Oxidative Radical Cyclisations for the Synthesis of Lactones

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Abstract

The object of study of this thesis lies on the optimisation of the oxidative radical cyclisation methodology for the preferential formation of γ-lactones from unsaturated alkyl malonate derivatives.

Chapter 1 introduces the concept of free-radical cyclisation; more extensive explanations are given for the intramolecular oxidative radical cyclisation using manganese(III) and copper(II) salts as oxidants. An overview of the contribution of the Burton group in the field is given, in which both the applicability and the limitations of the transformation are showcased.

Chapter 2 is concerned with the synthesis of the ethisolide family of natural products and one non-natural analogue, in which the oxidative radical cyclisation is key for the construction of the *bis*-γ-lactone moiety present in such natural products. The initial limitations of the methodology allowed for the discovery of new conditions for the formation of chloro monocyclic systems and for the development of copper-free oxidative cyclisation conditions for γ-lactone formation.

Chapter 3 reports the developments on the metal-free oxidative radical cyclisation. Bicyclic γ-lactones were synthesised from all-carbon alkyl malonate derivatives through anodic oxidation *via* constant current electrolysis. The development of a novel ionic oxidative cyclisation is also discussed.

Chapter 4 describes our efforts towards the formation of both fused and spiro γ-lactam-β-lactone molecules, as potential analogues to proteasome inhibitors, from either γ-lactam-γ-lactones or *exo*-γ-lactams precursors, previously synthesised through oxidative radical cyclisation.

Full experimental details, NMR spectra for the natural products and for the non-natural analogue, and a comparison between the obtained and the previously reported NMR data are also provided.

Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated. Work that was done as part of a collaboration with a research colleague has been fully acknowledged and referenced within the text.

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

Sandra Ainsua Martinez

July 2017

A mi padre, Ramón Ainsua.

Acknowledgments

These four years have flown by and I feel a single page will not be enough to express my gratitude to all the people who made my time in Oxford such a unique and unforgettable experience.

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I also would like to thank the OxIOSCR IDP programme for all the training we received, the European

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I would not have reached the end without the good friends I have made in Oxford. Patri, Anais and Allegra, it was such good fun having you around; and Ali, thanks for cheering me up whenever I needed. My mum Elisa and my brother Javi have always played an important role in my life. I am thankful for all the unconditional love they never stop giving me.

Contents

Abbreviations

Ac	acetyl
acac	acetylacetone
AIBN	α,α'-azoisobutyronitrile (2,2′-azobis(2-methylpropionitrile))
Ar	aryl
aq.	aqueous
atm	atmosphere(s)
ATP	adenosine-5′-triphosphate
bmim	1-butyl-3-methylamidazolium
Bn	benzyl
b.p.	boiling point
CAN	ceric ammonium nitrate
cat.	catalytic
Cp	cyclopentadienyl
d	day(s)
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEM	diethyl malonate
DIBAL-H	diisobutylaluminium hydride
DIPA	diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	*N*,*N*-dimethylpyridin-4-amine
DMF	dimethyl formamide

DMM	dimethyl malonate
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
d.e.	diastereomeric excess
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
FI	field ionisation
FID (NMR)	free induction decay
ESI	electrospray ionisation
GC	gas chromatography
h	hour(s)
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
IPA	isopropyl alcohol
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
MAN	$Mn(OAc)_3 \cdot 2H_2O$
m-CPBA	*meta*-chloroperbenzoic acid
maj	major
min	minor
min	minute(s)
m.p.	melting point
Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
NBS	*N*-bromosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine

NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
p-ABSA	*para*-acetamidobenzenesulfonyl azide
PE	petroleum ether
PG	a protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
Piv	pivaloyl
Py	pyridine
r.t.	room temperature
sat.	saturated
SET	single electron transfer
SM	starting material
SOMO	single occupied molecular orbital
TBACl	tetrabutylammonium chloride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
Ts	4-methylbenzenesulfonyl
T3P	propylphosphonic anhydride solution

1

General Introduction

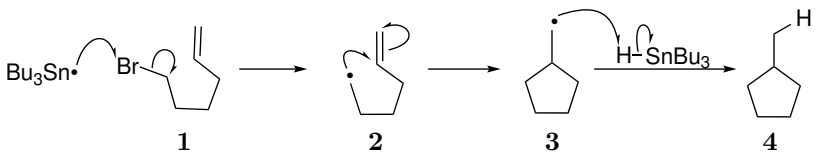
This thesis focuses on the development of new methodologies in the area of oxidative radical cyclisations. The combination of halides and manganese triacetate, as one-electron oxidant, proved to be a useful method for the construction of both γ-lactones and chloro monocyclic systems. Using this methodology, *bis*-γ-lactones were formed efficiently, thus allowing for the synthesis of the ethisolide family of natural products. As a result of the stoichiometric amounts of metal oxidants needed for the transformation, a more sustainable metal-free oxidative radical cyclisation alternative for the formation of γ-lactones was also studied. This introductory chapter gives an overview of oxidative free-radical cyclisation and on the use of manganese triacetate as a reagent for this transformation. Comments will also be addressed to the effect of the experimental conditions on the outcome of the reaction. Special attention will be given to those reaction conditions leading to the formation of γ-lactones.

1.1 Free-Radical Cyclisations

Over the past years, the use of radical transformations has increased in popularity within the synthetic community as a consequence of some of their synthetic advantages over classical ionic transformations.[1] Due to the high reactivity of carbon-centered radicals, mild and neutral conditions are usually required; however, low chemo-, regio- and stereoselectivities are sometimes associated with this type of reaction. Nevertheless, when the molecule presents conformational restrictions, higher stereoselectivities can often be achieved in the radical cyclisation. Moreover, their high reactivity and electronic neutrality makes them relatively unsolvated species and hence the formation of sterically hindered bonds is more easily achieved.[2] A wide range of methodologies have been reported where radical mechanisms are involved. Metal-metal, metal-hydrogen and non-metal-hydrogen initiators have found their use in atom-transfer cyclisations, couplings, rearrangements and cascade reactions; however, the focus of this chapter will be on free-radical cyclisations.[3]

1.1.1 Reductive Free-Radical Cyclisation

Radical cyclisations onto alkenes are particularly relevant for the synthesis of cyclic molecules.[4] Traditionally, the transformation consisted of the *in situ* activation of *n*-Bu_3SnH with sub-stoichiometric amounts of radical initiators such as AIBN, peroxides or UV light. The generated trialkyl stannane radical is responsible for the reduction of C-X bonds to a radical where X is usually a halide group, *e.g.* compound **1**. The formed primary radical **2** then cyclises onto the alkene, thus forming a primary adduct radical **3**, which is reduced through hydrogen abstraction, giving methycyclopentane **4** and releasing a second molecule of trialkyl stannane radical. (**Scheme 1.1**)



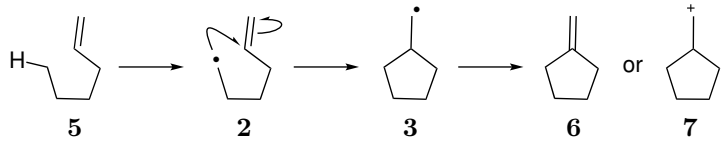
Scheme 1.1: Trialkyltin Hydride Mediated 5-Hexenyl Radical Cyclisation.

Despite the high yields associated with these reactions and their use in numerous syntheses, there are some important limitations: aside from the toxicity in handling organotin derivatives, the obtained products are relatively less functionalised as a result of a net two-electron reduction. In addition, since tin derivatives are not incorporated into the molecule, the reaction generates an important waste stream

of R_3Sn-X, which renders the methodology 'non-atom economical'.[5]

1.1.2 Oxidative Free-Radical Cyclisations

In contrast to reductive free-radical cyclisations, oxidative radical cyclisations oxidatively generate a radical, *e.g.* compound **2** which is also terminated in an oxidative manner to give either the *exo*-alkene **6** or the carbocation **7**, thus offering a major synthetic potential since higher levels of oxidation are achieved and more functionalised products can be derived from simple precursors, such as **5** (**Scheme 1.2**).

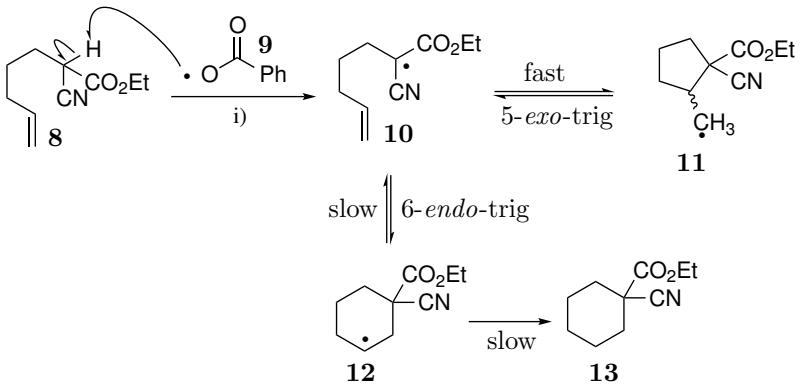


Scheme 1.2: Oxidative Free-Radical Cyclisation.

As shown in **Scheme 1.2**, formal loss of a hydrogen atom would lead to the acyclic radical **2**; however, in practical terms, a deprotonation happens in the first instance, followed by a one-electron oxidation of the resulting anion with a suitable one-electron oxidant. The oxidative termination is a versatile step, which can offer a wide range of products depending on the nature of the radical formed after the cyclisation and on the experimental conditions, such as solvent, and presence and type of co-oxidants.

Early studies on oxidative radical cyclisations were carried out by Julia[6,7] with unsaturated cyanoacetates **8** as substrates (**Scheme 1.3**). Benzoyl peroxide was used as the radical initiator, which upon reflux in cyclohexane formed benzoyloxyl radical **9**, which led to hydrogen abstraction at the most acidic position of precursor **8** to give the most stable radical **10**. The formed radical **10** could either cyclise through a 5-*exo*-trig cyclisation giving **11** or through a 6-*endo*-trig annulation for the formation of **12**. Considering that the slow hydrogen abstraction from cyclohexane was the only termination pathway and that cyclisation of **10** to give **11** was reversible, as a result of the stabilisation of the acyclic radical by the two electron-withdrawing groups, the thermodynamic product **13** was formed preferentially over the kinetic product **11** (**Scheme 1.3**).

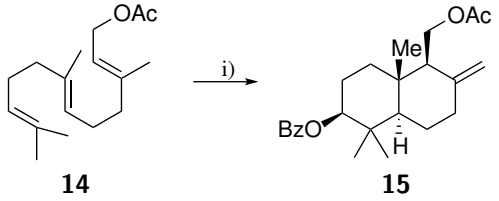
Reversibility of the radical addition to alkenes have previously been observed by Huang *et al.* in their intermolecular addition of ethyl cyanoacetate to *cis*-cinnamonitrile.[8] Because benzoyloxyl radicals cannot be used as oxidative terminators, these transformations, despite having an oxidative initiation, terminate in a reductive manner, meaning that the product offers the same oxidation state as the starting material and limited possibilities for further functionalisation.



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

Scheme 1.3: Early Days of Oxidative Radical Initiation, Reported by Julia.[6,7]

In order to force the formed radicals to undergo oxidative termination and increase synthetic practicality, Breslow[9,10] considered the use of cupric benzoate as a co-oxidant terminator in the oxidative cyclisation of farnesyl acetate **14** to form the highly functionalised bicyclic compound **15** in moderate yields (**Scheme 1.4**). The oxidative radical initiator was also benzoyloxy radical, which was generated this time by a CuCl-catalysed thermal decomposition of the corresponding peroxide. Although in this example, both molecular complexity and oxidation level were increased through the transformation, the use of benzoyl peroxide as oxidative initiator did not have general application.



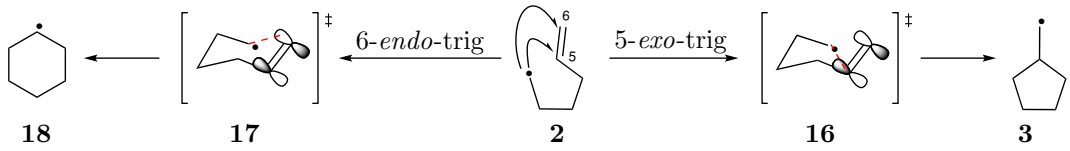
Reagents & Conditions: i) $(PhCO_2)_2$, CuCl, $Cu(OC(O)Ph)_2$, MeCN, reflux, 20-30% .

Scheme 1.4: Breslow's Farnesyl Acetate Oxidative Radical Cyclisation with Copper(II) as Co-Oxidant.[9,10]

1.1.3 Studies on Regiochemistry and Stereoselectivity

As it can be seen from the examples displayed on **Scheme 1.3** and **Scheme 1.4**, ring formation can either go through a 5-*exo*-trig or a 6-*endo*-trig cyclisation for the formation of 5- and 6-membered rings respectively (**Scheme 1.5**). Despite the reversibility observed in Julia's study[6,7] (**Scheme 1.3**), it should be mentioned that in the simpler case of 5-hexenyl radical **2**, both cyclisations are considered irreversible,[11] meaning that kinetic factors prevail over thermodynamic ones (**Scheme 1.5**). By only considering the thermodynamic stability of the formed radical adducts **3** and **18** and the corresponding

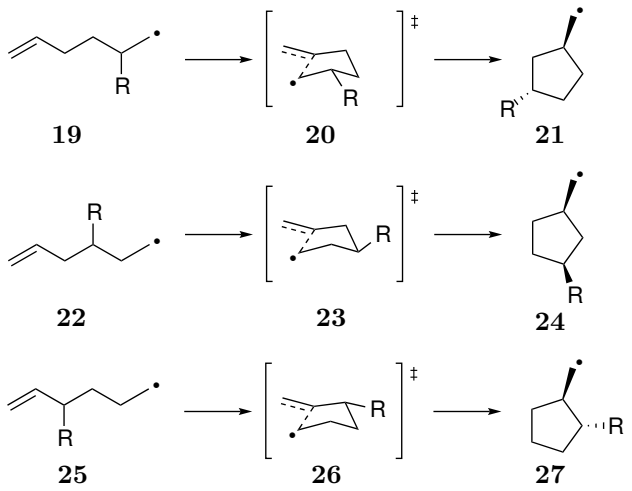
ring strain, we would imagine that the 6-*endo*-trig cyclisation would be more favourable since secondary radicals are more stable than primary ones. Nevertheless, experimental kinetic data showed that the ratio between the rate constants for 5-*exo*-trig over 6-*endo*-trig cyclisations was $\frac{k_{1,5}}{k_{1,6}} \approx 50$ (at 328 K).[12] On the basis of such experimental data, it was proposed that the radical cyclisation is under stereoelectronic control. For the cyclisation to occur, the singly occupied molecular orbital (SOMO) needs to overlap with the lowest unoccupied orbital (LUMO) of the alkene. The energy needed for such interaction is lower in the case of the transition state **16** than in the case of the transition state **17**. The strain originated in **17** when accommodating the needed disposition of the reactive centers, which outweighs the steric and thermodynamic factors, would favour six-membered ring formation.



Scheme 1.5: Transition States for 5-*exo*-trig and 6-*endo*-trig cyclisations for hexenyl radical **2**

The above analysis was confirmed by computational studies by Beckwith, and Houk and Spellmeyer.[13–17] Furthermore, these computational studies provided a rationale for the stereoselectivity observed in 5-*exo*-trig radical cyclisations. The Beckwith-Houk model for 5-*exo*-trig cyclisations proposed that the hexenyl radical **2** adopts a 'chair-like' conformation during the cyclisation transition state, and substituents preferentially adopt pseudo-equatorial positions to avoid allylic and 1,3-diaxial strains.[14] A study reported by Beckwith (**Scheme 1.6**) showed that 3-substituted radicals **22** preferentially form *cis*-products **24**; while 2- and 4-substituted radicals **19** and **25** mainly form *trans*-products **21** and **27**.[15]

Force field calculations for substituted 5-hexenyl radicals reported by Beckwith and Houk supported the experimental observations.[14] The authors found that the activation energy for the transition state with the 4-substituent in pseudo-axial position was 1.1 kcal mol^{-1} higher that for the one with the substituent in pseudo-equatorial position. The results suggest that the use of bulky groups as substituents could increase their conformational preference in the transition state, thus leading to a higher degree of diastereoselectivity.



Scheme 1.6: Stereoselectivity in 5-*exo*-trig Cyclisation of Substituted 5-Hexenyl Radicals.[15]

1.2 Use of Manganese(III) as Oxidant

The lack of general applicability of benzoyl peroxide for oxidative radical cyclisations (see **Scheme 1.4** and **Scheme 1.3**) led to the development of alternative oxidative radical reagents. Due to their ability to readily change oxidation state, (transition) metals appeared to be an excellent choice to mediate such reactions.[18] Some of the most popular one-electron metal oxidants are $Mn(OAc)_3 \cdot 2H_2O$ (MAN), cerium(IV) ammonium nitrate (CAN) and various Fe(III) salts.[19] The chemistry involved in such initiation results in the generation of electrophilic radicals from C-H acidic compounds, which then propagate to form a new C-C bond, giving an adduct radical. Such adduct radicals can terminate *via* oxidative elimination or substitution, ligand transfer to form C-X bonds or reductive hydrogen abstraction from either the solvent or the substrate. The termination pathway is highly dependent on the type of radical adduct formed, the solvent and the type/presence of co-oxidants in the reaction medium.[19] This section will solely focus on the use of $Mn(OAc)_3 \cdot 2H_2O$ in oxidative radical cyclisation while examples in which CAN[20–23] and Fe(III)[24] are employed can be consulted in the corresponding literature.

1.2.1 Properties

Manganese shows ample redox chemistry in acidic conditions, with oxidation states +2, +3, +4, +6 and +7.[25] Under the slightly acidic conditions associated with the use of $Mn(OAc)_3 \cdot 2H_2O$ in solution in oxidative radical reactions,[4] the reduction of Mn(III) to Mn(II) is a favourable process, with a standard

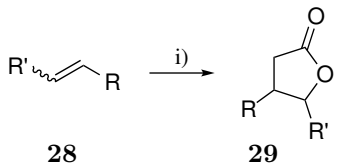
reduction potential of +1.50 V (**Equation 1.1**, with reference to the H_2/H^+).

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

As in the case of a number of transition metal(III) acetates,[26,27] anhydrous $Mn(OAc)_3$ has been reported as a trinuclear oxo-centered cluster with bridging acetates with the formula $Mn_3O(OAc)_6$.[28] Its use in synthesis generally involves the dihydrated form and it is proposed that the trimeric form is likely to persist during the transformation according to mechanistic studies. Nevertheless, for simplification purposes, we will represent the Mn(III) complex in its monomeric form $Mn(OAc)_3 \cdot 2H_2O$.

1.2.2 Intermolecular Oxidative Radical Cyclisation: Synthesis of γ-Lactones

Heiba and Dessau,[29] in the same year as Bush and Finkbeiner,[30] were the pioneers in the use of manganese(III) acetate as one-electron oxidant for oxidative free-radical cyclisations. The methodology that later will be considered as a general approach for this type of transformations,[4] gave access to a number of different γ-lactones **29** from treating mono and disubstituted alkenes **28** in refluxing acetic acid with stoichiometric amounts of $Mn(OAc)_3 \cdot 2H_2O$ (**Scheme 1.7**).



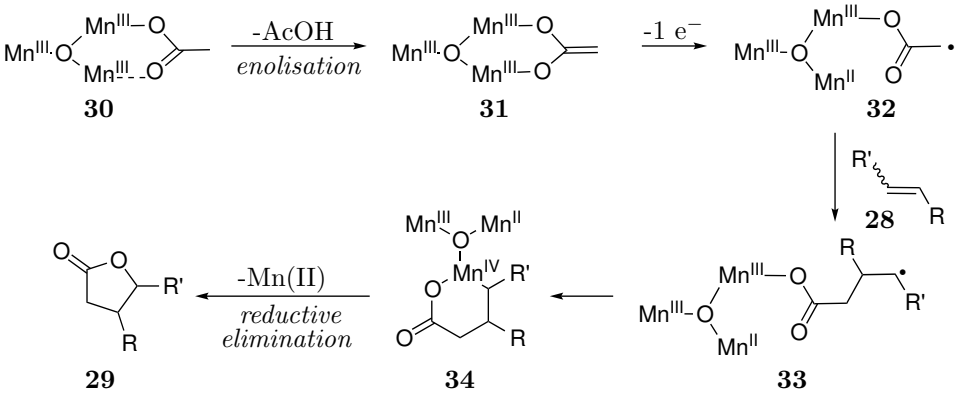
28 **29**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, AcOH, 135 °C; R, R' = H, alkyl; 44-79% .

Scheme 1.7: First Syntheses of γ-Lactones through Oxidative Radical Cyclisation, Reported by Heiba and Dessau,[29] and Bush and Finkbeiner.[30]

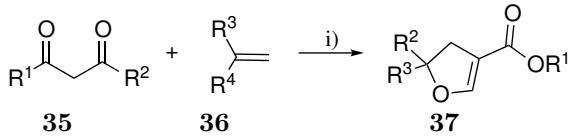
Early mechanistic studies in the oxidative addition of acids to alkenes were first published by Heiba and Dessau;[31] however, a more extensive mechanistic description including the structure of $Mn(OAc)_3$ did not appear until Fristad and Peterson reported in the 1980s their studies on the γ-lactone annulation system.[32–34] The general mechanism was proposed to start with the acidity increase of H_α of the carbonyl through complexation of the acetate to the Mn(III) coordination sphere to give **30** (**Scheme 1.8**). Then follows a rate-determining deprotonation step of a bridging acetate to form the Mn(III)-enolate **31**, which undergoes a single electron oxidation (SET) and generates the electrophilic radical complex **32** with loss of Mn(II). The C-C bond is formed upon regioselective addition of **32** to the alkene **28** to give the most stable secondary adduct radical **33**, which is further converted into the lactone **29** through a second

electron transfer, thus releasing Mn(II). The detailed mechanism of the last oxidation remains unknown; however it is well-known that Mn(III) will oxidise γ-carboxy radicals (unlike secondary and primary radicals) to cations, and a number of mechanisms has been proposed for this step.[35] One possibility is shown in **Scheme 1.8** where the radical **33** is trapped by a second Mn(III) cluster atom to form the Mn(IV) complex **34**, which undergoes a reductive elimination to form the lactone **29** with loss of Mn(II).



Scheme 1.8: General Mechanism for γ-Lactone Formation

Considering that the higher the acidity of the H_α, the higher is the enolisation rate, which is considered as the rate-determining step,[33] Heiba and Dessau kept exploring intermolecular oxidative radical additions in acetic acid between olefins and a wide range of more enolisable substrates including aliphatic and aromatic ketones,[36,37] β-diketones and β-keto esters.[38] In the case of using ketones instead of esters, dihydrofurans **37** could be generated after participation in the reaction of the carbonylic oxygen (**Scheme 1.9**).



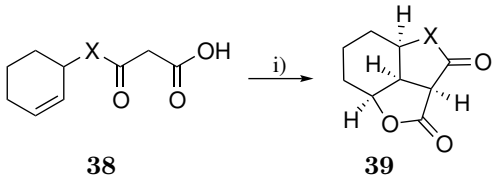
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, AcOH, 45 °C; R^1 = alkyl, R^2 = alkyl, alkoxy; R^3 = Ph, alkyl; R^4 = H, alkyl; 10-100% yield.

Scheme 1.9: Formation of Dihydrofurans through Mn(III)-based Oxidative Radical Cyclisation[38]

Extensive literature can be found for Mn(III)-based intermolecular oxidative radical cyclisations;[4,39] nevertheless, a more comprehensive focus will be given to the intramolecular version of such transformation.

1.2.3 Intramolecular Oxidative Radical Cyclisation

Intermolecular oxidative radical additions mediated by Mn(III) are efficient for the formation of cyclic systems; however, an intramolecular version was seen as a more attractive method since polycyclic compounds could be formed. It has been shown that, due to their higher enolisability, diketones and β-keto ester undergo oxidation more readily than acetate and acetic acid, a fact that convinced Corey that intramolecular oxidative radical cyclisations were possible with the adequate choice of substrate, greatly widening the scope of this transformation. Tricyclic fused cyclic systems **39** were synthesised from unsaturated 3-oxo acids **38** (**Scheme 1.10**), thus proving that the Mn(III) oxidative cyclisation could be extended intramolecularly for a greater increase of the molecule complexity in a single step.[40]

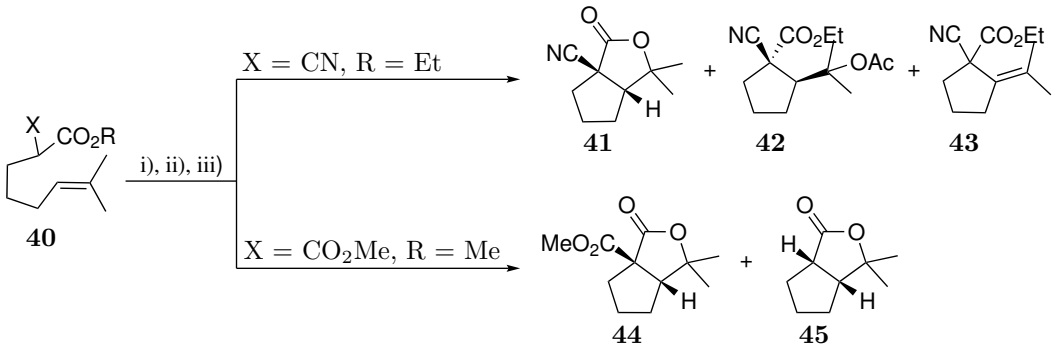


38 **39**

Reagents & Conditions: $Mn(OAc)_3 \cdot 2H_2O$ (1.3 eq.), AcOH, 23 °C when X = CH_2, 63%; $Mn(OAc)_3 \cdot 2H_2O$ (1.3 eq.), AcOH, 40 °C when X = O, 64% yield.

Scheme 1.10: First Mn(III)-based Intramolecular Oxidative Radical Cyclisation, Reported by Corey.[40]

Corey's results marked the debut for intramolecular Mn(III)-based oxidative radical reactions. Fristad reported the synthesis of bicyclic lactones **41** and **44** from unsaturated alkyl malonates and alkyl cyanoacetates **40** (**Scheme 1.11**).[41]



40 **41** **42** **43** **44** **45**

Reagents & Conditions: i) KOH, EtOH; ii) $Mn(OAc)_3 \cdot 2H_2O$, AcOH, T (°C) ; iii) CH_2N_2. **X = CN, R = Et: 41**: 17%; **42**: 17%; **43**: 9% at T = 70 °C ; **X = CO_2Me, R = Me: 44**: 41%; **45**: 3% at 25 °C.

Scheme 1.11: Mn(III)-based Intramolecular Oxidative Radical Cyclisation, Reported by Fristad.[41]

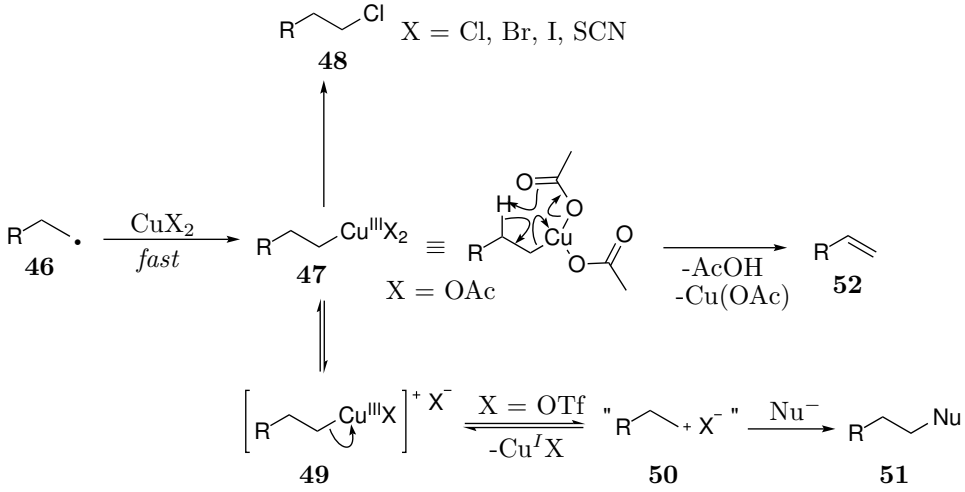
The modest yields obtained in Fristad's cyclisations are due to the side-product formation (compounds **45**, **42** and **43**) and hence optimisation of the reaction conditions was required. The nature of the

oxidants and the solvent all play a crucial role in determining the outcome of the reaction, which is mainly dictated by the termination step. Initiation of the reaction is efficiently accomplished by MAN; however, the performance of Mn(III) in the termination step varies depending on the stability of the adduct radical. Oxidation of stabilised radicals such as γ-carboxy radicals, tertiary radicals, allylic radicals and cyclohexadienyl radicals is efficiently performed by Mn(III); however, the oxidation rate of primary and secondary radicals is extremely low, meaning that, if no co-oxidant is present in the reaction, the reductive hydrogen abstraction remains the main termination pathway.

1.2.4 Product Ratio Control

1.2.4.1 Cu(II) Salts as Co-oxidants

Already in the 1960's, Kochi and co-workers demonstrated that copper(II) salts react rapidly with alkyl radicals **46** ($k \approx 10^6$ s^1 M^{-1}) to give alkylcopper(III) complexes **47** (**Scheme 1.12**). Different termination pathways could follow depending on the copper salt counterion: formation of alkenes **52** after a β-hydride elimination of the alkylcopper(III) intermediate **47** when the ligands are acetates, a ligand transfer reaction for the formation of **48** when dealing with copper(II) halides, or a nucleophilic substitution to give **51** with very stable counterions.[42,43]



Scheme 1.12: Kochi Studies on the Formation of Alkylcopper(III) Complexes.[42,43]

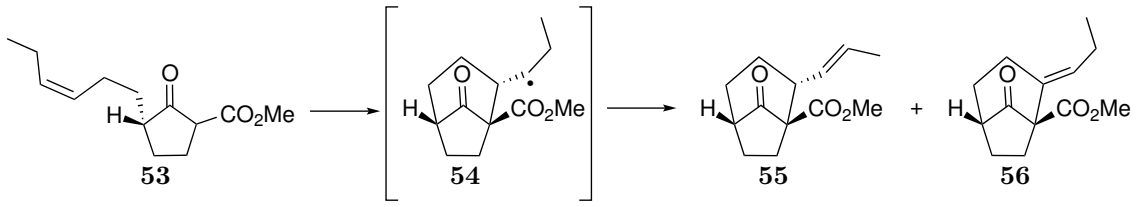
The major pathway is dictated by the coordinative character of the ligand in the metal complex; or, in other words, by the stability and the affinity of the ligands for copper(II/III). For the more stable ligands, oxidative nucleophilic substitution dominated, giving products **51**. The carbocation **50** was

proposed as the formal precursor, which was generated through an S_N1-like reaction, first initiated by the dissociation of one or both ligands in the copper(III) intermediate complex **47** to give the unsaturated complex **49**. Such dissociation would increase the electronic deficiency of the complex **47**, thus favouring the nucleophilic substitution (**Scheme 1.12**).

Around the same time, Heiba and Dessau[36,37] found out that not only is the use of Cu(II) salts compatible with MAN in the oxidative radical cyclisation, but also that such salts oxidise secondary radicals 350 times faster than Mn(III) does, thus corroborating Kochi's findings concerning the high rate by which alkylcopper(III) complexes are formed between Cu(II) salts and alkyl radicals **46**.[42,43] Despite the greater effectiveness of Cu(II) in oxidising secondary and primary radicals, the metal has a lower reduction potential than Mn(III) (**Equation 1.2** and **Equation 1.1**, **Section 1.2.1**), meaning that it is possible to take advantage of this property and render the transformation catalytic in Cu(II) by adding a second equivalent of Mn(III) to regenerate Cu(II) from Cu(I).

$$Cu^{2+} + e^- \rightarrow Cu^+ = +0.16 \text{ V} \tag{1.2}$$

When alkenes were formed from secondary radicals, it was observed that the reaction was both regio- and stereoselective. The less substituted (*E*)-alkenes (Hofmann elimination product) were isolated as major products of the oxidative radical addition. A representative example reported by Snider showed that a 14:1 mixture of Hofmann elimination and Zaitsev elimination products **55** and **56** respectively were obtained when exposing the β-keto ester **53** to the oxidative system MAN / $Cu(OAc)_2$ in AcOH (**Scheme 1.13**).[44]



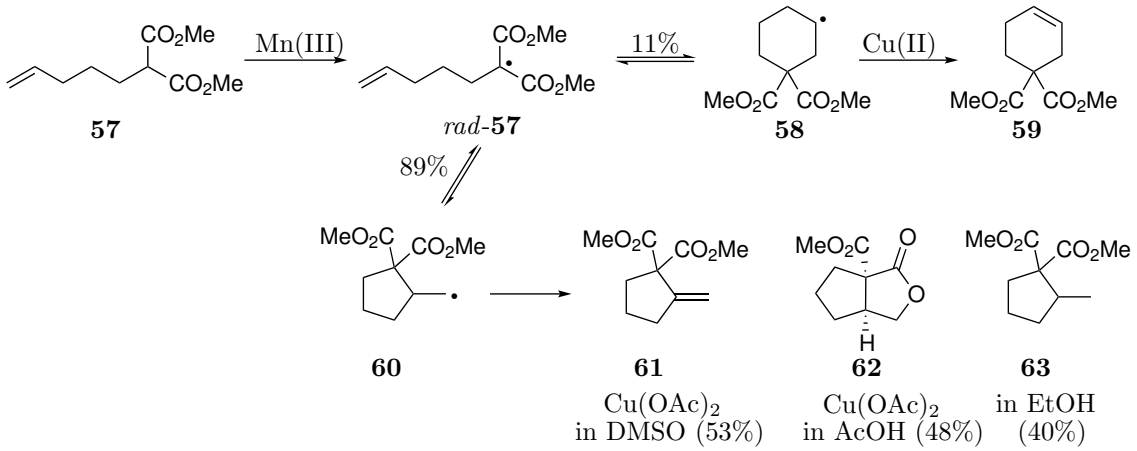
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2$, AcOH; **55**: Hofmann elimination, 70%; **56**: Zaitsev elimination, 5%.

Scheme 1.13: Regio- and Stereochemistry in the Formation of Alkenes through Cu(III)-Mediated β-Hydride Elimination.[44]

Following the discovery of Cu(II) as co-oxidant, the MAN / $Cu(OAc)_2$ oxidant system has gained popularity and the methodology has been further applied to a number of substrates such as unsaturated β-keto esters, di-ketones, and malonate esters.[4]

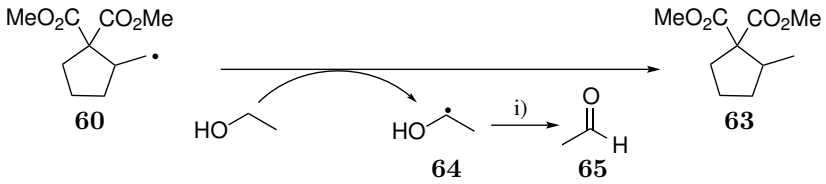
1.2.4.2 Solvent Effect

Acetic acid has always been the standard solvent for oxidative radical reactions using MAN; except when forming vinyl radicals, where ethanol was used instead to favour hydrogen abstraction, as oxidation by either Mn(III) or Cu(II) is not efficient enough.[45] Due to the lack of examples in the use of alternative solvents, Snider and co-workers decided to explore the effect of various solvents in the Mn(III)-based oxidative radical cyclisation of dimethyl 4-pentenylmalonate **57** (**Scheme 1.14**).[46]



Scheme 1.14: Solvent Effect on the Mn(III)-Based Oxidative Radical Cyclisation, Reported by Snider.[46]

Not only did Cu(II) salts have an impact on the termination step, but also so did the solvent in the product ratio between *exo*-methylene cyclopentane **61** and the bicyclic lactone **62**. DMSO was found to be the solvent of choice for the preferential formation of *exo*-methylene compound **61**; while AcOH was still the preferred solvent to form the lactone **62** in higher yields. Higher selectivity towards the formation of the lactone **62** was observed with MeCN; however, yields were lower than with AcOH. When using EtOH as solvent, hydrogen abstraction remained the preferred pathway, thus giving the saturated product **63** as major product and acetaldehyde **65** as a result of the oxidation of the radical **64** formed after the hydrogen abstraction (**Scheme 1.15**).



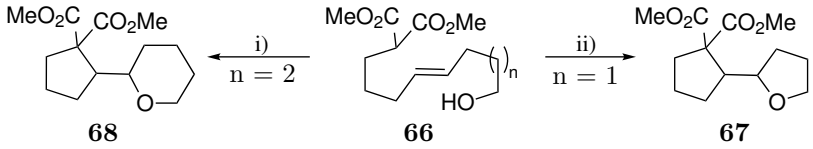
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$.

Scheme 1.15: Hydrogen Abstraction from a Molecule of EtOH.[46]

1.2.5 The Burton Group Contribution: Efficient Syntheses of γ-Lactones

1.2.5.1 Early days

$Cu(OAc)_2$ has been the co-oxidant of choice for the termination step in the oxidative radical cyclisation; nevertheless, Burton and co-workers reconsidered Kochi's pioneering studies[42,43] in which the nature of the counterion strongly modulated the outcome of the reaction (see **Section 1.2.4**). In the studies towards the formation of oxygen heterocycles tethered to carbocycles (**Scheme 1.16**), Burton and co-workers introduced the use of Cu(II) salts bearing highly stabilised counterions, such as $Cu(OTf)_2$ and $Cu(BF_4)_2$, in MeCN with the aim of increasing the ratio of oxidative substitution products over β-hydride elimination products in the MAN-based methodology.[47]



68 **66** **67**

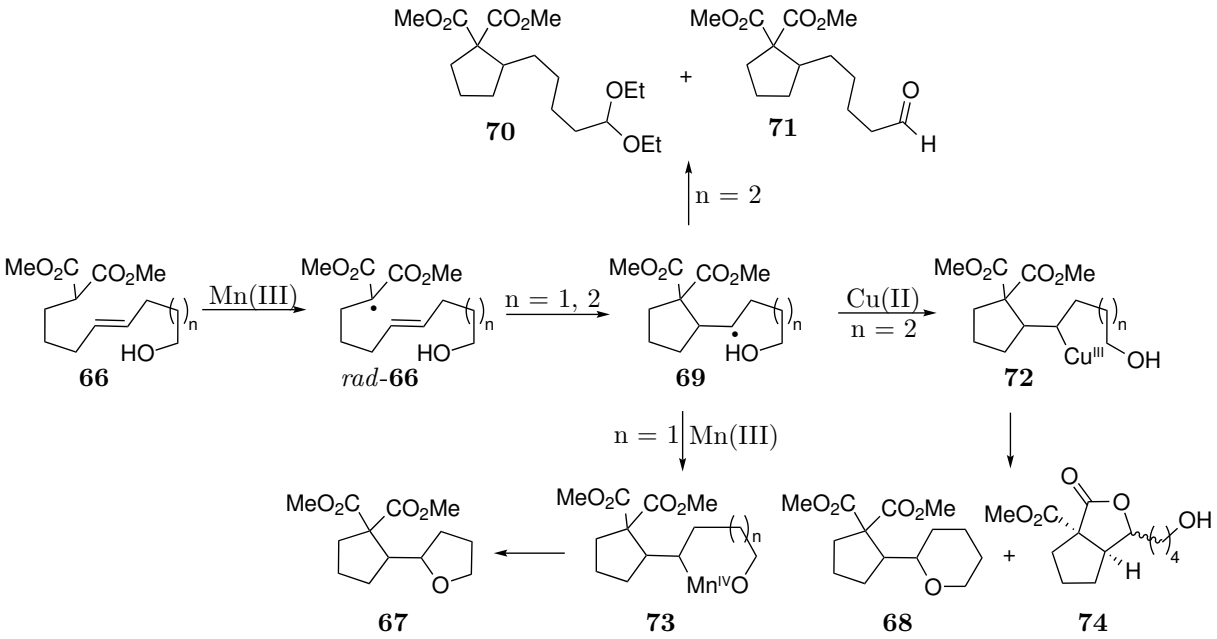
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OTf)_2$, MeCN, reflux, 30% ; ii) $Mn(OAc)_3 \cdot 2H_2O$, MeCN, reflux, 46%.

Scheme 1.16: Formation of THFs and THPs linked to Carbocycles, Reported by Hulcoop *et al.*[47]

The aim of the study was to develop a general oxidative substitution procedure in which pendant alcohols **66** would react with a radical adduct, previously formed from the cyclisation of the radical generated with MAN in the initiation step. While Cu(II) additives appeared to be unnecessary and even detrimental to the product yield in the formation of THF **67**, Cu(II) salts with poorly coordinated anions were essential for the synthesis of THP **68** (**Scheme 1.16** and **Scheme 1.17**).

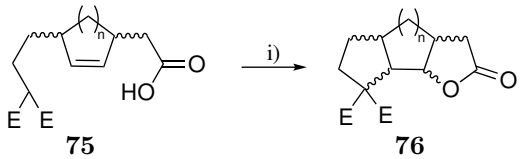
The THF **67** was proposed to be formed after the reductive elimination of the metallopyran system **73** (n = 1). In the case of the THP product **68**, the formation of its corresponding metallooxepane **73** (n = 2) was considered less favourable since a 1,5-H-atom transfer to yield the corresponding α-hydroxy radical (not shown) was a faster process. Such α-hydroxy radical (not shown in scheme) was oxidised by Mn(III) to deliver the aldehyde **71**, which was transformed into the acetal **70** under the reaction conditions in EtOH. To avoid the formation of **71** and **70**, Cu(II) was necessary to form the corresponding organocopper intermediate **72**, which was considered the precursor for the desired THP **68** and also to the lactone **74** after participation of one of the esters. Lower yields were observed for the THF **67** when Cu(II) was present, as a consequence of having the possibility for β-hydride elimination as the termination step (**Scheme 1.17**). In line with Kochi's studies, the use of $Cu(OAc)_2$ gave a higher

proportion of β-hydride elimination, whereas $Cu(OTf)_2$ and $Cu(BF_4)_2$ are the copper salts of choice for oxidative substitution.



Scheme 1.17: Cyclisation Mechanism for the Formation of THFs and THPs linked to Carbocycles, Reported by Hulcoop *et al.*[47]

In both cases, modest yields were obtained for the THFs and THPs products due to the number of side-products often formed. Nevertheless, the results showed that Cu(II) salts with poorly coordinated anions favoured the oxidative substitution. The methodology was further extended to a high-yielding synthesis of tricyclic γ-lactones **76** from the malonate-containing cyclic unsaturated acids **75** (**Scheme 1.18**).[48] This example demonstrates the high applicability of the methodology for the construction of molecular complexity in one step, which proves to be highly valuable in natural product synthesis.

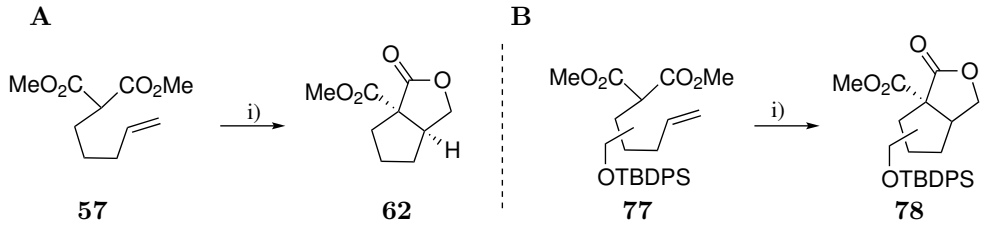


Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OTf)_2$, MeCN, reflux; n = 1, 2, 3; E = CO_2Me; 23-94%, 6 examples.

Scheme 1.18: Formation of Tricyclic γ-Lactones, Reported by Hulcoop *et al.*[48]

1.2.5.2 Efficient Synthesis of Polycyclic γ-Lactones in All-Carbon Systems

Since $Cu(OTf)_2$ was known to have a strong effect in the outcome of the MAN-based oxidative radical cyclisation, Burton and co-workers decided to revisit Snider's study on the effect of the solvent in the oxidative radical cyclisation of dimethyl 4-pentenyl malonate **57** (see **Scheme 1.14**).[46] Due to their adjacent quaternary and tertiary stereocenters and differentiated oxygen functionalities, [3.3.0]-bicyclic γ-lactones **62** were considered highly versatile intermediates in natural product synthesis. For this reason, Burton and co-workers considered that the optimisation of the reaction conditions was essential for the MAN-based methodology to be applicable. Pleasingly, the previously reported MAN / $Cu(OTf)_2$ oxidative system in acetonitrile was found to be more powerful (**Scheme 1.19**) than the conditions described by Snider consisting on MAN and $Cu(OAc)_2$ in acetic acid (**Scheme 1.14**), giving the desired product **62** in an improved yield of 92%.[49]



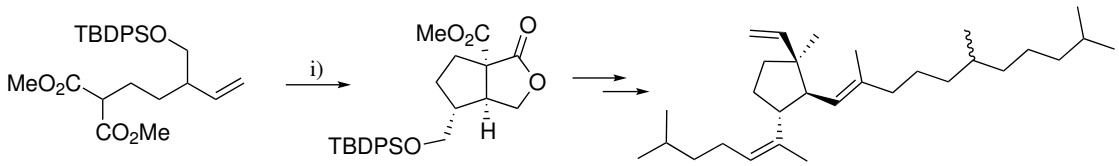
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OTf)_2$, MeCN, reflux. **A**) 92% ;**B**) 88-92%, 3 examples.

Scheme 1.19: Optimisation of the Experimental Conditions for the Preferential Formation of Fused Bicyclic γ-Lactones, Reported by Powell *et al.*[49]

The methodology was further extended to more complex substrates. Pendant protected alcohols **77** were compatible under the reaction conditions (**Scheme 1.19**) and a good yielding formation of bicyclic and tricyclic γ-lactones from 1,2-disubstituted and trisubstituted alkenes also proved possible.[49] The value of the substrates containing pendant protected alcohols **77** was shown in the total synthesis of the racemic 7,11-cyclobotryococca-5,12,26-triene natural product **81**. The substrate 4-pentenyl methyl malonate **79** cyclised in good yields to the γ-lactone **80**, which after chemical manipulations was converted into the natural product **81** (**Scheme 1.20**).[50]

A more recent application was published in 2016 for the synthesis of the sesquiterpene natural product aphanamol I **84** in both racemic and enantiopure forms from 4,6-heptadienyl malonate **82** through formation of a vinyl-substituted [3.3.0]-bicyclic lactone **83** (**Scheme 1.21**).

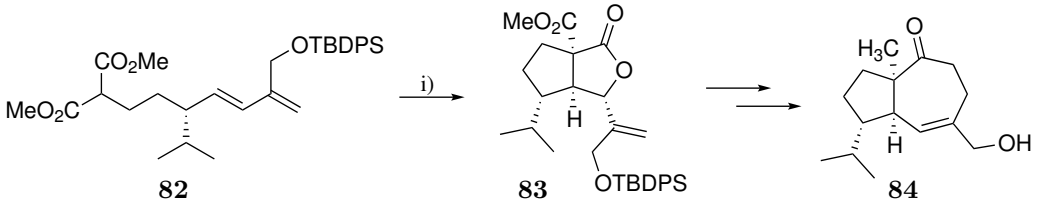
Expansion of the methodology to create vicinal quaternary, tertiary, tertiary stereocentres; quaternary, quaternary, tertiary stereocentres; and the more challenging all quaternary stereocentres was also



79 **80** **81**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OTf)_2$, MeCN, reflux; 75-88%, 13:1 *dr.*

Scheme 1.20: Total Synthesis of Racemic 7,11-Cyclobotryococca-5,12,26-triene, Reported by Davies *et al.*[50]



82 **83** **84**

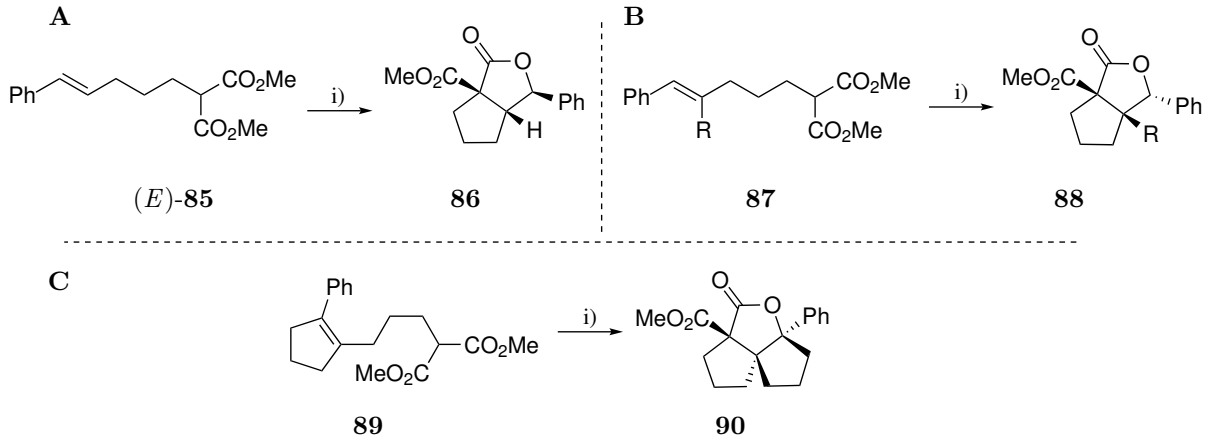
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OTf)_2$, MeCN, reflux, 89%, 6:1 *dr.*

Scheme 1.21: Total Synthesis of Aphanamol I, Reported by Ferrara *et al.*[51]

documented.[52] Cyclisation of the styrene-derived substrate (*E*)-**85** to the γ-lactone **86** occurred in 84% yield (**Scheme 1.22**). Substitution at the aromatic ring with both electron-rich and electron-poor substituents were well tolerated although electron-donating substituents decreased the diastereomeric ratio. The purpose of using styrene derivatives was to favour the cyclisation and the second oxidation by stabilising the generated carbocation. Trisubstituted alkenes **87** also performed efficiently under the oxidative conditions with good diastereoselectivities, even in the presence of sensitive functional groups such as alkynes and silyl protecting groups. The tetrasubstituted alkene **89** gave access to the single diastereoisomer **90** in good yield, which again was a showcase of the robustness of the methodology (**Scheme 1.22**).[52]

1.2.5.3 Amido Malonates for the Synthesis of Fused γ-Lactone-γ-Lactams

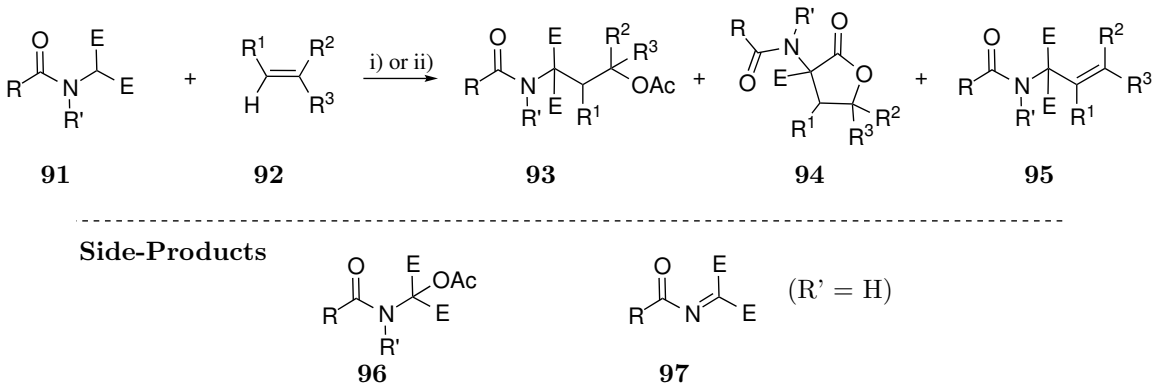
All-carbon systems with mono, di, tri and tetrasubstituted alkenes all perfomed very well under MAN-based conditions; however, these results raised the question of whether a further extension of the methodology towards the synthesis of fused γ-lactone heterocyclic motifs was possible. Pioneering work on this strategy was first reported by Citterio *et al.*,[53] with the study of the reactivity of ambiphilic radicals towards alkenes and metal oxidants. Oxidative C-C bond processes rely on the use of highly electrophilic carbon radicals sources. In that way, the formed radical presents a high oxidation potential due to the presence of the electron-withdrawing groups, meaning that the reaction with the alkene should be faster than a second oxidation with the radical initiator (metal oxidants). The reactivity of carbon radicals



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OTf)_2$, MeCN (0.4 M), 80 °C. **A**: 84%, 4.1:1 *dr*; **B**: R = alkyl, propargyl, $(CH_2)_2$OTBDPS, 74-96%, 8.0:1-11.9:1 *dr*; **C**: 86%)

Scheme 1.22: Extension of the MAN-Based Methodology to di-, tri- and tetrasubstituted Alkenes, Reported by Logan *et al.*[52]

sources bearing both electron-withdrawing and electron-donating groups (ambiphilic character) was less obvious, a fact that stimulated Citterio and co-workers to work on substituted α-amidomalonyl radicals and conjugated olefins. A range of products (**93**, **94** and **95**) resulting from addition/acetoxylation, addition/lactonisation or addition/elimination respectively were observed depending on the type of substrate **91** and alkene **92** used. (**Scheme 1.23**).



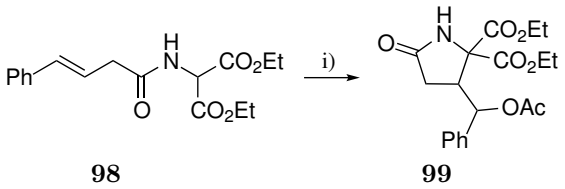
Reagents & Conditions: **E** = CO_2Et; **R′** = H, Me; **R**^{1} = H, CH=CHCH$_2$, CH=CH-O, CH=CH-S; **R**^{2} = Ph, Me, CH=CHCH$_2$, CH=CH-O, CH=CH-S; **R**^{3} = H, Ph, C(Me)=CH$_2$. i) $Mn(OAc)_3 \cdot 2H_2O$, AcOH, 80 °C, 8 h; ii) $Mn(OAc)_3 \cdot 2H_2O$, neat, 65 °C, 12 h.

Scheme 1.23: MAN-Based Oxidative Addition of α-Amido Ester Malonates to Substituted Alkenes, Reported by Citterio *et al.*[53]

Acetoxy derivatives **93** and lactones **94** were preferentially obtained with terminal alkenes; while alkenes **95** were the major products when alkenes **92** were part of a heteroaromatic ring such as furan and thiophene. Oxidation products **96** and **97** of the amido ester malonate **91** were also observed in the

less electrophilic substrates in low yields (4-16%).[53]

The first intramolecular oxidative addition was also reported with the cyclisation of **98** to give the γ-lactam **99** (**Scheme 1.24**).

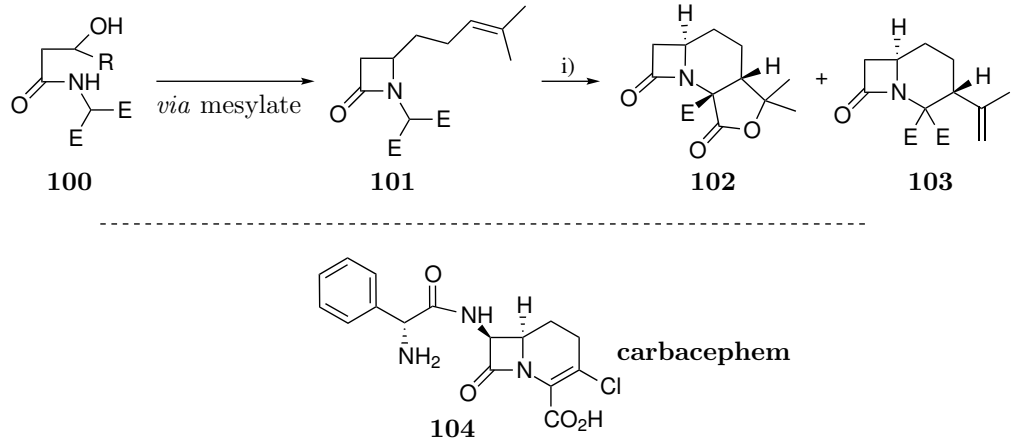


98 **99**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$.

Scheme 1.24: Intramolecular MAN-Based Oxidative Addition for the Formation of γ-Lactams, Reported by Citterio *et al.* (yield not reported).[53]

An additional contribution to the field was made two years later by Miller and co-workers, who used the MAN-based methodology in β-lactam-containing substrates **101** for the MAN-based oxidative radical cyclisation with the aim of developing an efficient route towards the antibiotics carbacephems **104** *via* formation of **102** and **103** (**Scheme 1.25**) .[54]



100 **101** **102** **103**

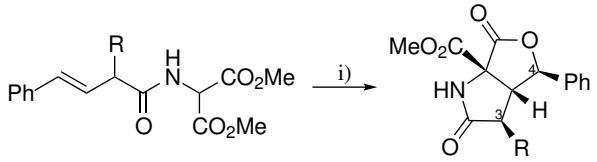
104

Reagents & Conditions: E = CO_2Et; i) $Mn(OAc)_3 \cdot 2H_2O$, AcOH, 55 °C, 1 h. **102**: racemic, 20%; **103**: racemic, 15%.

Scheme 1.25: Intramolecular MAN-Based Oxidative Cyclisation of Unsaturated β-Lactams, Reported by Miller *et al.*[54]

On the basis of these precedents, Burton and co-workers extended the previous methodology (see **Section 1.2.5.2**) to α-amido alkyl malonates **105** to create a general, mild and diastereocontrolled procedure for the synthesis of fused γ-lactams γ-lactones **106** (**Scheme 1.26**). This structural framework is an important intermediate in the synthesis of natural products. In contrast to the experimental conditions optimised for all-carbon systems (see **Scheme 1.22** and **Scheme 1.19**), the reaction could be performed at room temperature with high levels of diastereoselectivity. An additional stereocenter

could be introduced into the molecule (when R ≠ H), which also gave products with four stereocentres in good yields and diastereoselectivities (**Scheme 1.26**).



105 **106**

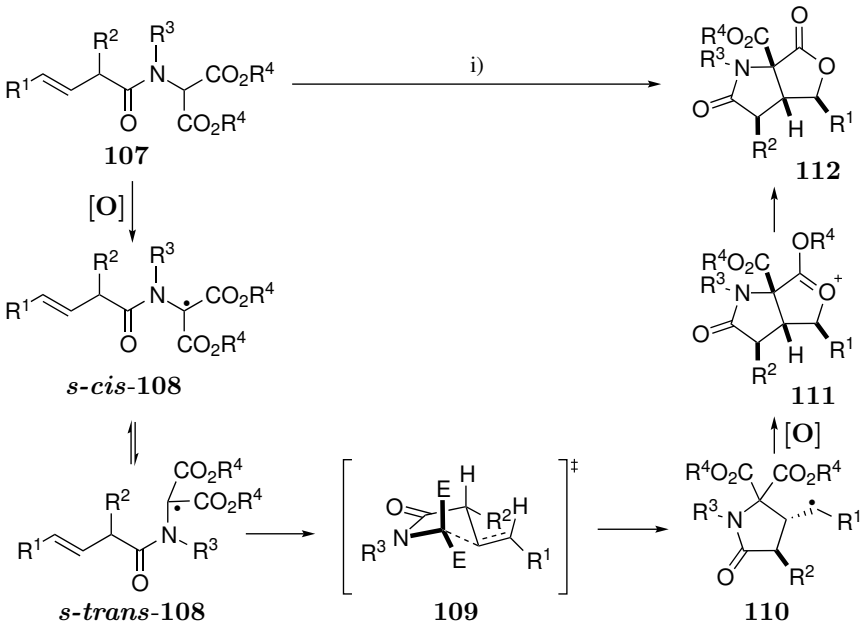
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN (0.05 M), 25 °C. **R = H**: 72%, 14:1 *dr*; **R = alkyl**: 65-84%, 6.6:1->25:1 *dr*; **R = propargyl**: 76%, 18:1 *dr*; **R = allyl**: 74%, 19:1 *dr*; **R = Bn**: 87%, 11:1 *dr*; **R = benzyloxyethyl**: 70%, 25:1 *dr*.

Scheme 1.26: Diastereocontrolled Synthesis of Fused γ-Lactam γ-Lactones, Reported by Logan *et al.*[55]

In all cases the observed diastereoselectivities were in accordance with a modified Beckwith-Houk model **109** for the chair-like transition state (see **Section 1.1.3**) characteristic of 5-*exo*-trig cyclisations, in which all substituents should adopt pseudo-equatorial positions in order to minimise 1,3-diaxial strain.[14,15,17] Mechanistically, a single electron oxidation occurs at the α-position of the amide **107** (**Scheme 1.27**). The formed radical **108** is likely to be present as a mixture of *s-cis* and *s-trans* rotamers **108**. In order to avoid geometric restrictions in the cyclisation, the radical **108** needs to be in the *s-trans* form, meaning that interconversion between *s-cis* and *s-trans* should not be highly energetic to allow the molecule to assemble as depicted in **109** before the 5-*exo*-trig cyclisation takes place. Once the radical adduct **110** is formed, a second oxidation follows, which after participation of the ester gives **111**, further hydrolysed to the substituted γ-lactam γ-lactone **112** (**Scheme 1.27**).

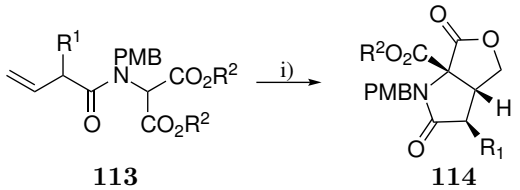
The examples depicted in **Scheme 1.26** all shared a common structural framework: the unprotected amide and a phenyl 1,2-disubstituted alkene. The methodology was later expanded to encompass terminal alkenes which gave the corresponding γ-lactam γ-lactones in good yields and with good diastereoselectivities (**Scheme 1.28**).

Synthetic utility was later shown in the Burton group by Foster and Logan with the efficient synthesis of Danishefsky's intermediate **118** in the formal synthesis of salinosporamide A **119** (**Scheme 1.29**).[55] The precursor **116** was synthesised in 5 steps from γ-butyrolactone **115** and subjected to the standard conditions to form γ-lactam γ-lactone **117** in 65% yield. A single chemical manipulation led to Danishefsky intermediate **118**, which was converted by Danishefsky into salinosporamide A **119**.[56] A total synthesis of salinosporamide A was also completed in the Burton group by Marx.[57]



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN. E = CO_2R^4

Scheme 1.27: Proposed Mechanism for the Synthesis of Fused γ-Lactam γ-Lactones, Reported by Logan *et al.*[55]



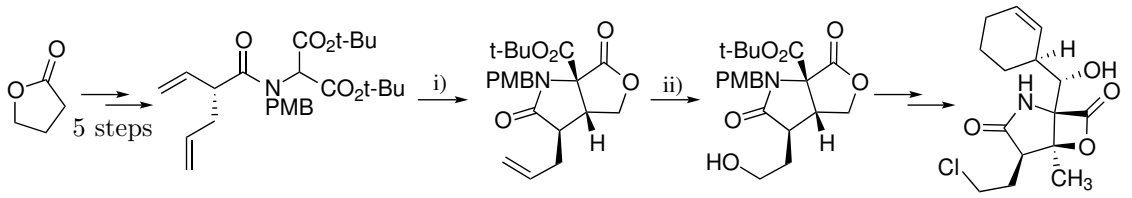
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN (0.40 M), 40 °C. $\mathbf{R^1}$ **= H, Bn, allyl** and $\mathbf{R^2}$ **= Me, Et, *t*-Bu**: 10-75%, >15:1 *dr*.

Scheme 1.28: Cyclisation of Terminal Alkene Substrates, Reported by Logan *et al.*[55]

1.2.5.4 Fused THF-γ-Lactones and *bis*-γ-Lactones. Captodative Radicals.

THF motifs are particularly interesting since they are ubiquitous in a number of biologically active natural products such as polyketides, acetogenins,[58] halogenated natural products and numerous terpenes.[59] The formation of THF-linked carbocycles have already been published in the group;[47] however, the success encountered in the formation of γ-lactams-γ-lactones motifs pushed the group to extend the methodology towards unsaturated ether and ester alkyl malonates for the formation of fused THF γ-lactones and *bis*-γ-lactones respectively.[60]

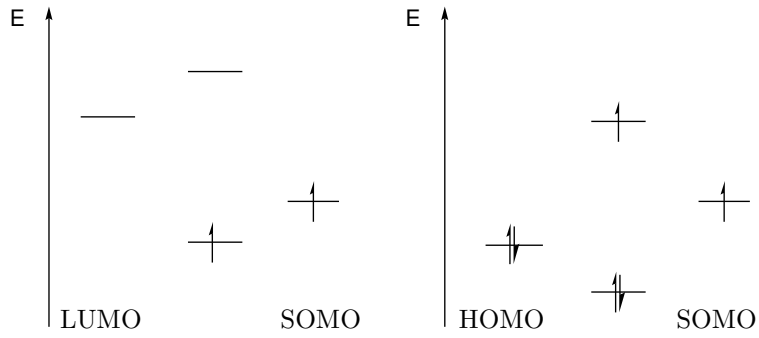
Captodative Radicals: An Explanation. A radical is considered captodative when the carbon is substituted by both electron-withdrawing and electron-donating groups, hence the free radical can be



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), MeCN (0.40 M), 40 °C, 65%; ii) O_3/O_2, 3:1 DCM/MeOH, -78 °C; then $NaBH_4$, MeOH, 88%.

Scheme 1.29: Formal and Total Synthesis of Salinosporamide A, studied by Marx *et al.*[55,57]

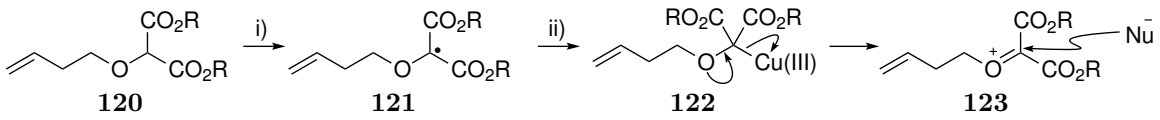
thermodynamically stabilised by both groups through conjugation of the unpaired electron. Frontier orbital theory gives a representation of the orbital interactions responsible for such stabilisation. The interaction between the LUMO of the electron-accepting group and the SOMO of the unpaired electron results in lowering the energy of the SOMO. In addition, the SOMO also interacts with the HOMO of the electron-donating substituent leading to a general stabilisation of the system, despite having the unpaired electron in a more energetic orbital, which consequently makes it more nucleophilic. Substituents of opposite polarity are then acting in synergy for the stabilisation of the radical (**Scheme 1.30**).[61]



Scheme 1.30: Frontier Orbital Theory Representation for Captodative Radicals.[61]

Due to the captodative character associated with ether malonyl radicals, the Burton group was first sceptical in their use as substrates.[61] Their higher stability was proposed to make the oxidation at the malonic position more likely to happen since these radicals (*e.g.* **121**, **Scheme 1.31**) have a longer half-life and formation of the Cu(III) complex **122** could be faster than the desired cyclisation. Participation of the oxygen lone pairs could reduce Cu(III) to Cu(I), thus forming the oxocarbenium ion **123**, which would be susceptible for attack by a nucleophile (**Scheme 1.31**). The same character is found in unsaturated amido malonates and ester malonates; however, since the nitrogen and oxygen lone pairs are delocalised onto the carbonyl, it was thought that the stabilising character would be less

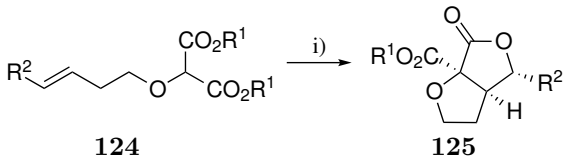
problematic.



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ ii) $Cu(OTf)_2$.

Scheme 1.31: Oxidation of Ether Malonyl Radicals. Captodative Radicals.

THFs and *bis*-γ-Lactones. Despite the inherent stabilisation present in ether malonyl radicals, these gratifyingly cyclised to give the desired fused THF-γ-lactones **125** in good to excellent yields with substrates containing both terminal and phenyl-substituted alkenes and methyl and *tert*-butyl esters malonates **124** (**Scheme 1.32**). As in the case of the all-carbon series,[49] the alkyl-substituted alkene ether malonates (R^2 = Et) did not perform with the same efficiency, giving products in modest yield and diasteroselectivity.



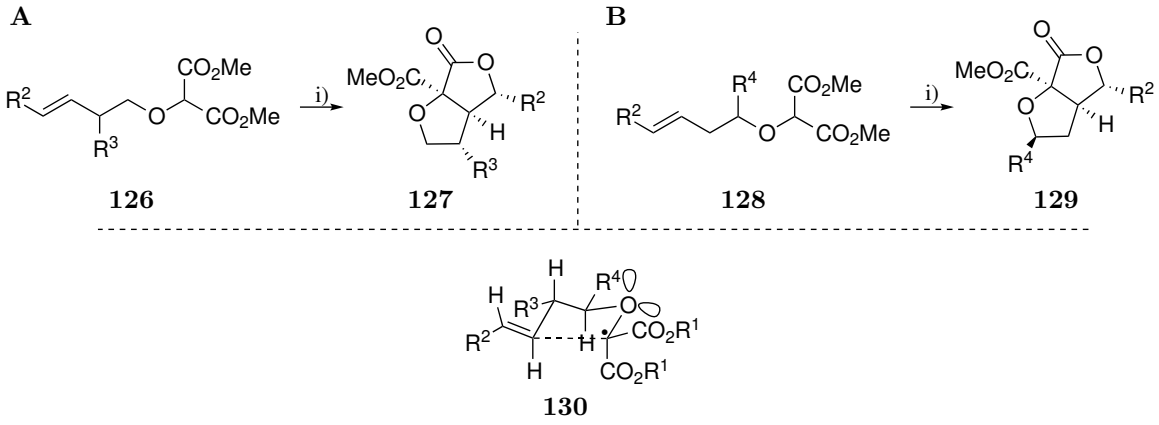
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OTf)_2$, MeCN, 40 °C. $\mathbf{R^1}$ **= Me, *t*-Bu** and $\mathbf{R^2}$ **= H, Ph**: 62-92%, 14:1-16:1 *dr*; $\mathbf{R^1}$ **= Me** and $\mathbf{R^2}$ **= Et**: 50%, 2:1 *dr*.

Scheme 1.32: THF-γ-Lactone Formation, Reported by Chany *et al.*[60]

Allylic and homo-allylic substituted ether malonates **126** and **128** also cyclised to give **127** and **129** respectively in good to excellent yields (**Scheme 1.33**); however, diastereocontrol was found to be more moderate than in the all-carbon systems, except with more sterically encumbered substituents. By analyzing the Houk-Beckwith chair-like transition state **130** associated to ether malonates (**Scheme 1.33**), it was found that allylic substituents in pseudo-axial positions have a minimised 1,3-diaxial interactions with one of the lone pairs of the oxygen, which accounts for the lower reported diastereoselectivities.[60]

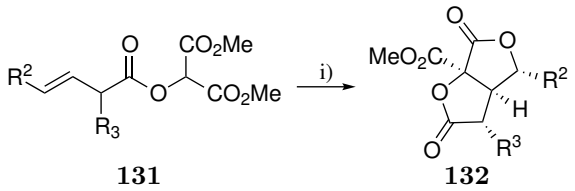
Concerning the synthesis of fused *bis*-lactones **132**, four examples were reported in good yields and diastereoselectivities from terminal unsaturated and styrene-derived ester malonates **131** as substrates (**Scheme 1.34**).

In conclusion, the standard methodology developed for all-carbon systems was applicable not only to α-amido malonates (see **Section 1.2.5.3**), but also to α-ether and α-ester unsaturated malonates, despite the captodative character associated with this type of malonyl radicals. The oxidant system MAN



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$,$Cu(OTf)_2$, MeCN, 40 °C. **A**: $\mathbf{R^2}$ **= H, Ph** and $\mathbf{R^3}$ **= Me, CH_2CO_2t-Bu, *i*-Pr**: 69-92%, 3:1-28.1 *dr*; $\mathbf{R^2}$ **= H, Ph** (6 examples). **B**: $\mathbf{R^2}$ **= H, Ph** and $\mathbf{R^4}$ **= Me, *i*-Pr, C_2H_3, Ph**: 61-96%, 2.6:1-7.5:1 *dr* (8 examples).

Scheme 1.33: Cyclisation of Allylic and Homoallylic Substituted Ether Malonates, Reported by Chany *et al.*[60]



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$,$Cu(OTf)_2$, MeCN, 40 °C. $\mathbf{R^2}$ **= H, Ph** and $\mathbf{R^3}$ **= H, *i*-Pr**: 62-77%, 9.6:1-24:1 *dr*.

Scheme 1.34: Formation of *bis*-Lactones, Reported by Chany *et al.*[60]

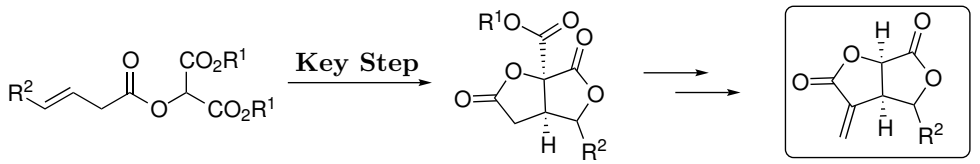
/ $Cu(OTf)_2$ was proven to be a robust methodology for the synthesis of small densely functionalised products with differentiated oxygens (fused THF-γ-lactones and *bis*-γ-lactones) and nitrogen functional groups (γ-lactam-γ-lactones) through the creation of a C-C and a C-O bonds, two rings and three stereocentres in a single step.

1.3 Methodology Limitations and Ph.D. Goals

As seen in **Section 1.2**, the MAN-based intramolecular oxidative radical cyclisation proved to be a highly versatile methodology for the formation of γ-lactone-containing molecules, *exo*-methylene-containing and saturated cyclic compounds.[4] For a number of years, the Burton group studied the transformation and developed standard experimental conditions to efficiently synthesise fused bicyclic γ-lactones (see **Section 1.2.5.2**),[49,52] γ-lactams-γ-lactones (see **Section 1.2.5.3**),[55] THF-γ-lactones and *bis*-γ-lactones (see **Section 1.2.5.4**).[60] The utility of this methodology was illustrated in the synthesis of 7,11-cyclobotryococca-5,12,26-triene (see **Scheme 1.20** and **Section 1.2.5.2**),[50] salinosporamide A (see

Section 1.2.5.3, **Scheme 1.29**);[55] and, more recently, aphanamol I (see **Scheme 1.21** in **Section 1.2.5.2**).[51]

Synthesis of Natural Products. The *bis*-γ-lactone framework represents the main core of the ethisolide family of natural products. On the basis of the Burton group precedents in the formation of such moieties, it was thought that the standard methodology could be key in delivering the corresponding alkyl-substituted *bis*-γ-lactone structure **134**, thus allowing for rapid and efficient synthesis of the natural product family **135** (**Scheme 1.35**).



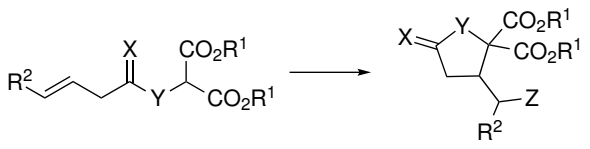
133 **134** **135**
Ethisolide Family

R^1 = Me, Et, *t*-Bu; R^2 = Et, C_8H_{17}, $C_{10}H_{21}$.

Scheme 1.35: Ph.D. Goal: Synthesis of the Ethisolide Family of Natural Products.

Nevertheless, it has also been seen that alkyl-substituted alkenes did not perform well in the oxidative radical cyclisation (see **Scheme 1.32**), and consequently, an optimisation of the standard methodology would be needed for the formation of the *bis*-γ-lactones in good yields. The application of the methodology in the synthesis of the ethisolide family of natural products will be discussed in **Chapter 2**.

Halo-γ-Lactones Formation. The optimisation studies performed for the preferential formation of *bis*-γ-lactones when R^2 = alkyl gave access to an unexplored reactivity of the oxidant system MAN / $Cu(OTf)_2$ with halides. Halo monocyclic systems **137** were formed from both the oxygen and nitrogen series of the alkyl malonates substrates *via* the new methodology (**Scheme 1.36**). A comprehensive discussion concerning the development and extension of the methodology will be given in **Chapter 2**.



136 **137**

$\mathbf{R}^1$ = alkyl, $\mathbf{R}^2$ = H, alkyl, $\mathbf{X}$ = H_2, O; $\mathbf{Y}$ = O, N-PG, NH; $\mathbf{Z}$ = Cl, I. PG = Protecting Group

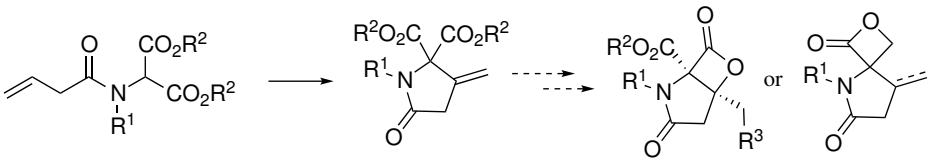
Scheme 1.36: Halo-lactone Formation.

Metal-Free Oxidative Radical Cyclisation. Despite the efficiency and robustness associated with the methodology, concerns about the waste production and the atom-economy of the transformation emerged as a result of the use of stoichiometric amounts of metals. An alternative procedure to perform a chemical oxidation in a metal-free fashion could involve the use of electrochemistry; hence, pioneering studies in the formation of bicyclic γ-lactones **139** from **138** (**Scheme 1.37**) through anodic oxidation will be presented in **Chapter 3**.

138 **139**

Scheme 1.37: Alternative Metal-Free Methodology for the Synthesis of Bicyclic γ-Lactones.

Towards Proteasome Inhibitors Analogues: β-Lactones γ-Lactams. Aside from the effective formation of γ-lactones, an additional interest grew for the formation of *exo*-methylene cyclic compounds for further derivatisation. After the development of the optimised conditions for all-carbon systems,[49] it was thought that the same conditions could be applied to α-amido malonates **140** to form *exo*-methylene γ-lactam products **141** (**Scheme 1.38**). Such structures were appealing as they were considered potential precursors of both fused and spiro β-lactones γ-lactams **142** and **143**, which would be analogues of the proteasome inhibitor salinosporamide A **119** (see **Scheme 1.29**). Studies towards the synthesis of β-lactones-γ-lactams through the formation of *exo*-methylene γ-lactam and / or γ-lactams γ-lactone molecules will be discussed in **Chapter 4**.

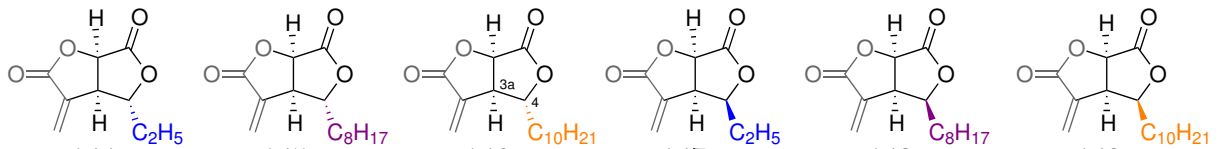


140 **141** **142** **143**

Scheme 1.38: Studies towards Fused and Spiro γ-Lactam β-Lactone

2

The Ethisolide Family of Natural Products



Scheme 2.1: Ethisolide Family of Natural Products.

2.1 The Ethisolide Family: Isolation and Biological Activities

2.1.1 Avenaciolide, *iso*-Avenaciolide and Ethisolide

Avenaciolide **145** was isolated from a strain of *Aspergillus avenaceus* and was the first of the five natural products to be structurally determined from both degradation and NMR studies.[62] Naturally-occurring avenaciolide **145** was initially suggested to have the configuration 3a*S*, 4*S*, 6a*S*; however, the first enantioselective synthesis of (–)-avenaciolide indicated the opposite absolute configuration.[63] Avenaciolide **145** displays antifungal activity for a wide range of fungi such as *Botrytis allii* and *Penicillium gladioli*; however, bacterial inhibition was weaker in assays against *B. subtilis*.[62] The same compound has also been isolated from a strain of *Aspergillus fischeri* var. glaber.[64] *iso*-Avenaciolide **148** was further isolated as a minor metabolite from a large scale growing of *Aspergillus avenaceus* and identified as a diastereoisomer of avenaciolide.[65] At the same time, ethisolide **147** was isolated from unidentified *Penicillium* species and structurally characterised with mass spectrometry and NMR spectroscopy, and by data comparison with avenaciolide **145** and *iso*-avenaciolide **148**.[65] Crystallographic data for (–)-avenaciolide was later published by Hughes.[66] A number of years later, ethisolide **147** was also found in *Penicillium capsulatum* cultures and for the first time was shown to have very high and specific antibacterial activity.[67] More recently, avenaciolide and three of its derivatives have been studied as new leads for combating MRSA (methicillin-resistant *Straphylococcus aureus*) infections. MRSA is a drug-resistant bacteria considered as the major pathogen responsible for nosocomial and community-acquired bacterial infections worldwide.[68]

2.1.2 Discosiolide and *epi*-Ethisolide

Discosiolide **146** was first isolated from *Discosia* sp. strains and was structurally identified by Krohn *et al.*[69] Comparison of $C_{3a}H$–C_4H coupling constants between discosiolide **146** and avenaciolide **145**, *iso*-avenaciolide **148**, and ethisolide **147** allowed for the assignment of the stereochemistry at C_4H. *epi*-Ethisolide **144** was isolated from the *Pezicula livida* strain, and showed a spectroscopic data very similar to those found for discosiolide **146**, except for the signals corresponding to the ethyl chain.[69] Thus, the metabolite was identified as epimeric to ethisolide **147**. Both discosiolide **146** and *epi*-ethisolide **144** were found to be biologically active against bacteria, fungal and algae test organisms; however herbicidal activity was only observed for *epi*-ethisolide **144**.[69] As the isolation of the diastereoisomer of discosolide **149** has not been reported in the literature, we considered the molecule **149** as a non-natural analogue

of discosiolide **146**, which we took the liberty of naming '*iso*-discosiolide'.

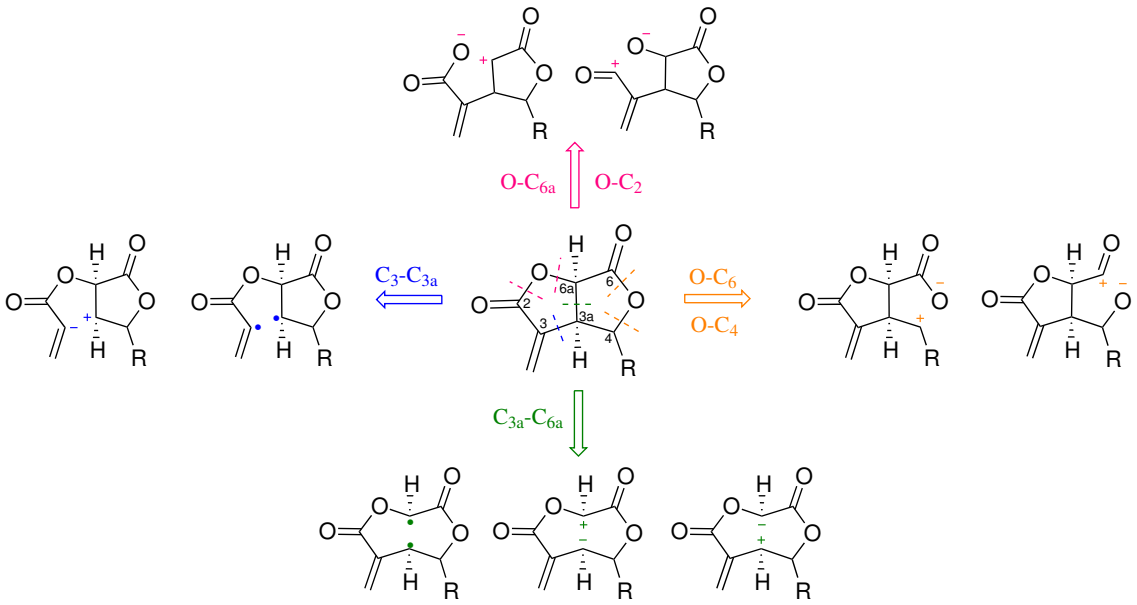
2.1.3 Other Biological Activities

Glutamate Transport. Glutamate transport across the mitochondrial membrane is proposed to have a regulatory function in the physiology of liver cells by providing intramitochondrial ammonia for the synthesis of carbamoyl phosphate, intermediary metabolite in nitrogen disposal.[70] Inhibition of the glutamate transport in the rat liver mitochondria was observed with avenaciolide **145**, while *iso*-avenaciolide **148** was found to be much less effective and ethisolide **147** not active at all.[70] The described mode of action implied covalent binding between thiol groups present in the glutamate carrier and the *exo*-methylene moiety of the inhibitor. Experimental data suggested that the SH group(s) of the carrier were located in the hydrophobic part of the membrane.[70] Although the *exo*-methylene moiety is a common feature in the family of natural products, it seemed that the length and disposition of the hydrophobic chain was essential in accommodating the natural product into the lipophilic part of the membrane so as to allow the covalent bond to occur.[70,71]

Protein Phosphatases. Additional biological activity for the natural products was later reported by Ueda *et al.*,[72] in which they identified *iso*-avenaciolide **148** as a potent inhibitor of a human dual-specificity phosphatase (DSPase) called VHR (vaccinia H1 related). Protein phosphatases control phosphorylation levels of proteins, which is a fundamental regulation mechanism of intracellular signal transduction involved in cellular events such as growth and differentiation. Inhibition of protein phosphatases is considered a useful tool to reveal signal transduction pathways of immune responses as well as to cure immunological diseases. The authors reported that *iso*-avenaciolide **148** binds covalently to the SH-group of cysteine residues by a 1,4-addition to the *exo*-methylene moiety. The same mechanism has been reported for the interaction between cytotoxic α-methylene γ-lactone-containing natural products and model biological nucleophiles.[73]

The five natural products **144**, **147**, **148**, **145** and **146**, and the non-natural *iso*-discosiolide **149** are all considered as highly reactive Michael acceptors due to the *exo*-methylene moiety in the α-position to the carbonyl of the γ-lactone. Differences and efficacies in their biological activities are then dependent on the length and disposition of the alkyl chain in C_4. Despite their relatively small size, the family of natural products attracted the attention of the synthetic community as a result of their densely functionalised structures and their diverse reported biological activities.

2.2 Synthetic Antecedents



Scheme 2.2: Retrosynthetic Analysis for the Ethisolide Family of Natural Products.[74]

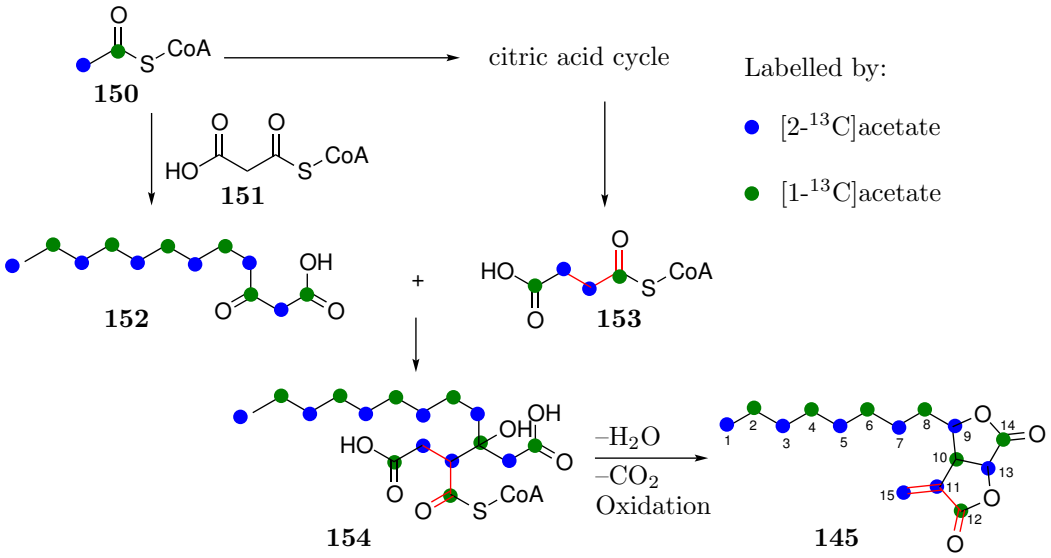
The crucial part in the synthesis of these molecules is the construction of the *bis*-lactone framework. Carbon-carbon, carbon-oxygen or a combination of both bond formation have been studied by a number of research groups.[74] Strategies have included the formation of one ring at a time or considered the simultaneous construction of both rings either through radical and/or ionic strategies (**Scheme 2.2**).

2.2.1 Biosynthetic Origins

In 1974, Tanabe *et al.* reported biosynthetic studies based on ^{13}C-NMR techniques.[75] ^{13}C- Enriched avenaciolide **145** was prepared in two parallel experiments from growing cultures of *Aspergillus avenaceus* fortified with sodium [1-^{13}C]acetate in one experiment and sodium [2-^{13}C]acetate in the other one. Based on the fortified medium, the *bis*-lactones were labelled at alternate carbon positions as indicated by the ^{13}C-NMR intensity signals (**Scheme 2.3**).

The studies revealed that 3-oxododecanoic acid **152** was an intermediate formed from acetyl-coenzyme A (Acetyl-CoA) **150** and malonyl-CoA **151**. Condensation of the ketoacid **152** with succinyl-CoA **153**, previously synthesised from the citric acid cycle (Krebs cycle), led to **154**, which was converted into avenaciolide **145** after loss of water, decarboxylation and oxidation (**Scheme 2.3**). Despite the enrichment with ^{13}C-acetate, the signal corresponding to C_{12} appeared to be weaker than that of the

C_{14} carbonyl peak. This observation was an indication that the C_{12}-containing fragment was derived from succinyl-CoA **153**, in which ^{13}C-labels were diluted through the citric acid cycle.



Scheme 2.3: ^{13}C-NMR Biosynthetic Studies of Avenaciolide, Reported by Tanabe.[75]

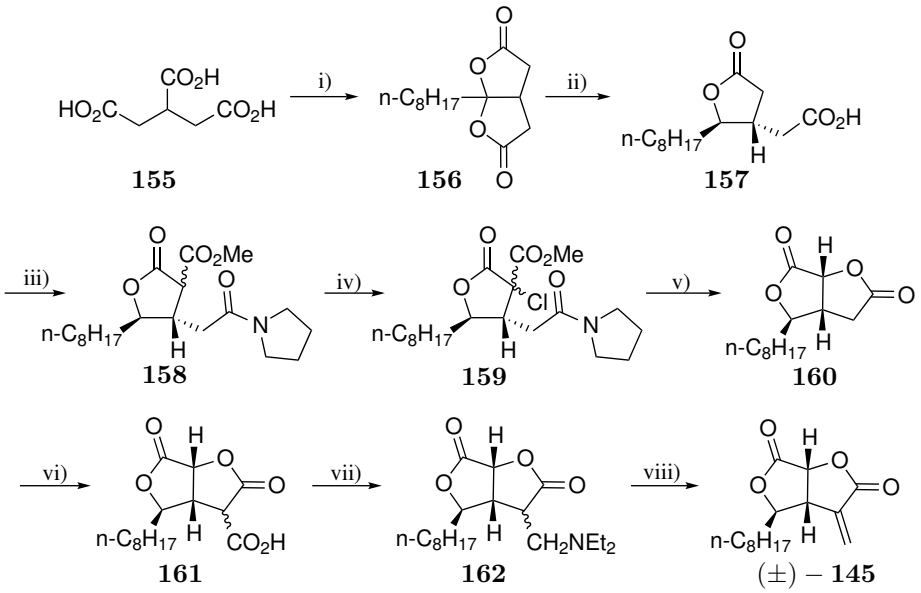
2.2.2 Avenaciolide and *iso*-Avenaciolide Synthetic Studies

2.2.2.1 First Syntheses: Avenaciolide

The Parker and Johnson Approach Avenaciolide **145** has been the most synthetically studied natural product in the family.[74] The first total synthesis of avenaciolide **145** in racemic form was published by Parker and Johnson,[76,77] which served as a corroboration for the structure proposed and reported by Brooks.[62] By taking advantage of the methodology previously developed in Johnson's and Parker's laboratories for the formation of α-methylene butyrolactones,[78] the authors opted for a late-stage methylenation from the *bis*-lactone **160** (**Scheme 2.4**). The efficiency of this step was such that it became a standard method for this type of transformation and a number of the syntheses published thereafter incorporated this methylenation step in their 'end-game' strategy.[74]

Parker and Johnson submitted tricarballylic acid **155** to an acylative decarboxylation with *n*-nonanoic anhydride to give the *bis*-lactone **156**,[79] which was further reduced to the *trans*-disubstituted γ-lactone **157** in high yield. The carboxylic acid was protected as an amide *via* acyl chloride formation, which allowed the α-carbomethoxylation of the γ-lactone to give the β-dicarbonyl compound **158**. Chlorination at the most acidic position gave the haloamidoester **159**, which after heating at reflux in acid, cyclised

to form the *bis*-lactone framework **160** after decarboxylation. Treatment with the Stile's reagent[78,80] gave the acid **161**, which after a second decarboxylation, reacted with the iminium ion formed from formaldehyde and diethyl amine to give **162**, which under thermal conditions created the *exo*-methylene moiety, *i.e.* avenaciolide **145** in racemic form (**Scheme 2.4**).

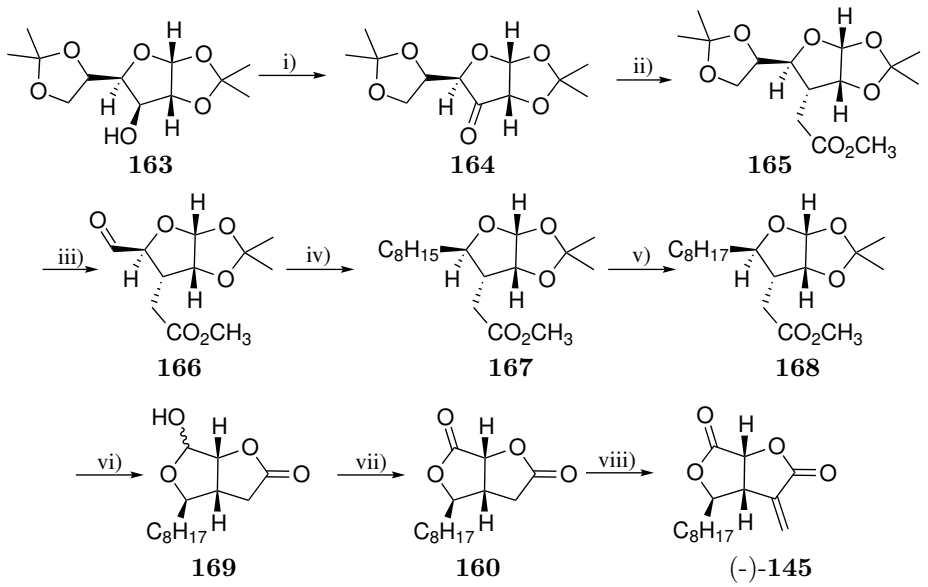


Reagents & Conditions: i) (n-$C_8H_{17}CO)_2O$, 185 °C, 49%; ii) $NaBH_4$, NaOH, H_2O, 91%; iii) 1: $SOCl_2$, pyrrolidine, 81%, 2: $(MeO)_2CO$, NaH, 82%; iv) NaClO; v) HBr, Δ, 57%; vi) $MeOMg(OCO_2Me)$ (Stile's reagent), 75%; vii) $HNEt_2$, HCHO; viii) Δ, 66%.

Scheme 2.4: First Total Synthesis of Avenaciolide **145** in Racemic Form, Reported by Parker and Johnson.[76,77]

First Asymmetric Syntheses from D-Glucose. The first synthesis of avenaciolide **145** as a single enantiomer was reported by Anderson and Fraser-Reid two years after Parker and Johnson's synthesis of avenaciolide **145** in racemic form.[63] The authors took advantage of the enantiopurity of diacetone-D-glucose **163** (**Scheme 2.5**) and started with the alcohol oxidation to give **164**, followed by a Wittig / hydrogenation sequence to give **165**.[81,82] Hydrolysis of the acetonide, followed by oxidative cleavage formed the aldehyde **166**, which was converted into the desired aliphatic chain **168** after a Wittig / hydrogenation sequence *via* the formation of **167**. In the next steps, strong acidic conditions resulted in the removal of the remaining acetonide, thus triggering the lactonisation to form the hemiacetal **169**, which was subsequently oxidised to form Parker and Johnson's intermediate **160** (**Scheme 2.5**).[76,77]

The measured specific rotation $[\alpha]_D^{29.5}$ = -41.08°, which was in accordance with the reported literature value $[\alpha]_D^{26.5}$ = -41.6° ,[62] allowed the reassignment of the absolute configuration of the naturally-occurring enantiomer to 3aR, 4R, 6aR, thus correcting the originally proposed assignment proposed by Turner (see



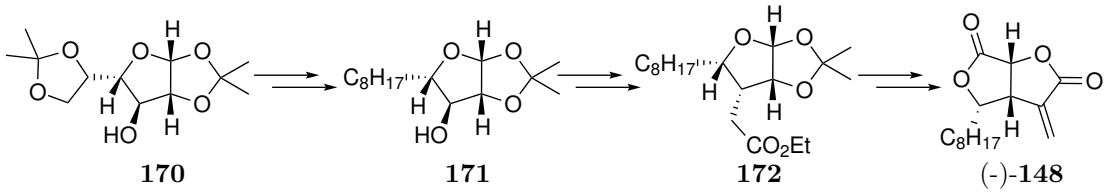
Reagents & Conditions: i) pyridinum dichromate (PDC); ii) 1. $(CH_3O)_2P(O)CH_2CO_2CH_3$, *t*-BuOK, DMF; 2. H_2, Pd;[82] iii) 1. AcOH / H_2O; 2. $NaIO_4$; iv) $C_7H_{15}PPh_3Br$, BuLi, THF, r.t., 70%; v) H_2, Pd-C, EtOH, 87%; vi) 0.5% H_2SO_4, H_2O-dioxane, 95%; vii) Jones' reagent, 77%; viii) Parker and Johnson's methylenation.[76–78]

Scheme 2.5: First Asymmetric Total Synthesis of (-)-Avenaciolide, Reported by Anderson and Fraser-Reid.[63]

Section 2.1.1).[62]

Both (+)- and (–)-avenaciolide **145** were also synthesised in the same year by Ohrui *et al.* by following the same glucose-based approach.[83] They used the same synthetic sequence reported by Anderson and Fraser-Reid to form the natural (–)-avenaciolide. In contrast, for the formation of (+)-avenaciolide (reported $[\alpha]_D^{25} = +41.3°$) the enantiomer of **164** was employed as starting material, which was synthesised by following the procedure reported by Tracey and co-workers.[84]

(–)-*iso*-Avenaciolide was also synthesised by Anderson and Fraser-Reid through the same strategy from diacetone galactose **170** (**Scheme 2.6**).[85]

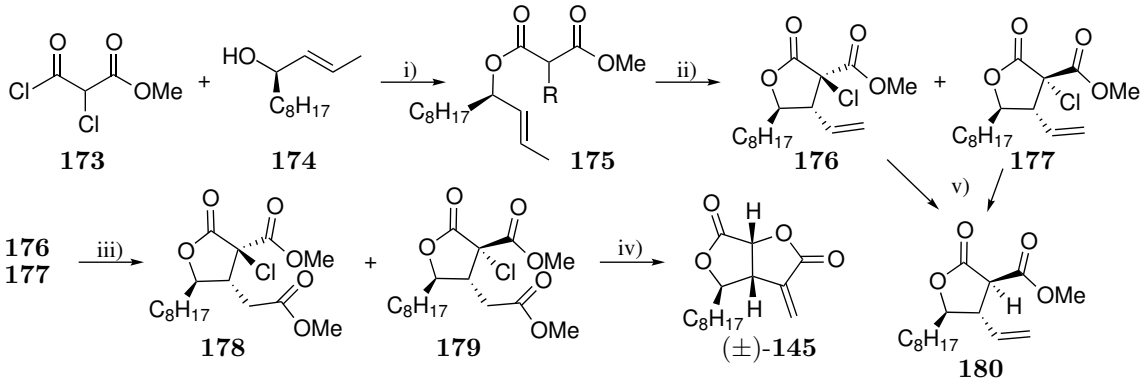


Scheme 2.6: First Asymmetric Total Synthesis of (-)-*iso*-Avenaciolide, Reported by Anderson and Fraser-Reid.[85]

2.2.2.2 C_3-C_{3a} Bond Formation: A Popular Strategy

With more than forty syntheses published for avenaciolide **145** and *iso*-avenaciolide **148**, the aim of this section is not to give a comprehensive review of the different synthetic strategies. The reader is directed to the various cited references in Martin's review for full details.[74] Nevertheless, a more detailed description will be given to the C_3-C_{3a} disconnection, since it has been the most exploited strategy.

Radical Approaches. Snider and co-workers published the synthesis of racemic avenaciolide **145**;[86] however, the initial goal of their studies was the formation of mono α-substituted γ-lactones such as **180** without concomitant polymerisation (**Scheme 2.7**). The challenge involved was that the resulted γ-lactone **180** was more oxidisable than its precursor **175** (R = H) under MAN conditions. An elegant way to overcome this limitation consisted of α-chlorination of the malonate to give precursors such as **175** where R = Cl, which would cyclise to the chloro γ-lactones **176** and **177**. A final reductive cleavage with Zn would give access to the desired γ-lactone **180** (**Scheme 2.7**).



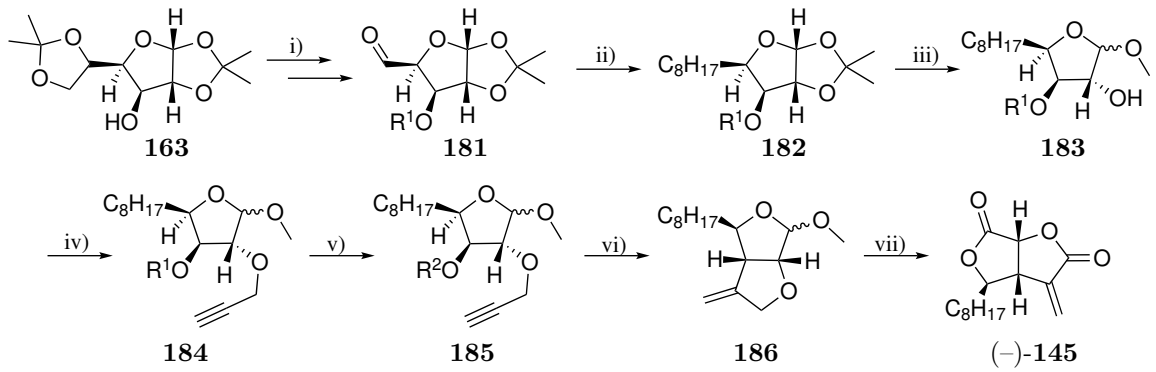
Reagents & Conditions: i) Et_3N, DCM, 78%; ii) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2$, EtOH, 75 °C, compound **176**: 62%, compound **177**: 20%; iii) (1) $H_3B \cdot SMe_2$; (2) CrO_3, AcOH; (3) CH_2N_2, compound **178**: 78%, compound **179**: 67%; iv) (1) HBr, H_2O, dioxane, reflux, 39% from compounds **176** and **177** (2) Parker and Johnson's methylenation;[76,77] v) Zn, AcOH, 95%.[86]

Scheme 2.7: MAN-based Oxidative Radical Cyclisation as Key Step for the Synthesis of (±)-Avenaciolide, Reported by Snider and co-workers.[86]

The synthesis began with the esterification of the acid chloride **173** with the alcohol **174**, followed by the oxidative radical cyclisation of **175** with $Mn(OAc)_3 \cdot 2H_2O$ as initiator and $Cu(OAc)_2$ as co-oxidant in EtOH, to provide the α-chloro γ-lactones **176** and **177**. The *n*-octyl substituent controlled the stereochemistry of the cyclisation, leading to two diastereoisomers at the chlorine-containing stereocenter. Hydroboration of the alkene followed by oxidation and methylation formed the diester γ-lactones **178** and **179**, which after a hydrolysis, decarboxylation, cyclisation[87] and methylenation[76,77] sequence was

converted into (±)-avenaciolide **145** (**Scheme 2.7**).

Success in the formation of the natural (–)-avenaciolide **145** was also achieved by Sharma and co-workers through a radical approach, with diacetone D-glucose **163** as starting material (**Scheme 2.8**). The work of Anderson and Fraser-Reid (see **Scheme 2.5**) was reflected in the first steps of their synthesis in the formation of the aldehyde **181**. The alkyl chain was introduced *via* a Wittig / hydrogenation sequence[81,82] to form **182**. Removal of the acetal and methanolysis led to **183**, from which the free alcohol was deprotonated and alkylated with propargyl bromide to give **184**. Removal of the PMB protecting group and re-protection to form the xantate ester **185** was essential to initiate the reductive radical cyclisation with the alkyne moiety, which led to *exo*-methylene fused *bis*-THFs **186** with the desired configuration. Finally, hydrolysis of the acetal and subsequent oxidation of the formed hemiacetal and the allylic methylene functionalities gave (–)-avenaciolide **145** (**Scheme 2.8**). Additional radical approaches for avenaciolide **145** and *iso*-avenaciolide **148** were also studied by Cossy,[88] Wee,[89] Dugger, and Martin research groups.[90]

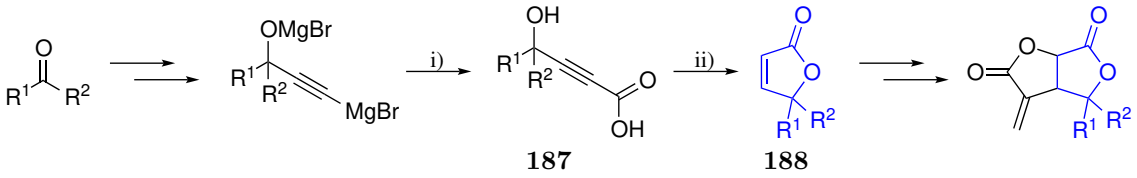


Reagents & Conditions: i) Refer to Anderson and Fraser-Reid synthesis;[63] ii) 1. $C_7H_{15}PPh_3Br$, BuLi, THF, r.t.; 2. H_2, Pd-C, EtOH, r.t., 60%; iii) MeOH, Amberlite, 80 °C; iv) C_3H_3Br, NaH, THF, r.t., 80%; v) 1. DDQ, DCM, r.t.; 2. NaH, CS_2, MeI, THF; vi) *n*-Bu_3SnH, AIBN cat., reflux benzene, 80%; vii) 1. AcOH, HCl, H_2O, 80 °C; 2. CrO_3-Py, DCM, 45 °C (*yield not reported for step vii*); R^1 = PMB; R^2 = C(S)SCH_3.[91]

Scheme 2.8: Radical Approach for the Synthesis of (–)-Avenaciolide, Reported by Sharma and co-workers.[91]

Ionic Pathways. Apart from radical strategies, ionic approaches have also been widely investigated for this type of disconnection. Common precursors involved butenolides **188**, which were available from their corresponding propargylic acids **187** according to the Nobuhara procedure (**Scheme 2.9**).[92] Michael additions of stabilised nucleophiles were the standard method to functionalise the α,β-unsaturated γ-lactones **188** for the construction of the *bis*-lactone moiety.

A representative example that fell into this strategy and involved an alternative method for the introduction of the *exo*-methylene moiety was published by Schlessinger and co-workers.[93,94] Their



Reagents & Conditions: i) $CO_2(s)$, 20 atm, r.t., then H_2SO_4; ii) H_2, Pd-$BaSO_4$, MeOH. *Yields are not reported.*[92]

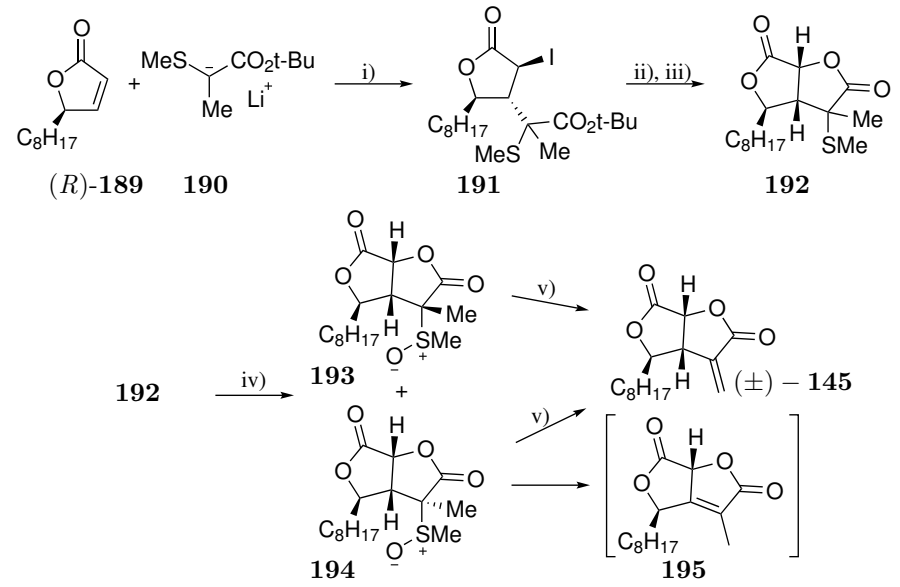
Scheme 2.9: Butenolides as Common Precursors for C_3-C_{3a} Bond Formation Strategy.

initial approach relied on the addition of an acetate enolate to furanone **189** (not shown); however, the 1,4-addition did not appear to be *trans*-stereoselective but epimeric at the *n*-octyl side-chain. As a consequence, to increase the *trans*-stereoselectivity of the Michael addition, a more hindered nucleophile such as the anion of *tert*-butyl thiomethylpropionate **190** was chosen (**Scheme 2.10**). Apart from the steric bulk, the importance of having a methyl sulfide geminal to a methyl group allowed a late-stage introduction of the *exo*-methylene moiety. After conjugate addition of **190** to the Michael acceptor **189**, quenching with iodine gave the all-*trans* α-iodo lactone **191**. Acidic hydrolysis of the ester before subsequent treatment with a sodium bicarbonate solution led to the desired *bis*-γ-lactone **192** in 92% yield. Introduction of the *exo*-methylene at the α position was finally achieved through oxidation of the methyl sulfide to the sulfoxides **193** and **194**, which after pyrolytic elimination gave access to avenaciolide (±)-**145**. It was proposed that the formation of the unstable *endo*-methylene product **195** was the reason for the 74% yield obtained in the pyrolysis of sulfoxide **194** (**Scheme 2.10**).

The same research group published the synthesis of *iso*-avenaciolide **148** from (*S*)-**189**. However, the synthetic route was redefined and included the formation of Yamada's intermediate[95] to achieve the correct configuration of the natural product.[96]

Takei *et al.* decided to form a doubly functionalised butenolide **196** in order to promote a sequential conjugate addition and cyclisation using the malonate derivative **197** (**Scheme 2.11**). The addition proceeded with *trans*-stereoselectivity with respect to the alkyl chain and cyclisation took place to form the fused *cis* aminodihydrofuran **198** in 64% yield. Hydrolysis with nitrosyl chloride gave access to the *bis*-lactone **199**, in which the α-ester was further hydrogenated to the carboxylic acid **161**. Standard Parker and Johnson's methylenation conditions[76,77] followed to form racemic avenaciolide **145** in 60% yield (**Scheme 2.11**). A slightly modified synthetic route was employed by the authors for the preparation of the analogue *epi*-ethisolide **144**.[97]

Optically active butenolides were synthesised by Tsuboi *et al.* in order to achieve the enantioselective synthesis of (–)-avenaciolide **145** (**Scheme 2.12**).[98] Ethyl 3-chloro-4-acetatedodecanoate **202** was pre-



Reagents & Conditions: i) I_2, THF, 97%; ii) *p*-TsOH, benzene; iii) $NaHCO_3$ aq., r.t., 92%; iv) *m*-CPBA, DCM, 96%; v) 140 °C, succinic anhidride, 74%.

Scheme 2.10: Total Synthesis of (±)-Avenaciolide, Reported by Schlessinger and co-workers.[93,94]

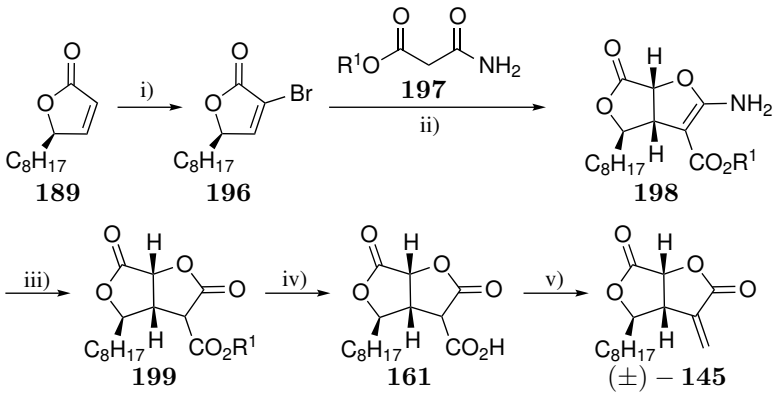
pared from **200** *via* reduction to form the alcohol **201** and subsequent treatment with acetic anhydride. Regioselective enzymatic hydrolysis gave the optically active alcohol (–)-**201** in 31% yield and 94% *ee* (**Scheme 2.12**). Butenolide **189** was formed in 59% after ester hydrolysis and dehydrochlorination under basic conditions from (–)-**201**. Finally, enantiopure avenaciolide (–)-**145** was formed from butenolide **189** by following a modified procedure previously reported by Schlessinger and co-workers (see **Scheme 2.10**).[93,94]

In addition to the C_3-C_{3a} bond disconnection, a number of alternative synthetic strategies for both avenaciolide and *iso*-avenaciolide involving disconnection at O-C_{6a}, O-C_2, O-C_4, O-C_6, and C_{3a}-C_{6a} bonds have also been reported in the past and can be consulted in the relevant literature.[74]

2.2.2.3 Most Recent Syntheses

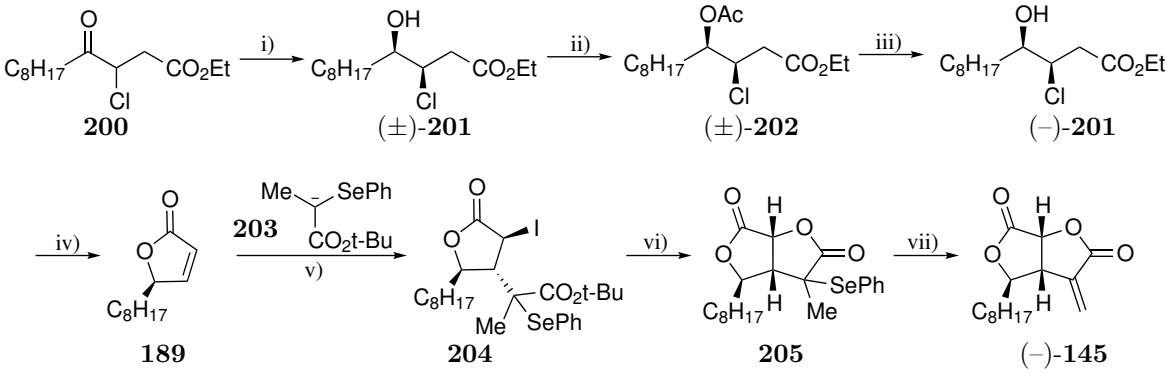
A recent formal synthesis of *iso*-avenaciolide was published by Sharma and co-workers by using the diacetone glucose strategy (**Scheme 2.13**). Despite the similarities with the enantioselective synthesis of (–)-avenaciolide (see **Scheme 2.8**),[91] in this case the formation of the *exo*-methylene moiety occurred from the radical addition of an alkenyl bromide to an alkene in order to obtain the correct configuration for the the alkyl chain.

Methyl glycoside **183** was prepared from diacetone glucose **163** (see **Scheme 2.8**),[91] separated from



Reagents & Conditions: i) Br_2, CCl_4; then Et_3N, benzene, 85%; ii) NaH, 64%; iii) NOCl, 70%; iv) H_2, Pd-C, quantitative; v) Parker and Johnson methylenation, 60%; R^1 = PMB.[76,77]

Scheme 2.11: Total Synthesis of (±)-Avenaciolide, Reported by Takei *et al.*[97]

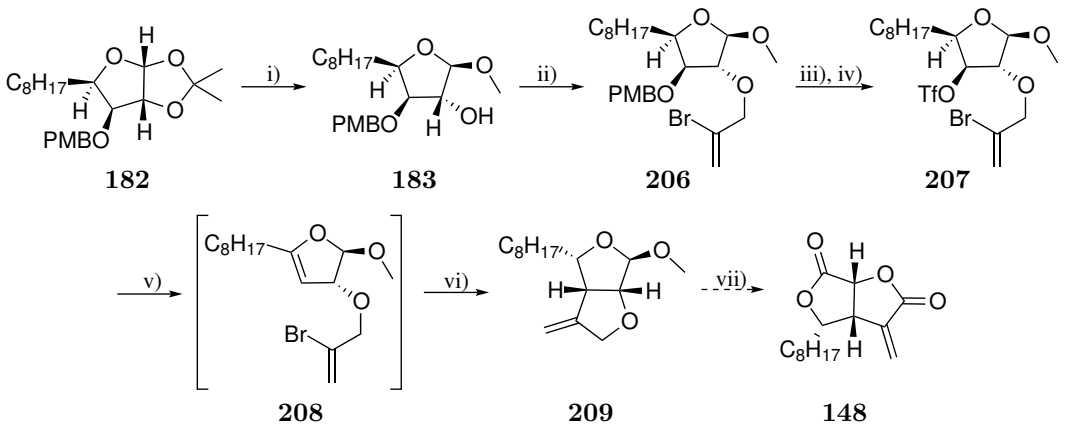


Reagents & Conditions: i) $NaBH_4$, EtOH, 73%; ii) Ac_2O, pyridine; iii) Lipase (Amano P.), 31%, 94% *ee*; iv) 1. HCl; 2. Et_3N, Et_2O, 59%, 94% *ee*; v) 1. compound **203**; 2. I_2, 89%; vi) 140 °C, DMSO, 47%; vii) AcOH, H_2O_2, 31%.[98]

Scheme 2.12: Total Synthesis of (−)-Avenaciolide, Reported by Tsuboi *et al.*[98]

its α-anomer and treated with 2,3-dibromopropene under basic conditions to give the bromo derivative **206** in 64% yield. Oxidative removal of the PMB group and subsequent re-protection of the alcohol led to the triflate **207** in 93% yield. E1cB elimination of the triflate gave the furanoid glycal **208**, which upon treatment with *n*-Bu_3SnH in the presence of AIBN cyclised to the *cis*-fused bicyclic system **209** in 65% yield. According to Cossy and co-workers' procedure,[88] a final hydrolysis followed by an oxidation would lead to the desired *iso*-avenaciolide **148** (**Scheme 2.13**). The same synthetic sequence has been applied by Sharma in his formal synthesis of ethisolide **147**.[99]

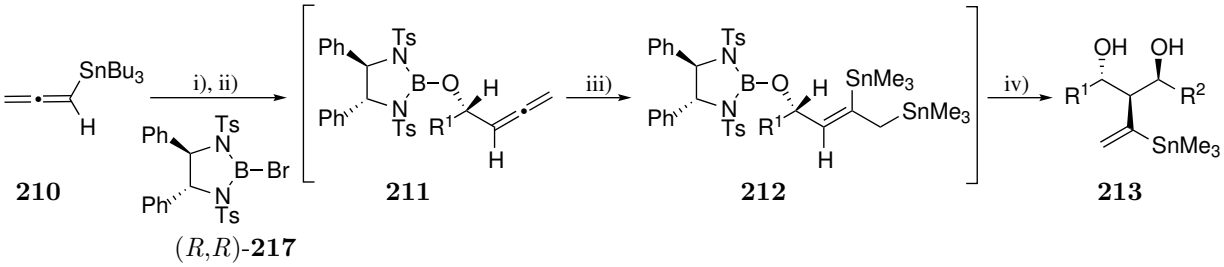
In 2006, Yu *et al.* published the enantioselective syntheses of both avenaciolide **145** and *iso*-avenaciolide **148**, in which the key step involved an asymmetric synthesis of stannylvinyl 1,3-diols **213** through an allylic transfer reaction (**Scheme 2.14**).[100] The methodology consisted of the use of the allene **210** in the presence of the chiral Lewis acid (*R*,*R*)-**217** for the first allylic transfer to an aldehyde, thus forming



Reagents & Conditions: i) acid, MeOH, 0 °C to r.t., 57%; ii) NaH, 2,3-dibromopropene, THF, 0 °C to r.t., 64%; iii) DDQ, DCM, H_2O, r.t., 82%; iv) Tf_2O, Py, DCM, 20 °C, 93%; v) DBU, DMSO, 0 °C to r.t.; vi) *n*-Bu_3SnH, AIBN, benzene, 80 °C, 65%; Cossy and co-workers' conditions.[88,99]

Scheme 2.13: Radical Approach for the Synthesis of *iso*-Avenaciolide, Reported by Sharma and co-workers.[99]

211. Distannation reaction with $(Me_3Sn)_2$ in the presence of $[(\pi\text{-allyl})_2Pd_2Cl_2]$ led to **212**, which then added to a second molecule of aldehyde to finally give the diol **213**.

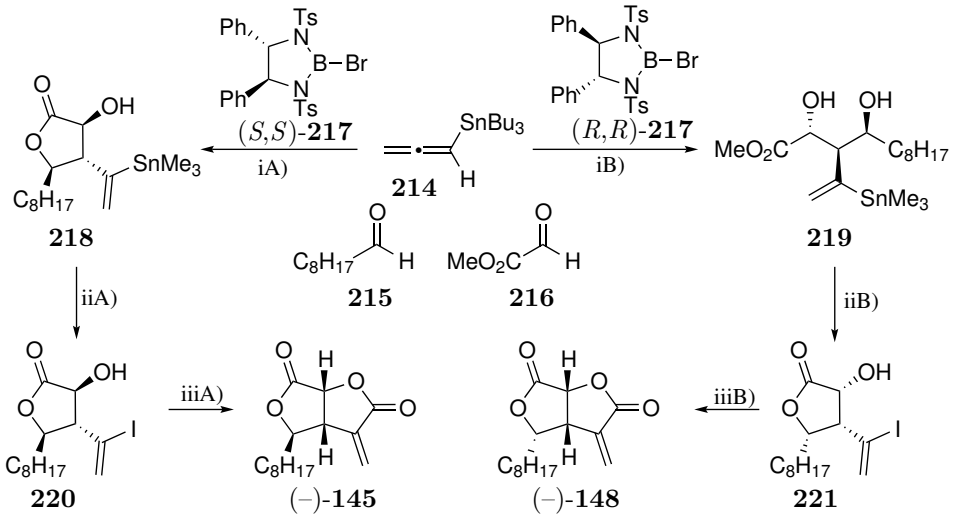


Reagents & Conditions: All reactions were run in CH_2Cl_2; i) boronyl LA promoter (*R*,*R*)-**217** -10 °C; ii) R^1CHO, -78 °C; iii) $(Me_3Sn)_2$ (1.3 eq.), $[(\pi\text{-allyl})_2Pd_2Cl_2]$ (3 mol%), -40 °C; iv) R^2CHO, -78 °C.[100]

Scheme 2.14: Stereospecific Allylic Transfer Reaction for the Enantioselective Synthesis of 2-(1-Stannylvinyl)-1,3-Diols, Reported by Yu *et al.*[100]

In order to achieve the synthesis of both (–)-avenaciolide **145** and (–)-*iso*-avenaciolide **148**, the order of addition of the aldehydes **215** and **216** to a mixture of the organotin reagent **214** and the corresponding chiral bromo borane **217** was inverted (**Scheme 2.15**). Two diastereoisomers were obtained; namely, the cyclised lactone **218** and the diol **219**. Treatment of the lactone **218** with NIS gave the vinyl iodide **220**, which cyclised and epimerised under Stille modified conditions to give avenaciolide **145** in 67% yield. On the other hand, exposure of the diol **219** to NIS gave the vinyl iodide, which upon acidic treatment, cyclised to the corresponding lactone **221** in 77% yield. Stille conditions led to the formation of the isomer *iso*-avenaciolide **148** in 78% yield (**Scheme 2.15**).

An enantioselective synthesis of *iso*-avenaciolide (–)-**148** was also reported in 2013 by Santos *et al.*,[101]



Reagents & Conditions: iA) 1. Borane (*S*,*S*)-**217**, -10 °C, 2. aldehyde **215**, -78 °C, 3. $(Me_3Sn)_2$ (1.3 eq.), $[(\pi\text{-allyl})_2Pd_2Cl_2]$ (3 mol%), -40 °C, 4. aldehyde **216**, -78 °C, 75%; iiA) NIS, -78 °C, DCM, 88%; iiiA) $[Pd(PPh_3)]_4$, CO (100 atm), K_2CO_3, MeCN, 70 °C, 67%; iB) 1. Borane (*R*,*R*)-**217**, 2. aldehyde **216**, 3. $(Me_3Sn)_2$, $[(\pi\text{-allyl})_2Pd_2Cl_2]$ (3 mol%), -40 °C; 4. aldehyde **215**, 54%; iiB) NIS, -78 °C, DCM, then CF_3CO_2H (10 mol%), 77%; iiiB) Same as iiiA), 78%.[100]

Scheme 2.15: Stereospecific Allylic Transfer Reaction for the Enantioselective Synthesis of Avenaciolide and *iso*-Avenaciolide, Reported by Yu *et al.*[100]

in which they made use of their developed stereoselective tandem hydroboration/aldehyde addition process for the preparation of 1,3-diols as a key step of the synthesis. Enantioselective formal syntheses were also published by Labeeuw[102] and Alcázar,[103] and total syntheses of both natural products in racemic form *via* tungsten-π-allyl complexes were also reported by Liu and co-workers.[104,105]

Overall, around thirty syntheses can be found in the literature for avenaciolide **145** and more than fifteen for *iso*-avenaciolide **148**.

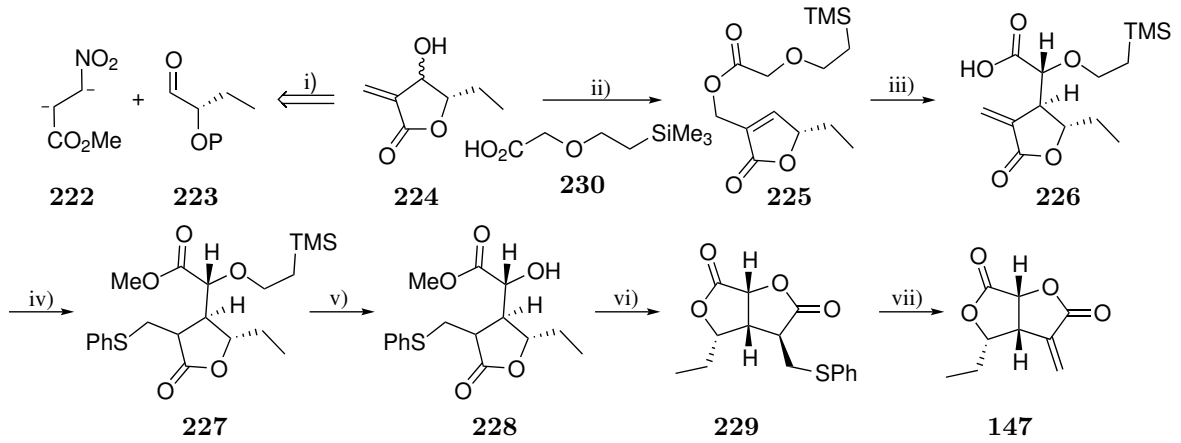
2.2.3 Ethisolide and *epi*-Ethisolide: Synthetic Studies

Diacetone-D-glucose **163** proved to be a highly versatile starting material for the enantioselective synthesis of the ethisolide family of natural products. Sharma *et al.* extended their use of radical reactions in carbohydrates for the first and unique enantioselective synthesis of *epi*-ethisolide (–)-**144**,[106] by following the same synthetic sequence employed for the enantioselective synthesis of avenaciolide (–)-**145** (see **Scheme 2.8**).[91]

Ethisolide **147** was much more popular among the synthetic community. The first synthesis was published by Burke and co-workers in both racemic and enantioselective fashion. The strategy involved the simultaneous construction of both rings by a double lactonisation, and also allowed for the syntheses

of *iso*-avenaciolide **148** and avenaciolide **145**.[107]

The lactone **224** was prepared according to Seebach's procedure involving the addition of the dianion of methyl 3-nitropropionate **222** to the aldehyde **223** (**Scheme 2.16**).[108] The mixture of allylic alcohols **224** was then transformed into the single butenolide **225** upon S_N2' displacement through a Mitsunobu coupling in 80% yield. Deprotonation with LiHMDS triggered the glycolate Claisen rearrangement to give the single diastereoisomer **226**. In order to favour the two sequential transacylations needed to form the *bis*-lactone moiety, the methylene fragment needed to be rehybridised with the addition of sodium phenyl sulfide, thus giving **227** after diazomethane esterification. Cleavage of the trimethyl silyl ether led to alcohol **228**, which cyclised to form the *bis*-lactone **229** under acidic conditions. Oxidation to the sulfoxide, followed by thermolysis gave the racemic ethisolide **147** in 70% yield (**Scheme 2.16**).



Reagents & Conditions: i) Seebach's conditions;[108] ii) Ph_3P, DEAD, THF, compound **230**, 80%; iii) LiHMDS, TMSCl, THF, -100 to 25 °C, 71%; iv) PhSNa, CH_2N_2, 79%; v) $BF_3 \cdot Et_2O$, 86%; vi) CSA cat. toluene, reflux, 89%; vii) *m*-CPBA, $CHCl_3$, -20 °C, K_2CO_3, reflux, 70%.[107]

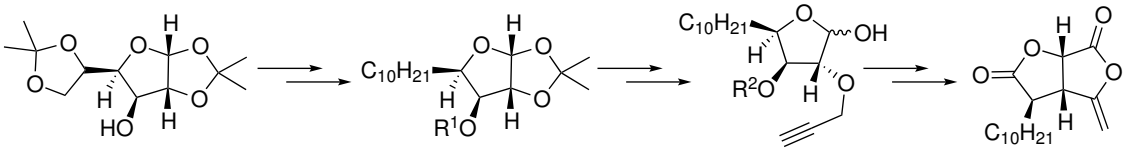
Scheme 2.16: First Synthesis of Ethisolide, Reported by Burke *et al.*[107]

The synthesis of ethisolide has also been studied by Cossy,[88] Ogawa,[109] and more recently by Sharma through the use of diacetone glucose (see **Scheme 2.13**),[99] and by Metzner through a stereocontrolled thio-Claisen transposition as a key step for the formation of butenolides as the starting materials (see **Section 2.2.2.2**).[110] Overall, eight syntheses have been published for ethisolide **147**; while only one for *epi*-ethisolide **144**.

2.2.4 Discosiolides: Synthetic Studies

To the best of our knowledge, only one synthesis of discosiolide **146** has been reported in the literature. Sharma *et al.* used diacetone-D-glucose **163** as starting material for the asymmetric formation of the

natural product **146** by following the same synthetic sequence reported for avenaciolide (–)-**145** (see **Scheme 2.8**) (**Scheme 2.17**).[111] At the time of writing, no syntheses have been reported for its isomer *iso*-discosiolide **149**.



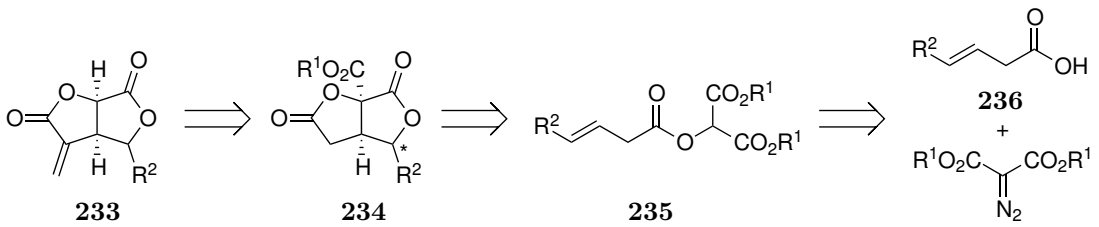
163 **231** **232** (–)-**146**

Reagents & Conditions: R^1 = PMB; R^2 = C(S)SCH_3.[111]

Scheme 2.17: Radical Approach for the Synthesis of (–)-Discosiolide, Reported by Sharma and co-workers.[111]

2.3 Results and Discussion: Synthesis of the Ethisolide Family

Previous results in the group showed the applicability of the MAN-based oxidative radical cyclisation for the synthesis of bicyclic γ-lactone systems with $Cu(OTf)_2$ as co-oxidant in MeCN (see **Section 1.2.5**). Particularly relevant was the application of the methodology for the cyclisation of unsaturated ester alkyl malonates to form fused *bis*-γ-lactones (see **Section 1.2.5.4**, **Scheme 1.34**),[60] which are the key structural framework of the ethisolide family of natural products. On the basis of Chany's *et al.* results,[60] we herein propose the following retrosynthetic strategy (**Scheme 2.18**) towards the preparation of the ethisolide family of natural products (see **Scheme 2.1**). A dealkoxycarbonylation / methylenation sequence would lead to the desired compound **233** from the *bis*-γ-lactone **234**, which would be formed from the ester alkyl malonate **235** through an oxidative radical cyclisation. An OH-insertion between the β,γ-unsaturated carboxylic acid **236** and the diazo alkyl malonate **237** would lead to the oxidative cyclisation precursor **235** (**Scheme 2.18**). Despite the numerous syntheses present in the literature for this family of natural products, the above mentioned methodology would give an efficient and fast access to the five natural products and to the non-natural analogue by following the same synthetic sequence. In order to reach such a goal, it would be beneficial if both diastereoisomers were formed in the oxidative cyclisation of the ester malonates **235**. At the time of writing, the MAN-based methodology would allow for the first total synthesis of the non-natural *iso*-discosiolide **149** and it would be the first time the same synthetic strategy provides the six components of the family.



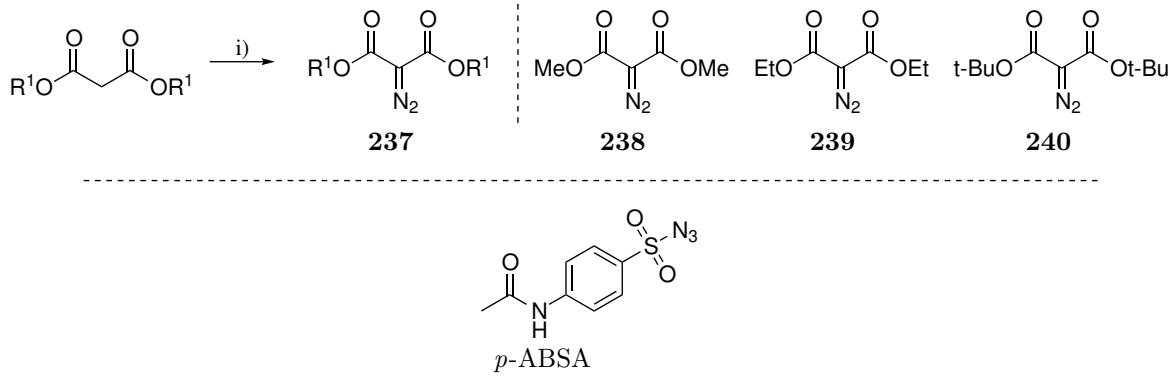
$\mathbf{R}^1$ = Me, Et, *t*-Bu; $\mathbf{R}^2$ = Et, C_8H_{17}, $C_{10}H_{21}$.

Scheme 2.18: Retrosynthetic Analysis of the Ethisolide Family of Natural Products.

2.3.1 Synthesis of Ester Malonate Precursors

Alkyl diazo malonates **237** were prepared in good yields (70-97%) from their corresponding alkyl malonates upon treatment with the azide *p*-ABSA through a diazo-transfer process (**Table 2.1**).[112] IR data provided evidence of the formation of the diazo moiety with an absorbance at 2130 cm^{-1}.

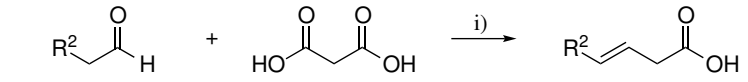
Table 2.1: Formation of the Diazo Alkyl Malonates.



Reagents & Conditions: i) *p*-ABSA, Et_3N, MeCN, 0 °C to r.t.

Entry	R^1 group	Diazomalonate	Yield / %
1	Me	**238**	70
2	Et	**239**	97
3	*t*-Bu	**240**	97

The unsaturated ester malonates **235** were subsequently formed *via* a Rh-catalysed OH-insertion reaction between the corresponding β,γ-unsaturated carboxylic acid **236** and the diazo malonate **237** (see **Scheme 2.18**).[113] Since unsaturated acids bearing longer alkyl chains ($R^2 = C_8H_{17}$ and $C_{10}H_{21}$) were not commercially available, they were synthesised through a Knoevenagel condensation / decarboxylation sequence between decanal **242** and dodecanal **244** with malonic acid **241**, thus giving (*E*)-dodec-3-enoic acid **243** and (*E*)-tetradec-3-enoic acid **245** in 91 and 92% respectively (**Scheme 2.19**).[114]



$R^2 = C_8H_{17}$: **242** **241** $R^2 = C_8H_{17}$: **243**

$R^2 = C_{10}H_{21}$: **244** $R^2 = C_{10}H_{21}$: **245**

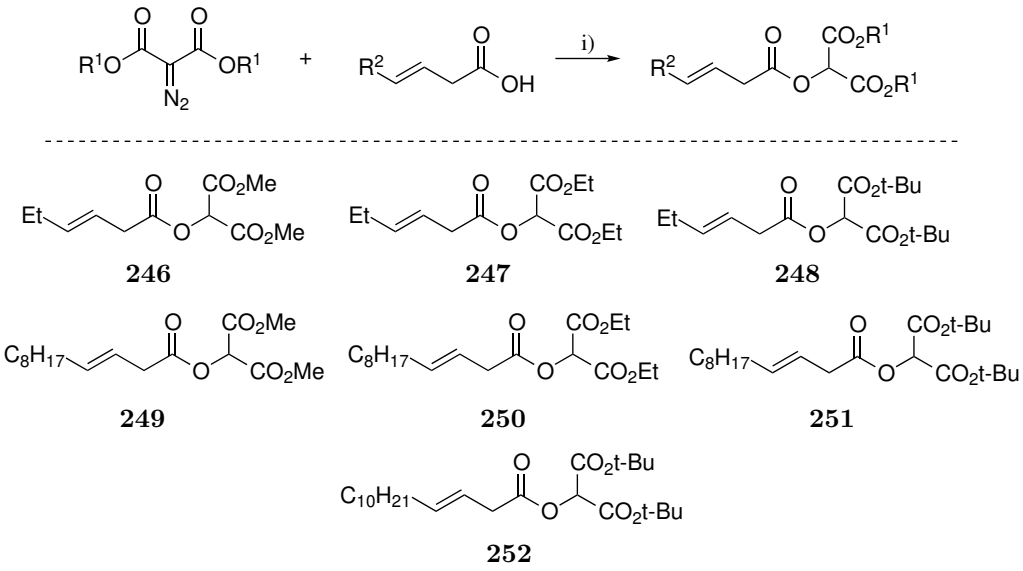
Reagents & Conditions: i) NMM, 80 °C 7 h; $\mathbf{R^2} = C_8H_{17}$: β,γ-unsaturated acid **243**: 91%; $\mathbf{R^2} = C_{10}H_{21}$: β,γ-unsaturated acid **245**: 92%.

Scheme 2.19: Formation of Unsaturated Carboxylic Acids

Good yields (78-83%) were obtained for the OH-insertion between trans-3-hexenoic acid and the diazo compounds **240**, **238** and **239** (**Table 2.2**, **Entries 1-3**). The acids **243** and **245** also perfomed well in the insertion with the diazo malonate **240** (**Entries 6** and **7**); however, modest yields were observed between the acid **243** and the diazo malonates **238** and **239** (**Entries 4** and **5**).

The formation of the ester malonates was confirmed by ^{1}H-NMR analysis with a singlet appearing between 5.30 and 5.60 ppm for the proton in the α-position to the oxygen and to the esters of the malonate. Also ^{13}C-NMR indicated the presence of the three ester carbonyls with resonances between

Table 2.2: Formation of the Precursor Unsaturated Ester Malonates.



246 **247** **248**

249 **250** **251**

252

Reagents & Conditions: i) $Rh_2(OAc)_4$, Benzene, 60 °C 2 h.

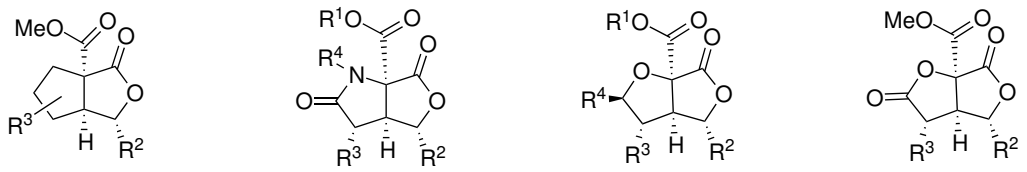
Entry	R^1 (Diazo Compound)	R^2 (Acid Compound)	Ester Malonate / Yield / %
1	Me (**238**)	C_2H_5	**246** / 82
2	Et (**239**)	C_2H_5	**247** / 83
3	*t*-Bu (**240**)	C_2H_5	**248** / 78
4	Me (**238**)	C_8H_{17} (**243**)	**249** / 41
5	Et (**239**)	C_8H_{17} (**243**)	**250** / 66
6	*t*-Bu (**240**)	C_8H_{17} (**243**)	**251** / 81
7	*t*-Bu (**240**)	$C_{10}H_{21}$ (**245**)	**252** / 88

165.0 and 170.0 ppm.

2.3.2 Towards the Synthesis of *bis*-γ-Lactones: MAN-based Standard Conditions

Despite the versatility of the MAN-based methodology (see **Section 1.2.5**) in the formation of different types of fused bicyclic γ-lactones, good to excellent yields were limited to primary alkene- and styrene-containing malonate derivatives; *i.e.*, substrates leading to primary or benzylic adduct radicals after the cyclisation (**Scheme 2.20**).[49,52,55,60] A single example with R^2 = *n*-Bu was reported in the all-carbon systems; however, a modest 58% yield of the corresponding γ-lactone was obtained under the standard reaction conditions with $Cu(OTf)_2$ as co-oxidant in MeCN (**Scheme 2.20**).[49]

The yield of the oxidative cyclisation was modest when R^2 = *n*-Bu; however, it was still considered practical, thus we exposed the ester malonates **248**, **247**, **246**, **249** and **250** to the standard reaction conditions ($Mn(OAc)_3 \cdot 2H_2O$ and $Cu(OTf)_2$ in MeCN) previously developed in the group for the form-



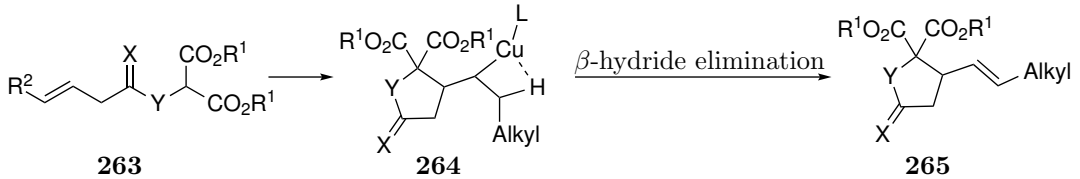
all-C γ-Lactones **γ-Lactam-γ-Lactones** **THF-γ-Lactones** ***bis*-γ-Lactones**

All-C γ-lactones: 9 examples, R^2 = H, Ph: 74-96%; R^2 = *n*-Bu: 58%; **γ-lactam-γ-lactones**: 14 examples, R^2 = H, Ph: 52-87%; **THF-γ-lactones**: 18 examples, R^2 = H, Ph: 61-96%; ***bis*-γ-lactones**: 4 examples, R^2 = H, Ph: 62-77%.

Scheme 2.20: Fused Bicyclic γ-Lactones, Reported by Burton and co-workers.

ation of *bis*-lactones.[60] Unfortunately, the desired *bis*-γ-lactones **253**, **254** , **255**, **256** and **257** were obtained as the minor product with formation of the alkenyl mono-lactones **258**, **259**, **260**, **261** and **262** as major products in approximately 1:2 ratio (**Table 2.3**, **Entries 1-5**). Replacement of $Cu(OTf)_2$ by $Cu(OAc)_2$ led to no conversion (**Entry 6**) and $Cu(BF_4)_2$ gave the alkenyl lactone **262** in 39% yield with no formation of the corresponding *bis*-lactone **257** (**Entry 7**). The yields of the *bis*-lactones were not likely to be high enough to allow completion of the natural products syntheses.

Our rationale for the formation of the alkenes over the *bis*-lactones when R^2=alkyl is likely due to the organocopper(III) intermediate **264** formed after the cyclisation of **263** which could undergo a β-hydride elimination to give **265** (**Scheme 2.21**). Despite the high dissociative character associated with $Cu(OTf)_2$ which would tend to form lactones through formal generation of a carbocation (see **Section 1.2.4**), the possibility to form the least substituted alkene **265** (Hofmann elimination product, see **Section 1.2.4**) remains and in the above instance is the kinetically-favourable competitive termination pathway. These results are in keeping with the Hofmann distribution of products reported by Snider in MAN-based oxidative radical cyclisation.[44]



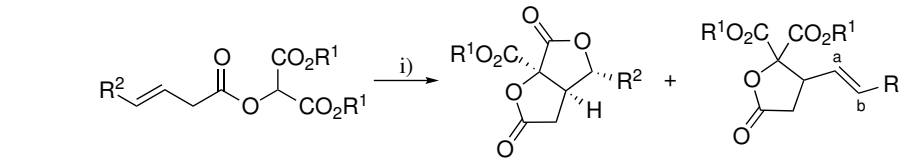
263 **264** **265**

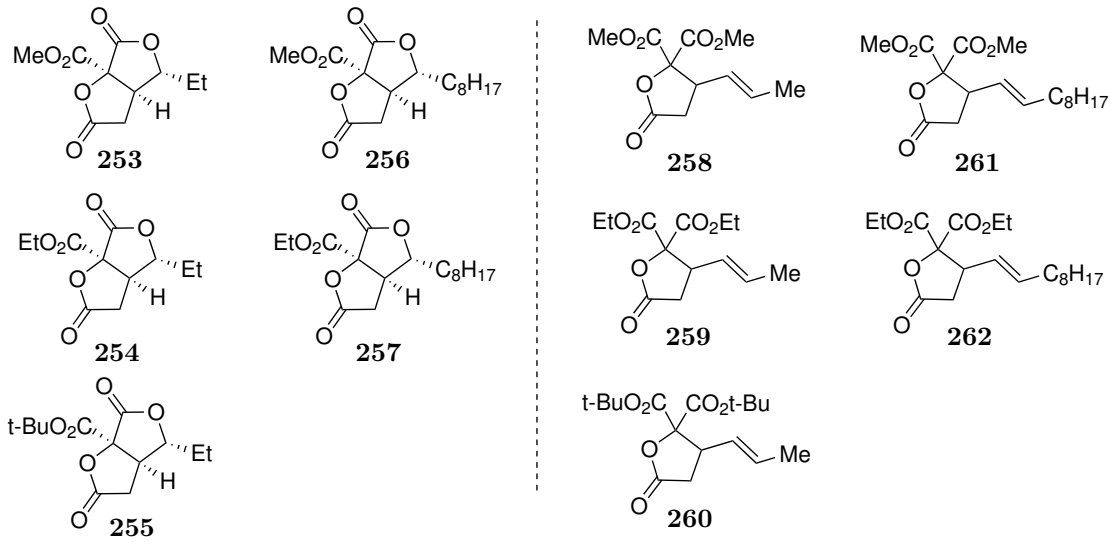
$\mathbf{R}^1$, $\mathbf{R}^2$ = Alkyl; **X** = H_2, O; **Y** = CH_2, N, O; **L** = Ligand.

Scheme 2.21: β-Hydride Elimination as Competitive Termination Mode.

Considering that the MAN-based oxidative radical cyclisation was the key step of the synthesis of the ethisolide family of natural products, the low-yielding standard conditions were no longer optimal for the formation of the *bis*-lactone framework, and hence the natural products. In order to overcome this limitation, an optimisation of the reaction conditions and a study of the conversion of the alkenyl

Table 2.3: Application of the Standard MAN-Based Conditions for the Formation of *bis*-γ-Lactones.





Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1.0 eq.), MeCN, 40 °C.

Entry	R^1	R^2	SM	*bis*-lactone / Yield / % / *dr*	alkenyl lactone / Yield / % / *E*:*Z* ratio	$^3J_{ab}$ (maj) /Hz
1	Me	C_2H_5	**246**	**253** / 32 / 4:1	**258** / 66 / 5.3:1	15.3
2	Et	C_2H_5	**247**	**254** / 39 / 2.3:1	**259** / 64 / 8.1:1	15.3
3	*t*-Bu	C_2H_5	**248**	**255** / 24 / 1.2:1	**260** / 40 / 3.8:1	15.3
4	Me	C_8H_{17}	**249**	**256** / 24 / 3.3:1	**261** / 58 / 19:1	15.3
5	Et	C_8H_{17}	**250**	**257** / 14 / 2.0:1	**262** / 32 / 24:1	15.4
6[a],[c]	Et	C_8H_{17}	**250**	**257** / -	**262** / -	-
7[b]	Et	C_8H_{17}	**250**	**257** / -	**262** / 39 / 32:1	15.4

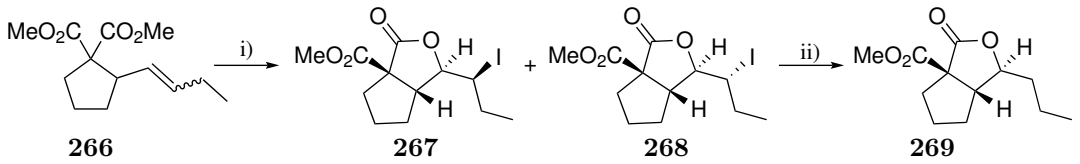
[a] $Cu(OAc)_2$ was used a copper salt; [b] $CuBF_4$ was used as copper salt; [c] no conversion.

γ-lactone into the *bis*-γ-lactone was performed.

2.3.3 Towards the *bis*-Lactones: Electrophile-Driven Lactonisation Studies

Iodolactonisation. Previous work in the group showed that iodolactonisation was an excellent method to synthesise bicyclic γ-lactones such as **269** diastereoselectively in high yields from vinyl cyclopentanes **266**. The transformation occurs through formation of the iodo bicyclic γ-lactones **267** and **268**, followed by reduction with tributyl tin hydride (**Scheme 2.22**).[115]

The success in the synthesis of γ-lactones in the all-carbon systems made us consider such strategy for the conversion of the alkenyl mono-lactones into the *bis*-lactones; however, no conversion was observed for **260** under the reported conditions of I_2 in DCM at r.t. (**Table 2.4**, **Entry 1**). Heating the diester

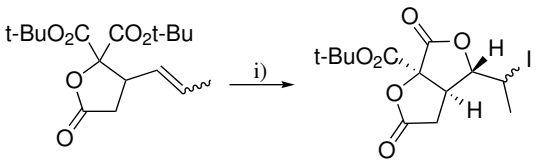


Reagents & Conditions: **266** is present in a 1.6:1 E/Z ratio. i) I_2, DCM, 0 °C, **267**: 54%, **268**: 38%; ii) *n*-Bu_3SnH, AIBN, MeCN, reflux, 97% from **268**, 63% from **267**.

Scheme 2.22: Iodo-Lactonisation Followed by Radical Reduction for the Formation of Bicyclic γ-Lactones, reported by Burton and co-workers.[115]

260 with I_2 in $CHCl_3$ at reflux led to no conversion (**Entry 3**). Mostinski *et al.* reported an iodolactonisation of *tert*-butyl esters with iodine in MeCN at room temperature,[116] yet our substrate did not undergo iodolactonisation under these conditions (**Entry 2**). The addition of silver triflate to activate the iodine led to a complicated mixture of unidentified products; while the use of NIS as a source of electrophilic iodine in MeCN[117] gave no conversion (**Entries 4** and **5**). Treatment of the alkenyl mono-lactone dicarboxylic acid with I_2 in MeCN led to decomposition of the starting material (**Entry 6**).

Table 2.4: Iodo-Lactonisation Attempts



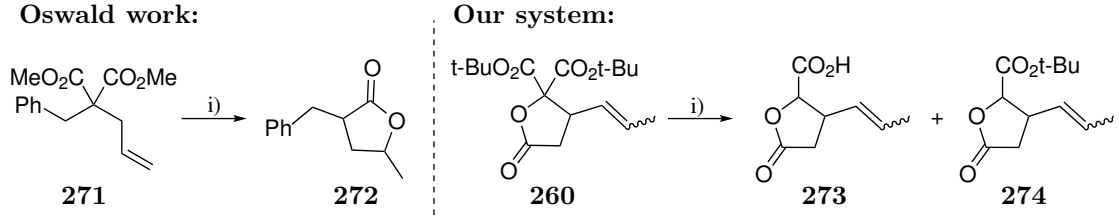
Reagents & Conditions: i) I^+ Source, Solvent, Temperature.

Entry	R I^+ Source	Solvent	T / °C	Compound **270** Yield / %
1	I_2	DCM	0 to r.t.	–
2	I_2	MeCN	0 to r.t.	–
3	I_2	$CHCl_3$	reflux	–
4	I_2, AgOTf	$CHCl_3$	r.t.	–
5	NIS	$CHCl_3$	r.t. to 40	–
6[a]	I_2	MeCN	0 to r.t.	–

[a] *tert*-butyl esters were hydrolysed to carboxylic acids.

Acid-Promoted Lactonisation. Oswald *et al.* published a sequential dealkoxycarbonylation and lactonisation of unsaturated malonates in ionic liquids.[118] The ionic liquid bmim[BF_4] was used in combination with bmimBr and LiCl to trigger a one-pot acid-promoted lactonisation and dealkoxycarbonylation forming **272** from **271** (**Scheme 2.23**). After applying the same conditions to the alkenyl monolactone **260**, traces of **273** and **274** were proposed to be present in a complex mixture of products isolated after purification by column chromatography. The challenge of using Oswald's methodology on **260** was that

lactonisation must happen before the dealkoxycarbonylation takes places to guarantee that one of the esters is *syn* to the activated alkene for the lactonisation to occur.



Reagents & Conditions: i) bmim[BF_4], bmimBr, LiCl, H_2O, 160 °C. Compound **272**: 89%; Compounds **273** and **274**: traces.

Scheme 2.23: Dealkoxycarbonylation / Acid-Promoted Lactonisation Sequence.[118]

To conclude, the conditions studied for the iodo- and acid-promoted lactonisation did not appear to be successful in forming the desired *bis*-γ-lactone. Instead of undertaking a more extensive study on alternative conditions for such strategy, it was thought that the optimisation of the MAN-based conditions for the preferential formation of the *bis*-γ-lactone moiety was more desirable. The iodo-lactonisation strategy, although it was effective in all-carbon systems, was not suitable for the synthesis of *bis*-lactones such as **270**.

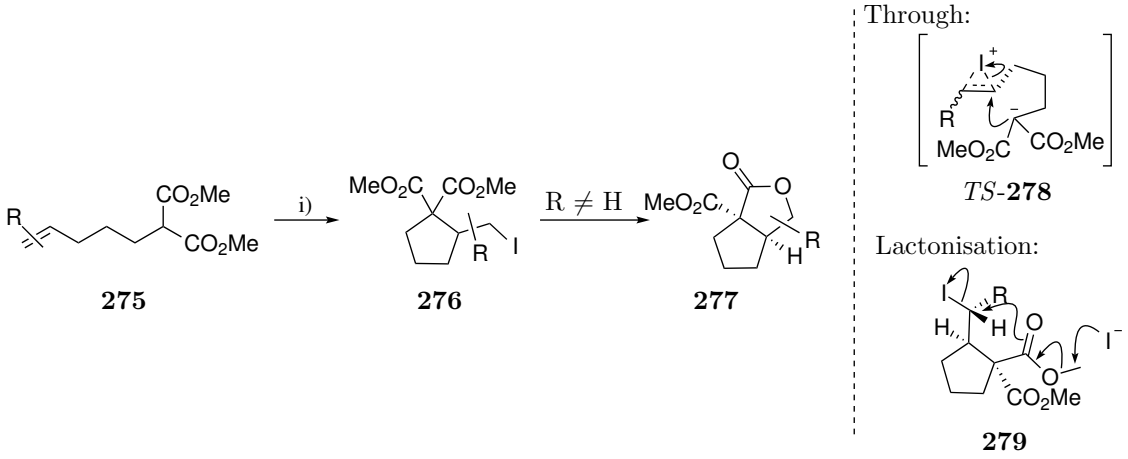
2.3.4 Towards the *bis*-Lactones: Optimisation of the MAN Conditions

Before commenting on the modifications in the experimental conditions of the MAN-based oxidative radical cyclisation, a few comments will be given to the work that inspired the experiments which ultimately led to the successful synthesis of the ethisolide family of natural products.

2.3.4.1 Ionic Carbocyclisations

We have seen that oxidative cyclisations with MAN follow a radical pathway; however, the ionic alternative, *i.e.* carbocyclisation by an ionic pathway, has also been reported with the use of Ti-based Lewis acids. Taguchi and co-workers, on the basis of the previously reported halocyclisation of unsaturated carboxylic acids (halolactonisation), alcohols (haloetherification) and amines, developed a methodology to achieve halocarbocyclisations. The transformation implied an intramolecular attack of a carbon nucleophile onto a double bond activated by an electrophilic halogenating agent, thus providing a method for the stereoselective construction of functionalised carbocycles.[119] A number of unsaturated methyl ester malonates **275** were cyclised in the presence of Ti(O*t*-Bu)$_4$ as Lewis acid and iodine to form primary iodo carbocycles **276** (R = H) and bicyclic γ-lactones **277** when the formed iodides **276** were secondary

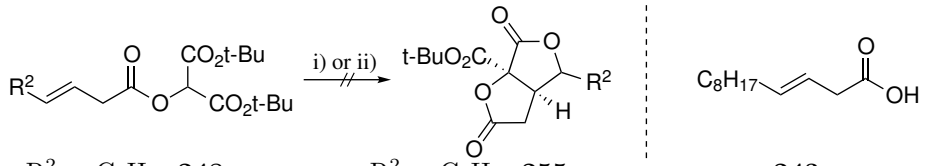
or tertiary (R ≠ H) (**Scheme 2.24**). Taguchi described the cyclisation as the result of the 5-*exo-trans* attack of the malonate carbanion or the Ti-enolate on the three-membered iodonium ion (***TS*-278**, **Scheme 2.24**). In the case of the formation of the bicyclic γ-lactones **277**, the same author also noted that iodide might be contributing in the lactonisation by attacking the alkyl group of the cyclising lactone (model **279**, **Scheme 2.24**).



Reagents & Conditions: i) Ti(O*t*-Bu)$_4$ (1 eq.), I_2 (1.5 eq.), DCM, r.t.; R = H, alkyl.

Scheme 2.24: Ionic Halocarbocyclisation, Reported by Taguchi and co-workers.[119]

In view of Taguchi's results, we exposed the ester malonate **248** to Taguchi's ionic carbocyclisation conditions. Unfortunately, no reaction was observed (**Scheme 2.25**). On the basis of Taguchi's work, a similar methodology has been developed in the Burton group by Shepherd using ethyl magnesium bromide as base with iodine to trigger the halocarbocyclisation for the synthesis of bicyclic γ-lactones.[120] Such conditions were tested on the ester malonate **251**; however, only the unsaturated acid **243** was isolated in 7% yield after purification by column chromatography (**Scheme 2.25**).



Reagents & Conditions: i) Ti(O*t*-Bu)$_4$, I_2, DCM, r.t. $R^2 = C_2H_5$, ester malonate **248** gave no conversion; ii) EtMgBr, I_2, DCM, -78 °C to r.t. $R^2 = C_8H_{17}$ ester malonate **251**, isolated product: unsaturated carboxylic acid **243**: 7%.

Scheme 2.25: Ionic Carbocyclisation Attempts for the Formation of *bis*-γ-Lactones.

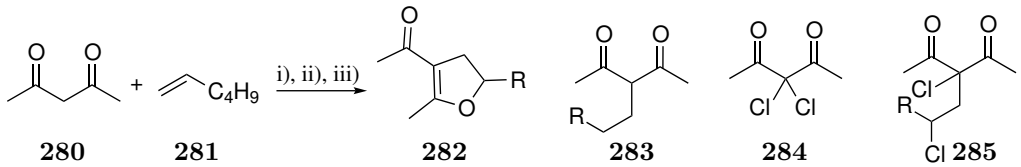
Despite the negative results regarding the halo-carbocyclisation of unsaturated ester alkyl malonates, the idea of forming a γ-lactone through nucleophilic substitution between the ester and a leaving group

gave us some hints on how to make the lactonisation step a more favourable termination mode compared to the β-hydride elimination in the MAN-based oxidative radical cyclisation.

2.3.4.2 Halides Salts as Additives in the MAN-based Oxidative Radical Cyclisation

Halide salts are proposed to have a potential double role in the oxidative cyclisation that would favour the lactonisation. The first one has been described in Taguchi's work and considered to be a halide attack (iodide in that example) on the alkyl residue of an ester group to trigger the lactonisation through nucleophilic substitution (see **Scheme 2.24**).[119] Such an attack is also represented in the Krapcho dealkoxycarbonylation mechanism with LiCl.[121,122] The second role would be the trapping of the formal carbocation generated from the organocopper(III) triflate intermediate by halides or through halide exchange to form a halo carbo- or heterocyclic system. The halide exchange would include reaction of an adduct radical with CuX or MnX followed by reductive elimination to form a C-X bond. Nucleophilic substitution *via* an ester attack would follow to form the desired γ-lactone. Among the halides, we initially considered LiCl since its precedent use in the MAN-based oxidative radical cyclisation has already been reported in the literature.

Use of Lithium Chloride in MAN-based Oxidative Radical Cyclisation: Vinogradov and Snider Work. During their studies on the oxidative addition of acetylacetone **280** to 1-hexene **281** under MAN (or $Co(OAc)_3$) conditions, Vinogradov *et al.* discovered that the presence of LiCl had a sharp impact on the product distribution of the reaction.[123] In the absence of LiCl, the main products obtained were the dihydrofuran **282** and the saturated diketone **283** in 38% and 55% yields respectively in AcOH with MAN. In contrast, when $CuCl_2$ was present, the participation of the alkene was no longer observed and dichlorination of diketone **280** occurred instead leading to **284**. In the presence of MAN and LiCl and in the absence of copper salts, both chlorination at the most acidic site and participation of the alkene took place giving the chlorinated diketone **285** (**Scheme 2.26**).

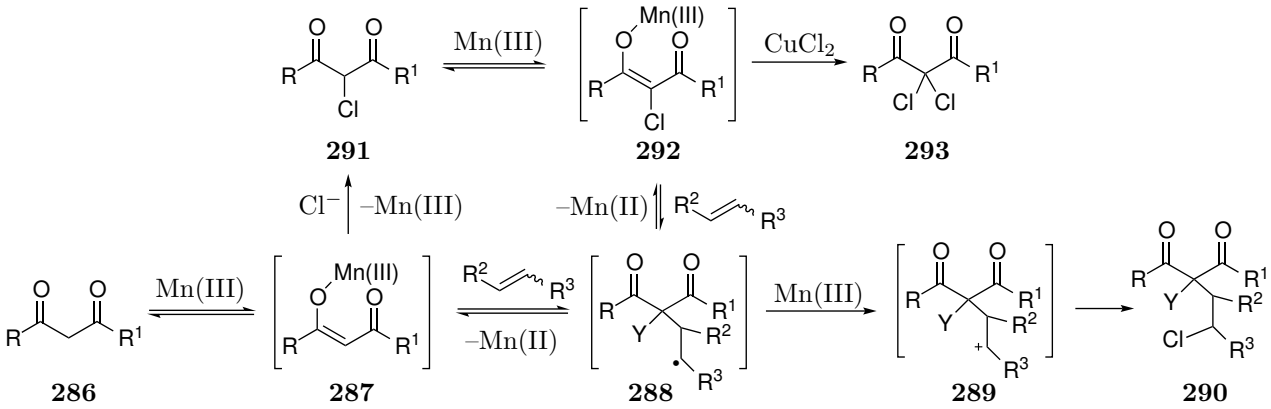


280 **281** **282** **283** **284** **285**

Conditions & Product Distribution: i) $Mn(OAc)_3 \cdot 2H_2O$, AcOH, 70 °C: Compounds **282**, 38% and **283**, 55%; ii) $Mn(OAc)_3 \cdot 2H_2O$, $CuCl_2$, 40 °C: Compound **284**, 94%; iii) $Mn(OAc)_3 \cdot 2H_2O$, LiCl, 50 °C: Compound **285**, 92%; R = C_4H_9.

Scheme 2.26: Effect of LiCl on the MAN-based Oxidative Radical Cyclisation, Reported by Vinogradov *et al.*[123]

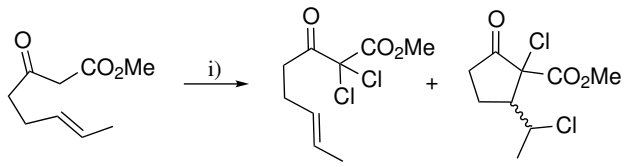
Additional investigations on ethyl acetoacetate and ethyl malonate as 1,3-dicarbonyl compounds with a number of different olefins under the LiCl / MAN system were also published by the same group.[124] The product distribution, which was dependent on the 1,3-dicarbonyl compound and on the type of alkene, was explained in their proposed mechanism (**Scheme 2.27**). It was proposed that after MAN coordination to the 1,3-diketone **286** three different pathways could follow. On the one hand, a one-electron oxidation from **287** followed by the attack of the alkene to give the adduct radical **288**, which is further oxidised to the carbocation **289** would lead to the chloro compound **290** (Y = H) after chloride trapping. On the other hand, chloride could participate in the reaction before the first one-electron oxidation and give the chloro 1,3 diketone **291**, which after MAN coordination, a one-electron oxidation and the attack to the alkene would lead to the adduct radical **288** with Y = Cl. A second oxidation and chloride trapping would give the dichloro compound **290** (Y = Cl). When $Cu(OAc)_2$ was present in the reaction mixture, it was proposed that $CuCl_2$ would form and dichlorination at the most acidic sites of the 1,3-dicarbonyl compound **286** would follow with no participation of the alkene to give **293** (**Scheme 2.27**).



Y = H, Cl; R = alkyl, alkoxide; R^1 = alkyl, alkoxide: R^2 = alkyl; R^3 = alkyl, phenyl .

Scheme 2.27: Participation of LiCl in the MAN-Based Oxidative Radical Cyclisation: Proposed Mechanism, Reported by Vinogradov and co-workers.[124]

The incompatibility of the chloride anion with $Cu(OAc)_2$ was later corroborated by Snider and co-workers in the intramolecular cyclisation of the unsaturated β-keto ester **294** (**Scheme 2.28**). The desired cyclised compound **296** was observed in less than 3% yield; with the dichlorinated uncyclised substrate **295** as the major product in 45% yield.[125]



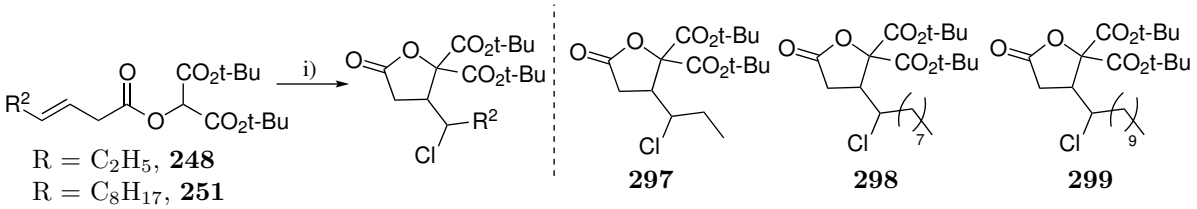
294 **295** **296**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, LiCl, AcOH, 25 °C; product **295**: 45%; product **296**: <3% yield.

Scheme 2.28: MAN / $Cu(OAc)_2$ / LiCl System for the Intramolecular Oxidative Radical Cyclisation, Reported by Snider and co-workers.[125]

2.3.4.3 The MAN / $Cu(OTf)_2$ / LiCl Oxidant System

Despite the reported incompatibility of LiCl with $Cu(OAc)_2$, LiCl was incorporated into the MAN-based standard conditions, with the expectation that the chloride would help direct the reaction towards the formation of bicyclic γ-lactones by attacking the alkyl residue of the cyclising ester (see **Section 2.3.4.1**). Unfortunately, the desired *bis*-γ-lactones were not obtained under such conditions; however, cyclisation was observed despite the presence of the copper salt and chloro mono-lactones **297**, **298** and **299** were isolated from their corresponding ester malonates **248**, **251** and **252** (**Scheme 2.29**). NMR analysis showed a doublet of triplets resonance for the C*H*-Cl bond at 4.20 ppm for the major diastereoisomer and a doublet of doublet of doublet resonance at 4.09 ppm for the minor; while mass analysis confirmed the presence of the chloride in the molecule with the isotopic distribution: 385.13900 ($[M+Na]^+$, 100%) and 387.13599 (30%) for compound **297**. IR analysis indicated the presence of a γ-lactone with absorptions between 1805-1807 cm^{-1}.



R = C_2H_5, **248**
R = C_8H_{17}, **251**
R = $C_{10}H_{21}$, **252**

297 **298** **299**

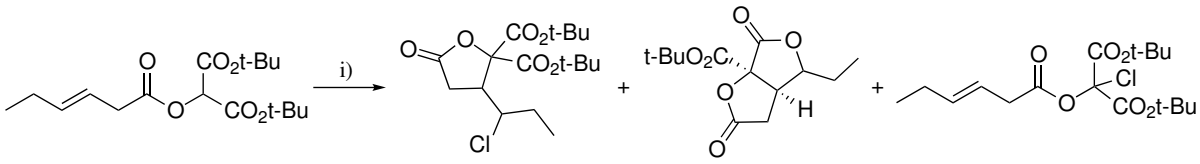
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), LiCl (1.2 eq.), MeCN (0.15 M), 40 °C; chloro mono-lactones: **297**, 74%, 4.8:1 *dr*; **298**, 66%, 5.3:1 *dr*; **299**, 64%, 5.7:1 *dr*

Scheme 2.29: MAN / $Cu(OTf)_2$ / LiCl Oxidant System for the Formation of Chloro mono-γ-Lactones.

Copper Salt Screening: Control Experiments. These results were in sharp contrast with the results of Vinogradov[123,124] and Snider,[125] in which no participation of the alkene was observed when $Cu(OAc)_2$ was present. In order to understand such reactivity differences, control experiments were

undertaken having $Cu(OAc)_2$ instead of $Cu(OTf)_2$ as the copper salt (**Table 2.5**).

Table 2.5: Control Experiments for the Formation of Chloro mono-γ-Lactones.



248 **297** **255** **300**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), Cu Salt (1.0 eq.) , LiCl (1.2 eq.), MeCN (0.15 M), T / °C, 22 h.

Entry	Cu salt	T / °C	Ratio **248**:**297**	Yield **297** / %	Yield **255**
1[a]	$Cu(OAc)_2$	40	1.17:1	38 (4.9:1 *dr*)	-
2	$Cu(OAc)_2$	80	0:1	63 (4.26:1 *dr*)	2 (1.8:1 *dr*)
3[a],[b]	$CuCl_2$	40	1.33:1	33 (5.7:1 *dr*)	-
4[b]	$CuCl_2$	80	0:1	62 (4.3:1 *dr*)	6 (1.94:1 *dr*)
5[c]	$Cu(OTf)_2$	40	-	-	-
6[b],[c],[d]	$CuCl_2$	80	1:0	-	-
7	-	40	1:0	-	-

[a] NMR yield; [b] LiCl not added; [c] $Mn(OAc)_3 \cdot 2H_2O$ not added; [d] unidentified compounds present with starting material.

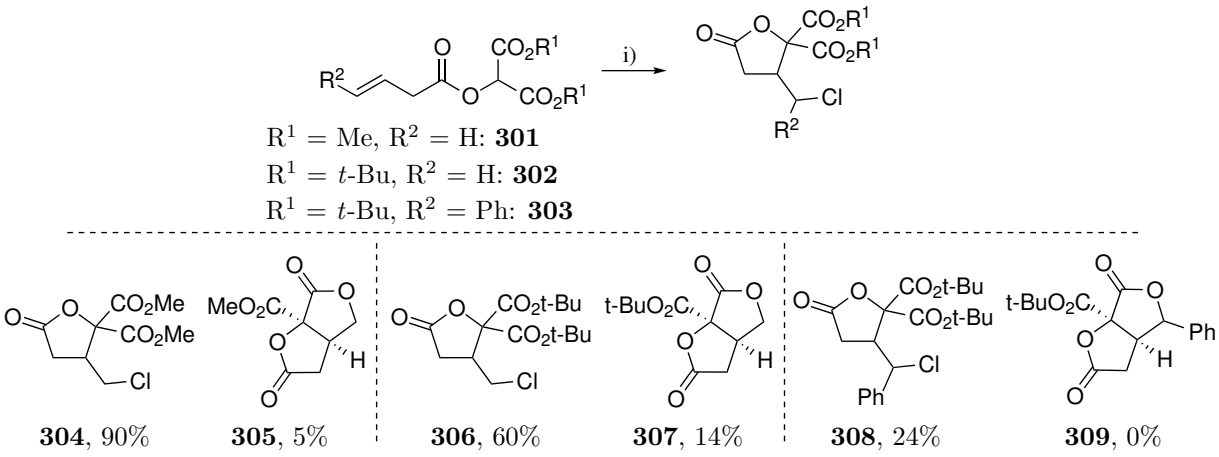
The formation of the chloro compounds were slower with $Cu(OAc)_2$ compared to $Cu(OTf)_2$ as deduced from the conversion obtained when T = 40 °C (**Table 2.5**, **Entry 1**). Increase of the temperature to 80 °C led to full conversion; however the observed yield was lower than in the case of using $Cu(OTf)_2$ (**Table 2.5**, **Entry 2**). Snider reported that the combination of $Cu(OAc)_2$ and LiCl was equivalent to adding $CuCl_2$,[125] hence we also performed the reaction with $CuCl_2$ in the absence of LiCl for further comparison. Low reaction rates were also observed with $CuCl_2$ at 40 °C, giving a similar conversion and yield for the chloro mono-lactone **297** (**Table 2.5**, **Entry 3**) when comparing with the $Cu(OAc)_2$ / LiCl combination. Higher temperatures also favoured the conversion and yield with $CuCl_2$ (**Table 2.5**, **Entry 4**), being the results equal to the ones obtained with $Cu(OAc)_2$ and LiCl, thus supporting Snider's observation that the combination of LiCl and $Cu(OAc)_2$ as the equivalent of $CuCl_2$. MAN-free conditions in the presence of $Cu(OTf)_2$ led to decomposition of the starting material (**Table 2.5**, **Entry 5**), and no conversion was observed with $CuCl_2$ (**Table 2.5**, **Entry 6**). The copper salt appeared essential for the transformation, as indicated by the lack of conversion of the copper-free experiment (**Table 2.5**, **Entry 7**). Traces of *bis*-γ-lactone **255** were observed when full conversion were obtained (**Table 2.5**, **Entries 2** and **4**), and less than 1% yield was observed for the uncyclised chloro ester malonates **300**.

As deduced from the control experiments, both MAN and copper salt were essential for the cyclisation to occur and it seemed that reactions driven by $Cu(OAc)_2$ were slower than those with $Cu(OTf)_2$. We corroborated Snider's observation in that the combination of $Cu(OAc)_2$ and LiCl is equivalent to $CuCl_2$. Nevertheless, in contrast with Vinogradov's and Snider's results, the alkene of the ester malonates

participates in the reaction regardless of the copper salt used with less than 1% yield observed for the chlorinated starting material **300**.

Extension of the Methodology. The methodology was extended to styrene-containing and primary alkene ester, ether, amido and amino malonates for the formation of primary and benzylic chloro mono-heterocyclic systems, in collaboration with Gillard[i].[126]

Ester Malonates. The chloro lactone **304** was isolated in 90% yield from the cyclisation of the ester **301** at 80 °C, with 5% of the *bis*-lactone **305**; while the ester malonate **302** led to 60% yield of **306** with 14% of the corresponding *bis*-lactone **307** at the same temperature (**Scheme 2.30**). Modest yields were observed for the chloro lactone **308**, which was obtained in 24% yield from the ester **303** with no presence of the *bis*-lactone **309** (**Scheme 2.30**).



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.) , LiCl (1.2 eq.), MeCN (0.15 M), T = 40 °C for the formation of **308** and T = 80 °C for **304** and **306**. Compound **308**: 99:1 *dr*

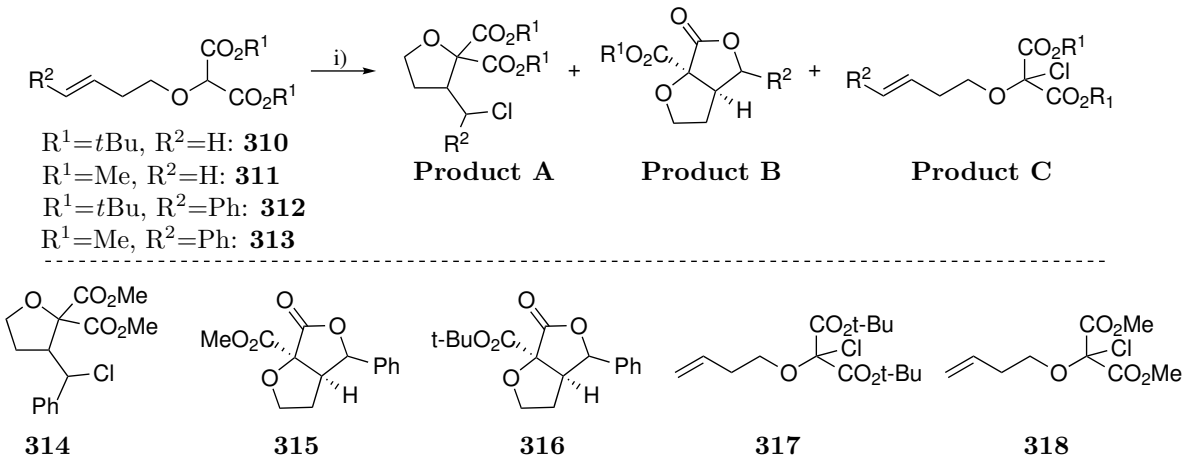
Scheme 2.30: Methodology Extension for the Formation of Chloro mono-Lactones, performed by Gillard.[126]

Ether Malonates. A special attention should be given to the case of ether alkyl malonates as substrates. Due to the higher captodative character of their malonyl radicals (see **Section 1.2.5.4**), participation of the alkene was only observed in the presence of the stabilising phenyl group in the α-position of the formed adduct radical (**Table 2.6**, **Entry 5** and **6**). In the absence of such a stabilisation effect, chlorination at the most acidic position occurred instead, giving the chlorinated ether malonates **317** and **318** in 42% and 51% yields respectively at 40 °C (**Table 2.6**, **Entries 1** and **3**). Increase of the

[i]Martin Gillard was a Master student in the Burton group who worked under my supervision in the formation of chloro monocyclic systems.

temperature to 80 °C did not trigger the cyclisation, but gave **317** in a much higher yield (**Table 2.6**, **Entry 2**). Substitution of $Cu(OTf)_2$ and LiCl by $CuCl_2$ also led to the chloro ether malonate **318** in 66% at 40 °C (**Table 2.6**, **Entry 4**). The outcome of the reaction changed dramatically with the styrene-containing substrates. No chlorination at the malonyl position was observed and the fused THF-γ-lactone **316** was obtained in 71% when the ester had *tert*-butyl residues (**Table 2.6**, **Entry 5**). Gratifyingly, the isolation of the desired chloro mono-THF system **314** was achieved in 40% yield with 56% yield for the fused THF-γ-lactone **315** when the ester alkyl residues were methyl groups (**Table 2.6**, **Entry 6**). We assume the methyl groups are slower than the *tert*-butyl residues in the lactonisation, which allowed for the isolation of the desired chloro THF system.

Table 2.6: Formation of Chloro-THF Systems, Performed by Gillard.[126]



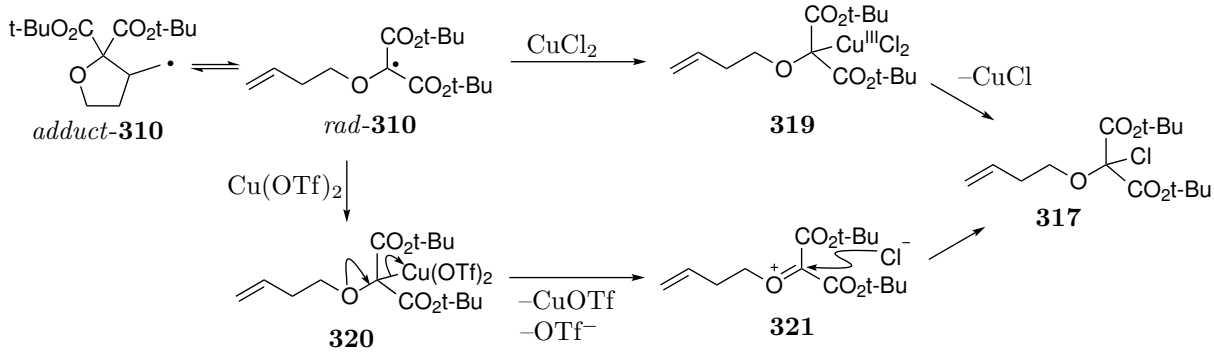
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), LiCl (1.2 eq.), MeCN (0.15 M), 40 °C, 22 h.

Entry	R^1	R^2	Substrate	Product A / Yield / %	Product B / Yield / %	Product C / Yield / %
1	*t*Bu	H	**310**	-	-	**317** / 42
2[a]	*t*Bu	H	**310**	-	-	**317** / 85
3	Me	H	**311**	-	-	**318** / 51
4[b]	Me	H	**311**	-	-	**318** / 66
5	*t*Bu	Ph	**312**	-	**316** / 71 (15:1 *dr*)	-
6	Me	Ph	**313**	**314** / 40 (99:1 *dr*)	**315** / 56 (32.3:1 *dr*)	-

[a] T = 80 °C; [b] $CuCl_2$ was used instead of LiCl.

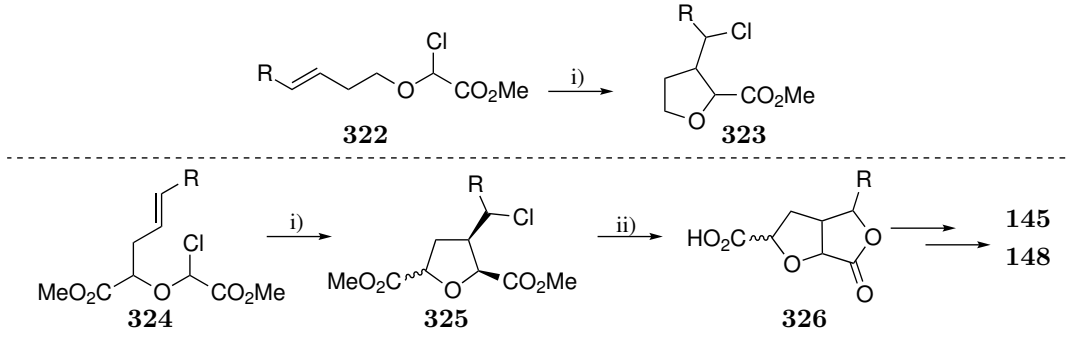
We attributed the lack of cyclisation in **310** and **311** as a consequence of the higher stability of the ether malonyl radical due to the captodative effect coming from its substituents. Their longer lifetime enabled the reaction with the copper salts $CuCl_2$ or $Cu(OTf)_2$, leading to the organocopper(III) complexes **319** and **320** respectively (**Scheme 2.31**). These could evolve either through a ligand transfer with release of CuCl or through the formation of an oxocarbenium ion **321** followed by chloride attack for the formation of the chlorinated ether malonate **317** (**Scheme 2.31**). We assume that this type of

ether malonate cyclises to the radical adduct *adduct*-**310**; however, since an unstable primary radical is formed, the ring opening towards the stabilised *rad*-**310** seemed to be more favoured. In the case of forming a more stable benzylic and secondary adduct radical, such reversibility is no longer present.



Scheme 2.31: Proposed Pathways for the Formation of Chloro Alkyl Ether Malonates.

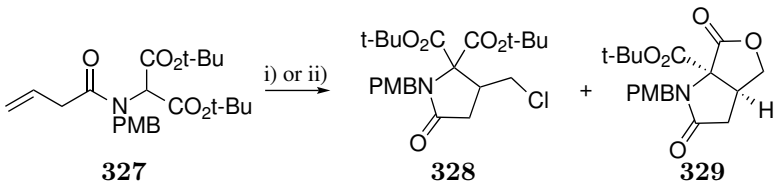
The synthesis of chloro THF systems has been reported by Udding *et al.* through a Cu-catalysed chlorine transfer radical cyclisation (**Scheme 2.32**).[127] Alkenes **322** and alkynes cyclised to give their corresponding chloro-containing systems such as **323** in yields between 64 and 95%. Application of the methodology was found in the synthesis of avenaciolide **145** and *iso*-avenaciolide **148**, after basic hydrolysis of the chloro THF **325** and further chemical manipulations.



Reagents & Conditions: i) CuCl (0.3 eq.), bpy (0.3 eq.), $ClCH_2CH_2Cl$, reflux, 18 h, 64-95% yield (7 examples); ii) KOH, MeOH, H_2O. R = alkyl group.

Scheme 2.32: Chloro THF Systems and Synthesis of Avenaciolide and *iso*-Avenaciolide, Reported by Udding *et al.*[127]

Nitrogen Series. The primary chloro PMB-protected lactam **328** was isolated in 31% yield with LiCl and in 40% yield with TBACl after the cyclisation of the amido malonate **327**, with the formation of the corresponding γ-lactam-γ-lactone **329** in 24% and 22% yield respectively (**Scheme 2.33**).[126]

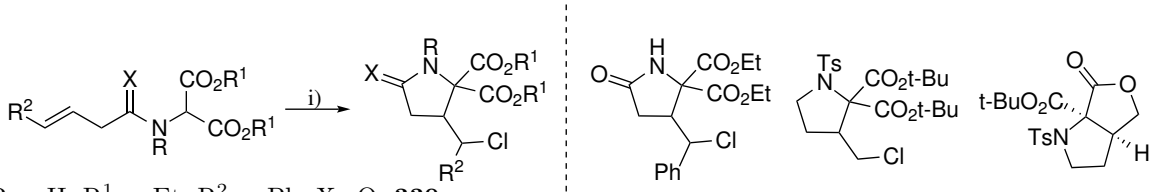


327 **328** **329**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.) , LiCl (1.2 eq.), MeCN (0.15 M), 40 °C, 22 h, **328**: 31%, **329**: 24%; ii) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), TBACl (1.2 eq.), MeCN (0.15 M), 40 °C, 22 h, **328**: 40%, **329**: 22%.

Scheme 2.33: Formation of the Primary Chloro mono-Lactam **328**, Performed by Gillard.[126]

The unprotected amido malonate **330** also cyclised to give the chloro γ-lactam **332** in 53% yield without the production of the corresponding γ-lactam-γ-lactone (**Scheme 2.34**). The amino malonate **331** was also tolerated, yet the N-tosyl-protected chloro pyrrolidine **333** was obtained in a lower yield (33%). Its corresponding γ-lactone **334** was observed in the crude of the reaction mixture, however the compound could not be isolated, thus a yield cannot be specified (**Scheme 2.34**).



R = H, R^1 = Et, R^2 = Ph, X=O: **330**

R = Ts, R^1 = *t*-Bu, R^2 = H, X=CH_2: **331**

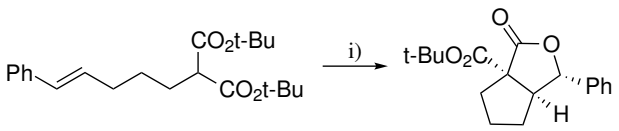
332, 53% **333**, 33% **334**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (.02 eq.), $Cu(OTf)_2$ (1.0 eq.), LiCl (1.2 eq.), MeCN (0.15 M), 40 °C, 22 h. Compound **332**: 1.2:1 *dr*.

Scheme 2.34: Extension to the Nitrogen Series.

Limitations of the Methodology. The methodology did not appear to be suitable for the all-carbon systems. When exposing the styrene-containing *tert*-butyl malonate (*E*)-**335**, the chloride did not seem to participate in the transformation, leading to the fused bicyclic γ-lactone **336** in 70% at both 40 °C and 80 °C (**Scheme 2.35**).

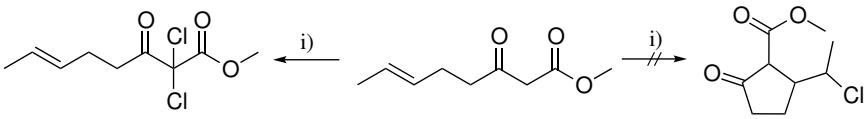
The submission of Snider's substrate **294**[125] (see **Scheme 2.28**) to our experimental conditions led to a mixture of starting material **294**, chlorinated β-ketoester **295** and other unidentified compounds. Increase of the temperature to 80 °C did not favour the reaction, but gave a complicated mixture of unidentified compounds (**Scheme 2.36**).



335 ***maj*-336**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), LiCl (1.5 eq.), MeCN (0.15 M); T = 40 °C: 70%, 49:1 *dr*; T = 80 °C: 70%, 13:1 *dr*.

Scheme 2.35: Application of MAN / $Cu(OTf)_2$ / LiCl System to All-Carbon Systems.



295 **294** **296**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), LiCl (1.5 eq.), MeCN (0.15 M), 40 °C.

Scheme 2.36: Application of MAN / $Cu(OTf)_2$ / LiCl System to Snider's Substrate **294**.

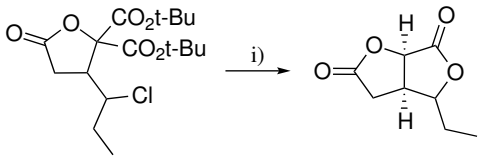
The conditions developed for the creation of chloro monocyclic compounds were highly substrate-dependent. All-carbon systems intramolecularly cyclised and lactonised at a higher rate than the chlorination process. In the case of Snider's substrate, the acidity of the unsubstituted α-protons was higher compared to those in the malonate series, which means that the chlorination step was faster than the cyclisation. Since the addition to the alkene was likely the rate determining step for this type of substrate, we assume alternative faster pathways were occurring before such cyclisation.[35]

2.3.4.4 Chloro mono-γ-Lactones as Precursors for the *bis*-γ-Lactones

With the chloro mono-γ-lactones **297**, **298**, **299** in hand (see **Scheme 2.29**), we attempted to convert them into the corresponding *bis*-γ-lactones. Halide exchange with NaI in refluxing acetone did not convert **297** into **337** (**Table 2.7**, **Entry 1**); while treatment with TBAI in DMSO at 140 °C only gave 6% of the decarboxylated *bis*-lactone **337** (**Entry 2**). Bromide exchange with LiBr in a mixture of DMSO and water at 140 °C gave a 32% yield for **337** (**Entry 6**); however, the yield could not be improved in an alternative solvent such as DMF (**Entry 8**) or in the presence of MgO as base to neutralise any HCl that could be formed during the reaction (**Entry 7**). Krapcho conditions[121,122] were not suitable, giving only 4% of the product (**Entry 5**). MgO in a mixture of DMSO and water led to 21% of the *bis*-lactone **337** (**Entry 4**); while the same reagent in refluxing toluene did not convert the chloro mono-γ-lactones **297** into **337** (**Entry 3**). Surprisingly, mild acidic conditions with the use of silica in refluxing toluene converted the starting material into **337** in 32% (**Entry 9**). The use of silica under solvent-free conditions decreased the yield to 12% (**Entry 10**). Silver salts did not convert the

starting material or led to decomposition (**Entries 11** and **12**). Solvent-free thermal conditions gave no conversion or decomposition (**Entries 14** and **15**) and only a 5% of product in a mixture of DMSO in water (**Entry 13**).

Table 2.7: Attempts for the Formation of *bis*-γ-Lactones from Chloro mono-γ-Lactones.



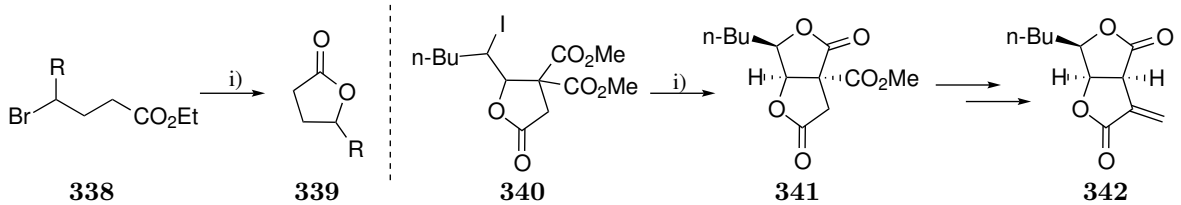
297 **337**

Reagents & Conditions: i) salt or base, solvent, T / °C, t / h.

Entry	Reagent(s)	Solvent(s)	T / °C	t / h	Ratio[d] **297**:**337**	Yield / %
1	NaI	acetone (0.05 M)	reflux	16	1:0	-
2	TBAI	DMSO (0.24 M)	140	1.5	0:1	6
3	MgO	toluene (0.05 M)	reflux	12	1:0	-
4	MgO	DMSO (0.24 M) / H_2O (11.8 M)	140	3	0:1	21
5	LiCl	DMSO (0.24 M)	160	1	0:1	4
6	LiBr	DMSO (0.24 M) / H_2O (11.8 M)	140	1.5	0:1	32
7	LiBr / MgO	DMSO (0.24 M) / H_2O (11.8 M)	140	1.5	1:0	-
8	LiBr	DMF (0.24 M)	140	1.5	1:0	-
9	SiO_2	toluene (0.2 M)	reflux	3	0:1	32
10	SiO_2	-	110	3	0:1	12
11[a]	$AgNO_3$	DMSO (0.24 M)	100	18	-	-
12	$AgBF_4$	MeCN (0.2 M)	40 to 80	20	1:0	-
13	-	DMSO (0.24 M) / H_2O (11.8 M)	140	3	0:1	5
14[b]	-	-	140	0.5	-	-
15[c]	-	-	100	3	1:0	-

[a] chloro-lactone **298** as substrate; [b] Kugelrohr was used; [c] heating under an Ar flow; [d] crude ratio.

The use of silica gel has already been reported for the formation of γ-lactones **339** from γ-halo esters **338** by Takeda and co-workers.[128] Several examples have been reported using silica gel in refluxing xylene for up to 15 h to produce cyclisation. The methodology has been applied to the synthesis of the key intermediate **341** for the synthesis of (±)-canadensolide **342** (**Scheme 2.37**).[129]



338 **339** **340** **341** **342**

Reagents & Conditions: i) silica gel, anhydrous xylene (0.4 M), reflux, t = 12-15 h, 66-79%; *bis*-lactone **341**: 62%, t = 3h.[128,129]

Scheme 2.37: Silica Gel-Mediated Lactonisation of γ-Halo Esters, Reported by Takeda and co-workers.[128]

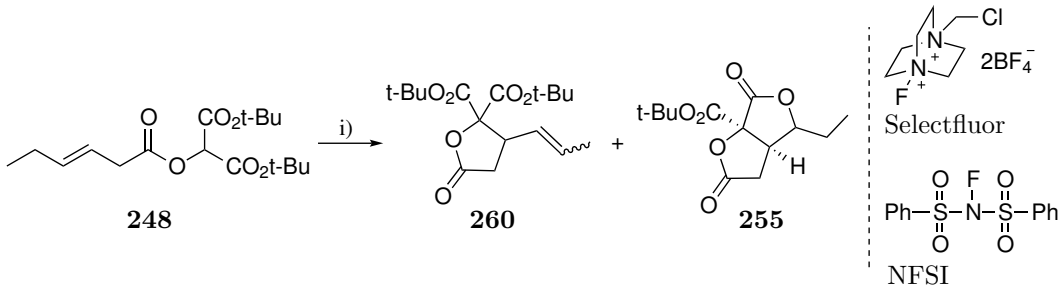
Despite the similarity of the chloro mono-lactones **297**, **298** and **299** with Takeda's γ-lactone **340**, no success has been found when applying their reported conditions in our system. We assumed the main

issue was the chloride as leaving group. We therefore decided to investigate the formation of other halo γ-lactones for a subsequent cyclisation to the *bis*-γ-lactones.

2.3.4.5 Towards Fluoro and Bromo mono-γ-Lactones

Fluoro-Containing Analogues. It is well known that fluoride is a poor leaving group in S_N2 reactions, implying that fluoro mono-γ-lactones would not cyclise to the desired *bis*-lactones. However, due to their importance in medicinal chemistry,[130] a number of reaction conditions towards their formation were studied.

Table 2.8: Attempts towards the Formation of Fluoro mono-γ-Lactones.



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), F^- / $F^\cdot$ source, MeCN (0.15 M), T / °C.

Entry	F^- / $F^\cdot$ source (eq.)	T / °C	t / h	Ratio[c] **260**:**255**
1	LiF (1.0)	40	24	66:34
2	KF (1.5)	80	21	72:28
3	CsF (1.5)	80	21	88:12
4	TBAF (1.5)	80	21	72:28
5	Selectfluor (1.5)	80	3	degradation
6[a]	Selectfluor (1.5)	80	3	degradation
7	NFSI (1.5)	80	3	38:62
8[a]	NFSI (1.5)	80	17	no conversion
9	CuF_2 (1.0)	80	22	1:0[d]
10[b]	CuF_2 (3.0)	80	19	-[e]

[a] Cu-free; [b] $Mn(OAc)_3 \cdot 2H_2O$ (1 eq.); [c] by ^{1}H-NMR analysis of the crude reaction mixture; [d] **260**: 40%, **255**: 8%, **248**: 10% recovered; [e] unidentified compound(s)

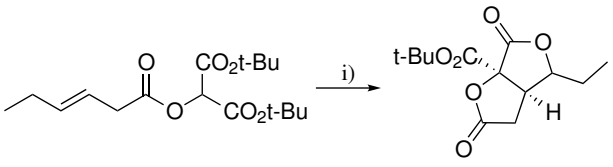
The ester malonate **248** was treated with the alkali fluorides LiF, KF and CsF under the MAN-based conditions; however, the fluoride anion did not appear to participate in the transformation, thus leading to the formation of the alkenyl γ-lactone **260** as the major compound, with the *bis*-γ-lactone **255** as the minor product (**Table 2.8**, **Entries 1-3**). The use of a more soluble salt such as alkyl ammonium fluoride did not favour the participation of the fluoride ion in the reaction (**Entry 4**). The use of fluorides as nucleophiles has always remained a challenge due to their poor solubility in common organic solvents and their high tendency for hydrogen bonding that typically lowers their nucleophilicity. On the other hand, if the fluoride is unsolvated, its high basicity would lead to side-product formation.[131] Consequently, in

order to avoid solvation issues, fluoro radical sources such as Selectfluor® and NFSI were selected for further study.[132] Unfortunately, product degradation was observed in the case of Selectfluor (**Entries 5** and **6**), and formation of the vinyl lactone **260** and no conversion were observed with NFSI in the presence (**Entry 7**) and in the absence of the copper salt (**Entry 8**) respectively. The use of CuF_2 gave **260** with recovery of starting material in 10% yield (**Entry 9**); while the use of three equivalents of CuF_2 with 1 equivalent of $Mn(OAc)_3 \cdot 2H_2O$ led to a mixture of unidentified compounds (**Entry 10**).

Despite the negative results with the development of this methodology, we consider that there is still room for further studies, including the use of alternative fluorides anions that would mainly act as non-solvated nucleophiles,[131] or with the use of radical sources of fluorine under modified reaction conditions.[132,133]

Bromo mono-γ-Lactones. Next on the list was the formation of bromo mono-γ-lactones as intermediates for the synthesis of the desired *bis*-γ-lactone frameworks. The *bis*-lactone **255** was isolated in yields between 16% and 21% when the temperature reached 80 °C with KBr and $CuBr_2$ (**Table 2.9**, **Entries 3** and **5**). The desired bromo mono-γ-lactone was not isolated. Lower temperatures gave complicated mixtures of unidentified compounds (**Entries 1**, **2** and **4**).

Table 2.9: Attempts towards the Formation of Bromo mono-γ-Lactones.



248 **255**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OTf)_2$ (1 eq.), Br^- source, MeCN (0.15 M), 21 h, T / °C.

Entry	Br^- Source (eq.)	T °C	Isolated Product / Yield / %
1	LiBr (1.5)	40	-
2	LiBr (1.5)	80	-
3	KBr (1.5)	80	**255** / 21
4[a]	$CuBr_2$ (1.0)	40	-
5[a]	$CuBr_2$ (1.0)	80	**255** / 16

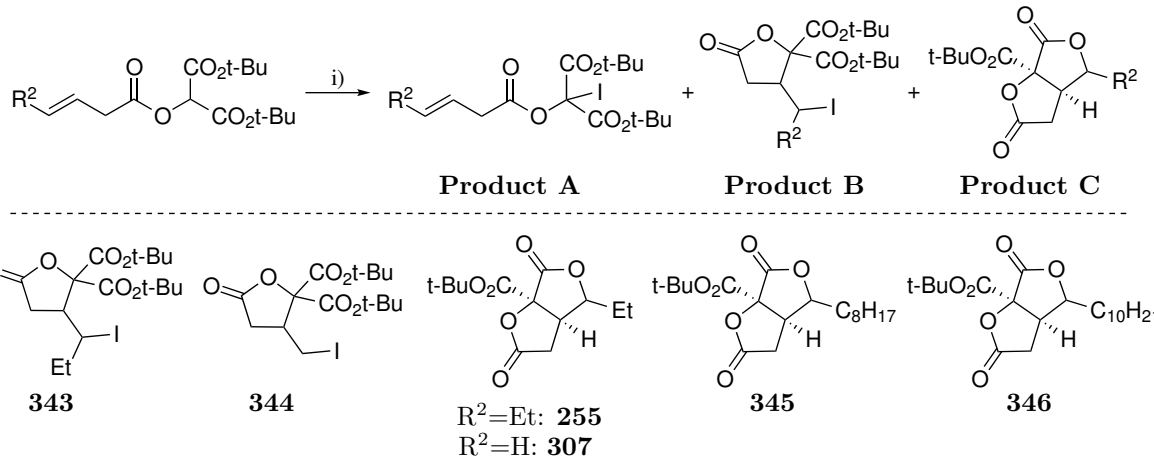
[a] $Cu(OTf)_2$ not present.

Previous work concerning the formation of α-bromo esters was reported by Curran and co-workers who used them as substrate for atom transfer radical cyclisations. It appeared that, after comparison with their iodo analogues, bromo esters were much less reactive towards the radical initiation needed for such radical cyclisations.[134]

2.3.4.6 Iodo mono-γ-Lactones: Key Intermediates

Fluorides, chlorides and bromides salts were incorporated into the MAN-based conditions; however, we were at first not very optimistic about the use of iodides in such oxidative conditions. Iodides are known as mild reducing agents and our first thought was that they would react with $Mn(OAc)_3 \cdot 2H_2O$ thus interfering with the oxidative radical cyclisation pathway. Nevertheless, LiI was used at 40 °C as an initial attempt (**Table 2.10**, **Entry 1**). ^{1}H-NMR analysis of the crude reaction mixture indicated the presence of the iodo ester malonate **357** as the major component of the mixture (the singlet at 5.32 ppm for the malonyl proton was not present) with the iodo mono-γ-lactone **343** and the *bis*-γ-lactone **255** as minor products of the transformation (**Entry 1**).

Table 2.10: Iodo mono-γ-Lactones as Intermediates for *bis*-γ-Lactones.



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), I^- salt (eq.), MeCN (0.15 M), T / °C 19 h

Entry	R^2 (compound)	I^- salt (eq)	T / °C	Product A	Product B	Product C
1[a]	C_2H_5 (**248**)	LiI	40	50 (**357**)	13 (**343**)	28 (**255**)
2[b],[c]	H (**302**)	KI	60	traces	41% (**344**)	12% (**307**)
3[a]	C_2H_5 (**248**)	KI	40	28 (**357**)	41 (**343**)	25 (**255**)
4[b]	C_2H_5 (**248**)	KI	80	-	-	74% (**255**) (2.3:1 *dr*)
5[b]	C_8H_{17} (**251**)	KI	80	-	-	57% (**345**) (2.7:1 *dr*)
6[b]	$C_{10}H_{21}$ (**252**)	KI	80	-	-	53% (**346**) (2.0:1 *dr*)

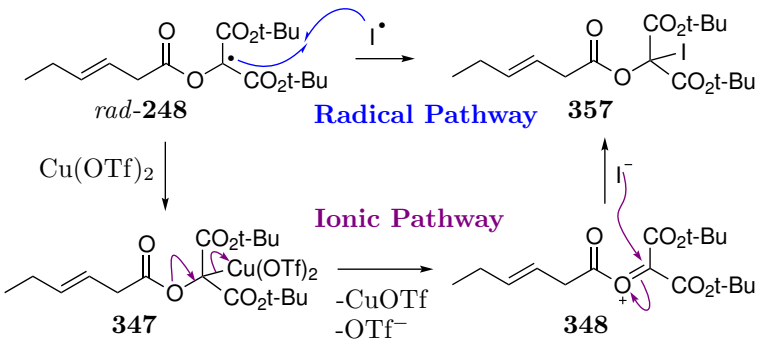
[a] NMR distribution of products (9% corresponds to starting material in **Entry 1** and 6% in **Entry 3**; [b] isolated yields; [c] experiment done by Gillard.[126]

The same study was performed for the terminal alkene **302** with KI by Gillard and 41% and 12% yields were obtained for the terminal iodo mono-γ-lactone **344** and the *bis*-lactone **307** respectively with traces of the uncyclised iodo malonate (**Entry 2**). Gillard's result has shed light on the investigation of KI as iodide source, which led to a higher proportion of the iodo mono-lactone **343** (**Entry 3**). We assumed that secondary iodides might convert into the *bis*-lactone after ester substitution under thermal conditions as reported by Taguchi in his ionic carbocyclisation (see **Section 2.3.4.1**). Consequently,

temperatures were increased by 40 °C and we observed a 74% yield for the desired *bis*-γ-lactone **255** without formation of the uncyclised iodo ester malonate **357** and the iodo mono-lactone **343** (**Entry 4**). The same conditions were applied to the octyl **251** and decyl **252** ester malonate analogues and 57% and 53% yield were obtained respectively for the corresponding *bis*-lactones **345** and **346** (**Entries 5** and **6**).

Yields were still moderate for the octyl and decyl *bis*-γ-lactones **345** and **346**; however, they represented a great improvement since alkenyl mono-lactones were not detected, which contrasts with the reported standard MAN-method (see **Section 2.3.2**).

Control Experiments. In view of the previous positive results, studies aimed at understanding the process were undertaken. Due to the mild reducing character associated with the iodide anion, we suspected that under the oxidative conditions iodine radicals might be formed, which would explain the formation of the iodo ester malonate **357** (radical pathway, **Scheme 2.38**). On the other hand, an alternative ionic pathway might happen through the formation of the oxocarbenium ion **348** with subsequent attack of the iodide to form **357** (**Scheme 2.38**).

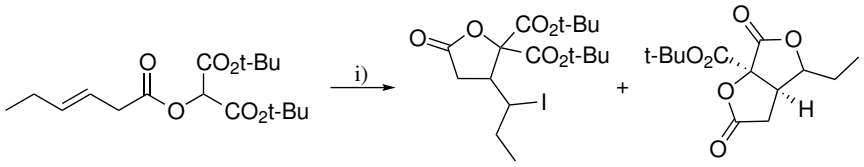


Scheme 2.38: Proposed Pathways for the Formation of α-Iodo Ester Malonate.

Mn(III) and Cu(II) Role. Considering the radical pathway (**Scheme 2.38**), we would expect formation of molecular iodine during the transformation. Consequently, a control experiment with molecular iodine as the iodine radical source was performed. However, the desired *bis*-γ-lactone **255** was not formed. Instead, 8% of starting material **248** was recovered along with unidentified products (**Table 2.11**, **Entry 1**). Nevertheless, this result does not negate the *in situ* formation of iodine radical or molecular iodine, since these could be formed in low concentrations and react with the most reactive species, *i.e.* the generated radicals. Shorter reaction times allowed the isolation of **343** in 21% yield

with 53% of the *bis*-γ-lactone **255**, thus confirming the iodo mono-γ-lactone **343** as an intermediate of the transformation (**Entry 2**). Further confirmation was given by Gillard when heating compound **344** (see **Table 2.10**) in MeCN at 80 °C for 8 h, which led to the formation of the corresponding *bis*-lactone **307** in 25% yield (50% conversion).[126] Due to the radical character of the reaction, MAN-based experiments were generally run in an O_2-free atmosphere; however, to monitor the influence of oxygen on the reaction, an open-air experiment was performed. The intermediate **343** was not observed despite the short reaction time and the *bis*-lactone **255** was obtained in lower yield despite complete consumption of the starting material (**Entry 3**).

Table 2.11: MAN / KI Methodology: Control Experiments.



248 **343** **255**

Reagents & Conditions: $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), copper salt (eq.), KI (eq.), MeCN, 80 °C.

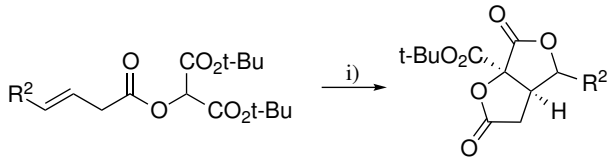
Entry	copper salt / eq	I^- Source / eq.	t / h	**343** / Yield / %	**255** / Yield / %
1	$Cu(OTf)_2$ /1.0	I_2 / 1.5	19	-	-[e]
2	$Cu(OTf)_2$ /1.0	KI / 1.5	2.5	21 (3.5:1 *dr*)	53 (1.9:1 *dr*)
3[a]	$Cu(OTf)_2$ / 1.0	KI / 1.5	3.5	-	46 (2.3:1 *dr*)
4	-	KI / 0.5	19	-	78[c] (2.0:1 *dr*)
5[b]	-	KI / 0.5	19	-	73 (1.1:1 *dr*)
6[b]	-	KI / 0.2	19	-	63 (1.1:1 *dr*)
7[d]	$Cu(OTf)_2$ / 3.0	KI / 0.5	3	-	decomposition
8[b][f]	-	-	19	-	n.a.
9[g]	-	-	19	-	n.a.

[a] Open-air flask; [b] $Mn(OAc)_3 \cdot 2H_2O$ (3 eq); [c] NMR yield (ratio **248**:**255** = 1:3); [d] MAN-free conditions; [e] 8% starting material **248** recovered; [f] **248**:**255** crude ratio = 82:18; [g] **248**:**255** crude ratio = 93:7 .

The role of the copper salt was next investigated and Cu-free conditions were studied. It appeared that copper salts were not essential for the oxidative cyclisation to occur and 78% NMR yield was obtained for the desired *bis*-lactone **255** in a mixture containing starting material **248** in a ratio **248**: **255** = 1:3 (**Entry 4**). The amount of iodide salt was reduced to sub-stoichiometric quantities (0.5 equivalents), as we assumed iodine was being regenerated in the medium. The number of MAN equivalents was increased from two to three and full conversion was obtained with 73% isolated yield for the *bis*-γ-lactone (**Entry 5**). Decrease in the KI stoichiometry also gave the *bis*-lactone; however, lower yields were obtained (**Entry 6**). MAN proved to be essential for the oxidative cyclisation by the result of the MAN-free experiment (**Entry 7**). KI-free conditions led to traces of the *bis*-γ-lactone **255** (**Entries 8** and **9**); meaning that the presence of KI assists and help the cyclisation to happen through an atom-transfer

radical process from the iodo malonate **357**. The kinetics of iodine-transfer reactions were studied by Curran and co-workers and they concluded that iodine transfer from an α-iodocarbonyl compound to a simple alkyl radical were very rapid processes.[135]

The isolation and purification of the *bis*-γ-lactones were more straightforward when copper-free conditions were used, an observation that might explain the much higher yields obtained for the *bis*-γ-lactones **345** and **346** (**Scheme 2.39**).

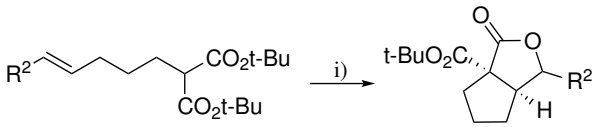


$R^2 = C_8H_{17}$: **251** $R^2 = C_8H_{17}$: **345**
$R^2 = C_{10}H_{21}$: **252** $R^2 = C_{10}H_{21}$: **346**

Reagents & Conditions: $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq), KI (0.5 eq), MeCN (0.15 M), 80 °C 21 h. **345**: 72% (1.9:1 *dr*); **346**: 74% (2.0:1 *dr*).

Scheme 2.39: Cu-Free MAN / KI Methodology.

Extension to All-Carbon Systems. All-carbon systems were also tolerated by the MAN / KI system for the oxidative radical cyclisation. The methodology proved to be highly efficient for the styrene-containing malonate **335**, with a 88% yield for the bicyclic γ-lactone **336**; however, a moderate yield was observed for the cyclisation of the terminal alkene malonate **349** into the γ-lactone **350** (**Scheme 2.40**). In the last case, NMR analysis showed the presence of olefinic protons in the side products. Assuming that the cyclisation might be reversible, the primary radical adduct would ring open and led to the formation of the uncyclised side-products, which are believed to be either dimers of **349** or oxidised starting materials.



R^2 = Ph, **335** R^2 = Ph, **336**
R^2 = H, **349** R^2 = H, **350**

Reagents & Conditions: $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq.), KI (0.5 eq.), MeCN (0.15 M), 80 °C, 21 h; Lactone **336**: 88%, 9:1 *dr* (ratio **335**:**336** = 7:93); Lactone **350**: 46%.

Scheme 2.40: MAN / KI Methodology Extension to All-Carbon Systems.

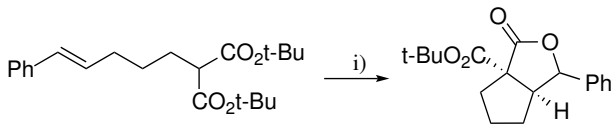
While the Cu-free and the standard methodology (see **Section 1.2.5.2**) gave similar yields for **336** (84% (4.1:1 *dr*) using the MAN / $Cu(OTf)_2$ oxidant system); the yield was much higher for **350** with

the standard method (92%) than with the MAN / KI system.

KI-free conditions in the presence of three equivalents of MAN were also attempted for **335**; however, in this case, 70% of starting material **335** was recovered, which was in accordance with the results obtained for **248** when running the same experiment (see **Table 2.11**, **Entry 8** and **9**).

Salt and Solvent Screening. Iodides salts other than KI also led to good yields for the bicyclic γ-lactone **336** with similar conversions (**Table 2.12**, **Entries 1** and **2**). Common solvents used in MAN-based oxidative cyclisations were tolerated giving yields between 72% and 78% (**Entries 3-5**).

Table 2.12: Iodide Salt and Solvent Screening in the All-Carbon Series.



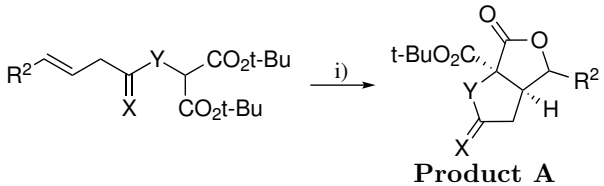
335 **336**

Reagents & Conditions: $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq), Iodide Salt (0.5 eq.), Solvent (0.15 M), 80 °C, 21 h.

Entry	I^- Salt	Solvent	Ratio **335**:**336**	**336** / Yield / %
1	TBAI	MeCN	10:90	78 (9:1 *dr*)
2	NaI	MeCN	6:94	83 (9:1 *dr*)
3	KI	AcOH	0:1	78 (10:1 *dr*)
4	KI	EtOH	6:94	72 (13.3:1 *dr*)
5	KI	DMSO	12:88	76 (9:1 *dr*)

Extension to Ethers Malonates and to the Nitrogen Series The MAN / KI methodology was developed for ester malonates and also showed applicability in the all-carbon malonate series. As a consequence, extension of the methodology to ether, amino and amido alkyl malonates was undertaken. The PMB-protected amido malonate **327** cyclised to give the γ-lactam γ-lactone **329** in a similar yield than the one obtained with the standard method (**Table 2.13**, **Entry 1**).

Table 2.13: MAN / KI Methodology Extension to the Oxygen and Nitrogen Series.



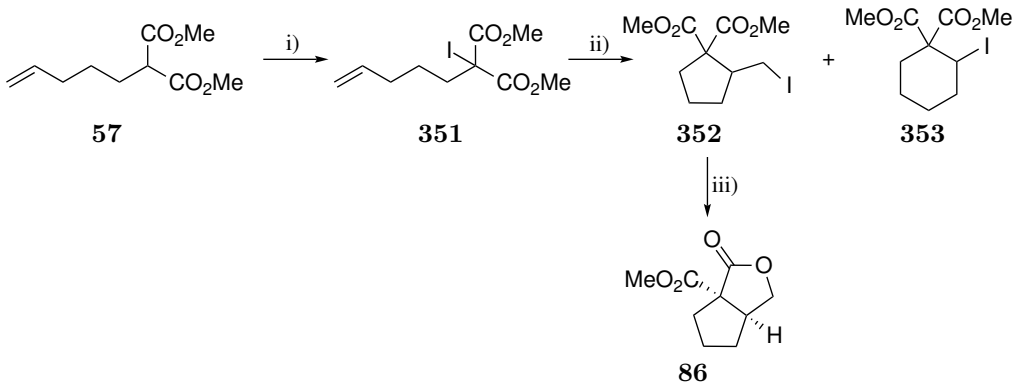
Product A

Reagents & Conditions: $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq.), KI (0.5 eq.), MeCN (0.15 M), 80 °C 21 h.

Entry	X	Y	R^2	Substrate	Product A / Yield / %
1	O	N-PMB	H	**327**	**329** / 83
2	H_2	N-Ts	H	**331**	**334** / 44
3	H_2	O	Ph	**312**	**316** / 63 (13.3:1 *dr*)
4	H_2	O	H	**310**	**498** / 68

The fused pyrrolidine γ-lactone **334** has also been isolated in 44% from the amino malonate **331** (**Entry 2**). Ether malonates **312** and **310** were also compatible with the present methodology and were converted to the fused THF-γ-lactones **316** and **498** in 63% and 68% yield respectively (**Entries 3** and **4**). The yield for the phenyl-containing lactone **316** was similar in both copper-free and standard methods (62%, 16:1 dr); however, in the case of the terminal alkene ether malonate **310**, the yield of the lactone **498** was substantially lower under the copper-free conditions with 68% yield compared to the 83% yield obtained in the presence of $Cu(OTf)_2$ (see **Section 1.2.5.4**).[60]

Proposed Mechanism The presence of the iodo ester malonate **357** (**Table 2.10**) in the preliminary experiments made us consider that it might be an intermediate during the transformation. Iodo malonates have already been studied by Curran and co-workers for atom transfer radical cyclisations (ATRC).[134] In this method, a C-X (X = halogen) bond reacts with an radical initiator to form the first radical, which adds intramolecularly across a multiple bond. Iodine was considered a much better donor than bromine in the halogen atom transfer process, thus explaining the choice of substrate. In Curran's work, dimethyl malonate **57** was converted into the α-iodo malonate **351**, which was then irradiated (275 W sunlamp) in the presence of the radical initiator to form an inseparable mixture of 5-*exo* **352** and 6-*endo* **353** cyclisation products in 86% yield. Further thermal treatment of the mixture converted the 5-*exo*-product **352** into the fused bicyclic γ-lactone **86** (**Scheme 2.41**).[134]



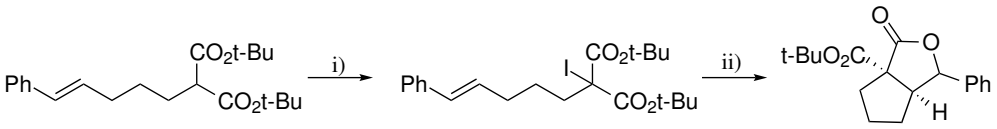
Reagents & Conditions: i) KH, NIS, THF, -78 °C **351**: 90%; ii) 5-10% $(Me_3Sn)_2$, hν (275 W, sunlamp), benzene (0.3 M), 40-80 °C 10 min, 86% ratio **352**:**353** = 9:1; iii) 110 °C 2 h.

Scheme 2.41: Atom Transfer Radical Cyclisation of α-Iodo Malonates, Reported by Curran and co-workers.[134]

Taking into account Curran's work on the atom transfer radical cyclisation, we proposed both iodo malonate **357** and the cyclic iodo compound **343** (see **Table 2.10**) as intermediates in the oxidative cyclisation of the ester malonates to the *bis*-γ-lactones. Since copper(II) salts were not essential for the

transformation, it is proposed that the formation of the iodo malonate **357** followed a radical mechanism rather than an ionic pathway which would imply the participation of the copper salt (see **Scheme 2.38**).

Since the all-carbon systems also cyclised under the copper-free methodology, the iodo styrene-derived *tert*-butyl malonate **354** was synthesised by treatment of the starting material **335** with NaH and NIS as electrophilic source of iodine. It was found that conversion to the fused γ-lactone **336** was achieved by leaving a sample of **354** in a $CDCl_3$ solution for 5 days at room temperature in a brown NMR tube (**Scheme 2.42**), thus supporting our hypothesis concerning compound **354** as an intermediate in the transformation.



335 **354** **336**

Reagents & Conditions: i) NaH (1.2 eq.), NIS (1.2 eq.), THF (0.1 M), -78 °C to r.t., 4.5 h; ii) r.t. 5 d, $CDCl_3$, in dark NMR tube; **336**:**354** ratio = 84:16; 13.3:1 *dr*

Scheme 2.42: Iodo Malonate **354** Formation and Evolution to the γ-Lactone **336**.

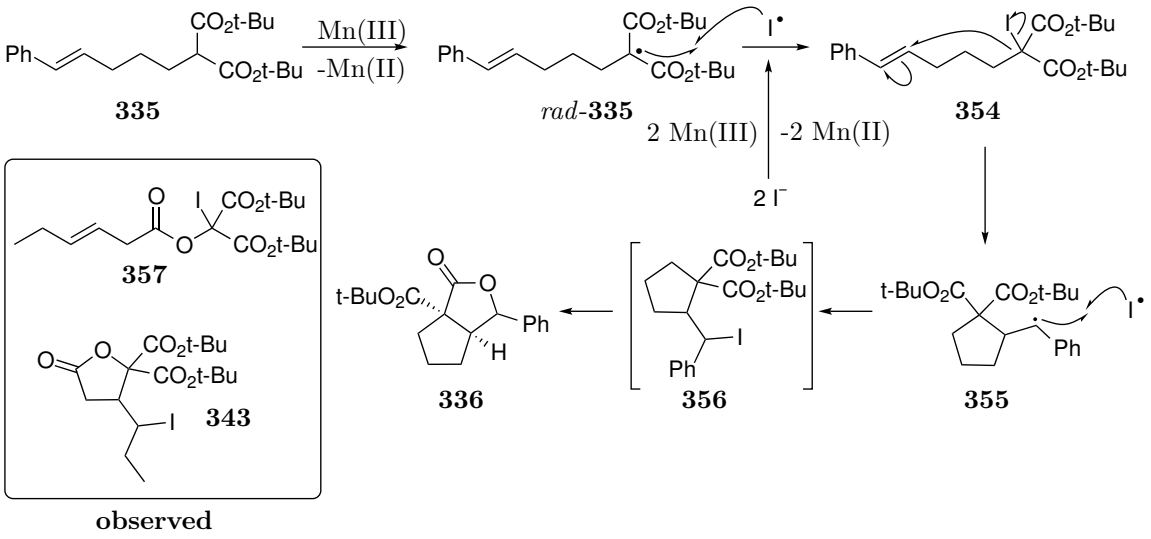
Finally, we proposed that after formation of the iodo malonate **354** from MAN-based initiation and reaction with iodine radical, an atom transfer radical cyclisation would follow to form the iodo cyclopentane **356** as reported previously by Curran.[134] The intermediate **356** has not been observed; however, its analogue **343** has been isolated when treating the ester malonate **248** under the oxidative conditions (see **Table 2.10**). Thermal treatment would follow to form the desired fused γ-lactone **336** after lactonisation (**Scheme 2.43**).

2.3.5 Endgame

The development of the methodology for the formation of *bis*-γ-lactones from ester malonates bearing an alkyl chain as alkene substituent equipped us to perform the two remaining reactions to complete the synthesis of the ethisolide family of natural products (see **Scheme 2.1**). As a result of the reactivity associated with *exo* α-methylene lactones as powerful Michael acceptors, dealkoxycarbonylation conditions were first investigated.

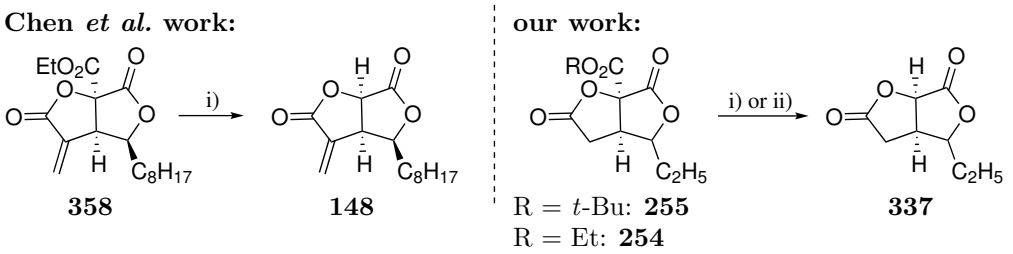
2.3.5.1 Dealkoxycarbonylation

Chen *et al.* published the use of magnesium salts for a late-stage dealkoxycarbonylation of *bis*-γ-lactones in their synthesis of (±)-*iso*-avenaciolide.[136] Despite the compatibility displayed with the *exo*-methylene



Scheme 2.43: Proposed Mechanism for the MAN / KI Oxidant System for the Synthesis of γ-Lactones.

moiety in **358** and the good yield obtained for *iso*-avenaciolide **148**, Chen's conditions did not give useful yields for the dealkoxycarbonylation of the *tert*-butyl ester *bis*-lactone **255** and ethyl ester *bis*-lactone **254** in either DMF or DMA as solvents (**Scheme 2.44**).



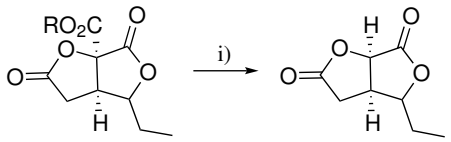
Reagents & Conditions: i) $MgCl_2 \cdot 6H_2O$, DMA, 150 °C, 3 h, **148**: 59%, **337**: 19% (1:1 *dr*); ii) $MgCl_2 \cdot 6H_2O$, DMF, 150 °C, 3 h, **337**: 18% NMR yield (4:1 *dr*) from **255**, 7% NMR yield (1:1 *dr*) from **254**.

Scheme 2.44: Dealkoxycarbonylation Attempts, Reported by Chen *et al.*[136]

The barrier encountered with the reported dealkoxycarbonylation of *bis*-γ-lactones,[136] drove us to study classical dealkoxycarbonylation conditions such as Krapcho conditions. A number of alkyl ester *bis*-lactones were treated with LiCl in a mixture of DMSO and H_2O and it appeared that 160 °C was necessary for high conversions (**Table 2.14**, **Entries 1** and **2**). Dealkoxycarbonylation of ethyl and methyl ester residues were found to be slower than the corresponding *tert*-butyl esters, in which their low yields could be explained by the decomposition of the product when longer reaction times were used (**Entries 2-4**). As already reported by Krapcho,[121,122] dealkoxycarbonylation of *tert*-butyl esters was much faster and 70% yield of the desired *bis*-lactone **337** was isolated (**Entry 7**) after 1 h at 160 °C.

Longer reaction times were not beneficial as displayed by the yields obtained after two and three hours reaction time (**Entries 5** and **6**).

Table 2.14: Dealkoxycarbonylation Attempts



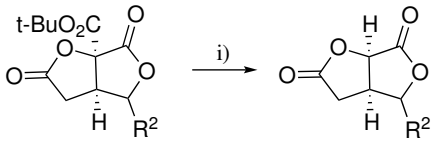
337

Reagents & Conditions: LiCl (3.5 eq.), DMSO (0.24 M), H_2O (11.8 M), T (°C), t (h).

Entry	R	Substrate	T / °C	t / h	Substrate: **337**	Yield / %
1	Me	**253**	150	8	40:60	n.a.
2	Me	**253**	160	10	10:90	28
3[a]	Me	**253**	160	12	9:91	18
4	Et	**254**	160	6	50:50	n.a.
5	*t*Bu	**255**	160	2	0:1	65
6	*t*Bu	**255**	160	3	0:1	51
7	*t*Bu	**255**	160	1	0:1	70 (2.1:1 *dr*)

[a] 5.8 eq. of LiCl used.

The optimal reaction conditions were applied to the *bis*-lactone analogues **345** and **346**, giving the decarboxylated *bis*-lactones **480** and **481** in 69% and 77% yield respectively (**Scheme 2.45**). It should be mentioned that no chromatography of **480** and **481** was needed as a result of the increase of hydrophobicity originating from the long aliphatic chains, which in contrast with their analogue **337**, made the isolation of the product from the highly polar solvent more straightforward.



R = C_8H_{17}: **345** R = C_8H_{17}: **480**

R = $C_{10}H_{21}$: **346** R = $C_{10}H_{21}$: **481**

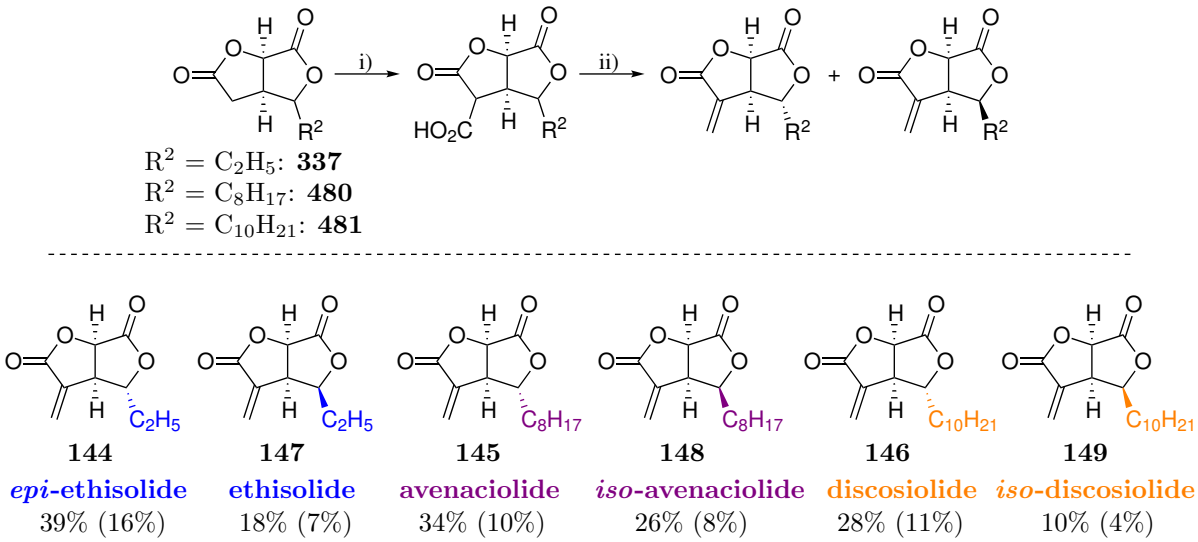
Reagents & Conditions: LiCl (3.5 eq.), DMSO (0.24 M), H_2O (11.8 M), 160 °C, 1 h; **480**: 69% (2.8:1 *dr*); **481**: 77% (3:1 *dr*).

Scheme 2.45: Krapcho Dealkoxycarbonylation.

2.3.5.2 Methylenation

Due to the popularity of Parker and Johnson's conditions[78] as late-stage strategy for the introduction of the *exo*-alkene moiety (see **Section 2.2**), we applied the same conditions to the diastereomeric mixture of the decarboxylated *bis*-lactones **337**, **480** and **481** (**Scheme 2.46**). Treatment of **337**, **480** and **481** with Stile's reagent led to the corresponding carboxylic acids. Addition of a stock solution of diethyl

amine and formalin in a buffer solution of NaOAc in AcOH led to CO_2 evolution and formation of the corresponding β-diethylamino lactone. Heating at 100 °C led to formation of the desired α-*exo*-methylene moiety. The diastereoisomers were separated by column chromatography, giving the five natural products **144**, **147**, **145**, **148** and **146**, and the non-natural analogue *iso*-discosiolide **149** in the following stated yields (**Scheme 2.46**).



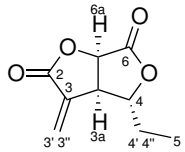
Reagents & Conditions: i) $MeOMgOCO_2Me$ (Stile's Reagent), DMF, 120 °C, 5 h; ii) formalin solution (37 wt. % CH_2O in H_2O), Et_2NH, NaOAc, AcOH, r.t. to 100 °C, 5-10 min; yields stated between parenthesis represent the overall yields for the synthesis.

Scheme 2.46: Late-Stage Methylenation for the Synthesis of the Ethisolide Family of Natural Products.

As it can be observed, the natural products have been isolated in low yields, especially for the minor diastereoisomers **147**, **148** and **149**, which proved difficult to purify. Separation of the two diastereoisomers was not trivial and fractions with mixtures of both diastereoisomers were often recovered, thus lowering the isolation yield of the pure compound. Attempts to increase the yield were made by changing the temperature and reaction times for the deprotonation / elimination step. Rodriguez *et al.* reported a modified procedure by treating the carboxylic acid with the iminium ion in the buffer solution at room temperature for two hours,[137] however, such conditions did not give any improvement. Also an increase in the number of equivalents of the stock solution and the reaction time at 100 °C for up to 20 min did not improve the yields.

NMR Data Comparison. Comparison with literature NMR data is shown below for *epi*-ethisolide **144** (**Table 2.15**).[69] NMR data comparison of ethisolide **147**, avenaciolide **145**, *iso*-avenaciolide **148** and discosiolide **146** can be consulted in **Section 7**.

Table 2.15: NMR Data Comparison of *epi*-Ethisolide.[69]



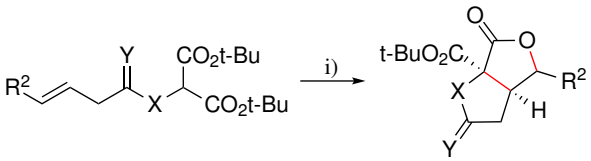
144

NMR data reported by Krohn *et al.* and recorded in $CDCl_3$ with a Bruker AM 400.[69]

Atom	^{1}H / ppm	^{1}H (Lit.) / ppm	Δ^1H / ppm	^{13}C/ ppm	^{13}C (Lit.) / ppm	Δ^{13}C / ppm
2	-	-	-	167.6 or 169.9	167.0 or 169.8	0.6 or 0.1
3	-	-	-	134.7	134.6	0.1
3′	5.88	5.90	-0.02	126.5	126.4	0.1
3″	6.47	6.48	-0.01	126.5	126.4	0.1
3a	3.58	3.59	-0.01	43.8	43.7	0.1
4	4.39	4.41	-0.02	86.4	86.3	0.1
4′	1.85	1.85	0.00	29.1	29.0	0.1
4″	1.87	1.85	0.02	29.1	29.0	0.1
5	1.08	1.09	-0.01	9.2	9.1	0.1
6	-	-	-	167.6 or 169.9	167.0 or 169.8	0.6 or 0.1
6a	5.06	5.05	0.01	74.4	74.3	0.1

2.3.6 Conclusions and Future Work

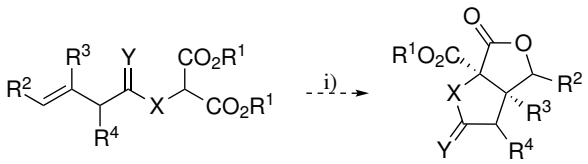
A new copper-free MAN-based methodology has been developed for the preferential formation of γ-lactones when R^2= H, Ph and alkyl groups (**Scheme 2.47**). The conditions were superior to the reported standard ones (MAN and $Cu(OTf)_2$) for substrates with R^2= alkyl groups, as the γ-lactones were isolated in the last case between 14 and 32% yield.



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq.), KI (0.5 eq.), MeCN (0.15 M), 80 °C; R^2= H, alkyl, Ph; X= CH_2, N, O; Y= H_2, O; 44-88% yield; 9 examples.

Scheme 2.47: Cu-Free MAN-Based Methodology for the Formation of γ-Lactones.

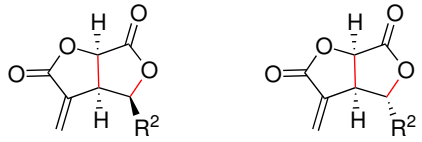
In order to evaluate and compare the efficiency of the copper-free MAN-based methodology with the standard method, a further expansion of the scope towards more hindered substrates in the all-carbon, oxygen and nitrogen series would be desirable (**Scheme 2.48**).



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq.), KI (0.5 eq.), MeCN (0.15 M), 80 °C; R^1= alkyl; R^2= H, alkyl, Ar; R^3= alkyl; R^4= alkyl, allyl, Bn, propargyl; X= O, N; Y= H_2, O.

Scheme 2.48: Methodology Expansion towards More Hindered Substrates.

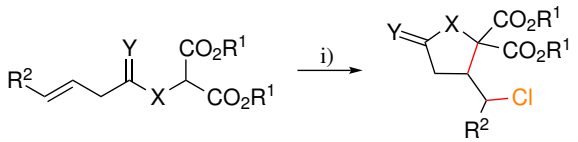
The copper-free MAN-based methodology allowed for the synthesis of the ethisolide family, composed of five natural products and one non-natural analogue in six and seven steps depending on the length of the alkyl chain R^2 (**Scheme 2.49**). Anticancer properties are currently being evaluated for the six molecules.



R^2= Et	**ethisolide**	***epi*-ethisolide**
R^2= C_8H_{17}	***iso*-avenaciolide**	**avenaciolide**
R^2= $C_{10}H_{21}$	***iso*-discosiolide**	**discosiolide**

Scheme 2.49: Ethisolide Family of Natural Products

In addition, during the course of our studies towards the synthesis of the natural products, the addition of LiCl in the MAN-based oxidative radical cyclisation emerged as a novel methodology for the creation of chloro mono-cyclic systems (**Scheme 2.50**). The methodology was applied to the oxygen and nitrogen series; however it did not appear suitable for the all-carbon substrates, as lactonisation appeared to be the fastest termination pathway in that case. The present results contrasted Vinogradov's and Snider's studies on the use of LiCl in MAN-based oxidative radical cyclisation, in which they reported that no participation of the alkene was ever observed when copper salts and LiCl were present in the reaction.[124,125]



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), LiCl (1.2 eq.), MeCN (0.15 M), 40 °C; R^2= H, Ph, alkyl, X= O, N; Y= H_2, O; 24-90% yield (8 examples).

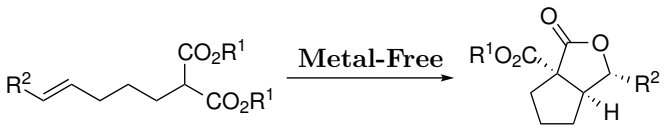
Scheme 2.50: LiCl as Additive in the MAN-based Oxidative Radical Cyclisation.

The resulting methodology is highly substrate-dependent and higher yields should be achievable with appropriate optimisation of the substrate structure. For example, the ester residues in the all-carbon systems could be modified to convert the lactonisation in a slower termination mode, thus allowing for the chloride transfer to occur preferentially for the formation of chloro cyclopentane derivatives. The formation of fluoro mono-cyclic systems was not successful; nevertheless, we believed that a more extensive study on the reaction conditions should be undertaken before discarding the possibility of formation of fluoro derivatives through a MAN-based oxidative radical cyclisation.

3

Metal-Free Oxidative Radical Cyclisation

The formation of bicyclic γ-lactones in high yields has been limited to malonate derivatives with R^2= H and Ph until the development of the Cu-free MAN / KI based methodology, which led to bicyclic γ-lactones with R^2= alkyl groups also in good yields (see **Section 2.3.4.6**). Nevertheless, the methodology still suffered from another limitation and this was that stoichiometric amounts of Mn(III) were needed to perform the oxidation. Although MAN remains a 'non-expensive' metal, a considerable amount of waste is produced during the transformation, which makes the reaction 'non-atom economical' and thus less suitable for large scale processes. Herein, this chapter will described our efforts towards converting the MAN-based oxidative radical cyclisation into a metal-free methodology. For simplification purposes, we began our study with all-carbon malonate systems (**Scheme 3.1**).



Scheme 3.1: Metal-Free Oxidative Radical Cyliclisation.

3.1 Electrochemical Methods

3.1.1 Brief Historical Introduction

Early Days. Pioneering electroorganic experiments were first made in 1834 by Faraday with the electrolysis of an acetate solution for the production of ethane to demonstrate the validity of the postulate that now bears his name *i.e.*, the Faraday's Law **3.1**.[138]

$$Q = nNF \tag{3.1}$$

where Q = charge consumed, n = moles of electrons involved per mole of compound being transformed, N = moles of the compound being transformed, F = Faraday's constant.

Kolbe was the first to develop the first synthetically useful electrolysis with the anodic oxidation of fatty acids salts to dimeric alkanes with loss of carbon dioxide (**3.2**), a reaction that was used on an industrial scale until the middle of the 1980's.

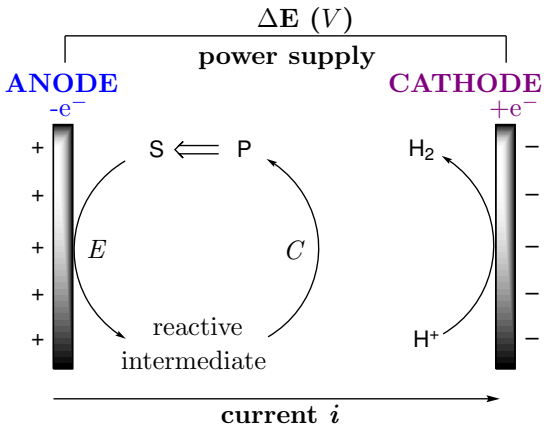
$$2RCOO^- \rightarrow R - R + 2CO_2 + 2e^+ \tag{3.2}$$

Numerous advantages have been associated with the use of electrochemistry in synthesis.[139] The selectivity of the reaction can be controlled with the adequate application of potential at the working electrode. Control of the reaction rate and the degree of transformation are possible by adjusting the current density and by managing the charge consumption of the electrolysis. The reaction conditions are typically mild in terms of temperature and pressure and electrons are inherently clean reactants, meaning that less waste is produced compared to conventional methods. All these advantages triggered a special interest in the methodology from both industrial and academic sides during the past 20^{th} century and numerous applications can be found in the literature.[140]

3.1.2 Basic Concepts

3.1.2.1 General Description

In an organic electrochemical reaction, electrons are removed from or added to the organic molecules for their activation at the surface of an electrode *via* a heterogeneous process. Removal of an electron occurs at the anode; while the addition of an electron takes place at the cathode. Oxidation will occur from the compound that oxidises most easily and the same applies for the reduction. The rate of electrons removed or added, *i.e.* the current intensity i, can be modified at will by using a direct current (DC) power supply that connects both electrodes through a wire as electronic conductor (**Scheme 3.2**).[139]



Current i (Amperes), Potential E (Volts); S = Substrate, P = Product, E = electron transfer, C = chemical process.

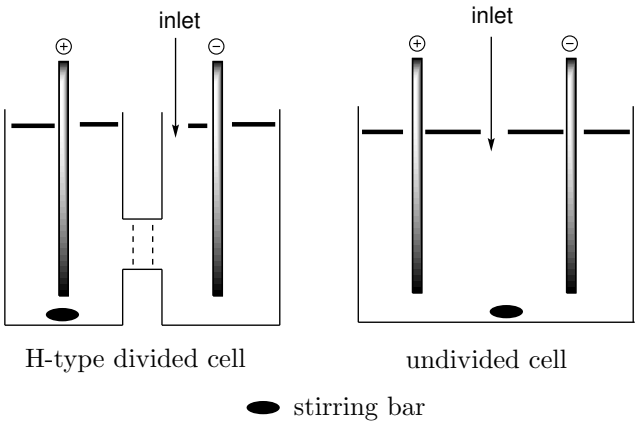
Scheme 3.2: Two Electrodes System for Constant Current Electrolysis.

Two basic events occur during an electrochemical reaction: a heterogeneous electron transfer (abbreviated as E) between the molecule and the surface of the electrode, that leads to the formation of reactive species (radical cations or radical anions), and a chemical process (C) that happens in the bulk of the solution or at the surface of the electrode (**Scheme 3.2**). The two processes can be repeated and / or combined during the reaction depending on the nature of the transformation. The solution in contact with the electrodes usually contains an electrolyte to increase the conductivity of the system. For this reason, electrolytic solvents must be polar enough to allow the electrolyte to fully dissociate in the medium and also must have low viscosity to facilitate the diffusion of the substrate between the bulk and the electrode surface.[139,141]

3.1.2.2 Parameters to Control

Organic electrosyntheses have a greater number of controllable parameters compared with ordinary organic syntheses. We have already mentioned the importance of the solvent and the presence of a supporting electrolyte; however, other parameters such as electrolytic cells (divided or undivided), electrolytic methods (constant current or constant potential) and type of electrodes must be considered when planning an electrolysis.

Cells. Divided cells (H-type cells) should be used whenever the product formed at one electrode can interfere with the other electrode. A separator (porous material such as a glass frit or ceramic) is present in such cells which allows ion exchange to maintain a high conductivity in the medium with a minimal exchange of solvent and neutral molecules. Nevertheless, for simplification purposes, undivided cells remain the most popular in electrosynthesis. In both cells, a gas inlet is generally present to allow the electrolysis to be run under O_2-free conditions. (**Scheme 3.3**).[141]



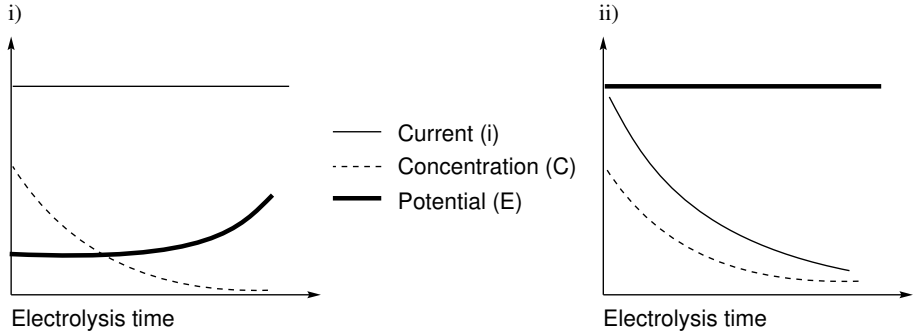
Scheme 3.3: Types of Electrolytic Cells.

Electrolytic Methods.

Constant Current Methods. Constant current methods (**Scheme 3.2**) are generally preferred over constant potential methods as their setup and the operation of the power supply are simpler. The current flowing between the anode and the cathode and the electrode active surface area are selected according to the concentration of the substrate. For the same current density, larger scale reactions require a larger electrode surface area. Since there is no control of the potential at the surface of the working electrode (anode if we are interested in the oxidation and cathode if reduction), selectivity can

be an issue if different functional groups of the molecule present similar oxidation potentials. After completion of the first oxidation, the potential at the working electrode will increase until meeting the potential of the following most easily oxidisable functional group (**Scheme 3.4**). Nevertheless, selectivity and degree of transformation can be improved with a careful control of the current density J and the amount of electricity passed, *i.e.*, the electrolysis reaction time.[141] For more elaborate explanations concerning the current density J and the electrolysis time, the reader is directed to **Section 6.5.1**.

Constant Potential Methods. If selectivity presents a serious issue in the transformation, constant potential electrolysis would be the method of choice. In order to control the potential at the working electrode, a reference electrode is needed, which allows the selection of the oxidation potential (if the anode is the working electrode) using a potentiostat. Reference electrodes suitable for organic solvents are not as common as for aqueous solutions; however, the Ag/Ag^+ electrode has found use in non-aqueous systems. Apart from the complexity and price of the setup, the method also suffers from conversion issues due to the decrease of current i over reaction time, a fact that makes the method unsuitable for large-scale reactions (**Scheme 3.4**). On the other hand, a preliminary analysis of the starting materials through cyclic voltammetry is possible with a potentiostat. This gives valuable information about the oxidation potential(s) of the different functional group(s) present in the molecule under the reaction conditions, which helps selecting the most suitable conditions for a succesful electrolysis.[141]



Conditions: i) Constant Current Mode, ii) Constant Potential Mode

Scheme 3.4: Electrolysis Profiles, adapted from Fuchigami's *et al.* book.[141]

Type of Electrodes. While a wide number of materials can be used as cathodes, the number of materials suitable for use as anodes are limited, since most metals are easily oxidised, with the exception of noble metals such as platinum and gold. Thus, carbon, graphite and metal oxides are generally used as anodes. Radicals are easily captured by carbon electrodes to be further oxidised to cationic intermediates.

The reason for such selectivity is due to the presence of traces of iron in the electrode surface which makes it paramagnetic. On the contrary, platinum anodes tend to generate radical intermediates, which make them more suitable for Kolbe-type electrolyses. In terms of cathodes, carbon and graphite electrodes can also be used; however platinum electrodes remain the most popular in aprotic organic solvents.[141]

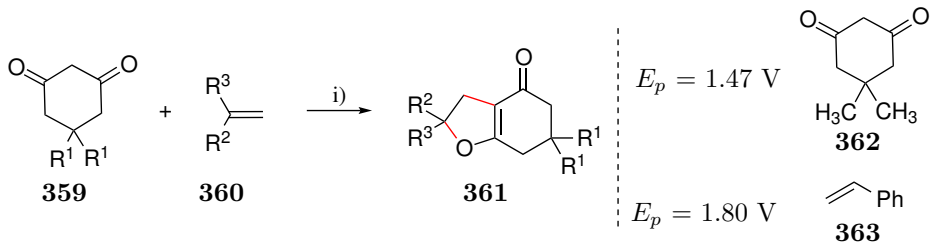
When water is present in the reaction system, oxygen and hydrogen gas can be generated competitively due to the discharge (anodic and cathodic interaction) of water during the electrolytic reaction. To avoid these reactions, cathode and anode materials with respectively high hydrogen and oxygen overpotential (potential difference between the standard potential and the potential at which the redox event is experimentally observed) should be selected. Nevertheless, when the reaction of interest is the anodic oxidation and the reaction at the counter electrode (cathode) is production of hydrogen, cathodes with low hydrogen overpotential such as platinum would be preferable. When using aprotic solutions, hydrogen and oxygen overpotentials are no longer an important criteria to have in mind to achieve the desired electrochemical reaction.[141]

Another aspect to take into consideration is the surface of such electrodes. Depending on the reaction scale and on the target reaction electrolysis time, electrochemical synthesis may require currents between 10 and 100 mA; hence, the use of a large electrode surface area is then recommended to complete the electrolysis. Both working and counter electrodes should have the same active surface area and are typically shaped as a plate, rod or mesh.

When running constant potential electrolysis in non-aqueous systems, the Ag/Ag^+ reference electrode is the most convenient as it can be placed near the working electrode surface without a salt bridge.

3.1.3 Precedents in Oxidative Radical Cyclisations

Pioneering work in the use of electrochemistry for oxidative radical cyclisation has been reported by Yoshida *et al.*[142] They were interested in the anodic oxidation of neutral 1,3-diketones **359** in the presence of an olefin **360** to form the formal [3+2] cycloadducts **361** (**Scheme 3.5**). A voltammetric study to examine the anodic behaviour of 1,3-diketones **359** revealed that dimedone **362** had an anodic peak at 1.47 V vs Ag/AgCl in MeCN; while styrene **363** showed its peak at 1.80 V under the same conditions. Such results suggested that neutral 1,3-diketones **359** could be oxidised at a reasonable potential without competing with the oxidation of the alkene **360** (**Scheme 3.5**).

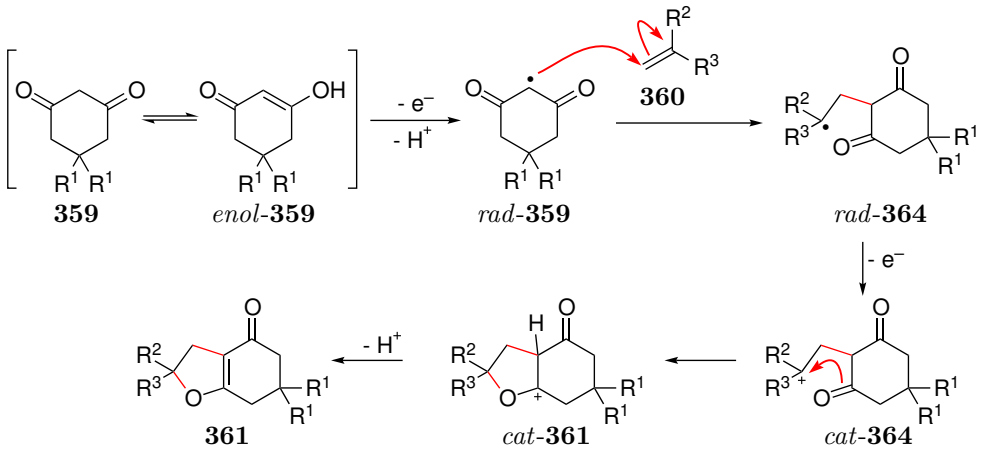


Reagents & Conditions: i) C rod (anode), Pt plate (cathode), 3 F/mol of electricity, i = 10 mA, Et_4NOTs, MeCN, r.t., undivided cell. $\mathbf{R^1}$ = $\mathbf{R^2}$ = H, Me; $\mathbf{R^3}$ = Ph, Oalkyl, OAc, vinyl, CH_2SiMe_3; 8 examples, 44-97% yield. E_p = potential (anodic) peak vs Ag/AgCl in MeCN.

Scheme 3.5: Anodic Oxidative [3+2] Cycloaddition of 1,3-Diketone and Olefin, Reported by Yoshida *et al.*[142]

Concerning the scope of the transformation, cyclic 1,3-diketones such as dimedone **362**, 1,3-cyclohexanedione and 1,3-cyclopentanedione reacted effectively with styrene derivatives, enol ethers and esters, allyltrimethylsilane, and 1,3-dienes, while the reactivity of alkyl-subtituted and electrodeficient olefins appeared to be lower (not shown). The addition took place with high regioselectivity, with the enol ether oxygen atom added exclusively onto the more substituted end of the terminal olefin. Acyclic 1,3-diketones were not tolerated under the oxidative conditions.

Mechanistically, the reaction was proposed to proceed first by the anodic oxidation of the 1,3-diketone **359** or its enol form *enol*-**359**, as deduced by the oxidation potentials measured *via* cyclic voltammetry. After a proton loss, the radical *rad*-**359** is formed and acts as a *C*-centered radical in the addition to the least substituted carbon of the olefin to produce the radical *rad*-**364**. A second one-electron oxidation follows at the anode to give the cation *cat*-**364**, which is then trapped by the carbonyl oxygen to form *cat*-**361**. A final proton loss leads to the desired final compound **361** (**Scheme 3.6**).



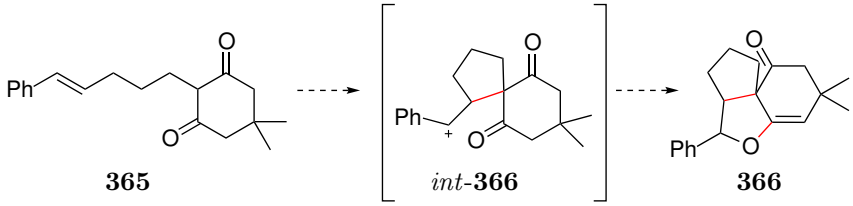
Scheme 3.6: Mechanism for the Anodic Oxidative [3+2] Cycloaddition of 1,3-Diketone and Olefin, Proposed by Yoshida *et al.*[142]

The higher reactivity of the electron-rich olefins compared to the electron-deficient ones can be understood by analysing the nature of the *C*-centered radical in *rad*-**359**. The radical is flanked by two carbonyl groups, thus making the radical highly electron-deficient. Therefore the addition of the radical to an electron-rich olefin will be more favourable than the addition to an electron-deficient olefin. In addition, the oxidation of *rad*-**364** will also be more favourable with electron-rich olefins.

3.1.4 Results and Discussion: Electrochemically-Driven Oxidative Radical Cyclisations

3.1.4.1 Intramolecular Version of Yoshida's Electrolysis

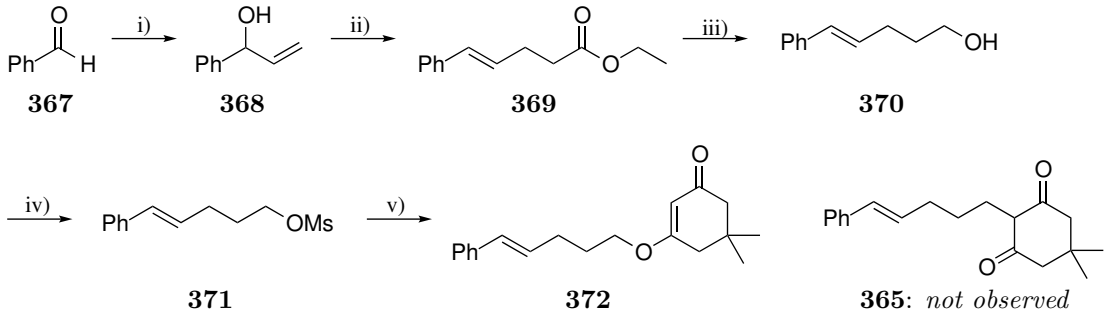
In view of Yoshida's results,[142] our first contact with electrochemistry consisted in attempting the intramolecular version of Yoshida's electrolysis with the substrate **365** (**Scheme 3.7**). Due to the similarities in structure between **365** and the all-carbon alkyl malonate systems studied for the MAN-based oxidative radical cyclisation, we considered the system **365** was a logical starting point for our study.



Scheme 3.7: Plan for the Intramolecular Version of Yoshida's Electrolysis.

The synthesis of the substrate began with the addition of vinylmagnesium bromide to benzaldehyde **367** to give the allylic alcohol **368** in 98% yield (**Scheme 3.8**). Further treatment with triethyl orthoacetate under acidic conditions led to the ester **369** in 66% yield after a Johnson-Claisen rearrangement under thermal conditions. The ester was reduced and the obtained alcohol **370** was converted into the mesylate **371** in 98% yield. Unfortunately, attempts to form the desired substrate **365** failed in the presence of *t*-BuOK in *t*-BuOH under the conditions reported by Groutas *et al.*,[143] giving the compound **372** instead (**Scheme 3.8**).

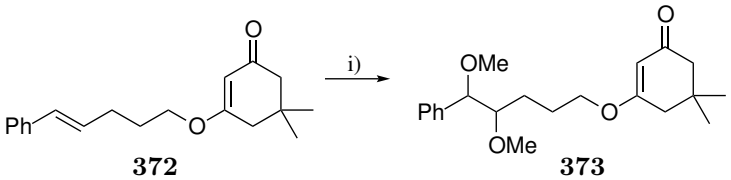
Despite not having formed the desired substrate **365**, compound **372** was submitted under Yoshida's experimental conditions, with a carbon graphite rod as cathode instead of a platinum plate. A complicated mixture of starting material and unidentified compounds was obtained under such conditions (not shown). The polarity and thus conductivity of the system was increased with the use of MeOH as solvent and the participation of the alkene was observed in the electrolysis of **372** with the formation of



Reagents & Conditions: i) vinylmagnesium bromide, THF, 0 °C, 3h, 98%; ii) triethyl orthoacetate, propionic acid (cat.), 145 °C, 7 h, 66%; iii) $LiAlH_4$, Et_2O, 0 °C to r.t., 4.5 h, 48%; iv) MsCl, Et_3N, DCM, 0 °C to r.t., 1.5 h, 98%; v) dimedone **362**, *t*-BuOK, *t*-BuOH, 50 °C, 9h, 72%.

Scheme 3.8: Substrate Synthesis.

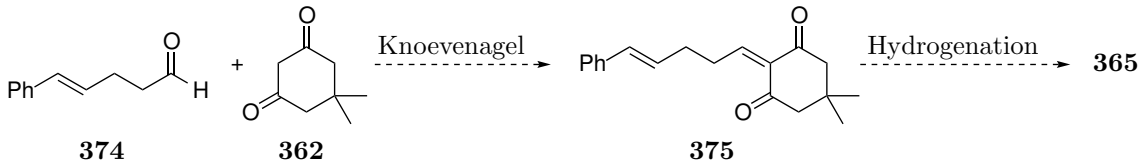
373 in 13% yield (**Scheme 3.9**).



Reagents & Conditions: i) C graphite rod (anode), C graphite rod (cathode), 3.0 F/mol, i = 10 mA, 0.2 M Et_4NOTs in MeOH, 2 h 50 min, r.t., 13% yield.

Scheme 3.9: Electrolysis of Compound **372**.

An alternative synthetic strategy for the formation of **365** would have been a Knoevenagel condensation between the aldehyde **374** and dimedone **362**, followed by hydrogenation to give **365** (**Scheme 3.10**). Nevertheless, such synthesis has not been attempted in the laboratory. Instead, we decided to focus on the application of Yoshida's experimental conditions to the all-carbon alkyl malonate substrates.

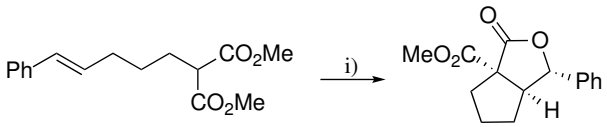


Scheme 3.10: Alternative Synthetic Sequence for Compound **365**.

3.1.4.2 All-Carbon Systems: Electrolyses

Application of Yoshida's Conditions. It is known that malonate **85** oxidatively cyclises under MAN-based conditions to form the fused bicyclic γ-lactone **86** in 84% yield (see **Section 1.2.5.2**) (**Scheme 3.11**).[52] Considering the similarities between the mechanism proposed for Yoshida's oxidative

cycloaddition (see **Scheme 3.6**) and the proposed mechanism for the MAN-based oxidative radical cyclisation (see **Section 1.2.2**), we considered Yoshida's electrolysis conditions as a sensible starting point for our investigations towards the metal-free conditions.

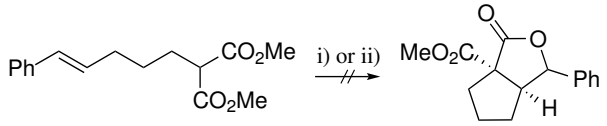


85 **86**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), MeCN, 80 °C, 84% yield (4.1:1 *dr*).

Scheme 3.11: MAN-based Oxidative Radical Cyclisation for the Synthesis of Fused Bicyclic γ-Lactones.[52]

Unfortunately, the application of Yoshida's electrolysis conditions to the malonate **85** did not convert the starting material **85** into the desired product **86** (**Scheme 3.12**, **conditions *i***). The crude was mainly composed of starting material **85** with traces of decomposition. At this point, it was not clear which factor was preventing the starting material **85** from undergoing oxidative cyclisation. Under MAN-based conditions, Mn(III) coordinates to the malonate carbonyls, thus decreasing the pKa of the malonyl proton before the formation of the enolate prior to the one-electron oxidation. In this case, such coordination could not happen, meaning that the pKa of the malonyl proton might not be sufficiently low to undergo enolate formation under the electrolysis conditions. Consequently, K_2CO_3 was added as a base to the reaction mixture; nevertheless, the same negative results were still observed under such experimental conditions (**Scheme 3.12**, **conditions *ii***). Solubility issues of ionic bases were thought to be the reason for such unsuccessful result. On the other hand, the use of organic amine bases was thought not to be ideal as they could interfere in the anodic oxidation.[144]



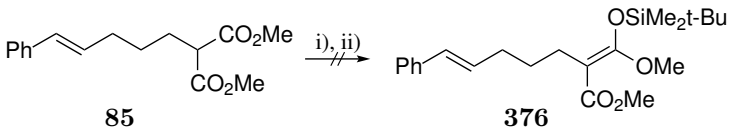
85 **86**

Reagents & Conditions: i) graphite rod (anode), graphite rod (cathode), 2.5 F/mol of electricity (2 h 20 min electrolysis time), i= 10 mA, 0.2 M Et_4NOTs in MeCN, r.t., *No conversion*; ii) Same as i) in the presence of K_2CO_3 as base (2.0 eq.), *No conversion.*

Scheme 3.12: Yoshida's Electrolysis Conditions for Oxidative Radical Cyclisation of **85**.

In order to favour the one-electron anodic oxidation at the malonyl position, the formation of silyl ketene acetals **376** was considered (**Scheme 3.13**). Unsuccessful results were obtained under the conditions reported by Denmark *et al.*,[145] consisting on the treatment of the malonate **85** with LDA formed *in*

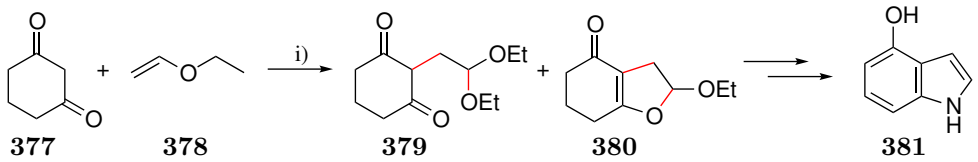
situ at -78 °C and with *t*-BuMe$_2$SiCl (**Scheme 3.13**). The high reactivity of the silylketeneacetal **376** suggests that protonation might have occurred during the work-up. The handling difficulty associated with product **376** made us abandon the idea of forming this type of compound before the electrolysis.



Reagents & Conditions: i) (*i*-Pr)$_2$NH, *n*-BuLi, THF, 0 °C, 30 min; then added **85** at -78 °C, ii) *t*-BuMe$_2$SiCl, THF, HMPA, -78 °C to r.t., 17 h; *no conversion*.

Scheme 3.13: Attempts on the Synthesis of Silyl Ketene Acetal Derived from **85**.[145]

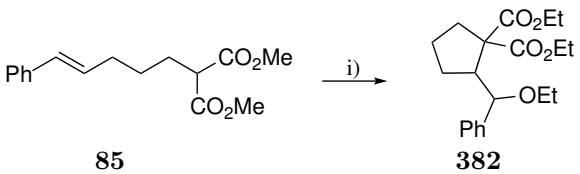
Torii's Conditions The need for a base under the electrolysis conditions made us consider more polar reaction conditions. In their work towards the formation of 4-hydroxyindol **381**, Torii *et al.* developed an electrochemical methodology to synthesise its precursors **379** and **380** in 65% yield (**Scheme 3.14**). Platinum foils were used as both anode and cathode and the oxidation took place by passing 2.0 F/mol of electricity through the system in the presence of EtONa as basic electrolyte in EtOH.[146]



Reagents & Conditions: i) Pt foil (anode), Pt foil (cathode), 2.0 F/mol of electricity, EtONa, EtOH anhydrous, undivided cell, 65% yield (**379** / **380** = 49:51).

Scheme 3.14: Electrochemical Oxidative C-C Coupling, Reported by Torii *et al.*[146]

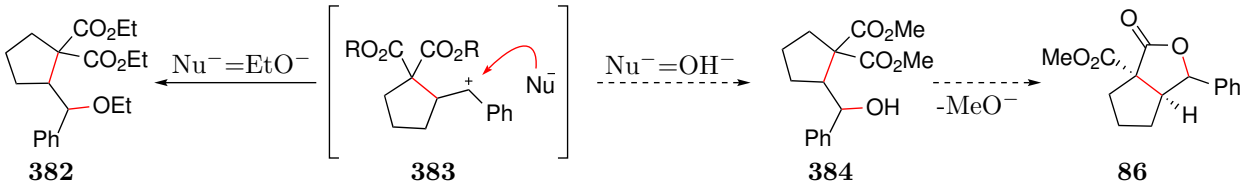
Gratifyingly, the use of EtOH as electrolytic solvent and NaOEt as base and electrolyte in our system delivered the cyclised compound **382** in 16% yield from the malonate derivative **85**. Despite the low yield obtained, this was the first time an intramolecular oxidative cyclisation of malonate derivatives was observed under electrochemical conditions (**Scheme 3.15**).



Reagents & Conditions: i) C graphite rod (anode), C graphite rod (cathode), NaOEt, EtOH, 2.0 F/mol of electricity (3 h electrolysis time), i = 10 mA, 16% yield (3.5:1 *dr*)

Scheme 3.15: Application of Torii's Conditions on the Malonate **85**.

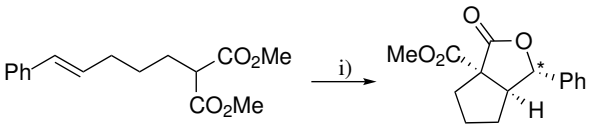
New Developed Conditions. Taking into account the mechanism proposed by Yoshida *et al.* for their oxidative addition (see **Scheme 3.6**), we assumed that the formation of compound **382** would have arisen from the nucleophilic attack of an ethoxide anion onto the carbocation **383**, previously formed under anodic conditions. By the same logic, replacement of ethoxide by hydroxide anions would lead to the alcohol **384**, which in turn would add to the ester forming the desired fused bicyclic γ-lactone **86** (**Scheme 3.16**).



Scheme 3.16: Proposed Formation of **382** and **86**.

Pleasingly, the malonate **85** cyclised to the desired fused bicyclic γ-lactone **86** in 25% yield after passing 2.0 F/mol of electricty through a solution of **85** in MeOH containing NaOH (**Table 3.1**, **Entry 1**).

Table 3.1: Electrolysis for the Formation of Fused Bicyclic γ-Lactone **86**.



Reagents & Conditions: C graphite rod (anode), C graphite rod (cathode), NaOH (1.4-1.6 eq.), MeOH (0.07 M), i= 10 mA, electricity (F/mol), r.t.

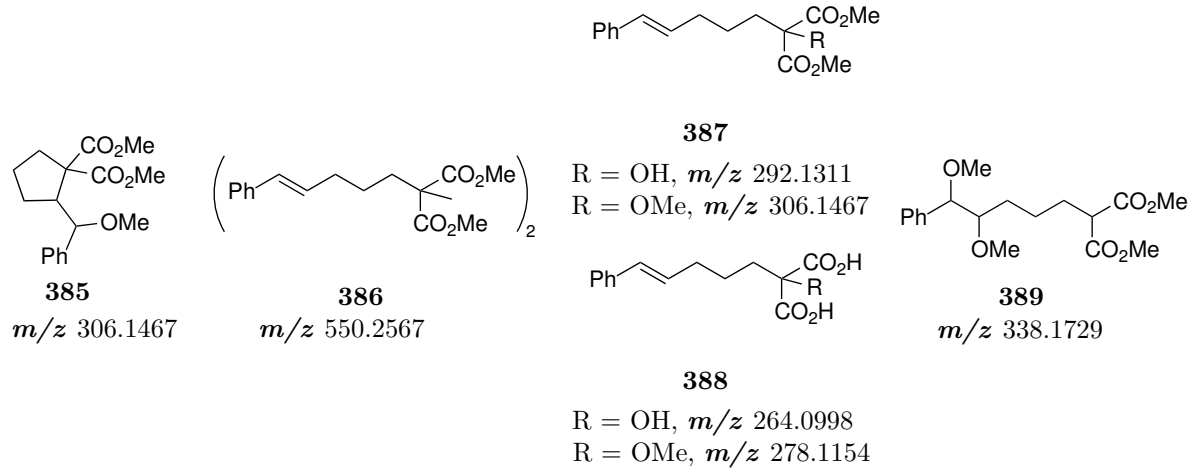
Entry	Electricity / F/mol	*dr**	Yield / %
1	2.0	3.3:1	25
2[a]	2.0	8.1:1	23
3	3.0	4.6:1	35
4	5.0	8.1:1	38
5	8.0	7.3:1	29
6[b]	5.0	4.2:1	29
7[c]	2.0	-	-
8[d]	2.0	4.3:1	42

[a] Pt plate as cathode; [b] NaOH (5.0 eq.); [c] NaOMe (3.0 eq.) as base; [d] T = 40 °C in a more concentrated system (0.1 M in MeOH). Standard conditions led to 84% yield (4.1:1 *dr*).

Replacement of the carbon graphite rod by a platinum plate as cathode did not improved the electrolysis (**Entry 2**). Increase of the electricity, *i.e.* equivalents of electrons, led to higher yields, up to 38% yield when 5.0 F/mol of electricity were passed (**Entry 4**); while 8.0 F/mol did not make any improvement (**Entry 5**). Increment of the number of equivalents of base under 5.0 F/mol of electricity

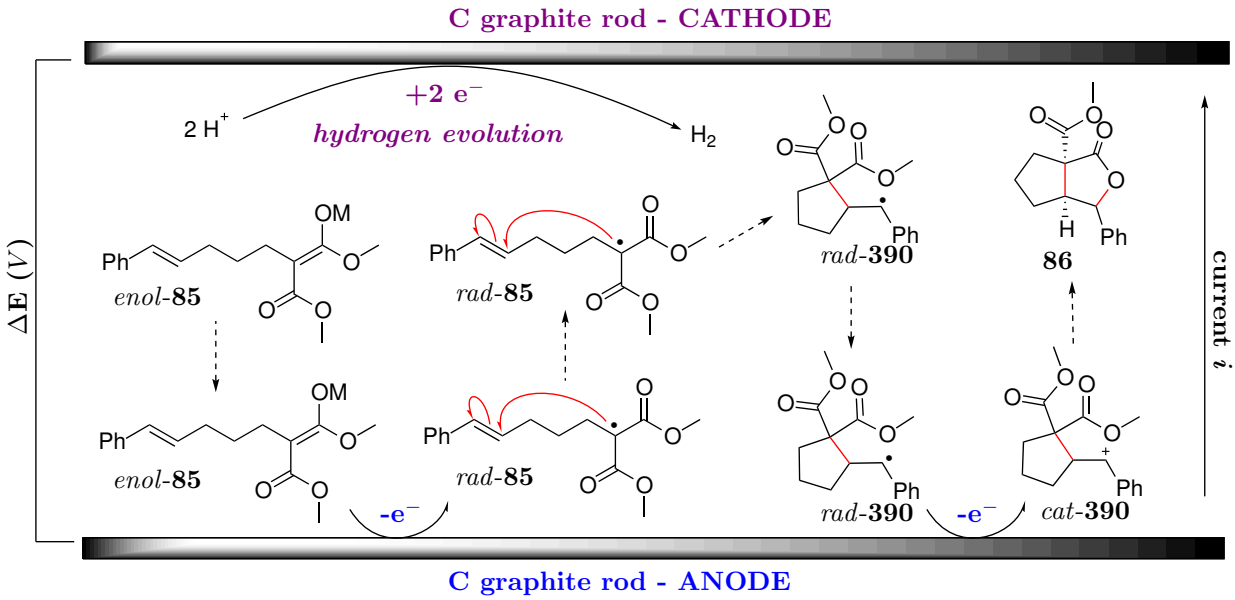
was not beneficial for the transformation (**Entry 6**). The use of NaOMe consumed the product but led to unidentified mixture of compounds (**Entry 7**). Finally, increase of the temperature to 40 °C in order to favour the cyclisation gave the desired product in 42% yield with 2.0 F/mol of electricity (**Entry 8**).

In all cases, the starting material **85** was fully consumed as indicated by the absence of the triplet signal at 3.39 ppm for the malonyl proton in the ^{1}H-NMR spectrum. A complicated mixture of inseparable side-products were generated during the electrolysis, which on the basis of m/z analysis and mechanistic hypotheses probably contained the cyclised compound **385** (found 329.1 $[M+Na]^+$ and 635.3 $[2M+Na]^+$), the dimer **386** (***m/z*** not found), the uncyclised ester malonate **387** (R = OMe, found 329.1 $[M+Na]^+$ and 635.3 $[2M+Na]^+$; R = OH, ***m/z*** 315.1 $[M+Na]^+$ found), the malonic acid derivative **388** (R = OH, ***m/z*** 265.1 $[M+H]^+$ found; R = OMe, ***m/z*** not found) and **389** (361.1 $[M+Na]^+$ found) (**Scheme 3.17**). We assumed that dimerisation and overoxidation at the anode are particularly favoured when a high concentration of radicals surrounds the surface of the anode.



Scheme 3.17: Possible Side-Products in the Electrolysis of **85**.

Proposed Mechanism. On the basis of Yoshida's proposed mechanism (see **Scheme 3.6**), we proposed that the electrolysis begins with the formation of the enolate *enol*-**85** in the bulk of the solution (**Scheme 3.18**). Diffusion of *enol*-**85** towards the anode surface follows for the first one-electron oxidation to give *rad*-**85**. Cyclisation could take place either at the surface of the electrode or after the diffusion of the radical into the bulk of the solution. Once *rad*-**390** is formed, the molecule has to diffuse towards the anode surface for the second one-electron oxidation to form the cation *cat*-**390**. The lactone **86** could be formed *via* several pathways, including the attack of the ester onto the anodically generated cation or participation of the hydroxide anion as depicted in **Scheme 3.16**.



Scheme 3.18: Proposed Mechanism for the Anodic Radical Cyclisation.

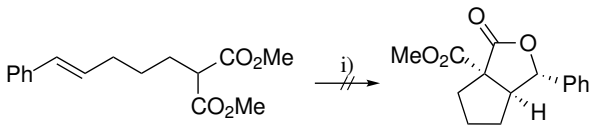
Optimisation of Conditions. As observed in **Table 3.1**, the current efficiency was poor as indicated by the amount of electricity used and the yield of the product, and it can also be understood by considering the number of side-products generated (**Scheme 3.17**). In any case, the current efficiency of any electrolysis is usually below 100%, since the solvent and/or the electrolyte are discharged simultaneously during the electrolytic reaction.[141]

Solvent Screen. Since we suspected that the solvent was also participating in the transformation, a solvent screen was first performed with the aim of finding a more inert and good conductor solvent for the electrolysis. A first attempt was made with DMSO (**Table 3.2**, **Entry 1**), as the solvent is polar enough to dissolve the base and ensure good conductivity. Water was added to the system in order to favour the reduction process, *i.e.* the reduction of protons to hydrogen. Unfortunately, the electrolysis did not proceed. A reason might be the high viscosity of the system that does not favour the migration of the substrate towards the anode surface despite the constant stirring during the electrolysis.

MeOH was then replaced by *t*-BuOH as the steric bulk of the *tert*-butyl group might prevent the attack of the *tert*-butoxide to the formed carbocation. Electrolyte salts were needed under such conditions as the system was showing a high resistance otherwise. The base did not dissolve in such solvent system and 96% of starting material **85** was recovered (**Entry 2**).

Finally, considering that the electrolyte could also act as a phase-transfer reagent, we performed the

Table 3.2: Electolytic Solvent Screening



85 **86**

Reagents & Conditions: C graphite rod (anode), C graphite rod (cathode), NaOH (1.4-1.6 eq.), electrolyte, solvent (0.07 M), i = 10 mA, 2.0 F/mol of electricity, r.t.

Entry	Solvent (Concentration / M)	Electrolyte (Concentration / M)	**85**:**86** ratio	Yield / %
1	DMSO / H_2O (9:1, 0.06)	-	1:0	-
2	*t*-BuOH (0.07)	Et_4NOTs (0.7)	1:0	-
3[a]	H_2O (0.07)	Et_4NOTs (0.14)	1:0	-

[a] NaOH not added.

reaction in water in the absence of NaOH as base. The proposal was that the hydroxide anions could be generated *in situ* after the cathodic reduction of the protons. The concentration of electrolyte in the medium was twice the concentration of the substrate to aid the interaction between the solvent and the substrate; however, the system was observed as an emulsion and no conversion was obtained (**Entry 3**).

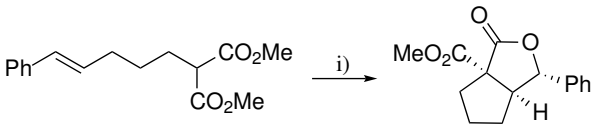
The selection of the solvent for the electrolysis remains a challenge since it must be sufficiently conducting and of low viscosity to favour the migration of the substrate to the surface of the electrode. In addition, it has to dissolve the starting material and any additives needed and ideally it should not participate in the chemical reaction happening in the bulk of the system or react under the potential window of the electrolysis. Protic solvents normally meet all these advantages, however the alkoxide anions generated in the medium are prone to give side reactions.

Effect of the Electrolyte. Electrolytes (R_4NOTs, R_4NBF_4, R_4NOH, $LiClO_4$, etc.) are generally present in any electrolysis as they decrease the electrical resistance of the system, and they also offer stabilisation to the ionic species involved in the transformation. Nevertheless, the chosen electrolyte should be stable under the potential window of the electrochemical reaction. In our initial system, the added NaOH was acting as both electrolyte and base; nevertheless, the presence of additional tetraalkylammonium salts, as well as the dilution of the system were subjected for further study.

Diluted systems are generally preferred in electrochemical reaction since they offer a higher difference in concentration between the electrode surface and the bulk of the solution, thus promoting a higher diffusion rate between these two. In our case, more diluted systems did not appear to have a strong effect on the outcome of the reaction (**Table 3.3**, **Entries 1** and **2**). On the other hand, since we are under constant stirring during the electrolysis, the dilution parameter might become less important.

The presence of electrolyte did not favour the electrolysis of the malonate **85**, as observed with the yield decrease when Et_4NOTs was present at the same concentration as the substrate (**Entry 3**). The electrolyte concentration is commonly fixed to ten times the concentration of the starting material; nevertheless, these experimental conditions were detrimental for the electrolysis (**Entry 4**). The use of Et_4NBF_4 instead of Et_4NOTs did not lead to any improvement (**Entry 5**). We suspect the electrolyte was interfering in the migration of the substrate to the surface of the anode.

Table 3.3: Study of the Presence of Electrolyte.



85 **86**

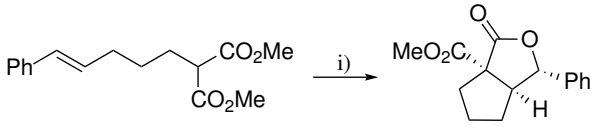
Reagents & Conditions: C graphite rod (anode), C graphite rod (cathode), NaOH (1.4-1.6 eq.), electrolyte, MeOH, i = 10 mA, 2.0 F/mol of electricity, r.t.

Entry	Et_4NOTs Concentration / M	**85** Concentration / M	*dr*	Yield / %
1	-	0.07	3.3:1	25
2[a]	-	0.02	4.6:1	29
3	0.07	0.07	8.1:1	20
4	0.2	0.02	n.a.	n.a.
5[b]	0.07	0.07	4.3:1	<15

[a] 15% of starting material **85** was recovered; [b] Et_4BF_4 was used as electrolyte.

Electrolytes are not supposed to interfere in the chemical transformation; however, we selected Et_4NOH as salt to do exactly the opposite. We envisaged that the hydroxide anion would act as a base and nucleophile to form the lactone according to **Scheme 3.16**. A complicated mixture of side-products were obtained when 2.0 F/mol of electricity was passed through the system (**Table 3.4**, **Entries 1** and **2**). Increase of the electricity to 5.0 F/mol led to less than 25% yield for the lactone **86**, being the formation of side-products still the dominant issue of the transformation (**Entry 3**).

Table 3.4: Et_4NOH as Electrolyte.



85 **86**

Reagents & Conditions: C graphite rod (anode), C graphite rod (cathode), Et_4NOH (eq.), MeOH (0.07 M), i = 10 mA, electricity (F/mol), r.t.

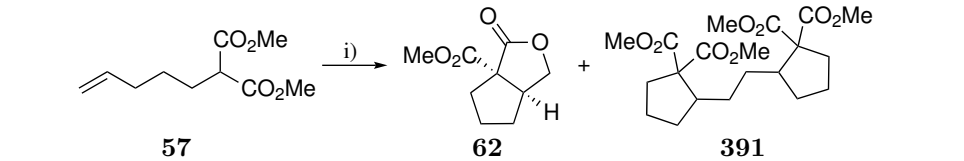
Entry	Et_4NOH (eq.)	Electricity / F/mol	*dr*	Yield / %
1	1.5	2.0	n.a.	n.a.
2	5.0	2.0	n.a.	n.a.
3	1.5	5.0	3.3:1	<25

Methodology Extension

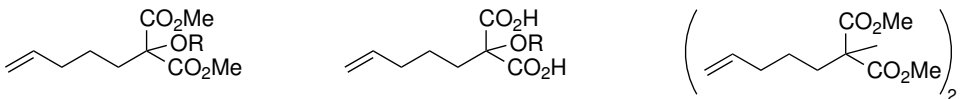
Presence of the Phenyl Group. The styrene-derived compound **85** had been initially selected for the study as we assumed that stabilisation of the carbocation by the phenyl group would favour and convert the cyclisation to an irreversible step. In order to verify this assumption, the terminal alkene malonate derivative **57** has also been under study (**Table 3.5**).

The presence of a stabilising group was shown to be essential for the cyclisation (**Table 3.5**, **Entry 1**). The starting material reacted under the electrolysis conditions, but the alkene did not participate in the transformation. The identity of the product(s) remains unclear; however, on the basis of mass analysis and mechanistic hypotheses, we proposed a mixture of dimer **394** (***m/z*** 421.1 $[M+Na]^+$ found) and the uncyclised compound **392** (R = Me, ***m/z*** 253.1 $[M+Na]^+$ found; R = H, ***m/z*** 239.1 $[M+Na]^+$ found) and **393** (R = Me, ***m/z*** not found; R = H, ***m/z*** 399.2 $[2M+Na]^+$ found) were present in the mixture (**Table 3.5**). Since stabilisation of the carbocation was essential for the cyclisation to proceed, electrolyte was added to the system as we have seen that its role could also be ionic stabilisation. The lactone **62** was formed in 2% yield when passing 2.0 F/mol of electricity, with 23% of the cyclised dimer **391** (**Entry 2**). The absence of the phenyl group clearly open the competition between the lactonisation and the dimerisation after the cyclisation step. Increase of the electricity to 5.0 F/mol led to a 21% yield for the desired lactone **62** with 25% for the dimer **391** (**Entry 3**).

Table 3.5: Electrolysis of Terminal Alkene Alkyl Malonate Derivative **57**



57 **62** **391**



392 **393** **394**

R = Me, ***m/z*** 230.1154 R = Me, ***m/z*** 202.0841 ***m/z*** 398.1941

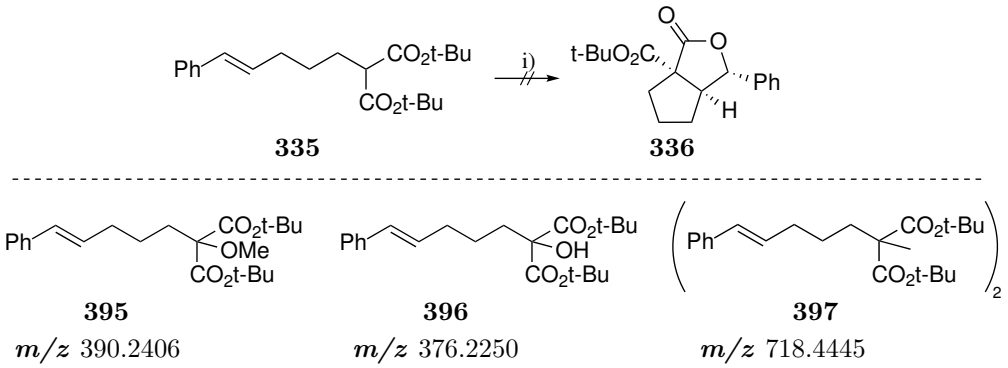
R = H, ***m/z*** 216.0998 R = H, ***m/z*** 188.0685

Reagents & Conditions: i) C graphite rod (anode), C graphite rod (cathode), NaOH (1.2 eq.), electrolyte, MeOH (0.07 M), i = 10 mA, electricity (F/mol), r.t.

Entry	Electrolyte (concentration / M)	Electricity / F/mol	**391** Yield / %	**62** Yield / %
1	-	2.0	-	-
2	Et_4BF_4 (0.09)	2.0	23	2
3	Et_4BF_4 (0.09)	5.0	25	21

Aside from the nature of the solvent which did not prove to be ideal for the electrolysis, the methodology was shown to be highly substrate-dependant. In the case of not having a phenyl group for stabilisation, the intermediate was exposed to additional competitive pathways that led to complicated mixture of side-products, thus reducing the yield for the desired lactone **62**.

Effect of the Ester Residues. Previous experience had shown that *tert*-butyl esters lactonise better than methyl esters (see **Section 2.3.4.3**), thus an attempt on the electrolysis of compound **335** was made (**Scheme 3.19**). The cyclisation did not happen as ^{1}H-NMR analysis confirmed the presence of the olefinic signals. On the other hand, the triplet associated to the malonic proton was missing, suggesting that substitution at this position occurred during the electrochemical reaction. It is not clear whether dimerisation to give **397** (***m/z*** not found) or / and substitution to give **395** (***m/z*** 413.2 $[M+Na]^+$ found) and **396** (***m/z*** 399.1 $[M+Na]^+$ found) took place during the transformation. Increase of the temperature to 40 °C did not trigger the cyclisation and led to the same mixture of compounds.

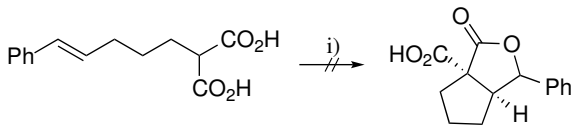


Reagents & Conditions: i) C graphite rod (anode), C graphite rod (cathode), NaOH (1.2 eq.), MeOH (0.07 M), i = 10 mA, 2.0 F/mol of electricity (2 h 15 min electrolysis time), T = r.t., 40 °C.

Scheme 3.19: Electrolysis of the *tert*-Butyl Ester Malonate Derivative **335**

Unfortunately, use of the acids **398** did not lead to cyclisation and lactonisation to form **399** (**Scheme 3.20**). Instead a complicated mixture was again found after the electrolysis. Carboxylic acids are also known to undergo Kolbe electrolysis for the formation of dimers, a fact that makes the oxidative cyclisation of malonic acid derivatives even more challenging.

A More Acidic Substrate. The need for an ionic base in the previous electrolyses necessitated the use of highly polar solvents such as alcohols. As a result, a more acidic substrate was thought to be more suitable for the anodic oxidation, as an external base may not be required. As the β-ketoester **400** has been reported to undergo MAN-based oxidative radical cyclisation, its electrolysis was considered.[147]



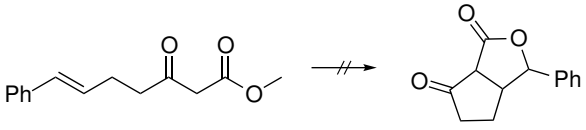
398 **399**

Reagents & Conditions: i) C graphite rod (anode), C graphite rod (cathode), NaOH (1.2 eq.), MeOH (0.07 M), i = 10 mA, 2.0 F/mol of electricity (2 h 10 min electrolysis time), r.t.

Scheme 3.20: Electrolysis of the Malonic Acid Derivative **398**.

The electrolysis of the β-ketoester **400** in a solution of electrolyte Et_4NOTs in MeCN in both the absence and presence of base led to the recovery of the starting material and decomposition (**Table 3.6**, **Entry 1** and **2**). Unfortunately, the same result was observed when running the reaction in MeOH with NaOMe as base with no electrolyte (**Table 3.6**, **Entry 3**).

Table 3.6: Electrolysis of the β-Keto Ester **400**



400 **401**

Reagents & Conditions: i) C graphite rod (anode), C graphite rod (cathode), Base (1.2 eq.), electrolyte, Solvent (0.07 M), i = 10 mA, 2.0 F/mol, r.t.

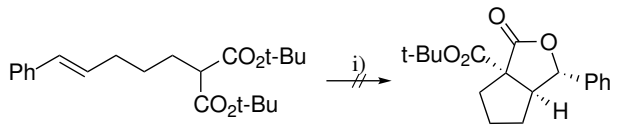
Entry	Electrolyte (concentration / M)	Solvent	Base	**401** Yield / %
1	Et_4NOTs (0.2)	MeCN	-	-
2	Et_4NOTs (0.2)	MeCN	Et_3N	-
3	-	MeOH	NaOMe	-

3.2 Results and Discussion: Ionic Methods

3.2.1 A Serendipitous Discovery

While conducting control experiments on the MAN/KI methodology for the preferential formation of fused γ-lactones (see **Section 2.3.4.6**), compound **335** was treated with MAN and NIS in MeCN at 80 °C. The purpose of this reaction was to confirm that iodine radicals were involved in the transformation as NIS is considered a radical source of iodine; nevertheless, the reaction failed and decomposition was observed (**Scheme 3.21**). We attributed this failure to the electrophilic nature of both malonyl and iodine radicals, which make them electronically not compatible for the interaction.

Since NIS is also an electrophilic source of iodine, a second control experiment was run, this time in the presence of NaOAc as base for enolate formation in the malonate derivative **335**. Surprisingly, the



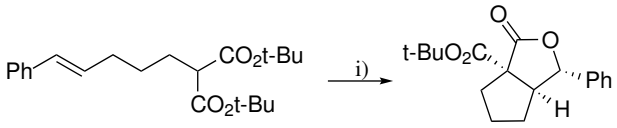
335 **336**

Reagents & Conditions: $Mn(OAc)_3 \cdot 2H_2O$ (1.2 eq.), NIS (1.2 eq.), MeCN, 80 °C.

Scheme 3.21: Control Experiment Using NIS as a Radical Source of Iodine.

reaction proceed with success giving the lactone **336** in 90% NMR yield in MeCN (**Table 3.7**, **Entry 1**). Full conversion was not achieved, which was attributed to the poor solubility of NaOAc in MeCN. A much better conversion was found when running the reaction in DMSO, which led to the lactone **336** in 79% isolated yield (**Entry 2**). Lastly, the reaction in EtOH also led to the desired product **336** with a lower conversion and yield (**Entry 3**). Replacement of NIS by iodine did not improve the conversion, giving a 67% NMR yield for the lactone **336** (**Entry 4**).

Table 3.7: NIS and Base for the Formation of Fused Bicyclic γ-Lactones.



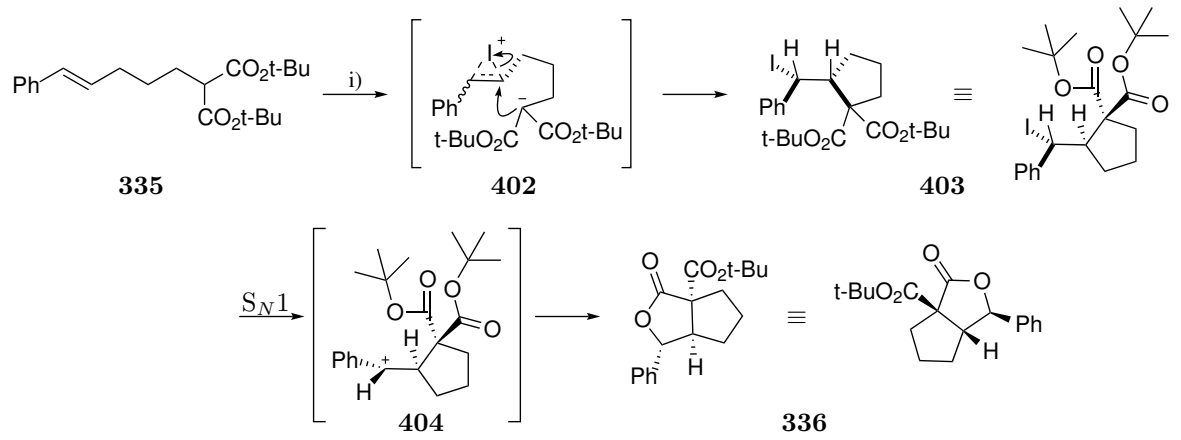
335 **336**

Reagents & Conditions: i) NaOAc (1.2 eq.), NIS (1.2 eq.), Solvent (0.15 M), 80 °C, 21 h.

Entry	Solvent	**335**:**336** ratio	*dr*	**336** Yield / %
1	MeCN	22:78	12:1	90[a]
2	DMSO	10:90	32:1	79
3	EtOH	32:68	10:1	66[a]
4[b]	DMSO	20:80	24:1	67[a]

[a] NMR yield, [b] NIS was replaced by I_2.

Standard conditions with MAN and $Cu(OTf)_2$ in MeCN gave comparable yields (84% and 4.1:1 *dr*); however, the diastereomeric ratio was much higher in the case of using NaOAc and NIS with a 32:1 *dr* in DMSO . This difference in value showed that an ionic pathway was likely to occur when forming the lactone. As in the work of Taguchi in ionic carbocyclisation (see **Section 2.3.4.1**),[119] the alkene would be activated by NIS forming an iodonium ion **402**, which would then be attacked by the enolate formed by the action of NaOAc. Further displacement of the secondary iodide **403** by the *tert*-butyl esters is proposed to take place *via* an S_N1 pathway through formation of the carbocation **404** (**Scheme 3.22**).

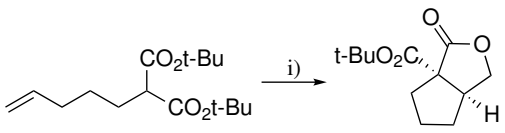


Reagents & Conditions: NaOAc (1.2 eq.), NIS (1.2 eq.), DMSO, 80 °C, 21 h.

Scheme 3.22: Proposed Mechanism for NIS-Driven Formation of γ-Lactones.

3.2.1.1 Towards the Methodology Extension

All-Carbon Series. The terminal alkene malonate **349** was also treated under the NIS/NaOAc conditions in DMSO (**Scheme 3.23**); however the yield for lactone **350** was substantially lower than in the case of using the standard MAN-based conditions (92% yield).[49] The reason behind such low yield was the poor conversion with the recovery of starting material **349** in 38% yield.



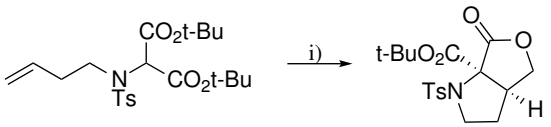
Reagents & Conditions: NaOAc (1.2 eq.), NIS (1.2 eq.), DMSO, 80 °C, 21 h, 43% yield .

Scheme 3.23: Terminal Alkene Malonates under NaOAc/NIS Conditions.

Nitrogen Series. The amino malonate **331** was tested under the metal-free conditions; however, the substrate gave the bicyclic pyrrolidine **334** in low yields at temperatures between 40 and 100 °C (**Table 3.8**, **Entries 1-3**). Unidentified side-products have been isolated at all tested temperatures, which would explain the low yields obtained for the desired compound **334**.

Unfortunately, attempts to form the γ-lactam γ-lactone **329** from amidomalonate **327** failed under the metal-free conditions (**Scheme 3.24**). Full conversion was achieved; however, the reaction led to a a mixture of unidentified compounds.

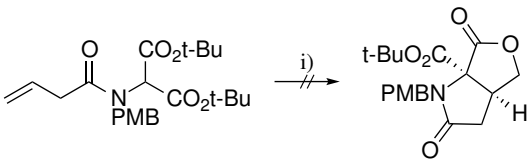
Table 3.8: Metal-Free Conditions for the Formation of Fused Bicyclic Pyrrolidine **334**.



331 **334**

Reagents & Conditions: i) NaOAc (1.2 eq.), NIS (1.2 eq.), DMSO (0.15 M), T (°C), 21 h.

Entry	T / °C	**334** / Yield / %
1	80	17
2	100	-
3	40	23

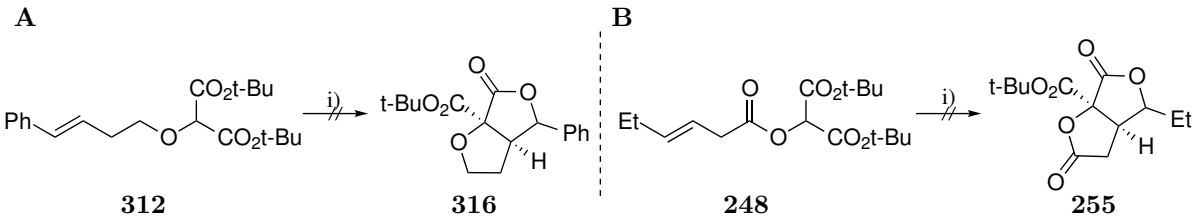


327 **329**

Reagents & Conditions: NaOAc (1.2 eq.), NIS (1.2 eq.), DMSO, 80 °C, 21 h.

Scheme 3.24: Attempts on Metal-Free Conditions for the Formation of Fused γ-Lactam γ-Lactone **329**.

Oxygen Series. The metal-free cyclisation of the ether malonate **312** to the THF γ-lactone **316** were not successful at both 40 and 80 °C (**Scheme 3.25**, **A**) and for the ester malonate **248** to the *bis*-lactone **255** (**Scheme 3.25**, **B**). As in the other cases, full conversion was achieved but a mixture of unidentified compounds was obtained.



312 **316** **248** **255**

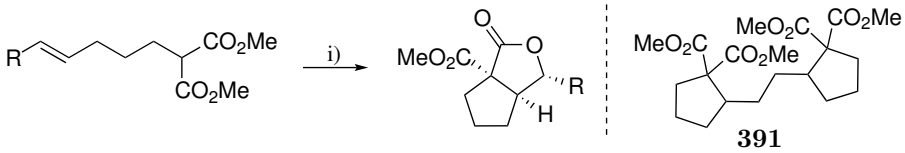
Reagents & Conditions: $Mn(OAc)_3 \cdot 2H_2O$ (1.2 eq.), NIS (1.2 eq.), DMSO, T = 40, 80 °C, 21 h.

Scheme 3.25: Attempts on Metal-Free Conditions for the Formation of Fused THF and *bis*-γ-Lactones.

3.3 Conclusions and Future Work

3.3.1 Anodic Oxidation

Electrochemical methods for a metal-free oxidative radical cyclisation were shown to be possible. After an extensive study of the experimental conditions, the styrene-containing malonate derivative **85** has been anodically oxidised and cyclised in a solution of NaOH in MeOH to give the fused γ-lactone **86** in 42% yield at 40 °C (**Scheme 3.26**). The terminal alkene **57** also cyclised to **62** in 21% yield with isolation of the dimer **391** in 25% yield.



391

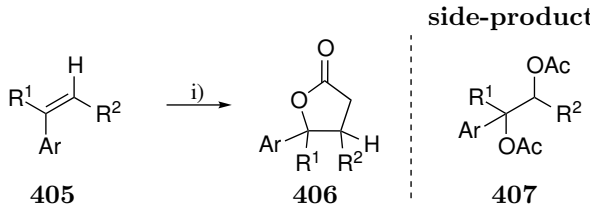
Reagents & Conditions: Substrate **85**, **R= Ph**: i) C graphite rod (anode), C graphite rod (cathode), NaOH (1.2 eq.), MeOH (0.1 M), i = 10 mA, 2.0 F/mol of electricity, 40 °C, 42% yield for lactone **86**, 4.3:1 *dr*; Substrate **57**, **R= H**: C graphite rod (anode), C graphite rod (cathode), NaOH (1.2 eq.), Et_4NBF_4 (0.09 M), MeOH (0.07 M), i = 10 mA, 5.0 F/mol of electricity, r.t., 21% yield for lactone **62**, 25% for dimer **391**

Scheme 3.26: Summary for the Electrochemical Generation of γ-Lactones.

As a result of the number of side-products formed during the electrolysis (see **Scheme 3.17**), a further study of the reaction conditions should be focused towards finding a solvent that does not participate in the reaction and that is stable under the potential window of the electrolysis. In addition, the optimal solvent should allow for a base and temperature screening. Higher temperatures might favour the cyclisation over dimerisation or overoxidation of the substrate. In addition, the use of a divided cell might reduce the amount of side-products in EtOH as a result of having the formation of ethoxide anions exclusively in the cathodic compartment. Constant potential methods are a possibility; nevertheless, a preliminary cyclic voltammetry study of the substrate needs to be performed under the selected electrolysis conditions.

Alternatively, stoichiometric MAN-based oxidative radical cyclisation could also be converted into catalytic with the regeneration of Mn(II) to Mn(III) at the anode surface. Work in this area has been reported by Shundo *et al.* with the use of $Mn(OAc)_2 \cdot 2H_2O$ as electromediator for the carboxymethylation of styrene derivatives **405** to form aryl γ-butyrolactones **406** in acetic acid in a divided cell (**Scheme 3.27**).[148]

On the basis of Shundo's work, the Cu-free MAN-based methodology developed for the preferential formation of γ-lactones (**Section 2.3.4.6**) would be an interesting reaction to study under indirect



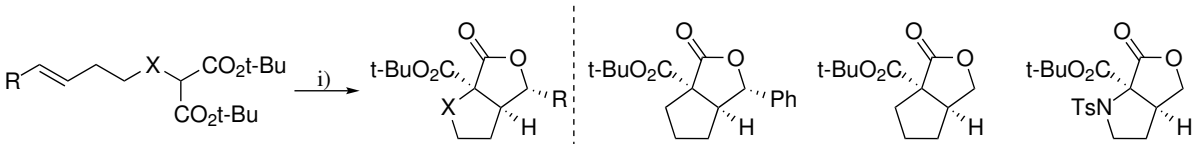
Reagents & Conditions: carbon rod (anode), carbon rod (cathode), $Mn(OAc)_2 \cdot 2H_2O$ (0.06 eq.), $Cu(OAc)_2$ (0.02 eq.), AcONa (0.7 eq.), $AcOH/Ac_2O$ (2:1, 1.2 M), 95-97 °C, 2 F/mol of electricity, divided cell. $\mathbf{R}^1$ = H, Me; $\mathbf{R}^2$ = H, CH_2OH, C_6H_5, CO_2Et, -CH_2-; **lactone 406**: 58-80% (8 examples); side-product **407**: 3-23%.

Scheme 3.27: Indirect Electrolysis for an Intermolecular Mn-Catalysed Oxidative Radical Cyclisation for the Synthesis of Lactones, Reported by Shundo *et al.*[148]

electrolysis conditions, as the oxidative radical transformation tolerated a number of polar solvents. The electromediator $Mn(OAc)_2 \cdot 2H_2O$ would be used in combination with iodide salts to trigger the oxidation, iodomalonate formation and atom transfer reaction to give the desired lactone.

3.3.2 Ionic Oxidation

While the styrene-containing *tert*-butyl malonate derivative **335** did not cyclise under electrochemical conditions, an alternative metal-free method was found to promote such cyclisation and lactonisation. The combination of NaOAc as base and NIS and electrophilic source of iodine in DMSO converted the malonate **335** into the desired lactone **336** in 79% isolated yield. (see **Scheme 3.28**). The methodology was found to be highly substrate dependant, with modest yields found for the lactones **350** and **334** from the malonate **349** and **331** respectively.



Reagents & Conditions: NaOAc (1.2 eq.), NIS (1.2 eq.), DMSO, T = 40, 80 °C, 21 h.

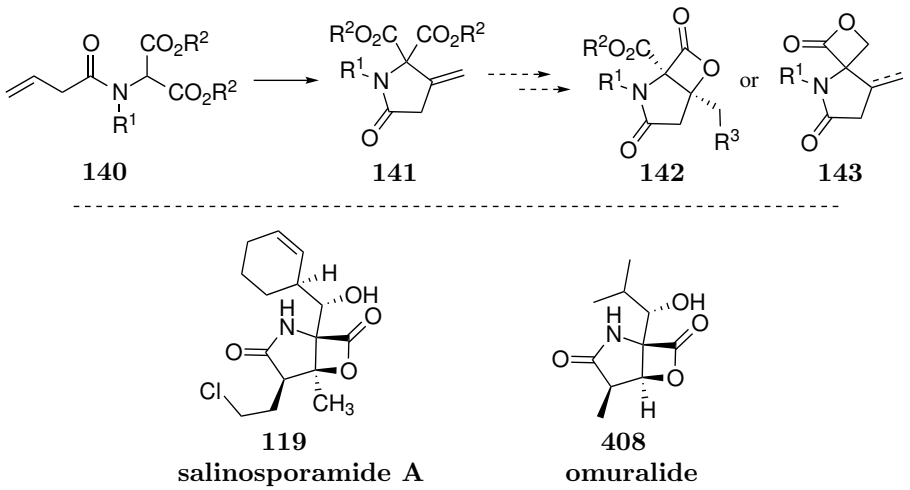
Scheme 3.28: Conclusive Remarks for the NIS/NaOAc Carbocyclisation/Lactonisation.

Ether, ester and amido malonates did not appear to cyclise under such conditions; however, a further screening of bases should be performed in these substrates in order to confirm the incompatibility of the methodology with this type of malonates derivatives.

4

Synthetic Studies towards Novel Proteasome Inhibitors

We have seen that fused γ-lactam-γ-lactones can be prepared under MAN-based oxidative conditions (see **Section 1.2.5.3**). Apart from bicyclic γ-lactones, cyclic *exo*-alkenes could also be prepared from all-carbon systems with the correct selection of the experimental conditions (see **Section 1.2.4**).[49] On the basis of these precedents, the aim of this work was to provide an efficient methodology for the preferential formation of *exo*-methylene γ-lactams **141** from the amido malonate **140** (**Scheme 4.1**). Such a structural framework was proposed to be a key intermediate in the synthesis towards both fused and spiro γ-lactam-β-lactones **142** and **143** respectively. The γ-lactam-β-lactone moiety was considered an important building block, as it has been reported to be responsible for the proteasome inhibition activity shown by the natural product salinosporamide A **119** and its analogue omuralide **408**.



Scheme 4.1: Synthesis of *exo*-Alkene-γ-Lactams as Intermediates towards γ-Lactam-β-Lactones.

4.1 Proteasome Inhibition as a Basis for Anticancer Activity

4.1.1 The Ubiquitin-Proteasome System

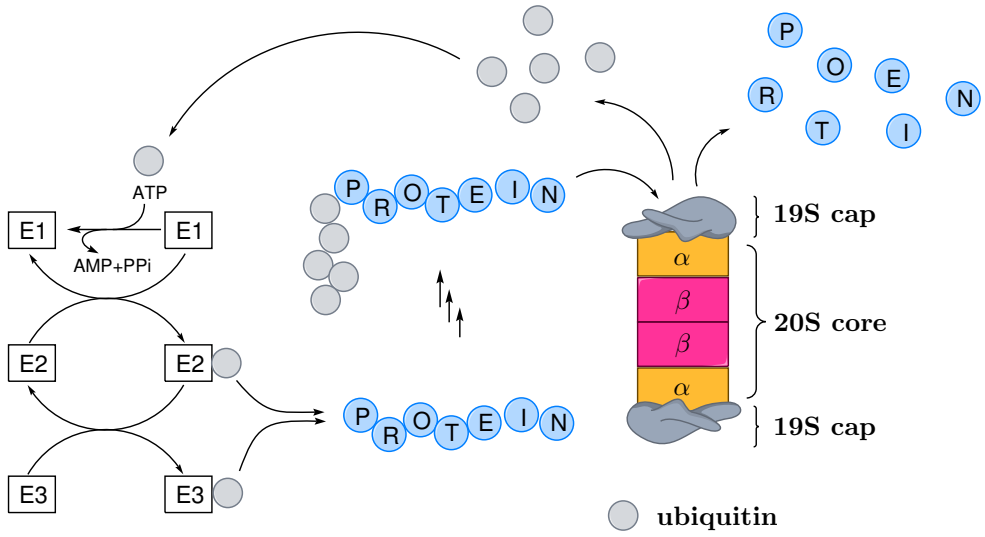
'The ubiquitin-proteasome system is the major proteolytic mechanism for non-lysosomal degradation of cellular proteins. The Nobel Prize of Chemistry was awarded to Aaron Ciechanoever, Avram Hershko and Irvine Rose for their description of the ubiquitin-mediated degradation of proteins'.[149]

Proteasomes are protein complexes found in the nucleus and in the cytoplasm of eukaryotes systems, and are responsible for the degradation of unneeded or defective proteins inside the cell. This process is catalysed by proteases enzymes, and the regulation of such process influences a number of crucial cellular processes, such as the cell cycle, signal transduction, transcription, stress signalling, cell differentiation and apoptosis.[150,151]

The proteins selected for degradation are differentiated *via* an iterative addition of multiple ubiquitin units (small regulatory proteins) through a cascade of enzymatic reactions to form a polyubiquitin chain. Thus, the proteins are 'tagged' by the action of three distinct enzymes (E1-E3). The ubiquitin-activating enzyme E1 binds to the ubiquitin through a thioester bond after consumption of one molecule of ATP. The activated ubiquitin is then transferred to the ubiquitin-conjugating enzyme E2 (also called *ubiquitin-carrier enzymes*), which facilitates the transfer of ubiquitin to the ubiquitin ligase E3, being this the responsible for the attachment of ubiquitin to a lysine residue of the target protein (**Scheme 4.2**).[151]

The formed 'activated' substrate is further recognised by the 26S proteasome, which is a large multi-

subunit complex composed of one or two 19S caps and a 20S core unit. The 19S caps of the proteasome have a regulatory function as they are in charge of recognising the tagged protein, cleave the ubiquitin units and unfold the protein before entering the catalytic 20S core. The latter is a symmetrical tube-shaped structure formed by four rings of seven subunits each ($\alpha_7\beta_7\beta_7\alpha_7$ subunits). Depending on the subunit, a different proteolytic activity is exerted, in which the selectivity is dictated by the composition of their respective pockets. Nevertheless, the degradation of the target protein follows the same mechanism in each of these proteolytic sites; *i.e.*, the side-chain hydroxy group of the N-terminal threonine unit (Thr1) gets deprotonated by the amine Thr1NH_2, thus leading to the nucleophilic cleavage of the peptide into small fragments (**Scheme 4.2**).



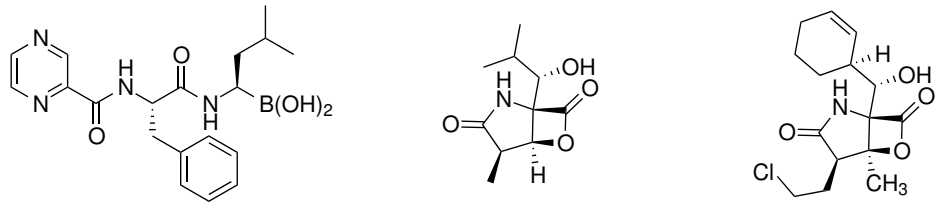
Scheme 4.2: The Proteasome-Ubiquitin System, Adapted from Gulder's Work.[151]

4.1.2 Proteasome Inhibition

When the proteolytic activity is inactive, the cell is unable to remove damaged proteins, which can lead to apoptosis of the cell. Cancer cells are known for having a higher proteasome activity than non transformed cells due to their increased metabolism and higher level of oxidative stress, cytokines and growth factors, fact that make them more sensitive to the proteasome inhibition. As a consequence, the inhibition of the proteasomal activity is viewed as an anticancer mechanism.[150]

Among the proteasome inhibitors we find small peptides bearing electrophilic groups for a covalent binding to the proteasome by nucleophilic attack of the Thr1 hydroxy groups (Thr1O^{γ}) of the active β subunits. The first proteasome inhibitor approved by the US Food and Drug Administration (FDA) was

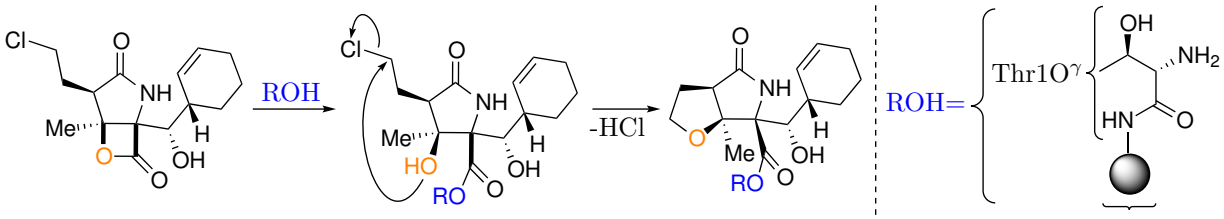
the peptidic proteasome inhibitor boronate bortezomib **409** (Velcade®), used for treatment of multiple myeloma (**Scheme 4.3**). Apart from boronates, suitable acceptor functionalities also include aldehydes, vinyl sulfones, and β-lactones. The importance of the latter functionality has been showcased with the natural product salinosporamide A **119**, which entered phase I human clinical trials for the treatment of multiple myeloma only three years after its discovery in 2003.[150]



409 **bortezomib (Velcade®)** | **408** **omuralide** | **119** **salinosporamide A**

Scheme 4.3: Examples of Proteasome Inhibitors.[151]

The molecular mode of action of salinosporamide A **119** has been elucidated after X-ray crystallographic studies of salinosporamide A **119** with the 20S proteasome.[152] In the first step of inhibition, the alcohol (Thr1O$^{\gamma}$) attacks the β-lactone ring, thereby leading to the salinosporamide-proteasome adduct **410** (**Scheme 4.4**). The released tertiary alcohol is subsequently deprotonated by Thr1NH$_2$ and a nucleophilic displacement of the chlorine follows to form the THF ring-containing salinosporamide-proteasome adduct **411**. As a result of the formation of the THF ring, active water molecules are displaced from the active site, thus preventing re-formation of the β-lactone ring, a fact that renders the inhibitor irreversibly bound to the proteasome.[151]

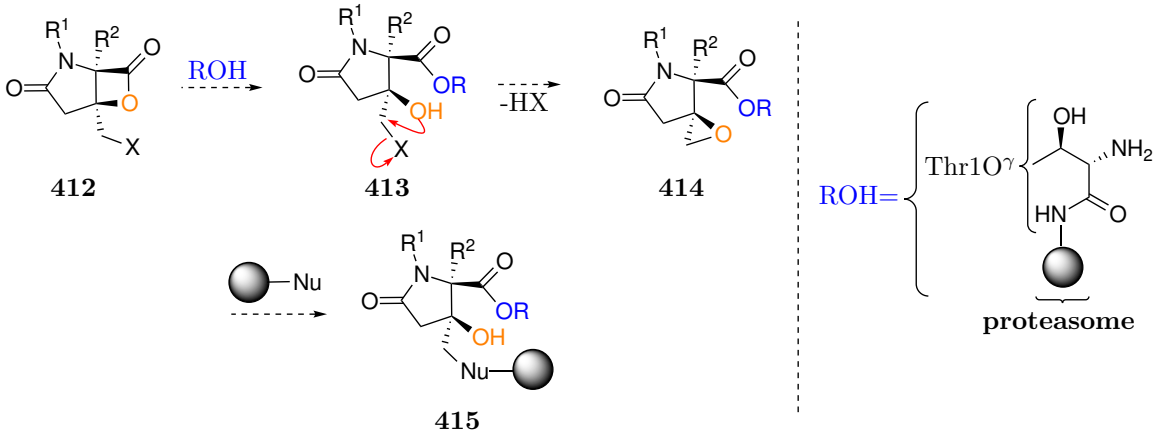


119 | **410** | **411**

Scheme 4.4: Molecular Mode of Action for Salinosporamide A.[151]

Salinosporamide A **119** is 35 times more active than omuralide **408** as a consequence of the formation of the THF ring. In the case of omuralide, the active water molecules surrounding the adduct omuralide-proteasome are not displaced, thus leading to saponification of the inhibitor-proteasome ester linkage and recovery of the proteasomal activity within 24 h.[150]

On the basis of the mode of action published for salinosporamide A **119**, it was thought that novel γ-lactam-β-lactones **412** could be developed. The formation of a spiro oxirane ring **414** instead of a fused THF ring after the interaction with the proteasome would create an additional potential attack site for the nucleophilic proteasome, which would lead to **415** and to a potential increase of the biological efficiency of the inhibition (**Scheme 4.5**).

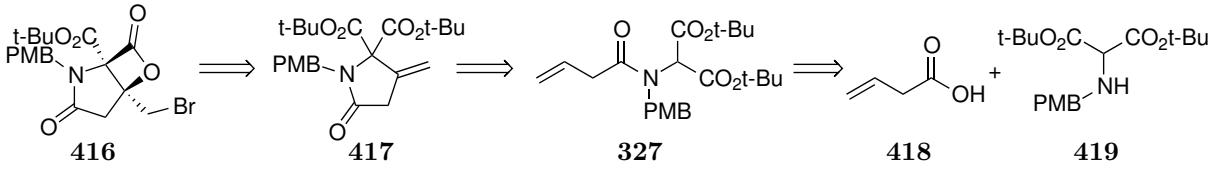


Scheme 4.5: Proposed Mode of Action for Novel Proteasome Inhibitors.

4.2 Oxidative Radical Cyclisation for the Formation of exo-Alkenes

4.2.1 Retrosynthetic Plan

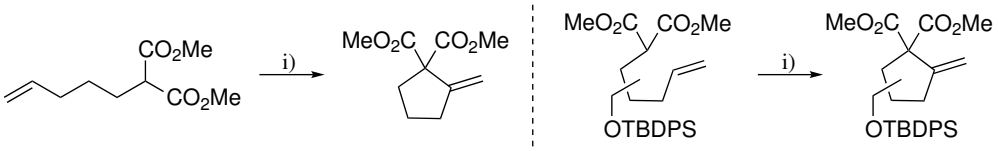
We selected the γ-lactam-β-lactone **416** as the first goal in our study, as we knew that the amido malonate **327** efficiently cyclises under MAN-based oxidative conditions for the formation of γ-lactam-γ-lactones (see **Section 1.2.5.3**). Nevertheless, in this study we aimed to oxidatively cyclise **327** preferentially to the *exo*-alkene **417** under MAN-based conditions, followed by an electrophile-mediated β-lactonisation that would lead to the desired fused β-lactone **416** (**Scheme 4.6**).



Scheme 4.6: Retrosynthetic Plan for Novel Proteasome Inhbitors.

4.2.2 Precedents in the Formation of *exo*-Alkenes

On the basis of the Snider study on the effect of the solvent in the MAN-based oxidative radical cyclisation (see **Section 1.2.4.2**),[46] methylenecyclopentanes **61** and **420** were synthesised in the Burton group from dimethyl 4-pentenyl malonate **57** and **77** respectively with the MAN / $Cu(OAc)_2$ oxidant system in DMSO (**Scheme 4.7**).[49]

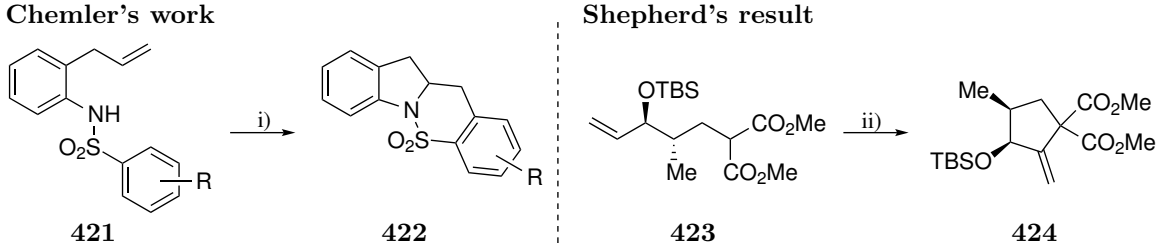


57 **61** **77** **420**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OAc)_2$ (1 eq.), DMSO (0.2 M), 80 °C, 24 h. **compound 61**: 77% yield; **compounds 420**: 50-80% yield, 3 examples.

Scheme 4.7: MAN-Based Oxidative Radical Cyclisation for the Synthesis of *exo*-Alkenes.[49]

In addition and based on the work of Chemler and co-workers in $Cu(OAc)_2$-promoted intramolecular carboamination,[153,154] a MAN-free Cu(II)-based strategy was also developed in the Burton group by Shepherd (unpublished results) for the formation of the *exo*-alkene **424** from the malonate **423** with the use of K_2CO_3 in DMSO (**Scheme 4.8**).[120]



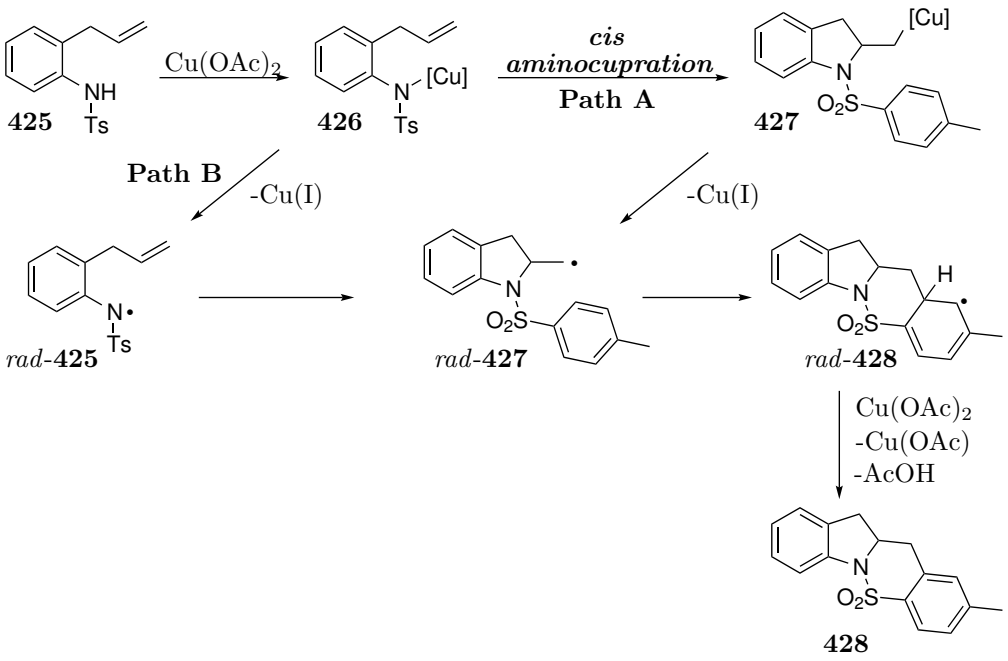
421 **422** **423** **424**

Reagents & Conditions: i) $Cu(OAc)_2$ (3 eq.), $CsCO_3$ (1 eq.), DMF/DMSO, 120 °C, R = Me, OMe, Cl, Br, NO_2, 24-73% yield (8 examples); ii) $Cu(OAc)_2$ (4 eq.), K_2CO_3 (4 eq.), DMSO, 80 °C, 76% yield.

Scheme 4.8: MAN-Free Cu-Promoted Formation of *exo*-Alkene, Based on Chemler's Work and Developed by Shepherd.[120,154]

Mechanistically, Chemler and co-workers proposed that the oxidative cyclisation was taking place after coordination of the Cu(II) salt to the amine **425** to give the organocopper **426**, from which two different pathways could follow (**Scheme 4.9**). In *Path A*, an intramolecular *cis*-aminocupration occurs that leads to the organocopper intermediate **427**. Subsequent homolysis of the Cu-C bond in **427** gives the primary carbon radical *rad*-**427**, which then adds to the aryl group to form an aryl radical *rad*-**428**. A final radical oxidation promoted by Cu(II) and loss of H^+ provides the product **428**. Alternatively the complex **426** could undergo homolysis to form the nitrogen-centered radical *rad*-**425**, which would

lead to a 5-*exo*-trig cyclisation to form the primary radical *rad*-**427**, which was also generated in *Path A*.

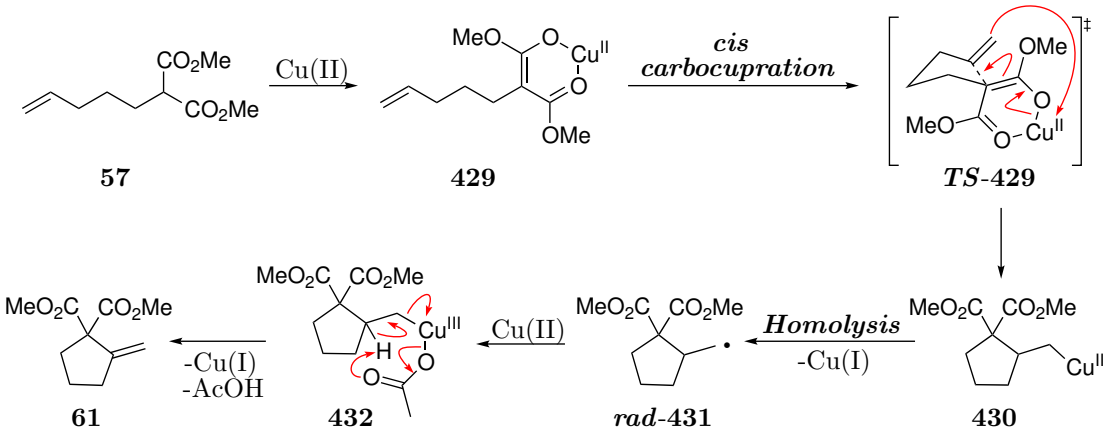


Scheme 4.9: Mechanism for the Cu-Promoted Carboamination, Reported by Chemler and co-workers.[154]

Based on Chemler's proposed mechanism, the MAN-free Cu(II)-promoted oxidative cyclisation for the formation of *exo*-alkenes was proposed to proceed first with enolisation of the malonate **57** and co-ordination of the Cu(II) to give the complex **429** (**Scheme 4.10**). *cis*-Carbocupration *via* the transition state ***TS*-429** would lead to the organocopper(II) complex **430**, which after homolysis would form the primary radical ***rad*-431**. Trapping of such radical by a second molecule of $Cu(OAc)_2$ would give the organocopper(III) **432**, which after a β-hydride elimination, would form the cyclic *exo*-alkene **61**.

The purpose of having a MAN-free Cu-promoted methodology was to further develop an asymmetric variant of the transformation. Due to the oxo-centered trinuclear structure associated to MAN, the design of a ligand for Mn(III) was considered an arduous task. Studies on the development of an asymmetric synthesis of carbocycles were done in the Burton group by Hopes.[155]

Equipped with both MAN-based and MAN-free Cu(II)-promoted methodologies for the formation of *exo*-alkenes, we studied their application on the oxidative cyclisation of amido malonates for the formation of *exo*-methylene γ-lactams.

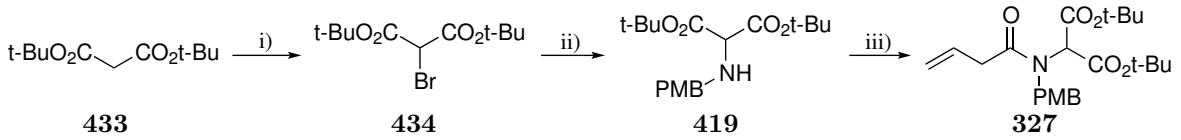


Scheme 4.10: Proposed Mechanism for the Cu-Based Oxidative Radical Cyclisation for the Synthesis of *exo*-Alkenes.[155]

4.2.3 *exo*-Alkene Formation *via* Oxidative Cyclisation

4.2.3.1 Amido Malonates as Substrates

Synthesis of the Precursor. The malonate **433** was brominated under Perrault's conditions[156] to form the bromo malonate **434** in 88% yield, which was then transformed into the amino malonate **419** in 88% yield.[55] A final coupling between **419** and butenoic acid with T3P® as coupling agent led to the desired amido malonate **327** in 96% yield (**Scheme 4.11**).[157]



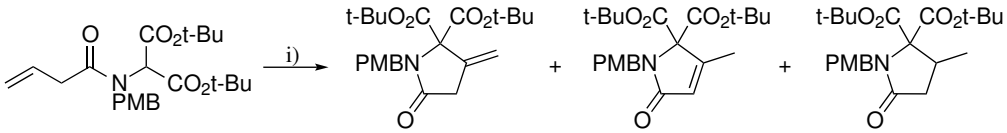
Reagents & Conditions:i) DBU (1 eq.), CBr_4 (1 eq.), THF, -78 °C, 3 h, 88%; ii) $PMBNH_2$ (1.2 eq), Et_3N (2.5 eq.), $CHCl_3$, 65 °C, 10 h, 88%; iii) 3-butenoic acid (1.2 eq.), T3P (1.6 eq.), pyridine (4.2 eq.), EtOAc, 0 °C to r.t. 14 h, 96%.

Scheme 4.11: Synthesis of the Amido Malonate **327**.

Studies towards the Formation of *exo*-Alkene γ-Lactams The amido malonate **327** cyclised with the oxidant system MAN / $Cu(OAc)_2$; however, a unseparable mixture of the desired methylene γ-lactone ***exo*-417** with the isomer ***endo*-417** and the saturated γ-lactam **436** was obtained (**Table 4.1**, **Entry 1**). The MAN-free methodology was also tolerated by the substrate; however the same mixture of compounds was isolated. A screening of bases having $Cu(OAc)_2$ as oxidant was made. Two equivalents of K_2CO_3 with four equivalents of $Cu(OAc)_2$ gave the γ-lactam ***exo*-417** in 37% NMR yield (**Entry 2**); while reducing the stoichiometry to two and one equivalents for the copper salt and the base respectively

did not lead to a yield increase (**Entry 3**). Anhydrous conditions and the use of Na_2CO_3 and NaOAc as bases were not beneficial for the oxidative cyclisation (**Entries 4-6**). The best result was obtained with Cs_2CO_3, giving a 49% NMR yield with no formation of the saturated γ-lactam **436** (**Entry 7**). Leaving the reaction overnight led to the isomerisation of ***exo*-417** into ***endo*-417**, meaning that the reaction time was an important parameter to control (**Entry 8**). Changes in the stoichiometry of the reaction and anhydrous conditions did not make ant improvement of the outcome of the reaction (**Entries 9** and **10**). The problem of isomerisation of the γ-lactam ***exo*-417** made us consider the amino malonates an alternative precursors for the oxidative cyclisation.

Table 4.1: Reaction Condition Optimisation for the Formation of *exo*-Methylene γ-Lactams.



327 ***exo*-417** ***endo*-417** **436**

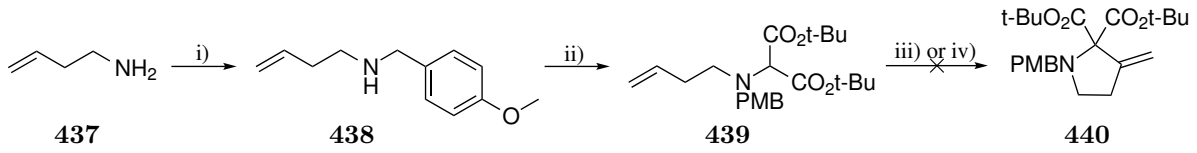
Reagents & Conditions: Oxidant(s), Base, DMSO (0.2 M), r.t., t (h).

Entry	Oxidant(s) (eq.)	Base (eq.)	t / h	***exo*-417**:***endo*-417**:**436** ratio	***exo*-417** NMR Yield / %
1[a]	MAN (2), $Cu(OAc)_2$ (1)	-	2.5	73:6:21	30
2	$Cu(OAc)_2$ (4)	K_2CO_3 (2)	2.5	85:8:7	37
3	$Cu(OAc)_2$ (2)	K_2CO_3 (1)	4.0	70:30:0	23
4[b]	$Cu(OAc)_2$ (4)	K_2CO_3 (2)	3.0	83:4:13	20
5	$Cu(OAc)_2$ (4)	Na_2CO_3 (2)	5.5	79:4:17	23
6	$Cu(OAc)_2$ (2)	NaOAc (1)	3.5	46:0:54	13
7	$Cu(OAc)_2$ (4)	Cs_2CO_3 (2)	3.5	90:10:0	49
8	$Cu(OAc)_2$ (4)	Cs_2CO_3 (2)	22	0:1:0	-
9	$Cu(OAc)_2$ (2)	Cs_2CO_3 (1)	3.0	72:20:8	40
10[b]	$Cu(OAc)_2$ (4)	Cs_2CO_3 (2)	3.0	83:13:4	51

[a] T= 40 °C, 0.4 M ;[b] anhydrous conditions.

4.2.3.2 Amino Malonates as Substrates

PMB-Protected Amino Malonates. The PMB-protected amino malonate **439** was synthesised from the amine **437** through a reductive amination to form the amine **438**, which was then treated with bromo malonate **434** to give the final product **439** (**Scheme 4.12**). The substrate was subjected to both MAN-based and MAN-free conditions for the oxidative cyclisation; however, the reaction did not proceed for the formation of the *exo*-methylene pyrrolidine **440** at both r.t. and 40 °C. A mixture of unidentified compounds was obtained in both cases. It was proposed that the failure of the reaction might be a result of the coordination of the nitrogen to the copper coordination sphere, thus altering the redox potential unfavourably.

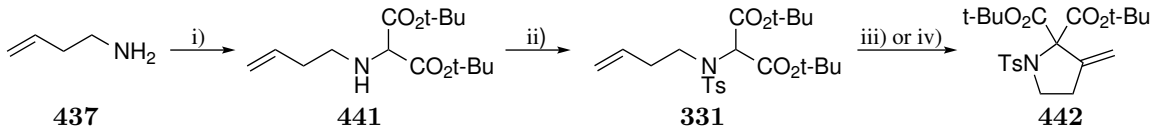


437 **438** **439** **440**

Reagents & Conditions: i) 1. 4-anisaldehyde (1.0 eq.), Et_3N (2.0 eq.), $MgSO_4$ (2.0 eq.), DCM, r.t., 20 h; 2. $NaBH_4$ (1.1 eq.), MeOH, 0 °C, 4 h, 88% yield over 2 steps;[158] ii) bromo malonate **434** (1.1 eq.), Et_3N (2.0 eq.), $CHCl_3$, 80 °C, 3 d., 79% yield;[159] iii) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OAc)_2$ (1.0 eq.), DMSO, T = r.t. and 40 °C; iv) $Cu(OAc)_2$ (4.0 eq.) Cs_2CO_3 (2.0 eq.), DMSO, T = r.t. and 40 °C.

Scheme 4.12: Synthesis and Cyclisation Attempts of the PMB-protected Amino Malonate **439**.

Tosyl-Protected Amino Malonates. As a result of the probable coordination of the nitrogen to the copper coordination sphere, the amine was protected with a tosyl group for the delocalisation of the nitrogen lone pairs, which would disfavour any coordination to the metal. Thus, the amine **437** was alkylated with the bromo malonate **434** to give the unprotected amino malonate **441**, which was further protected with TsCl, leading to the tosyl-protected amino malonate **331** (**Scheme 4.13**). MAN-based conditions were successful leading to the formation of *exo*-methylene pyrrolidine **442** in 48% yield. In contrast, MAN-free conditions did not appear to be suitable, giving the desired compound **442** in yields between 3 and 7% at temperatures between r.t. and 60 °C.



437 **441** **331** **442**

Reagents & Conditions: i) bromo malonate **434** (1.1 eq.), Et_3N (2.5 eq.), $CHCl_3$, 70 °C, 28 h, 73%; ii) TsCl (1.5 eq.), pyridine (1.0 M), 0 °C to r.t., 16 h, 87%; iii) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OAc)_2$ (1.0 eq.), DMSO, r.t., 3h, 48%; iv) $Cu(OAc)_2$ (4.0 eq.), base (2.0 eq.): Cs_2CO_3, K_2CO_3, DMSO, T= r.t, 40 °C, 60 °C, 3-7% yield.

Scheme 4.13: Synthesis and Oxidative Cyclisation of the Tosyl-Protected Amino Malonate **331**.

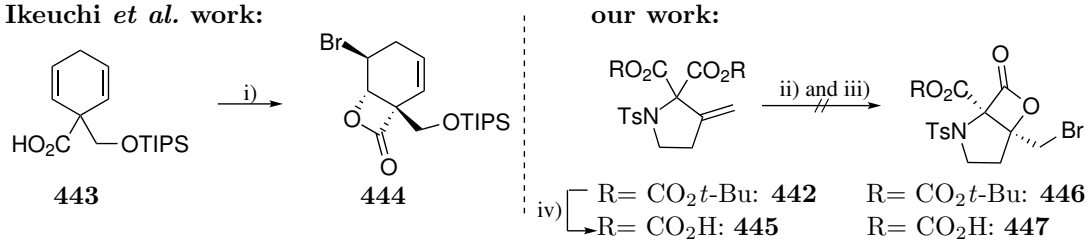
Several copper salts were screened in an attempt to increase the yield of the oxidative cyclisation. Unfortunately the use of $Cu(ethylhexanoate)_2$ (39% yield), $Cu(acac)_2$ (34% yield), $Cu(BF_4)_2$ (42% yield) and $CuSO_4$ (40% yield) did not improve the outcome of the reaction.

4.2.4 Towards the Formation of β-Lactones

The *exo*-methylene pyrrolidine **442** was taken as model substrate for the study of fused β-lactonisation conditions.

4.2.4.1 Direct β-Lactonisation

An asymmetric NBS-promoted bromo-β-lactonisation of prochiral cyclohexadienes has been reported by Ikeuchi *et al.* with the use cinchona alkaloids as chiral catalysts, giving 87% yield of **444** in 91% *ee*.[160] Unfortunately, the conditions did not trigger the β-lactonisation in the *exo*-alkene **442** and **445** (**Scheme 4.14**, **conditions *ii***). The starting material was recovered when submitting **442**, and a mixture of unidentified compounds was obtained when treating **445** under the above mentioned experimental conditions.

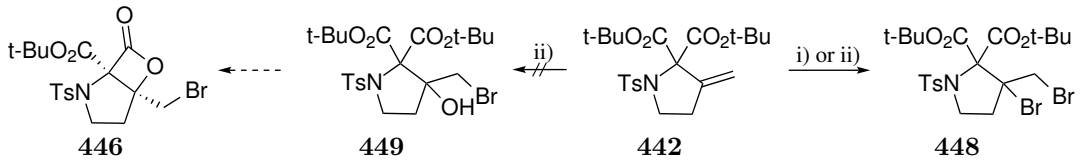


Reagents & Conditions: i) NBS (1.2 eq.), $(DHQD)_2PHAL$ (10 mol%), $CHCl_3$/*n*-Hexane, -40 °C, 1 h, 87%, 91% *ee*; ii) NBS (1.2 eq), $(DHQD)_2PHAL$ (10 mol%), $CHCl_3$ / *n*-Hexane 1:1, T= -40 °C, -20 °C, 0 °C and r.t.; R= CO_2t-Bu, CO_2H; iii) PhSeBr (3.5 eq.), $AgBF_4$ (2.5 eq.), DCM / MeCN (1:1), r.t., 5 h; iv) TFA, DCM (0.5 M), r.t., 10 h, quantitative yield.

Scheme 4.14: Electrophile-Promoted β-Lactonisation Conditions.[56,57,160]

Since a γ-lactonisation was efficiently performed in the group with the use of PhSeBr in the presence of a silver salt,[56,57] the conditions were applied to our system **442** for β-lactonisation; however, the compound decomposed under such conditions (**Scheme 4.14**, **Conditions *iii***).

Molecular bromine has also been reported in the literature as electrophilic agent for the formation of bromo γ-lactones,[161] however the ester did not lactonise over the activated alkene. Instead, an alkene dibromination occurred to give **448** in 50% yield (**Scheme 4.15**, **conditions *i***). A more polar solvent was next employed to favour the formation of the halohydrin **449**, which would lead to the desired β-lactone **446**; nevertheless, the same dibrominated product **448** was again isolated in 46% yield (**conditions *ii***).



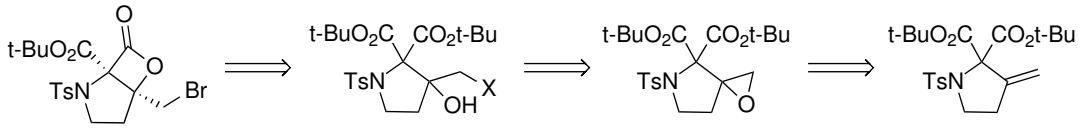
446 **449** **442** **448**

Reagents & Conditions: i) Br_2 (6 eq.), $NaHCO_3$ 0.5 M / Et_2O 1:1, 0 °C to r.t. 5.5 h, 50%; ii) Br_2 (6 eq.), $NaHCO_3$ 0.5 M / THF 1:1, 3 d., 46%.[161]

Scheme 4.15: Br_2-Promoted β-Lactonisation Conditions.[161]

4.2.4.2 Alternative Strategy towards β-Lactonisation

Due to the lack of success with the electrophile-mediated lactonisation conditions, an alternative synthetic route was envisaged. The β-lactone **446** would come from the halohydrin **451**, which would be formed from the epoxide **450** (**Scheme 4.16**)

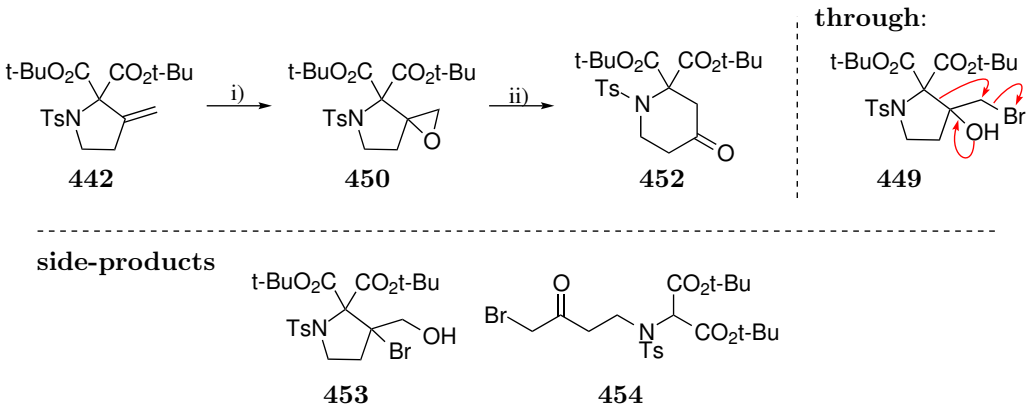


446 **451** **450** **442**

Scheme 4.16: Alternative Synthetic Strategy for the Synthesis of β-Lactones.

The epoxide **450** was successfully formed in 49% from the *exo*-alkene **442** after treatment with *m*-CPBA. Unfortunately, attempts on the epoxide opening under Bajwa's conditions for the formation of the halohydrin **449**,[162] resulted on the formation of the six-membered ring **452** in 20% yield, presumably formed after the rearrangement of the desired halohydrin **449** (**Scheme 4.17**). A mixture of side-products was also isolated, which, on the basis of mechanistic hypotheses and on mass analysis (found 556.2 ($[M+Na]^+$, 100%), 558.2 (100%)), we proposed was composed of the halohydrin **453** and the acyclic compound **454**.

The modest yield encountered for the formation and epoxidation of the *exo*-alkene pyrrolidine **442** and the unstability of the halohydrin **449** made us abandon the use of the *exo*-alkene pyrrolidine core as model substrate for the formation of fused β-lactones. We thus considered an alternative synthetic strategy for the preparation of the γ-lactam-β-lactone moiety from the amido malonate **327**, which would in addition allow us to form spiro β-lactones.

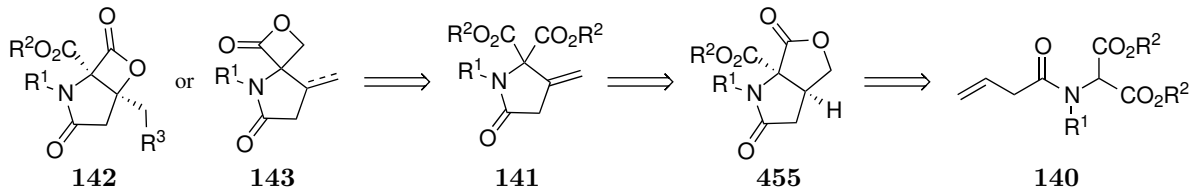


Reagents & Conditions: i) *m*-CPBA (6 eq.), DCM (0.2 M), 0 °C to r.t., 5 d. 49%; ii) LiBr (1.6 eq.), AcOH (3 eq.), THF (0.1 M), r.t. 30 h, 20% for **452**.[162]

Scheme 4.17: Epoxidation and Attempts on the Formation of a Halohydrin under Bajwa's Conditions.[162]

4.3 From γ-Lactam γ-Lactones to γ-Lactam β-Lactones

Pyrrolidinone-γ-lactones have already been synthesised in the Burton group under MAN-based oxidative radical cyclisation conditions.[55] Consequently, based on the synthetic sequence developed by Marx *et al.* for the total synthesis of salinosporamide A **119**,[55,57] we herein proposed the following retrosynthetic plan towards the synthesis of both spiro and fused γ-lactam-β-lactones as potential novel proteasome inhibitors (**Scheme 4.18**). In this case, the formation of the *exo*-alkene γ-lactam molecule **141** would arise from the γ-lactam-γ-lactone **455** and not directly from the amido malonate **140** after an oxidative cyclisation.

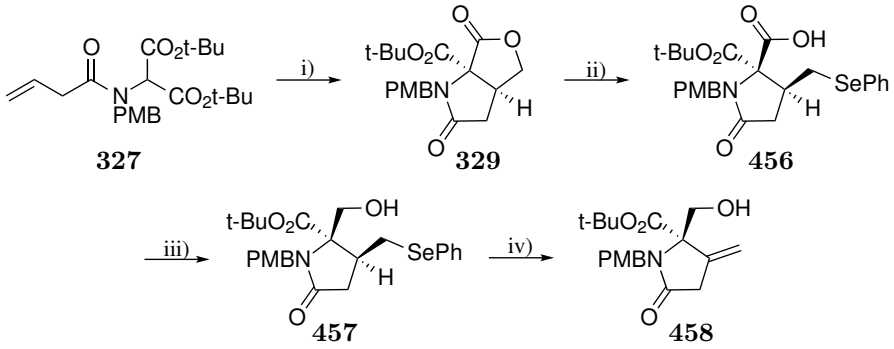


Scheme 4.18: Retrosynthetic Plan for the Formation of γ-Lactam β-Lactones.

4.3.1 Formation of an *exo*-Alkene from a γ-Lactone

The developed Cu-free MAN/KI-based oxidative radical cyclisation conditions (see **Section 2.3.4.6**) were applied to the amido malonate **327** to form the desired γ-lactam-γ-lactone **329** in 83% yield (**Scheme 4.19**). The lactone opened with phenyl selenide anion, previously formed from the treatment

of diphenyl diselenide with $NaBH_4$ in DMF, thus giving the acid **456**. The polarity associated with the acid **456** made its isolation from the selenide by-products not a straightforward process. While an acid-base extraction was leading to low yields, a filtration over a silica pad, followed by elution with a mixture of EtOAc and MeOH proved to be a more optimal work-up (For more information, see **Section 6.6**). Reduction of the acid **456** *via* formation of the acid chloride led to the alcohol **457** in 53% overall yield over the lactone opening and reduction steps. Formation of the *exo*-alkene **458** was achieved after oxidation of the selenide with $NaIO_4$ and further thermal elimination of the selenoxide, giving **458** in 93% yield with no presence of the *endo*-alkene isomer.



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (3 eq.), KI (0.5 eq.), MeCN (0.15 M), 80 °C, 21 h., 83%; ii) $(PhSe)_2$ (2 eq.), $NaBH_4$ (4 eq.), DMF, EtOH, 60 °C, 5 h; iii) 1. oxalyl chloride (5.4 eq.), DMF (1.8 eq), DCM, 0 °C to r.t., 30 min; 2. LiAl(O*t*-Bu)$_3$H (1.0 M in THF, 10 eq), THF, MeCN, -78 °C to r.t., 2 h., 53% over 2 steps; (iv) 1. $NaIO_4$ (4 eq.), $NaHCO_3$ (4 eq.), THF / MeOH / H_2O 1:1:1, r.t., 30 min; 2. $CHCl_3$ (0.06 M), 75 °C, 1 h., 93%.

Scheme 4.19: Synthesis of *exo*-Alkene **458** from the γ-Lactam γ-Lactone **329**.

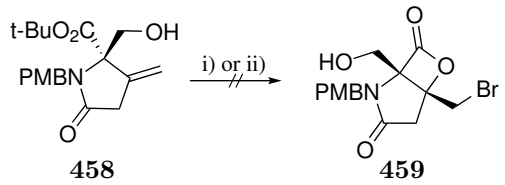
4.3.2 Towards the β-Lactone Formation

4.3.2.1 Direct Lactonisation for Fused β-Lactone Formation

The application of Ikeuchi's conditions for the NBS-promoted bromo lactonisation to the *exo*-alkene γ-lactam **458** led to the recovery of the starting material **458** (**Scheme 4.20**, **conditions *i***);[160] while the use of PhSeBr as electrophile gave decomposition (**conditions *ii***).[56,57] The participation of the alcohol was likely to occur under such conditions; nevertheless, the corresponding THF ring has not been detected.

4.3.2.2 Alternative Strategies towards Fused β-Lactones

The application of the synthetic sequence shown in **Scheme 4.16** was first envisaged for the *exo*-alkene **458**. Unfortunately, the epoxidation of the *exo*-alkene **458** did not give the desired epoxide **460** in good

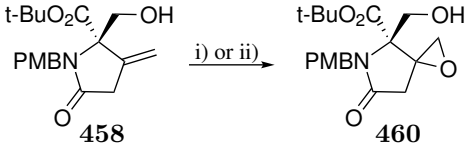


458 **459**

Reagents & Conditions: i) NBS (1.2 eq), $(DHQD)_2PHAL$ (10 mol%), $CHCl_3$ / *n*-Hexane 1:1, -40 °C to r.t.; ii) PhSeBr (3.5 eq.), $AgBF_4$ (2.5 eq.), DCM / MeCN (1:1), r.t, 21 h.

Scheme 4.20: Electrophile-Mediated β-Lactonisation.

yields, with 10% when using *m*-CPBA and 38% with $VO(acac)_2$ under the procedure described by Li *et al.* (**Scheme 4.21**).[163]

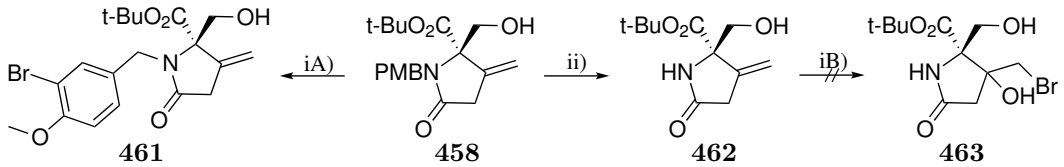


458 **460**

Reagents & Conditions: i) *m*-CPBA (6 eq.), $NaHCO_3$ (9 eq.), DCM (0.2 M), 6 d., 10%; ii) $VO(acac)_2$ (0.08 eq.), TBHP (1.5 eq., 5 M in DCM), DCM (2 M), 0 °C to r.t., 38%.[163]

Scheme 4.21: Epoxidation of the *exo*-Alkene **458**.

Halohydrin formation this time with NBS instead of molecular bromine was next attempted as the electrophilic character of the bromine source would avoid dibromination of the alkene in a mixture of THF and H_2O as solvent system. Nevertheless, the alkene did not react and bromination at the *ortho*-position with respect to the methoxy group in the aromatic ring led to **461** in 53% isolated yield (**Scheme 4.22**). The presence of the bromide was confirmed with high resolution mass spectrometry with the isotopic distribution at 426.09008 ($[M+H]^+$, 100%) and 428.08804 (100%) (see **Section 6.6**). Consequently, deprotection of the lactam with CAN under Corey's conditions followed to give the unprotected lactam **462** in 61% yield.[164] Unfortunately, treatment of **462** with NBS did not formed the desired product **463**, giving 77% of recovered starting material **462**.



461 **458** **462** **463**

Reagents & Conditions: i) NBS (1.2 eq.), THF / H_2O (1.5:1, 0.2 M), r.t., 24 h, A: 53% of **461**, B: 77% recovered **462**; ii) CAN (3.0 eq.), MeCN / H_2O (3:1, 0.15 M), 0 °C, 1.5 h., 61%.[164]

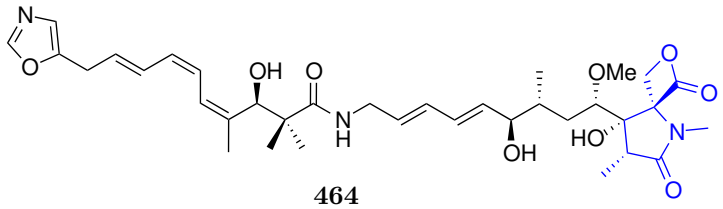
Scheme 4.22: Attempts towards the Halohydrin Formation.

The formation of fused β-lactones did not seem straightforward as the alkene was shown not to

be nucleophilic enough for electrophilic activation and thus functionalisation, as deduced from the low yields or lack of reactivity in the above mentioned transformations. As a result, our efforts were directed towards the construction of a spiro β-lactone moiety.

4.3.2.3 Studies towards the Formation of Spiro β-Lactones

In addition to the fused β-lactones found in the natural products salinosporamide A **119** and omuralide **408** (**Scheme 4.3**), spiro γ-lactam-β-lactones are also found in the antibacterial and antiviral oxazolomycin family of natural products (oxazolomycin A shown in **Scheme 4.23**). To date, only one synthesis has been published for oxazolomycin A,[165] yet a number of research groups focused their efforts towards the construction of the pyrrolidinone core containing the spiro β-lactone.[166–169]

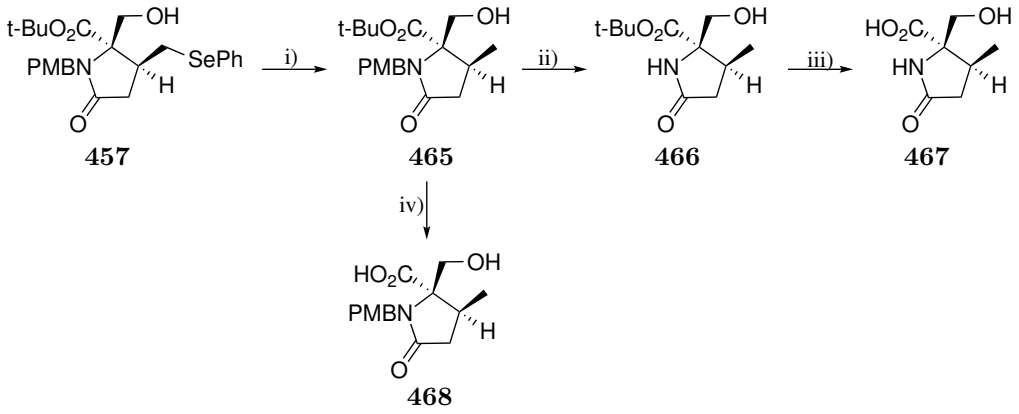


464
oxazolomycin A

Scheme 4.23: Structure for the Natural Product Oxazolomycin A.

Synthesis of the Substrates. Despite the inherent low reactivity of the *exo*-alkene **458**; investigations towards the formation of the spiro β-lactone were performed with the acids **467** and **468** (**Scheme 4.24**). The methylene moiety has been replaced by a methyl group not only to guarantee the reaction between the geminal methyl alcohol and the carboxylic acid, but also to reduce the strain in the γ-lactam. The syntheses began with the radical reduction of the seleno derivative **457** (synthesis shown in **Scheme 4.19**) under Danishefsky's conditions with *n*-Bu_3SnH in the presence of AIBN as radical initiator, giving the lactam **465** in 87% yield.[56] Deprotection of the lactam was successfully achieved with CAN,[164] leading to **466** in 64% yield, followed by ester hydrolysis with TFA to form the acid **467** in 83% yield. Alternatively, the PMB-containing acid **468** was synthesised in quantitative yield from **465** after hydrolysis of the ester.

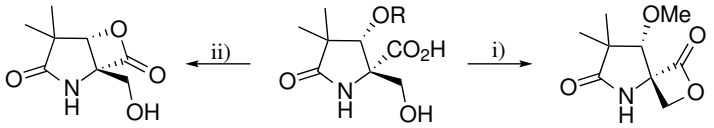
β-Lactonisation Attempts. Josa-Culleré *et al.* reported the synthesis of both fused and spiro β-lactone-containing tetramate cores as mimics of the natural products salinosporamide A, omuralide and oxazolomycins, which were then biologically evaluated for antibacterial and proteasome inhibition activities.[170] During their studies on the lactonisation conditions, Josa-Culleré *et al.* found that spiro



Reagents & Conditions: i) AIBN (0.1 eq.), *n*-Bu_3SnH (2.5 eq.), toluene (0.2 M), 100°C, 15 min, 87%;[56] ii) CAN (3.0 eq.), MeCN / H_2O (3:1, 0.06 M), 0 °C, 1.5 h, 64%;[164] iii) TFA (0.4 M), DCM (0.5 M), 0 °C to r.t., 6 h, 83%; iv) TFA (0.2 M), DCM (0.5 M), 0 °C to r.t., 19 h, quantitative yield.

Scheme 4.24: Synthesis of the Precursors for the Spiro β-Lactonisation.

and fused β-lactones required different coupling agents for their formation as depicted in **Scheme 4.25**. The synthesis of the spiro β-lactone **471** was only achieved with HATU as coupling agent; while BOPCl was the coupling agent of choice for the formation of the fused β-lactone **472** from the substrates **470** and **469** respectively.



R= H: **469**
R= Me: **470**

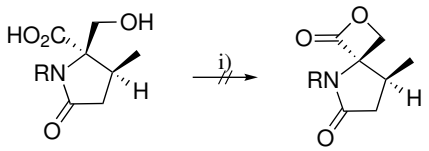
Reagents & Conditions: i) HATU, DIPEA, THF, 0 °C to r.t., 36 h, 27%, R= Me,; ii) BOPCl, Et_3N, DCM, r.t., 19 h, 45% over 2 steps (second step not shown), R= H.[170]

Scheme 4.25: Synthesis of Spiro and Fused β-Lactones Tetramates, Reported by Josa-Culleré *et al.*[170]

Based on Josa-Culleré *et al.* work,[170,171] the same HATU-based conditions were applied to the PMB-protected lactam **468** (**Table 4.2**, **Entry 1**). Unfortunately, a complex mixture was obtained with no presence of the β-lactone moiety as confirmed with IR spectroscopy. In order to decrease steric encumbrance into the molecule as we initially thought this could present an issue, the deprotected lactam **467** was subjected for study under Josa-Culleré's conditions; however a complex mixture of unidentified compounds was found with no presence of the β-lactone moiety according to IR analysis (**Entry 2**). An attempt to lactonise **467** with BOPCl was made despite its precendents on forming fused β-lactones; nevertheless decomposition was obtained (**Entry 3**). Donohoe and co-workers published the use of TsCl as coupling agent for the β-lactonisation in the synthesis of the pyrrolidinone core of the antibiotic

KSM-2690 B, belonging to the oxazolomycin family.[166] The application of Donohoe's conditions was not successful either, with decomposition as outcome of the reaction (**Entry 4**). The coupling agent HBTU was also reported by Donohoe and co-workers in the asymmetric synthesis of the pyrrolidinone core of oxazalomycin A,[167] however those conditions did not lead to the desired β-lactone (**Entry 5**).

Table 4.2: Attempts towards the Formation of Spiro β-Lactones.



R= PMB: **468** R= PMB: **473**
R= H: **467** R= H: **474**

Reagents & Conditions: i) coupling agent, solvent, base, T (°C), t (h).

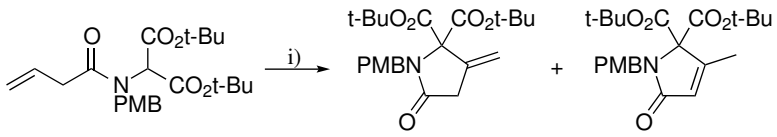
Entry	R (compound)	coupling agent	base	solvent	T / °C	t / h	**473** or **474** Yield / %
1	PMB (**468**)	HATU	DIPEA	THF	0 °C to r.t.	48	- (**473**)
2	H (**467**)	HATU	DIPEA	THF	0 °C to r.t.	42	- (**474**)
3	H (**467**)	BOPCl	Et_3N	DCM	r.t.	24	- (**474**)
4	H (**467**)	TsCl	Py	DCM	-5 °C to r.t.	19	- (**474**)
5	H (**467**)	HBTU	Et_3N	DCM	0 °C to r.t.	19	- (**474**)

We suspected the negative results encountered for the β-lactonisation of **467** were a consequence of the structural features of the molecule which did not position the alcohol and the activated carboxylic acid in proximity for their chemical interaction. Formation of the β-lactone followed by concomitant CO_2 evolution was also proposed as an explanation for the non success found in this transformation.

4.4 Conclusions and Future Work

The *exo*-alkene γ-lactam **417** was formed under the MAN-free methodology with the use of stoichiometric amounts of copper salt and base; however, isomerisation of the double bond occurred during the transformation. Control of the reaction time was necessary to minimise such isomerisation. The best conditions consisted of using four equivalents of $Cu(OAc)_2$ in the presence of two equivalents of Cs_2CO_3 for 3.5 h at r.t., which led to a 49% NMR yield for the desired *exo*-alkene **417** (**Scheme 4.26**).

In order to avoid formation of the *endo*-isomer, the PMB-protected amino malonate **439** was subjected to the MAN-free and MAN-based conditions for the oxidative cyclisation, however, decomposition was obtained as a result of a potential coordination of the nitrogen to the copper coordination sphere, thus altering its redox potential (see **Scheme 4.12**). Consequently, tosyl-protected amino malonate **331** was the substrate of choice for the oxidative cyclisation, which gave the desired *exo*-alkene **442** in 48%

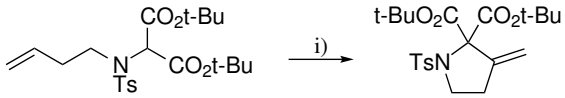


327 ***exo*-417** ***endo*-417**

Reagents & Conditions: i) $Cu(OAc)_2$ (4 eq.), Cs_2CO_3 (2 eq.), DMSO (0.2 M), r.t., 3.5 h, ***exo*-417**:***endo*-417** = 9:1, 49% NMR yield for *exo*-**417**.

Scheme 4.26: MAN-free Conditions for the Formation of *exo*-Alkene γ-Lactam **417**.

yield under MAN-based conditions (**Scheme 4.27**); while low yields were observed under MAN-free conditions (see **Scheme 4.13**).

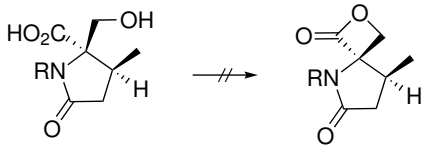


331 **442**

Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2 eq.), $Cu(OAc)_2$ (1 eq.), DMSO, r.t., 3h, 48%.

Scheme 4.27: MAN-based Conditions for the Formation of *exo*-Alkene Pyrrolidine **442**.

The *exo*-alkene **442** was taken as a model substrate for the study of fused β-lactonisation; however no success was found *via* an electrophile-mediated β-lactonisation, formation of a halohydrin or opening of the epoxide **450** (see **Scheme 4.14**, **Scheme 4.15** and **Scheme 4.17**). A synthetic alternative strategy was undertaken through the formation of γ-lactam-γ-lactone **329**, which opened the possibility for both spiro and fused β-lactonisations (see **Scheme 4.19**). Functionalisation at the *exo*-alkene moiety proved challenging, thus we focused our efforts towards the spiro β-lactonisation from both acids **468** and **467** (**Scheme 4.28**). Unfortunately, treatment under the reported lactonisation conditions did not lead to the desired spiro β-lactones **473** and **474** (see **Table 4.2**).

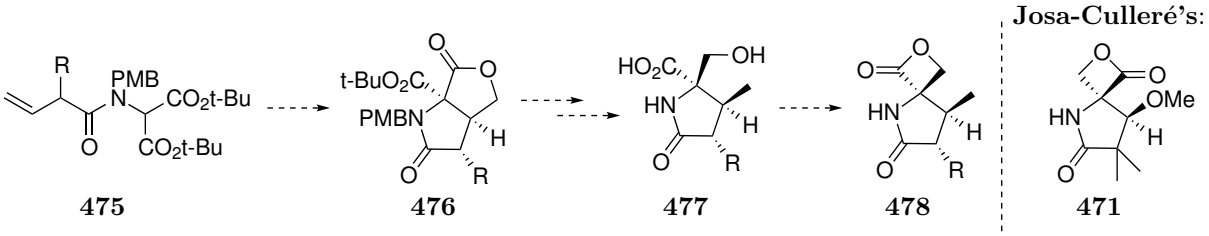


R= PMB: **468** R= PMB: **473**
R= H: **467** R= H: **474**

Scheme 4.28: Towards Spiro β-Lactones.

Given the structural similarity between Josa-Culleré's substrate **470** (see **Scheme 4.25**) and our substrate **467**, the negative results obtained for the spiro β-lactonisation were surprising.[170] The instability of the resulting product **474** (see **Table 4.2**) or the lack of steric encumbrance of the pyrrolidinone core

might be at the root of the issue. Since a number of γ-lactam-γ-lactones **476** were synthesised *via* MAN-based radical cyclisation by Logan *et al.*,[55] we propose that the lactonisation limitation might be circumvent with acids such as **477**, formed from their corresponding γ-lactam-γ-lactone **476** (**Scheme 4.29**).



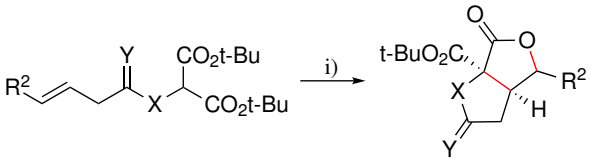
Scheme 4.29: Towards Spiro β-Lactones from More Substituted γ-Lactam-γ-Lactones.

5

General Conclusions and Future Work

5.1 MAN-based Oxidative Radical Cyclisation

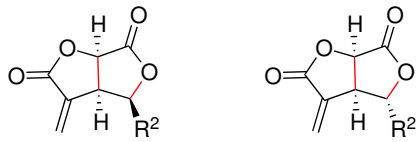
The MAN-based oxidative radical cyclisation was proved to be a powerful methodology for the construction of molecular complexity consisting of the formation of γ-lactone-containing bicyclic systems from linear substrates, including all-carbon, amino, amido, ether and ester malonate derivatives.[49,52,55,60] The scope of the methodology was extended to alkyl substituted alkene malonate derivatives with Cu-free conditions based on the use of MAN combined with substoichiometric amounts of KI (**Scheme 5.1**). Future work in this area requires the expansion of the methodology towards more hindered substrates.



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq.), KI (0.5 eq.), MeCN (0.15 M), 80 °C; R^2= H, alkyl, Ph; X= CH_2, N, O; Y= H_2, O; 44-88% yield; 9 examples.

Scheme 5.1: Cu-Free MAN-Based Methodology for the Formation of γ-Lactones.

The above mentioned methodology allowed us to efficiently synthesise the ethisolide family of natural products and one non-natural analogue, which we took the liberty of naming '*iso*-discosiolide' (**Scheme 5.2**). Anticancer properties are currently being evaluated for the six members of this family.

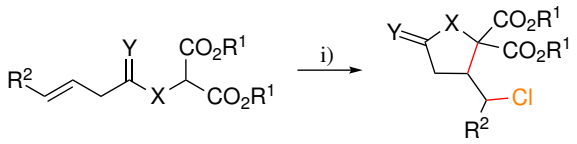


R^2= Et	**ethisolide**	***epi*-ethisolide**
R^2= C_8H_{17}	***iso*-avenaciolide**	**avenaciolide**
R^2= $C_{10}H_{21}$	***iso*-discosiolide**	**discosiolide**

Scheme 5.2: Ethisolide Family of Natural Products

While developing the Cu-free MAN/KI-based methodology, novel conditions for the formation of chloro monocyclic systems were discovered, which were based on the participation of LiCl in the standard MAN-based oxidative radical cyclisation (**Scheme 5.3**). The methodology was shown to be highly substrate-dependant as the all-carbon systems mainly gave lactonisation with no participation of the chloride. The structure of the all-carbon substrates needs to be optimised in order to favour the chlorination over the lactonisation pathway. Concerning the formation of fluoro monocyclic compounds, a more extensive study on the reaction conditions needs to be undertaken before discarding the possibility

of formation of fluoro derivatives *via* MAN-based oxidative radical cyclisation.



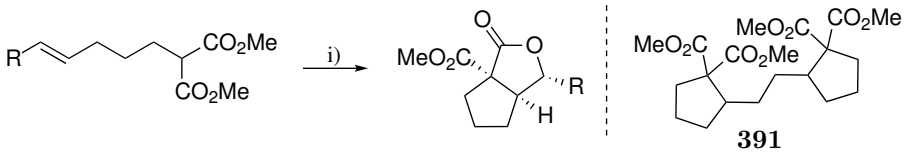
Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), LiCl (1.2 eq.), MeCN (0.15 M), 40 °C; R^2= H, Ph, alkyl, X= O, N; Y= H_2, O; 24-90% yield (8 examples).

Scheme 5.3: LiCl as Additive in the MAN-based Oxidative Radical Cyclisation.

Overall, the MAN-based methodology allowed for the construction of one carbon-carbon, one carbon-oxygen or carbon-chloride bonds; one or two rings; two or three stereocenters and the formation of quaternary, tertiary, tertiary centers; and was applied to the syntheses of five natural products and one non-natural analogue.

5.2 Metal-Free Oxidative Radical Cyclisation

We demonstrated that electrochemical techniques could be used for the anodic oxidation of all-carbon-based malonate derivatives in the synthesis of fused bicyclic γ-lactones (**Scheme 5.4**). Despite the limited applicability of the technique and the number of side-products formed during the transformation, these two example are a representation that metal-free conditions are possible in oxidative radical cyclisation for the synthesis of lactones. More extensive investigations concerning the solvent, cell and the electrochemical method to run the electrolysis should be undertaken to diminish the amount of side-reactions and to increase the scope of the transformation. Alternatively, conditions for a metal-catalysed oxidative radical cyclisation with Mn(II) as electromediator needs to be considered.

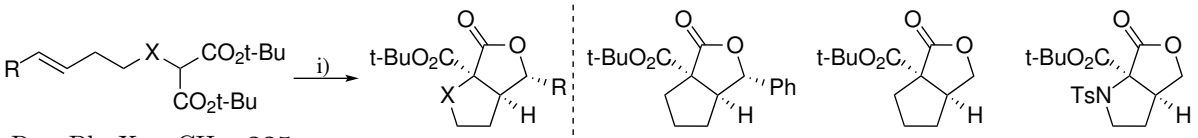


Reagents & Conditions: Substrate **85**, **R= Ph**: i) C graphite rod (anode), C graphite rod (cathode), NaOH (1.2 eq.), MeOH (0.1 M), i = 10 mA, 2.0 F/mol of electricity, 40 °C, 42% yield for lactone **86**, 4.3:1 *dr*; Substrate **57**, **R= H**: C graphite rod (anode), C graphite rod (cathode), NaOH (1.2 eq.), MeOH (0.07 M), i = 10 mA, 5.0 F/mol of electricity, r.t., 21% yield for lactone **62**, 25% for dimer **391**

Scheme 5.4: Summary for the Electrochemical Generation of γ-Lactones.

An ionic alternative has also been discovered with the use of a base (NaOAc) combined with NIS as electrophilic iodine. The method was applied to the all-carbon series and to the amino malonate **331** (**Scheme 5.5**). The highest yield was obtained for the cyclisation of the styrene-derived malonate **335**

with a 79% for the γ-lactone **336**. The high diasteroselectivity obtained implied that an ionic pathway might be governing the transformation. The methodology was found to be highly substrate-dependant; however additional studies on the experimental conditions would be essential before confirming the incompatibility of the methodology with the amido malonates and the oxygen series.



R = Ph, X = CH_2: **335**
R = H, X = CH_2: **349**
R = H, X = NTs: **331**

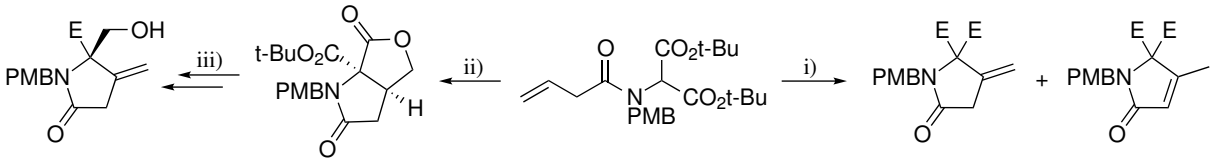
336: 79% (32:1 *dr*) **350**: 43% **334**: 23%

Reagents & Conditions: NaOAc (1.2 eq.), NIS (1.2 eq.), DMSO, T = 40, 80 °C, 21 h.

Scheme 5.5: Conclusive Remarks for the NIS/NaOAc Carbocyclisation/Lactonisation.

5.3 From exo-Alkenes-γ-Lactams towards γ-Lactams-β-Lactones

The *exo*-alkene γ-lactam **417** and **458** were synthesised respectively from the amido malonate **327** through a MAN-free Cu-promoted oxidative cyclisation in 49% NMR yield with the presence of the *endo*-isomer and from the γ-lactam γ-lactone **329** (which was previously synthesised *via* Cu-free MAN/KI-based oxidative cyclisation) in 50% isolated yield over 3 steps with no presence of the *endo*-isomer (**Scheme 5.6**).



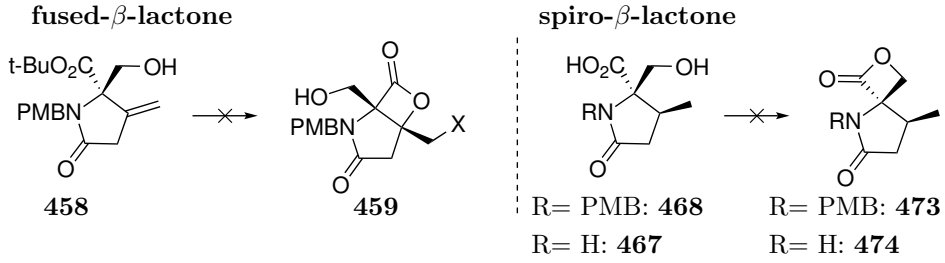
458 **329** **327** ***exo*-417** ***endo*-417**

Reagents & Conditions: i) $Cu(OAc)_2$ (4 eq.), Cs_2CO_3 (2 eq.), DMSO (0.2 M), r.t., 3.5 h, ***exo*-417**:***endo*-417** = 9:1, 49% NMR yield for *exo*-**417**; ii) $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq.), KI, (0.5 eq.), MeCN (0.15 M), 80 °C, 21 h, 83%; iii) 50% yield over 3 steps. E = CO_2t-Bu.

Scheme 5.6: Formation of *exo*-Alkene γ-Lactam **417** and **458**.

Attempts on the formation of the fused β-lactone **459** from **458** were not successful either *via* direct electrophile-mediated lactonisation or through formation of a halohydrin (**Scheme 5.7**). The same negative results were observed for the lactonisation of **468** and **467** when applying the conditions for β-lactonisation reported by Josa-Culleré *et al.* and Donohoe and co-workers.[166,167,170]

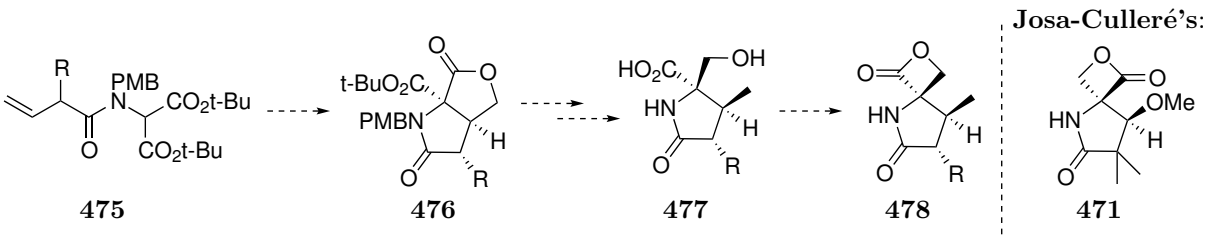
In the case of having **458** as substrate, we proposed the negative outcomes were a result of the low



Scheme 5.7: Attempts towards both Fused and Spiro β-Lactonisation.

nucleophilicity of the *exo*-alkene for the creation of the fused β-lactone **459**. On the other hand, we proposed that the non-success encountered for the spiro β-lactonisation of **467** resulted from either the unstability of the resulting product **474** or the lack of steric encumbrance of the pyrrolidinone core to position the alcohol and the carboxylic acid in proximity for the chemical interaction.

As future work, we consider that more hindered carboxylic acid such as **477** should be treated under the reported β-lactonisation conditions to give **478**, as the molecule shows more ressemblance with Josa-Culleré's substrate **471** (**Scheme 5.8**). Access to the acids **477** would easily be achieved from γ-lactamγ-lactone molecules **476**, which in their turn can be synthesised through MAN-based oxidative radical cyclisation from the amido malonates **475**.[55]



Scheme 5.8: Towards Spiro β-Lactones from More Substituted γ-Lactam-γ-Lactones.

6

Experimental Section

6.1 General Remarks

^{1}H and ^{13}C spectra were recorded on a Bruker AVF-400 (400/100 MHz), Bruker AVH-400 (400/100 MHz) or Bruker AVG-400 (400 / 100 MHz) spectrometer. Proton ($\boldsymbol{\delta_H}$) and carbon ($\boldsymbol{\delta_C}$) chemical shifts are quoted in ppm and are internally referenced to the residual protonated solvent signal. Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC data, relative intensities and comparison with spectra of related compounds. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), m (multiplet), dd (double doublet) and so on. Coupling constants (J) are given in Hz and are rounded to the nearest 0.1 Hz. H and H$'$ refer to diastereotopic protons attached to the same carbon and imply no particular stereochemistry.

High resolution mass spectra were recorded by the Mass Spectrometry Service at the University of Oxford Chemical Research Laboratory using a Bruker Daltronics microTOF spectrometer (ES). Mass values ($\boldsymbol{m/z}$) are reported in Daltons, with their relevant fragment ions in square parentheses. High resolution values are calculated to at least four decimal places from the molecular formula, with all found values reported within a tolerance of 5 ppm. Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ES).

Infrared spectra were recorded using a Bruker Tensor 27 Fourier Transform spectrophotometer using thin films on a diamond ATR. Absorption maxima (ν_{max}) are classified as strong (s), medium (m), weak (w) and broad (br) and are quoted in wavenumbers (cm^{-1}). Melting points were determined using a Leica Galen III Compound Microscope apparatus and are uncorrected.

Analytical TLC was performed on Merck DC-Alufolien 60 F_{254} 0.2 mm precoated plates and visualised using a ultraviolet lamp, acidic vanillin or basic potassium permanganate dips. Retention factors (R_f) are reported with the solvent system used in parentheses. Flash column chromatography was performed on Merck 60 silica (particle size 4063 μm, pore diameter 60 $\mathring{A}$) and the solvent system used is in parentheses.

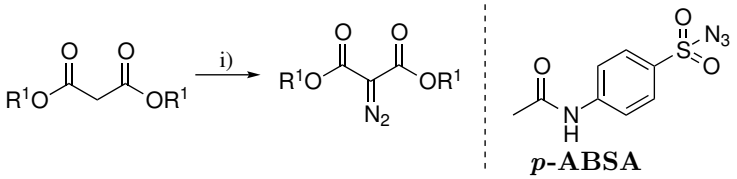
All non-aqueous reactions were carried out in oven-dried glassware sealed with a rubber septum under a positive pressure of dry nitrogen or argon from a manifold or balloon during the course of the reaction. Reactions were stirred using Teflon-coated magnetic stirrer bars. Elevated temperature reactions were maintained using a Thermowatch-controlled DrySyn heating block or oil bath. Reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Dry solvents were purified using standard techniques. Water used experimentally was deionised. Organic solutions were concentrated using a Büchi rotary evaporator with a water bath temperature of 30 °C. Brine

refers to a saturated solution of sodium chloride in water. For the preparation of the pH = 2.0 buffer, concentrated sulfuric acid (28 mL) was carefully added dropwise to a solution of sodium sulfate (213 g, 1.50 mol) in water (2 L). 'Petrol' refers to the fraction of light petroleum ether with a boiling point in the range of 40–60 °C unless otherwise stated. Compound names are generated by ChemDraw Professional 15.1. The relative configuration of the product [3.3.0]-bicyclic-γ-lactones was assigned on the basis of ^{1}H-NMR nOe experiments or by analogy. Where nOe data were not obtained, it was assumed that the [3.3.0]-bicyclic-γ-lactones were *cis*-configured in keeping with those [3.3.0]-bicyclic γ-lactones for which nOe data was readily obtained and from previous precedent.[52,55,60]

6.2 bis-γ-Lactones, Chloro and Alkenyl mono-γ-Lactones

6.2.1 General Procedures

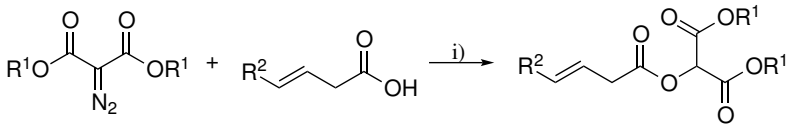
General Procedure 1: Formation of Diazomalonates



Reagents & Conditions: i) *p*-ABSA (1.2 eq.), Et_3N (3.0 eq.), MeCN, 0 °C to r.t.

According to the procedure of Baum *et al.*,[112] Et_3N (3.0 eq) was added at 0 °C to a solution of dialkyl malonate (1.0 eq.) and *p*-ABSA (1.2 eq.) in anhydrous MeCN (0.40 M). The reaction mixture was allowed to react at r.t. for 2 days. A blast shield was used during the reaction. Once the reaction was completed, the solids were filtered off and washed with Et_2O and the solvent was removed under reduced pressure in a water bath at T<20 °C. The residue was further purified by FC (PE_{40-60} / Et_2O).

General Procedure 2: Rh-Catalysed OH-Insertion

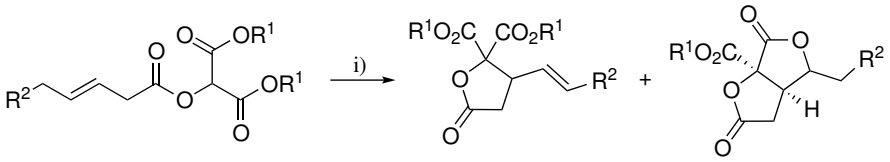


Reagents & Conditions: $Rh_2(OAc)_4$ (6 mol%), benzene, 60 °C, 2 h.

According to the procedure of Maguire *et al.*,[113] $Rh_2(OAc)_4$ (6 mol%) was added to a solution of alkenoic acid (1.0 eq) and diazo alkyl malonate (1.12 eq) in benzene (0.25 M). The reaction mixture was

allowed to reach and react at 60 °C for 2 h. After cooling down the system, volatiles were removed under pressure, giving the residue which was purified by FC (PE_{40-60} / Et_2O).

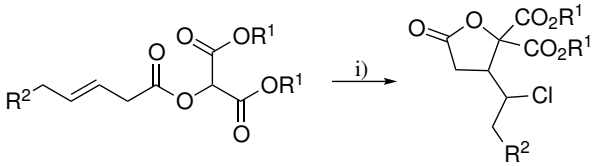
General Procedure 3: Manganese-Based Oxidative Radical Cyclisation



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), MeCN, 40 °C.

To a solution (0.15 M) of the alkene malonate derivative (1.0 eq) in MeCN (previously sparged with Ar for 15 min) were added $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq) and $Cu(OTf)_2$ (1.0 eq). The system was allowed to react at 40 °C overnight. The reaction was quenched with water and extracted with EtOAc. The collected organic fractions were washed with NH_4Cl sat. sol. and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was further purified by FC (PE_{40-60} / EtOAc).

General Procedure 4: Formation of Halo-γ-Lactones through Manganese-Based Oxidative Radical Cyclisation

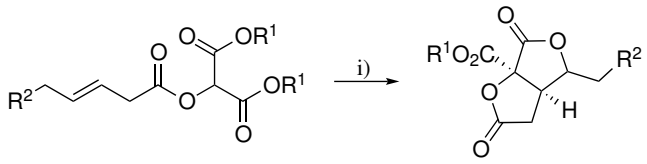


Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), LiCl (1.2 eq.), MeCN, 40 °C.

To a solution (0.15 M) of the alkene malonate derivative (1.0 eq) in MeCN (previously sparged with Ar for 15 min) were added $Mn(OAc)_3 \cdot 2H_2O$ (2.0 eq), $Cu(OTf)_2$ (1.0 eq) and LiCl (1.2 eq). The system was allowed to react at 40 °C for 22 h. The reaction was quenched with water and extracted with EtOAc. The collected organic fractions were then washed with NH_4Cl sat. sol. and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was further purified by FC (PE_{40-60} / EtOAc).

General Procedure 5: Formation of *bis*-γ-Lactones through Iodide-Mediated Manganese-Based Oxidative Radical Cyclisation

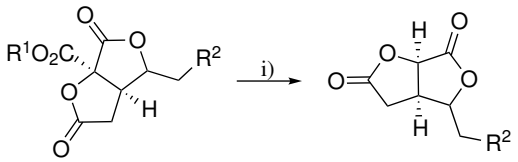
To a solution (0.15 M) of the alkene malonate derivative (1.0 eq) in MeCN (previously sparged with Ar for 15 min) were added $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq) and KI (0.5 eq). The system was allowed to react



Reagents & Conditions: i) $Mn(OAc)_3 \cdot 2H_2O$ (3.0 eq.), KI (0.5 eq.), MeCN, 80 °C.

at 80 °C for 22 h in the absence of light. The reaction was quenched with $Na_2S_2O_3$ sat. solution and extracted with EtOAc. The collected organic fractions were washed with brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was further purified by FC (PE_{40-60} / EtOAc).

General Procedure 6: Dealkoxycarbonylation

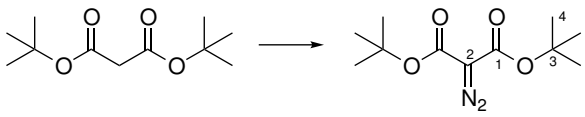


Reagents & Conditions: LiCl (3.5 eq.), DMSO / H_2O, 160 °C.

To a solution of *bis*-lactone (1 eq) in a mixture of DMSO (0.24 M) and H_2O (11.8 M) was added LiCl (3.5 eq). The mixture was left to reach and react at 160 °C for 1 h. The system was diluted with H_2O and extracted with Et_2O (unless otherwise noted). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was used without previous purification (unless otherwise noted).

6.2.2 The Ethisolide Family of Natural Products: Characterisation

di-*tert*-Butyl 2-diazomalonate 240

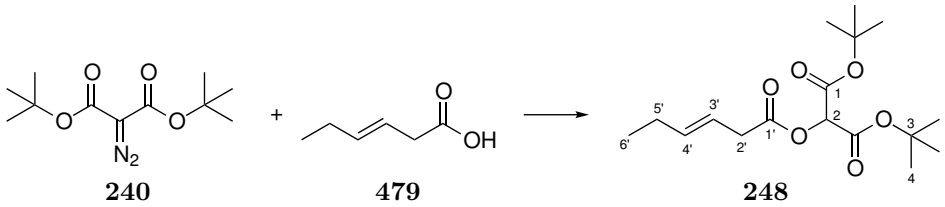


433 **240**

The title compound **240** was synthesised by following the **General Procedure 1** for the formation of diazomalonates. The malonate **433** (5.2 mL, 23.1 mmol), *p*-ABSA (6.7 g, 27.7 mmol), anhydrous Et_3N (9.7 mL, 69.4 mmol) in anydrous MeCN (58 mL) were reacted for 3 days at r.t. The residue was purified by FC (PE_{40-60} / Et_2O, gradient from 8:1 to 4:1), giving the title compound **240** as a yellow

oil (5.5 g, 97% yield). R_f (PE_{40-60} / Et_2O, 4:1) = 0.6; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 1.50 (s, 18 H, C(4)H_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 28.3 (C(4)), 82.7 (C(3)), 160.3 (C(1)) (*note: the diazo carbon was not detected*); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2130m (C=N=N); 1730m (C=O), 1328s (C-O); ***m/z*** LRMS (ESI^+) 507.3 ($[2M+Na]^+$, 100%); Data in accordance with literature values.[172]

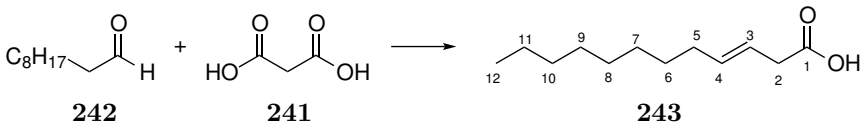
di-*tert*-Butyl (*E*)-2-(hex-3-enoyloxy)malonate 248



240 **479** **248**

The title compound **248** was synthesised by following the **General Procedure 2** for the Rh-catalysed OH insertion. Diazomalonate **240** (3.8 g, 15.5 mmol), *trans*-hexenoic acid **479** (1.6 mL, 13.9 mmol) and $Rh_2(OAc)_4$ (37 mg, 0.08 mmol) in benzene (55 mL) were used. The residue was purified by FC (PE_{40-60} / Et_2O, gradient from 15:1 to 7:1), giving the title compound **248** as a colourless oil (3.9 g, 78% yield). R_f (PE_{40-60} / Et_2O, 7:1) = 0.6; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 0.98 (t, 3 H, J= 7.5 Hz, C(6′)H_3), 1.49 (s, 18 H, C(4)H_3), 2.05 (tquint, 2 H, J= 1.2, 7.4 Hz, C(5′)H_2), 3.20 (dd, 2 H, J= 1.2, 6.7 Hz, C(2′)H_2), 5.32 (s, 1 H, C(2)H), 5.53 (ttd, 1 H, J= 1.5, 6.7, 15.3 Hz, C(3′)H), 5.65 (ttd, 1 H, J= 1.2, 6.2, 15.4 Hz, C(4′)H) ; $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 13.4 (C(6′)), 25.5 (C(5′)), 27.8 (C(4)), 37.3 (C(2′)), 72.9 (C(2)), 83.4 (C(3)), 119.6 (C(3′)), 136.9 (C(4′)), 163.6 (C=O), 170.9 (C=O) ; $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2979w (C-H), 1746s (C=O), 1143s (C-O-C); ***m/z*** LRMS (ESI^+): 351.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 329.19600; $C_{17}H_{28}O_6$ $[M+H]^+$ requires 329.19587.

(*E*)-Dodec-3-enoic acid 243

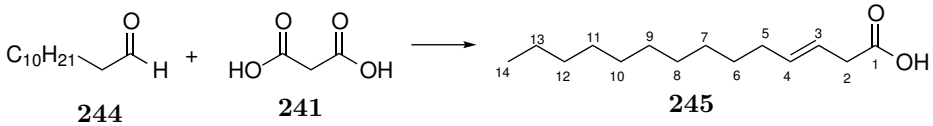


242 **241** **243**

According to the procedure reported by Zhang *et al.*,[114] a solution of malonic acid **241** (2.2 g, 21.1 mmol) and decanal **242** (3.6 mL, 19.2 mmol) in NMM (2.3 mL) was heated to 80 °C and left to react at this temperature for 7 h. H_2SO_4 11% aqueous solution (10 mL) was added to the reaction mixture at r.t. and left to stir for additional 30 min. The system was extracted with DCM (3 x 30 mL) and

the recovered organic layers were washed with H_2O, dried ($MgSO_4$), filtered and concentrated under vacuum. A colourless gel was obtained as residue, which was further used without previous purification (3.5 g, 17.7 mmol, 91% yield). R_f (PE_{40-60} / Et_2O, 4 :1) = 0.6; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 0.88 (t, 3 H, J= 7.0 Hz, C(12)H_3), 1.23-1.38 (m, 12 H, C(6, 7, 8. 9, 10, 11)H_2), 2.03 (q, 2 H, J= 7.4 Hz, C(5)H_2), 3.07 (dd, 2 H, J= 0.9, 6.6 Hz, C(2)H_2), 5.50 (ttd, 1 H, J= 1.2, 6.8, 15.3 Hz, C(3)H), 5.59 (td, 1 H, J= 6.5, 15.3 Hz, C(4)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 14.3 (C(12)), 22.8 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 32.0 (CH_2), 32.6 (C(5)), 37.9 (C(2)), 120.7 (C(3)), 135.8 (C(4)), 178.5 (C=O); ***m/z*** LRMS (ESI^-): 197.2 ([M-H]$^-$, 100%). *Data in accordance with literature values.*[114]

(*E*)-Tetradec-3-enoic acid 245

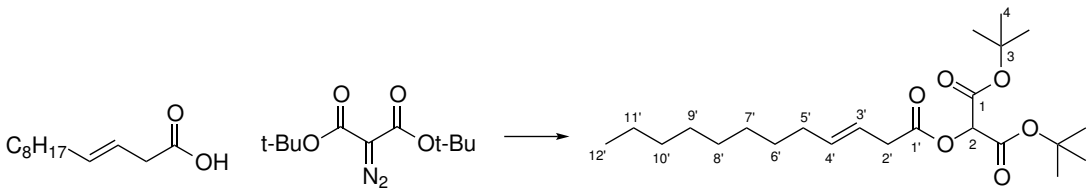


244 **241** **245**

According to the procedure reported by Zhang *et al.*,[114] a solution of malonic acid **241** (4.1 g, 39.6 mmol) and dodecanal **244** (8.0 mL,36.0 mmol) in NMM (4.4 mL) was heated at 80 °C and left to react for 7 h. H_2SO_4 11% aqueous solution (24 mL) was added to the reaction mixture at r.t. and left to stir for additional 30 min. The system was extracted with DCM (3 x 50 mL) and the recovered organic layers were washed with H_2O, dried ($MgSO_4$), filtered and concentrated under vacuum. A colourless gel was obtained as residue, which was further used without previous purification (7.5 g, 33.1 mmol, 92% yield). R_f (PE_{40-60} / Et_2O, 5:1) = 0.2; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 0.88 (t, 3 H, J= 7.1 Hz, C(14)H_3), 1.26-1.38 (m, 16 H, C(6,7,8,9,10,11,12,13)H_2), 2.03 (q, 2 H, J= 6.8 Hz, C(5)H_2), 3.07 (dd, 2 H, J= 1.3, 6.8 Hz, C(2)H_2), 5.50 (tdd, 1 H, J= 1.3, 6.8, 15.3 Hz, C(3)H), 5.59 (tdd, 1 H, J= 1.3, 6.6, 15.3 Hz, C(4)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 14.3 (C(14)), 22.8 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 32.1 (CH_2), 32.6 (C(5)), 37.8 (C(2)), 120.7 (C(3)), 135.8 (C(4)), 177.6 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2922s (O-H), 2853m (C-H), 1710s (C=O); ***m/z*** LRMS (ESI^-): 225.2 ([M-H]$^-$, 100%); HRMS (ESI^-) found 225.18571; $C_{14}H_{26}O_2$ [M-H]$^-$ requires 225.18600.

di-*tert*-Butyl (*E*)-2-(dodec-3-enoyloxy)malonate 251

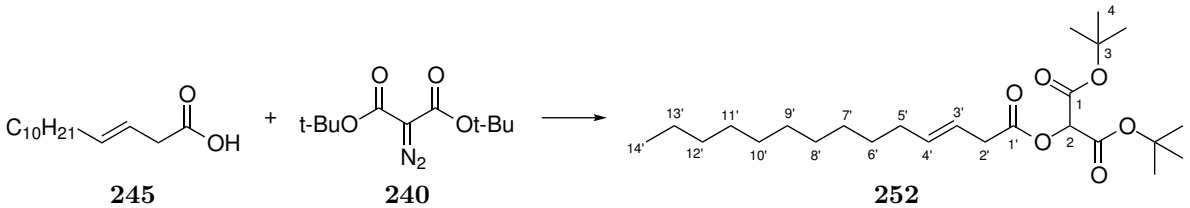
The title compound **251** was synthesised by following the **General Procedure 2** for the Rh-catalysed OH insertion. Diazomalonate **240** (4.4 g, 17.9 mmol), (*E*)-dodec-3-enoic acid **243** (3.2 g, 16.1 mmol) and $Rh_2(OAc)_4$ (43 mg, 0.09 mmol) in benzene (58 mL) were used. The residue was purified by FC



243 **240** **251**

(PE_{40-60} / Et_2O, gradient from 20:1 to 8:1), giving the title compound **251** as a colourless oil (6.0 g, 14.5 mmol, 81% yield). R_f (PE_{40-60} / Et_2O, 10:1) = 0.4; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 0.87 (t, 3 H, J= 7.1 Hz, C(12′)H_3), 1.25-1.36 (m, 12 H, C(6′, 7′, 8′, 9′, 10′, 11′)H_2), 1.49 (s, 18 H, C(4)H_3), 2.02 (q, 2 H, J= 7.1 Hz, C(5′)H_2), 3.19 (dd, 2 H, J= 1.2, 6.5 Hz, C(2′)H_2), 5.32 (s, 1 H, C(2)H), 5.53 (ttd, 1 H, J= 1.2, 6.7, 15.4 Hz, C(3′)H), 5.60 (td, 1 H, J= 6.6, 15.3 Hz, C(4′)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 14.3 (C(12′)), 22.8 (CH_2), 27.9 (C(4)), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 32.0 (CH_2), 32.6 (C(5′)), 37.5 (C(2′)), 73.0 (C(2)), 83.6 (C(3)), 120.6 (C(3′)), 135.8 (C(4′)), 163.7 (C=O), 171.0 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2927m (C-H), 2856w (C-H), 1748s (C=O), 1144s (C-O-C); *m/z* LRMS (ESI^+): 435.3 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 435.27119; $C_{23}H_{40}O_6$ $[M+Na]^+$ requires 435.27171.

di-*tert*-Butyl (*E*)-2-(tetradec-3-enoyloxy)malonate 252

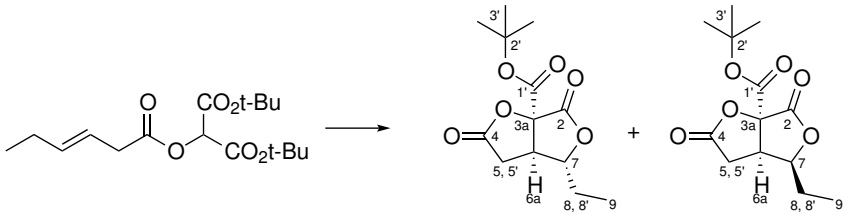


245 **240** **252**

The title compound **252** was synthesised by following the **General Procedure 2** for the Rh-catalysed OH insertion. Diazomalonate **240** (5.1 g, 20.9 mmol), (*E*)-tetradec-3-enoic acid **245** (4.2 g, 18.7 mmol) and $Rh_2(OAc)_4$ (50.0 mg, 0.11 mmol) in benzene (67 mL) were used. The residue was purified by FC (PE_{40-60} / Et_2O, gradient from 20:1 to 7:1), giving the title compound **252** as a yellowish oil (7.2 g, 16.4 mmol, 88% yield). R_f (PE_{40-60} / Et_2O 10:1) = 0.4; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) 0.88 (t, 3 H, J= 7.2 Hz, C(14′)H_3), 1.25-1.36 (m, 16 H, C(6′-13′)H_2), 1.49 (s, 18 H, C(4)H_3), 2.02 (q, 2 H, J= 7.4 Hz, C(5′)H_2), 3.18 (dd, 2 H, J= 0.9, 6.5 Hz, C(2′)H_2), 5.32 (s, 1 H, C(2)H), 5.52 (ttd, 1 H, J= 1.3, 6.8, 15.4 Hz, C(3′)H), 5.60 (ttd, 1 H, J= 1.2, 6.6, 15.4 Hz, C(4′)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) 14.3 (C(14′)), 22.8 (CH_2), 28.0 (C(4)), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 32.1 (CH_2), 32.7 (C(5′)), 37.5 (C(2′)), 73.0 (C(2)), 83.6 (C(3)), 120.6 (C(3′)), 135.8 (C(4′)), 163.7 (C=O),

171.0 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2925m (C-H), 1747s (C=O), 1142s (C-O-C) ; ***m/z*** LRMS (ESI$^+$): 463.2 ([M+Na]$^+$; 100%) HRMS (ESI$^+$) found 463.30211; $C_{25}H_{44}O_6$ [M+Na]$^+$ requires 463.30301.

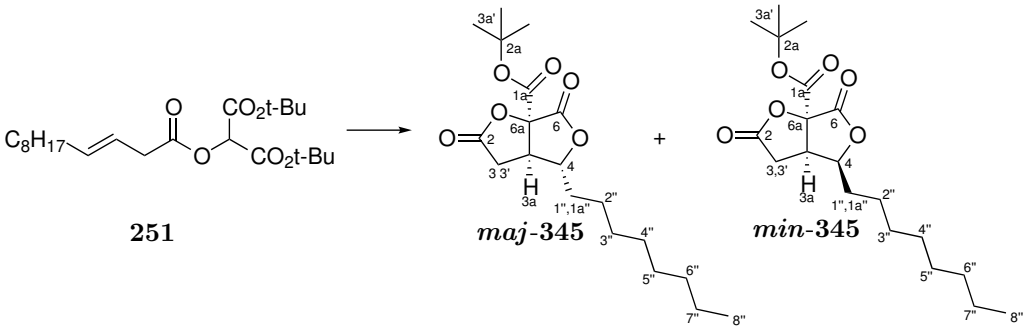
***tert*-Butyl (3a*R*,4*R*,6a*R*)-4-ethyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate *maj*-255** and ***tert*-butyl (3a*R*,4*S*,6a*R*)-4-ethyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate *min*-255**



248 ***maj*-255** ***min*-255**

The title compounds **255** were synthesised by following the **General Procedure 5** for the formation of *bis*-lactones. Alkenyl malonate **248** (0.50 g, 1.52 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (1.22 g, 4.57 mmol) and KI (0.13 g, 0.76 mmol) in MeCN (10.0 mL) were used. The residue was purified by FC (PE_{40-60} / EtOAc, gradient from 3:1 to 1:1), giving the title compounds **255** as a yellowish solid (0.32 g, 1.17 mmol, 77% yield, inseparable mixture of diastereoisomers 2.8:1 *dr*). R_f (PE_{40-60} / EtOAc, 1:1) = 0.7; *m.p.* = 110-114 °C; $\boldsymbol{\delta_H}$ (500 MHz MHz, $CDCl_3$) ***maj*-255**: 1.08 (t, 3 H, *J*= 7.4 Hz, C(9)H_3), 1.54 (s, 9 H, C(3′)H_3), 1.58-1.65 (m, 1 H, C(8)H), 1.80-1.94 (m, 1 H, C(8′)H), 2.68 (dd, 1 H, *J*= 9.1, 18.3 Hz, C(5)H), 2.75 (dd, 1 H, *J*= 9.9, 18.3 Hz, C(5′)H), 3.40 (m, 1 H, C(6a)H), 4.69 (td, 1 H, *J*= 6.0, 8.5 Hz, C(7)H); ***min*-255**: 1.07 (t, 3 H, *J*= 7.4 Hz, C(9)H_3), 1.53 (s, 9 H, C(3′)H_3), 1.58-1.65 (m, 1 H, C(8)H), 1.80-1.94 (m, 1 H, C(8′)H), 2.57 (dd, 1 H, *J*= 2.4, 18.3 Hz, C(5)H), 2.97 (dd, 1 H, *J*= 9.4, 18.3 Hz, C(5′)H), 3.06 (ddd, 1 H, *J*= 2.3, 5.9, 9.3 Hz, C(6a)H), 4.21 (td, 1 H, *J*= 5.9, 6.9 Hz, C(7)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) ***maj*-255**: 10.1 (C(9)), 27.9 (C(8 or 5)), 28.0 (C(3′)), 28.1 C(5 or 8)), 44.2 (C(6a)), 80.7 (C(7)), 86.2 (C(2′)), 163.9 (C=O),168.4 (C=O), 172.2 (C=O); ***min*-255**: 9.3 (C(9)), 24.5 (C(8)), 27.9 (C(3′)), 33.3 (C(5)), 44.8 (C(6a)), 85.9 (C(7)), 85.5 (C(2′)), 164.7 (C=O), 167.3 (C=O), 172.6 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 1787s (C=O), 1759m (C=O), 1108m (C-O-C); ***m/z*** LRMS (ESI$^+$): 563.2 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) found 563.20947; $C_{13}H_{18}O_6$ [2M+Na]$^+$ requires 563.20990.

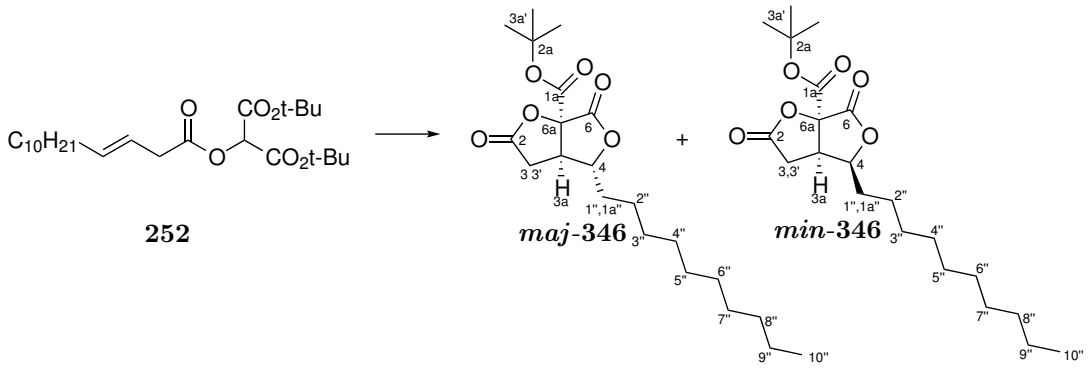
***tert*-Butyl (3a*R*,4*R*,6a*R*)-4-octyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate *maj*-345** and ***tert*-butyl (3a*R*,4*S*,6a*R*)-4-octyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate *min*-345**



The title compounds **345** have been synthesised by following the **General Procedure 5** for the synthesis of *bis*-lactones. Alkenyl malonate **251** (4.9 g, 11.97 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (9.6 g, 35.92 mmol), and KI (0.9 g, 5.99 mmol) were used in MeCN (80.0 mL). The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 12:1 to 1:1), giving the title compounds **345** as a yellowish solid (3.07 g, 8.66 mmol, 72% yield, inseparable mixture of diastereoisomers 2.3:1 *dr*). R_f (PE_{40-60}/ EtOAc, 8:1) = 0.2; *m.p.*= 70-72 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): ***maj*-345**: 0.87 (t, 3 H, *J*= 7.1 Hz, C(8″)H_3), 1.25-1.43 (m, 12 H, C(2″-7″)H_2), 1.51 (s, 9 H, C(3a′)H_3), 1.71-1.78 (m, 1 H, C(1″)H), 1.81-1.89 (m, 1 H, C(1a″)H), 2.58 (dd, 1 H, *J*= 2.5, 18.3 Hz, C(3)H), 2.96 (dd, 1 H, *J*= 9.5, 18.3 Hz, C(3′)H), 3.05 (ddd, 1H, *J*= 2.4, 5.6, 9.3 Hz, C(3a)H), 4.27 (td, 1 H, *J*= 5.6, 7.6 Hz, C(4)H); ***min*-345**: 0.87 (t, 3 H, *J*= 7.1 Hz, C(8″)H_3), 1.25-1.43 (m, 12 H, C(2″-7″)H_2), 1.52 (s, 3 H, C(3a′)H_3), 1.71-1.78 (m, 1 H, C(1″)H), 1.81-1.89 (m, 1 H, C(1a″)H), 2.68 (dd, 1 H, *J*= 9.1, 18.3 Hz, C(3)H), 2.74 (dd, 1 H, *J*= 9.8, 18.3 Hz, C(3′)H), 3.40 (ddd, 1 H, *J*= 5.8, 9.1, 9.7 Hz, C(3a)H), 4.74 (td, 1 H, *J*= 5.4, 8.6 Hz, C(4)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): ***maj*-345**: 14.2 (C(8″)), 22.7 (CH_2), 25.0 (CH_2), 27.9 (C(3a′)), 29.2 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 33.3 (C(3,3′)), 35.1 (C(1″,1a″)), 45.1 (C(3a)), 85.8 (C(4)), 84.8 (C), 85.0 (C), 164.7 (C=O), 167.5 (C=O), 172.8 (C=O); ***min*-345**: 14.2 (C(8″)), 22.7 (CH_2), 25.7 (CH_2), 28.0 (C(3a′)), 28.0 (C(3,3′)), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.1 (C(1″,1a″)), 31.8 (CH_2), 44.3 (C(3a)), 79.6 (C(4)), 85.4 (C), 86.0 (C), 163.9 (C=O), 168.5 (C=O), 172.4 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2929m (C-H), 2957w (C-H), 1789s (C=O), 1759s (C=O); ***m/z*** LRMS (ESI^+): 377.2 ($[M+Na]^+$, 100%) ; HRMS (ESI^+) found 377.19313; $C_{19}H_{30}O_6$ $[M+Na]^+$ requires 377.19346.

tert-Butyl (3a*R*,4*R*,6a*R*)-4-decyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate *maj*-346 and *tert*-butyl (3a*R*,4*S*,6a*R*)-4-decyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate *min*-346

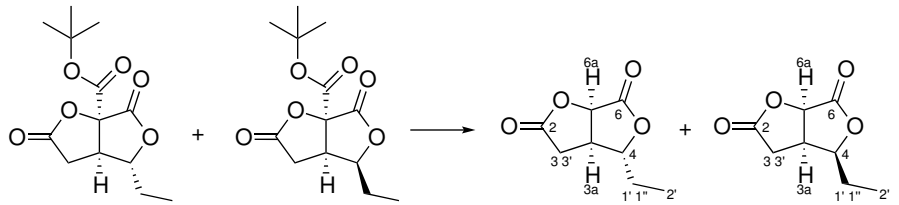
The title compounds **346** have been synthesised by following the **General Procedure 5** for the synthesis of *bis*-lactones. Alkenyl malonate **252** (5.09 g, 11.56 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (9.30 g, 34.67 mmol) and



KI (0.96 g, 5.78 mmol) were used in MeCN (77.0 mL). The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 14:1 to 5:1), giving the title compounds **346** as a yellowish solid (3.28 g, 8.58 mmol, 74% yield, inseparable mixture of diastereoisomers 1.7:1 *dr*). R_f (PE_{40-60} / EtOAc, 8:1) = 0.2; *m.p.* = 83-88 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): ***maj*-346**: 0.88 (t, 3 H, *J*= 7.2 Hz, C(10″)H_3), 1.26-1.53 (m, 16 H, C(2″-9″)H_2), 1.53 (s, 9 H, C(3a′)H_3), 1.71-1.78 (m, 1 H, C(1″)H), 1.83-1.91 (m, 1 H, C(1a″)H), 2.56 (dd, 1 H, *J*= 2.3, 18.2 Hz, C(3)H), 2.96 (dd, 1 H, *J*= 9.4, 18.2 Hz, C(3′)H), 3.04 (ddd, 1 H, *J*= 2.3, 5.9, 9.3 Hz, C(3a)H), 4.24 (td, 1 H, *J*= 5.7, 7.8 Hz, C(4)H); ***min*-346**: 0.88 (t, 3 H, *J*= 7.2 Hz, C(10″)H_3), 1.26-1.53 (m, 16 H, C(2″-9″)H_2), 1.54 (s, 9 H, C(3a′)H_3), 1.71-1.78 (m, 1 H, C(1″)H), 1.83-1.91 (m, 1 H, C(1a″)H), 2.68 (dd, 1 H, *J*= 9.2, 18.3 Hz, C(3)H), 2.74 (dd, 1 H, *J*= 9.8, 18.3 Hz, C(3′)H), 3.38 (dt, 1 H, *J*= 5.7, 9.5 Hz, C(3a)H), 4.75 (td, 1 H, *J*= 5.5, 8.8 Hz, C(4)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): ***maj*-346**: 14.3 (C(10″)), 22.8 (CH_2), 25.1 (CH_2), 28.0 (C(3a′)), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 33.3 (C(3,3′)), 35.2 (C(1″,1a″)), 45.3 (C(3a)), 84.8 (C(4)), 84.9 (C), 85.9 (C), 164.7 (C=O), 167.3 (C=O), 172.6 (C=O); ***min*-346**: 14.3 (C(10″)), 22.8 (CH_2), 25.7 (CH_2), 27.8 (CH_2), 28.0 (C(3a′)), 28.0 (C(3,3′)), 29.4 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 31.2 (C(1″,1a″)), 32.0 (CH_2), 44.4 (C(3a)), 79.5 (C(4)), 85.4 (C), 86.1 (C), 164.0 (C=O), 168.4 (C=O), 172.2 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2926m (C-H), 2855w (C-H),1789s (C=O), 1759m (C=O); ***m/z*** LRMS (ESI^+): 405.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 405.22464; $C_{21}H_{34}O_6$ $[M+Na]^+$ requires 405.22476. .

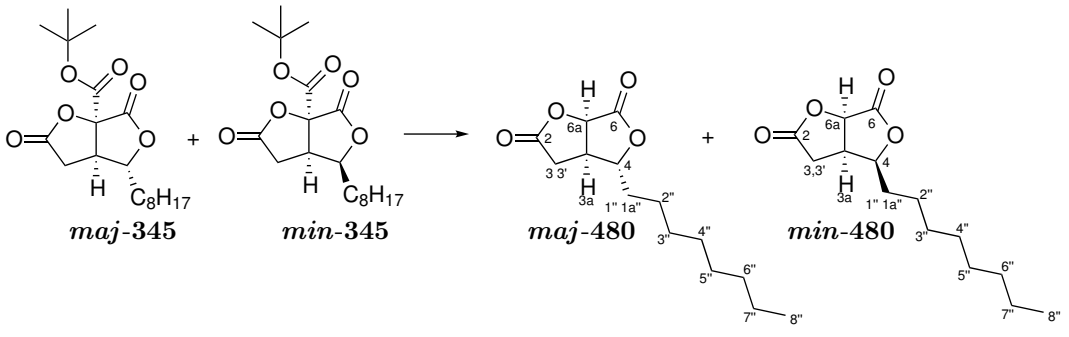
(3a*R*,4*R*,6a*R*)-4-Ethyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione *maj*-337 and (3a*R*,4*S*,6a*R*)-4-ethyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione *min*-337

The title compounds **337** have been synthesised by following the **General Procedure 6**. The *bis*-lactones **255** (3.95 g, 14.61 mmol), LiCl (2.17 g, 51.15 mmol) in DMSO (60.0 mL) and H_2O (1.25 mL) were used. The work-up extraction was made with EtOAc (4 x 75 mL). The residue was purified by FC (PE_{40-60} / EtOAc, gradient from 3:1 to 1:1), giving the title compounds **337** as a yellowish liquid (2.08



mg, 12.22 mmol, 80% yield, inseparable mixture of diastereoisomers 2.03:1 *dr*). R_f (PE_{40-60} / EtOAc, 2:1) = 0.2; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): ***maj*-337**: 1.05 (t, 3 H, J= 7.5 Hz, C(2′)H_3), 1.79 (ddq, 1 H, J= 3.4, 5.9, 7.3 Hz, C(1′)H), 1.81 (dqd, 1 H, J= 4.7, 7.5, 10.5 Hz, C(1″)H), 2.56 (dd, 1 H, J= 4.1, 18.2 Hz, C(3)H), 2.95 (dd, 1 H, J= 9.5, 18.2 Hz, C(3′)H), 3.05 (m, 1 H, C(3a)H), 4.30 (ddd, 1 H, J= 4.8, 5.9, 6.9 Hz, C(4)H), 5.01 (d, 1 H, J= 7.8 Hz, C(6a)H); ***min*-337**: 1.07 (t, 3 H, J= 7.5 Hz, C(2′)H_3), 1.63 (dqd, 1 H, J= 6.1, 7.4, 10.9 Hz, C(1′)H), 1.89 (sept, 1 H, J= 7.4 Hz, C(1″)H), 2.63 (dd, 1 H, J= 9.5, 18.2 Hz, C(3)H), 2.64 (d, 1 H, J= 9.5, 18.2 Hz, C(3′)H), 3.44-3.53 (m, 1 H, C(3a)H), 4.55 (td, 1 H, J= 5.9, 8.3 Hz, C(4)H), 5.16 (d, 1 H, J= 8.4 Hz, C(6a)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): ***maj*-337**: 9.3 (C(2′)), 24.8 (C(1′,1″)), 33.0 (C(3,3′)), 39.9 (C(3a)), 77.1 (C(6a)), 86.0 (C(4)), 169.9 (C=O), 173.6 (C=O); ***min*-337**: 9.9 (C(2′)), 24.8 (C(1′,1″), 26.9 (C(3,3′)), 39.3 (C(3a)), 77.1 (C(6a)), 80.1 (C(4)), 170.5 (C=O), 173.7 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2973w (C-H), 1777s (C=O), 1212m (C-O-C), 1150m (C-O-C), 1069m (C-O-C); ***m/z*** LRMS (ESI^+): 363.0 ($[2M+Na]^+$, 40%); HRMS (ESI^+) found 363.10498; $C_8H_{10}O_4$ $[2M+Na]^+$ requires 363.10504.

(3a*R*,4*R*,6a*R*)-4-Octyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione *maj*-480 and
(3a*R*,4*S*,6a*R*)-4-octyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione *min*-480

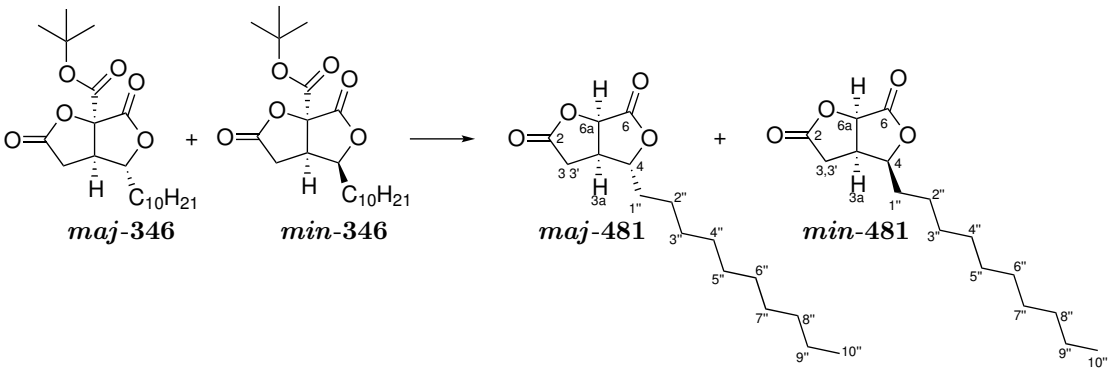


The title compounds **480** have been synthesised by following the **General Procedure 6**. *bis*-Lactones **345** (350 mg, 0.99 mmol), LiCl (147 mg, 3.46 mmol) were used in DMSO (6.6 mL) / H_2O (0.08 mL). A brown oil was obtained as crude which was used without previous purification (194 mg, 0.76 mmol, 77%

yield, inseparable mixture of diastereoisomers 2.23:1 *dr*). R_f (PE_{40-60} / EtOAc, 5:1) = 0.16, 0.22; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): ***maj*-480**: 0.88 (t, 3 H, J= 7.1 Hz, C(8″)H_3), 1.25-1.84 (m, 14 H, C(1″-7″)H_2), 2.55 (dd, 1 H, J= 4.1, 18.2 Hz, C(3)H), 2.94 (dd, 1 H, J= 9.4, 18.2 Hz, C(3′)H), 3.04 (dddd, 1 H, J= 4.1, 4.9, 7.9, 9.4 Hz, C(3a)H), 4.34 (td, 1 H, J= 5.2, 7.6 Hz, C(4)H), 5.01 (d, 1 H, J= 7.9 Hz, C(6a)H); ***min*-480**: 0.88 (t, 3 H, J= 7.1 Hz, C(8″)H_3), 1.25-1.84 (m, 14 H, C(1″-7″)H_2), 2.63 (s apparent, 1 H, C(3)H), 2.64 (s apparent, 1 H, C(3′)H), 3.46 (ddt, 1 H, J= 5.7, 8.4, 9.6 Hz, C(3a)H), 4.60 (td, 1 H, J= 5.7, 8.7 Hz, C(4)H), 5.16 (d, 1 H, J= 8.4 Hz, C(6a)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): ***maj*-480**: 14.2 (C(8″)), 22.8 (CH_2), 25.1 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 32.9 (C(3,3′)), 35.6 (C(1″,1a″)H_2), 40.4 (C(3a)), 77.1 (C(6a)), 84.9 (C(4)), 169.9 (C=O), 173.6 (C=O); ***min*-480**: 14.2 (C(8″)), 22.8 (CH_2), 25.6 (CH_2), 27.0 (C(3,3′)), 29.3 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.6 (C(1″,1a″)), 31.9 (CH_2), 39.6 (C(3a)), 77.1 (C(6a)), 78.8 (C(4)), 170.6 (C=O), 173.7 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2925m (C-H), 2856w (C-H), 1781s (C=O), 1216w (C-O-C), 1150w (C-O-C); ***m/z*** LRMS (ESI^+): 531.4 ($[2M+Na]^+$, 100%); HRMS (ESI^+) found 277.14117; $C_{14}H_{22}O_4$ $[M+Na]^+$ requires 277.14103.

(3a*R*,4*R*,6a*R*)-4-Decyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione *maj*-481 and

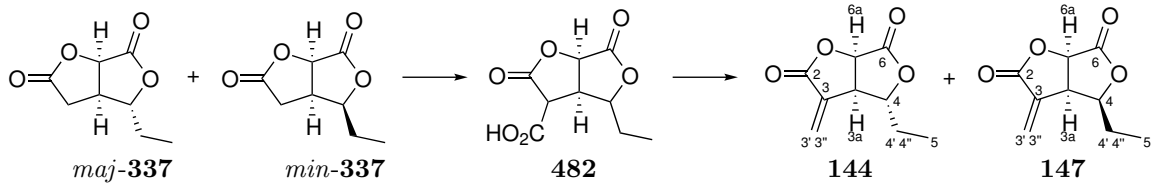
(3a*R*,4*S*,6a*R*)-4-decyldihydrofuro[3,4-b]furan-2,6(3*H*,4*H*)-dione *min*-481



The title compounds **481** have been synthesised by following the **General Procedure 6**. *bis*-Lactones **346** (3.28 g, 8.58 mmol), LiCl (1.27 g, 30.01 mmol) in DMSO (36.0 mL) and H_2O (0.73 mL) were used. A brown oil was obtained as crude which was used without previous purification (2.33 g, 8.25 mmol, 96%, inseparable mixture of diastereoisomers 2.23:1 *dr*). R_f (PE_{40-60} / EtOAc, 1:1) = 0.6, 0.7; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): ***maj*-481**: 0.88 (t, 3 H, J= 7.1 Hz, C(10″)H_3), 1.26-1.85 (m, 18 H, C(1″-9″)H), 2.55 (dd, 1 H, J= 4.1, 18.2 Hz, C(3)H), 2.94 (dd, 1 H, J= 9.4, 18.2 Hz, C(3′)H), 3.03 (ddd, 1 H, J= 4.3, 7.8, 11.9 Hz, C(3a)H), 4.34 (td, 1 H, J= 5.2, 7.7 Hz, C(4)H), 5.00 (d, 1 H, J= 7.7 Hz, C(6a)H); ***min*-481**: 0.88 (t, 3 H, J= 7.1 Hz, C(10″)H_3), 1.26-1.85 (m, 18 H, C(1″-9″)H), 2.63 (d, 2 H, J= 9.5 Hz, C(3,3′)H_2),

3.46 (ddt, 1 H, J= 5.7, 8.4, 9.5 Hz, C(3a)H), 4.60 (td, 1 H, J= 5.7, 8.7 Hz, C(4)H), 5.15 (d, 1 H, J= 8.4 Hz, C(6a)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): ***maj*-481**: 14.3 (C(10″)), 22.8 (CH_2), 25.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 32.9 (C(3,3′)), 35.6 (CH_2), 40.4 (C(3a)), 77.1 (C(6a)), 84.9 (C(4)), 173.6 (C=O), 173.7 (C=O); ***min*-481**: 14.3 (C(10″)), 22.8 (CH_2), 25.6 (CH_2), 27.0 (C(3,3′)), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.5 (CH_2), 32.0 (CH_2), 39.6 (C(3a)), 77.1 (C(6a)), 78.8 (C(4)), 169.9 (C=O), 170.6 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2922m (C-H), 2854 (C-H), 1780s (C=O), 1214 (C-O-C), 1151 (C-O-C), 1074 (C-O-C); ***m/z*** HRMS (ESI^+) found 305.17230; $C_{16}H_{26}O_4$ $[M+Na]^+$ requires 305.17233.

***epi*-Ethisolide** (major) **144** and **ethisolide** (minor) **147**



maj-**337** *min*-**337** **482** **144** **147**

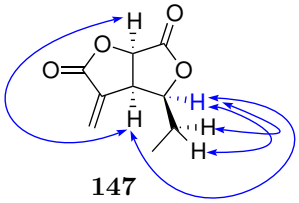
According to the procedure reported by Parker and Johnson,[77] to a solution of *bis*-lactones **337** (0.1 g, 0.59 mmol) in anhydrous DMF (2.9 mL) was added $MeOMgOCO_2Me$ (Stile's reagent 2.0 M in DMF, 1.8 mL, 3.53 mmol). The mixture was left to reach and react at 120 °C for 5 h. After cooling down, the reaction mixture was quenched with HCl 6 N (40 mL) at 0 °C and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The acid crude **482** was further engaged in the following reaction without previous purification.

The acid intermediate **482** was treated with a stock solution (0.65 mL; prepared by combining a solution of AcOH (4 mL) and NaOAc (0.105 g) with a solution of formalin (2.9 mL) and Et_2NH (1.0 mL)). The mixture was stirred vigorously at r.t. until the carbon dioxide evolution ceased. The solution was then heated to 100 °C for 10 min, cooled and diluted in H_2O. The mixture was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with $NaHCO_3$ sat. sol. and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude (4.3:1 *dr*) was purified by FC (PE_{40-60} / EtOAc, gradient from 2:1 to 1:2), giving the title compounds as white solids (*epi*-ethisolide **144**: 34 mg, 0.19 mmol, 34% yield and ethisolide **147**: 3.6 mg, 0.02 mmol, 18% yield).

***epi*-ethisolide 144**: R_f (PE_{40-60} / EtOAc, 1:1) = 0.6; *m.p.* = 53-58 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.08 (t, 3 H, J= 7.5 Hz, C(5)H_3), 1.85 (dq, 1 H, J= 0.6, 7.0 Hz, C(4′)H), 1.87 (dq, 1 H, J= 0.9, 7.4 Hz, C(4″)H), 3.58 (tdd, 1 H, J= 2.4, 3.9, 8.6 Hz, C(3a)H), 4.39 (dt, 1 H, J= 3.9, 6.5 Hz, C(4)H), 5.06 (dd,

1 H, J= 0.3, 8.9 Hz, C(6a)H), 5.88 (d, 1 H, J= 2.2 Hz, C(3′)H), 6.47 (d, 1 H, J= 2.5 Hz, C(3″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 9.2 (C(5)), 29.1 (C(4′,4″)), 43.8 (C(3a)), 74.4 (C(6a)), 86.4 (C(4)), 126.5 (C(3′, 3″), 134.7 (C(3)), 167.6 (C=O), 169.9 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2973w (C-H), 1771s (C=O), 1293m (C-O-C), 1216m (C-O-C), 1099m (C-O-C), 1059m (C-O-C); ***m/z*** LRMS (ESI$^+$): 183.0 ([M+H]$^+$, 100%), 205.0 ([M+Na]$^+$, 30%); HRMS (ESI$^+$) found 205.04734; $C_9H_{10}O_4$ [M+Na]$^+$ requires 205.04713.

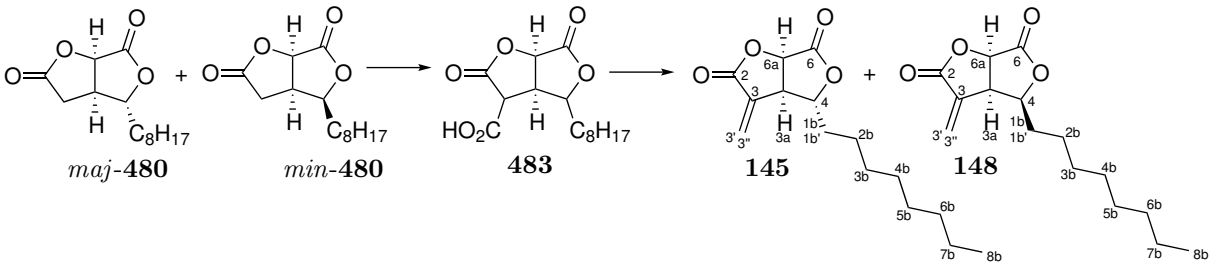
ethisolide 147: R_f (PE_{40-60} / EtOAc, 1:1) = 0.3; *m.p.* = 94-101 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.12 (t, 3 H, J= 7.3 Hz, C(5)H_3), 1.55-1.64 (m, 1 H, C(4′)H), 1.72-1.80 (m, 1 H, C(4″)H), 4.00 (tt, 1 H, J= 2.5, 8.3 Hz, C(3a)H), 4.68 (ddd, 1 H, J= 3.8, 7.9, 10.1 Hz, C(4)H), 5.11 (d, 1 H, J= 8.8 Hz, C(6a)H), 5.88 (d, 1 H, J= 2.3 Hz, C(3′)H), 6.60 (d, 1 H, J= 2.7 Hz, C(3″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 10.8 (C(5)), 25.9 (C(4′,4″)), 41.8 (C(3a)), 74.9 (C(6a)), 81.9 (C(4)), 129.0 (C(3′,3″)), 130.9 (C(3)), 167.9 (C=O), 170.0 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2973w (C-H), 1772s (C=O), 1208m (C-O-C); ***m/z*** HRMS (ESI$^+$) found 205.04738; $C_9H_{10}O_4$ [M+Na]$^+$ requires 205.04713.



147

key nOe interactions

Avenaciolide (major) **145** and ***iso*-avenaciolide** (minor) **148**

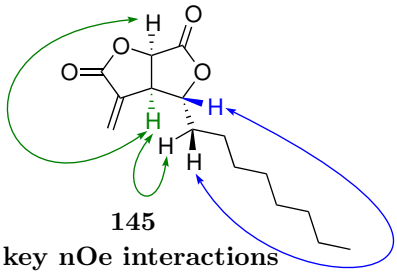


maj-**480** *min*-**480** **483** **145** **148**

According to the procedure reported by Parker and Johnson,[77] to a solution of *bis*-lactones **480** (1.65 g, 6.49 mmol) in anhydrous DMF (15 mL) was added $MeOMgOCO_2Me$ (Stile's reagent 2.0 M in DMF, 20.0 mL, 38.9 mmol). The mixture was left to reach and react at 120 °C for 5 h. After cooling down, the reaction mixture was quenched with HCl 6 N (400 mL) at 0 °C and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude **483** was further engaged in the following reaction without previous purification.

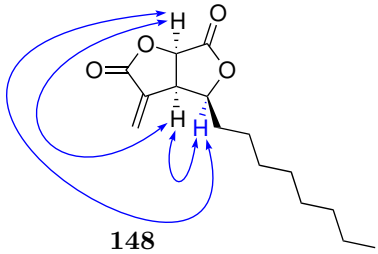
The acid **483** was treated with a stock solution (7.20 mL; prepared by combining a solution of AcOH (10 mL) and NaOAc (0.263 g) with a solution of formalin (7.25 mL) and Et_2NH (2.5 mL)). The mixture was stirred vigorously at r.t. until the carbon dioxide evolution ceased. The solution was then heated to 100 °C for 10 min, cooled and diluted in H_2O. The mixture was extracted with EtOAc (3 x 150 mL) and the combined organic layers were washed with $NaHCO_3$ sat. sol. and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude (7.3:1 *dr*) was purified by FC (PE_{40-60}/ EtOAc, gradient from 3:1 to 1:2), giving the title compounds as white solids (avenaciolide **145**: 510 mg, 1.91 mmol, 34% yield; *iso*-avenaciolide **148**: 51 mg, 0.19 mmol, 26% yield).

avenaciolide 145: R_f (PE_{40-60} / EtOAc, 2:1) = 0.7; *m.p.* = 51-56 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 0.88 (t, 3 H, J= 7.1 Hz, C(8b)H_3), 1.27-1.53 (m, 12 H, C(2b-7b)H_2), 1.75-1.86 (m, 2 H, C(1b)H and C(1b′)H), 3.53-3.57 (m, 1 H, C(3a)H), 4.42 (ddd, 1 H, J= 3.9, 5.9, 7.4 Hz, C(4)H), 5.05 (d, 1 H, J= 8.5 Hz, C(6a)H), 5.87 (d, 1 H, J= 2.2 Hz, C(3′)H), 6.48 (d, 1 H, J= 2.5 Hz, C(3″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 14.2 (C(8b)), 22.8 (CH_2), 24.9 (CH_2), 29.3 (2 x CH_2), 29.5 (CH_2), 31.9 (CH_2), 36.2 (C(1b,1b′)), 44.3 (C(3a)), 74.4 (C(6a)), 85.2 (C(4)), 126.4 (C(3′,3″)), 134.7 (C(3)), 167.6 (C=O), 169.8 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2927m (C-H), 2856w (C-H), 1779s (C=O), 1294w, 1218w, 1105w, 1062w; ***m/z*** HRMS (ESI^+) found 267.15937; $C_{15}H_{22}O_4$ $[M+H]^+$ requires 267.15909.



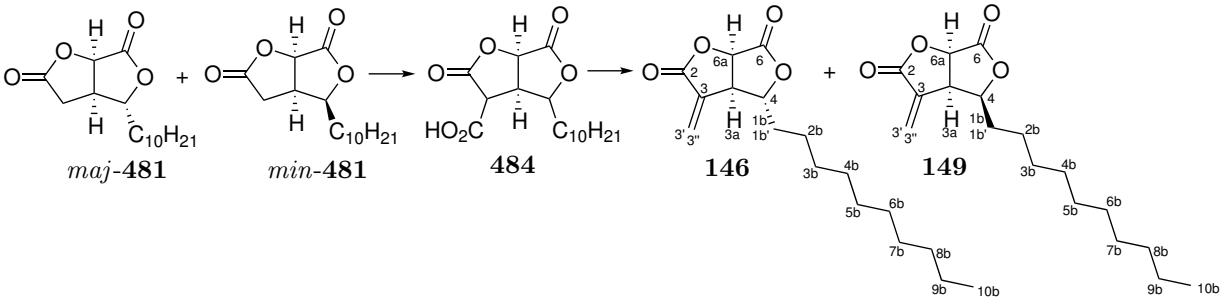
145
key nOe interactions

iso*-avenaciolide 148**: R_f (PE_{40-60} / EtOAc, 2:1) = 0.3; *m.p.* = 95-100 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 0.88 (t, 3 H, J= 7.1 Hz, C(8b)H_3), 1.26-1.45 (m, 12 H C(2b-7b)H_2), 1.59-1.71 (m, 2 H, C(1b)H and C(1b′)H), 3.99 (tt, 1 H, J= 2.4, 8.5 Hz, C(3a)H), 4.76 (ddd, 1 H, J= 3.4, 7.9, 10.0 Hz, C(4)H), 5.11 (d, 1 H, J= 8.8 Hz, C(6a)H), 5.88 (d, 1 H, J= 2.3 Hz, C(3′)H), 6.60 (d, 1 H, J= 2.7 Hz, C(3″)H) ; $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 14.2 (C(8b)), 22.8 (CH_2), 26.2 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 32.5 (C(1b,1b′)), 41.9 (C(3a)), 74.9 (C(6a)), 80.6 (C(4)), 129.1 (C(3′,3″)), 130.9 (C(3)), 167.9 (C=O), 170.1 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2924w (C-H), 2854w (C-H), 1767 (C=O), 1218m (C-O-C), 1053m (C-O-C); ***m/z LRMS (ESI^+): 289.0 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 289.14135; $C_{15}H_{22}O_4$ $[M+Na]^+$ requires 289.14103.



148
key nOe interactions

Discosiolide (major) **146** and ***iso*-discosiolide** (minor) **149**



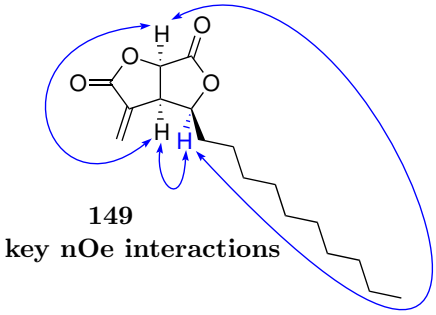
According to the procedure reported by Parker and Johnson,[77] to a solution of *bis*-lactones **481** (1.62 g, 5.74 mmol) in anhydrous DMF (15.0 mL) was added $MeOMgOCO_2Me$ (Stile's reagent 2.0 M in DMF, 17.0 mL, 34.4 mmol). The mixture was left to reach and react at 120 °C for 5 h. After cooling down, the reaction mixture was quenched with HCl 6 N (300 mL) at 0 °C and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude **484** was further engaged in the following reaction without previous purification.

The acid **484** was treated with a stock solution (6.40 mL, prepared by combining a solution of AcOH (10 mL) and NaOAc (0.263 g) with a solution of formalin (7.25 mL) and Et_2NH (2.5 mL)). The mixture was stirred vigorously at r.t. until the carbon dioxide evolution ceased. The solution was then heated to 100 °C for 10 min, cooled and diluted in H_2O. The mixture was extracted with EtOAc (3 x 200 mL) and the combined organic layers were washed with $NaHCO_3$ sat. sol. and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude (9:1 *dr*) was purified by FC (PE_{40-60} / EtOAc, gradient from 3:1 to 1:1), giving the title compounds as white solids (discosiolide **146** (420 mg, 1.43 mmol, 28% yield) and *iso*-discosiolide **149** (17 mg, 0.06 mmol, 10% yield).

discosiolide 146: R_f (PE_{40-60} / EtOAc, 2:1) = 0.8; *m.p.* = 53-60 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 0.88 (t, 3 H, J= 7.2 Hz, C(10b)H_3), 1.27-1.50 (m, 16 H, C(2b-9b)H_2), 1.75-1.86 (m, 2 H, C(1b)H and C(1b′)H), 3.55 (tdd, 1 H, J= 2.3, 4.3, 8.5 Hz, C(3a)H), 4.43 (ddd, 1 H, J= 3.9, 5.9, 7.3 Hz, C(4)H),

5.05 (d, 1 H, J= 8.5 Hz, C(6a)H), 5.87 (d, 1 H, J= 2.2 Hz, C(3′)H), 6.48 (dd, 1 H, J= 2.5 Hz, C(3″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 14.3 (C(10b)), 22.8 (CH_2), 24.9 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 36.3 (C(1b,1b′)), 44.4 (C(3a)), 74.4 (C(6a)), 85.2 (C(4)), 126.4 (C(3′,3″)), 134.7 (C(3)), 167.6 (C=O), 169.8 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2924m (C-H), 2854m, 1780s (C=O); ***m/z*** HRMS (ESI^+) found 295.19097; $C_{17}H_{26}O_4$ $[M+H]^+$ requires 295.19039.

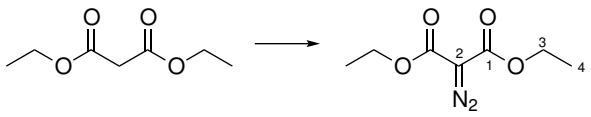
iso*-discosiolide 149**: R_f (PE_{40-60}/ EtOAc, 2:1) = 0.3; *m.p.* = 85-91 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 0.88 (t, 3 H, J= 7.1 Hz, C(10b)H_3), 1.26-1.69 (m, 18 H, C(1b-9b)H_2), 3.98 (tt, 1 H, J= 2.4, 8.5 Hz, C(3a)H), 4.75 (ddd, 1 H, J= 3.5, 8.0, 10.2 Hz, C(4)H), 5.10 (d, 1 H, J= 8.7 Hz, C(6a)H), 5.88 (d, 1 H, J= 2.3 Hz, C(3′)H), 6.61 (d, 1 H, J= 2.6 Hz, C(3″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 14.3 (C(10b), 22.8 (CH_2), 26.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 32.6 (C(1b,1b′)), 41.9 (C(3a)), 74.8 (C(6a)), 80.1 (C(4)), 129.1 (C(3′,3″)), 130.9 (C(3)), 167.9 (C=O), 170.0 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2924m, 2853w (C-H), 1767s (C=O), 1218w; ***m/z HRMS (ESI^+) found 295.19044; $C_{17}H_{26}O_4$ $[M+H]^+$ requires 295.19039.



149
key nOe interactions

6.2.3 Chloro mono-γ-Lactones and Precursors: Characterisation

Diethyl 2-diazomalonate 239

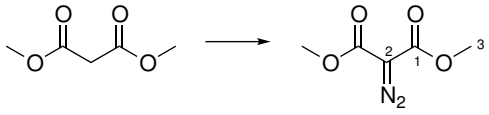


485 **239**

The title compound **239** was synthesised by following the **General Procedure 1** for the synthesis of diazo alkyl malonates. Diethyl malonate **485** (4.7 mL, 31.2 mmol), *p*-ABSA (7.7 g, 31.8 mmol), Et_3N (13.0 mL, 93.7 mmol) in MeCN (78 mL) were used. The residue was purified by FC (PE_{40-60}/ Et_2O, gradient from 5:1 to 1:1), giving the title compound **239** as a yellow oil (5.7 g, 97% yield). R_f

(PE_{40-60} / Et_2O, 4:1) = 0.4; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.31 (t, 6 H, J= 7.2 Hz, C(4)H_3); 4.29 (q, 4 H, J= 7.1 Hz, C(3)H_2); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 13.9 (C(4)), 61.3 (C(3)), 160.7 (C(1)); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2134m (C=N=N), 1734 (C=O), 1371s, 1077s; ***m/z*** LRMS (ESI^+): 395.1 ($[2M+Na^+]^+$, 100%); HRMS (ESI^+) found 187.07136; $C_7H_{10}N_2O_4$ $[M+H]^+$ requires 187.07133. Data in accordance with the literature.[173]

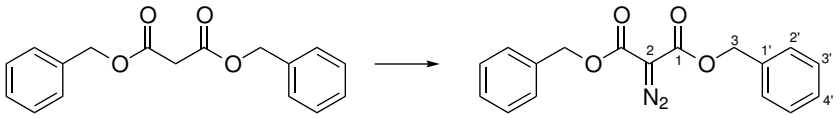
Dimethyl 2-diazomalonate 238



486 **238**

The title compound **238** was synthesised by following the **General Procedure 1** for the synthesis of diazo alkyl malonates. Dimethyl malonate **486** (4.3 mL, 37.8 mmol), *p*-ABSA (9.3 g, 38.6 mmol), Et_3N (15.8 mL, 113.4 mmol) in MeCN (95 mL) were used. The residue was purified by FC (PE_{40-60}/ Et_2O, gradient from 5:1 to 1:2), giving the title compound **238** as a yellow oil (4.2 g, 70% yield). R_f (PE_{40-60} / Et_2O, 3:1) = 0.2; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 3.84 (s, 6 H, C(3)H_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 52.5 (C(3)), 161.5 (C(1)); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2134m (C=N=N), 1737s (C=O), 1089s (C-O-C); ***m/z*** LRMS (ESI^+): 339.0 ($[2M+Na]^+$, 100%); HRMS (ESI^+) found 159.04021; $C_5H_6N_2O_4$ $[M+H]^+$ requires 159.04003.

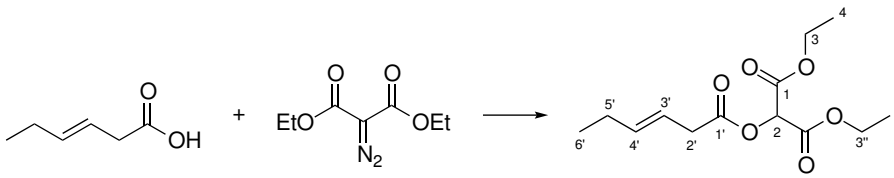
Dibenzyl 2-diazomalonate 488



487 **488**

The title compound **488** was synthesised by following the **General Procedure 1** for the synthesis of diazo alkyl malonates. Dibenzyl malonate **487** (5.1 mL, 20.4 mmol), *p*-ABSA (5.0 g, 20.8 mmol), Et_3N (8.5 mL, 61.2 mmol) in MeCN (51 mL) were used. The residue was purified by FC (PE_{40-60}/ Et_2O, gradient from 5:1 to 1:1), giving the title compound **488** as a white solid (6.1 g, 96% yield). R_f (PE_{40-60} / Et_2O, 4:1) = 0.3; *m.p.* 49-51 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 5.28 (s, 4 H, C(3)H_2), 7.32-7.37 (m, 10 H, C(Ar)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 67.2 (C(3)), 128.4 (C(2′) or C(3′)), 128.6 (C(4′)), 128.8 (C(2′) or C(3′)), 135.4 (C(1′)), 160.9 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2138m (C=N=N), 1757s (C=O), 1731s (C=O), 1308s (C-O-C); ***m/z*** LRMS (ESI^+): 333.0 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 333.08403; $C_{17}H_{14}N_2O_4$ $[M+Na]^+$ requires 333.08458.

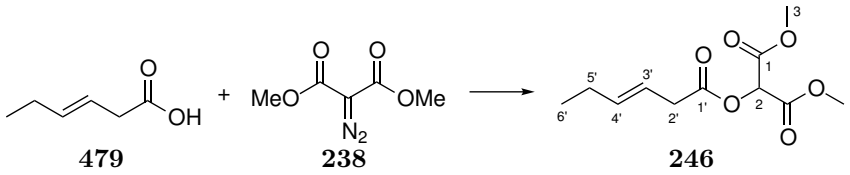
Diethyl (*E*)-2-(hex-3-enoyloxy)malonate 247



479 **239** **247**

The title compound **247** was synthesised by following the **General Procedure 2** for the Rh-catalysed OH insertion. Diazomalonate **239** (5.6 g, 29.9 mmol), (*E*)-hexenoic acid **479** (3.2 mL, 26.7 mmol) and $Rh_2(OAc)_4$ (70 mg, 0.16 mmol) in benzene (106 mL) were used. The residue was purified by FC (PE_{40-60} / Et_2O, gradient from 12:1 to 3:1), giving the title compound **247** as a colourless oil (6.8 g, 83% yield). R_f (PE_{40-60}/ Et_2O, 5:1) = 0.4; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 0.99 (t, 3 H, J= 7.4 Hz, C(6′)H_3), 1.30 (t, 6 H, J= 7.1 Hz, C(4)H_3), 2.06 (ddquint, 2 H, J= 1.0, 1.2, 7.4 Hz, C(5′)H_2), 3.20 (ddd, 2 H, J= 1.0, 1.2, 6.8 Hz, C(2′)H_2), 4.28 (q, 2 H, J= 7.1 Hz, C(3 or 3″)H_2), 4.29 (q, 2 H, J= 7.2 Hz, C(3 or 3″)H_2), 5.51 (ttd, 1 H, J= 1.5, 6.8, 15.3 Hz, C(3′)H), 5.53 (s, 1 H, C(2)H), 5.66 (ttd, 1 H, J= 1.0, 6.0, 15.3 Hz, C(4′)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 13.4 (C(6′)), 13.9 (C(4)), 25.5 (C(5′)), 37.2 (C(2′)), 62.5 (C(3 and 3″)), 71.8 (C(2)), 119.3 (C(3′)), 137.2 (C(4′)), 164.4 (C=O), 170.8 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2967w (C-H), 1748s (C=O), 1149m (C-O-C); ***m/z*** LRMS (ESI^+): 295.1 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 273.13330; $C_{13}H_{20}O_6$ $[M+H]^+$ requires 273.13326.

Dimethyl (*E*)-2-(hex-3-enoyloxy)malonate 246

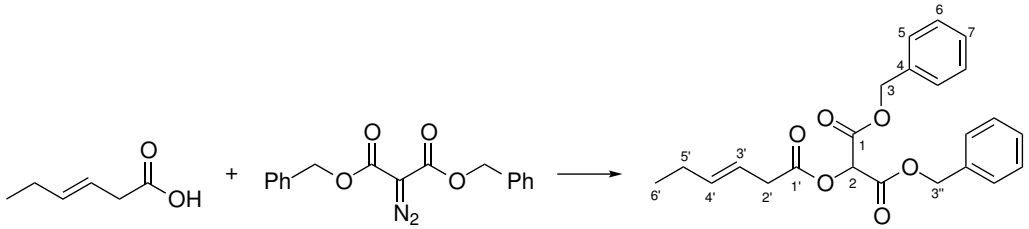


479 **238** **246**

The title compound **246** was synthesised by following the **General Procedure 2** for the Rh-catalysed OH insertion. Diazomalonate **238** (4.1 g, 26.1 mmol), (*E*)-hexenoic acid **479** (2.8 mL, 23.3 mmol) and $Rh_2(OAc)_4$ (62 mg, 0.14 mmol) in benzene (90 mL) were used. The residue was purified by FC (PE_{40-60} / Et_2O, gradient from 15:1 to 4:1), giving the title compound **246** as a colourless oil (5.2 g, 82% yield). R_f (PE_{40-60} / Et_2O, 5:1) = 0.3; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 0.99 (t, 3 H, J= 7.5 Hz, C(6′)H_3), 2.06 (ddquint, 2 H, J= 1.0, 1.2, 7.4 Hz, C(5′)H_2), 3.20 (dd, 2 H, J= 1.1, 6.8 Hz, C(2′)H_2), 3.83 (s, 3 H, C(3)H_3), 5.51 (ttd, 1 H, J= 1.5, 6.8, 15.4 Hz, C(3′)H), 5.57 (s, 1 H, C(2)H), 5.66 (ttd, 1 H, J= 1.1,

6.1, 15.4 Hz, C(4′)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 13.3 (C(6′)), 25.5 (C(5′)), 37.1 (C(2′)), 53.3 (C(3)), 71.5 (C(2)), 119.2 (C(3′)), 137.3 (C(4′)), 164.8 (C=O), 170.7 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2962w (C-H), 1750s (C=O), 1149m (C-O-C); ***m/z*** LRMS (ESI^+): 267.1 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 245.10210; $C_{11}H_{16}O_6$ $[M+H]^+$ requires 245.10196.

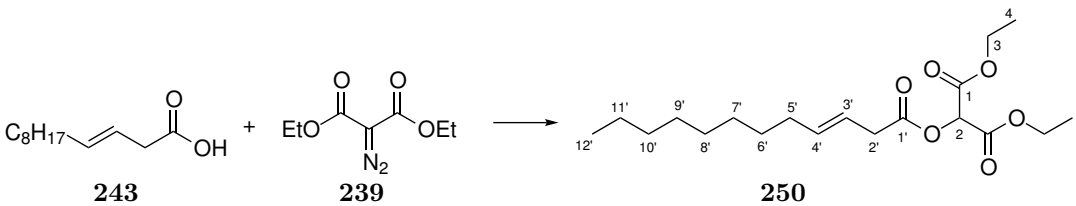
Dibenzyl (*E*)-2-(hex-3-enoyloxy)malonate 489



479 **488** **489**

The title compound **489** was synthesised by following the **General Procedure 2** for the Rh-catalysed OH insertion. Diazomalonate **488** (5.9 g, 19.3 mmol), (*E*)-hex-3-enoic acid **479** (2 mL, 17.2 mmol) and $Rh_2(OAc)_4$ (46.0 mg, 0.10 mmol) in benzene (60 mL) were used. The residue was purified by FC (PE_{40-60}/ Et_2O, gradient from 8:1 to 1:1), giving the title compound **489** as a colourless oil (6.1 g, 15.4 mmol, 80% yield). R_f (PE_{40-60} / EtOAc, 6:1) = 0.3; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 0.98 (t, 3 H, J= 7.5 Hz, C(6′)H_3), 2.04 (ddquint, 2 H, J= 1.2, 2.7, 7.5 Hz, C(5′)H_2), 3.20 (ddd, 2 H, J= 1.2, 2.4, 6.8 Hz, C(2′)H_2), 5.19 (d, 2 H, J= 12.2 Hz, C(3″)H), 5.22 (d, 2 H, J= 12.2 Hz, C(3)H), 5.50 (ttd, 1 H, J= 1.6, 6.8, 15.4 Hz, C(3′)H), 5.64 (ttd, 1 H, J= 1.3, 6.3, 15.4 Hz, C(4′)H), 5.64 (s, 1 H, C(2)H), 7.27-7.35 (m, 10 H, C(Ar)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 13.5 (C(6′)), 25.6 (C(5′)), 37.3 (C(2′)), 68.2 (C(3 and 3″)), 71.9 C(2)), 119.4 (C(3′)), 128.4 (C(Ar)), 128.7 (C(7)), 128.8 (C(Ar)), 134.7 (C(4)), 137.5 (C(4′)), 164.3 (C=O), 170.9 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2964w (C-H), 1749s (C=O), 1149m (C-O-C); ***m/z*** LRMS (ESI^+): 419.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 419.14595; $C_{23}H_{24}O_6$ $[M+Na]^+$ requires 419.14651.

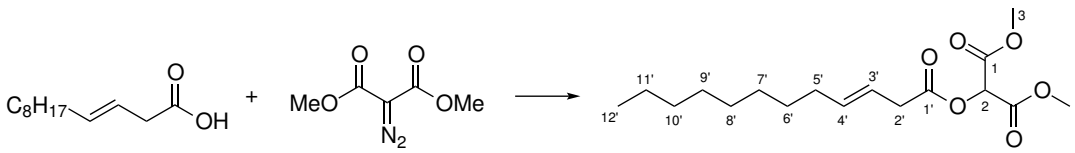
Diethyl (*E*)-2-(dodec-3-enoyloxy)malonate 250



243 **239** **250**

The title compound **250** was synthesised by following the **General Procedure 2** for the Rh-catalysed OH insertion. Diazomalonate **239** (3.4 g, 18.4 mmol), (*E*)-dodec-3-enoic acid **243** (3.3 g, 16.4 mmol) and $Rh_2(OAc)_4$ (44 mg, 0.1 mmol) in benzene (60 mL) were used. The residue was purified by FC (PE_{40-60} / Et_2O, gradient from 10:1 to 6:1), giving the title compound **250** as a colourless oil (3.9 g, 10.9 mmol, 66% yield). R_f (PE_{40-60} / Et_2O, 5:1) = 0.3; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 0.87 (t, 3 H, J= 7.0 Hz, C(12′)H_3), 1.24-1.37 (m, 12 H, C(6′-11′)H_2), 1.30 (t, 6 H, J= 7.1 Hz, C(4)H_3), 2.02 (q, 2 H, J= 7.0 Hz, C(5′)H_2), 3.20 (dd, 2 H, J= 0.9, 6.5 Hz, C(2′)H_2), 4.28 (q, 2 H, J= 7.1 Hz, C(3 or 3″)H_2), 4.29 (q, 2 H, J= 7.2 Hz, C(3 or 3″)H_2), 5.52 (ttd, 1 H, J= 1.3, 6.6, 15.3 Hz, C(3′)H), 5.52 (s, 1 H, C(2)H), 5.62 (ttd, 1 H, J= 1.1, 6.6, 15.3 Hz, C(4′)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 13.9 (C(4)), 14.1 (C(12′)), 22.7 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.9 (CH_2), 32.5 (C(5′)), 37.2 (C(2′)), 62.5 (C(3 and 3″)), 71.8 (C(2)), 120.2 (C(3′)), 135.9 (C(4′)), 164.4 (C=O), 170.8 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2926w (C-H), 1750s (C=O), 1146m (C-O-C); ***m/z*** LRMS (ESI^+): 357.2 ($[M+H]^+$, 40%), 379.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 357.22705; $C_{19}H_{32}O_6$ $[M+H]^+$ requires 357.22717.

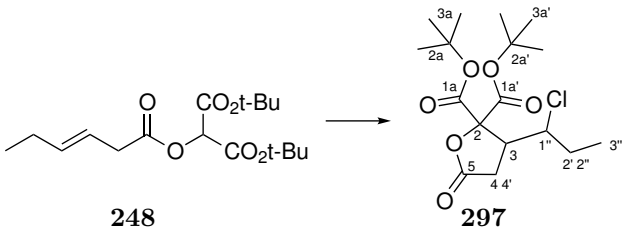
Dimethyl (*E*)-2-(dodec-3-enoyloxy)malonate 249



243 **238** **249**

The title compound **249** was synthesised by following the **General Procedure 2** for the Rh-catalysed OH insertion. Diazomalonate **238** (5.6 g, 35.6 mmol), (*E*)-dodec-3-enoic acid **243** (6.3 g, 31.8 mmol) and $Rh_2(OAc)_4$ (84 mg, 0.2 mmol) in benzene (114 mL) were used. The residue was purified by FC (PE_{40-60} / Et_2O, gradient from 9:1 to 5:1), giving the title compound **249** as a colourless oil (4.8 g, 14.7 mmol, 41% yield). R_f (PE_{40-60} / Et_2O, 4:1) = 0.3; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 0.87 (t, 3 H, J= 7.1 Hz, C(12′)H_3), 1.24-1.36 (m, 12 H, C(6′-11′)H_2), 2.02 (q, 2 H, J= 6.7 Hz, C(5′)H_2), 3.20 (dd, 2 H, J= 1.1, 6.7 Hz, C(2′)H_2), 3.83 (s, 6 H, C(3)H_3), 5.50 (ttd, 1 H, J= 1.4, 6.8, 15.3 Hz, C(3′)H), 5.57 (s, 1 H, C(2)H), 5.61 (ttd, 1 H, J= 1.2, 6.7, 15.3 Hz, C(4′)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 14.2 (C(12′)), 22.8 (C(11′)), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 32.0 (CH_2), 32.6 (C(5′)), 37.3 (C(2′)), 53.4 (C(3)), 71.6 (C(2)), 120.2 (C(3′)), 136.1 (C(4′)), 164.9 (C=O), 170.9 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2925w (C-H), 2854w (C-H), 1751s (C=O), 1144m (C-O-C); ***m/z*** LRMS (ESI^+): 329.2 ($[M+H]^+$, 90%), 351.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 351.17778; $C_{17}H_{28}O_6$ $[M+Na]^+$ requires 351.17781.

di-*tert*-Butyl 3-(1-chloropropyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 297

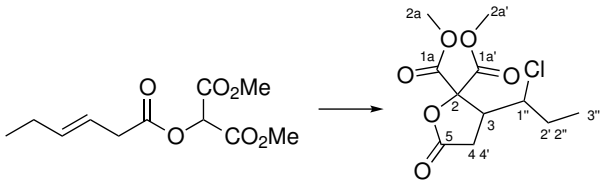


248 **297**

The title compound **297** has been synthesised by following the **General Procedure 4** for the formation of the halo-lactones through Mn(III)-based oxidative radical cyclisation. Alkenyl malonate **248** (1.0 g, 3.0 mmol) (synthesis described in **Section 6.2.2**), $Mn(OAc)_3 \cdot 2H_2O$ (1.6 g, 6.1 mmol), $Cu(OTf)_2$ (1.1 g, 3.0 mmol) and LiCl (155 mg, 3.6 mmol) in MeCN (20 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 10:1 to 0:1), giving the halo-lactone **297** as a colourless oil (0.89 g, 2.4 mmol, 80% yield, 3.3:1 *dr*). R_f (PE_{40-60} / EtOAc, 4:1) = 0.7; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): ***maj*-297**: 1.08 (t, 3 H, J= 7.3 Hz, C(3″)H_3), 1.50 (s, 9 H, C(3a or 3a′)H_3), 1.54 (s, 9 H, C(3a or 3a′)H_3), 1.69-1.79 (m, 1 H, C(2′)H), 1.86 (dqd, 1 H, J= 4.4, 7.3, 14.5 Hz, C(2″)H), 2.72 (dd, 1 H, J= 9.0, 17.7 Hz, C(4)H), 2.85 (dd, 1 H, J= 9.2, 17.7 Hz, C(4′)H), 3.40 (dt, 1 H, J= 3.7, 9.1 Hz, C(3)H), 4.20 (td, 1 H, J= 4.1, 9.3 Hz, C(1″)H); ***min*-297**: 1.05 (t, 3 H, J= 7.2 Hz, C(3″)H_3), 1.50 (s, 9 H, C(3a)H_3), 1.54 (s, 9 H, C(3a′)H_3), 1.69-1.79 (C(2′)H and C(2″)H, *masked*), 2.68 (dd, 1 H, J= 6.3, 17.8 Hz, C(4)H), 2.82 (dd, 1 H, J= 8.9, 17.8 Hz, C(4′)H), 3.57 (ddd, 1 H, J= 5.6, 6.2, 11.8 Hz, C(3)H), 4.08 (ddd, 1 H, J= 2.2, 5.4, 10.8 Hz, C(1″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) ***maj*-297**: 11.5 (C(3″), 27.9 (C(3a)), 28.0 (C(3a′)), 30.5 (C(4,4′)), 31.3 (C(2′, 2″)), 46.6 (C(3)), 62.6 (C(1″)), 84.6 (C), 85.2 (C), 86.6 (C), 164.7 (C=O), 165.3 (C=O), 173.4 (C=O); ***min*-297**: 11.4 (C(3″)), 27.2 (C(2′,2″)), 27.8 (C(3a)), 28.0 (C(3a′)), 30.9 (C(4,4′)), 47.5 (C(3)), 62.5 (C(1″)), 84.7 (C), 85.1 (C), 86.9 (C), 164.4 (C=O), 164.7 (C=O), 173.3 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2978w (C-H), 1805m (C=O), 1738s (C=O), 1151s (C-O-C); ***m/z*** LRMS (ESI^+): 385.1 ($[M+Na]^+$, 100%), 387.2 ($[M+Na]^+$, 30%); HRMS (ESI^+) found 385.13900 (100%), 387.13599 (30%); $C_{17}H_{27}ClO_6$ $[M+Na]^+$ requires 385.13993 (100%) and 387.13698 (30%).

Dimethyl 3-(1-chloropropyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 490

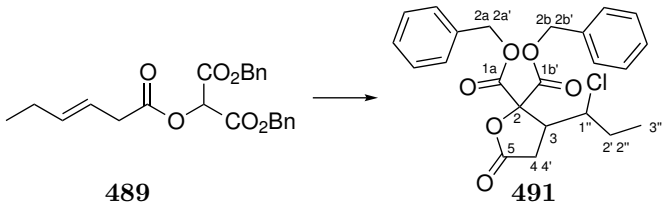
The title compound **490** has been synthesised by following the **General Procedure 4** for the formation of the halo-lactones through manganese-based oxidative radical cyclisation. Alkenyl malonate **246** (4.1 g, 16.8 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (9.0 g, 33.7 mmol), $Cu(OTf)_2$ (6.1 g, 16.8 mmol) and LiCl (0.9 g, 21.2 mmol) in MeCN (112 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc,



246 **490**

gradient from 5:1 to 0:1), giving the halo-lactone **490** as a colourless oil (3.7 g, 13.2 mmol, 79% yield, 3:1 *dr*). R_f (PE_{40-60} / EtOAc, 4:1) = 0.4; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) ***maj*-490**: 1.06 (t, 3 H, J= 7.4 Hz, C(3″)H_3), 1.71-1.84 (m, 2 H, C(2′)H and C(2″)H), 2.66 (dd, 1 H, J= 9.0, 17.7 Hz, C(4)H), 2.92 (dd, 1 H, J= 9.9, 17.7 Hz, C(4′)H), 3.42 (dt, 1 H, J= 2.2, 9.2 Hz, C(3)H), 3.83 (s, 3 H, C(2a)H_3), 3.84 (s, 3 H, C(2a′)H_3), 4.28 (ddd, 1 H, J= 2.2, 4.9, 9.0 Hz, C(1″)H); ***min*-490**: 1.04 (t, 3 H, J= 7.2 Hz, C(3″)H_3), 1.57-1.66 (m, 2 H, C(2′)H and C(2″)H), 2.72 (dd, 1 H, J= 8.1, 17.8 Hz, C(4)H), 2.79 (dd, 1 H, J= 8.8, 17.8 Hz, C(4′)H), 3.64 (dt, 1 H, J= 5.8, 8.3 Hz, C(3)H), 3.85 (s, 3 H, C(2a)H_3), 3.86 (s, 3 H, C(2a′)H_3), 4.01 (ddd, 1 H, J= 2.5, 5.7, 10.4 Hz, C(1″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) ***maj*-490**: 11.4 (C(3″)), 28.8 (C(4,4′)), 31.5 C(2′,2″), 46.9 (C(3)), 53.9 (C(2a)), 54.0 (C(2a′)), 61.9 (C(1″)), 85.4 (C(2)), 165.9 (C=O), 166.7 (C=O), 172.7 (C=O); ***min*-490**: 14.3 (C(3″)), 27.8 C(2′,2″), 30.9 (C(4,4′)), 47.9 (C(3)), 53.7 (C(2a)), 54.1 (C(2a′)), 62.2 (C(1″)), 85.8 (C(2)), 165.8 (C=O), 166.2 (C=O), 172.4 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2959w (C-H), 1804m (C=O, lactone), 1747s (C=O, ester), 1192m (C-O-C), 1162m (C-O-C); ***m/z*** LRMS (ESI^+): 301.1 ($[M+Na]^+$, 100%), 303.0 ($[M+Na]^+$, 30%); HRMS (ESI^+) found 301.04488 ($[M+Na]^+$, 100%), 303.04199 ($[M+Na]^+$, 30%); $C_{11}H_{15}ClO_6$ $[M+Na]^+$ requires 301.04494 (100%) and 303.04199 (30%).

Diphenyl 3-(1-chloropropyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 491

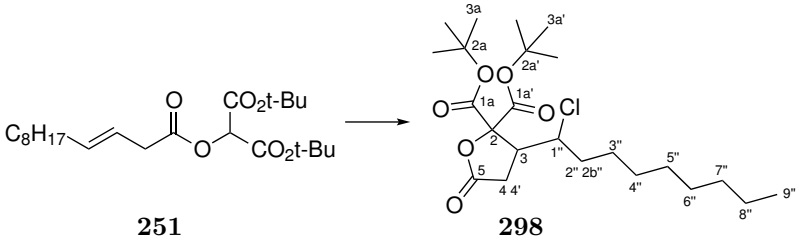


489 **491**

The title compound **491** has been synthesised by following the **General Procedure 4** for the formation of the halo-lactones through manganese-based oxidative radical cyclisation. Alkenyl malonate **489** (500 mg, 1.3 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (676 mg, 2.5 mmol), $Cu(OTf)_2$ (456 mg, 1.3 mmol) and LiCl (64 mg, 1.5 mmol) in MeCN (8.4 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc,

gradient from 8:1 to 1:1), giving the halo-lactone **491** as a colourless oil (357 mg, 0.83 mmol, 66% yield, 3.3:1 *dr*). R_f (PE_{40-60}/ EtOAc, 5:1) = 0.4; *m.p.* = 46-50 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) ***maj*-491**: 0.99 (t, 3 H, *J*= 7.3 Hz, C(3″)H_3), 1.65-1.80 (m, 2 H, C(2′)H and C(2″)H), 2.67 (dd, 1 H, *J*= 8.9, 17.6 Hz, C(4)H), 2.92 (dd, 1 H, *J*= 9.9, 17.6 Hz, C(4′)H), 3.47 (dt, 1 H, *J*= 2.6, 9.8 Hz, C(3)H), 4.21 (ddd, 1 H, *J*= 2.6, 4.9, 9.0 Hz, C(1″)H), 5.17 (d, 1 H, *J*= 12.2 Hz, C(2a)H), 5.19 (d, 1 H, *J*= 12.1 Hz, C(2b′)H), 5.23 (d, 1 H, *J*= 12.1 Hz, C(2b)H), 5.25 (d, 1 H, *J*= 12.2 Hz, C(2a′)H), 7.25-7.35 (m, 10 H, C(Ar)H); ***min*-491**: 0.85 (t, 3 H, *J*= 7.2 Hz, C(3″)H_3), 1.46-1.53 (m, 1 H, C(2′)H), 1.60 (ddd, 1 H, *J*= 2.5, 7.2, 14.4 Hz, C(2″)H), 2.68 (dd, 1 H, *J*= 7.5, 17.8 Hz, C(4)H), 2.76 (dd, 1 H, *J*= 8.8, 17.8 Hz, C(4′)H), 3.63 (ddd, 1 H, *J*= 5.8, 7.7, 8.6 Hz, C(3)H), 3.87 (ddd, 1 H, *J*= 2.5, 5.7, 10.6 Hz, C(1″)H), 5.11-5.31 (C(2a)H, C(2a′)H, C(2b)H, C(2b′)H, *masked*), 7.25-7.35 (m, 10 H, C(Ar)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) ***maj*-491**: 11.4 (C(3″)), 29.2 (C(4,4′)), 31.5 (C2′,2″)), 47.0 (C(3)), 61.9 (C(1″)), 68.9 (C(2a,2a′)), 69.1 (C(2b,2b′)), 85.6 (C(2)), 128.4 (2 x C(Ar)), 128.7 (2 x C(Ar)), 128.8 (4 x C(Ar)), 128.8 (C(Ar)), 128.9 (C(Ar)), 165.3 (C=O), 165.9 (C=O), 172.7 (C=O); ***min*-491**: 11.2 (C(3″)), 27.5 (C2′,2″)), 30.9 (C(4,4′)), 47.9 (C(3)), 62.0 (C(1″)), 68.8 (C(2a,2a′)), 68.9 (C(2b,2b′)), 86.0 (C(2)), 128.4-129.1 (10 x C(Ar), *masked*), 165.1 (C=O), 165.5 (C=O), 172.6 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2970w (C-H), 1805m (C=O, lactone), 1744s (C=O, ester), 1284m (C-O-C), 1161s (C-O-C); ***m/z*** LRMS (ESI^+): 453.2 ([M+Na]$^+$, 100%), 455.0 ([M+Na]$^+$, 30%); HRMS (ESI^+) found 453.10719 ([M+Na]$^+$, 100%), 455.10407 ([M+Na]$^+$, 30%); $C_{23}H_{23}ClO_6$ [M+Na]$^+$ requires 453.10754 (100%) and 455.10459 (30%).

di-*tert*-Butyl 3-(1-chlorononyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 298

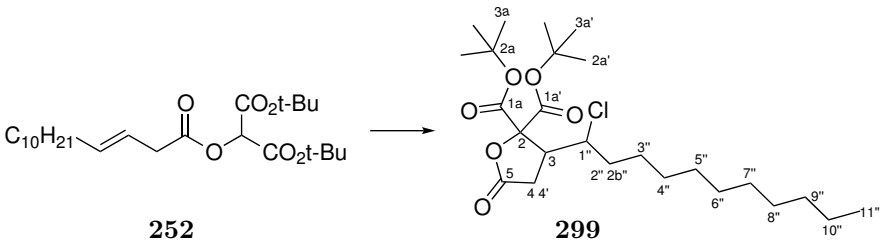


251 **298**

The title compound **298** has been synthesised by following the **General Procedure 4** for the formation of the halo-lactones through manganese-based oxidative radical cyclisation. Alkenyl malonate **251** (3.1 g, 7.4 mmol) (synthesis described in **Section 6.2.2**), $Mn(OAc)_3 \cdot 2H_2O$ (3.9 g, 14.8 mmol), $Cu(OTf)_2$ (2.7 g, 7.4 mmol) and LiCl (315 mg, 7.4 mmol) in MeCN (50 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 7:1 to 0:1), giving the halo-lactone **298** as a yellow oil (2.35 g, 5.3 mmol, 71% yield, 4.9:1 *dr*). R_f (PE_{40-60}/ EtOAc, 6:1) = 0.8; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$)

maj*-298**: 0.86 (t, 3 H, J= 7.2 Hz, C(9″)H_3), 1.23-1.61 (m, 12 H, C(3″-8″)H_2), 1.48 (s, 9 H, C(3a)H_3), 1.51 (s, 9 H, C(3a′)H_3), 1.67-1.77 (m, 2 H, C(2″)H and C(2b″)H), 2.70 (dd, 1 H, J= 9.1, 17.7 Hz, C(4)H), 2.82 (dd, 1 H, J= 8.8, 17.7 Hz, C(4′)H), 3.37 (dt, 1 H, J= 3.3, 8.9 Hz, C(3)H), 4.28 (ddd, 1 H, J= 3.4, 4.8, 8.3 Hz, C(1″)H); ***min*-298**: 0.85 (t, 3 H, J= 7.1 Hz, C(9″)H_3), 1.23-1.61 (m, 14 H, C(2″-8″)H_2), 1.48 (s, 9 H, C(3a)H_3), 1.51 (s, 9 H, C(3a′)H_3), 2.66 (dd, 1 H, J= 5.9, 17.8 Hz, C(4)H), 2.79 (dd, 1 H, J= 8.9, 17.8 Hz, C(4′)H_3), 3.53 (td, 1 H, J= 5.6, 8.8 Hz, C(3)H), 4.14 (ddd, 1 H, J= 2.0, 5.4, 10.9 Hz, C(1″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) ***maj*-298**: 14.2 (C(9″)), 22.7 (CH_2), 26.7 (CH_2), 27.8 (C(3a)), 27.9 (C(3a′)), 29.0 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 30.2 (C(4,4′)), 31.9 (CH_2), 37.9 (C(2″)), 46.6 (C(3)), 60.8 (C(1″)), 84.5 (C), 84.9 (C), 86.6 (C), 164.6 (C=O), 165.3 (C=O), 173.4 (C=O); ***min*-298**: 14.3 (C(9″)), 26.8 (CH_2), 27.8 (C(3a)), 27.9 (C(3a′)), 27.9 (CH_2), 28.0 (CH_2), 28.9 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.0 (CH_2), 33.8 (C(4,4′)), 47.6 (C(3)), 60.8 (C(1″)), 84.6 (C), 84.9 (C), 86.9 (C), 164.3 (C=O), 164.9 (C=O), 173.3 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2929m (C-H), 1806s (C=O, lactone), 1738s (C=O, ester), 1151s (C-O-C); ***m/z LRMS (ESI$^+$): 469.2.1 ([M+Na]$^+$, 100%), 471.2 ([M+Na]$^+$, 40%); HRMS (ESI$^+$) found 469.23305 (100%) and 471.22996 (30%); $C_{23}H_{39}ClO_6$ [M+Na]$^+$ requires 469.23274 (100%) and 471.22979 (30%).

di-*tert*-Butyl 3-(1-chloroundecyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 299



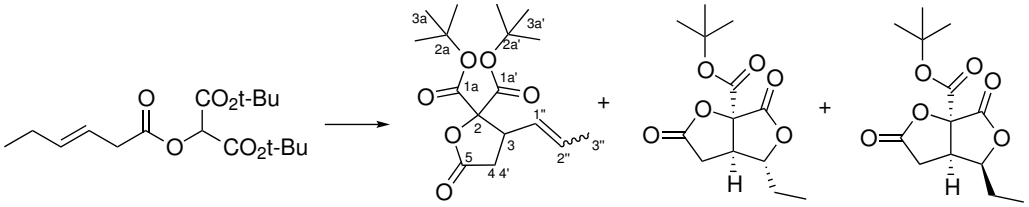
252 **299**

The title compound **299** has been synthesised by following the **General Procedure 4** for the formation of halo-lactones through manganese-based oxidative radical cyclisation. Alkenyl malonate **252** (1.0 g, 2.3 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (1.2 g, 4.5 mmol), $Cu(OTf)_2$ (0.8 g, 2.3 mmol) and LiCl (120 mg, 2.7 mmol) in MeCN (15 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 18:1 to 10:1), giving the halo-lactone **299** as a colourless oil (0.7 g, 1.5 mmol, 65% yield, 6.1:1 *dr*). R_f (PE_{40-60} / EtOAc, 15:1) = 0.6; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) ***maj*-299**: 0.86 (t, 3 H, J= 7.2 Hz, C(11″)H_3), 1.24-1.61 (m, 16 H, C(3-10″)H_2), 1.48 (s, 9 H, C(3a)H_3), 1.51 (s, 9 H, C(3a′)H_3), 1.66-1.78 (m, 2 H, C(2″)H and C(2b″)H), 2.70 (dd, 1 H, J= 9.0, 17.7 Hz, C(4)H), 2.82 (dd, 1 H, J= 8.8, 17.7 Hz), 3.37 (dt, 1 H, J= 3.3, 8.9 Hz, C(3)H), 4.28 (ddd, 1 H, J= 3.3, 4.7, 8.4 Hz, C(1″)H); $\boldsymbol{\delta_C}$ (125

MHz, $CDCl_3$) ***maj*-299**: 14.2 (C(11″)), 22.8 (CH_2), 26.7 (CH_2), 27.8 (C(3a)), 27.9 (C(3a′)), 29.0 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 30.2 (C(4,4′)), 31.9 (CH_2), 37.9 (C(2″)), 46.6 (C(3)), 60.8 (C(1″)), 84.5 (C), 84.9 (C), 86.6 (C), 164.6 (C=O), 165.3 (C=O), 173.4 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2926m (C-H), 1807s (C=O, lactone), 1739s (C=O, ester), 1150s (C-O-C); ***m/z*** LRMS (ESI$^+$): 497.2 ([M+Na]$^+$, 100%), 499.2 ([M+Na]$^+$, 35%); HRMS (ESI$^+$) found 497.26389 (100%) and 499.26064 (30%); $C_{25}H_{43}ClO_6$ [M+Na]$^+$ requires 497.26404 (100%) and 499.26109 (30%).

6.2.4 Alkenyl mono-γ-Lactones and Precursors: Characterisation

di-*tert*-Butyl 5-oxo-3-(prop-1-en-1-yl)dihydrofuran-2,2(3*H*)-dicarboxylate 260

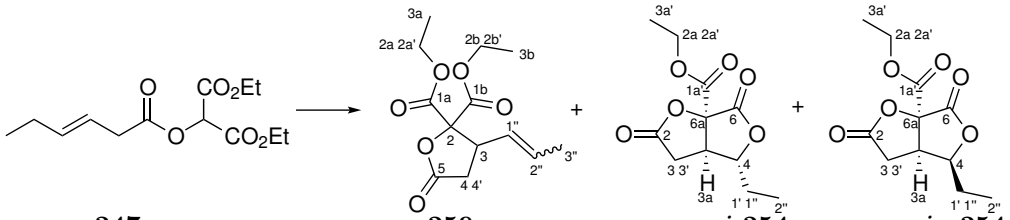


248 **260** ***maj*-255** ***min*-255**

The title compounds **260** and **255** have been synthesised by following the **General Procedure 3** for the Mn-based radical oxidative cyclisation. Alkenyl malonate **248** (3.9 g, 11.8 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (6.3 g, 23.6 mmol) and $Cu(OTf)_2$ (4.3 g, 11.8 mmol) in MeCN (79 mL) were used. The residue was purified by FC (PE_{40-60} / Et_2O, gradient from 7:1 to 0:1) giving the title compounds *maj*-**255** and *min*-**255** as a white solid (770 mg, 2.9 mmol, 24% yield, mixture of diastereoisomers 1.2:1 *dr*) and compound **260** as a white solid (1.6 g, 4.8 mmol, 40% yield, E/Z ratio: 3.8:1). (For full characterisation of the *bis*-lactones ***maj*-255** and ***min*-255**, see **Section 6.2.2**). **Compound 260**: R_f (PE_{40-60} / Et_2O, 7:1) = 0.4; *m.p.* = 63-78 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) (***E*)-260**: 1.46 (s, 9 H, C(3a)H_3), 1.50 (s, 9 H, C(3a′)H_3), 1.70 (ddd, 3 H, J= 1.0, 1.5, 6.5 Hz, C(3″)H_3), 2.65 (dd, 1 H, J= 10.2, 17.4 Hz, C(4)H), 2.69 (dd, 1 H, J= 8.7, 17.4 Hz, C(4′)H), 3.64 (tdd, 1 H, J= 0.9, 8.7, 17.3 Hz, C(3)H), 5.42 (dddd, 1 H, J= 1.5, 3.2, 7.2, 15.3 Hz, C(1″)H), 5.66 (dqd, 1 H, J= 1.2, 6.5, 15.3 Hz, C(2″)H); (***Z*)-260**: 1.48 (s, 9 H, C(3a)H_3), 1.49 (s, 9 H, C(3a′)H_3), 1.75 (dd, 3 H, J= 1.8, 6.9 Hz, C(3″)H_3), 2.43 (dd, 1 H, J= 7.8, 17.6 Hz, C(4)H), 2.81 (dd, 1 H, J= 8.8, 17.6 Hz, C(4′)H), 4.04 (dtd, 1 H, J= 0.9, 7.9, 10.4 Hz, C(3)H), 5.22 (qt, 1 H, J= 1.8, 10.7 Hz, C(1″)H), 5.63-5.70 (m, 1 H, C(2″)H, *masked*); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) (***E*)-260**: 18.1 (C(3″)), 27.9 (C(3a)), 28.1 (C(3a′)), 33.2 (C(4,4′)), 43.7 (C(3)), 83.8 (C), 84.3 (C), 87.7 (C), 125.7 (C(1″)), 130.1 (C(2″)), 165.0 (C=O), 165.1 (C=O), 174.2 (C=O); (***Z*)-260**: 13.4 (C(3″)),

27.9 (C(3a)), 28.0 (C(3a′)), 34.9 (C(4,4′)), 38.4 (C(3)), 83.9 (C), 84.1 (C), 87.9 (C), 125.4 (C(1″)), 129.6 (C(2″)), 164.6 (C=O), 165.0 (C=O), 173.2 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2979w (C-H), 1803s (C=O), 1738s (C=O), 1153s (C-O-C); ***m/z*** LRMS (ESI$^+$): 349.2 ([M+Na]$^+$, 60%), 675.3 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) found 349.16193; $C_{17}H_{26}O_6$ [M+Na]$^+$ requires 349.16216.

Ethyl (3a*R*,4*R*,6a*S*)-4-ethyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate *maj*-254 and **ethyl (3a*R*,4*S*,6a*S*)-4-ethyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate *min*-254** and **diethyl 5-oxo-3-(prop-1-en-1-yl)dihydrofuran-2,2(3*H*)-dicarboxylate 259**



247 **259** ***maj*-254** ***min*-254**

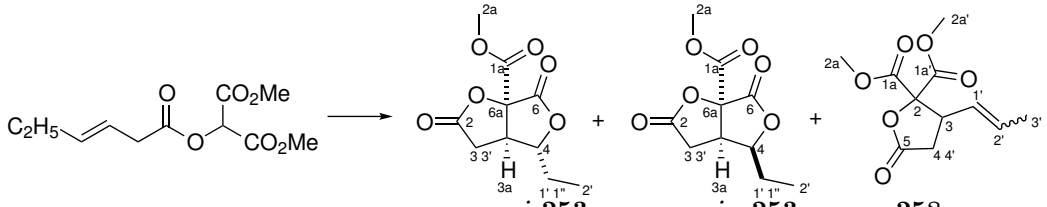
The title compounds **259** and **254** have been synthesised by following the **General Procedure 3** for the Mn-based radical oxidative cyclisation. Alkenyl malonate **247** (6.6 g, 24.2 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (13.0 g, 48.4 mmol) and $Cu(OTf)_2$ (8.8 g, 24.2 mmol) in MeCN (161 mL) were used. The residue was purified by FC (PE_{40-60} / EtOAc, gradient from 7:1 to 1:2) giving the *bis*-lactones **254** as a white solid (2.3 g, 9.5 mmol, 39% yield, 2.3:1 *dr*) and the alkene **259** as a colourless oil (4.2 g, 15.5 mmol, 64% yield, *E*/*Z* ratio: 8.1:1).

Compound 259: R_f = 0.3 (PE_{40-60} / EtOAc, 6:1); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) (***E***)-**259**: 1.24 (t, 3 H, *J*= 7.2 Hz, C(3a)H_3), 1.28 (t, 3 H, *J*= 7.1 Hz, C(3b)H_3), 1.66 (ddd, 1 H, *J*= 0.9, 1.6, 6.6 Hz, C(3″)H_3), 2.61 (dd, 1 H, *J*= 9.9, 17.5 Hz, C(4)H), 2.71 (dd, 1 H, *J*= 8.7, 17.5 Hz, C(4′)H), 3.68 (q, 1 H, *J*= 8.6 Hz, C(3)H), 4.09 (q, 1 H, *J*= 7.2 Hz, C(2a)H), 4.21-4.35 (m, 3 H, C(2a′,2b,2b′)H), 5.34 (qdd, 1 H, *J*= 1.6, 7.4, 15.3 Hz, C(1″)H), 5.69 (dqd, 1 H, *J*= 1.1, 6.5, 15.3 Hz, C(2″)H); (***Z***)-**259**: 1.21-1.30 (m, 6 H, C(3a)H_3 and C(3b)H_3, *masked*), 1.72 (dd, 3 H, *J*= 1.9, 6.7 Hz, C(3″)H_3), 2.45 (dd, 1 H, *J*= 8.3, 17.6 Hz, C(4)H), 2.79 (dd, 1 H, *J*= 8.8, 17.6 Hz, C(4′)H), 4.06-4.09 (m, 1 H, C(3)H, *masked*), 4.25-4.35 (m, 4 H, C(2a,2a′,2b,2b′)H), 5.12 (qt, 1 H, *J*= 1.8, 10.7 Hz, C(2″)H), 5.65-5.72 (m, 1 H, C(1″)H, *masked*); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) (***E***)-**259**: 13.9 (C(3a)), 14.2 (C(3b)), 18.0 (C(3″)), 33.0 (C(4,4′)), 43.9 (C(3)), 60.5 (C(2a)), 62.6 (C(2a′)), 62.8 (C(2b)), 62.8 (C(2b′)), 87.2 (C(2)), 124.9 (C(1′)), 130.9 (C(1′)), 165.8 (C=O), 165.9 (C=O), 173.6 (C=O); (***Z***)-**259**: 13.0 (C(3″)), 14.1 (C(3a), *C(3b) is*

masked), 34.5 (C(4,4′)), 38.7 (C(3)), 62.7 (C(2a)), 62.9 (C(2a′)), 63.0 (C(2b,2b′), 87.4 (C(4)), 124.6 (C(1′)), 130.5 (C(2′)), 165.8 (C=O), 165.9 (C=O), 173.7 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2985w (C-H), 1802s (C=O), 1742s (C=O), 1302m (C-O-C), 1225m (C-O-C), 1093m (C-O-C); ***m/z*** LRMS (ESI$^+$): 563.2 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) found 271.11757; $C_{13}H_{18}O_6$ [M+H]$^+$ requires 271.11761.

Compound 254: R_f = 0.7 (PE_{40-60} / EtOAc, 1:1); *m.p.* = 62-70 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) ***maj*-254**: 1.07 (t, 3 H, *J*= 7.5 Hz, C(2″)H$_3$), 1.34 (t, 3 H, *J*= 7.2 Hz, C(3a′)H$_3$), 1.63 (m, 1 H, C(1′)H), 1.84-1.94 (m, 1 H, C(1″)H), 2.71 (dd, 1 H, *J*= 9.0, 18.3 Hz, C(3)H), 2.77 (dd, 1 H, *J*= 9.9, 18.3 Hz, C(3′)H), 3.48 (dt, 1 H, *J*= 5.8, 9.4 Hz, C(3a)H), 4.35 (q, 1 H, *J*= 7.2 Hz, C(2a)H), 4.36 (q, 1 H, *J*= 7.1 Hz, C(2a′)H), 4.74 (td, 1 H, *J*= 5.9, 8.4 Hz, C(4)H); ***min*-254**: 1.06 (t, 3 H, *J*= 7.5 Hz, C(2″)H$_3$), 1.33 (t, 3 H, *J*= 7.2 Hz, C(3a′)H$_3$), 1.79-1.94 (m, 2 H, C(1′)H and C(1″)H, *masked*), 2.61 (dd, 1 H, *J*= 2.4, 18.4 Hz, C(3)H), 2.98 (dd, 1 H, *J*= 9.3, 18.4 Hz, C(3′)H), 3.13 (ddd, 1 H, *J*= 2.4, 6.0, 9.3 Hz, C(3a)H), 4.24 (td, 1 H, *J*= 5.7, 7.5 Hz, C(4)H), 4.32-4.38 (m, 2 H, C(2a)H and C(2a′)H, *masked*); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) ***maj*-254**: 9.9 (C(2″)), 14.1 (C(3a′)), 24.4 (C(1′,1″)), 27.8 (C(3,3′)), 44.1 (C(3a)), 63.8 (C(2a,2a′)), 80.8 (C(4)), 85.3 (C(6a)), 165.2 (C=O), 168.2 (C=O), 172.3 (C=O); **min-254**: 9.4 (C(2″)), 14.1 (C(3a′)), 28.1 (C(1′,1″)), 33.1 (C(3,3′)), 44.9 (C(3a)), 63.8 (C(2a,2a′)), 84.8 (C(6a)), 86.2 (C(4)), 165.9 (C=O), 167.1 (C=O), 172.7 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2978w (C-H), 1785s (C=O), 1763s (C=O), 1210m (C-O-C), 1106s (C-O-C); ***m/z*** LRMS (ESI$^+$): 507.2 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) found 243.08648; $C_{11}H_{14}O_6$ [M+H]$^+$ requires 243.08631.

Methyl (3a*R*,4*R*,6a*S*)-4-ethyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate *maj*-253, **methyl (3a*R*,4*S*,6a*S*)-4-ethyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate *min*-253** and **dimethyl 5-oxo-3-(prop-1-en-1-yl)dihydrofuran-2,2(3*H*)-dicarboxylate 258**



The title compounds **253** and **258** have been synthesised by following the **General Procedure 3** for the Mn-based radical oxidative cyclisation. Alkenyl malonate **246** (5.1 g, 20.7 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (11.1 g, 41.4 mmol) and $Cu(OTf)_2$ (7.5 g, 20.7 mmol) in MeCN (138 mL) were used. The residue

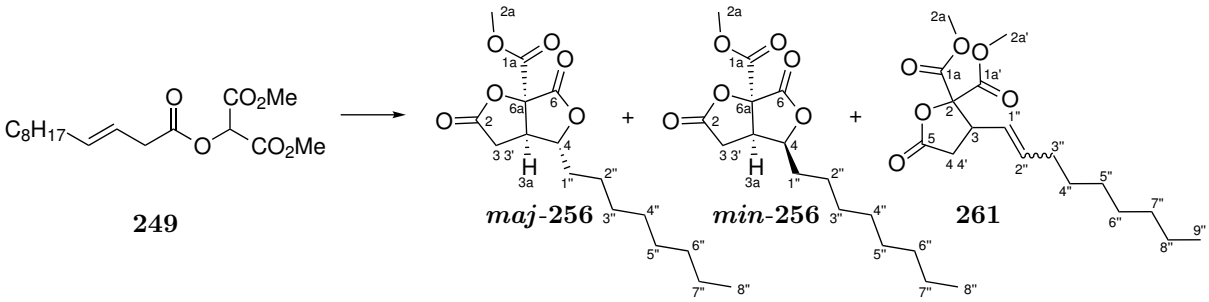
was purified by FC (PE_{40-60} / EtOAc, gradient from 5:1 to 1:2) giving the title compounds **253** as a white solid (1.5 g, 6.6 mmol, 32% yield, 4:1 *dr*) and compound **258** as a colourless oil (3.3 g, 13.6 mmol, 66% yield).

Compound 253: R_f (PE_{40-60} / EtOAc, 1:1) = 0.4; *m.p.* = 114-120 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) ***maj*-253**: 1.08 (t, 3 H, *J*= 7.4 Hz, C(2′)H_3), 1.63 (sept, 1 H, *J*= 7.4 Hz, C(1′)H), 1.85-1.93 (m, 1 H, C(1″)H), 2.71 (dd, 1 H, *J*= 9.0, 18.3 Hz, C(3)H), 2.77 (dd, 1 H, *J*= 9.8, 18.3 Hz, C(3′)H), 3.49 (dt, 1 H, *J*= 5.6, 9.6 Hz, C(3a)H), 3.92 (s, 3 H, C(2a)H_3), 4.76 (td, 1 H, *J*= 5.9, 8.5 Hz, C(4)H); ***min*-253**: 1.07 (t, 3 H, *J*= 7.4 Hz, C(2′)H_3), 1.78-1.95 (m, 2 H, C(1′)H and C(1″)H), 2.60 (dd, 1 H, *J*= 2.4, 18.5 Hz, C(3)H), 2.98 (dd, 1 H, *J*= 9.2, 18.4 Hz, C(3′)H), 3.14 (ddd, 1 H, *J*= 2.3, 6.2, 9.2 Hz, C(3a)H), 3.90 (s, 3 H, C(2a)H_3), 4.24 (td, 1 H, *J*= 5.9, 7.3 Hz, C(4)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) ***maj*-253**: 10.0 (C(2′)), 24.4 (C(1′,1″)), 27.8 (C(3,3′)), 44.1 (C(3a)), 54.2 (C(2a)), 80.7 (C(4)), 85.2 (C(6a)), 165.7 (C=O), 167.9 (C=O), 172.1 (C=O); ***min*-253**: 9.4 (C(2′)), 28.1 (C(1′,1″)), 32.9 (C(3,3′)), 45.1 (C(3a)), 54.2 (C(2a)), 84.9 (C(6a)), 86.1 (C(4)), 166.4 (C=O), 166.9 (C=O), 172.5 (C=O); $\boldsymbol{\nu_{max}}$ **/ $\mathbf{cm^{-1}}$** 2974w (C-H), 1787s (C=O), 1738s (C=O), 1212m (C-O-C), 1109m (C-O-C); ***m/z*** LRMS (ESI^+): 479.1 ($[2M+Na]^+$, 60%); HRMS (ESI^+) found 229.07089; $C_{10}H_{12}O_6$ $[M+H]^+$ requires 229.07066.

Compound 258: *E*/*Z* ratio = 5.3:1. R_f (PE_{40-60} / EtOAc, 1:1) = 0.8; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) (***E***)**-258**: 1.67 (ddd, 3 H, *J*= 0.8, 1.6, 6.5 Hz, C(3′)H_3), 2.61 (dd, 1 H, *J*= 9.9, 17.5 Hz, C(4)H), 2.71 (dd, 1 H, *J*= 8.7, 17.5 Hz, C(4′)H), 3.69 (q, 1 H, *J*= 8.7 Hz, C(3)H), 3.76 (s, 3 H, C(2a or 2a′)H_3), 3.83 (s, 3 H, C(2a or 2a′)H_3), 5.32 (qdd, 1 H, *J*= 1.7, 7.5, 15.3 Hz, C(1′)H), 5.70 (dqd, 1 H, *J*= 1.1, 6.5, 15.3 Hz, C(2′)H); (***Z***)**-258**: 1.72 (dd, 3 H, *J*= 1.9, 7.0 Hz, C(3′)H_3), 2.47 (dd, 1 H, *J*= 8.2, 17.7 Hz, C(4)H), 2.80 (dd, 1 H, *J*= 8.8, 17.7 Hz, C(4′)H), 3.78 (s, 3 H, C(2a or 2a′)H_3), 3.82 (s, 3 H, C(2a or 2a′)H_3), (3.67-3.84, 1 H, C(3)H, *masked*), 5.09 (qt, 1 H, *J*= 1.8, 10.7 Hz, C(2′)H), 5.67-5.74 (m, 1 H, C(1′)H, *masked*); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) (***E***)**-258**: 18.0 (C(3′)), 32.9 (C(4,4′)), 44.1 (C(3)), 53.2 (C(2a or 2a′)), 53.6 (C(2a or 2a′)), 87.3 (C(2)), 124.6 (C(1′)), 131.3 (C(2′)), 166.3 (C=O), 166.4 (C=O), 173.5 (C=O); (***Z***)**-258**: 14.3 (C(3′)), 34.3 (C(4,4′)), 38.8 (C(3)), 53.2 (C(2a or 2a′)), 53.7 (C(2a or 2a′)), 86.3 (C(6a)), 124.4 (C(1′)), 125.2 (C(2′)), 166.2 (C=O), 166.4 (C=O), 173.5 (C=O); $\boldsymbol{\nu_{max}}$ **/ $\mathbf{cm^{-1}}$** 2959w (C-H), 1802s (C=O), 1744s (C=O); ***m/z*** LRMS (ESI^+): 507.2 ($[2M+Na]^+$, 100%); HRMS (ESI^+) found 243.08632; $C_{11}H_{14}O_6$ $[M+H]^+$ requires 243.08631.

Methyl (3a*R*,4*R*,6a*S*)-4-octyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate (*maj*)-256, methyl (3a*R*,4*S*,6a*S*)-4-octyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate (*min*)-256

and **dimethyl 3-(non-1-en-1-yl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 261**



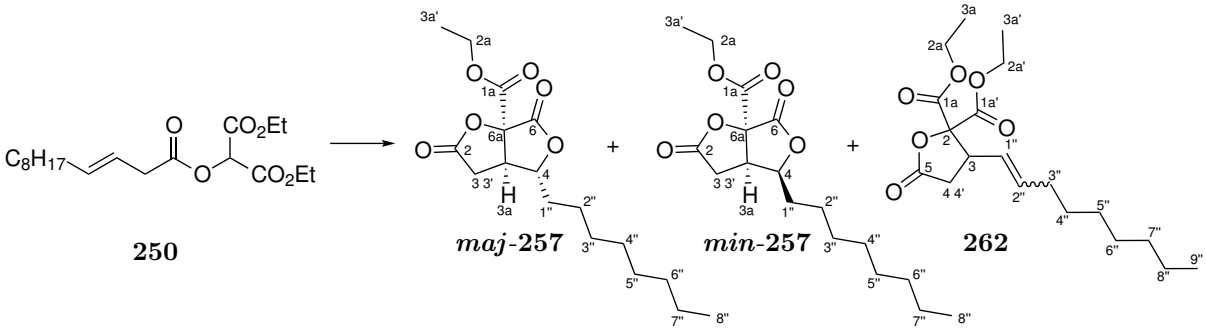
The title compounds **256** and **261** have been synthesised by following the **General Procedure 3** for the Mn-based radical oxidative cyclisation. Alkenyl malonate **249** (4.5 g, 13.8 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (7.4 g, 27.5 mmol) and $Cu(OTf)_2$ (4.9 g, 13.8 mmol) in MeCN (92.0 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 6:1 to 0:1) giving the title compound **261** as a colourless oil (2.6 g, 7.9 mmol, 58% yield, 19:1 E/Z ratio) and the title compounds **256** as a white solid (0.94 g, 3.0 mmol, 22% yield, 3.2:1 *dr*).

Compound 256: R_f (PE_{40-60} / EtOAc, 1:1) = 0.3; *m.p.* = 55-63 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) ***maj*-256**: 0.88 (t, 3 H, J= 7.2 Hz, C(8)H_3), 1.26-1.92 (m, 14 H, (C(1″-7″)H_2), 2.71 (dd, 1 H, J= 9.1, 18.3 Hz, C(3)H), 2.76 (dd, 1 H, J= 9.8, 18.3 Hz, C(3′)H), 3.47 (dt, 1 H, J= 5.8, 9.6 Hz, C(3a)H), 3.92 (s, 3 H, C(2a)H_3), 4.82 (td, 1 H, J= 5.4, 8.8 Hz, C(4)H)); ***min*-256**: 0.87-0.89 (C(8)H_3, *masked*), 1.26-1.92 (m, 14 H, (C(1″-7″)H_2), 2.58 (dd, 1 H, J= 2.3, 18.4 Hz, C(3)H), 2.97 (dd, 1 H, J = 9.1, 18.4 Hz, C(3′)H), 3.12 (ddd, 1 H, J= 2.2, 6.2, 9.2 Hz, C(3a)H), 3.91 (s, 3 H, C(2a)H_3), 4.27 (td, 1 H, J= 5.6, 7.9 Hz, C(4)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) ***maj*-256**: 14.2 (C(8)), 22.8 (CH_2), 25.7 (CH_2), 27.9 (C(3,3′)), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.2 (CH_2), 31.9 (CH_2), 44.4 (C(3a)), 54.2 (C(2a)), 79.5 (C(4)), 85.2 (C(6a)), 165.8 (C=O), 167.9 (C=O), 171.9 (C=O); ***min*-256**: 14.3 (C(8)), 25.2 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 32.9 (C(3,3′)), 35.1 (CH_2), 45.6 (C(3a)), 84.8 (C(6a)), 84.9 (C(4)), 166.5 (C=O), 166.8 (C=O), 171.3 (C=O) (*2 x CH_2 are masked*); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2927m (C-H), 2856w (C-H), 1790s (C=O), 1740m (C=O), 1161m (C-O-C); ***m/z*** HRMS (ESI^+) found 313.16429; $C_{16}H_{24}O_6$ $[M+H]^+$ requires 313.16456.

Compound 261 (19:1 E/Z ratio). Only (***E*)-261** was characterised: R_f (PE_{40-60} / EtOAc, 5:1) = 0.6; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) (***E*)-261**: 0.87 (t, 3 H, J= 7.1 Hz, C(9″)H_3), 1.25-1.45 (m, 10 H, C(4″-8″)H_2), 2.00 (q, 2 H, J= 7.2 Hz, C(3″)H_2), 2.65 (dd, 1 H, J= 9.8, 17.5 Hz, C(4)H), 2.74 (dd, 1 H, J= 8.6, 17.5 Hz, C(4′)H), 3.71 (q, 1 H, J= 8.4 Hz, C(3)H), 3.77 (s, 3 H, C(2a)H_3), 3.85 (s, 3 H, C(2a′)H_3), 5.33 (tdd, 1 H, J= 1.3, 7.5, 15.3 Hz, C(1″)H), 5.70 (dtd, 1 H, J= 1.0, 6.9, 15.3 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (125

MHz, $CDCl_3$) (***E***)-**261**: 14.2 (C(9″)), 22.8 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 31.9 (CH_2), 32.6 (C(3″)), 32.9 (C(4,4′)), 44.1 (C(3)), 53.2 (C(2a)), 53.7 (C(2a′)), 87.5 (C(2)), 123.4 (C(1″)), 136.8 (C(2″)), 166.3 (C=O), 166.5 (C=O), 173.5 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2926w (C-H), 2855w (C-H), 1805s (C=O), 1747s (C=O), 1159m (C-O-C), 1047m (C-O-C); ***m/z*** HRMS (ESI^+) found 327.18035; $C_{17}H_{26}O_6$ $[M+H]^+$ requires 327.18022.

Ethyl (3a*R*,4*R*,6a*S*)-4-octyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate (*maj*)-257, ethyl (3a*R*,4*S*,6a*S*)-4-octyl-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate (*min*)-257 and **diethyl 3-(non-1-en-1-yl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 262**



The title compounds **257** and **262** have been synthesised by following the **General Procedure 3** for the Mn-based radical oxidative cyclisation. Alkenyl malonate **250** (3.0 g, 8.4 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (4.5 g, 16.8 mmol) and $Cu(OTf)_2$ (3.1 g, 8.4 mmol) in MeCN (56 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 7:1 to 0:1) giving the title compound **262** as a colourless oil (0.95 g, 2.7 mmol, 32% yield, 24:1 *E*/*Z* ratio) and the title compounds **257** as a white solid (0.43 g, 1.3 mmol, 14% yield, 2.0:1 *dr*).

Compound 257: R_f (PE_{40-60} / EtOAc, 7:1) = 0.3; *m.p.* = 60-69 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) ***maj*-257**: 0.88 (t, 3 H, *J*= 7.1 Hz, (C(8″)H_3), 1.27-1.91 (m, 14 H, C(1″-7″)H_2), 1.35 (t, 3 H, *J*= 7.2 Hz, C(3a′)H_3), 2.71 (dd, 1 H, *J*= 9.2, 18.3 Hz, C(3)H), 2.76 (dd, 1 H, *J*= 9.8, 18.3 Hz, C(3′)H), 3.45 (dt, 1 H, *J*= 5.8, 9.5 Hz, C(3a)H), 4.37 (q, 2 H, *J*= 7.2 Hz, C(2a)H_2), 4.80 (td, 1 H, *J*= 5.5, 8.8 Hz, C(4)H); ***min*-257**: 0.88 (t, 3 H, *J*= 7.0 Hz, C(8″)H_3), 1.27-1.91 (m, 14 H, C(1″-7″)H_2, *masked*), 1.35 (t, 3 H, *J*= 7.2 Hz, C(3a′)H_3), 2.58 (dd, 1 H, *J*= 2.4, 18.4 Hz, C(3)H), 2.97 (dd, 1 H, *J*= 9.2, 18.3 Hz, C(3′)H), 3.11 (ddd, 1 H, *J*= 2.3, 6.1, 9.2 Hz, C(3a)H), 4.24-4.30 (m, 1 H, C(4)H), 4.36 (q, 2 H, *J*= 7.1 Hz, C(2a)H_2); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) ***maj*-257**: 14.1 (CH_3), 14.2 (CH_3), 22.8 (CH_2), 25.7 (CH_2),

27.9 (C(3,3′)), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 31.2 (CH_2), 31.9 (CH_2), 44.4 (C(3a)), 63.8 (C(2a)), 79.5 (C(4)), 84.9 (C(6a)), 165.3 (C=O), 168.1 (C=O), 172.1 (C=O); ***min*-257**: 14.1 (CH_3), 14.1 (CH_3), 25.2 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 33.0 (C(3,3′)), 35.1 (CH_2), 36.1 (CH_2), (1×(CH_2) is masked), 45.5 (C(3a)), 63.8 (C(2a)), 85.2 (C(4)), 84.8 (C(6a)), 165.9 (C=O), 166.9 (C=O), 172.5 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2927m (C-H), 1788s (C=O), 1766s (C=O), 1737m, 1206m, 1110m; ***m/z*** LRMS (ESI$^+$): 327.2 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 327.18007 ; $C_{17}H_{26}O_6$ [M+H]$^+$ requires 327.18022.

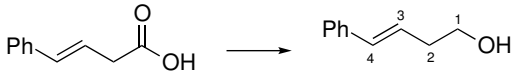
Compound 262 (24:1 *E*/*Z* ratio). Only (***E*)-262** was characterised: R_f (PE_{40-60} / EtOAc, 7:1) = 0.6; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) (***E*)-262**: 0.86 (t, 3 H, *J*= 7.1 Hz, C(9″)H_3), 1.26 (t, 3 H, *J*= 7.2 Hz, C(3a)H_3), 1.30 (t, 3 H, *J*= 7.2 Hz, C(3a′)H_3), 1.20-1.44 (m, 10 H, C(4″-8″)H_2), 1.99 (q, 2 H, *J*= 7.2 Hz, C(3″)H_2), 2.64 (dd, 1 H, *J*= 9.9, 17.5 Hz, C(4)H), 2.72 (dd, 1 H, *J*= 8.6, 17.4 Hz, C(4′)H), 3.70 (q, 1 H, *J*= 9.1 Hz, C(3)H), 4.16-4.36 (m, 4 H, C(2a)H_2 and C(2a′)H_2), 5.34 (tdd, 1 H, *J*= 1.2, 7.4, 15.4 Hz, C(1″)H), 5.68 (dtd, 1 H, *J*= 0.9, 6.8, 15.4 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) (***E*)-261**: 14.0 (CH_3), 14.2 (CH_3), 14.2 (CH_3), 22.8 (CH_2), 29.1(CH_2), 29.2 (CH_2), 29.2 (CH_2), 31.9 (CH_2), 32.6 (C(3″)), 33.1 (C(4,4′)), 43.9 (C(3)), 62.6 (C(2a)), 62.9 (C(2a′)), 87.3 (C(2)), 123.6 (C(1″)), 136.5 (C(2″)), 165.9 (C=O), 166.0 (C=O), 173.7 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2926w (C-H), 2855w (C-H), 1805s (C=O), 1743s (C=O), 1223m, 1159m, 1076m; ***m/z*** LRMS (ESI$^+$): 355.2 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 355.21122; $C_{19}H_{30}O_6$ [M+H]$^+$ requires 355.21152.

6.3 Towards the Formation of Chloro mono-Cyclic Systems

Part of this work was done by Martin Gillard. The compounds with Gillard's reference were prepared by Gillard.[126]

6.3.1 Synthesis of the Precursors

(*E*)-4-Phenylbut-3-en-1-ol 493[126]

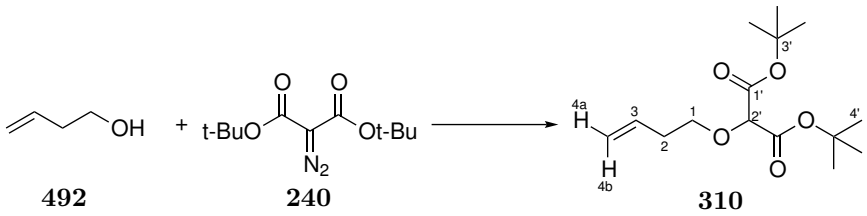


(*E*)-**494** (*E*)-**493**

To a solution of acid **494** (2.00 g, 12.3 mmol) in anhydrous Et_2O (12 mL), was added dropwise a solution of $LiAlH_4$ (234 mg, 6.15 mmol) in anhydrous Et_2O (15 mL) at 0 °C. The reaction was quenched after 2 h at r.t. by the successive addition of 0.3 ml of water, 0.3 ml of NaOH (15%) and 1.5 ml of water.

The yellow solid precipitate was filtered off and the solvent was removed under vacuum. The crude was purified by FC (PE_{40-60} / EtOAc, 85:15), giving the title compound **493** as a yellow oil (872 mg, 5.88 mmol, 48%). R_f = 0.7 (PE_{40-60} / EtOAc, 85:15); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.61 (s, 1 H, O*H*), 2.50 (dq, 2 H, *J*= 1.4, 6.3 Hz, C(2)H_2), 3.76 (t, 2 H, *J*= 6.2 Hz, C(1)H_2), 6.21 (td, 1 H, *J*= 7.2, 15.8 Hz, C(3)H), 6.51 (d, 1 H, *J*= 15.8 Hz, C(4)H), 7.25-7.19 (m, 1 H, C(Ar)H), 7.38-7.28 (m, 4 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 36.6 (C(2)), 62.2 (C(1)), 126.2 (C(Ar)), 126.4 (C(3)), 127.4 (C(Ar)), 128.7 (C(Ar)), 133.0 (C(Ar)), 137.3 (C(4)); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3339m (O-H), 2931w (C-H), 1493m (C=C), 1045s, 965s, 743s, 692s. *Data are in accordance with literature.*[174]

di-*tert*-Butyl 2-(but-3-en-1-yloxy)malonate 310[126]

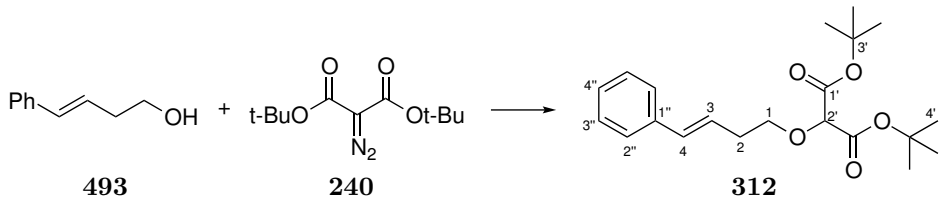


492 **240** **310**

The title compound **310** has been synthesised[126] by following the **General Procedure 2** for Rh-catalysed OH-insertion. The diazomalonate **240** (3.93 g, 16.2 mmol) (synthesis in **Section 6.2.2**) and 3-buten-1-ol **492** (1.11 mL, 15.4 mmol) were used in benzene (62 mL). The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 10:1 to 2:1), giving the title compound **310** as a colourless oil (3.33 g, 11.6 mmol, 76%). R_f = 0.4 (PE_{40-60} / Et_2O, 10:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.48 (s, 18 H, C(4′)H_3), 2.43 (tq, 2 H, *J*= 1.1, 7.0 Hz, C(2)H_2), 3.61 (t, 2 H, *J*= 7.0 Hz, C(1)H_2), 4.25 (s, 1 H, C(2′)H), 5.04 (ddd, 1 H, *J*= 1.2, 2.9, 10.2 Hz, C(4a)H), 5.10 (ddd, 1 H, *J*= 1.6, 3.4, 17.2 Hz, C(4b)H), 5.82 (tdd, 1 H, *J*= 6.8, 10.2, 17.2 Hz, C(3)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 28.0 (C(4′)), 34.0 (C(2)), 70.4 (C(1)), 80.4 (C(2′)), 82.7 (C(3′)), 116.9 (C(4)), 134.6 (C(3)), 166.0 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2980w (C-H), 1761m (C=O), 1739s (C=O), 1370m (C-O-C), 1294m (C-O-C), 1143s. *Data are in accordance with literature.*[60]

di-*tert*-Butyl (*E*)-2-((4-phenylbut-3-en-1-yl)oxy)malonate 312[126]

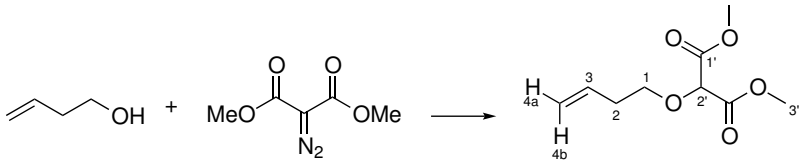
The title compound **312** was prepared by following the **General Procedure 2** for the Rh-catalysed OH-insertion. The diazomalonate **240** (1.82 g, 7.65 mmol) and 4-phenyl-but-3-en-1-ol **493** (1.00 g, 7.29 mmol) were used in benzene (30 mL). The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 9:1 to 3:1), giving the title compound **312** as a yellow oil (2.01 g, 5.55 mmol, 74%). R_f = 0.4 (PE_{40-60} / EtOAc, 9:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.48 (s, 18 H, C(4′)H_3), 2.52 (dtd, 2 H, *J*= 1.3, 6.9, 7.0 Hz,



493 **240** **312**

C(2)H_2), 3.69 (t, 2 H, J= 7.0 Hz, C(1)H_2), 4.28 (s, 1 H, C(2′)H), 6.23 (td, 1 H, J= 7.0, 15.8 Hz, C(3)H), 6.46 (d, 1 H, J= 15.8 Hz, C(4)H), 7.36-7.17 (m, 5 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 28.0 (C(4′)), 33.4 (C(2)), 70.6 (C(1)), 80.5 (C(3′)), 82.8 (C(2′)), 126.2 (2 x C(Ar)), 127.2 (C(3)), 128.5 (2 x C(Ar)), 128.6 (C(Ar)), 132.1 (C(4)), 138.0 (C(Ar)), 166.0 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2978w (C-H), 1736s (C=O), 1369m, 1137s (C-O-C). *Data are in accordance with literature.*[60]

Dimethyl 2-(but-3-en-1-yloxy)malonate 311[126]

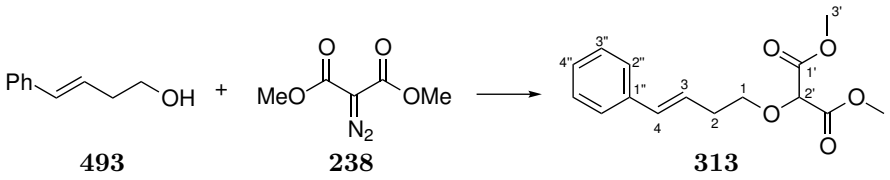


492 **238** **311**

The title compound **311** was prepared by following the **General Procedure 2** for the Rh-catalysed OH-insertion. The diazomalonate **238** (2.60 g, 16.5 mmol) (synthesis in **Section 6.2.3**) and 3-buten-1-ol **492** (1.32 mL, 15.7 mmol) in benzene (63 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 7:1 to 2:1), giving the title compound **311** as a colourless oil (2.22 g, 11.0 mmol, 70%). R_f = 0.3 (PE_{40-60} / Et_2O, 4:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 2.43 (tq, 2 H, J= 1.3, 6.9 Hz, C(2)H_2), 3.64 (t, 2 H, J= 6.9 Hz, C(1)H_2), 3.81 (s, 6 H, C(3′)H_3), 4.53 (s, 1 H, C(2′)H), 5.06 (ddd, 1 H, J= 1.1, 2.8, 10.2 Hz, C(4a)H), 5.11 (ddd, 1 H, J= 1.6, 3.2, 17.2 Hz, C(4b)H), 5.81 (tdd, 1 H, J= 6.7, 10.3, 17.2 Hz, C(3)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 33.9 (C(2)), 53.0 (C(3′)), 70.9 (C(1)), 79.1 (C(2′)), 117.2 (C(4)), 134.2 (C(3)), 167.1 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2957w (C-H), 1743s (C=O), 1371m, 1129s. *Data are in accordance with literature.*[60]

Dimethyl (*E*)-2-((4-phenylbut-3-en-1-yl)oxy)malonate 313[126]

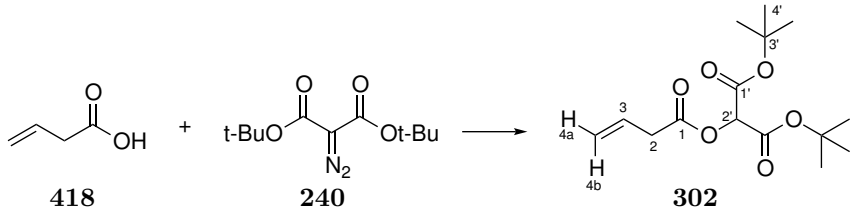
The title compound **313** has been synthesised by following the **General Procedure 2** for the Rh-catalysed OH-insertion. Diazomalonate **238** (963 mg, 6.10 mmol) and 4-phenyl-but-3-en-1-ol **493** (860 mg, 5.80 mmol) in benzene (23 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc,



493 **238** **313**

gradient from 10:1 to 2:1), giving the title compound **313** as a yellow oil (1.32 g, 4.76 mmol, 82%). R_f = 0.4 (PE_{40-60} / EtOAc, 9:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 2.59 (dq, 2 H, J= 1.4, 6.9 Hz, C(2)H_2), 3.72 (t, 2 H, J= 6.9 Hz, C(1)H_2), 3.81 (s, 6 H, C(3′)H_3), 4.56 (s, 1 H, C(2′)H), 6.21 (td, 1 H, J= 6.9, 15.9 Hz, C(3)H), 6.47 (d, 1 H, J= 15.9 Hz, C(4)H), 7.20 (tt, 1 H, J= 1.4, 7.2 Hz, C(4″)H), 7.27-7.36 (m, 4 H, C(2″)H and C(3″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 33.2 (C(2)), 53.1 (C(3′)), 71.2 (C(1)), 79.2 (C(2′)), 125.8 (C(3)), 126.2 (2 x C(Ar)), 127.3 (C(4″)), 128.6 (2 x C(Ar)), 132.4 (C(4)), 137.5 (C(Ar)), 167.1 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2955w (C-H), 1766m (C=O), 1746s (C=O), 1202m, 1136m. *Data are in accordance with literature.*[60]

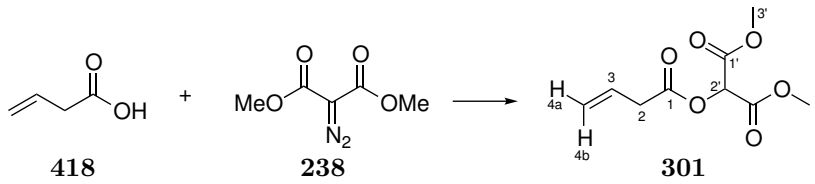
di-*tert*-Butyl 2-(but-3-enoyloxy)malonate 302[126]



418 **240** **302**

The title compound **302** has been synthesised by following the **General Procedure 2** for the Rh-catalysed OH-insertion. Diazomalonate **240** (3.80 g, 15.7 mmol) and 3-butenoic acid **418** (1.27 mL, 14.9 mmol) in benzene (60 mL). The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 12:1 to 6:1), giving the title compound **302** as a colourless oil (3.66 g, 12.2 mmol, 82%). R_f = 0.9 (PE_{40-60} / EtOAc, 10:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.49 (s, 18 H, C(4′)H_3), 3.25 (td, 2 H, J= 1.4, 6.9 Hz, C(2)H_2), 5.20 (ddd, 1 H, J= 1.4, 2.8, 10.3 Hz, C(4a)H), 5.21 (ddd, 1 H, J= 1.6, 3.0, 17.2 Hz, C(4b)H), 5.32 (s, 1 H, C(2′)H), 5.94 (tdd, 1 H, J= 6.9, 10.3, 17.1 Hz, C(3)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 28.0 (C(4′)), 38.5 (C(2)), 73.1 (C(2′)), 83.6 (C(3′)), 119.3 (C(4)), 129.5 (C(3)), 163.6 (C=O), 170.3 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2981w (C-H), 1744s (C=O), 1369m, 1250m, 1141s; ***m/z*** LRMS (ESI$^+$) 301.2 ([M+H]$^+$, 100%); HRMS (ESI$^+$) found 323.14615; $C_{15}H_{24}O_6$ [M+Na]$^+$ requires 323.14651.

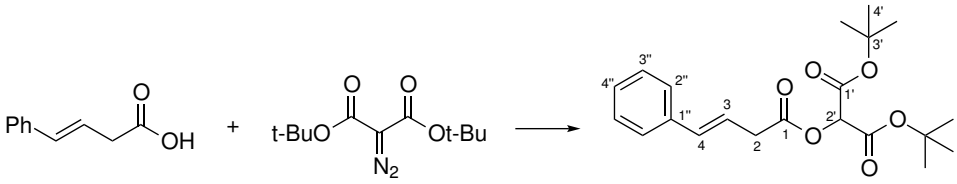
Dimethyl 2-(but-3-enoyloxy)malonate 301[126]



418 **238** **301**

The title compound **301** has been prepared by following the **General Procedure 2** for the Rh-catalysed OH-insertion. Diazomalonate **238** (600 mg, 3.8 mmol) and 3-butenoic acid **418** (0.3 mL, 3.5 mmol) in benzene (14 mL) were used. The crude has been purified by FC (PE_{40-60} / EtOAc ,4:1), giving the title compound **301** as a colourless oil (750 mg, 3.47 mmol, 99%). R_f = 0.6 (PE_{40-60} / EtOAc, 7:3); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 3.27 (td, 2 H, J= 1.4, 6.9 Hz, C(2)H_2), 3.83 (s, 6 H, C(3′)H_3), 5.22 (ddd, 1 H, J= 1.4, 2.7, 9.8 Hz C(4a)H), 5.23 (ddd, 1 H, J= 1.6, 2.9, 16.2 Hz, C(4b)H)), 5.58 (s, 1 H, C(2′)H), 5.93 (tdd, 1 H, J= 6.9, 9.8, 16.7 Hz, C(3)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 38.3 (C(2)), 53.5 (C(3′)), 71.6 (C(2′)), 119.7 (C(4)), 129.1 (C(3)), 164.9 (2 x C=O), 170.2 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$2959 (C-H), 1747s (C=O), 1438w, 1151m, 1025m. *Data are in accordance with literature.*[60]

di-*tert*-Butyl (*E*)-2-((4-phenylbut-3-enoyl)oxy)malonate 303[126]



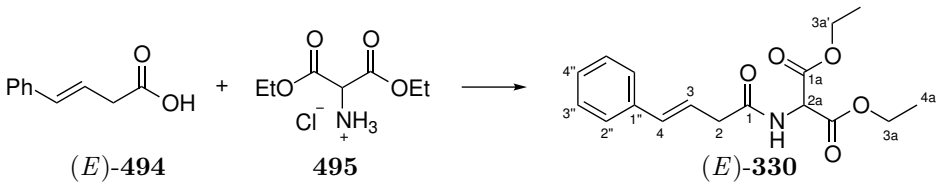
(*E*)-**494** **240** (*E*)-**303**

The title compound **303** was prepared by following the **General Procedure 2** for the Rh-catalysed OH-insertion. Diazomalonate **240** (2.70g, 11.1 mmol) and (*E*)-4-phenylbut-3-enoic acid **494** (1.72 g, 10.6 mmol) in benzene (42 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 11:1 to 6:1), giving the title compound **303** as a white solid (2.72 g, 7.23 mmol, 68%).

R_f = 0.4 (PE_{40-60} / EtOAc, 9:1); *m.p.* = 75-78 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.49 (s, 18 H, C(4′)H_3), 3.42 (dd, 2 H, J= 1.4, 7.1 Hz, C(2)H_2), 5.36 (s, 1 H, C(2′)H), 6.31 (td, 1 H, J= 7.1, 15.9 Hz, C(3)H), 6.53 (d, 1 H, J= 15.9 Hz, C(4)H), 7.23 (tt, 1 H, J= 2.4, 7.2 Hz, C(4″)H), 7.30 (t, 2 H, J= 7.6 Hz, C(3″)H), 7.37 (d, 2 H, J= 7.1 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 28.0 (C(4′)), 37.7 (C(2)), 73.2 (C(2′)), 83.7 (C(3′)), 120.4 (C(3)), 120.9 (C(Ar)), 126.5 (C(Ar)), 127.8 (C(Ar)), 128.7 (C(Ar)), 134.2 (C(4)), 136.9 (CAr), 163.6 (C=O), 170.4 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2980w (C-H), 1745s (C=O), 1369m, 1252m, 1141s (C-O-C); ***m/z*** LRMS (ESI^+) 399.2 ($[M+Na]^+$, 90%); HRMS (ESI^+) found 399.17687;

$C_{21}H_{28}O_6$ $[M+Na]^+$ requires 399.17781.

Diethyl (*E*)-2-(4-phenylbut-3-enamido)malonate 330



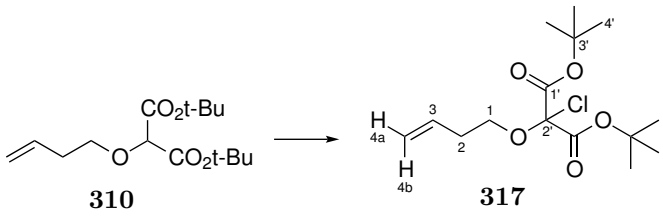
(*E*)-**494** **495** (*E*)-**330**

According to the procedure reported by Marx *et al.*,[57] to a solution of diethyl aminomalonate salt **495** (150 mg, 0.71 mmol), *trans*-styryl acetic acid **494** (100 mg, 0.62 mmol) and freshly distilled DIPEA (0.22 mL, 1.24 mmol) in anhydrous DMF (3 mL) was added portionwise HATU (248 mg, 0.65 mmol) at 0 °C. The reaction system was left to react at r.t. for 4 h. The reaction was quenched with a pH 2.0 buffer solution and diluted with EtOAc (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic fractions were washed with pH 2.0 buffer (10 mL), followed $NaHCO_3$ aq. sat. sol. (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by FC (PE_{40-60} / EtOAc, gradient from 3:1 to 2:1), giving the title compound **330** as a white solid (193 mg, 0.6 mmol, 97% yield). R_f = 0.3 (PE_{40-60} / EtOAc, 3:1) ; *m.p.* = 90 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.29 (t, 6 H, *J*= 6.8 Hz, C(4a)H_3), 3.25 (dd, 2 H, *J*= 1.2, 7.2 Hz, C(2)H_2), 4.25 (q, 2 H, *J*= 7.2 Hz, C(3a)H_2), 4.27 (q, 2 H, *J*= 6.8 Hz, C(3a′)H_2), 5.16 (d, 1 H, *J*= 6.8 Hz, C(2a)H), 6.30 (td, 1 H, *J*= 7.2, 16.0 Hz, C(3)H), 6.58 (d, 1 H, *J*= 16.0 Hz, C(4)H), 6.62 (d, 1 H, *J*= 6.8 Hz, N*H*), 7.24 (tt, 1 H, *J*= 1.6, 7.2 Hz, C(4″)H, 7.32 (t, 2 H, *J*= 7.6 Hz, C(3″)H), 7.38 (d, 2 H, *J*= 7.2 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 13.9 (C(4a)), 40.1 (C(2)), 56.4 (C(2a)), 62.7 (C(3a,3a′)), 121.5 (C(3)), 126.4 (C(2″)), 127.8 (C(4″)), 128.6 (C(3″)), 134.9 (C(4)), 166.2 (C=O), 170.4 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3301br (N*H*), 1742s (C=O), 1666m (C=O); ***m/z*** LRMS (ESI^+): 320.1 ($[M+H]^+$, 60%), 342.1 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 320.14877; $C_{17}H_{21}NO_5$ $[M+H]^+$ requires 320.14925.

6.3.1.1 Cyclisations and Side-Product Formation

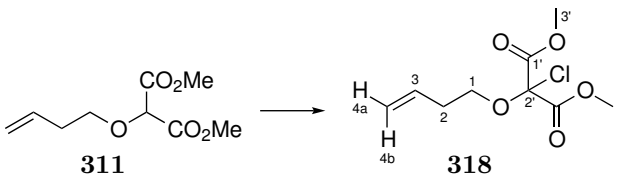
di-*tert*-Butyl 2-(but-3-en-1-yloxy)-2-chloromalonate 317[126]

The title compound **317** has been isolated when submitting the ether malonate **310** to the conditions described in **General Procedure 4** for the oxidative cyclisation for the synthesis of chloro monocyclic systems. Ether malonate **310** (60 mg, 0.21 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (113 mg, 0.42 mmol), $Cu(OTf)_2$ (76 mg, 0.21 mmol) and LiCl (11 mg, 0.25 mmol) in MeCN (1.4 mL) reacted at 80°C. The crude was purified



by FC (PE_{40-60} / EtOAc, gradient from 12:1 to 2:1), giving the title compound **317** as a colourless oil (57 mg, 0.18 mmol, 85%). R_f = 0.5 (PE_{40-60} / Et_2O, 10:1); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.48 (s, 18 H, C(4′)H_3), 2.45 (tq, 2 H, J= 1.3, 6.8 Hz, C(2)H_2), 3.72 (t, 2 H, J= 6.8 Hz, C(1)H_2), 5.07 (ddd, 1 H, J= 1.2, 2.9, 10.2 Hz, C(4a)H), 5.12 (qd, 1 H, J= 1.6, 17.2 Hz, C(4b)H), 5.82 (tdd, 1 H, J= 6.7, 10.2, 17.2 Hz, C(3)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 27.8 (C(4′)), 33.5 (C(2)), 66.7 (C(1)), 80.4 (C(2′)), 84.6 (C(3′)), 117.3 (C(4)), 134.0 (C(3)), 162.8 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2981w (C-H), 1744s (C=O), 1370m, 1290m, 1141s; ***m/z*** LRMS (ESI^+) 343.2 ($[M+Na]^+$, 100%) and 345.2 ($[M+Na]^+$, 33%); HRMS (ESI^+) found 343.12817 [100%] and 345.12529 [33%]; $C_{15}H_{25}ClO_5$ $[M+Na]^+$ requires 343.12827 [100%] and 345.12532 [33%].

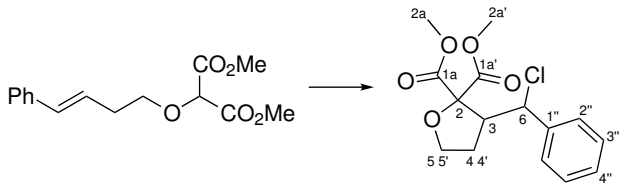
Dimethyl 2-(but-3-en-1-yloxy)-2-chloromalonate 318[126]



The title compound **318** has been isolated when submitting the ether malonate **311** to the conditions described in **General Procedure 4** for the oxidative cyclisation for the synthesis of chloro monocyclic systems. Ether malonate **311** (40 mg, 0.20 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (107 mg, 0.40 mmol), $Cu(OTf)_2$ (72 mg, 0.20 mmol) and LiCl (10 mg, 0.24 mmol) in MeCN (1.3 mL) reacted at 80°C. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 12:1 to 2:1), giving the title compound **318** as a colourless oil (38 mg, 0.16 mmol, 79%). R_f = 0.5 (PE_{40-60} / Et_2O, 10:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 2.44 (tq, 2 H, J= 1.3, 6.8 Hz, C(2)H_2), 3.75 (t, 2 H, J= 6.8 Hz, C(1)H_2), 3.87 (s, 6 H, C(3′)H_3), 5.07 (qd, 1 H, J= 1.2, 2.9, 10.2 Hz, C(4a)H), 5.12 (ddd, 1 H, J= 1.6, 17.2 Hz, C(4b)H), 5.79 (tdd, 1 H, J= 6.7, 10.2, 17.1 Hz, C(3)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 33.4 (C(2)), 54.3 (C(3′)), 67.3 (C(1)), 95.9 (C(2′)), 117.5 (C(4)), 133.6 (C(3)), 164.4 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2958w (C-H), 1763s (C=O), 1749s (C=O), 1280m, 1145s, 1051m; ***m/z*** LRMS (ESI^+) 259.0 ($[M+Na]^+$, 100%) and 261.0 ($[M+Na]^+$, 33%); HRMS (ESI^+) found

259.03439 [100%] and 261.03149 [33%]; $C_9H_{13}ClO_5$ $[M+Na]^+$ requires 259.03437 [100%] and 261.03142 [33%].

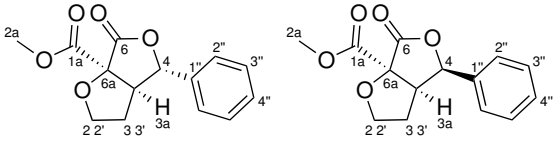
Dimethyl 3-(chloro(phenyl)methyl)dihydrofuran-2,2(3*H*)-dicarboxylate 314[126]



313 **314**

The title compound **314** has been prepared by following the **General Procedure 4** for the oxidative cyclisation for the synthesis of chloro monocyclic systems. Styrene-derived ether malonate **313** (100 mg, 0.36 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (193 mg, 0.72 mmol), $Cu(OTf)_2$ (130 mg, 0.36 mmol) and LiCl (18 mg, 0.43 mmol) in MeCN (2.4 mL) reacted at 40 °C. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 3:1 to 1:1), giving the title compound **314** as a colourless oil (45 mg, 0.14 mmol, 40%, 99:1 *dr*). R_f = 0.4 (PE_{40-60} / EtOAc, 9:1); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 2.14 (dtd, 1 H, *J*= 3.2, 7.2, 12.4 Hz, C(4)H), 2.47 (ddd, 1 H, *J*= 9.1, 12.4, 19.0 Hz, C(4′)H), 3.45 (ddd, 1 H, *J*= 4.0, 7.5, 10.2 Hz, C(3)H), 3.74 (s, 3 H, C(2a)H_3), 3.74 (s, 3 H, C(2a′)H_3), 3.92 (m, 1 H, C(5)H), 4.32 (dt, 1 H, *J*= 3.2, 8.5 Hz, C(5′)H), 5.52 (d, 1 H, *J*= 4.0 Hz, C(6)H), 7.30 (tt, 1 H, *J*= 2.7, 7.3 Hz, C(4″)H), 7.36 (t, 2 H, *J*= 7.6 Hz, C(3″)H), 7.45 (d, 2 H, *J*= 7.0 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 27.0 (C(4,4′)), 53.3 (C(2a)), 53.4 (C(2a′)), 53.6 (C(3)), 61.8 (C(6)), 69.0 (C(5,5′)), 87.1 (C(2)), 127.3 (C(2″)), 128.4 (C(4″)), 128.7 (C(3″)), 140.8 (C(1″)), 168.9 (C=O), 169.3 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2954w (C-H), 1739s (C=O), 1435w, 1286m, 1211m, 1090m; ***m/z*** LRMS (ESI^+) 335.0 ($[M+Na]^+$, 100%) and 337.0 ($[M+Na]^+$, 33%); HRMS (ESI^+) found 335.04731 [100%] and 337.06267 [33%]; $C_{15}H_{17}ClO_5$ $[M+Na]^+$ requires 335.06567 [100%] and 337.06272 [33%].

Methyl (3a*R*,4*S*,6a*S*)-6-oxo-4-phenyltetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate 315[126]

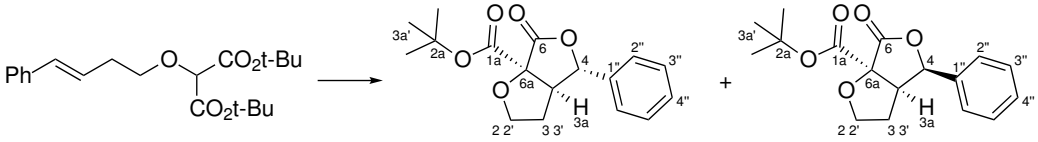


***maj*-315** ***min*-315**

The title compound **315** has been isolated in 56% yield (32.3:1 *dr*) as a side-product when submitting the ether malonate **313** to the conditions described in the **General Procedure 4** for the oxidative

cyclisation for the synthesis of chloro monocyclic systems. Characterisation is given for ***maj*-315**. R_f = 0.1 (PE_{40-60} / EtOAc, 5:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 2.18 (dddd, 1 H, J= 2.2, 3.9, 6.3, 13.0 Hz, C(3)H), 2.35 (tdd, 1 H, J= 7.9, 9.0, 13.0 Hz, C(3′)H), 3.36 (ddd, 1 H, J= 2.2, 5.7, 7.9 Hz, C(3a)H), 3.81 (s, 3 H, C(2a)H_3), 4.19 (dt, 1 H, J= 6.3, 9.1 Hz, C(2)H), 4.37 (ddd, 1 H, J= 7.9, 8.0, 9.0 Hz, C(2′)H), 5.19 (d, 1 H, J= 5.7 Hz, C(4)H), 7.44-7.34 (m, 5 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 31.9 (C(3,3′)), 53.4 (C(2a)), 54.5 (C(3a)), 70.8 (C(2,2′)), 84.9 (C(4)), 88.0 (C(6a)), 125.8 (2×C(Ar)), 129.1 (2× C(Ar)), 129.2 (C(4″)), 138.3 (C(1″)), 168.7 (C=O), 170.9 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2957w (C-H), 1778s (C=O), 1761s (C=O), 1731m (C=O), 1288m, 1254m, 1215m, 1049m, 1090m. *Data are in accordance with literature.*[60]

tert-Butyl (3a*R*,4*S*,6a*R*)-6-oxo-4-phenyltetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate **316**[126]

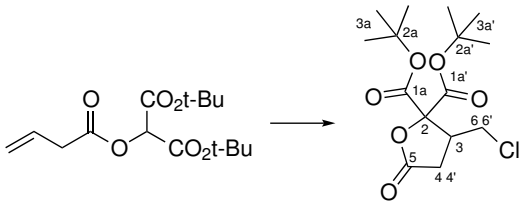


312 ***maj*-316** ***min*-316**

The title compound **316** has been isolated when submitting the ether malonate **312** to the conditions described in the **General Procedure 4** for the oxidative cyclisation for the synthesis of chloro monocyclic systems. Ether malonate **312** (80 mg, 0.22 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (118 mg, 0.44 mmol), $Cu(OTf)_2$ (80 mg, 0.22 mmol) and LiCl (11 mg, 0.26 mmol) reacted in MeCN (1.50 mL) at 40 °C. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 8:1 to 4:1), giving the title compound **316** as a colourless oil (48 mg, 0.16 mmol, 71%, 16:1 *dr*). R_f = 0.2 (PE_{40-60} / EtOAc, 4:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.43 (s, 9 H, C(3a′)H_3), 2.15 (dddd, 1 H, J= 1.1, 3.9, 6.2, 12.8 Hz, C(3)H), 2.37 (ddd, 1 H, J= 8.1, 12.9, 16.4 Hz, C(3′)H), 3.29 (ddd, 1 H, J= 2.8, 5.0, 8.0 Hz, C(3a)H), 4.16 (dt, 1 H, J= 6.3, 8.9 Hz, C(2)H), 4.34 (ddd, 1 H, J= 4.2, 7.6, 9.0 Hz, C(2′)H), 5.19 (d, 1 H, J= 5.1 Hz, C(4)H), 7.45-7.23 (m, 5 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 27.9 (C(3a′)), 32.6 (C(3,3′)), 54.3 (C(3a)), 70.7 (C(4)), 84.3 (C(2a)), 84.9 (C(2,2′)), 87.8 (C(6a)), 125.7 (2×C(Ar)), 128.9 (C(4″)), 129.0 (2×C(Ar)), 138.9 (C(1″)), 167.0 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2985w (C-H), 1783s (C=O), 1753s (C=O) 1256m, 1156m, 1104m, 1020s. *Data are in accordance with literature.*[60]

di-*tert*-Butyl 3-(chloromethyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate **306**[126]

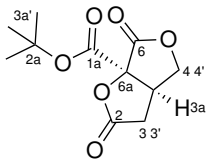
The title compound **306** has been synthesised by following the conditions described in the **General Procedure 4** for the oxidative cyclisation for the synthesis of chloro monocyclic systems. The ester



302 **306**

malonate **302** (100 mg, 0.33 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (177 mg, 0.66 mmol), $Cu(OTf)_2$ (119 mg, 0.33 mmol) and LiCl (17 mg, 0.40 mmol) reacted in MeCN (2.2 mL) at 80 °C. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 10:1 to 2:1), giving the title compound **306** as a white solid (71 mg, 0.20 mmol, 60%). R_f = 0.6 (PE_{40-60} / EtOAc 85:15); *m.p.* = 111-114 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.50 (s, 9 H, C(3a)H_3), 1.51 (s, 9 H, C(3a′)H_3), 2.62 (dd, 1 H, J= 9.6, 17.7 Hz, C(4)H), 2.88 (dd, 1 H, J= 8.2, 17.7 Hz, C(4′)H), 3.33-3.40 (m, 1 H, C(3)H), 3.39-3.44 (m, 1 H, C(6)H), 3.87 (dd, 1 H, J= 2.9, 9.9 Hz, C(6′)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 27.8 (C(3a)), 28.0 (C(3a′)), 32.9 (C(4,4′)), 43.2 (C(3)), 43.3 (C(6,6′)), 84.6 (C(2a)), 85.6 (C(2a′)), 86.0 (C(2)), 164.6 (2×C=O), 171.8 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2981w (C-H), 1808s (C=O), 1737s (C=O) 1371m, 1313m, 1251m, 1151s, 1084m; ***m/z*** LRMS (ESI^+) 357.0 ($[M+Na]^+$, 100%) and 359.0 ($[M+Na]^+$, 33%); HRMS (ESI^+) found 357.10756 [100%] and 359.10459 [33%], $C_{15}H_{23}ClO_6$ $[M+Na]^+$ requires 357.10754 [100%] and 359.10459 [33%].

tert-Butyl (3a*R*,6a*R*)-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate 307[126]

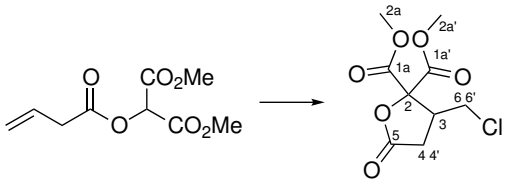


307

The title compound **307** has been isolated in 14% yield as side product after treatment of the ester malonate **302** to the conditions described in **General Procedure 4** for the synthesis of chloro monocyclic systems. Full caracterisation can be found in **Section 6.4**.

Dimethyl 3-(chloromethyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 304[126]

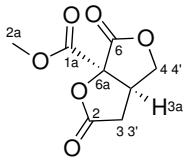
The title compound **304** has been prepared by following the conditions described in the **General Procedure 4** for the oxidative cyclisation for the synthesis of chloro monocyclic systems. Ester malonate **301** (100 mg, 0.46 mmol), $Mn(OAc)_3 \cdot 2H_2O$(247 mg, 0.92 mmol), $Cu(OTf)_2$ (166 mg, 0.46 mmol) and



301 **304**

LiCl (24 mg, 0.56 mmol) reacted in MeCN (3.1 mL) at 80 °C. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 3:1 to 1:1), giving the title compound **304** as a colourless oil (112 mg, 0.45 mmol, 90%). R_f = 0.3 (PE_{40-60} / EtOAc, 3:1); $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 2.74 (dd, 1 H, J= 10.5, 17.7 Hz, C(4)H), 2.86 (dd, 1 H, J= 8.6, 17.8 Hz, C(4′)H), 3.48 (m, 1 H, C(3)H), 3.57 (dd, 1 H, J= 7.8, 11.3 Hz, C(6)H), 3.85 (dd, 1 H, J= 3.9, 11.3 Hz, C(6′)H), 3.86 (s, 3 H, C(2a)H_3), 3.86 (s, 3 H, C(2a′)H_3); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 31.9 (C(4,4′)), 42.8 (C(3)), 43.3 (C(6,6′)), 54.0 (C(2a) and C(2a′)), 85.1 (C(2)), 165.9 (C=O), 166.2 (C=O), 172.2 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2959w (C-H), 1807s (C=O), 1747s (C=O), 1438m, 1303m, 1241m, 1169s, 1053m; ***m/z*** LRMS (ESI$^+$) 273.0 ([M+Na]$^+$, 100%) and 275.0 ([M+Na]$^+$, 33%); HRMS (ESI$^+$) found 273.01368 [100%] and 275.01071 [33%], $C_9H_{11}ClO_6$ [M+Na]$^+$ requires 273.01364 [100%] and m/z 275.01069 [33%].

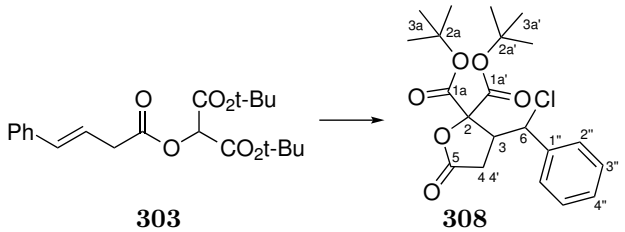
methyl (3a*R*,6a*S*)-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate[126]



305

The title compound **305** has been isolated in 5% yield as side product after treatment of the ester malonate **302** to the conditions described in **General Procedure 4** for the synthesis of chloro monocyclic systems. R_f = 0.1 (PE_{40-60} / EtOAc, 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 2.65 (dd, 1 H, J= 5.5, 18.6 Hz, C(3)H), 3.05 (dd, 1 H, J= 9.7, 18.5 Hz, C(3′)H), 3.56 (dddd, 1 H, J= 3.9, 5.5, 7.5, 9.5 Hz, C(3a)H), 3.92 (s, 3 H, C(2a)H_3), 4.25 (dd, 1 H, J= 3.9, 9.8 Hz, C(4)H), 4.74 (dd, 1 H, J= 7.4, 9.8 Hz, C(4′)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 33.3 (C(3,3′)), 40.1 (C(3a)), 54.2 (C(2a)), 70.9 (C(4,4′)), 171.9 (C=O) (quaternary carbons C(6), C(2) and C(6a) signals were not intense enough to be distinguished). *Data in accordance with the literature.*[60]

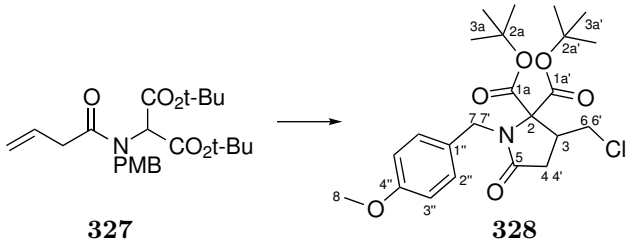
di-*tert*-Butyl 3-(chloro(phenyl)methyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 308[126]



303 **308**

The title compound **308** has been prepared by following the conditions described in the **General Procedure 4** for the synthesis of chloro monocyclic systems. Styrene-derived ester malonate **303** (125 mg, 0.33 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (177 mg, 0.66 mmol), $Cu(OTf)_2$ (119 mg, 0.33 mmol) and LiCl (34 mg, 0.40 mmol) reacted in MeCN (2.2 mL) at 40 °C. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 10:1 to 1:1), giving the title compound **308** as a white solid (33 mg, 0.080 mmol, 24%, 99:1 *dr*). R_f = 0.5 (PE_{40-60} / EtOAc, 9:1); *m.p.* = 106-109 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.50 (s, 9 H, C(3a)H_3), 1.58 (s, 9 H, C(3a′)H_3), 2.59 (dd, 1 H, *J*= 8.9, 17.6 Hz, C(4)H), 3.02 (dd, 1 H, *J*= 9.0, 17.6 Hz, C(4′)H), 3.57 (dt, 1 H, *J*= 2.1, 8.9 Hz, C(3)H), 5.61 (d, 1 H, *J*= 2.0 Hz, C(6)H), 7.32 (tt, 1 H, *J*= 2.5, 7.2 Hz, C(4″)H), 7.38 (t, 2 H, *J*= 7.7 Hz, C(3″)H), 7.43 (d, 2 H, *J*= 7.1 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 27.9 (C(3a)), 28.0 (C(3a′)), 29.0 (C(4,4′)), 48.9 (C(3)), 60.5 (C(6)), 84.7 (C), 85.3 (C), 86.4 (C), 126.9 (2×C(Ar)), 128.7 (C(4″)), 129.0 (2×C(Ar)), 139.7 (C(1″)), 164.6 (C=O), 165.3 (C=O), 173.2 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2985w (C-H), 1805s (C=O), 1736s (C=O), 1313m, 1251m, 1148s, 1080m; ***m/z*** LRMS (ESI$^+$) 433.2 ([M+Na]$^+$, 100%) and 435.2 ([M+Na]$^+$, 33%); HRMS (ESI$^+$) found 433.13809 [100%] and 435.13517 [33%], $C_{21}H_{27}ClO_6$ [M+Na]$^+$ requires 433.13884 [100%] and 435.13589 [33%].

di-*tert*-Butyl 3-(chloromethyl)-1-(4-methoxybenzyl)-5-oxopyrrolidine-2,2-dicarboxylate 328[126]

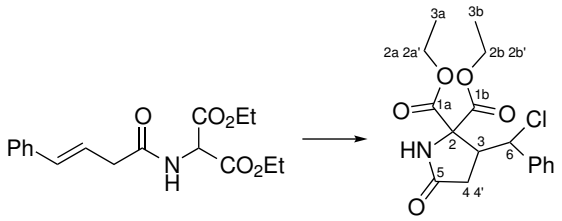


327 **328**

The title compound **328** was synthesised by following the conditions described in the **General Procedure 4** for the synthesis of chloro monocyclic systems. PMB-protected amidomalonate **327** (100 mg, 0.24 mmol) (synthesis described in **Section 6.4.2**), $Mn(OAc)_3 \cdot 2H_2O$ (129 mg, 0.48 mmol), $Cu(OTf)_2$ (87 mg, 0.24 mmol) and TBACl (79 mg, 0.29 mmol) reacted in MeCN (1.6 mL) at 40 °C.

The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 4:1 to 2:1), giving the title compound **328** as a white solid (43 mg, 0.095 mmol, 40%). R_f = 0.6 (PE_{40-60} / EtOAc, 85:15); *m.p.* = 113-117 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.22 (s, 9 H, C(3a)H_3), 1.46 (s, 9 H, C(3a′)H_3), 2.29-2.38 (m, 1 H, C(4)H), 2.80-2.89 (m, 1 H, C(4′)H), 3.33-3.41 (m, 1 H, C(3)H), 3.33-3.41 (m, 1 H, C(6)H, *masked*), 3.75 (s, 3 H, C(8)H_3), 3.86-3.88 (m, 1 H, C(6′)H), 4.28 (d, 1 H, *J*= 16.0 Hz, C(7)H), 4.88 (d, 1 H, *J*= 16.0 Hz, C(7′)H), 6.79 (d, 2 H, *J*= , 8.7 Hz, C(3″)H), 7.07 (d, 2 H, *J*= 8.7 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 27.4 (C(3a)), 28.0 (C(3a′)), 34.2 (C(4,4′)), 41.9 (C(3)), 44.3 (C(6,6′)), 45.8 (C(7,7′)), 55.5 (C(8)), 75.2 (C(2)), 84.3 (C(2a)), 84.8 (C(2a′)), 114.0 (C(3″)), 127.7 (C(2″)), 129.7 (C(1″)), 158.7 (C(4″)), 165.3 (C=O), 166.4 (C=O), 174.6 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2981w (C-H), 1808s (C=O), 1737s (C=O) 1371m, 1313m, 1251m, 1151s; ***m/z*** HRMS (ESI^+) found 476.18056 [100%] and 478.17740 [33%], $C_{23}H_{32}ClNO_6$ $[M+Na]^+$ requires 476.18104 [100%] and 478.17809 [33%].

Diethyl 3-(chloro(phenyl)methyl)-5-oxopyrrolidine-2,2-dicarboxylate 332

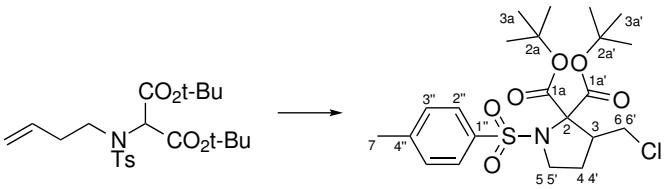


330 **332**

The title compound **332** has been synthesised by following the conditions described in the **General Procedure 4** for the oxidative cyclisation for the synthesis of chloro monocyclic systems. Amido malonate **330** (100 mg, 0.31 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (168 mg, 0.63 mmol), $Cu(OTf)_2$ (113 mg, 0.31 mmol) and LiCl (20 mg, 0.47 mmol) reacted in MeCN (2.0 mL) at 40 °C. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 6:1 to 0:1), giving the title compound **332** as a white solid (59 mg, 0.17 mmol, 53% yield, 1.17:1 *dr*). R_f = 0.2 (PE_{40-60} / EtOAc, 2:1); *m.p.* = 101-108 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$) ***major diastereosiomer***: 1.31 (t, 3 H, *J*= 7.2 Hz, C(3a)H_3), 1.34 (t, 3 H, *J*= 7.2 Hz, C(3b)H_3), 2.37 (dd, 1 H, *J*= 8.8, 16.7 Hz, C(4)H), 2.89 (dd, 1 H, *J*= 9.2, 17.0 Hz, C(4′)H), 3.60 (dt, 1 H, *J*= 2.3, 8.9 Hz, C(3)H), 4.22-4.38 (m, 4 H, C(2a)H, C(2a′)H, C(2b)H and C(2b′)H), 5.63 (d, 1 H, *J*= 2.3 Hz, C(6)H), 6.13 (brs, 1 H, N*H*), 7.31-7.47 (m, 5 H, C(Ar)H); ***minor diastereoisomer***: 1.32 (t, 3 H, *J*= 7.2 Hz, C(3a or 3b)H_3), 1.29-1.35 (t, 3 H, C(3a or 3b)H_3, *masked*), 2.52 (dd, 1 H, *J*= 1.7, 17.8 Hz, C(4)H), 2.75 (dd, 1 H, *J*= 8.8, 17.9 Hz, C(4′)H), 3.45 (t, 1 H, *J*= 7.2 Hz, C(3)H), 4.22-4.38 (m, 4 H, C(2a)H, C(2a′)H, C(2b)H and C(2b′)H), 5.23 (d, 1 H, *J*= 7.2 Hz, C(6)H), 6.43 (brs, 1 H,

N*H*), 7.31-7.47 (m, 5 H, C(Ar)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$) ***major diastereoisomer***: 14.1 (C(3a) and C(3b)), 30.3 (C(4,4′)), 48.6 (C(3)), 61.6 (C(6)), 63.2 (C(2a,2a′) or (2b,2b′)), 63.5 (C(2a,2a′) or (2b,2b′)), 70.0 (C(2)), 126.9 (2 x C(Ar)), 128.7 (C(Ar)), 128.9 (2 x C(Ar)), 139.9 (C(Ar)), 167.6 (C=O), 167.9 (C=O), 174.7 (C=O); ***minor diastereoisomer***: 14.0 (C(3a) and C(3b)), 34.4 (C(4,4′)), 48.1 (C(3)), 63.7 ((C(2a,2a′) and (2b,2b′)), 69.3 (C(2)), 85.5 (C(6)), 126.1 (2 x C(Ar)), 129.4 (2 x C(Ar)), 129.8 (C(Ar)), 136.9 (C(Ar)), 167.7 (C=O), 169.9 (C=O), 174.3 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3208br (N-H), 1780m (C=O), 1715s (C=O), 1275m; ***m/z*** LRMS (ESI$^+$) 354.2 ([M+H]$^+$, 100%) and 356.2 ([M+H]$^+$, 33%); HRMS (ESI$^+$) found 354.11048 [80%] and 356.10977 [100%], $C_{17}H_{20}ClNO_5$ [M+H]$^+$ requires 354.11028 [100%] and 356.10733 [33%].

di-*tert*-Butyl 3-(chloromethyl)-1-tosylpyrrolidine-2,2-dicarboxylate 333



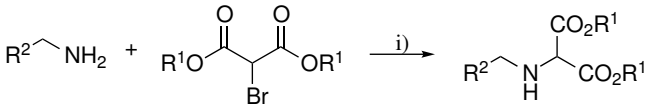
331 **333**

The title compound **333** has been synthesised by following the conditions described in the **General Procedure 4** for the oxidative cyclisation for the synthesis of chloro monocyclic systems. Tosyl-protected aminomalonate **331** (100 mg, 0.23 mmol) (synthesis described in **Section 6.4.2**), $Mn(OAc)_3 \cdot 2H_2O$ (122 mg, 0.46 mmol), $Cu(OTf)_2$ (82 mg, 0.23 mmol) and LiCl (15 mg, 0.34 mmol) reacted in MeCN (1.5 mL) at 40 °C. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 8:1 to 7:1), giving the title compound **333** as a white solid (36 mg, 0.075 mmol, 33% yield). R_f = 0.6 (PE_{40-60} / EtOAc, 7:1); *m.p.* = 122-126 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.55 (s, 9 H, C(3a)H_3), 1.56 (s, 9 H, C(3a′)H_3), 1.88 (quint, 1 H, *J*= 8.9 Hz, C(4)H), 2.21 (dtd, 1 H, *J*= 2.7, 6.6, 12.7 Hz, C(4′)H), 2.41 (s, 3 H, C(7)H_3), 2.92 (ddt, 1 H, *J*= 4.2, 6.2, 10.5 Hz, C(3)H), 3.20 (dt, 1 H, *J*= 6.9, 9.2 Hz, C(5)H), 3.45 (t, 1 H, *J*= 10.7 Hz, C(6)H), 3.49 (dt, 1 H, *J*= 2.7, 8.8 Hz, C(5′)H), 3.87 (dd, 1 H, *J*= 4.2, 10.9 Hz, C(6′)H), 7.28 (d, 2 H, *J*= 8.1 Hz, C(3″)H), 7.88 (d, 2 H, *J*= 8.3 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 21.7 (C(7)), 27.9 (C(3a) and C(3a′)), 28.8 (C(4,4′)), 43.9 (C(6)), 46.4 (C(5,5′)), 52.3 (C(3)), 77.3 (C(2)), 83.5 (C(2a)), 84.2 (C(2a′)), 128.2 (C(2″)), 129.4 (C(3″)), 137.5 (C(Ar)), 143.3 (C(Ar)), 166.2 (C=O), 167.2 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2979w (C-H), 1730m (C=O), 1151s (C-O-C); ***m/z*** LRMS (ESI$^+$) 496.2 ([M+Na]$^+$, 100%) and 498.2 ([M+Na]$^+$, 33%); HRMS (ESI$^+$) found 496.15211 [100%] and 498.14887 [33%], $C_{22}H_{32}ClNO_6S$ [M+Na]$^+$ requires 496.15311 [100%] and 498.15016 [33%].

6.4 MAN / KI Methodology Extension

6.4.1 General Procedures

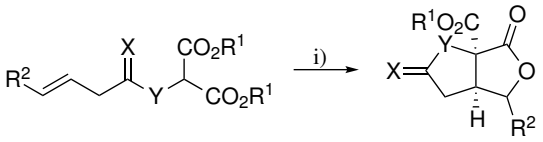
General Procedure 7: Alkylation of Amines



Reagents & Conditions: i) Et_3N, $CHCl_3$, reflux, 1-3 d.

According to the general procedure reported by Hess *et al.* for the alkylation of amines,[158,159] di-alkyl 2-bromomalonate (1 eq), the primary amine (1.2 eq) and triethylamine (2.5 eq) were dissolved in dry $CHCl_3$ (0.33 M) and heated under reflux for 1-3 days. The evolution of the reaction was followed by TLC analysis. After completion, the reaction mixture was cooled down to r.t. and quenched with H_2O (the volume used equals the volume of solvent used). The organic phase was decanted off and the aqueous layers were extracted (DCM). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by FC.

General Procedure 8: Cu-Free Oxidative Radical Cyclisation

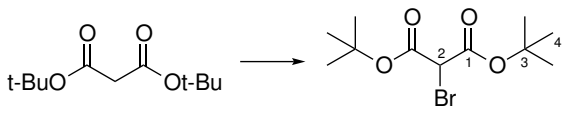


To a solution of the malonate derivative (1.0 eq.) in MeCN (0.15 M) (previously sparged with Ar over 15 min) were added $Mn(OAc)_3 \cdot 2H_2O$ (3 eq.) and KI (0.5 eq.) and the system was left to react at 80 °C for 21 h in the absence of light. The reaction was quenched with $Na_2S_2O_3$ aq. sat. sol. and the aqueous phase was extracted with EtOAc (3 x). The combined organic layers were washed with brine (1 x), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (PE_{40-60} / EtOAc).

6.4.2 Characterisation

6.4.2.1 Synthesis of the Substrates

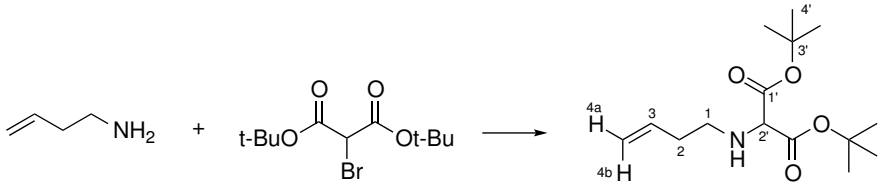
di-*tert*-Butyl 2-bromomalonate 434



433 **434**

According to the procedure of Perreault *et al.*,[156] DBU (9.7 mL, 65.0 mmol) was slowly added to a solution of *tert*-butyl malonate **433** (14.6 mL, 65.0 mmol) in anhydrous THF (520 mL) at 0 °C. The reaction mixture was left to stir at 0 °C for 30 min and was then cooled down to -78 °C. CBr_4 (21.6 g, 65.0 mmol) was then added in one portion at this temperature. The reaction mixture was left to stir and react at -78 °C for 2 h. The reaction was quenched by the slow addition of NH_4Cl aq. sat. sol. (200 mL/ 400 mL of THF) and the system was left to warm to r.t. The organic layer was decanted off and washed with brine. The combined aqueous layers were extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude was then fractionally distilled under reduced pressure (0.6 mmHg, *b.p.* = 82 °C), giving the title compound **434** as a colourless oil (16.9 g, 57.3 mmol, 88% yield). R_f = 0.4 (PE_{40-60} / EtOAc, 19:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.48 (s, 18 H, C(4)H_3), 4.65 (s, 1 H, C(2)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 27.5 (C(4)), 45.5 (C(2)), 83.7 (C(3)), 163.4 (C=O); ***m/z*** LRMS (ESI^+): 317.1 ($[M+Na]^+$). *Data in accordance with the literature.*[175]

di-*tert*-Butyl 2-(but-3-en-1-ylamino)malonate 441

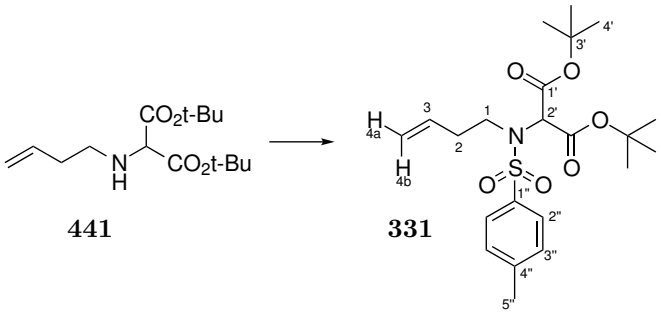


496 **434** **441**

The title compound **441** was synthesised by following the **General Procedure 7** for the alkylation of amines. The amine **496** (1.03 mL, 11.2 mmol), di-*tert*-butyl 2-bromomalonate **434** (3.65 g, 12.4 mmol) and Et_3N (3.90 mL, 28.1 mmol) reacted in $CHCl_3$ (43 mL) for 28 h. The crude was purified by FC (PE_{40-60} / EtOAc, 9:1), giving the title compound **441** as a yellow liquid (2.35 g, 8.23 mmol, 73% yield). R_f = 0.6 (PE_{40-60} / EtOAc, 9:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.47 (s, 18 H, C(4′)H_3), 1.89 (brs, N*H*), 2.27 (dq, 2 H, *J*= 1.1, 6.9 Hz, C(2)H_2), 2.65 (t, 2 H, *J*= 6.9 Hz, C(1)H_2), 3.85 (s, 1 H, C(2′)H), 5.04 (d, 1 H, *J*= 10.0 Hz, C(4a)H), 5.11 (td, 1 H, *J*= 1.6, 17.2 Hz, C(4b)H), 5.78 (tdd, 1 H, *J*= 6.8, 10.2, 17.1 Hz, C(3)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 28.1 (C(4′)), 34.4 (C(2)), 46.7 (C(1)), 66.6 (C(2′)), 82.3

(C(3′)), 116.7 (C(4)), 136.1 (C(3)), 168.0 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2979w (C-H), 1734s (C=O), 1369m, 1144s (C-O-C); ***m/z*** LRMS (ESI^+): 286.2 ($[M+H]^+$, 100%); HRMS (ESI^+) found 286.2013; $C_{15}H_{27}NO_4$ $[M+H]^+$ requires 286.2013.

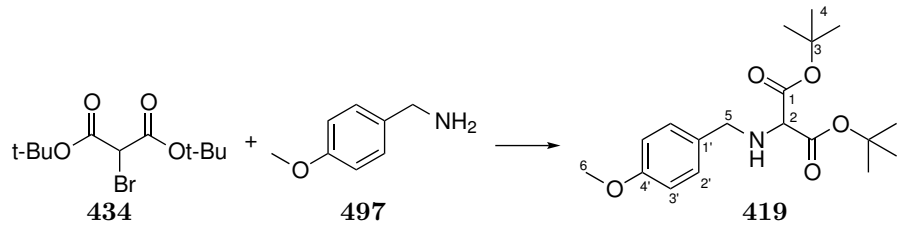
di-*tert*-Butyl 2-((*N*-(but-3-en-1-yl)-4-methylphenyl)sulfonamido)malonate 331



To a stirred solution of compound **441** (2.3 g, 8.1 mmol) in freshly distilled pyridine (8.0 mL) was added portionwise TsCl (2.30 g, 12.1 mmol) at 0 °C. The mixture was left to reach and react at r.t. for 17 h. The reaction was quenched with a solution of NaOH 2 M (12 mL) and DCM (20 mL). The organic phase was decanted off and the aqueous phase was extracted with DCM (2 x 20 mL). The collected organic phase was then washed with HCl 1.0 M (2 x 20 mL), brine, dried ($MgSO_4$) and filtered. After evaporation of the solvent *in vacuo*, the crude was purified by FC (PE_{40-60} / Et_2O, 6:1), giving the title compound **331** as a white solid (3.3 g, 7.5 mmol, 93% yield). R_f = 0.4 (5:1 PE_{40-60} / Et_2O); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.42 (s, 18 H, C(4′)H_3), 2.40 (s, 3 H, C(5″)H_3), 2.45 (m, 2 H, C(2)H_2), 3.38 (dt, 2 H, J= 5.2, 8.4 Hz, C(1)H_2), 4.99 (d, 1 H, J= 10.4 Hz, C(4a)H), 5.03 (dd, 1 H, J= 2.0, 17.2 Hz, C(4b)H), 5.07 (s, 1 H, C(2′)H), 5.69 (tdd, 1 H, J= 6.8, 10.3, 17.2 Hz, C(3)H), 7.27 (d, 2 H, J= 8.4 Hz, C(3″)H), 7.71 (d, 2 H, J= 8.4 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 21.6 (C(5″)), 27.9 (C(4′)), 34.9 (C(2)), 47.1 (C(1)), 64.4 (C(2′)), 83.3 (C(3′)), 116.7 (C(4)), 127.5 (C(2″)), 129.6 (C(3″)), 134.9 (C(3)), 136.9 (C(1″)), 143.6 (C(4″)), 165.3 (C=O); ***m/z*** LRMS (ESI^+) 462.2 ($[M+Na]^+$, 100%).*Data in accordance with the literature.*[176]

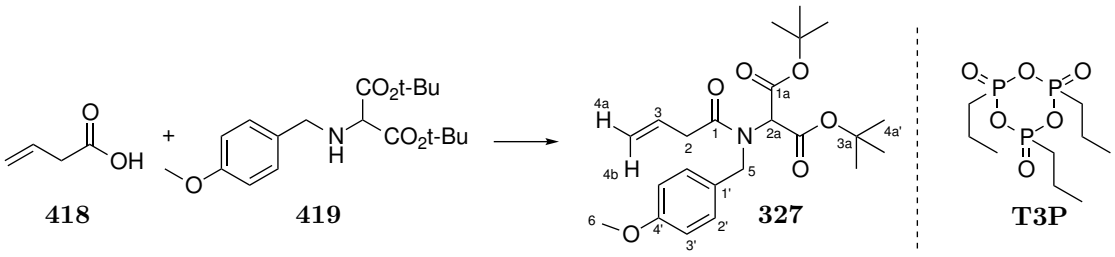
di-*tert*-Butyl 2-((4-methoxybenzyl)amino)malonate 419

The title compound **419** was synthesised by following the **General Procedure 7** for the alkylation of amines. Bromomalonate **434** (16.9 g, 57.3 mmol), *para*-methoxybenzyl amine **497** (14.9 mL, 114.6 mmol) and Et_3N (15.9 mL, 114.6 mmol) reacted in $CHCl_3$ (270 mL) for 10 h under reflux conditions. The crude was purified by FC (PE_{40-60} / EtOAc, 9:1), giving the title compound **419** as a yellowish oil



(17.9 g, 50.9 mmol, 88% yield). R_f = 0.8 (PE_{40-60} / EtOAc, 4:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.47 (s, 18 H, C(4)H_3), 3.73 (s, 2 H, C(5)H_2), 3.79 (s, 3 H, C(6)H_3), 3.84 (s, 1 H, C(2)H), 6.85 (d, 2 H, J= 8.0 Hz, C(3′)H), 7.26 (d, 2 H, J= 8.0 Hz, C(2′)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 28.1 (C(4)), 50.9 (C(5)), 55.4 (C(6)), 65.6 (C(2)), 82.3 (C(3)), 113.9 (C(3′)), 129.8 (C(2′)), 131.0 (C(1′)), 158.9 (C(4′)), 167.8 (C=O); ***m/z*** LRMS (ESI^+): 352.2 ([M+H]$^+$, 100%). *Data in accordance with the literature.*[175]

di-*tert*-Butyl 2-(*N*-(4-methoxybenzyl)but-3-enamido)malonate 327



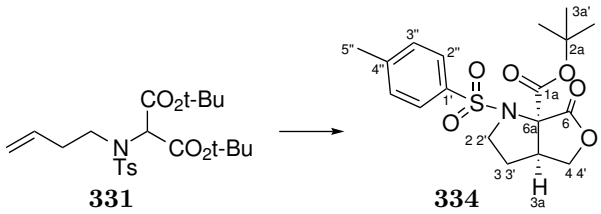
According to the modified procedure reported by Dunetz *et al.*,[157] to a solution of butenoic acid **418** (5.2 mL, 60.9 mmol) in EtOAc (20 mL) were added at 0 °C freshly distilled pyridine (17.2 mL, 213.0 mmol) and a solution of amino malonate **419** (17.9 g, 50.8 mmol) in EtOAc (20 mL). The coupling agent T3P (48 mL, 81.3 mmol, 50 wt% in EtOAc) was then added dropwise at 0 °C over 30 min. The reaction was left to react at 0 °C and then at r.t for 14 h. The reaction was quenched with a mixture of H_2O / NH_4Cl aq. sat. sol. (1:1, 50 mL) and the organic phase was decanted off. The aqueous phase was extracted (EtOAc, 3 x 50 mL) and the collected organic fractions were washed with a pH = 2.0 buffer solution, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (PE_{40-60} / EtOAc, 4:1), giving the title compound **327** as a yellowish solid (20.5 g, 48.9 mmol, 96% yield). R_f = 0.4 (PE_{40-60} / EtOAc, 4:1); *m.p.* = 48-51 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) a mixture of rotamers **R1** (major) and **R2** (minor) is present (ratio 89:11): 1.34 (s, 18 H, C(4a′)H_3, [R2]), 1.37 (s, 18 H, C(4a′)H_3, [R1]), 3.09 (d, 2H, J= 6.4 Hz, C(2)H_2, [R1]), 3.17 (d, 2 H, J= 6.2 Hz, C(2)H_2, [R2]), 3.74 (s, 3 H, C(6)H_3, [R2]) 3.79 (s, 3 H, C(6)H_3, [R1]), 4.67 (s, 2 H, C(5)H_2, [R1]), 4.71 (s, 2 H, C(5)H_2,

[R2]), 5.08 (d, 1 H, J= 17.2 Hz, C(4b)H, [R1; *R2 masked*]), 5.13 (d, 1 H, J= 10.4 Hz, C(4a)H, [R1]), 5.17 (d, 1 H, J= 9.5 Hz, C(4a)H, [R2]), 5.42 (s, 1 H, C(2a)H, [R1]), 5.53 (s, 1 H, C(2a)H, [R2]), 5.93 (tdd, 1 H, J= 6.4, 10.3, 17.0 Hz, C(3)H, [R1]), 6.07 (d, 1 H, J= 15.0 Hz, C(3)H, [R2]), 6.78 (d, 2 H, J= 8.4 Hz, C(3′)H, [R2]), 6.85 (d, 2 H, J= 8.4 Hz, C(3′)H, [R1]), 6.99 (d, 2 H, J= 8.8 Hz, C(2′)H, [R2]), 7.15 (d, 2 H, J= 8.4 Hz, C(2′)H, [R1]); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) a mixture of rotamers *R1* (major) and *R2* (minor) is present: 27.5 (C(4a′), [R1+R2]), 38.3 (C(2), [R1+R2]), 49.7 (C(5), [R1+R2]), 55.0 (C(6), [R1]), 55.3 (C(6), [R2]), 62.2 (C(2a), [R1+R2]), 82.5 (C(3a), [R1]), 83.3 (C(3a), [R2]), 113.4 (C(3′), [R2]), 113.8 (C(3′), [R1]), 117.8 (C(4), [R1+R2]), 127.1 (C(2′), [R1+R2]), 128.7 (C(1′)), 130.1 (C(3), [R1+R2]), 158.7 (C(4′), [R1+R2]), 165.2 (C=O, [R1+R2]), 172.2 (C=O, [R1+R2]); ***m/z*** LRMS (ESI^+): 442.1 ($[M+H]^+$, 100%). *Data in accordance with the literature.*[175]

6.4.2.2 Oxidative Cyclisations

tert-Butyl (3a*S*,6a*R*)-6-oxo-1-tosyltetrahydro-1*H*-furo[3,4-b]pyrrole-6a(6*H*)-carboxylate

334

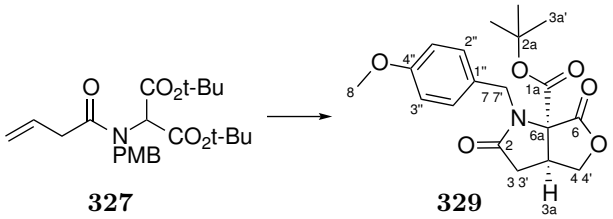


The title compound **334** has been synthesised by following the **General Procedure 8** for the oxidative cyclisation. Aminomalonate **331** (100 mg, 0.23 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (183 mg, 0.68 mmol) and KI (19 mg, 0.11 mmol) in MeCN (1.5 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 3:1 to 1:1), giving the title compound **334** as a white solid (38 mg, 0.09 mmol, 44% yield). R_f = 0.3 (PE_{40-60} / EtOAc, 1:1); *m.p.* = 163-166 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.56 (s, 9 H, C(3a′)H_3), 1.81 (ddd, 1 H, J= 7.8, 9.8, 12.8 Hz, C(3)H), 2.28 (dddd, 1 H, J= 2.8, 6.4, 7.5, 12.8 Hz, C(3′)H), 2.39 (s, 3 H, C(5″)H_3), 3.23 (dtd, 1 H, J= 2.0, 6.2, 13.4 Hz, C(3a)H), 3.31 (ddd, 1 H, J= 2.9, 8.1, 9.4 Hz, C(2)H), 3.58 (ddd, 1 H, J= 6.4, 9.3, 9.8 Hz, C(2′)H), 4.05 (dd, 1 H, J= 2.1, 9.6 Hz, C(4)H), 4.36 (dd, 1 H, J= 6.3, 9.6 Hz, C(4′)H), 7.27 (dd, 2 H, J= 0.7, 8.6 Hz, C(3″)H), 7.92 (td, 2 H, J= 2.0, 8.7 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 21.7 (C(5″)), 27.9 (C(3a′)), 29.5 (C(3,3′)), 48.8 (C(3a)), 49.1 (C(2,2′)), 67.8 (C(4,4′)), 73.9 (C(6a)), 84.9 (C(2a)), 128.2 (C(2″)), 129.5 (C(3″)), 137.0 (C(Ar)), 143.7 (C(Ar)), 166.9 (C=O), 170.6 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2979w (C-H), 1789m (C=O), 1724m, 1671m,

1344m (S=O), 1160s (C-O-C); ***m/z*** HRMS (ESI$^+$) found 404.11287; $C_{18}H_{23}NO_6S$ [M+Na]$^+$ requires 404.11383.

tert-Butyl (3a*S*,6a*R*)-1-(4-methoxybenzyl)-2,6-dioxotetrahydro-1*H*-furo[3,4-*b*]pyrrole-6a(6*H*)-carboxylate

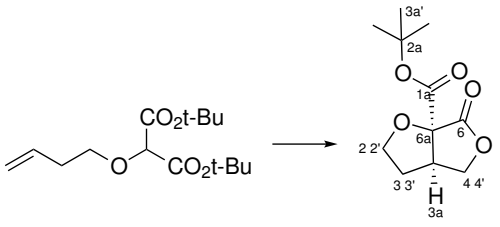
329



327 **329**

The title compound **329** has been synthesised by following the **General Procedure 8** for the Cu-free oxidative cyclisation. Amido malonate **327** (4.1 g, 9.8 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (7.9 g, 29.5 mmol), KI (0.82 g, 4.9 mmol) in MeCN (65 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 2:1 to 1:2), giving the title compound **329** as a yellow oil (2.9 g, 8.0 mmol, 83% yield). R_f= 0.2 (PE_{40-60} / EtOAc, 1:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.42 (s, 9 H, C(3a′)H_3), 2.36 (d, 1 H, J= 17.6 Hz, C(3)H), 2.74 (ddd, 1 H, J= 1.6, 8.4, 17.6 Hz, C(3′)H), 3.30 (q, 1 H, J= 8.0 Hz, C(3a)H), 3.76 (s, 3 H, C(8)H_3), 3.93 (t, 1 H, J= 7.8 Hz, C(4)H), 4.45 (dd, 1 H, J= 1.6, 15.2 Hz, C(7)H), 4.62 (t, 1 H, J= 9.3 Hz, C(4′)H), 4.70 (d, 1 H, J= 15.2 Hz, C(7′)H), 6.80 (d, 2 H, J= 8.8 Hz, C(3″)H), 7.27 (d, 2 H, J= 8.8 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 27.9 (C(3a′)), 34.1 (C(3,3′)), 39.4 (C(3a)), 45.2 (C(7,7′)), 55.2 (C(8)), 71.3 (C(6a)), 71.4 (C(4,4′)), 85.0 (C(2a)), 113.9 (C(3″)), 128.6 (C(1″)), 130.3 (C(2″)), 159.1 (C(4″)), 166.4 (C=O), 169.7 (C=O), 173.2 (C=O); ***m/z*** LRMS (ESI$^+$): 384.1 ([M+Na)$^+$, 100%). *Data in accordance with the literature.*[55]

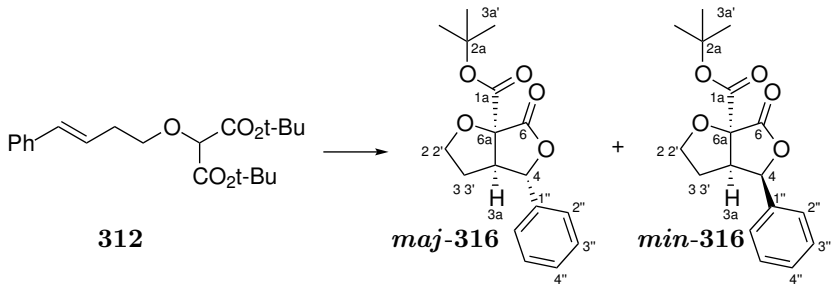
tert-Butyl (3a*R*,6a*R*)-6-oxotetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate 498



310 **498**

The title compound **498** has been synthesised by following the **General Procedure 8** for the Cu-free oxidative cyclisation. Ether malonate **310** (100 mg, 0.35 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (281 mg, 1.05 mmol), KI (29 mg, 0.18 mmol) in MeCN (2.3 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 2:1 to 1:2), giving the title compound **498** as a yellowish solid (54 mg, 0.24 mmol, 68% yield). R_f = 0.2 (PE_{40-60} / EtOAc, 2:1) $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.50 (s, 9 H, C(3a′)H_3), 1.93 (qd, 1 H, *J*= 7.1, 13.4 Hz, C(3)H), 2.38 (dtd, 1 H, *J*= 5.9, 6.6, 8.9, 12.6 Hz, C(3′)H), 3.22 (dtd, 1 H, *J*= 2.3, 6.7, 11.2 Hz, C(3a)H), 4.07 (ddd, 1 H, *J*= 5.9, 7.2, 8.9 Hz, C(2)H), 4.13 (td, 1 H, *J*= 6.9, 8.9 Hz, C(2′)H), 4.20 (dd, 1 H, *J*= 2.3, 9.4 Hz, C(4)H), 4.53 (dd, 1 H, *J*= 7.0, 9.4 Hz, C(4′)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 28.0 (C(3a′)), 33.1 (C(3,3′)), 45.6 (C(3a)), 70.8 (C(4,4′) and C(2,2′)), 84.2 (C), 86.8 (C), 166.7 (C=O), 172.4 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2980w (C-H), 2921w (C-H), 1781s (C=O), 1754s (C=O), 1372m, 1158m, 1117m; ***m/z*** HRMS (ESI^+) found 251.08909; $C_{11}H_{16}O_5$ $[M+Na]^+$ requires 251.08899. *Data in accordance with the literature.*[60]

tert-Butyl (3a*R*,4*S*,6a*R*)-6-oxo-4-phenyltetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate _maj_-316 and **_tert_-butyl (3a*R*,4*R*,6a*R*)-6-oxo-4-phenyltetrahydrofuro[3,4-*b*]furan-6a(6*H*)-carboxylate _min_-316**



The title compound **316** has been synthesised by following **General Procedure 8** for the Cu-free oxidative cyclisation. Ether malonate **312** (100 mg, 0.28 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (222 mg, 0.83 mmol) and KI (23 mg, 0.14 mmol) in MeCN (1.8 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 6:1 to 3:1), giving the title compound **316** as a yellowish oil (53 mg, 0.17 mmol, 63%, 13.3:1 *dr*). R_f = 0.4 (PE_{40-60} / EtOAc, 3:1); *only the major diastereoisomer is characterised*; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.42 (s, 9 H, C(3a′)H_3), 2.15 (dddd, 1 H, *J*= 2.9, 4.1, 9.1, 10.4 Hz, C(3)H), 2.36 (qd, 1 H, *J*= 8.0, 12.9 Hz, C(3′)H), 3.28 (ddd, 1 H, *J*= 2.8, 5.1, 8.0 Hz, C(3a)H), 4.14 (dt, 1 H, *J*= 6.2, 8.9 Hz, C(2)H), 4.32 (ddd, 1 H, *J*= 4.2, 7.6, 8.9 Hz, C(2′)H), 5.19 (d, 1 H, *J*= 5.1 Hz, C(4)H), 7.34-7.43 (m, 5 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 27.9 (C(3a′)), 32.6 (C(3,3′)), 54.2 (C(3a)), 70.7 (C(2,2′)),

84.2 (C), 84.8 (C(4)), 87.8 (C), 125.6 (3×C(Ar)H), 129.0 (2×C(Ar)), 138.9 (C(1″)), 166.9 (C=O), 171.5 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2979w (C-H), 1780s (C=O), 1751s (C=O), 1327m, 1256m, 1156s (C-O-C), 1092s (C-O-C), 1019s; ***m/z*** HRMS (ESI$^+$) found 327.12031; $C_{17}H_{20}O_5$ [M+Na]$^+$ requires 327.12029. *Data in accordance with the literature.*[60]

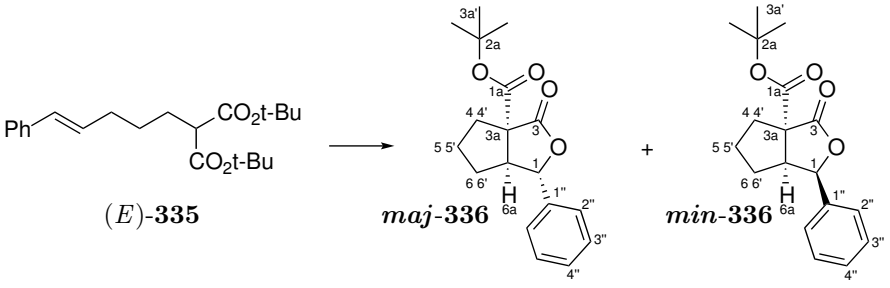
***tert*-Butyl**

(1*S*,3a*S*,6a*S*)-3-oxo-1-phenyltetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate

***maj*-336** and ***tert*-butyl**

(1*R*,3a*S*,6a*S*)-3-oxo-1-phenyltetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate

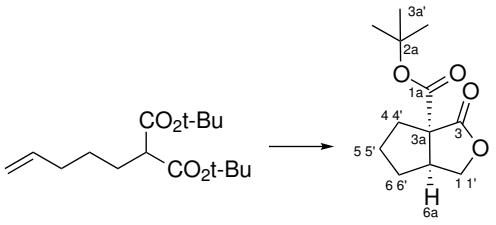
***min*-336**



The title compounds **336** have been synthesised by following the **General Procedure 8** for the Cu-free oxidative cyclisation. Malonate **335** (60 mg, 0.17 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (134 mg, 0.49 mmol) and KI (28 mg, 0.17 mmol) in MeCN (1.1 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 20:1 to 10:1), giving the title compounds **336** as a white solid (49 mg, 0.16 mmol, 88% yield, 9:1 *dr*). R_f = 0.2 (PE_{40-60} / EtOAc, 12:1); *m.p.* = 89-94 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.38 (s, 9 H, C(3a′)H_3), 1.70 (m, 1 H, C(5)H), 1.89-2.05 (m, 3 H, C(5′)H, C(6)H and C(6′)), 2.27 (ddd, 1 H, *J*= 2.3, 6.7, 12.8 Hz, C(4)H), 2.41 (ddd, 1 H, *J*= 6.7, 11.3, 13.4 Hz, C(4′)H), 3.06-3.09 (m, 1 H, C(6a)H), 5.02 (d, 1 H, *J*= 4.6 Hz, C(1)H); $\boldsymbol{\delta_C}$ (500 MHz, $CDCl_3$): 25.7 (C(5,5′)), 27.8 (C(3a′)), 34.0 (C(6,6′)), 35.0 (C(4,4′)), 54.8 (C(6a)), 63.3 (C(3a)), 82.9 (C(2a)), 86.1 (C(1)), 125.5 (2×C(Ar)), 128.5 (C(4″)), 128.8 (2×C(Ar)), 140.4 (C(1″)), 169.5 (C=O), 176.6 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2976w (C-H), 1773s (C=O), 1732s (C=O), 1455w (C=C), 1394m, 1256m, 1144s (C-O-C); ***m/z*** LRMS (ESI$^+$): 325.2 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 325.14102; $C_{18}H_{22}O_4$ [M+Na]$^+$ requires 325.14103.

***tert*-Butyl (3a*S*,6a*S*)-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate 350**

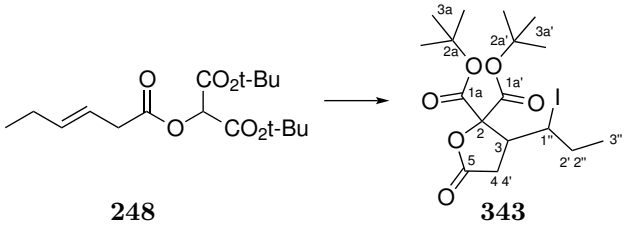
The title compound **350** has been synthesised by following the **General Procedure 8** for the Cu-free oxidative cyclisation. Malonate **349** (100 mg, 0.35 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (282 mg, 1.1 mmol)



349 **350**

and KI (29 mg, 0.18 mmol) in MeCN (2.4 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 14:1 to 12:1), giving the title compound **350** as a white solid (37 mg, 0.16 mmol, 46% yield). R_f = 0.4 (PE_{40-60} / EtOAc, 8:1); *m.p.* =63-68 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.46 (s, 9 H, C(3a′)H_3), 1.57-1.66 (m, 2 H, C(6)H and C(5′)H), 1.74-1.83 (m, 1 H, C(5)H), 1.99-2.09 (m, 1 H, C(6′)H), 2.14-2.21 (m, 1 H, C(4)H), 2.29-2.37 (m, 1 H, C(4′)H), 2.98-3.04 (m, 1 H, C(6a)H), 4.07 (dd, 1 H, J= 2.2, 9.2 Hz, C(1)H), 4.52 (dd, 1 H, J= 7.4, 9.2 Hz, C(1′)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 26.1 (C(5,5′)), 27.9 (C(3a′)), 34.1 (C(6,6′)), 34.2 (C(4,4′)), 46.1 (C(6a)), 62.7 (C(3a)), 73.2 (C(1,1′)), 82.9 (C(2a)), 169.0 (C=O), 177.1 (C=O); $\boldsymbol{\nu_{max}}$ **/** $\mathbf{cm^{-1}}$ 2975w (C-H), 2874w (C-H), 1769s (C=O), 1732s (C=O), 1369m, 1257m (C-O-C), 1139s (C-O-C); ***m/z*** LRMS (ESI^+): 227.0 ($[M+H]^+$, 100%); HRMS (ESI^+) found 227.12802; $C_{12}H_{18}O_4$ $[M+H]^+$ requires 227.12779.

di-*tert*-Butyl 3-(1-iodopropyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 343

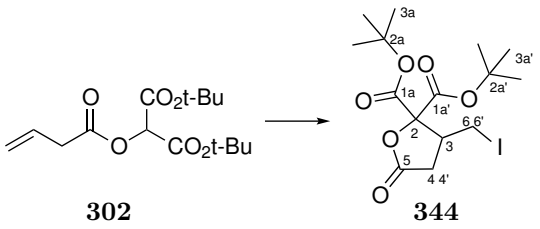


248 **343**

To a solution of alkenyl malonate **248** (500 mg, 1.5 mmol) in MeCN (previously sparged with argon over 15 min, 10 mL) was added $Mn(OAc)_3 \cdot 2H_2O$ (818 mg, 3.1 mmol), $Cu(OTf)_2$ (550 mg, 1.5 mmol) and KI (379 mg, 2.3 mmol). The suspension was left to reach and react at 80 °C for 2.5 h in the absence of light. The reaction mixture was then left to cool down and was quenched with a $Na_2S_2O_3$ aq. sat. solution. The aqueous phase was extracted with EtOAc (3 x 40 mL) and the recovered organic layers were washed with brine (1 x 50 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 4:1 to 1:1), giving the halo-lactone **343** as a yellow oil (146 mg, 0.32 mmol, 21% yield, 3.5:1 *dr*). R_f (PE_{40-60}/ EtOAc, 5:1) = 0.7; $\boldsymbol{\delta_H}$

(400 MHz, $CDCl_3$) ***maj*-343**: 1.05 (t, 3 H, J= 7.2 Hz, C(3″)H_3), 1.49 (s, 9 H, C(3a)H_3), 1.54 (s, 9 H, C(3a′)H_3), 1.79-1.87 (m, 2 H, C(2′)H and C(2″)H), 2.66 (dd, 1 H, J= 9.4, 17.7 Hz, C(4)H), 2.93 (dd, 1 H, J= 8.7, 17.7 Hz, C(4′)H), 3.32 (dt, 1 H, J= 7.4, 8.9 Hz, C(3)H), 4.13 (ddd, 1 H, J= 5.2, 7.4, 8.3 Hz, C(1″)H); ***min*-343**: 0.99 (t, 3 H, J= 7.0 Hz, C(3″)H_3), 1.49 (s, 9 H, C(3a)H_3), 1.53 (s, 9 H, C(3a′)H_3), 1.47-1.49 (C(2′)H and C(2″)H, *masked*), 2.74 (dd, 1 H, J= 3.9, 18.0 Hz, C(4)H), 2.97 (dd, 1 H, J= 9.0, 18.0 Hz, C(4′)H), 3.79 (td, 1 H, J= 3.8, 8.9 Hz, C(3)H), 4.40 (ddd, 1 H, J= 2.3, 3.4, 11.6 Hz, C(1″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) ***maj*-343**: 15.0 (C(3″)), 27.7 (C(3a)), 27.9 (C(3a′)), 32.9 (C(2′,2″)), 37.8 (C(4,4′) and C(1″)), 47.3 (C(3)), 81.6 (C), 84.5 (C), 85.1 (C), 164.9 (C=O), 166.2 (C=O), 172.2 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 1798m (C=O, lactone), 1736s (C=O, ester), 1147s (C-O-C); ***m/z*** LRMS (ESI$^+$): 477.0 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 477.07407; $C_{17}H_{27}IO_6$ [M+Na]$^+$ requires 477.07445.

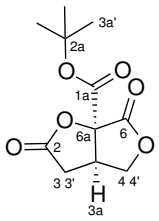
di-*tert*-Butyl 3-(iodomethyl)-5-oxodihydrofuran-2,2(3*H*)-dicarboxylate 344[126]



302 **344**

To a solution of ester malonate **302** (500 mg, 1.66 mmol) in MeCN (previously sparged with Ar over 15 min) (11 mL) were added $Mn(OAc)_3 \cdot 2H_2O$ (890 mg, 3.32 mmol), $Cu(OTf)_2$ (600 mg, 1.66 mmol) and KI (331 mg, 1.99 mmol). The reaction was left to react at 60 °C for 21 h. The system was quenched with a $Na_2S_2O_3$ aq. sat. sol. (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by FC (PE_{40-60} / EtOAc, 85:15), giving the title compound **344** as a white solid (349 mg, 0.83 mmol, 50%). R_f = 0.8 (PE_{40-60} / EtOAc, 85 : 15); *m.p.* = 114-117 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.50 (s, 9 H, C(3a)H_3), 1.51 (s, 9 H, C(3a′)H_3), 2.54 (dd, 1 H, J= 11.0, 17.6 Hz, C(4)H), 2.88 (dd, 1 H, J= 9.6, 11.9 Hz, C(6)H), 2.92 (dd, 1 H, J= 8.5, 17.5 Hz, C(4′)H), 3.37 (dtd, 1 H, J= 3.4, 8.5, 11.9 Hz, C(3)H), 3.55 (dd, 1 H, J= 3.5, 9.6 Hz, C(6′)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 0.7 (C(6,6′)), 27.9 (C(3a)), 28.1 (C(3a′)), 35.7 (C(4,4′)), 44.6 (C(3)), 84.5 (C(2a)), 85.7 (C(2a′)), 86.3 (C(2)), 164.4 (C=O), 164.7 (C=O), 171.8 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2979w (C-H), 1807s (C=O), 1736s (C=O) 1371m, 1313m, 1253m, 1150s; ***m/z*** LRMS (ESI$^+$) 449.0 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 449.04311; $C_{15}H_{23}IO_6$ [M+Na]$^+$ requires 449.04315.

***tert*-Butyl (3a*R*,6a*R*)-2,6-dioxotetrahydrofuro[3,4-b]furan-6a(6*H*)-carboxylate 307**[126]



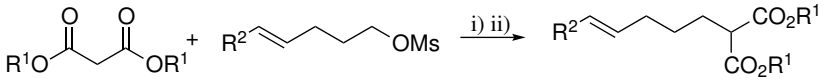
307

The title compound **307** has been isolated as a minor product (5% yield) in the oxidative cyclisation of **302** for the formation of **344** through oxidative cyclisation. R_f = 0.2 (PE_{40-60} / EtOAc, 85:15); *m.p.* = 117-121 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.53 (s, 1 H, C(3a′)H_3), 2.62 (dd, 1 H, *J*= 5.9, 18.4 Hz, C(3)H), 3.04 (dd, 1 H, *J*= 9.8, 18.4 Hz, C(3′)H), 3.42 (dddd, 1 H, *J*= 3.5, 5.9, 7.2, 9.6 Hz, C(3a)H), 4.24 (dd, 1 H, *J*= 3.5, 9.7 Hz, C(4)H), 4.68 (dd, 1 H, *J*= 7.2, 9.7 Hz, C(4′)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 28.0 (C(3a′)), 33.5 (C(3,3′)), 40.1 (C(3a)), 70.9 (C(4,4′)), 83.4 (C), 86.1 (C), 164.1 (C=O), 168.3 (C=O), 172.3 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2927w (C-H), 1797s (C=O), 1783s (C=O), 1745s (C=O), 1107s; ***m/z*** HRMS (ESI^+) found 265.06831; $C_{11}H_{14}O_6$ $[M+Na]^+$ requires 265.06826.

6.5 Metal-Free Methods for the Synthesis of γ-Lactones

6.5.1 General Procedures

General Procedure 9: Alkylation of Alkyl Malonates

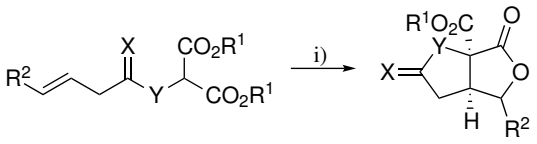


Reagents & Conditions: i) NaH, DMF, 0 °C; ii) THF, KI, 80 °C.

According to the procedure of Logan *et al.*,[177] NaH (60 wt% in mineral oil, 3.0 eq.) was suspended in anhydrous DMF (0.2 M) and cooled down to 0 °C. Dialkyl malonate (3.0 eq.) was added dropwise and the mixture was stirred for 20 min. A solution of alkenyl mesylate (1 eq.) in anhydrous THF (0.2 M) was then added dropwise, followed by KI (1 eq.). The resultant mixture was then heated to 80 °C overnight. After cooling down to r.t., NH_4Cl aq. sat. sol. (7 mL/mmol alkenyl mesylate) was added, and the reaction system was extracted with EtOAc (3 x 10 mL/mmol alkenyl mesylate). The combined

organic layers were washed with water and brine, and dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was further purified by FC (PE_{40-60} / EtOAc).

General Procedure 10: Metal-Free Oxidative Cyclisation



To a solution of malonate (1 eq.) and NaOAc (1.2 eq.) in DMSO (0.15 M) was added NIS (1.2 eq.), and the system was left to react at 80 °C in the dark for 21 h. The reaction was quenched with $Na_2S_2O_3$ aq. sat. sol. (10 mL) and extracted with EtOAc (3×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by FC (PE_{40-60} / EtOAc).

6.5.1.1 Anodic Oxidation

Constant Current Method. Constant current electrolyses were run with a Keithley 2200-72-1 programmable power supply (72 V, 1.2 A). All the experiments were carried out in an oven-dried glass tube (undivided cell) equipped with two graphite carbon rods electrodes, an inert gas inlet and a stirring bar. The carbon rods (diameter $\oslash$ = 0.5 cm) were spaced 0.3 cm apart and the working electrode surface ($WE_{surface}$ (m^2)) of each experiment (anode in our case) can be calculated by using the following **equation 6.1**:

$$WE_{surface} = 2\pi rh + \pi r^2 \tag{6.1}$$

where r is the radius (m) of the working electrode (anode in our case) and h (m) the immersion of the electrode into the solution.

The current density J (A/m^2) is calculated with the following **equation 6.2**:

$$J = I/WE_{surface} \tag{6.2}$$

where $I(A)$ refers to the current intensity passing through the solution measured in Amperes (A).

The number of equivalents of electrons passing through the system (amount of electricity) is controlled with the reaction time t for a given current intensity I. To know such reaction time, for a reaction with 3

equivalents of electrons passing through the system, *i.e.* 3.0 F/mol of electricity, at the selected current $I = 10\ mA$, we need to calculate:

1. the number of moles of electrons on the basis of the number of moles of the limitant reagent. For example, for 1 mmol of limitant reagent and 3.0 F/mol of electricity, we will have 3 mmol of electrons passing through the system.

2. the charge $Q(C)$ going through the solution, knowing that 1.0 mol of electrons contains 96500 C according to the **equation 6.3**:

$$F = 96500\ C/mol\ e^- \tag{6.3}$$

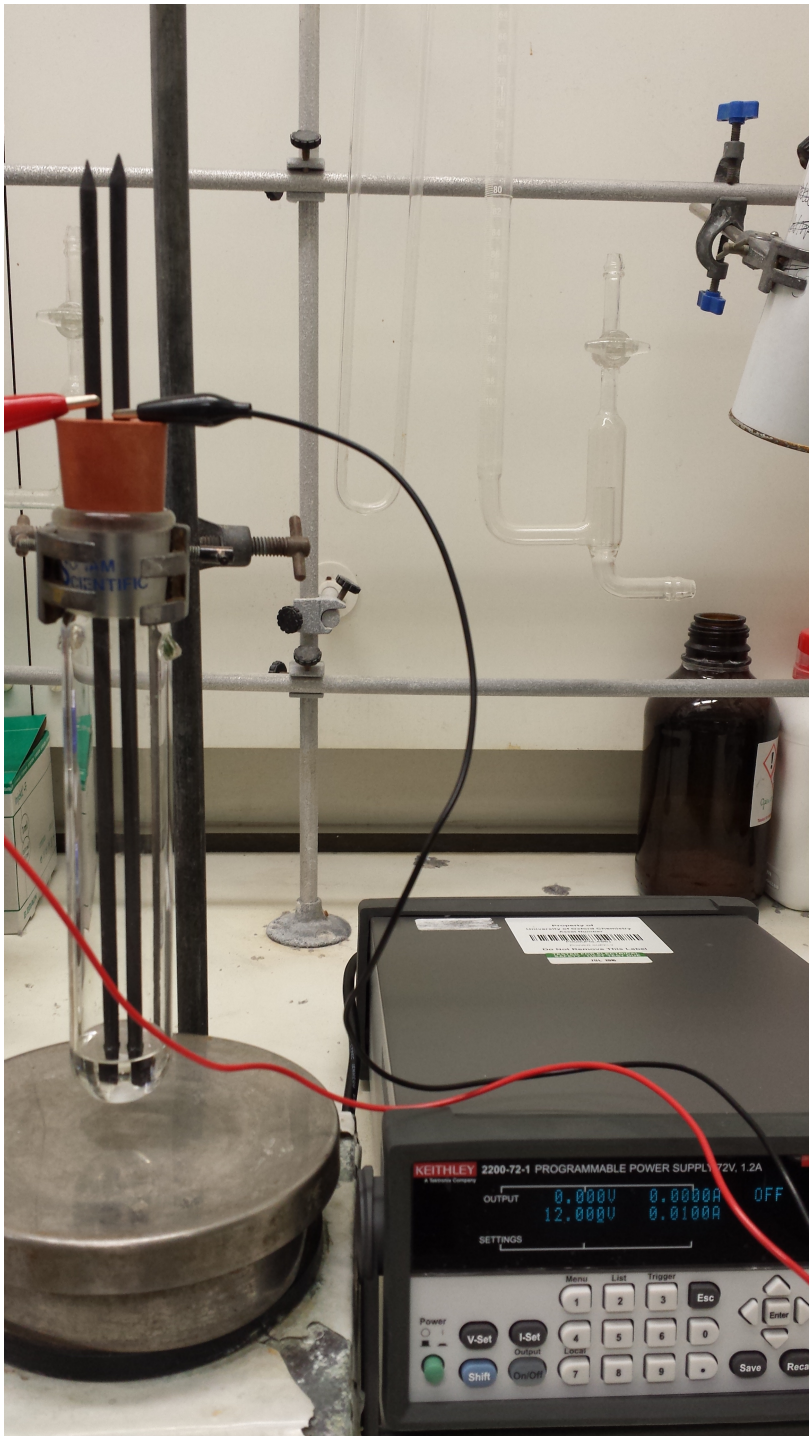
   where F is the Faraday constant and C refers to Coulomb, the unit of charge. Hence for 3 mmol of electrons, 289.5 C of charge will pass through the system.

3. Knowing the charge $Q(C)$ and the current $I(A)$ (the one we have selected in the power supply), the reaction time $t(s)$ for 3.0 F/mol of electricity will be calculated according to the **equation 6.4**:

$$I = Q/t \tag{6.4}$$

   where $Q(C)$ refers to charge in Coulombs (C) and $t(s)$ to time in seconds (s). In the example we thus have 0.01 A = 289.5 C / t, then t = 28950 s = 8 h would be the reaction time in such experimental conditions.

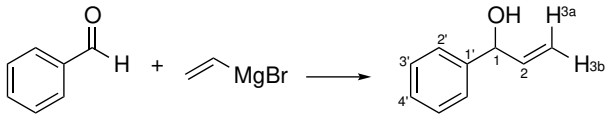
Undivided cell connected to the power supply during constant current electrolysis.



6.5.2 Characterisation

6.5.2.1 Synthesis of the Substrates

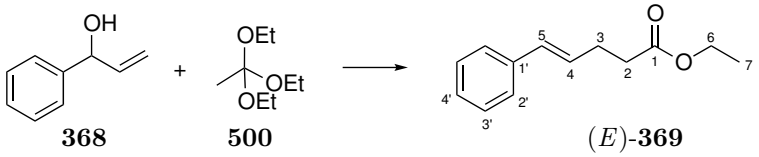
1-Phenylprop-2-en-1-ol 368



367 **499** **368**

Following the procedure of Jautze and Peters,[178] vinylmagnesium bromide **499** (1.0 M in THF, 25 mL, 25 mmol) was added slowly to a stirred solution of freshly distilled (distillation made over $CaCl_2$) benzaldehyde **367** (2.54 mL, 25 mmol) in THF (125 mL) at 0 °C. The reaction mixture was left to stir at 0 °C for 10 min and then left to reach and react at r.t. for 3 h. The reaction was quenched with NH_4Cl sat. aq. sol. (80 mL) and extracted with Et_2O (3 x 100 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under vacuum, giving the title compound **368** as a yellow liquid (4.02 g, 30.0 mmol, 98% yield), which was further used without purification. R_f = 0.6 (PE_{40-60} / Et_2O, 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.98 (brs, 1 H, O-*H*), 5.21 (td, 1 H, J = 1.2, 10.4 Hz, C(3b)H), 5.21-5.22 (m, 1 H, C(1)H, *masked*), 5.36 (td, 1 H, *J*= 1.6, 17.2 Hz, C(3a)H), 6.06 (ddd, 1 H, *J*= 6.0, 10.4, 17.2 Hz, C(2)H), 7.29-7.39 (m, 5 H, ArH) ; $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 75.4 (C(1)), 115.1 (C(3)), 126.3 (2×C(Ar)), 127.8 (C(4′)), 128.6 (2×C(Ar)), 140.2 (C(2)), 142.5 (C(1′)); ***m/z*** (ESI^+) 135.1 $[M+H]^+$. Data in accordance with the literature.[179]

Ethyl (*E*)-5-phenylpent-4-enoate 369

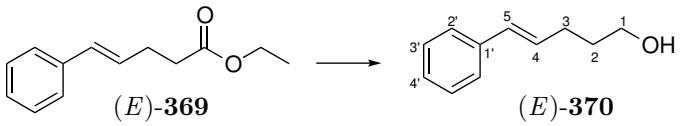


368 **500** (*E*)-**369**

According to the modified procedure of Johnson *et al.*,[180] propionic acid (0.13 mL, 1.75 mmol) was added to a stirred solution of phenyl propanol **368** (3.29 g, 24.5 mmol) in triethyl orthoacetate **500** (36.8 mL, 201 mmol) and the reaction was heated to 145 °C and stirred for 7 h. The reaction mixture was allowed to cool to r.t. and was diluted with EtOAc (25 mL) and washed successively with 1.0 M HCl (25 mL), $NaHCO_3$ aq. sat. sol. (25 mL), H_2O (25 mL) and brine (25 mL). The organic layer was dried

($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by FC (PE_{40-60} / EtOAc 99:1 to 98:2), giving the title compound **369** as a colourless oil (3.32 g, 16.3 mmol, 66% yield). R_f = 0.8 (PE_{40-60} / EtOAc 15:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.26 (t, 3 H, J= 7.1 Hz, C(7)H_3), 2.48 (dt, 2 H, J= 2.6, 9.2 Hz, C(2)H_2), 2.53 (t, 2 H, J= 6.8 Hz, C(3)H_2), 4.15 (q, 2 H, J= 7.1 Hz, C(6)H_2), 6.20 (td, 1 H, J= 6.8 Hz, 16.0 Hz, C(4)H), 6.43 (d, 1 H, J= 16.0 Hz, C(5)H), 7.20 (tt, 1 H, J= 1.6, 7.1 Hz, C(4′)H), 7.26-7.35 (m, 4 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 14.4 (C(7)), 28.5 (C(3)), 34.2 (C(2)), 60.6 (C(6)), 126.2 (2×C(Ar)), 127.2 (C(4′)), 128.6 (2×C(Ar) and C(4)), 131.0 (C(5)), 137.5 (C(1′)), 173.1 (C(1)). *Data in accordance with the literature.*[181]

(*E*)-5-Phenylpent-4-en-1-ol 370

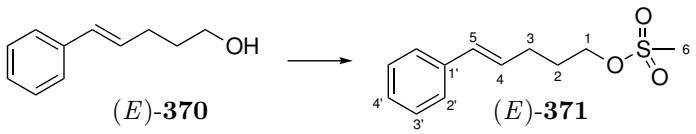


(*E*)-**369** (*E*)-**370**

To a suspension of $LiAlH_4$ (308 mg, 8.13 mmol) in anhydrous Et_2O (20.3 mL) was added dropwise at 0 °C a solution of the ester **369** (3.32 g, 16.3 mmol) in anhydrous Et_2O (16.3 mL). After 2.5 h stirring at 0 °C, the reaction was quenched cautiously with the successive addition of water (0.30 mL), 2.0 M NaOH (0.60 mL) and water (0.9 mL). The solid precipitate was filtered off and washed with Et_2O (3 x 5 mL) and the organic phase was concentrated under reduced pressure. The recovered residue was purified by FC (PE_{40-60} / EtOAc 3:1 to 2:1), giving the title compound **370** as a colourless oil (1.27 g, 7.82 mmol, 48% yield). R_f = 0.7 (PE_{40-60} / EtOAc 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.34 (bs, 1 H, O*H*), 1.76 (quint, 2 H, J= 6.6 Hz, C(2)H_2), 2.31 (dq, 2 H, J= 1.4, 7.2 Hz, C(3)H_2), 3.72 (t, 2 H, J= 6.5 Hz, C(1)H_2), 6.23 (td, 1 H, J= 6.9, 15.8 Hz, C(4)H), 6.42 (d, 1 H, J= 15.8 Hz, C(5)H), 7.20 (tt, 1 H, J= 1.5, 7.2 Hz, C(4′)H), 7.26-7.35 (m, 4 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 29.4 (C(3)), 32.3 (C(2)), 62.4 (C(1)), 126.0 (2×C(Ar)), 127.0 (C(4′)), 128.6 (2×C(Ar)), 130.1 (C(4)), 130.4 (C(5)), 137.7 (C(1′)); ***m/z*** HRMS (ESI^+) found 163.11186; $C_{11}H_{14}O$ $[M+H]^+$ requires 163.11174. *Data in accordance with the literature.*[181]

(*E*)-5-Phenylpent-4-en-1-yl methanesulfonate 371

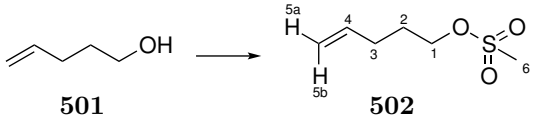
To a solution of the alcohol **370** (1.27 g, 7.83 mmol) in anhydrous DCM (39 mL) was added Et_3N (1.63 mL, 11.7 mmol). The solution was left to cool to 0 °C and MsCl (0.73 mL, 9.39 mmol) was added to the system. The mixture was allowed to warm to r.t. and react for 1.5 h. The reaction was quenched



(*E*)-**370** (*E*)-**371**

with 0.5 M HCl (35 mL). The layers were separated and the aqueous phase was extracted with DCM (3 x 30 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under vacuum, giving the title compound **371** as a yellowish oil (1.85 g, 7.69 mmol, 98% yield), which was used without previous purification. R_f = 0.7 (PE_{40-60} / EtOAc 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.94 (quint, 2 H, J= 6.9 Hz, C(2)H_2), 2.36 (dq, 2 H, J= 1.4, 7.1 Hz, C(3)H_2), 3.01 (s, 3 H, C(6)H_3), 4.28 (t, 2 H, J= 6.4 Hz, C(1)H_2), 6.17 (td, 1 H, J= 6.9, 15.8 Hz, C(4)H), 6.44 (d, 1 H, J= 15.8 Hz, C(5)H), 7.22 (tt, 1 H, J= 1.6, 7.2 Hz, C(4′)H), 7.28-7.37 (m, 4 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 28.7 (C(2)), 28.8 (C(3)), 37.4 (C(6)), 69.4 (C(1)), 125.9 (2×C(Ar)), 127.2 (C(4′)), 128.2 (C(4)), 128.5 (2×C(Ar)), 131.4 (C(5)), 137.2 (C(1′)); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3026w, 2939w, 1350s (S=O), 1170s; ***m/z*** (ESI$^+$) 263.0 ([M+Na]$^+$, 100%). *Data in accordance with the literature.*[177]

Pent-4-en-1-yl methanesulfonate 502

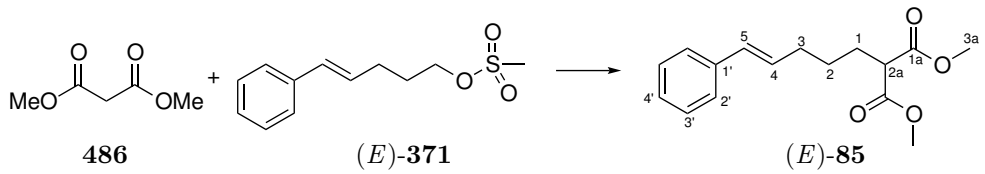


501 **502**

According to the procedure of Logan *et al.*,[177] Et_3N (2.4 mL, 17.4 mmol) was added to a stirred solution of pent-4-en-1-ol **501** (1.2 mL, 11.6 mmol) in DCM (58 mL). The system was cooled down to 0 °C and MsCl (1.1 mL, 13.9 mmol) was added. The solution was allowed to reach r.t. and react for 4 h. The reaction was quenched with HCl 0.5 M (50 mL) and the organic phase was decanted off. The aqueous phase was extracted with DCM (3 x 50 mL) and the recovered organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. A yellow oil was obtained as crude, which was used without previous purification (quantitative yield). R_f = 0.5 (PE_{40-60} / Et_2O 1:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.84 (quint, 2 H, J= 6.8 Hz, C(2)H_2), 2.17 (q, 2 H, J= 7.2 Hz, C(3)H_2), 2.99 (s, 3 H, C(6)H_3), 4.23 (t, 2 H, J= 6.5 Hz, C(1)H_2), 5.02 (d, 1 H, J= 9.6 Hz, C(5a)H), 5.06 (dd, 1 H, J= 1.4, 17.0 Hz, C(5b)H), 5.77 (tdd, 1 H, J= 6.7, 10.2, 17.2 Hz, C(4)H). *Data in accordance with the literature.*[182]

Dimethyl (*E*)-2-(5-phenylpent-4-en-1-yl)malonate 85

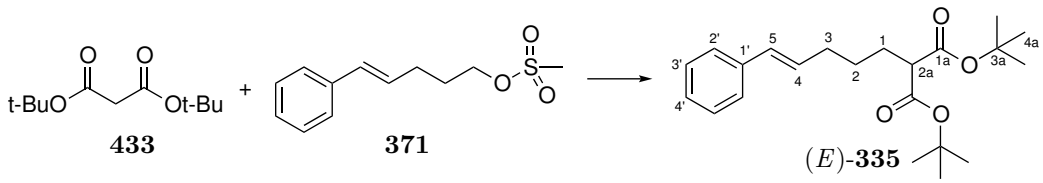
The title compound **85** was synthesised by following the **General Procedure 9** for the alkylation



486 (*E*)-**371** (*E*)-**85**

of alkyl malonates. Dimethyl malonate **486** (4.5 mL, 39.1 mmol) and NaH (1.6 g, 39.1 mmol, 60 wt% in mineral oil) in DMF (80 mL), and mesylate **371** (3.1 g, 13.0 mmol) and KI (2.2 g, 13.0 mmol) in THF (65 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 19:1 to 9:1) giving the title compound **85** as a yellow oil (2.6 g, 9.6 mmol, 71%). R_f = 0.4 (9:1 PE_{40-60} / EtOAc); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.41-1.58 (2 H, m, C(2)H_2), 1.84-1.94 (2 H, m, C(1)H), 2.26 (q, 2 H, J= 6.5 Hz, C(3)H_2), 3.41 (t, 1 H, J= 7.6 Hz, C(2a)H), 3.75 (s, 6 H, C(3a)H_3)), 6.18 (td, 1 H, J= 6.9, 15.9 Hz, C(4)H), 6.40 (d, 1 H, J= 15.9 Hz, C(5)H), 7.40-7.15 (m, 5 H, Ar*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 27.2 (C(2)), 28.5 (C(1)), 32.7 (C(3)), 51.7 (C(2a)), 52.6 (C(3a)), 126.1 (2×C(Ar)), 127.1 (C(4′)), 128.6 (2×C(Ar)), 129.8 (C(4)), 130.6 (C(5)), 137.7 (C(1′)), 169.9 (C=O); HRMS (ESI^+) found 277.14348; $C_{16}H_{20}O_4$ $[M+H]^+$ requires 277.14344. *Data in accordance with the literature.*[52]

di-*tert*-Butyl (*E*)-2-(5-phenylpent-4-en-1-yl)malonate (*E*)-**335**

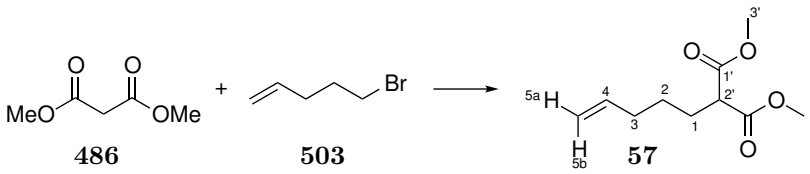


433 **371** (*E*)-**335**

The title compound **335** was synthesised by following the **General Procedure 9** for the alkylation of alkyl malonates. Di-*tert*-butyl malonate **433** (8.4 mL, 37.4 mmol) and NaH (1.5 g, 37.4 mmol, 60 wt% in mineral oil) in DMF (65 mL), and mesylate **371** (3.0 g, 12.5 mmol) and KI (2.1 g, 12.5 mmol) in THF (30 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 50:1 to 40:1) giving the title compound **335** as a white solid (2.4 g, 6.7 mmol, 53% yield). R_f = 0.3 (PE_{40-60} / EtOAc, 20:1); *m.p.* = 39-45 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.46 (s, 18 H, C(4a)H_3), 1.40-1.52 (m, 2 H, C(2)H_2), 1.86 (td, 2 H, J= 7.8, 8.1 Hz, C(1)H_2), 2.24 (q, 2 H, J= 7.2 Hz, C(3)H_2), 3.14 (t, 1 H, J= 7.6 Hz, C(2a)H), 6.19 (td, 1 H, J= 6.9, 15.8 Hz, C(4)H), 6.38 (d, 1 H, J= 15.8 Hz, C(5)H), 7.17-7.20 (m, 1 H, C(4′)H), 7.26-7.34 (m, 4 H, C(Ar)H); $\boldsymbol{\delta_C}$ (400 MHz, $CDCl_3$): 27.1 (C(2)), 28.1 (C(4a)), 28.3 (C(1)), 32.9 (C(3)), 53.9 (C(2a)), 81.5 (C(3a)), 126.1 (2×C(Ar)), 127.0 (C(4′)), 128.6 (2×C(Ar)), 130.3 (C(4)), 130.4 (C(5)), 137.8 (C(1′)), 169.1 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2978w (C-H), 2934w (C-H), 1725s (C=O), 1368m (C=C),

1252m, 1139s (C-O-C); ***m/z*** HRMS (ESI^+) found 361.23725 ; $C_{22}H_{32}O_4$ $[M+H]^+$ requires 361.23734.

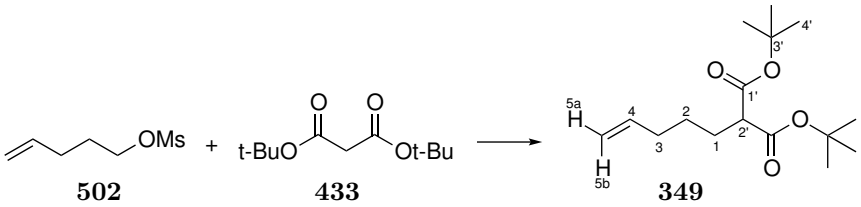
Dimethyl 2-(pent-4-en-1-yl)malonate 57



486 **503** **57**

According to the modified procedure reported by Kammerer *et al.*,[183] NaH (1.15 g, 30 mmol, 60 wt% dispersion in mineral oil) was suspended in dry DMF (65 mL) and cooled to 0 °C. Dimethyl malonate **486** (3.4 mL, 30 mmol) was added to the suspension and the mixture was left to react at 0 °C for 20 min. A solution of bromo pentene **503** (1.2 mL, 10 mmol) in anhydrous THF (50 mL) was added afterwards to the reaction mixture and the system was left to react at 80 °C overnight. The reaction mixture was cooled down and quenched with NH_4Cl sat. aq. solution (50 mL). The organic layers were separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (1 x 40 mL) and brine (1 x 40 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (gradient from 15:1 to 10:1 PE_{40-60} / EtOAc), giving the title compound **57** as a colourless oil (1.23 g, 6.14 mmol, 61% yield). R_f = 0.7 (PE_{40-60} / EtOAc, 10:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.41 (quint, 2 H, J= 7.4 Hz, C(2)H_2), 1.91 (q, 2 H, J= 7.6 Hz, C(1)H_2), 2.07 (tdd, 2 H, J= 1.3, 7.4, 14.0 Hz, C(3)H_2), 3.36 (t, 1 H, J= 7.5 Hz, C(2′)H), 3.74 (s, 6 H, C(3)H_3), 4.96 (d, 1 H, J= 10.2 Hz, C(5a)H), 5.01 (dd, 1 H, J= 1.6, 17.2 Hz, C(5b)H)), 5.76 (tdd, 1 H, J= 6.7, 10.2, 17.2 Hz, C(4)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 26.7 (C(2)), 28.4 (C(1)), 33.4 (C(3)), 51.7 (C(2′)), 52.6 (C(3′)), 115.2 (C(5)), 137.9 (C(4)), 169.9 (C=O); ***m/z*** LRMS (ESI+) 223.1 ($[M+Na]^+$, 100%). *Data in accordance with the literature.*[183]

di-*tert*-Butyl 2-(pent-4-en-1-yl)malonate 349



502 **433** **349**

The title compound **349** was synthesised by following the **General Procedure 9** for the alkylation of alkyl malonates. NaH (1.2 g, 28.9 mmol, 60 wt% in mineral oil), di-*tert*-butyl malonate **433** (6.5

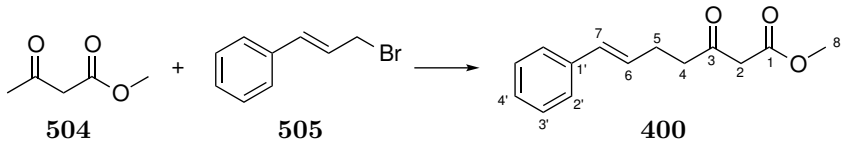
mL, 28.9 mmol) in anhydrous DMF (90 mL), and compound **502** (1.9 g, 11.6 mmol) and KI (1.9 g, 11.6 mmol) in anhydrous THF (58 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc 95:5), giving the title compound as a colourless oil (2.36 g, 8.3 mmol, 72% yield). R_f = 0.8 (PE_{40-60} EtOAc 95:5); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.40-1.44 (m, 2 H, C(2)H_2, *masked*), 1.45 (s, 18 H, C(4′)H_3), 1.81 (td, 2 H, *J*= 7.6, 8.2 Hz, C(1)H_2), 2.07 (tdd, 2 H, *J*= 1.3, 6.9, 14.2 Hz, C(3)H_2), 3.12 (t, 1 H, *J*= 7.6 Hz, C(2′)H), 4.95 (tdd, 1 H, *J*= 1.2, 2.0, 10.2 Hz, C(5a)H), 5.01 (qd, 1 H, *J*= 1.6, 17.2 Hz, C(5b)H), 5.78 (tdd, 1 H, *J*= 6.8, 10.4, 17.2 Hz, C(4)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 26.5 (C(2)), 27.9 (C(4′)), 28.0 (C(1)), 33.4 (C(3)), 53.8 (C(2′)), 81.2 (C(3′)), 114.8 (C(5)), 138.2 (C(4)), 168.9 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2979w (C-H), 1727s (C=O), 1393m, 1138s (C-O-C); ***m/z*** LRMS (ESI^+): 307.2 ($[M+Na]^+$, 67%), 591.4 ($[2M+Na]^+$, 100%); HRMS (ESI^+) found 307.18743; $C_{16}H_{28}O_4$ $[M+Na]^+$ requires 307.18798.

(*E*)-2-(5-Phenylpent-4-en-1-yl)malonic acid 398

85 **398**

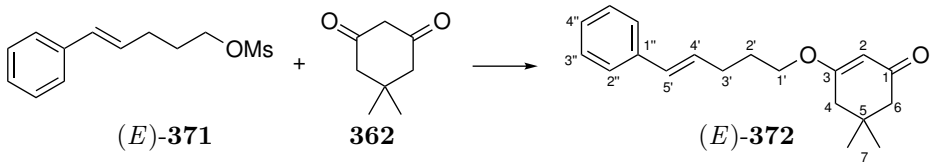
To a solution of KOH in a mixture of EtOH / H_2O (1:1, 12 mL) was added a solution of malonate **85** (500 mg, 1.8 mmol) in EtOH (0.8 mL). The reaction was left to react at r.t. overnight and the system mas quenched with the addition of H_2O (5 mL). EtOH was removed *in vacuo* and the aqueous phase was washed with Et_2O (15 mL). The aqueous layers were acidified at 0 °C with HCl (1.0 M, 15 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. A white solid (390 mg, 1.6 mmol, 87% yield) was obtained as product which was used without previous purification. R_f = 0.1 (PE_{40-60} / EtOAc, 1:2); *m.p.* = 138-143 °C; $\boldsymbol{\delta_H}$ (500 MHz, MeOD): 1.51 (quint, 2 H, *J*= 7.5 Hz, C(2)H_2), 1.88 (m, 2 H, C(1)H_2), 2.22 (q, 2 H, *J*= 7.2 Hz, C(3)H_2), 6.20 (td, 1 H, *J*= 6.9, 15.8 Hz, (C(4)H), 6.38 (d, 1 H, *J*= 15.8 Hz, C(5)H), 7.13 (tt, 1 H, *J*= 1.1, 7.4 Hz, C(4b)H), 7.23 (t, 2 H, *J*= 7.9 Hz, C(3b)H), 7.31 (d, 2 H, *J*= 7.3 Hz, C(2b)H) (*signal for C(2a)H masked in solvent residual signal)*; $\boldsymbol{\delta_C}$ (125 MHz, MeOD): 28.2 (C(2)), 29.6 (C(1)), 33.7 (C(3)), 52.9 (C(2a)), 126.9 (C(2b)), 127.9 (C(4b)), 129.4 (C(3b)), 130.9 ((C(4)), 131.7 ((C(5)), 139.1 (C(1b)), 173.2 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3026br (O-H), 2926br (O-H), 1712s (C=O), 1277m, 1209m; ***m/z*** HRMS (ESI^-) found 247.09741; $C_{14}H_{16}O_4$ $[M-H]^-$ requires 247.09758.

Methyl (*E*)-3-oxo-7-phenylhept-6-enoate 400



According to the procedure reported by Huckin *et al.*,[184] to a suspension of NaH (0.38 g, 9.5 mmol, 60 wt% dispersion in mineral oil) in anhydrous THF (22 mL) was added methyl acetoacetate **504** (0.93 mL, 8.6 mmol) and the system was left to stir at 0 °C for 10 min. To this solution was added *n*-BuLi (3.8 mL, 9.0 mmol, 2.37 M in hexanes) and the orange solution was left to stir at 0 °C for other 10 min. A solution of cinnamyl bromide **505** (1.9 g, 9.5 mmol) in THF (1.9 mL) was then added to the solution of the dianion at 0 °C and the mixture was left to react at r.t. for 40 min. The reaction was quenched with HCl 1.0 M (10 mL) and the organic layers were separated. The aqueous layers were extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine (1 x 40 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by FC (PE_{40-60} EtOAc, gradient from 6:1 to 4:1), giving the title compound **400** as a yellow oil (1.5 g, 6.3 mmol, 74% yield). R_f (PE_{40-60} / EtOAc, 4:1) = 0.7; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 2.51 (dtd, 2 H, J= 1.4, 6.9, 7.4 Hz, C(5)H_2), 2.73 (t, 2 H, J= 7.3 Hz, C(4)H_2), 3.48 (s, 2 H, C(2)H_2), 3.74 (s, 3 H, C(8)H_3), 6.18 (td, 1 H, J= 6.8, 15.8 Hz, C(6)H), 6.41 (td, 1 H, J= 1.5, 15.8 Hz, C(7)H), 7.20 (tt, 1 H, J= 1.6, 7.0 Hz, C(4′)H), 7.27-7.34 (m, 4 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 26.8 (C(5)), 42.5 (C(4)), 49.1 (C(2)), 52.4 (C(8)), 126.0 (2×C(Ar)), 127.2 (C(4′)), 128.2 (C(6)), 128.5 (2×C(Ar)), 131.0 (C(7)), 137.2 (C(1′)), 167.5 (C=O), 201.8 (C=O); ***m/z*** HRMS (ESI^+) found 233.11739; $C_{14}H_{16}O_3$ $[M+H]^+$ requires 233.11722. *Data in accordance with the literature.*[184]

(*E*)-5,5-Dimethyl-3-((5-phenylpent-4-en-1-yl)oxy)cyclohex-2-en-1-one 372



According to the modified procedure reported by Groutas *et al.*,[143] to a solution of dimedone **362** (729 mg, 5.20 mmol) in *t*-BuOH (26 mL) was added *t*-BuOK (583 mg, 5.20 mmol) at r.t. and left to stir for 15 min. Compound **371** (500 mg, 2.1 mmol) was added and the system was left to reach and react at 50 °C for 9 h. The reaction was quenched with 1.0 M HCl (10 mL), which turned the system from being a suspension to a colourless solution, which was further concentrated under reduced pressure. Brine (15

mL) and EtOAc (15 mL) were added and the layers were separated. The aqueous phase was extracted with EtOAc (2 x 15 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by FC (PE_{40-60} / EtOAc, gradient from 3:1 to 2:1), giving the title compound **372** as a white solid (425 mg, 1.5 mmol, 72% yield). R_f = 0.5 (PE_{40-60} / EtOAc 2:1); *m.p.* 71-77 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.07 (s, 6 H, C(7)H_3), 1.91 (quint, 2 H, J= 6.8 Hz, C(2′)H_2), 2.21 (s, 2 H, C(6)H_2), 2.28 (s, 2 H, C(4)H_2), 2.33 (dq, 2 H, J= 1.2, 7.0 Hz, C(3′)H_2), 3.88 (t, 2 H, J= 6.4 Hz, C(1′)H_2), 5.35 (s, 1 H, C(2)H), 6.19 (td, 1 H, J= 7.2, 16.0 Hz, C(4′)H), 6.41 (d, 1 H, J= 15.6 Hz, C(5′)H), 7.19-7.23 (m, 1 H, C(4″)H), 7.28-7.35 (m, 4 H, Ar); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 28.2 (C(2′)), 28.3 (C(7)), 29.4 (C(3′)), 32.5 (C(5)), 42.9 (C(4)), 50.7 (C(6)), 67.8 (C(1′)), 101.6 (C(2)), 125.9 (2×C(Ar)), 127.1 (C(4″)), 128.5 (2×C(Ar)), 128.9 (C(4′)), 130.9 (C(5′)), 137.4 (C(1″)), 176.2 (C(3)), 199.6 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2955w (C-H), 1652m, 1604s (C=O), 1367m, 1218m (C-O-C); ***m/z*** LRMS (ESI$^+$): 285.2 ([M+H]$^+$, 62%), 307.2 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) found 285.18451; $C_{19}H_{24}O_2$ [M+H]$^+$ requires 285.18491.

6.5.2.2 Anodic Oxidations

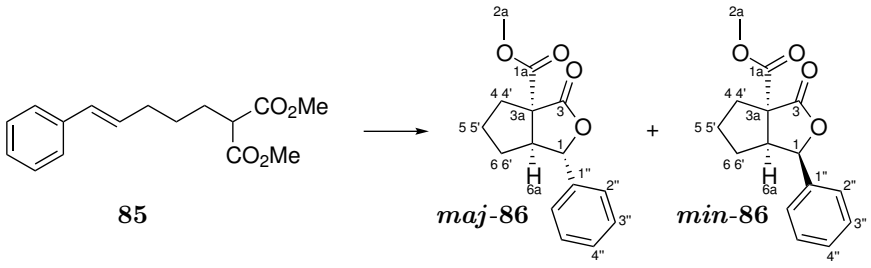
Methyl

(1*S*,3a*R*,6a*S*)-3-oxo-1-phenyltetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate

(*maj*)-86 and **Methyl**

(1*R*,3a*R*,6a*S*)-3-oxo-1-phenyltetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate

(*min*)-86

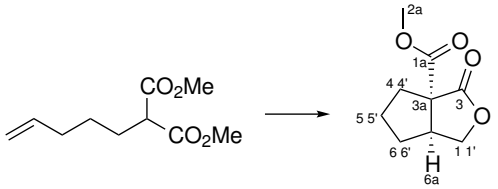


85 ***maj*-86** ***min*-86**

Malonate **85** (150 mg, 0.54 mmol) and NaOH (32 mg, 0.80 mmol) were dissolved in MeOH (7.8 mL, previously sparged with N_2 over 15 min) and the solution was left to stir at r.t. for 15 min before applying the current. The anodic oxidation was performed with graphite carbon rods as electrodes, under constant current conditions (10 mA, 5.19 mA / cm^2) for 7 h 15 min (5.0 F/mol). The solvent was then removed *in vacuo* and the resulting residue was dissolved in EtOAc (10 mL) and washed with brine (1 x 10 mL). The aqueous layers were extracted with EtOAc (3 x 10 mL) and the recovered organic

fractions were dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (PE_{40-60}/ EtOAc, gradient from 15:1 to 8:1), giving the title compound **86** as a colourless oil (54 mg, 0.21 mmol, 38%, 8.1:1 *dr*). R_f = 0.3 (PE_{40-60} / EtOAc 8:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) ***maj*-86**: 1.69-1.81 (m, 1 H, C(5)H), 1.90-2.06 (m, 3 H, C(5′)H, C(6)H and C(6′)H), 2.33-2.40 (m, 1 H, C(4)H), 2.41-2.49 (m, 1 H, C(4′)H), 3.16 (ddd, 1 H, J= 1.6, 4.8, 6.8 Hz, C(6a)H), 3.72 (s, 3 H, C(2a)H_3), 5.04 (d, 1 H, J= 4.8 Hz, C(1)H), 7.32-7.40 (m, 5 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) ***maj*-86**: 25.5 (C(5,5′)), 33.6 (C(6,6′)), 35.3 (C(4,4′)), 53.1 (C(2a), 54.4 (C(6a)), 62.3 (C(3a)), 86.1 (C(1)), 125.4 (2×C(Ar)), 128.5 (C(Ar)), 128.8 (2×C(Ar)), 139.7 (C(1″)), 170.9 (C=O); ***m/z*** LRMS (ESI^+): 543.2 ($[2M+Na]^+$, 100%). *Data are consistent with literature values.*[52]

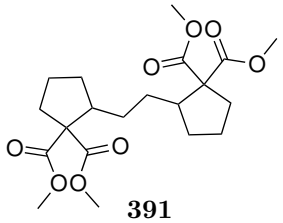
Methyl (3a*R*,6a*S*)-3-oxotetrahydro-1*H*-cyclopenta[c]furan-3a(3*H*)-carboxylate 62



57 **62**

Alkene malonate **57** (100 mg, 0.50 mmol), NaOH (24 mg, 0.60 mmol) and the electrolyte Et_4NBF_4 (108 mg, 0.50 mmol) were dissolved in MeOH (5.0 mL, previously sparged with Ar over 15 min). The solution was left to stir at r.t. for 10 min before applying the current. The anodic oxidation was performed under constant current conditions (10 mA, 5.65 mA / cm^2) for 6 h 40 min (5.0 F / mol). The solvent was then removed *in vacuo* and the resulting residue was dissolved in EtOAc (10 mL) and washed with brine (1 x 10 mL) and HCl 1.0 M (1 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by FC (PE_{40-60} / EtOAc, gradient from 15:1 to 5:1), giving the title compound **62** as a colourless oil (19 mg, 0.1 mmol, 21% yield). R_f = 0.10 (PE_{40-60} / EtOAc, 10:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.58-1.69 (m, 2 H, C(6)H and C(5)H), 1.78-1.84 (m, 1 H, C(5′)H), 2.04-2.09 (m, 1 H, C(6′)H), 2.24-2.30 (m, 1 H, C(4)H), 2.34-2.41 (m, 1 H, C(4′)H), 3.07-3.13 (m, 1 H, C(6a)H), 3.77 (s, 3 H, C(2a)H_3), 4.07 (dd, 1 H, J= 2.5, 9.3 Hz, C(1)H), 4.55 (dd, 1 H, J= 7.8, 9.2 Hz, C(1′)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 25.9 (C(5,5′)), 34.1 (C(6,6′)), 34.7 (C(4,4′)), 45.6 (C(6a)), 53.1 (C(2a)), 61.5 (C(3a)), 72.9 C(1,1′)), 170.5 (C=O), 176.4 (C=O); ***m/z*** LRMS (ESI^+) 391.1 ($[2M+Na]^+$, 100%). *Data in accordance with the literature.*[49]

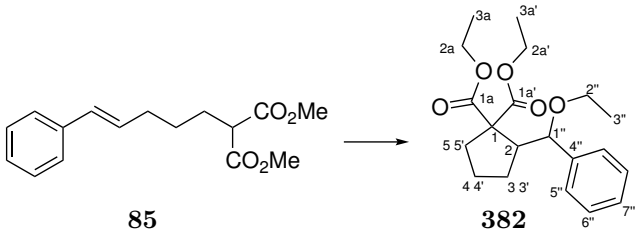
Tetramethyl 2,2'-(ethane-1,2-diyl)bis(cyclopentane-1,1-dicarboxylate) 391



391

The title compound **391** has been isolated as a colourless oil (50 mg, 0.13 mmol, 25% yield) in the anodic oxidation of the alkene malonate **57** for the formation of fused bicyclic γ-lactone **62**. R_f = 0.2 (PE_{40-60} / EtOAc, 10:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 0.81-0.87 (m, 2 H, 2 x C*H*), 0.97-1.03 (m, 1 H, C*H*), 1.06-1.14 (m, 1 H, C*H*), 1.29-1.33 (m, 1 H, C*H*), 1.35-1.31 (m, 1 H, C*H*), 1.41-1.48 (m, 4 H, 4 x C*H*), 1.76-1.87 (m, 2 H, 2 x C*H*), 1.89-2.01 (m, 2 H, 2 x C*H*), 2.35-2.45 (m, 3 H, 3 x C*H*), 2.48-2.55 (m, 1 H, C*H*), 3.68 (s, 6 H, 2×OCH_3), 3.69 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3); $\boldsymbol{\delta_C}$ (400 MHz, $CDCl_3$): 23.1 (CH_2), 29.7 (CH_2), 30.5 (CH_2), 30.7 (CH_2), 30.9 (CH_2), 34.5 (CH_2), 34.6 (CH_2), 45.7 (CH), 47.1 (CH), 52.1 (O-CH_3), 52.5 (O-CH_3), 63.6 (C), 172.1 (C=O), 172.1 (C=O), 173.1 (2 x C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2952w (C-H), 1729s (C=O), 1263m; ***m/z*** LRMS (ESI^+) 399.2([M+H]$^+$, 40%), 421.2 ([M+Na]$^+$, 100%); HRMS (ESI^+) found 421.18255; $C_{20}H_{30}O_8$ [M+Na]$^+$ requires 421.18329.

Diethyl 2-(ethoxy(phenyl)methyl)cyclopentane-1,1-dicarboxylate 382

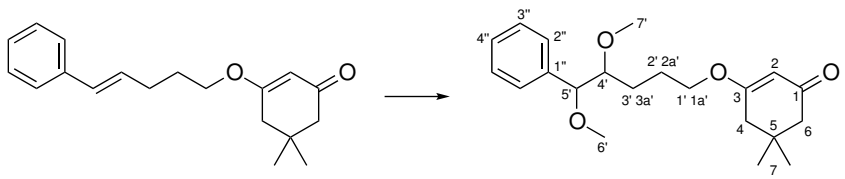


85 **382**

Malonate **85** (150 mg, 0.54 mmol) and NaOEt (50 mg, 0.74 mmol) were dissolved in EtOH (7.8 mL, previously sparged with N_2 over 15 min) and the solution was left to stir at r.t. for 15 min before applying the current. Anodic oxidation was performed by using graphite carbon rods as electrodes under constant current conditions (10 mA, 3.9 mA / cm^2) for 3 h (2.0 F / mol). The solvent was removed *in vacuo* and the obtained residue was dissolved in EtOAc (10 mL) and washed with brine (1 x 10 mL). The aqueous layers were extracted with EtOAc (3 x 10 mL) and the recovered organic fractions were dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (PE_{40-60} / EtOAc, 15:1 to 8:1), giving the title compound **382** as a colourless oil (31 mg, 16%, 3.5:1 *dr*). R_f = 0.5, 0.6 (PE_{40-60} / EtOAc, 8:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) ***major diastereoisomer***: 1.13 (t, 3 H, *J*=

7.1 Hz, C(3″, 3a′ or 3a)H_3), 1.23 (t, 3 H, J= 7.1 Hz, C(3″, 3a′ or 3a)H_3), 1.33 (t, 3 H, J= 7.1 Hz, C(3″, 3a′ or 3a)H_3), 1.61-1.72 (m, 3 H, C(3)H, C(4)H, C(4′)H), 1.91-1.99 (m, 1 H, C(3′)H), 2.03-2.11 (m, 1 H, C(5)H), 2.35-2.41 (m, 1 H, C(5′)H), 3.31-3.37 (m, 1 H, C(2)H), 3.59-3.71 (m, 4 H, 4× CH*H*-O), 4.21 (dq, 2 H, J= 0.8, 7.1 Hz, 2×CH*H*-OCH_3), 4.45 (d, 1 H, J= 8.1 Hz, C(1″)H), 7.27-7.37 (m, 4 H, Ar*H*), 7.48-7.51 (m, 1 H, Ar*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) ***major diastereoisomer***: 14.3 (CH_3), 15.1 (CH_3), 15.2 (CH_3), 26.6 (CH_2), 29.4 (CH_2), 32.1 (CH_2), 57.3 (CH_2)-O), 57.3 (C(2)), 58.9 ((CH_2)-O), 61.2 ((CH_2)-O), 69.5 (C(1)), 83.9 (C(1″)), 126.9 (2×C(Ar)), 127.9 (C(Ar)), 128.4 (2×C(Ar)), 141.0 (C(Ar)), 173.9 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2979w (C-H), 1726s (C=O), 1256s (C-O-C); ***m/z*** LRMS (ESI$^+$) 719.4 ([2M+Na]$^+$, 100%); HRMS (ESI$^+$) found 719.37645; $C_{20}H_{28}O_5$ [2M+Na]$^+$ requires 719.37657.

3-((4,5-Dimethoxy-5-phenylpentyl)oxy)-5,5-dimethylcyclohex-2-en-1-one 373



(*E*)-**372** **373**

A solution of compound **372** (100 mg, 0.35 mmol), electrolyte Et_4NOTs (422 mg, 1.40 mmol) and K_2CO_3 (6 mg, 0.05 mmol) in anhydrous MeOH (7 mL) was sparged with N_2 over 20 min. The anodic oxidation was run with two graphite carbon rods as electrodes under constant current conditions (10 mA, 5.6 mA / cm^2) for 2 h 40 min (3.0 F / mol). Solvent was removed under reduced pressure and brine (10 mL) and EtOAc (10 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic fractions were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product was purified by FC (PE_{40-60} / EtOAc, gradient from 3:1 to 2:1), giving the title compound **373** as a colourless oil (15 mg, 0.044 mmol, 13% yield). R_f = 0.3 (PE_{40-60} / EtOAc, 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.04 (s, 6 H, C(7)H_3), 1.24-1.32 (m, 1 H, C(3′)H), 1.38-1.45 (m, 1 H, C(3a′)H), 1.65-1.72 (m, 1 H, C(2′)H), 1.78-1.86 (m, 1 H, C(2a′)H), 2.18 (brs, 2 H, C(4)H_2 or C(6)H_2), 2.20 (brs, 2 H, C(4)H_2 or C(6)H_2), 3.25 (s, 3 H, C(7′)H_3 or C(6′)H_3), 3.33-3.37 (m, 1 H, C(4′)H), 3.45 (s, 3 H, C(7′)H_3 or C(6′)H_3), 3.74 (t, 2 H, J= 6.4 Hz, C(1′,1a′)H_2), 4.17 (d, 1 H, J= 6.0 Hz, C(5′)H), 5.27 (s, 1 H, C(2)H), 7.26-7.35 (m, 5 H, C(Ar)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 24.6 (C(2′,2a′)), 27.1 (C(3′,3a′)), 28.2 (C(7)), 32.4 (C(5)), 42.8 (C(4) or C(6)), 50.7 (C(4) or C(6)), 57.1 (C(6′) or C(7′)), 59.1 (C(6′) or C(7′)), 68.4 (C(1′)), 83.9 (C(4′)), 85.8 (C(5′)), 101.5 (C(2)),

127.5 (2×C(Ar)), 127.9 (C(4″)), 128.3 (2×C(Ar)), 138.8 (C(1″)), 176.2 (C(3)), 199.6 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2943w (C-H), 1654m (C=C), 1605vs (C=O), 1364m, 1219s (C-O), 1096s; ***m/z*** LRMS (ESI^+): 347.2 ($[M+H]^+$, 35%), 369.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 347.22133; $C_{21}H_{30}O_4$ $[M+H]^+$ requires 347.22169 .

6.5.2.3 Alternative Metal-Free Conditions for the γ-Lactone Synthesis

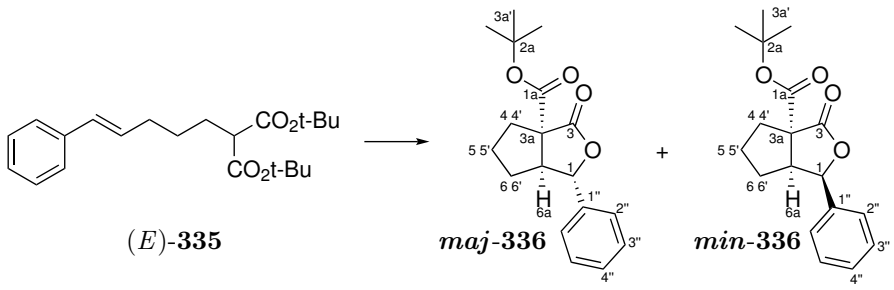
***tert*-Butyl**

(1*S*,3a*S*,6a*S*)-3-oxo-1-phenyltetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate

maj-**336** and ***tert*-butyl**

(1*R*,3a*S*,6a*S*)-3-oxo-1-phenyltetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate

min-**336**

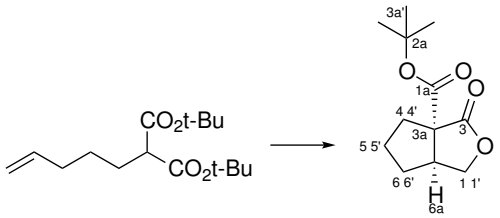


(*E*)-**335** ***maj*-336** ***min*-336**

The title compound **336** has been synthesised by following the **General Procedure 10** for the metal-free oxidative cyclisation. Malonate **335** (50 mg, 0.14 mmol), NaOAc (14 mg, 0.17 mmol) and NIS (38 mg, 0.17 mmol) in DMSO (0.9 mL) were used. The reaction was quenched with $Na_2S_2O_3$ aq. sat. sol. (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 12:1 to 8:1), giving the title compound **336** as a yellowish solid (33 mg, 0.11 mmol, 79% yield, 49:1 *dr*). Full caracterisation can be found in **Section 6.4**.

***tert*-Butyl (3a*S*,6a*S*)-3-oxotetrahydro-1*H*-cyclopenta[*c*]furan-3a(3*H*)-carboxylate 350**

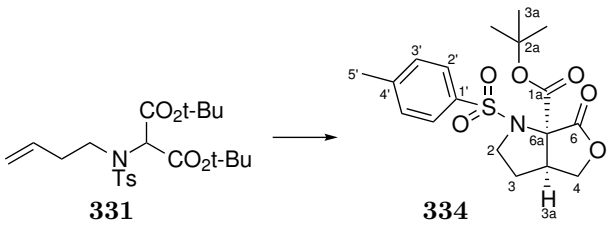
The title compound **350** has been synthesised by following the **General Procedure 10** for the metal-free oxidative cyclisation. Malonate **349** (100 mg, 0.35 mmol), NaOAc (35 mg, 0.42 mmol) and NIS (95 mg, 0.42 mmol) in DMSO (2.3 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 12:1 to 6:1), giving the title compound **350** as a white solid (34 mg, 0.15 mmol, 43% yield). Full caracterisation can be found in **Section 6.4**.



349 **350**

***tert*-Butyl (3a*S*,6a*R*)-6-oxo-1-tosyltetrahydro-1*H*-furo[3,4-b]pyrrole-6a(6*H*)-carboxylate**

334



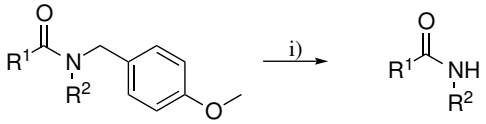
331 **334**

The title compound **334** has been synthesised by following the **General Procedure 10** for the metal-free oxidative cyclisation. The amino malonate **331** (60 mg, 0.14 mmol), NaOAc (14 mg, 0.16 mmol) and NIS (37 mg, 0.16 mmol) in DMSO (0.9 mL) were used at 40 °C. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 4:1 to 0:1), giving the title compound **334** as a white solid (12 mg, 0.03 mmol, 23% yield). Full caracterisation can be found in **Section 6.4**.

6.6 Towards the Synthesis of Proteasome Inhibitors

6.6.1 General Procedures

General Procedure 11: Deprotection of PMB-Protected Amides

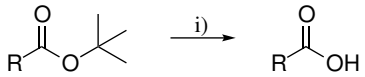


Reagents & Conditions: i) CAN (3.0 eq.), MeCN (0.08 M), H_2O (0.7 M), 0 °C .

According to the procedure reported by Corey and co-workers,[164] to a solution of amide in MeCN (0.08 M) was added at 0 °C a solution of CAN in H_2O (0.7 M). The system was left to react at 0 °C for 1 h and was then diluted with H_2O and extracted with EtOAc. The combined organic fractions were

washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by FC (PE_{40-60} / EtOAc).

General Procedure 12: Hydrolysis of *tert*-Butyl Esters.

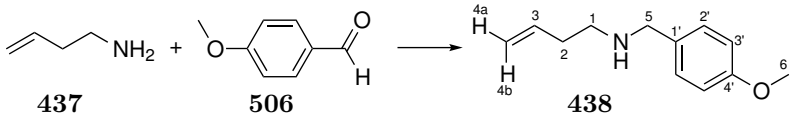


Reagents & Conditions: i) TFA (0.2 M), DCM (0.2 M), 0 °C to r.t.

To a solution of *tert*-butyl ester in DCM (0.2 M) was added TFA (0.2 M) at 0 °C. The system was allowed to reach and react at r.t. Oxygen-free conditions were not necessary; however, the flask was closed with a glass stopper to avoid evaporation of the solvent. Once the reaction completed, the residue was dissolved in $CHCl_3$ and concentrated under reduced pressure (3×) until a solid was obtained. No further purification was necessary.

6.6.2 Characterisation

***N*-(4-methoxybenzyl)but-3-en-1-amine 438**

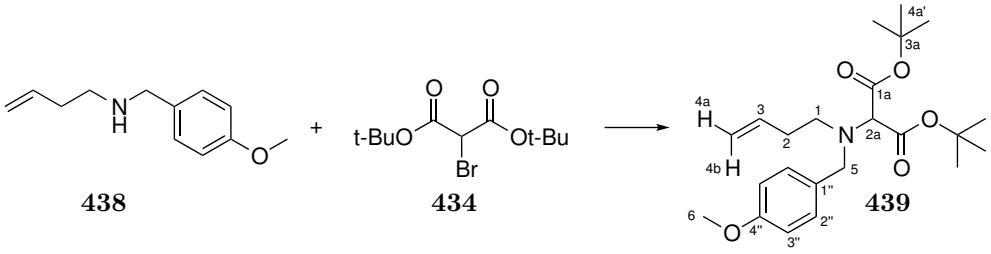


437 **506** **438**

According to the procedure of Dieltiens *et al.*,[158] to a solution of but-3-ene-1-amine **437** (0.64 mL, 7.03 mmol) in anhydrous CH_2Cl_2 (30 mL) were added $MgSO_4$ (1.70 g, 14.1 mmol), anhydrous Et_3N (1.96 mL, 14.1 mmol) and *p*-anisaldehyde **506** (0.85 mL, 7.03 mmol). The reaction system was left to stir at r.t. for 20 h. After filtration of the solids and evaporation of the solvent *in vacuo*, the residue was dissolved in MeOH (33 mL) and left to reach 0 °C. $NaBH_4$ (0.27 g, 7.26 mmol) was added portionwise at 0 °C. After 4 h, the reaction was quenched with H_2O and MeOH was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) and HCl 1.0 M (5 mL), the organic phase was decanted off and the aqueous phase was extracted with EtOAc (3 x 10 mL). The recovered organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*, giving the title compound **438** as a yellow liquid (1.18 g, 6.17 mmol, 88% yield over 2 steps). $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 1.69 (brs, 1 H, N*H*), 2.27 (q, 2 H, J= 6.8 Hz, C(2)H_2), 2.68 (t, 2 H, J= 6.8 Hz, C(1)H_2), 3.72 (s, 2 H, C(5)H_2), 3.79 (s, 3 H, C(6)H_3), 5.03 (d, 1 H, J= 10.0 Hz, C(4a)H), 5.08 (d, 1 H, J= 16.8 Hz, C(4b)H), 5.77 (dtdd, 1 H, J= 1.4, 6.8, 10.0, 17.0 Hz,

C(3)H), 6.86 (d, 2 H, J= 8.4 Hz, C(3′)H), 7.23 (d, 2 H, J= 8.4 Hz, C(2′)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 34.2 (C(2)), 48.2 (C(1)), 53.3 (C(5)), 55.3 (C(6)), 113.9 (C(3′)), 116.5 (C(4)), 128.7 (C(1′)), 129.4 (C(2′)), 136.5 (C(3)), 158.7 (C(4′)); ***m/z*** LRMS (ESI^+): 192.2 ($[M+H]^+$, 100 %). Data in accordance with the literature.[158]

di-*tert*-Butyl 2-(but-3-en-1-yl(4-methoxybenzyl)amino)malonate 439

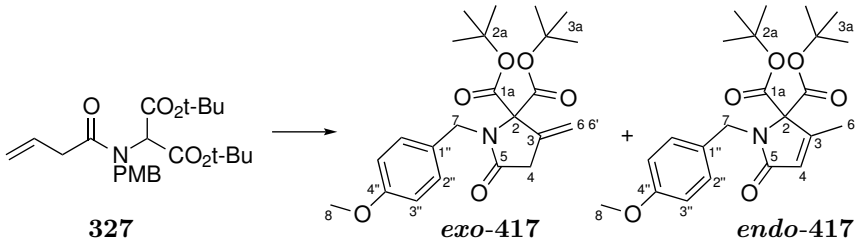


438 **434** **439**

The title compound was synthesised by following the **General Procedure 7** for the alkylation of amines. The amine **438** (0.50 g, 2.61 mmol), bromomalonate **434** (0.85 g, 2.87 mmol), and Et_3N (0.73 mL, 5.22 mmol) reacted in $CHCl_3$ (13 mL) for 3 days. The crude was purified by FC (9:1 PE_{40-60}/ EtOAc) giving the title compound **439** as a yellowish liquid (0.84 g, 2.07 mmol, 79% yield). R_f = 0.8 (PE_{40-60}/ EtOAc, 9:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.48 (s, 18 H, C(4a′)H_3), 2.24 (q, 2 H, J= 7.6 Hz, C(2)H_2), 2.77 (t, 2 H, J= 7.6 Hz, C(1)H_2), 3.80 (s, 5 H, C(6)H_3 and C(5)H_2), 3.99 (s, 1 H, C(2a)H), 4.96 (d, 1 H, J= 10.4 Hz, C(4a)H), 5.01 (tdd, 1 H, J= 1.5, 1.8, 17.2 Hz, C(4b)H), 5.77 (tdd, 1 H, J= 6.8, 10.4, 17.2 Hz, C(3)H), 6.84 (d, 2 H, J= 8.4 Hz, C(3″)H), 7.31 (d, 2 H, J= 8.8 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 28.2 (C(4a′)), 33.1 (C(2)), 51.2 (C(1)), 55.2 (C(6 or 5)), 55.3 (C(6 or 5)), 67.9 (C(2a)), 81.9 (C(3a)), 113.7 (C(3″)), 115.6 (C(4)), 129.9 (C(2″)), 131.8 (C(1″)), 136.7 (C(3)), 158.8 (C(4″)), 167.8 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2979w (C-H), 1729m (C=O), 1247w (C-O-C), 1137s (C-O-C); ***m/z*** LRMS (ESI^+) 406.3 ($[M+H]^+$, 100%); HRMS (ESI^+) found 428.2410; $C_{23}H_{35}NO_5$ $[M+Na]^+$ requires 428.2407.

Di-*tert*-Butyl 1-(4-methoxybenzyl)-3-methylene-5-oxopyrrolidine-2,2-dicarboxylate (*exo*)-417

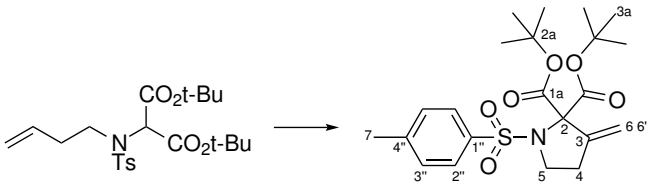
To a round-bottom flask charged with $Cu(OAc)_2$ (0.86 g, 4.76 mmol) and Cs_2CO_3 (0.78 g, 2.35 mmol) was added a solution of amido malonate **327** (0.50 g, 1.19 mmol) (synthesis in **Section 6.4.2**) in DMSO (6.0 mL; previously sparged with N_2 for 30 min). The system was left to react at r.t. for 3.5 h. The reaction was quenched with Et_2O (10 mL) and the suspension was filtered through a silica pad. The recovered organic phase was washed with an NH_4OH aq. sat. sol. (2 N) (1×20 mL), NH_4Cl aq.



327 ***exo*-417** ***endo*-417**

sat. sol. (1×20 mL), and brine (1×20 mL). The collected organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (PE_{40-60} / Et_2O, 1:3), giving the title compounds **417** as a white solid (0.24 g, 0.57 mmol, 49% yield, *exo*:*endo* ratio = 9:1); $R_f = 0.7$ (PE_{40-60} / Et_2O, 1:3); *m.p.* = 116-121 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) ***exo*-417**: 1.31 (s, 18 H, C(3a)H_3), 3.27 (t, 2 H, J= 2.4 Hz, C(4)H_2), 3.75 (s, 3 H, C(8)H_3), 4.67 (s, 2 H, C(7)H_2), 5.44 (t, 1 H, J= 2.4 Hz, C(6)H), 5.56 (t, 1 H, J= 2.8 Hz, C(6′)H), 6.79 (d, 2 H, J= 8.8 Hz, C(3″)H); 7.07 (d, 2 H, J= 8.8 Hz, C(2″)H); ***endo*-417**: 1.31 (s, 18 H, C(3a)H_3), 2.16 (d, 3 H, J= 1.2 Hz, C(6)H_3), 3.75 (s, 3 H, C(8)H_3), 4.69 (s, 2 H, C(7)H_2), 6.04 (q, 1 H, J= 1.6 Hz, C(4)H), 6.79 C(3″)H, *masked*), 7.10 (d, 2 H, J= 8.4 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) ***exo*-417**: 27.6 (C(3a)), 35.6 (C(4)), 45.6 (C(7)), 55.2 (C(8)), 77.4 (C(2)), 83.5 (C(2a)), 113.7 (C(3″)), 114.5 (C(6,6′)), 127.6 (C(2″)), 129.3 (C(1″)), 135.9 (C(3)), 158.5 (C(4″)), 165.6 (C=O), 173.7 (C=O); ***endo*-417**: 14.8 (C(6)), 27.6 (C(3a)), 44.8 (C(7)), 55.4 (C(8)), 84.2 (C(2a)), 113.9 (C(3″)), 125.3 (C(4)), 128.1 (C(2″)), 130.5 (C(1″)), 154.5 (C(3)), 158.7 (C(4″)), 164.2 (C=O), 172.1 (C=O);$\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2978w (C-H), 1734s (C=O), 1715s (C=O), 1515m (C=C), 1247s (C-O-C), 1155s (C-O-C); ***m/z*** LRMS (ESI^+): 418.2 ($[M+H]^+$, 100%), 440.2 ($[M+Na]^+$, 48%); HRMS (ESI^+) found 440.2049; $C_{23}H_{31}NO_6$ $[M+Na]^+$ requires 440.2044.

di-*tert*-Butyl 3-methylene-1-tosylpyrrolidine-2,2-dicarboxylate 442

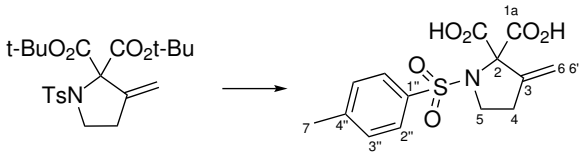


331 **442**

To a round-bottom flask charged with $Mn(OAc)_3 \cdot 2H_2O$ (2.4 g, 9.1 mmol), $Cu(OAc)_2$ (0.8 g, 4.6 mmol) and amino malonate **331** (2.0 g, 4.6 mmol), was added DMSO (23 mL) and the system was left to react at r.t. for 3 h. The reaction was quenched with Et_2O (10 mL) and the reaction mixture was filtered through a silica pad. The recovered organic phase was washed with NH_4OH 2 N aq. sol. (10

mL), NH_4Cl aq. sat. sol. (10 mL) and brine (10 mL). The collected organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (PE_{40-60} /Et_2O, 2:1), giving the title compound **442** as a white solid (0.96 g, 2.19 mmol, 48% yield). R_f = 0.4 (PE_{40-60} / Et_2O, 2:1); *m.p.* = 92-95 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.52 (s, 18 H, C(3a)H_3), 2.41 (s, 3 H, C(7)H_3), 2.62 (tt, 2 H, *J*= 2.0, 6.8 Hz, C(4)H_2), 3.39 (t, 2 H, *J*= 7.2 Hz, C(5)H_2), 5.16 (t, 1 H, *J*= 2.0 Hz, C(6)H), 5.36 (t, 1 H, *J*= 2.4 Hz, C(6′)H), 7.28 (d, 2 H, *J*= 8.4 Hz, C(3″)H), 7.91 (d, 2 H, J = 8.4 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 21.3 (C(7)), 27.5 (C(3a)), 31.4 (C(4)), 46.4 (C(5)), 82.6 (C(2a)), 110.6 (C(6,6′)), 127.9 (C(2″)), 128.9 (C(3″)), 137.4 (C(3 or 4″)), 142.9 (C(3 or 4″)), 146.2 (C(1″)), 165.9 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2978w (C-H), 1747m (C=O), 1157s (C-O-C); ***m/z*** LRMS (ESI^+): 460.2 ($[M+Na]^+$, 70%, 483.3 ($[M+2Na)^{2+}$, 100%); HRMS (ESI^+) found 460.1763; $C_{22}H_{31}NO_6S$ $[M+Na]^+$ requires 460.1764.

3-Methylene-1-tosylpyrrolidine-2,2-dicarboxylic acid 445

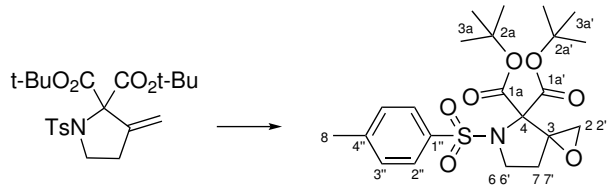


442 **445**

To a solution of *exo*-alkene **442** (600 mg, 1.37 mmol) in anhydrous DCM (2.80 mL) was added TFA (1.40 mL, 17.8 mmol) dropwise at 0 °C. The system was left to react at 0 °C for 2 h and then for additional 8 h at r.t to favour full conversion. Once the reaction was completed, the reaction mixture was concentrated under vacuum and the residual TFA was dissolved in toluene (4 x 2 mL) and evaporated. The title compound **445** was obtained as a white solid in quantitative yield (0.45 g, 1.38 mmol). R_f = 0.5 (PE_{40-60} / Et_2O, 1:2); *m.p.* = 135-140 °C; $\boldsymbol{\delta_H}$ (400 MHz, MeOD): 2.39 (s, 3 H, C(7)H_3), 2.74 (tt, 2 H, *J*= 2.0, 7.2 Hz, C(4)H_2), 3.49 (t, 2 H, *J*= 6.8 Hz, C(5)H_2), 5.19 (d, 1 H, *J*= 0.8 Hz, C(6)H), 5.33 (d, 1 H, *J*= 0.8 Hz, C(6′)H), 7.33 (d, 2 H, *J*= 8.0 Hz, C(3″)H), 7.77 (d, 2 H, *J*= 8.0 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, MeOD): 21.5 (C(7)), 32.7 (C(4)), 48.0 (C(5)), 110.9 (C(6,6′)), 129.1 (C(2″)), 130.4 (C(3″)), 137.9 (C), 145.3 (C), 148.3 (C), 172.3 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2963w (O-H), 1771m (C=O), 1333m, 1155s (C-O-C), 1101m; ***m/z*** LRMS (ESI^+): 348.0 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 348.0376; $C_{14}H_{15}NO_6S$ $[M+Na]^+$ requires 348.0512.

di-*tert*-Butyl 5-tosyl-1-oxa-5-azaspiro[2.4]heptane-4,4-dicarboxylate 450

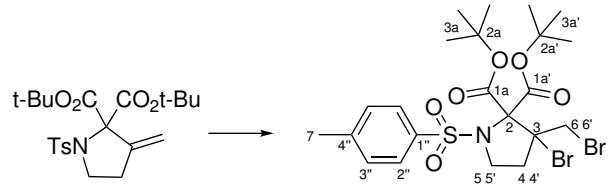
To a solution of *exo*-alkene **442** (200 mg, 0.46 mmol) in anhydrous DCM (2.30 mL) was added *m*-CPBA (473 mg, 2.74 mmol) at 0 °C. The white suspension was left to reach r.t. and react for 5 days.



442 **450**

The reaction was neutralised with $NaHCO_3$ sat. sol. (10 mL), followed by the addition of $Na_2S_2O_3$ sat. solution (10 mL). The system was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with $NaHCO_3$ aq. sat. sol. (1 x 10 mL) and brine (1 x 10 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (PE_{40-60} / Et_2O, 2:1), giving the title compound **450** as a white solid (102 mg, 0.22 mmol, 49% yield). R_f = 0.3 (PE_{40-60} / Et_2O, 2:1); *m.p.* = 72-75 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.49 (s, 9 H, C(3a)H_3), 1.53 (s, 9 H, C(3a′)H_3), 1.75 (ddd, 1 H, *J*= 2.5, 6.7, 13.3 Hz, C(7)H), 2.41 (s, 3 H, C(8)H_3), 2.62 (td, 1 H, *J*= 9.5 Hz, 13.3 Hz, C(7′)H), 2.91 (d, 1 H, *J*= 4.4 Hz, C(2)H), 3.10 (d, 1 H, *J*= 4.4 Hz, C(2′)H), 3.45 (dt, 1 H, *J*= 6.8, 8.9 Hz, C(6)H), 3.60 (td, 1 H, *J*= 2.4, 8.8 Hz, C(6′)H), 7.29 (d, 2 H, *J*= 8.0 Hz, C(3″)H), 7.91 (d, 2 H, *J*= 8.4 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 21.5 (C(8)), 27.8 (C(3a)), 27.9 (C(3a′)), 31.6 (C(7,7′)), 46.2 (C(6,6′)), 48.3 (C(2,2′)), 66.7 (C(4)), 75.5 (C(3)), 83.2 (C(2a and 2a′)), 127.9 (C(2″)), 129.1 (C(3″)), 137.4 (C(4″)), 143.3 (C(1″)), 162.7 (C=O), 165.9 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 2979w (C-H), 1754m (C=O), 1159s (C-O-C); ***m/z*** LRMS (ESI^+): 476.2 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 476.17077; $C_{22}H_{31}NO_7S$ $[M+Na]^+$ requires 476.17134.

di-*tert*-Butyl 3-bromo-3-(bromomethyl)-1-tosylpyrrolidine-2,2-dicarboxylate 448

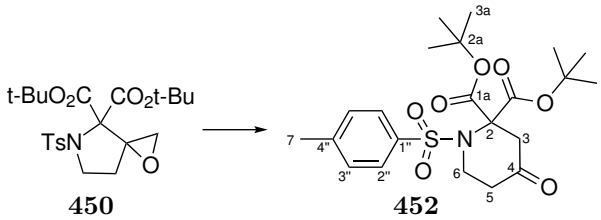


442 **448**

According to the procedure of Grudniewska *et al.*,[161] a solution of *exo*-alkene **442** (20.0 mg, 0.05 mmol) in Et_2O (0.30 mL) and $NaHCO_3$ 0.5 M aq. sol. (0.30 mL) was stirred at r.t. for 30 min and then left to reach 0 °C. Br_2 (6 eq) was added dropwise to the stirred solution at 0 °C and left to reach r.t. and react for 6 h. The reaction was diluted with Et_2O and quenched with $Na_2S_2O_3$ aq. sat. sol. The organic phase was decanted off and washed with $NaHCO_3$ 0.5 M aq. sol. (10 mL) and brine. The

recovered organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (PE_{40-60} / Et_2O, 2:1), giving the title compound **448** as a colorless oil (13.0 mg, 0.022 mmol, 50% yield). R_f = 0.5 (PE_{40-60} / Et_2O, 2:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.52 (s, 9 H, C(3a)H_3), 1.58 (s, 9 H, C(3a′)H_3), 2.41 (s, 3 H, C(7)H_3), 2.54 (dd, 1 H, J= 5.2, 13.6 Hz, C(4)H), 2.84 (ddd, 1 H, J= 8.8, 10.4, 13.6 Hz, C(4′)H), 3.60 (ddd, 1 H, J= 5.6, 8.8, 10.4 Hz, C(5)H), 3.71 (d, 1 H, J= 11.2 Hz, C(6)H), 4.03 (t, 1 H, J= 8.8 Hz, C(5′)H), 4.21 (d, 1 H, J= 11.6 Hz, C(6′)H), 7.29 (d, 2 H, J= 8.0 Hz, C(3″)H), 7.93 (d, 2 H, J= 8.4 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 21.5 (C(7)), 27.8 (C(3a and 3a′)), 38.6 (C(6,6′)), 41.5 (C(4,4′)), 47.1 (C(5,5′)), 75.0 (C), 83.3 (C), 84.1 (C), 85.3 (C), 127.6 (C(2″)), 129.2 (C(3″)), 138.6 (C(4″)), 142.9 (C(1″)), 163.5 (C=O), 165.5 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2979w (C-H), 1759m (C=O), 1154s (C-O-C); ***m/z*** LRMS (ESI^+): 618.0 ($[M+Na]^+$, 50%), 620.0 ($[M+Na]^+$, 100%), 622.0 ($[M+Na]^+$, 50%); ***m/z*** HRMS (ESI^+) found 596.03012 (50%), 598.02803 (100%), 600.02580 (50%); $C_{23}H_{33}Br_2NO_5S$ $[M+H]^+$ requires 596.03116 (50%), 598.02911 (100%), 600.02707 (50%).

di-*tert*-Butyl 4-oxo-1-tosylpiperidine-2,2-dicarboxylate 452

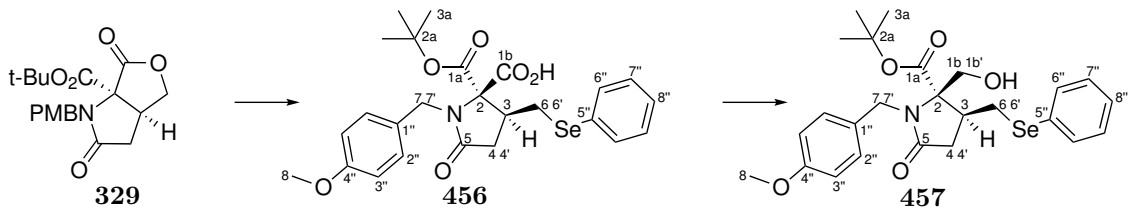


The title compound **452** was obtained as by-product when using the conditions reported by Bajwa *et al.* for epoxide opening.[162] The epoxide **450** (45.0 mg, 0.09 mmol) was dissolved in anhydrous THF (1.0 mL) and AcOH (2 eq) was added to the system. Anhydrous LiBr (14.0 mg, 0.16 mmol) was then added to the solution and the mixture was left to react at r.t for 30 h. The reaction was quenched with distilled water and extracted with Et_2O (3 x 5 mL). The combined organic fractions were then washed with distilled water, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by FC (PE_{40-60} / Et_2O, 1:1), giving the title compound **452** as a colourless oil (9 mg, 0.02 mmol, 20% yield). R_f = 0.4 (PE_{40-60} / Et_2O, 1:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.52 (s, 18 H, C(3a)H_3), 2.39 (t, 2 H, J= 6.4 Hz, C(5)H_2), 2.43 (s, 3 H, C(7)H_3), 3.02 (s, 2 H, C(3)H_2), 3.54 (t, 2 H, J= 6.0 Hz, C(6)H_2), 7.31 (d, 2 H, J= 8.0 Hz, C(3″)H), 7.96 (d, 2 H, J= 8.4 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 21.9 (C(7)), 28.0 (C(3a)), 39.5 (C(5)), 42.9 (C(6)), 48.2 (C(3)), 72.4 (C(2)), 84.4 (C(2a)), 128.3 (C(2″)), 129.8 (C(3″)), 137.9 (C(4″)), 143.9 (C(1″)), 166.7 (C=O), 203.9 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2980w (C-H),

1734s (C=O), 1341m, 1257m, 1158s (C-O-C); ***m/z*** LRMS (ESI^+): 476.2 ($[M+Na]^+$, 80%); HRMS (ESI^+) found 476.16984; $C_{22}H_{31}NO_7S$ $[M+Na]^+$ requires 476.17134.

tert-Butyl (2*R*,3*S*)-2-(hydroxymethyl)-1-(4-methoxybenzyl)-5-oxo-3-((phenylselanyl)methyl)pyrrolidine-2-carboxylate

457

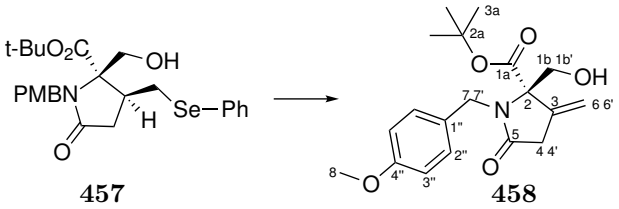


Compound 456: $NaBH_4$ (960 mg, 25.4 mmol) was added to a solution of $(PhSe)_2$ (4.0 g, 12.7 mmol) in DMF (26 mL) (previously sparged with Ar for 30 min). The solution was then allowed to react at 100 °C for 5 min and cooled down to r.t. The system at that point turned from yellow to a colourless solution. In the meantime, a solution of pyrrolidinone--lactone **329** (2.29 g, 6.3 mmol) in EtOH (26 mL) was sparged with Ar for 30 min and added afterwards to the phenyl selenide anion solution at r.t. The system was left to react at r.t. for 30 min. and then at 60 °C for 5 h. The reaction was quenched with NH_4Cl sat. sol. (10 mL) at r.t. and the solvents were removed *in vacuo* (the rotary evaporator was connected to the high vacuum pump (P = 15 mbar at 40 °C)). The crude was filtered through a silica pad with the first elution done with PE_{40-60} / EtOAc (4:1) to remove selenium by-products and then with EtOAc / MeOH (gradient from 2:1 to 0:1) to recover the product. The organic fraction containing the compound **456** was concentrated under reduced pressure. The residue was treated with a pH 2.0 buffer and extracted with EtOAc (2 x 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum, giving the compound **456** as a yellow oil (2.65 g, 5.11 mmol, 81% yield). R_f = 0.4 (PE_{40-60} / EtOAc / AcOH, 1:2:0.2); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.19 (s, 9 H, C(3a)H_3), 2.36 (dd, 1 H, *J*= 10.8, 16.8 Hz, C(4 or 6)H), 2.66 (t, 1 H, *J*= 12.0 Hz, C(4 or 6)H), 2.83 (dd, 1 H, *J*= 8.4, 16.8 Hz, C(4′ or 6′)H), 3.02-3.11 (m, 1 H, C(3)H), 3.31 (d, 1 H, *J*= 12.0 Hz, C(4′ or 6′)H), 3.74 (s, 3 H, C(8)H_3), 4.38 (d, 1 H, *J*= 15.6 Hz, C(7)H), 4.75 (d, 1H, *J*= 15.6 Hz, C(7′)H), 6.78 (d, 2 H, *J*= 8.8 Hz, C(3″)H), 7.09 (d, 2 H, *J*= 8.4 Hz, C(2″)H), 7.25-7.27 (m, 3 H, C(7″ and 8″)H), 7.52 (m, 2 H, C(6″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 27.3 (C(3a)), 27.7 (C(6,6′) or C(4,4′)), 35.6 (C(6,6′) or C(4,4′))), 41.0 (C(3)), 46.1 (C(7,7′)), 55.2 (C(8)), 75.3 (C(2)), 84.9 (C(2a)), 113.7 (C(3″)), 127.5 (C(8″)), 128.5 (C), 128.6 (C), 128.8 (C(2″)), 129.3 (C(7″)), 131.4 (C), 133.3 (C(6″)), 158.8 (C), 168.9 (C=O), 176.1 (C=O); $\boldsymbol{\nu_{max}}$

/ cm^{-1} 3000br (O-H), 2362s, 1730s (C=O), 1685s (C=O), 1514s, 1248s, 1154s; ***m/z*** LRMS (ESI^+): 520.1 ($[M+H]^+$, 100%), 542.1 ($[M+Na]^+$, 37%); HRMS (ESI^+) found 520.12243; $C_{25}H_{29}NO_6Se$ $[M+H]^+$ requires 520.12329; HRMS (ESI^-) found 518.10872; $C_{25}H_{29}NO_6Se$ $[M-H]^-$ requires 518.10873.

Compound 457: To a solution of DMF (0.88 mL, 11.4 mmol) in anhydrous DCM (43 mL) at 0 °C was added oxalyl chloride (2.9 mL, 34.2 mmol) over 5 min. The reaction was stirred for 30 min. at r.t. and all volatiles were removed under reduced pressure. The residual white salt was dried under high vacuum for additional 20 min before being re-dissolved in anhydrous THF (43 mL) and MeCN (31 mL). A solution of the crude carboxylic acid **456** (2.65 g, 5.11 mmol) in MeCN (32 mL) was added over 10 min at 0 °C and the reaction was stirred at this temperature for 30 min. and cooled down to -78 °C. A solution of $LiAl(OtBu)_3H$ (9.7 g, 9.45 mmol) in anhydrous THF (30 mL) and $LiAl(OtBu)_3H$ (25 mL, 1.0 M in THF) were added over 15 min at -78 °C. The reaction mixture was stirred for 20 min. at -78 °C and then allowed to warm to r.t. The system was stirred for 3.5 h at r.t. and was quenched at -78 °C by the successive addition of NH_4Cl sat. aq. sol. (14 mL), water (14 mL) and Rochelles salts sat. aq. sol. (32 mL). After 12 h stirring, the mixture was extracted with EtOAc (3 x 50 mL) and the organic layer was washed with water (1 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The title compound **457** was obtained as a white solid (1.69 g, 3.4 mmol, 53% over 2 steps) and was engaged in the further reactions without previous purification. R_f = 0.7 (PE_{40-60} / EtOAc / AcOH, 1:2:0.2); *m.p.* = 63-66 °C; **δ_H** (400 MHz, $CDCl_3$): 1.34 (s, 9 H, C(3a)H_3), 1.57 (t, 1 H, *J*= 6.6 Hz, O*H*), 2.44 (dd, 1 H, *J*= 12.0, 19.2 Hz, C(4)H), 2.65-2.75 (m, 2 H, C(4′)H and C(3)H), 2.93 (dd, 1 H, *J*= 10.4, 12.0 Hz, C(6)H), 3.25 (dd, 1 H, *J*= 4.0, 12.0 Hz, C(6′)H), 3.47 (dd, 1 H, *J*= 4.8, 12.8 Hz, C(1b)H), 3.78 (s, 3 H, C(8)H_3), 3.81 (dd, 1 H, *J*= 7.6, 12.8 Hz, C(1b′)H, 3.94 (d, 1 H, *J*= 15.2 Hz, C(7)H), 4.97 (d, 1 H, *J*= 15.2 Hz, C(7′)H), 6.83 (d, 1 H, *J*= 8.8 Hz, C(3″)H), 7.25-7.28 (m, 5 H, C(2″)H, C(7″)H, C(8″)H), 7.49-7.51 (m, 2 H, C(6″)H); **δ_C** (100 MHz, $CDCl_3$): 27.7 (C(3a) and C(6,6′)), 36.9 (C(4,4′)), 40.8 (C(3)), 44.3 (C(7,7′)), 55.2 (C(8)), 61.2 (C(1b,1b′)), 72.9 (C(2)), 83.2 (C(2a)), 114.3 (C(3″)), 127.5 (C(8″)), 128.9 (C), 129.2 (C(2″ or 7″)), 129.3 (C(2″ or 7″)), 130.1 (C), 133.3 (C(6″)), 159.2 (C(4″)), 170.1 (C=O), 175.1 (C=O); **ν_{max} / cm^{-1}** 2364s, 1615m (C=O); ***m/z*** LRMS (ESI^+): 506.1 ($[M+H]^+$, 80%), 528.1 ($[M+Na]^+$, 100%); HRMS (ESI^+) found 506.14348; $C_{25}H_{31}NO_5Se$ $[M+H]^+$ requires 506.14512.

tert-Butyl (*R*)-2-(hydroxymethyl)-1-(4-methoxybenzyl)-3-methylene-5-oxopyrrolidine-2-carboxylate 458

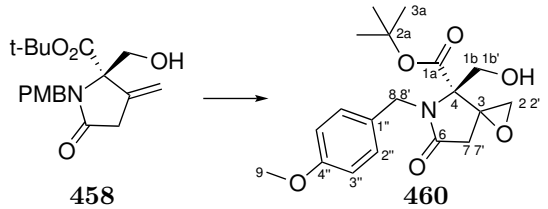


457 **458**

According to the modified procedure of Kocienski *et al.*,[185] to a mixture of lactam **457** (553 mg, 1.1 mmol) and $NaHCO_3$ (368 mg, 4.4 mmol) in MeOH / H_2O / THF (1:1:1, 18.0 mL) was added portionwise $NaIO_4$ (938 mg, 4.4 mmol) at 25 °C. The reaction mixture was stirred under air at 25 °C for 45 min. $CHCl_3$ (10.0 mL) was added and the system was filtered through a silica pad, using $CHCl_3$ (2 x 5 mL) for elution. The organic phase was decanted off and the aqueous phase was extracted with $CHCl_3$ (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and heated under reflux at 75 °C for 60 min. The system was allowed to cool down, and was concentrated under reduced pressure. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 1:1 to 1:2), giving the title compound **458** as a white solid (355 mg, 1.02 mmol, 93% yield). R_f = 0.4 (PE_{40-60} / EtOAc, 1:1); *m.p.* = 111-114 °C; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.38 (s, 9 H, C(3a)H_3), 3.21 (d, 1 H, J= 2.0 Hz, C(4)H), 3.22 (d, 1 H, J= 2.0 Hz, C(4′)H), 3.78 (s, 3 H, C(8)H_3), 3.84 (bs, 1 H, C(1b)H), 3.85 (bs, 1 H, C(1b′)H), 3.99 (d, 1 H, J= 15.2 Hz, C(7)H), 4.97 (d, 1 H, J= 15.2 Hz, C(7′)H), 5.24 (dt, 1 H, J= 0.6, 2.4 Hz, C(6)H), 5.28 (dt, 1 H, J= 0.6, 2.4 Hz, C(6′)H), 6.84 (d, 2 H, J= 8.8 Hz, C(3″)H), 7.32 (d, 2 H, J= 8.8 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 27.6 (C(3a)), 36.2 (C(4,4′)), 44.4 (C(7,7′)), 55.3 (C(8)), 64.2 (C(1b,1b′)), 75.4 (C(2)), 83.0 (C(2a)), 110.1 (C(6,6′)), 114.3 (C(3″)), 129.6 (C(2″)), 139.7 (C(1″)), 159.2 (C(4″)), 168.9 (C=O), 174.0 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3443w (O-H), 2361s, 1685m (C=O), 1663m (C=O), 1514m, 1248m; ***m/z*** LRMS (ESI$^+$): 348.1 ([M+H]$^+$, 100%), 370.1 ([M+Na]$^+$, 75%); HRMS (ESI$^+$) found 348.18024; $C_{19}H_{25}NO_5$ [M+H]$^+$ requires 348.18165.

tert-Butyl (4*S*)-4-(hydroxymethyl)-5-(4-methoxybenzyl)-6-oxo-1-oxa-5-azaspiro[2.4]heptane-4-carboxylate

460

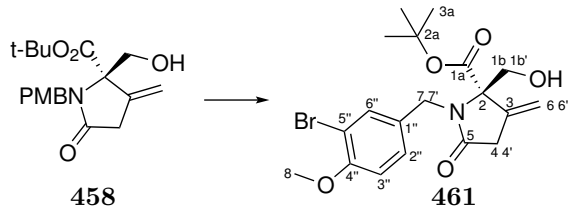


458 **460**

According to the modified procedure of Li *et al.*,[163] to a solution of *exo*-alkene **458** (60 mg, 0.173 mmol) in anhydrous DCM (0.13 mL) was added TBHP (5.0 M in DCM, 0.05 mL, 0.259 mmol). The solution was left to reach 0 °C and a solution of $VO(acac)_2$ (3.8 mg, 0.014 mmol) in DCM (0.1 mL) was added. The system was then left to reach r.t. TBHP (0.05 mL) and a solution of $VO(acac)_2$ (3.0 mg, 0.011 mmol) in anhydrous DCM (0.1 mL) were added every 2 h in order to favour the conversion (In total 21 mg of $VO(acac)_2$ in 0.5 mL of DCM were employed and 0.45 mL of TBHP). The reaction was quenched with Na_2SO_3 sat. aq. sol. at 0 °C and extracted with EtOAc (3 x 5 mL). The organic phase was washed with Na_2SO_3 sat. aq. sol., dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 1:1 to 1:3), giving the title compound **460** as a yellow oil (24 mg, 0.066 mmol, 38% yield). R_f = 0.5 (PE_{40-60} / EtOAc, 1:2); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.22 (s, 9 H, C(3a)H_3), 2.09 (bs, 1 H, O*H*), 2.48 (d, 1 H, *J*= 18.4 Hz, C(7)H), 2.93 (d, 1 H, *J*= 4.0 Hz, C(2)H), 2.99 (d, 1 H, *J*= 3.6 Hz, C(2′)H), 3.06 (d, 1 H, *J*= 18.0 Hz, C(7′)H), 3.68 (d, 1 H, *J*= 13.2 Hz, C(1b)H), 3.77 (s, 3 H, C(9)H), 3.81-3.86 (m, 1 H, C(1b′)H), 4.39 (d, 1 H, *J*= 14.8 Hz, C(8)H), 4.73 (d, 1 H, *J*= 14.8 Hz, C(8′)H), 6.82 (d, 2 H, *J*= 8.8 Hz, C(3″)H), 7.30 (d, 2 H, *J*= 8.8 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 27.6 (C(3a)), 36.2 (C(7,7′)), 44.2 (C(8,8′)), 47.9 (C(2,2′)), 55.3 (C(9)), 58.5 (C(1b,1b′)), 60.4 (C(3)), 70.9 (C(4)), 83.5 (C(2a)), 113.9 (C(3″)), 128.7 (C(1″)), 130.4 (C(2″)), 159.2 (C(4″)), 168.5 (C=O), 172.6 (C=O); $\boldsymbol{\nu_{max}}$ **/ cm^{-1}** 3400br (O-H), 2935w (C-H), 1693s (C=O), 1246s (C-O), 1155s (C-O); ***m/z*** LRMS (ESI^+): 364.1 ($[M+H]^+$, 100%), 749.2 ($[2M+Na]^+$, 46%); HRMS (ESI^+) found 364.17486; $C_{19}H_{25}NO_6$ $[M+H]^+$ requires 364.17546.

tert-Butyl (*R*)-1-(3-bromo-4-methoxybenzyl)-2-(hydroxymethyl)-3-methylene-5-oxopyrrolidine-2-carboxylate

461

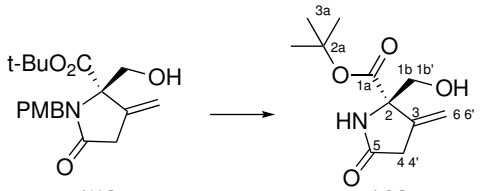


458 **461**

To a solution of lactam **458** (20 mg, 0.058 mmol) in a THF / H_2O mixture (3:2, 0.30 mL) was added NBS (12.3 mg, 0.069 mmol) at r.t. The system was left to react for 24 h. NaCl was added to the reaction mixture to saturate the aqueous phase, which was extracted with EtOAc (3 x 10 mL). The recovered organic fractions were washed with brine (1 x 15 mL), dried ($MgSO_4$), filtered and concentrated under

reduced pressure. The obtained residue was purified by FC (PE_{40-60} / EtOAc, gradient from 1:1 to 1:2), giving the title compound **461** as a colourless oil (13 mg, 0.030 mmol, 53% yield). R_f = 0.3 (PE_{40-60} / EtOAc, 1:1); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.34 (s, 9 H, C(3a)H_3), 1.77 (bs, 1 H, O*H*), 3.21 (t, 1 H, *J*= 2.4 Hz, C(4)H), 3.23 (t, 1 H, *J*= 2.4 Hz, C(4′)H), 3.86 (s, 3 H, C(8)H_3), 3.88-3.96 (m, 2 H, C(1b)H and C(1b′)H), 4.19 (d, 1 H, *J*= 15.2 Hz, C(7)H), 4.77 (d, 1 H, *J*= 15.2 Hz, C(7′)H), 5.25 (dt, 1 H, *J*= 0.6, 2.4 Hz, C(6)H), 5.28 (dt, 1 H, *J*= 0.6, 2.8 Hz, C(6′)H), 6.82 (d, 1 H, *J*= 8.4 Hz, C(3″)H), 7.30 (dd, 1 H, *J*= 2.0, 8.4 Hz, C(2″)H), 7.57 (d, 1 H, *J*= 2.4 Hz, C(6″)H); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 27.6 (C(3a)), 36.1 (C(4,4′)), 44.0 (C(7,7′)), 56.3 (C(8)), 64.5 (C(1b,1b′)), 74.9 (C(2)), 83.2 (C(2a)), 110.4 (C(6,6′)), 111.8 (C(3″)), 111.8 (C(5″)), 128.6 (C(2″)), 131.0 (C(1″)), 133.3 (C(6″)), 139.4 (C(3)), 155.4 (C(4″)), 169.0 (C=O), 174.0 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3400br (O-H), 2977w (C-H), 1708s (C=O), 1662s (C=O), 1498m (C=C), 1287m, 1256s (C-O), 1155s (C-O); ***m/z*** LRMS (ESI^+): 426.0 ($[M+H]^+$, 100%), 428.0 ($[M+H]^+$, 100%), 448 ($[M+Na]^+$, 55%), 450.0 ($[M+Na]^+$, 55%); HRMS (ESI^+) found 426.09008 (100%) and 428.08804 (100%); $C_{19}H_{24}BrNO_5$ $[M+H]^+$ requires 426.09106 (100%) and 428.08902 (100%).

***tert*-Butyl (*R*)-2-(hydroxymethyl)-3-methylene-5-oxopyrrolidine-2-carboxylate 462**

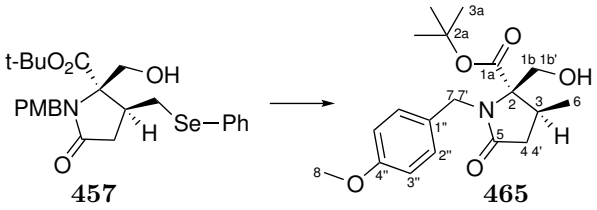


458 **462**

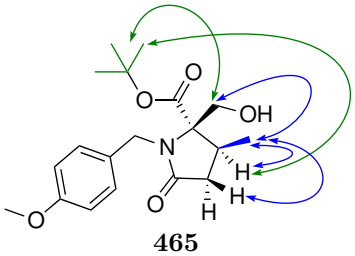
The title compound **462** has been synthesised by following the **General Procedure 11** for the deprotection of PMB-protected amides. PMB-protected lactam **458** (20 mg, 0.058 mmol) in MeCN (0.30 mL) and a solution of CAN (95 mg, 0.173 mmol) in H_2O (0.10 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, gradient from 1:1 to 0:1), giving the title compound **462** as colourless oil (8 mg, 0.035 mmol, 61% yield). R_f = 0.1 (PE_{40-60} / EtOAc, 1:3); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$): 1.47 (s, 9 H, C(3a)H_3), 3.12 (d, 1 H, *J*= 2.4 Hz, C(4)H), 3.13 (d, 1 H, *J*= 2.8 Hz, C(4′)H), 3.14 (bs, 1 H, O*H*), 3.64 (dd, 1 H, *J*= 5.6, 11.2 Hz, C(1b)H), 4.10 (dd, 1 H,*J*= 5.0, 11.0 Hz, C(1b′)H), 5.21 (t, 1 H, *J*= 2.0 Hz, C(6)H), 5.39 (t, 1 H, *J*= 2.8 Hz, C(6′)H), 6.90 (bs, 1 H, N*H*); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$): 27.8 (C(3a)), 36.4 (C(4,4′)), 68.2 (C(1b,1b′)), 71.6 (C(2)), 83.1 (C(2a)), 111.6 (C(6,6′)), 139.5 (C(3)), 169.6 (C=O), 175.2 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3336br (O-H and N-H), 2978w (C-H), 1703s (C=O), 1662s (C=O), 1369m, 1156m (C-O-C); ***m/z*** LRMS (ESI^+): 455.2 ($[2M+H]^+$, 48%), 477.2 ($[2M+Na]^+$, 100%); HRMS (ESI^+) found 455.23798; $C_{11}H_{17}NO_4$ $[2M+H]^+$ requires 455.23879.

tert-Butyl (2*R*,3*S*)-2-(hydroxymethyl)-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylate

465



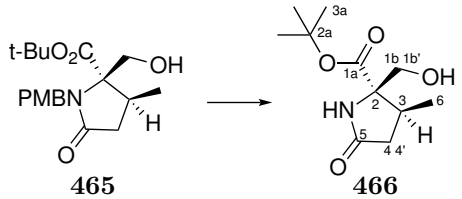
According to the procedure reported by Danishefsky and co-workers,[56] to a solution of lactam **457** (1.2 g, 2.37 mmol) in toluene (10 mL), were added AIBN (70 mg, 0.24 mmol) and *n*-Bu_3SnH (0.9 mL, 5.91 mmol). The system was left to react at 100 °C for 15 min and then cooled down to r.t. The reaction mixture was filtered and eluted (PE_{40-60} / EtOAc, 4:1 to EtOAc / MeOH, 19:1) through a pad of silica and K_2CO_3 (10%) to remove tin residues.[186] The organic phase was concentrated under reduced pressure and the crude was purified by FC (PE_{40-60} / EtOAc, gradient from 4:1 to 1:1), giving the title compound **465** as a white solid (717 mg, 2.05 mmol, 87% yield). R_f = 0.5 (PE_{40-60} / EtOAc, 1:2); *m.p.* = 134-139 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.14 (d, 3 H, *J*= 6.8 Hz, C(6)H_3), 1.45 (s, 9 H, C(3a)H_3), 1.45-1.48 (m, 1 H, O*H*), 2.21 (dd, 1 H, *J*= 6.3, 15.5 Hz, C(4)H), 2.53 (dq, 1 H, *J*= 2.0, 6.7 Hz, C(3)H), 2.58 (dd, 1 H, *J*= 8.6, 15.5 Hz, C(4′)H), 3.50 (dd, 1 H, *J*= 6.2, 12.5 Hz, C(1b)H), 3.76 (dd, 1 H, *J*= 4.5, 6.7 Hz, C(1b′)H), 3.79 (s, 3 H, C(8)H_3), 3.99 (d, 1 H, *J*= 15.3 Hz, C(7)H), 5.01 (d, 1 H, *J*= 15.2 Hz, C(7′)H), 6.83 (td, 2 H, *J*= 3.0, 8.7 Hz, C(3″)H), 7.29 (d, 2 H, *J*= 8.6 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 15.2 (C(6)), 28.1 (C(3a)), 35.4 (C(3)), 38.6 (C(4,4′)), 44.5 (C(7,7′)), 55.4 (C(8)), 61.9 (C(1b,1b′)), 73.3 (C(2)), 83.1 (C(2a)), 114.4 (C(3″)), 129.6 (C(2″)), 130.6 (C(1″)), 159.3 (C(4″)), 171.6 (C=O), 176.1 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3413br (O-H), 2975w (C-H), 2932w (C-H), 1730s (C=O), 1675s (C=O), 1514s (C=C), 1247s (C-O-C), 1150s (C-O-C); ***m/z*** HRMS (ESI^+) found 350.19623; $C_{19}H_{27}NO_5$ $[M+H]^+$ requires 350.19620.



465

key nOe interactions

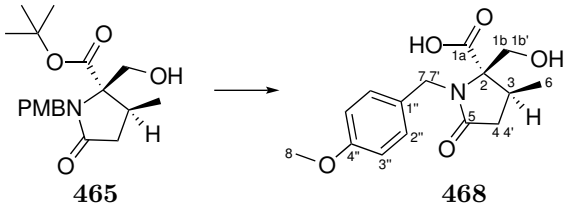
tert-Butyl (2*R*,3*S*)-2-(hydroxymethyl)-3-methyl-5-oxopyrrolidine-2-carboxylate 466



465 **466**

The title compound **466** has been synthesised by following the **General Procedure 11** for the deprotection of PMB-protected amides. PMB-protected lactam **465** (615 mg, 1.8 mmol) in MeCN (22 mL) and CAN (2.8 g, 5.3 mmol) in H_2O (7.5 mL) were used. The crude was purified by FC (PE_{40-60} / EtOAc, 1:2), giving the title compound **466** as a yellow solid (258 mg, 1.13 mmol, 64% yield). R_f = 0.8 (PE_{40-60} / EtOAc, 1:2); *m.p.* = 110-114 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.22 (d, 3 H, J= 7.0 Hz, C(6)H_3), 1.49 (s, 9 H, C(3a)H_3), 2.16 (dd, 1 H, J= 9.4, 16.7 Hz, C(4)H), 2.48 (dd, 1 H, J= 8.8, 16.7 Hz, C(4′)H), 2.61 (dq, 1 H, J= 2.1, 7.0 Hz, C(3)H), 2.65 (t, 1 H, J= 6.2 Hz, O*H*), 3.78 (dd, 1 H, J= 6.5, 11.2 Hz, C(1b)H), 3.92 (dd, 1 H, J= 5.7, 11.2 Hz, C(1b′)H), 6.38 (brs, 1 H, N*H*); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 14.7 (C(6)), 28.1 (C(3a)), 36.4 (C(3)), 38.9 (C(4,4′)), 64.6 C(1b,1b′)), 69.3 (C(2)), 82.9 (C(2a)), 171.6 (C=O), 176.8 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3342br (O-H and N-H), 2976w (C-H), 1696s (C=O), 1369m (C-O-C), 1255m (C-N), 1159m (C-O-C) ***m/z*** HRMS (ESI^+) found 252.12071; $C_{11}H_{19}NO_4$ $[M+Na]^+$ requires 252.12063.

(2*R*,3*S*)-2-(Hydroxymethyl)-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid 468

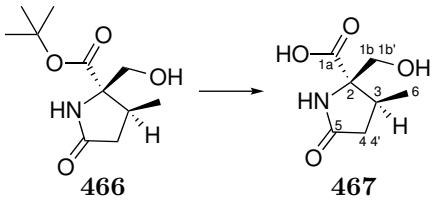


465 **468**

The title compound **468** has been synthesised by following the **General Procedure 12** for the hydrolysis of *tert*-butyl esters. Lactam **465** (296 mg, 0.85 mmol) in a mixture of TFA (4.23 mL) and DCM (1.7 mL) was used. The reaction was left for 19 h. The title compound **468** was obtained as a white solid (254 mg, quantitative yield) and was used without previous purification. R_f = 0.1 (PE_{40-60} / EtOAc, 1:3); *m.p.* = 143-145 °C; $\boldsymbol{\delta_H}$ (500 MHz, $CDCl_3$): 1.17 (d, 3 H, J= 6.6 Hz, C(6)H_3), 2.28 (dd, 1

H, J= 10.4, 19.9 Hz, C(4)H), 2.63-2.70 (m, 2 H, C(3)H and C(4′)H), 3.63 (d, 1 H, J= 12.4 Hz, C(1b)H), 3.78 (s, 3 H, C(8)H_3), 3.81 (d, 1 H, J= 12.5 Hz, C(1b′)H), 4.08 (d, 1 H, J= 15.3 Hz, C(7)H), 5.04 (d, 1 H, J= 15.5 Hz, C(7′)H), 6.84 (d, 2 H, J= 8.8 Hz, C(3″)H), 7.29 (d, 2 H, J= 8.6 Hz, C(2″)H); $\boldsymbol{\delta_C}$ (125 MHz, $CDCl_3$): 15.1 (C(6)), 35.4 (C(3)), 38.3 (C(4,4′)), 44.9 (C(7,7′)), 55.4 (C(8)), 61.6 (C(1b,1b′)), 73.3 (C(2)), 114.4 (C(3″)), 129.5 (C(2″)), 129.9 (C(1″)), 159.3 (C(4″)), 175.1 (C=O), 177.2 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 2933br (O-H), 1729s (C=O), 1636s (C=O), 1513s, 1246s (C-O), 1177m; ***m/z*** LRMS (ESI^+): 316.0 ([M+Na^+], 100%); (ESI^-): 292.1 ([M-H]$^-$, 100%); HRMS (ESI^-) found 292.11910; $C_{15}H_{19}NO_5$ [M-H]$^-$ requires 292.11905.

(2*R*,3*S*)-2-(Hydroxymethyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid 467



466 **467**

The title compound **467** has been synthesised by following the **General Procedure 12** for the hydrolysis of *tert*-butyl esters. Lactam **466** (258 mg, 1.13 mmol) in a mixture of TFA (3 mL) and DCM (2.3 mL) reacted for 6 h. The acid **467** was isolated as a white solid (162 mg, 0.94 mmol, 83 % yield), which was used without previous purification. R_f = 0.3 (EtOAc / MeOH, 19:1); *m.p.* = 136-146 °C; $\boldsymbol{\delta_H}$ (500 MHz, MeOD): 1.23 (d, 3 H, J= 7.1 Hz, C(6)H_3), 2.18 (dd, 1 H, J= 9.7, 16.6 Hz, C(4)H), 2.42 (dd, 1 H, J= 8.8, 16.6 Hz, C(4′)H), 2.63 (dqd, 1 H, J= 1.9, 6.9, 9.1 Hz, C(3)H), 3.82 (d, 1 H, J= 11.3 Hz, C(1b)H), 3.86 (d, 1 H, J= 11.2 Hz, C(1b′)H); $\boldsymbol{\delta_C}$ (500 MHz, MeOD): 14.4 (C(6)), 37.8 (C(3)), 39.8 (C(4,4′)), 64.3 (C(1b,1b′)), 70.7 (C(2)), 175.5 (C=O), 179.6 (C=O); $\boldsymbol{\nu_{max}}$ / $\mathbf{cm^{-1}}$ 3293-2974br (O-H and N-H), 1700s (C=O), 1672s (C=O), 1243m (C-O-C); ***m/z*** LRMS (ESI^-): 172.1 ([M-H]$^-$, 100%); HRMS (ESI^-) found 172.06150; $C_7H_{11}NO_4$ [M-H]$^-$ requires 172.6153.

7

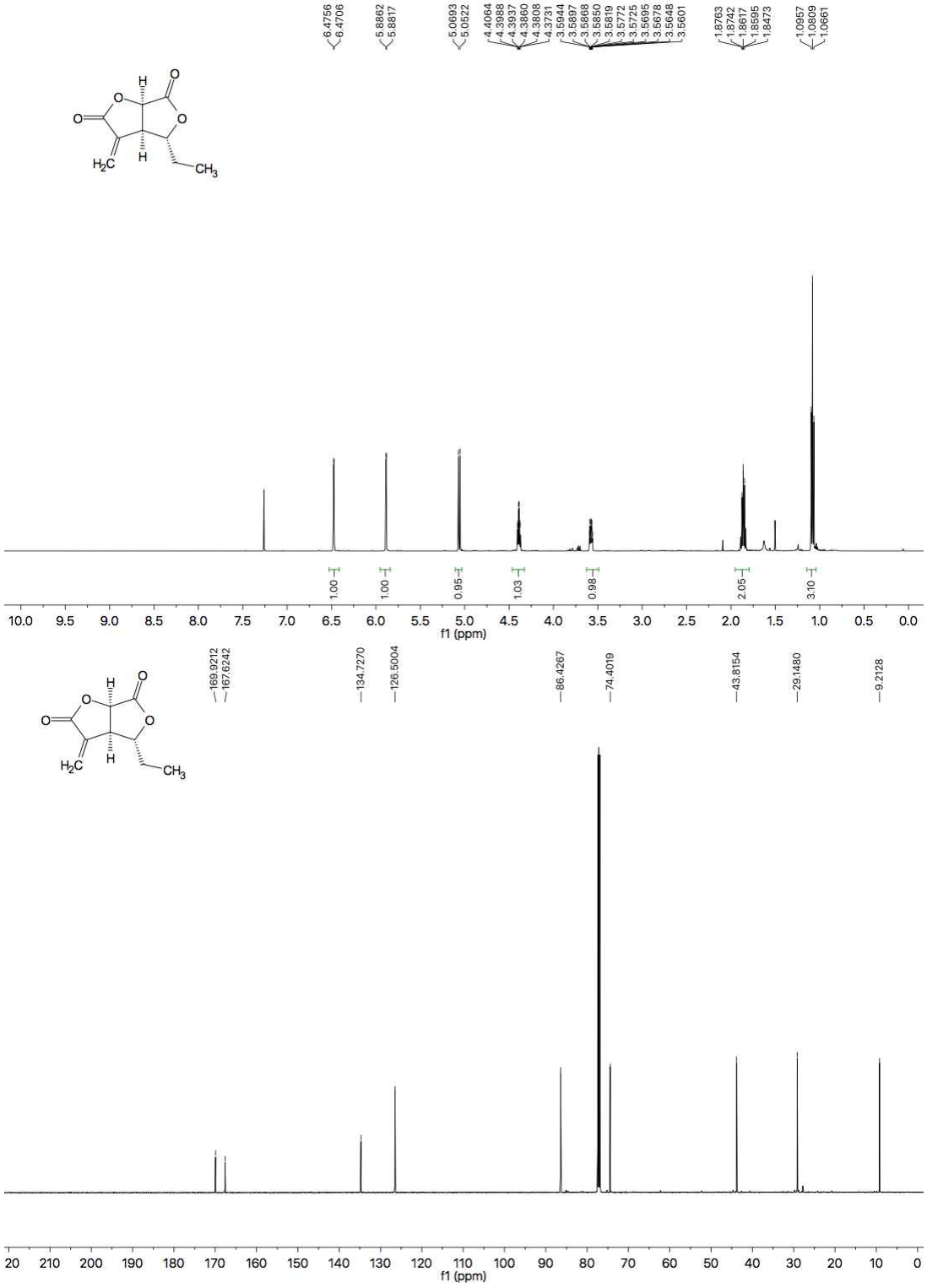
Appendix

7.1 Selected Spectra and NMR Comparison

The following section contains NMR data for the natural products *epi*-ethisolide **144**, ethisolide **147**, avenaciolide **145**, *iso*-avenaciolide **148** and discosiolide **146**, and for the non-natural compound *iso*-discosiolide **149**. In addition, the obtained NMR data for the natural products are compared with those reported in the literature (**Table 7.1**, **Table 7.2**, **Table 7.3**, **Table 7.4** and **Table 7.5**).

7.1.1 *epi*-Ethisolide and Ethisolide

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra for *epi*-ethisolide **144** in $CDCl_3$.



^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra for ethisolide **147** in $CDCl_3$.

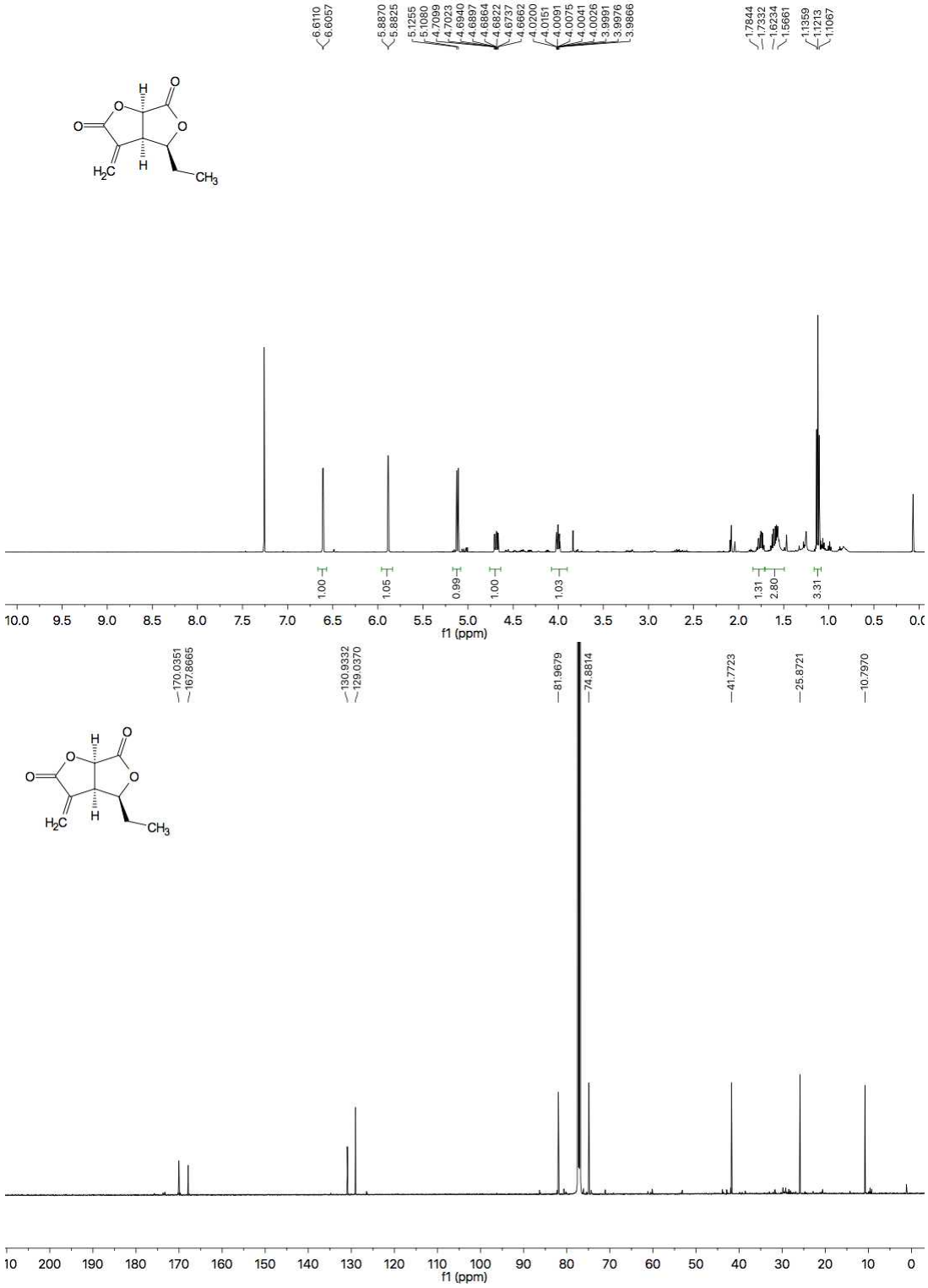
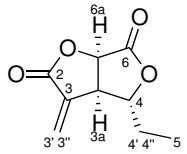


Table 7.1: NMR Data Comparison of *epi*-Ethisolide.[69]

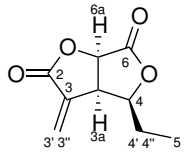


144

NMR data reported by Krohn *et al.* and recorded in $CDCl_3$ with a Bruker AM 400.[69]

Atom	^{1}H / ppm	^{1}H (Lit.) / ppm	Δ^1H / ppm	^{13}C/ ppm	^{13}C (Lit.) / ppm	Δ^{13}C / ppm
2	-	-	-	167.6 or 169.9	167.0 or 169.8	0.6 or 0.1
3	-	-	-	134.7	134.6	0.1
3′	5.88	5.90	-0.02	126.5	126.4	0.1
3″	6.47	6.48	-0.01	126.5	126.4	0.1
3a	3.58	3.59	-0.01	43.8	43.7	0.1
4	4.39	4.41	-0.02	86.4	86.3	0.1
4′	1.85	1.85	0.00	29.1	29.0	0.1
4″	1.87	1.85	0.02	29.1	29.0	0.1
5	1.08	1.09	-0.01	9.2	9.1	0.1
6	-	-	-	167.6 or 169.9	167.0 or 169.8	0.6 or 0.1
6a	5.06	5.05	0.01	74.4	74.3	0.1

Table 7.2: NMR Data Comparison of Ethisolide.



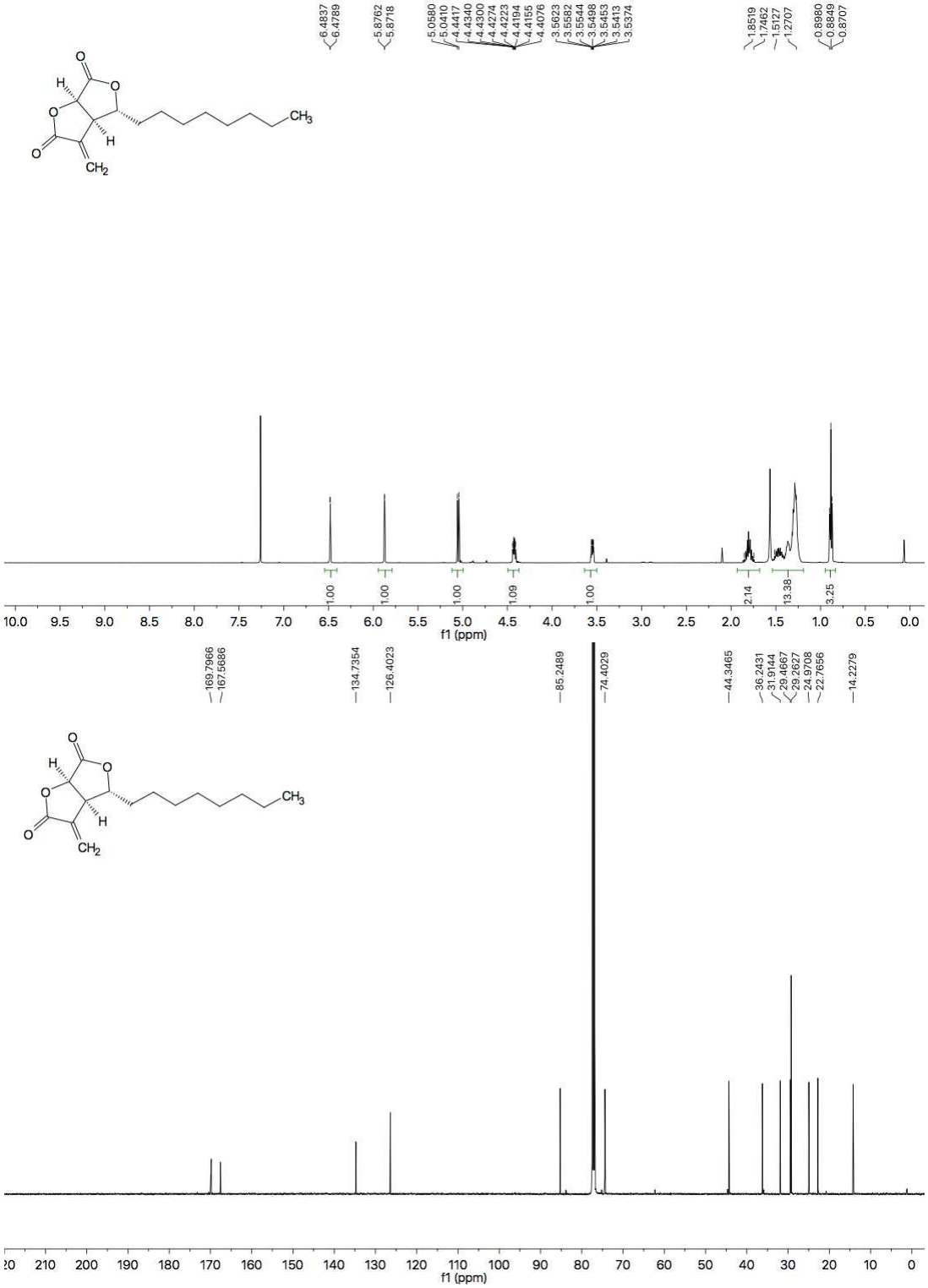
147

NMR data reported by Wee and recorded in $CDCl_3$ with a Bruker WH 200 instrument.[89]

Atom	^{1}H / ppm	^{1}H (Lit.) / ppm	Δ^1H / ppm	^{13}C/ ppm	^{13}C (Lit.) / ppm	Δ^{13}C / ppm
2	-	-	-	167.9 or 170.0	167.5 or 170.0	0.4 or 0.0
3	-	-	-	130.9	130.8	0.1
3′	5.88	5.86	0.02	129.0	128.9	0.1
3″	6.60	6.59	0.01	129.0	128.9	0.1
3a	4.00	3.97	0.03	41.8	41.6	0.2
4	4.68	4.66	0.02	81.9	81.8	0.1
4′	1.55-1.64 (m)	1.50-1.57 (m)	n.a.	25.9	25.7	0.2
4″	1.72-1.80 (m)	1.50-1.57 (m)	n.a.	25.9	25.7	0.2
5	1.12	1.10	0.02	10.8	10.6	0.2
6	-	-	-	167.9 or 170.0	167.5 or 170.0	0.4 or 0.0
6a	5.11	5.10	0.01	74.9	74.8	0.1

7.1.2 Avenaciolide and *iso*-Avenaciolide

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra for avenaciolide **145** in $CDCl_3$.



^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra for *iso*-avenaciolide **148** in $CDCl_3$.

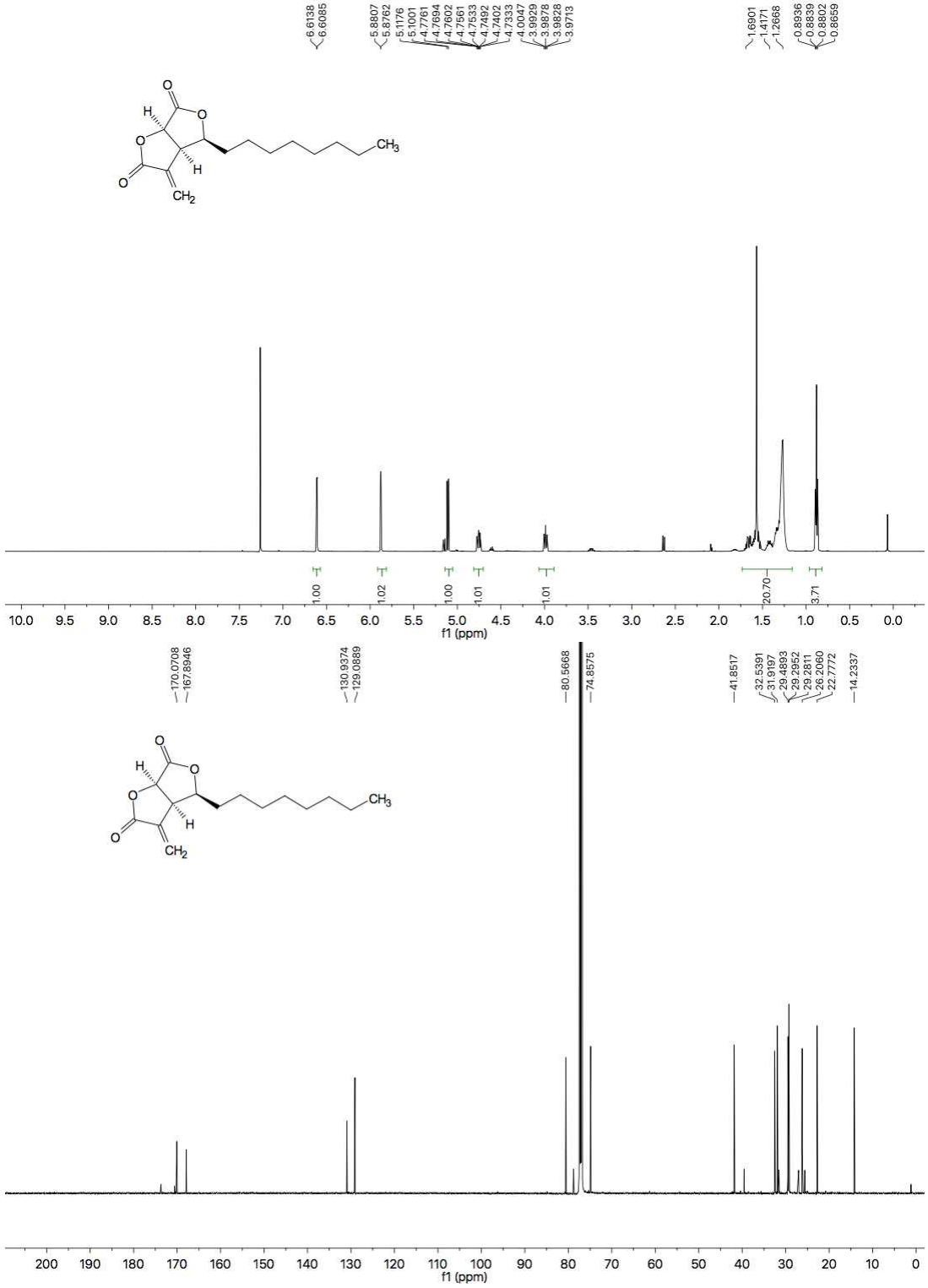
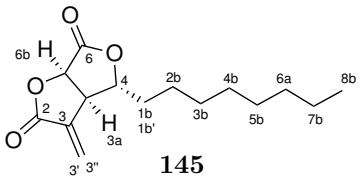


Table 7.3: NMR Data Comparison of Avenaciolide.[90]



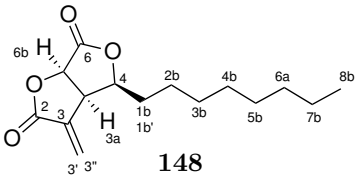
145

NMR data reported by Rodriguez *et al.* and recorded in $CDCl_3$. The model of the NMR spectrometer is not specified.[90]

Atom	^{1}H / ppm	^{1}H (Lit.) / ppm	Δ^1H / ppm	^{13}C/ ppm	^{13}C (Lit.) / ppm	Δ^{13}C / ppm
2	-	-	-	167.6 or 169.8	167.4 or 169.6	0.2
3	-	-	-	134.7	134.6	0.1
3′	5.87	5.87	0.00	126.4	126.2	0.2
3″	6.48	6.48	0.00	126.4	126.2	0.2
3a	3.53-3.57 (m)	3.55 (m)	n.a.	44.3	44.2	0.1
4	4.42	4.43	-0.1	85.2	85.1	0.1
6	-	-	-	167.6 or 169.8	167.4 or 169.6	0.2
6a	5.05	5.04	0.01	74.4	74.2	0.2
1b	1.75-1.86 (m)	1.80 (m)	n.a.	35.2	36.0	-0.8
1b′	1.75-1.86 (m)	1.80 (m)	n.a.	35.2	36.0	-0.8
2b-7b[a]	1.27-1.53 (m)	1.28 (m)	n.a.	22.8-31.9	22.6-31.8	0.1-0.2
8b	0.88	0.89	-0.1	14.2	14.0	0.2

[a] ^{13}C-NMR resonances appeared between the stated ppm range.

Table 7.4: NMR Data Comparison of *iso*-Avenaciolide.[90]



148

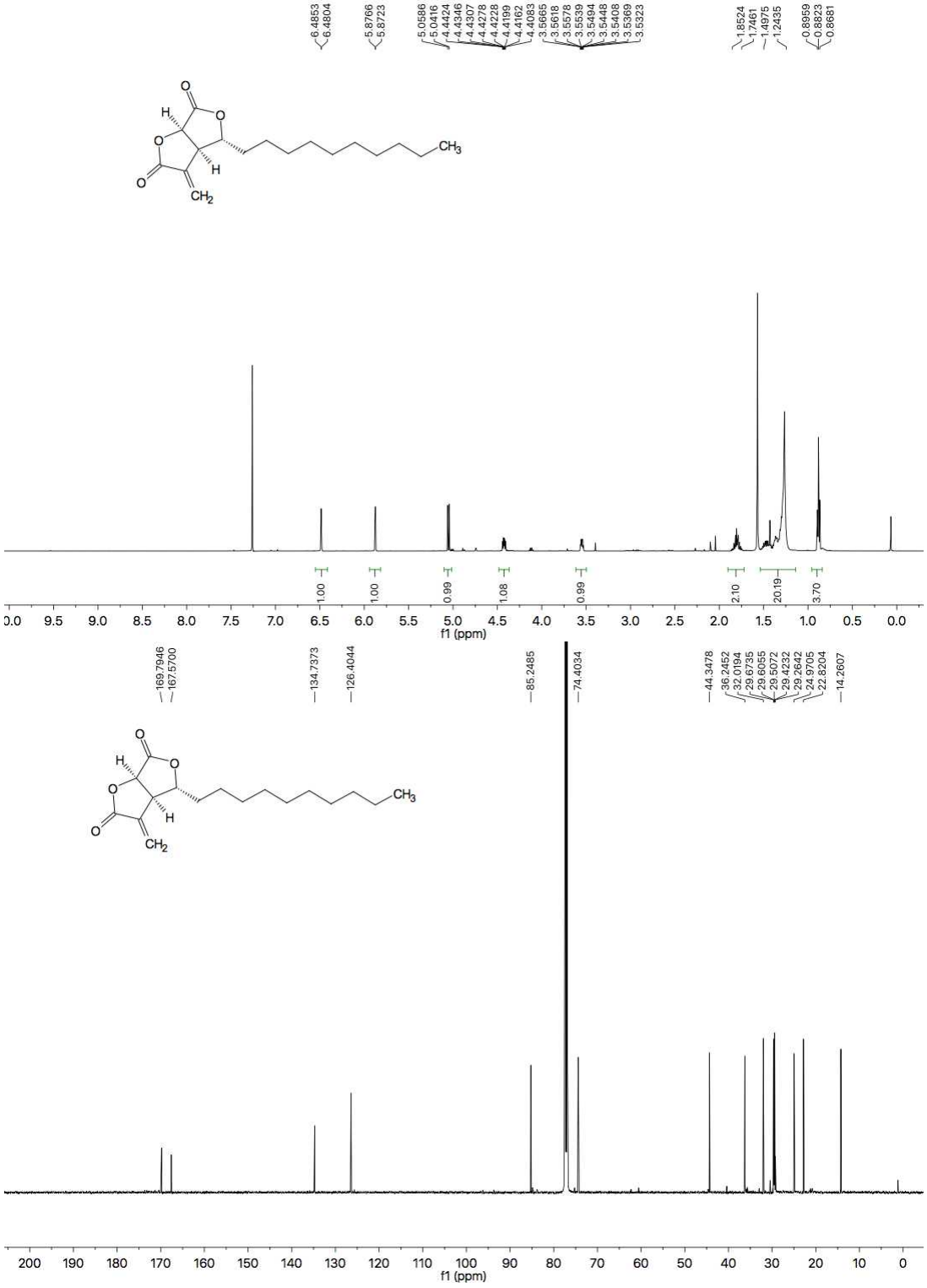
NMR data reported by Rodriguez *et al.* and recorded in $CDCl_3$. The model of the NMR spectrometer is not specified.[90]

Atom	^{1}H / ppm	^{1}H (Lit.) / ppm	Δ^1H / ppm	^{13}C/ ppm	^{13}C (Lit.) / ppm	Δ^{13}C / ppm
2	-	-	-	167.9 or 170.1	167.7 or 169.8	0.2 or 0.3
3	-	-	-	130.9	130.8	0.1
3′	5.88	5.87	0.01	129.1	128.8	0.3
3″	6.60	6.61	-0.01	129.1	128.8	0.3
3a	3.99	3.98	0.01	41.9	41.7	0.2
4	4.76	4.75	0.01	80.6	80.3	0.3
6	-	-	-	167.9 or 170.1	167.7 or 169.8	0.2 or 0.3
6a	5.11	5.10	0.01	74.9	74.6	0.3
1b	1.59-1.71 (m)	1.61 (m)	n.a.	32.5	32.4	0.1
1b′	1.59-1.71 (m)	1.61 (m)	n.a.	32.5	32.4	0.1
2b-7b[a]	1.26-.1.45 (m)	1.27 (m)	n.a.	22.8-31.9	22.6-31.7	0.1-0.2
8b	0.88	0.88	0.00	14.2	14.0	0.2

[a] ^{13}C-NMR resonances appeared between the stated ppm range.

7.1.3 Discosiolide and *iso*-Discosiolide

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra for discosiolide **146** in $CDCl_3$.



^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra for *iso*-discosiolide **149** in $CDCl_3$.

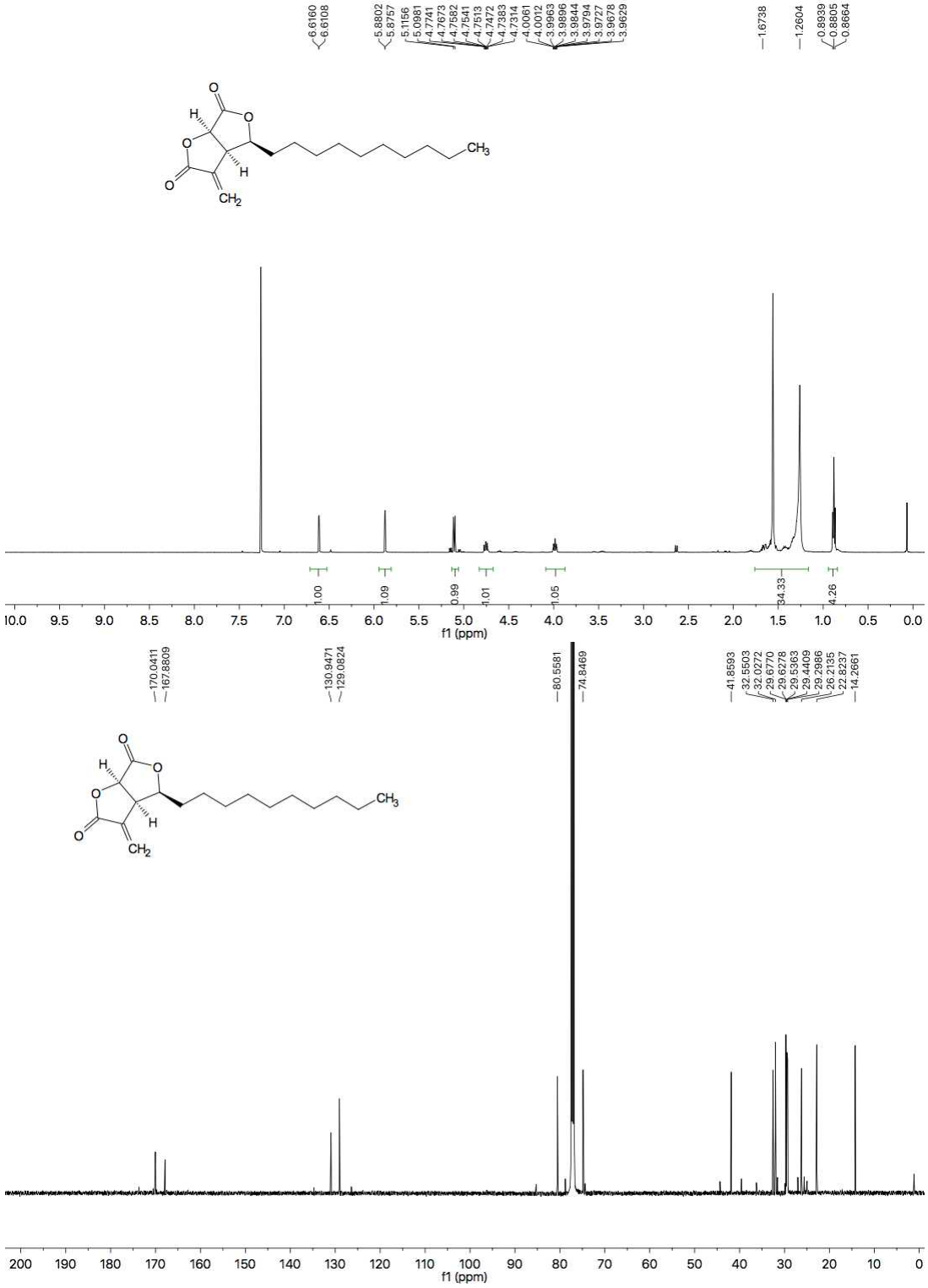
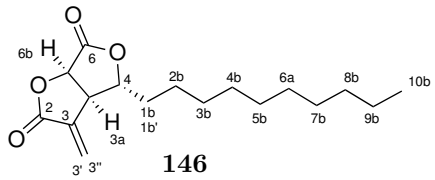


Table 7.5: NMR Data Comparison of Discosiolide.[69]



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NMR data reported by Krohn *et al.* and recorded in $CDCl_3$ with a Bruker AM 400.[69]

Atom	^{1}H / ppm	^{1}H (Lit.) / ppm	Δ^1H / ppm	^{13}C/ ppm	^{13}C (Lit.) / ppm	Δ^{13}C / ppm
2	-	-	-	167.6 or 169.8	167.5 or 169.8	0.1 or 0.0
3	-	-	-	134.7	134.6	0.1
3′	5.87	5.88	-0.01	126.4	126.3	0.1
3″	6.48	6.47	0.01	126.4	126.3	0.1
3a	3.55	3.58	-0.03	44.4	44.2	0.2
4	4.43	4.43	0.00	85.2	85.2	0.0
6	-	-	-	167.6 or 169.8	167.5 or 169.8	0.1 or 0.0
6a	5.05	5.0	0.05	74.4	74.3	0.1
1b	1.76-1.86	1.82	0.04-0.06	36.3	36.1	0.2
1b′	1.75-1.86 (m)	1.82 (m)	n.a.	36.3	36.1	0.2
2b-9b[a]	1.27-1.50 (m)	1.26-1.55 (m)	n.a.	22.8-32.0	22.7-31.9	0.1
10b	0.88	0.88	0.0	14.3	14.1	0.02

[a] ^{13}C-NMR resonances appeared between the stated ppm range.

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