse addition[150] of vinylmagnesium bromide to a solution of cinnamyl bromide with 20 mol% $Li_2[CuCl]_4$ gave diene **414** in 83% yield.

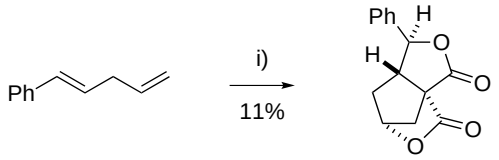


415 X=Br
416 X=OPiv
414

Entry	X	Catalyst		Yield / %
1	OPiv	CuI	5 mol%	8
2	OPiv	CuI	50 mol%	26
3	OPiv	CuI	100 mol%	36
4	Br	$Li_2[CuCl_4]$	5 mol%	28
5	Br	$Li_2[CuCl_4]$	20 mol%	83

Table 5.1: Synthesis of skipped 1,4-diene **414**.

With a scalable synthesis of diene **414** established, an intermolecular synthesis of tricyclic *bis*-lactone **303** was attempted. Treatment of two equivalents of diene **414** with one equivalent of malonic acid, four equivalents of MAN, and one equivalent of $Cu(OTf)_2$ in a 0.01 M MeCN solution gave a small amount of *bis*-lactone **303**, apparently as a single diastereomer (**Scheme 5.5**). The reaction was not clean by ^{1}H NMR spectroscopy, with many excess resonances visible. The high metal loading also complicated product isolation. Attemps to monitor the reaction by HPLC analysis were also unsuccessful in a number of mobile phases, which again precluded optimisation by multivariate analysis.



414 **303**

Reagents & Conditions: i) 2 eq. diene **414**, 1 eq. malonic acid, 4 eq. $Mn(OAc)_3{\cdot}2H_2O$, 1 eq. $Cu(OTf)_2$, MeCN, 80 °C.

Scheme 5.5: Intermolecular synthesis of tricyclic *bis*-lactone **303**.

This demonstrated the proof-of-principle for reaction mediated by MAN which generates a high level of molecular complexity. The simple skipped diene **414** was transformed in a single step to a structure containing four stereocentres with the formation of two C-C bonds and two C-O bonds. This is clearly a powerful synthetic method and further optimisation should allow access to a range of useful small molecule building blocks with selective reactivity as shown in **Section 3.3**.

5.3 Conclusions

The oxidative radical cyclisation methodology discussed in **Chapter 2** showed that radical methods are effective in the stereocontrolled formation of highly congested cyclopentanes (**Figure 5.2**). The direct formation of up to three contiguous quaternary centres, with two all-carbon stereocentres, is unprecedented and represents an important development in radical cyclisation methodology. The inherently low reactivity of 2,2-disubstituted alkenes was overcome by the use of an aryl (or dialkyl) substituent to stabilise the adduct radical. As the reactions proceed under oxidative conditions, the products are amenable to further transformations. Two differentiated carbonyls are present, and potentially fragile functionality was retained during the course of the reaction.

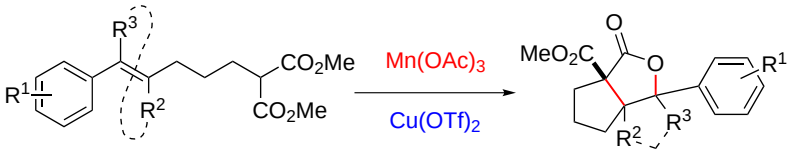


Figure 5.2: Summary of oxidative radical cyclisations presented in **Chapter 2**.

This methodology was developed further to allow the synthesis of highly strained tricyclic *bis*-lactones, as shown in **Chapter 3** (**Figure 5.3**). Complementary diastereomers could be selectively synthesised by the choice of MAN or CAN as the transition metal oxidant. This difference in selectivity was maintained with a range of different substrates, although the reasons for this are still unclear. The utility of the tricyclic *bis*-lactones was demonstrated by various chemo- and regioselective transformations.

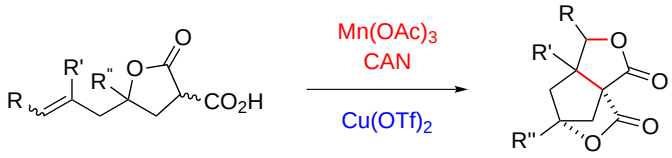


Figure 5.3: Summary of oxidative radical cyclisations presented in **Chapter 3**.

Finally, the application of oxidative radical cyclisations to the synthesis of complex heterocycles in natural product synthesis was demonstrated in **Chapter 4**. In conjunction with Robert Foster,[128] a formal asymmetric synthesis of the clinically relevant proteasome inhibitor (–)-salinosporamide **335** was acheived with a diastereoselective MAN-mediated oxidative radical cyclisation as the key step (**Figure 5.4**). The data obtained were in excellent agreement with literature data.[125] The route delivered an intermediate in 10 fewer steps than reported by Endo and Danishefsky. This synthesis should serve as

an impetus for the synthesis of other pyrrolidinone containing natural products with oxidative radical methodology as a key bond forming step.

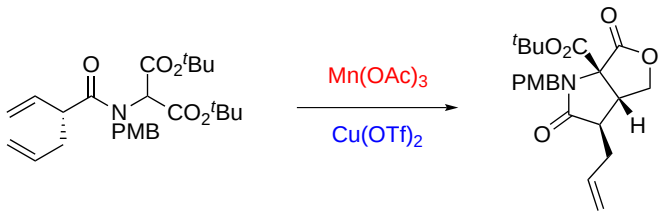


Figure 5.4: Key oxidative radical cyclisation in the formal synthesis of (+)-salinosporamide A **335** presented in **Chapter 4**.

6

Experimental Details and Compound Characterisation

6.1 General Remarks

Chemicals were used as received from Sigma-Aldrich, Acros Organics, and Alfa-Aesar, unless otherwise stated. Commercial manganese(III) acetate dihydrate was washed with AcOH until the the filtrate ran clear, washed on the plate with Et_2O and then dried under high vacuum. The pale brown solid thus obtained was then stored under N_2.

All non-aqueous reactions were conducted under an atmosphere of nitrogen unless otherwise stated.

All ^1H and ^{13}C spectra were recorded on Bruker DPX200, DPX250, DPX400, AV400, DRX500, and AVC500 spectrometers using the stated solvent as an internal deuterium lock. Chemical shifts are quoted as ppm relative to tetramethylsilane ($\boldsymbol{\delta} = 0$ ppm) and referenced to residual solvent signal. Multiplicities are abbreviated as s – singlet, d – doublet, t – triplet, q – quartet, qn – quintet, m – muliplet, br – broad, and combinations thereof. Coupling constants are quoted as J Hz and are rounded to 0.1 Hz. Coupling to magnetically inequivalent protons are quoted individually, even if the coupling constants are the same. 2D NMR experiments (COSY, HSQC, HMBC) were used as appropriate to aid assignment. Some ^{13}C assignments were made on the basis of intensities where appropriate.

Low resolution ESI mass spectra were recorded on a MicroMass LCT Premier. High resolution mass spectra *of novel compounds* were recorded by the University of Oxford Chemical Research Laboratory Mass Spectrometry Service.

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected.

FT-IR spectra *of novel compounds* were recorded on a Bruker Tensor 27 FTIR as a neat film on NaBr discs for liquids and oils and as KBr discs for solids, or on a diamond ATR probe.

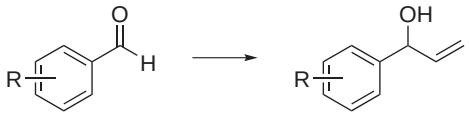
Analytic thin-layer chromatography was performed on Merck aluminium backed sheets coated with 60 F_{254} silica gel, and visualised as appropriate (ultraviolet or chemical stain). Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh).

HPLC analysis was carried out on an Agilent 1200 equipped with normal phase Agilent Zorbax RX-SIL 5 μm semi-preparative, ChiralPak AD-H, and ChiralPak OD-H columns. Compounds were detected by DAD ($\lambda = 254, 230, 210$ nm).

6.2 Cyclisation of Linear ϵ-Styrl Malonates

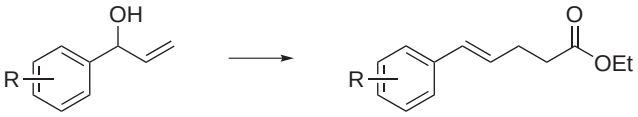
6.2.1 General Procedures

General Procedure 1: Addition of Vinylmagnesium Bromide to Aryl Aldehydes



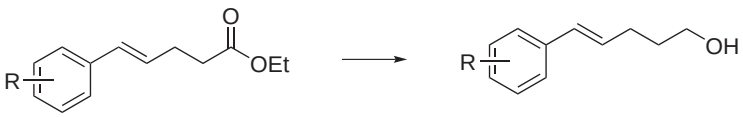
Following the procedure of Jautze and Peters,[151] vinylmagnesium bromide (1 eq., 1 M in THF) was added a slowly to a stirred solution of freshly distilled aldehyde (1 eq.) in dry THF (0.2 M) maintaining an internal temperature <5 °C. After 15 min the reaction was allowed to warm to RT and stirred for an additional 1–3 h. The reaction was quenched by the addition of saturated NH_4Cl solution and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, which gave the crude product.

General Procedure 2: Johnson-Claisen Rearrangement of 1-Arylprop-2-en-1-ol



Following the modified procedure of Johnson *et al.*,[79] propionic acid (0.07 eq.) was added to a stirred solution of arylpropenol (1 eq.) in triethyl orthoacetate (1.5 mL/mmol arylpropenol) and the reaction was heated to 145 °C and stirred for 4–18 h. After cooling to RT, the solution was diluted with EtOAc (1 mL/mmol arylpropenol) and washed successively with 1 M aqueous HCl solution (1 mL/mmol arylpropenol), saturated aqueous $NaHCO_3$ solution (1 mL/mmol arylpropenol), water (1 mL/mmol arylpropenol), and brine (1 mL/mmol arylpropenol). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, which gave the crude product.

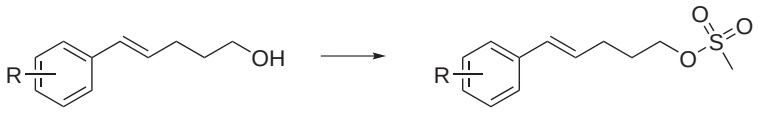
General Procedure 3: Reduction of Ethyl 5-arylpent-4-enoate



A solution of ethyl 5-arylpent-4-enoate (1 eq.) in dry Et_2O (1 M) was added dropwise to a stirred suspension of $LiAlH_4$ (0.5 eq.) in dry Et_2O (0.4 M) at 0 °C. After stirring for 2 h, water (n mL/n g

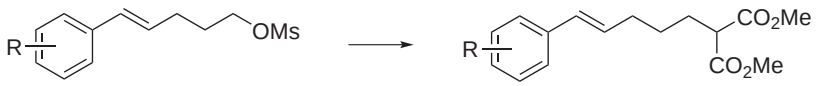
$LiAlH_4$) was added cautiously followed by 15% aqueous NaOH solution (n mL/n g $LiAlH_4$) and then water ($3n$ mL/n g $LiAlH_4$).[152] The solid precipitate was filtered off with washings of Et_2O and the solvent removed *in vacuo*, which gave the crude product.

General Procedure 4: Mesylation of 5-Arylpent-4-en-1-ol



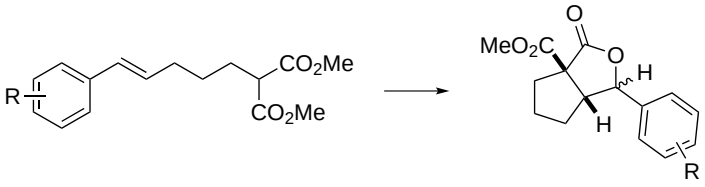
To a stirred solution of 5-arylpent-4-en-1-ol (1 eq.) in dry DCM (0.2 M) was added triethylamine (1.5 eq.) and cooled to 0 °C after which MsCl (1.2 eq.) was added. The solution was allowed to warm to RT and stirred for 1.5 h after which time aqueous 0.5 M HCl solution (4.5 mL/mmol alcohol) was added. The layers were separated and the aqueous layer was extracted with DCM (3×4.5 mL/mmol). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, which gave the crude product.

General Procedure 5: Alkylation of 5-Arylpent-4-enyl methanesulfonate



Sodium hydride (60 wt% in mineral oil, 2.5 eq.) was suspended in dry DMF (0.2 M) and cooled to 0 °C, after which dimethyl malonate (2.5 eq.) was added dropwise and the mixture was stirred for 20 minutes. A solution of the mesylate (1 eq.) in dry THF (0.2 M) was added followed by potassium iodide (1 eq.) and the solution was stirred at 80 °C overnight. After cooling to RT, the solution was poured onto saturated NH_4Cl solution (7 mL/mmol mesylate) and extracted with EtOAc (3×7 mL/mmol mesylate). The combined organic extracts were washed with water, dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, which gave the crude product.

General Procedure 6: Manganese(III) Acetate-Mediated Oxidative Radical Cyclisation of Dimethyl 2-(5-Arylpent-4-enyl)malonate



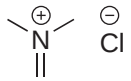
Copper(II) triflate (1 eq.) and manganese(III) acetate dihydrate (2 eq.) were placed under vacuum and heated to 80 °C for 10 minutes and then quenched to N_2. A solution of aryl malonate (1 eq.) in MeCN (0.4 M) was then added rapidly under N_2 and the solution stirred overnight at 80 °C. Water and EtOAc (1:1, 10 mL/mmol malonate) were added and the layers separated. The aqueous layer was extracted with EtOAc (3×5 mL/mmol) and the combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*, which gave the crude product. The cyclised products were obtained as a mixture of diastereomers, which were epimeric at the C1 position adjacent to the aryl group.

General Procedure 7: Installation of Methylene Group *via* a Mannich Reaction

According to the modifed procedure of Ragoussis *et al.*,[86] a solution of α-unsubtituted aldehyde (1 eq.), diethylammonium chloride (1.2 eq.) and formaldehyde (37% aqueous solution, 1.2 eq.) was stirred at 70 °C for 24 h. After cooling to RT, the layers were separated and the aqueous layer was extracted with Et_2O (3×0.5 mL/mmol of aldehyde). The combined organic extracts were dried (Na_2SO_4) and filtered, which gave the crude product.

6.2.2 Reagent Syntheses

***N*-Methyl-*N*-methylenemethanaminium chloride**

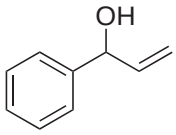


417

According to the procedure of Böhme and Hartke,[90] acetyl chloride (10.2 mL, 75 mmol) in dry Et_2O (70 mL) was added to a stirred solution of *N*,*N*,*N'*,*N'*-tetramethyldiaminemethane (5.33 mL, 75 mmol) in dry Et_2O (140 mL) over 30 min. The precipitate so formed was filtered off under a blanket of N_2 and dried under high vacuum, which gave Böhme's salt, *N*-methyl-*N*-methylenemethanaminium chloride, (5.62 g, 60.0 mmol, 80%) as a highly hygroscopic white powder which was stored under N_2.

6.2.3 Experimental Details and Data

1-Phenylprop-2-en-1-ol



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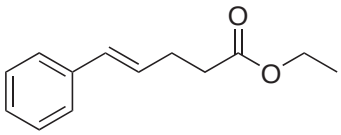
According to GP 1, benzaldehyde (4.25 g, 40.0 mmol) was treated with vinylmagnesium bromide, which gave alcohol **141** (5.30 g, 39.5 mmol, 99%) as a pale yellow oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.39–7.27 (5H, m, Ar*H*), 6.05 (1H, ddd, J = 17.1, 10.3, 6.0 Hz, H_2C=C*H*), 5.36 (1H, dt, J = 6.0, 1.4 Hz, HOC*H*), 5.22–5.16 (2H, m, CH=CH_2), 2.60 (1H, br s, O*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 142.7 (*Ar*), 140.3 (H_2C=*C*H), 128.5 (*Ar*), 127.7 (*Ar*), 126.3 (*Ar*), 115.1 (H_2C=CH), 75.3 (HO*C*H). *Data are consistent with literature values.*[153]

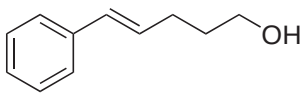
(*E*)-Ethyl 5-phenylpent-4-enoate



142

According to GP 2, alcohol **141** (5.30 g, 39.5 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (15:1 PE:EtOAc), gave ester **(*E*)-142** (4.56 g, 22.3 mmol, 57%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.44-7.20 (5H, m, Ar*H*), 6.46 (1H, d, J = 15.9 Hz, PhC*H*=CH), 6.24 (1H, dt, J = 15.9, 6.5 Hz, PhCH=C*H*), 4.17 (2H, q, J = 7.1 Hz, OCH_2CH$_3$), 2.60–2.47 (4H, m, (CH_2)$_2$), 1.28 (3H, t, J = 7.1 Hz, OCH$_2$CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 171.9 (*C*=O), 137.4 (*Ar*), 131.0 (Ph*C*H=CH), 128.5 (*Ar* & PhCH=*C*H), 127.1 (*Ar*), 126.1 (*Ar*), 60.4 (O*C*H$_2$), 34.1 (*C*H$_2$), 28.3 (*C*H$_2$), 14.3 (*C*H$_3$). *Data are consistent with literature values.*[154]

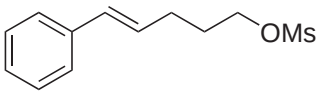
(*E*)-5-Phenylpent-4-en-1-ol



143

According to GP 3, ester **(*E*)-142** (3.69 g, 18.1 mmol) was treated with $LiAlH_4$, which after flash column chromatography (2:1 PE:EtOAc), gave alcohol **(*E*)-143** (2.60 g, 16.0 mmol, 89%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.39–7.29 (4H, m, Ar*H*), 7.22 (1H, t, J = 7.1 Hz, Ar*H*), 6.44 (1H, d, J = 15.8 Hz, PhC*H*=CH), 6.25 (1H, dt, J = 15.8, 6.7 Hz, PhCH=C*H*), 3.71 (2H, t, J = 6.7 Hz, HOCH_2), 2.37–2.29 (2H, m, PhCH=CHCH_2), 1.77 (2H, tt, J = 6.7, 6.7 Hz, HOCH$_2$CH_2); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 137.6 (*Ar*), 130.4 (PhCH=*C*H), 130.1 (*Ar*), 128.5 (*Ar*), 127.0 (Ph*C*H=CH), 126.0 (*Ar*), 62.3 (HO*C*H$_2$), 32.2 (*C*H$_2$), 29.3 (*C*H$_2$). *Data are consistent with literature values.*[154]

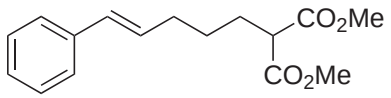
(*E*)-5-Phenylpent-4-enyl methanesulfonate



418

According to GP 4, alcohol **(*E*)-143** (2.60 g, 16.0 mmol) was treated with MsCl, which gave mesylate **(*E*)-418** (3.85 g, 16.0 mmol, 100%) as a pale yellow oil, which was used without purification. $\mathbf{R}_f$ 0.31 (1:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.38–7.26 (5H, m, Ar*H*), 6.45 (1H, d, J = 15.8 Hz, PhC*H*=CH), 6.19 (1H, dt, J = 15.8, 7.2 Hz, PhCH=C*H*), 4.28 (2H, t, J = 6.6 Hz, MsOCH_2), 3.01 (3H, s, SO_2C*H*$_3$), 2.36 (2H, dt, J = 7.2, 7.2 Hz, PhCH=CHCH_2), 1.95 (2H, tt, J = 7.2, 6.6 Hz, MsOCH$_2$CH_2); $\boldsymbol{\delta_H}$ (100 MHz, $CDCl_3$) 137.2 (*Ar*), 131.4 (PhCH=*C*H), 128.6 (*Ar*), 128.3 (*Ar*), 127.2 (Ph*C*H=CH), 126.0 (*Ar*), 69.4 (MsO*C*H$_2$), 37.3 (OSO$_2$*C*H$_3$), 28.8 (*C*H$_2$), 28.7 (*C*H$_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2940 (m, C-H), 1576 (w, C=C), 1353 (s, SO_2), 1173 (s, SO_2); **m/z** (ESI+) 263.1 ([M+Na]$^+$, 100%), HRMS found 263.0710, $C_{12}H_{16}O_3NaS$ requires 263.0712.

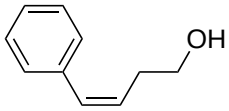
(*E*)-Dimethyl 2-(5-phenylpent-4-enyl)malonate



144

According to GP 5, mesylate **(*E*)-418** (3.85 g, 16.0 mmol) was treated with DMM, which after flash column chromatography (15:1→10:1 PE:EtOAc), gave malonate **(*E*)-144** (3.57 g, 12.9 mmol, 81%) as a colourless oil. $\mathbf{R}_f$ 0.21 (10:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.37–7.26 (4H, m, Ar*H*), 7.23–7.18 (1H, m, Ar*H*), 6.40 (1H, d, J = 15.8 Hz, PhC*H*=CH), 6.19 (1H, dt, J = 15.8, 7.3 Hz, PhCH=C*H*), 3.75 (6H, s, CO_2CH_3), 3.41 (1H, t, J = 7.5 Hz, $CH_2CH(CO_2Me)_2$), 2.26 (2H, dtd, J = 7.3, 7.3, 1.4 Hz, PhCH=CHCH_2), 2.02–1.93 (2H, m, $(MeO_2C)_2CHCH_2$), 1.56–1.47 (2H, m, CH=CHCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.8 (*C*=O), 137.6 (*Ar*), 130.5 (Ph*C*H=CH), 129.7 (*Ar*), 128.5 (*Ar*), 127.0 (PhCH=*C*H), 126.0 (*Ar*), 52.5 (CO_2CH_3), 51.6 ($(MeO_2C)_2CH$), 32.5 (PhCH=CH*C*H$_2$), 28.4 (*C*H$_2$), 27.0 (*C*H$_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2954 (m, C-H), 1735 (s, C=O), 1598 (w, C=C); **m/z** (ESI+) 299.1 ([M+Na]$^+$, 100%), 575.3 ([2M+Na]$^+$, 92%), HRMS found 299.1255, $C_{16}H_{20}O_4Na$ requires 299.1254.

(*Z*)-5-Phenylpent-4-en-1-ol

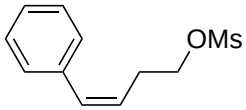


143

According to the method of Liu and Stahl,[85] to a stirred solution of $(PPh_3)_2NiBr_2$ (723 mg, 1.0 mmol) in dry toluene (100 mL) was added PhMgBr (3 M in Et_2O, 0.33 mL, 1.0 mmol) at RT. After 15 min, PhMgBr (3 M in Et_2O, 3.33 mL, 10.0 mmol) was added followed by 3,4-dihydropyran **419** (3.0 mL, 33 mmol). The solution was heated at reflux overnight, allowed to cool to RT, and then poured on to saturated aqueous NH_4Cl (100 mL). The layers were separated and the aqueous was extracted with Et_2O (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (5→1:1 PE:EtOAc), which gave alcohol **(*Z*)-143** (1.04 g, 6.4 mmol, 64%) as a colourless oil. $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.40–7.29 (4H, m, Ar*H*), 7.29–7.23 (1H, m, Ar*H*), 6.49 (1H, dt, J = 11.6, 1.8 Hz, PhC*H*=CH), 5.70 (1H, dt, J = 11.6, 7.3 Hz, PhCH=C*H*), 3.66 (2H, t, J = 6.5 Hz,

HOCH_2), 2.45 (2H, tdd, J = 7.5, 7.3, 1.8 Hz, PhCH=CHCH_2), 1.96 (1H, br s, OH), 1.78–1.70 (2H, m, HOCH$_2$CH_2); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 137.9 (Ar), 132.5 (PhCH=CH), 129.9 (PhCH=CH), 129.2 (Ar), 128.6 (Ar), 127.0 (Ar), 62.7 (HOCH$_2$), 33.2 (HOCH$_2$$CH_2$), 25.3 (PhCH=CH$CH_2$). *Data are consistent with literature values.*[85]

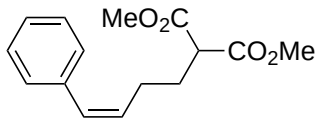
(*Z*)-5-Phenylpent-4-enyl methanesulfonate



418

According to GP 4, alcohol **(*Z*)-143** (700 mg, 4.32 mmol) was treated with MsCl, which gave mesylate **(*Z*)-418** (1.03 g, 4.30 mmol, 100%) as a pale yellow oil, which was used without purification. $\mathbf{R}_f$ 0.42 (1:1 PE:EtOAc), $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.40-7.23 (5H, m, ArH), 6.52 (1H, br d, J = 11.6 Hz, PhCH=CH), 5.64 (1H, dt, J = 11.6, 7.3 Hz, PhCH=CH), 4.23 (2H, t, J = 6.4 Hz, MsOCH_2), 2.89 (3H, s, SO_2CH_3), 2.48 (2H, tdd, J = 7.3, 7.3, 1.8 Hz, PhCH=CHCH_2), 1.96–1.85 (2H, m, PhCH=CHCH$_2$CH_2); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 137.2 (Ar), 130.5 (PhCH=CH), 130.4 (PhCH=CH), 128.7 (Ar), 128.3 (Ar), 126.9 (Ar), 69.3 (MsOCH$_2$), 37.2 (SO_2CH$_3$), 29.2 (PhCH=CHCH$_2$$CH_2$), 24.4 (PhCH=CH$CH_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2919 (m, C-H), 1645 (w, C=C), 1599 (w, C=C), 1354 (s, SO_2), 1075 (m); **m/z** (ESI+) 263.1 ([M+Na]$^+$, 100%), HRMS found 263.0709, $C_{12}H_{16}O_3NaS$ requires 263.0712.

(*Z*)-Dimethyl 2-(5-phenylpent-4-enyl)malonate

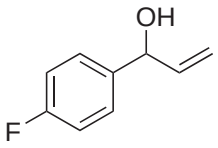


144

According to GP 5, mesylate **(*Z*)-418** (1.03 g, 4.30 mmol) was treated with DMM, which after flash column chromatography (10→7:1 PE:EtOAc), gave malonate **(*Z*)-144** (982 mg, 3.56 mmol, 83%) as a colourless oil. $\mathbf{R}_f$ 0.38 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.44–7.15 (5H, ArH), 6.44 (1H, br d, J = 11.6 Hz, PhCH=CH), 5.63 (1H, dt, J = 11.6, 7.2 Hz, PhCH=CH), 3.72 (6H, s, CO_2CH_3), 3.36 (1H, t, J = 7.5 Hz, $(CO_2Me)_2$CH), 2.37 (2H, tdd, J = 7.4, 7.2, 1.7 Hz, PhCH=CHCH_2), 1.98–1.89 (2H, m, $(CO_2Me)_2$CHCH_2), 1.53–1.43 (2H, m, PhCH=CHCH$_2$CH_2), $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.8 (C=O), 137.5 (Ar), 131.8 (PhCH=CH), 129.5 (PhCH=CH), 128.7 (Ar), 128.2 (Ar), 126.6 (Ar), 52.4 (CO_2CH$_3$), 51.5

($(CO_2Me)_2CH$), 28.4 (PhCH=CHCH_2), 28.1 ($(CO_2Me)_2CHCH_2$), 27.6 (PhCH=$CHCH_2CH_2$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2953 (m, C-H), 1735 (s, C=O), 1599 (w, C=C) 1437 (m), 1149 (m), **m/z** (ESI+) 299.1 ($[M+Na]^+$, 100%), HRMS found 299.1251, $C_{16}H_{20}O_4Na$ requires 299.1254.

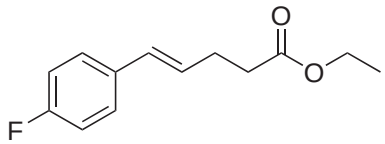
1-(4-Fluorophenyl)prop-2-en-1-ol



145

According to GP 1, 4-fluorobenzaldehyde (1.24 g, 10.0 mmol) was treated with vinylmagnesium bromide, which gave alcohol **145** (1.45 g, 9.50 mmol, 95%) as an amber oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.33 (2H, dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HF}$ = 5.5 Hz, ArH), 7.04 (2H, dd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HF}$ = 8.6 Hz, ArH), 6.01 (1H, ddd, J = 17.0, 10.3, 6.0 Hz, H_2C=CH), 5.33 (1H, d, J = 17.0 Hz, CH=CHH), 5.20 (1H, d, J = 10.3 Hz, CH=CHH), 5.17 (1H, d, J = 6.0 Hz, CHOH), 2.34 (1H, br s, OH); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 162.3 (d, $^1J_{CF}$ = 246 Hz, CF), 140.1 (H_2C=CH), 138.3 (d, $^4J_{CF}$ = 3 Hz, FC(CHCH)$_2C$), 128.1 (d, $^3J_{CF}$ = 8 Hz, FC(CHCH)$_2$), 115.3 (d, $^2J_{CF}$ = 22 Hz, FC(CH)$_2$), 115.3 (CH=CH$_2$), 74.6 (CHOH); $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$) -115. *Data are consistent with literature values.*[153]

(*E*)-Ethyl 5-(4-fluorophenyl)pent-4-enoate

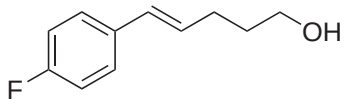


146

According to GP 2, alcohol **145** (1.40 g, 9.20 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (10:1 PE:EtOAc), gave ester **146** (1.08 g, 4.06 mmol, 53%) as a colourless oil. $\mathbf{R}_f$ 0.58 (5:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.30–7.26 (2H, m, ArH), 6.97 (2H, dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{HF}$ = 8.7 Hz, ArH), 6.38 (1H, d, J = 15.9 Hz, ArCH=CH), 6.11 (1H, dt, J = 15.9, 6.4 Hz, ArCH=CH), 4.15 (2H, q, J = 7.1 Hz, OCH_2), 2.56–2.43 (4H, m, CH_2), 1.25 (3H, t, J = 7.1 Hz, OCH_2CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 172.9 (C=O), 162.0 (d, $^1J_{CF}$ = 246 Hz, CF), 133.5 (d, $^4J_{CF}$ = 3 Hz, FC(CHCH)$_2C$), 129.7 (ArCH=CH), 128.2 (ArCH=CH), 127.5 (d, $^3J_{CF}$ = 8 Hz, FC(CHCH)$_2$), 115.3 (d, $^2J_{CF}$ = 22 Hz, FC(CH)$_2$), 60.4 (OCH$_2$), 34.0 (CH$_2$), 28.2 (CH$_2$), 14.2 (OCH_2CH_3); $\boldsymbol{\delta_F}$ (377

MHz, $CDCl_3$) -115. *Data are consistent with literature values.*[155]

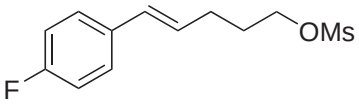
(*E*)-5-(4-Fluorophenyl)pent-4-en-1-ol



147

According to GP 3, ester **146** (445 mg, 2.00 mmol) was treated with $LiAlH_4$, which after flash column chromatography (2:1 PE:EtOAc) gave alcohol **147** (270 mg, 1.50 mmol, 75%) as a colourless oil. $\mathbf{R}_f$ 0.21 (2:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.30 (2H, dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HF}$ = 5.7 Hz, Ar*H*), 6.99 (2H, dd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HF}$ = 8.6 Hz, Ar*H*), 6.39 (1H, d, *J* = 15.8 Hz, ArC*H*=CH), 6.15 (1H, dd, *J* = 15.8, 7.0 Hz, ArCH=C*H*), 3.71 (2H, br s, HOCH_2), 2.31 (2H, dt, *J* = 7.2, 7.2 Hz, CH=CHCH_2), 1.75 (2H, tt, *J* = 7.2, 7.2 Hz, $HOCH_2CH_2$), 1.53 (1H, br s, O*H*); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 161.9 (d, $^1J_{CF}$ = 245 Hz, *C*F), 133.8 (d, $^4J_{CF}$ = 3 Hz, FC(CHCH)$_2$*C*), 129.8 (Ar*C*H=CH), 129.2 (ArCH=*C*H), 127.4 (d, $^3J_{CF}$ = 8 Hz, FC(CH*C*H)$_2$), 115.3 (d, $^2J_{CF}$ = 22 Hz, FC(*C*H)$_2$), 62.3 (HO*C*H$_2$), 32.2 ($HOCH_2CH_2$), 29.2 (CH=CH*C*H$_2$); $\boldsymbol{\delta}_\mathbf{F}$ (377 MHz, $CDCl_3$) -115; $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 3350 (br, O-H), 2937 (m, C-H), 1655 (w C=C), 1508 (s), 1228 (s, C-F), 967 (m); **m/z** HRMS (FI) found 180.0944, $C_{11}H_{13}FO$ requires 180.0950.

(*E*)-5-(4-Fluorophenyl)pent-4-enyl methanesulfonate

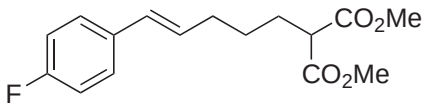


420

According to GP 4, alcohol **147** (240 mg, 1.33 mmol) was treated with MsCl, which gave mesylate **420** (340 mg, 1.32 mmol, 99%) as a pale yellow oil, which was used without purification. $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.30 (2H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HF}$ = 5.6 Hz, Ar*H*), 6.99 (2H, dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{HF}$ = 8.7 Hz, Ar*H*), 6.41 (1H, d, *J* = 15.8 Hz, ArC*H*=CH), 6.09 (1H, dt, *J* = 15.8, 7.2 Hz, ArCH=C*H*), 4.28 (2H, t, *J* = 6.4 Hz, MsOCH_2), 3.02 (3H, s, SO_2CH_3), 2.35 (2H, tt, *J* = 7.2, 7.2 Hz, $MsOCH_2CH_2$), 1.98–1.90 (2H, m, ArCH=CHCH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 162.1 (d, $^1J_{CF}$ = 247 Hz, *C*F), 133.4 (d, $^4J_{CF}$ = 3 Hz, FC(CHCH)$_2$*C*), 130.2 (Ar*C*H=CH), 128.0 (ArCH=*C*H), 127.5 (d, $^3J_{CF}$ = 8 Hz, FC(CH*C*H)$_2$), 115.4 (d, $^2J_{CF}$ = 22 Hz, FC(*C*H)$_2$), 69.2 (MsO*C*H$_2$), 37.4 (SO_2CH_3), 28.7 (*C*H$_2$), 28.7 (*C*H$_2$); $\boldsymbol{\delta}_\mathbf{F}$ (377 MHz, $CDCl_3$) -115; $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2941 (m, C-H), 1509 (s), 1353 (s, SO_2), 1226 (s, C-F), 1174 (s, SO_2), 972

(m); **m/z** (ESI+) 281.1 ([M+Na]$^+$, 100%), HRMS found 281.0613, $C_{12}H_{15}FNaO_3S$ requires 281.0618.

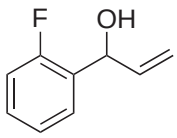
(*E*)-Dimethyl 2-(5-(4-fluorophenyl)pent-4-enyl)malonate



148

According to GP 5, mesylate **420** (309 mg, 1.20 mmol) was treated with DMM, which after flash column chromatography (10:1 PE:EtOAc), gave malonate **148** (173 mg, 0.59 mmol, 49%) as a colourless oil. $\mathbf{R}_f$ 0.19 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.29 (2H, dd, $^3J_{HH}$ = 8.6 Hz, $^4J_{HF}$ = 5.5 Hz, Ar*H*), 6.98 (2H, dd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HF}$ = 8.6 Hz, Ar*H*), 6.35 (1H, d, *J* = 15.8 Hz, ArC*H*=CH), 6.09 (1H, dt, *J* = 15.8, 6.9 Hz, ArCH=C*H*), 3.75 (6H, s, $(CO_2CH_3)_2$), 3.40 (1H, t, *J* = 7.5 Hz, $(MeO_2C)_2CH$), 2.24 (2H, dt, *J* = 6.9, 6.9 Hz, ArCH=CHCH_2), 1.97 (2H, dt, *J* = 7.5, 5.5 Hz, $(MeO_2C)_2CHCH_2$), 1.55–1.46 (2H, m, $CH_2CH_2CH_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.8 (*C*=O), 161.9 (d, $^1J_{CF}$ = 247 Hz, *C*F), 133.7 (d, $^4J_{CF}$ = 3 Hz, $FC(CHCH)_2C$), 129.4 (*C*H=CH), 129.3 (*C*H=CH), 127.4 (d, $^3J_{CF}$ = 8 Hz, $FC(CHCH)_2$), 115.3 (d, $^2J_{CF}$ = 22 Hz, $FC(CH)_2$), 52.5 (CO_2CH_3), 51.6 ($(MeO_2C)_2CH$), 32.5 (ArCH=CH*C*H_2), 28.4 ($(MeO_2C)_2CHCH_2$), 27.0 ($CH_2CH_2CH_2$); $\boldsymbol{\delta}_\mathbf{F}$ (377 MHz, $CDCl_3$) -115; $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2955 (m, C-H), 1735 (s, C=O), 1602 (w, C=C), 1510 (m), 1226 (s, C-F), 1156 (m); **m/z** (ESI+) 317.1 ([M+Na]$^+$, 100%), 611.3 ([2M+Na]$^+$, 20%), HRMS found 317.1160, $C_{16}H_{19}FNaO_4$ requires 317.1160.

1-(2-Fluorophenyl)prop-2-en-1-ol

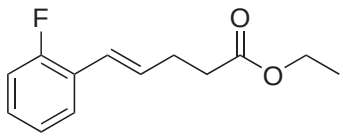


149

According to GP 1, 2-fluorobenzaldehyde (1.24 g, 10.0 mmol) was treated with vinylmagnesium bromide, which after flash column chromatography (10→5:1 PE:EtOAc), gave alcohol **149** (1.17 g, 7.7 mmol, 77%) as a colourless oil. $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.46 (1H, td, *J* = 7.5, 1.7 Hz, Ar*H*), 7.28 (1H, tdd, *J* = 7.5, 5.3, 1.7 Hz, Ar*H*), 7.20–7.13 (1H, m, Ar*H*), 7.08–7.01 (1H, m, Ar*H*), 6.08 (1H, ddd, *J* = 16.5, 10.4, 5.6 Hz, H_2C=C*H*), 5.53 (1H, d, *J* = 5.6 Hz, HOC*H*), 5.37 (1H, d, *J* = 16.5 Hz, CH=*H*H), 5.22 (1H, d, *J* = 10.4 Hz, CHH*H*), 2.05 (1H, br s, O*H*); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 160.1 (d, $^1J_{CF}$ = 246 Hz, *Ar*), 138.9 (H_2C=*C*H), 129.7 (d, $^2J_{CF}$ = 13 Hz, *Ar*), 129.2 (d, $^3J_{CF}$ = 8 Hz, *Ar*), 127.6 (d, $^3J_{CF}$ =

4 Hz, *Ar*), 124.4 (d, $^4J_{CF}$ = 4 Hz, *Ar*), 115.4 (d, $^2J_{CF}$ = 22 Hz) 115.3 (CH=*C*H$_2$), 69.2 (d, $^3J_{CF}$ = 3 Hz, HO*C*H); $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$) -119. *Data are consistent with literature values.*[153]

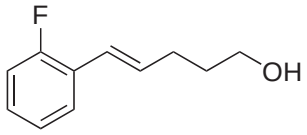
(*E*)-Ethyl 5-(2-fluorophenyl)pent-4-enoate



150

According to GP 2, alcohol **149** (1.10 g, 7.23 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (15:1 PE:EtOAc), gave ester **150** (1.43 g, 6.45 mmol, 89%) as a colourless oil. $\mathbf{R}_f$ $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.41 (1H, ddd, J = 7.7, 7.7, 1.7 Hz, Ar*H*), 7.17 (1H, dddd, J = 7.7, 7.7, 5.2, 1.7 Hz, Ar*H*), 7.10–7.04 (1H, m, Ar*H*), 7.03–6.97 (1H, m, Ar*H*), 6.59 (1H, d, J = 16.0 Hz, ArC*H*=CH), 6.29 (1H, dt, J = 16.0, 6.6 Hz, ArCH=C*H*), 4.16 (2H, q, J = 7.1 Hz, CO_2CH_2), 2.62–2.52 (2H, m, ArCH=CHCH_2), 2.53–2.45 (2H, m, EtO_2CCH_2), 1.26 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 172.8 (*C*=O), 160.0 (d, $^1J_{CF}$ = 249 Hz, *Ar*), 131.2 (d, $^4J_{CF}$ = 4 Hz, ArCH=*C*H), 128.3 (d, $^3J_{CF}$ = 8 Hz, *Ar*), 127.1 (d, $^4J_{CF}$ = 4 Hz, *Ar*), 125.1 (d, $^2J_{CF}$ = 12 Hz, *Ar*), 124.0 (d, $^3J_{CF}$ = 4 Hz, *Ar*), 123.3 (d, $^3J_{CF}$ = 4 Hz, Ar*C*H=CH), 115.6 (d, $^2J_{CF}$ = 22 Hz, *Ar*), 60.4 ($CO_2CH_2CH_3$), 33.9 (ArCH=CH*C*H$_2$), 28.7 (EtO_2CCH_2), 14.2 ($CO_2CH_2CH_3$); $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$) -119; $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2983 (m, C-H), 1735 (s, C=O), 1614 (w, C=C), 1579 (w, C=C), 1488 (m), 1230 (s, C-F); **m/z** (ESI+) 245.1 ($[M+Na]^+$, 80%), 261.1 ($[M+K]^+$, 100%), HRMS found 245.0949, $C_{13}H_{15}FNaO_2$ requires 245.0948.

(*E*)-5-(2-Fluorophenyl)pent-4-en-1-ol

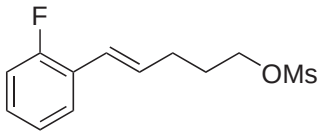


151

According to GP 3, ester **150** (667 mg, 3.00 mmol) was treated with $LiAlH_4$, which after flash column chromatography (4→2:1 PE:EtOAc), gave alcohol **151** (402 mg, 2.23 mmol, 74%) as a colourless oil. $\mathbf{R}_f$ 0.13 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.43 (1H, t, J = 7.6 Hz, Ar*H*), 7.17 (1H, dd, J = 13.2, 7.0 Hz, Ar*H*), 7.08 (1H, t, J = 7.6 Hz, Ar*H*), 7.05–6.99 (1H, m, Ar*H*), 6.58 (1H, d, J = 16.0 Hz,

ArC*H*=CH), 6.32 (1H, dt, J = 16.0, 7.0 Hz, ArCH=C*H*), 3.73 (2H, t, J = 6.4 Hz, HOCH_2), 2.35 (2H, dt, J = 7.1, 7.0 Hz, ArCH=CHCH_2), 1.83–1.73 (2H, m, HOCH$_2$CH_2), 1.47 (1H, br s, O*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 159.9 (d, $^1J_{CF}$ = 248 Hz, *Ar*), 132.8 (d, $^4J_{CF}$ = 5 Hz, ArCH=*C*H), 128.1 (d, $^3J_{CF}$ = 8 Hz, *Ar*), 127.0 (d, $^3J_{CF}$ = 3 Hz, Ar*C*H=CH), 125.3 (d, $^2J_{CF}$ = 12 Hz, *Ar*), 124.0 (d, $^3J_{CF}$ = 4 Hz, *Ar*), 122.8 (d, $^4J_{CF}$ = 3 Hz, *Ar*), 115.6 (d, $^2J_{CF}$ = 22 Hz, *Ar*), 62.4 (HO*C*H$_2$), 32.1 (HOCH$_2$*C*H$_2$), 29.7 (ArCH=CH*C*H$_2$); $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$) -119; $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3336 (br, O-H), 2937 (m, C-H), 1652 (w, C=C), 1487 (s), 1229 (s, C-F), 969 (s), 753 (s); **m/z** HRMS (FI) found 180.0949, $C_{11}H_{13}FO$ requires 180.0950.

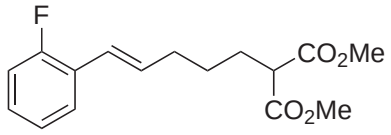
(*E*)-5-(2-Fluorophenyl)pent-4-enyl methanesulfonate



421

According to GP 4, alcohol **151** (180 mg, 1.00 mmol) was treated with MsCl, which gave mesylate **421** as a pale yellow oil (258 mg, 1.00 mmol, 100%), which was used without purification. $\mathbf{R}_f$ 0.20 (1:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.41 (1H, dd, J = 10.9, 4.5 Hz, Ar*H*), 7.19 (1H, dt, J = 7.2, 3.7 Hz, Ar*H*), 7.09 (1H, t, J = 7.4 Hz, Ar*H*), 7.06–6.99 (1H, m, Ar*H*), 6.59 (1H, d, J = 16.0 Hz, ArC*H*=CH), 6.27 (1H, dt, J = 16.0, 7.0 Hz, ArCH=C*H*), 4.29 (2H, t, J = 6.3 Hz, MsOCH_2), 3.02 (3H, s, SO_2CH_3), 2.39 (2H, dt, J = 7.0, 7.0 Hz, ArCH=CHCH_2), 2.00–1.93 (2H, m, MsOCH$_2$CH_2); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 159.97 (d, $^1J_{CF}$ = 249 Hz, *Ar*), 131.08 (d, $^4J_{CF}$ = 5 Hz, ArCH=*C*H), 128.43 (d, $^3J_{CF}$ = 8 Hz, *Ar*), 127.15 (d, $^3J_{CF}$ = 4 Hz, Ar*C*H=CH), 125.0 (d, $^2J_{CF}$, 12 Hz, *Ar*), 124.07 (d, $^3J_{CF}$ = 4 Hz, *Ar*), 123.88 (d, $^4J_{CF}$ = 3 Hz, *Ar*), 115.67 (d, $^2J_{CF}$ = 22 Hz, *Ar*), 69.2 (MsO*C*H$_2$), 37.4 (SO_2CH_3), 29.2 (*C*H$_2$), 28.6 (*C*H$_2$); $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$) -119; $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2941 (m, C-H), 1652 (w, C=C), 1487 (m), 1353 (s, SO_2), 1229 (m, C-F), 1173 (s, SO_2), 972 (s), 928 (s), 720 (m); **m/z** (ESI+) 281.1 ($[M+Na]^+$, 100%) HRMS found 281.0619, $C_{12}H_{15}FNaO_3S$ requires 281.0618.

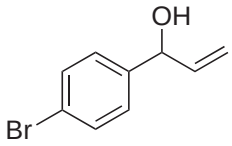
(*E*)-Dimethyl 2-(5-(2-fluorophenyl)pent-4-enyl)malonate



152

According to GP 5, mesylate **421** (258 mg, 1.00 mmol) was treated with DMM, which after flash column chromatography (10:1 PE:EtOAc), gave malonate **152** (205 mg, 0.700 mmol, 70%) as a colourless oil. $\mathbf{R}_f$ 0.45 (1:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.42 (1H, t, J = 7.7 Hz, ArH), 7.21–7.13 (1H, m, ArH), 7.07 (1H, t, J = 7.4 Hz, ArH), 7.04–6.98 (1H, m, ArH), 6.55 (1H, d, J = 15.9 Hz, ArCH=CH), 6.26 (1H, dt, J = 15.9, 7.0 Hz, ArCH=CH), 3.75 (6H, s, (OCH_3)$_2$), 3.41 (1H, t, J = 7.5 Hz, (MeO_2C)$_2$CH), 2.28 (2H, dt, J = 7.0, 7.0 Hz, ArCH=CHCH_2), 1.98 (2H, td, J = 7.9, 7.5 Hz, (MeO_2C)$_2$CHCH_2), 1.57–1.48 (2H, m, ArCH=CHCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.8 (C=O), 159.9 (d, $^1J_{CF}$ = 248 Hz, Ar), 132.4 (ArCH=CH), 128.1 (d, $^3J_{CF}$ = 8 Hz, Ar), 115.6 (d, $^2J_{CF}$ = 22 Hz, Ar), 52.5 (CO_2CH$_3$), 51.6 ((MeO_2C)$_2C$H), 32.9 (ArCH=CHCH$_2$), 28.4 ((MeO_2C)$_2$CHCH$_2$), 26.9 (ArCH=CHCH$_2C$H$_2$); $\boldsymbol{\delta}_\mathbf{F}$ (377 MHz, $CDCl_3$) -119; $\boldsymbol{\nu}_\mathbf{max}$ **/ cm^{-1}** 2955 (m, C-H), 1736 (s, C=O), 1438 (m), 1229 (s, C-F), 1112 (s), 792 (s); **m/z** (ESI+) 317.1 ([M+Na]$^+$, 100%), 638.4 ([2M+Na]$^+$, 27%), HRMS found 317.1161, $C_{16}H_{19}FNaO_4$ requires 317.1160.

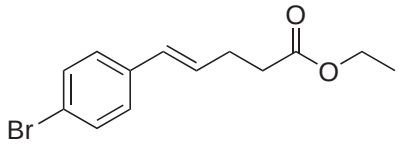
1-(4-Bromophenyl)prop-2-en-1-ol



153

According to GP 1, 4-bromobenzaldehyde (1.85 g, 10.0 mmol) was treated with vinylmagnesium bromide, which gave alcohol **153** (2.08 g, 9.85 mmol, 99%) as an amber oil, which was used without purification. $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.49 (2H, d, J = 8.4 Hz, ArH), 7.25 (2H, d, J = 8.4 Hz, ArH), 6.00 (1H, ddd, J = 17.0, 10.3, 6.1 Hz, CH=CH$_2$), 5.34 (1H, dd, J = 17.0, 1.3 Hz, CH=CHH), 5.21 (1H, dd, J = 10.3, 1.3 Hz, CH=CHH), 5.16 (1H, d, J = 6.1 Hz, CHOH), 2.05 (1H, br s, OH); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 141.5 (Ar), 139.8 (CH=CH$_2$), 131.6 (Ar), 128.6 (Ar), 128.0 (Ar), 115.7 (CH=CH$_2$), 74.7 (CHOH). *Data are consistent with literature values.*[156]

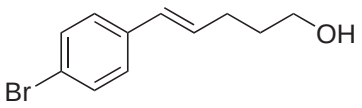
(*E*)-Ethyl 5-(4-bromophenyl)pent-4-enoate



154

According to GP 2, alcohol **153** (1.18 g, 5.53 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (30→10:1 PE:EtOAc), gave ester **154** (867 mg, 3.06 mmol, 55%) as a colourless oil. $\mathbf{R}_f$ 0.42 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.41 (2H, d, J = 8.4 Hz, ArH), 7.20 (2H, d, J = 8.4 Hz, ArH), 6.37 (1H, d, J = 15.9 Hz, ArCH=CH), 6.20 (1H, dt, J = 15.9, 6.4 Hz, ArCH=CH), 4.15 (2H, q, J = 7.1 Hz, OCH_2), 2.60–2.41 (4H, m, CH_2CH_2), 1.26 (3H, t, J = 7.1 Hz, OCH$_2$CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 172.8 (C=O), 136.3 (Ar), 131.6 (ArCH=CH), 129.8 (ArCH=CH), 129.4 (Ar), 127.6 (Ar), 120.8 (Ar), 60.4 (OCH$_2$), 33.9 (CH$_2$), 28.2 (CH$_2$), 14.3 (OCH$_2$$CH_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2981 (m, C-H), 1734 (s, C=O), 1653 (w, C=C), 1486 (m), 1159 (m), 1036 (s, C-Br); **m/z** HRMS (FI) found 282.0252, $C_{13}H_{15}{}^{79}BrONa_2$ requires 282.0255.

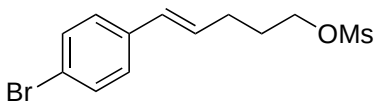
(*E*)-5-(4-Bromophenyl)pent-4-en-1-ol



155

According to GP 3, ester **154** (820 mg, 2.90 mmol) was treated with $LiAlH_4$, which after flash column chromatography (1→2:1 Et_2O:PE), gave alcohol **155** (592 mg, 2.47 mmol, 85%) as a waxy white solid, *m.p.* 43–46 °C. $\mathbf{R}_f$ 0.17 (1:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.44–7.36 (2H, m, ArH), 7.24–7.16 (2H, m, ArH), 6.36 (1H, d, J = 15.9 Hz, ArCH=CH), 6.22 (1H, dt, J = 15.9, 6.8 Hz, ArCH=CH), 3.70 (2H, t, J = 6.5 Hz, HOCH_2), 2.30 (2H, tdd, J = 7.2, 6.8, 1.4 Hz, ArCH=CHCH_2), 1.80–1.69 (3H, m, HOCH$_2$CH_2 & OH); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 136.5 (Ar), 131.6 (PhCH=CH), 131.0 (Ar), 129.2 (PhCH=CH), 127.5 (Ar), 120.6 (Ar), 62.3 (HOCH$_2$), 32.1 (HOCH$_2$$CH_2$), 29.3 (PhCH=CH$CH_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2940 (m, C-H), 1652 (w, C=C), 1588 (w, C=C), 1353 (s), 1173 (s); **m/z** HRMS (FI) found 240.0154, $C_{11}H_{13}{}^{79}BrO$ requires 240.0150.

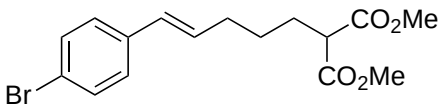
(*E*)-5-(4-Bromophenyl)pent-4-enyl methanesulfonate



422

According to GP 4, alcohol **154** (552 mg, 2.30 mmol) was treated with MsCl, which gave mesylate **422** (730 mg, 2.30 mmol, 100%) as a pale yellow oil, which was used without purification. $\mathbf{R}_f$ 0.42 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.45–7.37 (2H, m, Ar*H*), 7.23–7.17 (2H, m, Ar*H*), 6.38 (1H, d, J = 15.8 Hz, ArC*H*=CH), 6.17 (1H, dt, J = 15.8, 6.9 Hz, ArCH=C*H*), 4.27 (2H, t, J = 6.4 Hz, MsOCH_2), 3.01 (3H, s, SO_2CH_3), 2.34 (2H, tdd, J = 6.9, 6.9, 1.1 Hz, ArCH=CHCH_2), 1.99–1.89 (2H, m, $MsOCH_2CH_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 136.2 (*Ar*), 131.6 (*Ar*), 130.3 (Ar*C*H=CH), 129.2 (ArCH=*C*H), 127.6 (*Ar*), 120.9 (*Ar*), 69.2 (MsO*C*H_2), 37.4 (SO_2*C*H_3), 28.8 (*C*H_2), 28.6 (*C*H_2); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2940 (m, C-H), 1652 (w, C=C), 1589 (w, C=C), 1487 (m), 1353 (s, SO_2), 1174 (s, SO_2), 971 (m); **m/z** (ESI+) 341.0 (100%, [M(^{79}Br)+Na]$^+$), 343.0 (100%, [M(^{81}Br)+Na]$^+$), 357.0 (51%, [M(^{79}Br)+K]$^+$), 359.0 (50%, [M(^{81}Br)+K]$^+$), HRMS found 340.9828, $C_{12}H_{15}{}^{79}BrO_3S$ requires 340.9823.

(*E*)-Dimethyl 2-(5-(4-bromophenyl)pent-4-enyl)malonate

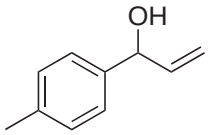


156

According to GP 5, mesylate **422** (730 mg, 2.30 mmol) was treated with DMM, which after flash column chromatography (5:1 PE:EtOAc)) gave malonate **156** (412 mg, 1.16 mmol, 51%) as a colourless oil. $\mathbf{R}_f$ 0.35 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.40 (2H, d, J = 8.5 Hz, Ar*H*), 7.19 (2H, d, J = 8.5 Hz, Ar*H*), 6.32 (1H, d, J = 15.9 Hz, ArC*H*=CH), 6.17 (1H, dt, J = 15.9, 6.8 Hz, ArCH=C*H*), 3.74 (6H, s, CO_2CH_3), 3.39 (1H, t, J = 7.5 Hz, $(CO_2Me)_2CH$), 2.23 (2H, dt, J = 6.8, 6.8 Hz, ArCH=CHCH_2), 2.00–1.88 (2H, m, CHCH_2), 1.55–1.45 (2H, m, ArCH=CHCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.8 (*C*=O), 136.5 (*Ar*), 131.5 (*Ar*), 130.6 (ArCH=*C*H), 129.4 (Ar*C*H=CH), 127.5 (*Ar*), 120.6 (*Ar*), 52.5 (CO_2*C*H_3), 51.5 (*C*H(CO_2Me)$_2$), 32.5 (ArCH=CH*C*H_2), 28.4 (CH*C*H_2), 26.9 (ArCH=CHCH$_2$*C*H_2); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2953 (m, C-H), 1735 (s, C=O), 1652 (w, C=C), 1589 (w, C=C), 1437 (s), 1151 (s); **m/z** (ESI+) 377.1 (87%, [M(^{79}Br)+Na]$^+$), 379.1 (87%, [M(^{81}Br)+Na]$^+$), HRMS found 377.0374, $C_{16}H_{19}{}^{79}BrNaO_4$ requires

377.0364.

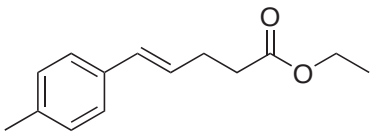
1-*p*-Tolylprop-2-en-1-ol



157

According to GP 1, 4-methylbenzaldehyde (2.40 g, 20.0 mmol) was treated with vinylmagnesium bromide, which gave alcohol **157** (2.96 g, 20.0 mmol, 100%) as a pale yellow oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.28 (2H, d, J = 7.9 Hz, ArH), 7.19 (2H, d, J = 7.9 Hz, ArH), 6.06 (1H, ddd, J = 17.0, 10.3, 6.0 Hz, H_2C=CH), 5.19 (1H, d, J = 10.3 Hz, CH=CHH), 5.35 (1H, d, J = 17.0 Hz, CH=CHH), 5.16 (1H, d, J 6.0 Hz, HOCH), 2.50 (1H, br s, OH), 2.37 (3H, s, ArCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 140.4 (H_2C=CH), 139.8 (Ar), 137.4 (Ar), 129.1 (Ar), 126.3 (Ar), 114.8 (CH=CH$_2$), 75.1 (HOCH), 21.1 (ArCH$_3$). *Data are consistent with literature values.*[157]

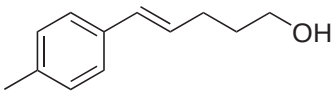
(*E*)-Ethyl 5-*p*-tolylpent-4-enoate



158

According to GP 2, alcohol **157** (3.00 g, 20.0 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (15:1 PE:EtOAc), gave ester **158** (919 mg, 4.22 mmol, 21%) as a colourless oil. $\mathbf{R}_f$ = 0.56 (5:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.25 (2H, d, J = 8.0 Hz, ArH), 7.12 (2H, d, J = 8.0 Hz, ArH), 6.42 (1H, d, J = 15.8 Hz, ArCH=CH), 6.17 (1H, dt, J = 15.8, 6.5 Hz, ArCH=CH), 4.17 (2H, q, J = 7.1 Hz, OCH_2CH$_3$), 2.58–2.45 (4H, m, CH_2CH_2), 2.35 (3H, s, ArCH_3), 1.28 (3H, t, J = 7.1 Hz, OCH$_2$CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.0 (C=O), 136.8 (Ar), 134.6 (Ar), 130.8 (ArCH=CH), 129.2 (Ar), 127.4 (ArCH=CH), 125.9 (Ar), 60.4 (OCH$_2$), 34.1 (CH$_2$), 28.3 (CH$_2$), 21.1 (OCH$_2$$CH_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2981 (m), 1735 (s, C=O), 1610 (w, C=C), 1158 (m), 967 (m); **m/z** (ESI+) 219.1 ([M+H]$^+$, 17%), 241.1 ([M+Na]$^+$, 100%), HRMS found 241.1199, $C_{14}H_{18}NaO_2$ requires 241.1199.

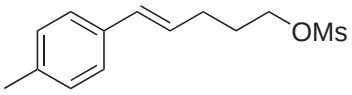
(*E*)-5-*p*-Tolylpent-4-en-1-ol



159

According to GP 3, ester **158** (919 mg, 4.21 mmol) was treated with $LiAlH_4$, which after recrystallisation from hexane/EtOAc, gave alcohol **159** (589 mg, 3.33 mmol, 79%) as a white solid *m.p.* 42–43 °C (*lit.*[158] 43 °C). $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.25 (2H, d, J = 8.0 Hz, ArH), 7.12 (2H, d, J = 8.0 Hz, ArH), 6.40 (1H, d, J = 15.8 Hz, ArCH=CH), 6.19 (1H, dt, J = 15.8, 6.9 Hz, ArCH=CH), 3.72 (2H, t, J = 6.4 Hz, HOCH_2), 2.38–2.25 (5H, m, CH_3 & CH_2), 1.81–1.72 (2H, m, CH_2), 1.43 (1H, br s, OH); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 136.7 (*Ar*), 134.8 (*Ar*), 130.2 (Ar*C*H=CH), 129.2 (*Ar*), 129.0 (ArCH=*C*H), 125.8 (*Ar*), 62.4 (HO*C*H_2), 32.3 (HOCH$_2$*C*H_2), 29.3 (ArCH=CH*C*H_2), 21.1 (*C*H_3). *Data are consistent with literature values.*[158]

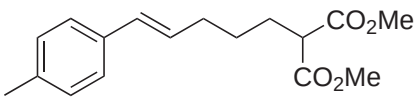
(*E*)-5-*p*-Tolylpent-4-enyl methanesulfonate



423

According to GP 4, alcohol **159** (176 mg, 1.00 mmol) was treated with MsCl, which gave mesylate **423** (250 mg, 0.98 mmol, 98%) as a pale yellow oil, which was used without purification. $\mathbf{R}_f$ 0.37 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.24 (2H, d, J = 8.1 Hz, ArH), 7.12 (2H, d, J = 8.1 Hz, ArH), 6.41 (1H, d, J = 15.8 Hz, ArCH=CH), 6.12 (1H, dt, J = 15.8, 7.0 Hz, ArCH=CH), 4.29 (2H, t, J = 6.4 Hz, MsOCH_2), 3.01 (3H, s, SO_2CH_3), 2.42–2.30 (m, 2H, ArCH=CHCH_2), 2.34 (3H, ArCH_3), 2.01–1.88 (2H, MsOCH$_2$CH_2); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 137.0 (*Ar*), 134.4 (*Ar*), 131.3 (Ar*C*H=CH), 129.2 (*Ar*), 127.2 (ArCH=*C*H), 125.9 (*Ar*), 69.3 (MsO*C*H_2), 37.4 (SO_2*C*H_3), 28.8 (*C*H_2), 28.8 (*C*H_2), 21.1 (Ar*C*H_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2940 (m, C-H), 1513 (m), 1353 (s, SO_2), 1173 (s, SO_2), 970 (m), 926 (m); **m/z** (ESI+) 277.1 ([M+Na]$^+$, 100%), HRMS found 277.0866, $C_{13}H_{18}NaO_3S$ requires 277.0869.

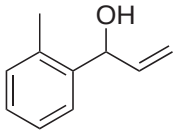
(*E*)-Dimethyl 2-(5-*p*-tolylpent-4-enyl)malonate



160

According to GP 5, mesylate **423** (250 mg, 0.98 mmol) was treated with DMM. which after flash column chromatography (4:1 PE:Et_2O), gave malonate **160** (188 mg, 0.65 mmol, 66%) as a colourless oil. $\mathbf{R}_f$ 0.34 (3:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.25 (2H, d, J = 8.0 Hz, ArH), 7.11 (2H, d, J = 8.0 Hz, ArH), 6.38 (1H, d, J = 15.8 Hz, ArCH=CH), 6.14 (1H, dt, J = 15.8, 7.0 Hz, ArCH=CH), 3.75 (6H, s, (OCH_3)$_2$), 3.41 (1H, t, J = 7.5 Hz, CH(CO_2Me)$_2$), 2.34 (3H, s, ArCH_3), 2.25 (2H, td, J = 7.1, 7.0 Hz, ArCH=CHCH_2), 1.98 (2H, td, = 7.5, 5.7 Hz, (MeO_2C)$_2$CHCH_2), 1.56–1.47 (2H, m, CH=CHCH_2CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.8 (C=O), 136.6 (Ar), 134.8 (Ar), 130.3 (ArCH=CH), 129.1 (Ar), 128.7 (ArCH=CH), 125.9 (Ar), 52.5 (CO_2CH$_3$), 51.6 ((MeO_2C)$_2C$H), 32.5 (ArCH=CHCH$_2$), 28.4 ((MeO_2C)$_2$CHCH$_2$), 27.1 (CH=CHCH$_2C$H$_2$), 21.1 (ArCH$_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2953 (m, C-H), 1737 (s, C=O), 1610 (w, C=C), 1437 (s), 1151 (m); **m/z** (ESI+) 313.1 ([M+Na]$^+$, 100%), 603.3 ([2M+Na]$^+$, 61%), HRMS found 313.1417, $C_{17}H_{22}NaO_4$ requires 313.1410.

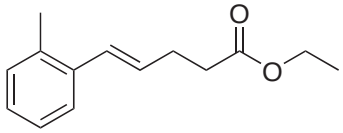
1-*o*-Tolylprop-2-en-1-ol



161

According to GP 1, *o*-tolualdehyde (1.20 g, 10.0 mmol) was treated with vinylmagnesium bromide, which gave alcohol **161** (1.41, 9.51 mmol, 95%) as a golden oil, which was used without purification. $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.48–7.44 (1H, m, ArH), 7.28–7.14 (3H, m, ArH), 6.03 (1H, ddd, J = 17.1, 10.3, 5.7 Hz, H_2C=CH), 5.41 (1H, d, J = 5.7 Hz, HOCH), 5.31 (1H, dd, J = 17.1, 1.3 Hz, CH=CHH), 5.21 (1H, dd, J = 10.3, 1.3 Hz, CH=CHH), 2.36 (3H, s, ArCH_3), 2.17 (1H, br s, OH); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 140.4 (Ar), 139.4 (COHCH=CH_2), 135.3 (Ar), 130.5 (Ar), 127.6 (Ar), 126.3 (Ar), 125.8 (Ar), 115.2 (COHCH=CH$_2$), 72.0 (ArCHOH), 19.1 (ArCH$_3$). *Data are consistent with literature values.*[153]

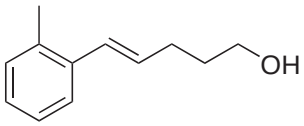
(*E*)-Ethyl 5-*o*-tolylpent-4-enoate



162

According to GP 2, alcohol **161** (1.40 g, 9.50 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (20:1 PE:EtOAc), gave ester **162** (1.30 g, 6.00 mmol, 63%) as a colourless oil. $\mathbf{R}_f$ 0.49 (5:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.43–7.38 (1H, m, ArH), 7.22–7.09 (3H, m, ArH), 6.66 (1H, d, J = 15.7 Hz, ArCH=CH), 6.10 (1H, dt, J = 15.7 Hz, 6.6 Hz, ArCH=CH), 4.18 (2H, q, J = 7.1 Hz, OCH_2), 2.59 (2H, td, J = 6.8, 6.6 Hz, ArCH=CHCH_2), 2.54–2.48 (2H, m, EtO_2CCH_2), 1.29 (3H, t, J = 7.1 Hz, OCH_2CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 173.0 (C=O), 136.6 (Ar), 135.0 (Ar), 130.2 (Ar), 129.9 (ArCH=CH), 128.8 (ArCH=CH), 127.1 (Ar), 126.0 (Ar), 125.5 (Ar), 60.4 (OCH_2CH_3), 34.2 (EtO_2CCH_2), 28.6 (ArCH=CHCH_2), 19.8 (ArCH_3), 14.3 (OCH_2CH_3); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2981 (m, C-H), 1735 (s, C=O), 1650 (w, C=C), 1179 (m), 966 (m); **m/z** (ESI+) 241.1 ($[M+Na]^+$, 100%), HRMS found 241.1198, $C_{14}H_{18}NaO_2$ requires 241.1199.

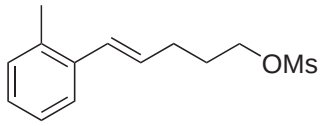
(*E*)-5-*o*-tolylpent-4-en-1-ol



163

According to GP 3, ester **162** (1.26 g, 5.8 mmol) was treated with $LiAlH_4$, which after flash column chromatography (1:1 PE:Et_2O), gave alcohol **163** (762 mg, 4.32 mmol, 75%) as a colourless oil. $\mathbf{R}_f$ 0.19 (1:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.46 (1H, d, J = 6.2 Hz, ArH), 7.24–7.15 (3H, m, ArH), 6.67 (1H, d, J = 15.7 Hz, ArCH=CH), 6.15 (1H, dt, J = 15.7, 6.9 Hz, ArCH=CH), 3.74 (2H, t, J = 6.5 Hz, HOCH_2), 2.41–2.32 (5H, m, ArCH_3 & ArCH=CHCH_2), 2.22 (1H, br s, OH), 1.85–1.75 (2H, m, $HOCH_2CH_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 136.8 (Ar), 135.0 (Ar), 131.5 (ArCH=CH), 130.2 (Ar), 128.2 (ArCH=CH), 127.0 (Ar), 126.1 (Ar), 125.5 (Ar), 62.3 ($HOCH_2$), 32.4 ($HOCH_2CH_2$), 29.7 (ArCH=CHCH_2), 19.9 (ArCH_3); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 3334 (br, O-H), 2935 (s, C-H), 1649 (w, C=C), 1601 (w, C=C), 1483 (m), 1056 (m), 996 (s); **m/z** HRMS (FI) found 176.1201, $C_{12}H_{16}O$ requires 176.1201.

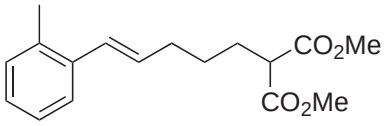
(*E*)-5-*o*-tolylpent-4-enyl methanesulfonate



424

According to GP 4, alcohol **163** (696 mg, 3.95 mmol) was treated with MsCl, which gave mesylate **424** (1.00 g, 3.95 mmol, 100%) as a pale yellow oil, which was used without purification. $\mathbf{R}_f$ 0.12 (2:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.44–7.38 (1H, m, Ar*H*), 7.21–7.09 (3H, m, Ar*H*), 6.65 (1H, d, J = 15.7 Hz, ArC*H*=CH), 6.05 (1H, dt, J = 15.7, 7.0 Hz, ArCH=C*H*), 4.29 (2H, t, J = 6.4 Hz, MsOCH_2), 3.01 (3H, s, SO_2CH_3), 2.42–2.35 (2H, m, ArCH=CHCH_2), 2.34 (3H, s, ArCH_3), 1.95 (2H, tt, J = 6.4, 6.4 Hz, $MsOCH_2CH_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 136.4 (*Ar*), 135.0 (*Ar*), 130.2 (*Ar*), 129.7 (ArCH=*C*H), 129.3 (Ar*C*H=CH), 127.2 (*Ar*), 126.1 (*Ar*), 125.5 (*Ar*), 69.4 (MsO*C*H_2), 37.3 ($SO_2C$$H_3$), 29.1 (ArCH=CH*C*$H_2$), 28.8 ($MsOCH_2C$$H_2$), 19.8 (Ar*C*$H_3$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2941 (m, C-H), 1648 (w, C=C), 1482 (m), 1353 (s, SO_2), 1174 (s, SO_2), 970 (s), 927 (s); **m/z** (ESI+) 277.1 ($[M+Na]^+$, 94%), HRMS found 277.0869, $C_{13}H_{18}NaO_3S$ requires 277.0869.

(*E*)-Dimethyl 2-(5-*o*-tolylpent-4-enyl)malonate

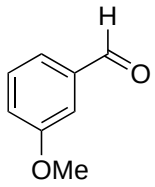


164

According to GP 5, mesylate **424** (941 mg, 3.70 mmol) was treated with DMM, which after flash column chromatography (4:1 PE:Et_2O), gave malonate **164** (919 mg, 3.17 mmol, 86%) as a colourless oil. $\mathbf{R}_f$ 0.35 (2:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.41 (1H, d, J = 6.2 Hz, Ar*H*), 7.21–7.09 (3H, m, Ar*H*), 6.60 (1H, d, J = 15.7 Hz, ArC*H*=CH), 6.06 (1H, dt, J = 15.7, 7.0 Hz, ArCH=C*H*), 3.76 (6H, s, CO_2CH_3), 3.42 (1H, t, J = 7.5 Hz, $(MeO_2C)_2CH$), 2.34 (3H, s, ArCH_3), 2.29 (2H, tdd, J = 7.4, 7.0, 0.9 Hz, ArCH=CHCH_2), 2.04–1.94 (2H, m, $(MeO_2C)_2CHCH_2$), 1.58–1.48 (2H, m, $ArCH{=}CHCH_2CH_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.8 (*C*O_2Me), 136.8 (*Ar*), 134.9 (*Ar*), 131.1 (ArCH=*C*H), 130.2 (*Ar*), 128.4 (Ar*C*H=CH), 126.9 (*Ar*), 126.0 (*Ar*), 125.5 (*Ar*), 52.5 ($CO_2C$$H_3$), 51.6 ($(MeO_2C)_2C$H), 32.8 (ArCH=CHC$H_2$), 28.4 ($(MeO_2C)_2CHC$$H_2$), 27.1 ($ArCH{=}CHCH_2C$$H_2$), 19.8 (Ar*C*$H_3$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2953 (m, C-H), 1737

(s, C=O), 1649 (w, C=C), 1601 (w, C=C), 1437 (m), 1151 (m), 968 (m); **m/z** (ESI+) 313.1 ($[M+Na]^+$, 100%), 603.3 ($[2M+Na]^+$, 62%), HRMS found 313.1411, $C_{17}H_{22}NaO_4$ requires 313.1410.

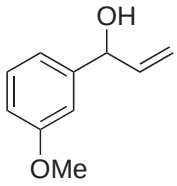
3-Methoxybenzaldehyde



425

To a stirred solution of 3-hydroxybenzaldehyde (1.22 g, 10.0 mmol) and K_2CO_3 (2.76 g, 20.0 mmol) in acetone (50 mL) at 0 °C was added MeI (0.93 mL, 15.0 mmol). The solution was heated under reflux for 3 h. After cooling to RT, the solution was poured on to water (50 mL). The aqueous layer was extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*, which gave aldehyde **425** (1.32 g, 9.69 mmol, 97%) as a pale yellow oil which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.99 (1H, s, C*H*O), 7.18–7.45 (4H, m, Ar*H*), 3.88 (3H, s, OCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 192.2 (*C*HO), 160.2 (*Ar*), 137.9 (*Ar*), 130.1 (*Ar*), 123.5 (*Ar*), 121.5 (*Ar*), 112.2 (*Ar*), 55.5 (O*C*H_3). *Data are consistent with literature values.*[159]

1-(3-Methoxyphenyl)prop-2-en-1-ol

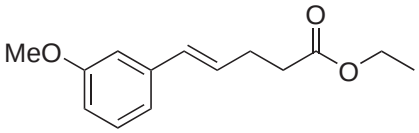


165

According to GP 1, 3-methoxybenzaldehyde (1.40 g, 10.3 mmol) was treated with vinylmagnesium bromide, which after flash column chromatography (1:1 PE:EtOAc), gave alcohol **165** (1.07 g, 6.50 mmol, 63%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.31–7.26 (1H, m, Ar*H*), 6.98–6.93 (2H, m, Ar*H*), 6.88–6.80 (1H, m, Ar*H*), 6.05 (1H, ddd, J = 17.0, 10.2, 6.1 Hz, H_2C=C*H*), 5.37 (1H, ddd, J = 17.0, 1.3, 1.3 Hz, CH=C*H*H), 5.25–5.16 (2H, m, CH=CH*H* & HOC*H*), 3.82 (3H, OCH_3), 1.98 (1H, br s, O*H*); $\boldsymbol{\delta_C}$ (50 MHz, $CDCl_3$) 160.3 (*Ar*), 144.2 (*Ar*), 140.6 (H_2C=*C*H), 130.0 (*Ar*), 119.1 (*Ar*), 115.6 (*Ar*), 113.8

(*Ar*), 112.2 (CH=*C*H$_2$), 75.7 (HO*C*H), 55.7 (O*C*H$_3$). *Data are consistent with literature values.*[160]

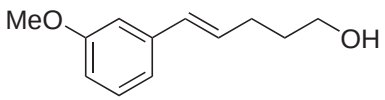
(*E*)-Ethyl 5-(3-methoxyphenyl)pent-4-enoate



166

According to GP 2, alcohol **165** (1.07 g, 6.50 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (15→10:1 PE:EtOAc), gave ester **166** (866 mg, 3.70 mmol, 57%) as a colourless oil. $\mathbf{R}_f$ 0.53 (4:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.28–7.18 (1H, m, *Ar*), 6.97–6.74 (3H, m, *Ar*), 6.41 (1H, d, J = 15.8 Hz, ArC*H*=CH), 6.22 (1H, dt, J = 15.8, 6.4 Hz, ArCH=C*H*), 4.16 (2H, q, J = 7.1 Hz, OCH_2), 3.81 (3H, s, OCH_3), 2.60–2.45 (4H, m, CH_2CH_2), 1.27 (3H, t, J = 7.1 Hz, OCH$_2$CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 173.0 (*C*=O), 159.8 (*Ar*), 138.9 (*Ar*), 130.8 (Ar*C*H=CH), 129.5 (ArCH=*C*H), 128.8 (*Ar*), 118.7 (*Ar*), 112.7 (*Ar*), 111.4 (*Ar*), 60.4 (CO*C*H$_2$), 55.2 (O*C*H$_3$), 34.0 (*C*H$_2$), 28.3 (*C*H$_2$), 14.3 (OCH$_2$*C*H$_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2940 (m, C-H), 1734 (s, C=O), 1651 (w, C=C), 1600 (m, aromatic), 1582 (m, aromatic), 1262 (m), 1158 (s), 1044 (m); **m/z** (ESI+) 257.1 ([M+Na]$^+$, 100%), HRMS found 257.1149, $C_{14}H_{18}NaO_3$ requires 257.1148.

(*E*)-5-(3-Methoxyphenyl)pent-4-en-1-ol

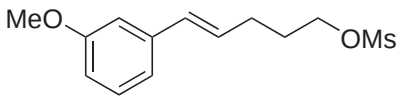


167

According to GP 3, ester **166** (577 mg, 2.46 mmol) was treated with $LiAlH_4$, which after flash column chromatography (3→1:1 PE:EtOAc), gave alcohol **167** (355 mg, 2.19 mmol, 89%) as a colourless oil. $\mathbf{R}_f$ 0.10 (4:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.28–7.19 (1H, m, Ar*H*), 6.95 (1H, d, J = 8.0 Hz, Ar*H*), 6.89 (1H, s, *Ar*), 6.77 (1H, dd, J = 8.0, 2.5 Hz, Ar*H*), 6.40 (1H, d, J = 15.8 Hz, ArC*H*=CH), 6.24 (1H, dt, J = 15.8, 7.0 Hz, ArCH=C*H*), 3.82 (3H, s, OCH_3), 3.72 (2H, J = 6.5 Hz, HOCH_2), 2.32 (2H, td, J = 7.2, 7.0 Hz, ArCH=CHCH_2), 1.82–1.71 (2H, m, HOCH$_2$CH_2), 1.53 (1H, br s, O*H*); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 159.8 (*Ar*), 139.1 (*Ar*), 130.4 (*Ar*), 130.3 (Ar*C*H=CH), 129.5 (ArCH=*C*H), 118.6 (*Ar*), 112.6 (*Ar*), 111.3 (*Ar*), 62.4 (HO*C*H$_2$), 55.2 (O*C*H$_3$), 32.2 (ArCH=CH*C*H$_2$), 29.3 (HOCH$_2$*C*H$_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 3357 (br, O-H), 2938 (m, C-H), 1653 (w, C=C), 1601 (s, aromatic), 1581 (s, aromatic), 1263

(s), 1157 (s), 1046 (s), 968 (m); **m/z** (FI) found 192.1149, $C_{12}H_{16}O_2$ requires 192.1150.

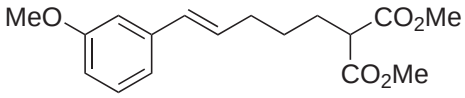
(*E*)-5-(3-Methoxyphenyl)pent-4-enyl methanesulfonate



426

According to GP 4, alcohol **167** (192 mg, 1.00 mmol) was treated with MsCl, which gave mesylate **426** (270 mg, 1.00 mmol, 100%) as a pale yellow oil, which was used without purification. $\mathbf{R}_f$ 0.39 (1:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.28–7.20 (1H, m, Ar*H*), 6.94 (1H, d, J = 8.0 Hz, Ar*H*), 6.89 (1H, s, Ar*H*), 6.78 (1H, d, J = 8.0 Hz, Ar*H*), 6.42 (1H, d, J = 15.8 Hz, ArC*H*=CH), 6.23–6.13 (1H, m, ArCH=C*H*), 4.28 (2H, t, J = 7.1 Hz, MsOCH_2), 3.82 (3H, s, OCH_3), 3.01 (3H, s, SO_2CH_3), 2.36 (2H, dt, J = 7.1, 7.1 Hz, ArCH=CHCH_2), 1.95 (2H, tt, J = 7.1, 7.1 Hz, MsOCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 159.8 (*Ar*), 138.7 (*Ar*), 131.3 (*Ar*), 129.5 (Ar*C*H=CH), 128.6 (ArCH=*C*H), 118.7 (*Ar*), 112.8 (*Ar*), 111.4 (*Ar*), 69.3 (MsO*C*H$_2$), 55.2 (O*C*H$_3$), 37.4 (SO_2*C*H$_3$), 28.8 (ArCH=CH*C*H$_2$), 28.7 (MsOCH$_2$*C*H$_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2940 (m), 1651 (w C=C), 1600 (w C=C), 1352 (s SO_2), 1173 (s SO_2), 970 (m); **m/z** (ESI+) 293.1 ([M+Na]$^+$, 100%), HRMS found 293.0819, $C_{13}H_{18}NaO_4S$ requires 293.0818.

(*E*)-Dimethyl 2-(5-(3-methoxyphenyl)pent-4-enyl)malonate

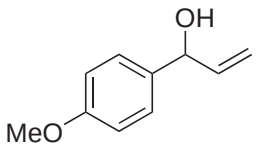


168

According to GP 5, mesylate **426** (270 mg, 1.00 mmol) was treated with DMM, which after flash column chromatography (10:1 PE:EtOAc), gave malonate **168** (213 mg, 0.700 mmol, 70%) as a colourless oil. $\mathbf{R}_f$ 0.38 (1:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.20 (1H, t, J = 7.6 Hz, Ar*H*), 6.94 (1H, d, J = 7.6 Hz, Ar*H*), 6.88 (1H, s, Ar*H*), 6.77 (1H, d, J = 7.6 Hz Ar*H*), 6.37 (1H, d, J = 15.8 Hz, ArC*H*=CH), 6.18 (1H, dt, J = 15.8, 7.0 Hz, ArCH=C*H*), 3.82 (3H, s, ArOCH_3), 3.75 (6H, s, CO_2CH_3), 3.40 (1H, t, J = 7.5 Hz, (MeO$_2$C)$_2$C*H*), 2.25 (2H, dt, J = 7.0, 7.0 Hz, CH=CHCH_2), 1.97 (2H, td, J = 7.7, 7.5 Hz, ((MeO$_2$C)$_2$CHCH_2), 1.57–1.45 (2H, m, CH=CHCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.8 (*C*=O), 159.8 (*Ar*), 139.1 (*Ar*), 130.4 (Ar*C*H=CH), 130.1 (ArCH=*C*H), 129.4 (*Ar*), 118.6 (*Ar*), 112.6 (*Ar*), 111.3 (*Ar*), 55.2 (ArO*C*H$_3$), 52.5 (CO_2*C*H$_3$), 51.6 ((MeO$_2$C)$_2$*C*H), 32.5 (CH=CH*C*H), 28.4 ((MeO$_2$C)$_2$CH*C*H$_2$), 27.0 (CH=CHCH$_2$*C*H$_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2954 (m, C-H), 1735 (s, C=O), 1656 (s, aromatic), 1581 (s,

aromatic), 1435 (m), 1154 (s), 967 (m); **m/z** (ESI+) 329.1 ([M+Na]$^+$, 100%), 635.3 ([2M+Na]$^+$, 30%), HRMS found 329.1366, $C_{17}H_{22}NaO_5$ requires 329.1359.

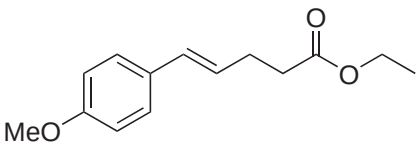
1-(4-Methoxyphenyl)prop-2-en-1-ol



169

According to GP 1, 4-methoxybenzaldehyde (5.45 g, 40.0 mmol) was treated with vinylmagnesium bromide, which gave alcohol **169** as a yellow oil (6.43 g, 39.1 mmol, 98%), which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.30 (2H, d, J = 8.6 Hz, ArH), 6.90 (2H, d, J = 8.6 Hz, ArH), 6.05 (1H, ddd, J = 17.1, 10.3, 5.9 Hz, H_2C=CH), 5.35 (1H, dd, J = 17.1, 1.4 Hz, CH=CHH), 5.16–5.22 (2H, CH=CHH & CHOH), 3.81 (3H, s, OCH_3), 1.94 (1H, br s, OH); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 159.2 (Ar), 140.4 (H_2C=CH), 134.9 (Ar), 127.7 (Ar), 114.7 (CH=CH$_2$), 113.9 (Ar), 74.8 (CHOH), 55.3 (OCH$_3$). *Data are consistent with literature values.*[156]

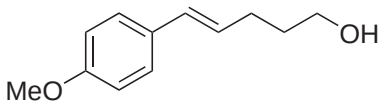
(*E*)-Ethyl 5-(4-methoxyphenyl)pent-4-enoate



170

According to GP 2, alcohol **169** (6.40 g, 39.0 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (15:1 PE:EtOAc) gave ester **170** (1.85 g, 7.9 mmol, 20%) as a colourless oil, characterised as a 3:1 mixture of E:Z isomers. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.31–7.22 (2H, m, ArH), 6.84 (2H, d, J = 8.8 Hz, ArH), 6.38 (1H, d, J = 15.8 Hz, ArCH=CH), 6.07 (1H, dt, J = 15.8, 6.1 Hz, ArCH=CH), 4.15 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.80 (3H, s, ArOCH_3), 2.57–2.43 (4H, m, CH_2CH_2), 1.27 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.1 (C=O), 158.8 (Ar), 130.3 (ArCH=CH), 127.8 (Ar), 127.1 (Ar), 126.3 (ArCH=CH), 113.9 (Ar), 60.3 ($CO_2CH_2CH_3$), 55.3 (ArOCH$_3$), 34.2 (CH$_2$), 28.3 (CH$_2$), 14.3 ($CO_2CH_2CH_3$). *Data are consistent with literature values.*[155]

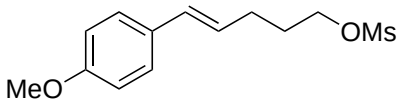
(*E*)-5-(4-Methoxyphenyl)pent-4-en-1-ol



171

According to GP 3, ester **170** (1.83 g, 7.82 mmol) was treated with $LiAlH_4$, which after recrystallisation from hexane/EtOAc gave alcohol **171** (783 mg, 4.08 mmol, 52%) as a white solid *m.p.* 71–73 °C. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.28 (2H, d, J = 8.8 Hz, ArH), 6.85 (2H, d, J = 8.8 Hz, ArH), 6.37 (1H, d, J = 15.8 Hz, ArCH=CH), 6.10 (1H, dt, J = 15.8, 6.9 Hz, ArCH=CH), 3.81 (3H, s, OCH_3), 3.71 (2H, t, J = 6.2 Hz, HOCH_2), 2.30 (2H, dt, J = 6.9, 6.7 Hz, ArCH=CHCH_2), 1.75 (2H, tt, J = 6.7, 6.7 Hz, HOCH$_2$CH_2); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 158.7 (*Ar*), 129.7 (ArCH=*C*H), 127.9 (*Ar*), 127.7 (*Ar*), 127.0 (*Ar*), 113.9 (Ar*C*H=CH), 62.5 (HO*C*H$_2$), 55.3 (ArO*C*H$_3$), 32.4 (HOCH$_2$*C*H$_2$), 29.3 (ArCH=CH*C*H$_2$). *Data are consistent with literature values.*[154]

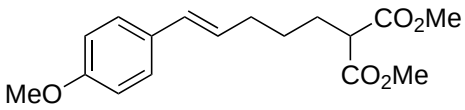
(*E*)-5-(4-Methoxyphenyl)pent-4-enyl methanesulfonate



427

According to GP 4, alcohol **171** (806 mg, 4.23 mmol) was treated with MsCl, which gave mesylate **427** as a pale yellow oil (1.19 g, 4.22 mmol, 100%), which was used without purification. A small amount was purified by flash column chromatography (2:1 PE:EtOAc), which gave an analytically pure sample. $\mathbf{R}_f$ 0.43 (1:1 PE:EtOAC) $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.29 (2H, d, J = 8.8 Hz, ArH), 6.86 (2H, d, J = 8.8 Hz, ArH), 6.39 (1H, d, J = 15.8 Hz, ArCH=CH), 6.04 (1H, dt, J = 15.8, 7.0 Hz, ArCH=CH), 4.29 (2H, t, J = 6.4 Hz, MsO*C*H$_2$), 3.82 (3H, s, ArO*C*H$_3$), 3.02 (3H, s, SO$_2$*C*H$_3$), 2.34 (2H, app q, J = 7.2 Hz, ArCH=CH*C*H$_2$), 2.00–1.89 (2H, m, MsOCH$_2$*C*H$_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 159.3 (*Ar*), 131.2 (*Ar*), 130.5 (ArCH=*C*H), 127.5 (*Ar*), 126.5 (*Ar*), 114.4 (Ar*C*H=CH), 69.8 (MsO*C*H$_2$), 55.7 (ArO*C*H$_3$), 37.8 (SO$_2$*C*H$_3$), 29.3 (MsOCH$_2$*C*H$_2$), 29.2 (ArCH=CH*C*H$_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2938 (m, C-H), 1607 (w, C=C), 1509 (s), 1350 (s, SO$_2$), 1246 (s), 1172 (s, SO$_2$); **m/z** (ESI+) 271.1 ([M+H]$^+$, 45%), 291.1 ([M+Na]$^+$, 100%), 563.2 ([2M+Na]$^+$, 20%), HRMS found 293.0819, $C_{13}H_{18}NaO_4S$ requires 293.0818.

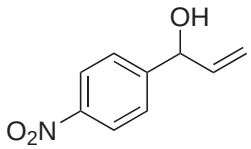
(*E*)-Dimethyl 2-(5-(4-methoxyphenyl)pent-4-enyl)malonate



172

According to GP 5, mesylate **427** (1.14 g, 4.23 mmol) was treated with DMM, which after flash column chromatography (10→5:1 PE:EtOAc), gave malonate **172** (802 mg, 2.62 mmol, 62%) as a colourless oil characterised as a 10:1 mixture with *p*-anisaldehyde*. $\mathbf{R}_f$ 0.40 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.30–7.24 (2H, m, Ar*H*), 6.84 (2H, d, $J = 6.6$ Hz, Ar*H*), 6.34 (1H, d, $J = 15.8$ Hz, ArC*H*=CH), 6.11–5.93 (1H, m, ArCH=C*H*), 3.75 (6H, s, CO_2CH_3), 3.81 (3H, s, $ArOCH_3$), 3.44–3.37 (1H, m, $(MeO_2C)_2CH$), 2.31–2.17 (2H, m, ArCH=CHCH_2), 2.04–1.89 (2H, m, CHCH_2), 1.58–1.40 (2H, m, $CHCH_2CH_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 170.2 (*C*=O), 159.1 (*Ar*), 132.7 (*Ar*), 130.2 (ArCH=*C*H), 128.0 (*Ar*), 127.4 (*Ar*), 114.3 (Ar*C*H=CH), 55.7 ($ArOCH_3$), 52.9 (CO_2CH_3), 52.0 ($(MeO_2C)_2CH$), 32.9 (ArCH=CH*C*H_2), 28.8 (CH*C*H_2), 27.6 ($CHCH_2CH_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2954 (s, C-H), 1734 (s, C=O), 1607 (m, C=C), 1578 (w, C=C), 1512 (m), 1033 (m), 835 (m); **m/z** (ESI+) 329.1 ($[M+Na]^+$, 100%), 635.3 ($[2M+Na]^+$, 32%), HRMS found 329.1360, $C_{17}H_{22}NaO_5$ requires 329.1359.

1-(4-Nitrophenyl)prop-2-en-1-ol



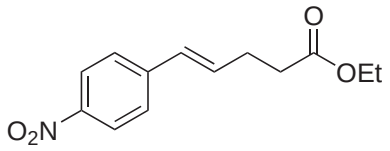
177

According to the modified GP 1, 4-nitrobenzaldehyde (151 mg, 1.00 mmol) was dissolved in dry THF (5 mL) and cooled to -78 °C after which vinylmagnesium bromide (1 M in THF, 1.00 mL, 1.00 mmol) was added dropwise. The solution was stirred for 2 h and quenched by the addition of 80% saturated aqueous NH_4Cl solution (5 mL) followed by EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*, which gave alcohol **177** (166 mg, 0.927 mmol, 93%) as a yellow oil, which was used without purification. $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 8.10 (2H, d, $J = 8.6$ Hz, Ar*H*), 7.50 (2H, d, $J = 8.6$ Hz, Ar*H*), 5.94 (1H, ddd, $J = 17.0$, 10.2, 6.4 Hz, C*H*=CH_2), 5.33 (1H, d, $J = 17.0$ Hz,

*The product is prone to aerobic oxidation, with *p*-anisaldehyde evident by both ^{1}H and ^{13}C NMR.

CH=C*H*H), 5.26 (1H, d, J = 6.4 Hz, ArC*H*OH), 5.20 (1H, dd, J = 10.3, 0.6 Hz, CH=CH*H*), 3.21 (1H, br s, O*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 150.0 (*Ar*), 147.1 (*Ar*), 139.1 (*C*H=CH_2), 127.0 (*Ar*), 123.6 (*Ar*), 116.6 (CH=*C*H_2), 74.4 (Ar*C*HOH). *Data are consistent with literature values.*[153]

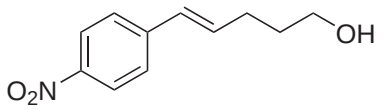
(*E*)-Ethyl 5-(4-nitrophenyl)pent-4-enoate



178

According to GP 2, alcohol **177** (1.09 g, 6.10 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (8:1 PE:EtOAc), gave ester **178** (1.22 g, 4.90 mmol, 80%) as yellow crystals, *m.p.* 27–29 °C. $\mathbf{R}_f$ 0.18 (10:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.14 (2H, d, J = 8.6 Hz, *Ar*), 7.45 (2H, d, J = 8.6 Hz, *Ar*), 6.53–6.38 (2H, m, C*H*=C*H*), 4.15 (2H, q, J = 7.1 Hz, OC$H_2$$CH_3$), 2.59 (2H, dt, J = 6.9, 6.8 Hz, ArCH=CHCH_2), 2.51 (2H, t, J = 6.8 Hz, EtO_2CCH_2), 1.25 (3H, t, J = 7.1 Hz, OCH_2CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$); 172.6 (*C*=O), 146.6 (*Ar*), 143.8 (*Ar*), 133.9 (*C*H=*C*H), 129.2 (*C*H=*C*H), 126.5 (*Ar*), 123.9 (*Ar*), 60.5 (O*C*H_2), 33.5 (ArCH=CH*C*H_2), 28.3 (EtO_2C*C*H_2), 14.2 (OCH_2*C*H_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2983 (m) 1732 (s C=)) 1650 (w C=C) 1596 (m) 1516 (s N=O) 1343 (s N=O); **m/z** (ESI+) 272.1 ([M+Na]$^+$, 100%), 521.2 ([2M+Na]$^+$, 51%), HRMS found 272.0896, $C_{13}H_{15}NNaO_4$ requires 272.0893.

(*E*)-5-(4-Nitrophenyl)pent-4-en-1-ol

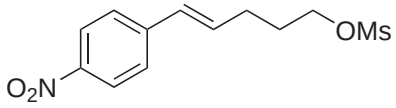


179

To a stirred solution of ester **178** (100 mg, 0.40 mmol) in dry DCM (2.9 mL) was added DiBAl-H (1.5 M in toluene, 0.55 mL, 0.82 mmol) dropwise at –78 °C. After 3 h, the reaction was quenched with Rochelle's salt (2.9 mL) and the solution was stirred vigourously overnight. The layers were separated and the aqueous was extracted with EtOAc (3×5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (1:1 PE:EtOAc), which gave **179** (64 mg, 0.31 mmol, 77%) as orange crystals *m.p.* 42–44 °C

(lit. 53–54 °C). $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.12 (2H, d, J = 8.8 Hz, ArH), 7.43 (2H, d, J = 8.8 Hz, ArH), 6.47–6.42 (2H, m, ArCH=CH), 3.70 (2H, t, J = 6.4 Hz, HOCH_2), 2.40–2.32 (2H, m, ArCH=CHCH_2), 1.93 (1H, br s, OH), 1.82–1.72 (2H, m, $HOCH_2CH_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 146.4 (Ar), 144.2 (Ar), 135.6 (CH=CH), 128.6 (CH=CH), 126.4 (Ar), 123.9 (Ar), 62.1 (HOCH$_2$), 31.8 ($HOCH_2CH_2$), 29.5 (ArCH=CHCH$_2$). *Data are consistent with literature values.*[154]

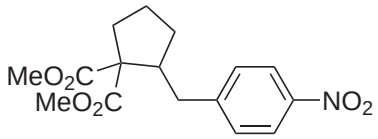
(*E*)-5-(4-Nitrophenyl)pent-4-enyl methanesulfonate



185

According to GP 4, alcohol **179** (207 mg, 1.00 mmol) was treated with MsCl, which gave **185** (285 mg, 1.00 mmol, 100%) as a yellow oil, which was used without purification. $\mathbf{R}_f$ 0.34 (Et_2O), $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.16 (2H, d, J = 8.8 Hz, ArH), 7.46 (2H, d, J = 8.8 Hz, ArH), 6.52 (1H, d, J = 15.9 Hz, ArCH=CH), 6.39 (1H, dt, J = 15.9, 6.8 Hz, ArCH=CH), 4.30 (1H, t, J = 6.3 Hz, MsOCH_2), 3.03 (3H, s, SO_2CH_3), 2.46–2.39 (2H, m, ArCH=CHCH_2), 2.02–1.94 (2H, m, $MsOCH_2CH_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 146.7 (Ar), 143.7 (Ar), 133.6 (ArCH=CH), 129.6 (ArCH=CH), 126.5 (Ar), 124.0 (Ar), 69.0 (MsOCH$_2$), 37.4 (SO_2CH_3), 29.0 (CH_2), 28.4 (CH_2); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2937 (w, C-H), 1650 (w, C=C), 1513 (m), 1341 (s, S=O & N=O), 1172 (m, S=O); **m/z** (ESI+) 308.1 ($[M+Na]^+$, 100%), HRMS found 308.0556, $C_{12}H_{15}NNaO_5S$ requires 308.0563.

Dimethyl 2-(4-nitrobenzyl)cyclopentane-1,1-dicarboxylate

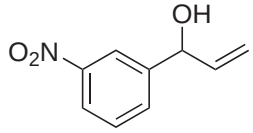


180

According to GP 5, mesylate **185** (285 mg, 1.00 mmol) was treated with DMM, which after flash column chromatography (3:1 PE:Et_2O) gave cyclopentane **180** (222 mg, 0.69 mmol, 69%) as a colourless oil. $\mathbf{R}_f$ 0.39 (3:2 PE:Et_2O); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 8.14 (2H, d, J = 8.6 Hz, ArH), 7.37 (2H, d, J = 8.6 Hz, ArH), 3.76 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.19 (1H, dd, J = 13.1, 3.4 Hz, ArCHH), 2.75 (1H, tdd, J = 10.8, 7.0, 3.5 Hz, $ArCH_2CH$), 2.48 (1H, ddd, J = 14.0, 8.7, 6.9 Hz, $(MeO_2C_2)CCHH$), 2.34 (1H, dd, J = 12.9, 11.5 Hz, ArCHH), 2.06 (1H, ddd, J = 13.9, 9.8, 5.2 Hz, $CHCH_2CHH$), 1.90–1.82 (1H, m,

$CHCH_2CHH$), 1.72–1.65 (1H, m, $CHCHH$), 1.54 (1H, tddd, J = 12.7, 9.6, 8.7, 7.4 Hz, $(MeO_2C)_2CCHH$), 1.47–1.38 (1H, m, $CHCH_2CHH$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 172.6 (C=O), 171.6 (C=O), 149.0 (Ar), 146.5 (Ar), 129.6 (Ar), 123.6 (Ar), 62.9 ($(MeO_2C)_2C$), 52.6 (OCH_3), 52.3 (OCH_3), 48.2 ($ArCH_2CH$), 37.5 ($ArCH_2$), 34.3 ($CHCH_2CH_2$), 30.2 ($CHCH_2$), 22.6 ($CHCH_2CH_2CH_2$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2955 (m, C-H), 1730 (s, C=O), 1602 (m), 1521 (s, N=O), 1437 (m) 1348 (s, N=O), 1205 (s); **m/z** (ESI+) 344.1 ($[M+Na]^+$, 100%), 665.2 ($[2M+Na]^+$, 93%), HRMS found 344.1105, $C_{16}H_{19}NNaO_6$ requires 344.1105.

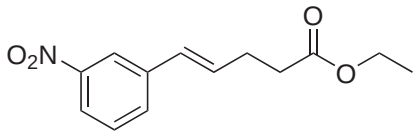
1-(3-Nitrophenyl)prop-2-en-1-ol



173

A solution of 3-nitrobenzaldehyde (1.51 g, 10.0 mmol) in dry THF (50 mL) was cooled to -78 °C and vinylmagnesium bromide (1 M in THF, 10.0 mL, 10.0 mmol) was added dropwise. The solution was stirred for 2.5 h, after which 70% saturated aqueous NH_4Cl solution (50 mL) was added at -78 °C. After warming to RT, the layers were separated and the aqueous was extracted with EtOAc (3×50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, which gave alcohol **173** (1.86 g, 10.0 mmol, 100%) as a red oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.25 (1H, s, ArH), 8.13 (1H, d, J = 8.1 Hz, ArH), 7.72 (1H, d, J = 7.6 Hz, ArH), 7.53 (1H, t, J = 7.9 Hz, ArH), 6.01 (1H, ddd, J = 17.0, 10.2, 6.4 Hz, $H_2C=CH$), 5.41 (1H, dd, J = 17.0, 0.9 Hz, $CH=CHH$), 5.32 (1H, d, J = 6.4 Hz, $HOCH$), 5.28 (1H, dd, J = 10.2, 0.9 Hz, $CH=CHH$), 2.41 (1H, br s, OH); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 148.3 (Ar), 144.6 (Ar), 139.3 ($H_2C=CH$), 132.4 (Ar), 129.4 (Ar), 122.6 (Ar), 121.3 (Ar), 116.8 ($H_2C=CH$), 74.4 ($HOCH$). *Data are consistent with literature values.*[153]

(*E*)-Ethyl 5-(3-nitrophenyl)pent-4-enoate

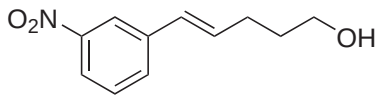


174

According to GP 2, alcohol **173** (1.72 g, 10.0 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (15→5:1 PE:EtOAc), gave ester **174** (1.96 g, 7.84 mmol, 78%) as a

pale yellow oil. $\mathbf{R}_f$ 0.40 (8:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 8.19 (1H, s, Ar*H*), 8.06 (1H, d, J = 8.1 Hz, Ar*H*), 7.63 (1H, d, J = 8.1 Hz, Ar*H*), 7.46 (1H, dd, J = 8.1, 8.1 Hz, Ar*H*), 6.50 (1H, d, J = 15.9 Hz, ArC*H*=CH), 6.38 (1H, dt, J = 15.9, 6.4 Hz, ArCH=C*H*), 4.17 (2H, q, J = 7.1 Hz, OCH_2H$_3$), 2.60 (2H, td, J = 7.0, 6.4 Hz, ArCH=CHCH_2), 2.51 (2H, t, J = 7.0 Hz, EtO_2CCH_2), 1.28 (3H, t, J = 7.1 Hz, OCH$_2$CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 172.7 (*C*=O), 166.2 (*Ar*), 139.1 (*Ar*), 132.0 (Ar*C*H=CH), 131.9 (*Ar*), 129.4 (*Ar*), 128.9 (ArCH=*C*H), 121.7 (*Ar*), 120.6 (*Ar*), 60.5 (CO_2CH$_2$), 33.6 (CH$_2$), 28.2 (CH$_2$), 14.3 (CO_2CH_2CH$_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2983 (m), 1733 (s, C=O), 1653 (w, C=C), 1531 (s, N=O), 1442 (m), 1351 (s N=O), 1255 (s), 1183 (s), 967 (m); **m/z** (ESI+) 272.1 ([M+Na]$^+$, 100%), HRMS found 272.0894, $C_{13}H_{15}NNaO_4$ requires 272.0893.

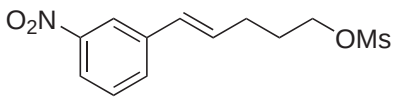
(*E*)-5-(3-Nitrophenyl)pent-4-en-1-ol



175

DiBAl-H (1.5 M in PhMe, 4.1 mL, 6.15 mmol) was added dropwise to a stirred solution of ester **174** (748 mg, 3.0 mmol) in dry Et_2O (22 mL) at -78 °C. The solution was allowed to warm to RT overnight after which time saturated aqueous Rochelle's salt solution (30 mL) was added and stirred for a further 2 h. The layers were separated and the aqueous was extracted with EtOAc (3×25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (3→1:1 PE:EtOAc), which gave alcohol **175** (423 mg, 2.04 mmol, 68%) as a yellow oil. $\mathbf{R}_f$ 0.21 (1:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 8.19 (1H, s, Ar*H*), 8.04 (1H, d, J = 8.0 Hz, Ar*H*), 7.62 (1H, d, J = 7.7 Hz, Ar*H*), 7.45 (1H, dd, J = 8.0, 7.7 Hz, Ar*H*), 6.48 (1H, d, J = 16.0 Hz, ArC*H*=CH), 6.47–6.35 (1H, m, ArCH=C*H*), 3.73 (2H, t, J = 6.4 Hz, HOCH_2), 2.37 (2H, td, J = 7.0, 7.0 Hz, ArCH=CHCH_2), 1.83–1.73 (2H, m, HOCH$_2$CH_2), 1.59 (1H, br s, O*H*); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 148.6 (*Ar*), 139.4 (*Ar*), 133.6 (ArCH=*C*H), 131.9 (*Ar*), 129.3 (*Ar*), 128.3 (Ar*C*H=CH), 121.5 (*Ar*), 120.5 (*Ar*), 62.2 (HO*C*H$_2$), 31.9 (HOCH$_2$*C*H$_2$), 29.3 (ArCH=CH*C*H$_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 3358 (br, O-H), 2936 (m), 1653 (w, C=C), 1527 (s, N=O), 1350 (s, N=O), 966 (m); **m/z** (ESI+) 230.1 ([M+Na]$^+$, 100%), HRMS found 230.0788, $C_{11}H_{13}NNaO_3$ requires 230.0788.

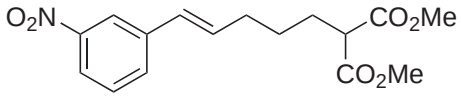
(*E*)-5-(3-Nitrophenyl)pent-4-enyl methanesulfonate



428

According to GP 4, alcohol **175** (218 mg, 1.05 mmol) was treated with MsCl, which gave mesylate **428** (299 mg, 1.05 mmol, 100%) as a yellow oil, which was used without purification. $\mathbf{R}_f$ 0.56 (1:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 8.19 (1H, s, Ar*H*), 8.06 (1H, d, J = 8.1 Hz, Ar*H*), 7.63 (1H, d, J = 7.6 Hz, Ar*H*), 7.47 (1H, dd, J = 8.1, 7.6 Hz, Ar*H*), 6.51 (1H, d, J = 15.9 Hz, ArC*H*=CH), 6.34 (1H, dt, J = 15.9, 7.1 Hz, ArCH=C*H*), 4.30 (2H, t, J = 6.3 Hz, MsOCH_2), 3.03 (3H, s, SO_2CH_3), 2.41 (2H, dt, J = 7.1, 7.1 Hz, ArCH=CHCH_2), 2.02–1.92 (2H, m, MsOCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 148.6 (*Ar*), 139.0 (*Ar*), 132.0 (ArCH=*C*H), 131.8 (*Ar*), 129.4 (*Ar*), 129.3 (Ar*C*H=CH), 121.8 (*Ar*), 120.5 (*Ar*), 69.0 (MsO*C*H$_2$), 37.4 (SO_2CH_3), 28.8 (ArCH=CH*C*H$_2$), 28.5 (MsOCH$_2$*C*H$_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2941 (m), 1655 (w, C=C), 1528 (s, NO_2), 1351 (s, NO_2, SO_2), 1173 (s, SO_2), 970 (m), 929 (m); **m/z** (ESI+) 308.1 ([M+Na]$^+$, 100%), 593.2 ([2M+Na]$^+$, 13%), HRMS found 308.0563, $C_{12}H_{15}NNaO_5S$ requires 308.0563.

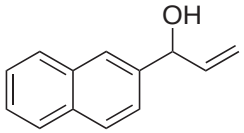
(*E*)-Dimethyl 2-(5-(3-nitrophenyl)pent-4-enyl)malonate



176

According to GP 5, mesylate **428** (278 mg, 0.98 mmol) was treated with DMM, which after flash column chromatography (10→5:1 PE:EtOAc), gave malonate **176** (230 mg, 0.72 mmol, 73%) as a pale yellow oil. $\mathbf{R}_f$ 0.51 (1:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 8.19 (1H, s, Ar*H*), 8.05 (1H, d, J = 8.0 Hz, Ar*H*), 7.62 (1H, d, J = 7.8 Hz, Ar*H*), 7.46 (1H, dd, J = 8.0, 7.8 Hz, Ar*H*), 6.46 (1H, d, J = 15.9 Hz, ArC*H*=CH), 6.34 (1H, dt, J = 15.9, 6.7 Hz, ArCH=C*H*), 3.76 (6H, s, OCH_3), 3.41 (1H, t, J = 7.5 Hz, $(MeO_2C)_2CH$), 2.30 (2H, td, J = 7.0, 6.7 Hz, ArCH=CHCH_2), 2.02–1.94 (2H, m, $(MeO_2C)_2$CHCH_2), 1.62–1.49 (2H, m, ArCH=CHCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.7 (*C*=O), 148.6 (*Ar*), 139.3 (*Ar*), 133.2 (ArCH=*C*H), 131.9 (*Ar*), 129.3 (*Ar*), 128.5 (Ar*C*H=CH), 121.6 (*Ar*), 120.5 (*Ar*), 52.5 (O*C*H$_3$), 51.5 ($(MeO_2C)_2CH$), 32.5 (ArCH=CH*C*H$_2$), 28.3 ($(MeO_2C)_2$CH*C*H$_2$) 26.7 (ArCH=CHCH$_2$*C*H$_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2954 (m), 1735 (s, C=O), 1654 (w, C=C), 1529 (s, N=O), 1437 (m), 1351 (s N=O), 1099 (m); **m/z** (ESI+) 344.1 ([M+Na]$^+$, 100%), HRMS found 344.1108, $C_{16}H_{19}NNaO_6$ requires 344.1105.

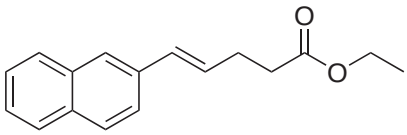
1-(Naphthalen-2-yl)prop-2-en-1-ol



181

According to GP 1, 2-naphthaldehyde (1.56 g, 10.0 mmol) was treated with vinylmagnesium bromide, which gave alcohol **181** (1.81 g, 9.80 mmol, 98%) as an amber oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.87–7.82 (4H, m, Ar*H*), 7.54–7.47 (3H, m, Ar*H*), 6.14 (1H, ddd, J = 17.0, 10.3, 6.0 Hz, CHOHC*H*=CH_2), 5.42 (1H, dt, J = 17.0, 1.1 Hz, CH=C*H*H), 5.37 (1H, d, J = 6.0 Hz, C*H*OH), 5.26 (1H, dt, J = 10.3, 1.1 Hz, CH=CH*H*), 2.33 (1H, br s, O*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 140.1 (*Ar*), 140.0 (*C*H=CH_2), 133.3 (*Ar*), 133.0 (*Ar*), 128.4 (*Ar*), 128.0 (*Ar*), 127.7 (*Ar*), 126.2 (*Ar*), 126.0 (*Ar*), 125.0 (*Ar*), 124.5 (*Ar*), 115.4 (CH=*C*H_2), 75.4 (*C*HOH). *Data are consistent with literature values.*[161]

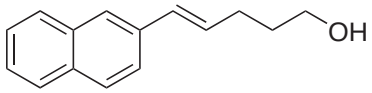
(*E*)-Ethyl 5-(naphthalen-2-yl)pent-4-enoate



182

According to GP 2, alcohol **181** (1.78 g, 9.65 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (25→20:1 PE:EtOAc), gave ester **182** (858 mg, 3.37 mmol, 35%) as a colourless oil. $\mathbf{R}_f$ 0.17 (25:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.88–7.43 (7H, m, Ar*H*), 6.65 (1H, d, J = 15.8 Hz, ArC*H*=CH), 6.40 (1H, dt, J = 15.8, 6.6 Hz, ArCH=C*H*), 4.23 (2H, q, J = 7.1 Hz, OCH_2), 2.66 (2H, td, J = 7.2, 6.6 Hz, ArCH=CHCH_2), 2.57 (2H, t, J = 7.1 Hz, COCH_2), 1.33 (3H, t, J = 7.1 Hz, OCH_2CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.0 (*C*=O), 134.9 (*Ar*), 133.7 (*Ar*), 132.8 (*Ar*), 131.1 (Ar*C*H=CH), 129.0 (ArCH=*C*H), 128.1 (*Ar*), 127.9 (*Ar*), 127.7 (*Ar*), 126.2 (*Ar*), 125.7 (*Ar*), 125.7 (*Ar*), 123.5 (*Ar*), 60.4 (O*C*H_2), 34.1 (CO*C*H_2), 28.5 (ArCH=CH*C*H_2), 14.3 (OCH_2*C*H_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2982 (m), 1733 (s, C=O), 1627 (m, C=C), 1347 (m), 1179 (s), 965 (s); **m/z** (ESI+) 277.1 ([M+Na]$^+$, 100%), 531.3 ([2M+Na]$^+$, 31%), HRMS found 277.1198, $C_{17}H_{18}NaO_2$ requires 277.1199.

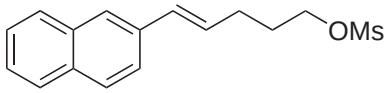
(*E*)-5-(Naphthalen-2-yl)pent-4-en-1-ol



183

According to GP 3, ester **182** (445 mg, 2.00 mmol) was treated with $LiAlH_4$, which gave alcohol **183** (383 mg, 1.80 mmol, 90 %) as a white solid, *m.p.* 68–70 °C, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.89–7.37 (7H, m, Ar*H*), 6.60 (1H, d, J = 15.8 Hz, ArC*H*=CH), 6.38 (1H, dt, J = 15.8, 7.0 Hz, ArCH=C*H*), 3.75 (2H, t, J = 6.5 Hz, HOCH_2), 2.39 (2H, td, J = 7.1, 7.0 Hz, ArCH=CHCH_2), 1.86–1.76 (2H, m, $HOCH_2CH_2$), 1.58 (1H, br s, O*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 135.1 (*Ar*), 133.7 (*Ar*), 132.7 (*Ar*), 130.5 (*C*H=CH & CH=*C*H), 128.1 (*Ar*), 127.8 (*Ar*), 127.6 (*Ar*), 126.2 (*Ar*), 125.5 (*Ar*), 124.4 (*Ar*), 123.5 (*Ar*), 62.5 ($HOCH_2$), 32.3 (ArCH=CHCH_2), 29.5 ($HOCH_2CH_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3331 (br m, O-H), 2934 (m), 1688 (w, C=C), 1440 (m), 1056 (s), 965 (s); **m/z** HRMS (FI) found 212.1197, $C_{15}H_{16}O$ requires 212.1201.

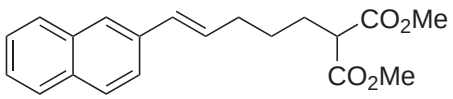
(*E*)-5-(Naphthalen-2-yl)pent-4-enyl methanesulfonate



429

According to GP 4, alcohol **183** (282 mg, 1.33 mmol) was treated with MsCl, which gave mesylate **429** (386 mg, 1.33 mmol, 100 %) as a pale yellow oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.84–7.41 (7H, m, Ar*H*), 6.61 (1H, d, J = 15.8 Hz, ArC*H*=CH), 6.32 (1H, dt, J = 15.8, 7.0 Hz, ArCH=C*H*), 4.32 (2H, t, J = 6.4 Hz, MsOCH_2), 3.02 (3H, s, SO_2CH_3), 2.42 (2H, dt, J = 7.0, 6.9 Hz, ArCH=CHCH_2), 2.04–1.94 (2H, m, $MsOCH_2CH_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 134.7 (*Ar*), 133.6 (*Ar*), 132.8 (*Ar*), 131.5 (*C*H=CH & CH=*C*H), 128.7 (*Ar*), 128.1 (*Ar*), 127.9 (*Ar*), 127.6 (*Ar*), 126.2 (*Ar*), 125.7 (*Ar*), 123.4 (*Ar*), 69.3 (MsOCH_2), 37.4 (SO_2CH_3), 28.9 (ArCH=CHCH_2), 28.8 ($MsOCH_2CH_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2948 (m, C-H), 1691 (w, aromatic), 1625 (w, aromatic), 1597 (w, C=C), 1352 (s, SO_2), 1173 (s, SO_2), 969 (m); **m/z** (ESI+) 313.1 ([M+Na]$^+$, 100%), HRMS found 313.0870, $C_{16}H_{18}NaO_3S$ requires 313.0874.

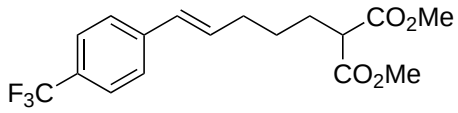
(*E*)-Dimethyl 2-(5-(naphthalen-2-yl)pent-4-enyl)malonate



184

According to GP 5, mesylate **429** (382 mg, 1.32 mmol) was treated with DMM, which after flash column chromatography (10:1 PE:EtOAc), gave malonate **184** as a colourless oil (309 mg, 0.95 mmol, 72%). $\mathbf{R}_f$ 0.16 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.79 (3H, t, J = 8.6 Hz, ArH), 7.68 (1H, s, ArH), 7.58 (1H, dd, J = 8.6, 1.4 Hz, ArH), 7.49–7.39 (2H, m, ArH), 6.57 (1H, d, J = 15.8 Hz, ArCH=CH), 6.33 (1H, dt, J = 15.8, 6.9 Hz, ArCH=CH), 3.76 (6H, s, $(CO_2CH_3)_2$), 3.43 (1H, t, J = 7.5 Hz, $(MeO_2C)_2CH$), 2.32 (2H, dt, J = 6.9, 6.9 Hz, ArCH=CHCH_2), 2.05–1.98 (2H, m, $(MeO_2C)_2CHCH_2$), 1.62–1.51 (2H, m, ArCH=CHCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.8 (C=O), 135.1 (Ar), 133.7 (Ar), 132.7 (Ar), 130.6 (C=CH), 130.2 (CH=CH), 128.1 (Ar), 127.8 (Ar), 127.6 (Ar), 126.1 (Ar), 125.5 (Ar), 125.5 (Ar), 123.4 (Ar), 52.5 (OCH$_3$), 51.6 ($(MeO_2C)_2CH$), 32.7 (ArCH=CHCH$_2$), 28.4 ($(MeO_2)_2CHCH_2$), 27.1 (ArCH=CHCH$_2$$CH_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2953 (m), 1735 (s, C=O), 1627 (w, C=C), 1436 (m), 1152 (m); **m/z** (ESI+) 349.2 ([M+Na]$^+$, 100%), HRMS found 349.1410, $C_{20}H_{22}NaO_4$ requires 349.1410.

(*E*)-Dimethyl 2-(5-(4-(trifluoromethyl)phenyl)pent-4-en-1-yl)malonate



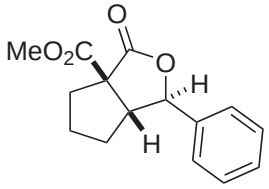
191

To a N_2 sparged suspension of Grubbs 1st Generation catalyst **190** (21 mg, 5.0 μmol) was added a solution of *para*-trifluoromethylstyrene **189** (172 mg, 1.00 mmol) and dimethyl 4-pentenyl malonate **430** (100 mg, 0.50 mmmol) in DCM (2.0 mL). The solution was heated at 40 °C overnight. The volatiles were removed *in vacuo*, and the residue was purified by flash column chromatography (5→3:1 PE:Et_2O), which gave malonate **191** (101 mg, 0.294 mmol, 59%) as a pale green oil. $\mathbf{R}_f$ 0.19 (4:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.53 (2H, d, J = 8.2 Hz, ArH), 7.41 (2H, d, J = 8.2 Hz, ArH), 6.42 (1H, d, J = 15.8 Hz, ArCH=CH), 6.28 (1H, dt, J = 15.8, 7.3 Hz, ArCH=CH), 3.74 (6H, s, CO_2CH_3), 3.40 (1H, t, J = 7.5 Hz, C$H$$(CO_2Me)_2$), 2.27 (2H, dt, J = 7.3, 7.3 Hz, ArCH=CHCH_2), 2.01–1.93 (2H, m, CHCH_2), 1.57–1.48 (2H, m, CHCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.7 (C=O), 141.1 (Ar), 132.6 (ArCH=CH),

129.3 (*Ar*), 126.1 (Ar*C*H=CH), 125.4 (*Ar*), 125.4 (*Ar*), 52.5 (CO_2CH_3), 51.5 ($(MeO_2C)_2CH$), 32.5 (ArCH=CHCH_2), 28.3 (CHCH_2), 26.8 ($CH_2CH_2CH_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}**2968 (m, C-H), 1739 (s, C=O), 1597 (w, C=C); **m/z** (ESI+) 367.1 ($[M+Na]^+$, 100%), HRMS found 367.1129, $C_{17}H_{19}F_3NaO_4$ requires 367.1128.

(1*R,3a*S**,6a*R**)-Methyl**

3-oxo-1-phenylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate



193

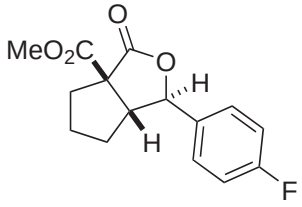
According to GP 6, malonate ***E*-144** (75 mg, 0.271 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (4:1 PE:EtOAc), gave cyclopentane-lactone **193** (*dr* 4.1:1, 59 mg, 0.226 mmol, 84%) as a colourless oil. The diastereomers were separated by semi-preparative HPLC. Data for major isomer **193**: $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.43–7.33 (5H, m, Ar*H*), 5.05 (1H, d, J = 4.8 Hz, C*H*Ph), 3.73 (3H, s, CO_2CH_3), 3.17 (1H, ddd, J = 6.9, 4.8, 1.9 Hz, PhCHC*H*), 2.46 (1H, ddd, J = 13.5, 11.0, 6.6 Hz, MeO_2CCCH*H*), 2.40–2.34 (1H, m, MeO_2CCCH*H*), 2.08–1.92 (3H, m, $CHCH_2$ & $CHCH_2CH$*H*), 1.81–1.70 (1H, m, $CHCH_2CH$*H*); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 175.9 (lactone *C*=O), 170.9 (ester *C*=O), 139.7 (*Ar*), 128.8 (*Ar*), 128.5 (*Ar*), 125.4 (*Ar*), 86.0 (Ph*C*H), 62.3 (MeO_2CC), 54.3 (PhCH*C*H), 53.1 (CO_2CH_3), 35.3 (MeO_2CCCH_2), 33.6 (CHCH_2), 25.5 ($CHCH_2CH_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2955 (m, C-H), 1774 (s, lactone C=O), 1740 (s, ester C=O), 1258 (m), 1150 (m); **m/z** (ESI+) 283.1 ($[M+Na]^+$, 82%), 543.2 ($[2M+Na]^+$, 100%), HRMS found 283.0941, $C_{15}H_{16}NaO_4$ requires 283.0941. Data for C1-*epi*-**193**: $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.40 (2H, t, J = 7.0 Hz, Ar*H*), 7.33 (1H, tt, J = 7.0, 1.0 Hz, Ar*H*), 7.30 (2H, td, J = 7.0, 1.0 Hz, Ar*H*), 5.88 (1H, d, J = 6.5 Hz, C*H*Ph), 3.86 (3H, s, CO_2CH_3), 3.32 (1H, ddd, J = 8.8, 6.5, 6.5 Hz, PhHC*H*), 2.42 (1H, ddd, J = 13.2, 7.6, 7.6 Hz, MeO_2CCCH*H*), 2.35 (1H, ddd, J = 13.2, 6.4, 6.4 Hz, MeO_2CCCH*H*), 1.71–1.62 (1H, m, $CHCH_2CH$*H*), 1.62–1.54 (1H, m, $CHCH_2CH$*H*), 1.50 (1H, dddd, J = 13.5, 8.7, 6.8, 6.8 Hz, CHC*H*H), 1.33–1.25 (1H, m, CHCH*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 175.9 (lactone *C*=O), 170.3 (ester *C*=O), 136.4 (*Ar*), 128.6 (*Ar*), 128.3 (*Ar*), 124.9 (*Ar*), 81.5 (Ph*C*H), 63.7 (MeO_2CC), 53.2 (PhCH*C*H), 51.3 (CO_2CH_3), 34.7 (MeO_2CCCH_2), 28.6 (CHCH_2), 26.0 ($CHCH_2CH_2$)0; $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2955 (m, C-H), 1778 (s, lactone C=O), 1742 (s, ester

C=O), 1255 (m), 1147 (m); **m/z** HRMS found 283.0946, $C_{15}H_{16}NaO_4$ requires 283.0941.

Following the same procedure, (***Z***)-**144** (75 mg, 0.271 mmol) was treated with $Mn(OAc)_3{\cdot}2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography gave cyclopentane-lactone **193** (dr 4.2:1, 53 mg, 0.216 mmol mmol, 82%) as a colourless oil.

(1*R,3a*S**,6a*R**)-Methyl**

1-(4-fluorophenyl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate



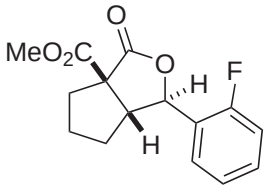
198

According to GP 6, malonate **148** (80 mg, 0.271 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (5:1 PE:EtOAc), gave cyclopentane-lactone **al472A** (4.1:1 dr, 54 mg, 0.194 mmol, 72%) as a colourless oil. The diastereomers were separated by semi-preparative HPLC (1% IPA in hexane). Data for major isomer **198**: $\mathbf{R}_f$ 0.22 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.36 (2H, dd, $^3J_{HH}$ = 8.5, $^4J_{HF}$ = 5.2 Hz, Ar*H*), 7.09 (2H, dd, $^3J_{HH}$ = 8.5, $^3J_{HF}$ = 8.5 Hz, Ar*H*), 5.03 (1H, d, J = 4.8 Hz, ArC*H*), 3.74 (3H, s, CO_2CH_3), 3.14 (1H, ddd, J = 4.8, 4.7, 1.7 Hz, ArCHC*H*), 2.45 (1H, ddd, J = 13.5, 10.9, 6.5 Hz, CC*H*H), 2.39–2.33 (1H, m, CCH*H*), 2.07–1.89 (3H, m, CCH_2CH_2CHH), 1.79–1.68 (1H, m, CCH_2CH_2CHH); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 175.7 (lactone *C*=O), 170.7 (ester *C*=O), 162.7 (d, $^1J_{CF}$ = 247 Hz, *Ar*), 135.5 (d, $^4J_{CF}$ = 3 Hz *Ar*), 127.4 (d, $^3J_{CF}$ = 8 Hz *Ar*), 115.7 (d, $^2J_{CF}$ = 22 Hz *Ar*), 85.5 (Ar*C*H), 62.3 (MeO_2CC), 54.2 (CH_2CH), 53.2 (CO_2CH_3), 35.2 (CH_2), 33.6 (CH_2), 25.5 (CH_2); $\boldsymbol{\delta}_\mathbf{F}$ (377 MHz, $CDCl_3$) -113; $\boldsymbol{\nu}_\mathbf{max}$ **/ cm^{-1}** 2957 (m, C-H), 1776 (s, lactone C=O), 1742 (s, ester C=O), **m/z** (ESI+) 301.1 ($[M+Na]^+$, 73%), 579.1 ($[2M+Na]^+$, 100%), HRMS found 301.0854, $C_{15}H_{15}FNaO_4$ requires 301.0847; Data for C1-*epi* **198**: $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.32 (2H, dd, $^3J_{HH}$ = 8.5, $^4J_{HF}$ = 5.5 Hz, Ar*H*), 7.14 (2H, dd, $^3J_{HH}$ = 8.5, $^3J_{HF}$ = 8.5 Hz, Ar*H*), 5.90 (1H, d, J = 6.5 Hz, ArC*H*), 3.90 (3H, s, CO_2CH_3), 3.34 (1H, ddd, J = 8.7, 7.0, 6.5 Hz, ArCHC*H*), 2.51–2.44 (1H, m, CC*H*H), 2.43–2.37 (1H, m, CCH*H*), 1.76–1.67 (1H, m, CCH_2CHH), 1.67–1.61 (1H, m, CCH_2CHH), 1.59–1.51 (1H, m, CHC*H*H), 1.36–1.28 (1H, m, CHCH*H*); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 175.6 (lactone *C*=O), 170.2 (ester *C*=O), 162.3 (d, $^1J_{CF}$ = 246 Hz, *Ar*), 132.2 (d, $^4J_{CF}$ = 3 Hz, *Ar*), 126.7 (d, $^3J_{CF}$ = 8 Hz, *Ar*), 115.6 (d, $^2J_{CF}$ = 22 Hz, *Ar*), 80.9 (Ar*C*H), 63.7 (MeO_2CC), 53.2 (CO_2CH_3), 51.3

(CH_2CH), 34.7 (CH_2), 28.5 (CH_2), 25.9 (CH_2), $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$) -114; $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2959 (m, C-H), 1779 (s, lactone C=O), 1743 (s, ester C=O), **m/z** HRMS found 301.0853, $C_{15}H_{15}FNaO_4$ requires 301.0847.

(1*R,3a*S**,6a*R**)-Methyl**

1-(phenyl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate

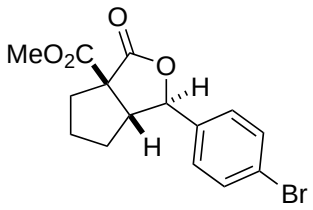


199

According to GP 6, malonate **6c** (88 mg, 0.299 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (4:1 PE:EtOAc), gave cyclopentane-lactone **199** (4.8:1 dr, 45 mg, 0.162 mmol, 54%) as a colourless oil characterised as a 5:1 mixture of diastereomers. $\mathbf{R}_f$ 0.59 (1:1 PE:Et_2O); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.56–7.46 (1H, m, Ar*H*), 7.42–7.33 (1H, m, Ar*H*), 7.28–7.19 (1H, m, Ar*H*), 7.19–7.08 (1H, m, Ar*H*), 6.07 (1H, d, J = 6.6 Hz, C1-*epi* ArC*H*), 5.40 (1H, d, J = 4.2 Hz, ArC*H*), 3.89 (3H, s, C1-*epi* CO_2CH_3), 3.73 (3H, s, CO_2CH_3), 3.50 (1H, dddd, $^3J_{HH}$ = 9.0, 6.6, 6.6 Hz, $^4J_{HF}$ = 2.4 Hz, C1-*epi* COArC*H*), 3.17–3.13 (1H, m, COArC*H*), 2.54–2.31 (2H, m, CH_2), 2.18–1.95 (3H, m, CH_2), 1.83–1.52 (1H, m, CH_2), 1.35–1.24 (1H, m, C1-*epi* CH_2); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 175.9 (lactone *C*=O), 175.5 (C1-*epi* *C*=O), 170.7 (ester *C*=O), 170.2 (C1-*epi* *C*=O), 159.4 (d, $^1J_{CF}$ = 246 Hz, *Ar*), 159.0 (d, $^1J_{CF}$ = 246 Hz, C1-*epi* *Ar*), 129.9 (d, $^3J_{CF}$ = 8 Hz, *Ar*), 127.5 (d, $^3J_{CF}$ = 13 Hz, C1-*epi* *Ar*), 126.4 (d, $^4J_{CF}$ = 4 Hz, *Ar*), 126.4 (d, $^4J_{CF}$ = 4 Hz, C1-*epi* *Ar*), 124.4 (d, $^2J_{CF}$ = 4 Hz, *Ar*), 124.1 (d, $^2J_{CF}$ = 14 Hz, C1-*epi* *Ar*), 115.5 (d, $^2J_{CF}$ = 21 Hz, *Ar*), 115.2 (d, $^2J_{CF}$ = 20 Hz, C1-*epi* *Ar*), 80.6 (d, $^3J_{CF}$ = 3 Hz, *C*HOAr), 77.4 (d, $^3J_{CF}$ = 6 Hz, C1-*C1*-*C*HOAr), 63.2 (C1-*epi* MeO_2CC), 61.9 (MeO_2CC), 53.7 (Ar*C*H), 53.3 (C1-*epi* CO_2CH_3), 53.1 (CO_2CH_3), 50.3 (C1-*epi* Ar*C*H), 35.7 (CCH_2), 34.7 (C1-*epi* CCH_2), 34.0 ($CHCH_2$), 28.8 (C1-*epi* $CHCH_2$), 26.1 (C1-*epi* $CHCH_2CH_2$), 25.7 ($CHCH_2CH_2$); $\boldsymbol{\delta_F}$ (377 MHz, $CDCl_3$) -118.0 (C1-*epi*), -118.1; $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2957 (w, C-H), 1781 (s, lactone C=O), 1742 (s, ester C=O), 1257 (m, C-F), 1104 (m); **m/z** (ESI+) 301.1 ($[M+Na]^+$, 96%), 579.1 ([2M+Na]+, 100%), HRMS found 301.0847, $C_{15}H_{15}FNaO_4$ requires 301.0847.

(1*R,3a*S**,6a*R**)-methyl**

1-(4-bromophenyl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate

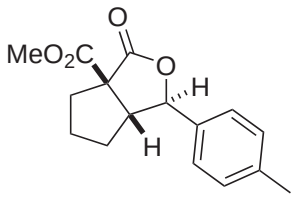


200

According to GP 6, malonate **156** (107 mg, 0.300 mmol) was treated with $Mn(OAc)_3{\cdot}2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (4:1 PE:EtOAc), gave cyclopentane-lactone **200** (4.2:1 dr, 75 mg, 0.221 mmol, 74%) as a colourless oil characterised as a 10:1 mixture of diastereomers, data given for the major diastereomer only. $\mathbf{R}_f$ 0.27 (4:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.59–7.47 (2H, m, Ar*H*), 7.30–7.23 (2H, m, Ar*H*), 5.01 (1H, d, J = 4.7 Hz, ArC*H*), 3.72 (3H, s, CO_2CH_3), 3.10 (1H, ddd, J = 7.0, 4.7, 2.0 Hz, CH_2CH), 2.49–2.39 (1H, m, C*H*H), 2.38–2.32 (1H, m, C*H*H), 2.07–2.00 (1H, CHC*H*H), 2.01–1.87 (2H, m, CHCH*H* & C*H*H), 1.79–1.66 (1H, m, C*H*H); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 175.6 (lactone *C*=O), 170.6 (ester *C*=O), 138.8 (*Ar*), 131.9 (*Ar*), 127.0 (*Ar*), 122.5 (*Ar*), 85.3 (Ar*C*H), 62.2 (MeO_2CC), 54.2 (CH_2CH), 53.2 (CO_2CH_3), 35.2 (CH_2), 33.7 (CH_2), 25.5 (CH_2); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2955 (m, C-H), 1777 (s, lactone C=O), 1742 (s, ester C=O), 1261 (m), 1150 (m), 1008 (m); **m/z** 361.0 (100%, $[M(^{79}Br)+Na]^+$), 363.0 (100%, $[M(^{81}Br)+Na]^+$), HRMS found 377.0036, $C_{15}H_{15}{}^{79}BrNaO_4$ requires 377.0046.

(1*R,3a*S**,6a*R**)-Methyl**

3-oxo-1-*p*-tolylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate



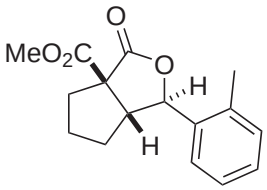
201

According to GP 6, malonate **160** (78 mg, 0.271 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (5:1 PE:EtOAc), gave cyclopentane-lactone **201** (1.5:1 dr, 46 mg, 0.168 mmol, 62%) as a colourless oil characterised as a 1.5:1 mixture of diastereomers.

$\mathbf{R}_f$ 0.22 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.28–7.23 (2H, m, Ar*H*), 7.22–7.15 (2H, m, Ar*H*), 5.85 (1H, d, J = 6.7 Hz, C1-*epi* ArC*H*), 5.00 (1H, d, J = 4.9 Hz, ArC*H*), 3.84 (3H, s, C1-*epi* CO_2CH_3), 3.74 (3H, s, CO_2CH_3), 3.28 (1H, ddd, J = 8.5, 6.7, 6.7 Hz, C1-*epi* CH_2CH), 3.17–3.13 (1H, m, CH_2CH), 2.49–2.30 (5H, m, MeO_2CCH_2 & $ArCH_3$), 2.06–1.87 (2H, m, CH_2), 1.80–1.43 (2H, m, CH_2), 1.35–1.25 (1H, m, C1-*epi*-$CHCH_2CHH$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 175.9 (lactone C=O & C1-*epi* lactone C=O), 170.9 (C1-*epi* ester C=O), 170.4 (ester C=O), 138.4 (*Ar*), 137.7 (*Ar*), 136.7 (*Ar*), 133.3 (*Ar*), 129.4 (*Ar*), 129.2 (*Ar*), 125.5 (*Ar*), 124.8 (*Ar*), 86.2 (Ar*C*H), 81.5 (C1-*epi* Ar*C*H), 63.7 (MeO_2CC), 62.4 (MeO_2CC), 54.4 (CH_2CH), 53.2 (C1-*epi* CO_2CH_3), 53.1 (CO_2CH_3), 51.4 (C1-*epi* CH_2CH), 35.2 (CH_2), 34.8 (C1-*epi* CH_2), 33.5 (CH_2), 28.5 (C1-*epi* CH_2), 25.9 (C1-*epi* CH_2), 25.5 (CH_2), 21.1 (ArCH_3), 21.1 (ArCH_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2956 (m, C-H), 1776 (s, lactone C=O), 1742 (s, ester C=O), 1450 (m), 1437 (m), 1257 (s), 1150 (s); **m/z** (ESI+) 297.1 ($[M+Na]^+$, 73%), 571.2 ($[2M+Na]^+$, 100%), HRMS found 297.1097, $C_{16}H_{18}NaO_4$ requires 297.1097.

(1*R,3a*S**,6a*R**)-Methyl**

3-oxo-1-*o*-tolylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate



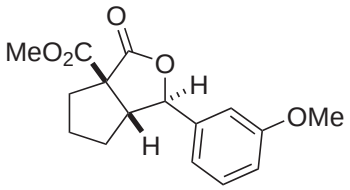
202

According to GP 6, malonate **164** (87 mg, 0.300 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (4:1 PE:EtOAc), gave cyclopentane-lactone **202** (1.3:1 dr, 60 mg, 0.219 mmol, 73%) as a colourless oil characterised as a mixture of diastereomers. $\mathbf{R}_f$ 0.24 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.44–7.36 (1H, m, Ar*H*), 7.28–7.11 (3H, m, Ar*H*), 5.95 (1H, d, J = 6.8 Hz, C1-*epi* ArC*H*), 5.31 (1H, d, J = 3.7 Hz, ArC*H*), 3.84 (3H, s, C1-*epi* OCH_3), 3.66 (3H, s, OCH_3), 3.41 (1H, ddd, J = 8.5, 6.8, 6.5 Hz, C1-*epi* CH_2CH), 3.05–3.00 (1H, m, CH_2CH), 2.33 (3H, s, $ArCH_3$), 2.28 (3H, s, C1-*epi* $ArCH_3$), 2.16–2.05 (1H, m, $CHCHH$), 2.02–1.89 (2H, m, $CHCHH$ & C1-*epi* CHH), 1.80–1.67 (1H, m, C1-*epi* CHH), 1.67–1.59 (1H, m, CHH), 1.53–1.38 (2H, m, CHH & C1-*epi* $CHCHH$), 1.24–1.17 (1H, m, C1-*epi* $CHCHH$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 176.2 (lactone *C*=O), 175.7 (C1-*epi* lactone *C*=O), 170.9 (ester *C*=O), 170.4 (C1-*epi* ester *C*=O), 138.1 (*Ar*), 134.6 (C1-*epi* *Ar*), 133.8 (*Ar*), 133.3 (C1-*epi* *Ar*), 130.6 (*Ar*), 130.4 (C1-*epi* *Ar*), 128.1 (*Ar*), 127.9 (C1-*epi* *Ar*), 126.2

(*Ar*), 126.1 (C1-*epi Ar*), 124.6 (*Ar*), 124.5 (C1-*epi Ar*), 83.6 (Ar*C*H), 80.1 (C1-*epi* Ar*C*H), 63.4 (C1-*epi* MeO_2CC), 62.0 (MeO_2CC), 53.3 (ArCH*C*H), 53.2 (CO_2CH_3), 52.9 (C1-*epi* CO_2CH_3), 49.3 (C1-*epi* ArCH*C*H), 35.8 (CH_2), 35.0 (C1-*epi* CH_2), 34.5 (CH_2), 28.5 (C1-*epi* CH_2), 26.0 (C1-*epi* CH_2), 25.9 (CH_2), 19.5 (Ar*C*H_3), 19.1 (C1-*epi* Ar*C*H_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2957 (m, C-H), 1777 (s, lactone C=O), 1742 (s, ester C=O), 1258 (m), 1148 (m), 1055 (m); **m/z** (ESI+) 297.1 ([M+Na]$^+$, 81%), 571.2 ([2M+Na]$^+$, 100%), HRMS found 297.1098, $C_{16}H_{18}NaO_4$ requires 297.1097.

(1*R,3a*S**,6a*R**)-Methyl**

1-(3-methoxyphenyl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate

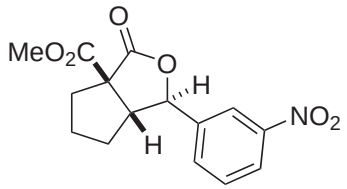


203

According to GP 6, malonate **168** (82 mg, 0.268 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (4:1 PE:EtOAc), gave cyclopentane-lactone **203** (6.1:1 dr, 57 mg, 0.197 mmol, 73%) as a colourless oil characterised as a mixture of diastereomers. $\mathbf{R}_f$ 0.47 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.31 (1H, t, J = 8.1 Hz, Ar*H*), 6.91–6.81 (2H, m, Ar*H*), 6.81 (1H, m, Ar*H*), 5.85 (1H, d, J = 6.5 Hz, C1-*epi* ArC*H*), 5.01 (1H, d, J = 4.8 Hz, ArC*H*), 3.85 (3H, s, C1-*epi* CO_2CH_3), 3.83 (3H, s, CO_2CH_3), 3.82 (3H, s, C1-*epi* ArOCH_3), 3.74 (3H, s, ArOCH_3), 3.34–3.28 (1H, m, C1-*epi* ArCHC*H*), 3.16 (1H, ddd, J = 7.0, 4.8, 2.3 Hz, ArCHC*H*), 2.45 (1H, ddd, J = 13.6, 11.1, 6.6 Hz, C*H*H), 2.40–2.33 (1H, m, C*H*H), 2.14–.188 (2H, m, CH_2), 1.82–1.62 (1H, m, C*H*H), 1.61–1.46 (1H, m, C*H*H), 1.42–1.17 (1H, m, C1-*epi* C*H*H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) *Only data for the major isomer are reported* 175.9 (lactone *C*=O), 170.8 (ester *C*=O), 159.9 (*Ar*), 141.3 (*Ar*), 129.8 (*Ar*), 117.6 (*Ar*), 114.0 (*Ar*), 110.9 (*Ar*), 85.9 (Ar*C*HO), 62.2 (MeO_2CC), 55.3 (CO_2CH_3), 54.3 (ArCH*C*H), 53.1 (ArO*C*H_3), 35.3 (CH_2), 33.7 (CH_2), 25.5 (CH_2); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2956 (m, C-H), 1776 (s, lactone C=O), 1742 (s, ester C=O), 1604 (m), 1456 (m), 1437 (m), 1261 (s), 1150 (m); **m/z** 313.1 ([M+Na]$^+$, 72%), HRMS found 313.1047, $C_{16}H_{18}NaO_5$ requires 313.1046.

(1*R,3a*S**,6a*R*)-Methyl**

1-(3-nitrophenyl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate

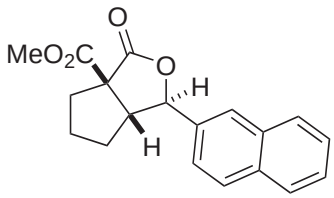


204

According to GP 6, malonate **176** (96 mg, 0.300 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (4→3:1 PE:EtOAc), gave cyclopentane-lactone **204** (3.4:1 dr, 60 mg, 0.197 mmol, 66%), which crystallised on standing, which gave white plate-like crystals *m.p.* 101–101 °C. The diastereomers could also be separated by semi-preparative HPLC, which gave a diastereomerically pure sample of cyclopentane-lactone **204** from which an X-ray crystal structure was obtained. Data for major isomer **204**: $\mathbf{R}_f$ 0.22 (2:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 8.29 (1H, br s, *Ar*), 8.23 (1H, d, J = 8.3 Hz, *Ar*), 7.72 (1H, d, J = 8.3 Hz, *Ar*), 7.61 (1H, dd, J = 8.3, 8.3 Hz, *Ar*), 5.16 (1H, d, J = 4.4 Hz, ArC*H*), 3.75 (3H, s, CO_2CH_3), 3.14 (1H, ddd, J = 7.7, 4.4, 2.3 Hz, ArCHC*H*), 2.46 (1H, ddd, J = 13.5, 11.2, 6.4 Hz, MeO_2CCCHH), 2.42–2.36 (1H, m, MeO_2CCCHH), 2.15–2.06 (1H, m, CHC*H*H), 2.05–1.96 (2H, m, CHCH*H* & $CHCH_2CHH$), 1.80–1.70 (1H, m, $CHCH_2CHH$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 175.4 (lactone *C*=O), 170.3 (ester *C*=O), 148.5 (*Ar*), 142.0 (*Ar*), 131.5 (*Ar*), 129.9 (*Ar*), 123.4 (*Ar*), 120.6 (*Ar*), 84.7 (Ar*C*H), 62.1 (MeO_2CC), 54.0 (ArCH*C*H), 53.3 (CO_2CH_3), 35.1 (MeO_2CCCH_2), 34.0 ($CHCH_2$), 25.5 ($CHCH_2CH_2$); Data for C1-*epi* **204**: $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 8.24–8.18 (2H, m, Ar*H*), 7.69–7.66 (1H, m, Ar*H*), 7.61 (1H, dd, J = 7.8, 7.8 Hz, Ar*H*), 5.95 (1H, d, J = 6.3 Hz, ArC*H*), 3.87 (3H, s, CO_2CH_3), 3.43–3.37 (1H, m, ArCHC*H*), 2.47 (1H, ddd, J = 14.0, 7.4, 7.4 Hz, MeO_2CCHH), 2.37 (1H, ddd, J = 14.0, 6.7, 6.7 Hz, MeO_2CCHH), 1.74–1.65 (1H, m, $CHCH_2CHH$), 1.65–1.58 (1H, m, $CHCH_2CHH$), 1.58–1.49 (1H, m, CHC*H*H); 1.24–1.16 (1H, m, CHCH*H*); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 175.0 (lactone *C*=O), 169.8 (ester *C*=O), 148.5 (*Ar*), 138.8 (*Ar*), 130.9 (*Ar*), 129.9 (*Ar*), 123.1 (*Ar*), 120.2 (*Ar*), 80.0 (Ar*C*H), 63.6 (MeO_2CC), 53.4 (CO_2CH_3), 51.1 (ArCH*C*H), 34.5 (MeO_2CCCH_2), 28.6 ($CHCH_2$), 25.9 ($CHCH_2CH_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2958 (m, C-H), 1779 (s, lactone C=O), 1743 (s, ester C=O), 1533 (s, N=O), 1350 (s, N=O), 1258 (m), 1097 (m), **m/z** (ESI+) 328.1 ($[M+Na]^+$, 100%), HRMS found 328.0792, $C_{15}H_{15}NNaO_6$ requires 328.0792.

(1*S,3a*S**,6a*R**)-Methyl**

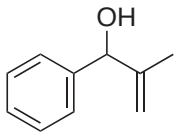
1-(naphthalen-2-yl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate



205

According to GP 6, malonate **184** (89 mg, 0.271 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (4:1 PE:EtOAc), gave cyclopentane-lactone **205** (1.6:1 dr, 70 mg, 0.226 mmol, 83%) as a pale yellow oil characterised as a 1.6:1 mixture of diastereomers. $\mathbf{R}_f$ 0.22 (4:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.92–7.81 (4H, m, Ar*H*), 7.55–7.50 (2H, m, Ar*H*), 7.48 (1H, dd, J = 8.5, 1.7 Hz, Ar*H*), 7.33 (1H, dd, J = 8.5, 1.6 Hz, C1-*epi* Ar*H*), 6.05 (1H, d, J = 6.5 Hz, C1-*epi* ArC*H*), 5.22 (1H, d, J = 4.8 Hz, ArC*H*), 3.88 (3H, s, C1-*epi* OCH_3), 3.71 (3H, s, OCH_3), 3.42 (1H, ddd, J = 8.7, 6.5, 6.5 Hz, C1-*epi* ArCHC*H*), 3.24 (1H, ddd, J = 7.2, 4.8, 2.2 Hz, ArCHC*H*), 2.50 (1H, dd, J = 13.5, 6.7 Hz, C(CO_2Me)C*H*H), 2.47 (1H, dd, J = 13.5, 6.5 Hz, C1-*epi* C(CO_2Me)C*H*H), 2.44–2.35 (1H, m, C(CO_2Me)CH*H*), 2.10–1.96 (2H, m, CHCH*H*), 1.84–1.74 (1H, m, CHC*H*H), 1.70–1.55 (2H, m, CH_2), 1.49 (1H, ddd, J = 14.0, 8.8, 6.7 Hz, C1-*epi* CHCH*H*), 1.31 (1H, ddd, J = 14.0, 4.0, 4.0 Hz, C1-*epi* CHCH*H*); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 176.0 (lactone *C*=O), 175.8 (lactone *C*=O), 170.9 (ester *C*=O), 170.3 (ester *C*=O), 137.0 (*Ar*), 133.8 (*Ar*), 133.2 (*Ar*), 133.1 (*Ar*), 133.0 (*Ar*), 132.9 (*Ar*), 128.9 (*Ar*), 128.5 (*Ar*), 128.0 (*Ar*), 128.0 (*Ar*), 127.8 (*Ar*), 127.7 (*Ar*), 126.6 (*Ar*), 126.6 (*Ar*), 126.5 (*Ar*), 126.3 (*Ar*), 124.5 (*Ar*), 123.8 (*Ar*), 122.9 (*Ar*), 122.7 (*Ar*), 86.2 (Ar*C*H), 81.5 (C1-*epi* Ar*C*H), 63.7 (MeO_2C*C*), 62.3 (MeO_2C*C*), 54.3 (*C*H), 53.3 (C1-*epi* CO_2*C*H_3), 53.1 (CO_2*C*H_3), 51.3 (C1-*epi* *C*H), 35.3 (*C*H_2), 34.8 (C1-*epi* *C*H_2), 33.7 (*C*H_2), 28.6 (C1-*epi* *C*H_2), 26.0 (C1-*epi* *C*H_2), 25.6 (*C*H_2); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2956 (m), 1775 (s, lactone C=O), 1741 (s, ester C=O), 1258 (m), 1148 (m); **m/z** (ESI+) 333.1 ($[M+Na]^+$, 69%), 643.2 ($[2M+Na]^+$, 100%), HRMS found 333.1100, $C_{19}H_{18}NaO_4$ requires 333.1097.

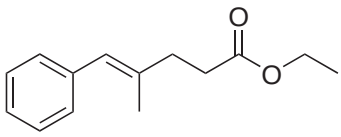
2-Methyl-1-phenylprop-2-en-1-ol



212

According to GP 1 with phenylmagnesium bromide in place of vinylmagnesium bromide, methacrolein (701 mg, 10.0 mmol) was treated with phenylmagnesium bromide, which gave alcohol **212** (1.48 g, 10.0 mmol, 100%) as a pale yellow oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.43–7.27 (5H, m, Ar*H*), 5.23 (1H, s, C*H*), 5.14 (1H, s, C*H*), 5.00–4.97 (1H, m, C*H*), 2.28 (1H, br s, O*H*), 1.64 (3H, s, CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 146.9 (*Ar* or $H_2C{=}C$), 142.0 (*Ar* or $H_2C{=}C$), 128.4 (*Ar*), 127.6 (*Ar*), 126.5 (*Ar*), 111.2 ($C{=}CH_2$), 77.8 (Ph*C*HOH), 18.3 (CH_3). *Data are consistent with literature values.*[153]

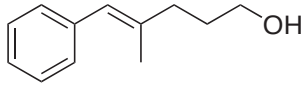
(*E*)-Ethyl 4-methyl-5-phenylpent-4-enoate



230

According to GP 2, alcohol **212** (1.47 g, 9.92 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (20:1 PE:EtOAc), gave ester **230** (1.46 g, 6.69 mmol, 67%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.41–7.28 (2H, m, Ar*H*), 7.28–7.17 (3H, m, Ar*H*), 6.34 (1H, s, PhC*H*=C(Me)), 4.18 (2H, q, J = 7.1 Hz, OCH_2CH_3), 2.59–2.52 (4H, m, CH_2CH_2), 1.90 (3H, s, PhCH=C(CH_3), 1.29 (3H, t, J = 7.1 Hz, OCH_2CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.2 (*C*=O), 138.2 (*Ar*), 137.1 (PhCH=*C*(Me)), 128.8 (*Ar*), 128.1 (*Ar*), 126.1 (*Ar*), 125.7 (Ph*C*H=C(Me)), 60.4 (OCH_2CH_3), 35.7 (CH_2), 33.2 (CH_2), 17.7 (PhCH=C(CH_3)), 14.3 (OCH_2CH_3). *Data are consistent with literature values.*[162]

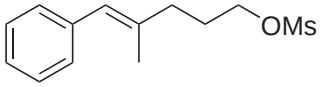
(*E*)-4-Methyl-5-phenylpent-4-en-1-ol



231

Accoding to GP 3, ester **230** (1.38 g, 6.32 mmol) was treated with $LiAlH_4$, which after flash column chromatography (3→0:1 PE:Et_2O), gave alcohol **231** (845 mg, 4.79 mmol, 76%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.34 (2H, t, J = 7.5 Hz, ArH), 7.26 (2H, d, J = 7.5 Hz, ArH), 7.21 (1H, t, J = 7.5 Hz, ArH), 6.34 (1H, s, PhCH=C), 3.72 (2H, t, J = 6.5 Hz, HOCH_2), 2.29 (2H, t, J = 7.5 Hz, CH=CCH_2), 1.90 (3H, s, CH_3), 1.87–1.78 (2H, m, $HOCH_2CH_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 138.5 (Ar or CH=C), 138.4 (Ar or CH=C), 128.8 (Ar), 128.1 (Ar), 125.9 (PhCH), 125.2 (Ar), 62.6 (HOCH$_2$), 37.0 (CH=CCH$_2$), 30.9 ($HOCH_2CH_2$), 17.8 (CH$_3$). *Data are consistent with literature values.*[163]

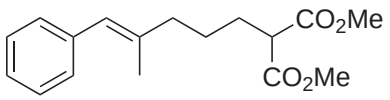
(*E*)-4-Methyl-5-phenylpent-4-enyl methanesulfonate



431

According to GP 4, alcohol **231** (749 mg, 4.25 mmol) was treated with MsCl, which gave mesylate **431** (1.07 g, 4.21 mmol, 99%) as a pale yellow oil, which was used without purification. $\mathbf{R}_f$ 0.59 (Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.33 (2H, t, J = 7.6 Hz, ArH), 7.28–7.17 (3H, m, ArH), 6.33 (1H, s, CH=C(CH$_3$)), 4.29 (2H, t, J = 6.4 Hz, MsOCH_2), 3.02 (3H, s, SO_2CH_3), 2.31 (2H, t, J = 7.5 Hz, CH=CCH_2), 2.04–1.96 (2H, m, $MsOCH_2CH_2$), 1.88 (3H, s, CH=C(CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 138.0 (Ar), 136.8 (CH=C(CH$_3$), 128.8 (Ar), 128.1 (Ar), 126.2 (Ar & PhCH=C(CH$_3$), 69.5 (MsOCH$_2$), 37.3 (SO_2CH_3), 36.3 (PhCH=CCH$_2$), 27.3 ($MsOCH_2CH_2$), 17.6 (CH=C(CH$_3$)); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3024 (s), 1651 (w, C=C), 1491 (w), 1354 (s, SO_2), 1174 (s, $S0_2$), 972 (m), 928 (m); **m/z** (ESI+) 277.1 ($[M+Na]^+$, 100%), HRMS found 277.0870, $C_{13}H_{18}NaO_3S$ requires 277.0869.

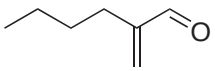
(*E*)-Dimethyl 2-(4-methyl-5-phenylpent-4-enyl)malonate



232

According to GP 5, mesylate **431** (1.02 g, 4.00 mmol) was treated with DMM, which after flash column chromatography (4:1 PE:Et_2O), gave malonate **232** (907 mg, 3.36 mmol, 84%) as a colourless oil. $\mathbf{R}_f$ 0.33 (2:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.32 (2H, t, J = 7.5 Hz, ArH), 7.24 (2H, d, J = 7.5 Hz, ArH), 7.19 (1H, t, J = 7.5 Hz, ArH), 6.29 (1H, s, PhCH=C(Me)), 3.76 (6H, s, CO_2CH_3), 3.44 (1H, t, J = 7.5 Hz, $(MeO_2C)_2CH$), 2.22 (2H, t, J = 7.5 Hz, PhCH=C(Me)CH_2), 2.01–1.93 (2H, m, $(MeO_2C)_2CHCH_2$), 1.85 (3H, s, PhCH=C(CH_3), 1.61–1.52 (2H, m, PhCH=C(Me)CH_2CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.8 (C=O), 138.4 (Ar), 138.0 (PhCH=C(Me)), 128.8 (Ar), 128.0 (Ar), 125.9 (Ar), 125.5 (PhCH=C(Me)), 52.5 (CO_2CH_3), 51.6 ($(MeO_2C)_2CH$), 40.1 (PhCH=C(Me)CH_2), 28.4 ($(MeO_2C)_2CHCH_2$), 25.6 (PhCH=C(Me)CH_2CH_2), 17.6 (PhCH=C(CH_3)); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2953 (m, C-H), 1737 (s, C=O), 1652 (w, C=C), 1491 (m), 1150 (m); **m/z** (ESI+) 313.2 ([M+Na]$^+$, 100%), HRMS found 313.1409, $C_{17}H_{22}NaO_4$ requires 313.1410.

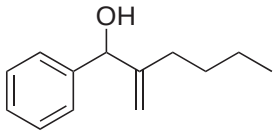
2-Methylenehexanal



215

According to GP 7, freshly distilled hexanal **213** (2.00 g, 20.0 mmol) was treated with aqueous formaldehyde. The solvent was removed *in vacuo* and the crude product was purified by Kugelrohr distillation (140 °C, 150 mBar), which gave α,β-unsaturated aldehyde **215** (1.86 g, 16.6 mmol, 83%) as a colourless oil. $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 9.53 (1H, s, CHO), 6.24 (1H, s, C=CHH), 5.98 (1H, s, C=CHH), 2.24 (2H, t, J = 7.6 Hz, OHCCCH_2), 1.47–1.38 (2H, m, CCH_2CH_2), 1.38–1.28 (2H, m, H_3CCH_2), 0.91 (3H, t, J = 7.3 Hz, CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 194.8 (CHO), 150.4 (H_2C=C), 133.9 (C=CH$_2$), 29.9 (CCH_2CH_2), 27.4 (OHCCCH$_2$), 22.3 (H_3CCH_2), 13.8 (CH_3). *Data are consistent with literature values.*[86]

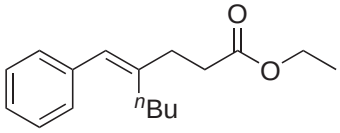
2-Methylene-1-phenylhexan-1-ol



217

According to GP 1, α,β-unsaturated aldehyde **215** (879 mg, 7.81 mmol) was treated with phenylmagnesium bromide, which gave alcohol **217** (1.32 g, 6.95 mmol, 89%) as a pale yellow oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.42–7.26 (5H, m, Ar*H*), 5.28 (1H, s, C=C*H*H), 5.16 (1H, s, PhC*H*OH), 5.00 (1H, s, C=CH*H*), 2.14 (1H, br s, O*H*), 1.98 (1H, dt, J = 15.7, 7.8 Hz, CH(OH)CC*H*H), 1.86 (1H, dt, J = 15.7, 7.6 Hz, CH(OH)CCH*H*), 1.91–1.81 (2H, m, CCH_2CH_2), 1.33–1.22 (2H, m, H_3CCH_2), 0.87 (3H, t, J = 7.3 Hz, CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 151.2 ($H_2C{=}C$), 142.2 (*Ar*), 128.4 (*Ar*), 127.7 (*Ar*), 126.7 (*Ar*), 109.6 ($C{=}CH_2$), 77.3 (Ph*C*HOH), 31.5 (CH(OH)C*C*H_2), 30.0 (CCH_2CH_2), 22.5 (H_3CCH_2), 14.0 (H_3C); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3359 (br s, O-H), 2929 (s), 1647 (w, C=C), 1453 (m), 1027 (m), 903 (s); **m/z** HRMS (FI) found 190.1351, $C_{13}H_{18}O$ requires 190.1358.

(*E*)-Ethyl 4-benzylideneoctanoate

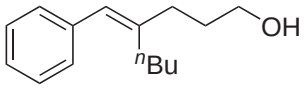


233

According to GP 2, alcohol **217** (951 mg, 5.00 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (20:1 PE:EtOAc) gave ester **233** (1.04 g, 4.00 mmol, 80%) as a colourless oil. $\mathbf{R}_f$ 0.62 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.39–7.29 (2H, m, Ar*H*), 7.25–7.16 (3H, m, Ar*H*), 6.31 (1H, s, PhC*H*=C), 4.18 (2H, q, J = 7.1 Hz, OCH_2), 2.57–2.50 (4H, m, $EtO_2CCH_2CH_2$), 2.28–2.22 (2H, m, $CH_2CH_2CH_2$), 1.56–1.42 (2H, m, $CH_2CH_2CH_3$), 1.39–1.30 (2H, m, $CH_2CH_2CH_3$), 1.29 (3H, t, J = 7.1 Hz, OCH_2CH_3), 0.91 (3H, t, J = 7.3 Hz, $CH_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.3 (*C*=O), 141.7 (PhCH=*C*), 138.2 (*Ar*), 128.6 (*Ar*), 128.1 (*Ar*), 126.1 (*Ar*), 125.5 (Ph*C*H=C), 60.4 (O*C*H_2), 33.3 ($EtO_2CCH_2CH_2$), 32.2 ($EtO_2CCH_2CH_2$), 30.5 ($CH_2CH_2CH_2$ & $CH_2CH_2CH_3$), 22.8 ($CH_2CH_2CH_3$), 14.3 (OCH_2CH_3), 13.9 ($CH_2CH_2CH_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2958 (m, C-H), 1737 (s, C=O), 1648 (w, C=C), 1175 (m); **m/z** (ESI+) 283.2 ($[M+Na]^+$, 100%), HRMS found 283.1669, $C_{17}H_{24}NaO_2$

requires 283.1669.

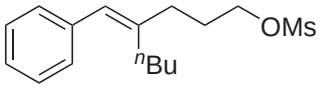
(*E*)-4-Benzylideneoctan-1-ol



234

According to GP 3, ester **233** (583 mg, 2.24 mmol) was treated with $LiAlH_4$, which after flash column chromatography (3:1→0:1 PE:Et_2O), gave alcohol **234** (486 mg, 2.23 mmol, 99%) as a colourless oil. $\mathbf{R}_f$ 0.55 (Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.32 (2H, t, J = 7.6 Hz, ArH), 7.24–7.17 (3H, m, ArH), 6.32 (1H, s, PhCH=C), 3.73 (2H, t, J = 6.5 Hz, HOCH_2), 2.31–2.22 (4H, m, CH=C(CH_2)(CH_2)), 1.81 (2H, tt, J = 7.2, 6.5 Hz, HOCH$_2$CH_2), 1.58 (1H, br s, OH), 1.52–1.43 (2H, m, CH_2CH$_2$CH$_3$), 1.38–1.28 (2H, m, CH_2CH$_3$), 0.90 (3H, t, J = 7.3 Hz, CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 143.1 (PhCH=C), 138.4 (Ar), 128.6 (Ar), 128.1 (Ar), 125.9 (Ar), 125.2 (PhCH=C), 62.8 (HOCH$_2$), 33.4 (CH=CCH$_2$), 31.1 (HOCH$_2$$CH_2$), 30.5 ($CH_2CH_2CH_3$), 30.4 (CH=C$CH_2$), 22.9 ($CH_2CH_3$), 13.9 ($CH_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 3330 (br s, OH), 2954 (m), 1645 (s, C=O), 1462 (m), 1059 (m); **m/z** HRMS (FI) found 218.1665, $C_{15}H_{22}O$ requires 218.1671.

(*E*)-4-Benzylideneoctyl methanesulfonate

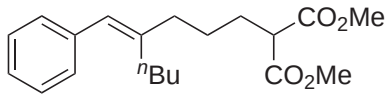


432

According to GP 4, alcohol **234** (316 mg, 1.45 mmol) was treated with MsCl, which gave mesylate **432** (425 mg, 1.45 mmol, 100%) as a pale yellow oil, which was used without purification. $\mathbf{R}_f$ 0.61 (Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.33 (2H, t, J = 7.6 Hz, ArH), 7.25–7.18 (3H, m, ArH), 6.32 (1H, s, PhCH=C), 4.31 (2H, t, J = 6.4 Hz, MsOCH_2), 3.04 (3H, s, SO_2CH_3), 2.31 (2H, t, J = 7.6 Hz, MsOCH$_2$CH$_2$CH_2), 2.28–2.21 (2H, m, H$_3$CCH$_2$CH$_2$CH_2), 2.05–1.95 (2H, m, MsOCH$_2$CH_2), 1.52–1.42 (2H, m, H$_3$CCH$_2$CH_2), 1.39–1.28 (2H, m, H$_3$CCH_2), 0.90 (3H, t, J = 7.3 Hz, CH$_2$CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 141.8 (PhCH=C), 138.5 (Ar), 129.0 (Ar), 128.5 (Ar), 126.6 (PhCH=C), 126.5 (Ar), 70.0 (MsOCH$_2$), 37.8 ($SO_2$$CH_3$), 33.2 (MsOCH$_2CH_2$$CH_2$), 30.9 (H$_3CCH_2$$CH_2$), 30.6 (H$_3CCH_2CH_2$$CH_2$), 28.0 (MsOCH$_2$$CH_2$), 23.2 (H$_3CCH_2$), 14.3 (CH$_2$$CH_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2957 (m, C-H), 1646 (w, C=C), 1599 (w, C=C), 1355 (s, SO_2), 1174 (s, SO_2); **m/z** (ESI+) 319.1 ([M+Na]$^+$, 100%) 615.3 ([2M+Na]$^+$,

37%), HRMS found 319.1339, $C_{16}H_{24}NaO_3S$ requires 319.1338.

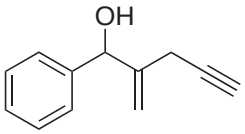
(*E*)-Dimethyl 2-(4-benzylideneoctyl)malonate



235

According to GP 5, mesylate **432** (401 mg, 1.35 mmol) was treated with DMM, which after flash column chromatography (4:1 PE:Et_2O), gave malonate **235** (323 mg, 0.97 mmol, 72%) as a colourless oil. $\mathbf{R}_f$ 0.22 (4:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.32 (2H, dd, J = 7.6, 7.6 Hz, ArH), 7.23–7.16 (3H, m, ArH), 6.28 (1H, s, PhCH=C), 3.77 (6H, CO_2CH_3), 3.45 (1H, t, J = 7.5 Hz, $(CO_2Me)_2CH$), 2.27–2.17 (4H, m, CH=C(CH_2)$_2$), 2.04–1.94 (2H, m, CHCH_2), 1.62–1.51 (2H, m, $CHCH_2CH_2$), 1.51–1.41 (2H, $CH_3CH_2CH_2$), 1.37–1.27 (2H, CH_3CH_2), 0.90 (3H, CH_2CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 170.3 (C=O), 143.0 (PhCH=C), 138.8 (Ar), 129.0 (Ar), 128.4 (Ar), 126.3 (PhCH=C), 125.8 (Ar), 52.9 (CO_2CH_3), 52.0 ($(CO_2Me)_2CH$), 37.0 (CH=CCH$_2$), 30.9 (CH=CCH$_2$), 30.6 ($H_3CCH_2CH_2$), 29.0 (CHCH$_2$), 26.2 ($CHCH_2CH_2$), 23.2 (H_3CCH_2), 14.4 (CH_2CH_3); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2955 (s), 1748 (s, C=O), 1646 (w, C=C), 1438 (m), 1150 (m); **m/z** (ESI+) 355.2 ([M+Na]$^+$, 100%), 687.4 ([2M+Na]$^+$, 66%), HRMS found 355.1880, $C_{20}H_{28}NaO_4$ requires 355.1880.

2-Methylene-1-phenylpent-4-yn-1-ol



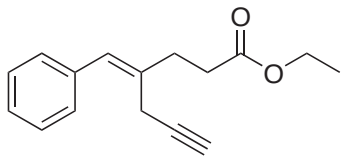
220

According to the procedure of Nicolaou *et al.*,[88] DMSO (3.55 mL, 50.0 mmol), triethylamine (6.93 mL, 50.0 mml), and 4-pentyn-1-ol (841 mg, 10.0 mmol) were dissolved in dry DCM (20 mL) and pyridine·SO_3 complex (3.18 g, 20.0 mmol) was added. The solution was stirred for 2 h, after which time *N*-methyl-*N*-methylenemethanaminium chloride (1.40 g, 15.0 mmol) was added. The solution was stirred overnight and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (15 mL). The layers were separated and the aqueous extracted with Et_2O (4×15 mL). The combined organic extracts were washed successively with 10% aqueous $CuSO_4$ solution (10 mL), 1 M aqueous HCl solution (10 mL), brine (10 mL), and then dried ($MgSO_4$) and filtered. The excess solvent was distilled off through a Vigreux column

and the residue filtered through a silica plug eluting with 25% Et_2O in 30–40 °C petrol. The solvent was removed carefully, which gave the crude α,β-unsaturated aldehyde.

According to GP 1 with phenylmagnesium bromide in place of vinylmagnesium bromide, the crude α,β-unsaturated aldehyde was treated with phenylmagnesium bromide (3 M in Et_2O, 3.33 mL, 10.0 mmol), which after flash column chromatography (3:1 PE:EtOAc), gave alkynol **220** (412 mg, 2.40 mmol, 24% from 4-pentyn-1-ol) as a foul smelling oil. $\mathbf{R}_f$ 0.35 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.46–7.19 (5H, m, Ar*H*), 5.41 (1H, s, C=C*H*H), 5.38 (1H, s, C=CH*H*), 5.29 (1H, s, C*H*OH), 2.95 (1H, d, J = 19.6 Hz, C*H*HC≡CH), 2.76 (1H, d, J = 19.6 Hz, CH*H*C≡CH), 2.27 (1H, br s, O*H*), 2.15 (1H, t, J = 2.6 Hz, C≡C*H*); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 145.2 (*Ar*), 141.1 (*C*=CH_2), 128.5 (*Ar*), 127.9 (*Ar*), 126.4 (*Ar*), 112.6 (C=*C*H_2), 81.0 (CH_2*C*≡CH), 76.5 (Ph*C*HOH), 71.2 (CH_2C≡*C*H), 21.7 (*C*H_2C≡CH); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 3381 (br m, O-H), 3298 (s, C≡C-H), 2120 (w, C≡C), 1653 (w, C=C), 1600 (w, C=C), 1452 (m), 1420 (m), 1081 (s); **m/z** (FI) HRMS found 172.0890, $C_{12}H_{12}O$ requires 172.0888.

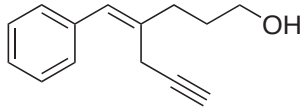
(*Z*)-Ethyl 4-benzylidenehept-6-ynoate



236

According to GP 2, alcohol **220** (375 mg, 2.18 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (30→15:1 PE:EtOAc), gave ester **236** (417 mg, 1.72 mmol, 79%) as an unstable colourless oil. Data are reported for partially pure material. $\mathbf{R}_f$ 0.51 (3:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.35 (2H, t, J = 7.5 Hz, Ar*H*), 7.30–7.21 (3H, m, Ar*H*), 6.41 (1H, s, PhC*H*=C), 4.17 (2H, q, J = 7.1 Hz, OCH_2), 3.13 (2H, d, J = 2.5 Hz, CH_2C≡CH), 2.74–2.68 (2H, m, CH_2), 2.67–2.59 (2H, m, CH_2), 2.07 (1H, t, J = 2.5 Hz, C≡C*H*), 1.28 (3H, t, J = 7.1 Hz, OCH_2CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 173.0 (*C*=O), 137.1 (*Ar*), 135.3 (PhCH=*C*), 128.7 (*Ar*), 128.3 (*Ar*), 127.4 (Ph*C*H=C), 126.8 (*Ar*), 81.9 (CH_2*C*≡CH), 69.3 (C≡*C*H), 60.4 (O*C*H_2), 33.0 (*C*H_2), 32.2 (*C*H_2), 21.1 (*C*H_2C≡CH), 14.3 (OCH_2*C*H_3); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 3287 (s, C≡C-H), 2935 (m, C-H), 1735 (s, C=O), 1651 (w, C=C), 1599 (w, C=C); **m/z** (ESI+) 265.1 ($[M+Na]^+$, 100%), HRMS found 265.1200, $C_{16}H_{18}NaO_2$ requires 265.1199.

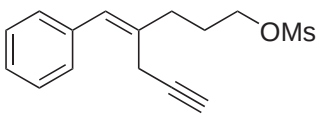
(*Z*)-4-Benzylidenehept-6-yn-1-ol



237

According to GP 3, ester **236** (379 mg, 1.56 mmol) was treated with $LiAlH_4$, which after flash column chromatography (1:1→1:2 PE:Et_2O), gave alcohol **237** (245 mg, 1.23 mmol, 79%) as a colourless oil. $\mathbf{R}_f$ 0.12 (1:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.36 (2H, t, J = 7.5 Hz, ArH), 7.31–7.22 (3H, m, ArH), 6.43 (1H, s, PhCH=C), 3.75 (2H, t, J = 6.5 Hz, HOCH_2), 3.13 (2H, d, J = 2.5 Hz, CH_2C≡CH), 2.48–2.42 (2H, m, CH=CCH_2), 2.07 (1H, t, J = 2.5 Hz, CH_2C≡CH), 1.93–1.84 (2H, m, HOCH_2CH_2) 1.83 (1H, br s, OH); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 137.3 (PhCH=C), 136.5 (Ar), 128.7 (Ar), 128.3 (Ar), 127.0 (Ar), 126.7 (PhCH=C), 82.3 (CH_2C≡CH), 69.1 (C≡CH), 62.5 (HOCH$_2$), 33.4 (CH=CCH$_2$), 30.8 (HOCH$_2C$H$_2$), 21.2 (CH$_2$C≡CH); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 3288 (s, C≡C-H), 2941 (m, C-H), 2115 (w, C≡C), 1650 (w, C=C), 1600 (w, C=C), 1054 (m); **m/z** HRMS (FI) found 200.1203, $C_{14}H_{16}O$ requires 200.1201.

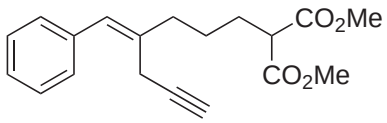
(*Z*)-4-Benzylidenehept-6-ynyl methanesulfonate



433

According to GP 4, alcohol **237** (240 mg, 1.20 mmol) was treated with MsCl, which gave mesylate **433** (326 mg, 1.17 mmol, 98%) as a pale yellow oil, which was used without purification. $\mathbf{R}_f$ 0.27 (2:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.40–7.33 (2H, m, ArH), 7.32–7.20 (3H, m, ArH), 6.44 (1H, s, PhCH=C), 4.33 (2H, t, J = 6.4 Hz, MsOCH_2), 3.12 (2H, d, J = 2.5 Hz, HC≡CCH_2), 3.04 (3H, s, SO_2CH_3), 2.49 (2H, t, J = 7.6 Hz, PhCH=CCH_2), 2.14–2.04 (3H, m, MsOCH$_2$CH_2 & C≡CH); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 137.3 (PhCH=C), 135.3 (Ar), 129.1 (Ar), 128.8 (Ar), 128.5 (PhCH=C), 127.3 (Ar), 82.3 (C≡CH), 69.8 (C≡CH & MsOCH$_2$), 37.8 (SO_2CH_3), 33.5 (PhCH=CCH$_2$), 27.7 (MsOCH$_2C$H$_2$), 21.5 (CH$_2$C≡CH); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 3288 (m, C≡C-H), 2940 (w, C-H), 2115 (w, C≡C), 1654 (w, C=C), 1599 (w, C=C), 1353 (s, SO_2), 1173 (s, SO_2), 933 (s); **m/z** (ESI+) 309.1 ([M+Na]$^+$, 100%), HRMS found 301.0871, $C_{15}H_{18}NaO_3S$ requires 301.0869.

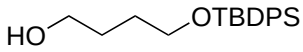
(*Z*)-Dimethyl 2-(4-benzylidenehept-6-ynyl)malonate



238

According to GP 5, mesylate **433** (306 mg, 1.10 mmol) was treated with DMM, which after flash column chromatography (4→3:1 PE:Et_2O), gave malonate **238** (307 mg, 0.98 mmol, 89%) as an unstable colourless oil. Data are reported for partly pure material. $\mathbf{R}_f$ 0.19 (4:1 PE:Et_2O); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.39–7.32 (2H, m, Ar*H*), 7.29–7.14 (3H, m, Ar*H*), 6.39 (1H, m, PhC*H*), 3.76 (6H, s, CO_2CH_3), 3.44 (1H, t, J = 7.5 Hz, $(CO_2Me)_2CH$), 3.09 (2H, d, J = 2.1 Hz, $CH_2C{\equiv}C$-H), 2.38 (2H, td, J = 7.7, 1.2 Hz, $CH{=}CCH_2$), 2.04 (1H, t, J = 2.1 Hz, $C{\equiv}CH$), 2.02 (2H, m, $CHCH_2$), 1.67–1.60 (2H, m, $CH{=}CCH_2CH_2$); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 169.8 (*C*=O), 137.3 (PhCH=*C*), 136.1 (*Ar*), 128.7 (*Ar*), 128.2 (*Ar*), 127.2 (*Ar*), 126.6 (Ph*C*H=C), 82.1 (*C*≡CH), 69.0 (C≡*C*H), 52.5 (CO_2CH_3), 51.6 ($(CO_2Me)_2CH$), 36.5 ($CH{=}CCH_2CH_2$), 28.4 ($CHCH_2$), 25.4 ($CH{=}CCH_2CH_2$), 20.9 ($CH_2C{\equiv}CH$); $\boldsymbol{\nu}_\mathbf{max}$ **/ cm^{-1}** 3288 (m, C≡C-H), 2953 (m, C-H), 2115 (w, C≡C), 1735 (s, C=O), 1600 (w, C=C), 1493 (m), 1153 (m); **m/z** (ESI+) 337.2 ($[M+Na]^+$, 100%), HRMS found 337.1409, $C_{19}H_{22}NaO_4$ requires 337.1410.

4-(*tert*-Butyldiphenylsilyloxy)butan-1-ol

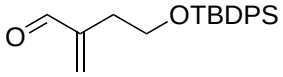


222

According to the procedure of Carter and Weldon,[164] DMAP (244 mg, 2.0 mmol) followed by butane-1,4-diol (5.12 mL, 58.0 mmol) were added to a stirred solution of TBDPSCl (5.50 g, 20.0 mmol) and NEt_3 (3.05 mL, 22.0 mmol) in DCM (150 mL). The reaction was stirred overnight and then quenched by the addition of saturated aqueous NH_4Cl (125 mL). The layers were separated and the aqueous was extracted with Et_2O (3×125 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (3:1→3:2 PE:EtOAc), which gave silyl ether **222** (6.04 g, 18.4 mmol, 92%) as a colourless oil. $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.74–7.60 (4H, m, Ar*H*), 7.51–7.32 (6H, m, Ar*H*), 3.71 (2H, t, J = 5.7 Hz, $TBDPSOCH_2$), 3.68–3.62 (2H, m, $HOCH_2$), 1.75–1.59 (4H, m, CH_2CH_2), 1.06 (9H, s, $SiC(CH_3)_3$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 135.6 (*Ar*), 133.6 (*Ar*), 129.6 (*Ar*), 127.7 (*Ar*), 64.0 ($HOCH_2$), 62.8 ($TBDPSOCH_2$), 29.8 (CH_2), 29.3

(CH$_2$), 26.8 (SiC(CH$_3$)$_3$), 19.2 (SiC(CH$_3$)$_3$). *Data are consistent with literature values.*[164]

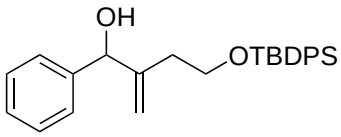
4-(*tert*-Butyldiphenylsilyloxy)-2-methylenebutanal



223

Following the same procedure as for α,β-unsaturated aldehyde **220** (985 mg, 3.0 mmol), alcohol **222** was treated with SO$_3$·py followed by Böhme's salt, which after flash column chromatography (9→3:1), which gave α,β-unsaturated aldehyde **223** (430 mg, 1.30 mmol, 42%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, CDCl$_3$) 9.53 (1H, s, CHO), 7.80–7.59 (4H, m, ArH), 7.54–7.33 (6H, m, ArH), 6.39 (1H, d, J = 0.8 Hz, C=CHH), 6.07 (1H, d, J = 0.8 Hz, C=CHH), 3.79 (2H, t, J = 6.2 Hz, TBDPSOCH_2), 2.56 (2H, t, J = 6.2 Hz, TBDPSOCH$_2$CH_2), 1.10 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, CDCl$_3$) 194.4 (CHO), 147.1 (CHOC=CH$_2$), 135.9 (Ar), 135.6 (Ar), 133.7 (Ar), 129.7 (Ar), 127.7 (C=CH$_2$), 61.8 (TBDPSOCH$_2$), 31.1 (OCH$_2$$CH_2$), 26.9 (SiC($CH_3$)$_3$), 19.2 (Si$C$(CH$_3$)$_3$). *Data are consistent with literature values.*[165]

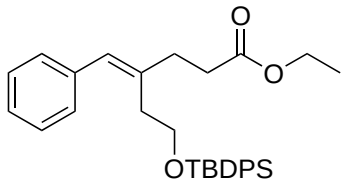
4-(*tert*-Butyldiphenylsilyloxy)-2-methylene-1-phenylbutan-1-ol



224

According to GP 1 with phenylmagnesium bromide in place of vinylmagnesium bromide, aldehyde **223** (542 mg, 1.60 mmol) was treated with phenylmagnesium bromide, which after flash column chromatography (4→3:1 PE:EtOAc), gave alcohol **224** (625 mg, 1.50 mmol, 94%) as a colourless oil. $\mathbf{R}_f$ 0.33 (4:1 PE:Et$_2$O); $\boldsymbol{\delta_H}$ (400 MHz, CDCl$_3$) 7.78–7.65 (4H, m, ArH), 7.54–7.21 (11H, m, ArH), 5.31 (1H, s, C=CHH), 5.25 (1H, d, J = 4.1 Hz, PhCHOH), 5.06 (1H, s, C=CHH), 3.83–3.69 (2H, m, TBDPSOCH_2), 2.37–2.27 (1H, m, CCHH), 2.19 (1H, dt, J = 14.6, 5.6 Hz, CCHH), 1.12 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, CDCl$_3$) 148.7 (PhCHOHC=CH$_2$), 142.5 (Ar), 135.7 (Ar), 135.6 (Ar), 133.2 (Ar), 133.2 (Ar), 129.8 (Ar), 128.3 (Ar), 127.8 (Ar), 127.3 (Ar), 126.5 (Ar), 113.8 (C=CH$_2$), 77.3 (PhCHOH), 64.4 (TBDPSOCH$_2$), 34.6 (CCH$_2$CH$_2$), 26.9 (SiC(CH$_3$)$_3$), 19.2 (SiC(CH$_3$)$_3$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3410 (br m, O-H), 3070 (m, Ar), 2932 (m, C-H), 2859 (m, C-H), 1647 (w, C=C), 1591 (w, C=C), 1109 (s); **m/z** (FI) HRMS found 439.2061, $C_{27}H_{32}NaO_2Si$ requires 439.2064.

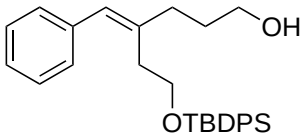
(*Z*)-Ethyl 4-benzylidene-6-(*tert*-butyldiphenylsilyloxy)hexanoate



239

According to GP 2, alcohol **224** (532 mg, 1.28 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (7:1 PE:EtOAc), gave ester **239** (514 mg, 1.02 mmol, 83%) as a colourless oil and characterised as a 10:1 mixture of Z:E isomers with data given for the major diastereomer. $\mathbf{R}_f$ 0.41 (4:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.74–7.62 (4H, m, ArH), 7.47–7.36 (6H, m, ArH), 7.33–7.16 (5H, m, ArH), 6.40 (1H, s, PhCH=C), 4.21–4.08 (2H, m, $CO_2CH_2CH_3$), 3.81 (2H, t, J = 6.9 Hz, TBDPSOCH_2), 2.57 (2H, t, J = 6.9 Hz, TBDPSOCH$_2$CH_2), 2.49 (4H, br s, CH_2CH_2CO$_2$Et), 1.33–1.24 (3H, m, $CO_2CH_2CH_3$), 1.05 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 173.1 (C=O), 138.2 (PhCH=C), 137.8 (Ar), 135.6 (Ar), 133.7 (Ar), 129.6 (Ar), 128.7 (Ar), 128.1 (Ar), 127.7 (PhCH=C), 126.3 (Ar), 62.5 (TBDPSOCH$_2$), 60.4 (CO_2CH$_2$CH$_3$), 33.7 (CH$_2$), 33.3 (CH$_2$), 32.5 (CH$_2$), 26.8 (SiC(CH$_3$)$_3$), 19.1 (SiC(CH$_3$)$_3$), 14.3 (CO_2CH_2CH$_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2931 (m, C-H), 1734 (s, C=O), 1427 (m), 1155 (s), 670 (s); **m/z** (ESI+) HRMS found 509.2472, $C_{31}H_{38}NaO_3Si$ requires 509.2482.

(*Z*)-4-Benzylidene-6-(*tert*-butyldiphenylsilyloxy)hexan-1-ol

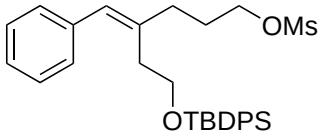


240

According to GP 3, a mixture of E and Z ester **239** (279 mg, 0.57 mmol) was treated with $LiAlH_4$, which after flash column chromatography (4→1:1 PE:EtOAc), gave alcohol **240** (185 mg, 0.42 mmol, 73%) as a colourless oil characterised as a mixture of E and Z diastereomers. $\mathbf{R}_f$ 0.25 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.78–7.64 (4H, m, ArH), 7.50–7.35 (7H, m, ArH), 7.35–7.25 (4H, m, ArH), 6.42 (1H, s, PhCH=C), 3.82 (2H, t, J = 6.9 Hz, TBDPSOCH_2), 3.67 (2H, t, J = 6.1 Hz, HOCH_2), 2.59 (2H, t, J = 6.9 Hz, TBDPSOCH$_2$CH_2), 2.24–2.18 (2H, m, HOCH$_2$CH$_2$CH_2), 1.79–1.69 (2H, m, HOCH$_2$CH_2), 1.34 (1H, br s, OH), 1.07 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 139.7 (PhCH=C),

138.4 (*Ar*), 136.0 (*Ar*), 134.2 (*Ar*), 130.0 (*Ar*), 129.1 (*Ar*), 128.5 (*Ar*), 128.1 (*Ar*), 127.8 (*Ar*), 126.5 (Ph*C*H=C), 63.1 (HO*C*H_2), 62.9 (TBDPSO*C*H_2), 34.1 (HOCH$_2$CH$_2$*C*H_2), 34.0 (TBDPSOCH$_2$*C*H_2), 31.5 (HOCH$_2$*C*H_2), 27.3 (SiC(*C*H_3)$_3$), 19.6 (Si*C*(CH$_3$)$_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3331 (br, O-H), 2931 (m, C-H), 1649 (w, C=C), 1599 (w, C=C), 1109 (s), 700 (s); **m/z** (ESI+) HRMS found 467.2373, $C_{29}H_{36}NaO_2Si$ requires 467.2377.

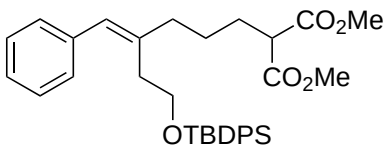
(*Z*)-4-Benzylidene-6-(*tert*-butyldiphenylsilyloxy)hexyl methanesulfonate



434

According to GP 4, a mixture of *E* and *Z* alcohol **240** (239 mg, 0.54 mmol) was treated with MsCl, which gave mesylate **434** (275 mg, 0.53 mmol, 98%) as a pale yellow oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.74–7.62 (4H, m, Ar*H*), 7.50–7.33 (6H, m, Ar*H*), 7.35–7.13 (5H, m, Ar*H*), 6.40 (1H, s, PhC*H*=C), 4.23 (2H, t, J = 6.4 Hz, MsOC*H*$_2$), 3.80 (2H, t, J = 6.8 Hz, TBDPSOC*H*$_2$), 2.99 (3H, s, OSO$_2$C*H*$_3$), 2.55 (2H, t, J = 6.8 Hz, TBDPSOCH$_2$C*H*$_2$), 2.24 (2H, t, J = 7.5 Hz, MsOCH$_2$CH$_2$C*H*$_2$), 1.95–1.84 (2H, m, MsOCH$_2$C*H*$_2$), 1.05 (9H, s, SiC(C*H*$_3$)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 138.2 (*Ar*), 138.0 (*Ar*), 136.0 (*Ar*), 134.0 (*Ar*), 130.1 (*Ar*), 129.1 (*Ar*), 128.6 (PhCH=*C*), 128.5 (*Ar*), 128.1 (Ph*C*H=C), 126.7 (*Ar*), 69.8 (MsO*C*H_2), 62.8 (TBDPSO*C*H_2), 37.8 (SO$_2$*C*H$_3$), 33.9 (TBDPSOCH$_2$*C*H_2), 33.5 (MsOCH$_2$CH$_2$*C*H_2), 27.9 (MsOCH$_2$*C*H_2), 27.2 (SiC(*C*H_3)$_3$), 19.6 (Si*C*(CH$_3$)$_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2956 (m, C-H), 1648 (w, C=C), 1594 (w, C=C), 1356 (s, SO_2), 1175 (s, SO_2), 1109 (s), 930 (m); **m/z** (ESI+) 523.3 ([M+H]$^+$, 42%), 540.3 ([M+NH$_4$]$^+$, 60%), 545.3 ([M+Na]$^+$, 100%), HRMS found 545.2146, $C_{30}H_{38}NaO_4SSi$ requires 545.2152.

(*Z*)-Dimethyl 2-(4-benzylidene-6-(*tert*-butyldiphenylsilyloxy)hexyl)malonate

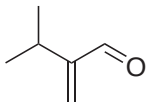


241

According to GP 5, mesylate **434** (261 mg, 0.500 mmol) was treated with DMM, which after flash column chromatography (6→4:1 PE:EtOAc), gave malonate **241** (188 mg, 0.336 mmol, 63%) as a viscous

colourless oil. $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.70–7.59 (4H, m, Ar*H*), 7.49–7.32 (6H, m, Ar*H*), 7.33–7.01 (5H, m, Ar*H*), 6.36 (1H, s, PhC*H*=C), 3.77 (2H, t, J = 7.0 Hz, TBDPSOCH_2), 3.75 (6H, s, CO_2CH_3), 3.38 (1H, t, J = 7.5 Hz, $(MeO_2C)_2CH$), 2.53 (2H, t, J = 7.0 Hz, $TBDPSOCH_2CH_2$), 2.14 (2H, t, J = 7.4 Hz, PhCH=CCH_2), 1.95–1.88 (2H, m, CHCH_2), 1.53–1.43 (2H, m, $CHCH_2CH_2$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 169.8 (*C*=O), 138.9 (*Ar*), 138.0 (*Ar*), 135.6 (*Ar*), 133.7 (PhCH=*C*), 129.6 (*Ar*), 128.7 (*Ar*), 128.0 (*Ar*), 127.6 (*Ar*), 127.5 (Ph*C*H=C), 126.1 (*Ar*), 62.4 (TBDPSO*C*H_2), 52.5 (CO_2CH_3), 51.6 ($(MeO_2C)_2CH$), 36.8 (PhCH=C*C*H_2), 33.5 ($TBDPSOCH_2CH_2$), 28.5 (CH*C*H_2), 26.8 (SiC(CH_3)$_3$), 25.8 ($CHCH_2CH_2$), 19.1 (Si*C*(CH_3)$_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3070 (s, Ar-H), 2955 (s, C-H), 1736 (s, C=O), 1649 (w, C=C), 1594 (w, C=C), 1463 (s), 1109 (s), 919 (m); **m/z** (ESI+) 576.3 ($[M+NH_4]^+$, 100%), 581.3 ($[M+Na]^+$, 97%), HRMS found 581.2685, $C_{34}H_{42}NaO_5Si$ requires 581.2694

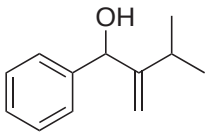
3-Methyl-2-methylenebutanal



216

According to GP 7, isovaleraldehyde (1.72 g, 20.0 mmol) was treated with aqueous formaldehyde. The solvent was distilled off and the crude product was purified by distillation at atmospheric pressure through a short Vigreux column, which gave α,β-unsaturated aldehyde **216** (1.24 g, 12.6 mmol, 63%) as a colourless oil *b.p.* 106 °C (*lit.*[166] 109 °C). $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.52 (1H, s, C*H*O), 6.23 (1H, d, J = 1.0 Hz, C=C*H*H), 5.94 (1H, br s, C=CH*H*), 2.78 (1H, hept d, J = 6.9, 1.0 Hz, C*H*(CH_3)$_2$), 1.06 (6H, d, J = 6.9 Hz, CH(CH_3)$_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 194.6 (*C*HO), 156.4 (H_2C=*C*), 132.1 (C=*C*H_2), 26.1 (*C*H(CH_3)$_2$), 21.3 (CH(*C*H_3)$_2$). *Data are consistent with literature values.*[166]

3-Methyl-2-methylene-1-phenylbutan-1-ol

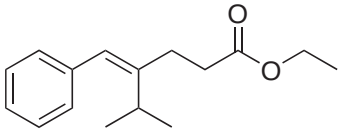


218

According to GP 1 with phenylmagnesium bromide in place of vinylmagnesium bromide, α,β-unsaturated aldehyde **216** (1.15 g, 11.7 mmol) was treated with phenylmagnesium bromide, which gave alcohol **218** (2.00 g, 11.3 mmol, 97%) as a pale yellow oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz,

$CDCl_3$) 7.40–7.26 (5H, m, Ar*H*), 5.27 (1H, dd, J = 1.0, 1.0 Hz, C=C*H*H), 5.22 (1H, s, C=CH*H*), 5.06 (1H, d, J = 1.0 Hz, PhC*H*OH), 2.12 (1H, hept d, J = 6.9, 1.0 Hz, C*H*$(CH_3)_2$), 1.00 (6H, d, J = 6.9 Hz, CH(C*H*$_3)_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 158.3 (*C*=CH_2), 138.6 (*Ar*), 129.3 (*Ar*), 128.3 (*Ar*), 125.9 (*Ar*), 107.3 (C=*C*H_2) 74.7 (Ph*C*HOH), 30.7 (*C*H$(CH_3)_2$), 22.4 (CH(*C*$H_3)_2$). *Data are consistent with literature values.*[166]

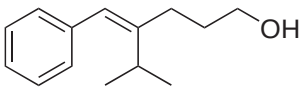
(*Z*)-Ethyl 4-benzylidene-5-methylhexanoate



242

According to GP 2, alcohol **218** (1.97 g, 11.1 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (40→20:1 PE:EtOAc), gave a mixture of E and Z ester **242** (2.21 g, 8.97 mmol, 81%) as a colourless oil characterised as a 1:5 mixture of diastereomers with data reported for the major diastereomer. $\mathbf{R}_f$ 0.53 (5:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.36–7.15 (5H, m, Ar*H*), 6.20 (1H, s, PhC*H*), 4.18 (2H, q, J = 7.1 Hz, OCH_2), 3.11 (1H, hept, J = 6.9 Hz, C*H*$(CH_3)_2$), 2.65–2.56 (2H, m, CH_2), 2.51–2.39 (2H, m, CH_2), 1.29 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.06 (6H, d, J = 6.9 Hz, CH(C*H*$_3)_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.4 (*C*=O), 146.7 (PhCH=*C*), 138.3 (*Ar*), 128.7 (*Ar*), 128.1 (*Ar*), 126.0 (*Ar*), 123.5 (Ph*C*H), 60.4 (O*C*H_2), 33.8 (*C*H_2), 29.2 (*C*H$(CH_3)_2$), 25.3 (*C*H_2), 21.2 (CH(*C*$H_3)_2$), 14.3 (OCH_2*C*H_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2964 (m, C-H), 1735 (s, C=O), 1645 (w, C=C), 1599 (w, C=C), 1158 (m); **m/z** (ESI+) 269.1 ([M+Na]$^+$, 100%), HRMS found 269.1510, $C_{16}H_{22}NaO_2$ requires 269.1512.

(*Z*)-4-Benzylidene-5-methylhexan-1-ol

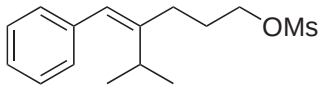


243

According to GP 3, a 1:5 mixture of E:Z ester **242** (2.07 g, 8.37 mmol) was treated with $LiAlH_4$, which after flash column chromatography (3→1:1, PE:Et_2O), gave **243** (1.50 g, 7.35 mmol, 88%) as a colourless oil characterised as a mixture of diastereomers with data reported for the major diastereomer. $\mathbf{R}_f$ 0.35 (1:1 PE:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.33 (2H, t, J = 7.6 Hz, Ar*H*), 7.28–7.18 (3H, m, Ar*H*), 6.25 (1H, s, PhC*H*=C), 3.76 (2H, t, J = 6.5 Hz, HOCH_2), 3.12 (1H, hept, J = 6.9 Hz, C*H*$(CH_3)_2$),

2.26–2.17 (2H, m, CH=CCH_2), 1.91–1.81 (2H, m, HOCH$_2$CH$_2$), 1.60 (1H, br s, OH), 1.06 (6H, d, J = 6.9 Hz, CH(CH$_3$)$_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 147.8 (PhCH=C), 138.6 (Ar), 128.7 (Ar), 128.1 (Ar), 125.9 (Ar), 123.5 (PhCH=C), 63.0 (HOCH$_2$), 32.3 (HOCH$_2$$CH_2$), 29.2 ($C$H(CH$_3$)$_2$), 26.5 (CH=C$CH_2$), 21.4 (CH($CH_3$)$_2$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3332 (br s, O-H), 2959 (m, C-H), 1642 (w, C=C), 1598 (w, C=C), 1059 (m); **m/z** (FI) HRMS found 204.1511, $C_{14}H_{20}O$ requires 204.1514.

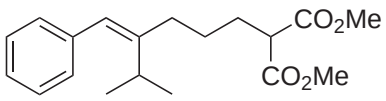
(*Z*)-4-Benzylidene-5-methylhexyl methanesulfonate



435

According to GP 4, a 1:5 mixture of *E*:*Z* alcohol **243** (1.46 g, 7.13 mmol) was treated with MsCl, which gave mesylate **435** (2.01 g, 7.10 mmol, 100%) as a pale yellow oil, which was used without purification as a mixture of diastereomers with data reported for the major diastereomer. $\mathbf{R}_f$ 0.42 (1:1 PE:Et$_2$O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.33 (2H, t, J = 7.5 Hz, ArH), 7.28–7.16 (3H, m, ArH), 6.24 (1H, s, PhCH=C), 4.34 (2H, t, J = 6.4 Hz, MsOCH_2), 3.12 (1H, hept, J = 6.9 Hz, CH(CH$_3$)$_2$), 3.04 (3H, s, SO$_2$CH_3), 2.25 (2H, t, J = 6.3 Hz, CH=CCH_2), 2.09–1.99 (2H, m, MsOCH$_2$CH_2), 1.05 (6H, d, J = 6.9 Hz, CH(CH_3)$_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 146.5 (PhCH=C), 138.2 (Ar), 128.7 (Ar), 128.1 (Ar), 126.1 (Ar), 124.2 (PhCH=C), 69.9 (MsOCH$_2$), 37.3 (SO$_2$$CH_3$), 29.2 ($C$H(CH$_3$)$_2$), 28.8 (MsOCH$_2$$CH_2$), 26.1 (CH=C$CH_2$), 21.3 (CH($CH_3$)$_2$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2962 (m, C-H), 1642 (w, C=C), 1598 (w, C=C), 1355 (s, SO$_2$), 1174 (s, SO$_2$); **m/z** (ESI+) 305.1 ([M+Na]$^+$, 100%), HRMS found 305.1182, $C_{15}H_{22}NaO_3S$ requires 305.1182.

(*Z*)-Dimethyl 2-(4-benzylidene-5-methylhexyl)malonate

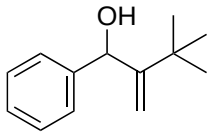


244

According to GP 5, a 1:5 mixture of *E*:*Z* mesylate **435** (2.00 g, 7.00 mmol) was treated with DMM, which after flash column chromatography (4:1 PE:Et$_2$O), gave malonate **244** (1.89 g, 5.94 mmol, 85%) as a colourless oil characterised as a mixture of diastereomers with data reported for the major diastereomer. $\mathbf{R}_f$ 0.29 (4:1 PE:Et$_2$O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.32 (2H, t, J = 7.5 Hz, ArH), 7.24–7.12 (3H, m, ArH), 6.20 (1H, s, PhCH=C), 3.77 (6H, s, CO$_2$CH_3), 3.45 (1H, t, J = 7.5 Hz, (CO$_2$Me)$_2$CH), 3.09 (1H,

hept, J = 6.9 Hz, $(CH_3)_2CH$), 2.21–2.10 (2H, m, PhCH=CCH_2), 2.09–1.97 (2H, m, $(CO_2Me)_2CHCH_2$), 1.65–1.54 (2H, m, PhCH=CHCH$_2$CH_2), 1.03 (6H, d, J = 6.9 Hz, $(CH_3)_2CH$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.9 (C=O), 147.4 (PhCH=C), 138.6 (Ar), 128.7 (Ar), 128.0 (Ar), 125.9 (Ar), 123.6 (PhCH=C), 52.5 (CO_2CH_3), 52.7 ($(CO_2Me)_2CH$), 39.9 (PhCH=CCH$_2$), 29.1 ($(CH_3)_2CH$), 28.9 ($(CO_2Me)_2CHCH_2$), 26.9 (PhCH=CHCH$_2C$H$_2$), 21.3 ($(CH_3)_2CH$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2958 (m, C-H), 1738 (s, C=O), 1643 (w, C=C), 1599 (w, C=C), 1438 (m), 1151 (m); **m/z** (ESI+) 341.2 ([M+Na]$^+$), HRMS found 341.1722, $C_{19}H_{26}NaO_4$ requires 341.1723.

3,3-Dimethyl-2-methylene-1-phenylbutan-1-ol



228

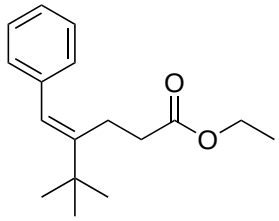
A solution of 3,3-dimethylbutan-1-ol (1.02 g, 10.0 mmol) in dry DCM was added rapidly to a slurry of PCC (3.23 g, 15 mmol) and Celite® (4.03 g) in dry DCM (18 mL) at 0 °C and then stirred at RT for 3.5 h. The solution was diluted with Et_2O (25 mL) and filtered through Florisil® with washings of Et_2O. The solvent was carefully removed *in vacuo*, which gave the crude aldehyde, which was used directly in the next step.

The aldehyde was redissolved in IPA (1.0 mL) and then formaldehyde (37% aqueous solution, 811 mg, 10.0 mmol), propionic acid (75 μL, 1.0 mmol), and pyrrolidine (84 μL, 1.0 mmol) were added successively. The solution was stirred at 45 °C overnight and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (2.5 mL). The aqueous was extracted with Et_2O (3×10 mL) and the combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*, which gave the crude α,β-unsaturated aldehyde, which was used directly in the next step.

The α,β-unsaturated aldehyde was dissolved in dry THF (50 mL) and PhMgBr (3 M in Et_2O, 4.8 mL, 14.0 mmol) was added dropwise at 0 °C. The solution was stirred for 2 h and quenched by the addition of 50% saturated aqueous NH_4Cl solution (25 mL). The layers were separated and the aqueous was extracted with EtOAc (3×25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, which gave the crude alcohol, which was purified by flash column chromatography (7:1 PE:EtOAc), which gave alcohol **228** (328 mg, 1.73 mmol, 17% from 3,3-dimethylbutanol) as a colourless oil. $\mathbf{R}_f$ 0.27 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$)

7.45–7.24 (5H, Ar*H*), 5.42 (1H, s, PhC*H*OH), 5.24 (1H, d, J = 1.5 Hz, C=C*H*H), 5.19 (1H, d, J = 1.5 Hz, C=CH*H*), 1.87 (1H, br s, O*H*), 1.12 (9H, s, C(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 160.4 (*C*=CH_2), 143.7 (*Ar*), 128.3 (*Ar*), 127.4 (*Ar*), 126.9 (*Ar*), 110.6 (C=*C*H_2), 72.8 (Ph*C*HOH), 35.6 (*C*(CH_3)$_3$), 29.8 (C(*C*H_3)$_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3339 (br m, O-H), 2963 (m, C-H), 1634 (w, C=C), 1603 (w, C=C), 1014 (m), 913 (m), 732 (s); **m/z** (FI) HRMS found 112.0887, $C_7H_{12}O$ requires 112.0888.

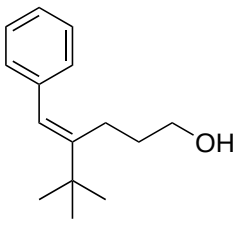
(*E*)-Ethyl 4-benzylidene-5,5-dimethylhexanoate



245

According to GP 2, alcohol **228** (312 mg, 1.69 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (15:1 PE:EtOAc), gave ester **245** (315 mg, 1.21 mmol, 72%) as a colourless oil. $\mathbf{R}_f$ 0.43 (9:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (200 MHz, $CDCl_3$) 7.57–7.06 (5H, m, Ar*H*), 6.51 (1H, s, PhC*H*=C), 4.14 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.81–2.58 (2H, m, CH_2CH_2), 2.46–2.27 (2H, m, CH_2CH_2), 1.38–1.13 (12H, m, (CH_3)$_3$ & CH_2CH_3); $\boldsymbol{\delta_C}$ (50 MHz, $CDCl_3$) 173.7 (*C*=O), 149.8 (PhCH=*C*), 139.2 (*Ar*), 128.9 (*Ar*), 128.8 (*Ar*), 126.6 (*Ar*), 124.3 (Ph*C*H=C), 60.7 ($CO_2CH_2CH_3$), 37.8 (PhCH=C*C*(CH_3)$_3$), 34.7 (*C*H_2CH_2)), 29.8 (C(*C*H_3)$_3$), 23.7 (*C*H_2CH_2), 14.6 ($CO_2CH_2CH_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2964 (m, C-H), 1732 (s, C=O), 1636 (w, C=C), 1598 (w, C=C), 1368 (m), 1164 (m); **m/z** (ESI+) 261.2 ([M+H]$^+$, 71%), 283.2 ([M+Na]$^+$, 100%), HRMS found 283.1667, $C_{17}H_{24}NaO_2$ requires 283.1669.

(*E*)-4-Benzylidene-5,5-dimethylhexan-1-ol

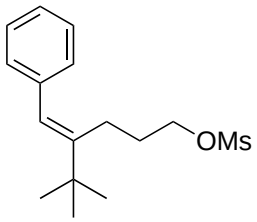


246

According to GP 3, ester **245** (284 mg, 1.09 mmol) was treated with $LiAlH_4$, which after flash column chromatography (5→1:1 PE:EtOAc), gave alcohol **246** (179 mg, 0.82 mmol, 75%) as a colourless oil.

$\mathbf{R}_f$ 0.29 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.37–7.14 (5H, m, Ar*H*), 6.42 (1H, s, PhC*H*=C), 3.49 (2H, t, J = 6.4 Hz, HOCH_2), 2.37–2.31 (2H, m, PhCH=CCH_2), 1.66–1.48 (3H, m, $HOCH_2CH_2$ & O*H*), 1.18 (9H, s, C(CH_{33}); $\boldsymbol{\delta_C}$ (62.5 MHz, $CDCl_3$) 151.3 (PhCH=*C*), 139.8 (*Ar*), 129.0 (*Ar*), 128.6 (*Ar*), 126.4 (*Ar*) 123.5 (Ph*C*H), 63.4 ($HOCH_2$), 37.7 ($HOCH_2CH_2$), 33.6 (*C*(CH_3)$_3$), 30.1 (C(*C*H_3)$_3$), 24.8 (PhCH=C*C*H_2); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3330 (br m, OH), 2958 (s, C-H), 1633 (w, C=C), 1597 (w, C=C), 1475 (m), 1362 (m), 1061 (m); **m/z** (ESI+) 241.2 ([M+Na]$^+$, 100%), HRMS found 241.1561, $C_{15}H_{22}NaO$ requires 241.1562.

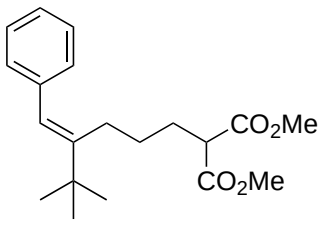
(*E*)-4-Benzylidene-5,5-dimethylhexyl methanesulfonate



436

According to GP 4, alcohol **246** (97 mg, 0.44 mmol) was treated with MsCl, which gave mesylate **436** (130 mg, 0.44 mmol, 100%) as a colourless oil, which was used without purification. $\mathbf{R}_f$ (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (250 MHz, $CDCl_3$) 7.43–7.30 (2H, m, Ar*H*), 7.28–7.16 (3H, m, Ar*H*), 6.47 (1H, s, PhC*H*=C), 4.07 (2H, t, J = 6.5 Hz, MsOCH_2), 2.91 (3H, s, SO_2CH_3), 2.47–2.33 (2H, m, PhCH=CCH_2), 1.83–1.66 (2H, m, $MsOCH_2CH_2$); $\boldsymbol{\delta_C}$ (63 MHz, $CDCl_3$) 150.0 (PhCH=*C*), 139.6 (*Ar*), 128.9 (*Ar*), 128.7 (*Ar*), 126.6 (*Ar*), 124.2 (Ph*C*H=C), 70.6 ($MsOCH_2$), 37.7 (SO_2CH_3), 37.6 (*C*(CH_3)$_3$), 29.9 (C(*C*H_3)$_3$), 29.8 ($MsOCH_2CH_2$), 24.5 (PhCH=C*C*H_2); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2963 (m, C-H), 1633 (w, C=C), 1597 (w, C=C), 1356 (s, S=O), 1174 (s, S=O), 926 (m); **m/z** (ESI+) 314.2 ([M+NH_4]$^+$, 85%), 319.1 ([M+Na]$^+$, 100%), HRMS found 319.1337, $C_{16}H_{24}NaO_3S$ requires 319.1338.

(*E*)-Dimethyl 2-(4-benzylidene-5,5-dimethylhexyl)malonate

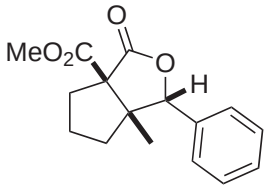


226

According to GP 5, mesylate **436** (130 mg, 0.44 mmol) was treated with DMM, which after flash column chromatography (7:1 PE:EtOAc), gave malonate **226** (135 mg, 0.41 mmol, 92%) as a colourless oil. $\mathbf{R}_f$ (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.35–7.28 (2H, m, Ar*H*), 7.23–7.15 (3H, m, Ar*H*), 6.39 (1H, s, PhC*H*=C), 3.68 (6H, s, CO_2CH_3), 3.25 (1H, t, J = 7.6 Hz, $(MeO_2C)_2CH$), 2.33–2.21 (2H, m, CH=CCH_2), 1.89–1.73 (2H, m, CHCH_2), 1.35 (2H, dtd, J = 10.6, 8.1, 5.3 Hz, CH=CCH$_2$CH_2), 1.16 (9H, s, C(CH_3)); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.7 (*C*=O), 150.6 (PhCH=*C*), 139.2 (*Ar*), 128.5 (*Ar*), 128.2 (*Ar*), 125.9 (*Ar*), 123.2 (Ph*C*H=C), 52.4 (CO_2CH$_3$), 51.3 ($(MeO_2C)_2C$H), 37.1 ($C(CH_3)_3$), 29.6 (C(CH$_3$)$_3$), 29.3 (CHCH$_2$), 28.0 (CH=CCH$_2$), 27.7 (CH=CCH$_2C$H$_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2956 (m, C-H), 1738 (s, C=O), 1632 (w, C=C), 1597 (w, C=C), 1438 (m), 1245 (m); **m/z** (ESI+) 333.2 ($[M+H]^+$, 59%), 355.2 ($[M+Na]^+$, 100%), HRMS found 355.1872, $C_{20}H_{28}NaO_4$ requires 355.1880.

(1*R,3a*S**,6a*R**)-Methyl**

6a-methyl-3-oxo-1-phenylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate

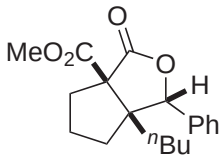


247

According to GP 6, malonate **232** (87 mg, 0.300 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (5:1 PE:EtOAc), gave cyclopentane-lactone **247** (7.9:1 dr, 69 mg, 0.252 mmol, 84%) as a colourless oil characterised as a mixture of diastereomers. $\mathbf{R}_f$ 0.26 (4:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.42–7.27 (5H, m, Ar*H*), 5.45 (1H, s, OC*H*Ph), 3.83 (3H, s, OCH_3), 2.57–2.48 (1H, m, C*H*H), 2.38–2.31 (1H, m, C*H*H), 1.80–1.54 (3H, m, C*H*H), 1.20 (3H, m, CCH_3), 1.02 (1H, ddd, J = 12.3, 6.1, 4.0 Hz, C*H*H); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 176.3 (lactone *C*=O), 169.2 (ester *C*=O), 135.3 (*Ar*), 128.4 (*Ar*), 128.3 (*Ar*), 125.4 (*Ar*), 86.7 (O*C*HPh), 66.9 (*C*), 56.1 (*C*), 52.8 (CO_2CH$_3$), 35.4 (CH$_2$), 33.0 (CH$_2$), 23.8 (CH$_2$), 20.7 (CCH$_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2962 (m, C-H), 1779 (s, lactone C=O), 1743 (s, ester C=O), 1453 (m), 1251 (s), 1126 (m), 1019 (m); **m/z** (ESI+) 297.1 ($[M+Na]^+$, 100%), HRMS found 297.1095, $C_{16}H_{18}NaO_4$ requires 297.1097.

(1*R,3a*S**,6a*R**)-Methyl**

6a-butyl-3-oxo-1-phenylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate

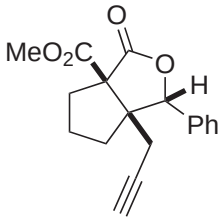


248

According to GP 6, malonate **234** (99 mg, 0.300 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (5:1 PE:EtOAc), gave cyclopentane-lactone **248** (10.7:1 dr, 86 mg, 0.271 mmol, 91%) as a colourless oil characterised as a mixture of diastereomers. $\mathbf{R}_f$ 0.31 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.41–7.28 (5H, m, Ar*H*), 5.51 (1H, s, PhC*H*) 3.82 (3H, s, PhCHCH_3), 2.45–2.39 (2H, m, MeO_2CCCH_2), 1.81–1.67 (2H, m, CH_2), 1.66–1.50 (3H, m, CH_2), 1.37–1.18 (5H, m, CH_2), 0.88 (3H, t, J = 7.0 Hz, CH_2CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 176.3 (lactone *C*=O), 169.2 (ester *C*=O), 135.7 (*Ar*), 128.4 (*Ar*), 128.3 (*Ar*), 126.4 (*Ar*), 87.5 (Ph*C*H), 67.2 (MeO_2C*C*), 58.8 (O*C*H_3), 52.7 (PhCH*C*), 35.2 (*C*H_2), 33.9 (*C*H_2), 32.1 (*C*H_2), 26.2 (*C*H_2), 23.6 (*C*H_2), 23.5 (*C*H_2), 13.8 (CH_2*C*H_3); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2957 (m, C-H), 1777 (s, lactone C=O), 1743 (s, ester C=O), 1454 (m), 1247 (s), 1021 (m); **m/z** 317.2 ($[M+H]^+$, 37%), 339.1 ($[M+Na]^+$, 98%), 655.3 ($[2M+Na]^+$, 100%), HRMS found 339.1565, $C_{19}H_{24}NaO_4$ requires 339.1567.

(1*R,3a*S**,6a*S**)-Methyl**

3-oxo-1-phenyl-6a-(prop-2-ynyl)hexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate

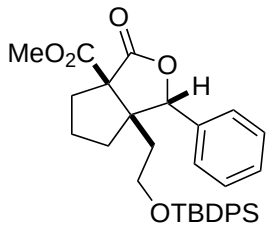


249

According to GP 6, malonate **238** (94 mg, 0.300 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (5:1 PE:EtOAc), gave cyclopentane-lactone **249** (11.9:1 dr, 66 mg, 0.221 mmol, 74%) as a colourless oil characterised as a 12:1 mixture of diastereomers. $\mathbf{R}_f$ 0.22 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.47–7.30 (5H, m, Ar*H*), 5.89 (1H, s, PhC*H*), 3.83

(3H, s, CO_2CH_3), 2.60 (1H, dd, J = 17.5, 2.7 Hz, C≡CCHH), 2.51–2.42 (2H, m, CH_2), 2.50 (1H, dd, J = 17.5, 2.7 Hz, C≡CCHH), 2.15 (1H, t, J = 2.7 Hz, C≡CH), 1.79–1.68 (2H, m CH_2), 1.60–1.48 (1H, m, CHH), 1.28–1.17 (1H, m, CHH) $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 175.5 (lactone C=O), 168.7 (ester C=O), 135.0 (Ar), 128.6 (Ar), 128.5 (Ar), 125.6 (Ar), 84.3 (PhCH), 79.4 (CH_2C≡CH), 72.4 (C≡CH), 65.8 (MeO_2CC), 57.7 (PhCHC), 52.8 (CO_2CH_3), 34.4 (CH_2), 34.2 (CH_2), 24.5 (CH_2C≡CH), 23.5 (CH_2); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3283 (m, C≡C-H), 2955 (m, C-H), 2120 (w, C≡C), 1778 (s, lactone C=O), 1742 (s, ester C=O), 1452 (m), 1250 (m); **m/z** (ESI+) 321.1 ([M+Na]$^+$, 100%), 619.2 ([2M+Na]$^+$, 66%), HRMS found 321.1093, $C_{18}H_{18}NaO_4$ requires 321.1097.

(1*R,3a*S**,6a*S**)-Methyl 6a-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-3-oxo-1-phenylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate**

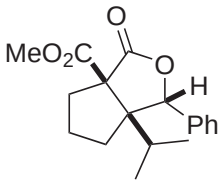


250

According to GP 6, malonate **241** (145 mg, 0.259 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (6→3:1 PE:EtOAc), gave cyclopentane-lactone **250** (11.6:1 dr, 135 mg, 0.249 mmol, 96%) as a colourless viscous oil characterised as a mixture of diastereomers. $\mathbf{R}_f$ 0.34 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.65–7.58 (4H, m, ArH), 7.49–7.28 (9H, m, ArH), 7.22–7.18 (2H, m, ArH), 5.46 (1H, s, PhCH), 3.73 (3H, s, CO_2CH_3), 3.70–3.56 (2H, m, TBDPSOCH_2), 2.45–2.52 (2H, m, CH_2), 1.99–1.89 (2H, m, TBDPSOCH$_2$CH_2), 1.74–1.60 (2H, m, CH_2), 1.58–1.45 (1H, m, CHH), 1.32–1.22 (1H, m, CHH), 1.03 (9H, s, SiC(CH_3)$_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 176.1 (C=O lactone), 169.0 (C=O ester), 135.5 (Ar, two resonances coincident), 135.4 (Ar), 133.4 (Ar), 133.3 (Ar), 129.8 (Ar), 129.8 (Ar), 128.5 (Ar), 128.3 (Ar), 127.8 (Ar), 127.7 (Ar), 126.5 (Ar), 87.0 (PhCH), 67.4 (MeO_2CC), 59.8 (TBDPSOCH$_2$), 57.7 (PhCHC), 52.8 (CO_2CH_3), 38.1 (TBDPSOCH$_2C$H$_2$), 33.5 (CH_2), 32.5 (CH_2), 26.8 (SiC(CH_3)$_3$), 23.7 (CH_2), 19.0 (SiC(CH$_3$)$_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2955 (m, C-H), 2852 (m, Ar-H), 1779 (s, C=O lactone), 1743 (s, C=O ester), 1430 (m), 1243 (m), 1109 (s), 704 (s); **m/z** (ESI+) 560.3 ([M+NH$_4$]$^+$, 100%), 565.2 ([M+Na]$^+$, 97%), HRMS found 565.2372, $C_{33}H_{38}NaO_5Si$ requires 565.2381.

(1*R,3a*S**,6a*S**)-Methyl**

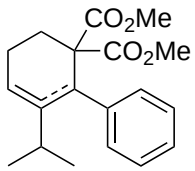
6a-isopropyl-3-oxo-1-phenylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate



252

According to GP 6, malonate **244** (96 mg, 0.300 mmol) was treated with $Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (5:1 PE:EtOAc), gave cyclopentane-lactone **252** (35 mg, 0.116 mmol, 39%) as colourless crystals, *m.p.* 95–97 °C. $\mathbf{R}_f$ 0.24 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.43–7.31 (5H, m, Ar*H*), 5.72 (1H, s, OC*H*Ph), 3.84 (3H, s, OCH_3), 2.54–2.46 (1H, m, C*H*H), 2.39–2.30 (1H, m, CH*H*), 1.94–1.75 (2H, m, C*H*HC*H*H), 1.56–1.47 (2H, m, CH*H*CH*H*), 2.20 (1H, hept, J = 6.8 Hz, C*H*$(CH_3)_2$), 0.93 (3H, d, J = 6.8 Hz, CH(CH_3)(CH_3)), 0.89 (3H, d, J = 6.8 Hz, CH(CH_3)(CH_3)); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 176.1 (lactone *C*=O), 169.6 (ester *C*=O), 136.5 (*Ar*), 128.5 (*Ar*), 128.2 (*Ar*), 127.9 (*Ar*), 87.4 (O*C*HPh), 67.1 (*C*), 62.2 (*C*), 52.8 (O*C*H_3), 34.8 (*C*H_2), 33.1 (*C*H$(CH_3)_2$), 29.7 (*C*H_2), 23.3 (*C*H_2), 18.8 (CH(*C*H_3)(CH_3)), 18.6 (CH(CH_3)(*C*H_3)); $\boldsymbol{\nu}_\mathbf{max}$ **/ cm^{-1}** 2957 (m, C-H), 1775 (s, lactone C=O), 1740 (s, ester C=O), 1258 (m); **m/z** (ESI+) 325.2 ($[M+Na]^+$, 100%), 627.3 ($[2M+Na]^+$, 96%), HRMS found 325.1410, $C_{18}H_{22}NaO_4$ requires 325.1410.

Dimethyl 3-isopropyl-2-phenylcyclohex-3-ene-1,1-dicarboxylate

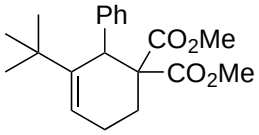


253

Isolated from the formation of lactone **9e**, cyclohexene **10e** (45 mg, 0.143 mmol, 48%) as a colourless oil characterised as a mixture which may contain some tetrasubstituted alkene. $\mathbf{R}_f$ 0.36 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.34–7.12 (5H, m, Ar*H*), 5.62 (1H, dd, J = 5.1, 2.6 Hz, C=C*H*), 4.21 (1H, s, PhC*H*), 3.74 (3H, s, CO_2CH_3), 3.47 (3H, s, CO_2CH_3'), 2.42–2.25 (1H, m, C=CHC*H*H), 2.19–2.07 (2H, m, CCH_2), 2.04–1.93 (1H, m, C=CHCH*H*), 1.89 (1H, qq, J = 6.9, 6.9 Hz, C*H*$(CH_3)_2$), 1.01 (3H, d, J = 6.9 Hz, CH(CH_3)(CH_3)), 0.94 (3H, d, J = 6.9 Hz, CH(CH_3)(CH_3)); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$)

171.3 (CO$_2$Me), 170.6 (CO$_2$Me), 143.6 (CH=C), 139.4 (Ar), 129.8 (Ar), 128.0 (Ar), 127.3 (Ar), 118.4 (CH=C), 59.0 ((MeO$_2$C)$_2C$), 52.6 (CO$_2C$H$_3$), 52.0 (CO$_2C$H$_3$), 47.2 (PhCH), 33.0 (CH(CH$_3$)$_2$), 22.5 (CH$_2$), 22.2 (CH$_2$), 22.0 (CH(CH$_3$)(CH$_3$)), 21.4 (CH(CH$_3$)(CH$_3$)); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2956 (m, C-H), 1740 (s, C=O), 1600 (w, C=C), 1252 (m); **m/z** (ESI+) 339.2 ([M+Na]$^+$, 100%), 655.3 ([2M+Na]$^+$, 39%), HRMS found 339.1559, $C_{19}H_{24}NaO_4$ requires 339.1567.

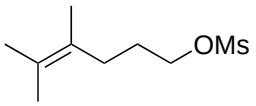
Dimethyl 3-*tert*-butyl-2-phenylcyclohex-3-ene-1,1-dicarboxylate



255

According to GP 6, malonate **226** (31.4 mg, 0.0945 mmol) was treated with Mn(OAc)$_3 \cdot 2$H$_2$O and Cu(OTf)$_2$, which after flash column chromatography (8→4:1 PE:EtOAc), gave cyclohexene **255** (7 mg, 21 μmol, 23%) as a colourless oil. $\mathbf{R}_f$ 0.48 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, CDCl$_3$) 7.26–7.17 (3H, m, ArH), 7.15 (2H, dd, J = 9.3, 7.7 Hz, ArH), 5.76 (1H, dd, J = 3.5, 2.4 Hz, C=CH), 4.40 (1H, s, PhCH), 3.73 (3H, s, CO$_2$CH_3), 3.52 (3H, s, CO$_2$CH_3), 2.43–2.26 (1H, m, C=CHCHH), 2.19–2.01 (3H, m, C=CHCHH & CCH_2), 0.92 (9H, s, C(CH_3)$_3$); $\boldsymbol{\delta_C}$ (125 MHz, CDCl$_3$) 171.0 (CO$_2$Me), 170.6 (CO$_2$Me), 144.7 (CH=CCH), 140.6 (Ar), 129.7 (Ar), 127.9 (Ar), 127.0 (Ar), 119.7 (C=CH), 59.6 (C(CO$_2$Me)$_2$), 52.5 (CO$_2C$H$_3$), 52.1 (CO$_2C$H$_3$), 45.4 (PhCH), 36.3 (C(CH$_3$)$_3$), 30.5 (C(CH$_3$)$_3$), 22.7 (C=CHCH$_2$), 21.2 (CCH$_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2954 (m, C-H), 1741 (s, C=O), 1601 (w, C=C), 1228 (m), 1069 (m), 707 (m); **m/z** (ESI+) 353.2 ([M+Na]$^+$, 100%), HRMS found 353.1728, $C_{20}H_{26}NaO_4$ requires 353.1723.

4,5-Dimethylhex-4-enyl methanesulfonate

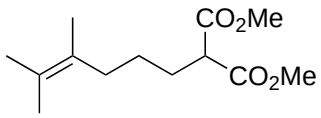


437

According to GP 4, 4,5-dimethylhex-4-en-1-ol (450 mg, 3.50 mmol) was treated with MsCl, which gave mesylate **437** (701 mg, 3.39 mmol, 97%) as a pale yellow oil, which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, CDCl$_3$) 4.18 (2H, t, J = 6.5 Hz, MsOCH_2), 3.00 (3H, s, SO$_2$CH_3), 2.18–2.07 (2H, m, C=CCH_2), 1.81 (2H, tt, J = 6.5, 6.5 Hz, MsOCH$_2$CH_2), 1.68–1.60 (9H, m, 3×CH_3); $\boldsymbol{\delta_C}$ (50 MHz, CDCl$_3$) 126.2 (C), 126.0 (C), 70.3 (MsOCH$_2$), 37.8 (SO$_2C$H$_3$), 30.5 (C=CCH$_2$), 28.0 (MsOCH$_2C$H$_2$),

21.0 (CH$_3$), 20.6 (CH$_3$), 18.6 (CH$_3$). *Data are consistent with literature values.*[167]

Dimethyl 2-(4,5-dimethylhex-4-enyl)malonate

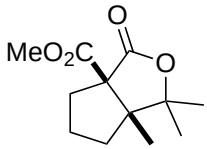


261

According to GP 5, mesylate **437** (680 mg, 3.3 mmol) was treated with DMM, which after flash column chromatography (7:1 PE:EtOAc), gave malonate **261** (439 mg, 1.81 mmol, 55%) as a colourless oil. $\mathbf{R}_f$ 0.27 (7:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, CDCl$_3$) 3.71 (6H, s, CO$_2$CH_3), 3.35 (1H, t, J = 7.6 Hz, (CO$_2$Me)$_2$CH), 2.05–1.99 (2H, m, C=CCH_2), 1.89–1.82 (2H, m, (CO$_2$Me)$_2$CHCH_2), 1.61 (6H, br s, C=C(CH_3)$_2$), 1.58 (3H, s, Me$_2$C=CCH_3), 1.36 (2H, tt, J = 9.7, 6.7 Hz, C=CCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, CDCl$_3$) 169.9 (C=O), 126.8 (C=C), 124.6 (C=C), 52.4 (CO$_2$$CH_3$), 51.6 ((CO$_2$Me)$_2$$C$H), 33.8 (C=C$CH_2$), 28.7 ((CO$_2$Me)$_2CHCH_2$), 25.8 (C=CCH$_2$$CH_2$), 20.5 (C($CH_3$)(CH$_3$)), 20.1 (C(CH$_3$)($CH_3$)), 18.1 (C$CH_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2953 (w, C-H), 1735 (s, C=O), 1436 (m), 1152 (s); **m/z** (ESI+) 265.2 ([M+Na]$^+$, 100%), HRMS found 265.1411, C$_{13}$H$_{22}$O4$_2$Na requires 265.1410.

(3a*S,6a*R**)-Methyl**

1,1,6a-trimethyl-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate

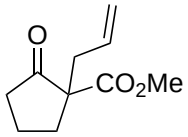


263

According to GP 6, malonate ester **261** (73 mg, 0.300 mmol) was treated with Mn(OAc)$_3$·2H$_2$O and Cu(OTf)$_2$, which after flash column chromatography (7:1 PE:EtOAc), gave cyclopentane-lactone **263** (50 mg, 0.221 mmol, 74%) as a colourless oil. $\mathbf{R}_f$ 0.33 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, CDCl$_3$) 3.74 (3H, s, OCH$_3$), 2.48 (1H, dddd, J = 13.7, 8.4, 5.2, 1.1 Hz, CHH), 2.28 (1H, ddd, J = 13.7, 7.7, 7.7 Hz, CHH), 1.97 (1H, ddd, J = 12.7, 9.8, 7.0 Hz, CHH), 1.87–1.75 (1H, m, CHH), 1.74–1.63 (1H, m, CHH), 1.59–1.49 (1H, m, CHH), 1.38 (3H, s, C(CH_3)(CH$_3$)), 1.37 (3H, s, C(CH$_3$)(CH_3)), 1.06 (3H, s, C(CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, CDCl$_3$) 176.2 (lactone C=O), 171.2 (ester C=O), 87.3 (quaternary C), 65.6 (quaternary C), 57.6 (quaternary C), 52.5 (CO$_2$$CH_3$), 38.7 ($CH_2$), 36.4 ($CH_2$), 25.9 (C($CH_3$)(CH$_3$)),

24.6 (CH$_2$), 23.5 (C(CH$_3$)(CH$_3$)), 18.5 (CCH$_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2956 (m, C-H), 1765 (s, lactone C=O), 1734 (s, ester C=O), 1272 (s), 1251 (s), 1106 (m); **m/z** (ESI+) 249.1 ([M+Na]$^+$, 100%), HRMS found 249.1101, $C_{12}H_{18}NaO_4$ requires 249.1097.

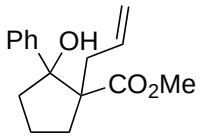
Methyl 1-allyl-2-oxocyclopentanecarboxylate



269

According to the procedure of Trost and Shi,[168] to a stirred suspension of pentane washed NaH (2.10 g, 52.5 mmol) in dry THF (110 mL) at 0 °C was added methyl 2-oxocyclopentanecarboxylate **268** (7.11 g, 50.0 mmol) so as maintain steady evolution of H_2. Allyl bromide (7.26 g, 60.0 mmol) was added, and the solution was stirred overnight at RT. The reaction was quenched with water (20 mL), and extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*, which gave alkene **269** (9.01 g, 49.5 mmol, 99%) as a colourless oil which was used without purification. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 5.69–5.56 (1H, m, H$_2$C=CH), 5.09–5.01 (2H, m, H_2C=CH), 3.65 (3H, s, CO$_2$CH_3), 2.61 (1H, dd, J = 13.9, 7.2 Hz, H$_2$C=CHCHH), 2.44–2.14 (4H, m), 2.02–1.82 (3H, m); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 214.4 (ketone C=O), 171.3 (ester C=O), 132.9 (H$_2$C=CH), 119.0 (H$_2C$=CH), 59.9 (C(O)C), 52.5 (CO$_2C$H$_3$), 38.0 (CH$_2$CH$_2$CH$_2$), 37.8 (H$_2$C=CHCH$_2$), 32.0 (CH$_2$CH$_2C$H$_2$), 19.4 (CH$_2C$H$_2$CH$_2$). *Data are consistent with literature values.*[168]

Methyl 1-allyl-2-hydroxy-2-phenylcyclopentanecarboxylate

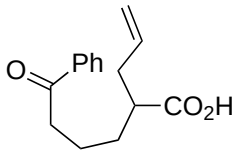


270

According to the modified procedure of Compernolle and co-workers,[169] to a stirred solution of PhMgBr (1.35 M in THF, 4.9 mL, 6.6 mmol) at –78 °C was added a solution of alkene **269** (1.00 g, 5.49 mmol) in dry THF (6.7 mL). The solution was allowed to warm over 5.5 h, and then quenched with sat. aq. NH_4Cl solution (25 mL). The layers were separated, and the aqueous was extracted with

Et_2O (3×25 mL). The combined organic extracts were successively washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (6→3:1 PE:EtOAc), which gave alcohol **270** (1.15 g, 4.43 mmol, 81%) as a colourless oil. $\mathbf{R}_f$ 0.45 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.47–7.42 (2H, m, Ar*H*), 7.40–7.34 (2H, m, Ar*H*), 7.33–7.28 (1H, m, Ar*H*), 5.67 (1H, dddd, J = 16.8, 10.1, 8.1, 6.4 Hz, H_2C=C*H*), 5.16–5.10 (1H, m, CH=C*H*H), 5.08–5.03 (1H, m, CH=CH*H*), 2.81 (1H, dd, J = 13.3, 6.4 Hz, H_2C=CHC*H*H), 2.70–2.63 (1H, m, H_2C=CHCH*H*), 2.52–2.45 (1H, m, PhC(OH)C*H*H), 2.39–2.32 (1H, m, PhC(OH)CH*H*), 2.29–2.19 (1H, m, O*H*), 2.09–1.90 (4H, m, C(O)CH_2C*H*$_2$C*H*$_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 175.7 (*C*=O), 144.1 (*Ar*), 135.6 (H_2C=*C*H), 128.3 (*Ar*), 127.8 (*Ar*), 126.0 (*Ar*), 118.1 (H_2*C*=CH), 85.7 (Ph*C*), 63.1 (*C*CO_2Me), 51.6 (CO_2*C*H_3), 39.1 (PhC*C*H_2), 36.6 (H_2C=CH*C*H_2), 32.0 (MeO_2CC*C*H_2CH_2), 20.7 (CH_2*C*H_2CH_2); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$3498 (br, O-H), 2949 (m, C-H), 1706 (s, C=O), 1639 (w, C=C), 1215 (s), 701 (s); **m/z** (FI) HRMS found 260.1419, $C_{16}H_{20}O_3$ requires 260.1412.

2-Allyl-6-oxo-6-phenylhexanoic acid

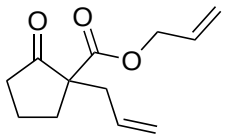


271

To a stirred solution of alcohol **270** (637 mg, 2.45 mmol) in MeOH (15 mL) was added aq. KOH solution (2 M, 4.9 mL, 9.8 mmol). The solution was stirred overnight and diluted with DCM (30 mL). The layers were separated and the organic layer was extracted with 2 M NaOH solution (2×30 mL). The combined aqueous extracts were acidified to pH 2 with conc. HCl. The acidified aqueous extracts were extracted with DCM (3×30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*, which gave acid **271** (441 mg, 1.79 mmol, 73%) as a white solid m.p. 52–57 °C. $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 10.20 (1H, br s, O*H*), 7.95 (2H, d, J = 7.6 Hz, Ar*H*), 7.56 (1H, dd, J = 7.6, 7.6 Hz, Ar*H*), 7.46 (2H, dd, J = 7.6, 7.6 Hz, Ar*H*), 5.78 (1H, dddd, J = 17.0, 10.1, 7.0, 7.0 Hz, H_2C=C*H*), 5.14–5.02 (2H, m, *H*$_2$C=CH), 3.04–2.97 (2H, m, PhC(O)C*H*$_2$), 2.57–2.48 (1H, m, C*H*CO_2H), 2.48–2.67 (1H, m, H_2C=CHC*H*H), 2.35–2.26 (1H, m, H_2C=CHCH*H*), 1.86–1.58 (4H, m, C*H*$_2$C*H*$_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 199.8 (ketone *C*=O), 181.5 (acid *C*=O), 136.9 (H_2C=*C*H), 134.9 (*Ar*), 133.0 (*Ar*), 128.6 (*Ar*), 128.0 (*Ar*), 117.2 (H_2*C*=CH), 45.0 (*C*HCO_2H), 38.2 (PhC(O)*C*H_2), 36.0 (H_2C=CH*C*H_2), 30.9 (*C*H_2CH_2), 21.8 (CH_2*C*H_2); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2948 (br, C-H & O-H), 1711 (s, ketone

C=O), 1684 (s, acid C=O), 1639 (m, C=C), 1445 (m), 1218 (m), 732 (s); **m/z** (ESI+) 269.1 ($[M+Na]^+$, 100%), HRMS found 269.1145, $C_{15}H_{18}NaO_3$ requires 269.1148.

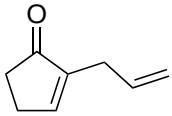
Allyl 1-allyl-2-oxocyclopentanecarboxylate



273

According to the procedure of Blechert and co-workers,[93] to a stirred suspension of NaH (60 wt% in mineral oil, 5.11 g, 128 mmol) in dry PhMe (110 mL) was added allyl alcohol (1.77 g, 30.4 mmol) dropwise at RT, followed by diallyl adipate **272** (25.5 g, 113 mmol) dropwise over 30 min. The reaction was then heated at 90 °C for 2 h after which time further NaH (60 wt% in mineral oil, 1.50 g, 37.0 mmol) was added. After stirring at 90 °C for a further 30 min, allyl alcohol was azeotropically distilled off at 110 °C. When no more allyl alcohol was present, allyl bromide (20.0 g, 165 mmol) was added over 10 min at 100 °C, and the reaction was stirred overnight. After cooling to RT, the solution was washed successively with 5 wt% aq. NaCl solution (50 mL), sat. aq. $NaHCO_3$ solution (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*. The residue was purified by distillation, which gave cyclopentanone **273** (13.9 g, 66.7 mmol, 59%) as a colourless oil b.p. 125–128 °C, 6.5 mBar (lit. 90 °C, 3 mBar). $\boldsymbol{\delta_H}$ (250 MHz, $CDCl_3$) 6.04–5.61 (2H, m, $H_2C{=}CH$), 5.40–4.99 (4H, m, $H_2C{=}CH$), 4.65–4.57 (2H, m, OCH_2), 2.71 (1H, ddt, J = 14.0, 7.2, 1.1 Hz, $CCHHCH{=}CH_2$), 2.59–2.17 (4H, m), 2.13–1.87 (3H, m); $\boldsymbol{\delta_C}$ (62.5 MHz, $CDCl_3$) 214.6 (ketone $C{=}O$), 170.7 (ester $C{=}O$), 133.0 ($H_2C{=}CH$), 131.7 ($H_2C{=}CH$), 119.3 ($H_2C{=}CH$), 118.5 ($H_2C{=}CH$), 66.0 (CCH_2), 60.0 (CO_2CH_2), 38.2 (CCH_2CH), 37.9 ($C(O)CH_2$), 32.2 (CCH_2CH_2), 19.6 (CH_2CH_2). *Data are in accordance with literature values.*[93]

2-Allylcyclopent-2-enone

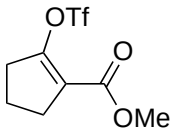


274

According to the procedure of Blechert and co-workers,[93] to a stirred solution of PPh_3 (151 mg,

0.576 mmol) in MeCN (50 mL) was added $Pd(OAc)_2$ (108 mg, 0.480 mg). The solution was heated to 80 °C and a solution of allyl ester **273** (10.0 g, 48.0 mmol) in MeCN (10 mL) was added over 10 min. The solution was stirred for 1 h, cooled to RT, and the solvent was removed *in vacuo*. The residue was purified by distillation, which gave enone **274** (1.01 g, 8.27 mmol, 17%) as a colourless oil b.p. 60–63 °C, 4 mBar (lit. 60 °C, 4 mBar). $\boldsymbol{\delta_H}$ (250 MHz, $CDCl_3$) 7.41–7.37 (1H, m, C=C*H*), 5.92 (1H, ddt, J = 17.0, 10.4, 6.7 Hz, H_2C=C*H*), 5.20–5.10 (2H, m, CH=CH_2), 3.02–2.95 (2H, m, C(O)CH_2), 2.68–2.60 (2H, m, CCH_2), 2.51–2.45 (2H, m, CHCH_2); $\boldsymbol{\delta_C}$ (62.5 MHz, $CDCl_3$) 209.3 (*C*=O), 158.3 (C=*C*H), 144.5 (*C*=CH), 134.5 (*C*H=CH_2), 116.5 (CH=*C*H_2), 34.4 (*C*H_2), 29.2 (*C*H_2), 26.5 (*C*H_2). *Data are in accordance with literature values.*[93]

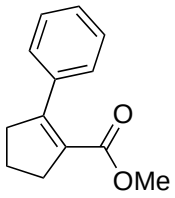
Methyl 2-(trifluoromethylsulfonyloxy)cyclopent-1-enecarboxylate



277

According to the procedure of Christensen *et al.*,[95] methyl 2-oxocyclopentanecarboxylate (1.42 g, 10.0 mmol) was dissolved in dry DCM (40 mL) and cooled to -78 °C, followed by the addition of Hünig's base (8.6 mL). After stirring for 10 mins, Tf_2O (1.24 mL, 12.0 mmol) was added over 30 mins by syringe pump. The solution was allowed to warm to RT overnight and then quenched by the addition of water (15 mL). The layers were separated and the organic layer was washed with 5% aqueous citric acid solution (2×15 mL), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The resultant black residue was purified by flash column chromatography (19→15:1 PE:EtOAc), which gave triflate **277** (2.74 g, 10.0 mmol, 100%) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 3.80 (3H, s, CO_2CH_3), 2.86–2.64 (4H, m, (C=CCH_2)$_2$), 2.13–1.93 (2H, m, $CH_2CH_2CH_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 162.5 (*C*=O), 122.9 (*C*F_3), 119.8 (*C*=C), 116.7 (C=*C*), 51.5 (CO_2CH_3), 32.6 (C=C*C*H_2), 29.0 (C=C*C*H_2), 18.7 ($CH_2CH_2CH_2$); $\boldsymbol{\delta_F}$ (376 MHz, $CDCl_3$) -74.9. *Data are consistent with literature values.*[95]

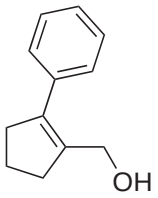
Methyl 2-phenylcyclopent-1-enecarboxylate



278

According to the procedure of Christensen *et al.*,[95] triflate **277** (2.15 g, 7.8 mmol), PPh_3 (205 mg, 0.78 mmol), $Pd(OAc)_2$ (88 mg, 0.39 mmol), Na_2CO_3 (1.66 g, 15.6 mmol) were dissolved in nitrogen sparged benzene/EtOH (3:1, 32 mL). Phenylboronic acid (1.15 g, 9.36 mmol) was added and the solution was heated to 75 °C for 20 h. The solution was concentrated *in vacuo* and filtered through Celite®. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (19:1 PE:EtOAc), which gave ester **278** (1.44 g, 7.12 mmol, 91%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.45–7.26 (5H, m, Ar*H*), 3.64 (3H, s, CO_2CH_3), 2.96–2.80 (4H, m, C=CCH_2), 2.11–1.94 (2H, m, $CH_2CH_2CH_2$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 166.6 (*C*=O), 153.6 (Ph*C*=C), 137.0 (*Ar*), 128.8 (MeO_2CC=C), 127.9 (*Ar*), 127.8 (*Ar*), 127.7 (*Ar*), 51.1 (CO_2CH_3), 40.2 (C=CCH_2), 35.2 (C=CCH_2), 22.0 ($CH_2CH_2CH_2$). *Data are consistent with literature values.*[95]

(2-Phenylcyclopent-1-enyl)methanol

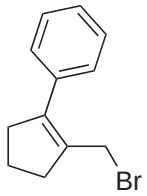


279

According to GP 3, ester **278** was treated with $LiAlH_4$, which after flash column chromatography (1:1 PE:Et_2O) gave alcohol **279** (1.11 g, 6.39 mmol, 91%) as needle like crystals *m.p.* 55–56 °C. $\mathbf{R}_f$ 0.38 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.40–7.30 (2H, Ar*H*), 7.32–7.21 (3H, Ar*H*), 4.33 (2H, d, J = 3.0 Hz, HOCH_2), 2.84–2.77 (2H, m, PhCCH_2), 2.72–2.66 (2H, m, CH_2CCH_2), 2.04–1.92 (2H, m, $CH_2CH_2CH_2$), 1.45 (1H, br s, O*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 139.5 (*Ar*), 137.6 (*C*=C), 137.5 (C=*C*), 128.2 (*Ar*), 127.7 (*Ar*), 126.9 (*Ar*), 59.9 (HO*C*H_2), 37.8 (PhC*C*H_2), 35.4 (CH_2CCH_2), 22.0 ($CH_2CH_2CH_2$); $\boldsymbol{\nu_{max}}$ **/** $\mathbf{cm^{-1}}$ 3347 (m, O-H), 2948 (m, C-H), 1599 (w, C=C), 993 (m), 764 (s), 704 (s); **m/z** (FI)

HRMS found 174.1051, $C_{12}H_{14}O$ requires 174.1045.

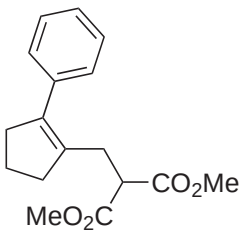
(2-(Bromomethyl)cyclopent-1-enyl)benzene



280

Alcohol **279** (1.10 g, 6.29 mmol) and pyridine (0.05 mL, 0.60 mmol) were dissolved in Et_2O/hexane (7:2, 9.7 mL) and cooled to 0 °C after which PBr_3 (0.23 mL, 2.40 mmol) was added dropwise. The reaction was stirred at 0 °C until TLC indicated complete consumption of starting material (∼45 min). Water (5 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3×5 mL), and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography† (PE), which gave allyl bromide **280** (677 mg, 2.46 mmol, 39%) as a colourless oil which rapidly turned pale yellow. By ^{1}H NMR, the purity was estimated to be ≈80%. $\mathbf{R}_f$ 0.64 (PE); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.46–7.11 (5H, m, Ar*H*), 4.08 (2H, s, BrCH_2), 2.87–2.73 (2H, m, C=CCH_2), 2.73–2.61 (2H, m, C=CCH_2), 2.04–1.91 (2H, m, $CH_2CH_2CH_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 140.5 (*Ar*), 137.7 (*C*=C), 135.9 (C=*C*), 128.1 (*Ar*), 127.8 (*Ar*), 126.8 (*Ar*), 67.2 (Br*C*H_2), 37.7 (C=C*C*H_2), 36.1 (C=C*C*H_2), 22.0 ($CH_2CH_2CH_2$); $\boldsymbol{\nu}_\mathbf{max}$ **/ cm^{-1}** 2950 (m, C-H), 2843 (m), 1493 (w), 1442 (w), 1050 (m), 761 (s, Ar), 699 (s, Ar); **m/z** (FI) HRMS found 236.0212, $C_{12}H_{13}{}^{87}Br$ requires 236.0201.

Dimethyl 2-((2-phenylcyclopent-1-enyl)methyl)malonate



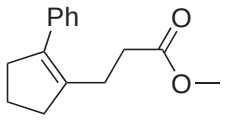
281

Allyl bromide **280** (648 mg, 2.73 mmol), DMM (0.62 mL, 5.47 mmol), and K_2CO_3 (1.89 g, 13.7

†A number of more polar impurities co-eluted with the desired product. Additionally, the silica turned deep red although the eluted product was colourless.

mmol) were dissolved in acetone (14 mL) and heated under reflux overnight. The reaction was cooled to RT after which 0.5 M aqueous HCl solution (5 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (12→6:1 PE:EtOAc), which gave malonate **281** (320 mg, 1.11 mmol, 41%) as a pale yellow oil. $\mathbf{R}_f$ 0.50 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.37–7.30 (2H, m, Ar*H*), 7.28–7.20 (3H, m, Ar*H*), 3.65 (6H, s, CO_2CH_3), 3.57 (1H, t, J = 7.8 Hz, $(MeO_2C)_2CH$), 2.89 (2H, d, J = 7.8 Hz, $CHCH_2$), 2.75–2.66 (2H, m, $C{=}CCH_2$), 2.47 (2H, br t, J = 7.4 Hz, $C{=}CCH_2$), 1.97–1.84 (2H, m, $CH_2CH_2CH_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.5 (*C*=O), 139.3 (*C*), 138.2 (*C*), 133.8 (*C*), 128.2 (*Ar*), 127.6 (*Ar*), 126.6 (*Ar*), 52.4 (CO_2CH_3), 50.4 ($(MeO_2C)_2CH$), 38.0 ($C{=}CCH_2$), 36.3 ($C{=}CCH_2$), 28.5 ($CHCH_2$), 22.1 ($CH_2CH_2CH_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2952 (w, C-H), 1734 (s, C=O), 1599 (w, C=C), 1574 (w, C=C), 1436 (m), 1242 (m), 762 (m, Ar), 701 (m, Ar); **m/z** (ESI+) 311.1 ($[M+Na]^+$, 100%), HRMS found 311.1255, $C_{17}H_{20}NaO_4$ requires 311.1254.

Methyl 3-(2-phenylcyclopent-1-enyl)propanoate

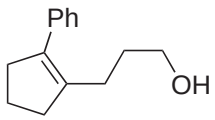


282

A stirred solution of malonate ester **281** (320 mg, 1.11 mmol), water (40 mg, 2.22 mmol), and NaCl (71 mg, 1.22 mmol) in dry DMSO (1.1 mL) was heated at 170 °C for 4.5 h. After cooling to RT, saturated aqueous NH_4Cl solution (0.25 mL) was slowly added, followed by water (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (10:1 PE:EtOAc), which gave ester **282** (182 mg, 0.79 mmol, 71%) as a pungent colourless oil. $\mathbf{R}_f$ 0.57 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.38–7.32 (2H, m, Ar*H*), 7.28–7.20 (3H, m, Ar*H*), 3.65 (3H, s, CO_2CH_3), 2.78–2.70 (2H, $C{=}CCH_2$), 2.64–2.57 (2H, m, $MeO_2CCH_2CH_2$) 2.54–2.42 (4H, m, $C{=}CCH_2$ & CH_2CO_2Me), 1.99–1.88 (2H, m, $CH_2CH_2CH_2$); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 173.7 (*C*=O), 138.4 (*Ar*), 137.0 (*C*=C), 136.7 (C=*C*), 128.2 (*Ar*), 127.6 (*Ar*), 126.4 (*Ar*), 51.6 (CO_2CH_3), 37.8 ($C{=}CCH_2$), 36.5 ($C{=}CCH_2$), 32.9 (MeO_2CCH_2), 24.8 ($MeO_2CCH_2CH_2$), 22.0 ($CH_2CH_2CH_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2950 (m, C-H), 1736 (s, C=O), 1436 (m), 1170 (s), 761 (s), 699 (s); **m/z** (ESI+) HRMS found 253.1199, $C_{15}H_{18}NaO_2$ requires

253.1199.

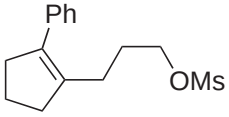
3-(2-Phenylcyclopent-1-enyl)propan-1-ol



283

According to GP 3, ester **282** (180 mg, 0.78 mmol) was treated with $LiAlH_4$, which gave alcohol **283** (156 mg, 0.77 mmol, 99%) as a colourless oil, which was used without purification. $\mathbf{R}_f$ 0.40 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.34 (2H, t, J = 7.6 Hz, ArH), 7.30–7.19 (3H, m, ArH), 3.61 (2H, t, J = 6.5 Hz, HOCH_2), 2.80–2.70 (2H, m, C=CCH_2), 2.52 (2H, dd, J = 7.4, 7.4, C=CCH_2), 2.33 (2H, t, J = 7.7 Hz, $HOCH_2CH_2CH_2$), 1.98–1.87 (2H, m, $CH_2CH_2CH_2$), 1.78–1.68 (2H, m, $HOCH_2CH_2$), 1.45 (1H, br s, OH); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 138.7 (C=C), 138.4 (Ar), 136.1 (C=C), 128.1 (Ar), 127.6 (Ar), 126.3 (Ar), 62.8 (HOCH$_2$), 37.8 (C=CCH$_2$), 36.8 (C=CCH$_2$), 31.1 ($HOCH_2CH_2$), 25.4 ($HOCH_2CH_2CH_2$), 22.1 ($CH_2CH_2CH_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 3329 (br m, O-H), 2937 (m, C-H), 1643 (w, C=C), 1600 (w, C=C), 1053 (m), 760 (m), 653 (m); **m/z** (FI) HRMS found 202.1357, $C_{14}H_{18}O$ requires 202.1358.

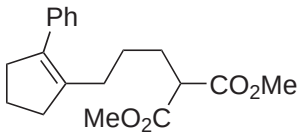
3-(2-Phenylcyclopent-1-enyl)propyl methanesulfonate



438

According to GP 4, alcohol **283** (156 mg, 0.77 mmol) was treated with MsCl, which gave mesylate **438** (210 mg, 0.75 mmol, 97%) as a pale yellow oil, which was used without purification. $\mathbf{R}_f$ 0.40 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.44–7.33 (2H, m, ArH), 7.30–7.24 (3H, m, ArH), 4.20 (2H, t, J = 6.5 Hz, MsOCH_2), 2.91 (3H, s, SO_2CH_3), 2.81–2.75 (2H, m, CH_2), 2.55 (2H, t, J = 7.5 Hz, CH_2), 2.42 (2H, dd, J = 7.7, 7.7 Hz, CH_2), 2.04–1.89 (4H, m, CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 138.9 (Ar), 137.7 (C=C), 137.2 (C=C), 128.6 (Ar), 128.1 (Ar), 126.9 (Ar), 70.1 (MsOCH$_2$), 38.3 (CH$_2$), 37.6 (SO_2CH_3), 37.1 (CH$_2$), 28.1 (CH$_2$), 25.5 (CH$_2$), 22.5 (CH$_2$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2942 (m, C-H), 1347 (s, SO_2), 1172 (s, SO_2), 967 (m), 927 (m), 762 (m), 703 (m); **m/z** 303.1 ([M+Na]$^+$, 100%), HRMS found 303.1020, $C_{15}H_{20}NaO_3S$ requires 303.1025.

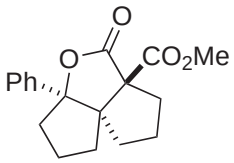
Dimethyl 2-(3-(2-phenylcyclopent-1-enyl)propyl)malonate



266

According to GP 5, mesylate **438** (200 mg, 0.71 mmol) was treated with DMM, which after flash column chromatography (12:1 PE:EtOAc) gave malonate **266** (161 mg, 0.51 mmol, 72%) as a colourless oil. $\mathbf{R}_f$ 0.55 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.39–7.29 (2H, m, Ar*H*), 7.26–7.18 (3H, m, Ar*H*), 3.73 (6H, s, CO_2CH_3), 3.33 (1H, t, J = 7.5 Hz, $(MeO_2C)_2CH$), 2.73 (2H, t, J = 7.4 Hz, $C{=}CCH_2(CH_2)_2CH$), 2.54–2.43 (2H, m, $C{=}CCH_2$), 2.27 (2H, dd, J = 7.7, 7.7 Hz, $C{=}CCH_2$), 1.97–1.83 (4H, m, CH_2), 1.55–1.42 (2H, m, CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (100 MHz, $CDCl_3$) 169.8 (*C*=O), 138.7 (*Ar*), 138.2 (*C*=C), 136.2 (C=*C*), 128.1 (*Ar*), 127.6 (*Ar*), 126.2 (*Ar*), 52.4 (CO_2CH_3), 51.5 ($(MeO_2C)_2CH$), 37.7 ($C{=}CCH_2(CH_2)_2CH$), 36.6 ($C{=}CCH_2$), 28.8 ($C{=}CCH_2$), 28.7 (CH_2), 25.9 (CH_2), 22.0 (CH_2); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2951 (m, C-H), 1752 (s, C=O asymmetric), 1735 (s, C=O symmetric), 1599 (w, C=C), 1574 (w, C=C), 1435 (m), 763 (m), 700 (m); **m/z** (ESI+) 339.2 ($[M+Na]^+$, 100%), HRMS found 339.1564, $C_{19}H_{24}NaO_4$ requires 339.1567.

(3a*S,5a*R**,8*R**)-Methyl 5-oxo-3a-phenyloctahydro-1*H*-dicyclopenta[*b*,*c*]furan-5a-carboxylate**



267

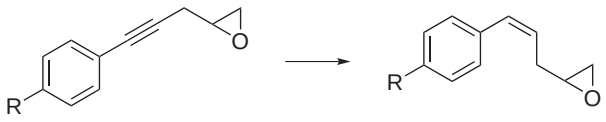
According to GP 6, malonate ester **266** (26 mg, 82.3 μmol mmol) was treated with $Mn(OAc)_2{\cdot}2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (5:1 PE:EtOAc), gave tricyclic lactone **267** (21 mg, 70.8 μmol, 86%) as a colourless oil. $\mathbf{R}_f$ 0.32 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.45–7.41 (4H, m, Ar*H*), 7.40–7.34 (1H, m, Ar*H*), 3.88 (3H, s, CO_2CH_3), 2.58 (1H, ddd, J = 13.5, 11.9, 7.5 Hz, $MeO_2CCCCHH$), 2.53–2.46 (1H, m, $PhCCCHH$), 2.39–2.30 (1H, m, $PhCCCHH$), 2.26 (1H, app ddt, J = 13.5, 7.5, 1.6 Hz, $MeO_2CCCCHH$), 1.98–1.86 (4H, m, $PhCCH_2CH_2CH_2$), 1.76 (1H, app ddt, J = 13.6, 6.2,

1.6 Hz, $MeO_2CCCH_2CH_2CHH$), 1.68–1.58 (1H, m, $MeO_2CCCH_2CH_2CHH$), 1.42 (1H, ddddd, J = 12.8, 7.5, 7.5, 1.6, 1.6 Hz, MeO_2CCH_2CHH), 0.82–0.69 (1H, m, MeO_2CCCH_2CHH); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 177.3 (lactone C=O), 171.6 (ester C=O), 141.1 (Ar), 128.4 (Ar), 128.1 (Ar), 126.1 (Ar), 97.9 (PhC), 68.2 (MeO_2CC), 66.3 (CH_2CCH_2), 53.2 (CO_2CH_3), 43.5 ($PhCCH_2$), 38.5 ($MeO_2CCCH_2CH_2CH_2$), 38.3 ($PhCCH_2CH_2$), 37.4 (MeO_2CCCH_2), 24.2 ($MeO_2CCCH_2CH_2$), 23.8 ($PhCCH_2CH_2CH_2$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2955 (m, C-H), 1770 (s, lactone C=O), 1735 (s, ester C=O), 1448 (m), 1240 (m), 1164 (m), 766 (m), 704 (m); **m/z** (ESI+) 323.2 ($[M+Na]^+$, 100%), HRMS found 323.1255, $C_{18}H_{20}NaO_4$ requires 323.1254.

6.3 Synthesis of Tricyclic bis-Lactones

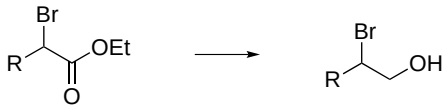
6.3.1 General Procedures

General Procedure 8: Semi-Reduction with Lindlar's Catalyst



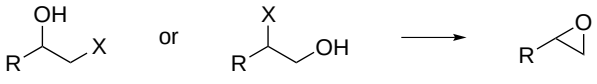
A vigourously stirred solution of aryl alkyne (1.0 eq.), quinoline (1.0 eq.), and Lindlar catalyst (Strem or Sigma-Aldrich, 15 wt%) in allyl alcohol (5 mL/mmol) was purged of oxygen by three times vacuum–N_2 flush and finally quenched to an atmosphere of H_2. The solution was stirred at RT until the reaction was judged complete (GC or TLC, ca. 3 h) and then purged of H_2 and quenched to N_2. The resultant solution was filtered through a plug of Celite®, diluted with EtOAc, washed with saturated aqueous NH_4Cl solution (water was added to dissolve precipitates), dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo*.

General Procedure 9: α-Bromoester Reduction with DiBAl-H



To a stirred solution of α-bromoester in DCM (5 mL/mmol) at –40 °C was added DiBAl-H (1.0 M in PhMe, 2.5 eq.) dropwise. When TLC analysis indicated complete consumption of starting material (≈2 h) the reaction was quenched by the addition of sat. aq. Rochelle's salt (2 mL/mmol). The solution was stirred vigorously until the aqueous and organic layers separated. The layers were separated and the aqueous layer was extracted with DCM (3×2 mL/mmol). The combined organic extracts were washed successively with water (2 mL/mmol) and brine (2 mL/mmol), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*.

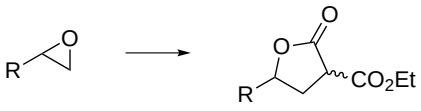
General Procedure 10: Halohydrin Epoxidation



To a stirred solution of halohydrin in ^{t}BuOH (5 mL/mmol) at 35 °C was added KO^{t}Bu (1.5 eq.). When TLC analysis indicated complete consumption of starting material (≈30 min) the reaction was

quenched by the addition of water (2 mL/mmol) and diluted with Et_2O (5 mL/mmol). The layers were separated and the aqueous layer was extracted with Et_2O (3×2 mL/mmol). The combined organic layers were washed successively with sat. aq. NH_4Cl solution (4 mL/mmol), water (2×4 mL/mmol), and brine (4 mL/mmol). The organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*.

General Procedure 11: Lactonisation by Epoxide Opening

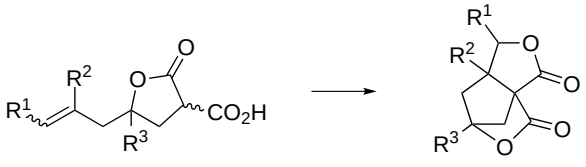


To a stirred solution of epoxide (1.0 eq.) and diethyl malonate (3.0 eq.) in EtOH (0.25 mL/mmol epoxide) at 0 °C was added NaOEt solution (2 M in EtOH, 3.0 eq.) freshly prepared by the addition of Na metal to an appropriate volume of EtOH at 0 °C. The solution was allowed to warm to RT and stirred overnight. The reaction was quenched with sat. aq. NH_4Cl solution (5 mL/mmol epoxide) and diluted with EtOAc (5 mL/mmol epoxide). The layers were separated and the aqueous was extracted with EtOAc (3×10 mL/mmol). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*.

General Procedure 12: Saponification of Lactone-Ester

To a stirred solution of lactone (1.0 eq.) in EtOH (5 mL/mmol lactone) at 0 °C was added aq. KOH solution (1 M, 2.0 eq.). The reaction was stirred until judged complete by TLC, and then diluted with NaOH solution (2 M, 5 mL/mmol lactone) and DCM (2.5 mL/mmol lactone). The layers were separated and the aqueous was acidified to pH ≈2 with conc. HCl. The aqueous was extracted with EtOAc (4×10 mL/mmol lactone). The combined organic extracts were washed with brine (5 mL/mmol lactone), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*, which gave the corresponding acid which was used without purification.

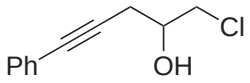
General Procedure 13: Oxidative Radical Cyclisation of Lactone-Acid



A solution of lactone-acid (1.0 eq.) in MeCN (10 μM) was sparged with N_2 for 30 min and then added to a degassed solution of $Mn(OAc)_3{\cdot}H_2O$ or CAN (2.0 eq.) and $Cu(OTf)_2$ (1.0 eq.) at the specified temperature. The solution was stirred for 2 h, and then quenched by the addition of 1 M aq. HCl solution (5 mL/mmol) and diluted with DCM (5 mL/mmol). The layers were separated, and the aqueous layer was extracted with DCM (3×5 mL/mmol). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*, which gave the crude product.

6.3.2 Experimental Details and Data

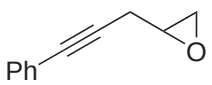
1-Chloro-5-phenylpent-4-yn-2-ol



294

According to the procedure of Yamaguchi and Hirao,[99] phenylacetylene (8.23 mL, 7.65 g, 75 mmol) was dissolved in dry THF (100 mL) and cooled to –78 °C after which ^{n}BuLi (2.35 M in pentane, 32 mL, 75 mmol) was added. After 10 min, $BF_3{\cdot}OEt_2$ (9.87 mL, 11.4 g, 80 mmol) was added and after a further 10 min epichlorohydrin (3.92 mL, 4.63 g, 50 mmol) in dry THF (20 mL) was added. After 30 min, saturated aqueous NH_4Cl solution (50 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The crude product was purified on a Biotage Isolere Four (6→50% MTBE in hexanes) which gave chlorohydrin **294** (8.29 g, 42.5 mmol, 85%) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.46–7.36 (2H, Ar*H*), 7.33–7.27 (3H, Ar*H*), 4.07 (1H, dddd, J = 11.9, 5.9, 5.9, 5.9 Hz, C*H*O), 3.78 (1H, dd, J = 11.2, 4.4 Hz, CHOHC*H*HCl), 3.69 (1H, dd, J = 11.2, 5.9 Hz, CHOHCH*H*Cl), 2.80 (1H, dd, J = 17.1, 5.9 Hz, C*H*HCHOH), 2.74 (1H, dd, J = 17.1, 6.8 Hz, CH*H*CHOH), 2.57 (1H, br s, O*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 131.6 (*Ar*), 128.3 (*Ar*), 128.1 (*Ar*), 123.0 (*Ar*), 84.3 (*C*≡C), 83.5 (C≡*C*), 69.9 (*C*HOH), 48.5 (CHOH*C*H_2Cl), 25.3 (CHOH*C*H_2C). *Data are consistent with literature values.*[99]

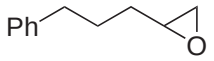
2-(3-Phenylprop-2-ynyl)oxirane



293

According to GP 10, chlorohydrin **294** (5.83 g, 29.9 mmol) was treated with KO^{t}Bu, which after purification on a Biotage Isolere 4 (6%→50% MTBE in hexanes) gave epoxide **293** (3.73 g, 23.6 mmol, 79%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.44–7.37 (2H, m, Ar*H*), 7.31–7.22 (3H, m, Ar*H*), 3.20–3.14 (1H, m, C*H*(OCH_2)), 2.85–2.78 (2H, m, C≡CC*H*H & CH(O)C*H*H), 2.71 (1H, dd, J = 4.8, 2.5 Hz, CH(O)CH*H*), 2.67 (1H, dd, J = 17.3, 5.1 Hz, C≡CCH*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 131.6 (*Ar*), 128.2 (*Ar*), 128.0 (*Ar*), 123.2 (*Ar*), 84.1 (*C*≡C), 82.6 (C≡*C*), 50.0 (*C*H(OCH_2)), 46.5 (CH(O*C*H_2)), 23.2 (C≡C*C*H_2). *Data are consistent with literature values.*[170]

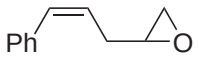
2-(3-Phenylpropyl)oxirane



298

A solution of alkyne **293** (335 mg, 2.12 mmol) in toluene (20 mL) was degassed 3 times and placed under an N_2 atmosphere after which Lindlar's catalyst (67 mg) was added. The solution was placed under vacuum, and then an H_2 atmosphere was established with vigorous stirring. After 5 h, the solution was filtered through cotton wool and the solvent removed *in vacuo* which gave epoxide **298** (326 mg, 2.01 mmol, 95%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.30–7.24 (2H, m, Ar*H*), 7.21–7.13 (3H, m, Ar*H*), 2.94–2.87 (1H, m, C*H*(O)CH_2), 2.74–2.69 (1H, m, CH(O)C*H*H), 2.66 (2H, t, J = 7.7 Hz, ArCH_2), 2.43 (1H, dd, J = 5.0, 2.7 Hz, CH(O)CH*H*), 1.88–1.68 (2H, m, $PhCH_2CH_2$), 1.65–1.47 (2H, m, CH_2CH(O)CH_2); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 142.0 (*Ar*), 128.4 (*Ar*), 128.3 (*Ar*), 125.8 (*Ar*), 52.1 (*C*H(OCH_2)), 47.0 (CH(O*C*H_2)), 35.6 (*C*H_2), 32.0 (*C*H_2), 27.7 (*C*H_2). *Data are consistent with literature values.*[171]

(*Z*)-2-(3-Phenylallyl)oxirane

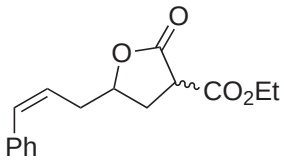


292

According to GP 8, alkyne **298** (500 mg, 3.16 mmol) was treated with H_2 gas, which after purification on a Biotage Isolere 4 (4%→32% MTBE in hexanes) gave alkene **292** (440 mg, 2.75 mmol, 87%) as a colourless oil. $\mathbf{R}_f$ $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.39–7.32 (2H, m, Ar*H*), 7.31–7.23 (3H, m, Ar*H*), 6.61 (1H, d, J = 11.6 Hz, PhC*H*=CH), 5.74 (1H, dt, J = 11.6, 7.4 Hz, PhCH=C*H*), 3.09–3.04 (1H, m, CH_2CHO), 2.79 (1H, dd, J = 5.0, 3.9 Hz, CH(O)C*H*H), 2.66–2.61 (2H, m, PhCH=CHCH_2), 2.56 (1H, dd, J = 5.0,

2.7 Hz, CH(O)CHH) $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 137.0 (Ar), 131.7 (PhCH=CH), 128.7 (Ar), 128.2 (Ar), 126.9 (Ar), 126.0 (PhCH=CH), 51.6 (CH_2CHO), 46.6 (CH(O)CH$_2$), 31.3 (PhCH=CHCH$_2$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3053 (w, epoxide C-H), 3016 (m, C-H), 1600 (w, C=C, Ar), 1574 (w, C=C, Ar), 1494 (m, Ar), 769 (s Ar), 698 (s, Ar); **m/z** (FI) HRMS found 160.0896, $C_{11}H_{12}O$ requires 160.0888.

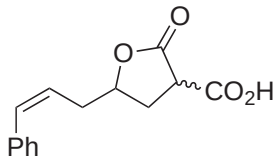
(*Z*)-Ethyl 2-oxo-5-(3-phenylallyl)tetrahydrofuran-3-carboxylate



301

According to GP 11, epoxide **292** (1.06 g, 6.64 mmol) was treated with DEM, which after flash column chromatography (9:1→4:1→1:1 hexanes:EtOAc) which gave an inseparable 1:1 diastereomeric mixture of lactone **301** (1.81 g, 6.61 mmol, 100%) as a colourless oil characterised as a mixture of diastereomers. $\mathbf{R}_f$ 0.47 (1:1 EtOAc:hexanes); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.36 (2H, t, J = 8.0 Hz, ArH), 7.29–7.22 (3H, m, ArH), 6.66 (1H, d, J = 11.6 Hz, PhCH=CH), 6.64 (1H, d, J = 11.6 Hz, PhCH=CH), 5.70 (1H, ddd, J = 7.1, 7.1, 11.6 Hz, PhCH=CH), 5.67 (1H, ddd, J = 7.1, 7.1, 11.6 Hz, PhCH=CH), 4.80–4.74 (1H, m, CH_2CHO-d1), 4.54 (1H, dddd, J = 9.5, 6.8, 5.9, 5.9 Hz, CH_2CHO-d2), 4.24 (2H, q, J = 7.1 Hz, CO_2CH_2), 3.62 (1H, dd, J = 11.1, 9.3 Hz, EtO_2CCH-d2), 3.57 (1H, dd, J = 9.5, 4.9 Hz, EtO_2CCH-d1), 2.90–2.81 (1H, m, PhCH=CHCHH-d2), 2.81–2.65 (2H, m, PhCH=CHCH_2-d1 & PhCH=CHCHH-d2 & CHCHH-d1), 2.55 (1H, ddd, J = 13.1, 9.4, 6.3 Hz, CHCHH-d2), 2.37 (1H, ddd, J = 13.1, 11.1, 9.5 Hz, CHCHH-d2), 2.13 (1H, ddd, J = 13.3, 9.7, 7.3 Hz, CHCHH-d1), 1.31 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 1.30 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 171.6 (lactone C=O), 171.5 (lactone C=O), 167.7 (ester C=O), 167.7 (ester C=O), 136.7 (Ar), 136.7 (Ar), 132.8 (PhCH=CH), 132.6 (PhCH=CH), 128.6 (Ar), 128.6 (Ar), 128.4 (Ar), 128.3 (Ar), 127.2 (Ar), 127.1 (Ar), 124.9 (PhCH=CH), 124.8 (PhCH=CH), 79.4 (CHO-d1), 78.7 (CHO-d2), 62.3 (CO_2CH_2), 62.2 (CO_2CH_2), 47.3 (EtO_2CCH-d2), 46.9 (EtO_2CCH-d1), 33.9 (PhCH=CHCH$_2$), 31.6 (CHOCH$_2$-d2), 31.3 (CHOCH$_2$-d1), 14.0 ($CO_2CH_2CH_3$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2984 (w, C-H), 1776 (s, lactone C=O), 1732 (s, ester C=O), 1161 (m), 1021 (m); **m/z** (ESI+) 297.1 ($[M+Na]^+$, 100%), HRMS found 297.1100, $C_{16}H_{18}NaO_4$ requires 297.1097.

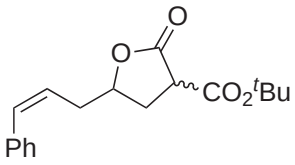
(*Z*)-2-Oxo-5-(3-phenylallyl)tetrahydrofuran-3-carboxylic acid



288

According to GP 12, lactone-ester **301** (750 mg, 2.74 mmol) was treated with aqueous KOH, which gave acid **288** (674 mg, 2.74 mmol, 100%) as a colourless viscous oil characterised as a mixture of diastereomers. $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 8.10 (1H, br, CO_2H), 7.36 (2H, t, J = 7.6 Hz, ArH), 7.30–7.22 (3H, m, ArH), 6.68 (1H, d, J = 11.6 Hz, PhCH=CH), 6.66 (1H, d, J = 11.6 Hz, PhCH=CH), 5.69 (1H, dt, J = 11.6, 7.2 Hz, PhCH=CH), 5.66 (1H, dt, J = 11.6, 7.2 Hz, PhCH=CH), 4.83–4.76 (1H, m, CHO-d1), 4.59 (1H, dddd, J = 9.7, 6.2, 6.2, 6.2 Hz, CHO-d2), 3.70 (1H, dd, J = 11.2, 9.4 Hz, HO_2CCH-d2), 3.63 (1H, dd, J = 9.8, 5.6 Hz, HO_2CCH-d1), 2.90–2.67 (3H, m, CH=CHCH_2 & CHCHH-d1), 2.63 (1H, ddd, J = 13.2, 9.3, 6.1 Hz, CHCHH-d2), 2.40–2.30 (1H, m, CHCHH-d2), 2.19 (1H, ddd, J = 14.2, 9.8, 6.8 Hz, CHCHH-d1); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 172.1 (lactone C=O), 171.8 (lactone C=O), 171.6 (acid C=O), 171.1 (acid C=O), 136.6 (Ar), 136.6 (Ar), 133.1 (PhCH=CH), 132.9 (PhCH=CH), 128.6 (Ar), 128.6 (Ar), 128.4 (Ar), 128.4 (Ar), 127.2 (Ar), 127.2 (Ar), 124.4 (PhCH=CH), 79.6 (CHO-d1), 79.2 (CHO-d2), 46.9 (HO_2CCH-d2), 46.5 (HO_2CCH-d1), 33.8 (CH=CHCH$_2$), 33.7 (CH=CHCH$_2$), 31.3 (CHCH$_2$-d2), 30.8 (CHCH$_2$-d1); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3468 (br, COO-H), 3023 (m, C-H), 1772 (s, lactone C=O), 1742 (s, acid C=O), 1600 (w, C=C), 1574 (w, C=C), 1175 (s, C-O); **m/z** (ESI+) 269.1 ([M+Na]$^+$, 100%), HRMS found 269.0792, $C_{14}H_{14}NaO_4$ requires 269.0784.

(*Z*)-*tert*-Butyl 2-oxo-5-(3-phenylallyl)tetrahydrofuran-3-carboxylate

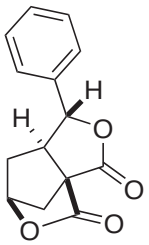


302

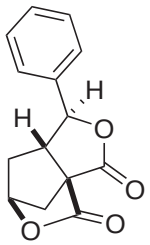
To a stirred solution of carboxylic acid **288** (80 mg, 0.33 mmol) in dry DCM (1.65 mL) at 0 °C was added ^{t}BuOH (24 mg, 0.33 mmol), DCC (68 mg, 0.33 mmol), and DMAP (2.0 mg, 17 μmmol) successively. The solution was allowed to slowly warm to RT and stirred overnight. The reaction was

filtered through Celite®, eluting with 1:1 DCM/Et_2O. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (4:1 PE:EtOAc), which gave an inseparable 1:1 mixture of diastereomers of *tert*-butyl ester **302** (65 mg, 0.22 mmol, 65%) as a colourless oil characterised as a mixture of diastereomers. $\mathbf{R}_f$ 0.30 (4:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.40–7.32 (2H, m, Ar*H*), 7.30–7.21 (3H, m, Ar*H*), 6.66 (1H, d, $J = 11.6$ Hz, PhC*H*=CH-d_1), 6.63 (1H, d, $J = 11.6$ Hz, PhC*H*=CH-d_2), 5.71 (1H, dt, $J = 11.6$, 7.2 Hz, PhCH=C*H*-d_2), 5.67 (1H, dt, $J = 11.6$, 7.2 Hz, PhCH=C*H*-d_1), 4.78–4.70 (1H, m, CH_2C*H*O-d_1), 4.51 (1H, dddd, $J = 9.6$, 6.2, 6.2, 6.2 Hz, CH_2C*H*O-d_2), 3.52 (1H, dd, $J = 10.9$, 9.3 Hz, CO_2C*H*-d_1), 3.47 (1H, dd, $J = 9.6$, 4.7 Hz, CO_2C*H*-d_2), 2.85 (1H, dddd, $J = 15.6$, 6.9, 6.9, 1.9 Hz, PhCH=CHC*H*H-d_1), 2.80–2.71 (1H, m, PhCH=CHC*H*H), 2.72–2.66 (1H, m, PhCH=CHCH*H*), 2.63 (1H, ddd, $J = 13.2$, 6.9, 4.7 Hz, CHOC*H*HCH-d_2), 2.52 (1H, ddd, $J = 13.0$, 9.3, 6.2 Hz, CHOC*H*HCH-d_1), 2.32 (1H, ddd, $J = 13.0$, 10.0, 9.3 Hz, CHOCH*H*CH-d_1), 2.09 (1H, ddd, $J = 13.2$, 9.6, 7.3 Hz, CHOCH*H*CH-d_2); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 171.9 (lactone *C*=O), 171.9 (lactone *C*=O), 166.8 (ester *C*=O), 166.8 (ester *C*=O), 136.7 (*Ar*), 136.7 (*Ar*), 132.7 (Ph*C*H=CH), 132.5 (Ph*C*H=CH), 128.6 (*Ar*), 128.6 (*Ar*), 128.3 (*Ar*), 128.3 (*Ar*), 127.1 (*Ar*), 127.1 (*Ar*), 125.0 (PhCH=*C*H), 124.9 (PhCH=*C*H), 83.1 ($CO_2C(CH_3)_3$), 82.8 ($CO_2C(CH_3)_3$), 79.2 (CH_2*C*HO-d_1), 78.5 (CH_2*C*HO-d_2), 48.2 (CO_2*C*H-d_1), 47.9 (CO_2*C*H-d_2), 34.0 (PhCH=CH*C*H_2), 34.0 (PhCH=CH*C*H_2), 31.5 (CHO*C*H_2CH), 31.5 (CHO*C*H_2CH), 27.9 ($CO_2C(CH_3)_3$), 27.9 ($CO_2C(CH_3)_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2995 (w, C-H), 1773 (s, lactone C=O), 1728 (s, ester C=O), 1169 (m), 998 (m); **m/z** (ESI+) 325.1 ($[M+Na]^+$, 100%), HRMS found 325.1410, $C_{18}H_{22}NaO_4$ requires 325.1410

(1*R,4*R**,5*R**,7*S**)-4-Phenyl-3,8-dioxatricyclo[5.2.1.0^{1,5}]decane-2,9-dione, 303;**
(1*R,4*S**,5*R**,7*S**)-4-Phenyl-3,8-dioxatricyclo[5.2.1.0^{1,5}]decane-2,9-dione, 291**



303

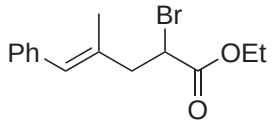


291

According to GP 13, lactone-acid **288** (24.6 mg, 100 μmmol) was treated with manganese(III) acetate dihydrate and copper(II) triflate which, after flash column chromatography (1:1 PE:EtOAc) gave cyclopentane *bis*-lactones **303**:**291** in 5.4:1 dr (15.9 mg, 65 μmol, 65%) as colourless plate-like crystals.

X-ray diffraction quality crystals were grown by slow diffusion of hexane into a DCM solution of lactone **303**. Data for **303**: $\mathbf{R}_f$ 0.14 (1:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.45–7.39 (3H, m, Ar*H*), 7.38–7.34 (2H, m, Ar*H*), 5.41 (1H, d, J = 10.9 Hz, PhC*H*), 5.17 (1H, dd, J = 2.2, 2.2 Hz, C*H*O), 3.16 (1H, ddd, J = 10.6, 10.6, 7.6 Hz, PhCHC*H*), 2.70 (1H, dt, J = 8.4, 1.4 Hz, CC*H*H) 2.22 (1H, ddd, J = 14.2, 10.6, 2.2 Hz, CHC*H*H), 2.16 (1H, br d, J = 10.6 Hz, CCH*H*) 1.98 (1H, ddd, J = 14.2, 7.6, 2.2 Hz, CHCH*H*); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 171.0 (*C*=O), 167.3 (*C*=O), 135.8 (*Ar*), 129.3 (*Ar*), 129.0 (*Ar*), 125.6 (*Ar*), 85.0 (CO_2CH), 83.5 (Ph*C*H), 62.2 (CO_2C), 53.3 (PhCH*C*H), 40.9 (C*C*H_2), 29.2 (CH*C*H_2); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2959 (m, C-H), 1782 (s, bridged lactone C=O), 1756 (s, lactone C=O), **m.p.** 157–159 °C. Data for **291**: $\mathbf{R}_f$ 0.11 (1:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.47–7.38 (3H, m, Ar*H*), 7.39–7.33 (2H, m, Ar*H*), 5.34 (1H, d, J = 9.8 Hz, PhC*H*O), 5.17 (1H, br s, C*H*O), 3.04 (1H, dddd, J = 9.7, 8.3, 4.6, 1.2 Hz, PhCHC*H*), 2.64 (1H, br d, J = 10.9 Hz, CC*H*H), 2.53 (1H, d, J = 10.9 Hz, CCH*H*), 2.34 (1H, ddd, J = 13.7, 8.4, 2.6 Hz, CHC*H*H), 2.24 (1H, ddd, J = 13.7, 4.6, 1.2 Hz, CHCH*H*); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 169.1 (*C*=O), 167.2 (*C*=O), 136.1 (*Ar*), 129.5 (*Ar*), 129.1 (*Ar*), 125.6 (*Ar*), 84.5 (CO_2CHPh), 82.2 (CO_2CH), 57.0 (CO_2C), 49.5 (COPh*C*H), 40.5 (C*C*H_2), 33.5 (CH*C*H_2); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 1799 (s, bridged lactone C=O), 1772 (s, lactone C=O), 1342 (m), 1119 (m), 1019 (m), 912 (m); **m/z** (ESI+) 267.1 ($[M+Na]^+$, 100%), HRMS found 267.0634, $C_{14}H_{12}NaO_4$ requires 267.0628.

(*E*)-Ethyl 2-bromo-4-methyl-5-phenylpent-4-enoate

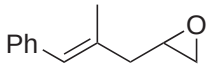


307

According to the modified procedure of Beaudry and Trauner,[119] to a stirred solution of ester **230** (1.31 g, 6.01 mmol) and TMSCl (1.22 mL, 9.63 mmol) in dry THF (60 mL) at –78 °C was added freshly prepared LDA (1.0 M in THF, 9.0 mL, 9.0 mmol) dropwise. The solution was stirred for 1 h, and then NBS (2.14 g, 12.0 mmol) in dry THF (60 mL) precooled to –78 °C was added dropwise. The solution was stirred for 1 h at –78 °C, and 1 h at –40 °C before being quenched by the addition of 50% sat. aq. NH_4Cl solution (30 mL) and diluted with EtOAc (30 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (25:1 PE:EtOAc), which gave α-bromoester **307** (1.25 g, 4.21 mmol, 70%) as a colourless oil. $\mathbf{R}_f$ 0.41

(25:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.34 (2H, t, J = 7.4 Hz, ArH), 7.26–7.20 (3H, m, ArH), 6.39 (1H, s, PhCH=C), 4.45 (1H, dd, J = 7.7, 7.7 Hz, CHBr), 4.29–4.22 (2H, m, CO_2CH_2), 3.02 (1H, dd, J = 14.1, 7.7 Hz, CHHCHBr), 2.83 (1H, dd, J = 14.1, 7.7 Hz, CHHCHBr), 1.90 (3H, s, CH=CCH_3), 1.31 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.6 (C=O), 137.5 (Ar), 133.4 (PhCH=C), 129.4 (PhCH=C), 128.8 (Ar), 128.1 (Ar), 126.5 (Ar), 62.0 (CO_2CH_2), 45.7 (CH$_2$CHBr), 43.8 (CHBr), 17.5 (PhCH=CCH$_3$), 14.0 ($CO_2CH_2CH_3$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2981 (m, C-H), 1736 (s, C=O), 1599 (w, C=C), 1575 (w, C=C), 1147 (s), 744 (m), 699 (s); **m/z** (ESI+) 319.0 ([M(^{79}Br)+Na]$^+$, 100%), 321.0 ([M(^{81}Br)+Na]$^+$, 100%), HRMS found 319.0304, $C_{14}H_{17}BrNaO_2$ requires 319.0304.

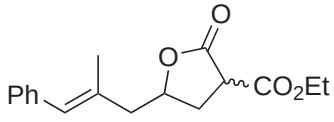
(*E*)-2-(2-Methyl-3-phenylallyl)oxirane



309

According to GP 9, ester **307** (1.15 g, 4.21 mmol) was treated with DiBAl-H, which gave the corresponding bromohydrin which was used without purification. According to GP 10, the bromohydrin was treated with KO^{t}Bu. The crude product was purified by flash column chromatography (25:1 PE:EtOAc), which gave epoxide **309** (570 mg, 3.75 mmol, 89%) as a colourless oil. $\mathbf{R}_f$ 0.50 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.34 (2H, t, J = 7.5 Hz, ArH), 7.29–7.18 (3H, m, ArH), 6.41 (1H, s, PhCH=C), 3.16–3.10 (1H, m, CH(O)CH$_2$), 2.85 (1H, dd, J = 5.0, 5.0 Hz, CH(O)CHH), 2.58 (1H, dd, J = 5.0, 2.7 Hz, CH(O)CHH), 2.44 (1H, dd, J = 14.5, 5.8 Hz, CH=CCHH), 2.39 (1H, dd, J = 14.5, 5.2 Hz, CH=CCHH), 1.94 (3H, s, CH=CCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 138.0 (Ar), 134.9 (PhCH=C), 128.9 (Ar), 128.1 (Ar), 127.0 (PhCH=C), 126.2 (Ar), 51.4 (CH(O)), 46.9 (CH(O)CH$_2$), 43.4 (PhCH=CCH$_2$), 18.5 (PhCH=CCH$_3$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2986 (m, C-H), 1599 (w, C=C), 1575 (w, C=C), 699 (m), 649 (s); **m/z** (FI) HRMS found 174.1042, $C_{12}H_{14}O$ requires 174.1045.

(*E*)-Ethyl 5-(2-methyl-3-phenylallyl)-2-oxotetrahydrofuran-3-carboxylate

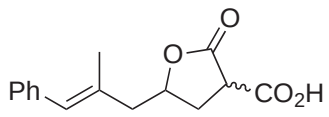


310

To a stirred solution of epoxide **309** (152 mg, 0.873 mmol) and DEM (0.40 mL, 2.62 mmol) in EtOH (0.10 mL) at 0 °C was added freshly prepared NaOEt (2.0 M in EtOH, 1.30 mL, 2.6 mmol) dropwise

over 30 min. The solution was allowed to warm to RT and stirred overnight, and then quenched by the addition of saturated aqueous NH_4Cl solution (3 mL) and diluted with EtOAc (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (9→4:1 PE:EtOAc), which gave an inseperable 3:2 mixture of diastereomeric lactones **310** (222 mg, 0.769 mmol, 88%) as a viscous colourless oil characterised as a mixture of diastereomers. $\mathbf{R}_f$ 0.14 (4:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.41–7.36 (2H, m, Ar*H*), 7.31–7.25 (3H, m, Ar*H*), 6.46 (1H, s, PhC*H*=C), 6.43 (1H, s, PhC*H*=C), 5.00–4.94 (1H, m, C*H*O-d1), 4.74 (1H, dddd, J = 9.3, 6.3, 6.3, 6.3 Hz, C*H*O-d2), 4.36–4.29 (2H, m, CO_2CH_2), 3.70 (1H, dd, J = 11.0, 9.4 Hz, EtO_2CCH), 3.68 (1H, dd, J = 9.5, 4.8 Hz, EtO_2CCH), 2.82–2.74 (2H, m, CHC*H*H-d1 & C(Me)C*H*H-d2) 2.70 (1H, dd, J = 14.0, 6.8 Hz, C(Me)C*H*H-d1), 2.64 (1H, ddd, J = 13.0, 9.3, 6.2 Hz, CHC*H*H-d2) 2.58 (1H, dd, J = 14.0, 6.1 Hz, C(Me)CH*H*-d1) 2.55–2.45 (2H, m, C(Me)CH*H*-d2 & CHCH*H*-d2), 2.29 (1H, ddd, J = 13.3, 9.6, 7.3 Hz, CHCH*H*-d1), 1.98 (3H, s, PhCH=CCH_3), 1.98 (3H, s, PhCH=CCH_3), 1.38 (3H, t, J = 7.2 Hz, $CO_2CH_2CH_3$), 1.37 (3H, t, J = 7.2 Hz, $CO_2CH_2CH_3$); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 172.1 (lactone *C*=O), 172.1 (lactone *C*=O), 168.3 (ester *C*=O), 138.0 (*Ar*), 138.0 (*Ar*), 133.5 (PhCH=*C*), 133.4 (PhCH=*C*), 129.3 (*Ar*), 129.3 (*Ar*), 129.3 (*Ar*), 129.3 (*Ar*), 128.6 (Ph*C*H=C), 128.6 (Ph*C*H=C), 127.0 (*Ar*), 126.9 (*Ar*), 79.2 (*C*HO), 78.5 (*C*HO), 62.8 (CO_2CH_2), 62.7 (CO_2CH_2), 47.7 (C(O)*C*HC(O)), 47.3 (C(O)*C*HC(O)), 46.6 (PhCH=C*C*H_2), 46.3 (PhCH-C*C*H_2), 32.4 (CH*C*H_2), 32.1 (CH*C*H_2), 18.8 (PhCH=C*C*H_3), 18.8 (PhCH=C*C*H_3), 14.5 ($CO_2CH_2CH_3$), 14.5 ($CO_2CH_2CH_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2982 (m, C-H) 1775 (s, lactone C=O), 1732 (s, ester C=O), 1599 (w, C=C), 1575 (w, C=C), 1157 (s), 747 (m), 701 (m); **m/z** (ESI+) 311.1 ($[M+Na]^+$, 100%), 599.2 ($[2M+Na]^+$, 80%), HRMS found 311.1258, $C_{17}H_{20}NaO_4$ requires 311.1254.

(*E*)-5-(2-Methyl-3-phenylallyl)-2-oxotetrahydrofuran-3-carboxylic acid

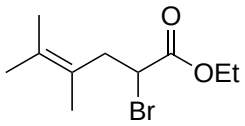


306

To a stirred solution of ester **310** (462 mg, 1.60 mmol) in EtOH (8.0 mL) at 0 °C was added aqueous KOH solution (1.0 M, 3.20 mL, 3.20 mmol). The reaction was stirred until TLC indicated complete consumption of starting material (∼3 h). The solution was diluted with DCM and the layers separated. The aqueous phase was acidified to pH 2 with conc. HCl and extracted with DCM (3×10 mL). The

combined organic extracts were dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*, which gave acid **306** (438 mg, 1.68 mmol, 100%) as a pale yellow gum. $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 8.20 (1H, br, O*H*), 7.34 (2H, dd, J = 7.6, 7.6 Hz, Ar*H*), 7.28–7.20 (3H, m, Ar*H*), 6.41 (1H, s, PhC*H*), 6.38 (1H, s, PhC*H*), 4.98–4.90 (1H, m, C*H*O-d1), 4.77–4.69 (1H, m, C*H*O-d2), 3.80–3.67 (1H, m, HO_2CCH), 2.81–2.61 (C(Me)C*H*H-d1) 2.53 (1H, dd, J = 14.1, 5.9 Hz, C(Me)CH*H*-d2), 2.30 (1H, ddd, J = 13.5, 9.7, 7.0 Hz, CHCH*H*-??) 1.93 (3H, s, CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 172.5 (lactone *C*=O), 172.2 (lactone *C*=O), 171.8 (acid *C*=O), 171.3 (acid *C*=O), 137.6 (PhCH=*C*). 137.5 (PhCH=*C*), 132.9 (*Ar*), 132.8 (*Ar*), 129.2 (Ph*C*H), 129.1 (Ph*C*H), 129.0 (*Ar*), 129.0 (*Ar*), 128.3 (*Ar*), 128.3 (*Ar*), 126.7 (*Ar*), 126.7 (*Ar*), 79.2 (*C*HO-d1), 78.7 (*C*HO-d2), 47.1 (HO_2CCH), 46.7 (HO_2CCH), 46.1 (C(Me)CH_2), 46.0 (C(Me)CH_2), 31.8 (CHCH_2), 31.3 (CHCH_2), 18.4 (CH_3), 18.4 (CH_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2995 (w, C-H), 1760 (s, lactone C=O), 1726 (m, acid C=O), 1642 (m, C=C), 1181 (s), 1164 (s); **m/z** (ESI+) 283.1 ($[M+Na]^+$, 100%), HRMS found 283.0939, $C_{15}H_{16}NaO_4$ requires 283.0941.

Ethyl 2-bromo-4,5-dimethylhex-4-enoate

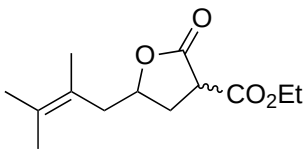


311

To a stirred solution of ester **260** (620 mg, 3.66 mmol) and TMSCl (0.75 mL, 5.5 mmol) in dry THF (37 mL) at –78 °C was added a freshly prepared solution of LDA (1.0 M in THF, 4.6 mL, 4.6 mmol) dropwise. The solution was stirred for 1 h and then NBS (1.35 g, 7.60 mmol) in dry THF (37 mL) precooled to –78 °C was added dropwise. The solution was allowed to warm slowly to RT and then quenched by the addition of 50% sat. aq. NH_4Cl solution (40 mL). The layers were separated and the aqueous was extracted with Et_2O (3×40 mL). The combined organic extracts were washed successively with 1 M aq. HCl solution (40 mL) and brine (40 mL) (40 mL), dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (15:1 PE:Et_2O), which gave α-bromo ester **311** (523 mg, 2.10 mmol, 53%) as a colourless oil. $\mathbf{R}_f$ 0.58 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 4.31 (1H, dd, J = 8.4, 7.4 Hz, C*H*Br), 4.25–4.16 (2H, m, CO_2CH_2), 2.88 (1H, dd, J = 14.1, 8.4 Hz, CHBrC*H*H), 2.75 (1H, dd, J = 14.1, 7.4 Hz, CHBrCH*H*), 1.70 (3H, s, CH_3), 1.66 (6H, s, CH_3), 1.29 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (62.5 MHz, $CDCl_3$) 170.4 (*C*=O), 130.1 (*C*=C), 123.2 (C=*C*), 62.3 (CO_2CH_2), 44.9 (*C*HBr), 40.4 (C=CCH_2), 21.3 (CH_3), 21.1 (CH_3), 18.6

(CH$_3$), 14.4 (CH$_2C$H$_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2921 (w, C-H), 1738 (s, C=O), 1371 (m), 1251 (m), 1147 (s); **m/z** (FI) HRMS found 248.0416, $C_{10}H_{17}{}^{79}BrO_2$ requires 248.0412.

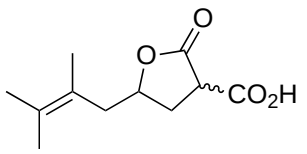
Ethyl 5-(2,3-dimethylbut-2-en-1-yl)-2-oxotetrahydrofuran-3-carboxylate



313

According to GPs 9, 10, and 11, α-bromoester **311** (456 mg, 1.83 mmol) was treated with DiBAl-H, KO^{t}Bu, and DEM respectively, which after flash column chromatography (10→6:1 PE:EtOAc) gave an inseperable 1:1 mixture of diastereomeric lactone-ester **313** (136 mg, 0.567 mmol, 40%) as a colourless oil. $\mathbf{R}_f$ 0.40 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 4.81–4.74 (1H, m, CHO-d1), 4.54 (1H, dddd, J = 9.3, 6.3, 6.3, 6.3 Hz, CHO-d2), 4.30–4.22 (2H, m, CO$_2$CH_2), 3.60 (1H, dd, J = 11.0, 9.1 Hz, EtO$_2$CCH-d2), 3.59 (1H, dd, J = 9.4, 5.1 Hz, EtO$_2$CCH-d1), 2.68–2.60 (2H, m, CHCHH-d1 & C(Me)CHH-d1), 2.56–2.48 (2H, m, CHCHH-d2 & C(Me)CHH-d1), 2.45–2.30 (3H, m, CHCHH-d2 & C(Me)CH_2-d2), 2.14 (1H, ddd, J = 13.2, 9.4, 7.1 Hz, CHCHH-d1), 1.73–1.65 (9H, m, CH_3), 1.32 (3H, t, J = 7.1 Hz, CO$_2$CH$_2$CH_3), 1.31 (3H, t, J = 7.1 Hz, CO$_2$CH$_2$CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 171.8 (lactone C=O), 171.7 (lactone C=O), 167.9 (ester C=O), 167.9 (ester C=O), 128.7 (C=C), 128.6 (C=C), 121.9 (C=C), 121.9 (C=C), 79.5 (CHO-d1), 78.7 (CHO-d2), 62.2 (CO$_2C$H$_2$), 62.1 (CO$_2C$H$_2$), 47.4 (EtO$_2$CCH-d2), 46.9 (EtO$_2$CCH-d1). 39.8 (C(Me)CH$_2$), 39.7 (C(Me)CH$_2$), 32.1 (CHCH$_2$-d2), 31.7 (CHCH$_2$-d1), 20.7 (CCH$_3$), 20.7 (CCH$_3$), 20.6 (CCH$_3$), 19.1 (CO$_2$CH$_2C$H$_3$), 19.0 (CO$_2$CH$_2C$H$_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2919 (w, C-H), 1776 (s, lactone C=O), 1734 (s, ester C=O), 1160 (s); **m/z** (ESI+) HRMS found 263.1254, $C_{13}H_{20}NaO_4$ requires 263.1254. NB. the intermediates from GPs 9 and 10 were highly volatile and so rigourous isolation and purification was not undertaken.

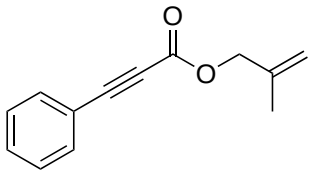
5-(2,3-Dimethylbut-2-en-1-yl)-2-oxotetrahydrofuran-3-carboxylic acid



314

According to GP 12, lactone-ester **313** (125 mg, 0.520 mmol) was treated with aqueous KOH, which gave lactone-acid **314** (108 mg, 0.509 mmol, 98%) as a colourless gum. $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.62 (1H, br s, O*H*), 4.84–4.77 (1H, m, C*H*O-d1), 4.59 (1H, dddd, J = 9.8, 6.3, 6.3, 6.3 Hz, C*H*O-d2), 3.67 (1H, dd, J = 11.5, 9.1 Hz, HO_2CC*H*), 3.66 (1H, dd, J = 9.6, 6.0 Hz, HO_2CC*H*), 2.72–2.57 (3H, m, C(Me)C*H*H-d2 & CHC*H*H-d1 & CHC*H*H-d2), 2.53 (1H, dd, J = 14.0, 6.9 Hz, C(Me)C*H*H-d1), 2.44 (1H, dd, J = 14.1, 6.2 Hz, C(Me)CH*H*-d2), 2.39 (1H, dd, J = 14.0, 6.5 Hz, C(Me)CH*H*-d1), 2.32 (1H, ddd, J = 13.1, 11.5, 9.8 Hz, CHH*H*-d2), 2.22 (1H, ddd, J = 13.4, 9.6, 6.5 Hz, CHCH*H*-d1), 1.72–1.67 (9H, m, C*C*H_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 172.5 (acid *C*=O), 172.1 (acid *C*=O), 171.5 (lactone *C*=O), 170.8 (lactone *C*=O), 129.0 (*C*=C), 128.9 (*C*=C), 121.7 (C=*C*), 121.5 (C=*C*), 79.8 (*C*HO), 79.4 (*C*HO), 46.9 (HO_2C*C*H), 46.4 (HO_2C*C*H), 39.6 (C(Me)*C*H_2), 31.7 (CH*C*H_2), 31.1 (CH*C*H_2), 20.7 (C*C*H_3), 20.7 (C*C*H_3), 20.7 (C*C*H_3), 19.1 (C*C*H_3), 19.1 (C*C*H_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3469 (br, CO_2-H), 2982 (w, C-H), 1768 (s, lactone C=O), 1733 (s, acid C=O), 1170 (s); **m/z** (FI) HRMS found 212.1044, $C_{11}H_{16}O_4$ requires 212.1049.

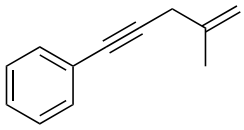
2-Methylallyl 3-phenylpropiolate



319

To a stirred solution of phenylpropiolic acid **320** (1.46 g, 10.0 mmol) and 2-methylallyl alcohol **321** (1.17 mL, 1.00 g, 14.0 mmol) in dry DCM (30 mL) at RT was added a solution of DIC (1.84 mL, 1.51 g, 12.0 mmol) and DMAP (122 mg, 1.00 mmol) in dry DCM (10 mL). The solution was stirred overnight, and then filtered through a silica plug eluting with 2:1 PE:EtOAc. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (10:1 PE:EtOAc), which gave ester **319** (1.73 g, 8.66 mmol, 87%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.59 (2H, d, J = 7.5 Hz, Ar*H*), 7.45 (1H, t, J = 7.2 Hz, Ar*H*), 7.38 (2H, dd, J = 7.5, 7.2 Hz, Ar*H*), 5.07 (1H, s, C=C*H*H), 5.00 (1H, s, C=CH*H*), 4.66 (2H, s, OCH_2), 1.82 (3H, s, CCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 153.8 (*C*=O), 139.2 (*Ar*), 133.0 (*Ar*), 130.7 (*Ar*), 128.6 (*Ar*), 119.6 (*C*=CH_2), 114.1 (C=*C*H_2), 86.5 (Ph*C*≡C), 80.5 (PhC≡*C*), 69.2 (O*C*H_2), 19.5 (C*C*H_3). *Data are consistent with literature values.*[120]

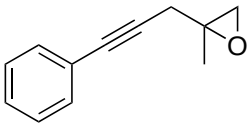
(4-Methylpent-4-en-1-yn-1-yl)benzene



322

According to the modified procedure of Tunge and Rayabarapu,[120] to a stirred suspension of $Pd(OAc)_2$ (113 mg, 0.50 mmol) in dry, argon sparged toluene was added PPh_3 (524 mg, 2.00 mmol) at RT. The solution was stirred under argon for 30 min, and a solution of ester **319** (1.00 g, 5.00 mmol) in dry, argon sparged toluene (20 mL) was added. The solution was stirred at 75 °C for 2 days. After cooling to RT, the solution was filtered through a silica/Celite® pad, eluting with DCM. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography (PE), which gave enyne **322** (483 mg, 3.10 mmol, 62%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.45–7.40 (2H, m, Ar*H*), 7.33–7.28 (3H, m, Ar*H*), 5.09 (1H, br s, C=C*H*H), 4.89 (1H, br s, C=CH*H*), 3.14 (CH_2), 1.86 (CH_3), $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 140.3 (*C*=CH_2), 131.4 (*Ar*), 128.0 (*Ar*), 127.6 (*Ar*), 123.6 (*Ar*), 111.8 (C=*C*H_2), 87.0 (PhC≡*C*), 82.6 (Ph*C*≡C), 28.0 (C≡C*C*H_2), 22.0 (*C*H_3). *Data are consistent with literature values.*[120]

2-Methyl-2-(3-phenylprop-2-yn-1-yl)oxirane

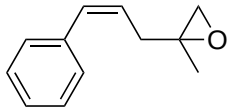


323

To a stirred solution of enyne **322** (260 mg, 1.67 mmol) in DCM (17 mL) was added *m*-CPBA (70 wt%, 535 mg, 2.17 mmol) at 0 °C. The solution was allowed to warm to RT and until TLC analysis showed complete consumption of starting material (24–48 h). The reaction was quenched with sat. aq. $Na_2S_2O_3$ solution (10 mL), and the layers were separated. The aqueous was extracted with DCM (3×15 mL mL), and the combined organic extracts were washed with sat. aq. $NaHCO_3$ solution (30 mL(, dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (9:1 PE:Et_2O), which gave epoxide **323** (208 mg, 1.49 mmol, 89%) as a colourless oil. $\mathbf{R}_f$ 0.34 (3:1 PE:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.46–7.39 (2H, m, Ar*H*), 7.34–7.27 (3H, m, Ar*H*), 2.87 (1H, d, J = 4.9 Hz, C(O)C*H*H), 2.78 (1H, d, J = 17.2 Hz, C≡CC*H*H), 2.69 (1H, d, J = 4.9 Hz,

C(O)CHH), 2.66 (1H, d, J = 17.2 Hz, C≡CCHH), 1.50 (3H, s, CCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 131.6 (Ar), 128.2 (Ar), 127.9 (Ar), 123.4 (Ar), 84.8 (C≡C), 82.8 (C≡C), 55.7 (C(O)CH_2), 53.4 (C(O)CH$_2$), 28.0 (C≡CCH$_2$), 20.8 (CCH$_3$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2987 (m, C-H), 1599 (w, C=C), 1572 (w, C=C), 1490 (m), 1071 (m), 757 (s), 692 (s); **m/z** (FI) HRMS found 172.0889, $C_{12}H_{12}O$ requires 172.0888. This compound has previously been reported however no data were available.[172]

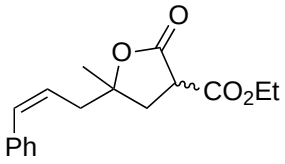
(*Z*)-2-Methyl-2-(3-phenylallyl)oxirane



324

According to GP 8, alkyne **323** (497 mg, 2.89 mmol) was treated with Lindlar's catalyst and H_2 overnight, which after flash column chromatography (19:1 PE:Et_2O) gave alkene **324** (376 mg, 2.16 mmol, 75%) as a colourless oil. $\mathbf{R}_f$ 0.48 (4:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.39–7.32 (2H, m, ArH), 7.30–7.22 (3H, m, ArH), 6.60 (1H, d, J = 11.7 Hz, PhCH=CH), 5.71 (1H, ddd, J = 11.7, 7.3, 7.3 Hz, PhCH=CH), 2.70 (1H, d, J = 4.8 Hz, C(O)CHH), 2.69–2.64 (1H, m, CH=CHCHH), 2.62 (1H, d, J = 4.8 Hz, C(O)CHH), 2.61–2.56 (1H, m, CH=CHHH), 1.36 (3H, s, CCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 137.1 (Ar), 131.5 (PhCH=CH), 128.7 (Ar), 128.2 (Ar), 126.8 (Ar), 126.5 (PhCH=CH), 56.8 (C(O)CH_2), 53.1 (C(O)CH$_2$), 35.2 (CH=CHCH$_2$), 21.4 (CCH$_3$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2981 (w, C-H), 1600 (w, C=C), 1575 (w, C=C), 1073 (m), 769 (s), 700 (s); **m/z** (FI) HRMS found 174.1051, $C_{12}H_{14}O$ requires 174.1045.

(*Z*)-Ethyl 5-methyl-2-oxo-5-(3-phenylallyl)tetrahydrofuran-3-carboxylate

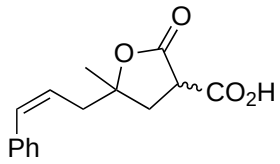


439

According to GP 11, epoxide **324** (424 mg, 2.44 mmol) was treated with DEM, which after flash column chromatography (5:1 PE:EtOAc) gave an inseparable 1:1 mixture of diastereomeric lactone-ester **439** (643 mg, 2.23 mmol, 92%) as a colourless oil. $\mathbf{R}_f$ 0.17 (5:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.39–7.33 (2H, m, ArH), 7.30–7.20 (3H, m, ArH), 6.69 (1H, d, J = 11.6 Hz, PhCH=CH), 6.68 (1H, d, J = 11.6 Hz, PhCH=CH), 5.73 (1H, ddd, J = 11.6, 7.0, 7.0 Hz, PhCH=CH), 5.67 (1H, ddd, J = 11.6, 7.3, 7.3 Hz,

PhCH=C*H*), 4.29–4.21 (2H, m, CO_2CH_2), 3.74 (1H, dd, J = 10.0, 10.0 Hz, $EtCO_2CH$), 3.65 (1H, dd, J = 10.0, 9.0 Hz, $EtCO_2CH$), 2.85–2.75 (1H, m, PhCH=CHC*H*H), 2.73–2.63 (1H, m, PhCH=CHCH*H*), 2.59 (1H, dd, J = 13.0, 10.0 Hz, C(O)C*H*H), 2.42 (1H, dd, J = 13.4, 9.0 Hz, C(O)C*H*H), 2.35 (1H, dd, J = 13.4, 10.0 Hz, C(O)CH*H*), 2.23 (1H, dd, J = 13.0, 10.0 Hz, C(O)CH*H*), 1.50 (3H, s, CCH_3), 1.39 (3H, s, CCH_3), 1.31 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 1.31 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 171.2 (lactone *C*=O), 171.1 (lactone *C*=O), 167.9 (ester *C*=O), 167.8 (ester *C*=O), 136.8 (*Ar*), 136.6 (*Ar*), 133.4 (Ph*C*H=CH), 132.8 (Ph*C*H=CH), 128.6 (*Ar*), 128.6 (*Ar*), 128.4 (*Ar*), 128.3 (*Ar*), 124.9 (PhCH=*C*H), 124.8 (PhCH=*C*H), 85.5 (O*C*CH_3), 85.1 (O*C*CH_3), 62.2 (CO_2CH_2), 62.2 (CO_2CH_2), 47.7 (C(O)*C*H), 47.2 (C(O)*C*H), 39.5 (PhCH=CH*C*H_2), 39.2 (PhCH=CH*C*H_2), 36.4 (EtO_2CCHCH_2), 36.1 (EtO_2CCHCH_2), 26.8 (CCH_3), 25.8 (CCH_3), 14.0 ($CO_2CH_2CH_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2981 (m, C-H), 1772 (s, lactone C=O), 1732 (s, ester C=O), 1600 (w, C=C), 1574 (w, C=C), 1177 (s), 701 (m); **m/z** (ESI+) 311.1 ($[M+Na]^+$, 100%), HRMS found 311.1251, $C_{17}H_{20}NaO_4$ requires 311.1254.

(*Z*)-5-Methyl-2-oxo-5-(3-phenylallyl)tetrahydrofuran-3-carboxylic acid



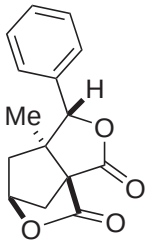
315

According to GP 12, ester **439** (100 mg, 0.35 mmol) was treated with aqueous KOH, which gave acid **315** (94 mg, 0.35 mmol, 100%) as a colourless gum. $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 8.12 (1H, br, O*H*), 7.39–7.33 (2H, m, Ar*H*), 7.30–7.21 (3H, m, Ar*H*), 6.72 (1H, d, J = 11.7 Hz, PhC*H*=CH) 6.70 (1H, d, J = 11.7 Hz, PhC*H*=CH), 5.69 (1H, ddd, J = 11.7, 7.2, 7.2 Hz, PhCH=C*H*), 5.66 (1H, ddd, J = 11.7, 7.2, 7.2 Hz, PhCH=C*H*), 3.80 (1H, dd, J = 10.4, 10.4 Hz, HO_2CCH), 3.70 (1H, dd, J = 9.8, 9.8 Hz, HO_2CCH), 2.83–2.76 (1H, m, CH=CHC*H*H), 2.74–2.65 (1H, m, CH=CHCH*H*), 2.57 (1H, dd, J = 13.0, 10.4 Hz, CHC*H*H), 2.44 (1H, dd, J = 13.0, 9.8 Hz, CHC*H*H), 2.40 (1H, dd, J = 13.0, 9.8 Hz, CHCH*H*), 2.30 (1H, dd, J = 13.0, 10.4 Hz, CHCH*H*), 1.51 (3H, s, CH_3), 1.41 (3H, s, CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 171.8 (lactone *C*=O), 171.1 (acid *C*=O), 171.0 (acid *C*=O), 136.7 (*Ar*), 136.5 (*Ar*), 133.7 (Ph*C*H), 133.2 (Ph*C*H). 128.6 (*Ar*), 128.5 (*Ar*), 128.4 (*Ar*), 128.3 (*Ar*), 127.3 (*Ar*), 127.1 (*Ar*), 124.4 (PhCH=*C*H), 86.4 (O*C*(Me)), 86.0 (O*C*(Me)), 47.2 (HO_2CCH), 46.7 (HO_2CCH), 39.3 (CH=CH*C*H_2), 38.9 (CH=CH*C*H_2), 35.9 (CH*C*H_2), 35.7 (CH*C*H_2), 26.8 (*C*H_3), 25.7 (*C*H_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3458 (w, O-H), 2970 (w, C-H), 1740 (s, C=O), 1447 (m), 1216 (m); **m/z** (FI) HRMS found 260.1059, $C_{15}H_{16}O_4$

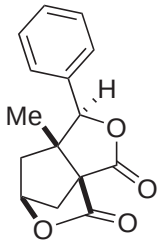
requires 260.1049.

(1*R,4*S**,5*R**,7*S**)-5-Methyl-4-phenyl-3,8-dioxatricyclo[5.2.1.0^{1,5}]decane-2,9-dione, 325;**

(1*R,4*R**,5*S**,7*S**)-5-Methyl-4-phenyl-3,8-dioxatricyclo[5.2.1.0^{1,5}]decane-2,9-dione, 326**



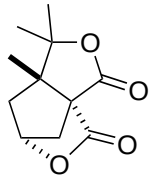
325



326

According to GP 13, acid **306** (26.0 mg, 100 μmol) was treated with $Mn(OAc)_3{\cdot}2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (2:1 PE:EtOAc) gave tricyclic *bis*-lactones **325**:**326** 3.2:1 (20.8 mg, 80.6 μmol, 81%). Data for **325**: **m.p.** 218–221 °C; $\mathbf{R}_f$ 0.22 (1:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (400 MHz, $CDCl_3$) 7.43–7.32 (3H, m, Ar*H*), 7.29–7.25 (2H, m, Ar*H*), 5.64 (1H, s, PhC*H*), 5.13 (1H, br s, C*H*O), 2.59 (1H, ddd, J = 11.2, 2.3, 1.2 Hz, O_2CCC*H*H), 2.43 (1H, dd, J = 11.2, 1.0 Hz, O_2CCCH*H*), 2.29 (1H, br d, J = 14.3 Hz, C(Me)C*H*H), 1.84 (1H, dd, J = 14.3, 2.3 Hz, C(Me)CH*H*), 1.02 (3H, s, CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (62.5 MHz, $CDCl_3$) 172.9 (*C*=O), 167.6 (*C*=O), 135.0 (*Ar*), 128.9 (*Ar*), 128.6 (*Ar*), 125.0 (*Ar*), 86.3 (Ph*C*H), 84.2 (*C*HO), 68.1 (O_2C*C*), 52.7 (*C*(Me)), 38.4 (O_2CC*C*H_2), 38.2 (C(Me)*C*H_2), 20.8 (*C*H_3); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2931 (w, C-H), 1799 (s, C=O), 1762 (s, C=O), 1373 (m), 919 (s); Data for **326**: **m.p.** 188–192 °C sublimed; $\mathbf{R}_f$ 0.13 (1:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.44–7.35 (3H, m, Ar*H*), 7.30–7.26 (2H, m, Ar*H*), 5.68 (1H, d, J = 2.7 Hz, PhC*H*), 5.12 (1H, d, J = 1.0 Hz, CH_2C*H*O), 2.77 (1H, d, J = 11.0 Hz, O_2CC*H*H), 2.68 (1H, ddd, J = 11.0, 3.0, 2.7 Hz, O_2CCH*H*), 2.53 (1H, dd, J = 13.6, 1.0 Hz, C(Me)C*H*H), 1.91 (1H, dd, J = 13.6, 3.0 Hz, C(Me)CH*H*), 0.87 (3H, s, CH_3); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 168.0 (*C*=O), 167.3 (*C*=O), 134.2 (*Ar*), 128.8 (*Ar*), 128.8 (*Ar*), 124.9 (*Ar*), 86.2 (Ph*C*H), 81.8 (CH_2C*C*HO), 62.1 (O_2C*C*), 51.3 (*C*Me), 42.1 (O_2CC*C*H_2), 40.4 (C(Me)*C*H_2), 19.9 (*C*H_3); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2934 (w, C-H), 1807 (s, C=O), 1767 (m, C=O), 1630 (m), 1032 (s); **m/z** (ESI+) HRMS found 281.0776, $C_{15}H_{14}NaO_4$ requires 281.0784.

(3a*S,6*R**,7a*S**)-1,1,7a-Trimethyltetrahydro-3a,6-methanofuro[3,4-*c*]pyran-3,4-dione**



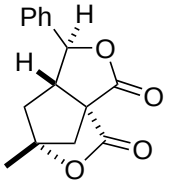
327

According to GP 13, acid **314** (21.2 mg, 0.100 mmol) was treated with $Mn(OAc)_3{\cdot}2H_2O$ and $Cu(OTf)_2$, which after flash column chromatography (2→0:1 PE:EtOAc) gave tricyclic *bis*-lactone **327** (5.0 mg, 24 μmol, 24%) as a colourless gum. $\mathbf{R}_f$ 0.37 (EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 5.06 (1H, br s, C*H*O), 2.72 (1H, d, J = 11.1 Hz, C*H*HCHOCH$_2$), 2.64 (1H, ddd, J = 11.1, 2.4, 2.4, CH*H*CHOCH$_2$), 2.37 (1H, d, J = 13.8 Hz, CH$_2$CHOC*H*H), 1.90 (1H, dd, J = 14.0, 2.7 Hz, CH$_2$CHOCH*H*), 1.64 (3H, s, C*H*$_3$), 1.48 (3H, s, C*H*$_3$), 1.31 (3H, s, C*H*$_3$); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 168.6 (*C*=O), 167.6 (*C*=O), 87.4 (*C*(Me)$_2$), 81.2 (*C*HO), 63.1 ((CO)$_2$*C*), 49.4 (*C*(Me)), 44.9 (*C*H$_2$CHOCH$_2$), 39.8 (CH$_2$CHO*C*H$_2$), 28.2 (*C*H$_3$), 26.6 (*C*H$_3$), 24.5 (*C*H$_3$); $\boldsymbol{\nu}_{\mathbf{max}}$ / $\mathbf{cm^{-1}}$ 2958 (w, C-H), 1801 (s, C=O), 1760 (s, C=O), 1338 (m), 1088 (m); **m/z** (ESI+) 233.1 ([M+Na]$^+$, 100%), HRMS found 233.0782, $C_{11}H_{14}NaO_4$ requires 233.0784.

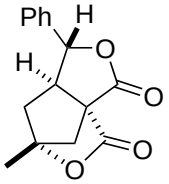
(1*S,3a*R**,6*R**,7a*S**)-6-Methyl-1-phenyltetrahydro-3a,6-methanofuro[3,4-*c*]pyran-3,4-dione, 328;**

(1*R,3a*R**,6*R**,7a*R**)-6-Methyl-1-phenyltetrahydro-3a,6-methanofuro[3,4-*c*]pyran-3,4-dione,**

329



328



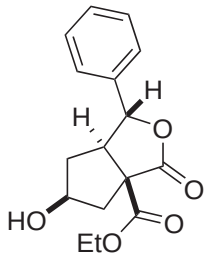
329

According to GP 13, acid **315** (26.0 mg, 100 μmol) was treated with $Mn(OAc)_3{\cdot}2H_2O$, which after flash column chromatography (2:1 PE:EtOAc) gave tricyclic *bis*-lactones **328**:**329** 2.0:1 (13.2 mg, 51.1 μmol, 51%) as a colourless gum. Data for **328**: $\mathbf{R}_f$ 0.27 (1:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.44–7.37 (3H, m, Ar*H*), 7.36–7.32 (2H, m, Ar*H*), 5.41 (1H, d, J = 10.9 Hz, PhC*H*), 3.15 (1H, ddd, J = 10.9,

10.5, 7.8 Hz, C*H*), 2.48 (1H, dd, J = 10.5, 1.5 Hz, O_2CCCHH), 2.12 (1H, d, J = 10.5 Hz, O_2CCCHH), 2.07 (1H, dd, J = 13.9, 10.5 Hz, CHC*H*H), 1.99 (1H, ddd, J = 13.9, 7.8, 1.5 Hz, CHH*H*), 1.68 (3H, s, CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 171.2 (*C*=O), 167.4 (*C*=O), 135.9 (*Ar*), 129.3 (*Ar*), 128.9 (*Ar*), 125.6 (*Ar*), 95.5 (O_2CC), 83.4 (Ph*C*H), 63.3 (Me*C*O), 54.3 (*C*H), 45.5 (O_2CCCH_2), 34.3 (CH*C*H_2), 19.3 (*C*H_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2940 (w, C-H), 1796 (s, C=O), 1765 (s, C=O), 1331 (m), 1000 (m); Data for **329**: $\mathbf{R}_f$ 0.20 (1:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.46–7.38 (3H, m, Ar*H*), 7.37–7.32 (2H, m, Ar*H*), 5.33 (1H, d, J = 9.8 Hz, PhC*H*), 3.07 (1H, ddd, J = 9.8, 8.4, 4.7 Hz, CHOC*H*), 2.54 (1H, d, J = 10.8 Hz, O_2CCCHH), 2.42 (1H, dd, J = 10.8, 2.8 Hz, O_2CCHH), 2.24 (1H, ddd, J = 13.7, 8.4, 2.8 Hz, CHC*H*H), 2.15 (1H, dd, J = 13.7, 4.7 Hz, CHCH*H*), 1.71 (3H, s, CH_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 169.2 (*C*=O), 167.2 (*C*=O), 136.2 (*Ar*), 129.4 (*Ar*), 129.1 (*Ar*), 125.6 (*Ar*), 92.2 (Ph_2CCH), 84.5 (*C*HO), 58.3 (Me*C*O), 50.9 (*C*H), 44.6 (O_2CCCH_2), 38.5 (CH*C*H_2), 18.4 (*C*H_3); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2935 (w, C-H), 1803 (s, C=O), 1773 (m, C=O), 1343 (m), 1068 (m); **m/z** (ESI+) 281.1 ([M+Na]$^+$, 100%), HRMS found 281.0782, $C_{15}H_{14}NaO_4$ requires 281.0784.

(1*R,3a*R**,5*S**,6a*R**)-Ethyl**

5-hydroxy-3-oxo-1-phenylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate

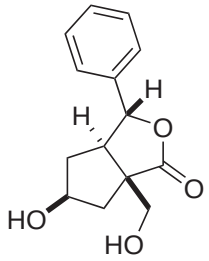


331

To a stirred solution of cyclopentane *bis*-lactone **303** (5.4 mg, 22 μmol) in EtOH (2.2 mL) was added potassium carbonate (0.1 mg, 2.2 μmol). After 3 h, the solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (2:1 PE:EtOAc) which gave ester **331** (4.4 mg, 15 μmol, 69%). $\mathbf{R}_f$ 0.21 (1:1 PE:EtOAc) $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.45 7.32 (5H, m, *Ar*), 5.47 (1H, d, J = 4.3 Hz, PhC*H*), 4.63 (1H, br s, C*H*OH), 4.20 (2H app. qd, J = 7.1, 2.5 Hz, CO_2CH_2), 3.10 (1H, ddd, J = 8.6, 4.3, 1.2 Hz, PhCHOC*H*), 2.59 (1H, dd, J = 14.3, 3.4 Hz, CC*H*H), 2.49 (1H, dd, J = 14.3, 2.1 Hz, CCH*H*), 2.22 2.16 (1H, m, CHC*H*H), 2.16 2.09 (1H, m, CHCH*H*), 1.67 (1H, t, J = 1.7 Hz, O*H*), 1.23 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 176.3 (lactone *C*=O), 170.3 (ester *C*=O), 140.5 (*Ar*), 128.7 (*Ar*), 128.3 (*Ar*), 125.4 (*Ar*), 87.2 (Ph*C*H), 74.2 (HO*C*H), 62.4 (CO_2CH_2), 61.5 (*C*),

52.8 (PhOCH*C*H), 44.1 (C*C*H_2), 41.4 (CH*C*H_2), 13.8 (CO_2CH_2C*H*$_3$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3498 (br, O-H), 2946 (w, C-H), 1768 (s, lactone C=O), 1737 (s, ester C=O), 1261 (s), 1157 (m), 973 (m); **m/z** (ESI+) 313.1 ([M+Na]$^+$, 100%), HRMS found 313.1047, $C_{16}H_{18}NaO_5$ requires 313.1046.

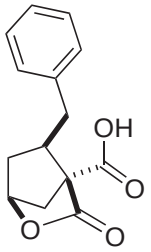
(3*R,3a*R**,5*S**,6a*R**)-5-Hydroxy-6a-(hydroxymethyl)-3-phenylhexahydro-1*H*-cyclopenta[*c*]furan-1-one**



334

To a stirred solution of tricyclic *bis*-lactone **303** (10.0 mg, 41 μmol) in THF (0.80 mL) was added $NaBH_4$ in EtOH (0.1 M, 0.82 mL, 82 μmol). The reaction was stirred until TLC analysis showed complete consumption of starting material (≈1.5 h). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (5% MeOH in DCM), which gave diol **334** (8.7 mg, 35 μmol, 86%) as a colourless oil. $\mathbf{R}_f$ 0.29 (EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.45–7.36 (4H, m, Ar*H*), 7.35–7.30 (1H, m, Ar*H*), 5.51 (1H, d, J = 5.1 Hz, PhC*H*), 4.57 (1H, app. t, J = 3.6 Hz, HOC*H*), 3.90 (1H, dd, J = 10.7, 6.9 Hz, HOC*H*H), 3.62 (1H, dd, J = 10.7, 4.7 Hz, HOCH*H*), 2.82 (1H, dd, J = 8.5, 5.1 Hz, PhCHOC*H*), 2.32 (1H, dd, J = 6.9, 4.7 Hz, *H*OCH_2), 2.29 (1H, dd, J = 14.3, 2.4 Hz, CC*H*H), 2.19 (1H, dd, J = 14.3, 2.4 Hz, CHC*H*H), 2.04 (1H, ddd, J = 14.3, 8.5, 3.8 Hz, CHCH*H*), 1.86 (1H, dd, J = 14.3, 3.8 Hz, CCH*H*), 1.78 (1H, br s, *H*OCH); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 181.6 (*C*=O), 141.0 (*Ar*), 128.7 (*Ar*), 128.2 (*Ar*), 125.6 (*Ar*), 87.0 (Ph*C*H), 74.0 (HO*C*H), 66.9 (HO*C*H_2), 57.9 (*C*), 49.9 (PhCHO*C*H), 43.8 (C*C*H_2), 40.8 (CH*C*CH_2); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3429 (br s, O-H), 2932 (w, C-H), 1744 (s, C=O), 939 (m); **m/z** (ESI+) 271.1 ([M+Na]$^+$, 100%), HRMS found 271.0948, $C_{14}H_{16}NaO_4$ requires 271.0941.

(1*S,4*S**,5*R**)-5-benzyl-3-oxo-2-oxabicyclo[2.2.1]heptane-4-carboxylic acid**



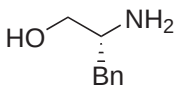
305

A solution of cyclopentane *bis*-lactone **303** (15.1 mg, 62 μmol) and Pd/C (10 wt% Pd, 0.6 mg) in EtOAc (1.5 mL) was vigourously stirred under H_2 atmosphere for 16 h. The mixture was filtered through Celite® eluting with EtOAc and the solvent was removed *in vacuo*, which gave carboxylic acid **305** (15.3 mg, 62 μmol, 100%) as white crystals **m.p.** 152–155 °C. $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 8.05 (1H, br s, CO_2H), 7.33–7.25 (2H, m, Ar*H*), 7.21 (1H, t, J = 7.2 Hz, Ar*H*), 7.16 (2H, d, J = 7.2 Hz, Ar*H*), 4.91 (1H, s, C*H*O), 3.19 (1H, dd, J = 13.6, 3.6 Hz, PhC*H*H), 3.08–2.98 (1H, m, C*H*CH_2Ph), 2.56 (1H, dt, J = 10.6, 2.6 Hz, CC*H*H), 2.34 (1H, dd, J = 13.6, 11.6 Hz, PhCH*H*), 2.22 (1H, d, J = 10.6 Hz, CCH*H*), 2.10 (1H, ddd, J = 13.8, 10.1, 2.1 Hz, CHC*H*HCHO), 1.67 (1H, ddd, J = 13.8, 5.0, 2.9 Hz, CHCH*H*CHO); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 174.5 (lactone *C*=O), 171.2 (acid *C*=O), 138.6 (*Ar*), 128.7 (*Ar*), 128.6 (*Ar*), 126.6 (*Ar*), 79.9 (CO_2CH), 59.2 (CO_2C), 44.7 (C*C*H_2), 42.3 (PhCH_2*C*H), 38.0 (Ph*C*H_2), 35.0 (CH*C*H_2CO); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3062 (br m, COO-H), 1779 (s, lactone C=O), 1713 (m, acid C=O), 1150 (m), 732 (m), 702 (m); **m/z** (ESI+) HRMS found 269.0790, $C_{14}H_{14}NaO_4$ requires 269.0784.

6.4 A Formal Synthesis of (–)-Salinosporamide A

The following compounds are labelled according to the numbering given in **Chapter 4.3.3**. This numbering does not necessarily correspond to the numbering given in the compound names.

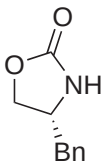
(*R*)-2-Amino-3-phenylpropan-1-ol



384

Following the procedure of Haaf *et al.*,[133] D-phenylalanine **383** (30.5 g, 0.184 mol) was added to a mechanically stirred solution of $LiAlH_4$ (17.5 g, 0.46 mol) in dry THF (350 mL) portionwise over 1 h at 60 °C (gas evolution and highly exothermic!). The solution was then heated under reflux for a 1 hour before being cooled to 0 °C. Water (20 mL) was added dropwise, followed successively by dropwise addition of 2 M NaOH (13 mL) and water (30 mL). The resulting slurry was stirred overnight, and then filtered through Celite®. The Celite® was extracted with DCM (3×250 mL), the combined organic extracts were dried (Na_2SO_4), and the solvent removed *in vacuo*, which gave yellow crystals. The crude product was recrystallised from EtOAc to give **384** as white crystals (19.59 g, 70%) *m.p.* 90–91 °C (*lit.* 91–93 °C. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.32 (2H, t, J = 7.0 Hz, $CH_2CCHCHCH$), 7.26–7.18 (3H, m, $CH_2CCHCHCH$), 3.65 (1H, dd, J = 10.6, 3.9 Hz, $HOCHH$), 3.40 (1H, dd, J = 10.6, 7.2 Hz, $HOCHH$), 3.13 (1H, dddd, J = 8.8, 7.3, 5.2, 4.0 Hz, H_2NCH), 2.81 (1H, dd, J = 13.5, 5.2 Hz, $PhCHH$), 2.54 (1H, dd, J = 13.5, 8.6 Hz, $PhCHH$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 138.6 (CH_2CCH), 129.2 (CH_2CCH), 128.6 (CH_2CCHCH), 126.4 ($CH_2CCHCHCH$), 66.3 ($HOCH_2$), 54.2 (H_2NCH), 40.9 ($PhCH_2$); $\boldsymbol{[\alpha]_D^{25}}$ +23.9 (c = 0.94, EtOH) (*lit.* -24.6 for enantiomer). *Data are consistent with literature values.*[133]

(*R*)-4-Benzyloxazolidin-2-one

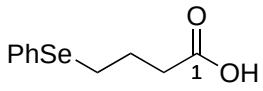


382

To a stirred solution of aminoalcohol **384** (23.9 g, 158 mmol) and diethyl carbonate (39 mL, 321 mmol) in an RBF equipped for distillation was added K_2CO_3 (2.18 g, 15.8 mmol). The solution was

heated at 135 °C until no further ethanol was collected by distillation. The yellow residue was cooled, dissolved in DCM (120 mL), and washed with water (120 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. Recrystallisation from EtOAc/hexane gave **440** (25.2 g, 142 mmol, 90%) as a white crystalline solid **m.p.** 86–88 °C (*lit.* 88–89 °C). $\boldsymbol{\delta_H}$ (400 MHz, DMSO-d_6) 7.80 (1H, br, N*H*), 7.33–7.20 (5H, m, Ph*H*), 4.25 (1H, t, J = 8.2 Hz, OC*H*H), 4.05 (1H, tt, J = 7.2, 5.4 Hz, HNC*H*Bn), 3.97 (1H, dd, J = 8.2, 5.4 Hz, OCH*H*), 2.82 (1H, dd, J = 13.6, 5.2 Hz, PhC*H*H), 2.74 (1H, dd, J = 13.6, 7.1 Hz, PhCH*H*); $\boldsymbol{\delta_C}$ (100 MHz, DMSO-d_6) 159.5 (*C*=O), 137.4 (CH_2C), 130.3 (CHC*H*CH), 129.3 (CHCH*C*H), 127.3 ((CH)*C*H(CH)), 68.9 (O*C*H_2), 53.3 (HN*C*HBn), 41.1 (Ph*C*H_2); $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ +64.7 (c = 1.00, $CHCl_3$) (*lit.* -63 for enantiomer). *Data are consistent with literature values.*[133]

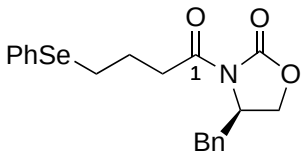
4-(phenylselanyl)butanoic acid



380

According to the modified procedure of Smith III and co-workers,[129] a solution of diphenyl diselenide (6.74 g, 21.6 mmol) in dry DMF (110 mL) was sparged with N_2 for 20 min after which $NaBH_4$ (1.86 g, 49.2 mmol) was added portionwise. The solution was heated to 100 °C and a solution of γ-butyrolactone **381** (3.44 g, 40.0 mmol) in dry DMF (22 mL) was added. The solution was heated to 120 °C for 2 h and then allowed to cool to RT. The reaction was quenched by the addition of 2 M aqueous NaOH solution (100 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic layer was extracted with 2 M aqueous NaOH solution (2×100 mL). The combined aquoues extracts were acidified to pH 2 with concentrated HCl and extracted with EtOAc (3×100 mL). The combined organic extracts were washed successively with sat. aq. NH_4Cl solution (3×50 mL), water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The solid obtained was recrystallised from hexane/Et_2O, which gave acid **380** (9.41 g, 38.7 mmol, 97%) as slightly yellow crystals **m.p.** 65–67 °C (lit 60–62 °C). $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.56–7.46 (2H, m, Ar*H*), 7.32–7.22 (3H, m, Ar*H*), 2.96 (2H, t, J = 7.1 Hz, C$H_2$$CO_2$H), 2.52 (2H, t, J = 7.2 Hz, PhSeCH_2), 2.02 (2H, tt, J = 7.1, 7.2 Hz, PhSeCH$_2$CH_2); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 178.9 (*C*=O), 132.3 (*Ar*), 129.7 (*Ar*), 129.1 (*Ar*), 127.0 (*Ar*), 33.5 (PhSe*C*H_2), 26.8 (*C*$H_2$$CO_2$H), 24.9 (PhSeCH$_2$*C*$H_2$). *Data are consistent with literature values.*[173]

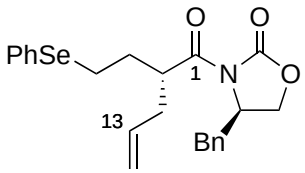
(*R*)-4-benzyl-3-(4-(phenylselanyl)butanoyl)oxazolidin-2-one



379

To a stirred solution of acid **380** (2.43 g, 10.0 mmol) in dry THF (80 mL) at -10 °C was added triethylamine (3.70 mL, 27.0 mmol) and pivaloyl chloride (1.35 mL, 11.0 mmol). After 1 h LiCl (466 mg, 11.0 mmol) and (*R*)-Evans auxiliary **382** (1.95 g, 11.0 mmol) were added and the solution was allowed to warm to RT overnight. The reaction was diluted with EtOAc (300 mL), washed with sat. aq. $NaHCO_3$ solution (75 mL) and brine (75 mL), dried (Na_2SO_4, filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (3:1 PE:EtOAc), which gave oxazolinone **379** (3.73 g, 9.20 mmol, 92%) as a colourless oil. $\mathbf{R}_f$ 0.37 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.53 (2H, dd, J = 7.8, 1.4 Hz, ArH), 7.34 (2H, t, J = 7.2 Hz, ArH), 7.31–7.22 (4H, m, ArH), 7.20 (2H, t, J = 7.1 Hz, ArH), 4.64 (1H, dddd, J = 10.0, 6.4, 3.3, 3.3 Hz, C(O)NCH), 4.19 (1H, dd, J = 14.6, 6.4 Hz, C(O)OCHH), 4.16 (1H, dd, J = 14.6, 3.3 Hz, C(O)OCHH), 3.28 (1H, dd, J = 13.4, 3.3 Hz, PhCHH), 3.09 (2H, t, J = 7.2 Hz, CH_2C(O)), 3.01 (2H, t, J = 7.2 Hz, PhSeCH_2), 2.75 (1H, dd, J = 13.4, 10.0 Hz, PhCHH), 2.11 (2H, tt, J = 7.2, 7.2 Hz, PhSeCH$_2$CH_2); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 172.4 (amide C=O), 153.4 (imide C=O), 135.2 (*Ar*), 132.7 (*Ar*), 130.0 (*Ar*), 129.4 (*Ar*), 129.1 (*Ar*), 129.0 (*Ar*), 127.4 (*Ar*), 126.9 (*Ar*), 66.2 (NCH), 55.1 (OCH$_2$), 37.9 (PhCH$_2$), 35.3 (C(O)CH$_2$), 27.0 (PhSeCH$_2C$H$_2$), 24.6 (PhSeCH$_2$); $\boldsymbol{\nu}_\mathbf{max}$ **/ cm^{-1}** 2925 (w, C-H), 1780 (s, amide C=O), 1699 (s, imide C=O), 1385 (m), 1150 (m); **m/z** (ESI+) 426 ([M+Na]$^+$, 100%), 829 ([2M+Na]$^+$, 29%), HRMS found 426.0593, $C_{20}H_{21}NNaO_3Se$ requires 426.0597; $[\boldsymbol{\alpha}]_\mathbf{D}^{\mathbf{25}}$ -39.1 (c = 1.03, $CHCl_3$).

(*R*)-4-benzyl-3-((*R*)-2-(2-(phenylselanyl)ethyl)pent-4-enoyl)oxazolidin-2-one

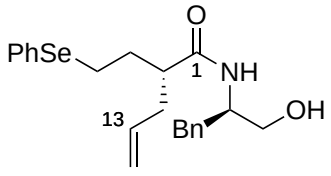


385

To a stirred solution of NaHMDS (2 M in THF, 5.00 mL, 10.0 mmol) at –78 °C was added dropwise

a solution of oxazolidinone **379** (3.44 g, 8.56 mmol) in dry THF (8.5 mL), maintaining an internal temperature <70 °C. After stirring for 30 min, allyl iodide (2.35 mL, 25.7 mmol) filtered through neutral alumina immediately prior to use was added dropwise maintaining an internal temperature <70 °C and the solution was stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl solution (22 mL) and diluted with EtOAc (100 mL). The layers were separated and the organic phase was washed successively with water (20 mL), 1 M aqueous $NaHCO_3$ solution (20 mL), and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (6:1 PE:EtOAc), which gave allylated oxazolidinone **385** (3.13 g, 7.06 mmol, 82%) as a colourless oil. $\mathbf{R}_f$ 0.24 (6:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.49 (2H, dd, J = 8.0, 1.6 Hz, Ar*H*), 7.34 (2H, d, J = 7.3 Hz, Ar*H*), 7.31–7.20 (6H, m, Ar*H*), 5.79 (1H, dddd, J = 17.1, 10.1, 7.1, 7.1, H_2C=C*H*), 5.08 (1H, d, J = 17.1, *H*HC=CH), 5.08–5.03 (1H, m, H*H*C=CH), 4.68–4.59 (1H, m, NC*H*), 4.17–4.09 (2H, m, OCH_2), 4.03 (1H, dddd, J = 8.9, 7.0, 6.7, 4.9 Hz, C(O)C*H*), 3.28 (1H, dd, J = 13.3, 3.3 Hz, PhC*H*H), 2.96 (1H, ddd, J = 12.2, 9.2, 5.5 Hz, PhSeC*H*H), 2.87 (1H, ddd, J = 12.2, 9.0, 6.6 Hz, PhSeCH*H*), 2.66 (1H, dd, J = 13.3, 10.0 Hz, PhCH*H*), 2.47 (1H, ddd, J = 13.9, 7.1, 7.0 Hz, H_2C=CHC*H*H), 2.32 (1H, ddd, J = 13.9, 7.1, 6.7 Hz, H_2C=CHCH*H*), 2.21 (1H, dddd, J = 14.2, 8.9, 8.9, 5.6 Hz, PhSeCH_2C*H*H), 1.89 (1H, dddd, J = 14.2, 9.3, 6.6, 4.9 Hz, PhSeCH_2CH*H*); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 175.0 (amide *C*=O), 153.0 (imide *C*=O), 135.3 (*Ar*), 134.6 (H_2C=*C*H), 132.6 (*Ar*), 130.0 (*Ar*), 129.4 (*Ar*), 129.0 (*Ar*), 128.9 (*Ar*), 127.3 (*Ar*), 126.8 (*Ar*), 117.6 (H_2*C*=CH), 66.0 (O*C*H_2), 55.4 (N*C*H), 42.5 (C(O)*C*H), 38.1 (Ph*C*H_2), 36.6 (H_2C=CH*C*H_2), 31.6 (PhSeCH_2*C*H_2), 25.1 (PhSe*C*H_2); $\boldsymbol{\nu}_\mathbf{max}$ **/ cm^{-1}** 2920 (w, C-H), 1777 (s, imide C=O), 1695 (s, amide C=O); **m/z** (ESI+) 466 ([M+Na]$^+$, 100%), 909 ([2M+Na]$^+$, 29%), HRMS found 466.0896, $C_{23}H_{25}NNaO_3Se$ requires 466.0892; $[\boldsymbol{\alpha}]_\mathbf{D}^{\mathbf{25}}$ -46.5 (c = 1.19, $CHCl_3$).

(*R*)-*N*-((*R*)-1-Hydroxy-3-phenylpropan-2-yl)-2-(2-(phenylselanyl)ethyl)pent-4-enamide

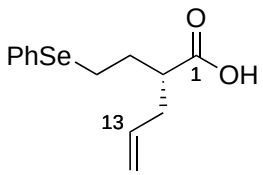


386

To a stirred solution of allylated oxazolidinone **385** (110 mg, 0.25 mmol) in THF (2.0 mL) with 4 drops of MeOH was added aqueous LiOH solution (1.0 M, 1.0 mL, 1.0 mmol) at 0 °C. The solution

was stirred until TLC showed complete consumption of starting material (≈4 h). The reaction was diluted with EtOAc, and washed with 2 M aqueous NaOH solution (). The organic layer was dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*, which gave amide **386** (84 mg, 0.20 mmol, 81%) as a white solid m.p. 58–65 °C. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.50–7.42 (2H, m, Ar*H*), 7.37–7.14 (8H, m, Ar*H*), 6.01 (1H, d, J = 8.1 Hz, N*H*), 5.48 (1H, ddt, J = 17.1, 10.1,7.1 Hz, H_2C=C*H*), 4.95 (1H, dd, J = 17.1, 1.7 Hz, CH=C*H*H), 4.88 (1H, dd, J = 10.1, 1.7 Hz, CH=CH*H*), 4.26–4.16 (1H, m, NHC*H*), 3.62 (1H, dd, J = 11.1, 3.8 Hz, HOC*H*H), 3.52 (1H, dd, J = 11.1, 5.3 Hz, HOCH*H*), 3.23 (1H, br, O*H*), 3.01–2.71 (4H, m, PhSeCH_2 & PhCH_2), 2.38–2.18 (2H, m H_2C=CHC*H*H & C(O)C*H*), 2.12–1.96 (2H, m, H_2C=CHCH*H* & CHC*H*H), 1.78–1.68 (1H, m, CHCH*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 174.8 (*C*=O), 137.7 (*Ar*), 135.0 (*C*H=CH_2), 132.5 (*Ar*), 129.2 (*Ar*), 129.1 (*Ar*), 129.0 (*Ar*), 128.6 (*Ar*), 126.9 (*Ar*), 126.6 (*Ar*), 117.0 (CH=*C*H_2), 64.2 (HO*C*H_2), 53.8 (NH*C*H), 52.7 (NH*C*H), 46.8 (C(O)*C*H), 37.0 (NH*C*H_2Ph), 36.8 (H_2C=CH*C*H_2), 32.3 (PhSeCH$_2$*C*H_2), 25.6 (PhSe*C*H_2), $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3296 (br, N-H & O-H), 1741 (s), 1640 (s, amide C=O), 1023 (m), 735 (s); $\boldsymbol{[\alpha]_D^{25}}$ -0.8 (c = 1.00, $CHCl_3$); **m/z** (ESI+) 440.1 ([M+Na]$^+$, 100%), HRMS found 440.1098, $C_{22}H_{27}NNaO_2Se$ requires 440.1099.

(*R*)-2-(2-(Phenylselanyl)ethyl)pent-4-enoic acid

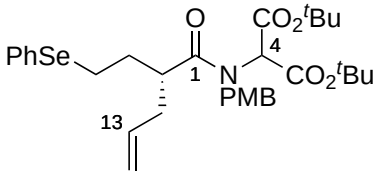


371

To a stirred solution of allylated oxazolidinone **385** (1.39 g, 3.13 mmol) in 4:1 THF:water (32 mL) at 0 °C was added a pre-cooled solution of 1 M LiO_2H (6.3 mL, 6.3 mmol). The reaction was stirred for 3 min, then quenched by the addition of sat. aq. sodium bisulfate solution (15 mL) and then diluted with DCM (20 mL). The layers were separated and the aqueous layer was extracted with DCM (20 mL). The aqueous layer was acidified to pH 2 with sulfate buffer and extracted with DCM (3×20 mL). The combined acidic organic extracts were dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (0.5%→4% MeOH in DCM), which gave acid **371** (576 mg, 2.03 mmol, 65%) as a colourless oil. $\mathbf{R}_f$ 0.17 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.52–7.49 (2H, m, Ar*H*), 7.30–7.25 (3H, m, Ar*H*), 5.73 (1H, m, H_2C=C*H*), 5.11–5.04 (2H, m, *H*$_2$C=CH), 2.99 (1H, m, PhSeC*H*H), 2.90 (1H, m, PhSeCH*H*), 2.67 (1H, m, C(O)C*H*), 2.41 (1H, m, H_2C=CHC*H*H), 2.28 (1H,

m, H_2C=CHCHH), 2.08 (1H, m, PhSeCH$_2$CHH), 1.90 (1H, m, PhSeCH$_2$CHH); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 181.4 (acid C=O), 134.6 (H_2C=CH), 132.7 (Ar), 129.8 (Ar), 129.1 (Ar), 127.0 (Ar), 117.6 (H_2C=CH), 44.9 (C(O)CH), 35.8 (H_2C=CHCH$_2$), 31.5 (PhSeCH$_2$$CH_2$), 25.0 (PhSe$CH_2$); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3068 (br m, O-H), 2927 (m, C-H), 1649 (s, C=O), 1438 (m), 1285 (m), 920 (m); **m/z** (ESI+) 307.0 ([M+Na]$^+$, 100%), HRMS found 307.0208, $C_{13}H_{16}NaO_2Se$ requires 307.0208; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -33.8 (c = 0.50, DCM).

(*R*)-Di-*tert*-butyl 2-(*N*-(4-methoxybenzyl)-2-(2-(phenylselanyl)ethyl)pent-4-enamido)malonate

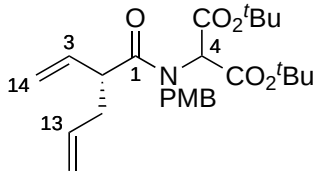


373

To a stirred solution of acid **371** (619 mg, 2.18 mmol) in dry DCM (5.6 mL) with a drop of DMF was added oxalyl chloride (171 μL, 2.0 mmol) dropwise. The solution was stirred for 1 h and then rapidly transferred to a vigourously stirred solution of malonate **372**‡ (547 mg, 1.56 mmol) in 1:1 DCM:sat. aq. $NaHCO_3$ solution (5.6 mL). The solution was stirred for 16 h and then filtered through a plug of silica eluting with 1:1 PE:Et_2O. The solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (9:1 DCM:EtOAc), which gave malonate **373** (575 mg, 0.936 mmol, 60%) as a colourless oil. $\mathbf{R}_f$ 0.57 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 7.43–7.42 (2H, m, ArH), 7.28–7.20 (5H, m, ArH), 6.86 (2H, d, J = 8.5 Hz, ArH), 5.60 (1H, m, H_2C=CH), 5.16 (1H, s, CH(CO_2^tBu)$_2$), 4.97–4.92 (2H, m, H_2C=CH), 4.73 (1H, d, J = 17.4 Hz, ArCHH), 4.62 (1H, d, J = 17.4 Hz, ArCHH), 3.79 (3H, s, OCH_3), 2.94 (1H, ddd, J = 12.0, 8.5, 5.7 Hz, PhSeCHH), 2.82–2.72 (2H, m, PhSeCHH & C(O)CH), 2.33 (1H, m, H_2C=CHCHH), 2.16–2.08 (2H, m, H_2C=CHCHH & PhSeCH$_2$CHH) 1.78 (1H, dddd, J = 12.0, 8.8, 6.9, 5.4, PhSeCH$_2$CHH), 1.41 (9H, s, CO_2C(CH_3)), 1.41 (9H, s, CO_2C(CH_3')); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 176.2 (lactam C=O), 165.3 (ester C=O), 159.1 (Ar), 135.3 (H_2C=CH), 132.3 (Ar), 130.1 (Ar), 129.7 (Ar), 129.0 (Ar), 127.9 (Ar), 126.6 (Ar), 117.1 (H_2C=CH), 114.0 (Ar), 82.6 (OC(CH$_3$)$_3$), 63.4 (CH(CO_2^tBu)$_2$), 55.4 (OCH$_3$), 50.4 (ArCH$_2$), 41.5 (C(O)CH), 36.7 (H_2C=CHCH$_2$), 32.5 (PhSeCH$_2$$CH_2$), 27.8 ($CO_2$C($CH_3$)$_3$), 25.0 (PhSe$CH_2$), $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2978 (s, C-H), 1732 (s, ester C=O), 1657 (s, amide C=O), 1478 (s), 1367 (s), 1249 (s); **m/z** (ESI+) 640.1 ([M+Na]$^+$, 100%), HRMS found 640.2157, $C_{32}H_{43}NNaO_6Se$ requires 640.2150; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ -10.8 (c = 0.49, DCM).

‡ *N*-PMB malonate **372** was supplied by Robert W. Foster.

(*R*)-Di-*tert*-butyl 2-(*N*-(4-methoxybenzyl)-2-vinylpent-4-enamido)malonate

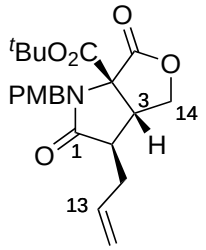


374

To a stirred solution of selenide **373** (306 mg, 0.500 mmol) in DCM (23 mL) at -15 °C was added *m*-CPBA (70–75% with water, 344 mg, 1.50 mmol) in DCM (2.9 mL). The solution was allowed to warm to RT and stirred for 30 min after which time DMS (73 μL, 1.00 mmol) and DiPA (0.42 mL, 3.00 mmol) were added and the solution was heated under reflux for 4 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (5:1 PE:EtOAc), which gave alkene **374** (183 mg, 0.400 mmol, 80%) as a colourless oil. $\mathbf{R}_f$ 0.40 (5:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.17 (2H, d, J = 8.6 Hz, ArH), 6.87 (2H, d, J = 8.6 Hz, ArH), 5.82 (1H, ddd, J = 17.3, 10.1, 7.9 Hz, H_2C=CHCH), 5.71 (1H, dddd, J = 17.3, 10.1, 7.3, 6.6 Hz, H_2C=CHCH_2), 5.29 (1H, s, CH(CO_2^tBu)$_2$), 5.14–5.00 (4H, m, (H_2C=CH)$_2$), 4.74 (1H, d, J = 17.7 Hz, ArCHH), 4.60 (1H, d, J = 17.7 Hz, ArCHH), 3.80 (3H, s, OCH_3), 3.20 (1H, m, C(O)CH), 2.57 (1H, m, H_2C=CHCHH), 2.24 (1H, m, H_2C=CHCHH), 1.41 (9H, s, CO_2C(CH_3)$_3$), 1.36 (9H, s, CO_2C(CH'_3)$_3$); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 174.3 (amide C=O), 165.4 (ester C=O), 159.0 (Ar), 136.3 (H_2C=CHCH), 135.5 (H_2C=CHCH_2), 129.1 (Ar), 127.5 (Ar), 117.2 (H_2C=CHCH), 116.9 (H_2C=CHCH_2), 114.0 (Ar), 82.7 (OC(CH_3)$_3$), 62.9 (CH(CO_2^tBu)$_2$), 55.3 (OCH$_3$), 49.7 (ArCH$_2$), 47.4 (C(O)CH), 37.2 (H_2C=CHCH$_2$), 27.7 (C(CH$_3$)$_3$); $\boldsymbol{\nu}_\mathbf{max}$ **/ cm^{-1}** 2980 (m, C-H), 1733 (s, ester C=O), 1660 (s, amide C=O), 1514 (m), 1368 (m), 1250 (s); **m/z** (ESI+) 482.3 ([M+Na]$^+$, 100%), HRMS found 482.2510, $C_{26}H_{37}NNaO_6$ requires 482.2510; $[\boldsymbol{\alpha}]_\mathbf{D}^{\mathbf{25}}$ -30.2 (c = 0.42, DCM).

(3*R*,3a*R*,6a*S*)-*tert*-Butyl

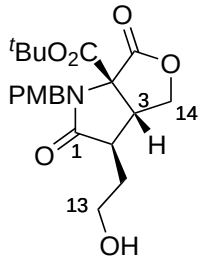
3-allyl-1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate



375

To a degassed mixture of $Mn(OAc)_3 \cdot 2H_2O$ (44.1 mg, 0.164 mmol), $Cu(OTf)_2$ (59.3 mg, 0.164 mmol), and alkene **374** (37.8 mg, 0.0822 mmol) at 40 °C was rapidly added sparged MeCN (0.21 mL). The solution was stirred for 2.5 h, allowed to cool to RT and filtered through a pad of silica eluting with EtOAc. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (2:1 PE:EtOAc), which gave pyrrolidinone-lactone **375** (21.0 mg, 0.052 mmol, 64%) as a colourless oil. $\mathbf{R}_f$ 0.65 (1:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.28 (2H, d, J = 8.8 Hz, ArH), 6.82 (2H, d, J = 8.8 Hz, ArH), 5.73 (1H, dddd, J = 17.0, 10.2, 8.0, 6.0, H_2C=CH), 5.14 (1H, dddd, J = 10.2, 1.3, 1.3, 1.3 Hz, CH=CHH), 5.09 (1H, dddd, J = 17.0, 1.6, 1.6, 1.3 Hz, CH=CHH), 4.80 (1H, d, J = 15.2 Hz, ArCHH), 4.61 (1H, dd, J = 9.3, 8.5 Hz, CHCHHO), 4.46 (1H, d, J = 15.2 Hz, ArCHH), 3.98 (1H, dd, J = 9.3, 6.5 Hz, CHCHHO), 3.78 (3H, s, OCH_3), 3.10 (1H, ddd, J = 8.8, 6.5, 3.0 Hz, C(O)CHCH), 2.65 (1H, ddddd, J = 8.8, 6.0, 4.3, 1.6, 1.3 Hz, C(O)CH), 2.47 (1H, ddd, J = 7.3, 4.3, 3.1 Hz, H_2C=CHCHH), 2.22–2.15 (1H, m, H_2C=CHCHH), 1.46 (9H, s, C(CH_3)$_3$); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 174.9 (lactam C=O), 170.1 (lactone C=O), 166.8 (ester C=O), 158.9 (Ar), 134.2 (H_2C=CH), 130.0 (Ar), 128.6 (Ar), 118.5 (H_2C=CH), 113.6 (Ar), 84.9 (OC(CH$_3$)$_3$), 71.2 (ArCH$_2$), 70.5 (C), 55.2 (OCH$_3$), 46.2 (C(O)CH), 45.6 (OCH$_2$CH), 44.0 (OCH$_2C$H), 34.9 (H_2C=CHCH$_2$), 27.7 (OC(CH$_3$)$_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2979 (m, C-H), 1781 (s, lactone C=O), 1736 (s, ester C=O), 1706 (s, lactam C=O), 1514 (s), 1371 (m), 1247 (s), 1152 (s); **m/z** (ESI+) 424.2 ([M+Na]$^+$, 100%), HRMS found 424.1721, $C_{22}H_{27}NNaO_6$ requires 424.1731; $[\boldsymbol{\alpha}]_\mathbf{D}^{\mathbf{25}}$ +5.7 (c = 0.32, DCM).

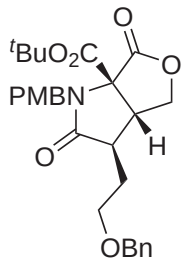
(3*R*,3a*R*,6a*S*)-*tert*-Butyl 3-(2-hydroxyethyl)-1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate



355

A solution of alkene **375** (60.0 mg, 0.149 mmol) win 3:1 DCM:MeOH (10 mL) was treated with O_3/O_2 at - 78 °C until a pale blue colour persisted. The solution was purged of O_3 with a stream of O_2 and then treated with $NaBH_4$ (7.3 mg, 0.194 mmol) in MeOH (1.0 mL) and stirred for 30 min. The solution was stirred for a further 30 min at 0 °C and then diluted with EtOAc (10 mL). The solution was washed successively with 5% aqueous citric acid solution (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (3:2→1:1 PE:EtOAc), which gave alcohol **355** (53.1 mg, 0.131 mmol, 88%) as a colourless oil. $\mathbf{R}_f$ 0.44 (EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.28 (2H, d, J = 8.7 Hz, ArH), 6.82 (2H, d, J = 8.7 Hz, ArH), 4.77 (1H, d, J = 15.2 Hz, ArCHH), 4.64 (1H, dd, J = 9.5, 8.0 Hz, CHCHHO), 4.48 (1H, d, J = 15.2 Hz, ArCHH), 4.08 (1H, dd, J = 9.5, 5.8 H CHCHHO), 3.87–3.77 (2H, m, HOCH_2), 3.77 (3H, s, OCH_3), 3.14 (1H, ddd, J = 8.0, 5.8, 3.8 Hz, OCH_2CH), 2.61 (1H, ddd, J = 7.0, 6.8, 3.8 Hz, C(O)CH), 2.54 (1H, t, J = 5.2 Hz, OH), 1.99 (1H, dddd, J = 14.4, 6.8, 6.8, 4.3 Hz, $HOCH_2$CHH), 1.78 (1H, dddd, J = 14.4, 7.3, 7.0, 4.3 Hz, $HOCH_2$CHH), 1.46 (9H, s, C(CH_3)$_3$); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 176.6 (lactam C=O) 170.7 (lactone C=O) 167.2 (ester C=O), 159.4 (*Ar*), 130.5 (*Ar*), 129.0 (*Ar*), 114.2 (*Ar*), 85.6 (OC(CH$_3$)$_3$), 71.7 (*C*), 71.3 (CHCH$_2$O), 61.4 (HOCH$_2$), 55.7 (OCH$_3$), 46.7 (C(O)CH), 46.3 (ArCH$_2$), 45.4 (OCH_2CH), 34.1 ($HOCH_2CH_2$), 28.3 (C(CH$_3$)$_3$); $\boldsymbol{\nu}_\mathbf{max}$ **/ cm^{-1}** 3400 (br m, O-H), 1782 (s, lactone C=O), 1743 (s, ester C=O), 1704 (s, lactam C=O), 1514 (s), 1248 (s), 1153 (s), 1034 (m); **m/z** (ESI+) 428.2 ([M+Na]$^+$, 100%), HRMS found 428.1673, $C_{22}H_{27}NNaO_6$ requires 428.1680; $[\boldsymbol{\alpha}]_\mathbf{D}^{\mathbf{25}}$ +22.7 (c = 0.52, $CHCl_3$).

(3*R*,3a*R*,6a*S*)-*tert*-Butyl 3-(2-(benzyloxy)ethyl)-1-(4-methoxybenzyl)-2,6-dioxohexahydro-1*H*-furo[3,4-*b*]pyrrole-6a-carboxylate

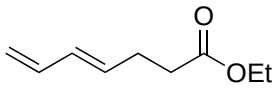


354

To a stirred solution of alcohol **355** (4.5 mg, 11.1 μmol) and benzyl trichloroimidate **391** (5.6 mg, 22.2 μmol) in DCM (0.80 mL) was added a solution of TMSOTf (10 μM in DCM, 0.22 mL, 2.2 μmmol). The solution was stirred overnight, and a further charge of benzyl trichloroimidate (5.6 mg, 22.2 μmol) and TMSOTf (10 μM in DCM, 1.10 mL, 11.1 μmol) was added and the solution was stirred for a futher 24 h. The volatiles were removed *in vacuo*, and the residue was redissolved in 2:1 PE:EtOAc (10 mL). The solution was filtered through silica, washed successively with sat. aq. $NaHCO_3$ (5 mL) and water (5 mL). The organic layer was dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (3→2:1 PE:EtOAc and 4% EtOAc in DCM), which gave benzyl ether **354** (1.3 mg, 2.6 μmol, 24%) as a colourless oil. $\mathbf{R}_f$ 0.22 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 7.37–7.27 (7H, m, Ar*H*), 6.80 (2H, d, J = 8.7 Hz, Ar*H*), 4.75 (1H, d, J = 15.1 Hz, ArC*H*H), 4.52–4.42 (4H, m, ArCH*H* & PhCH_2 & CHC*H*HO), 4.01 (1H, dd, J = 9.4, 5.4 Hz, CHCH*H*O), 3.77 (3H, s, OCH_3), 3.68–3.59 (2H, m, BnOCH_2), 3.18 (1H, ddd, J = 8.0, 5.4, 4.4 Hz, C*H*CH_2O), 2.51 (1H, ddd, J = 9.4, 4.4, 4.4 Hz, C*H*CH_2), 2.24–2.16 (1H, m, CHC*H*H), 1.76–1.67 (1H, m, CHCH*H*), 1.42 (9H, s, C(CH_3)$_3$); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 176.0 (lactam *C*=O), 170.9 (lactone *C*=O), 167.2 (ester *C*=O), 159.2 (*Ar*), 138.3 (*Ar*), 130.4 (*Ar*), 129.1 (*Ar*), 128.9 (*Ar*), 128.3 (*Ar*), 128.1 (*Ar*), 114.0 (*Ar*), 85.2 (O*C*(CH$_3$)$_3$), 73.6 (Ph*C*H$_2$O), 71.8 (O$_2$C*C*), 71.0 (CH*C*H$_2$O), 69.0 (BnO*C*H$_2$), 55.6 (O*C*H$_3$), 46.5 (C(O)*C*H), 46.1 (N*C*H$_2$Ar), 45.5 (*C*HCH$_2$O), 31.5 (CH*C*H$_2$), 28.1 (C(*C*H$_3$)$_3$); **m/z** (ESI+) 518.2 ([M+Na]$^+$, 100%), HRMS found 518.2150, $C_{28}H_{33}NNaO_7$ requires 518.2149.

6.5 Future Work & Conclusions

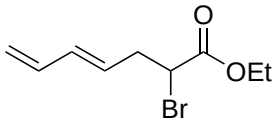
(*E*)-Ethyl hepta-4,6-dienoate



400

According to GP 2, 1,4-pentadien-3-ol **399** (1.26 g, 15.0 mmol) was treated with triethyl orthoacetate, which after flash column chromatography (19:1 PE:Et_2O) gave diene **400** (2.12 g, 13.8 mmol, 92%) as a colourless oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.29 (1H, dt, J = 16.9, 10.2 Hz, H_2C=CH), 6.09 (1H, dd, J = 15.0, 10.5 Hz, CHCH=CH), 5.73–5.65 (1H, m, CH=CHCH_2), 5.11 (1H, d, J = 16.9 Hz, CH=CHH), 4.99 (1H, d, J = 10.1 Hz, CH=CHH), 4.14 (2H, q, J = 7.1 Hz, CO_2CH_2), 2.42–2.39 (4H, m, CHCH_2CH_2), 1.26 (3H, t, J = 7.1 Hz, CH_2CH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.0 (C=O), 136.8 (H_2C=CH), 132.6 (CHCCH=CH), 131.9 (CH=CHCH_2), 115.7 (CH=CH$_2$), 60.4 (CO_2CH_2), 33.8 (CH_2), 27.8 (CH_2), 14.2 (CH_2CH_3). *Data are consistent with literature values.*[174]

(*E*)-Ethyl 2-bromohepta-4,6-dienoate

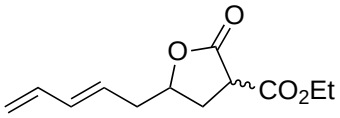


401

To a stirred solution of diene **400** (992 mg, 6.44 mmol) in dry THF (64 mL) at –78 °C was added TMSCl (1.31 mL, 10.3 mmol) and LDA (1.0 M, 10.3 mL, 10.3 mmol). The reaction was stirred for 1 h after which a solution of NBS (2.30 g, 12.9 mmol) in dry THF (64 mL) precooled to –78 °C was added dropwise. The solution was allowed to slowly warm to RT and when TLC analysis showed complete consumption of starting material, the reaction was quenched with 50% sat. aq. NH_4Cl solution (30 mL). The layers were separated, and the aqueous was extracted with Et_2O (3×40 mL). The combined organic extracts were successively washed with 1 M aq. HCl solution (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (4→8% Et_2O in PE 30–40 °C), which gave α-bromo ester **401** (1.11 g, 4.78 mmol, 74%) as a colourless oil. $\mathbf{R}_f$ 0.55 (3:1 PE:Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 6.30 (1H, ddd, J = 16.9, 10.4, 10.4 Hz, H_2C=CH), 6.16 (1H, dd, J = 15.2, 10.4 Hz, H_2C=CHCH), 5.61 (1H, ddd, J = 15.2, 7.1, 7.1 Hz, H_2C=CHCH=CH), 5.18 (1H,

d, J = 16.9 Hz, CH=CHH), 5.08 (1H, d, J = 10.4 Hz, CH=CHH), 4.27–4.18 (3H, m, CO_2CH_2 & CHBr), 2.89 (1H, ddd, J = 14.8, 7.1, 7.1 Hz, CHBrCHH), 2.75 (1H, ddd, J = 14.8, 7.1, 7.1 Hz, CHBrCHH); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 169.3 (C=O), 136.3 (H_2C=CH), 135.0 (H_2C=CHCH), 128.3 (H_2CHCH=CH), 117.3 (H_2C=CH), 62.0 ($CO_2CH_2CH_3$), 44.4 (CHBr), 37.9 (CHBrCH_2), 14.0 ($CO_2CH_2CH_3$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$2982 (w, C-H), 1737 (s, C=O), 1149 (m), 1004 (m); **m/z** (FI) HRMS found 232.0101, $C_9H_{13}O_2{}^{79}Br$ requires 232.0099.

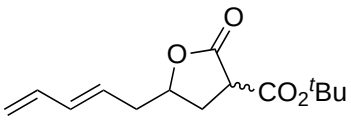
(*E*)-Ethyl 2-oxo-5-(penta-2,4-dien-1-yl)tetrahydrofuran-3-carboxylate



402

Ester **401** (1.11 g, 4.76 mmol) was treated successively with DiBAl-H, KO^{t}Bu, and DEM according to GPs 9, 10, and 11 respectively. The crude product was purified by flash column chromatography (6→3:1 PE:EtOAc), which gave an inseparable 1:1 mixture of diastereomeric lactones **402** (532 mg, 2.38 mmol, 50%) as a colourless oil. $\mathbf{R}_f$ 0.17 (3:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 6.31 (1H, ddd, J = 16.9, 10.3, 10.3 Hz, H_2C=CH), 6.18 (1H, ddd, J = 15.5, 10.3, 6.6 Hz, H_2C=CHCH=CH), 5.64 (1H, ddt, J = 14.8, 10.0, 7.4 Hz, H_2C=CHCH=CH), 5.17 (1H, d, J = 16.9 Hz, CH=CHH), 5.06 (1H, dd, J = 15.5, 10.3 Hz,CH=HH), 4.78–4.70 (1H, m, CH_2CHO-d1), 4.50 (1H, dddd, J = 9.2, 6.3, 6.3, 6.3 Hz, CH_2CHO-d2), 4.29–4.21 (2H, m, $CO_2CH_2H_3$), 3.62 (1H, dd, J = 10.9, 9.3 Hz, EtO_2CCH-d2), 3.57 (1H, dd, J = 9.7, 5.1 Hz, EtO_2CCH-d1), 2.68 (1H, ddd, J = 12.2, 7.0, 5.1 Hz, CHOCHH-d1), 2.66–2.42 (3H, m, CH=CHCH_2 & CHOCHH-d2), 2.36 (1H, ddd, J = 13.1, 10.9, 9.2 Hz, CHOCHH-d2), 2.17 (1H, ddd, J = 12.2, 9.7, 7.1 Hz, CHOCHH-d1), 1.34–1.28 ($CO_2CH_2CH_3$; $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 171.8 (lactone C=O), 171.7 (lactone C=O), 167.9 (ester C=O), 167.8 (ester C=O), 136.5 (H_2C=CH), 136.4 (H_2C=CH), 135.4 (H_2C=CHCH), 135.1 (H_2C=CHCH), 127.1 (H_2C=CHCH=CH), 126.9 (H_2C=CHCH=CH), 117.3 (CH=CH_2), 117.1 (CH=CH_2), 79.2 (CH_2CHO), 78.6 (CH_2CHO), 62.4 (CO_2CH_2-d1), 62.3 (CO_2CH_2-d2), 47.3 (EtO_2CCH-d2), 47.0 (EtO_2CCH-d1), 38.2 (CH=CHCH_2), 38.1 (CH=CHCH_2), 31.6 (CHCH_2-d2), 31.2 (CHCH_2-d2), 14.2 (CH_2CH_3), 14.2 (CH_2CH_3); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$2984 (w, C-H), 1774 (s, lactone C=O), 1731 (s, ester C=O), 1155 (s), 1006 (s); **m/z** (ESI+) 247.1 ($[M+Na]^+$, 94%), 263.1 ($[M+K]^+$, 65%), HRMS found 247.0939, $C_{12}H_{16}NaO_4$ requires 247.0941.

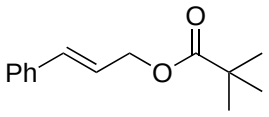
(E)-tert-butyl 2-oxo-5-(penta-2,4-dien-1-yl)tetrahydrofuran-3-carboxylate



405

Ester **401** (131 mg, 0.52 mmol) was treated successively with DiBAl-H, KO^{t}Bu, and di-*tert*-butyl malonate according to GPs 9, 10, and 11 respectively. The crude product was purified by flash column chromatography (6:1 PE:EtOAc), which gave an inseparable 1:1 mixture of diastereomeric lactones **402** (35 mg, 0.139 mmol, 27%) as a colourless oil. $\mathbf{R}_f$ 0.41 (3:1 PE:EtOAc); $\boldsymbol{\delta}_\mathbf{H}$ (500 MHz, $CDCl_3$) 6.32 (1H, ddd, J = 17.0, 10.3, 10.3 Hz, H_2C=CH), 6.23–6.13 (1H, m, CHCH=CH), 5.65 (1H, ddd, J = 11.3, 7.2, 7.2 Hz, CH=CHCH_2), 5.18 (1H, d, J = 17.0 Hz, CH=CHH), 5.09–5.05 (1H, m, CH=CHH), 4.75–4.68 (1H, m, CHO-d1), 4.47 (1H, dddd, J = 9.2, 6.4, 6.4, 6.4 Hz, CHO-d2), 3.52 (1H, dd, J = 10.7, 9.4 Hz, ^{t}BuO$_2$CCH-d2), 3.48 (1H, dd, J = 9.6, 5.0 Hz, ^{t}BuO$_2$CCH-d1), 2.66–2.58 (2H, m, CH=CHCHH-d2 & CHCHH-d1), 2.55–2.41 (4H, m, CH=CHCH_2-d1 & CH=CHCHH-d2 & CHCHH-d2), 2.32 (1H, ddd, J = 13.0, 10.8, 9.2 Hz, CHCHH-d2), 2.13 (1H, ddd, J = 13.3, 9.7, 7.2 Hz, CHCHH-d1), 1.51 (9H, s, C(CH_3)$_3$), 1.49 (9H, s, C(CH_3)$_3$); $\boldsymbol{\delta}_\mathbf{C}$ (125 MHz, $CDCl_3$) 172.0 (lactone C=O), 171.9 (lactone C=O), 166.9 (ester C=O), 166.8 (ester C=O), 136.4 (H_2C=CH), 136.3 (H_2C=CH), 135.2 (CHCH=CH), 134.9 (CHCH=CH), 127.2 (CH=CHCH$_2$), 126.9 (CH=CHCH$_2$), 117.1 (CH=CH$_2$), 116.9 (CH=CH$_2$), 83.1 (OC(CH$_3$)$_3$), 82.9 (OC(CH$_3$)$_3$), 78.9 (CHO-d1) 78.2 (CHO-d1), 48.1 (^{t}BuO$_2$CCH-d2), 47.9 (^{t}BuO$_2$CCH-d1), 38.1 (CH=CHCH$_2$), 38.1 (CH=CHCH$_2$), 31.4 (CHCH$_2$-d2), 31.2 (CHCH$_2$-d1), 27.9 (C(CH$_3$)$_3$), 27.9 (C(CH$_3$)$_3$); $\boldsymbol{\nu}_\mathbf{max}$ / $\mathbf{cm^{-1}}$ 2980 (w, C-H), 1776 (s, C=O), 1729 (s, C=O), 1369 (m), 1144 (s), 1007 (m); **m/z** (ESI+) 275.1 ([M+Na]$^+$, 100%), HRMS found 275.1249, $C_{14}H_{20}NaO_4$ requires 275.1254.

Cinnamyl Pivalate

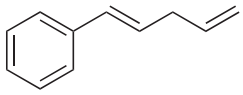


441

To a stirred solution of cinnamyl alcohol (6.71 g, 50.0 mmol) in dry DCM (100 mL) at 0 °C was added dry pyridine (6.07 mL, 75.0 mmol) and the solution was stirred for 30 minutes. Pivaloyl chloride (7.41

mL, 60 mmol) was added dropwise over 30 min, and the reaction mixture was allowed to warm to RT over 5 h. The reaction mixture was washed successively with 10% HCl solution (3×50 mL), saturated $NaHCO_3$ solution (3×50 mL), brine (70 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, which gave ester **441** (10.8 g, 50 mmol, 100%) as a pale yellow oil. $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.42-7.25 (5H, m, Ar*H*), 6.65 (1H, d, J = 15.9 Hz, PhC*H*=CH), 6.29 (1H, dt, J = 15.9, 6.3 Hz, PhCH=C*H*), 4.73 (2H, dd, J = 6.3, 1.3 Hz, OCH_2), 1.24 (9H, s, C(CH_3)$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 178.8 (O*C*(=O)), 136.8 (CH=CH*C*CH), 134.1 (Ph*C*H=CH), 129.1 (CCH*C*H), 128.4 (CCHCH*C*H), 127.0 (C*C*HCH), 124.1 (PhCH=*C*H), 65.4 (CH=CH*C*H_2O), 39.3 (*C*(CH$_3$)$_3$), 27.7 (C(*C*H$_3$)$_3$); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$1724 (s, C=O), 1656 (m, C=C), 1397 (w), 1164 (m) **m/z** (FI) HRMS found 218.1306, $C_{14}H_{18}O_2$ requires 218.1307.

(*E*)-Penta-1,4-dienylbenzene



414

To a stirred solution of cinnamyl bromide (591 mg, 3.0 mmol) and vinylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol) in dry THF (1.80 mL) at 0 °C was added $Li_2[CuCl_4]$ (100 μM in THF, 6.0 mL, 0.60 mmol) was added as a single portion. After 10 minutes, the reaction mixture was diluted with PE (30 mL) and washed successively with sat. aq. $NaHCO_3$ solution (20 mL), brine (20 mL), and water (20 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (PE), which gave diene **414** (355 mg, 2.46 mmol, 82%) as a bright yellow oil; $\mathbf{R}_f$ 0.65 (30:1 PE:EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.40–7.18 (5H, m, Ar*H*), 6.42 (1H, d, J = 16.1 Hz, PhCH), 6.24 (1H, dt, J = 15.8, 6.6 Hz, PhCH=C*H*), 5.92 (1H, ddt, J = 16.7, 10.1, 6.4 Hz, H_2C=C*H*), 5.13 (1H, dq, J = 17.2, 1.7 Hz, *H*HC=CH), 5.08 (1H, dd, J = 10.1, 1.3 Hz, H*H*C=CH), 2.98 (2H, ddd, J = 6.6, 6.6, 1.3 Hz, H_2C=CHCH_2); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 137.6 (CH=CH*C*), 136.5 (H_2C=*C*H), 130.8 (Ph*C*H), 128.5 (CCH*C*H), 128.2 (CCHCH*C*H), 127.0 (PhCH*C*H), 126.0 (C*C*HCH), 115.7 (H_2*C*=CH), 37.0 (H_2CH=CH*C*H_2); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$2978 (m, C-H), 1637 (m, C=C), 1496 (m), 965 (s); **m/z** (FI) HRMS found 144.0938, $C_{11}H_{12}$ requires 144.0939.

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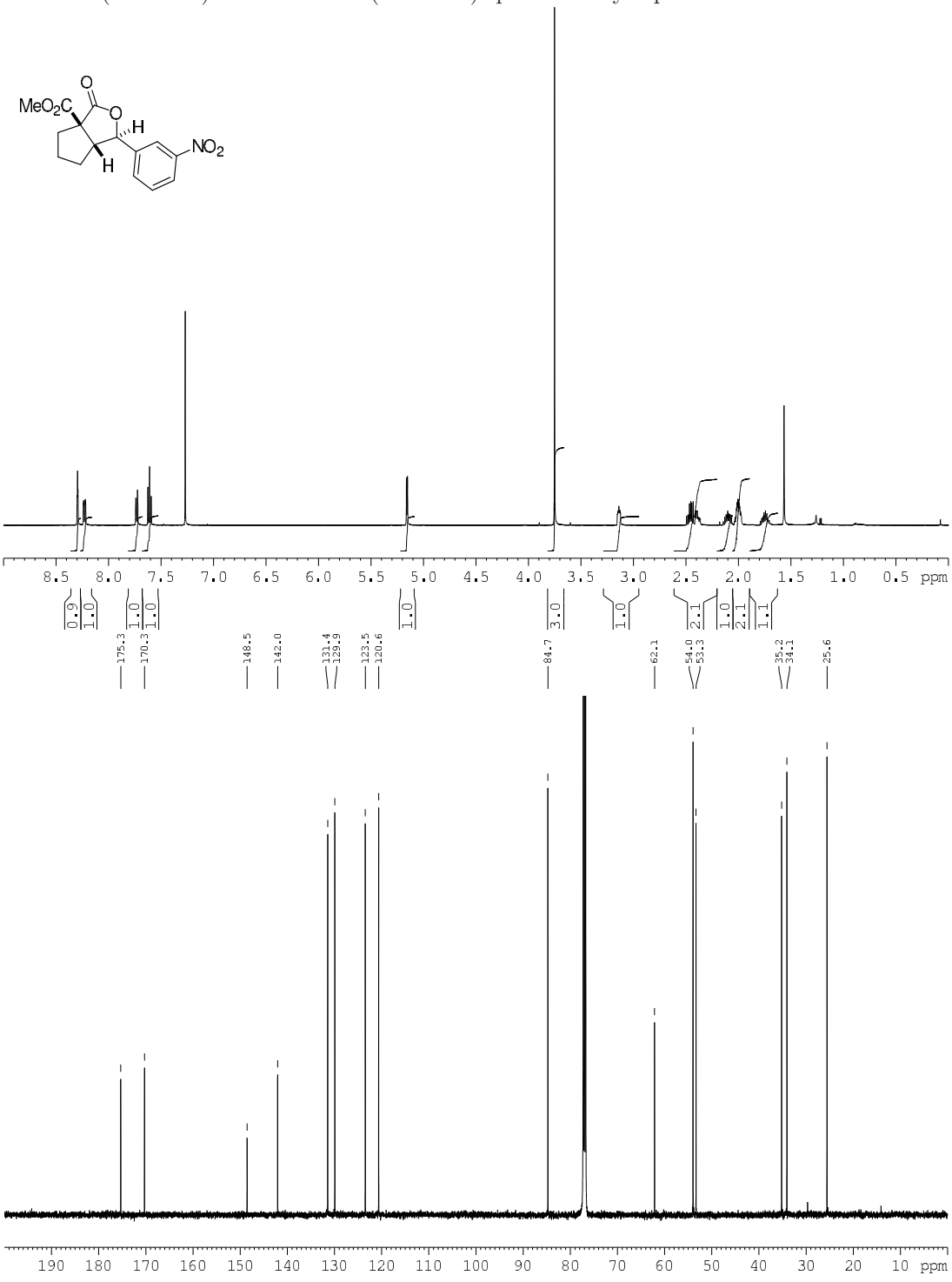
A

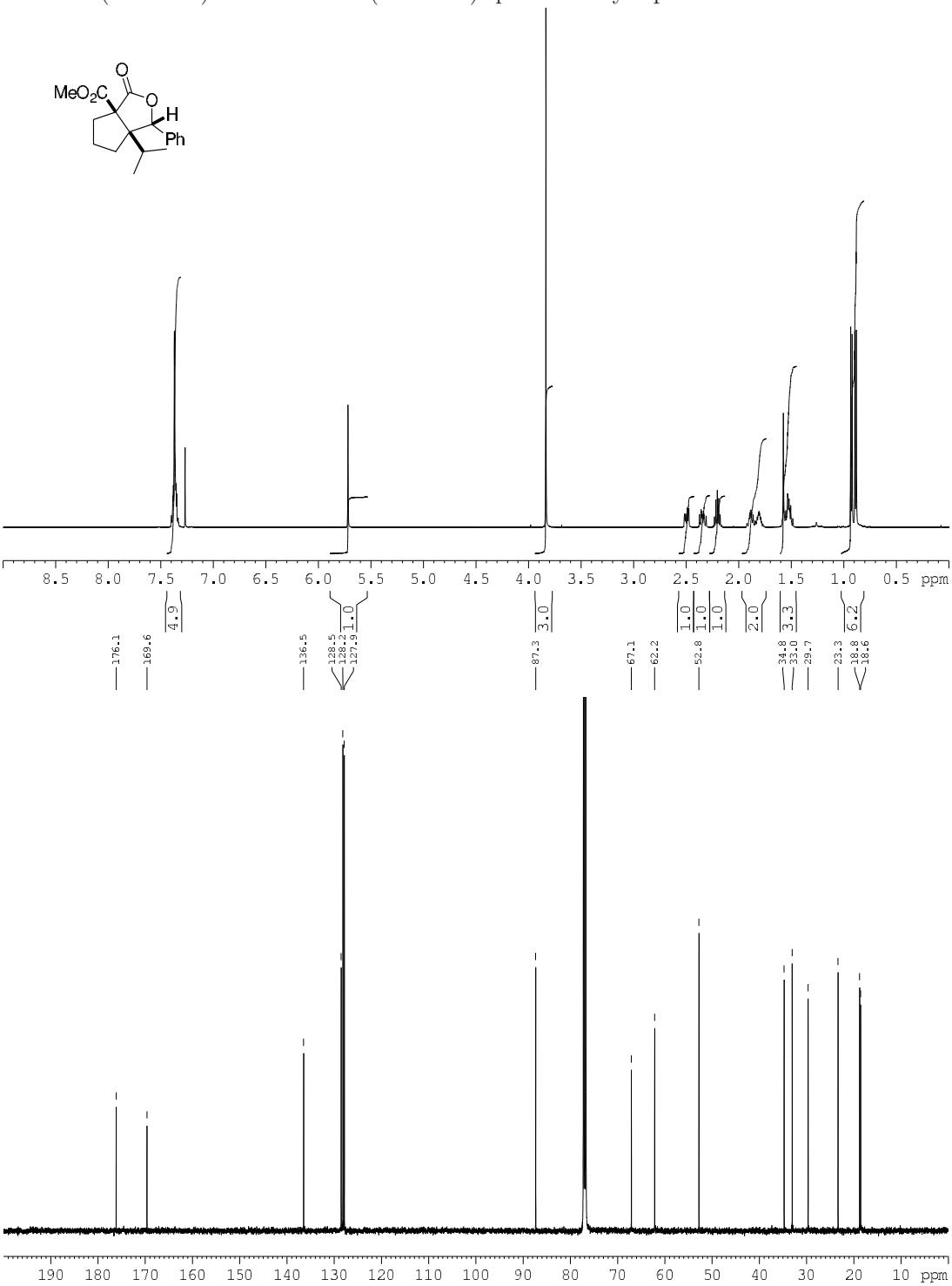
Selected Spectra

^{1}H and ^{13}C NMR spectra are included for cyclopentane-lactones **204** and **252**, and tricyclic *bis*-lactone **303**, alcohol **355**, and benzyl ether **354**. HPLC traces for acid **371** and alcohol **355** are also included.

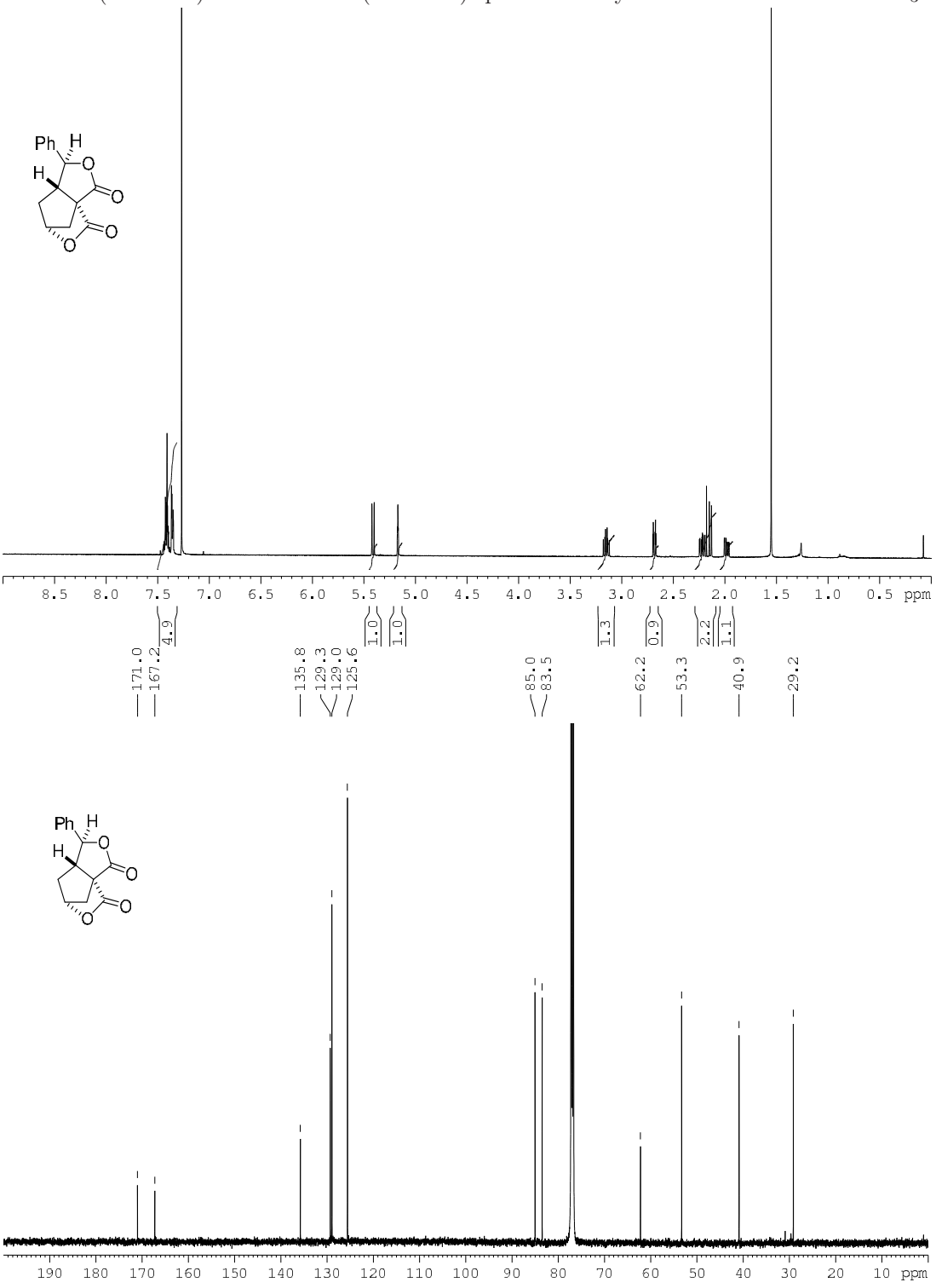
^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra for cyclopentane-lactone **204** in $CDCl_3$.



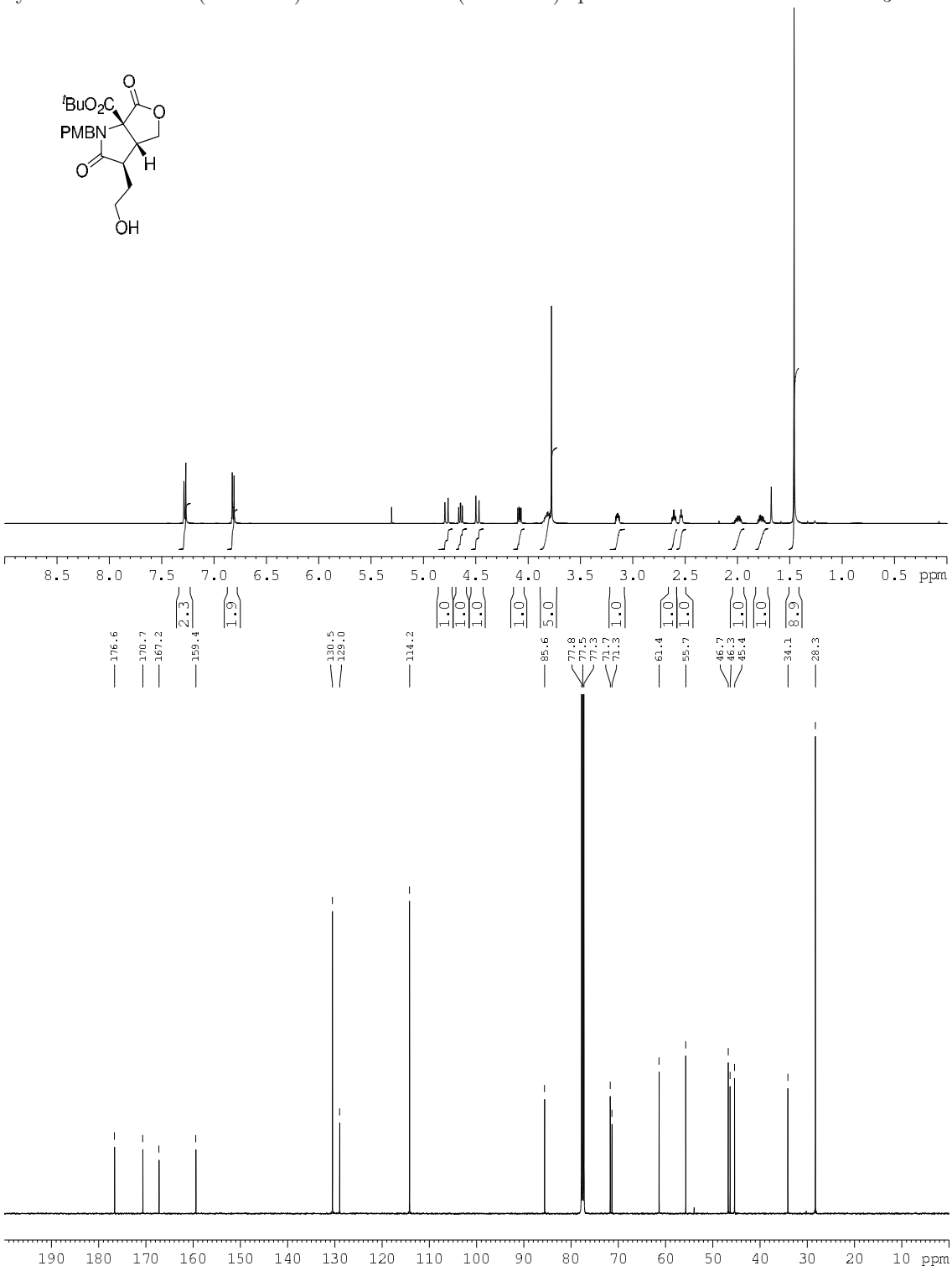
^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra for cyclopentane-lactone **252** in $CDCl_3$.



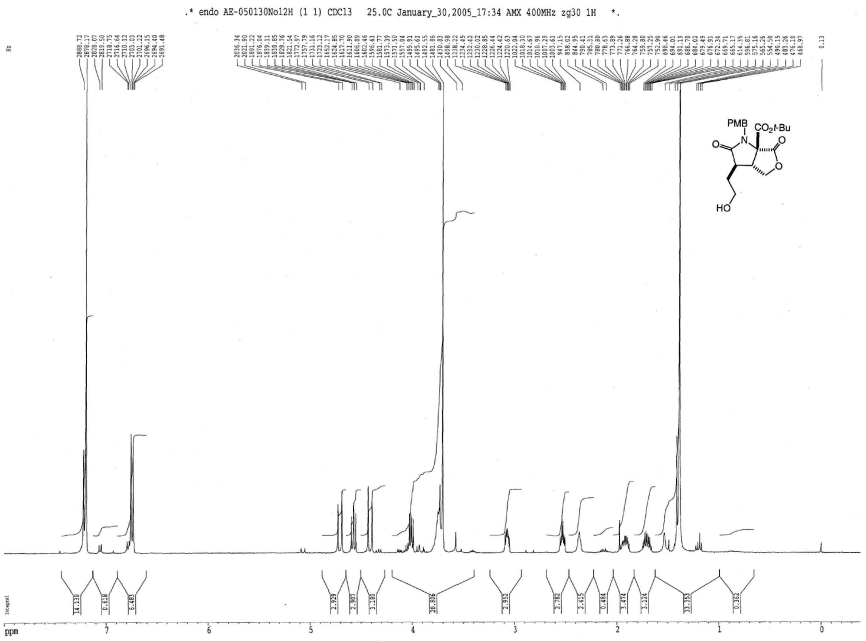
^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) specra for tricyclic *bis*-lactone **303** in $CDCl_3$.

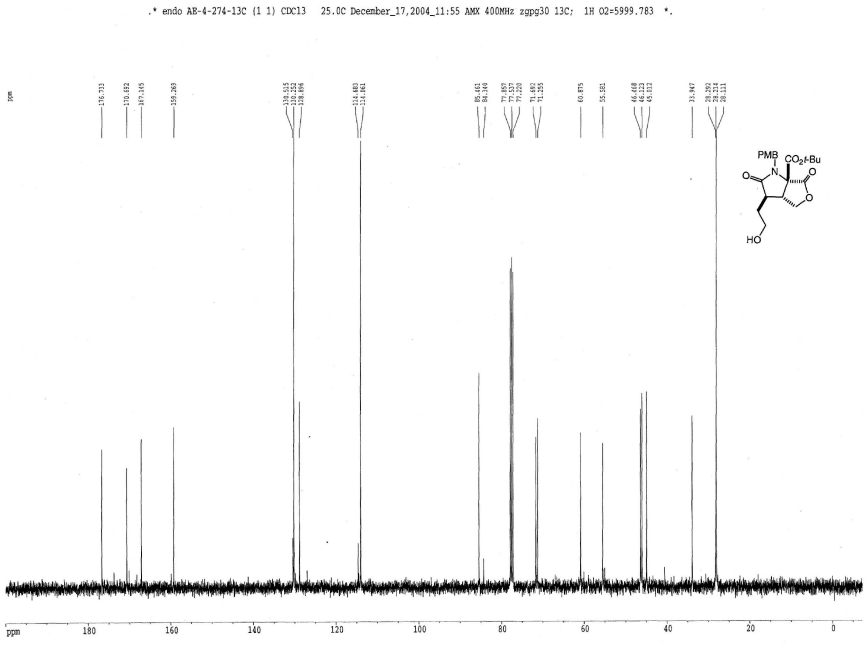


Synthetic ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra for alcohol **355** in $CDCl_3$.



Danishefsky's ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra for alcohol **355** in $CDCl_3$.



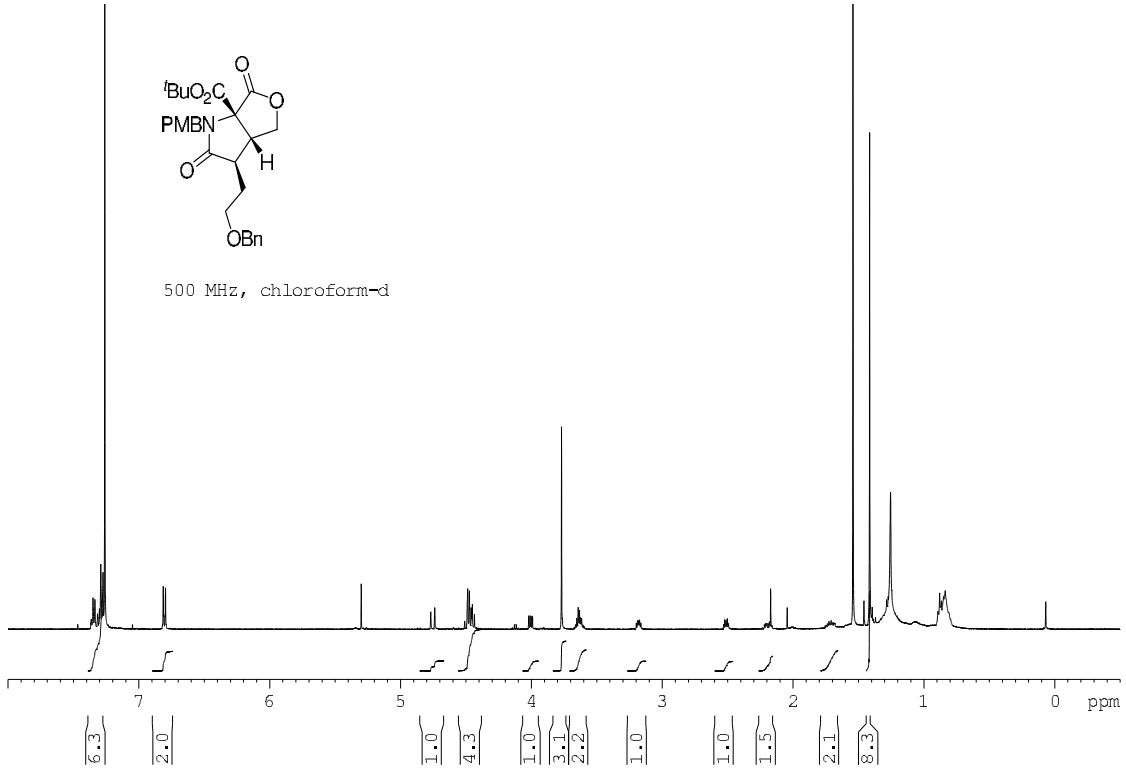


Synthetic ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra for benzyl ether **354** and comparison with literature data.

Entry	Assignment	Synthetic $\boldsymbol{\delta_H}$ / ppm (500 MHz, $CDCl_3$)	Lit. $\boldsymbol{\delta_H}$ [a] / ppm (400 MHz, $CDCl_3$)	$\lvert\boldsymbol{\Delta\delta_H}\rvert$ / ppm
1	ArH_5; $OCH_2C(CHCH)_2$	7.37–7.27, 7H, m	7.37–7.24, 7H, m	0.00
2	$MeOC(CHCH)_2$	6.80, 2H, d	6.80, 2H, d	0.00
3	$NCHH$	4.75, 1H, d	4.76, 1H, d	0.01
4	$PhCH_2$; $NCHH$; 14	4.52–4.42, 4H, m	4.52–4.42, 4H, m	0.00
5	14'	4.00, 1H, dd	4.00, 1H, dd	0.00
6	OCH_3	3.77, 3H, s	3.77, 3H, s	0.00
7	13	3.68–3.59, 2H, m	3.69–3.57, 2H, m	0.01
8	3	3.18, 1H, ddd	3.18, 1H, m	0.00
9	2	2.51, 1H, ddd	2.51, 1H, m	0.00
10	12	2.24–2.16, 1H, m	2.19, 1H, m	N/A
11	12'	1.76–1.67, 1H, m	1.71, 1H, m	N/A
12	$C(CH_3)_3$	1.42, 9H, s	1.40, 9H, s	0.02

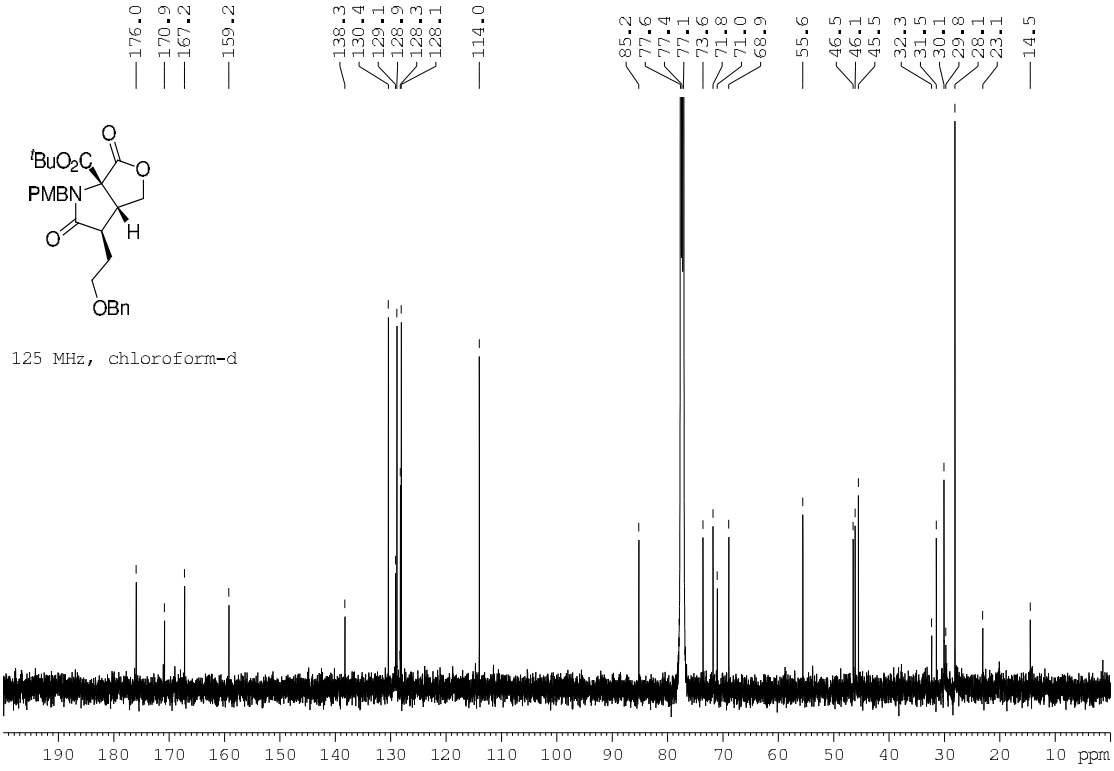
Table A.1: Comparison of synthetic benzyl ether (+)-**354** and literature ^{1}H NMR data.

[a] All literature data have been corrected by +0.07 ppm as the original spectrum was referenced with the $CHCl_3$ solvent residual at 7.20 ppm rather than 7.27 ppm.

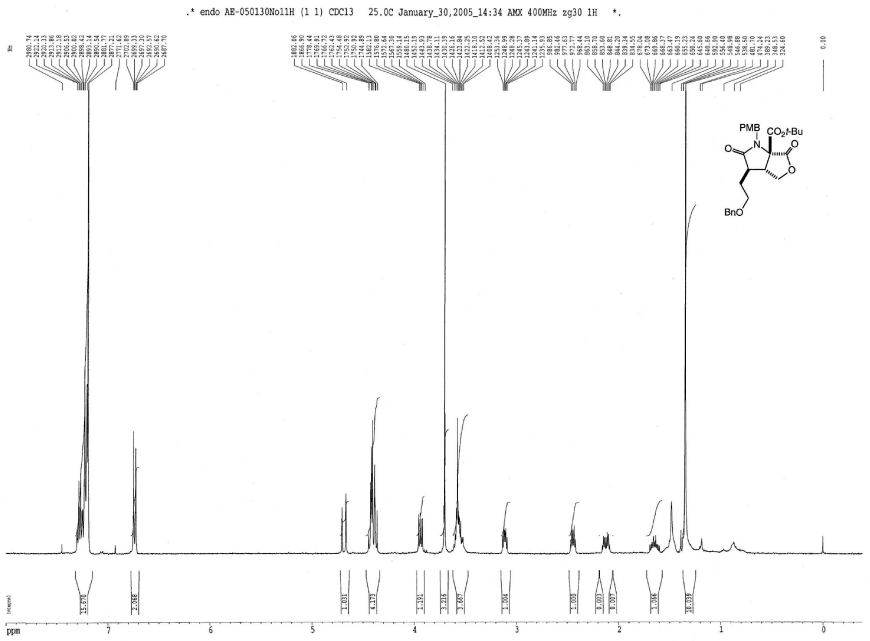


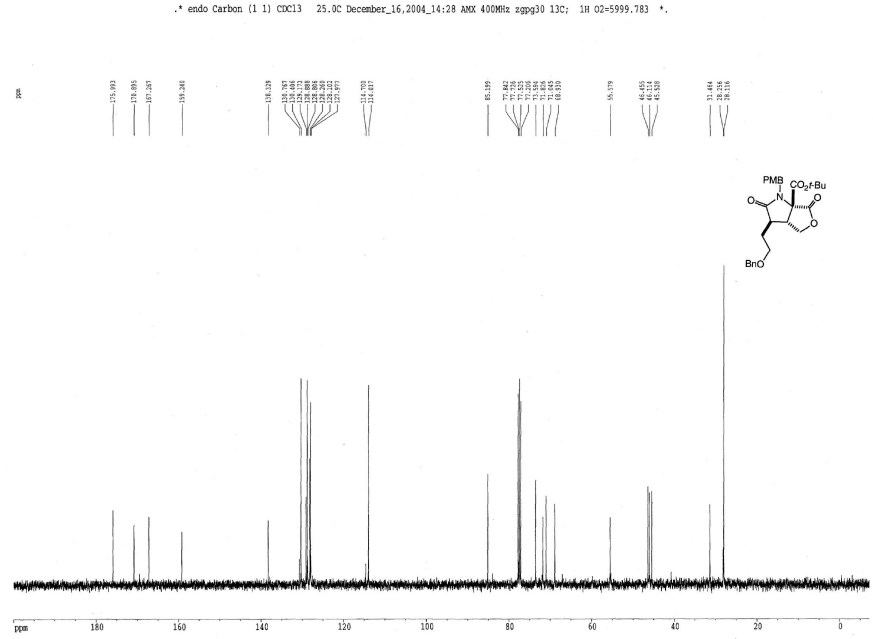
Entry	Assignment	Synthetic $\boldsymbol{\delta_C}$ / ppm (125 MHz, $CDCl_3$)	Lit. $\boldsymbol{\delta_H}$ / ppm (100 MHz, $CDCl_3$)	$\lvert\boldsymbol{\Delta\delta_C}\rvert$ / ppm
1	1	176.0	176.0	0.0
2	15	170.9	170.9	0.0
3	5	167.2	167.3	-0.1
4	$MeOC(CHCH)_2$	159.2	159.2	0.0
5	*Ar*	138.3	138.3	0.0
6	*Ar*	130.4	130.4	0.0
7	*Ar*	129.1	129.2	0.1
8	*Ar*	128.9	128.9	0.0
9	*Ar*	128.3	128.3	0.0
10	*Ar*	128.1	128.1	0.0
11	*Ar*	114.0	114.0	0.0
12	$C(CH_3)_3$	85.2	85.2	0.0
13	OCH_2Ph	73.6	73.6	0.0
14	4	71.8	71.8	0.0
15	14	71.0	71.1	0.1
16	13	69.0	68.9	0.1
17	OCH_3	55.6	55.6	0.0
18	2	46.5	46.5	0.0
19	CH_2Ar	46.1	46.1	0.0
20	3	45.5	45.5	0.0
21	12	31.5	31.5	0.0
22	$C(CH_3)_3$	28.1	28.1	0.0

Table A.2: Comparison of synthetic benzyl ether (+)-**354** and literature ^{13}C NMR data.

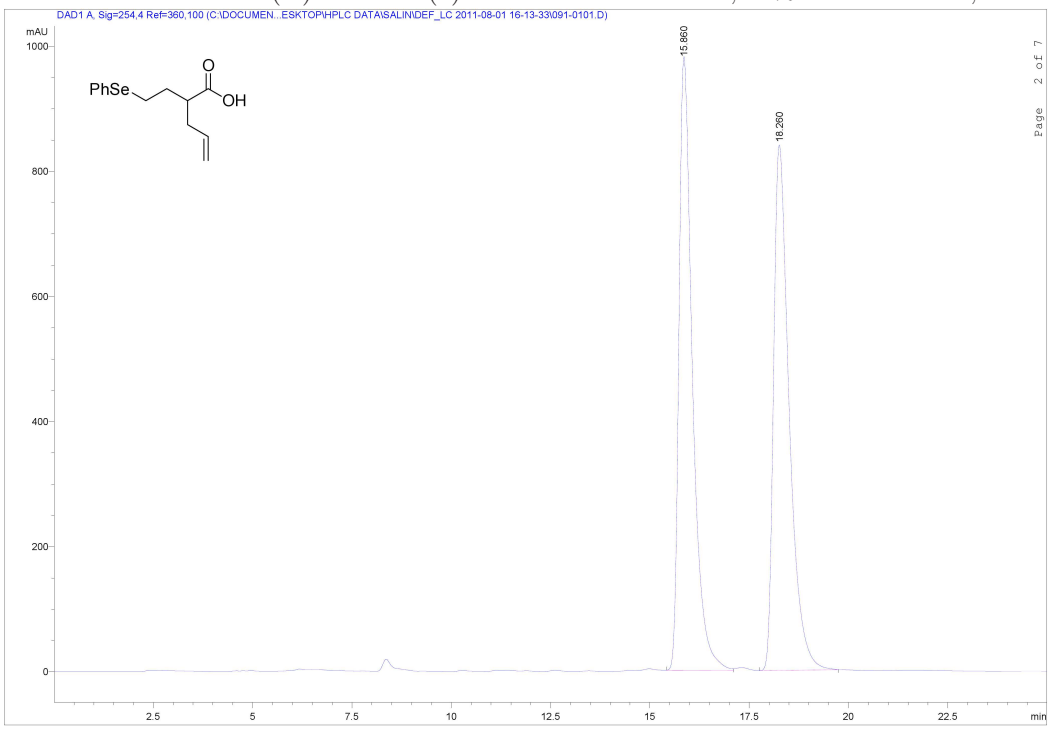


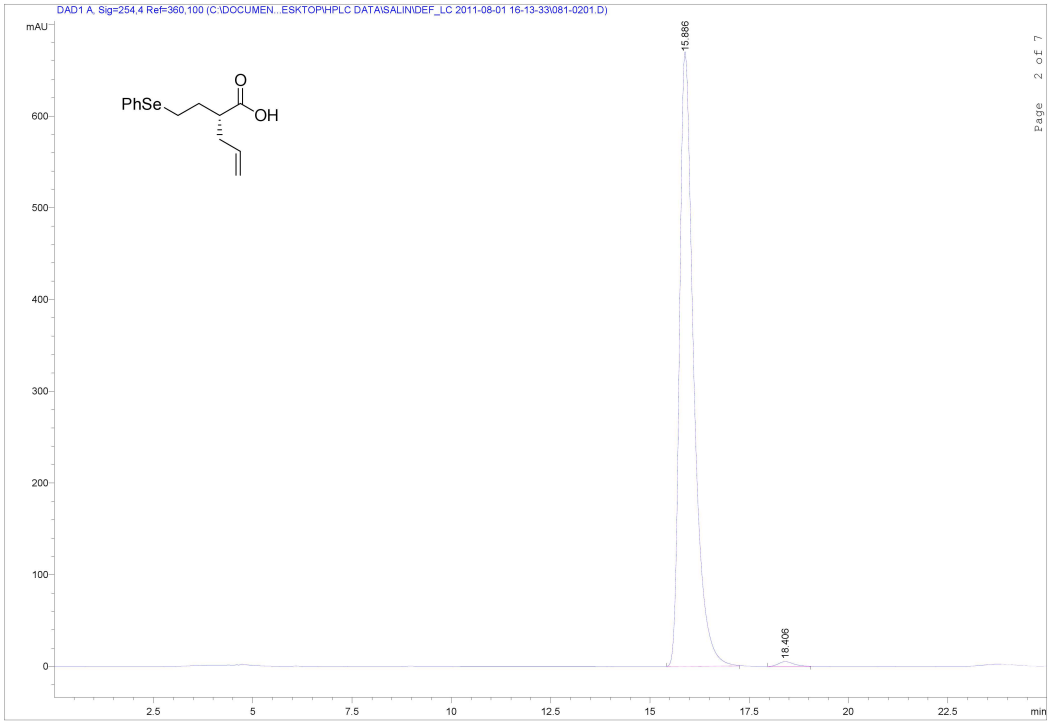
Danishefsky's ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra for benzyl ether **354**.



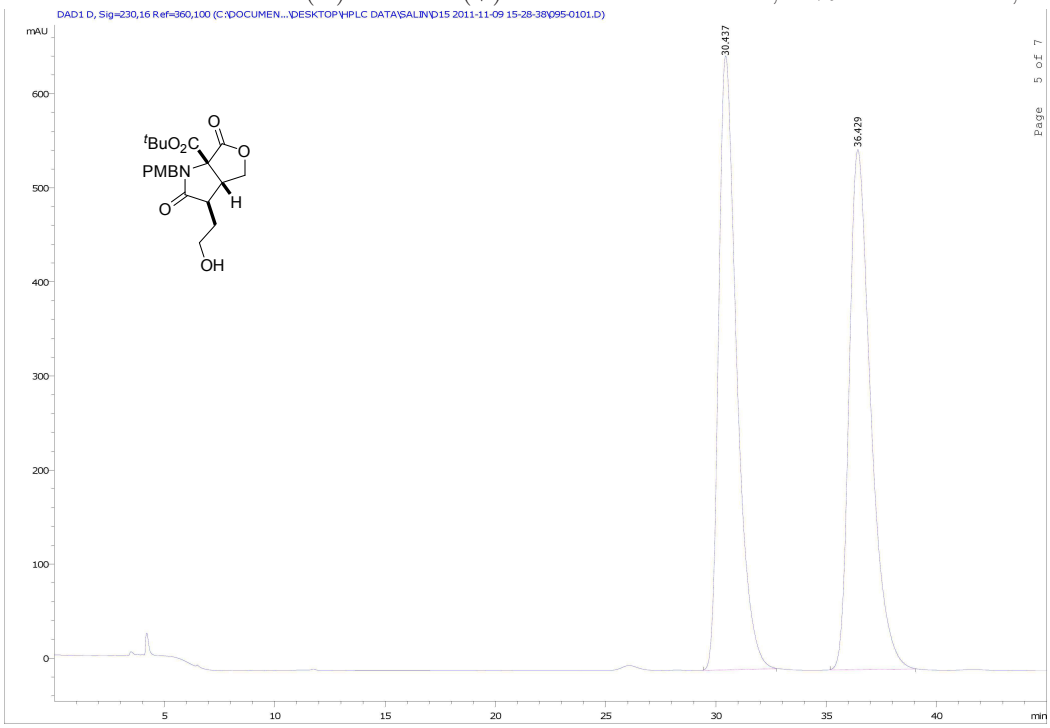


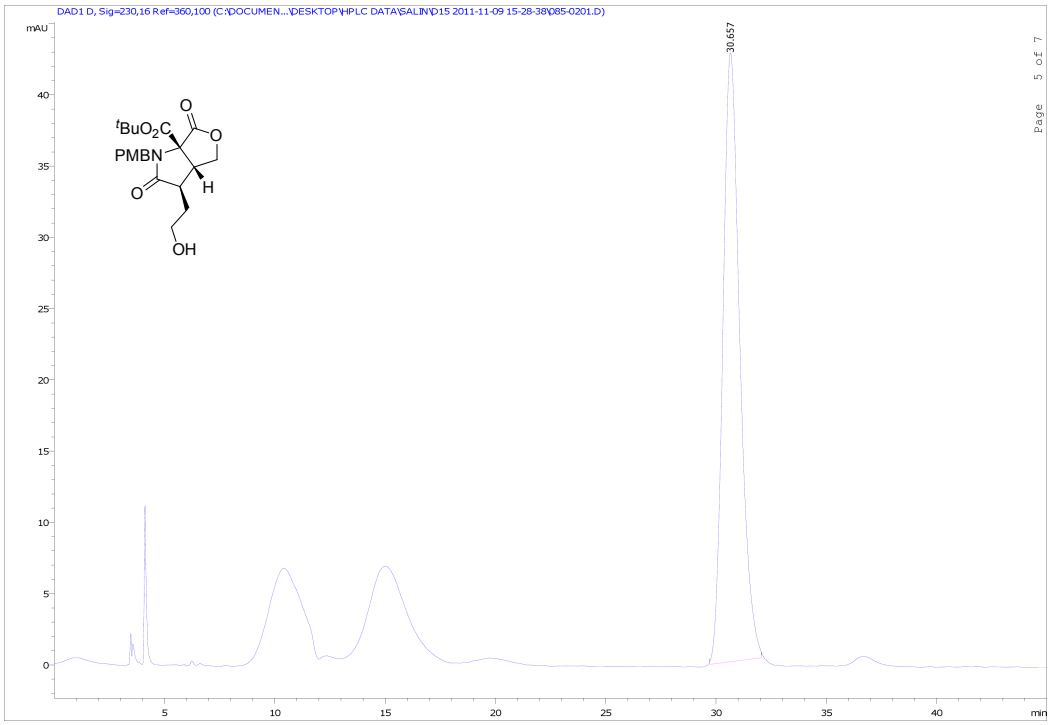
HPLC traces for acids (±)-**371** and (–)-**371**. ChiralPak AD-H, 10% IPA in hexane, 1.00 mL/min.





HPLC traces for alcohols (±)-**355** and (+)-**355**. ChiralPak AD-H, 10% IPA in hexane, 1.00 mL/min.





B

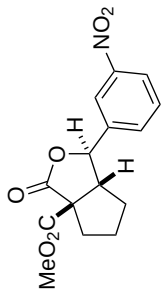
Crystallographic Data

Crystallographic data are provided for cyclopentane-lactones **204** and **252**, tricyclic *bis*-lactones **303**, **325**, **326**, and cyclohexene **378**.

(1*R**,3a*S**,6a*R*)-Methyl 1-(3-nitrophenyl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate **204**

Table 1. Crystal data and structure refinement for al558.

Identification code	al558
Empirical formula	C15 H15 N1 O6
Formula weight	305.29
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	a = 6.6885(2) Å α= 76.9115(15)°. b = 7.8890(3) Å β= 81.3249(15)°. c = 14.2710(5) Å γ = 83.2683(19)°.
Volume	722.36(4) Å^3
Z	2
Density (calculated)	1.403 Mg/m^3
Absorption coefficient	0.110 mm^{-1}
F(000)	320
Crystal size	0.600 x 0.400 x 0.200 mm^3
Theta range for data collection	5.136 to 27.604°.
Index ranges	-8<=h<=7, -9<=k<=10, -17<=l<=18
Reflections collected	10430
Independent reflections	3284 [R(int) = 0.029]
Completeness to theta = 25.947°	98.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.98 and 0.90
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2166 / 0 / 199
Goodness-of-fit on F^2	0.9500
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.1053
R indices (all data)	R1 = 0.0510, wR2 = 0.1157
Largest diff. peak and hole	0.21 and -0.23 e.Å^{-3}



204

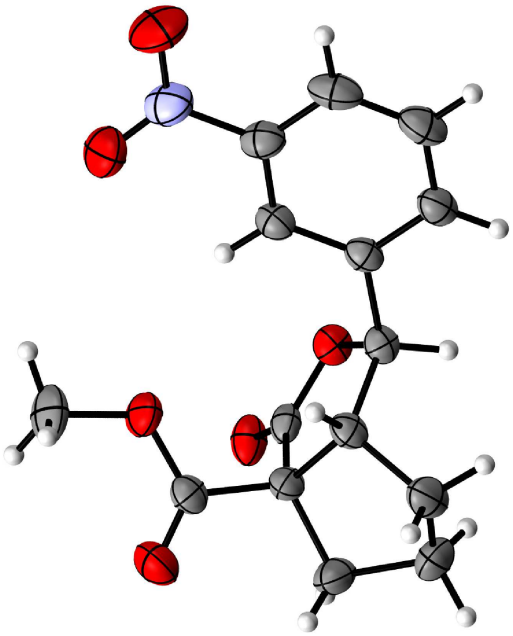


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for al558. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(4)	9782(3)	4054(3)	3995(2)	42
C(5)	7575(3)	3760(3)	4385(2)	47
C(6)	6712(3)	3489(3)	3507(2)	44
C(7)	7980(3)	-656(2)	2705(1)	30
C(8)	9515(3)	-907(2)	1968(1)	33
C(9)	9141(3)	-1819(2)	1300(1)	38
C(10)	7287(4)	-2461(3)	1333(2)	46
C(11)	5771(3)	-2186(3)	2061(2)	44
N(12)	10781(3)	-2104(2)	526(1)	50
O(13)	10493(3)	-3012(3)	-25(1)	76
O(14)	12347(3)	-1403(2)	460(1)	60
O(15)	12819(2)	759(2)	4217(1)	39
C(16)	6114(3)	-1301(2)	2750(2)	36
C(17)	11885(3)	3492(2)	2435(1)	33
O(18)	12241(2)	4985(2)	2159(1)	52
O(19)	12735(2)	2211(2)	1994(1)	43
C(20)	14162(4)	2711(3)	1129(2)	54
C(61)	8391(3)	2363(2)	3016(1)	31
C(1)	8275(3)	377(2)	3434(1)	29
O(2)	10180(2)	-273(2)	3824(1)	32
C(3)	11299(3)	1033(2)	3830(1)	30
C(31)	10399(3)	2781(2)	3308(1)	30

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for al558. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(4)	36(1)	45(1)	52(1)	-27(1)	-4(1)	-2(1)
C(5)	38(1)	46(1)	58(1)	-23(1)	6(1)	2(1)
C(6)	28(1)	34(1)	67(1)	-12(1)	-7(1)	1(1)
C(7)	31(1)	24(1)	33(1)	-3(1)	-7(1)	-3(1)
C(8)	36(1)	32(1)	32(1)	-4(1)	-5(1)	-8(1)
C(9)	50(1)	34(1)	31(1)	-7(1)	-7(1)	-4(1)
C(10)	63(1)	36(1)	45(1)	-10(1)	-21(1)	-10(1)
C(11)	41(1)	39(1)	58(1)	-10(1)	-17(1)	-11(1)
N(12)	69(1)	48(1)	34(1)	-13(1)	-2(1)	-8(1)
O(13)	100(2)	86(1)	57(1)	-46(1)	2(1)	-18(1)
O(14)	67(1)	70(1)	44(1)	-18(1)	13(1)	-19(1)
O(15)	27(1)	59(1)	31(1)	-8(1)	-5(1)	-3(1)
C(16)	31(1)	29(1)	49(1)	-6(1)	-8(1)	-3(1)
C(17)	27(1)	36(1)	36(1)	-7(1)	-8(1)	-5(1)
O(18)	50(1)	40(1)	63(1)	-6(1)	0(1)	-16(1)
O(19)	48(1)	44(1)	32(1)	-8(1)	10(1)	-6(1)
C(20)	51(1)	76(2)	30(1)	-5(1)	10(1)	-11(1)
C(61)	28(1)	31(1)	34(1)	-6(1)	-8(1)	-5(1)
C(1)	27(1)	31(1)	30(1)	-5(1)	-6(1)	-2(1)
O(2)	30(1)	34(1)	33(1)	-5(1)	-9(1)	0(1)
C(3)	25(1)	42(1)	23(1)	-11(1)	2(1)	-4(1)
C(31)	26(1)	32(1)	34(1)	-13(1)	-4(1)	-5(1)

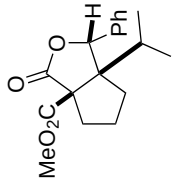
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for al558.

	x	y	z	U(eq)
H(41)	10696	3813	4499	50
H(42)	9897	5231	3618	50
H(52)	6866	4780	4612	57
H(51)	7479	2725	4911	57
H(62)	6480	4598	3065	52
H(61)	5441	2926	3679	53
H(81)	10772	-464	1907	40
H(101)	7094	-3092	868	56
H(111)	4514	-2617	2096	53
H(161)	5060	-1138	3257	42
H(201)	14544	1691	848	82
H(203)	15317	3135	1314	80
H(202)	13524	3637	670	80
H(611)	8411	2614	2314	36
H(11)	7173	188	3987	33

((1*R**,3a*S**,6a*S**)-Methyl 6a-isopropyl-3-oxo-1-phenylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate **252**

Table 1. Crystal data and structure refinement for al567.

Identification code	al567
Empirical formula	C18 H22 O4
Formula weight	302.37
Temperature	150 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 10.9324(3) Å α= 90°. b = 12.0646(3) Å β= 90°. c = 12.1689(4) Å γ = 90°.
Volume	1605.02(8) Å^3
Z	4
Density (calculated)	1.251 Mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	648
Crystal size	0.300 x 0.100 x 0.100 mm^3
Theta range for data collection	5.112 to 27.458°.
Index ranges	-14<=h<=14, -15<=k<=15, -15<=l<=15
Reflections collected	10957
Independent reflections	2077 [R(int) = 0.026]
Completeness to theta = 27.458°	99.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.99 and 0.94
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1649 / 0 / 199
Goodness-of-fit on F^2	0.9686
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0849
R indices (all data)	R1 = 0.0402, wR2 = 0.0896
Largest diff. peak and hole	0.19 and -0.20 e.Å^{-3}



204

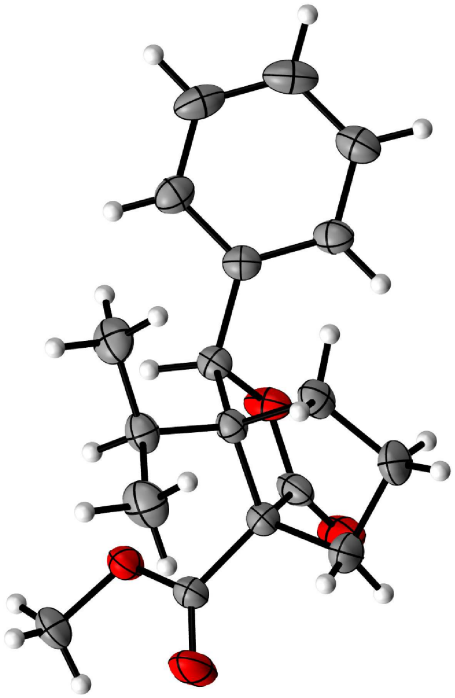


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for al567. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	10532(1)	5540(1)	8029(1)	31
C(2)	11659(2)	5306(2)	8600(2)	37
C(3)	10627(2)	6200(2)	7148(2)	29
O(4)	11565(2)	6606(2)	6845(2)	49
C(5)	9387(2)	6398(2)	6627(2)	27
C(6)	8679(2)	5364(2)	6154(2)	24
C(7)	7812(2)	5051(2)	7142(2)	25
O(8)	7707(1)	6052(1)	7813(1)	34
C(9)	8556(2)	6807(2)	7551(2)	32
O(10)	8598(2)	7692(1)	8001(2)	48
C(11)	6513(2)	4680(2)	6937(2)	27
C(12)	6182(2)	3577(2)	7111(2)	33
C(13)	4981(2)	3239(2)	6946(2)	40
C(14)	4095(2)	3992(2)	6642(2)	42
C(15)	4409(2)	5102(2)	6498(2)	37
C(16)	5615(2)	5435(2)	6637(2)	30
C(17)	8019(2)	5851(2)	5130(2)	32
C(18)	8153(2)	7108(2)	5184(2)	43
C(19)	9408(2)	7266(2)	5711(2)	42
C(20)	9499(2)	4361(2)	5869(2)	30
C(21)	8773(2)	3375(2)	5442(2)	39
C(22)	10523(2)	4621(2)	5037(2)	44

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for al567. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	25(1)	37(1)	31(1)	5(1)	-4(1)	-2(1)
C(2)	31(1)	43(1)	38(1)	4(1)	-11(1)	4(1)
C(3)	21(1)	31(1)	34(1)	3(1)	-1(1)	-1(1)
O(4)	24(1)	65(1)	56(1)	20(1)	1(1)	-10(1)
C(5)	23(1)	26(1)	33(1)	3(1)	-2(1)	0(1)
C(6)	22(1)	27(1)	24(1)	2(1)	1(1)	1(1)
C(7)	25(1)	26(1)	23(1)	-5(1)	0(1)	1(1)
O(8)	26(1)	41(1)	34(1)	-16(1)	5(1)	-5(1)
C(9)	20(1)	34(1)	42(1)	-8(1)	-4(1)	3(1)
O(10)	32(1)	38(1)	73(1)	-25(1)	-8(1)	0(1)
C(11)	27(1)	30(1)	24(1)	-4(1)	2(1)	-2(1)
C(12)	38(1)	32(1)	28(1)	2(1)	3(1)	-4(1)
C(13)	48(1)	39(1)	34(1)	0(1)	4(1)	-19(1)
C(14)	34(1)	59(2)	34(1)	-6(1)	2(1)	-17(1)
C(15)	27(1)	46(1)	39(1)	-6(1)	-1(1)	-1(1)
C(16)	26(1)	32(1)	32(1)	-6(1)	4(1)	-2(1)
C(17)	30(1)	39(1)	27(1)	5(1)	-2(1)	1(1)
C(18)	41(1)	41(1)	48(1)	15(1)	-12(1)	3(1)
C(19)	38(1)	36(1)	51(1)	16(1)	-8(1)	-3(1)
C(20)	29(1)	34(1)	26(1)	0(1)	2(1)	7(1)
C(21)	44(1)	36(1)	37(1)	-10(1)	-1(1)	7(1)
C(22)	36(1)	55(1)	41(1)	-1(1)	12(1)	8(1)

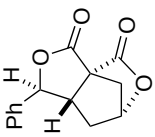
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for al567.

	x	y	z	U(eq)
H(21)	11469	4929	9278	57
H(23)	12058	5985	8751	59
H(22)	12188	4831	8164	57
H(71)	8255	4498	7577	29
H(121)	6764	3073	7350	39
H(131)	4751	2471	7029	49
H(141)	3284	3762	6515	49
H(151)	3803	5648	6306	44
H(161)	5837	6204	6525	35
H(171)	8464	5574	4476	38
H(172)	7186	5588	5093	39
H(181)	7538	7438	5660	52
H(182)	8107	7459	4465	52
H(191)	9513	8001	6026	49
H(192)	10057	7097	5192	49
H(201)	9907	4115	6557	35
H(211)	9326	2747	5307	59
H(213)	8171	3134	5965	59
H(212)	8343	3534	4779	59
H(222)	11083	3990	4982	67
H(221)	11014	5286	5266	67
H(223)	10153	4748	4313	67

((1*R**,4*R**,5*R**,7*S**)-4-Phenyl-3,8-dioxatricyclo[5.2.1.0^{1,5}]decane-2,9-dione, **303**

Table 1. Crystal data and structure refinement for al769a.

Identification code	al769a
Empirical formula	C14 H12 O4
Formula weight	244.24
Temperature	150 K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	P n a 21
Unit cell dimensions	a = 16.7310(11) Å α= 90°. b = 6.0624(4) Å β= 90°. c = 11.2928(7) Å γ = 90°.
Volume	1145.42(12) Å^3
Z	4
Density (calculated)	1.416 Mg/m^3
Absorption coefficient	0.867 mm^{-1}
F(000)	512
Crystal size	0.44 x 0.22 x 0.02 mm^3
Theta range for data collection	5.288 to 75.779°.
Index ranges	-15<=h<=21, -7<=k<=5, -14<=l<=12
Reflections collected	3612
Independent reflections	1895 [R(int) = 0.0473]
Completeness to theta = 73.505°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.63629
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1733 / 1 / 163
Goodness-of-fit on F^2	0.9301
Final R indices [I>2sigma(I)]	R1 = 0.0457, wR2 = 0.1209
R indices (all data)	R1 = 0.0476, wR2 = 0.1244
Largest diff. peak and hole	0.21 and -0.18 e.Å^{-3}



303

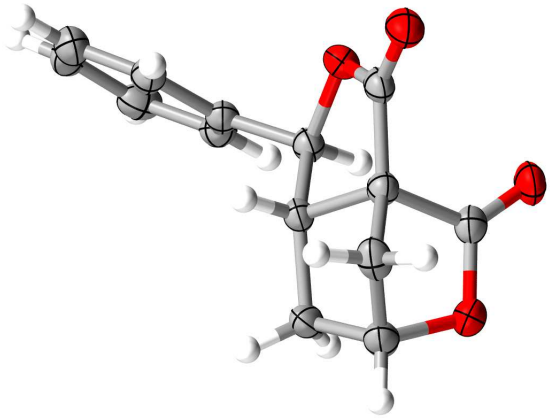


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for al769a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6341(1)	1174(3)	6453(2)	30
C(2)	6609(1)	3230(4)	5844(2)	26
C(3)	5986(1)	3794(3)	4933(2)	26
C(4)	5733(2)	2241(4)	4098(2)	32
C(5)	5129(2)	2768(5)	3305(3)	38
C(6)	4776(1)	4809(5)	3333(3)	38
C(7)	5034(2)	6384(4)	4137(3)	36
C(8)	5633(1)	5869(4)	4956(3)	29
C(9)	7433(1)	2548(4)	5399(2)	25
C(10)	7710(1)	1112(4)	6450(2)	26
C(11)	6966(1)	-142(4)	6740(2)	27
O(12)	6873(1)	-1936(3)	7173(2)	39
C(13)	7949(2)	2647(4)	7478(2)	29
O(14)	7613(1)	2988(3)	8392(2)	37
O(15)	8638(1)	3612(3)	7150(2)	34
C(16)	8800(1)	2842(4)	5937(3)	34
C(17)	8542(1)	401(4)	6022(3)	33
C(18)	8168(1)	4013(4)	5163(2)	31

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for al769a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	30(1)	34(1)	26(1)	3(1)	4(1)	-4(1)
C(2)	29(1)	27(1)	21(1)	0(1)	1(1)	-1(1)
C(3)	21(1)	34(1)	24(1)	0(1)	1(1)	-1(1)
C(4)	30(1)	38(1)	27(1)	-3(1)	-1(1)	-1(1)
C(5)	37(1)	50(2)	26(1)	-1(1)	0(1)	-6(1)
C(6)	26(1)	59(2)	30(1)	12(1)	-6(1)	-6(1)
C(7)	28(1)	37(1)	44(2)	10(1)	2(1)	3(1)
C(8)	26(1)	31(1)	31(1)	2(1)	1(1)	-2(1)
C(9)	27(1)	29(1)	20(1)	1(1)	0(1)	0(1)
C(10)	29(1)	26(1)	22(1)	-2(1)	-1(1)	-1(1)
C(11)	36(1)	27(1)	19(1)	-1(1)	1(1)	-4(1)
O(12)	53(1)	30(1)	32(1)	4(1)	-3(1)	-11(1)
C(13)	34(1)	29(1)	24(1)	0(1)	-3(1)	1(1)
O(14)	49(1)	41(1)	21(1)	-3(1)	-1(1)	-4(1)
O(15)	32(1)	43(1)	28(1)	0(1)	-5(1)	-7(1)
C(16)	26(1)	48(1)	27(1)	2(1)	0(1)	-1(1)
C(17)	31(1)	41(1)	27(1)	0(1)	0(1)	9(1)
C(18)	26(1)	38(1)	27(1)	7(1)	0(1)	-3(1)

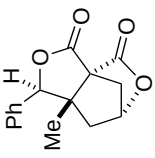
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for al769a.

	x	y	z	U(eq)
H(21)	6653	4370	6460	31
H(41)	5966	826	4099	40
H(51)	4959	1706	2739	46
H(61)	4358	5156	2812	47
H(71)	4797	7791	4147	46
H(81)	5794	6905	5520	39
H(91)	7356	1544	4726	32
H(161)	9351	3097	5690	40
H(171)	8853	-455	6586	43
H(172)	8521	-377	5280	43
H(182)	8104	5555	5416	38
H(181)	8311	3927	4308	39

(1R*,4S*,5R*,7S*)-5-Methyl-4-phenyl-3,8-dioxatricyclo[5.2.1.0^{1,5}]decane-2,9-dione, **325**

Table 1. Crystal data and structure refinement for 6437.

Identification code	6437		
Empirical formula	C15 H14 O4		
Formula weight	258.27		
Temperature	150 K		
Wavelength	1.54180 Å		
Crystal system	Monoclinic		
Space group	P 21/c		
Unit cell dimensions	a = 7.9425(1) Å	α= 90°.	
	b = 14.2285(2) Å	β= 107.4583(15)°.	
	c = 11.6215(2) Å	γ = 90°.	
Volume	1252.85(3) Å^3		
Z	4		
Density (calculated)	1.369 Mg/m^3		
Absorption coefficient	0.822 mm^{-1}		
F(000)	544		
Crystal size	0.200 x 0.150 x 0.100 mm^3		
Theta range for data collection	5.057 to 74.349°.		
Index ranges	-9<=h<=9, -17<=k<=17, -12<=l<=14		
Reflections collected	21121		
Independent reflections	2517 [R(int) = 0.015]		
Completeness to theta = 69.144°	99.5 %		
Absorption correction	Semi-empirical from equivalents		
Max. and min. transmission	0.92 and 0.86		
Refinement method	Full-matrix least-squares on F^2		
Data / restraints / parameters	2507 / 0 / 172		
Goodness-of-fit on F^2	1.0056		
Final R indices [I>2sigma(I)]	R1 = 0.0320, wR2 = 0.0789		
R indices (all data)	R1 = 0.0323, wR2 = 0.0792		
Largest diff. peak and hole	0.30 and -0.19 e.Å^{-3}		



325

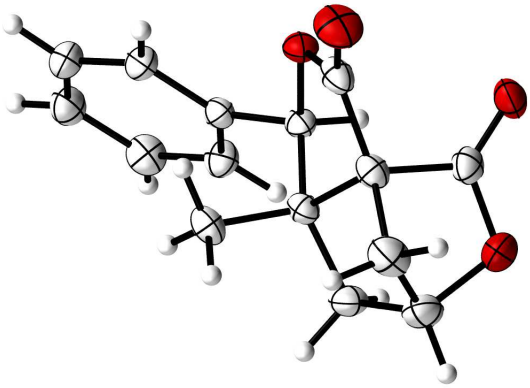


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6437. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2497(1)	5052(1)	5619(1)	36
C(2)	4010(1)	5456(1)	6286(1)	27
C(3)	4492(1)	5017(1)	7552(1)	25
C(4)	5155(1)	3999(1)	7469(1)	23
C(5)	3560(1)	3566(1)	6503(1)	30
C(6)	2124(1)	4319(1)	6411(1)	36
O(7)	4765(1)	6056(1)	5909(1)	33
C(8)	5503(2)	3472(1)	8669(1)	30
C(9)	2619(2)	4848(1)	7624(1)	36
C(10)	6131(2)	5480(1)	8329(1)	29
O(11)	7517(1)	5054(1)	8075(1)	27
C(12)	6918(1)	4249(1)	7246(1)	22
O(13)	6343(1)	6111(1)	9040(1)	44
C(14)	8319(1)	3503(1)	7514(1)	23
C(15)	9623(1)	3439(1)	8619(1)	28
C(16)	10834(1)	2706(1)	8841(1)	32
C(17)	10769(1)	2038(1)	7967(1)	33
C(18)	9484(2)	2106(1)	6855(1)	33
C(19)	8264(1)	2834(1)	6628(1)	28

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for 6437. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	27(1)	38(1)	37(1)	5(1)	2(1)	1(1)
C(2)	28(1)	24(1)	30(1)	1(1)	8(1)	5(1)
C(3)	31(1)	21(1)	26(1)	-1(1)	12(1)	1(1)
C(4)	26(1)	19(1)	23(1)	-1(1)	8(1)	-2(1)
C(5)	26(1)	26(1)	35(1)	-4(1)	7(1)	-7(1)
C(6)	24(1)	36(1)	47(1)	2(1)	10(1)	-4(1)
O(7)	38(1)	28(1)	35(1)	9(1)	11(1)	2(1)
C(8)	37(1)	27(1)	30(1)	5(1)	15(1)	0(1)
C(9)	35(1)	32(1)	48(1)	2(1)	22(1)	4(1)
C(10)	41(1)	22(1)	24(1)	-1(1)	10(1)	-2(1)
O(11)	30(1)	22(1)	26(1)	-4(1)	4(1)	-5(1)
C(12)	25(1)	21(1)	18(1)	-1(1)	4(1)	-4(1)
O(13)	62(1)	32(1)	38(1)	-16(1)	14(1)	-6(1)
C(14)	23(1)	24(1)	22(1)	2(1)	7(1)	-3(1)
C(15)	28(1)	29(1)	24(1)	1(1)	4(1)	-2(1)
C(16)	26(1)	34(1)	32(1)	6(1)	2(1)	0(1)
C(17)	28(1)	31(1)	42(1)	6(1)	12(1)	5(1)
C(18)	37(1)	31(1)	33(1)	-3(1)	14(1)	2(1)
C(19)	30(1)	31(1)	23(1)	-1(1)	7(1)	0(1)

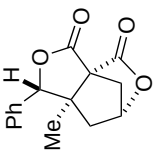
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for 6437.

	x	y	z	U(eq)
H(51)	3219	2968	6785	36
H(52)	3760	3495	5707	35
H(61)	894	4118	6070	42
H(81)	5976	2858	8567	45
H(83)	6369	3818	9341	45
H(82)	4377	3388	8871	44
H(91)	1938	5422	7565	42
H(92)	2606	4455	8311	42
H(121)	6684	4485	6412	23
H(151)	9666	3917	9224	32
H(161)	11744	2674	9612	39
H(171)	11621	1531	8123	39
H(181)	9479	1655	6241	40
H(191)	7368	2888	5853	33

(1*R**,4*R**,5*S**,7*S**)-5-Methyl-4-phenyl-3,8-dioxatricyclo[5.2.1.$0^{1,5}$]decane-2,9-dione, **326**

Table 1. Crystal data and structure refinement for DIA0173.

Identification code	DIA0173
Empirical formula	C15 H14 O4
Formula weight	258.27
Temperature	100 K
Wavelength	0.68890 Å
Crystal system	Monoclinic
Space group	P 21/n
Unit cell dimensions	a = 10.5566(1) Å α= 90°. b = 11.6218(1) Å β= 112.1374(15)°. c = 10.5824(1) Å γ = 90°.
Volume	1202.61(2) Å^3
Z	4
Density (calculated)	1.426 Mg/m^3
Absorption coefficient	0.104 mm^{-1}
F(000)	544
Crystal size	0.030 x 0.010 x 0.010 mm^3
Theta range for data collection	2.635 to 32.112°.
Index ranges	-15<=h<=15, -17<=k<=17, -15<=l<=16
Reflections collected	15885
Independent reflections	4116 [R(int) = 0.030]
Completeness to theta = 25.048°	97.4 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.77
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4110 / 0 / 172
Goodness-of-fit on F^2	0.9344
Final R indices [I>2sigma(I)]	R1 = 0.0414, wR2 = 0.0878
R indices (all data)	R1 = 0.0506, wR2 = 0.0988
Largest diff. peak and hole	0.46 and -0.32 e.Å^{-3}



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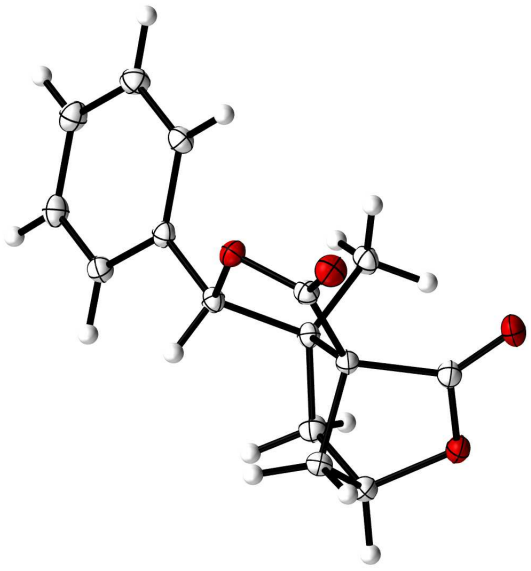


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DIA0173. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5452(1)	4658(1)	1419(1)	17
C(2)	6839(1)	4764(1)	1899(1)	16
C(3)	7144(1)	5863(1)	2709(1)	13
C(4)	6726(1)	5641(1)	3958(1)	12
C(5)	5140(1)	5675(1)	3297(1)	16
C(6)	4905(1)	5734(1)	1775(1)	17
O(7)	7575(1)	4062(1)	1703(1)	22
C(8)	7269(1)	4493(1)	4663(1)	17
C(9)	5964(1)	6612(1)	1749(1)	15
C(10)	8547(1)	6373(1)	3319(1)	14
O(11)	8736(1)	6781(1)	4579(1)	15
C(12)	7464(1)	6685(1)	4837(1)	13
O(13)	9411(1)	6446(1)	2842(1)	20
C(14)	7811(1)	6615(1)	6349(1)	13
C(15)	9002(1)	6081(1)	7221(1)	15
C(16)	9279(1)	6012(1)	8613(1)	18
C(17)	8354(1)	6454(1)	9142(1)	19
C(18)	7162(1)	6987(1)	8277(1)	18
C(19)	6900(1)	7079(1)	6886(1)	16

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3) for DIA0173. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\,h^2\,a^{*2}U^{11} + \ldots + 2\,h\,k\,a^*\,b^*\,U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	16(1)	15(1)	19(1)	-5(1)	5(1)	-1(1)
C(2)	18(1)	14(1)	15(1)	-2(1)	6(1)	0(1)
C(3)	13(1)	12(1)	13(1)	-1(1)	5(1)	0(1)
C(4)	13(1)	11(1)	13(1)	-1(1)	5(1)	-1(1)
C(5)	14(1)	17(1)	19(1)	-2(1)	7(1)	-2(1)
C(6)	15(1)	16(1)	18(1)	-3(1)	4(1)	1(1)
O(7)	23(1)	18(1)	24(1)	-6(1)	8(1)	3(1)
C(8)	21(1)	12(1)	17(1)	1(1)	7(1)	0(1)
C(9)	15(1)	14(1)	14(1)	1(1)	3(1)	2(1)
C(10)	14(1)	13(1)	15(1)	1(1)	5(1)	1(1)
O(11)	14(1)	16(1)	15(1)	-1(1)	6(1)	-3(1)
C(12)	13(1)	12(1)	14(1)	0(1)	6(1)	-1(1)
O(13)	17(1)	25(1)	22(1)	-1(1)	11(1)	-2(1)
C(14)	15(1)	12(1)	14(1)	-1(1)	6(1)	-1(1)
C(15)	16(1)	14(1)	16(1)	1(1)	7(1)	1(1)
C(16)	19(1)	18(1)	16(1)	3(1)	6(1)	1(1)
C(17)	23(1)	20(1)	15(1)	0(1)	8(1)	-2(1)
C(18)	20(1)	18(1)	18(1)	-3(1)	11(1)	-1(1)
C(19)	16(1)	15(1)	16(1)	-1(1)	6(1)	1(1)

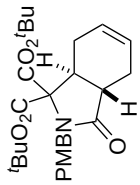
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for D1A\013.

	x	y	z	U(eq)
H(51)	4763	6366	3571	21
H(52)	4735	4988	3510	21
H(61)	3956	5840	1136	20
H(81)	7081	4421	5488	25
H(83)	8279	4431	4921	24
H(82)	6833	3845	4068	25
H(91)	5871	7360	2125	18
H(92)	5994	6714	843	18
H(121)	6930	7387	4470	15
H(151)	9652	5764	6866	19
H(161)	10124	5654	9207	22
H(171)	8549	6405	10100	23
H(181)	6518	7291	8614	23
H(191)	6088	7456	6287	19

(3a*S**,7a*S**)-Di-*tert*-butyl 2-(4-methoxybenzyl)-3-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-1,1-dicarboxylate, **378**

Table 1. Crystal data and structure refinement for DIA0174.

Identification code	DIA0174	
Empirical formula	C26 H35 N1 O6	
Formula weight	457.57	
Temperature	100 K	
Wavelength	0.68890 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.2769(1) Å	α= 90°.
	b = 19.0465(2) Å	β= 90°.
	c = 20.3494(4) Å	γ = 90°.
Volume	2432.83(7) Å^3	
Z	4	
Density (calculated)	1.249 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	984	
Crystal size	0.050 x 0.050 x 0.050 mm^3	
Theta range for data collection	2.073 to 31.898°.	
Index ranges	-9<=h<=9, -29<=k<=29, -28<=l<=20	
Reflections collected	32517	
Independent reflections	4716 [R(int) = 0.045]	
Completeness to theta = 25.199°	96.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.81	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4704 / 0 / 298	
Goodness-of-fit on F^2	0.9344	
Final R indices [I>2sigma(I)]	R1 = 0.0383, wR2 = 0.0921	
R indices (all data)	R1 = 0.0425, wR2 = 0.0999	
Largest diff. peak and hole	0.33 and -0.24 e.Å^{-3}	



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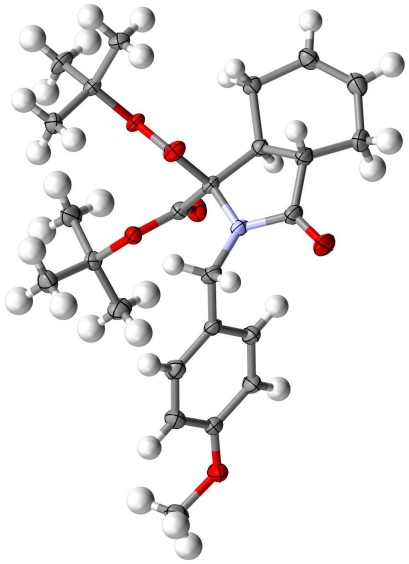

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DIA0174. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	7471(2)	5236(1)	2679(1)	20
C(2)	7088(3)	4963(1)	2068(1)	27
C(3)	5869(3)	5504(1)	1685(1)	26
C(4)	4916(2)	5978(1)	2210(1)	20
C(5)	6517(2)	5929(1)	2785(1)	18
C(6)	9052(2)	4928(1)	3112(1)	23
C(7)	8124(3)	4430(1)	3616(1)	22
C(8)	9309(3)	4253(1)	4169(1)	27
C(9)	8541(3)	3786(1)	4638(1)	29
C(10)	6527(3)	3494(1)	4555(1)	27
C(11)	5325(3)	3662(1)	4004(1)	30
C(12)	6123(3)	4127(1)	3540(1)	27
O(13)	5601(3)	3034(1)	4984(1)	35
C(14)	6700(3)	2891(1)	5582(1)	32
O(15)	7755(3)	4395(1)	1879(1)	38
C(16)	4143(4)	5288(1)	1201(1)	36
C(17)	2974(3)	5924(1)	998(1)	32
C(18)	3124(3)	6551(1)	1277(1)	28
C(19)	4389(2)	6683(1)	1900(1)	22
C(20)	5398(2)	5957(1)	3460(1)	19
O(21)	3495(2)	5917(1)	3530(1)	29
O(22)	6836(2)	6018(1)	3937(1)	20
C(23)	6187(3)	6101(1)	4634(1)	23
C(24)	4888(3)	6772(1)	4703(1)	32
C(25)	8327(3)	6169(1)	4979(1)	33
C(26)	4995(3)	5458(1)	4873(1)	32
C(27)	8210(2)	6508(1)	2732(1)	18
O(28)	9888(2)	6418(1)	2463(1)	24
O(29)	7463(2)	7104(1)	2986(1)	20
C(30)	8807(2)	7748(1)	2995(1)	21
C(31)	10784(3)	7613(1)	3406(1)	26
C(32)	7362(3)	8281(1)	3327(1)	31
C(33)	9334(3)	7975(1)	2299(1)	27

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for DIA0174. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2 a^{*2} U^{11} + \ldots + 2\, h\, k\, a^*\, b^*\, U^{12}\,]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	25(1)	13(1)	24(1)	-1(1)	2(1)	1(1)
C(2)	37(1)	17(1)	26(1)	-3(1)	1(1)	1(1)
C(3)	38(1)	18(1)	23(1)	-2(1)	1(1)	1(1)
C(4)	23(1)	17(1)	21(1)	-1(1)	0(1)	-3(1)
C(5)	18(1)	13(1)	21(1)	-2(1)	2(1)	-1(1)
C(6)	23(1)	16(1)	31(1)	1(1)	0(1)	3(1)
C(7)	25(1)	13(1)	28(1)	-1(1)	-1(1)	1(1)
C(8)	24(1)	23(1)	34(1)	1(1)	-5(1)	0(1)
C(9)	32(1)	25(1)	31(1)	3(1)	-8(1)	2(1)
C(10)	39(1)	17(1)	24(1)	1(1)	-7(1)	-4(1)
C(11)	36(1)	25(1)	30(1)	6(1)	-9(1)	-11(1)
C(12)	31(1)	21(1)	29(1)	5(1)	-8(1)	-6(1)
O(13)	49(1)	29(1)	28(1)	8(1)	-10(1)	-14(1)
C(14)	37(1)	30(1)	29(1)	4(1)	-1(1)	8(1)
O(15)	59(1)	20(1)	36(1)	-8(1)	-3(1)	9(1)
C(16)	57(1)	24(1)	28(1)	-6(1)	-11(1)	1(1)
C(17)	33(1)	40(1)	24(1)	0(1)	-3(1)	-5(1)
C(18)	26(1)	31(1)	26(1)	1(1)	-3(1)	3(1)
C(19)	22(1)	20(1)	24(1)	0(1)	1(1)	1(1)
C(20)	20(1)	16(1)	22(1)	-1(1)	0(1)	-1(1)
O(21)	19(1)	40(1)	27(1)	-2(1)	1(1)	-3(1)
O(22)	21(1)	19(1)	21(1)	-1(1)	0(1)	0(1)
C(23)	27(1)	21(1)	20(1)	-1(1)	0(1)	1(1)
C(24)	43(1)	28(1)	26(1)	-5(1)	1(1)	10(1)
C(25)	33(1)	38(1)	27(1)	0(1)	-8(1)	-1(1)
C(26)	40(1)	29(1)	28(1)	3(1)	8(1)	-6(1)
C(27)	19(1)	13(1)	22(1)	-1(1)	-1(1)	-1(1)
O(28)	21(1)	19(1)	34(1)	-2(1)	6(1)	-1(1)
O(29)	21(1)	12(1)	27(1)	-2(1)	2(1)	0(1)
C(30)	26(1)	13(1)	24(1)	-1(1)	-1(1)	-2(1)
C(31)	27(1)	24(1)	26(1)	-2(1)	-6(1)	-3(1)
C(32)	36(1)	16(1)	41(1)	-6(1)	3(1)	3(1)
C(33)	37(1)	19(1)	26(1)	5(1)	-2(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for DIA0174.

	x	y	z	U(eq)
H(31)	6925	5782	1437	31
H(41)	3598	5763	2360	24
H(61)	9820	5299	3331	28
H(62)	10050	4669	2837	29
H(81)	10659	4454	4222	33
H(91)	9363	3670	5013	36
H(111)	3959	3457	3946	36
H(121)	5285	4245	3164	33
H(141)	5907	2514	5800	48
H(143)	6718	3311	5852	48
H(142)	8155	2736	5474	48
H(162)	4719	5040	831	44
H(161)	3127	4959	1422	45
H(171)	2099	5884	586	40
H(181)	2428	6942	1070	34
H(192)	3580	6982	2209	26
H(191)	5694	6934	1779	26
H(241)	4610	6863	5160	50
H(243)	5659	7160	4515	49
H(242)	3554	6726	4482	49
H(252)	8125	6208	5453	49
H(251)	9047	6572	4815	48
H(253)	9176	5769	4880	48
H(262)	4825	5491	5346	47
H(263)	5772	5042	4751	48
H(261)	3597	5443	4673	47
H(313)	11575	8047	3441	38
H(311)	10378	7452	3837	38
H(312)	11665	7259	3197	37
H(321)	8109	8727	3352	45
H(323)	6971	8128	3768	45
H(322)	6078	8339	3067	45
H(332)	10159	8409	2312	42
H(331)	8070	8061	2066	40
H(333)	10118	7623	2074	40