APPLICATION OF DIOXINONE DERIVATIVES FOR SYNTHESIS OF AROMATIC COMPOUNDS

A Thesis submitted by

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ABSTRACT

The *de novo* synthesis of various aromatic compounds from derivatives of dioxinone **I** is reported (Scheme **I**). Using the vinyl dioxinone **II** for cross metathesis reactions allowed a series of dioxinone ketones **IV** to be constructed. The aromatization reaction the substrates, catalyzed by DABCO, was developed to allow synthesis of 6-aryl and 6-alkyl salicylates **V**.[1]
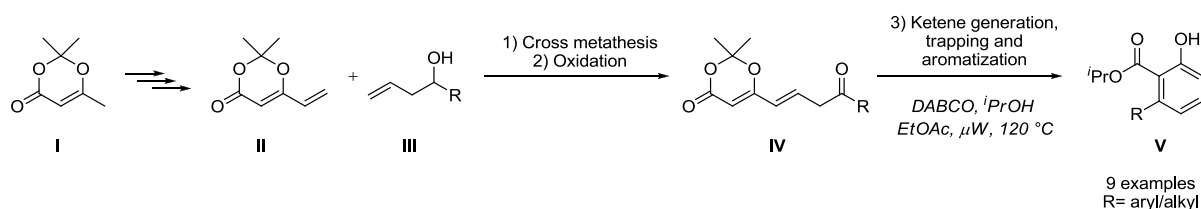
Scheme I. Sythesis of 6-substituted salicylates.

Furthermore, using the same intermediates **VI**, oxidation to the dioxinone-diones **VII** was discovered (Scheme **II**). These compounds were found to undergo a similar aromatization process but yielded hydroquinones **VIII**.
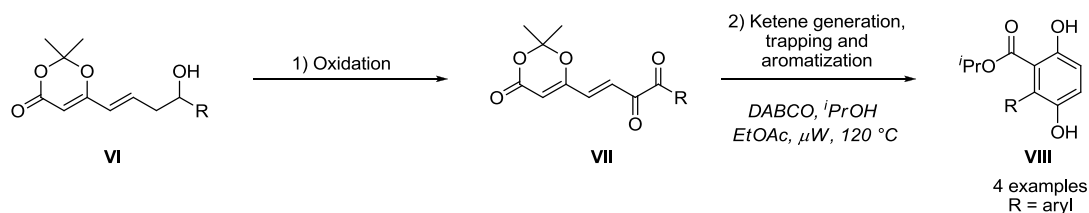
Scheme II. Synthesis of Hydroquinones **VIII**.

A novel *de novo* route to γ-resorcylates **XI**, **XV**, and **XIX** was also developed.[2] Aromatization proceeded under Appel-type reaction conditions to give the γ-resorcylates with various substitution patterns. Three complementary routes were developed for the synthesis of substrates. The first involved cross metathesis of vinyl dioxinone **II** with homoallylic esters **IX** to give the acid **X** (Scheme **III**).

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[1] Blencowe, P. S.; Barrett, A. G. M. *Can. J. Chem.* **2012**, *90* (11), 975.
[2] Blencowe, P. S.; Barrett, A. G. M. *Eur. J. Org. Chem.* **2014**, (22), 4844.
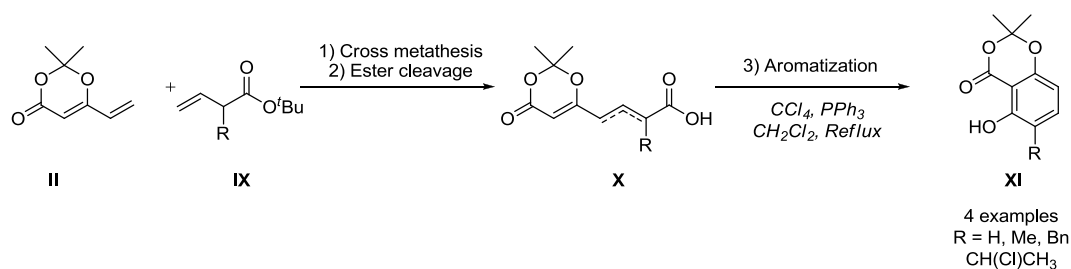
Scheme III. Synthesis of γ-resorcylates **XI**.

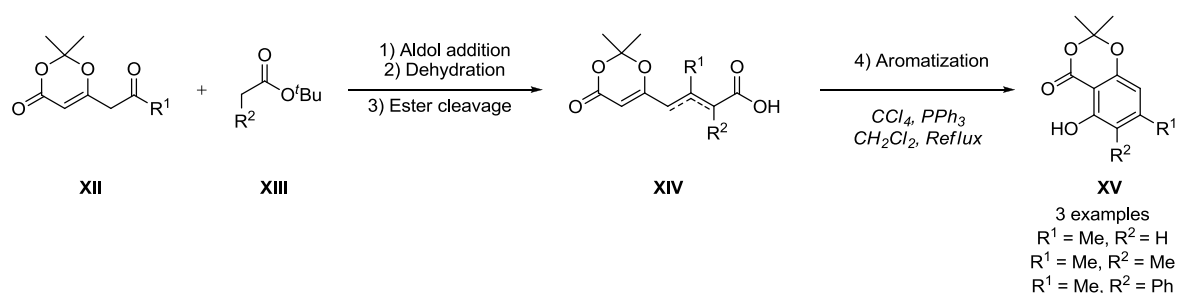A second route involved using keto-dioxinones **XII** as starting materials (Scheme **IV**). Aldol addition of *tert*-butyl acetate derivatives **XIII** to **XII** followed by dehydration and ester cleavage provided the aromatization substrates **XIV**.

Scheme IV. Synthesis of γ-resorcylates **XV**.

In a third route, the use of benzyl acetate derivatives **XVII** for aldol additions to keto-dioxinones **XVI** followed by hydrogenolysis, gave the β-hydroxy acid compounds **XVIII** (Scheme **V**). Aromatization of these substrates proceeded under the same Appel-type conditions to give the γ-resorcylates **XIX**.
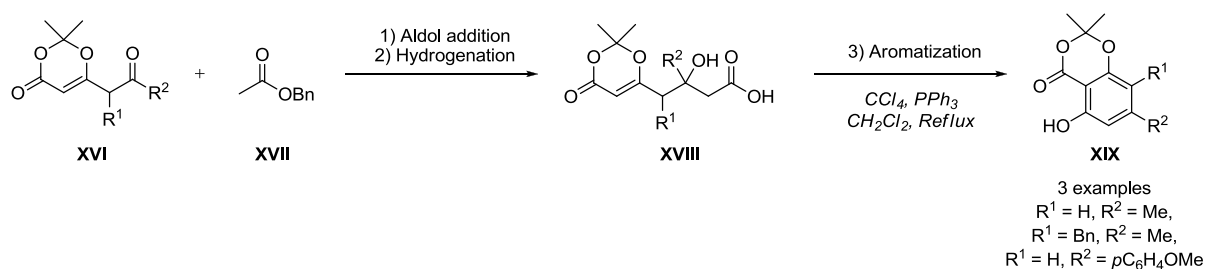
Scheme V. Synthesis of γ-resorcylates **XIX**.

Further expanding this methodology the unsaturated amide **XX** and β-hydroxy amide **XXII** were constructed in a similar manner to before (Scheme **VI**). Conditions were developed to allow the aromatization of these substrates giving 6-aminosalicylate **XXI**.

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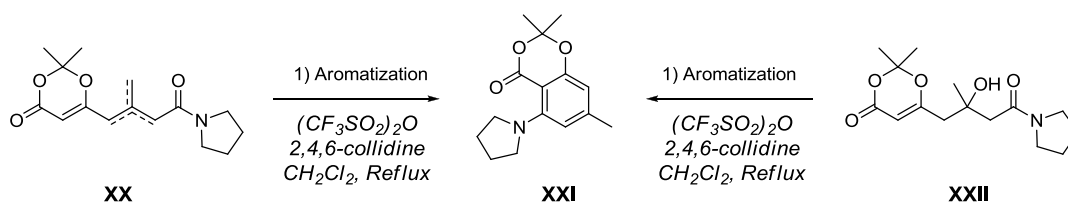
Scheme VI. Synthesis of 6-aminosalicylate **XXI**.

A route to acid chloride **XXIII** was explored in this work as it would be useful synthetic intermediate (Scheme **VII**). *In situ* IR evidence is presented for this compound however attempted isolation from solution resulted in formation of the dimer **XXIV**.
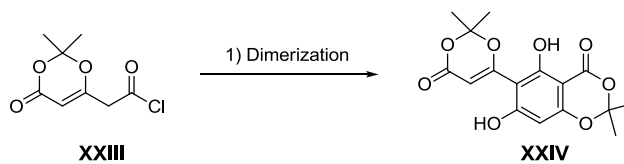
Scheme VII. Synthesis of dioxinone dimer **XXIV**.

ACKNOWLEDGMENTS

ABBREVIATIONS

Å	Angstrom (10^{-10} metres)
Ac	acetyl
Anal.	analysis
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
BHT	butylated hydroxytoluene
br	broad
Br	bromide
Bu	butyl
°C	degrees Celsius
calcd.	calculated
cat.	catalytic
CDI	carbonyl diimidazole
CI	chemical ionization
δ	chemical shift
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	*o*-dichlorobenzene
dd	doublet of doublets

DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMB	2,4-dimethoxybenzyl
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
EDCI	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et$_2$O	diethyl ether
Et$_3$N	triethylamine
EtOAc	ethyl acetate
h	hour
HAT	histone acetyltransferase
HeLa	Henrietta Lacks cells
HMDS	hexamethyldisilizane
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide

HRMS	high-resolution mass spectrometry
Hsp90	heat shock protein 90
Hz	Hertz
i	iso
IBX	2-iodoxybenzoic acid
IR	infrared spectroscopy
J	coupling constant
L	litre
LDA	lithium diisopropylamide
LDL	low-density lipoprotein
μ	micro (10^{-6})
μW	microwave
m	multiplet
M	molar
m	*meta*
Me	methyl
MeOH	methanol
MHz	mega (10^{6}) Hertz
min	minute(s)
mL	millilitre(s)
mol	mole(s)
MOM	methoxymethyl ether
mmol	millimole(s)
mp	melting point

MS	molecular sieves
n	normal
NF-κB	Nulcear Factor kappa B
NMO	N-methylmorpholine oxide
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser effect spectroscopy
Nu	nucleophile
o	*ortho*
OTf	triflate
p	*para*
PCC	pyridium chlorochromate
pH	potential hydrogen
Ph	phenyl
PhMe	toluene
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
*p*TSA	*para*-toluenesulfonic acid
q	quartuplet
quin.	quintuplet
R	general substituent
rr	regioisomeric ratio

s	singlet
s	secondary
sep	septuplet
t or *tert*	tertiary
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
td	triplet of doublets
tt	triplet of triplets
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate

Introduction

Aromatic compounds are ubiquitous throughout chemistry and its applications. Whether it is for the core of the latest blockbuster drug or functional material, the synthesis of aromatic hydrocarbons has been a feature of organic chemistry since the 19th century.[1] At that time, coal tar provided an inexpensive and abundant source of benzene, phenols, and polycyclic aromatic hydrocarbons (PAHs); and synthetic routes to substituted benzene compounds were by functionalization of one of these cheap starting materials. This led to the development of aromatic electrophilic and nucleophilic substitution reactions; reactions that have been taught to generations of chemistry.[2]

Another common area taught to chemistry students is heteroaromatic chemistry. Reactions taught in this context consist of, for example, the Paal-Knorr synthesis of pyrroles or the Fischer indole synthesis. In these cases, pre-functionalized, acyclic starting materials undergo an aromatization reaction to give the target heteroaromatic compound. This strategy of producing aromatic compounds beginning from non-aromatic precursors is often referred to as *de novo* aromatic synthesis (Scheme **1**).
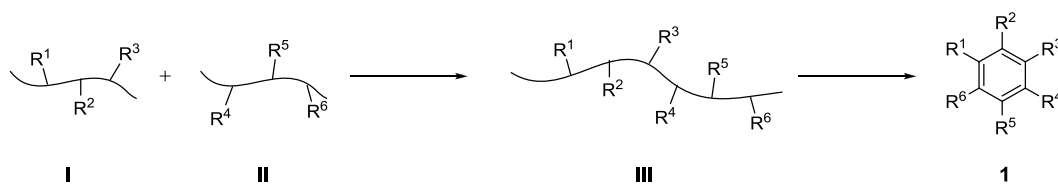
Scheme 1. A conceptual picture of *De novo* synthesis. Hexasubstituted-benzene **1** is made by cyclization of acyclic building block **III**, itself already constructed from **I** and **II**.

Classical aromatic substitution chemistry can often result in formation of *ortho*, *meta* and *para* mixtures. As such, the synthesis of highly substituted aromatic rings can often involve linear multi-step routes negating the use of cheap starting materials.[1] Using *de novo* approaches can avoid these problems; introducing substituents to an acylic starting material provides complete regioselectivity and can allow highly convergent synthesis of aromatic compounds. Furthermore, *de novo* synthesis can offer access to novel compounds not easily available by aromatic functionalization chemistry.

In the remainder of this introduction will be an outline of some of the strategies that have been used in the regioselective synthesis of densely functionalized benzenoid compounds from acyclic precursors. Of course there have been many reviews in this area of chemistry and rather than providing an exhaustive list of *de novo* methods, the outline will contain some of the main strategies that have been developed, including some of their applications as examples.[3] Some examples will also be shown to directly compare the efficiency of aromatic functionalization and *de novo* strategies. The methods

covered will mainly be *de* novo synthesis of benzene compounds; heteroaromatic synthesis and the synthesis of fused compounds are largely not covered.

Having introduced strategies for *de novo* synthesis, some of the synthetic methods nature employs for aromatic compounds will be discussed including chemists who have attempted to mimic them. At this point, a discussion of dioxinone compounds and their use in synthesis will ensue before returning to biomimetic concepts and how, when combined with dioxinone derivatives, they are leading to emerging methods in *de novo* aromatic synthesis.

Research within the Barrett group at Imperial College will then be discussed giving a detailed picture of what was known before the current research began, as well as developments that were made concurrently. Following this, the aims of the project will be outlined, and the research carried out will be presented in the subsequent results and discussion sections.

1.1 Benzenes by *De Novo* Synthesis

The following *de novo* methods of benzene synthesis are loosely divided into sections by virtue of their broad underlying strategy. This allows the many ways in which *de novo* synthesis has been explored to be appreciated.

1.1.1 Formation and Cyclization of Dienylketenes

Dienylketenes readily undergo 6π-electrocyclization resulting in benzene derivatives. There are many ways for their generation and the following sections cover the Danheiser benzannulation reaction, cyclization of hexadienoic acids, and the Wulff-Dötz reaction as methods for accessing this intermediate.

1.1.1.1   The Danheiser Benzannulation Reaction

The discovery of the Danhesier benzannulation was preceded by the benzannulation of enoic-ketenes and alkynes. This process was first discovered by Smith and Hoehn; reaction of diphenyl ketene (**2**) and phenylacetylene (**3**) gave 3,4-diphenylnaphthalen-1-ol (**4**) (Scheme **2**).[4] This was proposed to occur through a dienylketene intermediate.
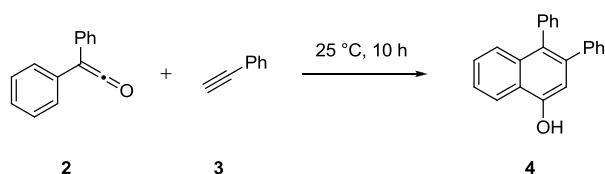
Scheme 2. Smith and Hoehn's naphthol synthesis.

Following numerous contributions one of the major examples of this process is the Danheiser benzannulation which sees the conversion of a cyclobutenone and acetylenic derivative to give a highly substituted aromatic compound in a regiocontrolled manner (Scheme **3**).[5] Heating of cyclobutenedione **5** leads to a reversible four-electron electrocyclic cleavage to give vinylketene **7** which undergoes a [2+2] regiospecific cycloaddition with acetylene component **6**. Four-electron cleavage of the 2-vinylcyclobutenone **8** forms dienylketene **9**. 6π-electrocyclization of the dienylketene affords a cyclohexadienone that can tautomerize to give phenol compound **10**.
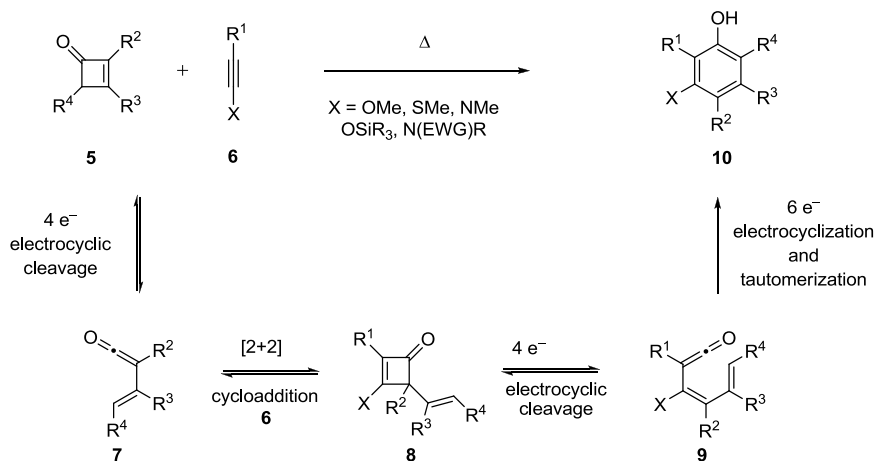
Scheme 3. Danheiser's aromatization of dienylketenes.

As alternative precursors to vinylketene intermediate **7** a route using a Wolff rearrangement was developed (Scheme **4**). Rearrangement of diazo compound **11** gave vinylketene **12** that could react with an alkyne as before. This expands the versatility of the cycloaddition method through the range of substrates available.[6]
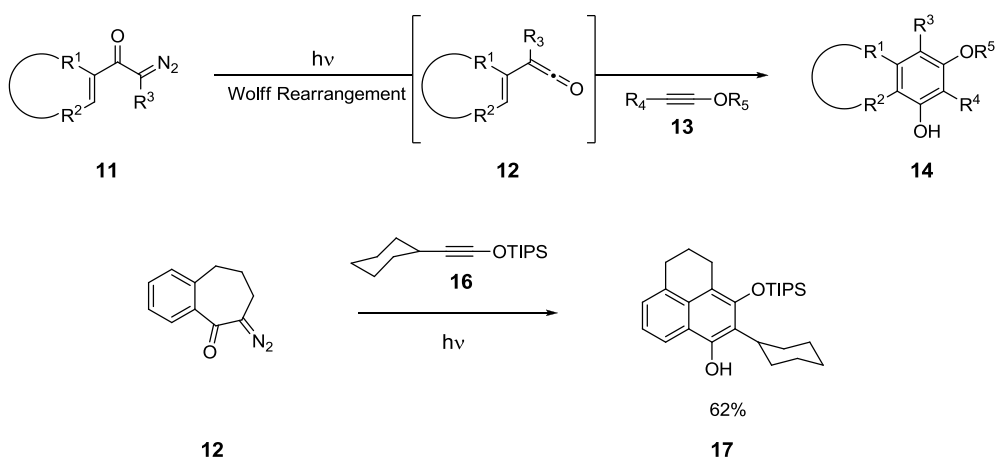
Scheme 4. Wolff rearrangement in the generation of dienylketenes.

The scope of these reactions was further increased by use of cyclobutenediones as starting materials in an intramolecular process (Scheme **5**).[7] Addition of aryllithium reagents to **18** gives cyclobutenol **19**, which undergoes conrotary ring opening to give dienylketene **20**. 6π-Electrocyclization of the dienylketene **20** gives fused 1,4-hydroquinones **21**. Alternatively, addition to fused dione **22** with an arylmagnesium reagent gave the cyclobutenol **23**. Aromatization of the cyclobutenol followed by oxidation gives quinone **24**. Further to this, the addition of alkynyl lithium reagents to **22** gives yne-eneylketene intermediates, an oxidation state higher, resulting in direct isolation of quinones (Moore cyclization, not pictured).[8]
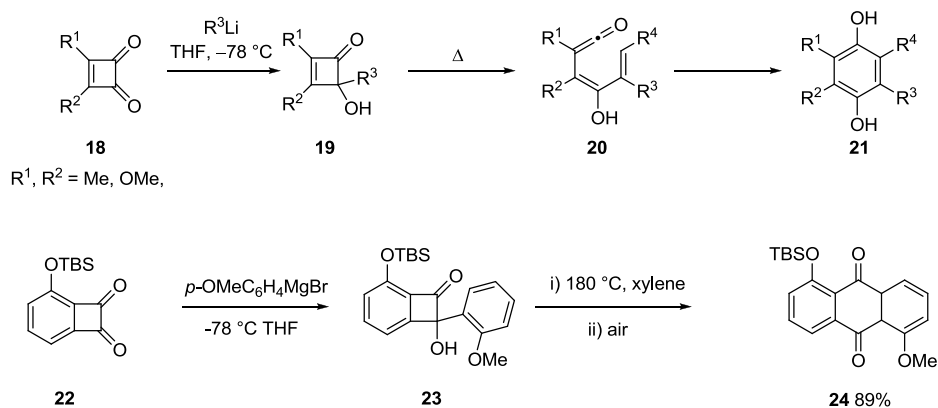
Scheme 5. Liebeskind's organometallic additions to cyclobutenediones and aromatization reactions.

1.1.1.2 Hexadienoic Acids

Activation of hexadienoic acids **25** also lead to formation of dienylketenes with subsequent 6π-electrocyclization (Tables **1** and **2**). The required substrates can easily be constructed *via* Stobbe condensation or by Wittig reaction.[9, 10] The first use of these substrates for aromatic synthesis was by

Ramage *et al.* who prepared phosphinic-carboxylic acid mixed anhydrides in the presence of base to give the *m*-hydroxybenzoic acids.[11]
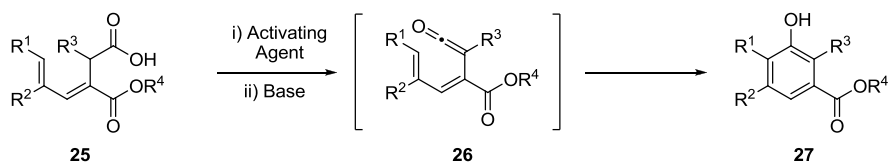
Entry[b]	R^1	R^2	Yield
1	H	Me	50
2	Me	H	59
3	Ph	Me	47
4	Me	Ph	62
5	Me	*o,o*-Br, NO_2-C_6H_3	56

a) R^3 = H, R^4 = Me. b) i) *N*-methylmorphiline, $P(O)Ph_2Cl$, CH_2Cl_2, −23 °C; ii) NEt_3, −23 to 25 °C.

Table 1. Activation of **25** as phosphinic-carboxylic mixed anhydrides by Ramage *et al*.

Entry	R^1	R^2	R^3	R^4	Yield (%)
1[12]	PhS	Me	Me	Et	95[c]
2	Br	Me	H	Et	89[b]
3	Ph	OMe	H	Et	88[b]
4[13]	β-glucopyranosyl	H	H	Et	91[b]
5[14]	*o*-BnO-napthyl	Et	H	Me	78[a]
6	2-furyl	Me	H	Me	87[a]
7[15]			H	Et	90[a]
8			H	Et	85[a]

a) $ClCO_2Et$, NEt_3, THF. b) i) $ClCO_2Et$, NEt_3, THF; ii) NaOH, EtOH. c) $(CF_3CO)_2$, NEt_3; ii) $NaBH_4$, EtOH.

Table 2. Activation of hexadienoic acids **25** by Serra.

Further work by Serra, who improved the activation by use of ethyl chloroformate as the activating agent, demonstrated applicability for a range of substrates. Heteroatom, aryl, alkyl, and glycosidyl substituents were all compatible with the cyclization protocol giving excellent yields. Similar to these

examples, but without the requirement for direct activation, was the intramolecular cyclization of the dienylacids **28** (Scheme **6**).[16] Due to the presence of the enol ether, heating of **28** alone provided phenols **29**.
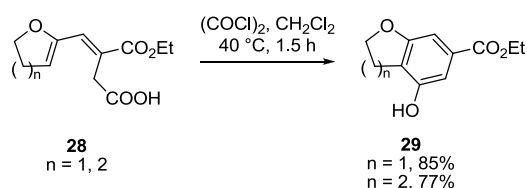
Scheme 6. Paquette's enol ether assisted aromatization reaction.

1.1.1.3 The Wulff-Dötz Benzannulation

The Wulff-Dötz reaction is the reaction of an α,β-unsaturated Fischer carbene complex with an alkyne to give an arene-Cr(CO)$_3$ complex: a [3+2+1]-benzannulation (Scheme **7**).[17] After initial loss of carbon monoxide from the carbene **30** by mild heating (typically 45–60 °C), coordination of a molecule of alkyne **31** forms α,β-unsaturated carbene intermediate **III**. Insertion of CO then generates the dienylketene-Cr(CO)$_3$ complex **IV**. Electrocyclic ring closure followed by tautomerization gives the arene-Cr(CO)$_3$ complex **32**. This is a similar dienylketene intermediate generated in methods highlighted above. In this case however, the formation of the dienylketene is within the coordination sphere of a metal allowing the phenols **32** to be formed under very mild conditions. Unsymmetrical alkynes are regiochemically incorporated in correlation with their steric differential; the larger substituent incorporated *ortho* to the hydroxy group. [18]
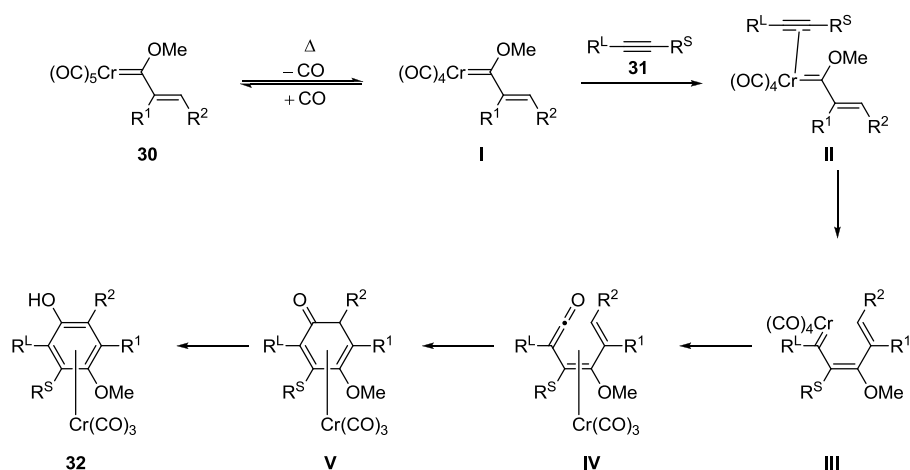
Scheme 7. Postulated mechanism for the Wulff-Dötz reaction.

In light of the effectiveness of the Wulff-Dötz reaction, it has been used widely in synthesis and in a number of natural products. En route to the macrocycle (–)-kendomycin, the reaction allowed a

heavily substituted benzene derivative **35** to be prepared from the alkyne **33** (Scheme **8**).[19] Here, mild air oxidation of the mixture liberated the phenol free from its chromium complex. Another densely functionalized phenol **37** was produced by a partial Wulff-Dötz reaction.[20] Preformed dienylcarbene complex **36**, underwent carbonylation and aromatization to give the carbazole in 65 % yield towards a synthesis of carbazoquinocin C.
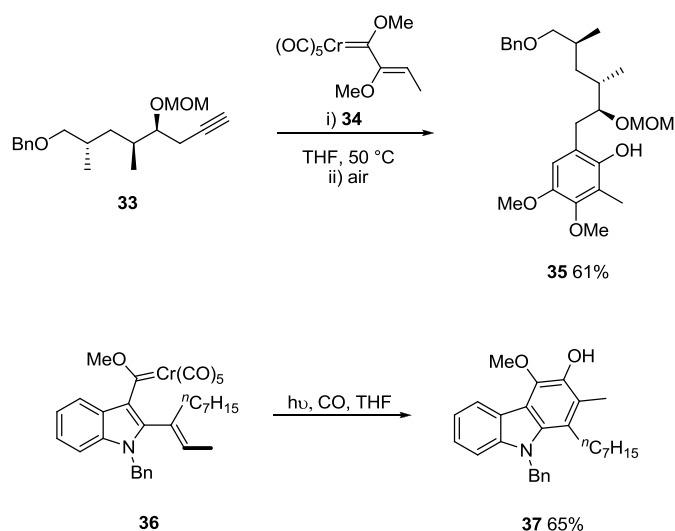
Scheme 8. Application of the Wulff-Dötz in synthetic steps towards (−)-kendomycin and carbazoquinocin C.

1.1.2 Eneyne Molecules as Substrates for Aromatization

Benzene synthesis involving eneynes cover a vast array of different reactions, mechanisms and strategies. Here, Bergmann cyclizations, dehydro Diels-Alder, Diels-Alder, and trimerization reactions are discussed.

1.1.2.1 Bergmann and Myers-Saito Cyclizations

The Bergmann cyclization was first applied to synthetic molecules before the discovery of its occurrence in nature.[21] The cyclization of acyclic enediynes **38** to give 1,4-biradical **39** was first discovered by Bergman and coworkers and the high temperature required suggested that it would not be possible at the ambient temperatures of nature (Scheme **9**).[22] Related to this, is the Myers-Saito Cyclization in which the cyclization of eneyne allene systems **41** gives biradical **42**.[23] Allenes of type **41** are highly reactive and so the Myers-Saito cyclization of acyclic molecules is generally more facile than Bergmann cyclization.[24]

Bergmann cyclization

Myers-Saito cyclization

Scheme 9. Mechanisms of the Bergmann and Myer-Saito cyclizations.

Natural cyclic enediynes occur in a number of antitumor antibiotics such as the calicheamicins, esperamicins, and neocarzinostatin. Elucidation of the mode of action of these antibiotics led to an understanding of how the substrates could be stabilized at ambient temperatures as well as triggered to undergo cyclization when required.[25] For example the active site of calicheamicins contain a cyclic enediyne, calicheamicinone (**44**) (Scheme **10**). In the laboratory, triggering of the Bergmann cyclization was achieved by addition of triphenylphosphine; attack at the allylic trisulfide of **44** led to Michael addition of the resulting thiol to generate the more highly strained intermediate **I**.[26] Now activated for cyclization, **I** gives the biradical **II**, which is deuterated by the solvent resulting in **45**.

Scheme 10. Triggering calicheamicinone (**44**) to undergo a Bergmann cyclization deuterium trapping of the biradical.

With regard to the rate of cyclization, a theory was postulated that the distance between the acetylenic carbon atoms governs the rate of cyclization.[27] More recently another more general theory was proposed based on the differential molecular strain between the ground and transition states.[28] With regard to the Myers-Saito cyclization, the formation of a s-*cis*-enyne-allene can be sufficient to trigger cyclization. For example, treatment of **46** with TFA in the presence of 1,4-cyclohexadiene forms the enyne-allene **47**, which undergoes a very facile Myers-Saito cyclization to give the aromatized product lactone **48** (Scheme **11**). [29]

Scheme 11. Acid mediated formation of a enyne-allene **46** and Myers-Saito cyclization.

In order to allow more facile aromatization of Bergmann enediyne substrates, rearrangement to the more reactive eneyne-allene forms have been attempted. One example of where this has been achieved is through formation of a vinylidene complex **50** (Scheme **12**).[30] Thermyolysis the complex **50** required heating at only 100 °C compared to 190 °C required for aromatization of the uncomplexed enediyne **49**.[31]
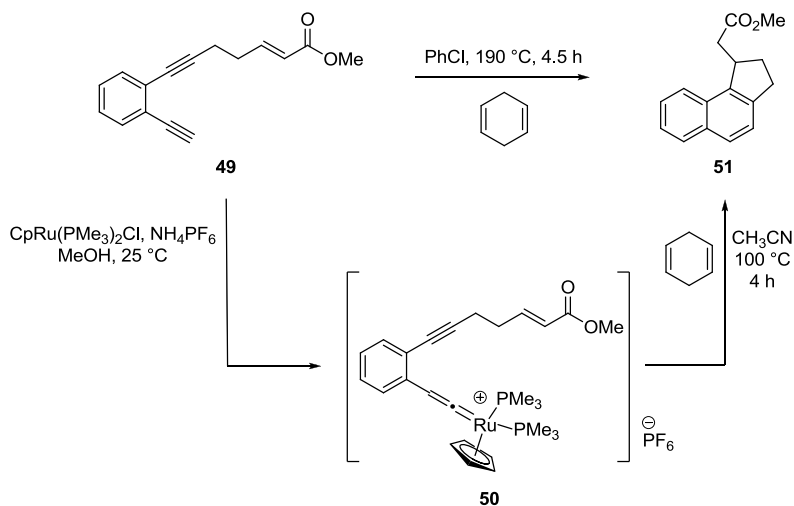
Scheme 12. Rearrangement of enediyne **49** to more reactive vinylidene complex **50**, that aromatizes to **51**.

1.1.2.2 Dehydro Diels-Alder Reactions for *De Novo* Aromatic Synthesis.

The "dehydrogenated" version of the Diels-Alder is known as the dehydro Diels-Alder; the tetradehydro-Diels-Alder being more highly oxidized is capable of generating bent cyclic allenes-isomers of benzenes.[32] Many variants on substrates and their synthesis have been envisaged based on intra- and intermolecular reactions, as well as variation in starting materials.[33]

Danheiser demonstrated that the conjugated enynes of **52a–c** undergo intramolecular [4+2] cycloaddition with alkynes to give benzene compounds **53a–c** under heat or with protic and Lewis acids (Scheme **13**).[34] The use of phenolic additives increased the yields obtained in these reactions but not the rate, while use of protic or Lewis acids enabled reactions to be carried out at 0 °C. The initial

isoaromatic cyclic allenes from these reactions are proposed to undergo rearrangement *via* either proton or radical mediated hydrogen atom transfer pathways.[35]
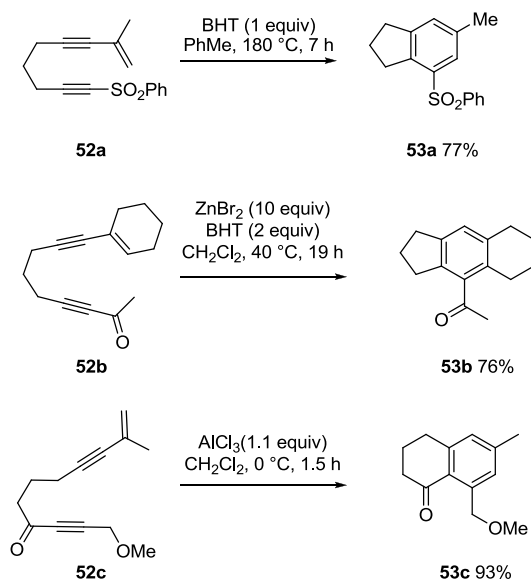
Scheme 13. Danheiser's cyclizations of eneynes under thermal and acid catalyzed reaction conditions.

Later, Yamamoto and co-workers reported a complimentary regiospecific palladium catalyzed intermolecular method for homodimerization of conjugated enynes (Scheme **14**).[36] Beginning with the enynes **54** or **55**, the conversion to homodimers was observed without trimerization and, in a regiospecific manner to give the benzene derivatives **56** and **57**. This was then extended to produce unsymmeterical compounds from cross cycloaddition of the enynes. Cycloaddition of **58** or **59**, with symmetrical diynes such as **60**, gave **61** and **62** respectively in a regioselective fashion.[37]
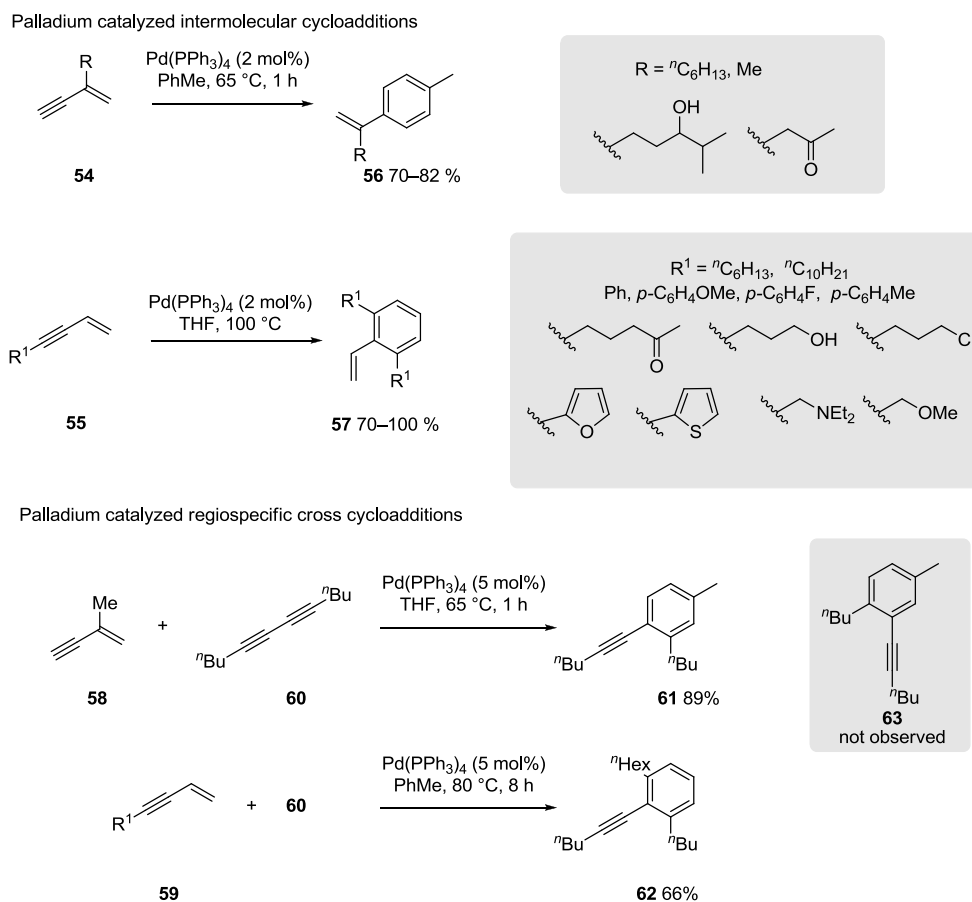
Scheme 14. Yamamoto's intermolecular eneyne homo-cycloadditions and cross-cycloadditions.

1.1.2.3 Diels Alder Reactions

Diels-Alder reactions of 2-pyrones are have been widely used for *de novo* construction of benzene compounds.[38] The general concept proceeds by [4+2] cycloaddition of alkynes to pyrones **63** generates highly strained bicyclooctadeienes **64**, which is followed by extrusion of CO_2 to give the aromatic products **65** (Scheme **15**). Cycloaddition of alkenes to pyrone **63** gives more stable bicyclooctenes **66**, and extrusion of CO_2 gives dihydrobenzenes **67**. Elimination of a leaving group can give the benzene **68**.
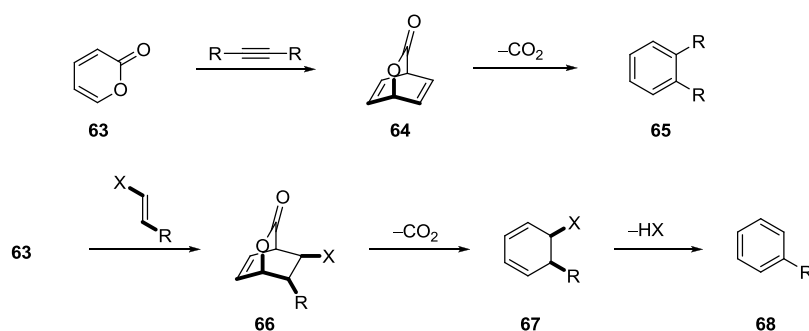
Scheme 15. General Diels-Alder reactions of alkynes or alkenes with 2-pyrone **63** as applied for benzene synthesis.

This method has been used in methodology and natural product chemistry alike. Towards highly functionalized benzene derivatives, alkylated pyrones **69** were heated with unsymmetrical alkynes **70** (Scheme **16**).[39] Use of unsymmetrical alkynes in such Diels Alder reactions can lead to mixtures of regioisomers however in this case, use an acetylenic ester **70** allowed sufficient distinction for highly regioselective formation of benzoate **71** over regioisomer **72**.
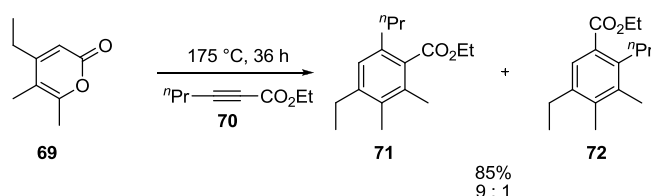
Scheme 16. Regioselectivity achieved in Diels-Alder reaction of an unsymmetrical alkyne **70** with 2-pyrone **69**.

Within natural product synthesis the Diels-Alder strategy for *de novo* benzene synthesis has solved numerous problems. In a synthesis of imeluteine (**73**), trimethoxy ethene is used as the reactive partner with pyrone **74** (Scheme **17**).[40] The Diels-Alder cyclization and decarboxylation was followed by treatment with base to facilitate loss of methanol to give **75**. Ester saponification followed by decarboxylation gave rise to the target natural product imeluteine (**73**).
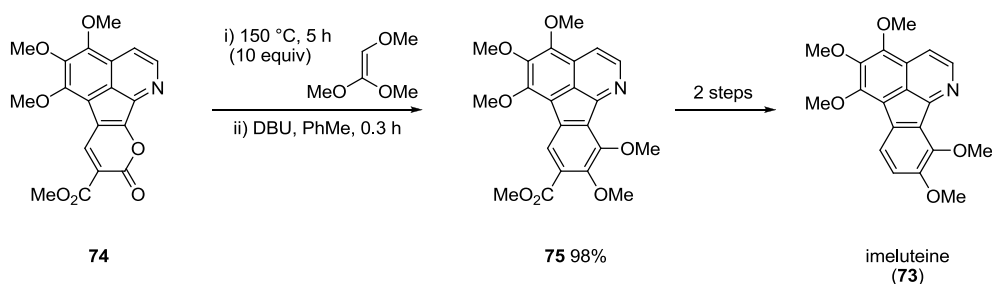
Scheme 17. Diels-Alder addition of trimethoxyethene and 2-pyrone **74** towards a synthesis of imeluteine (**73**).

In a synthesis of lasalocid A (**76**) a salicylate was required (Scheme **18**). Despite attempts of Diels-Alder reaction of pyrone **77** with alkoxy propynes or synthetic equivalents, none were found to be reactive.[41] However, it was found ynamines could also be active as dienophiles for the Diels-Alder

reactions with 2-pyrone **77**. Diels-Alder reaction of *N,N*-diethyl-1-amino-1-propyne with pyrone **77** occurred at room temperature in 89% yield. The required dibenzylalkyne **78** reacted similarly well to give the aminosalicylate **79** in 60% yield, which was further converted to lasalocid A.
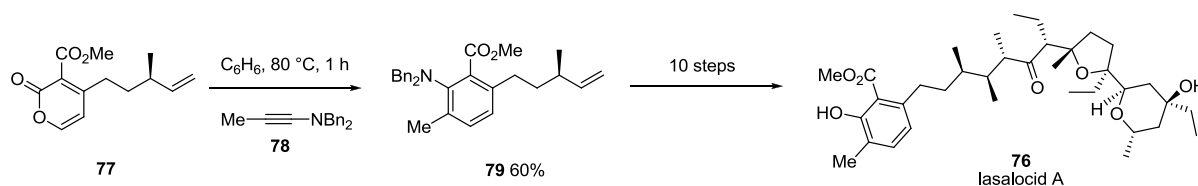
Scheme 18. Diels-Alder reaction of 2-pyrone **77** with a ynamine **78**.

Application of the Diels-Alder strategy also enabled a synthesis haouamine A (**80**); a architecturally unique alkaloid containing a cyclophane macrocycle and a highly deformed aromatic ring (Scheme **19**).[42] Formation of the macrocycle by biaryl synthesis methods or alkylation failed and so *de novo* approaches were investigated. This first involved the synthesis of pyrone **81**, with the nitrogen-tethered alkyne awaiting an intramolecular, macrocylization Diels-Alder reaction- a first of its kind. Reaction proceeded at 250 °C to give adduct **82** and treatment with potassium carbonate gave **80** in 21% yield (with 30% of recovered **81**) and 10:1 selectivity for the desired atropisomer. While the yield was low, this represented the first synthesis of **80** and a novel macrocyclization strategy.
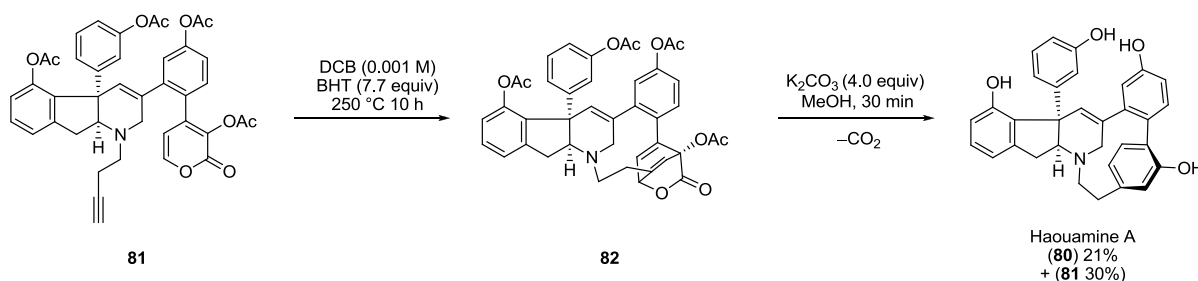
Scheme 19. *De novo* synthesis using a Diel's Alder reaction of pyrone **81** employed by Baran for synthesis of haouamine A (**80**).

To further improve the synthesis of haouamine A (**80**) and its atropisomer, an alternative *de novo* synthesis of the phenol ring was investigated (Scheme **20**).[43] This time the cyclohexenone intermediate **83** was chosen as the target for synthesis, the sp³ hybridization making this a less strained species. Oxidation of **83** would then allow access to the desired phenol. The oxidant of choice, to avoid oxidation of the core, was found to be *N-tert*-butylbenzenesulfinimidoyl chloride (**84**).[44] Brief exposure of **83** to the oxidant gave the desired phenol **85** in 60% yield (23% **83**) and demethylation provided the natural product **80**.
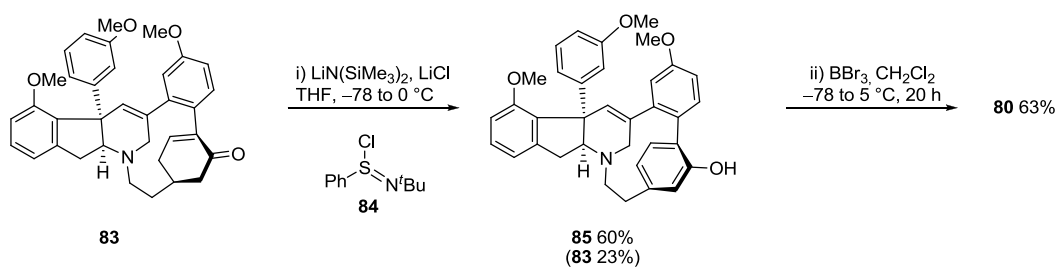
Scheme 20. *De novo* synthesis of haouamine A (**80**) by an oxidation strategy.

1.1.2.4   [2+2+2] Trimerizations

Trimerization of alkynes is a very useful and widely applied method for the synthesis of benzene derivatives.[45] In 1866 the thermal (ca 400 °C) cyclization of acetylene to give benzene was reported and later, in 1949 the first transition metal variant of the reaction was reported being catalyzed by a large number of transition metals.[46] In the case of homo-trimerization, the regioselectivity of 1,2,4 vs 1,3,5-substituted arenes must be considered (Scheme **21**). Excellent results are obtained with respect to this regioselectivity using titanium calixarene catalysts as illustrated by Ladipo *et al*.[47] Virtually complete regioselectivity is imparted by the steric effects directing insertion of the third alkyne into a titanacyclopentadiene.
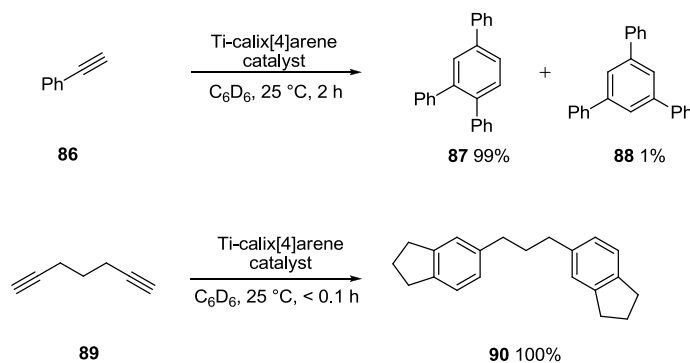
Scheme 21. Ladipo's highly regioselective alkyne trimerizations for formation of 1,2,4-substituted arenes.

Moving to a more complex situation, selective cross-trimerization is even more challenging as including regioselectivity issues, there are also chemoselective issues meaning multiple products may be obtained. For the intermolecular variant, selectivity can be achieved through selective formation of the intermediate metallocyclopentadiene and its further reaction with an alkyne, similar to the example above. Takahashi *et al*. were able to develop a one-pot sequential procedure to give highly selective benzene formation of three different alkynes (Scheme **22**).[48] Treatment of Cp_2ZrCl_2 (**91**), with *n*-Buli, followed by ethylene gives rise to a zirconacyclopentane **I** which selectively reacts with only one alkyne in the acetylene atmosphere. At 50 °C under a nitrogen atmosphere a second alkyne

is incorporated to give unsymmetrical zirconacyclopentadiene **II**. Introduction of the third alkyne with copper chloride gives benzene **92** in 85% yield. Only 2% of side product **93** was formed from unselective alkyne insertion.
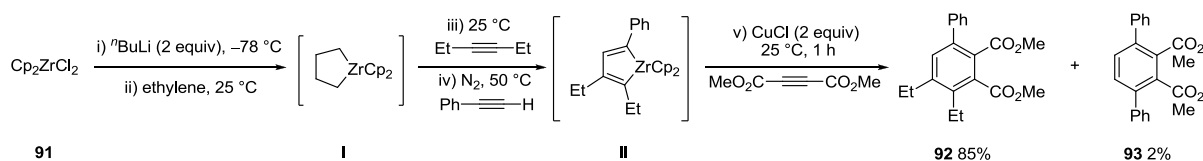
Scheme 22. Sequential trimerization of three different alkynes *via* a zirconiumcyclopentadiene **II**.

Moving towards catalytic processes and alternative mechanisms for selective cross-trimerization Yamamoto *et al.* have investigated the sequential formation of enynes, followed by [4+2] cyclo addition as a formal [2+2+2] process (Scheme **23**).[49] The first step is a regio and chemoselective coupling of a terminal alkyne **94** (donor alkyne) to an alkyne possessing an electron-withdrawing group **95** (acceptor alkyne). Further reaction with the diyne **96** gives pentasubstituted-benzene **97** in 56% yield.
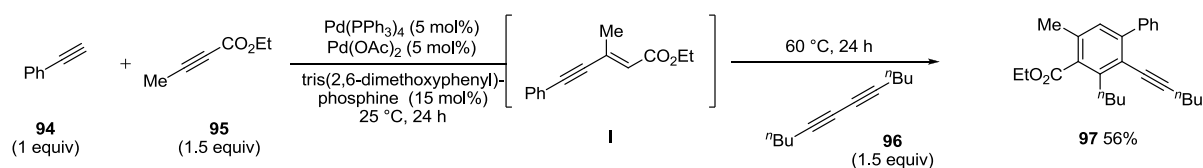
Scheme 23. Sequential alkyne trimerization *via* enynes **I** for formal [2+2+2] cyloadditions.

1.1.3 Synthesis of Aromatics by Condensation reactions.

Much early *de novo* synthesis of phenolic compounds revolved around condensation reactions of ketones **98** with dicarbonyl species such as dialdehydes **99** to give nitro-phenols **100** (Scheme **24**).[50] Expanding this concept, but combining disubstituted ketones **101**, with keto-aldehyes or 1,3-diketones (**102**) as the electrophile is more useful, giving rise to more highly substituted aromatics **103**. When using unsymmetrical ketones **101**, care must be taken to allow preferential enolization and, with regards to the β-diketone **102**, use of ketones, aryl ketones, or aldehydes can provide some selectivity.[51] A range of different electron withdrawing groups can be incorporated as exemplified in the synthesis of 1,3-cyano-nitro biaryl **106**.[52]
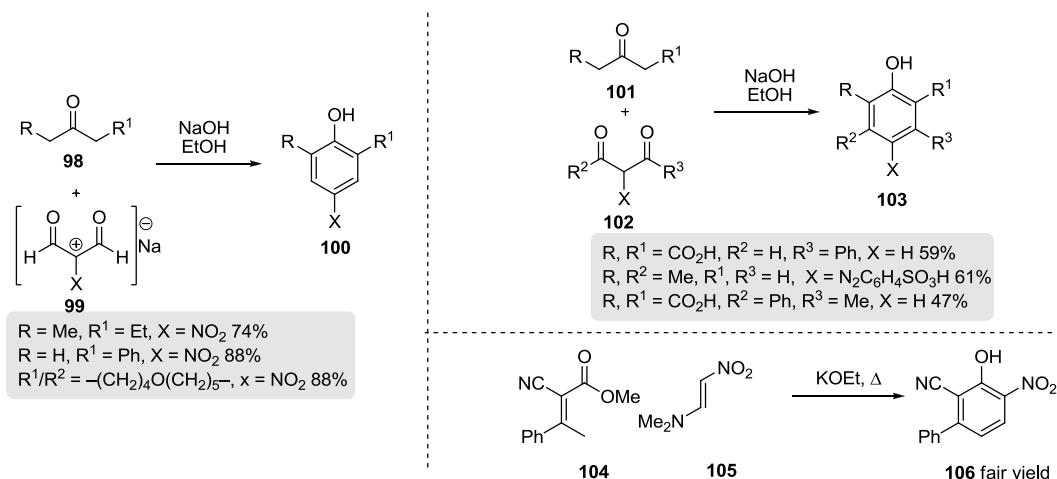
Scheme 24. Synthesis of phenols and hydroxy-benzoates through condensation reactions.

Similar concepts are again applied to produce dihydroxy benzoate derivatives (Scheme **25**). Here, use of aldol condensations is common, but also Claisen condensations to allow incorporation of the second hydroxy group. For example, self condensation of diethyl acetonedicarboxylate **107** proceeds by aldol condensation followed by Claisen condensation to give highly substituted aromatic **108**.[53] Crossed condensations can also be used, however reaction of **111** gives a mixture of **112** and **113**, arising from Claisen condensation and arising from aldol condensation respectively.[54].
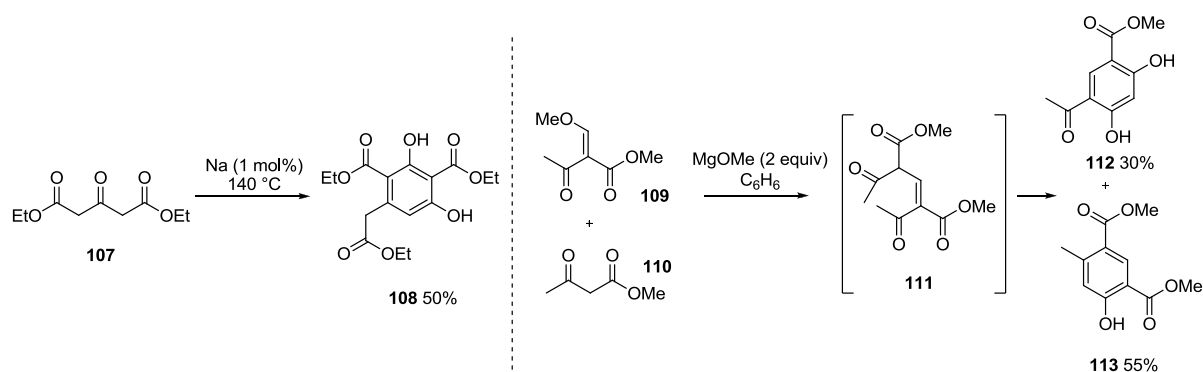
Scheme 25. Formation of dihydroxy-benzoates through intramolecular condensation reactions.

1.1.3.1 Isoxazoles

Aside from a judicious choice of functional groups present in condensation reactions, other methods for regiocontrol in condensation aromatizations have been investigated. Use of isoxazoles as masked β-dicarbonyl compounds were investigated as precursors for aromatic compounds (Scheme **26**).[55] Hydrogenation of **114** gives rise to the dienamine-dicarbonyl **115**. On treatment with aqueous hydrochloric acid, **115** is converted to a mixture of **116** and **117** arising from a choice of cyclizations.
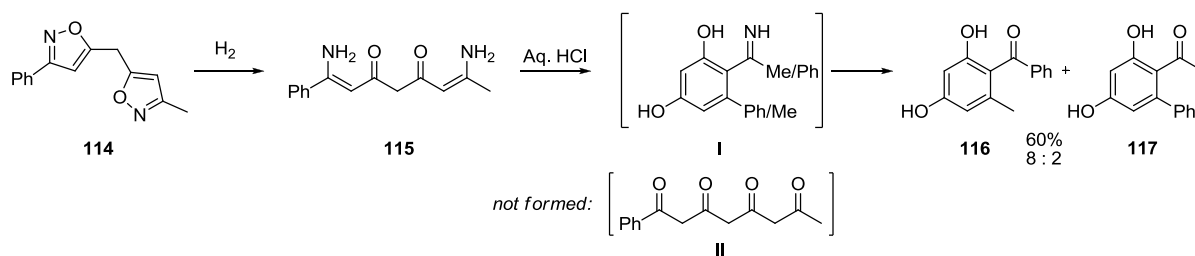
Scheme 26. Formation of β-resocinols **116** and **117** through intramolecular Mannich reaction.

In order to probe the intermediates in this process, partial hydrogenolysis of **114** gave **118** followed by hydrolysis to give **119** (Scheme **27**). When the second isoxazole was reduced, a mono enamine **120** was obtained. On treatment with aqueous hydrochloric acid the sole regioisomer formed was **117**. This demonstrated that cyclization of these systems involves direct loss of ammonia and that tetracarbonyl intermediates are not formed under the conditions; loss of ammonia is favored over loss of water. Utilizing this selectivity, double isoxazoles **121** and **114** could be hydrogenated, the bisenamine intermediates undergoing cyclization to give the respective resorcinols **116** and **117** selectively (< 5% of other regioisomers obtained).
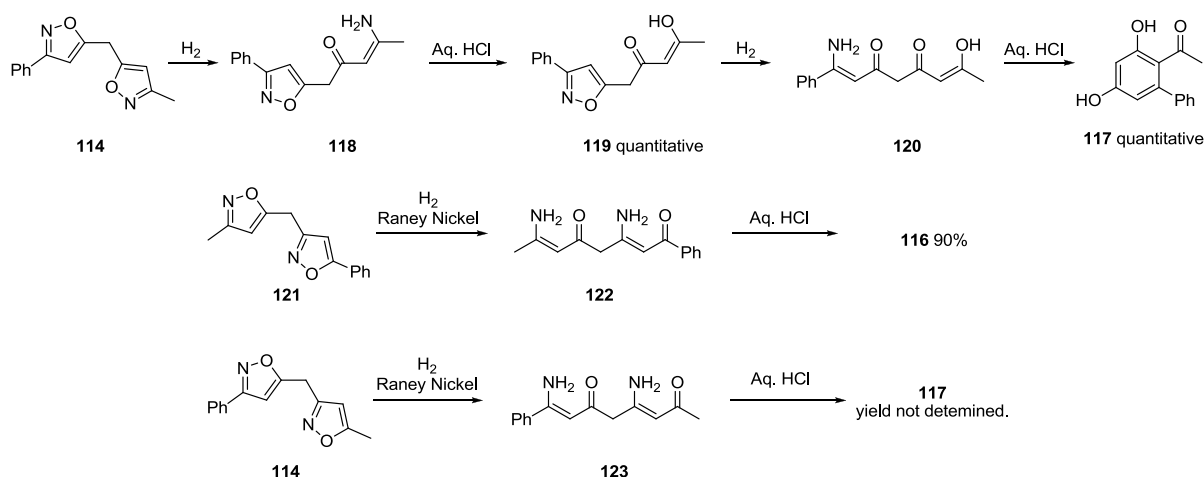
Scheme 27. Use of isoxazoles as masked β-dicarbonyls for synthesis of resorcinol products.

1.1.3.2   Lewis Acid Mediated Cyclizations

In the condensation reactions shown above, regioselectivity is an element that must be rigorously controlled to provide truly useful syntheses. One way such regioselectivity has been elegantly controlled is by use of 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1.3-diene **124** (Chan's diene) (Scheme **28**).[56] This bis-silylated reagent was introduced as the dianion equivalent of methyl acetoacetate. However, **124** can condense with various electrophiles under Lewis acidic conditions. It was found that the reactivity of **124** with electrophiles is as follows: aldehyde > conjugated position of

a β-oxy-α,β-unsaturated ketone ≈ isolated ketone > carbonyl positions of a β-oxy-α,β-unsaturated ketone > acetal or monothioacetal > conjugate position of β-oxy-α,β-unsaturated ester or ester carbonyl.[57]
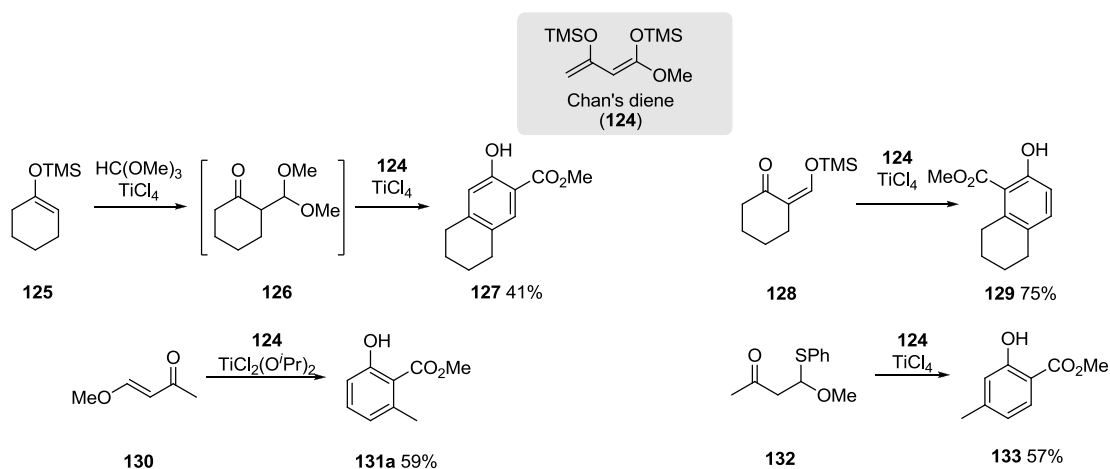
Scheme 28. Lewis acid mediated reactivity of Chan's diene with various electrophiles.

To illustrate this reactivity are the following examples. Reaction of **124** with acetal ketone **126** occurs first at the ketone to give **127** in 41% as the sole regioisomer. Alternatively, use of ketoaldehyde-silyl enol ether **128** gives alternative regioisomer **129**; the diene reacting firstly with the silyl enol ether. Continuing down the reactivity scale, with β-oxy-α,β-unsaturated ketone **130**, reaction occurs first at the β-position to give 6-methyl salicylate **131a**. Alternatively, addition of **124** to ketone **132** occurs first followed by ring closure at the mixed thioacetal/acetal to give the alternative regioisomer, 4-methyl salicylate **133**.

Chan's diene proved useful in more complex methodology and natural product synthesis (Scheme **29**). Reacting two equivalents of the diene **124** with a variety of electrophiles gave 4-substituted homophthalates **134** in a single step. Use of anhydrides as the electrophiles proved equally useful as orthoesters. In the case of isobutyric anhydride, significant quantities of methyl 6-methyl-3,5-dioxoheptanoate were also observed, presumably due to steric effects of the isopropyl group on the aromatization step.[58]
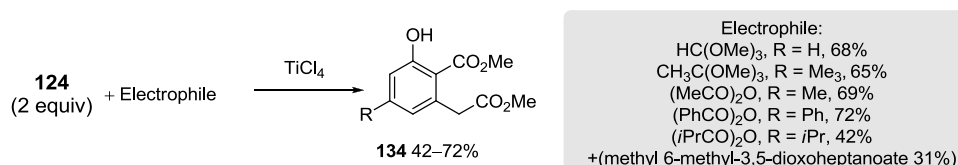
Scheme 29. Synthesis of homophthalates using Chan's diene (**124**).

This methodology for homophthalate synthesis was applied to the rapid construction of sclerin (**135**) (Scheme **30**).[59] Formation of a variant on Chan's diene from 3-oxo-methylpentanoate gave the bis-

silyl ether **137**, which when reacted in a 2:1 ratio with trimethyl orthoformate, gives penta-substituted homophthalate **138**. Further methylation with LDA gives **139**, and ring closure under basic conditions concludes this highly concise, biomimetic synthesis of sclerin (**135**).
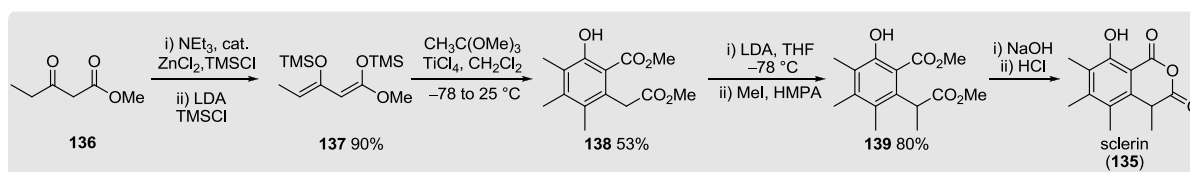
Scheme 30. Application of Chan's diene in synthesis of Sclerin (**135**).

Furthermore, towards syntheses of Δ^1-tetrahydrocannibol 1 (Δ^1-THC) (**140**), **141** could be converted through reaction with Chan's diene (**124**), to γ-resorcylate **142** which once decarboxylated gives a concise route to olivetol (not shown), used in conventional routes to Δ^1-THC (Scheme **31**).[60] Alternatively, conversion of **141** to the corresponding acid chloride **143**, resulted in a reversal of the reactivity with Chan's diene and gave the regioisomeric β-resorcylate **144**. Further selective electrophilic aromatic substitution at the 3-position and ether ring formation gives **145** with no chromenylation at the other vacant position. Alkaline hydrolysis and decarboxylation gave Δ^1-THC.
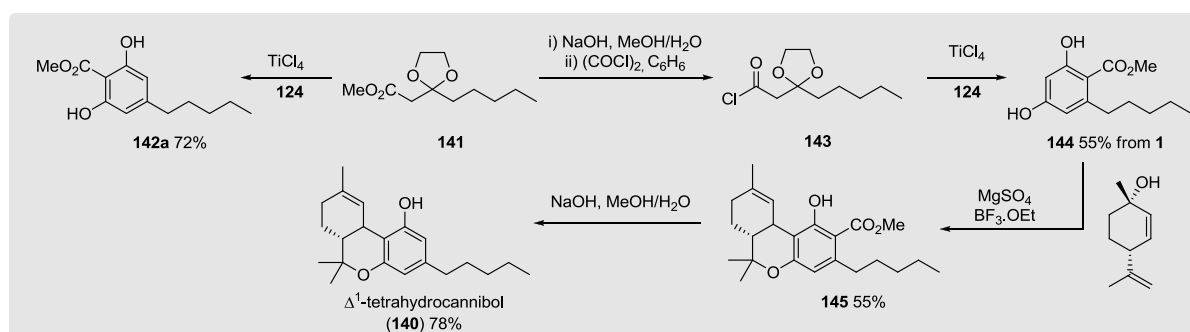
Scheme 31. Application of Chan's diene in synthesis of Δ^1-tetrahydrocannibol (**140**).

1.1.4 Synthesis of Aromatics Using Metathesis

Metathesis, for the synthesis of aromatics, is most common amongst syntheses of benzene-fused or heteroaromatic compounds and often may be used for substrate synthesis, but not as an actual aromatization reaction.[61] For example, Donohoe *et al*. have developed a synthesis of pyridines where a condensation reaction is used for the aromatization step (Scheme **32**).[62] In constructing the substrates however, cross metathesis of a homoallylic alcohol and enone, **146** and **147** for example, is the key step. Oxidation of this product gives the unsaturated 1,5-dicarbonyl compound **148** as the aromatization substrate.
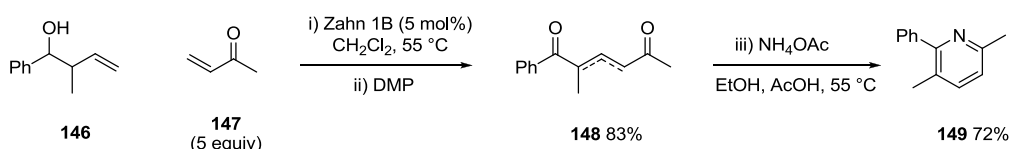
Scheme 32. Cross metathesis and oxidation for the synthesis of a 1,5-dicarbonyl compound **148** as precursor to pyridine **149**.

Huang and Wang made use of ring closing metathesis, again for substrate construction (Scheme **33**).[63] Here ring closing metathesis of the propen-1-ol **150** is used to form the second ring of the naphthalene product. Dehydration then occurs in presence of silica gel to give the desired aromatic product **151**.
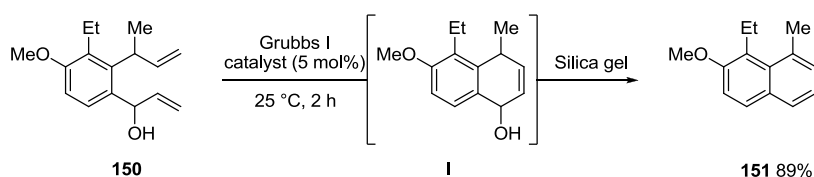
Scheme 33. Formation of naphthalene **151** by a cross metathesis-elimination sequence.

Using cross metathesis for direct formation of aromatic benzene derivatives is less common, but one example is the synthesis of naphthol **152** (Scheme **34**).[64] Here, treatment of α,β-unsaturated ketone **153** with Grubbs second generation metathesis catalyst gives rise to ring closing metathesis and spontaneous tautomerization gives the naphthol **152**.
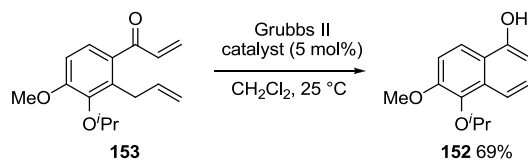
Scheme 34. Direct formation of naphthol **152** by cross metathesis.

The concept of ring closing metathesis of an α,β-unsaturated ketone with a suitable allyl fragment was further broadened allowing a synthesis of phenols (Scheme **35**).[65] The trienone **154** (from a vinyl lithium addition to 2-ethylacrolein and oxidation) underwent ring closing metathesis to give the phenol **155** in 97% yield, and using this methodology, tri-substituted phenols could be accessed in high yield. Furthermore, regioisomeric trienes such as **156** also underwent similar transformation.
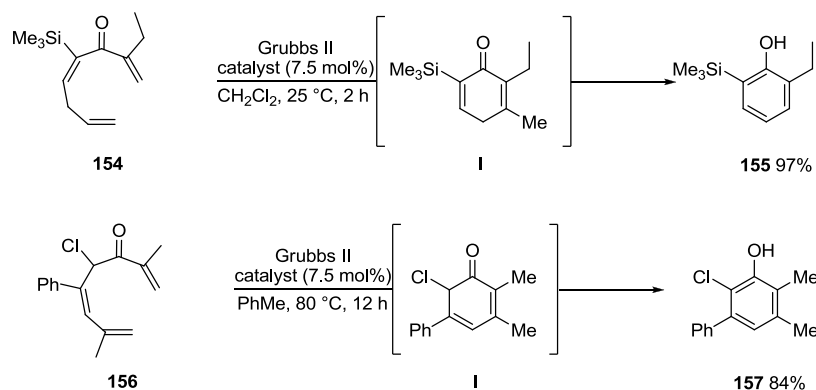
Scheme 35. Ring closing metathesis for formation of substituted phenols **155** and **157.**

Wishing to simplify the routes to substrate, trienes such as **158** were constructed by vinyl Grignard addition to 2,3-disubstituted acroleins, followed by oxidation (Scheme **36**).[66] On ring closing metathesis of **158**, the exo-alkene **159** was obtained in 86% yield. The phenol product **160** could be obtained by isomerization with [RhCl(cod)]$_2$ in 95 % yield. Wishing to utilize this second step to introduce further functionality, it was demonstrated that under Mizoroki-Heck conditions, cross coupling of **161** with a diazonium tetrafluoroborate salt **162** and aromatization, gave phenol **163**.
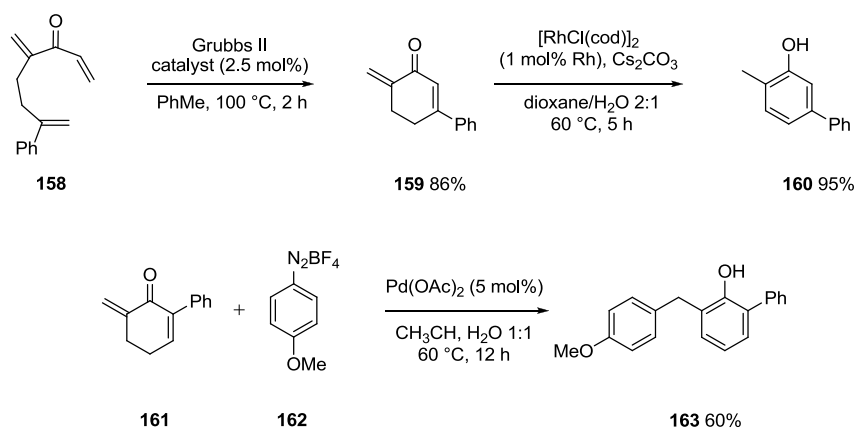
Scheme 36. Ring closing metathesis of **158** followed by isomerization to give phenol **160** and cross coupling-isomerization of exo-alkene **161** to give benzyl substituted phenol **163**.

1.1.5 De Novo Synthesis vs Aromatic Derivitization

Having examined some of the *de novo* methods that can be used in synthesis of small molecules and natural products, the following section will illustrate the effectiveness of *de novo* methods for benzene synthesis. Comparing *de novo* methods against traditional aromatic derivatization chemistries for the synthesis of a natural product and a synthetic drug compound will show that *de novo* methods can be most efficient in terms of yields and brevity of synthetic sequence.

1.1.5.1 Cribrostatin 6

The natural product cribrostatin 6 (**164**) was found to inhibit growth of antibiotic-resistant gram-positive bacteria and pathogenic fungi, as well as exhibiting some *in vitro* anticancer activity and so significant synthetic efforts have been put towards its synthesis. The synthesis of **164** has been reported four times in the literature, twice by *de novo* methods and twice by functionalization of a pre-existing aromatic molecule (Scheme **37**).
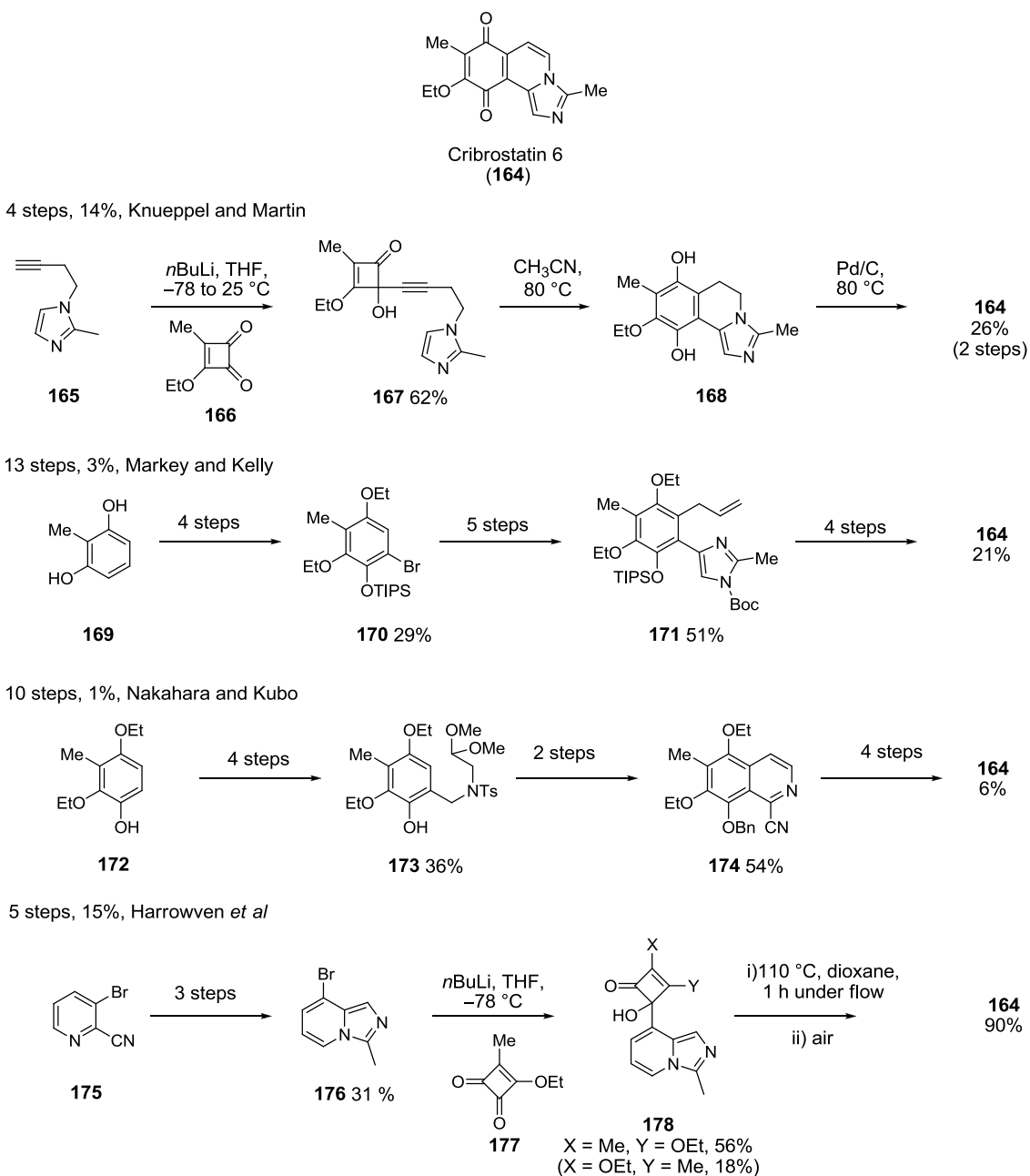
Scheme 37. Synthetic routes employed towards Cribrostatin 6 (**124**).

Martin's synthesis of Cribrostatin was based on the benzannulation developed by Moore and co-workers and begins with addition of a lithiated alkyne **165** to cyclobutenedione **166**.[67] Heating of **167** results in formation of a yne-eneylketene which can aromatize with radical interception of the imidazole ring to give **168**. While this final process occurs in a low 26% yield, the synthesis is concise (4 steps) with no protecting group manipulation, giving **164** in 14% overall yield.

The route employed by Markey and Kelly however, begins with 2-methyl resorcinol **169**, involving linear manipulations of the aromatic unit to form intermediate **170**.[68] Cross coupling of **170** with a SEM-protected imidazole, further bromination, cross coupling with allyltributyltin, and, a protecting-group swap gives intermediate **171**. Ring closure, deprotection, and oxidation complete the synthesis of **164** in 13 steps and a 3% overall yield. A similarly lengthy synthesis is that of Nakahara and Kubo.[69] Elaboration of a benzenoid precursor **172** allows a modified Pomeranz-Fritsch isoquinoline synthesis, which after reduction of nitrile **174** allows construction of the imidazole ring completing **164** in 10 steps in a 1% overall yield. Notably, although both Kelly and Kubo's syntheses were chronologically before Martin's synthesis, the main concept of Martin's synthesis was developed some 17 years previous to isolation of the natural product!

The only improvement in overall yield of **164** is by another *de novo* synthesis, from Harrowven and co-workers.[70] Their synthesis begins with a pyridine nitrile **175** which undergoes reduction, acylation, and treatment with POCl$_3$ to give imidazopyridine **176**. The addition of the squarate **177** occurs predominantly at the more electrophilic ketone to give **178**. The fundamental benzannulation step then follows and, using flow chemistry, cribrostatin 6 **164** is obtained on exposure to air.

1.1.5.2   Oxidation to Triphenyl Compounds

Another example of the power of *de novo* synthesis of aromatic compounds is the homogenous palladium catalysis dehydrogenation of substituted cyclohexenones to phenols (Scheme **38**).[71] The terphenyl **179** was identified as an allosteric inhibitor of the human luteinizing hormone receptor implicated in fertility and ovarian cancer.[72] While the synthesis of intermediate compound **180** can be made *via* two Suzuki cross couplings in 19 % overall yield, a more efficient route involves *de novo* construction of the central phenol. Aldol condensation of 4-methylacetophenone (**183**) with benzaldehyde (**184**) followed by a Robinson annulations gives cyclohexenone **185**.[73] Application of the dehydrogenative conditions then gives the terphenol **180** in 83% overall yield. The ready availability of Diels-Alder adducts such as **186**, which can be converted to 3,4-dimethylbenzoic acid **187**, further demonstrates the use of this method.

Heitman *et al*.
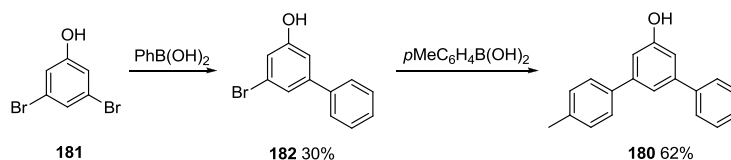
Stahl *et al*.
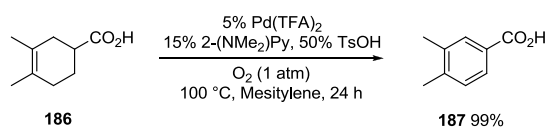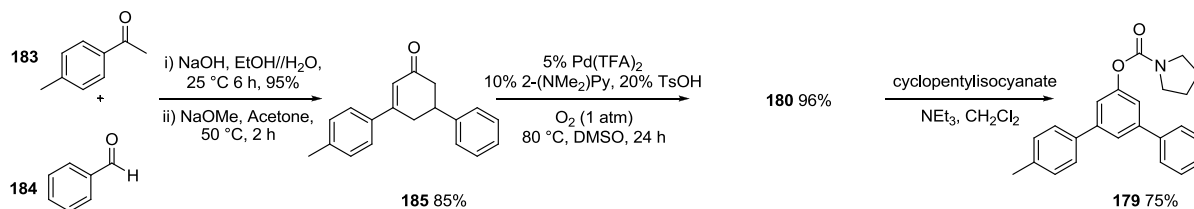
Scheme 38. Oxidation as a strategy towards terphenyl **180.**

At present it would be difficult for a *de novo* process to rival the efficiency and scale of synthesis for simple aromatic molecules that could be more easily obtained by classical aromatic chemistry. However, as illustrated in the above examples, *de novo* synthesis demonstrates more value for the synthesis of highly substituted aromatics or those with less common substitution patterns.

1.1.6 Biosynthesis and Biomimetic Synthesis of Aromatic Natural Products

Prior to invention of all laboratory methods covered, the first *de novo* synthesis of aromatic compounds was conducted by nature. Many of the aromatic units observed in polyketide natural products are produced through aromatization reactions of polycarbonyl chains, constructed themselves using a series of condensation reactions.[74]

1.1.6.1 The Polyketide Biosynthesis Hypothesis

The biosynthesis of polyketide natural products from polycarbonyls was first proposed by Collie. It wasn't until later that Birch confirmed, through radiolabelling experiments, their biosynthetic construction *via* acetate units and subsequent transformations to give aromatics and other polyketides; a theory that has come to be known as the Collie-Birch polyketide hypothesis.[74,75] Using radiolabelled acetic acid **188** Birch was able to predict the isotopic pattern that would be exhibited in the production of 6-methylsalicyclic acid (**190**) by the mould *Penicillium griseofulvum* (Scheme **39**).[76]
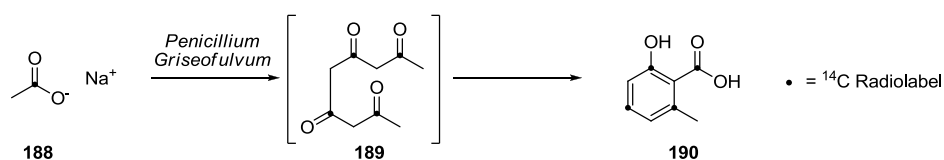
Scheme 39. A radiolabelling experiment by Birch, The isotopic pattern of the 6-methylsalicyclic acid (**190**) was predicted by his biosynthesis theory.

This was the first *in vivo* experimental support for the polyketide hypothesis, and similar studies show the same mechanisms occur in a wide range of natural products.[74] The currently accepted concepts of the polyketide hypothesis can be seen in the biosynthesis of 6-methylsalicyclic acid (**190**) (Scheme **40**).
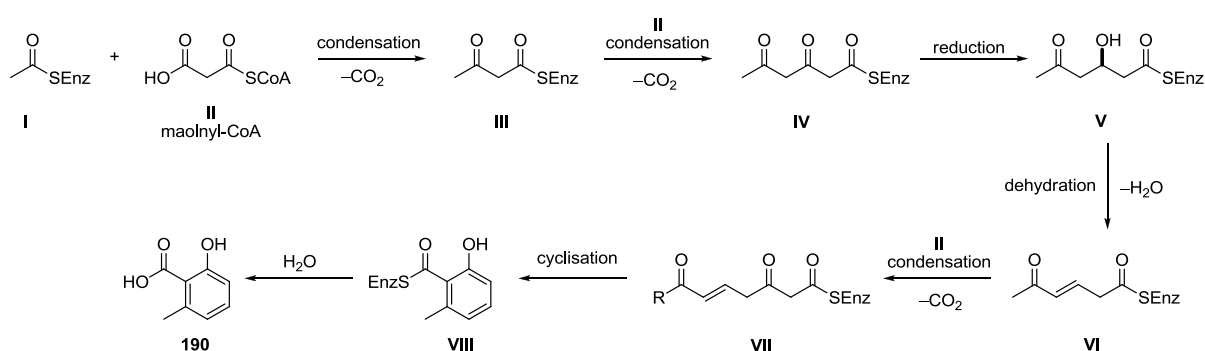
Scheme 40. Biosynthesis of 6-methylsalicylic acid (**190**).

Condensation of an acetate unit **I** with malonyl coenzyme A **II**, followed by decarboxylation gives an enzyme bound thioester **III**. A further decarboxylative condensation, again with malonyl coenzyme A, gives tri-carbonyl **IV**. Repeated iterations of this sequence can then allow longer polycarbonyl chains to be constructed. In addition to chain extension, further modification of intermediate **IV** is possible. For **190**, reduction followed by dehydration gives the enone **VI**. Further chain extension to the tri-carbonyl **VII**, cyclization and release from the enzyme provide **190**.

1.1.6.2 Biomimetic Synthesis of Resorcylates

Based on the biosynthetic route of aromatic compounds many groups became interested in reproducing such reactions in the laboratory. Harris *et al.*, has published extensively towards this goal.[77] In one instance the biomimetic synthesis of aromatic compounds based on triketo-ester compound **191a** was explored. (Scheme **41**)
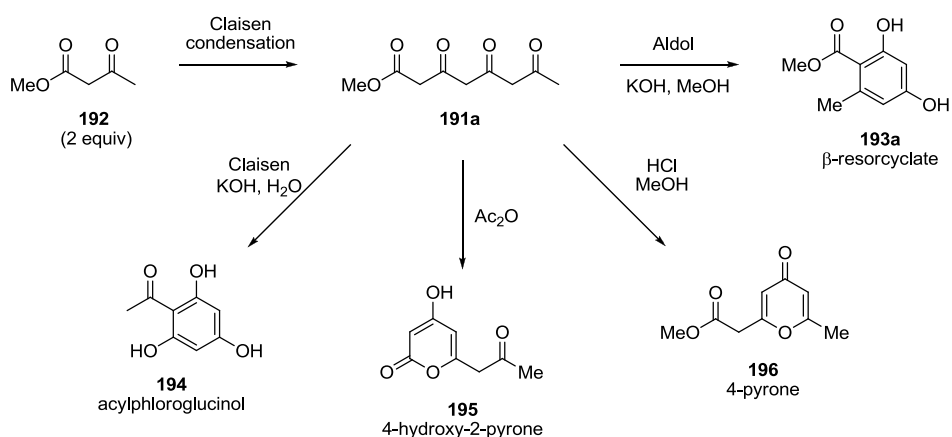
Scheme 41. Cyclizations of the triketo-ester 191a.

Harris found that 191a could be produced by self-Claisen condensation of 2 equivalents of methyl acetoacetate (192). Treatment of the 191a above pH 4, was found to result in a highly selective aldol condensation to give the β-resorcylate compound 193a. Furthermore, it was shown that with careful choice of reaction conditions, the 191a could undergo different possible cyclizations. Use of aqueous basic conditions resulted in Claisen condensation to give acylphloroglucinol 194. Treatment of 191a under acidic conditions, gave either 2-pyrone 195 or 4-pyrone 196.

This work showed that polycarbonyl compounds could be produced synthetically and, their cyclization to β-resorcylates may allow synthesis of natural products containing such moieties. There were limitations however as only simple substrates had been considered. Using highly basic conditions for the polycarbonyl synthesis and difficulties in handling such compounds would prevent its application in more complex β-resorcylate synthesis.

It was postulated by Barrett that combination of polycarbonyl synthesis using dioxinone chemistry may facilitate synthesis of more complex molecules based on this biomimetic concept. Dioxinone compounds and their use in the synthesis will now be introduced, before considering the unification of this chemistry with biomimetic aromatic synthesis.

1.2   Dioxinones and Their Application in Synthesis.

2,2,6-Trimethyl-4H-1,3-dioxin-4-one 197, otherwise known as the diketene-acetone adduct is a convenient precursor to acetylketene (198) (Scheme 42).[78] Despite commercial preparations of diketene (199) in acetone, the presence of 197 was not initially recognized until its structure was elucidated from IR and UV spectral properties by Carroll and Bader, later confirmed with ^{1}H NMR.[79] On heating, dioxinone 197 undergoes a reversible loss of acetone to give acylketene (198) which has been observed by IR spectroscopy at 5 K.[80]

Scheme 42. Synthesis of dioxinone **197** and generation of acylketene **198**.

Thermyolysis of dioxinone **197** alone will form the homodimer of acylketene. More usefully, thermyolysis of **197** is carried out in the presence of a suitable nucleophile such as an alcohol or amine to give β-ketoesters or β-ketoamides respectively. While this is not the only method to generate acetylketene, dioxinone **197** provides a convenient, safe and nonlachrymatory alternative to diketene for aceto-acetylation reactions.[81] Irradiation of dioxinone **197** at 254nm has been used for the generation of **198**.[82]

Apart from aceto-acetylation reactions the use of dioxinone molecules in synthesis has been applied for a diverse range of applications. The following examples display the reactivity of dioxinone derivatives and how they have been applied to solving synthetic challenges.

1.2.1 Dioxinones in Macrocycle Formation Strategies

Derivatives of dioxinone have been used extensively for the intramolecular capture of pendant nucleophiles, representing an excellent process for the formation of medium-sized rings and macrocycles (Scheme **43**).[83] This method was used for formation of formation of ring sizes 4–77 and, towards the synthesis of several macrocyclic natural products including, (+)-diplodialide A (**200**), (–)-kromycin (**201**), (–)-A26771B, ikarugamycin, Deschlorocallipeltoside A, and callipeltoside A.[84] The reported yields are generally good even for the least energetically favorable 8−10 membered rings **205** and **200**.

| Ring Size: | 4 | 5 | 7 | 8 | 10 | 12 |

Scheme 43. Formation of various size lactones and lactams from dioxinones.

In one instance, Hoye's synthesis of intermediate **206** towards callipeltoside A, a tetraol precursor underwent the desired dual macrolactonization and, hemiketal formation took place in 53% yield without the formation of any other constitutional isomers. Here the regioselective lactonization of the secondary alcohol in preference of the primary hydroxyl group was conformational in origin.

One limitation of this method is the formation of 6-membered lactones, where oligomerization is favored. Literature explanations for this are either that the correct orientation of the hydroxyl group required for nucleophilic addition is not possible or, hydrogen bonding between the hydroxyl and acetyl groups forms a favourable 6 membered conformation leading to oligomer formation.[85]

1.2.2 Tandem IMDA Macrocycle Formation

Using dioxinones for intramolecular macrocycle formation was a part of a strategy employed towards hirsutellone B (**210**) (Scheme **44**).[86] In this case however, a tandem procedure with an intramolecular Diels-Alder (IMDA) was also employed. Use of vinyl dioxinone **211** enabled an IMDA reaction with the pendant diene, while the tethered amine underwent macrocycle formation. This reaction generated three bonds, 3 rings and four stereocentres to give the correct diastereoisomer **212** in 50% yield *via* an endo transition state. Despite being later unable to effect the required ring contraction for the natural product, a highly convergent strategy for synthesis of the core was developed.
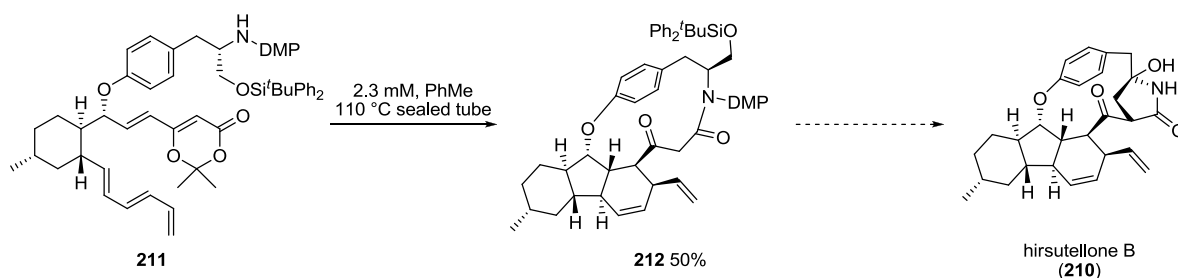
Scheme 44. Tandem IMDA-macrocycle formation of **212** towards a synthesis of hirsutellone B (**210**).

1.2.3 Dioxinones in Prins Cyclizations

Other than forming macrocycles dioxinone derivatives have been used in several other ways. In a synthesis of (−)-exiguolide (**213**), a key dioxinone fragment was employed twice as a partner in Prins cyclizations (Scheme **45**).[87] Firstly, dioxinone **214** and aldehyde **215** underwent and intermolecular Prins coupling to create a 2,6,-*cis*-tetrahydropyran ring **216**. After removal of the dioxinone fragment, a second dioxinone fragment could be introduced by Yamaguchi esterification and after several manipulations, **217** was obtained. The stage was set for a second Prins cyclization. Treatment of **217** with scandium triflate resulted in an intramolecular Prins reaction, building another pyran ring and forming the 16-membered macrocycle **218**.
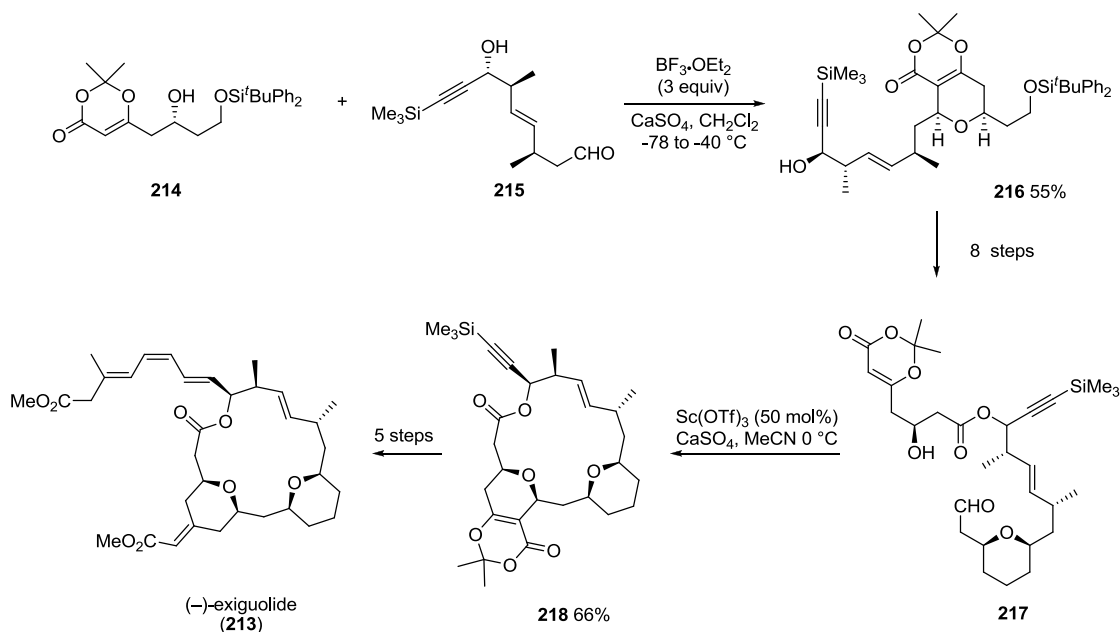
Scheme 45. Prins cyclizations of dioxinones for macrocycle and THP formation.

1.2.4 Dioxinones in Friedel-Crafts Type Reactions

While acylketenes generated from dioxinones are most widely reacted with oxygen and nitrogen nucleophiles, they also participate in Friedel-Crafts reactions with electron-rich aromatic rings (Scheme **46**). In a synthesis of taiwaniaquinol B a double annulation is performed by intramolecular Friedel-Crafts acylation followed by alkylation.[88] Silylation of the Meldrum's acid derivative **220** gives the dioxinone **I**, which after retro-Diels-Alder reaction, undergoes Friedel-Crafts acylation with the dimethoxy-benzene ring to give enol **II**. Trifluoromethanesulfonic acid acid then promotes the second ring formation and, decarboxylation of **III** under the thermal reaction conditions, generated the *cis*-fused tricycle **221** as a single diastereoisomer in 73% yield.
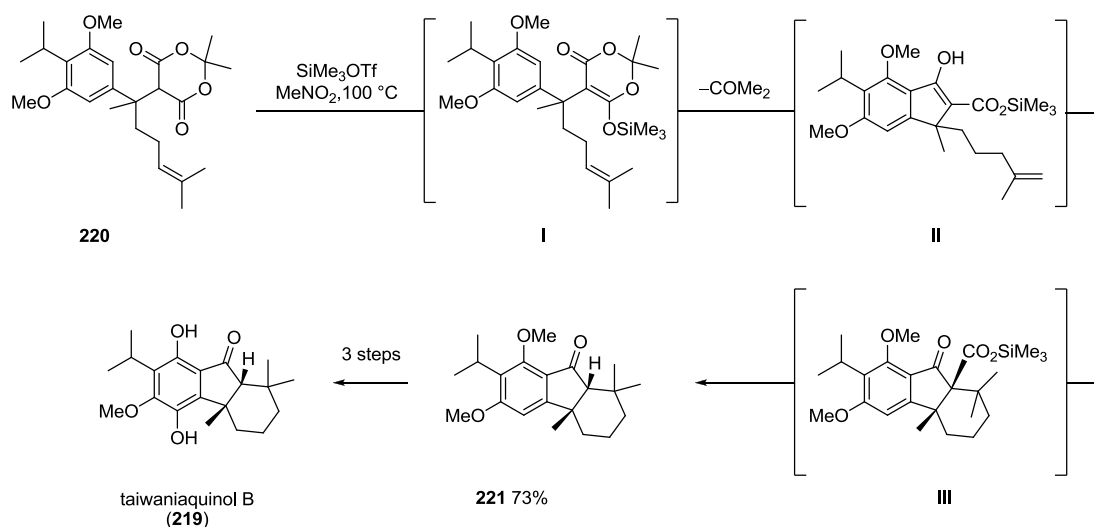
Scheme 46. Intramolecular Friedel-Crafts reaction of a dioxinone in a tandem sequence towards taiwanaquinol B (**219**).

1.2.5 Dioxinones in Heterocycle Synthesis.

Numerous heterocyclic compounds have also been constructed using dioxinone derivatives, demonstrating some different ways in which the thermally generated acylketene species react.[89] While the 6-lactones highlighted above are more difficult to form, pyrones such as **222** are more easily formed by 6π-electrocyclic ring closure of the enoneketene **II** (Scheme **47**).[85] Nucleophilic addition of urea (**224**) to the acetylketene from dioxinone **197**, followed by condensation gives uracil **225**.[90] Furthermore, the acylketene from dioxinone **197** also undergoes [2+4] cycloaddition with imines such as **226** to give the oxazine **227**.[91]
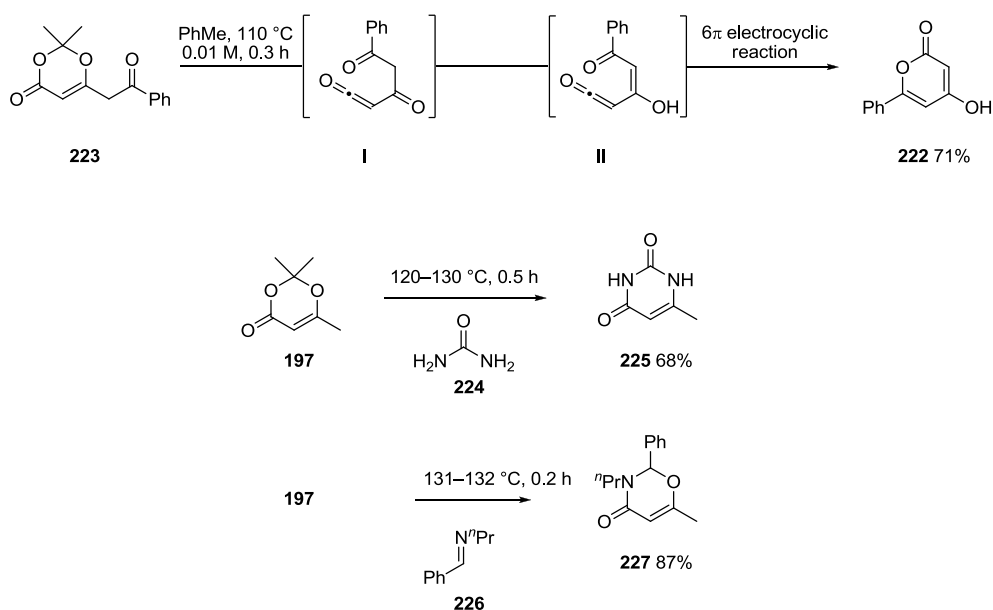
Scheme 47. Application of dioxinones in heterocycle synthesis.

1.3 Barrett's Resorcylate Synthesis: Combining Dioxinone Chemistry with Biomimetic Synthesis.

Syntheses of resorcylate natural products building from an aromatic core can often suffer setbacks due to protecting group manipulations and lengthy synthesis routes.[92] Inspired by the polyketide biosynthesis of aromatic natural products and, biomimetic synthesis of simple resorcylates by Harris, Barrett *et al.* saw the opportunity to apply dioxinone compounds for the synthesis of polycarbonyls and more complex natural product targets (Scheme **48**).
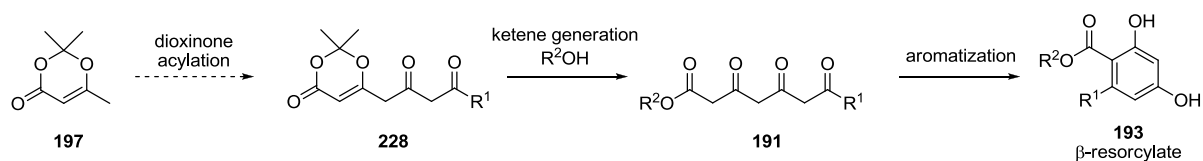
Scheme 48. Barrett's hypothesis for biomimetic synthesis of β-resorcylate compounds **193** from diketo-dioxinone precursors **228**.

Beginning with a dioxinone **197**, functionalization would give rise to the diketo-dioxinone **228**. This could then undergo ketene generation and reaction with an appropriate alcohol to generate a triketo-ester **191**. Aromatization using the known conditions would then lead to the β-resorcylate **193**.

With regards to the aromatization step of this hypothesis; while the aromatization of triketo-esters **191** was known at the outset, the aromatization of diketo-dioxinones **228** was discovered during Barrett's methodology studies (Scheme **49**).[93] More explicitly, thermyolysis of diketo-dioxinone **228a** in the

44

presence of methanol gave triketo-ester **191a** and, aromatization with caesium carbonate followed by acidification, gave resorcylate **193a** in 87% yield. In an alternative one-pot procedure, heating **228a** with methanol in a sealed tube gave rise to the resorcylate **193a** directly in 82%. However, diketo-dioxinone **228a** also undergoes aromatization itself, and when treated with triethylamine gave benzodioxinone **229a** in 96% yield. Aromatization of diketo-dioxinones similar to **228a** have been performed under a variety of other mild basic or acidic conditions, or in some cases, occur spontaneously. Furthermore, the benzodioxinones **229** obtained can undergo solvolysis under basic conditions to give the resorcylate **193**. Alternative transformations of benzodioxinones **229** are known including reduction, aminolysis, decarboxylation and, photolysis to the quinoketene, allowing a wide range of products to be obtained.[94]
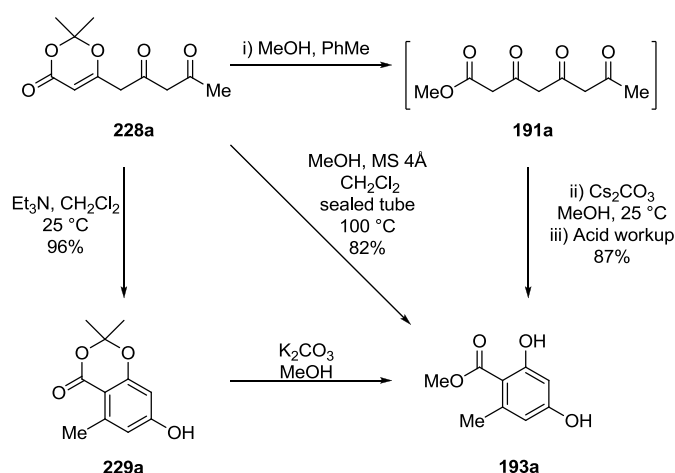
Scheme 49. Aromatization routes for diketo-dioxinone **228a**.

The following sections show how this initial hypothesis has come to fruition and, through development of natural product and methodology chemistry, how many aromatic compounds have been prepared from dioxinone derivatives.

1.3.1 Application of Dioxinone Derivatives in Synthetic Studies Towards Aromatic Compounds

1.3.1.1 Synthesis of S-(–)-Zearalenone

The first application by Barrett *et al.* of using dioxinone derivatives in *de novo* synthesis was the synthesis of resorcylate acid lactone *S*-(–)-zearalenone (**230**) (Scheme **50**).[95] The macrocycle would be formed using cross metathesis of aromatic diene **193b**. The aromatic **193b** would be available from ketene generation, trapping with the requisite alcohol **231**, followed by aromatization of the triketo-

ester **191b**. The key diketo-dioxinone fragment would be constructed by a vinylogous Mukaiyama Aldol reaction between the *O,O*-silyl ketene acetal **232** and aldehyde **233**.
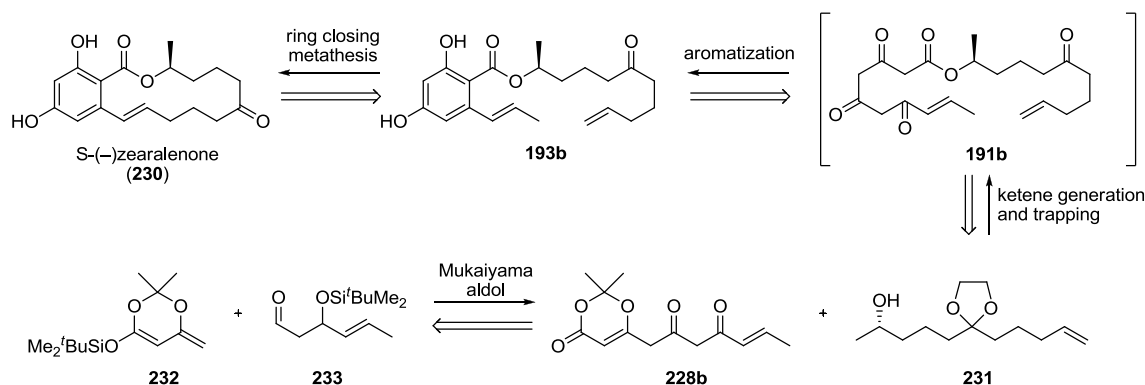
Scheme 50. Retrosynthetic analysis of *S*-(−)zearalenone (**230**).

In practice, the vinylogous Mukaiyama reaction of **232** and **233** gave mono-protected dioxinone diol **234** in 61% yield (Scheme **51**). Sequential oxidation of the free alcohol and then deprotection of the second alcohol followed by further oxidation gave diketo-dioxinone fragment **228b**. Thermyolysis and ketene generation of dioxinone **228b** followed by reaction with alcohol **231** gave triketo-ester **191b**. Base mediated intramolecular aldol addition followed by acidification resulted in condensation and hydrolysis of the ketal to give aromatic diene **193b**. The synthesis was completed by cross metathesis with Grubbs-Hoveyda second generation catalyst (G-H II) to give **230** in 71%. Attempted metathesis at of triketo-ester intermediate **191b** resulted in intractable mixtures but, did contain some of the natural product **230**. In a modified procedure, the last steps could be telescoped giving a slight increase in yield and more operational simplicity. Thus, thermyolysis of diketo-dioxinone **228b**, ketene trapping followed by aldol condensation (mediated by caesium carbonate and acidic Dowex resin) and, cross metathesis gave *S*-(−)-zearalenone **230** in 63% yield.
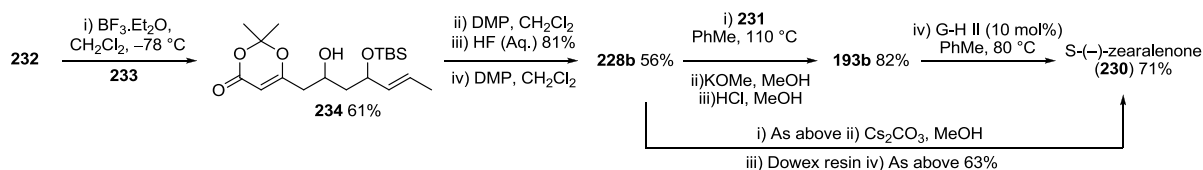
Scheme 51. Synthesis of S-(−)- zearalenone.

This report also contained further synthesis of three further natural products 15G256-β (**235**), 15G256-τ, and, 15G256-π all involving synthesis of diketo-dioxinone compounds **228** (Scheme **52**). It is the synthesis of such diketo-dioxinone derivatives that is incorporated in all routes for synthesis of beta-resorcylate containing molecules by Barrett.

To 15G256-β, vinylogous Mukaiyama aldol reaction between **232** and **236a** gave dioxinone keto-ester **237a** in 80% yield. More conveniently, lithium enolate addition of commercial dioxinone **197** to a

benzotriazole ester **238** (or acid chloride **236a**), gave **237a** in 63% yield. Dioxinone keto-ester **237a** is acylated by formation of its magnesium enolate and reaction with acid chloride **239** to give **240a**.[96] Treatment of **240a** with a Pd(0) source and a π-allyl scavenger (morpholine) led to deallylation and decarboxylation resulting in diketo-dioxinone intermediate **228c**. This intermediate was carried through aromatization to give marine antifungal agent 15G256-β **235** as well as the closely related compounds 15G256-π and 15G256-τ (not shown).
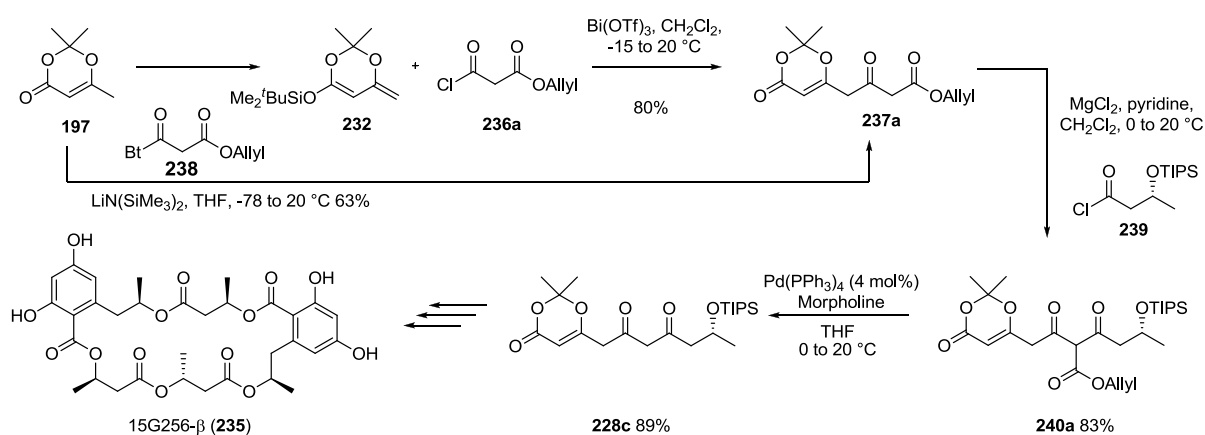
Scheme 52. Synthetic route to 15G256 antifungal agents.

The double acylation strategy used in the synthesis of 15G256 compounds was then used to form the diketo-dioxinone fragments required for the synthesis of other β-resorcylate molecules in methodology and natural product studies.

1.3.1.2   Hexasubstituted Benzene Synthesis

The double acylation of **197** has been applied to give an expedient synthesis of dioxinones **241** containing additional alkyl (R^2) and allyl (R^3) substituents, resulting in hexa-substituted benzene derivatives **242** (Scheme **53**).[97] Acylation of dioxinone keto-ester **237** proceeds as before to give diketo-dioxinones **240** and introduce a substituent R^2 (the ester fragment CO_2R^1 is kept in place, although if desired could easily be decarboxylated as above (Scheme **52**)). Allylation catalyzed by Pd(PPh$_3$)$_4$ proceeds in a regioselective manner to give **241** and introduce substituent R^3 and, in the same pot, aromatization by treatment with Cs$_2$CO$_3$ gives **242**. When R^2 was an α-branched group (^{i}Pr, cyclopropyl, phenyl, 2-furyl) the aromatization proceeded in a moderate 42-59% yield and in some cases required use of silica. However, in less substituted moieties (Me, Et, 2-phenylethyl) cyclization proceeded more efficiently in 83-90% yield.
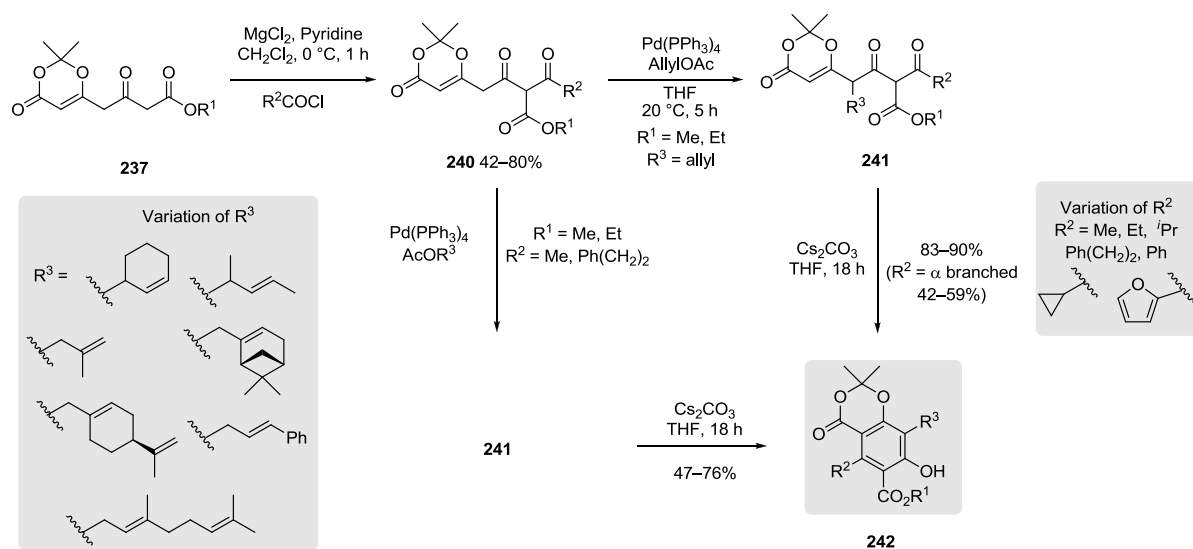
Scheme 53. Synthetic routes to hexasubstituted benzene compounds.

Rather than allylation of **240** with allyl acetate, various substituted allylic acetates could be used to introduce a variety of different allyl substituents R^3.[98] Cyclization of **241** in these cases proceeded well although slightly lower than when the allyl group was unsubstituted.

1.3.1.3   Synthetic Studies Towards Lactonamycin

The double acylation of dioxinone **197** was also applied in a route to lactonamycin for the synthesis of dihydroxy-isoindolinone-carboxylates (**243**) as EF-ring precursors (Scheme **54**).[99] Acylation of dioxinone keto-esters **237b–c** with sarcosine derived acid chloride **244** gave di-keto dioxinones **240b–c**. The ester moiety was desired in the final product so was kept in place, and treatment of **240b–c** with triethylamine gave benzodioxinones **242a–b**. Based induced methanolysis of **242a–b**, followed by removal of the SES group with Bu$_4$F and concurrent lactamization, gave the desired isoindolinones **243a–b**. After methylation and triflation of **243b** to give isoindoline **246**, conversion to a boronic ester provided a coupling partner for Suzuki coupling with bromide **247**. Subsequent ester hydrolysis and intramolecular Friedel-Crafts acylation of **248** provide pentacycle **249** after acetate protection.[100]
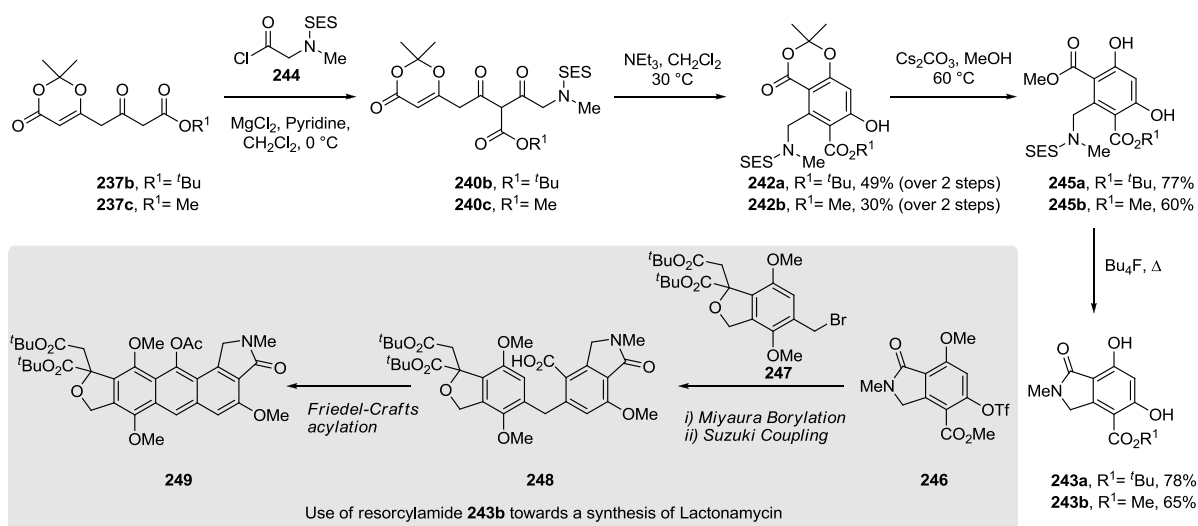
Scheme 54. Barrett's application of *de novo* synthesis towards lactonamycin.

1.3.1.4 Synthesis of Anthraquinones (**250**) and Macrosporin (**251**)

Use of an intramolecular Friedel-Crafts acylation was combined with the *de novo* synthesis chemistry once more for access to anthraquinones (**250**) and the natural product macrosporin (**251**) (Scheme **55**).[101] Dioxinone keto-ester **237a** was acylated with a phenylacetic acid derivative, as described previously, then subjected to Pd(PPh$_3$)$_4$ catalyzed deallylation and decarboxylation. The morpholine served as both a π-allyl scavenger, as well as a base for aromatization of diketo-dioxinone intermediate **252**, to give benzodioxinone **253** in a high yielding one-pot procedure.
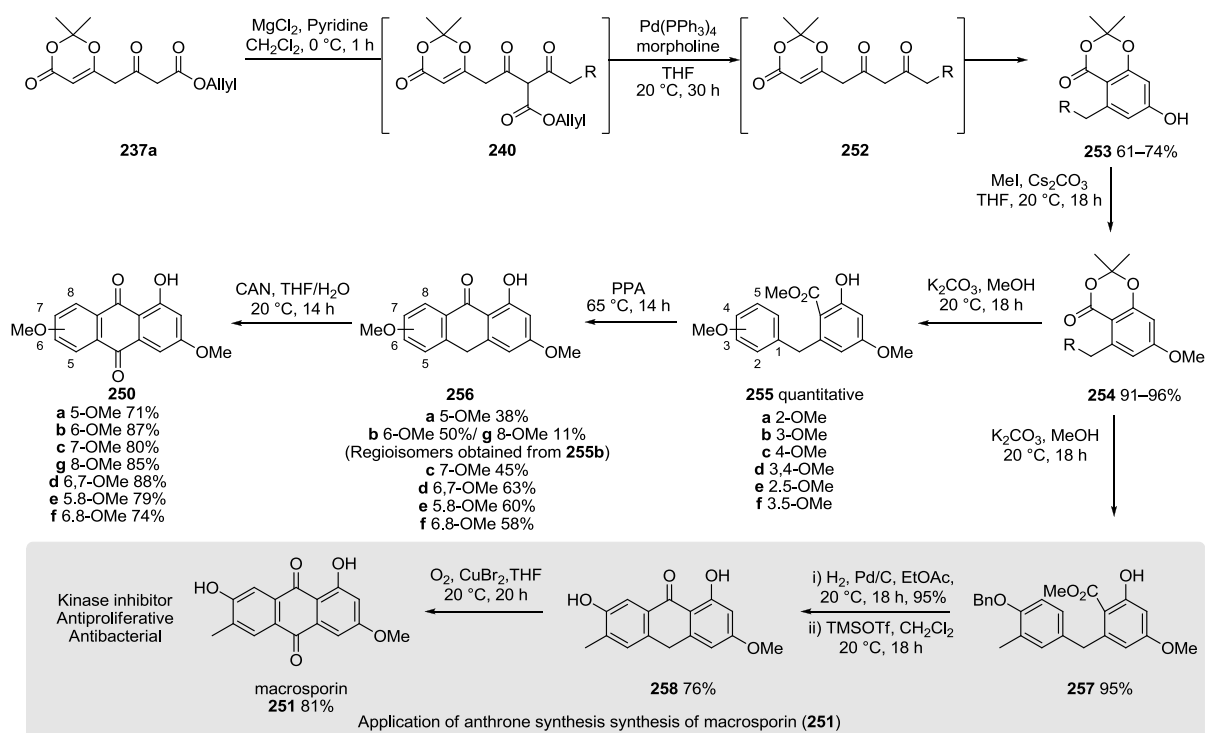
Scheme 55. Synthesis of anthraquinones (**250**) and application to macrosporin (**251**).

Methylation of **253** gave phenol-ethers **254**, however attempts at cyclization to the anthrones **256** directly were not successful. The ethers **254** were subjected to treatment with methanolic potassium carbonate to give 6-benzyl resorcylates **255** in quantitative yields. Cyclization of resorcylates **255** was achieved by heating in Polyphosphoric acid (PPA) to give anthrones **256** in 38–63% yields. Oxidation with cerium ammonium nitrate gave 9,10-anthraquinones **250** in good yield.

The methodology for synthesis of anthraquinones was used for a synthesis of anthraquinone fungi-derived macrosporin **251**. From intermediate **257** hydrogenolysis followed by treatment with trimethysilyl triflate gave anthrone **258** in 76% yield (2 steps). Attempted cyclization of benzyl protected **258** or debenzylated phenol of **258** with PPA gave only decomposition. Although **256a–f** contain unprotected phenols, these are deactivated through hydrogen-bonded to the ester.

Oxidation of **258** with CAN did not proceed as for **256a–g**, so it is likely the free phenol at C-7 is problematic again. Instead the oxidation of **258** was achieved with oxygen and copper bromide to give macrosporin (**251**) in 81% yield.

1.3.1.5   Allyl Migration in Diketo-dioxinone Synthesis

During the synthesis of related β-resorcylate natural products, an interesting observation was made. If morpholine was not used as a scavenger in the deallylation of **259**, then decarboxylation and Tsuji-Trost allylation can occur to give decarboxylation and migration of the allyl moiety (**I**) (Scheme **56**).
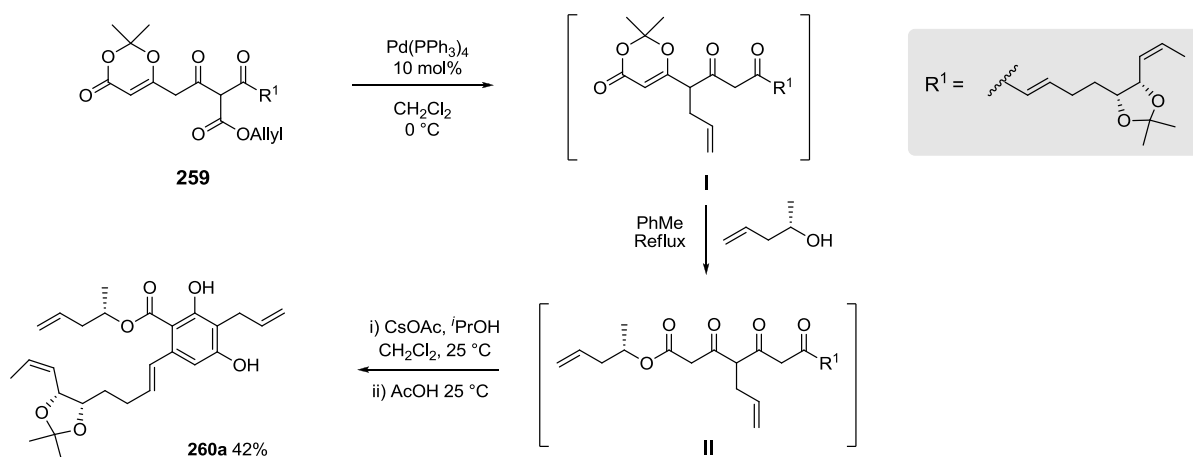
Scheme 56. Discovery of an allyl migration reaction.

This reaction was investigated further through the synthesis of angelicoin A (**261**) (Scheme **57**).[102] When the prenyl-substituted diketo-dioxinone **240d** was treated with Pd(PPh₃)₄ and caesium carbonate, it underwent prenyl migration and decarboxylation to give straight chain product **262a** in 50% yield and, branched intermediate **263a** in 10% yield. From crossover experiments (albeit on slightly different substrates) the reaction is proposed to occur through an intermolecular prenyl transfer. Finally, silyl-deprotection and lactonization under basic conditions gave angelicoin A (**261**) in 33% over 5 linear steps from dioxinone **197**.
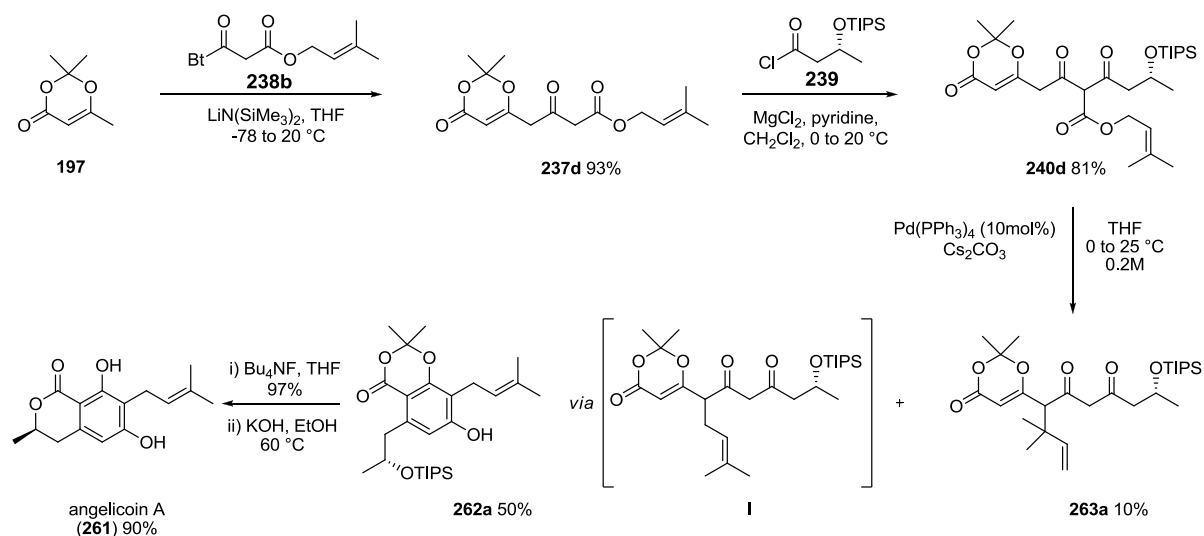
Scheme 57. Synthesis of angelecoin A (**261**).

Concentration was found to be an important factor in the prenyl-migration reaction. While normally conducted at 0.200 M concentration, if conducted at 0.014 M concentration, a different set of products was observed (Scheme **58**).[103] At 0.200 M concentration, compounds **262b** and **263b** are isolated. However, at 0.014 M concentration **242c** and **229a** were the dominant reaction products. The two products **242c** and **229a** arise, because at lower concentration the intramolecular aromatization

reaction becomes competitive with intermolecular decarboxylation/prenylation reaction. These results also suggest that **II** and **III** are intermediates on the pathway to **I**. The observed regiochemistry in the prenylation of **III** to **I** is identical to previously observed (cf. Synthesis of hexasubstituted-resorcylates, Scheme **53**), reaction occurring at the most acidic methylene position.

		Product, Yield (%)			
Entry	Concentration (M)	**262b**	**263b**	**242c**	**229a**
1	0.200	50	10	2	3
2	0.014	3	1	42	41

Pd(PPh$_3$)$_4$, Cs$_2$CO$_3$, THF, 0 to 25 °C
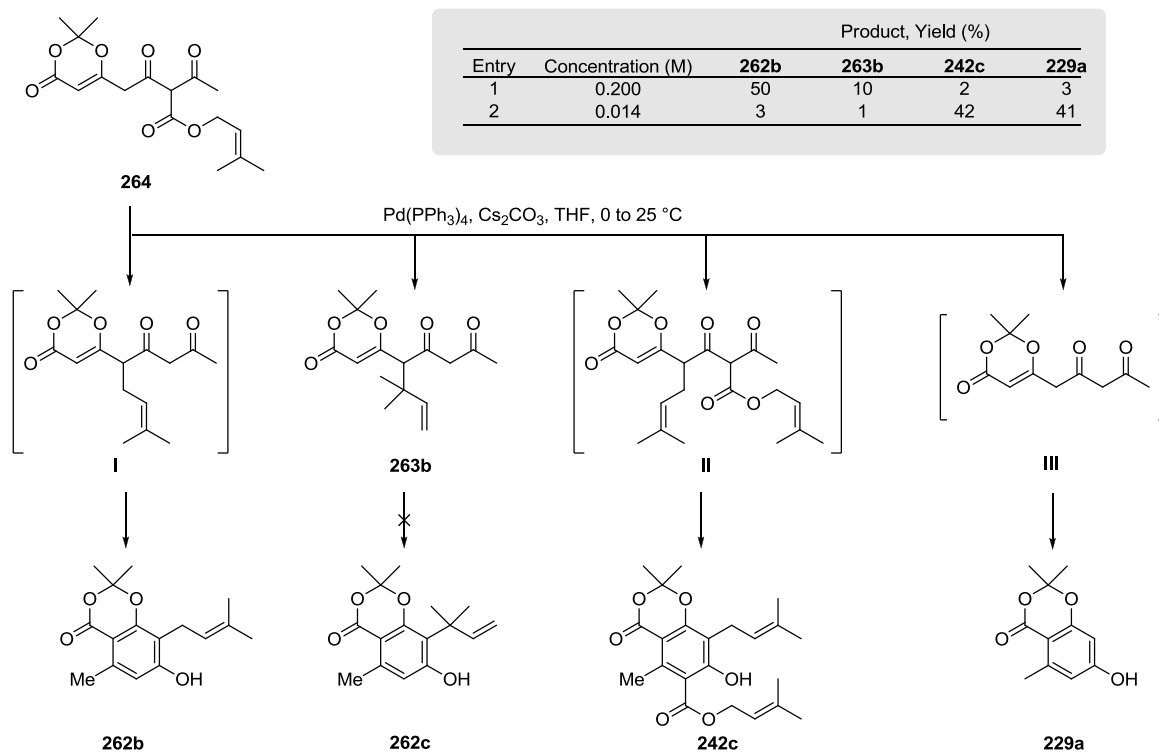
Scheme 58. Product distribution from prenyl migration reactions.

1.3.1.6   Synthesis of Hericenone J and Herecenol A

Application of the allyl-migration reaction of diketo-dioxinones was then extended in the synthesis of several other natural products.[104] In the synthesis of hericenone J (**265**) and herecenol A (**266**) the geranyl side chain was required (Scheme **59**). After acylation, dioxinone keto-ester **240e** was treated with (Pd(PPh$_3$)$_4$ but the conditions were changed from the synthesis of angelecoin A (**261**). Geranyl migration took significantly longer than allyl or prenyl migration, and the addition of base led to decomposition. After allowing 15 h for geranyl migration, addition of silica gel led to aromatization under acidic conditions to give benzodioxinone **262d** as the sole regioisomer, without branching and, in *trans* form. Methylation gave phenolic ether **268** which was either lactonized, to give hericenone J (**265**) (24%, 8 steps), or reduced to give hericenol A (**266**) (21%, 8 steps).
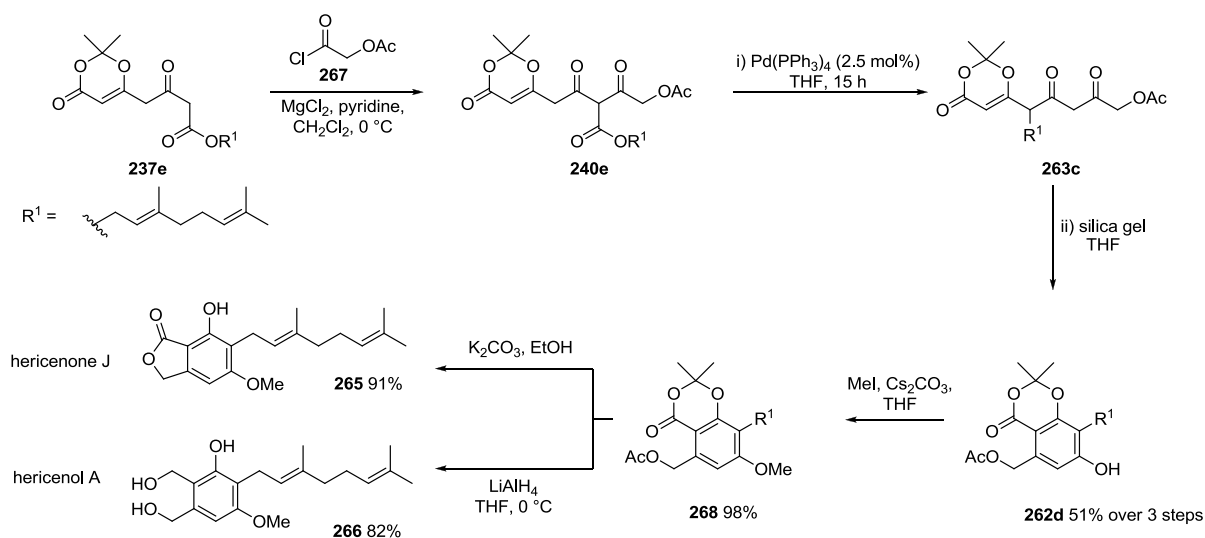
Scheme 59. Synthesis of hericenone J (**265**) and hericenol A (**266**).
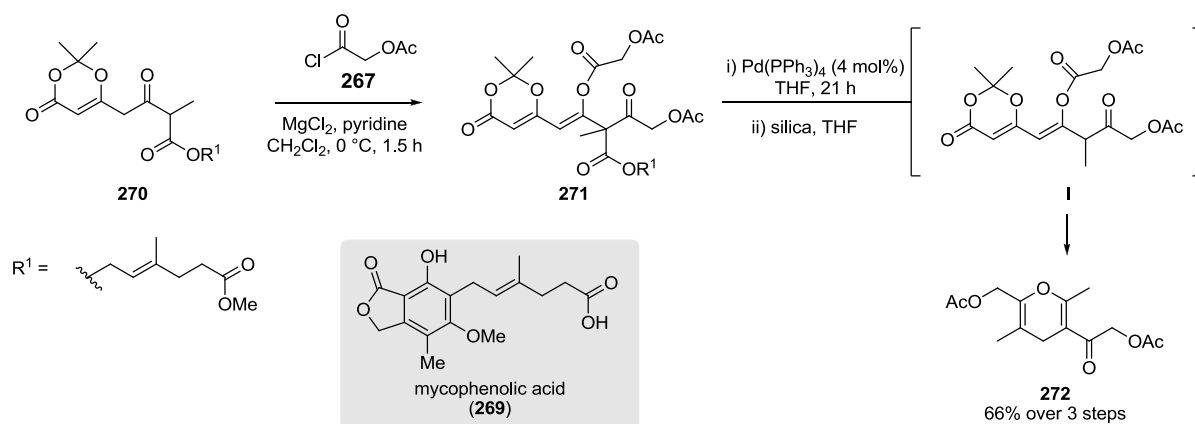
1.3.1.7 Synthesis of Mycophenolic Acid

Similar in structure to hericenone J (**265**) but with six aromatic substituents and a different sidechain is mycophenolic acid (**269**) (Scheme **60**).[105] During this synthesis, some limitations of the *de novo* strategy were encountered. The additional benzene substituent necessitated beginning the synthesis with methylated dioxinone keto-ester **270**. However, during the acylation of **270**, due to the presence of the methyl group, O-acylation could not be suppressed. Subjecting **271** to Pd(PPh$_3$)$_4$ did not result in the allyl migration, but gave pyrone **272**.

Scheme 60. Synthesis of mycophenolic acid (**269**).

Alternatively, the methyl substituent was installed after aromatic ring formation (Scheme **61**). The β-resorcylate **273** (constructed in a similar manner to hericenone J) was treated with iodine and *tert*-butyl amine to give iodoether **274** and diiodo compound **275**. The Iodo-ether of **274** acted as a protecting group for the double bond, allowing application of more forcing conditions for

electrophilic bromination which gave **276**. Treatment of **276** with DABCO-(AlMe$_3$)$_2$ complex and a palladium catalyst, resulted in methylation and deprotection of the double bond to give the hexa-substituted **277** in 72 % yield as only the (*E*) isomer. Hydrolysis with LiOH provided mycophenolic acid (**269**).
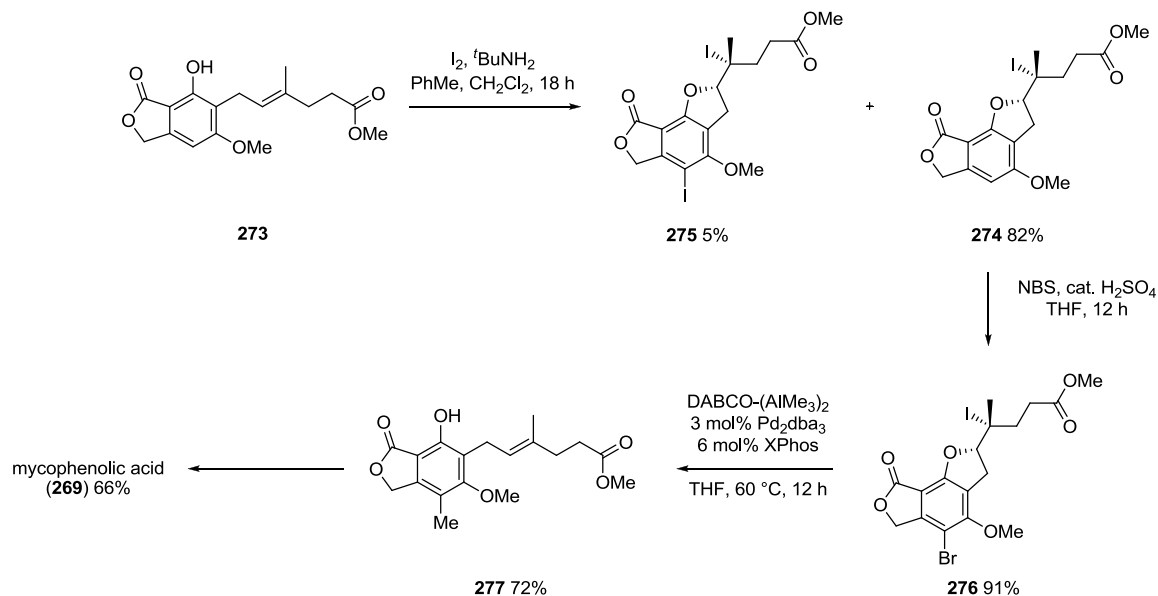
Scheme 61. Barrett's synthesis of mycophenolic acid (**269**).

1.3.1.8 Synthesis of Cristatic Acid Methyl Ester

Even larger allylic side chains have also been shown to be compatible in the migration reaction as demonstrated in the synthesis of cristatic acid methyl ester (**278**) (Scheme **62**).[106] While the migration reaction took 15 h for a geranyl moiety (Scheme **59**), 70 h were required for conversion of **275** to diketo-dioxinone **276**. This then underwent the usual aromatization reaction followed by isopropylidene cleavage to give cristatic acid methyl ester **278**. Here the delicate nature of the decarboxylative migration and aromatization conditions are typified in the compatibility with the delicate iso-butylene substituted furan.
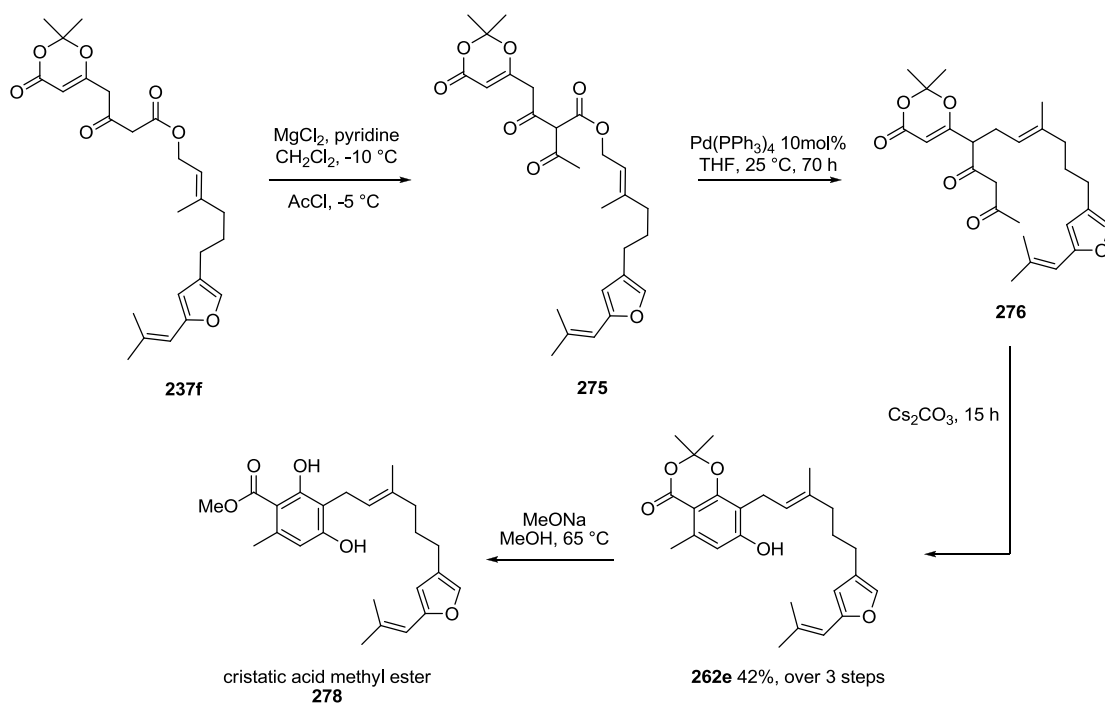
Scheme 62. Synthesis of cristatic acid methyl ester (**278**).

1.3.2 Use of Dianion chemistry in Synthesis of Aromatic Compounds from Dioxinones

The examples of natural product synthesis and methodology discussed so far have seen acylation of ketoester-dioxinones **237** to provide diketo-ester-dioxinones **240** (Scheme **63**). In most cases subsequent decarboxylation is carried out, with or without allyl migration, to give diketo-dioxinones **263** or **228**. The diketo-dioxinones then undergo ketene generation and trapping followed by aromatization to give **260**, or simply direct aromatization to give **262**.
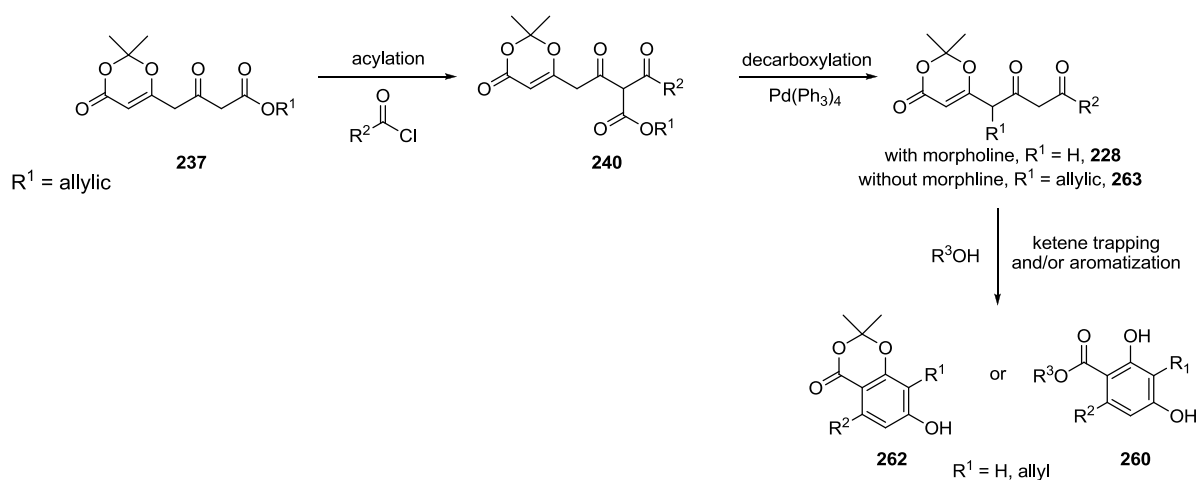
Scheme 63. General synthesis of diketo-dioxinones β-resorcylates **260** and **262** by acylation chemistry.

A more direct way to access diketo-dioxinones **228** is through the acylation of parent dioxinone **197**, as displayed in another synthesis of (*S*)-(−)-zearalenone (**230**) (Scheme **64**).[107] In this case, addition of dioxinone **197** to acylbenzotriazole **279** gave ketal-protected diketo-dioxinone **280**. Cross metathesis with alcohol **281** gives substrate **282**, with all the requisite functionality in position. In another divergence from the first synthesis of **230** (Scheme **51**), the macrocycle was formed through intramolecular ketene trapping—a tactic which has been previously employed in natural product synthesis as a solution to macrolactonization steps that can often be poor yielding. Intramolecular ketene trapping provides macrocycle **283** which, through aromatization, contracts to give 14-membered resorcylate acid lactone **230**.
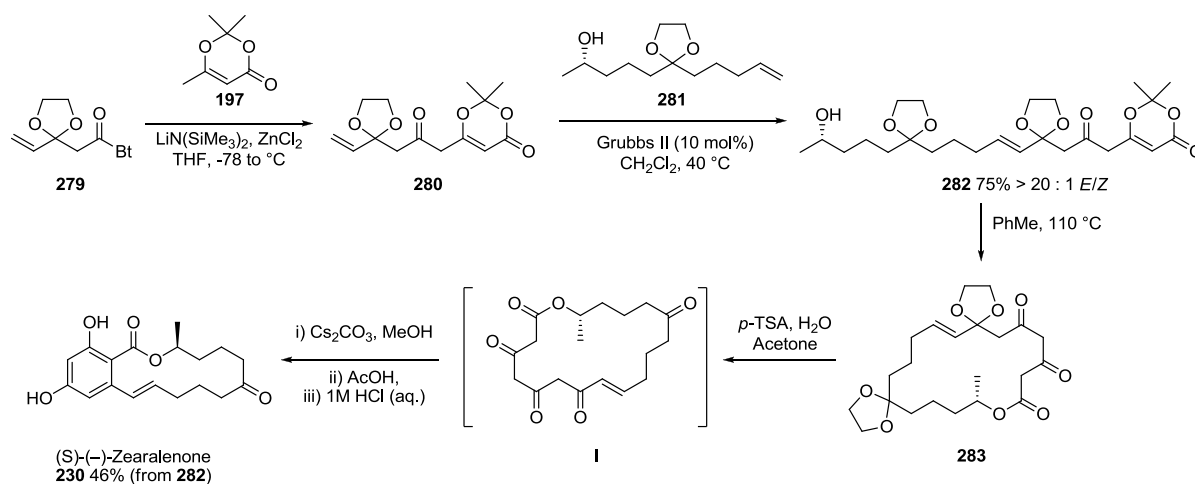
Scheme 64. A second generation synthesis of (S)-(−)-zearalenone (**230**).

Further developing the synthesis of diketo-dioxinones **228**, dioxinone **197** has been acylated to give keto-dioxinone **284a** (Scheme **65**).[108] The synthesis of keto-dioxinone **284a** was optimized and acylimidazole (**285**) was the optimum acylating agent, with the addition of diethylzinc to enhance the acylation.[109]
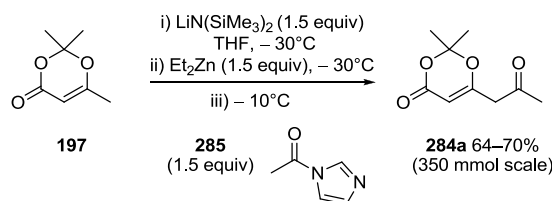
Scheme 65. Synthesis of keto-dioxinone **284a**.

Keto-dioxinone **284a** can be further acylated through formation of its dianion and as such, this molecule and analogues have been a key starting material for the synthesis of diketo-dioxinones **228**. These include synthesis of a number of different products and the following sections will disclose how keto-dioxinones **284** have been used in natural product and small molecule chemistry (Scheme **66**).
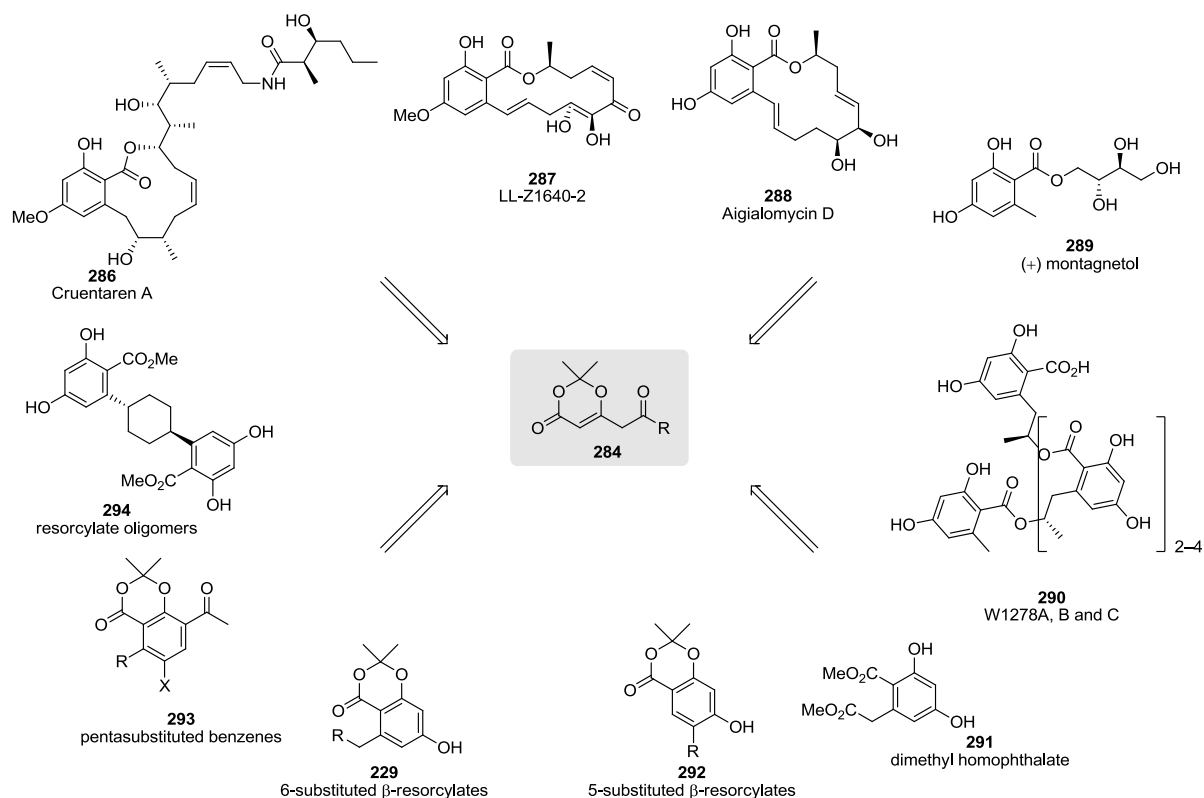
Scheme 66. Synthetic products produced from keto-dioxinones **284**.

1.3.2.1 Synthesis of Curentaren A

Perhaps the most ambitious resorcylate acid lactone syntheses attempted so far is the synthesis of cruentaren A (**286**) (Scheme **67**).[110] Previous syntheses of this molecule start from aromatic entities and involve lactonization and ring closing alkyne metathesis followed by lindlar reduction to give the desired (*Z*)-isomer. The first idea was that intramolecular macrolactonization by ketene trapping and aromatization could provide the macrocycle and aromatic unit in one step.
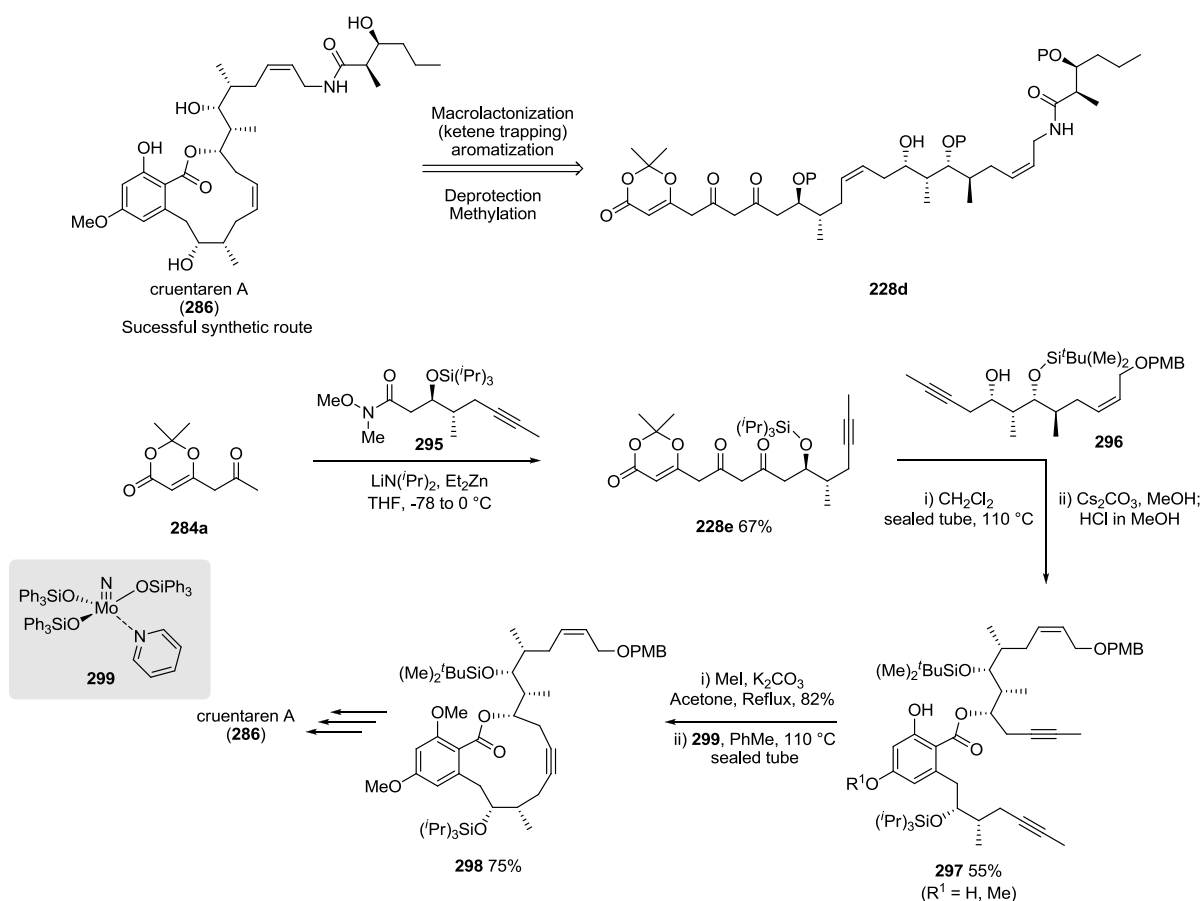
Scheme 67. Synthesis of Creuntaren A (**286**).

However, due to difficulties in the synthesis of the side chains the final strategy involved macrolactonization using ring closing alkyne metathesis. Nevertheless, use of the resorcylate formation strategy allowed formation of aromatic **286** in 55% yield. Interestingly, formation of the aromatic gave some of the methylated phenolic compound also, presumably due to dimethylacetal formation of the intermediate poly-carbonyl compounds. This reaction was also carried out on gram-scale presenting the largest scale that Barrett *et al.* has reported employing formation of tri-keto esters from ketene trapping and subsequent aromatization.

1.3.2.2   Synthesis of LL-Z1640-2

Once more, keto-dioxinone **284a** was used, applied to a synthesis of tumor inhibitor LL-X1640-2 **287** (Scheme **68**).[111] Acylation of **284a** with Weinreb amide **300** gave diketo-dioxinone **228f**, precursor for a macrocyclization/aromatization reaction. Heating of **228f** resulted in macrocycle formation and sequential treatment with caesium carbonate and acetic acid gave resorcylic acid lactone **301** in 55% yield. Selective methylation of the resorcylate core, deprotection and oxidation provided the desired natural product **287**.
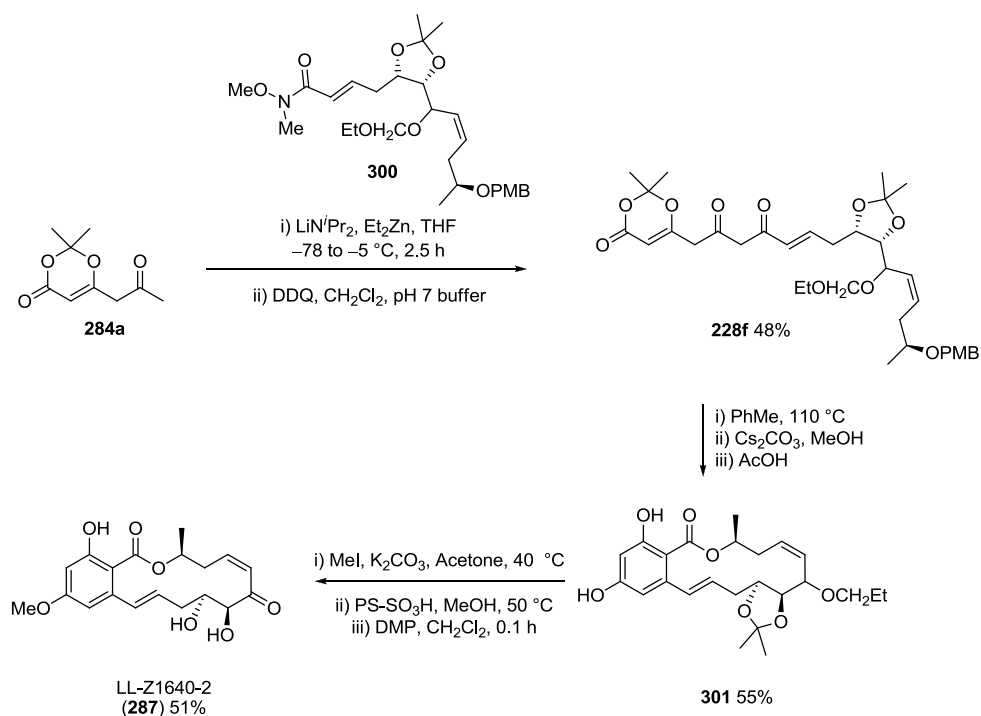
Scheme 68. Synthesis of LL-Z1640-2 (**287**).

1.3.2.3 Synthetic Studies Towards Tragoponol

A limitation of the methodology for resorcylic acid lactone synthesis was observed in studies towards unsymmetrical resorcylate dimer tragoponol (**302**) (Scheme **69**).[112] Highly functionalized resorcylate **303** had been synthesized using the developed resorcylate chemistry. Reaction of **303** with keto-dioxinone **284a** gave diketo-dioxinone **228g** in 76% yield; setting the stage for generation of the second aromatic ring. Selective desilylation with HF or N^{n}Bu$_4$F gave the desired alcohol **304**. However, in attempts to purify or isolate alcohol **304**, quantitative formation of δ-lactone **305** occurred. Attempts to carry out the desilylation during ketene trapping also failed to produce the desired macrocycle.
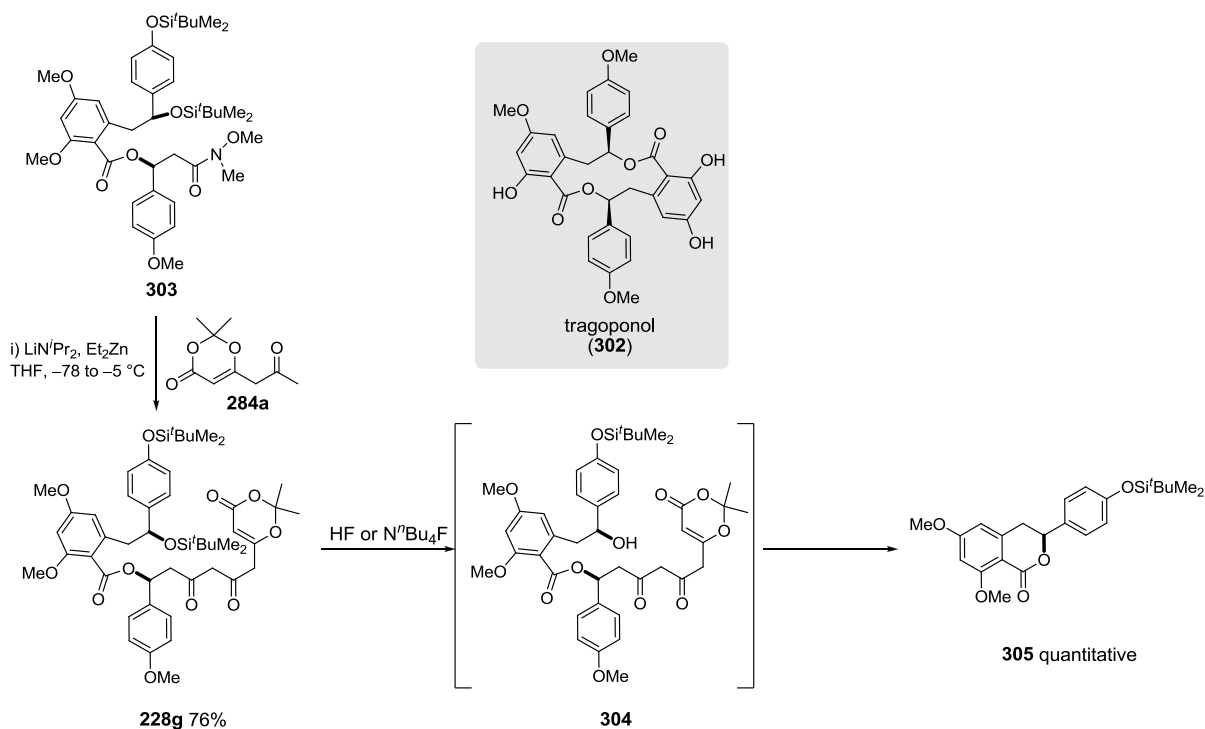
Scheme 69. Synthetic efforts towards tragoponol (**302**).

1.3.2.4 Synthesis of W1278 Oligo-esters

Towards oligo-esters W1278A, B and C (**290**) some interesting findings were made as regard to the thermyolysis of dioxinone molecules (Schemes **70** and **71**).[108a] As now commonplace, acylation of keto-dioxinone **284a** with a Weinreb amide **306** gave the desired diketo-dioxinone **228c** (Scheme **70**). Heating in the presence of alcohol **307,** followed by aromatization and deprotection gave the β-resorcylate **309**. This was then heated with another molecule of diketo-dioxinone **228c** and gave desired ester **310** in 45% yield. Unfortunately at the required reaction temperature for ketene generation, lactonization competed for reaction with **228c** and benzolactone **311** was also formed in 21%.
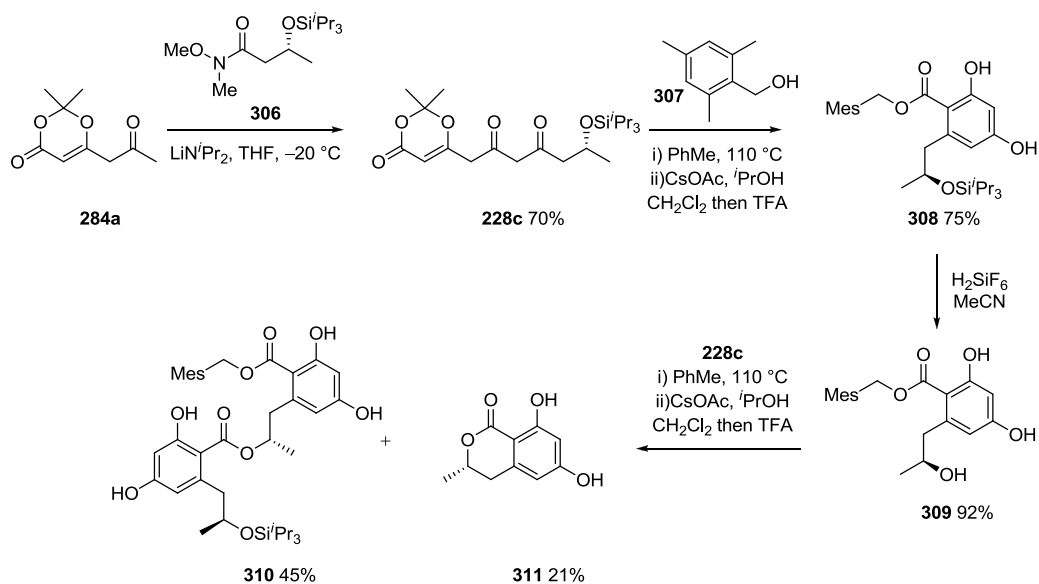
Scheme 70. Synthesis of intermediate **310**.

To overcome the use of such high temperature ketene generation the acylketene adduct was varied, affecting the temperature at which thermolysis was possible (Scheme **71**). Various dioxinones (**197** and **311a–c**) were heated with nucleophile **312** for a set period of time. The yield of keto-ester **313** ranged from 5–95% indicating different rates of thermyolysis. Acetophenone adduct **311c** appeared to give very rapid reaction, perhaps accelerated through overlap of the phenyl π-system with the σ* orbital the O–CO bond, or alternatively through the enhanced radical stabilizing ability of the diphenyl moiety.[113] The ability to tune the thermyolysis temperature of dioxinones makes them useful in cases where certain substrates are unstable.

Dioxinone	**311a**	**197**	**311b**	**311c**
Yield of **313**	5	15	55	95
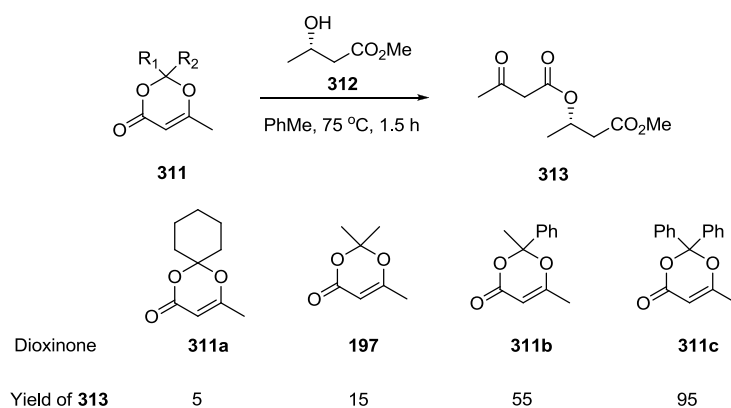
Scheme 71. Thermyolysis of various dioxinones.

Applied to the W1278 oligo-esters at hand, alternative diketo-dioxinone **228h** was constructed (Scheme **72**). Reaction of **309** with **228h** at a lower thermyolysis temperature of 80 °C gave aromatized product **310** in a much improved 72% yield. The synthesis of the W1278A, B and C (**290**) could then be completed. Following deprotection of the Silyl ether, repeated used of diketo-dioxinone

228h allows additional resorcylate units to be added to the molecule, in a yield of 60% yield per repeated sequence.
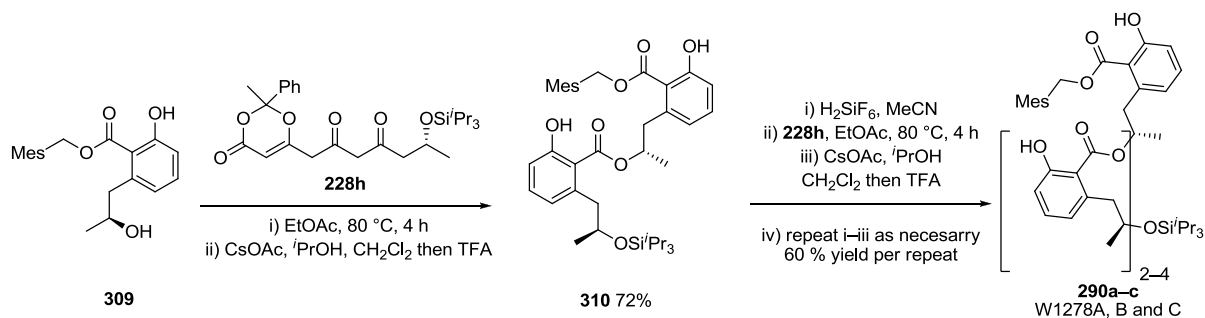
Scheme 72. Synthesis of W1278 oligo-esters (**290**).

1.3.2.5 Double β-Resorcylate Oligomers

Aside from the naturally occurring W1278 oligoesters, keto-dioxinone **284a** has also been used in the synthesis of novel double resorcylate oligomers **294a–e** (Scheme **73**).[114] Reaction of keto-dioxinone **284a** with bisamides **314a–e** resulted in formation of bisdiketo-dioxinone compounds **315a–e**. Treatment of **315 a–e** with triethylamine led to aromatization and opening of benzodioxinones **316a–e** gave the double resorcylate compounds **294a–e**. Notably, choice of appropriate amide partner allows a double resorcylate pyridine **294d** and a terphenyl resorcylate **294c** to be obtained.
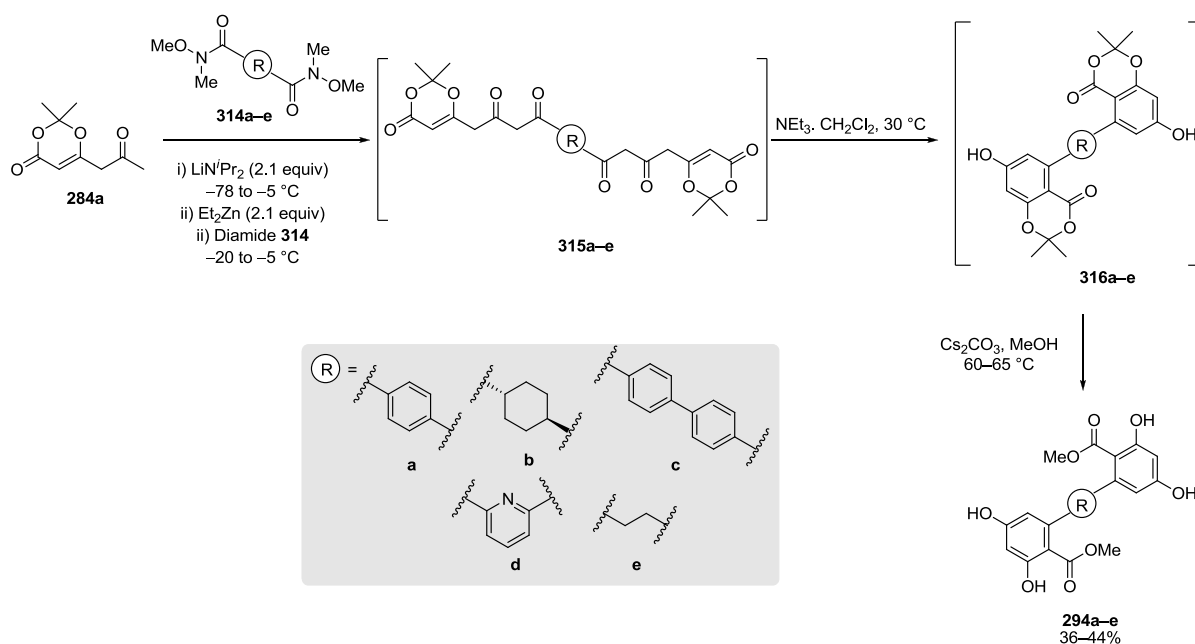
Scheme 73. Synthesis of double β-resorcylates.

1.3.2.6 Synthesis of 6-Amino-Resorcylates

Keto-dioxinone **284a** has also proved a key intermediate at the core of methodologies for the synthesis of an array of small resorcylate molecules. The first example is in the synthesis of 6-substituted β-resorcylates from a crossed Claisen condensation reaction with functionalized α-amino acids (Scheme **74**).[115] The dienolate of keto-dioxinone **284a** was treated with diethylzinc followed by addition of a Weinreb amide or an acyl imidazole (Acyl imidazoles were more reactive in this acylation when sterically hindered amino acids were used).[116] Treatment of diketo-dioxinones **317** with triethylamine and aromatization gave a range of β-resorcylates **318** and **319**. The novel amino resorcylates produced in this study were tested against various cancer cell lines and displayed promising ability as selective CDK2 inhibitors. This methodology also shows that it is possible to generate a wide array of novel resorcylate structures, which can serve as small molecule starting points for medicinal chemistry, with tolerance for a range of functional groups and without protecting groups.
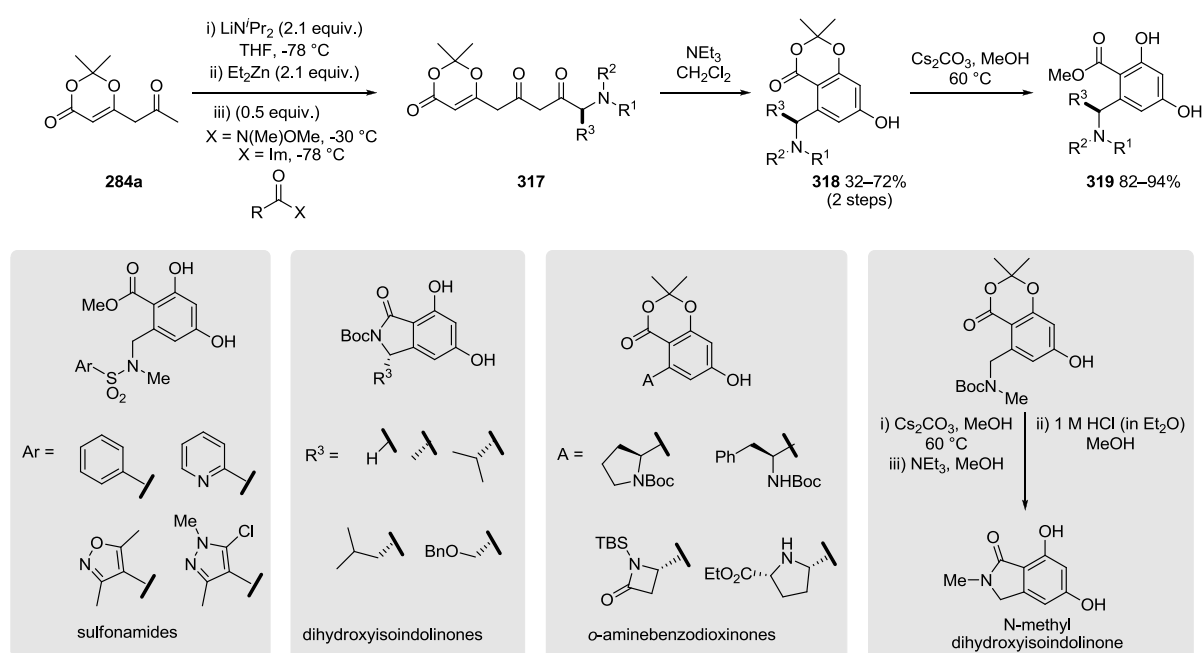
Scheme 74. Synthesis of 6-substituted β-resorcylates.

1.3.2.7 Synthesis of 2-Pyridones

Aside from the specific keto-dioxinone **284a**, analogues of this compound have also been used in development of methodology for synthesis of pyridinones **320** (Scheme **75**).[117] Synthesis of an array of keto dioxinones **284** proceeded by reaction of dioxinone **197** with acyl imidazole. Condensation of **284** with ammonium acetate gave enamine-dioxinones **321** that on heating underwent intramolecular

cyclization to give 6-substituted-4-hydroxy-2-pyridinones **320**. Use of slightly modified conditions gave an N-alkylated analogue **322**. This methodology gave overall yields of 45–64% from dioxinone **197** with only one purification required and again, a wide incorporation of functional groups were tolerated under the conditions.

6-substituted-4-hydroxy-2-pyridones
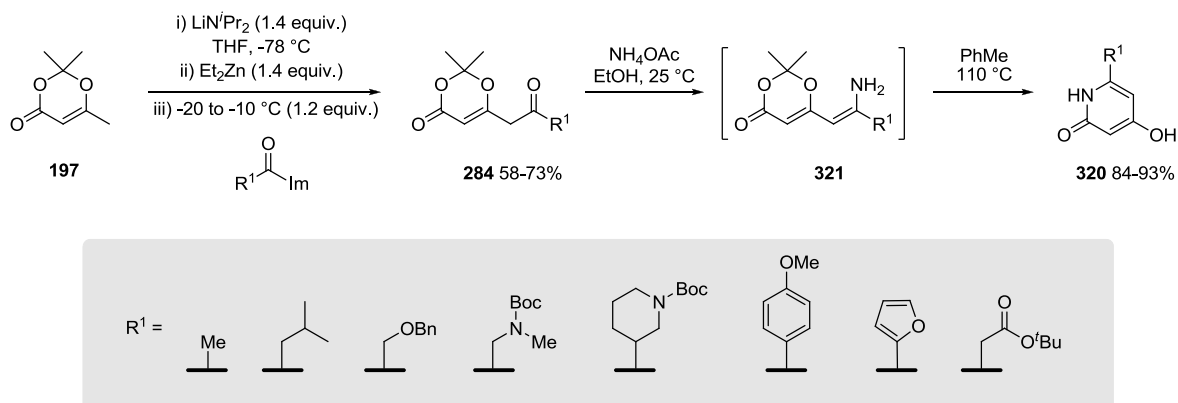
N-Benzyl-4-hydroxy-6-methyl-2-pyridone
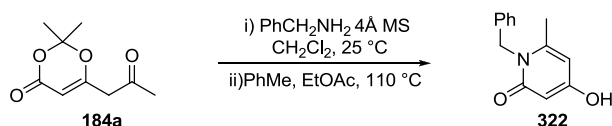
Scheme 75. synthesis of 4-hydroxy-2-pyridinones.

1.3.2.8 Synthesis of 5-Amino Resorcylates

The heat shock protein 90 HSP90 inhibitors **323** and **324** were developed by Astex and Pfizer pharmaceutical companies respectively for use in oncology (Scheme **76**).[118] The syntheses reported for these molecules involved beginning with a resorcylate starting material and use phenolic protection and derivatization of the aromatic core. It was hoped that a biomimetic *de novo* strategy applying diketo-dioxinone chemistry would offer a more suitable synthesis of these pharmaceutically relevant molecules.[119]
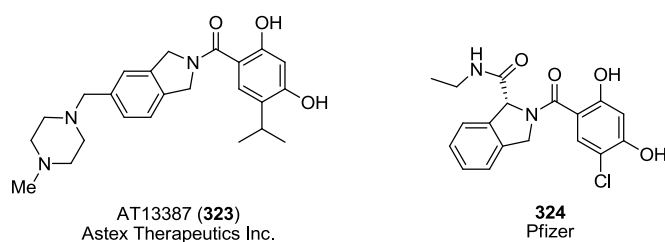
Scheme 76. β-resorcylamides developed for oncology treatments.

The synthesis of **323** began with conversion of *iso*-valeric acid (**325**) to imidazoyl **326** which was used for acylation of the lithium enolate of dioxinone **197** to give keto-dioxinone **284b** (Scheme **77**). Generation of the dienolate of keto-dioxinone **284b** with diethylzinc and use of ethyl formate as the electrophile gave keto-aldehyde dioxinone **327**. Without isolation, aldehyde **327** was aromatized to give 5-substituted β-resorcylate core **328**. Addition of *iso*-indoline **329** with *iso*-propylmagnesium chloride to benzodioxinone **328** yielded AT13387 (**323**) in 70%. Including synthesis of the *iso*-indoline sidechain, this route gave **323** in 13% yield over 9 synthetic manipulations in contrast to the reported synthesis (from a benzoic acid derivative) of 13 steps with an overall 3% yield. The chemistry was also extended to the core of Pfizer's compound **324**. Synthesis of the 5-chloro-substituted resorcylate **330** by the same route followed by opening with *iso*-indoline **331** gave **324**.
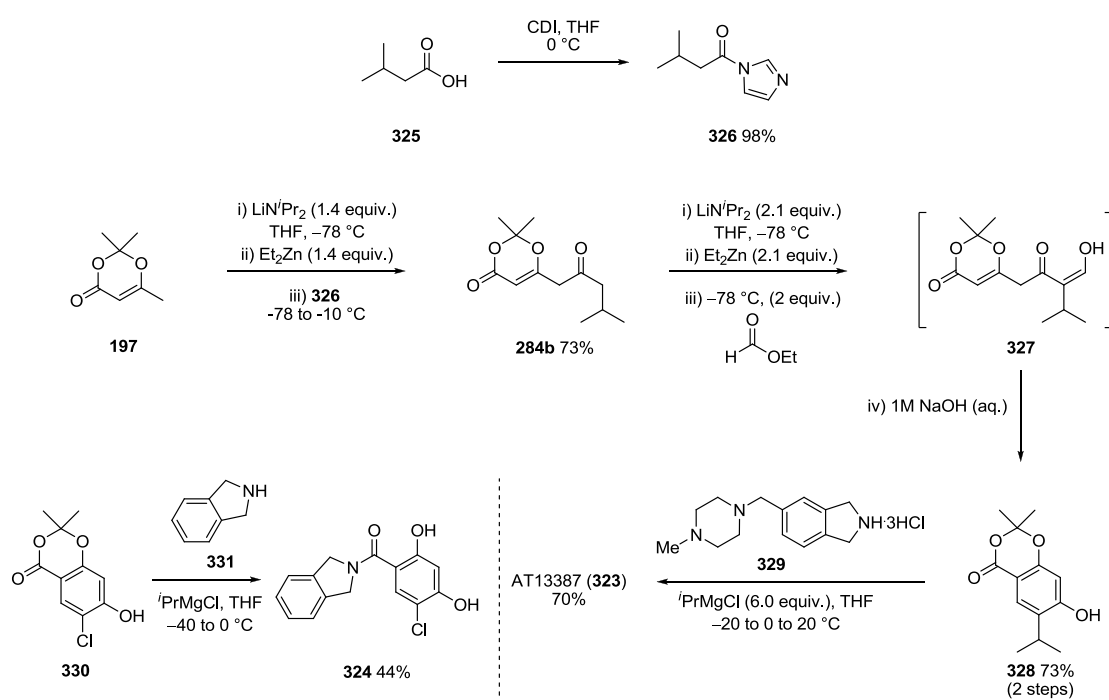
Scheme 77. Synthesis of the commercial resorcylamides **323** and **324**.

The development of the methodology shows that not only 6-alkyl resorcylates could be synthesized but 5-alykl resorcylates were readily available. Indeed, the formylation step was applied for the general synthesis of 5-substituted β-resorcylate derivatives.[120]

1.3.2.9   Synthesis of Pentasubstitued. Orthogonally Oxygenated Benzene Derivatives

Keto-dioxinone **284a** has also been used in an alternative aromatization mode within the Barrett group (Scheme **78**). Condensation of DMF-DMA at the active methylene position of keto-dioxinone **284a** gives rise to the enamine **332**.[121] Addition of various magnesium acetylides to **332** gave eneyne

dioxinone substrates **333**, predominantly as the desired *E*-isomer, and treatment with ICl or NBS gave rise to the halogenated aromatics **334**. The final compounds are of synthetic interest because they contain multiple sites for further selective functionalization.
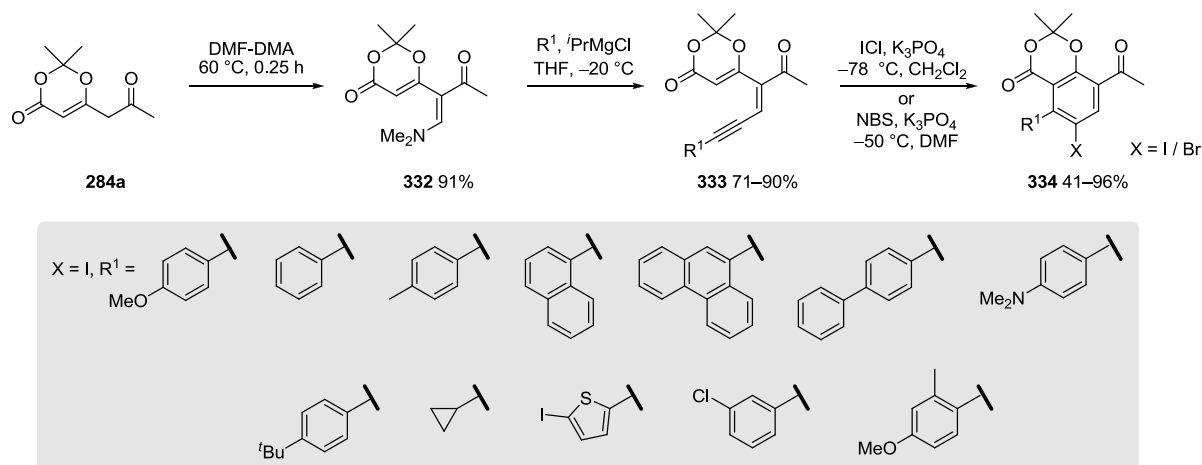
Scheme 78. Synthesis of orthogonally oxygenated benzene derivatives **334**.

1.3.3 Key Benefits of the Barrett Methodology

In Summary, by combining biomimetic synthesis of aromatic compounds with the synthetic utility of dioxinones for polycarbonyl synthesis, the methodology developed by Barrett *et al.* allows the concise synthesis of a diverse array of novel aromatic derivatives as well as larger natural products. There are several key advantages to this *de novo* methodology over synthesis from aromatic precursors.

The relative stability of dioxinone derivatives compared to polycarbonyl compounds (cf. Harris *et al.*) allows stepwise introduction of substituents under milder conditions. In the case of small molecules, this allows regioselective formation of resorcylate molecules without the requirement for protecting groups and with a wide variety and number of aromatic substituents incorporated. As the case of AT13387 (**323**) shows, these routes can be higher yielding when compared to aromatic derivatization chemistries.

The synthesis of resorcylic acid lactone natural products using the late-stage aromatization strategy allows for a highly efficient macrolactonization step to be conducted easily *via* ketene trapping and without the requirement for phenolic protecting groups. Excellent functional group tolerance is exhibited and high complexity is generated in a single step making this an attractive route to this class of natural products.

New classes of aromatics such as the amino resorcylates have been developed which have showed useful bioactivity. The fact that these are novel compounds suggest that traditional aromatic chemistries may be inefficient at forming them and have perhaps eluded the imagination of organic chemists. Whether such molecule classes would've been explored without the invention of this methodology could be debated. However, where synthesis of a certain class of molecule is restricted, then exploration of the chemical properties of that class is also restricted.

1.4 Research Aims and Description

The main aims of this project lie in the further development of synthetic methodology; in particular, *de novo* synthesis of aromatic compounds using dioxinone derivatives as starting materials. Previous methodology developed towards this goal was based on formation of diketo-dioxinones **228** and their aromatization to give β-resorcylates **193** (Scheme **79**).
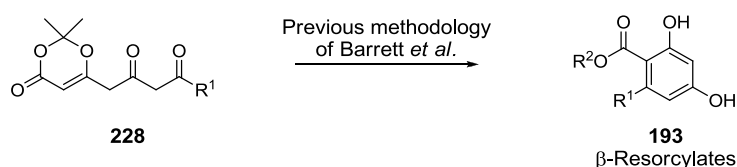
Scheme 79. Methodology previously developed by Barrett *et al.*

As shown earlier in the biosynthesis of 6-methylsaliclic acid **190**, partially reduced poly-carbonyl compounds are also aromatized in nature to give aromatic products (Scheme **40**). Based on these concepts, the hypothesis was that heating dioxinone **335** in an alcohol would form the partially reduced polycarbonyl compound **336** and aromatization *via* an intramolecular aldol condensation would give salicylates **131** (Scheme **80**).
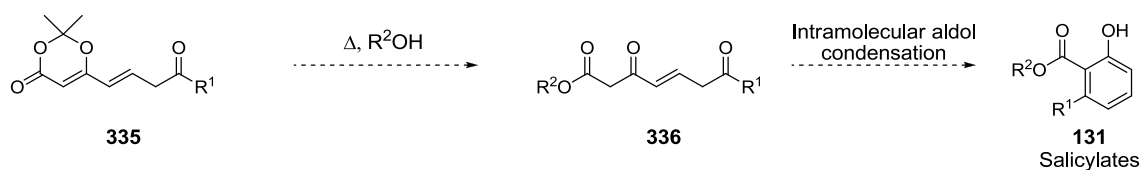
Scheme 80. Hypothesis for a synthesis of salicylates **131**.

Reduced polycarbonyl compounds could be further exploited (Scheme **81**). If dioxinone **337** could be constructed then the reduced polycarbonyl compound **338** would be easily accessible. Dieckmann cyclization of **338** could then give γ-resorcylates **142**. This would regioisomerically complement the Barrett methodology for synthesis of β-resorcylates **193**.
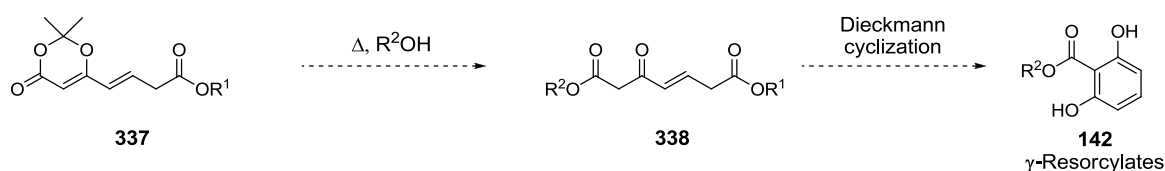
Scheme 81. Hypothesis for a synthesis of γ-resorcylates **142**.

Chapter **2** shows initial synthetic route for the synthesis of reduced substrates **335** and **337**. The salicylates **131** and γ-resorcylates **142** are important classes of molecules and information on their use and synthesis is provided in subsequent chapters. Chapter **3** provides details on the applications of salicylates **131** and the methodology that has developed for their synthesis. Chapter **4** provides similar information pertaining to γ-resorcylates **142**.

During the development of these methodologies, the synthesis of other types of aromatic molecules **339**, **340**, **341** were also explored (Figure **1**). In chapters **5** and **6** the methodology for synthesis of these molecules will be discussed.

339
6-Alkylamino-
salicylates

340
Hydroquinones

341
Dioxinone dimer
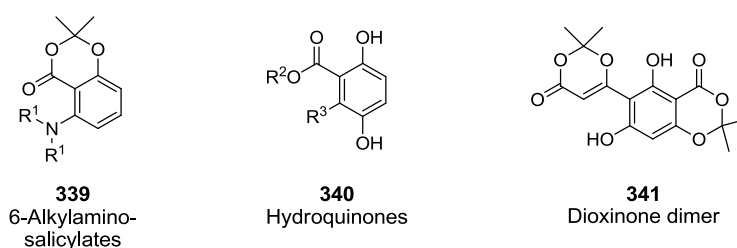
Figure 1. Methodology was developed for additional aromatic products.

Synthesis of Dioxinone Carbaldehyde **350** and Development of Routes to Cyclization Substrates

1.5 Retrosynthesis of Aromatization Substrates

Considering the substrates for the proposed aromatization processes outlined in the introduction (Chapter **1**, Schemes **80** and **81**, **335** and **337**), a retrosynthesis for compounds of the general structure **342** (R = aryl or alkyl, either regioisomer) was carried out (Scheme **82**). Depending on which regioisomer of **342** is chosen, then retrosynthetically breaking the double bond there is a choice of two different pathways for Wittig reactions to be carried out. Following route A, a combination of either dioxinone phosphonium salt **343** and malonaldehyde **344**, or dioxinone aldehyde **346** and phosphonium salt **347**, would give **342**. Alternatively, following route B, phosphonium salt **349** and dioxinone aldehyde **350** would give **342**. Furthermore, dioxinone aldehyde **350** could be prepared through several routes. Addition of the lithium enolate of dioxinone **197** to formaldehyde followed by oxidation or, direct formylation, would give aldehyde **350**. Alternatively, aldehyde **350** could be produced by reduction from either Weinreb amide **351** or thioester **352**. All of these strategies towards the substrates **342** were investigated and are detailed throughout this chapter.
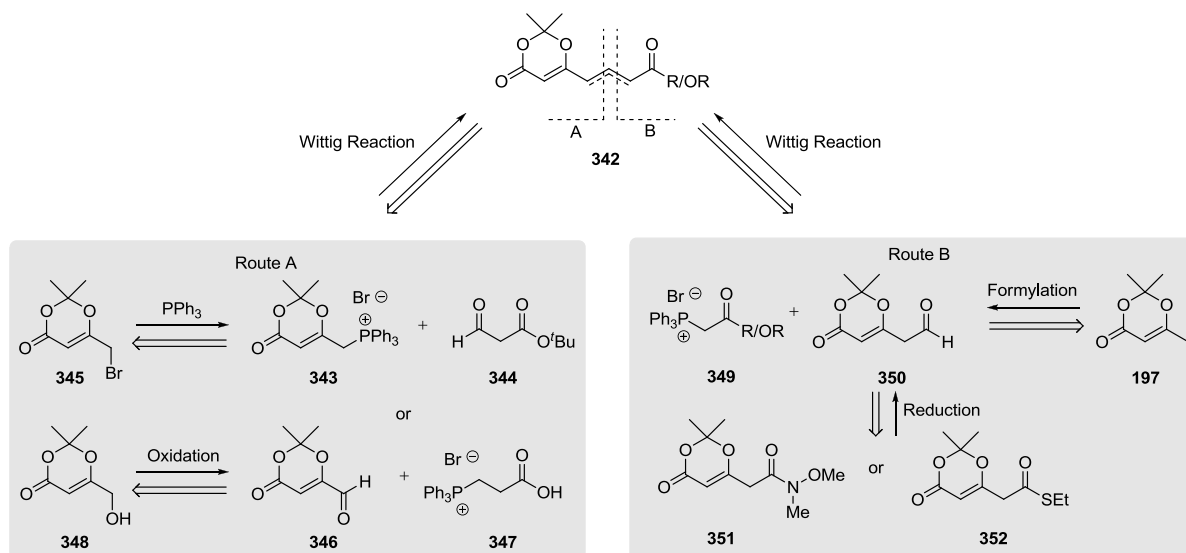
Scheme 82. Retrosynthesis for the dioxinone ketones and esters of the general structure **342**.

1.6 Synthesis of the Aromatization Substrates

1.6.1 Towards Route A Employing Dioxinone Phosphonium Salt 343
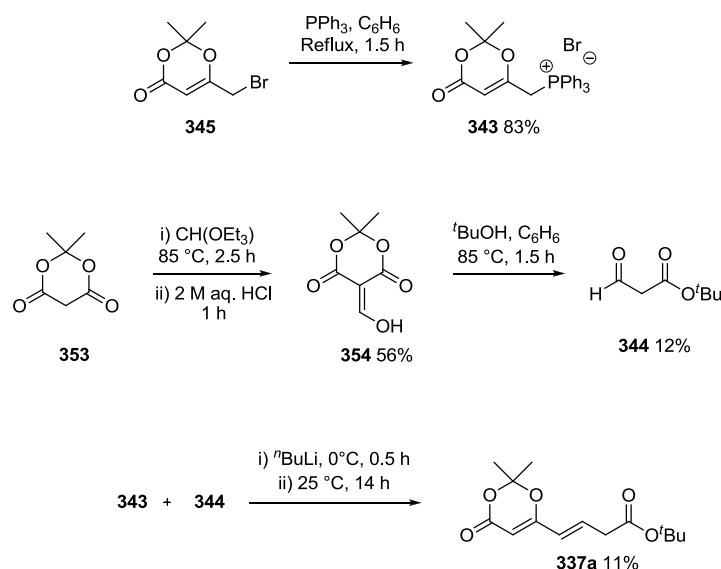
Scheme 83. Synthesis of dioxinone ester 337a through a Wittig reaction of phosphonium salt 343 and aldehyde 344.

Beginning with route A, the bromo dioxinone 345 was refluxed with triphenylphosphine in benzene to give phosphonium salt 343 in 83 % yield (Scheme 83).[122] The synthesis of the required aldehyde 344 proved to be more challenging due to its instability. According to the literature, Meldrum's acid 353 was heated with triethyl orthoformate to give the corresponding ethyl enol ether, which was then hydrolyzed to give formylmeldrum's acid 354.[123] Heating of 354 in *tert*-butanol gave after distillation aldehyde 344 that existed as a keto-enol mixture in solution. Using aldehyde 344 immediately, a Wittig reaction with 343 was conducted and gave ester 337a in 11% yield. Further attempts to improve the yield of this reaction were hindered by the instability of aldehyde 334 (which decomposed within 12 h even when stored at −20 °C), which due to its high degree of enolisation is prone to aldol condensations and polymerization.

1.6.2 Towards Route A Employing Dioxinone Aldehyde 346

Continuing with route A we considered the alternative Wittig pairing, dioxinone aldehyde 346 and phosphonium salt 347 (Scheme 84). Phosphonium salt 347 is known in the literature but the aldehyde 346 has only been obtained in very low yield (as a product during the oxygenation of a silyl dienol ether with triphenyl phosphate ozonide) and was only partially characterized.[124] Commencing with bromo dioxinone 345, displacement with sodium acetate gave 355 which was hydrolyzed to primary alcohol 348 (Scheme 84).[125] Oxidation of 348 to aldehyde 346 could be achieved using Dess-Martin

periodinane, however purification proved problematic due to the instability of aldehyde **346** to silica gel chromatography. Use of freshly prepared manganese dioxide proved optimal and gave desired aldehyde **346** in 84% yield.[126] Interestingly, the use of commercially sourced manganese dioxide for oxidation of **348** led to decomposition. This disparity is most likely due to differing morphologies of the catalyst in this heterogeneous reaction.
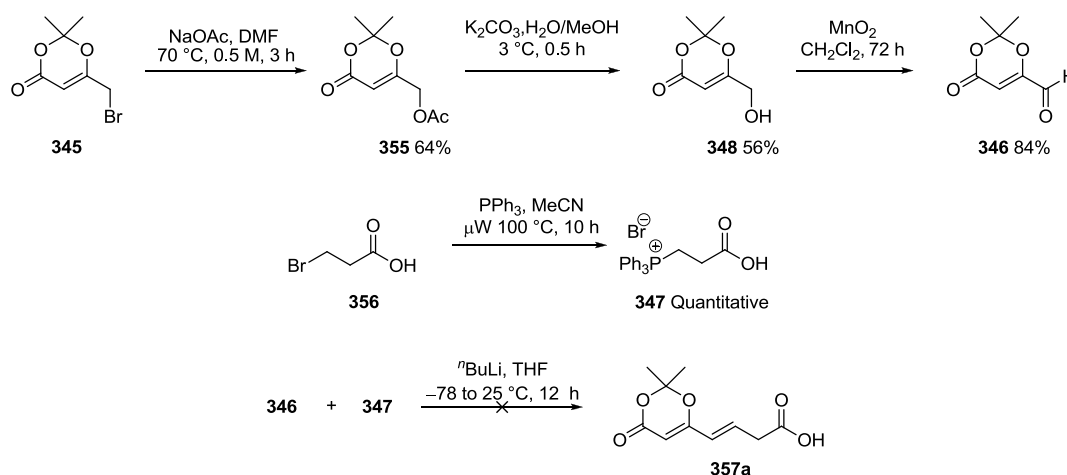
Scheme 84. Synthesis of dioxinone aldehyde **346** and attempted Wittig reaction with **347**.

The acid **356** was treated with triphenylphosphine to give phosphonium salt **347** as a Wittig partner for aldehyde **346**.[127] Unfortunately reaction of **346** and **347** failed to give any of acid **357a** and only decomposition of aldehyde **346** was observed.[128]

1.6.3 Towards Route B Employing Dioxinone Aldehyde **350**

With some success in route A, route B was also examined. Towards a synthesis of dioxinone aldehyde **350**, reaction of dioxinone **197** with formaldehyde was first attempted (Scheme **85**). Monomeric formaldehyde in THF was generated by codistillation from paraformaldehye in presence of *p*-toluenesulfonic acid.[129] This solution was added to the lithium enolate of dioxinone **197** however only alcohol **358** was isolated in 9% yield, from reaction at the α-position. A similar situation was observed in reaction with chloromethyl methyl ether (MOM-Cl) which gave methyl ether **359** in 28% yield.

Target: **350**

Formaldehyde in THF

LiN(^{i}Pr)$_2$, THF
−78 °C, 1 h

197

358 9%

LiN(^{i}Pr)$_2$, MOM-Cl
THF, −78 °C, 3 h

197

359 28%
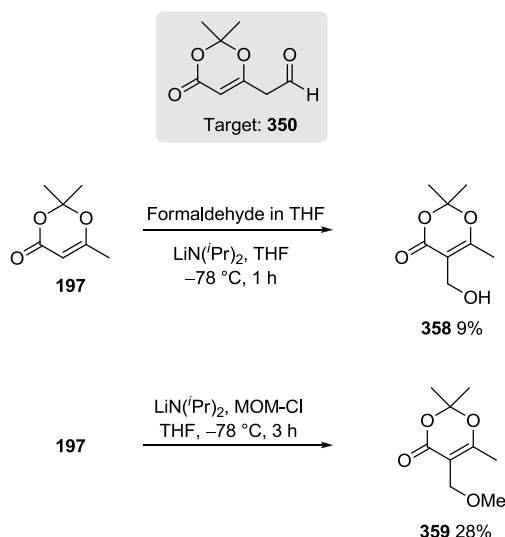
Scheme 85. Attempted reactions of the lithium enolate of dioxinone **197** with electrophiles formaldehyde and chloromethyl methyl ether towards aldehyde **350**.

Attempting a more direct route to **337b**, a one-pot formylation-Horner Wadsworth Emmons procedure was examined (Scheme **86**).[130] The lithium enolate of dioxinone **197** was added to *N*-formyl carbazole **361** followed by addition of triethylphosphonoacetate which resulted in successful reaction with isomerization to give **337b** in 9% yield. The parent carbazole **360** was isolated from this reaction in 70% which might suggest that formylation had taken place but the intermediate aldehyde **350** was unstable to the reaction conditions. Using tert-Butoxycarbonylmethyl)triphenylphosphonium bromide (**349a**) in place of the phosphonate **362** failed to give any of the corresponding Wittig product (not shown).

HCO$_2$H
Reflux, 9 h
55%

360

361

i) LiN(^{i}Pr)$_2$, THF
−78 °C, 45 min
ii) **361** 1 h, −78 to 10°C

iii) (EtO)$_2$P(O)CH$_2$CO$_2$Et **362**
10 to 25 °C, 14 h

197

+ **360** 70%

337b 9%
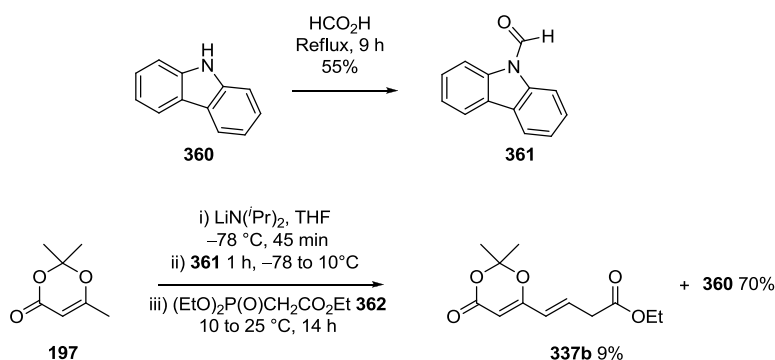
Scheme 86. A one-pot formylation-Horner Wadsworth Emmons procedure for synthesis of ester **337b**.

## 1.6.4 Synthesis of Aldehyde **350** by Reduction Methods

Continuing to target aldehyde **350** the reduction of Weinreb amide **351** was considered (Scheme **87**). Carbamoyl chloride **364** was produced in 78% yield by treatment of *N*,*O*-dimethylhydroxylamine

hydrochloride (**363**) with triphosgene. This was then used to acylate dioxinone **197** to give the desired Weinreb amide compound **351** in 71% yield.
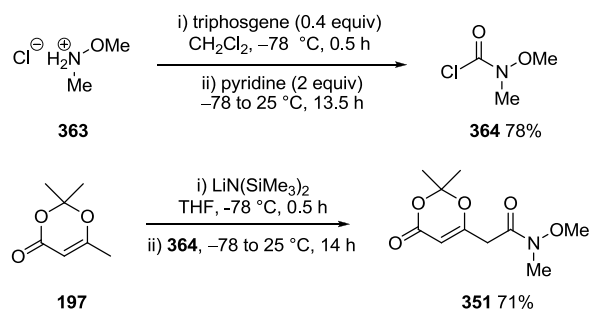
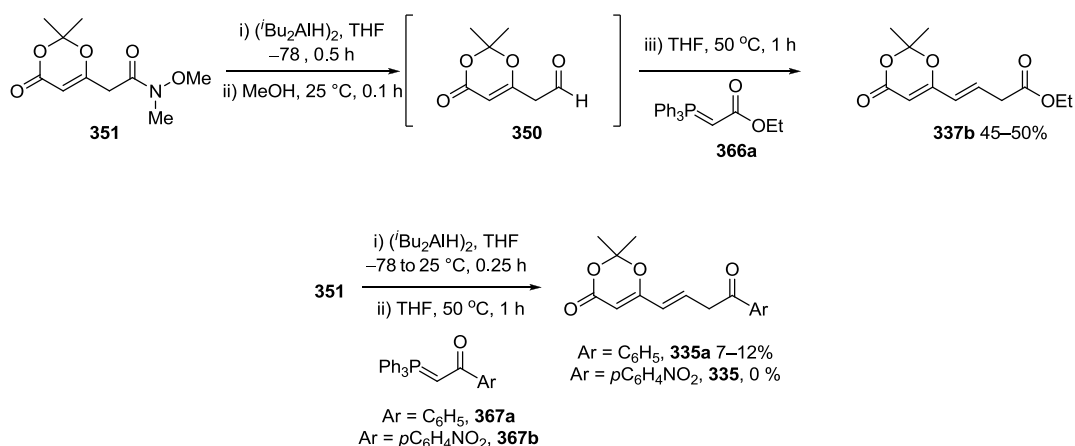**Scheme 87.** Synthesis of Weinreb amide **351**.

Weinreb amide **351** was treated with di-*iso*-butylaluminium hydride at −78 °C and then subjected to work up aided by Rochelle's salt (Scheme **88**). The main product isolated was not the desired aldehyde **350** but in fact enamine **365**. Traces of an aldehyde compound (tentatively assigned as **350**) were observed in the crude ^{1}H NMR spectrum of this reaction however this was not isolated after silica gel chromatography.[131]
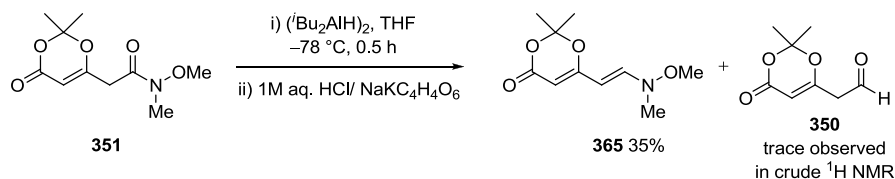
Scheme 88. Reduction of Weinreb amide **351** with (*i*Bu$_2$AlH)$_2$.

Taking into account the instability of aldehyde **350** and that it may also be consumed in formation of enamine **365**, the reduction was attempted again but in a telescoped procedure, whereby the reduction was followed immediately by Wittig reaction (Scheme **89**). A two step procedure was developed in which, after quenching the di-*iso*-butylaluminium hydride mediated reduction with methanol, the intermediate aldehyde **350** was directly subjected to Wittig reaction with a phosphorane.

In this way reaction with the phosphorane **366a** gave rise to ethyl ester **337b** in 45–50% yield. In a similar manner, keto-phosphoranes **367a** and **367b** were applied in the procedure however the ketone **355a** was only isolated in 7–12% yield and *p*-nitrophenylketone **355** was not observed at all.[132] Heating up to 80 °C for longer periods in these cases gave no improvement in yield. From the reaction mixtures the unreacted phosphorane could be mostly recovered but enamine **365** was observed in all cases as a major side product.

Scheme 89. A telescoped procedure for reduction of Weinreb amide 351 and subsequent Wittig rection to give 337b and 335a.

1.6.5 Attempted Isolatation of Aldehyde 350

Having limited charaterisation of aldehyde 350 an alternative synthesis was sought that would allow for its easy isolation and enable further reactions to be assayed. It was envisaged that a heterogeneous Fukuyama reduction would proceed under mild conditions and allow for simple isolation of aldehyde 350 by filtration.

Synthesis of the Fukuyama substrate thioester 352 began with carboxylic acid 368 (Scheme 90).[133] Addition of Ghosez's reagent to 368 was expected to form the corresponding acid chloride, and after addition of ethanethiol and pyridine the desired thioester 352 was obtained in 72%. Treatment of the thioester 352 with triethylsilane in the presence of 10 mol% palladium on charcoal gave an intermediate mixture A, the components of which were unknown. Attempted separation of this mixture by chromatography resulted in decomposition.
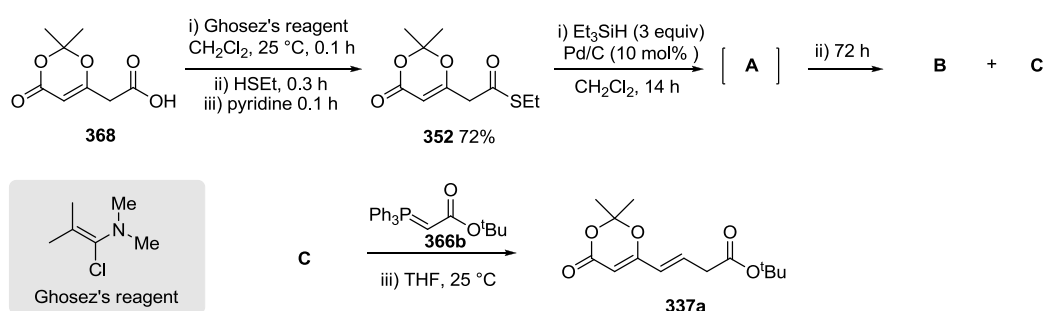
Scheme 90. Formation of thioester 352, its Fukuyama reduction and subsequent Wittig reaction.

Interestingly, when leaving **A** for several days the mixture partitioned into two separate oils **B** and **C**. The first oil **B** appears to be related to the triethylsilane. The second oil **C** however, is tentatively assigned as aldehyde **350**. Indeed, an aliquot of mixture **C** underwent reaction with phosphorane **366b** and the Wittig product **337a** was observed.
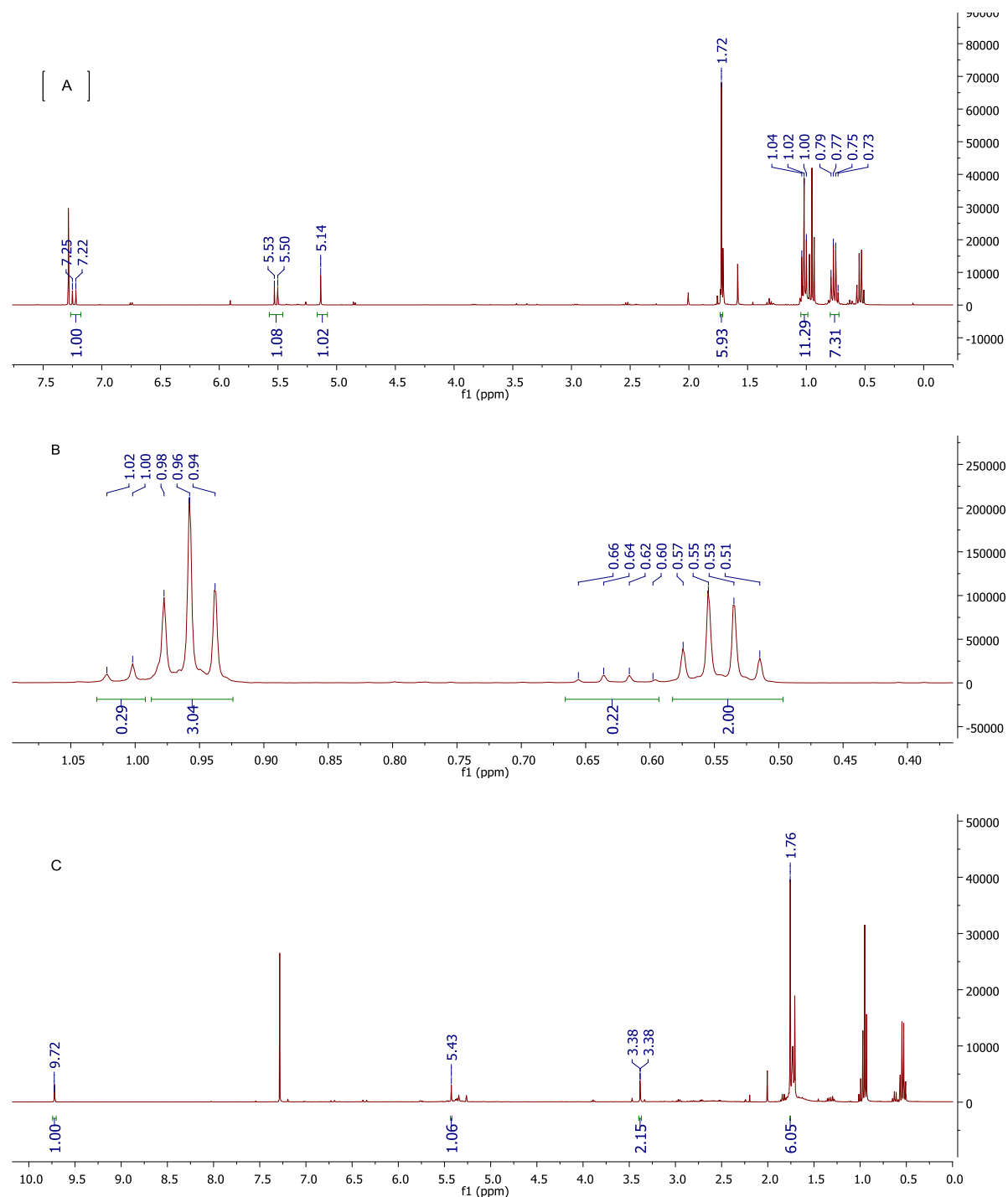
Figure 2. ^{1}H NMR spectra in CDCl$_3$ for Fukuyama reduction of thioester **352**. Top: Mixture **A**. Middle: Mixture **B**. Bottom: Mixture **C**.

Examining the ^{1}H NMR spectrum of **A** (Figure **2**; top spectrum) shows two doublets (7.23, 5.52 ppm, $J = 11.7$) indicative of a *trans* double bond. The spectrum of **B** (Figure **2**; middle spectrum) indicates the presence of two different silyl related impurities, possibly siloxanes. The spectrum of **C** (Figure **2**; bottom spectrum) appears to indicate a mixture of both the silyl impurities present in **B** and a new aldehyde compound. To explain these observations *trans*-silylenol ether **369** is proposed as a possible structure for an intermediate in mixture **A**, and **C** is proposed to be aldehyde **350** (Scheme **91**).
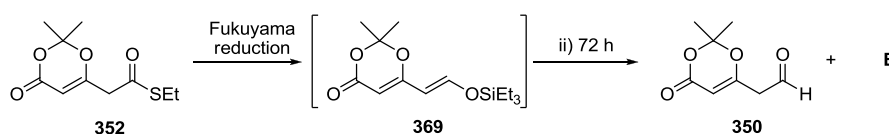

Scheme 91. Postulated intermediates formed during the Fukuyama reduction.

To determine if mixture A did in fact contain silyl enolether **369**, further derviatization of this mixture was attempted. Cookson's diene (4-phenyl-1,2,4-triazoline-3,5-dione) (**370**) is a highly reactive dienophile and is commonly used as a derivatization agent for dienes.[134] The unknown mixture A was added to the diene **370** however none of adduct **371** was detected (Scheme **92**). In a control reaction, reaction of vinyl dioxinone **372** reacted with Cookson's diene to give, after isomerization, adduct **373**.
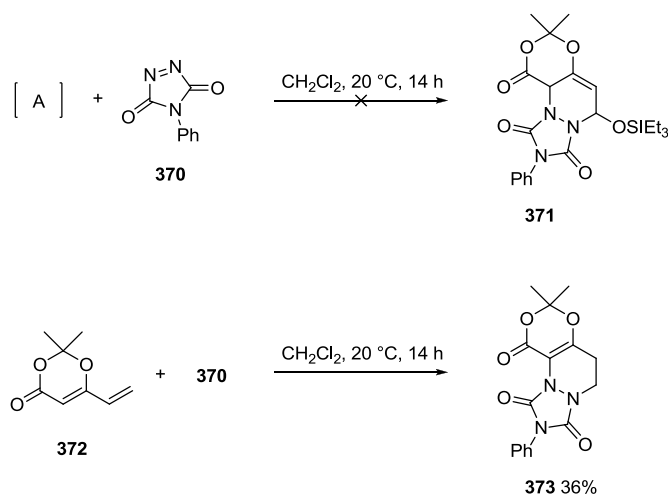
Scheme 92. Attempted derivatization of unknown A using Cookson's diene **370** and a control reaction.

1.7   Conclusion to Synthesis of Carbaldehyde **350** and Development of Route to Cyclization Substrates

After exploring several routes to **335** and **337**, use of Weinreb amide **351** in a telescoped reduction-Wittig procedure appeared to be the most viable route (Scheme **93**). The starting materials for this

reaction sequence were both stable and the Wittig reactions proceeded in moderate yields. Moreover, this route allowed an initial amount of dioxinone ester **337b** and ketone **335a** to be produced and this material was used to investigate the intramolecular aldol and Dieckmann cyclization reactions proposed in the introduction (Chapter **1**, Scheme **80** and **81**). These studies are covered in chapters **3** and **4**.
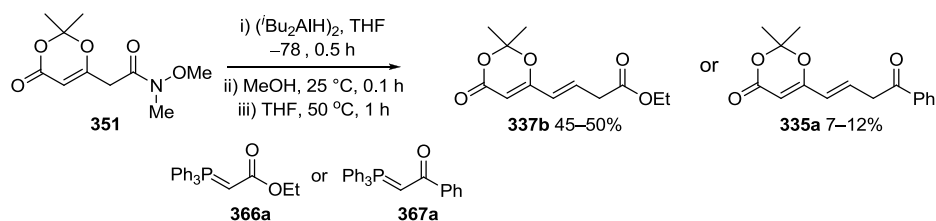
Scheme 93. Synthesis of target ester **335a** and ketone **337b**.

Synthesis of Salicylates from Dioxinone Derivatives

1.8 Introduction to Salicylic Acid Derivatives: Their Applications and Synthesis

1.8.1 Applications of Salicyclic Acid Derivatives

Salicylic acid derivatives have been used for a variety of purposes including medicine, flavouring, fragrances, cosmetics,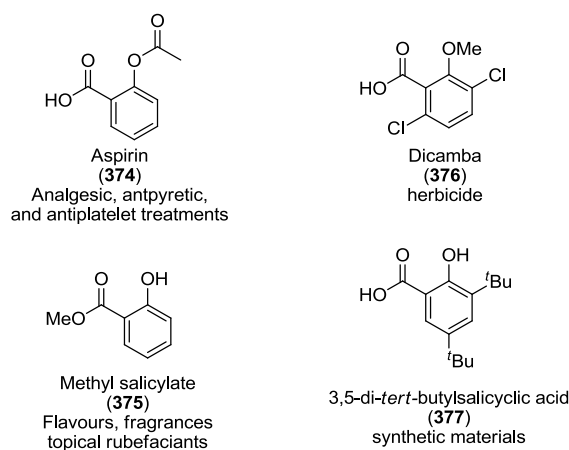 materials and agrochemicals (Figure **3**). In the simplest forms acetylsalicylic acid (aspirin, **374**) and salicylic acid have long been used for analgesic and antipyretic effects as well as prevention of myocardial infarction.[135] In fact, 40000 t is consumed each year.[136] Methyl salicylate (oil of wintergreen, (**375**) also has a long history as use in fragrance, flavours and in topical pain treatments.[135]

Aspirin
(374)
Analgesic, antpyretic,
and antiplatelet treatments

Dicamba
(376)
herbicide

Methyl salicylate
(375)
Flavours, fragrances
topical rubefaciants

3,5-di-*tert*-butylsalicyclic acid
(377)
synthetic materials

Figure 3. Simple salicylic acid derivatives and their industrial applications.

Within agrochemicals 3,6-dichloro-2-methoxybenzoic acid (Dicamba, **376**) is used widely as a herbicide to control broadleaved weeds and grassy weeds, but also has uses in fine chemicals manufacturing of chemiluminescence and color-developing agents.[137] Furthermore, 3,5-di-*tert*-butylsalicylic acid (**377**) is used in materials such as pressure sensitive recording paper and charge control additives in toner.[138]

Several natural products contain the salicyclic acid moiety within their framework and exhibit a wide range of biological activities (Figure **4**). Many of these are 6-substituted macrocyclic salicylates. Of these, Salicylihalamide A and B, Apicularen A (**378**), marinomycins A–D exhibit a range of anti-cancer activites.[139] The Marinomycins also exhibit antibacterial activity and the fungal metabolites

CJ-12,950 (**379**) and CJ-13,357 are potent inducers of the LDL recetor gene *in vitro*.[140] Other 6-substituted salicylates natural products include the long chain anacardic acid derivatives (**380**) that exhibit anti-bacterial properties and the diacetylenic natural product frutescin (**381**).[141]

(−)-Apicularen A
(**378**)
Anticancer (downregulates
tubulin synthesis)

Fungal metabolite CJ-12,950
(**379**)
Induces LDL receptor gene

Anacardic Acid and Dervatives
(**380**)
HAT and NF-κB Inhibitor
Antibacterial, Antioxidant

frutescin
(**381**)
Antibacterial and
HeLa inhibitor
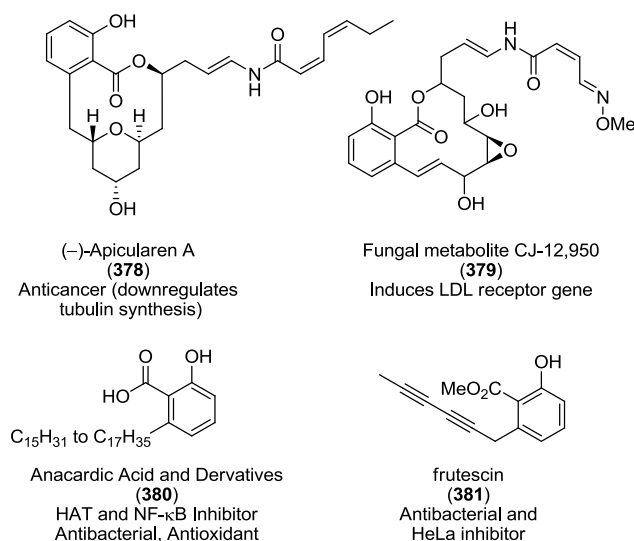
Figure 4. Some isolated natural products containing the salicylates motif and their biological activities.

1.8.2 Synthesis of Salicyclate Derivatives

Commonly synthesis of bulk salicylates is by the Kolbe-Schmitt reaction of a phenolic compounds.[142] Further modification can then be performed by esterification at the carboxylic acid or phenol groups, or *via* classical aromatic substitution chemistry. Typically syntheses of the more complex natural products detailed above are by derivatisation of aromatics often using cross coupling chemistries for introduction of the C_6 aromatic substituent.[143]

1.8.2.1   *De Novo* Sythesis of Salicylates

De novo methods for salicylate synthesis have also been examined but are less common. Oxidative cyclization of the β-keto ester **392** gave rise to methylsalicylate (**375**) (Scheme **94**).[144] Only one substrate was examined in this reaction so while the route may be generally applicable to other salicylate derivatives, further substitution of the aromatic ring was not examined.
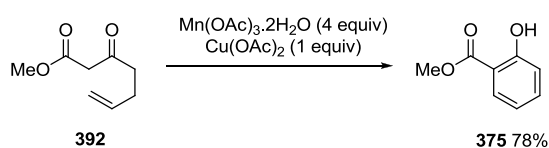
Scheme 94. Oxidative cyclization for the synthesis of methyl salicylate (**375**).

As outlined in the introduction, the reaction of 1,3-bis(silyl enol ethers) with β,β-dicarbonyl species gives rise to salicylates in a substrate controlled regioselective manner (Chapter **1**, Scheme **28**). Further to this It was found that use of 1,1-diacetylcyclopropane (**394**), in similar reaction with **393** mediated by TiX_4, gave rise to the ring opened, halogenated salicylates **395** (Scheme **95**).[145] Introduction of a substituent at R^1 did result in a significant drop in yield however a range of functionality was incorporated.

R = OMe, R^1 = H, X = Br, 80%
R = OMe, R^1 = H, X = Cl, 82%
R = Me, R^1 = H, X = Cl, 68%
R = OEt, R^1 = Et, X = Cl, 40%
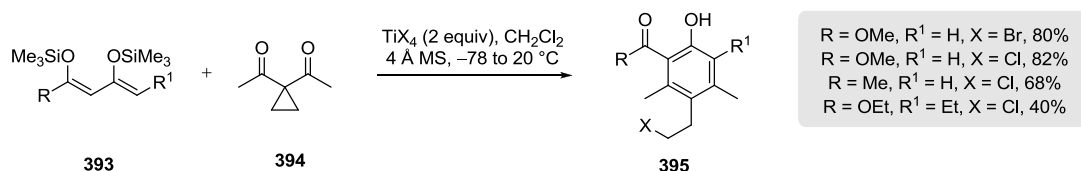
**Scheme 95.** Titanium(IV) chloride mediated [3+3] additions.

A more general approach to salicylates is the gold-catalyzed cycloaromatization of dienynes **396** to give a range of 6-substituted salicylates **131** (Scheme **96**).[146] Electron poor or rich aryl, linear or branched alkyl, alkenyl, alkynyl, and, silyl dienyne carboxylic acids underwent cyclization in 61-78% yield. A proposed mechanism for this reaction is that the gold catalyst co-ordinates to the electron rich alkyne **396** followed by *s-trans* to *s-cis* isomerization to give **II**. Intramolecular nucleophilic addition at the electrophilic carbon centre gives eight-membered ring **III**. Addition to the oxonium ion forms the bicycle **IV** which undergoes final aromatization causing opening of the four-membered ring to give the product **131** with regeneration of the catalytic species.
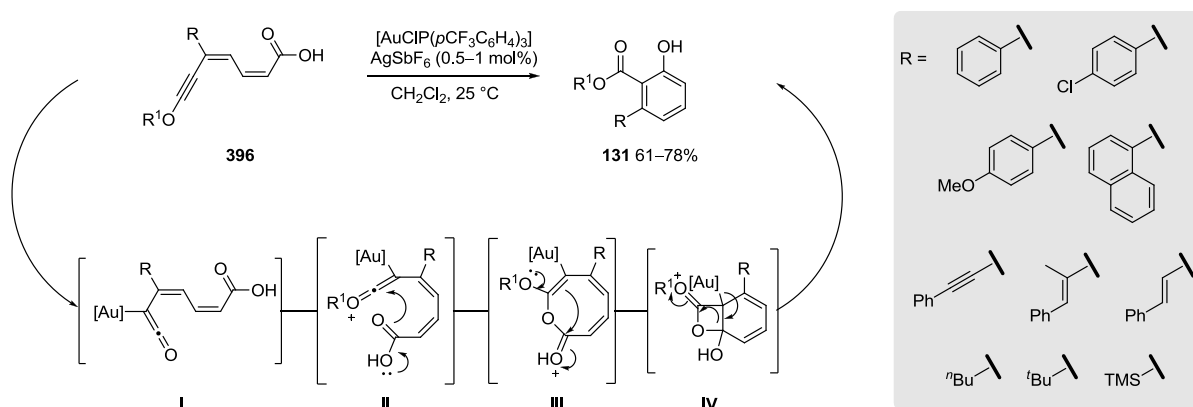
Scheme 96. Gold-catalyzed cycloaromatization of dienynes to give 6-substituted salicylates.

Intramolecular Wittig reactions have also been used for the *de novo* synthesis of salicylates (Scheme **97**). Reactions of the formyl chromones **397** *via* domino 'Michael-retro-Michael-Wittig' reactions with the phosphorane **398** resulted in 4-(2-hydroxybenzoyl) salicylate compounds **399**.[147] The domino process is proposed to involve a Michael addition of phosphorane **398** to the chromone **397**, followed by a retro-Micahel reaction opening to give **I**. An intramolecular Wittig reaction then forms the new

aromatic ring. A range of salicylates could be formed in moderate yields with substitution dependant on the availability of formyl chromones **397**.
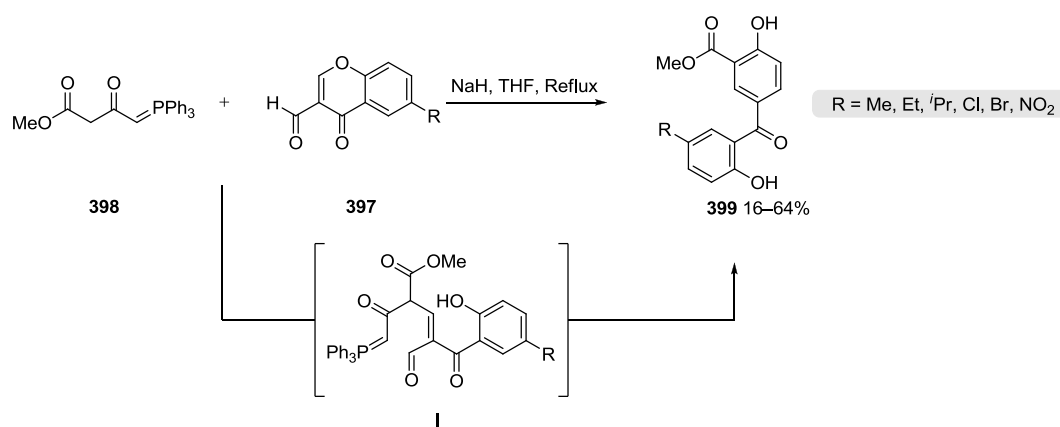
**Scheme 97.** Domino 'Michael-retro-Michael-Wittig' reactions for synthesis of 4-(2-hydroxybenzoyl) salicylate compounds **399**.

Given their prevalence in nature and the proposed biosynthesis of such aromatic compounds, some attempts of biomimetic syntheses of salicylates have been examined. These are based around reduced polycarbonyl pre-cursors and intramolecular aldol condensations. Scott found that reduction of tetraacetic lactone **195** gives the 6-acetonyl-5,6-dihydro-4-hydroxy-2-pyrone **400** (Scheme **98**).[148] Treatment of this pyrone with potassium hydroxide results in formation of a reduced trianion capable of intramolecular aldol addition and loss of water on acidification to give 6-methylsalicylic acid (**190**). In this case the substrate was limited to species that could be reduced selectively; reduction of 6-phenacyl-4-hydroxy-2-pyrone resulted in reduction of the side chain ketone preferentially to the alkene.
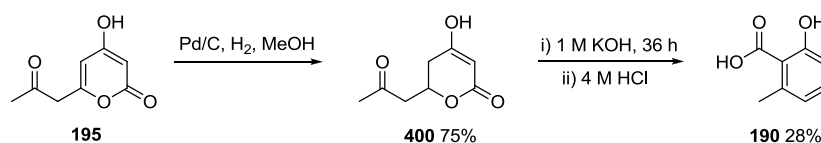
Scheme 98. Formation of methylsalicylic acid **190** from pyrone **195** reported by Scott.

In a similar vein, addition of acetoacetate dianions **401** to formylketones **402** gave partially reduced poly-carbonyls **403** capable of intramolecular aldol cyclization and dehydration to give salicylates **131** (Scheme **99**).[149] When employing formylacetone in this reaction, the more bulky *tert*-butyl acetoacetate had to be employed to prevent competing self condensation reactions.
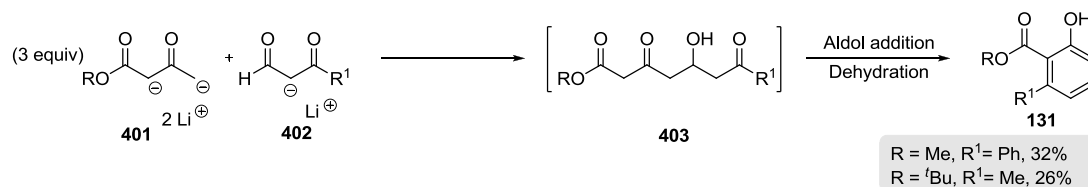
Scheme 99. Previously reported biomimetic syntheses of salicylates reported by Harris.

Bearing in mind the uses of salicylates outlined in this introduction we were encouraged to develop our initial results to provide a useful route to salicylates to incorporate a range of functional groups and to be able to develop regioselective methods for this process. Such a process would be of use to academic and industrial chemists involved in the development of new salicylate derivatives.

1.9   Results and Discussion

1.9.1 Aromatization of Ketone **335a**

As described earlier, the ketone **335a** was prepared through a telescoped reduction-Wittig procedure (Chapter **2**, Scheme **93**). With ketone **335a** in hand, formation of ester **336a** and subsequent aromatization reaction to salicylate **131b** could be explored (Scheme **100**).
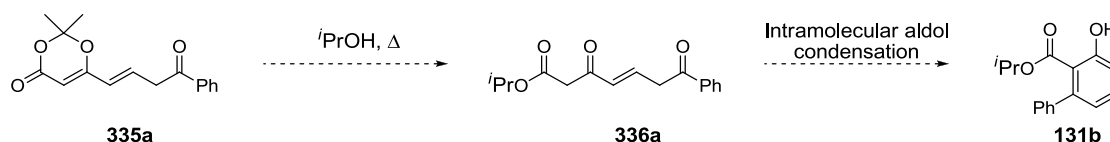
Scheme 100. The hypothesis that ketone **335a** woud undergo ester formation and intramolecular aldol condensation..

The ketone **335a** was subjected to heating at 120 °C in the presence of *iso*-propanol to give the enonic intermediate **336a** as a mixture of regioisomers and keto-enol forms (Scheme **xx**). On continued heating **336a** underwent aromatization with concomitant loss of water to give the salicylate **131b**. This initial result prompted the development of a more efficient synthetic route to ketone **335a**, as well as optimization of the aromatization reaction.
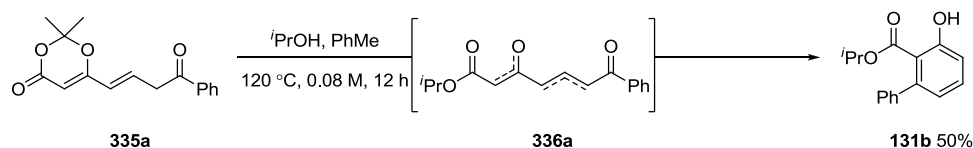
Scheme 101. Ketene trapping and aromatization of the ketone **335a**.

1.9.2 Retrosynthesis of Ketone **335a**: Proposal of a Cross Metathesis Route

The initial synthesis of ketone **335a** was a telescoped procedure consisting of reduction of a Weinreb amide and subsequent Wittig reaction (Chapter **2**, Scheme **93**). This reaction proceeded by intermediate aldehyde **350** that could not be isolated and only gave low yields of the ketone **335a**. Cross metathesis was considered as an alternative for the synthesis of ketone **335a** and also the regioisomeric ketone **404**, (which was expected to be able to form the same intermediate **336a**) (Scheme **102**).
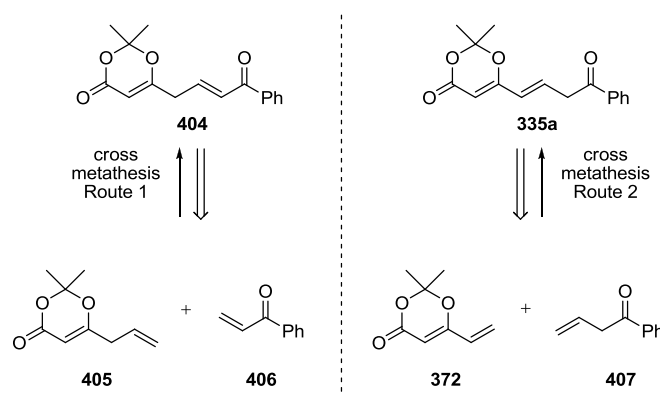

Scheme 102. Retrosynthetic analysis for the synthesis of **404** and **335a**.

The enone **404** could be produced by cross metathesis of the allylic dioxinone **405** and phenylvinyl ketone (**406**) (Route 1). Alternatively enone **335a** could be available from the known vinyl dioxinone **372** and homoallylic ketone **407** (Route 2). In developing a synthesis for the aromatization substrate, both of these possible syntheses were investigated.

1.9.3 Synthesis Towards Ketones **404** and **335a**

1.9.3.1 Synthetic Studies Towards Ketone **404** *via* Route 1

Investigations of route 1 began with attempts to synthesize novel allyl dioxinone **405** (Scheme **103**). *tert*-Butyl acetate **408** underwent Claisen condensation with ethyl but-3-enoate **409** to give the keto-ester **410**. Following literature precedent for synthesis of dioxinone derivatives, keto-ester **410** was treated with acetone, acetic anhydride and catalytic sulfuric acid however failed to give rise to the desired dioxinone **405**.[150]
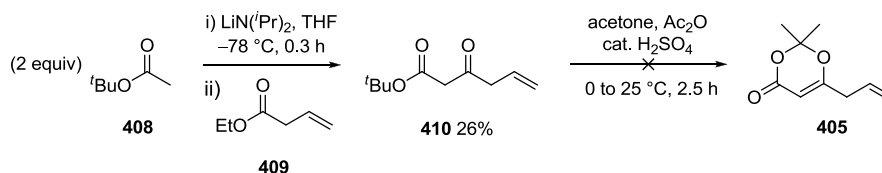
Scheme 103. Attempted synthesis of dioxinone **405** *via* condensation of acetone with **410**.

In an alternative route to dioxinone **405**, Meldrum's acid **353** was acylated with vinylacetic acid **411** which gave rise to a mixture of terminal and internal alkenes **412** and **413** (Scheme **104**). Heating of Meldrum's acid derivatives is expected to give rise to an acylketene which can then undergo cycloaddition with acetone to give dioxinones. [150,151] In this case, thermyolysis of **412** and **413** gave a complex mixture and only a small yield of isomerized dioxinone **414** could be isolated. Interestingly, protonation of the lithium enolate of **414**, generated with LiHMDS at −78 °C in THF, occurred to give a mixture of alkenes **415** and **414** (similar reaction of methyl sorbate, in the presence of HMPT or HMPA, gives solely the deconjugated product 1,3-diene [152]).
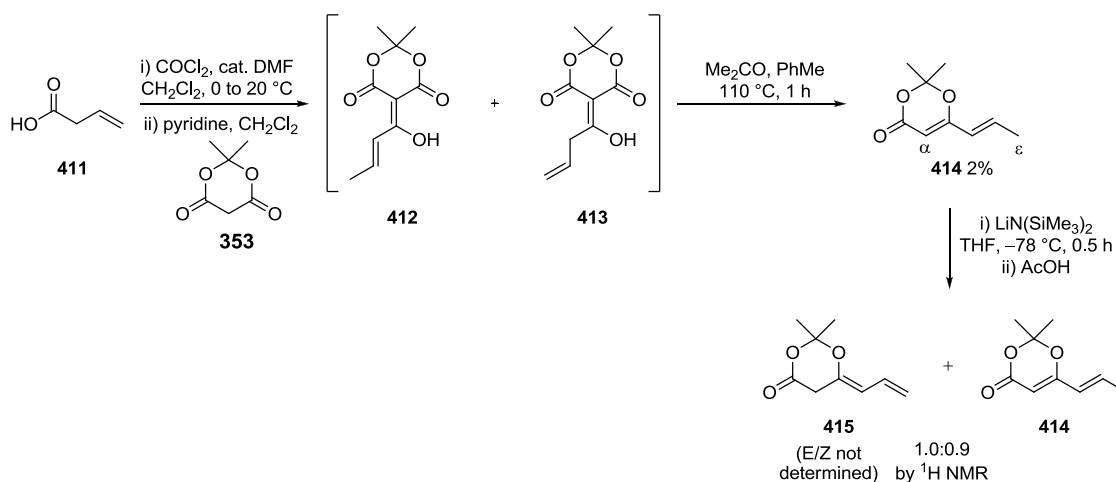
Scheme 104. Attempted synthesis of alkene **405** *via* cycloaddition of acetone to an acylketene.

As an alternative synthesis of terminal alkene **405**, use of elimination from chloro-dioxinone **418** was examined (Scheme **105**). The synthesis of **418** began with a Claisen condensation; reaction of *tert*-Butyl acetate (**408**) with ethyl 4-chlorobutanoate (**416**) gave 1,3-ketoester **417**. Treatment of **417** with acetone, acetic anhydride and catalytic sulfuric acid gave the desired chloro-dioxinone **418**.
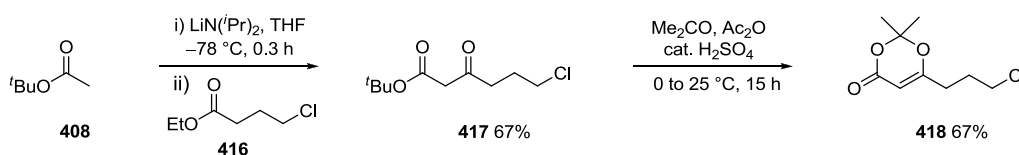
Scheme 105. Formation of the chloro-dioxinone **418**.

Treatment of **418** with triethylamine or sodium acetate gave no reaction, even on heating the mixtures for a prolonged period (Scheme **106**). Moving to a stronger sterically hindered base also proved ineffective. Treatment of **418** with potassium *tert*-butoxide resulted in formation of a cyclopropane compound **419**. With this in mind, it was clear that a more facile elimination would be required to give access to the dioxinone **405**.
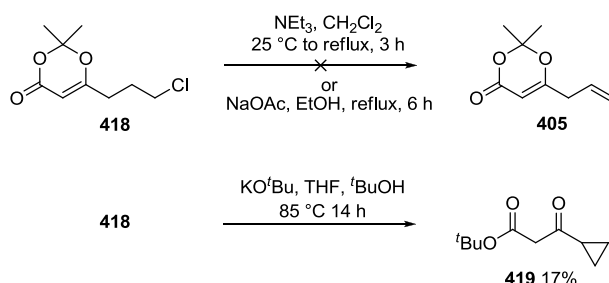

Scheme 106. Attempted synthesis of alkene **405** *via* elimination from halide **418.**

A very mild method for formation of double bonds is the elimination of selenoxides, a method that doesn't usually require addition of base and would occur at ambient temperatures.[153] To this end, the chloride **418** was treated with the lithium anion of benzeneselenol to give the selenide **420** in 72% yield (Scheme **107**). In the first instance, oxidation of the selenide **420** at −10 °C with *m*CPBA gave the selenoxide **421** that could be observed by crude ^{1}H NMR as a mixture of diasteromers contaminated with 3-chlorobenzoic acid. Warming to 40 °C resulted in elimination of the selenoxide **421** to give the desired alkene **405** in 20% yield (Table **3**, Entry **1**). The reaction was repeated without isolation of the intermediate selenoxide and gave **405** in 58% yield (Table **3**, Entry **2**). In both of these examples however, observation of starting material and other products in the crude mixtures were observed by ^{1}H NMR.
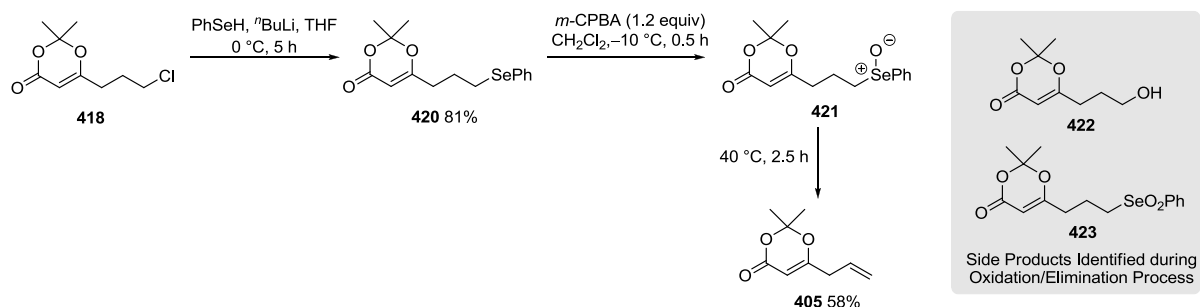
Scheme 107. Synthesis of selenide **420** and its oxidation and selenoxide elimination to give alkene **405**.

In order to improve conversion of the starting material (and oxidize the phenylselenic acid PhSeOH produced to phenyl seleninic acid, PhSeO$_2$H) increased amounts of *m*CPBA were used in subsequent trials (Table **3**, Entries **3–5**). In these entries a larger scale was used which allowed identification of some of the side products. The selenone **423** was isolated in two cases (Entries **4** and **5**) and results

from over-oxidation of the starting material, due to necessity for heating to effect the elimination. Another side product isolated was alcohol **422**, and some other unidentified impurities were observed in small amounts during this reaction.
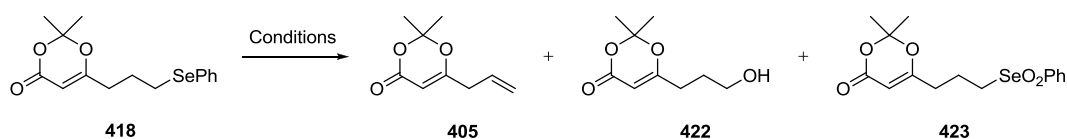
Entry[a]	Scale (mmol)	*m*CPBA	Yield of isolated Products			
			405	**422**	**423**	Selenide SM
1[b]	0.12	1	20	--	--	--
2	0.15	1.2	58	--	--	--
3	0.55	1.6	11	5	--	10
4	0.46	2	23	5	6	7
5[c]	0.46	2	28	11	14	9

a) Reaction Conditions: Oxidation with *m*-CPBA at -10 °C for 0.5 h, then reflux for 2.5 h, CH$_2$Cl$_2$. b) After elimination stirred at 25 °C and selenoxide isolated by workup, then subjected in reflux in CH$_2$Cl$_2$ to give **405**. c) vinyl acetate (10 equiv) added after oxidation step.

**Table 3.** Oxidation and elimination of selenide **420.**

The observation of side products **422** and **423** in this reaction are due to a number of factors. The *m*-chlorobenzoic acid produced in the reaction has a retarding effect on the selenoxide elimination step, and promotes electrophilic olefin addition.[154] Although not specifically observed, phenylselenic acid generated during the *syn* elimination is in equilibrium with diphenyl diselenide and phenylseleninic acid, that under the mildly acidic reaction conditions could also give rise to β-hydroxy selenides. In one case (Table **3**, entry **5**) a sacrificial alkene, vinyl acetate, was added however this didn't give a significant increase in yield.[155]

Applying the most optimal conditions (Table **3**, Entry **2**) on a 0.5 mmol scale proved to be problematical. The yields of **405** varied greatly (20–50% yield) and numerous side products in addition to **422** and **423** were encountered. As a result, adequate quantities of the alkene **405** were not available for cross metathesis reactions to be investigated. Returning to the retrosynthetic analysis (Scheme **102**), we then examined route 2.

### 1.9.3.2 Synthetic Studies Towards Ketone **335a** *via* Route 2

Towards known vinyl dioxinone **372**, Claisen condensation of *tert*-butylacetate **408** with ethyl 3-chloropropionate **424** gave *tert*-butyl 5-chloro-3-oxopentanoate **425** (Scheme **108**).[156] Condensation of

425 with acetone gave dioxinone **426** and elimination by treatment with triethylamine, according to the procedure of Blechert *et al.*, gave **372** in 73% yield over the 3 steps.[157]
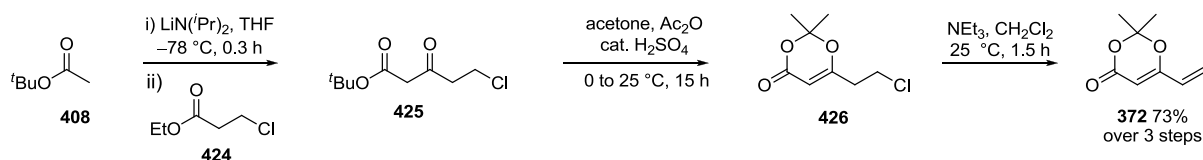
Scheme 108. Synthesis of vinyl dioxinone **372.**

Cross metathesis of vinyl dioxinone **372** with homoallylic ketone **407** (itself prepared by allyl Grignard addition to benzaldehyde followed by PCC oxidation) was then examined (Scheme **109**). In the presence of catalyst **427a** only small amounts of self-metathesis products **428** and **429** were obtained. Alternatively, cross metathesis of homoallylic alcohol **430a** with vinyl dioxinone **372**, provided the desired product **431a** in 81% yield. The cross metathesis of enones with homoallylic alcohols has been significantly developed by Donohoe *et al.* for construction of 1,5-dicarbonyls subsequently used in heterocycle synthesis.[158] Use of their conditions (Sealed Tube, CH_2Cl_2, 0.1 M, 55 °C, 18 h, Zhan-1B catalyst **432** (5 mol%)) for cross metathesis of **430a** and **372** however, gave **431a** in only 17% yield.
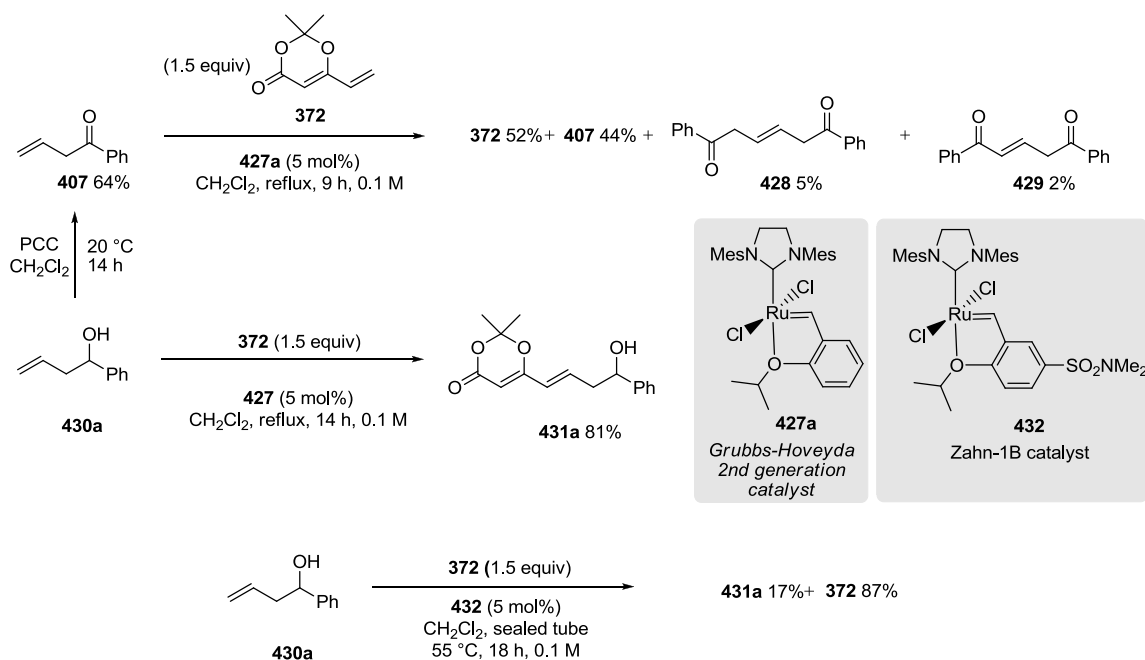

Scheme 109. Oxidation of **430a** and cross metathesis reactions of **407** and **430**.

1.9.3.3 Oxidation of the Dioxinone Alcohol 431a to Ketone 335a

The oxidation of the cross metathesis product **431a** to the ketone **335a** was then examined (Table **4**). First attempts with PCC or MnO_2 gave no reaction and after a prolonged period decomposition was observed (Table **4**, Entries **1** & **2**). Ley-Griffiths oxidation also resulted in no oxidation (a control reaction of *p*-anisyl alcohol giving full conversion to *p*-anisaldehyde) (Table **4**, Entry **3**).[159] Swern oxidation of **431a** gave a mixture of products containing ketone **335a** in 47% yield but also an intractable mixture of other products possibly due to chlorination as has been observed with aryl vinyl ketones (Table **4**, Entry **4**).[160] Modified Oppenhauer oxidation gave **335a** but it was heavily contaminated with excess 2,4-dinitrobenzaldehyde oxidant which could not be separated (Table **4**, Entry **5**).[161]

The use of IBX in DMSO for oxidation of **431a** gave over oxidation and resulted in isolation of the diketone **433a** (Table **4**, Entry **6**).[162] IBX is known to carry out α-hydroxylation of a variety of enolizable ketones.[163] Higher yields of **335a** were achieved by oxidation with IBX in EtOAc (Table **4**, Entry **7**) to give the desired compound in 67%, the reactivity of IBX tempered by its lower solubility in EtOAc.[164] The best results obtained were with use of Dess-Martin-periodinane (DMP), which at 0 °C gave **335a** in 77% yield (Table **4**, Entry **9**).[165]
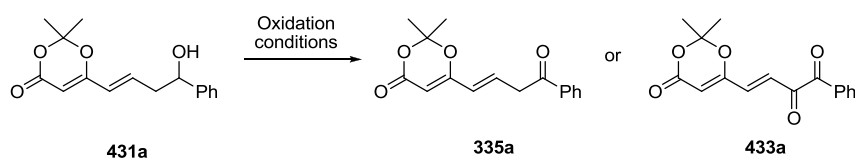

Entry	Oxidation conditions[a]	Reaction outcome: Yields (%)		
		431a	335a	433a
1	PCC, CH_2Cl_2.	100	--	--
2	MnO_2, CH_2Cl_2.	100	--	--
3	TPAP, NMO, CH_2Cl_2.	100	--	--
4	$(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 to −15 °C.	--	47[b]	--
5	$AlMe_3$ (10 mol%), 2,4-dinitrobenzaldehyde, PhMe, 3 h.	--	71[b]	--
6	IBX, DMSO, 24 h.	15	--	30
7	IBX, EtOAc, 80 °C.	--	67	--
8	DMP, CH_2Cl_2.	--	40	--
9	DMP, CH_2Cl_2, 0 °C.	--	77	--

a) Reactions performed at 25 °C unless otherwise stated. b) Yield of impure compound (see text).

Table 4. Conditions applied for the oxidation of alcohol **431a**.

## 1.9.4 Optimisation of the Aromatization Reaction of Ketone 335a

With a more efficient synthesis of ketone **335a** available, its aromatization to salicylate **131b** could then be investigated (Scheme **110**). The conversion of **335a** to **131b** can be broken down into two constituent steps: thermyolysis of dioxinone **335a** to generate a substituted acylketene and its reaction with an alcohol to give **336a**; aromatization of intermediate **336a** to salicylate **131b**.
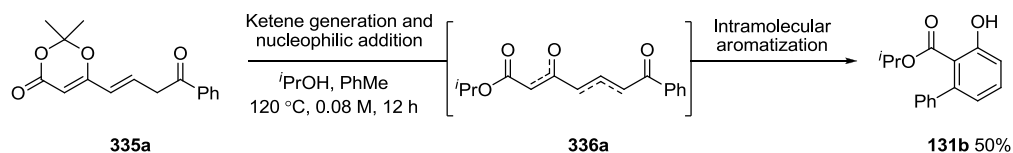
Scheme 110. Ketene generation, trapping and aromatization converting **335a** to **131b**.

We investigated the ketene generation and ester formation step first. Heating the dioxinone **335a** for 45 min, complete conversion to the enone **336a** was observed. This compound could not be isolated by chromatography however ^{1}H NMR of the crude mixture indicated good conversion in this process (Figure **5**, 2nd Spectrum).

Given that 12 h were required for complete aromatization under thermal conditions and that the ketene generation and trapping appeared complete in 45 min the addition of DABCO was considered. The use of a base would increase the rate of intramolecular aldol reaction, and DABCO may undergo conjugate addition to **336a** aiding isomerization of the double bond. Accordingly, after 45 min not only was trapping complete but aromatization had begun (Figure **5**, 3rd and 4th Spectra).
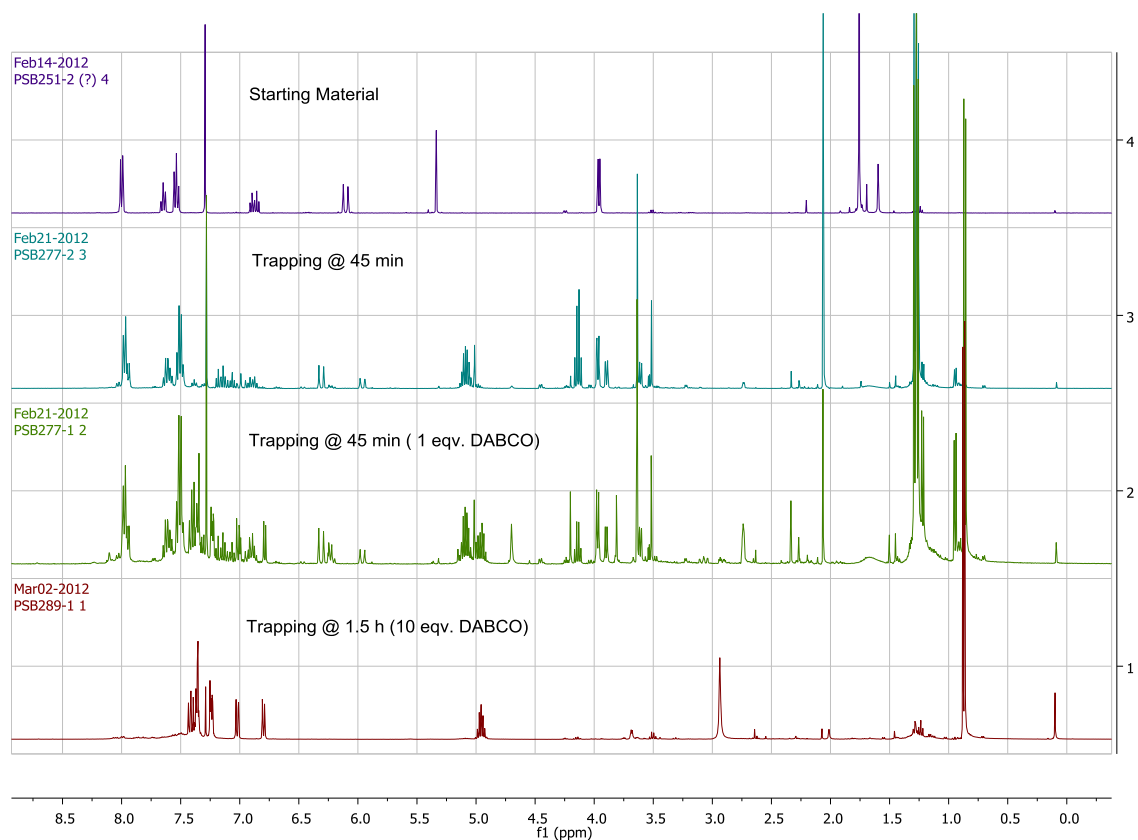
Figure 5. ^{1}H NMR spectra for converstion of **335a** to **131b**. 1st Spectrum: The starting material **335a**. 2nd Spectrum: Heating of **335a** at 120 °C for 45 min, ketene generation and trapping gave **336a**. 3rd Spectrum: Heating of **335a** at 120 °C for 45 min with DABCO (1 equiv), ketene generation and trapping gave **336a**; aromatization of **336a** has begun. 4th Spectrum) Heating of **335a** at 120 °C for 1.5 h with DABCO (10 equiv) results in full conversion to **131b**.

Following these initial observations it was unknown whether heat was required for the aromatization step or whether this could occur at room temperature. Following heating of dioxinone for 45 min the intermediate **336a** obtained was treated with Cs_2CO_3, quinuclidine or Barton's base however in each case only decomposition of the mixture was observed (Table **5**, Entries **1**, **2** & **3**). Addition of DABCO to intermediate **336a** did give some conversion to the desired product however, decomposition was also observed in this instance (Table **5**, Entry **4**). These results show that aromatization of **336a** was more efficient with heating.

90

Table 5. Attempted aromatization conditions of intermediate **336a** at 20 °C.
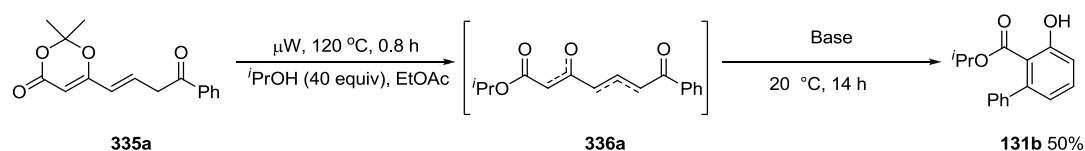
Entry	Additive	Conc., M	Time, h	Outcome
1	Cs$_2$CO$_3$	0.02	4	Decomposition
2	Quinuclidine	0.04	14	Decomposition
3	Barton's Base	0.04	14	Decomposition
4	DABCO	0.02	4	Trace **131b** with decomposition

In order to improve the yield of the ketene trapping/aromatization process a range of conditions were trialed for conversion of **335a** to **131b** (Table **6**). To repeat the earlier aromatization result the ketone **335a** was heated conventially for 26 h in toluene which gave **131b** in 53 % (Table **6**, Entry **1**). Addition of DABCO (10 eqv.) gave **131b** in 55% yield after 1.5 hours (Table **6**, Entry **2**). Similarly, **131b** was obtained in 47% with just 1 equivalent of DABCO, and prolonged heating gave no significant increase in yield (Table **6**, Entries **3** and **4**). Molecular sieves seem to impart little effect on the outcome and would prevent interference from any adventitious water (Table **6**, Entry **5**). Also, the presence of DABCO during the trapping had no effect on the overall yield (Table **6**, Entry **6**). The control experiment without any additional base gave only 14% of **131b** in 8 h and, given that trapping is complete within 45 min, it is clear DABCO has an accelerating effect on the aromatization process converting **336b** to **131b** (Table **6**, Entry **7**).

Other methods investigated for the aromatization reaction of **335a** involved a sealed tube method which gave **131b** in 28% yield (Table **6**, Entry **8**). Use of acetic acid as an additive gave **131b** in only 21% yield, a pyrone side product was also observed by ^{1}H NMR spectroscopy of the crude mixture (Table **6**, Entry **9**).
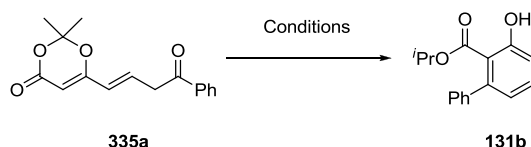
Entry	Additive (equiv)	Solvent	Conc., M	Temperature (method)	Time, h	Yield of **131b**, %
1	-	PhMe	0.08	120[b]	26	53
2	DABCO (10)	EtOAc	0.05	120 (μW)	1.5	55
3	DABCO (1)	EtOAc	0.05	120 (μW)	2	47
4	DABCO (1	EtOAc	0.05	120 (μW)	8	51
5	DABCO (10), 4 Å MS	EtOAc	0.03	120 (μW)	1.5	48
6[c]	DABCO (10)	EtOAc	0.01	120 (μW)	2.25	49
7	-	EtOAc	0.05	120 (μW)	8	14
8	4 Å MS	CH_2Cl_2	0.02	120 (sealed tube)	21	28
9	Acetic Acid (10)	PhMe	0.025	125 (sealed tube)	1.5	21

a) ^{i}PrOH (40 equiv) used in all Experiments b) Conventional reflux c) DABCO added after the ketene trapping was complete (45 min), and reaction heated for a further 1.5 h; purified by loading mixture directly onto silica.

Table 6. Conditions investigated for aromatization of **335a** to salicylates **131b**.

As discussed in the introduction, diketo-dioxinones underwent aromatization under basic conditions to give the corresponding benzodioxinones in high yield. In contrast to this, treatment of the reduced compound **335a** with triethylamine, Hunig's base or 5 M HCl resulted only in decomposition (Table **7**). This could be due to the *trans* geometry of the double bond preventing the required intramolecular aldol reaction.
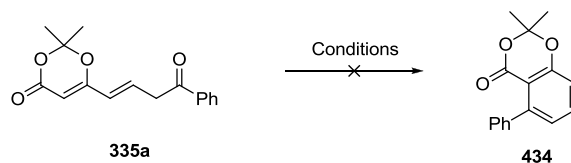
Entry	Reagent[a]	Solvent	Conc., M	Temperature	Time (h)	Outcome
14	NEt₃	DCM	0.1	25	14	Decomposition
15	AcOH	DCM	0.1	25	14	**335a**
16	DIPEA	DCM	0.05	25	4.5	**335a**
17	DIPEA	DCM	0.05	25	48	Decomposition
18	5M HCl	MeOAc	0.02	25	18	Decompoition
19	NH₄OAc	EtOH	0.25	45	14	Decomposition

a) Excess reagent used.

Table 7. Conditions attempted for the aromatization of **335a** to benzodioxinone **434**.

1.9.5 Aromatization of Further Substrates with Optimised Conditions

Having developed a synthetic route to the enone **335a** and optimized conditions for its aromatization to give salicylate **131b** the reaction was extended to incorporate a range of alkyl and aryl substituents (Scheme **111**). The homoallylic alcohols **430a–k** were prepared according to the literature by Grignard addition to the corresponding aldehydes. Cross metathesis of the homoallylic alcohols **430a–k** with vinyl dioxinone **372a** gave **431a–j** in 55–88% yields. In some cases an increased amount of catalyst (10 vs. 5 mol%) **427a** and vinyl dioxinone **372a** (2 vs. 1.5 equiv) was used which gave a significant increase in yield in the cross metathesis step (86 vs. 26% for furan **431a**). In these cases, self-metathesis of vinyl dioxinone **372a** was also observed but this was less than 10%. The pyridine containing alcohol **430k** failed to undergo cross metathesis under these conditions, probably due to the coordinating ability of the nitrogen lone pair.[166]

Initially the oxidation of **431a–j** to give the enones **355a–j** was investigated using the 2 best sets of conditions developed (Table **4**, Entries **7** and **9**). Comparing the oxidation of **431a–f**, yields of **335a–f** were 10–31% higher using DMP and so this oxidant was used in subsequent oxidations of **431g–i**. In the case of furan **431f** the yield for oxidation was slightly lower compared to other substrates which may have been due to butenolide formation from over-oxidation.

Aromatization of the ketones **335a–j** under the newly developed conditions gave rise to a range of 6-alkyl/aryl salicylates **131b–j** in 46–67% yield. Of note, is that the nature of the *para*-substituent on the aryl unit (R) had little effect on the aromatization yield with both electron donating (**335e**) and electron withdrawing groups (**335b**) undergoing aromatization with comparable efficiency. However, the yield of the aromatization was influenced by steric factors. The least sterically hindered ketone **335g** underwent aromatization in highest yield. Consistent with this is the observation that sterically hindered mesityl compound **335j** failed to undergo aromatization.
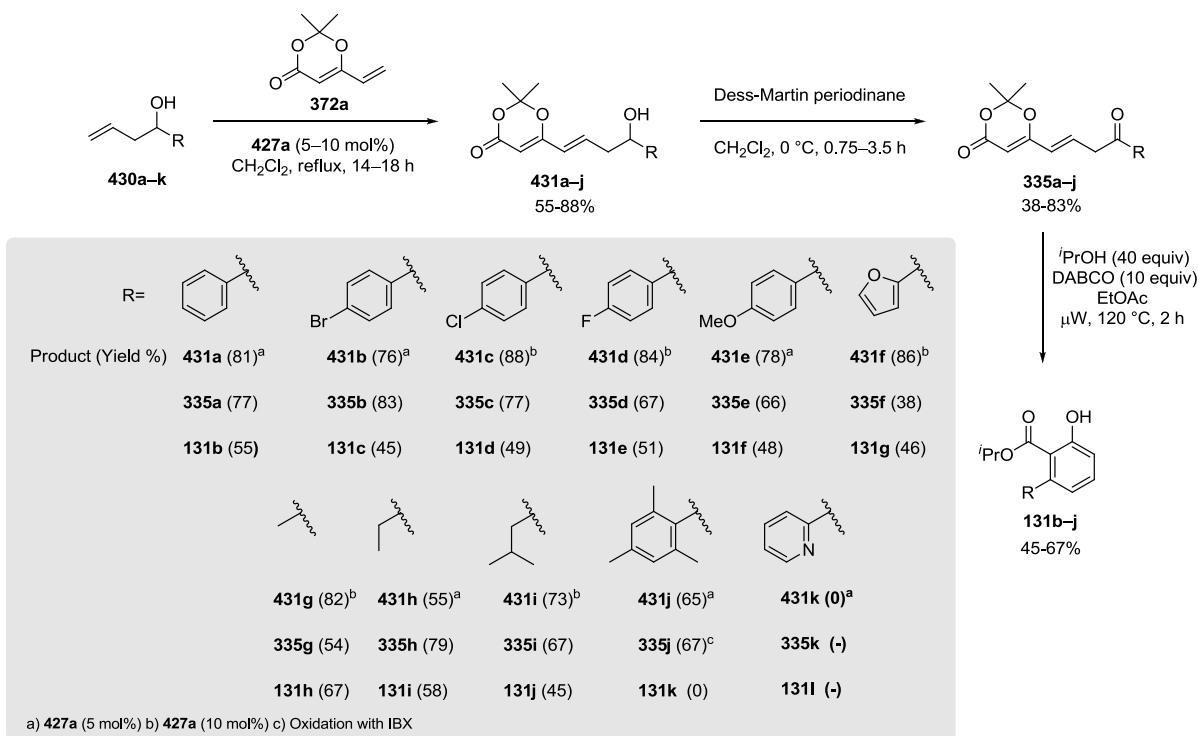
Scheme 111. Overall route to salicylates **131b–j**.

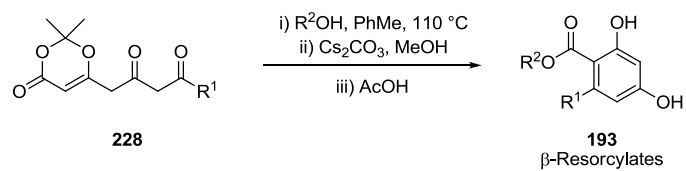# 1.10 Conclusion to Synthesis of Salicylates from Dioxinone Derivatives

A novel route to synthesize 6-aryl and alkyl salicylates has been developed (Scheme **111**). Cross metathesis of vinyl dioxinone **372a** with homoallylic alcohols **430a–k** gave dioxinone derivatives **431a–j**. Oxidation of **431a–j** was explored by a number of methods and DMP was the optimal oxidant. The ketene generation and trapping of the resultant enedione ketenes from **335a–j**, and their aromatization to salicylates **131b–j**, was investigated under several reaction conditions using **335a**. The use of DABCO as a catalyst provided a significant rate enhancement to the aromatization reaction.

The hypothesis made in the introduction was correct; the reduced compounds **355** underwent ketene generation, trapping and aromatization to give the salicylate products **131** (Scheme **112**). The reaction provides a novel route to the functionalized salicylates and an addition to the synthetic chemists armory. Furthemore, this work compliments the previously developed methodology for β-resorcylate synthesis, giving the 4-deshydroxy compounds.

This Work

355a–j

^{i}PrOH (40 equiv)
DABCO (10 equiv)

EtOAc
μW, 120 °C, 2 h

131b–j
Salicylates
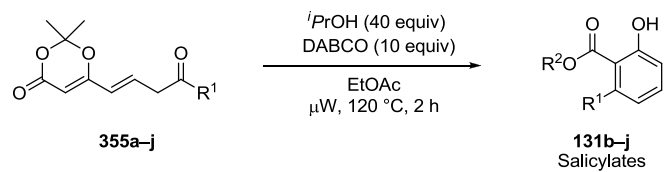
Previous methodology
of Barrett *et al*.

228

i) R^{2}OH, PhMe, 110 °C
ii) Cs$_2$CO$_3$, MeOH

iii) AcOH

193
β-Resorcylates

Scheme 112. Comparison of the reaction for salicylate formation to the previously developed reaction for β-resorcylates.

Synthesis of γ-Resorcylates from Dioxinone Derivatives

1.11 Introduction to γ-Resorcylic Acid Derivatives: Their Applications and Synthesis

1.11.1 Applications of γ-Resorcylic Acid Derivatives

γ-Resorcylic acid (**435**) (2,6-hydroxybenzoic acid) derivatives occur widely in nature and in man-made materials, exhibiting a wide range of uses in disparate fields. In the simplest form, the parent γ-resorcylic acid (**435**) and 3,5-di-*tert*-butyl-γ-resorcylic acid (**436**) have been used for forming complexes through the carboxylate anion coordination to lanthanide cations (Figure **6**).[167] As well as providing binding information on the novel complexes synthesized, they exhibited very high luminescence which could be useful in new luminescent materials or optical sensors. Furthermore, 3,5-Di-*tert*-butyl-γ-resorcylic acid (**436**) and its ester derivatives have shown effectiveness against platelet aggregation and atherosclerosis.[168]
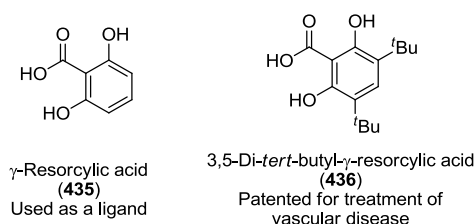

Figure 6. Applications of γ-resorcylic acid (**435**) and 3,5-di-*tert*-butyl-γ-resorcylic acid (**436**).

In biological applications, the γ-resorcylic anilides **437** are known as anthelmintics and the antibiotic methicillin **438** contains an important methylated resorcylic anilide that reduces affinity for β-lactamases (Figure **7**).[169] The hydroxamic derivatives **439** have been used for their acaricidal and mite ovicidal activity against citrus red mite, desert spider mite and european red mite.[170]
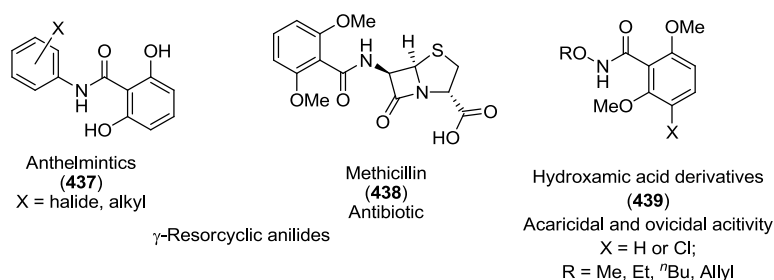

Figure 7. Biological applications of γ-resorcylic anilides **437** and **438**, and hydroxamic derivatives **439**.

Applied in polymer manufacturing, azo and disazo γ-resorcylic acids (**440** and **441**) were found to be excellent dyes and stabilizers for polypropylene and other thermoplastic resins, exhibiting excellent brilliance, and fastness to light and cleaning (Figure **8**).[171] A range of aromatic substituents on the azo side chains and γ-resorcylic acid core conferred different colours in the resultant dyes.

440

441

Azo and disazo
resorcyclic acid dyes
X^1 = H or Br, X = Halogen, NO_2, CF_3,
alkyl, alkoxy; Y = alkyl, alkoxy, Cl

Figure 8. Application of γ-resorcylic derivatives as dyes.

Furthermore, the γ-resorcylate moiety appears in several natural products that exhibit interesting biological activities (Figure **9**). The naturally occurring penicillide (**442**) and derivatives thereof show biological activity including inhibition of cholesterol ester transfer protein (CETP) and, oxytocin antagonism.[172] (–)-Berkelic acid (**443**) shows activity towards an aggressive ovarian cancer cell line OVCAR-3.[173]

Penicillide
(**442**)
Inhibition of CETP and
oxytonin antagonism

(–)-Berkelic acid
(**443**)
Activity towards ovarian
cancel cell line OVCAR-3

Figure 9. Naturally occurring γ-resorcylate containing compounds and their biological targets.

1.11.2 *De Novo* Synthesis of γ-Resorcylates

The synthesis of resorcinol derivatives from resorcinol (1,3-dihydroxybenzene) can be problematical and so *de novo* syntheses may be used as alternatives.[174] *De novo* synthesis of γ-resorcylate products is uncommon in the literature, but one example is from the work of Doyle *et al*. (Scheme **113**).

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Enedione-diazoester **444** undergoes aromatization on treatment with sub-stoichiometric amounts of sodium hydroxide to give mono-substituted γ-resorcylate **142b**. The reaction is postulated to proceed by first deprotonation of **44** then isomerization of the double bond to give **I**. A second isomerization is then followed by electrocyclic ring closure to give **III**. Subsequent loss of dinitrogen and a 1,2-methyl shift, followed by protonation and enolization gives the product **142b**.[175]
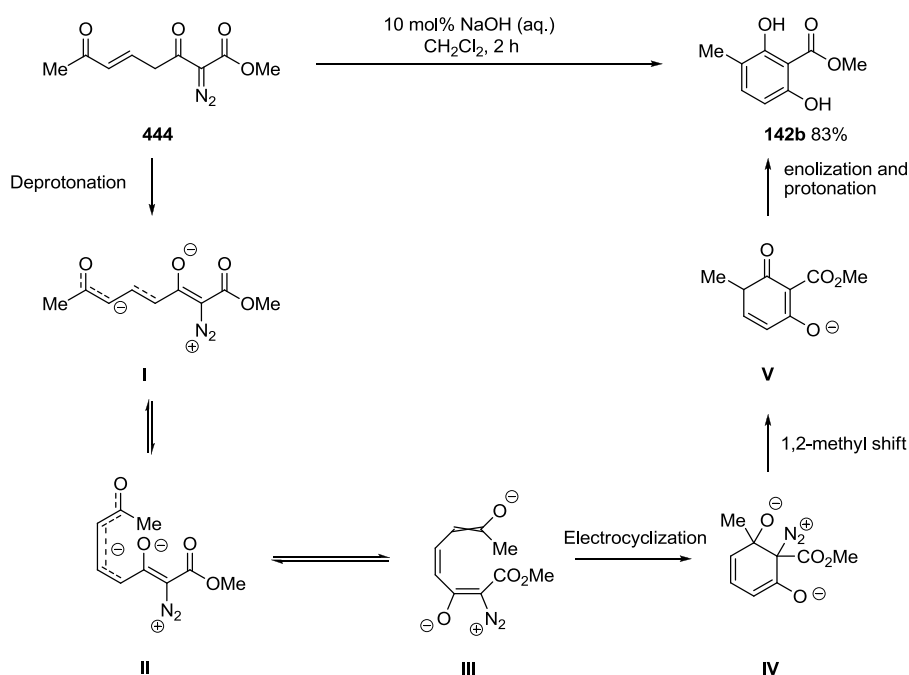
Scheme 113. Postulated mechanism for the aromatization of enedione-diazoesters as proposed by Doyle *et al.*

The reaction occurred at lower yields when more bulky esters were employed: an *iso*-propyl ester and *tert*-butyl ester gave the corresponding γ-resorcylates in 59% and 54%. The synthesis of the substrate and aromatization were combined into a one pot reaction (Scheme **114**). Here, the authors increased the scope of the methodology by intercepting the equivalent first anion **I** with a suitable Michael acceptor, such as β-nitro styrene, and were able to incorporate a variety of aromatic groups in this fashion.
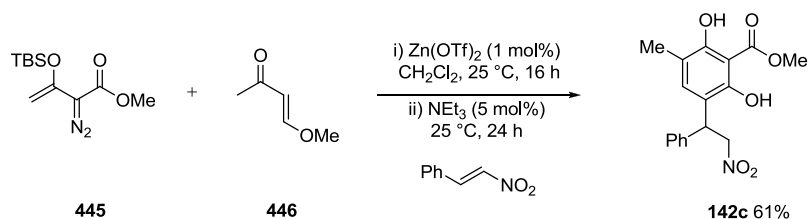
Scheme 114. One pot synthesis of γ-resorcylate **142c** including formation of a enedione-diazoester followed by addition to a Michael acceptor and aromatization.

Recent research within the Barrett research program outlined in the main introduction has been aimed at the synthesis of functionalized β-resorcylate derivatives, using diketo-dioxinones. Given the utility

of this chemistry, development of similar methods might also allow versatile and useful routes to regioisomeric γ-resorcylate products. Given the wide application of γ-resorcylates outlined, new methods for their synthesis would be of value to the synthetic chemistry community.

## 1.12 Investigation of Aromatization Reactions for the Synthesis of γ-Resorcylates

Using the route developed (chapter **2**) allowed the synthesis of **337b** (Scheme **115**). The generation of an acylketene intermediate from **337b** and ester formation to give triketone **338b** would be investigated. This triketone **338b** could subsequently be used in the proposed Dieckmann cyclization to give γ-resorcylates **142d**.
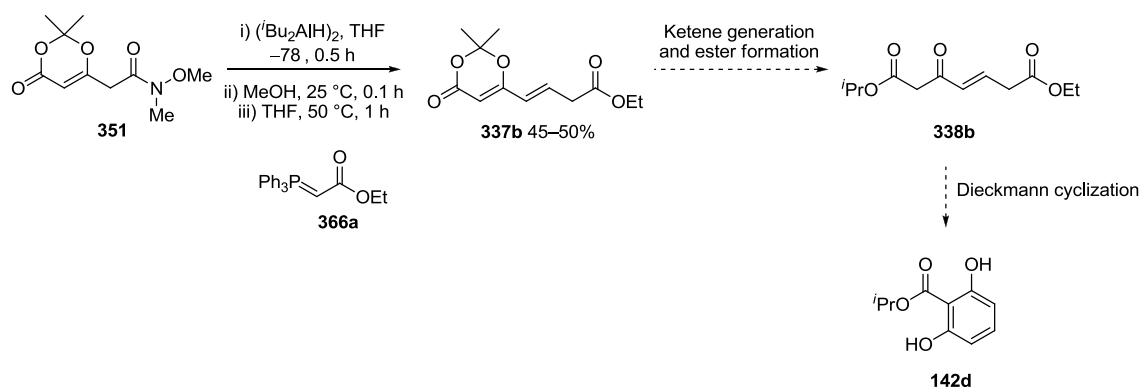
Scheme 115. Synthesis of ester **337b** and proposed Dieckmann cyclization.

1.12.1 Synthesis and Investigation into the Dieckmann Cyclisation of 5-Oxoheptenedioates

Heating of dioxinone **337b** in the presence of *iso*-propanol gave triketo compound **338b** as a mixture of *trans* regioisomers, and keto-enol forms (Scheme **116**). Dieckmann cyclisation of **338b** to give γ-resorcylate **142d** was then attempted using numerous bases. It was found that caesium carbonate and potassium *tert*-butoxide resulted in no formation of the desired product and only decomposition of the starting material was observed. When **338b** was treated with tertiary amines triethylamine, DIPEA, DABCO and DBU degradation of the starting material was observed and no desired product could be isolated. Cyclisation of **338b** was also attempted in 2 M aqueous potassium hydroxide; however, no aromatic products could be detected by NMR, only saponification of one or both esters.
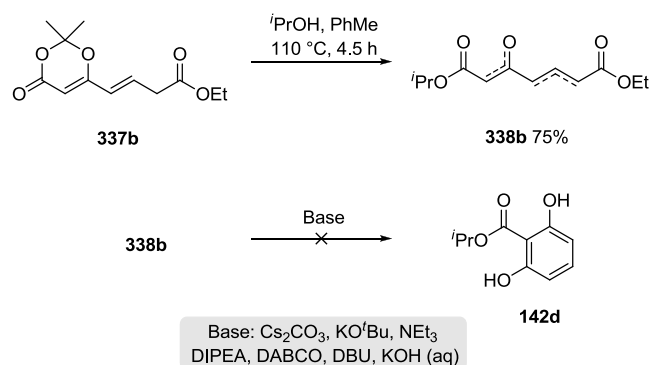
Scheme 116. Synthesis of diester **338b** and attempted Dieckmann cyclization with various bases.

Two reasons for the failure of the Dieckmann cyclization of **338b** were postulated. Firstly, the enoate in the cyclization was not electrophilic enough for the reaction to progress. Secondly, the double bond *E* geometry could prevent the intramolecular Claisen reaction.

Given the possibility that the double bond geometry could hinder the cyclization, Hunter isomerization of **338b** under basic catalytic conditions was attempted in order to induce isomerisation and aromatization (Scheme **117**). [176] However, the sulphide addition to the double bond was irreversible and only phenyl sulphide **447** was obtained. [177] Reaction of phenylsulphide **447** with potassium *tert*-butoxide in THF/*tert*-butanol resulted in liberation of thiophenol but no aromatic product **142d** was isolated.
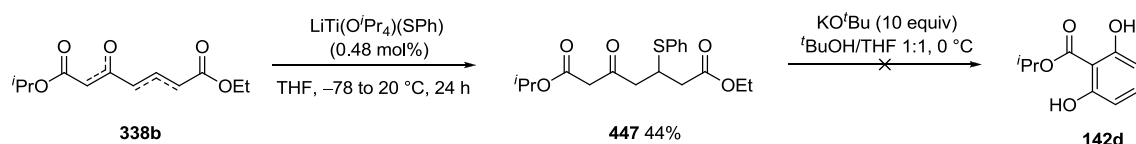
Scheme 117. Attempted Hunter isomerisation of **338b** to afford thioether **447** and subsequent attempted Dieckmann cyclization.

To increase the electrophilicity of the Dieckmann substrate **338**, a synthesis of phenyl ester **338c** was attempted (Scheme **118**). Reduction of Weinreb amide **351**, quenching with methanol and, Wittig reaction with phosphorane **366c** gave a mixture of phenyl and methyl esters **337c–d** in 33% combined yield. Heating this mixture with *iso*-propanol resulted formation of the *iso*-propyl diesters **338c–d** and, pyrone **448** although these could not be fully purified. Interestingly formation of the pyrone **448** shows that the diester **338c** is able to undergo an intramolecular acylation reaction. However, it also shows that in this case, O-acylation is favorable over the desired C-acylation.
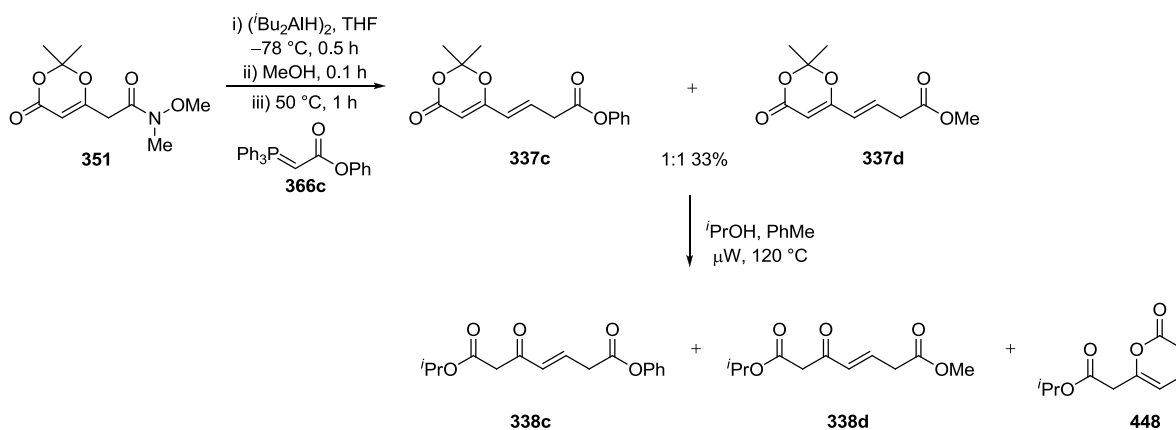
**Scheme 118.** Synthesis of phenyl ester **337c** and attempted trapping resulting in formation of pyrone **448**.

1.12.2 Synthesis and Investigation into the Dieckmann cyclisation of 3-hydroxy-5-oxoheptanedioates (**450**)

While investigating the 5-oxoheptenedioates (**338**) above, the use of more flexible β-hydroxy-esters **450** were investigated as alternative substrates for the synthesis of γ-resorcylates (Scheme **119**). The β-hydroxy-ester **450** would be available by thermyolysis of dioxinone **449**.
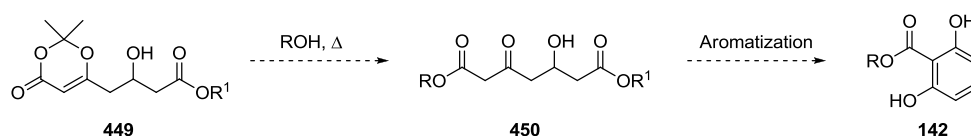
Scheme 119. 3-hydroxy-5-oxoheptanedioate **450** as a possible aromatization substrate.

The benzyl ester **449a** was chosen as the first substrate; this would allow its facile removal should the free carboxylic acid be required for future strategies (Scheme **120**). The synthesis of **449a** began with addition of the lithium enolate of dioxinone **197** to acid chloride **236b** which gave keto-ester **237g** in 42% yield. The ketone could then be selectively reduced to give the β-hydroxy ester **449a**.
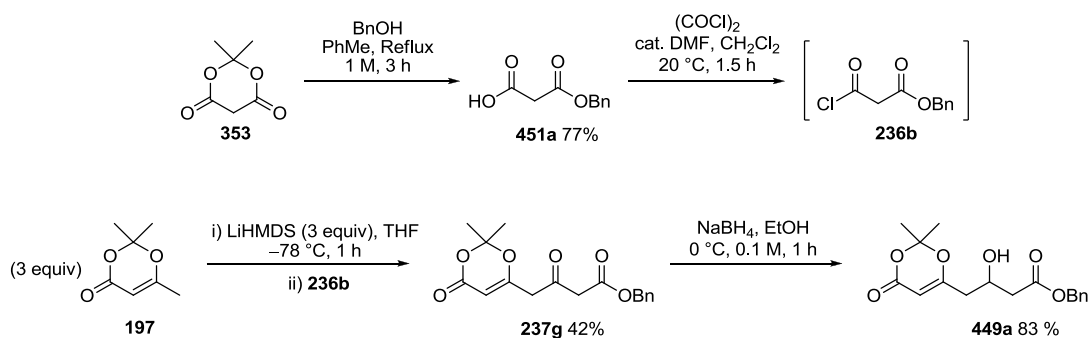
Scheme 120. Synthesis of β-hydroxy ester **449a**.

Upon heating, dioxinone **449a** underwent reaction with *iso*-propanol to give the desired di-ester **450a** and Dieckmann cyclization of this substrate was examined (Scheme **121**). Various conditions were investigated for conversion of β-hydroxy ester **450a** to resorcylate **142d**. Treatment with potassium *tert*-butoxide resulted in partial hydrolysis of the benzyl ester. The use of a milder procedure involving TBAF (as has previously been employed in Lacey-Deickmann reactions for acyltetronic acid synthesis), or Barton's guanidine base resulted in no reaction and recovery of starting material.[178]
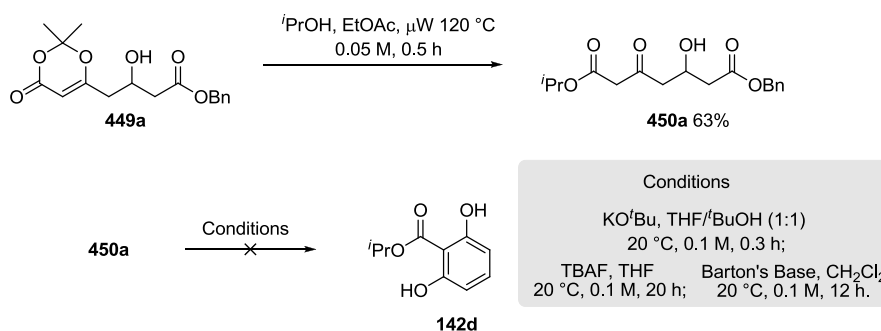
Scheme 121. Synthesis of the diester **450a** and subsequent attempted Dieckmann cyclization reactions.

As the β-hydroxy ester **450a** had failed to undergo aromatization to γ-resorcylate **142d**, conversion of the hydroxy functionality into a better leaving group was examined. Attempted mesylation of **449a** resulted in no reaction however it could be converted to its silyl ether **452** (Scheme **122**).
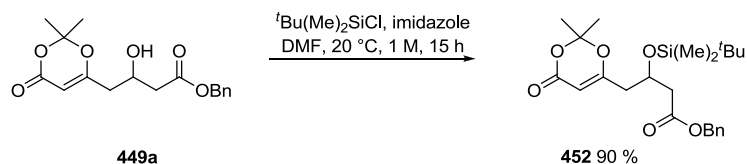
Scheme 122. Synthesis of silyl ether **452**.

The silyl ether **452** was heated in the presence of *iso*-propanol to give the diester **453** (Scheme **123**). Once again various conditions were tested for the desired Dieckmann cyclization. Treatment with NaN(SiMe$_3$)$_2$ or with LiN(SiMe$_3$)$_2$ at 20 °C resulted in no reaction. On heating with LiN(SiMe$_3$)$_2$ or reaction with potassium *tert*-butoxide, elimination of the silyl ether was observed but none of γ-resorcylate **142d** was obtained.
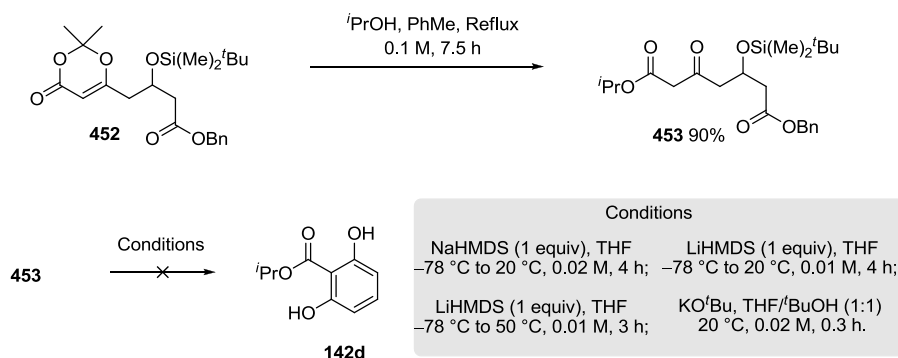
Scheme 123. Synthesis of the diester **453** and subsequent attempted Dieckmann cyclization reactions.

# 1.12.3 Intramolecular Acylation Reactions of Dioxinone-Esters for γ-Resorcylate Synthesis

Having explored Dieckmann cyclization of diesters for synthesis of γ-resorcylates to no avail, further activation of the substrates towards intramolecular acylation was required. The O-cyclization of phenyl ester **338c** to pyrone **448** (Scheme **118**) showed that introducing a phenyl ester sufficiently increased the electrophilicity of the carbonyl group to activate it towards intramolecular acylation. With this in mind, use of an acid chloride as an activated carbonyl species was then considered (Scheme **124**).

Hydrogenolysis of benzyl ester **453** gave the acid **454**. The acid **454** was then treated with Ghosez's reagent followed by 2,4,6-collidine resulting in formation of lactone **455**. The preferred pathway for reaction was again O-acylation.
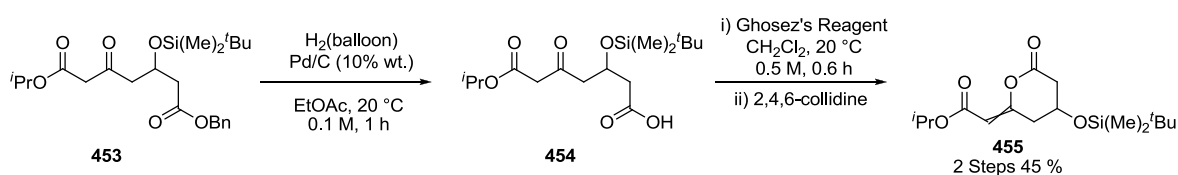
Scheme 124. Synthesis of carboxylic acid **454** and its conversion to lactone **455**.

In order to prevent O-acylation during the reaction a different starting material was chosen. Keeping the dioxinone fragment in place would prevent O-acylation leaving C-acylation as the only option. Thus, the keto-ester **449a** was subjected to hydrogenolysis to give β-hydroxy acid **456** (Scheme **125**). The hydroxyl functionality was left unprotected in order to allow for dehydration with Burgess reagent during the reaction.
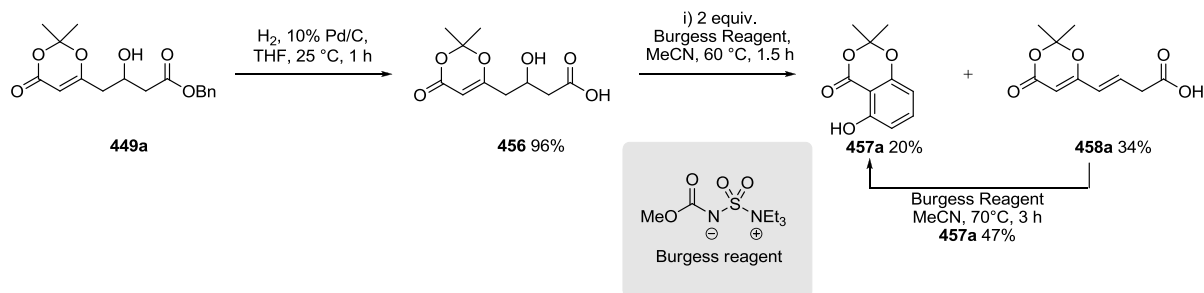
Scheme 125. Synthesis of β-hydroxy acid **456** and its aromatization reaction with Burgess reagent to give γ-resorcylate **457a.**

Accordingly, reaction of **456** with Burgess reagent gave the aromatized product **457a** in 20 % yield in addition to 34% of dehydrated acid **458a**. Treatment of the acid **458a** with more Burgess reagent also gave **457a**. In the conversion of β-hydroxy acid **456** to **457a** the order of the two dehydration events is not known. However, reaction of silyl ether **459** with Burgess reagent gave bisamide **460** in 77% yield (Scheme **126**). This suggests that in the above reaction (Scheme **125**, **456** to **457a**) the hydroxy group of **456** is first dehydrated to give **458a**, which once activated (as a ketene or sulfonamide), reacts in an intramolecular acylation reaction.
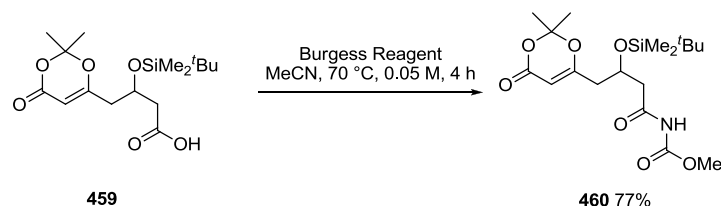
Scheme 126. Treatment of the protected β-hydroxy acid **459** with Burgess reagent to give acylcarbamate **460**.

In order to optimize the aromatization reaction of acid **458a**, a shorter synthesis of this substrate was developed (Scheme **127**). Based on the work developed for the synthesis of salicylates (Chapter **3**) cross metathesis was used once again. Treatment of crotonyl chloride **461** with *tert*-butanol and triethylamine gave homoallylic ester **462a** in 73% yield. Cross metathesis of **462a** with vinyl dioxinone **372a** was successful and gave **337a** in 82% yield. Treatment of **337a** with trifluoroacetic acid gave the required acid **458a**.
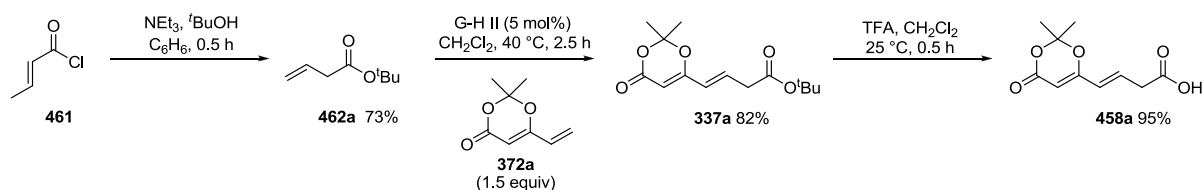
**Scheme 127.** Synthesis of the acid **458a** from crotonyl chloride **461**.

1.12.4   Optimisation of Conditions for Aromatization of Dioxinone Acid **458a**

Treatment of acid **458a** with Burgess reagent had resulted in successful reaction to give the desired aromatic product **457a** (Scheme **125**). Different conditions were then investigated to optimize conditions for this aromatization reaction. Considering the reactivity of acid **458a**, it was expected to form dienyl-ketene **463** that may undergo a 6 electrocyclization to give **457a** (Scheme **128**).
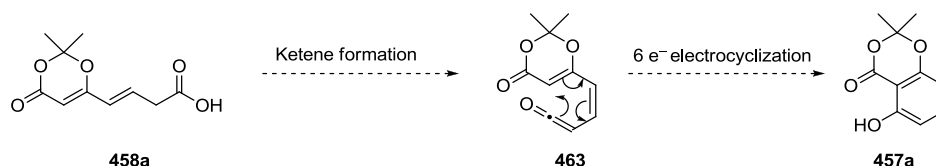

Scheme 128 Formation of γ-resorcylate **457a** may be possible from dienylketene **463**.

To form the dienyl ketene **463,** acid **458a** was treated with Ghosez's reagent followed by addition of 2,4,6-collidine (Scheme **129**). The aromatic **457a** was isolated in 33% yield. TLC analysis of this reaction indicated that conversion to the product **457a** started to occur before addition of the base, suggesting that it was superfluous. Accordingly, treatment of **458a** with Ghosez's reagent for an extended period gave the γ-resorcylate **457a** in a 74% yield.
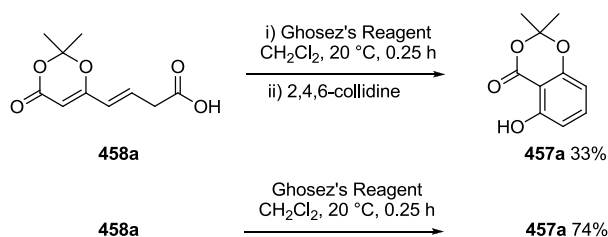
Scheme 129. Treatment of **458a** with Ghosez's reagent resulted in formation of γ-resorcylate **457a**.

The reactivity of **458a** upon activation with Ghosez's reagent is similar to the previous cyclizations of dienylketenes outlined in the introduction section. Thus, further conditions for the aromatization of **458a** were examined, some following literature procedures (Table **8**).

458a → 457a (Conditions)
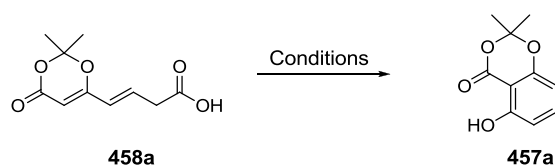
Entry	Reagents (equiv)	Temp (°C)	Solvent	Time (h)	Yield of 5a(%)
1	(COCl)$_2$ (5)	Reflux	CH$_2$Cl$_2$	48	9
2	(COCl)$_2$ (1.5), DMF (0.2)	25	CH$_2$Cl$_2$	20	50
3[a]	i) NaH (1.1), (COCl)$_2$ (1) DMF (1)	25	THF	19	38
4	Burgess Reagent (1.5)	70	MeCN	2	47
5	Ghosez's Reagent (1.3)	25	CH$_2$Cl$_2$	2	74
6	CCl$_4$ (1.2), PPh$_3$ (1.5).	25	CH$_2$Cl$_2$	18	26
7	CCl$_4$ (1.2), PPh$_3$ (1.5)	Reflux	CH$_2$Cl$_2$	3	76
8	CBr$_4$ (1.2), PPh$_3$ (1.5)	Reflux	CH$_2$Cl$_2$	3	73

a) Sequential addition: NaH 2 h; (COCl)$_2$ 1 h; DMF 16 h.

Table 8. Conditions for aromatization of **458a** to **457a**.

Initially methods using oxalyl chloride for generation of the acid chloride were examined. Treatment with Paquette's conditions refluxing the acid **458a** in oxalyl chloride gave the product **457a** in 9% yield (Table **8**, Entry **1**).[179] This was significantly improved by using a sub-stoichiometric amount of DMF and reducing the reaction temperature to 25 °C, to give **457a** in 50% yield (Table **8**, Entry **2**). Interestingly when **458a** was treated with excess oxalyl chloride and excess DMF, **457a** was not obtained but instead **464** was obtained in 33% (Scheme **130**). The occurrence of **464** could be explained through decarboxylation of **458a**, followed by formylation, aromatization and further formylation.
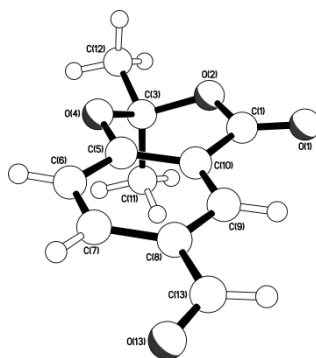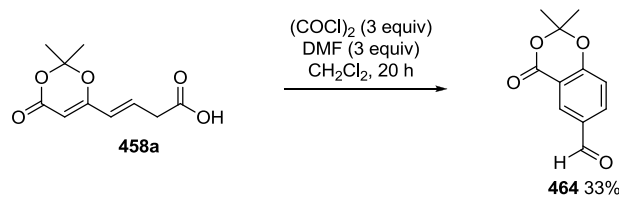
Scheme 130. Treatment of the acid **458a** resulted in the unexpected formation of the aldehyde **464**. An x-ray crystal structure of **464** confirmed its identity.

Generation of the acid chloride under neutral conditions, using sodium hydride to first generate the sodium salt of **458a**, followed by treatment with oxalyl chloride then DMF, gave **457a** in 38 % (Table **8**, Entry **3**). The remaining mass balance consisted solely of starting material **458a** and several attempts were made to increase the conversion. Increasing the amount of sodium hydride and reaction time to ensure full deprotonation, or increasing the amount of oxalyl chloride and DMF, resulted in no further increases in conversion or isolated yield.

Appel reactions conditions were used next as it was thought that not only would this create the acid chloride under mild conditions but the presence of triphenylphosphine could aid in the isomerisation of the double bond and thus promote aromatization. The reaction was tried at room temperature (Table **8**, Entry **6**) and gave **457a** in 26% yield and some other minor impurities observed by crude ^{1}H NMR. The same reaction in refluxing CH_2Cl_2 improved the yield giving the desired γ-resorcylate **457a** in 76 % (Table **8** Entry **7**), and when substituting CCl_4 for CBr_4, **457a** was isolated in 73% (Table **8**, Entry **8**). While use of Appel conditions didn't increase the yield over the initial result using Ghosez's reagent (Table **8**, Entry **5**), the two sets of conditions gave alternative protocols that could later be applied to further substrates.

1.12.5 Retrosynthesis for Substrate Synthesis of Dioxinone Acids Using Cross Metathesis Strategies

With conditions for the aromatization in hand, a larger range of substrates was explored to gain greater synthetic utility from this new intramolecular aromatization reaction. Ideally, 3 substituents

R^1–R^3 could be incorporated to allow synthesis of tri-substituted γ-resorcylates i.e. hexa-substituted benzene derivatives (Scheme **131**).
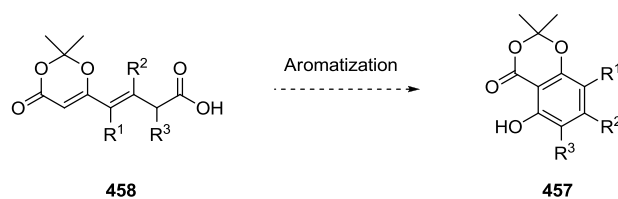
Scheme 131. Proposed synthesis of substituted γ-resorcylates.

As cross metathesis had be used for the synthesis of substrate **458a**, this route was used for more complex substrates (Scheme **132**). Retrosynthesis for substitution at position R^1 would be through synthesis of the appropriate dioxinone fragment **372**, available by acid-catalyzed condensation of acetone with a 1,3-ketoester such as **465**. Retrosynthesis for substitution at position R^2, or R^3 was proposed using vinyl dioxinone **372a**. The introduction of aryl groups directly attached to the homoallylic ester fragment **462** would come from deconjugative protonation of Horner-Wadsworth-Emmons adducts **466**. The alkyl substituted ester **462** would be available from *tert*-butyl crotonate (**471**) by deconjugative alkylation with appropriate electrophiles.
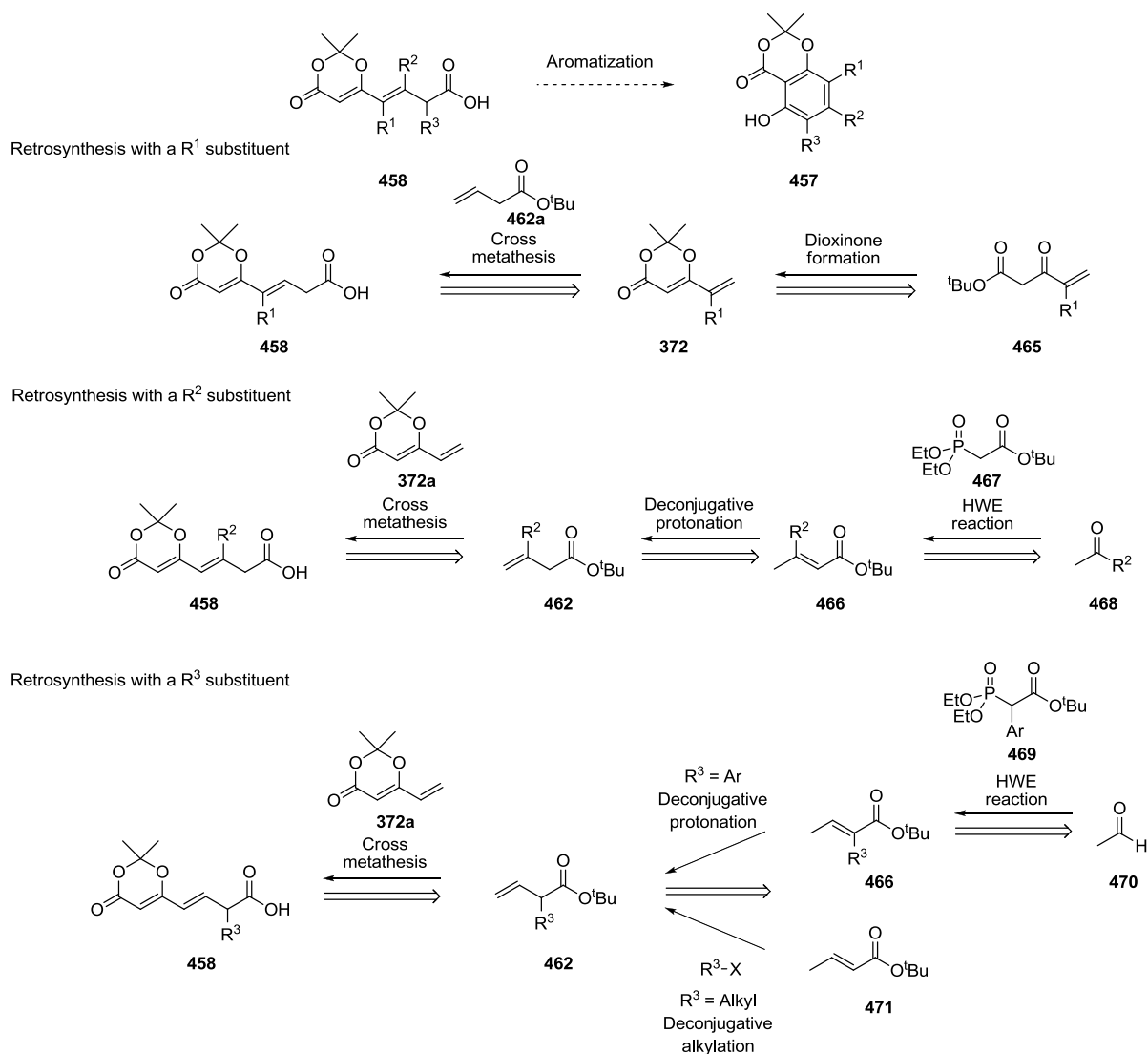
Scheme 132. Retrosynthetic analysis of the possible routes for substituted substrates **458** based on cross metathesis as the key step.

1.12.5.1 Synthesis of Cross Metathesis Substrates

Based on the synthetic plans developed (Scheme **132**), construction of the substrates **458** required for the cross metathesis reactions were investigated (Scheme **133–135**). Starting with R^1, introduction of a methyl substituent was examined meaning construction of a dioxinone ring was required (Scheme **133**). Addition of the lithium enolate of *tert*-butylacetate (**408**) to methacrolein gave hydroxy-ester **472** in 87% yield. Swern oxidation of **472** resulted in the formation of keto-ester **465a**, which after condensation with acetone gave dioxinone **372b**.
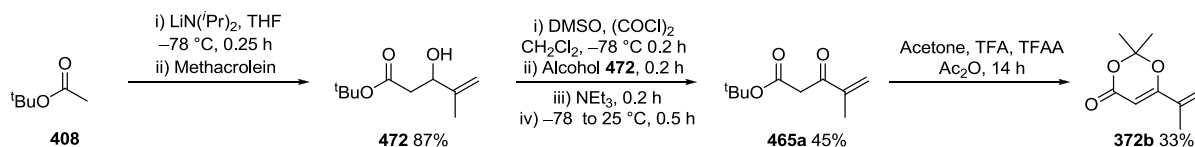
Scheme 133. Synthesis of methyl dioxinone **372b**.

The synthesis of aryl-substituted homoallylic ester **462d** was achieved as follows (Scheme **134**). Bromo *tert*-butylacetate (**473**) was subjected to an Arbuzov reaction with triethylphosphite to give phosphonate **467a**. Horner-Wadsworth-Emmons reaction of **467a** with acetophenone gave the internal alkene **466a** that was subjected to deconjugative protonation, giving terminal alkene **462d** in 52% yield.
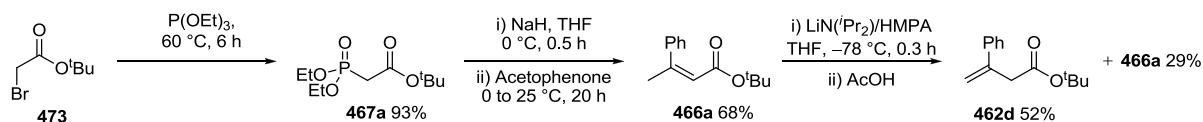
Scheme 134. Horner-Wadsworth-Emmons route to cross metathesis partner **462d**.

Introduction of an aryl substitutent at the ester α position began with bromo phenylacetic acid **474** (Scheme **135**). Reaction with thionyl chloride and catalytic DMF gave the corresponding acid chloride intermediate **I** which was reacted with *tert*-butanol to give ester **475**. Arbuzov reaction of **475** with triethylphosphite gave the phosphonate **469a**. Deprotonation of **473a** and reaction with acetaldehyde (**470**) installed the aryl group in the correct position. Unfortunately, attempted deconjugative protonation of **466b** as before, was unsuccessful; an inseparable mixture of **462g** and starting material, **466b**, was obtained.
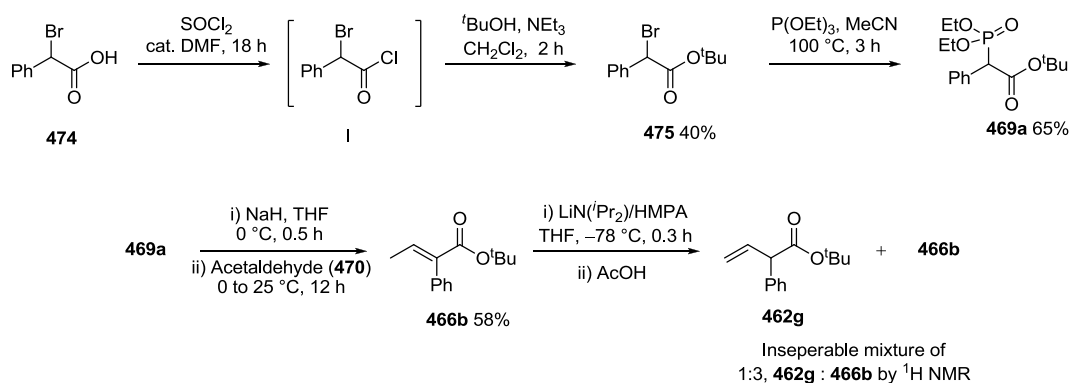
Scheme 135. Unsuccessful Horner-Wadsworth-Emmons route to the cross metathesis partner **462g**.

Installation of an alkyl group at the ester α position was achieved by deconjugative alkylation of *tert*-butyl crontonate (**475**) (Scheme **136**). The use of HMPA with LDA in this procedure means only α-alkylated products should be observed.[180] Use of methyl iodide and benzyl bromide as alkylating
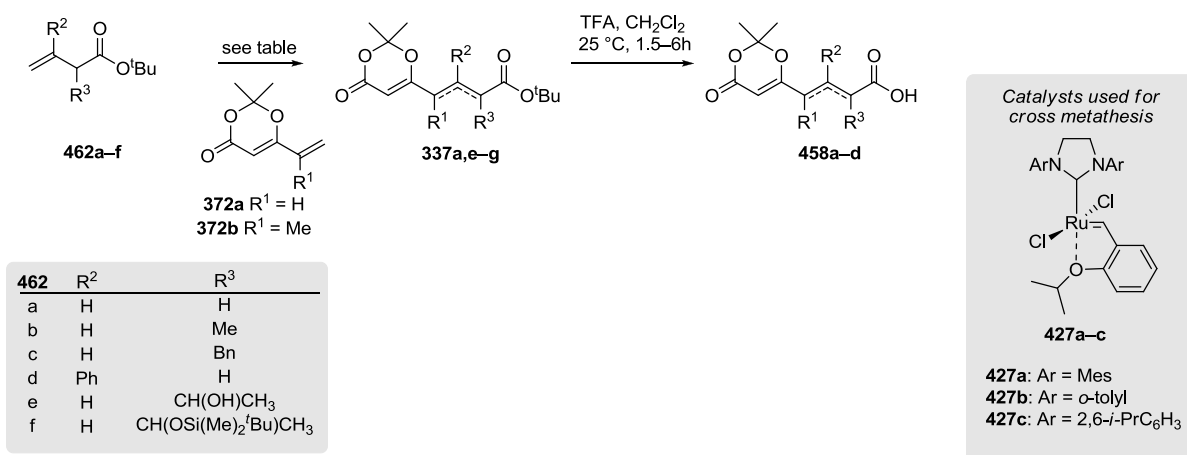
agents proved effective and the homoallylic esters **462b–c** were isolated in good yield. The use of secondary bromides was ineffective and did not result in alkylation. This was also the case for MOM-Cl, and use of 1,3-dibromopropane gave only mixtures of products that were inseparable by distillation or chromatography. Schlessinger has reported these latter two electrophiles to undergo alkylation in 94 and 92% yield respectively when using ethyl crotonate suggesting that the steric bulk is responsible for failure in these instances.[180] Use of acetaldehyde as the electrophile gave alcohol **462e** in 63%, which was protected as TBS ether **462f**.
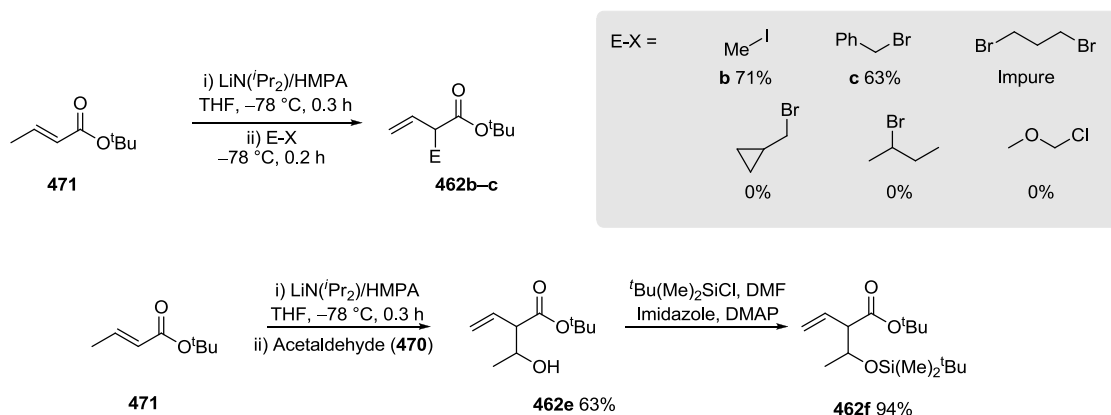
Scheme 136. Deconjugatve alkylation of *tert*-butyl acrylate (**471**) for synthesis of cross metathesis substrates.

1.12.6   Cross Metathesis for Synthesis of Aromatization Substrates

With some substrates in hand, their cross metathesis reactions were investigated (Table **9**). Cross metathesis reaction of vinyl dioxinone **372a** with t-butyl ester **462a** in dichloromethane at reflux gave the unsaturated ester **337a** in 82% yield (Table **9**, Entry **1**). Ester deprotection of **337a** with trifluoroacetic acid (TFA) gave the carboxylic acid **458a** in 95% yield as a single regioisomer.

TFA, CH$_2$Cl$_2$
25 °C, 1.5–6h

462a–f

372a R^1 = H
372b R^1 = Me

337a,e–g

458a–d

Catalysts used for cross metathesis

427a–c

427a: Ar = Mes
427b: Ar = o-tolyl
427c: Ar = 2,6-i-PrC$_6$H$_3$

462	R^2	R^3
a	H	H
b	H	Me
c	H	Bn
d	Ph	H
e	H	CH(OH)CH$_3$
f	H	CH(OSi(Me)$_2^t$Bu)CH$_3$

Entry	462 (equiv)	372 (equiv)	R^1	R^2	R^3	Cross Metathesis Conditions	337 (%)	458 (%)
1	**a** (1.0)	**a** (1.5)	H	H	H	**427a**[a], CH$_2$Cl$_2$, 2.5 h, 40 °C	**337a** (82)	**458a** (95)
2	**b** (1.0)	**a** (1.5)	H	H	Me	**427a**[a], CH$_2$Cl$_2$, 2.5 h, 40 °C	**337e** (0)	
3	**b** (1.0)	**a** (1.5)	H	H	Me	**427a**[b], C$_6$F$_5$CF$_3$, 16 h, 70 °C	**337e** (43)	
4	**b** (1.0)	**a** (1.5)	H	H	Me	**427a**[b], C$_6$F$_6$, 16 h, 70 °C	**337e** (46)	**458b** (97)
5	**b** (3.0)	**a** (1.0)	H	H	Me	**427a**[b], C$_6$F$_5$CF$_3$, 16 h, 70 °C	**337e** (24)	
6	**b** (1.0)	**a** (3.0)	H	H	Me	**427a**[b], C$_6$F$_5$CF$_3$, 2 h, 70 °C	**337e** (68)	
7	**c** (1.0)	**a** (3.0)	H	H	Bn	**427a**[b], C$_6$F$_5$CF$_3$, 2 h, 70 °C	**337f** (61)	**458c** (96)
8	**e** (1.0)	**a** (3.0)	H	H	CH(OH)CH$_3$	**427a**[b], C$_6$F$_5$CF$_3$, 2 h, 70 °C	--[c]	
9	**f** (1.0)	**a** (3.0)	H	H	CH(OSi(Me)$_2^t$Bu)CH$_3$	**427a**[b], C$_6$F$_5$CF$_3$, 4 h, 70 °C	**337g** (54)	**458d**[d] (91)
10	**d** (1.0)	**a** (3.0)	H	Ph	H	**427a,b** or **c**[b], C$_6$F$_5$CF$_3$, 14 h, 70 °C	--[c]	n/a
11	**a** (1.0)	**b** (3.0)	Me	H	H	**427a,b** or **c**[b], C$_6$F$_5$CF$_3$, 16 h, 70 °C	--[c]	n/a

a) 5 mol% catalyst used. b) 10 mol% catalyst used. c) No cross metathesis products observed. d) R^3 = CH(OH)CH$_3$.

Table 9. Conditions for cross metathesis reactions of **462** with **372** and ester cleavage for synthesis of **458a–d**.

In contrast, attempted cross metathesis of vinyl dioxinone **372a** with ester **462b** in dichloromethane was unsuccessful, however, reaction in perfluorotoluene as solvent at 70 °C with catalyst **427a** gave the desired product **337e** in 43% yield (Table **1**, Entries **2** and **3**). During purification of **337e** partial isomerization to the more substituted alkene meant **337e** was isolated as a mixture of regioisomers.[181] The use of perflourobenzene gave no significant increase in yield and subsequently perfluorotoluene was used, as it was the more economical of the two (Table **1**, Entry **4**). Use of excess ester **462b** resulted in a decrease in yield but when 3 equivalents of vinyl dioxinone **372a** were employed, product **337e** was obtained in 68% yield (Table **1**, Entries **5** and **6**). These reaction conditions were subsequently applied to the cross metathesis of vinyl dioxinone **372a** with ester **462c** giving the desired alkene **337f** in 61% yield as a mixture of regioisomers (Table **1**, Entry **7**). Cross metathesis of alkene **462e** with **372a** was not possible but cross metathesis of the corresponding TBS ether **462f**

with **372a** gave **337g** in 61% (Table **1**, Entries **8** and **9**). The use of di-substituted alkenes **462d** and **372b**, in cross metathesis reactions with **372a** and **462a** respectively, was attempted (Table **1**, Entries **10** and **11**), but none of the desired cross metathesis products were formed, even when the metathesis catalysts **427b** or **427c** were employed.[182] Deprotection of the t-butyl esters **337e**, **337f** and **337g** with TFA gave the carboxylic acids **458b**, **458c**, and **458d** in 97, 96, and 91% yield respectively. In the ester cleavage of **337g** the TBS group was also removed.

1.12.7   Aldol Addition Strategies for Synthesis of Aromatization Substrates **458**

The previous route allowed cross metathesis with alkyl substituents α to the ester, however other substituents were not tolerated in the substrates. Having encountered these limitations an alternative route to unsaturated acids **458**, which may allow greater functional group incorporation, was explored (Scheme **137**). Acid **458** would be available from dehydration of β-hydroxy ester **476**, itself the product of an aldol addition between a *tert*-butyl ester **477** and keto-dioxinone **284**. The route would begin with readily available starting materials; several derivatives of keto-dioxinones **284** are known and derivatives of phenylacetic acid are very common and easily accessible.[183]
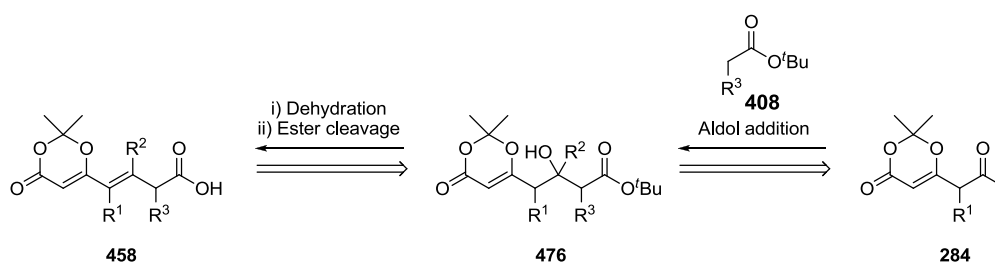
Scheme 137. Retrosynthetic analysis of **458** using an aldol addition and dehydration strategy.

1.12.7.1 Aldol Addition for Synthesis of Aromatization Substrates

The first aldol addition reaction carried out was between *tert*-butyl acetate (**408a**) and keto-dioxinone **284a** (Scheme **138**). When kept at −78 °C the reaction proceeded to give aldol product **476a** in a 48% yield. Given that the remaining unreacted keto-dioxinone **284a** could be recovered, this reaction was considered synthetically useful.
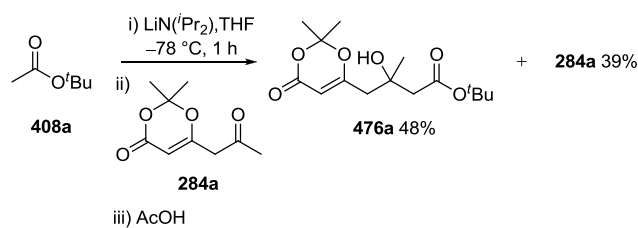
Scheme 138. Aldol addition strategy gives the desired β-hydroxy ester **476a** and unreacted keto-dioxinone **284a** is recovered.

Two more keto-dioxinones **284c** and **284d** were produced to enable further aromatization substrates to be constructed (Scheme **139**). Acylation of dioxinone **197** with the acylimidazole **477** gave keto-dioxinone **284c**.[184] The benzyl substituted keto-dioxinone **284d** was obtained by alkylation of **284a**.[183] Some of the regioisomer **284e** was obtained however this was a minor product.
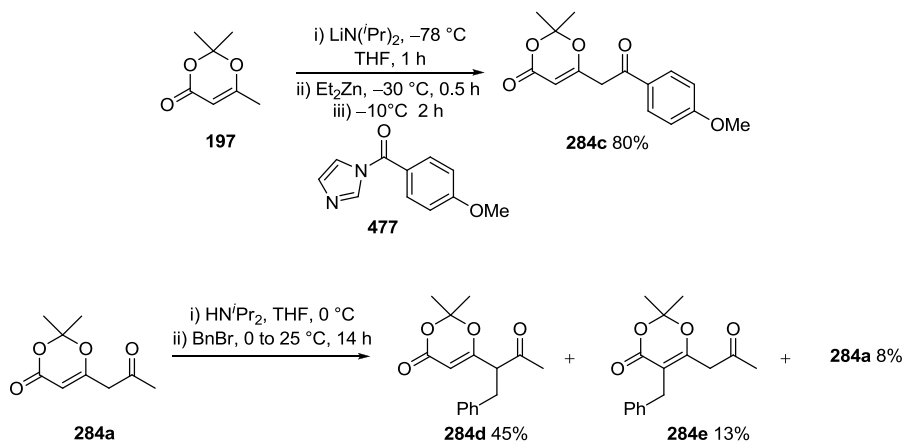
Scheme 139. Synthesis of the keto-dioxinones **284c** and **284d**.

Reaction of *tert*-butyl acetates **408a–c** with keto-dioxinones **248a, 248c** and **248d** resulted in the formation of β-hydroxy esters **476a–e** in 42–52% yield (Table **10**). The addition reactions showed few side products and so it was possible to recover 63–93% of the unreacted keto-dioxinones **248a, 248c** and **248d**. The esters **476a–e** underwent facile dehydration with Burgess reagent to give the enoate compounds **357h–l** as mixtures of regioisomers and these esters were treated with TFA to give the required acids **458e–h**, also as regioisomeric mixtures. The generation of the carboxylic acids **458** as mixtures of regioisomers was of little concern as when subjected to the aromatization reaction, the final products would be identical.
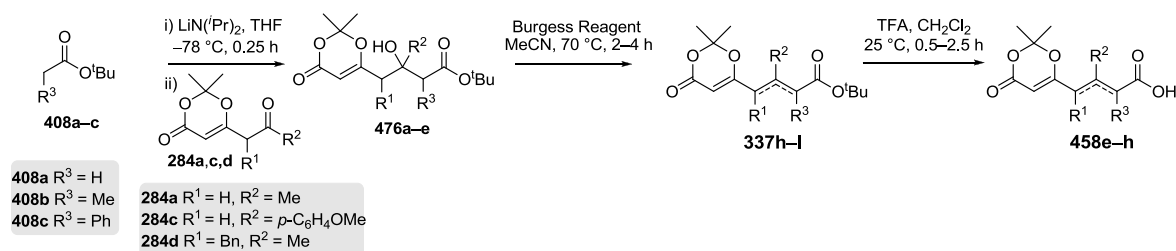
Entry	248	408	R^1	R^2	R^3	476 (%)	337 (%)	458 (%)
1	248a	408a	H	Me	H	476a 48	337h 77	458e 76
2	248a	408b	H	Me	Me	476b 50	337i 77	458f 97
3	248a	408c	H	Me	Ph	476c 42	337j 75	458g 98
4	248d	408b	Bn	Me	Me	476d 50	337k 82	458h 85
5	248c	408a	H	p-C$_6$H$_4$OMe	H	476e 52	337l 81	458i --

Table 10. Formation of β-hydroxy esters **476a–e** and their conversion to unsaturated acids **458e–h**.

When attempting the ester cleavage of **337l** with TFA the desired acid was not obtained but instead formation of pyrone **478** occurred (Scheme **140**). While in general the mixtures of isomers of **337** formed after dehydration were inseparable, in the case of **337l** two major isomers **337la** and **337lb** were isolated after chromatography. While the E/Z geometry of these isomers couldn't be conclusively determined, nOe measurements indicated the shown regioisomers. Treating each of these separately with TFA gave two different results; the more highly conjugated ester **337la** gave the pyrone **478** while the less conjugated isomer **337lb** gave the desired acid **458i**. Formation of the pyrone may be due to the highly conjugated nature of **337la** allowing facile hydrolysis of the dioxinone fragment. Prolonged exposure of the acid **458i** to TFA converted it fully to pyrone **478** perhaps *via* acid catalyzed isomerization and then pyrone formation.
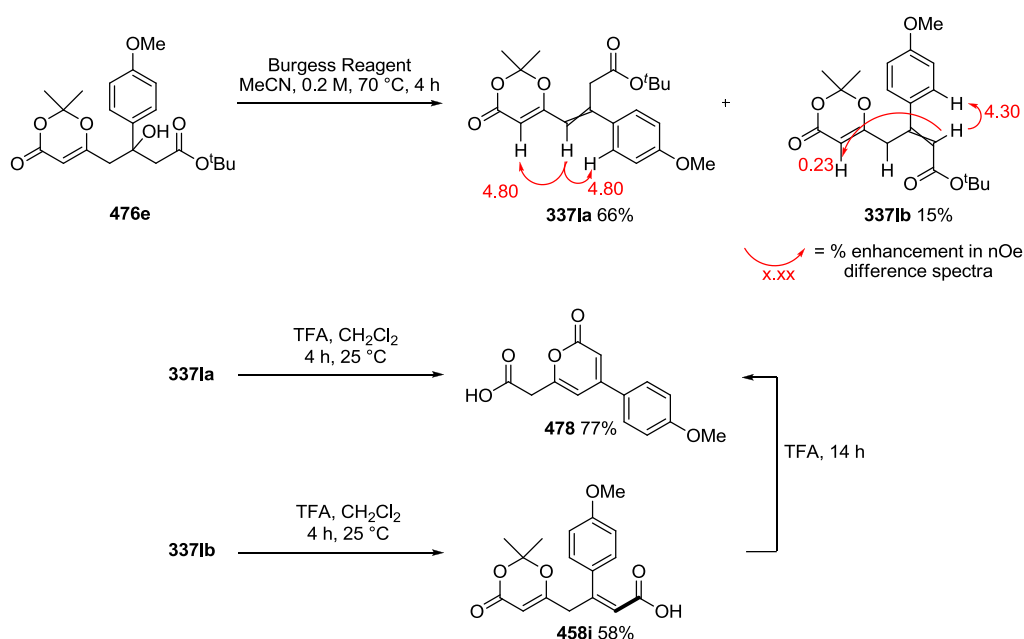
Scheme 140. Dehydration of **476** to give regioisomers **337la** and **337lb** and subsequent formation of pyrone **378**.

1.12.7.2 Aldol addition for Synthesis of β-Hydroxy Acid Aromatization Substrates

Incoporation of an aryl substituent R^2 to the aromatization substrate was not possible by the dehydration route above (Scheme **140**) as formation of the highly conjugated intermediate **337la** upon dehydration, led to formation of pyrone **478**. To avoid intermediate **337**, β-hydroxy acids **479** were considered as substrates for the aromatization reaction (Scheme **141**). To this end, β-hydroxy acid **479a** was subjected to the Appel reaction conditions and γ-resorcylate **457b** was obtained in 42% yield. The increased amount of reagents was to effect the two dehydrations required.
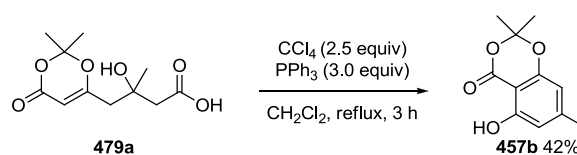
Scheme 141. Aromatization of β-hydroxy acid **479a** to γ-resorcylate **457b**.

The synthesis of the β-hydroxy acid substrates for this reaction was then expanded much in the same way as before (Table **11**). Aldol addition of benzyl acetates **480a–c** to the keto-dioxinones **284a**, **284c**, and **284d** followed by hydrogenolysis, proceeded to give **479a–e** with some unreacted keto-dioxinone **284** observed. The crude mixture of the aldol addition could be directly subjected to hydrogenolysis and the resultant acid easily extracted by work up. The unreacted keto-dioxinone **284** could also be recovered at this stage if desired.
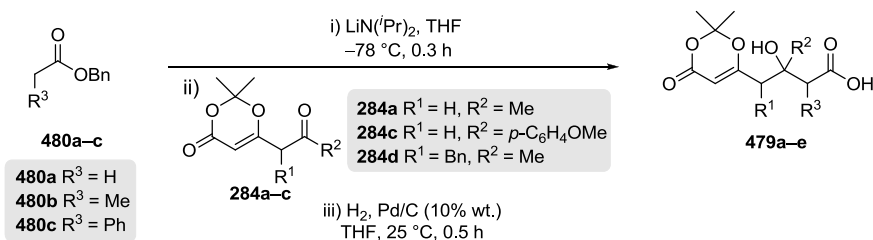
Entry	284	480	R^1	R^2	R^3	479 (%)
1	284a	480a	H	Me	H	479a 38
3	284d	480a	Bn	Me	H	479b 56
5	284c	480a	H	p-MeO-C$_6$H$_4$	H	479c 43
2	284d	480b	Bn	Me	Me	479d 41
4	284a	480c	H	Me	Ph	479e 19

Table 11. Synthesis of β-hydroxy acids **479a–e**.

For the synthesis of **479e** it was found that further simplification of the process was possible (Scheme **142**). Starting with double deprotonation of phenylacetic acid (**481**) using lithium diisopropylamide, addition to keto dioxinone **284a**, gave the desired β-hydroxy acid **479e** in 38 % yield.[185] This provides a more direct route to the desired β-hydroxy acids **479**, and although not fully investigated, the dianion of acetic or propanoic acid could also potentially provide substrates **479a–d** in a one step process.
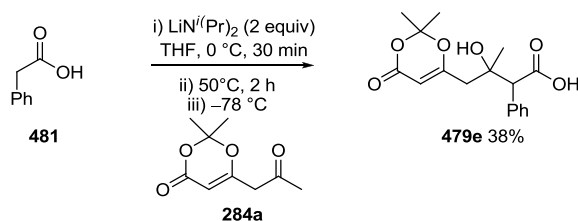
Scheme 142. Direct synthesis of β-hydroxy acid **479e**.

1.13 Aromatization of Methylated Substrates

With a range of substrates now available the developed aromatization conditions were applied to the methylated substrates **458b** and **458e** (Scheme **143** and **144**). Treatment of **458b** with Ghosez's reagent did not afford the desired compound **457c** but led to the formation of a mixture of products, of which the major constituent was acylated product **482** in 15% yield. This was in stark contrast to the earlier aromatization of the unsubstituted compound **458a** (Scheme **129**) that underwent aromatization in 74% when subjected to the same conditions. Some of the other aromatization conditions developed were then applied to the methylated substrate **458b**. Use of Burgess reagent resulted in a complex

mixture and no **457c** was isolated. Sequential treatment of **458b** with sodium hydride, oxalyl chloride and catalytic DMF gave **457c** in a 10% yield accompanied by decomposition of the starting material. When **458b** was subjected to Appel reaction conditions γ-resorcylate **457c** was obtained in 49% yield.

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Conditions	Yield of 457c
Burgess reagent MeCN, 70 °C, 3 h	0%
i) NaH, ii) (COCl)$_2$ iii) DMF (5 mol%)	10%
CCl$_4$ (1.2 equiv) PPh$_3$ (1.5 equiv) CH$_2$Cl$_2$, reflux , 3 h	49%
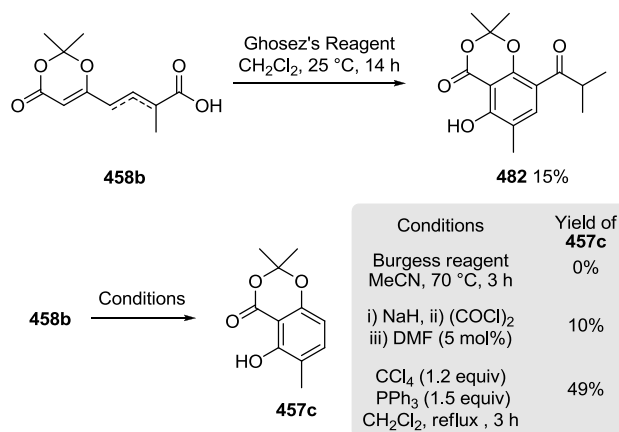
Scheme 143. Conditions employed for aromatization of methylated substrate **458b**.

Moving to the next methylated substrate **458e** it was found that use of Ghosez's reagent gave the γ-resorcylate **457b** in 45% yield (Scheme **144**). Once again, this was improved by using Appel conditions which allowed **457b** to be isolated in 62% yield. The lower yield for conversion of **458b** to **457c** than **458e** to **457b** is likely due to the increased steric hindrance as a result of the methyl group α to the carbonyl. When this substituent is in the β position (**458e**) then the steric hindrance for nucleophilic attack is reduced.

Conditions	Yield of 457b
Ghosez's Reagent CH$_2$Cl$_2$, 25 °C, 14 h	45%
CCl$_4$ (1.2 equiv) PPh$_3$ (1.5 equiv) CH$_2$Cl$_2$, reflux , 3 h	62%
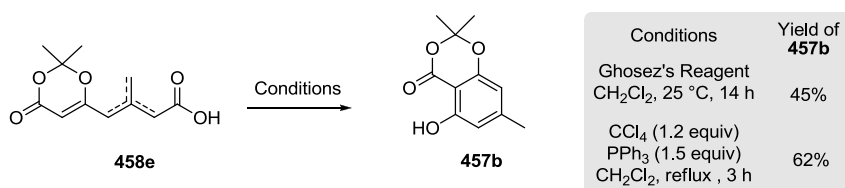
Scheme 144. Conditions employed for aromatization of methylated substrate **458e.**

The aromatization reaction of methylated substrates **458b** and **458e** indicated that the Appel reaction conditions were most general for the aromatization reaction. None of the electron rich aromatic products underwent further acylation reactions as had been observed in the presence of Ghosez reagent (Scheme **143**, **482**) or DMF (Scheme **130**, **464**). These optimal conditions were then used for aromatization of the rest of substrates **458**.

1.14 Application of the Optimised Aromatization Reaction

Having produced enoic acids **458a–h** and the β-hydroxy esters **479a–e** as cyclization substrates they were now subjected to the optimal aromatization reaction conditions (Scheme **145**).
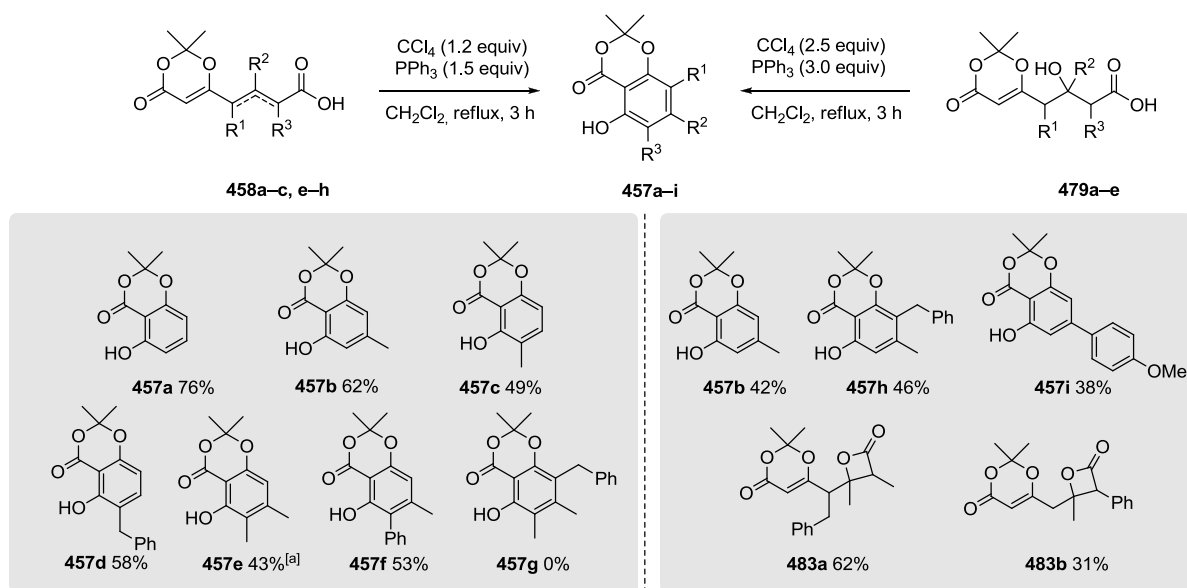
Scheme 145. Substrates for the aromatization reaction and the products obtained. a) 1,2-dichloroethane used as solvent at 70 °C.
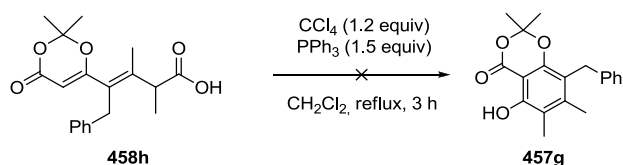

Scheme 146. Attempted aromatization of **458h** to give hexa-substituted γ-resorcylate **457g**.

Generally the aromatization reactions proceeded as expected to give the γ-resorcylates **457a–f**, **h** and **I**. In the case of **458f**, heating in DCE at 70 °C was necessary to increase the yield from 18% under the standard conditions to 42% of γ-resorcylate **457e**, the low reactivity presumably being due to steric hindrance. When applied to the more sterically demanding substrate **458h**, the desired hexa-substituted aromatic **458g** was not obtained and only decomposition of the starting material was observed (Scheme **146**). Targeting the same resorcylate **457g**, but from the β-hydroxy acid **479d**, resulted not in resorcylate **457g**, but in the β-lactone **483a** in 62% yield. Reaction of the β-hydroxy acid **479e** also resulted in formation of the corresponding β-lactone, **483b**, suggesting that this reaction pathway is favoured over aromatization when utilizing β-hydroxy acids substituted in the α-position. In this case however, the lactone formation could be avoided by performing a dehydration first, affording the desired γ-resorcylate **457f** from the unsaturated acid **458g** in 53% yield.

The substrate **458d** was also subjected to the reactions conditions and the chlorinated product **457j** was obtained in a 5% yield (Scheme **147**). On attempting to repeat this experiment the resorcylate

457a was obtained in 6% and none of the chlorinated product **457j** was obtained. This product likely arises through an acid catalyzed retro-aldol reaction of **458d** to give unsaturated acid **458a** which undergoes aromatization to give **457a**. In both cases starting material was fully consumed and the remaining mass balance consisted of polar compounds along with phosphorous based side products not isolated by silica gel chromatography. Further investigation of this process was not carried out.
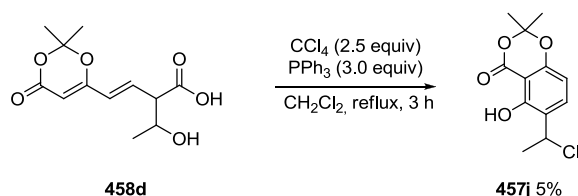
Scheme 147. Aromatization of the hydroxyl substituted compound **458d** to give the chlorinated product **457j**.

Comparing the efficiency of the two aromatization substrates, unsaturated acids **458** and β-hydroxy acids **479**, is possible for **458e** and **479a**. They both give the same product **457b** and aromatization occurred in 67 and 42% yields respectively for the two substrates. The lower yield for aromatization of the β-hydroxy acid **479a** may be the result of a competitive acid catalyzed retro-aldol reaction. In the reaction of **479e** to β-lactone **483b** in 31 % yield, keto-dioxinone **284a** was also obtained in 54% suggesting retro-aldol processes can be operative under the reaction conditions.[186]

1.14.1 Further Reactions of Benzodioxinone γ-Resorcylates **457**

γ-Resorcylate products **457** (benzodioxinones) obtained from the aromatization reaction can undergo several further transformations. For example, treatment of benzodioxinone **457** with methanolic caesium carbonate gave the γ-resorcylate methyl-2,6-dihydroxy-3,4-dimethylbenzoate **484** (a natural product isolated from the heartwood of *Picea morrisonicola* trees[187]) in 85% (Scheme **148**). Further functionalization of benzodioxinones **457** are known in the literature, for example undergoing reduction with (^{i}Bu$_2$AlH)$_2$, LiAlH$_4$, or LiBH$_4$, formation of quinoketenes or triflation followed by cross coupling reactions.[188]
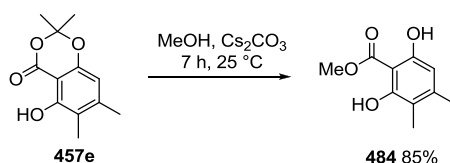
**Scheme 148.** Base mediated opening of the benzodioxinone **457e** gave **484**.

1.15 Conclusion to Synthesis of γ-Resorcylates from Dioxinone Derivatives

A number of strategies for the synthesis of γ-resorcylates from dioxinone derivatives were investigated. Dioxinones such as **337c** were constructed to allow synthesis of diesters for the proposed Dieckmann cyclization (Scheme **149**). However, upon ketene generation and formation of diester **338c**, cyclization to the pyrone **448** occurred showing the preferred mode of reactivity was through O-acylation. In another instance, acid **454** was activated as an acid chloride but the same reactivity was observed; the lactone **455** obtained as the result of O-acylation.
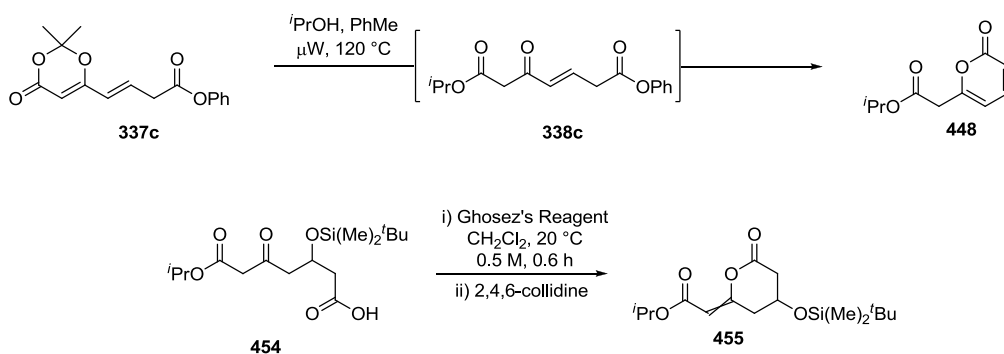
Scheme 149. O-Acylation was the preferred mode of reactivity rather than Dieckmann cyclization.

In order to prevent O-acylation, the aromatization of unsaturated dioxinone compounds **458** and **479** was investigated (Scheme **150**). Use of cross metathesis and aldol additions allowed the construction of several different substrate classes that successfully underwent aromatization to the desired γ-resorcylates.
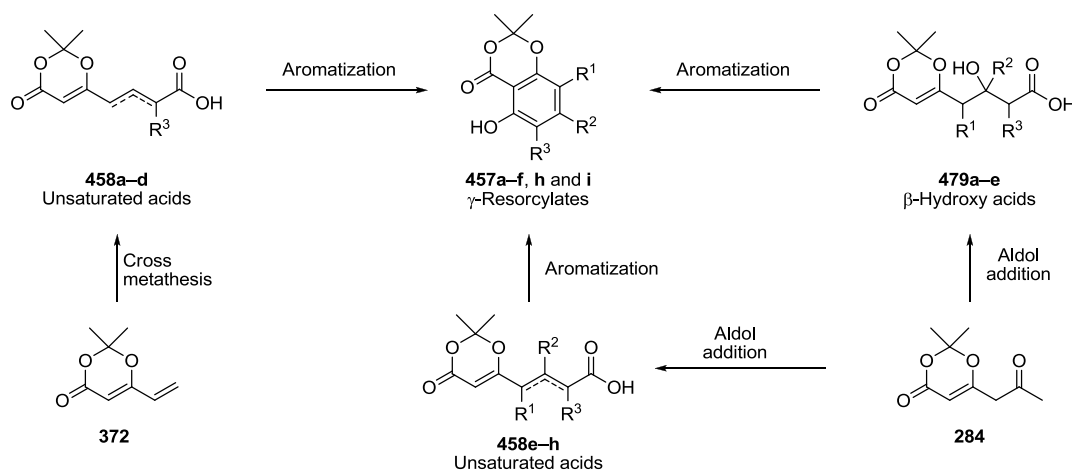
Scheme 150. Overview of γ-resorcylate synthesis routes.

Of the three substrate classes developed for the aromatization reaction and their requisite routes it is not possible to simply say one route is more efficient. While the aromatization reaction was more efficient with unsaturated acids **458** than β-hydroxy acids **479** (as demonstrated for **457b**) when the

whole synthetic route to γ-resorcylates is considered, they are closer in yield. The overall synthesis of resorcylate **457b** from keto-dioxinone *via* unsaturated acid **458e** is 17% and *via* **479a** is 16%. Furthermore, synthesis of γ-resorcylates from β-hydroxy acids **479** involves fewer synthetic steps.

Additionally, the three routes developed are complementary to one another. The use of cross metathesis with vinyl dioxinone **372** allows generation of γ-resorcylates **457** bearing an R^3 substituent where R^1 and R^2 = H. On the other hand use of aldol additions to keto-dioxinones **284** generated γ-resorcylates **457** where the R^2 substituent is always present (i.e. $R^2 \neq H$), but R^1 and R^3 could be incorporated conferring a higher level of substitution in some cases. When formation of resorcylate **457i** was not possible from **458i** due to formation of pyrone **478**, synthesis of the corresponding β-hydroxy acid **479c** and its aromatization to **457i** was possible. Equally, when attempted aromatization of the β-hydroxy acid **479e** gave rise to β-lactone **483b**, γ-resorcylate **457f** was available from the unsaturated acid **458g**.

Extension of Methodology to Other Aromatic Compounds

1.16 Introduction

The application of 6-(alkylamino)-salicylates in drug molecules and synthesis is limited. In one example, the 6-dimethylamino-salicylate **485** is patented as an inbititor of hyaluronan transport for treatment of several diseases including osteoarthrosis and certain types of cancer (Figure **10**).[189]
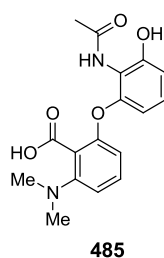
Figure 10. The 6-(dimethylamino)-salicylate **485** shows *in vitro* inhibition of hyaluronan transport.

Although there are relatively few examples highlighting the synthesis of these compounds in the literature, both Böhme and Hormi have reported *de novo* methods for the generation of substituted 6-alkylamino salicylates (Scheme **151**). Böhme has shown that the β-ester enamines **486** undergo a condensation with another molecule of **486** to give the amino-salicylates **487** when treated with CF$_3$CO$_2$H.[190] A range of amino and R^2 were tolerated substituents giving the amino-salicylates **487** in 8–90% yield. In a second example, Hormi has shown that the chloro-malonate **488** can be converted to an aniline malonate **489** which cyclizes upon heating to the amino salicylates **490**. This is proposed to occur via ketene generation and electrocyclization.[191]
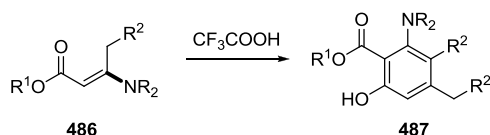
R^1	R^2	NR$_2$	Yield		R^1	R^2	NR$_2$	Yield
Me	H	HN^{n}Pr	42		Me	Me	N-morpholine	63
"	"	HNPh	40					
"	"	NMe$_2$	70		"	CO$_2$Me	N-pyrrolidine	78
"	"	N-piperidine	45					
"	"	N-methylpiperazine	8		Et	H	"	52
					"	"	NMe$_2$	90
					Me	"	38
					Ph	"	16

Table **12**
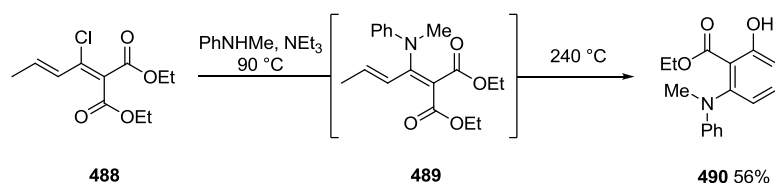
Scheme 151. Literature *de novo* syntheses of 6-alkylamino salicylates.

Given the relatively unknown application of these types of amino-salicylate molecules and the limited procedures for their synthesis, developing new methods for the selective synthesis of substituted examples would be beneficial.

## 1.16.1 Hypothesis for Synthesis of 6-Alkylamino-salicylates and 4-Oxy-pyridones

During the synthesis of the γ-resorcylates (chapter **4**) it was postulated that the acid substrates may cyclize be through formation of a dienyl-ketene such as **463** (Scheme **152**). Such an intermediate would be expected to undergo a 6π-electrocyclization to give the γ-resorcylate **457a**. Based on this principle it was believed that similar reactions using other cumulenes might be possible. For example, cyclization of a dienyl-keteniminium **491** would be expected to provide the 6-(dialkylamino)-salicylate **492**.
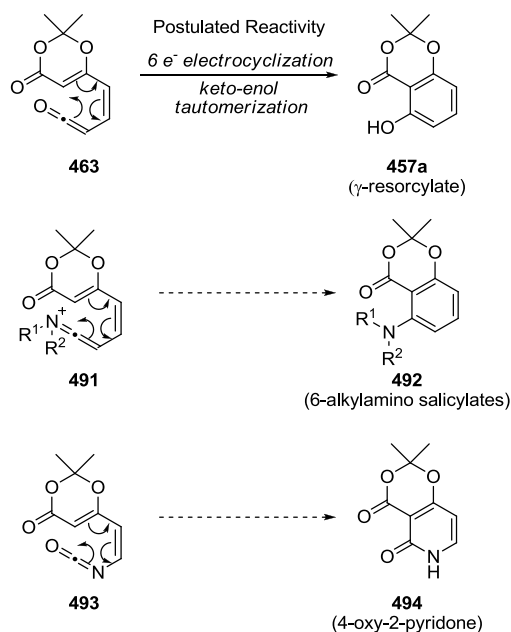
Scheme 152. Postulated cyclizations to give alkylamino salicylates **492** and 4-oxy-pyridones **494**.

Furthermore, cyclization of the dienylisocyanate **493** could provide 4-oxy-2-pyridones **494**, which represent a further class of important compounds present in numerous natural products.[192] In a similar literature example, acyl azide **495** undergoes Curtius rearrangement to give dienylisocyanate **496** and intramolecular acylation of resulted in pyridine **497**.[193] The iodine is postulated to catalyze double bond isomerization in this process so a lower temperature could be used; in a solely thermal processes a temperature of 230 °C was required.[194]
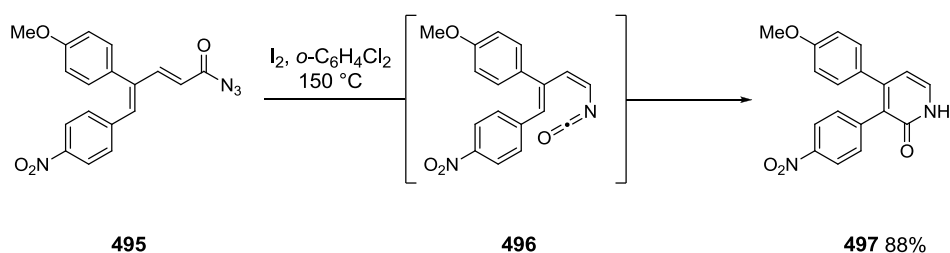
Scheme 153. Intramolecular acylation of isocyante **496** gives pyridone **497**.

1.16.1.1 Retrosynthetic Analysis of Substrates **498** and **493**

It was envisaged that the substrates for these cyclization reactions would be easily available using similar strategies to those employed in the synthesis of γ-resorcylates (chapter **xx**). Thus, the keteniminium salt **491-OTf** would be available from amide substrate **498** by treatment with triflic anhydride and collidine according to the conditions of Ghosez *et al.* (Scheme **154**).[195] The amide **498** could be formed after dehydration of the β-hydroxy amide **499** that would in turn be the product of an aldol addition reaction between keto-dioxinone **284a** and N-acetylpyrrolidine (**500**).
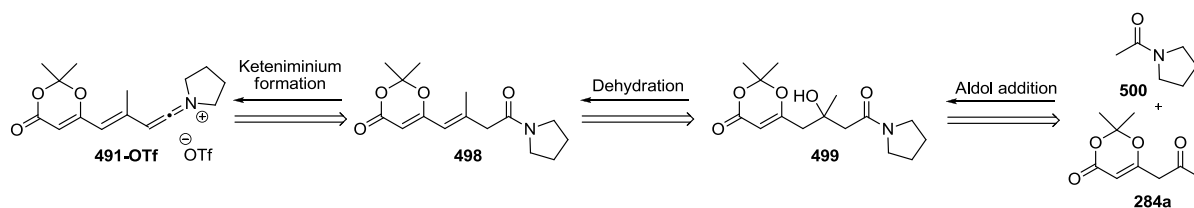
Scheme 154. Retrosynthesis of the substrate **498**.

The isocyanate **493** would be produced from a Curtius rearrangment of the acyl azide **501** (Scheme **155**). This would be made from the acid **502** which could be synthesized by cross metathesis of vinyl dioxinone **372** with *tert*-butylacrylate and ester cleavage. Alternatively, *N*-Boc-carbamates have been used to generate isocyanate intermediates at room temperature by treatment with Tf$_2$O and DMAP, to subsequently undergo intramolecular Friedel-Crafts-type cyclizations.[196] This would require synthesis of **503**.
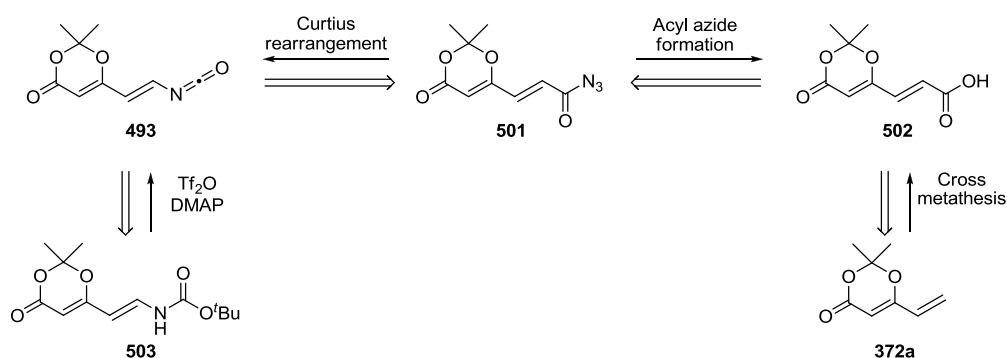
Scheme 155. Retrosynthesis of the substrates **501** and **503**.

1.16.2 Hypothesis for a Quinone Synthesis

During development of the salicylates synthesis (chapter **3**) an unexpected oxidation reaction was observed. Oxidation of alcohol **431a** with IBX, when carried out in DMSO resulted in over-oxidation to give the 1,2-diketone compound **433a** (Scheme **156**). It was reasoned that on heating this would undergo ketene generation and trapping. Then, as previously observed for the enone substrates, aldol condensation would follow yielding quinone **504**.
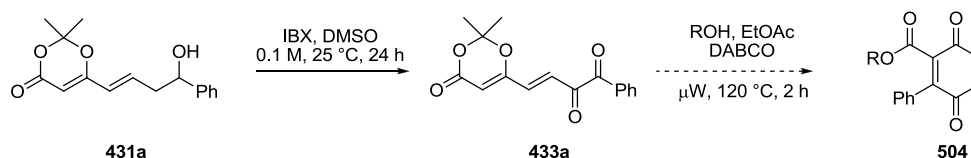
Scheme 156. Over oxidation of alcohol **431a** to **433a**, and the expected aromatization product **504**.

1.17 Results and Discussion

1.17.1 Synthesis and Aromatization Studies for 6-Alkylamino-salicylates

1.17.1.1 Synthesis of Substrates for Keteniminium Formation
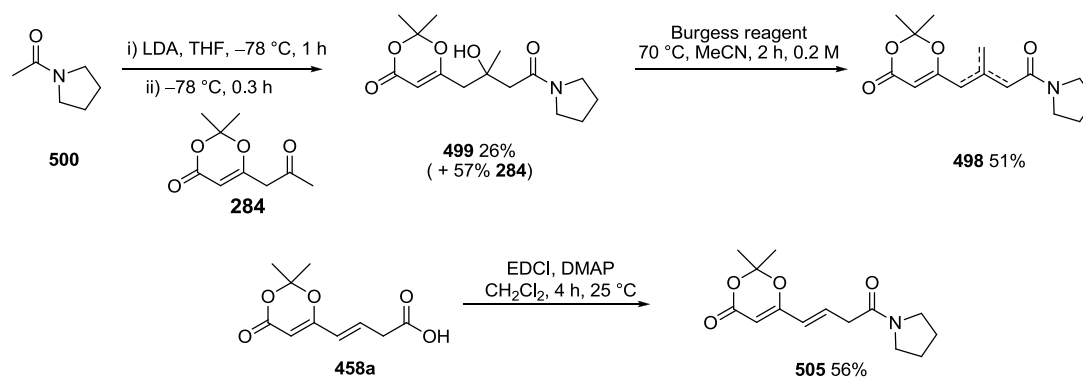
Scheme 157. Synthesis of the two substrates **498** and **505**.

The synthesis of the required amide substrate **498** was pursued as outlined in the retrosynthetic analysis (Scheme **157**). Thus, addition of acetyl pyrrolidine **500** to keto dioxinone **284** gave rise to the β-hydroxy amide **499** in 26% yield with 57% recovery of ketodioxinone **284**. Attempts to improve this yield by using three equivalents of amide nulceophile, or addition at −100 °C had little effect on the outcome. Transmetallation of the lithium enolate to zinc or cerium has not been investigated but may offer an increase in efficiency. Attempted dehydration of **499** with TFA resulted in no reaction but use of the Burgess reagent gave the dehydrated amide **498** in 51% yield. With some of the acid **458a** already in hand, a further substrate for aminosalicylate synthesis was produced by an amide coupling reaction with pyrrolidine to give amide **505** in 56% yield.

1.17.1.2 Aromatization Reactions Towards 6-Alkylamino-salicylates
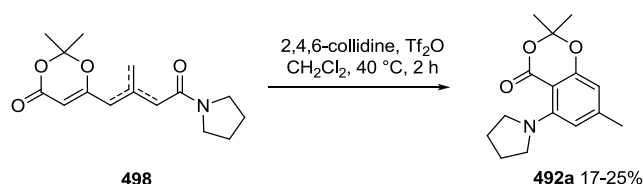
Scheme 158. Formation of methyl substituted aminosalicylate **492a** from the amide **498**.

The aromatization of **498** was then investigated using conditions developed by Ghosez *et al.* for generation on keteniminium salts (Scheme **158**).[195] Addition of the substrate **498** and collidine to a mixture of refluxing triflic anhydride in dichloromethane gave rise to the desired aniline product **492a** in 17−25% yield. The starting material was consumed in this process however the reaction appeared to be accompanied by decomposition which could be observed by ^{1}H NMR.

We investigated other methods for the aromatization that might give a cleaner reaction without any decomposition (Table **13**). Treatment of **505** with phosphorous oxychloride, with and without addition base led to decomposition (Table **13**, Entries **1** and **2**). Application of our previously developed Appel

aromatization conditions resulted in only starting material being recovered, as did the use of triphosgene or Meerwein's reagent (Table **13**, Entries **3**, **4** and **5**). Using Meerweins reagent with heating resulted in decomposition of the dioxinone fragment, while treatment of **505** with thionyl chloride led to complete decomposition (Table **13**, Entries **6** and **7**). Interestingly use of oxalyl chloride resulted in the formation of an adduct **506**, the structure of which was confirmed by x-ray crystallography (Table **13**, Entry **8**) (Scheme **159**).
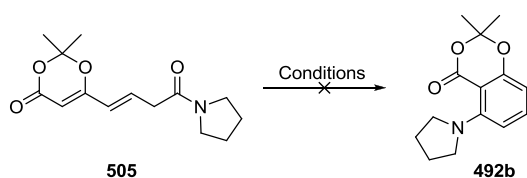
Entry	Reagent and Conditions[a]	Outcome
1	POCl$_3$ (1.2 equiv), NEt$_3$ (2.5 equiv), 3 h	Decomposition
2	POCl$_3$ (1.3 equiv), 24 h	Decomposition
3	PPh$_3$ (1.5 equiv), CCl$_4$ (1.2 equiv), 8 h	Starting Material
4	Triphosgene (0.4 equiv × 2), 2 × 4 h	Starting Material
5	Triethyloxonium tetrafluoroborate, 25 °C, 4 h	Starting Material
6	Triethyloxonium tetrafluoroborate, 12 h	Dioxinone decomposition
7	Thionyl Chloride	Decomposition
8	Oxalyl Chloride (2 equiv)	**506** 89% (see scheme **159**)

a) All reactions carried out in refluxing CH$_2$Cl$_2$ unless otherwise stated.

Table 13. Conditions attempted for conversion of **505** to **492b**.
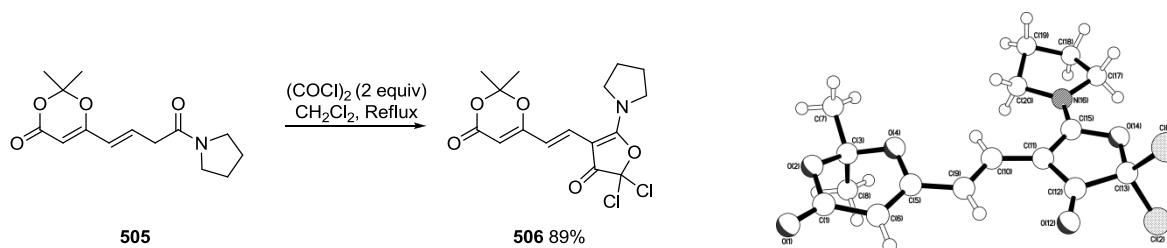
Scheme 159. Formation of the oxalyl chloride adduct **506** and its depiction from the crystal structure.[197]

Formation of these adducts have only been observed in a few instances in the literature and such dichloro furanones are rare.[198] A possible mechanism involves addition of oxalyl chloride leading to the imminium **I**, which on loss of carbon dioxide and carbon monoxide gives the chloroiminium **II** and subsequently the chloroenamine **III** (Scheme **160**). This would then undergo further acylation with oxalyl chloride to give **IV**. Attack by chloride, followed by ring closure gives **IV** and loss of HCl would give **506**.
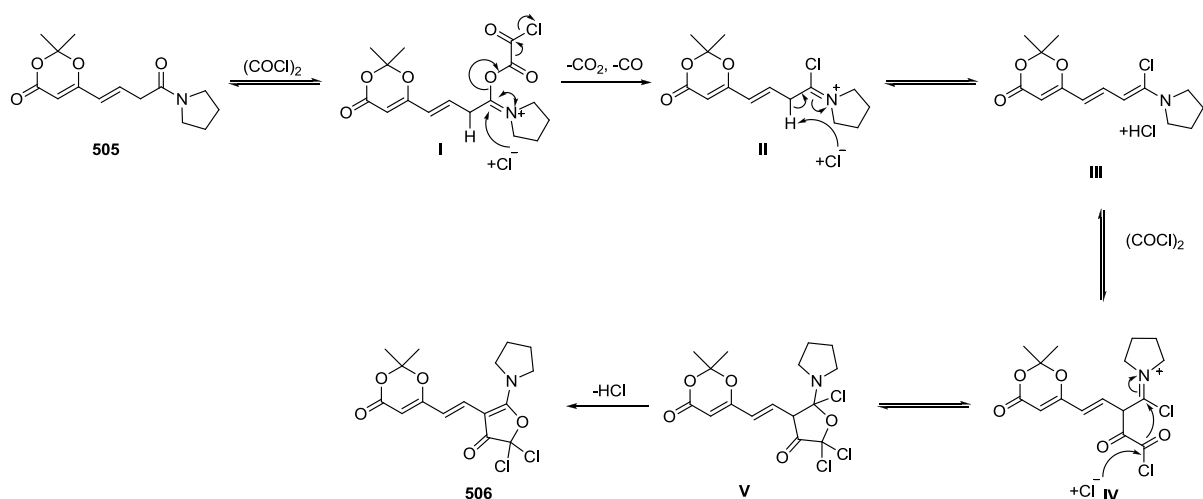
Scheme 160. Possible mechanism for the formation of **506** from **505**.

Following unsuccessful attempts to improve the yield for the synthesis of amino-salicylates **492**, an alternative substrate **499** was examined (Scheme **161**). It was observed in the synthesis of γ-resorcylates that β-hydroxy acids undergo aromatization (Chapter **4**), and so it was anticipated that β-hydroxy amide **499** might also be used as a substrate in this instance. Treatment of **499** with triflic anhydride and collidine led to aminosalicylate **492a** but in only a 7% yield, again accompanied by decomposition. Treatment under Appel conditions resulted in no reaction, however treatment with oxalyl chloride appeared to lead to the desired product **492a**. The resulting mixture of product and starting material was resubjected to the reaction conditions, this however led to decomposition. Upon repetition of this process, an unidentified oxalyl chloride adduct of the starting material was observed by ^{1}H NMR. Unfortunately this failed to convert to the product on prolonged heating. Further experiments are required to fully understand this reaction and improve yields of the aminosalicylate products **492**.
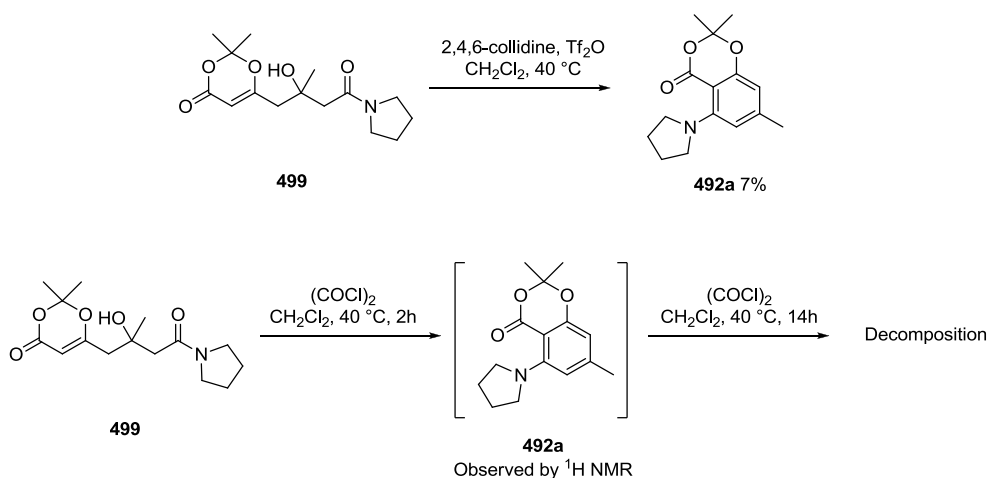
Scheme 161. Attempted cyclization reactions of β-hydroxy amide **499**.

1.17.2   Synthesis of Substrates and Attempted Aromatization Reactions for Synthesis of 4-Oxy-2-pyridones.

The synthesis of substrates towards 4-oxy-2-pyridones followed the retrosynthesis outlined earlier (Scheme **155**). Cross metathesis of vinyl dioxinone **372a** with tert-butyl acrylate using previously developed conditions gave the ester **507** which upon treatment with TFA gave carboxylic acid **508** (Scheme **162**). Conversion of the carboxylic acid **508** to the corresponding acid chloride using Ghosez's reagent, followed by direct treatment with NaN$_3$ resulted in formation of acyl azide **509**, the substrate for the planned Curtius rearrangement.

To prevent ketene formation of the dioxinone fragment the Curtius rearrangement was performed at a suitably mild temperature in the presence of *iso*-propanol. This gave rise to rearrangement and the carbamate **510** was obtained in 76% yield. The minor product **511** was isolated in 9% yield. While the desired isocyanate wasn't directly observed, its occurrence is inferred from isolation of these rearranged products.
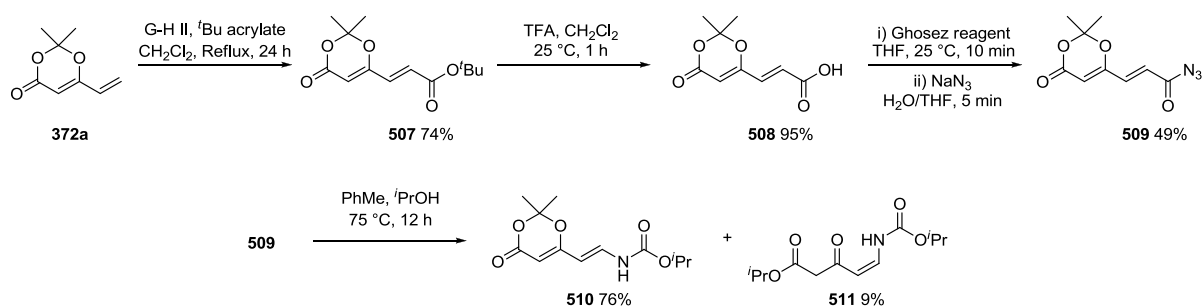
Scheme 162. Synthesis of acyl azide substrate **509**, Curtius rearrangement and reaction to carbamate **510**.

With the acyl azide **509** in hand, and suitable conditions for its Curtius rearrangement developed, the intramolecular acylation reaction was attempted (Scheme **163**). The acyl azide was heated at 75 °C in toluene, until the starting material was consumed. Carrying out the reaction at 0.02 M concentration provided a complex mixture of products that could not be separated. This result was not improved by using a more dilute concentration of 0.001 M and **494** was not observed.
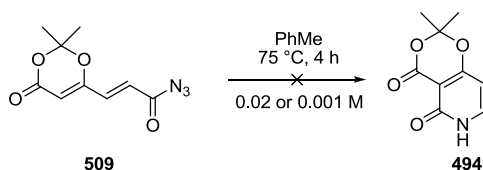
Scheme 163. Attempted Curtius rearrangement and aromatization.

As a complex mixture was observed, a second substrate *N*-Boc-carbamate **512** was then examined (Scheme **164**). This could be reacted under a difference set of conditions, perhaps more conducive to selective reaction. The acyl azide **509** was heated in toluene and *tert*-butanol resulting in a Curtius rearrangement and trapping of the isocyanate to give *N*-Boc carbamate **512**. This substrate was then subjected to variety of conditions for a Friedel-Crafts type acylation. Use of triflic anhydride and DMAP or triphosgene and pyridine failed to give the desired pyridone **494**; a complex mixture being obtained in both cases.[199]
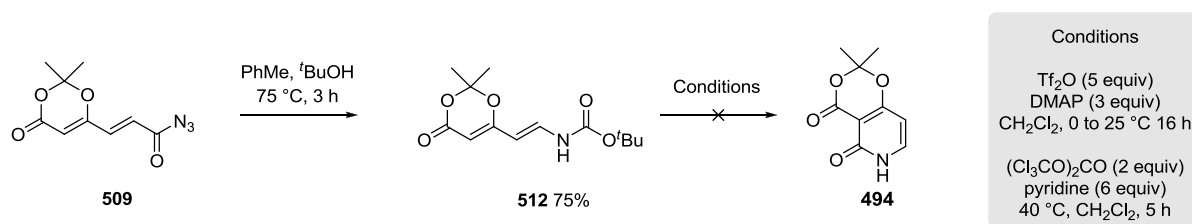
Scheme 164. Synthesis of the *tert*-butyl carbamate **512** and attempted aromatization to pyridone **494**.

Further investigations into the formation pyridone **494** were not attempted, however some further suggestions for experiments are as follows: splitting the process into two steps, first of all observing the isocyanate and then secondly, the intramolecular acylation reaction would be helpful. This would provide evidence that the isocyanate does indeed form and then allow different conditions to be applied for the subsequent step. While a thermal rearrangement may give the isocyanate, treatment with a Lewis acid such as BF$_3$.OEt at lower temperatures may also provide an effective solution to the problems encountered.[199]

1.17.3   Towards a Quinone Synthesis

1.17.3.1   1,2-Diketone Synthesis

IBX is commonly used in DMSO, one of the few solvents it is soluble in. Reactions of alcohol **431a** with IBX in DMSO however gave none of the ketone **335a**. Instead the over-oxidised product **433a** was obtained in 30% yield (Scheme **165**).[200] Given the ease at which IBX can carry out oxygen transfer and the varied outcomes with enolizable ketones this result isn't necessarily surprising.[201]
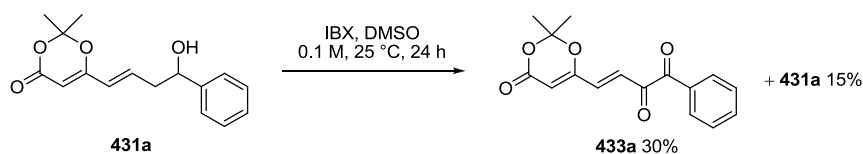
Scheme 165. Oxidation of the alcohol **431a** to give the α-dicarbonyl compound **433a**.

As previously mentioned, oxidation of alcohol **431a** was more efficient when facilitated by DMP (Chapter **xx**, Scheme **xx**). Schreiber's seminal contribution in this field shows that DMP can be also used to effect oxidation of acidic methylene positions.[202] Taking the ketone **335a**, conditions using triethylamine and collidine as base were attempted, the use of collidine giving a slightly higher 41% yield of the diketone **433a** (Scheme **166**). The best yields for formation of diketone **433a** were achieved by oxidation of alcohol **431a** with DMP under basic conditions. This gave diketone **433a** directly in a 45% yield. Starting the reaction at −15 °C the ketone **335a** is observed by TLC and by warming to room temperature further reaction occurs to the 1,2-diketone.
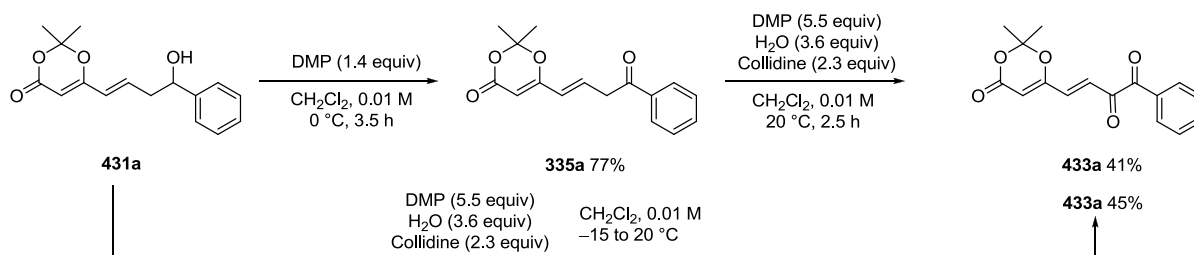
Scheme 166. Alternative routes to the α-dicarbonyl compound **433a**.

1.17.3.2 Aromatization of the 1,2-Diketones

Having developed a route to diketone **433a**, its intramolecular aldol condensation reaction was then examined (Scheme **167**). Submitting diketone **433a** to the previously developed ketene trapping/aromatization conditions we expected formation of the keto-ester **513** which would undergo Aldol condensation to give the quinone **504a**.
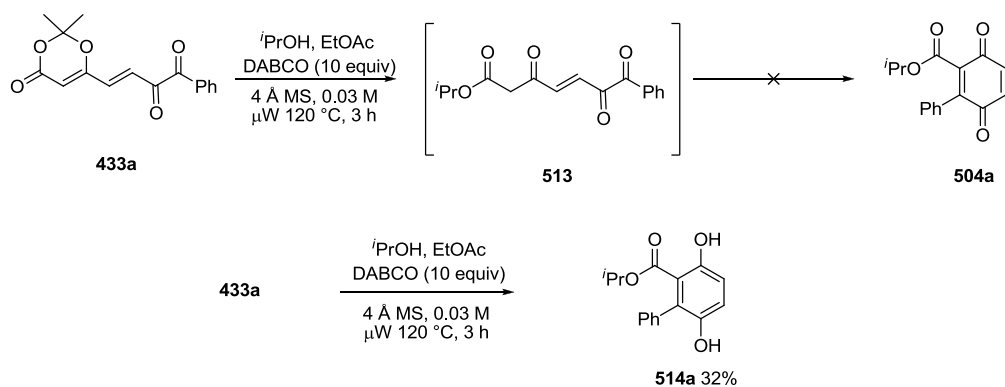
Scheme 167. Unexpected formation of the hydroquinone **514a**.

To our surprise the isolated product was actually hydroquinone **514a** in 32% yield. Thus, alongside aromatization, a reduction reaction had also taken place. No oxidized species could be isolated, therefore the reaction conditions were varied in an attempt to determine the reductant. The DABCO catalyst was removed but in this case reaction still occurred to give **514a** in 8 % (Table **14**, Entry **2**). It is likely that, as observed in the synthesis of salicylates, DABCO catalyzes the intramolecular Aldol reaction but is not strictly necessary and is not responsible for the reductive process. *Iso*-propanol could be oxidized, acting as a reductant, however changing the alcohol to *n*-propanol resulted in no increase in yield, hydroquinone **514b** being isolated in 31% yield (Table **14**, Entry **3**).

Another possibility to explain the formation of hydroquinone **514a** is that a disproportionation reaction is taking place in this process. The reaction was carried out in the presence of the hydroquinone 1,4-dihydroxybenzene. It was hoped this would be oxidized in preference, however the hydroquinone **514a** was again isolated in 35% yield (Table **14**, Entry **4**). This doesn't exclude the possibility of a disproportionation reaction, but could suggest that disproportion occurs before the Aldol condensation; however none of the expected oxidized products were ever isolated from product mixtures.

Carrying out the reaction open to air under conventional heating also failed to produce any of the quinone **504a** (Table **14**, Entry **5**). To improve yields the reaction was attempted at lower temperatures and to this end appearance of new products was observed only above 90 °C. Reaction at 100 °C required 5.5 h for consumption of starting material and no improvement in yield was observed (Table **14**, Entry **6**).

433a

R = ᶦPr **514a**
R = ⁿPr **514b**
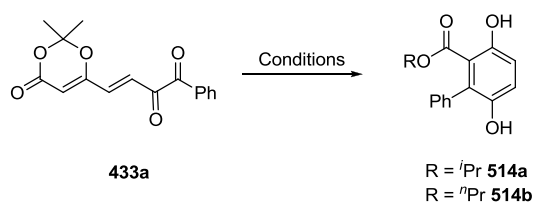
Entry[a]	DABCO (equiv)	Temperature °C	Time (h)	Additive	**Product** Yield (%)
1[b]	10	120	3	-	**514a** (32)
2[b]	0	120	3	-	**514a** (8)
3[c]	10	120	3	-	**514b** (31)
4[b]	10	120	2	1,4-dihydroxybenzene	**514a** (35)
5[d]	10	110	20	-[e]	**514a** (29)
6[b]	10	100	5.5	-	**514a** (27)

a) All reactions conducted at 0.03 M concentration b) ᶦPrOH/EtOAc solvent, microwave heating c) ⁿPrOH/EtOAc solvent, microwave heating d) ᶦPrOH/PhMe, conventional reflux. e) Reflux carried out open to atmosphere.

Table 14. Conditions for conversion of dicarbonyl **433a** to hydroquinones **514a** and **514b**.

The reactivity of the intermediates **513** and the high temperature required for cyclization suggested that it would be difficult to improve yields much further given that no distinct side-products have been observed or isolated. To be sure that the low yields during the synthesis and cyclization of diketone **433a** weren't substrate specific some other substrates were synthesized and subjected to the trapping/aromatization conditions (Scheme **168**).
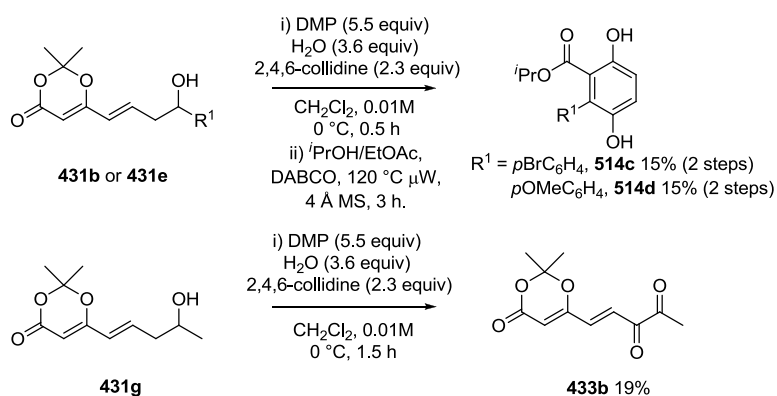
Scheme 168. Substrate synthesis and hydroquinone formation of further substrates.

The two substituted biaryl hydrquinones **514c** and **514d** were isolated both in 15% over 2 steps. The intermediate 1,2-diketone compounds **433** could not be isolated in pure-form in this instance but the contaminant in each case was tentatively assigned as the corresponding 1,4-diketone isomer. Upon aromatisation only the product of the 1,2-diketones **433b** were obtained and no other aromatic compounds were observed. The methyl substituted analogue **431g** was oxidized to give the 1,2-diketone **433b** in 19% yield but was not continued to the hydroquinone stage. These results confirmed that the low yields for formation of the hydroquinones **514** were general.
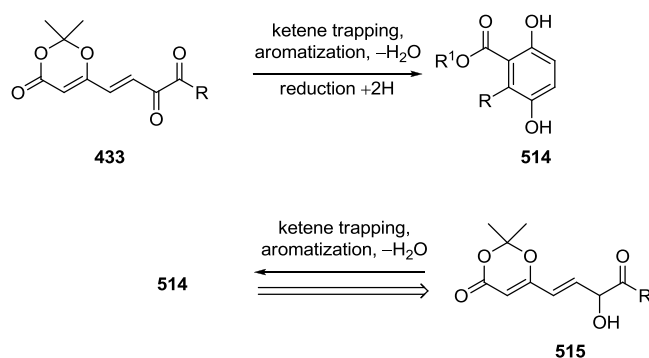
Scheme 169. Retrosynthetic analysis for hydroquinones reveals α-hydroxy ketones.

The low yield for all examples in conversion of the diketones **433** to the hydroquinones **514** is most likely due to the disproportionation that must occur to produce the reduced compound (Scheme **169**). By retrosynthetic analysis of the hydroquinone product **514** it can be seen that the most suitable starting material for this reaction is the α-hydroxy ketone **515**. With this in mind some attempts were made to produce such substrates.

1.17.4 Alternative Routes for Hydroquinone Substrates

1.17.4.1 α-Hydroxylation Routes

The first route chosen to target the α-hydroxy ketone **515** was to carry out a direct hydroxylation of the ketone **335a** (Scheme **170**). The alpha hydroxylation of **335a** was attempted with PhI(OAc)$_2$ in MeOH/KOH, this however resulted only in decomposition.[203] Treatment under acidic conditions (PhI(OAc)$_2$ / TFA) returned starting material and several decomposition products.[204]
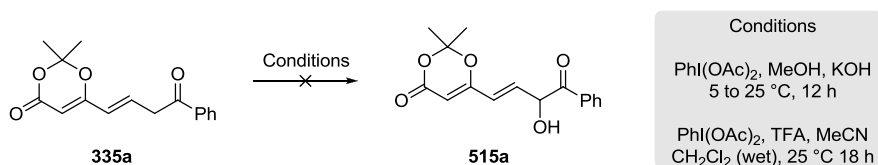
Scheme 170. Attempted formation of the α-hydroxy ketone **515a**.

The failure to functionalize **335a** by direct methods is not only due to its instability to basic conditions, but due to the highly conjugated nature of its enol form. This presents multiple reactive sites with no significant difference in nuleophilicty.[205] With direct hydroxylation methods failing, an alternative retrosynthetic analysis of the acyloin **515a** was considered.

1.17.4.2 Cross Metathesis for Synthesis of Dithiane Precursors

135

A common route for the synthesis of non-symmetrical acyloins is employing Umpolung chemistry, using an acyl anion equivalent.[206] In this case a dithiane was chosen as a masked acyl anion equivalent (Scheme **171**). If dithiane additions were successful, then there would be opportunities to produce more functionlized compounds through addition of the parent 1,3-dithiane followed by Brook rearrangement and further alkylation.[207]
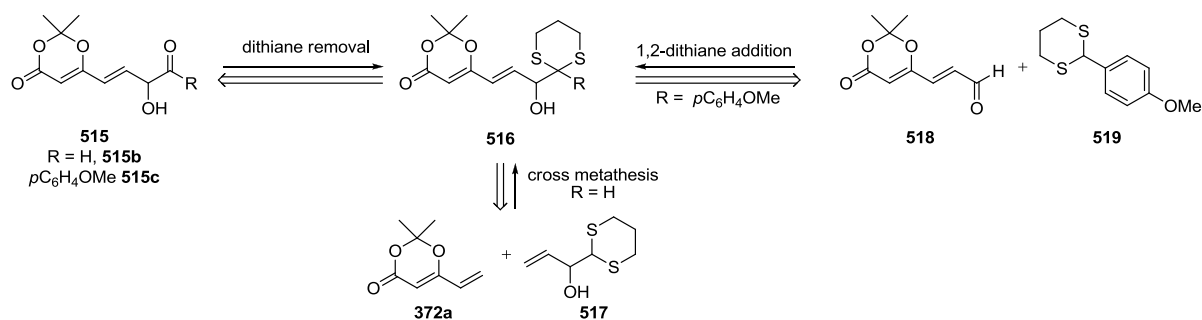
Scheme 171. Retrosynthetic routes of the acyloin **516**.

Retrosynthetically acyloin **515** is produced via unmasking of dithiane **516**. Deprotection of dithianes can be effected under mild conditions such as Fujitas conditions [Hg(ClO$_4$)$_2$, CHCl$_3$/MeOH] as exemplified in Smith's synthesis of a spongistatin 1.[208] The intermediate **516** could be produced either by cross metathesis of **372a** and dithiane **517** or alternatively, 1,2 dithiane addition of **519** to the aldehyde **518**.
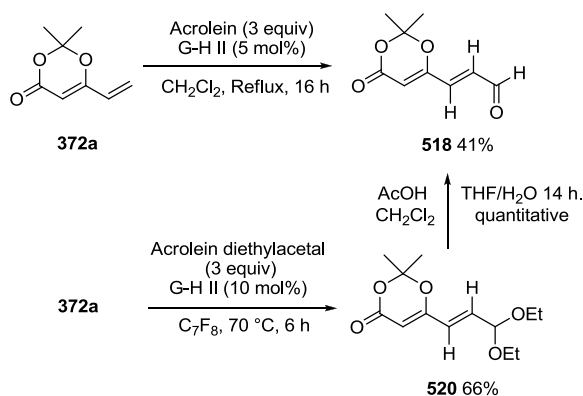
Scheme 172. Synthesis of dioxinone aldehyde **518**.

Cross metathesis of vinyl dioxinone **372a** with acrolein gave the desired aldehyde **518a** in 41% yield (Scheme **172**). Use of acrolein as solvent in this reaction failed to give any desired cross metathesis product. Cross metathesis of **372a** with acrolein diethyl acetal was also unsuccessful under these conditions however use of higher temperatures with perfluorotoluene gave the diethyl acetal **520** in 66% yield. Quantitative cleavage of the acetal **520** gave rise to the desired aldehyde **518** in a slightly higher overall yield than direct metathesis with acrolein.

Addition of dithianes to α, β-unsaturated carbonyl compounds has been the subject of several studies, discussing differences between 1,2 and 1,4-addition.[209] Addition of 2-phenyl-1,3-dithiane to cyclohex-2-enone at 25 °C results in solely 1,4 addition while addition at −78 °C, and quick quenching (after 10 min), gives a 13:7 mixture of 1,2 addition and 1-4 addition products; in hexane/THF (9:5), the ratio increases to 19:1.

The dithiane **519** was added to the aldehyde **518** at −78 °C in THF and the desired compound was isolated with some unidentified impurities in approximately 16% yield with starting material recovered in 47% yield (Scheme **173**). A second attempt in which the reaction as allowed to warm to 25 °C the starting material was fully consumed, however multiple side products were produced. Side products most likely arise from possible conjugate addition to the aldehyde or dioxinone moieties. In an attempt to circumvent these problems cerium chloride was used in order to promote 1,2-addition.[210] Again traces of the product were observed but could not be isolated in pure form.
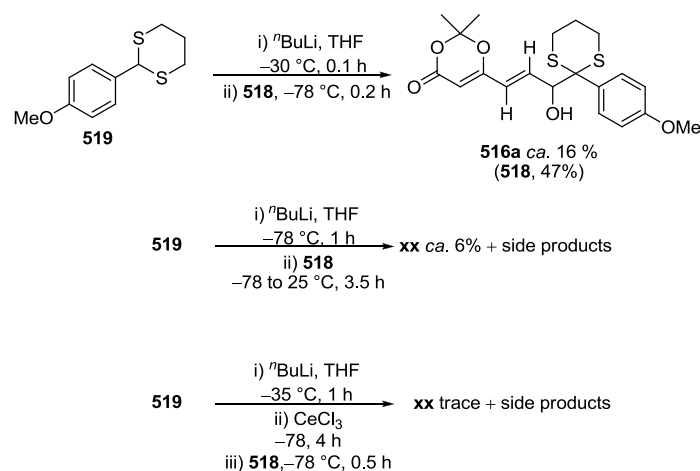
Scheme 173. Conditions for synthesis of the dithiane **516a**.

Pursuing the second route based on cross metathesis, construction of substrate **517** began with addition of 1,3-dithiane **521** to acrolein to give allylic alcohol **517** in 77% yield (Scheme **174**). This was subsequently protected as the TBS ether **522**. Unfortunately, on subjecting these two compounds to the two different sets of conditions developed for cross metathesis with vinyl dioxinone **372a**, none of the desired products **516b** or **516c** were isolated.
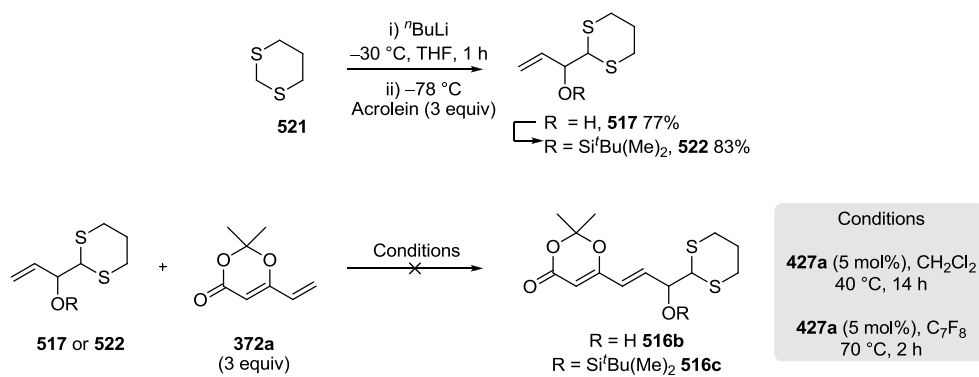
Scheme 174. Attempted synthesis of the dioxinone **516b** and **516c** by cross metathesis.

Failure of the dithiane moieties **xx** and **xx** to undergo cross metathesis is likely due to steric constraints. While first generation metathesis catalysts perform poorly in metathesis reactions of sulfides, second generation catalysts have been shown to be active in metathesis of compounds bearing sulfide, disulfide, dithiane functionalities.[211] The literature precedent for cross metathesis compatibility of dithianes suggests that steric effects must be responsible for the failure of cross metathesis in these cases.[212]

1.18 Conclusion of Extension of Methodology to Other Aromatic Compounds

The methodology previously developed for the synthesis of salicylates (Chapter **3**) and γ-resorcylates (Chapter **4**) enabled the synthesis of further aromatic classes of molecules. Intermediate alcohol-dioxinone derivatives **431**, developed previously for salicylate synthesis, were used in a synthesis of hydroquinones **514** (Scheme **175**). The alcohols **431** could be oxidized to the diketone compounds **433** that underwent ketene generation and trapping of the resultant ketene, followed by aromatization and reduction, to give the hydroquinones **514**. The hydroquinones obtained may be the result of a disproportionation reaction, but further investigation is required to confirm or disprove this.
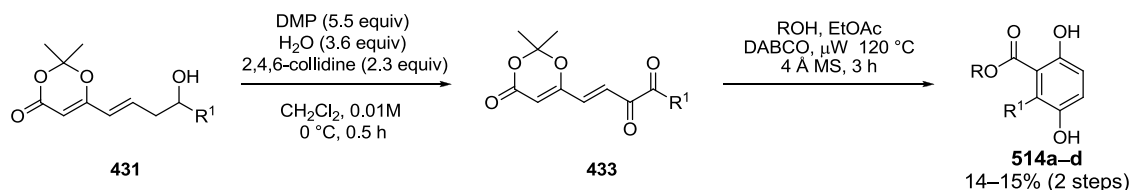
Scheme 175. Synthesis of hydroquinones **514a–d**.

Exploiting methodology for unsaturated dioxinone synthesis towards γ-resorcylates (Chapter **4**), gave unsaturated amide **498** and β-hydroxy-amide **499** (Scheme **176**). Conditions were explored for the aromatization of **498** and **499** to give 6-dialkylamino salicylate **492a**. It is postulated that these aromatization reactions proceed through a 6π-electrocyclization of a dienylketeniminium intermediate
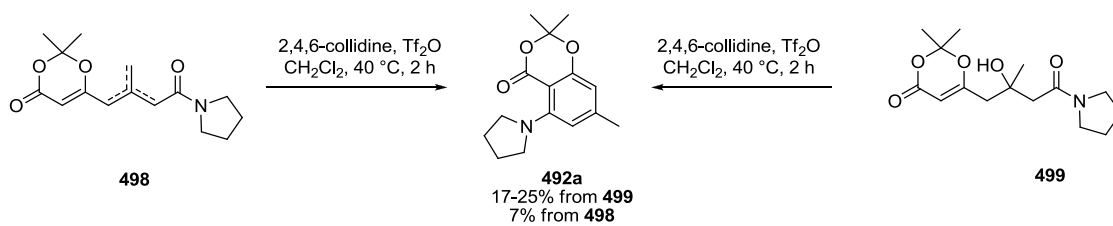
Scheme 176. Synthesis of 6-aminosalicylate **492a** from **498** or **499**.

A similar hypothesis was explored for synthesis of 4-oxo-2-pyridones (Scheme **177**). However, 6π-electrocyclization of isocyanate **493** failed to give **494**.
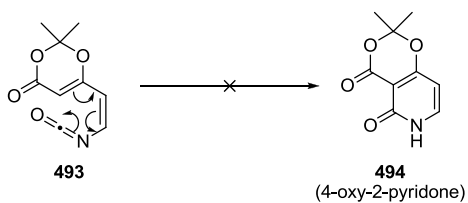
Scheme 177. Attempted formation of 2-pyridone **494** was unsuccessful.

# Towards the Synthesis of Higher Polycarbonyl Dioxinone Derivatives

1.19 Introduction

1.19.1   Biomimetic Synthesis of Naphthalenetriols

As outlined in the main introduction (chapter **1**) biomimetic syntheses of resorcylate and salicylate natural products have been carried out from tetracarbonyl compounds. When developed however, the polyketide biosynthesis hypothesis was also extended to larger aromatic systems such as napthols, hydroxyanthracenes and tetracycline structures.[213] Wishing to recreate such larger systems in a laboratory setting, Harris and co-workers set about producing hexacarbonyl compound **523** (Scheme **178**).[214]

Their initial approach to **523** was a β-ketoacylation of 1-phenyl-1,3,5,7-octanetetraone with ethyl benzoylacetate to give **523** in 19%. A higher yield was achieved through an *in situ* double β-ketoacylation of acetylacetone **524**, to give **523** in 40% yield. It was subsequently found that **523** could lead to several cyclization products depending on the reaction conditions. Treatment with aqueous KOH gave **526** as the major product (**527** was the minor product along with its hemiketal), and subsequent aldol condensation gave the naphthalenetriol **528**. Treatment of **523** with pH 8 silica gel resulted in isolation of naphthalenetriol **530** in 92% yield, intramolecular acylation of **529** occurring through the more acidic methylene position. These two naphthalenetriols were air sensitive but stable as triacetates. Furthermore, the cyclizations proved to be selective and the formation of **531** or **532** was not observed.
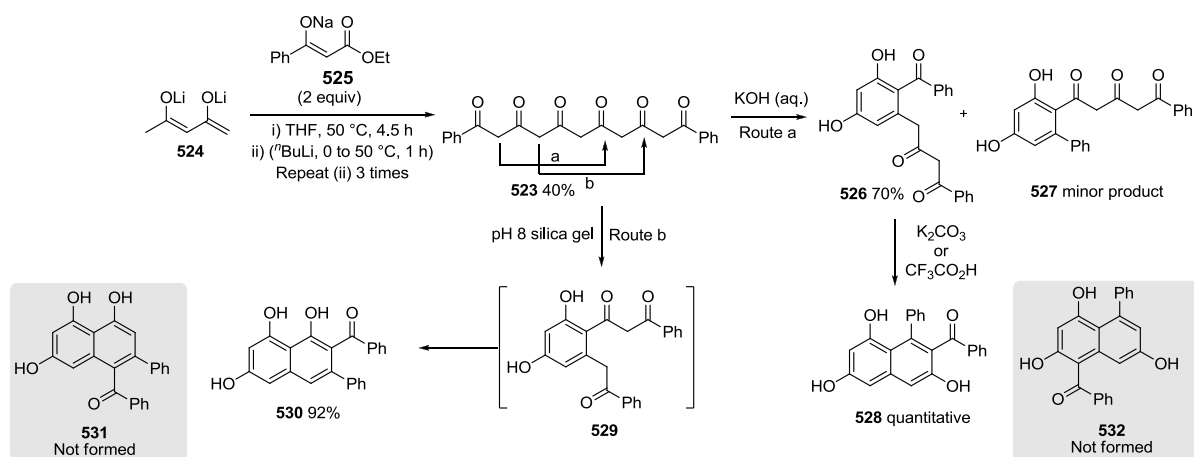
Scheme 178. Synthesis of hexacarbonyl compound **523** and cyclization to give naphthalenetriols under differing reaction conditions.

## 1.19.2 Biomimetic Synthesis of a Homophthalate

Most previous research using dioxinones for polycarbonyl synthesis, as outlined in the introduction, has been focused on the synthesis of tetra-carbonyl compounds and their aromatization to benzene derivatives, including the research presented in earlier sections. In one case the principle concept outlined in these syntheses was extended to produce a pentacarbonyl compound, dimethyl 3,5,7-trioxononanedioate **535** (Scheme **179**).[215] This was produced by a double acetylation of dioxinone **197** with bis(4-nitrophenyl) carbonate **533** to give the bisdioxinone derivative **534**. On heating to effect ketene generation and trapping, aromatization to the homophthalate **291** *via* the only available intramolecular aldol cyclization occurs.[216] Although no direct evidence was provided for formation of the pentacarbonyl compound **535**, the aromatization proceeded in high yield and without external base.
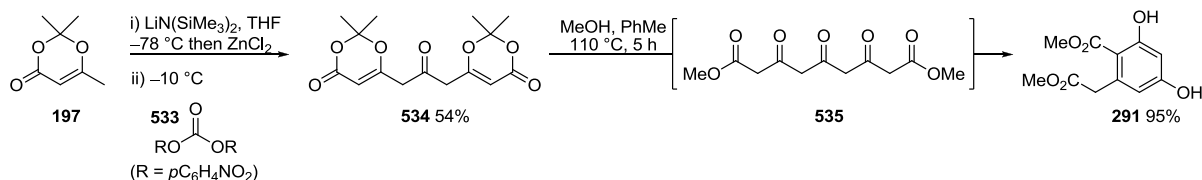
Scheme 179. Synthesis of dimethyl homophthalate **291** as reported by Barrett *et al*.

1.19.3 Naphthalenetetraol Natural Products

Related to the naphthalenetriols produced by Harris are the naphthalenetetraols which are common motifs in several natural products including rubrofusarin (**536**), nigerone (**537**) and hypoxyxylerone (**538**) (Scheme **180**).[217] These molecules all exhibit useful biological activities and, given that the reported syntheses of these structures involve napthalenetetrols as intermediates, new synthetic routes could be useful for their synthesis, and construction of related compounds.
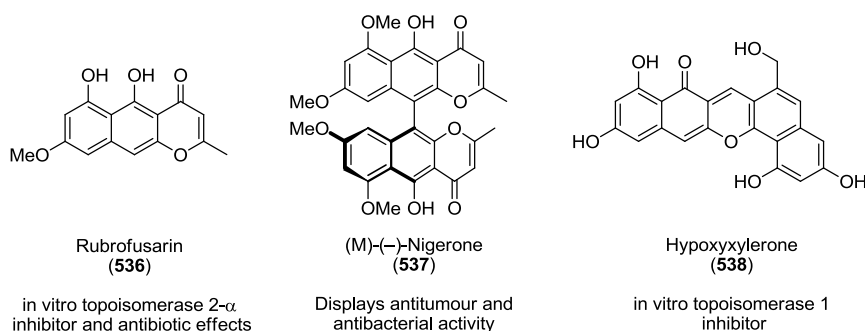
Scheme 180. Natural products produced *via* naphthalenetetrols and their biological activities.

1.19.4   Bisdioxinones as Naphthalenetetraol Precursors

Building on the precedent of bisdioxinone **534** and the selective cyclization of Harris, the diketo-bisdioxinone **539** is proposed as a possible precursor for naphthalenetetraols **543** and **544** (Scheme **181**). The product of double ketene trapping, diester **540** could undergo two possible aldol condensations *via* cyclization a or b to give **541** or **542** respectively. Upon further aromatization, **541** can only give **543** while **542** could lead to two possible products, attack through the more acidic position of **542** favoring naphthalenetetrol **543**. To test this hypothesis a synthesis of the starting bisdioxinone **539** would need to be developed.
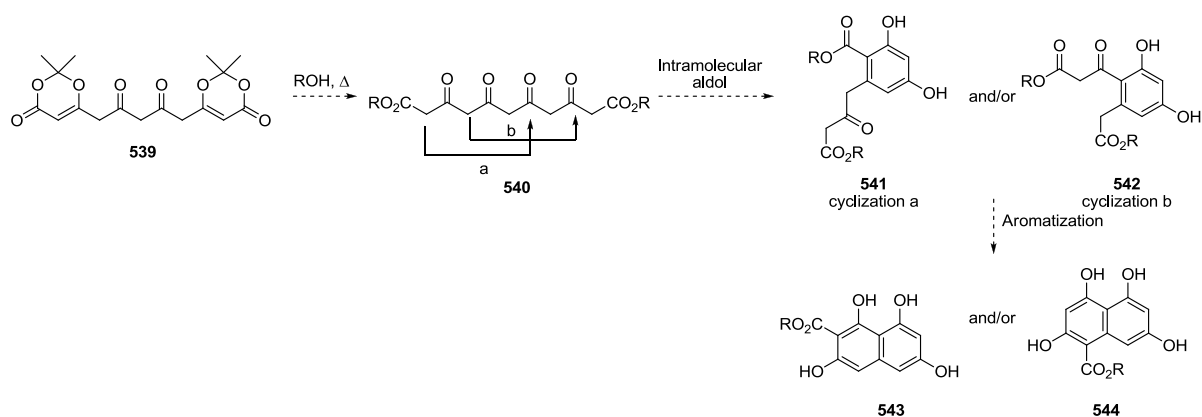
Scheme 181. Bisdioxinone **539** as a putative precursor to naphthalenetetrols.

Reviewing the literature, the methyl protected β-resorcylate **545** when treated with KOH underwent hydrolysis and decarboxylation to **546**, followed by cyclization to **547** - a pathway that could render naphthalenetetrol synthesis from **541** unfeasible and similar to problems encountered in our earlier Dieckmann cyclization attempts (Scheme **182**).[218] With regards to intermediate **542**, the similar protetrone **548** when treated under acidic conditions gave the Dieckmann cyclization product naphthacenequinone **549**, albeit with a malonamoyl rather than a malonyl moiety.[219]
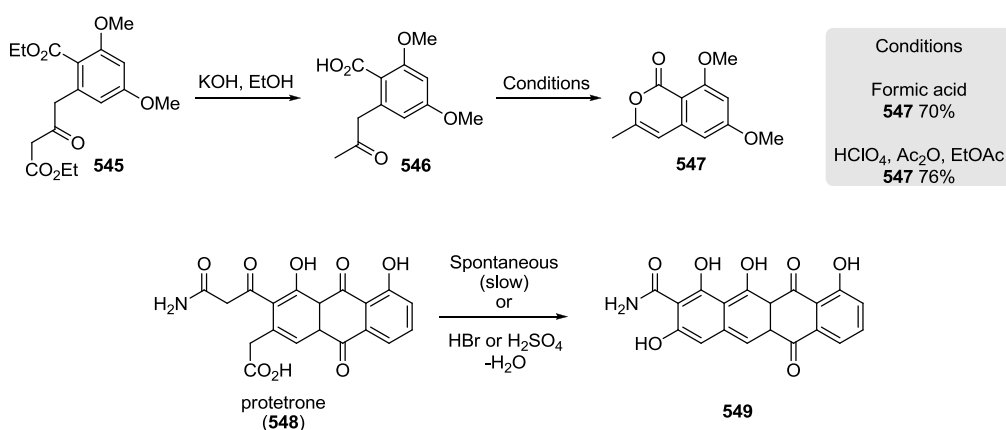
Scheme 182. Literature reactions of diester **545** and protetrone (**548**).

1.19.5   Retrosynthetic Analysis of Bisdioxinone **539**

Using the methodology previously developed in the Barrett group, a retrosynthesis of the bis-dioxinone **539** was proposed (Scheme **183**). It was anticipiated that **539** would be preceeded by palladium catalyzed deallylation and decarboxylation of bisdioxinone **550**, a product of intramolecular acylation of keto-ester-dioxinone **237a** and the acid chloride **551**.
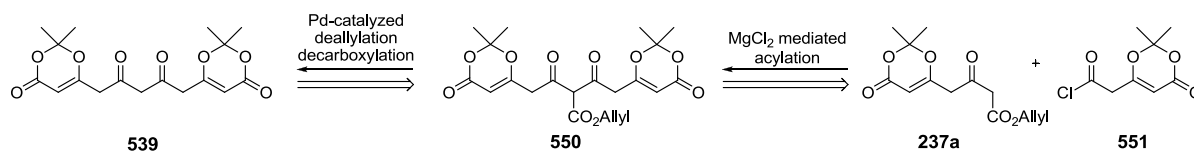
Scheme 183. Retrosynthetic analysis of the bisdioxinone **539**.

1.20 Results and Discussion

1.20.1   Synthetic Studies Towards the Bisdioxinone **550**

The synthesis of the required carboxylic acid **368** (precursor to acid chloride **551**) began with addition of the lithium enolate of dioxinone **197** to benzyl chloroformate which resulted in the two regioisomers **552** and **553**, which despite their very close elution values could be separated by chromatography (Scheme **184**). The desired regioisomer **553** was subjected to hydrogenolysis in the presence of palladium on charcoal to give acid **368** in a 42% overall yield from dioxinone **197**.
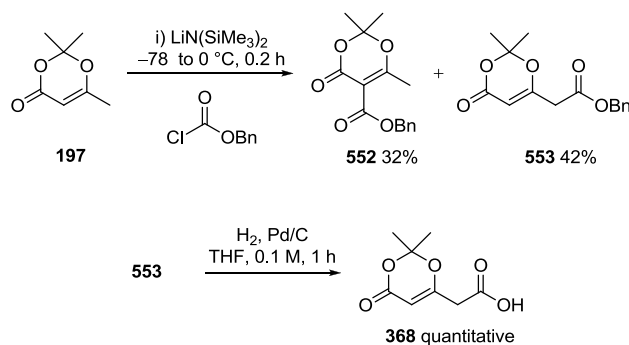
Scheme 184. Carboxylation of dioxinone **197** and subsequent hydrogenation to give the dioxinone acid **368**.

The next step in the synthesis was to convert acid **368** to the corresponding acid chloride **551** and investigate its use as an acylation agent. The acid **368** was treated with Ghosez's reagent at 0 °C for 0.2 h before being added to the pre-formed magnesium enolate of keto-ester **237a** (Scheme **185**). The starting keto-ester **237a** was isolated in 57% as well as a complex mixture of products which did not appear to contain the desired bisdioxinone compound **550**. In control reactions, taking acid **368** and treating with Ghosez's reagent followed by reaction with ethanol and pyridine gave, albeit in moderate yield, the expected ester **554**. Also, replacing the acid **368** with acetic acid in reaction with Ghosez's reagent followed by the magnesium enolate of keto-ester **237a** resulted in successful acylation to give the diketo-dioxinone **555**.
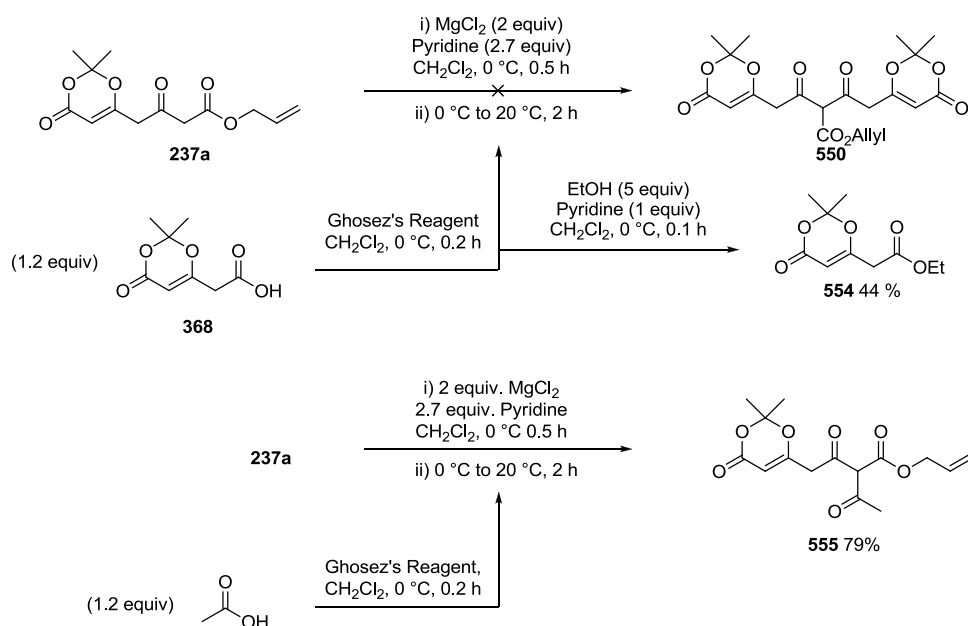
Scheme 185. Attempted acylation of keto-ester **237a** with the dioxinone acid chloride **551**, and control reactions.

It is clear that unsuccessful reaction of **237a** and **551** is due to this specific acid chloride. Given the presence of pyridine in these reaction mixtures, it is expected that in the case of acid chloride **551**, deprotonation at the acidic methylene position would be possible forming a ketene. If this is indeed the case, decomposition or polymerization of the ketene appears to out-compete reaction with the magnesium enolate of **237a**.

Due to the base sensitive nature of the acid chloride **551** an attempt was made to react it with Chan's diene (**124**) (Scheme **186**). Chan's diene (**124**) is known to react with acetyl chloride without an external catalyst to give methyl 3, 5-dioxohexanoate.[220] Unfortunately reaction of **124** with the acid chloride **551** failed to give the triketo-dioxinone **556**. A complex mixture of products was observed and only methyl acetoacetate was isolated in 15% yield.
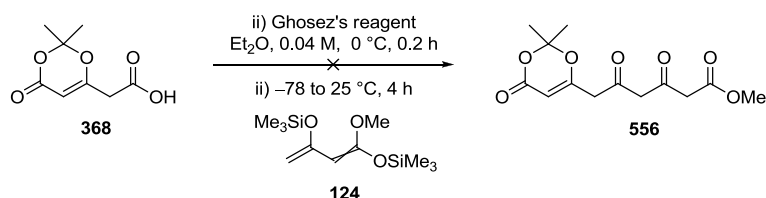
Scheme 186. Unsuccessful reaction of the corresponding acid chloride of carboxylic acid **368** with Chan's diene **124**.

1.20.2   Formation of a Dioxinone Dimer **557**

Taking the above acylation reaction in its constituent steps, characterization of the acid chloride **551** was attempted. After addition of Ghosez's reagent to the carboxylic acid **368** the mixture was concentrated *in vacuo*; however, the acid chloride was not detected but rather a new compound, **557** was observed (Scheme **187**). The product **557** corresponds to a dehydrative dimerization process occurring and its structure was confirmed by x-ray crystallography.[221]
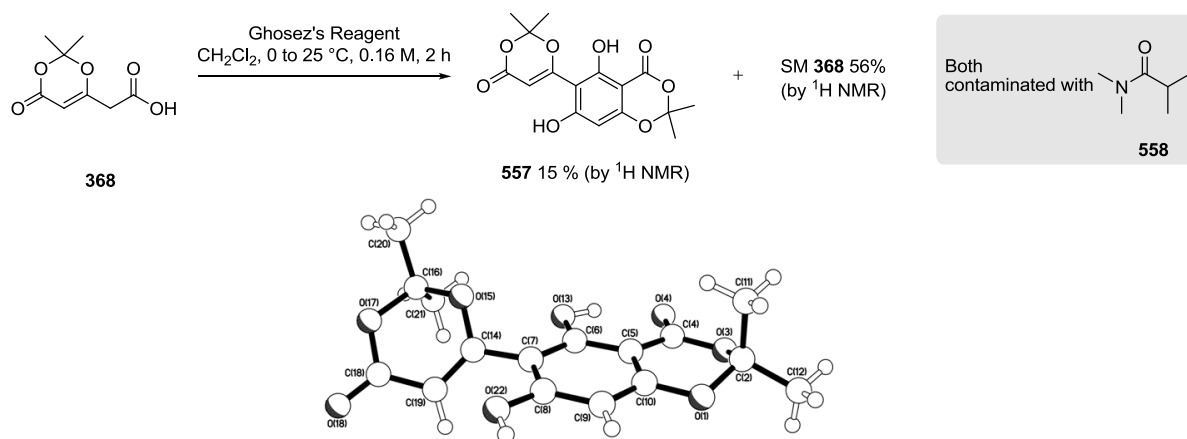
Scheme 187. Unexpected formation of a dioxinone dimer **557** and graphical representation of its structure as determined by X-ray crystallography.

To investigate the formation of dimer **557** and to produce an IR of the acid chloride **551** *in-situ*, the reaction was performed with a Mettler-Toledo ReactIR spectrometer (Graph **1**). IR measurements (16 scans) were taken every 15 seconds, the initial peaks at 0–30 min due to the introduction of substrate and solvent, with cooling taking place until the limitation of the equipment was reached at −14 °C. At this temperature, the addition of 1.3 equivalents of Ghosez's reagent was carried out by injection (timepoint: 1 h 20 min). The reaction was then allowed to warm to 25 °C at a rate of 2.5 °C/min so when a second 1.3 equivalents of Ghosez's reagent was added (timepoint: 2 h 12 min) the mixture was at room temperature. The reaction was carried out on a 1 mmol scale at 0.04 M concentration in CH_2Cl_2, the large reactor size necessitating more dilute reaction conditions.
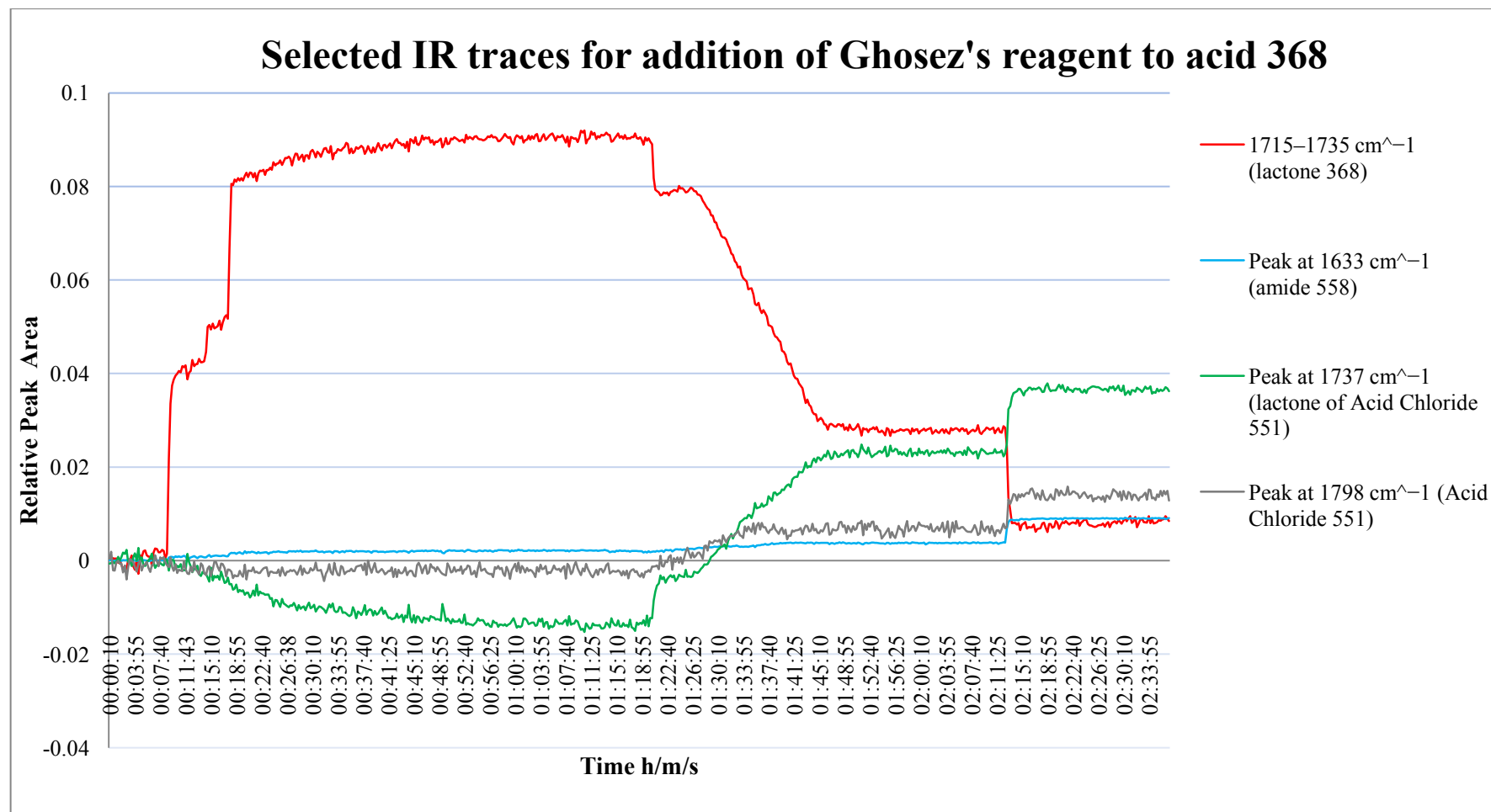
Graph 1. Monitoring the conversion of **368** to **551** by IR spectroscopy. Specific peaks were selected and their intensity during the course of reaction plotted. The peak at 1715–1735 cm^{-1} corresponds to the dioxinone lactone functionality in carboxylic acid **368**. The peaks at 1737 and 1798 cm^{-1} are indicative of the acid chloride **551**. The peak at 1633 cm^{-1} corresponds to the amide **558**.

After first addition of Ghosez's reagent the lactone peak of dioxinone **368** at 1715–1735 cm^{-1} (after an initial downward spike) appears to slowly decrease while a new lactone peak increases at 1737 cm^{-1} along with an additional peak at 1799 cm^{-1} which would correspond to formation of an acid chloride **551**. During this process the amide **558** (1633 cm^{-1}) is also produced at a constant rate matching decrease in the **368** lactone peak. When addition of Ghosez's reagent occurs at room temperature the reaction is much quicker and, in less than a minute, the starting acid **368** is consumed, along with further acid chloride **551** and amide **558** formation. An aliquot of the final mixture was quenched in Ethanol. TLC analysis of this aliquot shows formation of the ethyl ester **554** and none of product **557** or starting material **368** present.

These results suggest that when carboxylic acid **368** is treated with Ghosez's reagent, formation of acid chloride **551** occurs and under high dilution (0.04 M), is stable at room temperature for at least 1h without formation of **557** (Scheme **188**). In fact, when the reaction solution from the ReactIR experiment was kept at 3 °C under an inert atmosphere, reactions of this solution with ethanol gave the expected ethyl ester **554** for 1 week before acid **368** could be observed . Treatment of an aliquot of the solution with Hünigs base resulted only in decomposition; formation of the dimer **557** was observed on concentration of the solution without base.
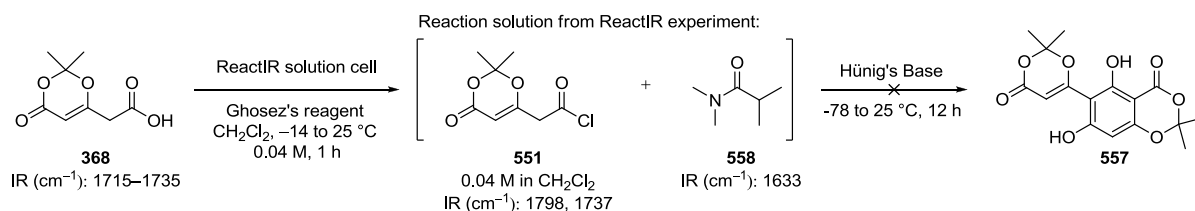
Scheme 188. ReactIR experiment and subsequent reaction of the solution of acid chloride **551** with Hünig's base.

1.20.3   Possible Mechanism for Formation of Dimer **557**

The mechanism for formation of dimer **557** is unknown but two possible pathways are given below (Scheme **189**). Path A proceeds *via* a quaternary ammonium salt and path B *via* ketene formation followed by a concerted [2+4] process. Following path A, the amide **558** is expected to add to acid chloride **551** giving the iminium chloride **I**. The enol form of **II** can then act as a nucleophile and is acylated by another molecule of **551** to give **IV**. Tautomerisation of **IV** followed by further intramolecular attack leads to the dimer **25** in a stepwise manner. More directly, pathway B follows elimination of amide salt from the iminium chloride **I** resulting in ketene **VI** that could undergo a [2+4] addition with another molecule of **VI** to give dimer **557**.
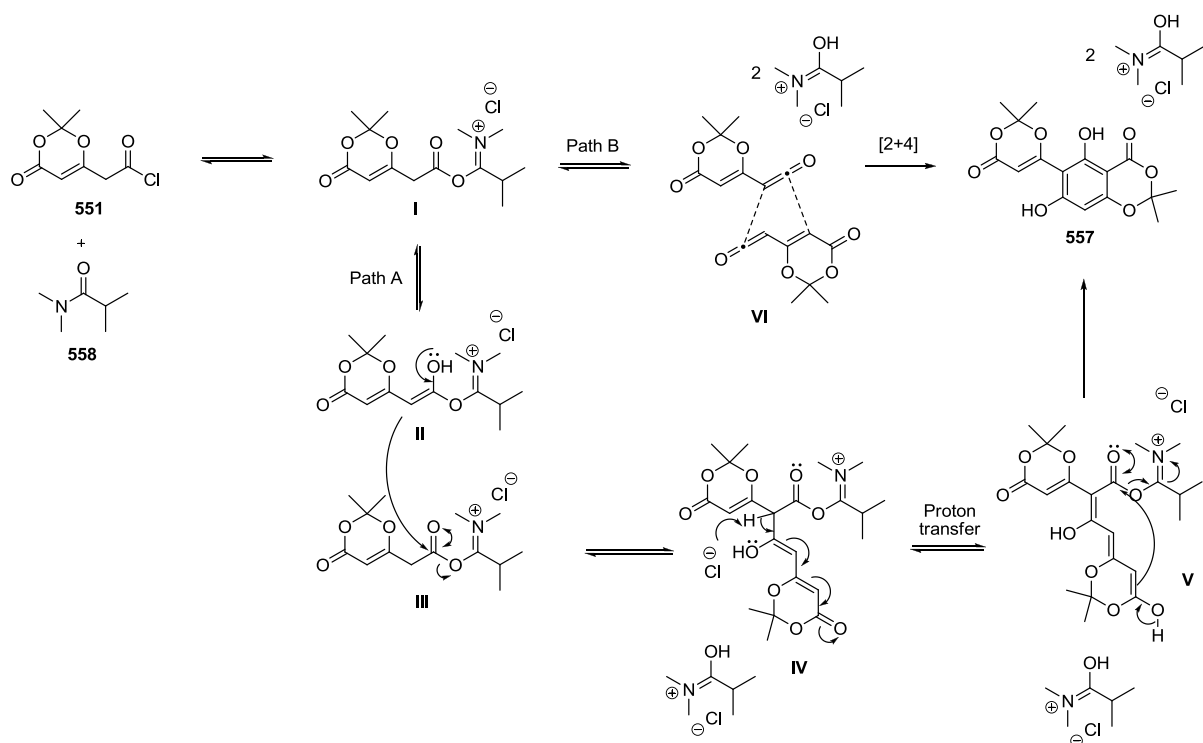
**Scheme 189.** Two possible mechanisms for the formation of dimer **557** from acid chloride **551**.

1.20.4 Further Synthesis of Dimer **557** and its Subsequent Reactions

Wishing to explore further reactions of dimer **557** some new routes to the carboxylic acid substrate **368** were developed (Scheme **190**). A regioselective formation of the ester **553** would avoid difficult purification and may provide a higher yield of dioxinone acid **368**. The lithium enolate dioxinone **197** could be regioselectively halogenated with hexachloroethane to give **559** in 55%, or 1,2-dibromotetrachloroethane to give **345** in 53%.[222] These halides could then be subjected to palladium catalyzed carbonylation to give the benzyl ester **553** in 43 and 47 % respectively.[223] In both cases dehalogenated starting material (**197**) was observed showing that, despite facile insertion, carbonylation appeared to be the problematic step.
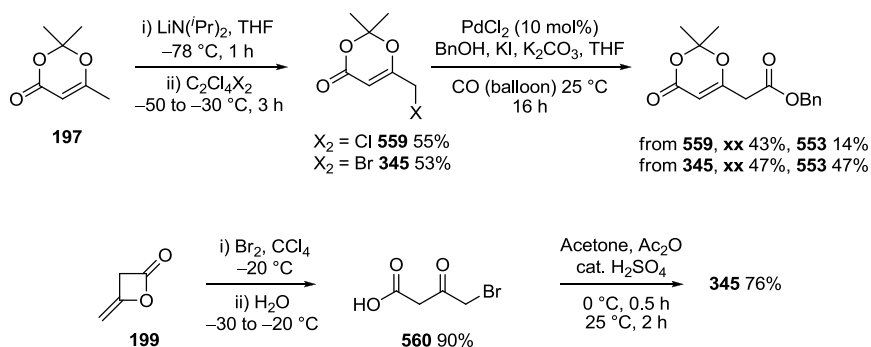
Scheme 190. Futher Routes developed to the benzyl ester **553**.

Pursuing a better route to bromo-dioxinone **345**, diketene **99** was converted to bromoacetoacetic acid **560** in 90% yield.[224] Despite formation of dioxinone **345** in 68% overall yield from **199**, the original carboxylation route to **553** was still most effective even though not regioselective. With further quantities of carboxylic acid **368** now in hand the dimerization reaction could be further examined. Carrying this out on 5.4 mmol scale gave an improved 27% yield of **557** (Scheme **191**). No doubt the low yield is in part due to the difficult isolation of **557**, the presence of amide **558** necessitating its isolation by crystallization.
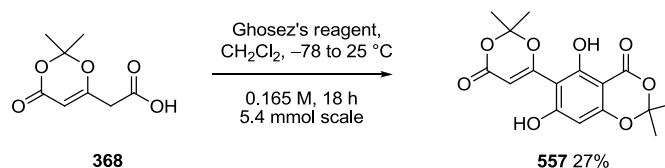
Scheme 191. Formation of the dimer **557** was carried out on preparative scale to allow a pure sample to be isolated by crystallization.

1.20.5   Further Reactions of Dimer **557**

Some reactions of **557** were first explored to understand its reactivity (Scheme **192**). On heating in methanol, the dimer **557** underwent transformation to give the keto-ester **561** in quantitative conversion (Scheme **192**). The ^{1}H NMR (THF-d_8) spectrum of **561** indicates both phenolic protons are hydrogen bonded and the compound exists solely in its keto-form. Reaction of the dimer **557** with caesium carbonate in methanol gave a mixture of hydroxy-coumarins **562** and **563** in a combined 72% yield.   Methylation of **557** gave the methylated compound **564** in quantitative yield.[225] Further reactions and synthetic use of the dimer **557** is yet to be explored.
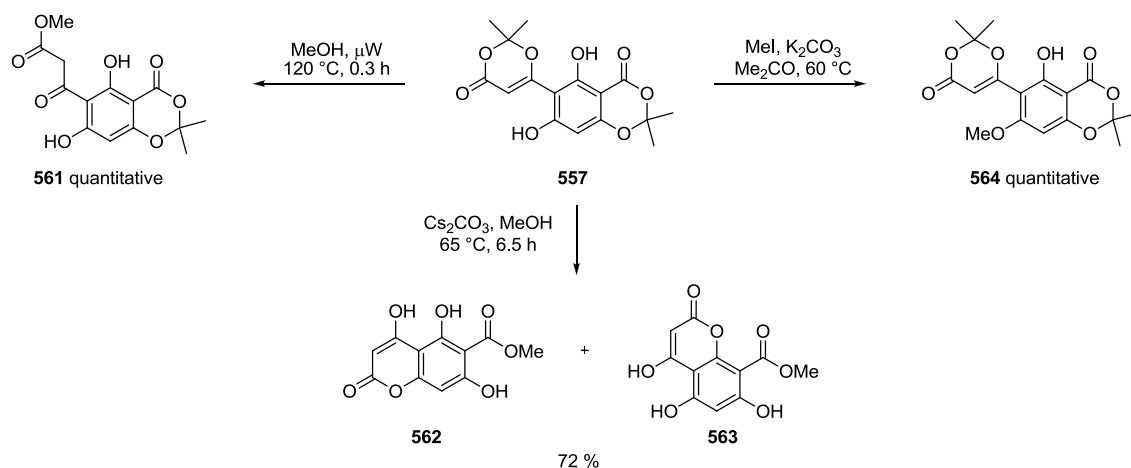
Scheme 192. Reactions of the dimer **557**.

1.21 Conclusions to the Synthesis of Higher Polycarbonyl Dioxinone Derivatives

Towards a hexacarbonyl compound and naphtalenetetrols, synthesis of bisdioxinone **550** was attempted using an acylation strategy (Scheme **193**). Unfortunately, bisdioxinone **550** was not formed and consequently, the hypothesis that after deallylation and decarboxylation, thermyolysis in an alcohol would give naphthalenetetrols **543** and **544** could not be tested.
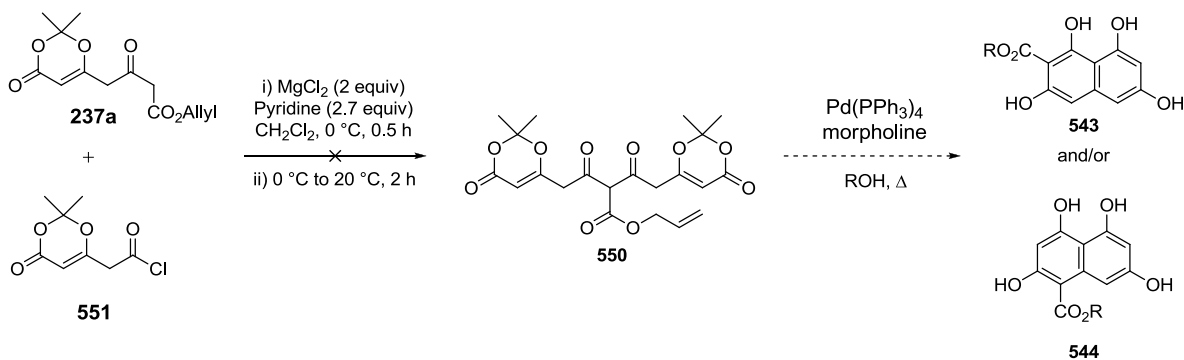
Scheme 193. The unsuccessful route to bisdioxinone **550**.

However, IR evidence for the formation of the acid chloride **551** was obtained and this appeared stable at 0.04 M (Scheme **194**). Interestingly, at a concentration of 0.165 M **551** dimerized to give highly substituted benzene compound **557**.
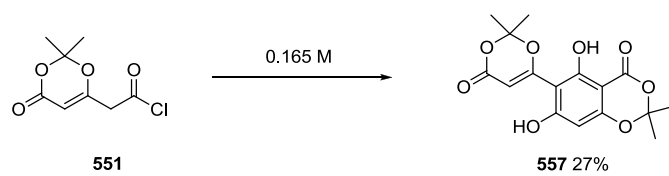
Scheme 194. Acid chloride **551** underwent dimerization to **557** at a concentration of 0.165 M.

Conclusion and Further Work

1.22 Conclusion

The research presented shows the application of dioxinone derivatives in the synthesis of aromatic compounds by *de novo* methodology. This work uses the key dioxinone derivatives vinyl dioxinone **372a**, keto-dioxinones **284a**, **c** and **d**, and the dioxinone acid chloride **551** to produce a range of aromatic products (Scheme **195**).
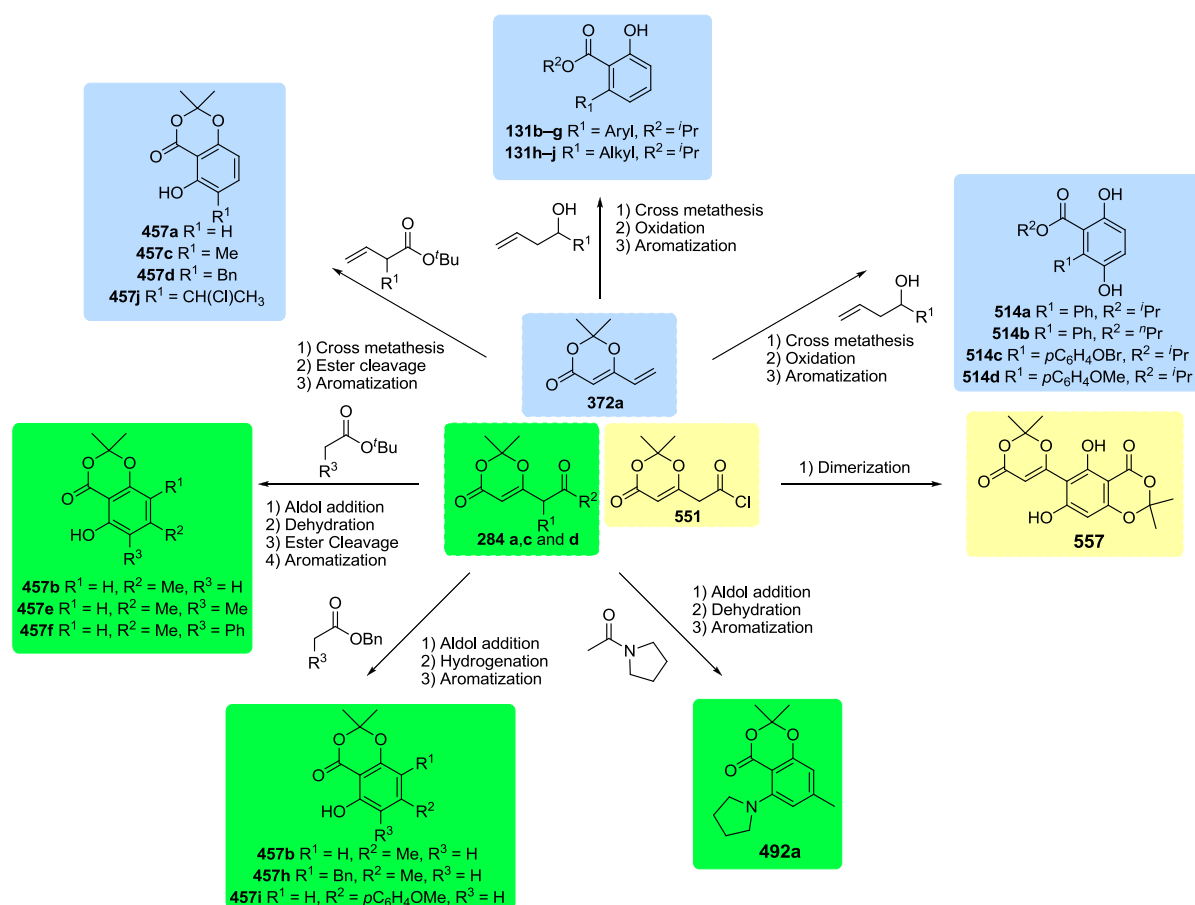
Scheme 195. Synthesis of aromatic compounds from dioxinone derivatives.

Firstly, the vinyl dioxinone **372a** was used in cross metathesis with homoallylic alcohols. After oxidation these compounds could undergo ketene generation, trapping and aromatization to give 6-aryl and 6-alkyl salicylates, **131b–g** and **131h–j**, in a novel biomimetic process (Chapter **3**). Building on the aromatization of diketo-dioxinones outlined in the introduction, this demonstrates that reduced compounds are also capable of aromatization.

An unexpected reaction during the synthesis of salicylates led to the synthesis of hydroquinones **514a–d** (Chapter **5**). Using cross metathesis once more allowed the construction of dioxinone-diones that underwent ketene generation and trapping followed by aromatization to give hydroquinones. Interestingly, the expected quinone products weren't observed and further work is required to investigate this reaction and improve the hydroquinone synthesis.

To complement the known pathways to β-resorcylates, a new aromatization reaction was developed for the synthesis of γ-resorcylate compounds **457a**, **c**, **d**, and **j** (Chapter **4**). Using vinyl dioxinone **372a** allowed construction of some mono-substituted γ-resorcylates. The limitations of cross metathesis with vinyl dioxinone **372a** were also realized, the reaction becoming less efficient for the synthesis sterically challenging substrates.

In addition to the cross metathesis route, a synthesis of γ-resorcylates **457b**, **e**, **f**, **h**, and **i**, from keto-dioxinones **284a**, **c** and **d** was also developed. Aldol additions of *tert*-butyl acetate derivatives to keto-dioxinones followed by dehydration and ester cleavage provided substrates for aromatization. Alternatively, aldol additions of benzyl acetate derivatives to keto-dioxinones followed by hydrogenation provided alternative substrates. Various conditions were investigated for aromatization reaction and these routes allowed access to more highly substituted γ-resorcylate compounds although a hexa-substituted benzene compound could not be made with the current methodology.

Keto-dioxinone **284a** was found to be useful once more for a synthesis of an amino-salicylate compound **492** (Chapter **5**). Further studies are required to improve the aromatization reaction in this instance however, once optimized, the strategy for substrate synthesis is developed which will provide a range of aminosalicylates.

Finally, the acid chloride **551** was made *in-situ* however could not be isolated (Chapter **6**). This compound showed interesting behavior and when concentrated underwent a dimerization reaction to give **557**. Some further reactions of this dimer were explored to understand its reactivity.

1.23 Further Work

1.23.1   Synthesis of More Highly Functionalized Salicylates

After the publication of our salicylate synthesis Liu *et al.* published a synthesis of 6-substituted salicylates (Scheme **196**). This involved using the iodinated benzodioxinone **565** for cross coupling with an aryl or alkenyl boronic acid to give biaryl **566**. Under the usual esterification conditions, a range of 6-substituted aryl and alkenyl salicylates **567** were synthesized.
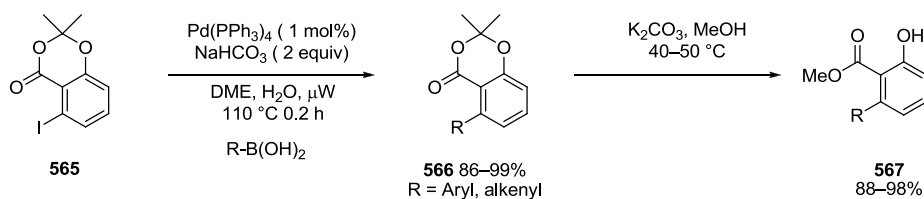
Scheme 196. Liu *et al.*'s synthesis of 6-substituted salicylate compounds.

Comparing this to the synthesis presented (Chapter **3**) from a synthetic view point, Liu *et al.*'s route is somewhat simpler for the construction of 6-aryl salicylates. It is a two-step process and proceeds in much higher overall yield. However, this route is limited by the availability of starting iodo-arene **565**, and the coupling partner must be aryl or alkenyl. The introduction of alkyl substituents is an important benefit of the presented methodology; the use of traditional Friedel-Crafts alkylation would be complicated by over-alkylation.

Furthermore Liu *et al.*'s route is also limited in its ester formation step. A large excess of alcohol is used and this could be problematic if a valuable alcohol is required. The ketene trapping involved in our methodology means that a large excess of alcohol does not necessarily have to be used.

Using the methodology later developed (chapter **4**), more substituted unsaturated dioxinones **569** could be constructed (Scheme **197**). Aldol addition of ketone enolates of **568** to keto-dioxinones **284** followed by dehydration would give ketones **569**. Aromatization would give the highly substituted salicylates **570**.
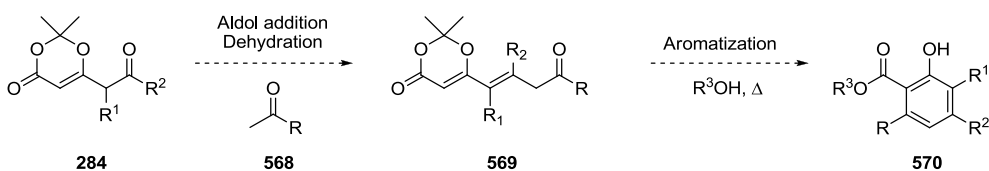
Scheme 197. Proposed synthesis of more densely functionalized salicylates.

1.23.2 Carbon Nucleophiles for Ketene Trapping

Another opportunity to note for the presented methodology is that ketene trapping can allow carbon nucleophiles to be used during the aromatization reaction (Scheme **198**). Some preliminary studies on this subject were carried out during this work. Reaction of N-methyl pyrrole **571** with dioxinone **197** gave 2-acetoacetyl pyrrole **572** in 62% yield. Using a more complex unsaturated dioxinone **337a** the acetylated pyrrole **573** was obtained in 53% yield.
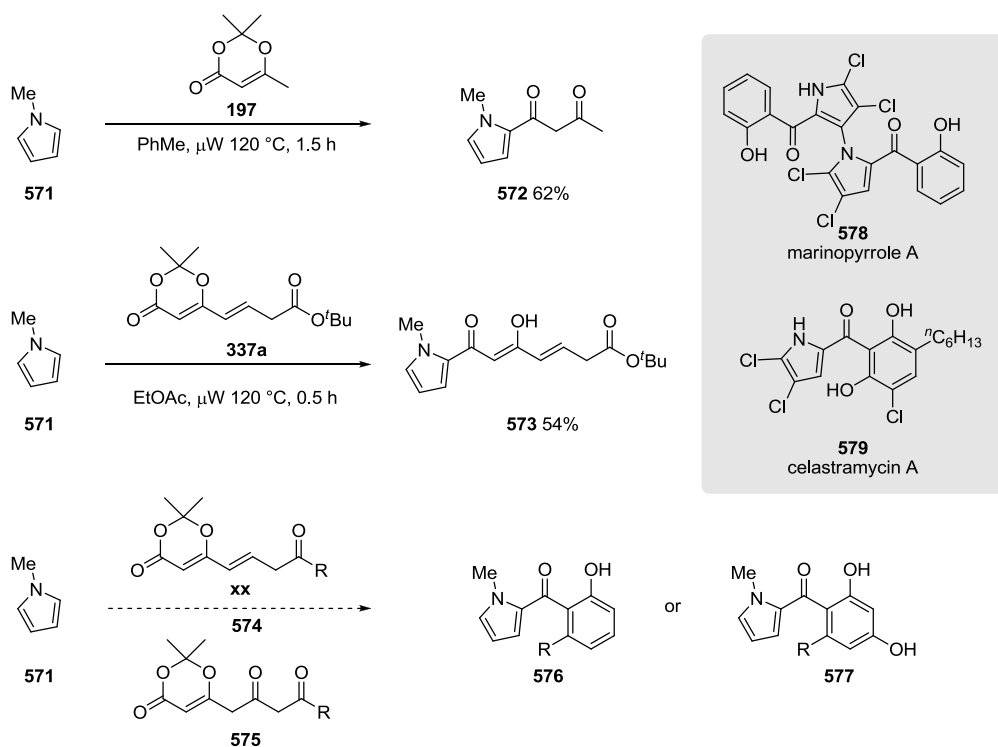
Scheme 198. *N*-methyl pyrrole for ketene trapping reactions in synthesis and, as proposed for use in aromatization reactions.

Developing these reactions further it may be possible to react **571** with unsaturated ketones **574** or diketo-dioxinones **575** to give, after aromatization, the resorcinol products **576** and **577** respectively. This would greatly expand the use of this methodology by incorporating a C–C bond formation into the aromatization reaction. These types of structures are also similar to the core natural products such as marinopyrrole A (**578**) and celastramycin A (**579**). Furthermore, other electron-rich aromatic compounds may also undergo similar acylation. A combination of ketene trapping with carbon nucleophiles and the chemistry developed within this work as well as previously by Barrett *et al*., could allow range of biaryl resorcinol molecules to be easily constructed.

1.23.3   Hydroquinone Synthesis

The 1,4-hydroquinones **514a–d** synthesized (Chapter **5**) are novel molecules. Some initial biological screens have indicated that **514a** and **514b** are active as anti-fungal agents towards *Uromyces viciae-fabae* and *Monographella nivalis* and this could warrant some further investigation.[226] A higher yielding route to such compounds and their analogues would be required however and this could be achieved by formation of α-hydroxy ketones **581**.

An ideal synthesis of hydroquinones **582** would allow rapid construction of such molecules and analogues. With further optimization, the use of dithianes presented (Chapter **5**) may be a viable option, but other masked acyl anion equivalents could also be explored. The use of an unmasked acyl

anion equivalent could allow very quick construction of the desired substrates from aldehyde **518** (Scheme **199**). Acyl zirconium species **580** would undergo1,2-addition to dioxinone aldehyde **518** leading directly to 1,2-acyloin **581**.[227] Under the thermal conditions developed, ketene trapping with an alcohol and aromatization would give 1,4-hydroquinones **582**.
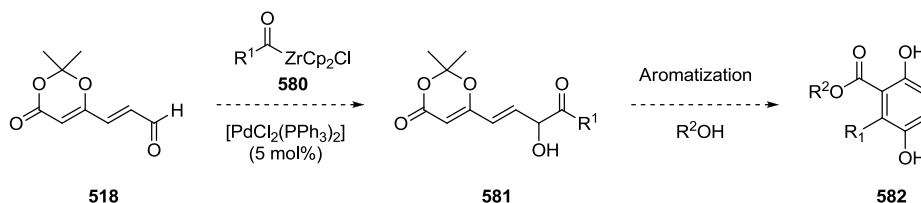
Scheme 199. Proposed synthesis of 1,4-hydroquinones.

Furthermore, regioisomeric 1,2-hydroquinones **587** could be constructed from the corresponding 1,4-acyloin **586** (Scheme **200**). A cationic zirconium species **583** can be carbonylated to the η^2-acyl complex **584** and insertion of an alkyne is known to afford the β-ketoalkenyl complex **585**.[228] An addition of this zirconium species to the dioxinone aldehyde **346** would then give the 1,4-acyloin **586** and aromatization would provide the 1,2-hydroquinone **587**.
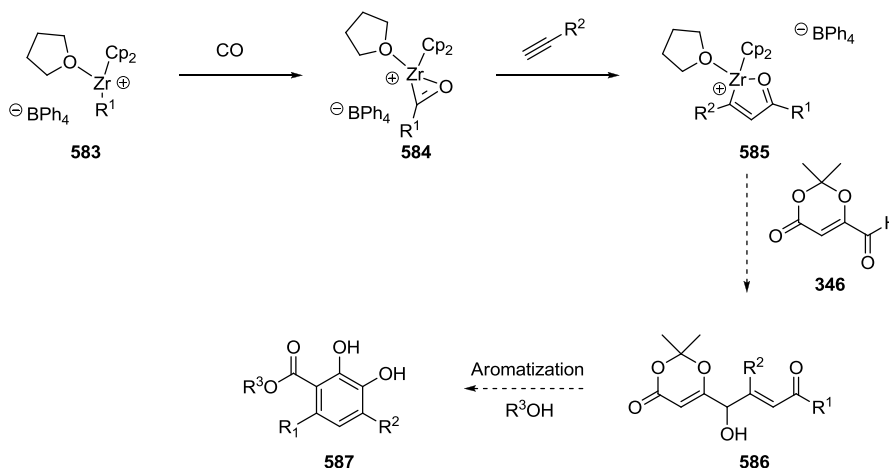
Scheme 200. Proposed synthesis of 1,2-hydroquinones.

1.23.4   Synthesis of Bisdioxinone **539**.

While efforts to produce the bisdioxinone compound **539** were thwarted (Chapter **6**) due to the instability of the acid chloride **551**, an alternative retro synthesis is proposed (Scheme **201**). Krische *et al.* have developed methodology employing 1,3-glycols as dialdehyde equivalents for iridium catalyzed transfer hydrogenative double allylation reactions.[229] Employing this method with the dioxinone acetate **355** may allow a double allylation reaction to give the bisdioxinone **589**, an oxidation step away from target biosdioxinone **539**.
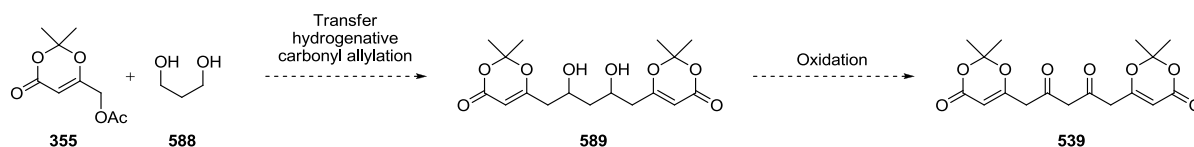
Scheme 201. Proposed synthesis of bisdioxinone **539**.

This method would avoid the formation of unstable dioxinone acid chloride **551** or, the use of highly basic conditions. Using this type of catalytic reaction is also known for allylation reactions with 1-(trifluoromethyl), 1-(trimethylsilyl), and 1-methyl-allyl acetate and so may be possible with the more functionalized dioxinone acetate **355**.[230]

1.24 Closing Remarks

Ultimately, dioxinone derivatives can be used to access a wide range of aromatic molecules. The optimization of substrate synthesis and aromatization reactions presented has made these discoveries possible and presents great opportunities for progress in novel routes to aromatic compounds. Building on inspiration from nature and *de* novo synthesis, further developments will allow the facile synthesis of a wider array of aromatic molecules.

Experimental

1.25 General Methods

All reactions were carried out in oven-dried glassware under N_2, using commercially supplied solvents and reagents unless otherwise stated. *n*-BuLi was obtained as a 2.5 M solution in hexanes and Et_2Zn was obtained as a 1.0 M solution in ether from commercial suppliers. CH_2Cl_2 and MeOH were redistilled from CaH_2 and THF was redistilled from Na–benzophenone ketyl. PhMe was redistilled from sodium. Flash chromatography was carried out on silica gel (eluents are given in parentheses). Analytical TLC was performed on pre-coated silica gel F_{254} aluminum plates with visualization under UV light and by staining with acidic vanillin or acidic potassium permanganate solutions. Melting points were determined using a hot-stage microscope. IR spectra are recorded as cm^{-1}. ^1H and ^{13}C NMR spectra were

recorded at 400 and 101 MHz respectively, with the solvent used in each case specified and spectra referenced to residual solvent peaks. Where mixtures of regioisomers (rr = regioisomer ratio) or diastereoisomers (dr = diastereoisomer ratio) have been characterized together, integrals are normalized to the major isomer. Low and high resolution mass spectra were recorded by Imperial College London mass spectrometry service. Microanalysis data was determined by the London Metropolitan University analytical service.

1.25.1 General Procedure for preparation of LDA and LiHMDS

n-BuLi in hexanes (2.5 M, 1.0 equiv) was added dropwise with stirring to (i-Pr)$_2$NH (1.0 equiv) or (SiMe$_3$)NH (1.0 equiv) in THF at 0 °C and stirred for 15 min.

1.25.2 General Procedure **A** For Synthesis of Homoallylic Alcohols **430a–k**

The corresponding aldehyde (3.5 mmol) was added dropwise to allylmagnesium bromide (1M in diethyl ether, 5 mL) at 0 °C and stirred at 25 °C until complete as indicated by T.L.C analysis. The mixture was quenched with addition of saturated aqueous NH$_4$Cl, diluted with water and then extracted with ether (× 3). The combined organics were dried (MgSO$_4$), rotary evaporated and either chromatographed or distilled (Kughelrohr) to give the homoallylic alcohols **430a–k**.

1.25.3 General procedure **B** for cross metathesis of homoallylic alcohols **430a–k**

Catalyst **427a** (5–10 mol%) was added with stirring to vinyl dioxinone **372a** (1.5–2 equiv) and homoallylic alcohol (**430a–k**, 0.1 M) in CH$_2$Cl$_2$ at reflux and heating was continued for 14–18 h. The mixture was rotary evaporated and chromatographed to give the corresponding dioxinone (**431a–j**).

1.25.4 General procedure **C** for oxidation of dioxinones **431a–j**

DMP (1.4 equiv) was added with stirring to dioxinone (**431a–j**, 0.1 M) in CH$_2$Cl$_2$ at 0 °C and stirring continued at this temperature for 0.75–3.5 h. The mixture was chromatographed eluting with Et$_2$O, and the fractions containing product were rotary evaporated. Chromatography of the residue gave the enone–dioxinone (**335a–j**).

1.25.5 General procedure **D** for aromatization of enone–dioxinones **335a–j**

Molecular sieves (100 mg per 0.1 mmol **335a–335j**), DABCO (10 equiv), *iso*-PrOH (40 equiv), and enone-dioxinone (**335a–j**) in EtOAc (0.02 M) were placed in a 10 mL microwave vial and microwave heated at 120 °C for 2 h. The resulting mixture was filtered and rotary evaporated. The residue was taken up in EtOAc (10 mL) and washed with 1 M aqueous HCl. The aqueous layer was extracted further with EtOAc (2 × 10 mL), and the combined organic layers were dried (MgSO$_4$), rotary evaporated, and chromatographed to give the salicylates **131b–131j**.

1.25.6 General Procedure **E** for deconjugative alkylation of *tert*-butyl crotonate or deconjugative protonation

HMPA (1.32 equiv) was added dropwise to LDA (1 equiv) in THF (8 mL) at −78 °C. After 30 min, the ester (1.0 equiv) in THF (5 mL) was added dropwise. After a further 10 min, the electrophile (1.0 equiv) was added dropwise. After a further 15 min, AcOH (1.3 equiv) in THF (5 mL) was added dropwise. Water (40 mL) was added was added and the mixture extracted with Et$_2$O (2 × 50 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$), rotary evaporated and purified by either chromatography or Kughelrohr distillation to give the the corresponding homoallylic esters.

1.25.7 General Procedure **F** for the Cross Metathesis of Alkenes **462a–f** with Alkenes **372a–b**

Catalyst **427a** (5–10 mol%) was added with stirring to vinyl dioxinone **372a** (1.5–3 equiv) and homoallylic ester (**462a–f**, 0.15 M) in CH$_2$Cl$_2$ at reflux or C$_6$F$_5$CF$_3$ at 70 °C and heating

was continued for 2–2.5 h. The mixture was rotary evaporated and chromatographed to give the corresponding dioxinone (**337a**, **e–g**).

1.25.8 General Procedure **G** for Deprotection of *t*-Butyl Esters

CF$_3$CO$_2$H (10 equiv) was added with stirring to ester (0.4 M) in CH$_2$Cl$_2$ at 25 °C. After 0.5–16 h, the resulting mixture was rotary evaporated and the residue dissolved in diethyl ether (10 mL) and extracted with saturated aqueous NaHCO$_3$ (5 × 5 mL). The aqueous layer was acidified to pH 1 using 3 M aqueous HCl and the mixture extracted with EtOAc (3 × 20 mL). The combined EtOAc layers were washed with brine, dried (MgSO$_4$), and rotary evaporated to give the carboxylic acid.

1.25.9 General Procedure **H** for the Aldol Addition Reaction to Ketones **284a–c**

The ester or amide (1.0 equiv) in THF (5 mL) was added dropwise to LDA (1.2 equiv) in THF (10 mL) at −78 °C. After a further 1 h, dioxinone ketone (**284a–c**, 1.0 equiv) in THF (5 mL) was added dropwise. After a further 15 min, AcOH (1.3 equiv) in THF (5 mL) was added dropwise. Water (20 mL) was added and the mixture extracted with EtOAc (3 × 40mL). The combined organic extracts were washed with brine, dried (MgSO$_4$), rotary evaporated, and chromatographed to give the corresponding products.

1.25.10 General Procedure **I** for the Dehydration of β-Hydroxy-Esters **476a–e** and β-Hydroxy-Amide **499**

Et$_3$N$^+$SO$_2$N$^-$CO$_2$Me (Burgess reagent) (1.5 equiv) was added with stirring to β-hydroxy-ester (**476a–476e**, **499** 0.2 M) in MeCN at 70 °C and heating continued for 2–4 h. The residue was rotary evaporated and chromatographed to give the corresponding esters **10h–10l** and amide **498**.

1.25.11 General Procedure **J** for the Aldol Reaction of Esters **480a–c** with Ketones **284a–c** Followed by Hydrogenolysis

The ester **480a–c** (1.0 equiv) in THF (5 mL) was added dropwise to LDA (1.2 equiv) in THF (10 mL) at −78 °C. After a further 1 h, dioxinone ketone **284a–c** (1.0 equiv) in THF (5 mL) was added dropwise. After a further 15 min, AcOH (1.3 equiv) in THF (5 mL) was added dropwise. Water (20 mL) was added and the mixture was extracted with EtOAc (3 × 40 mL) and the combined organic extracts were washed with brine, dried (MgSO$_4$), the solvent evaporated under vacuum and the residue dissolved in THF (20 mL). N$_2$ was bubbled through the mixture for 5 min, when Pd/C (10 % by wt.) was added and H$_2$ was bubbled through the mixture for 5 min, which was stirred under an H$_2$ atmosphere for 30 min. The mixture was filtered through celite, rotary evaporated and the residue worked up as in general procedure **G** to give carboxylic acids **479a–e**.

1.25.12   General Procedure **K** for the Aromatization of Carboxylic Acids **458** or **479**

CCl$_4$ (1.2 equiv for **458**, 2.5 equiv for **479**) was added with stirring to Ph$_3$P (1.5 equiv for **458**, 3.0 equiv for **479**) and carboxylic acid **458** or **479** (0.5 M) in CH$_2$Cl$_2$ and the mixture heated at reflux for 3 h. The mixture was rotary evaporated and chromatographed to give the corresponding γ-resorcylates **457a–i** or β-lactones **483a** and **483b**.

1.25.13   General Procedure **L** for α-Oxidation of Dioxinones **430**

DMP (5.5 equiv) and 2,4,6-collidine (2.3 equiv) were stirred in CH$_2$Cl$_2$ (0.1 M) to give a clear solution. Water (3.6 mmol) in CH$_2$Cl$_2$ (0.03 M) was added to the DMP solution dropwise with stirring over 1 h. The homoallylic alcohol (0.4 M) in CH$_2$Cl$_2$ was added dropwise. After 1 h the mixture was rotary evaporated and then redissolved in Et$_2$O. The mixture was washed with 10% Na$_2$S$_2$O$_3$/saturated aqueous NaHCO$_3$ (1:1, × 2), water and brine. The combined aqueous washings were reextracted with further Et$_2$O that was then washed with water and brine. The combined organic extracts were dried (Na$_2$SO$_4$) rotary evaporated and chromatographed to give the diones **433a** and **433b**.

1.25.13.1 Methoxy-2,2,8,8-tetramethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene (**124**)[231]
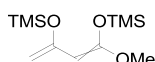
Methyl 3-(trimethylsilyloxy)but-2-enoate (1.10 g, 5.9 mmol) was added dropwise to LDA (7.1 mmol) at −78 °C in THF (25 mL) and stirred for 2 min. Trimethylsilyl chloride (1.20 mL, 9.5 mmol) was added to the mixture and stirred for 10 min then rotary evaporated. ^{n}Hexane was added, the solids removed by filtration and the mother liquors were rotary evaporated to give the title compound (917 mg, 60 %) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 4.48 (s, 1 H), 4.15 (d, J = 1.0 Hz, 1 H), 3.95 (d, J = 1.5 Hz, 1 H), 3.56 (s, 3 H), 0.25 (s, 9 H), 0.22 (s, 9 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 158.6, 153.4, 89.2, 77.5, 55.0, 0.5, 0.2. In agreement with the literature.

1.25.13.2 Isopropyl 3-hydroxybiphenyl-2-carboxylate (131b)
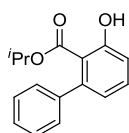
According to general procedure **D**, aromatization of enone–dioxinone **335a** (50 mg, 0.184 mmol) and chromatography (hexanes/Et$_2$O, 100:0 to 19:1) gave salicylate **131b** (26 mg, 55%) as a colorless solid; mp 53–55 °C (Et$_2$O/pentane). IR (cm^{-1}): 1650, 1606, 1597, 1441, 1370, 1278, 1225, 1178, 1097, 922, 897, 814. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.96 (s, 1 H), 7.48–7.30 (m, 4 H), 7.30–7.12 (m, 2 H), 7.01 (dd, J = 8.3, 1.0 Hz, 1 H), 6.78 (dd, J = 7.3, 1.0 Hz, 1 H), 5.05–4.85 (m, 1 H), 0.86 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.4, 161.5, 145.0, 143.2, 133.3, 128.3, 127.6, 126.6, 122.4, 116.6, 112.6, 69.1, 20.9. HR-MS (EI) m/z calcd for C$_{16}$H$_{17}$O$_3$: 257.1178 [M + H]$^+$; found: 257.1168. Anal. calcd for C$_{16}$H$_{16}$O$_3$: C 74.98, H 6.29; found: C 74.90, H 6.37.
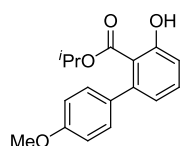
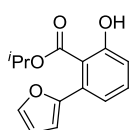### 1.25.13.3 Isopropyl 4′-bromo-3-hydroxybiphenyl-2-carboxylate (131c)
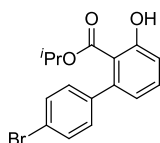
According to general procedure **D**, aromatization of enone–dioxinone **335b** (100 mg, 0.29 mmol) and chromatography (hexanes/Et$_2$O, 100:0 to 9:1) gave salicylate **131c** (43 mg, 45%) as a colorless solid; mp 79–83 °C (Et$_2$O/pentane). IR (cm^{-1}): 1663, 1600, 1575, 1492,

1444, 1363, 1314, 1273, 1209, 1173, 1100, 1066, 918, 807. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 11.04 (s, 1 H), 7.54–7.46 (m, 2 H), 7.40 (t, J = 8.1 Hz, 1 H), 7.14–7.06 (m, 2 H), 7.02 (dd, J = 8.3, 1.0 Hz, 1 H), 6.73 (dd, J = 7.3, 1.0 Hz, 1 H), 4.98 (spt, J = 6.2 Hz, 1 H), 0.91 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.1, 161.8, 143.6, 142.2, 133.5, 130.6, 130.0, 122.2, 120.7, 117.1, 112.2, 69.5, 21.0. MS (CI) m/z: 354 [M(^{81}Br) + NH$_4$]$^+$, 352 [M(^{79}Br) + NH$_4$]$^+$, 337 [M(^{81}Br) + H]$^+$, 335 [M(^{79}Br) + H]$^+$. HR-MS (CI) m/z calcd for C$_{16}$H$_{16}$BrO$_3$: 335.0283 [M + H]$^+$; found: 335.0274. Anal. calcd for C$_{16}$H$_{15}$BrO$_3$: C 57.33, H 4.51; found: C 57.25, H 4.56.

1.25.13.4 Isopropyl 4′-chloro-3-hydroxybiphenyl-2-carboxylate (**131d**)
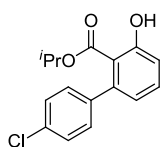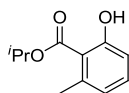

According to general procedure **D**, aromatization of enonedioxinone **335c** (69 mg, 0.23 mmol) and chromatography (hexanes/Et$_2$O, 100:0 to 97:3) gave salicylate **131d** (32 mg, 49%) as a colorless solid; mp 73–76 °C (CHCl$_3$). IR (cm^{-1}): 1665, 1601, 1576, 1492, 1444, 1363, 1314, 1272, 1172, 1101, 807. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 11.04 (s, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.37–7.30 (m, 2 H), 7.20–7.12 (m, 2 H), 7.02 (dd, J = 8.6, 1.2 Hz, 1 H), 6.73 (dd, J = 7.6, 1.2 Hz, 1 H), 4.98 (spt, J = 6.3 Hz, 1 H), 0.91 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.1, 161.8, 143.6, 141.7, 133.5, 132.7, 129.6, 127.7, 122.3, 117.1, 112.3, 69.4, 21.0. MS (CI) m/z: 310 [M(^{37}Cl) + H$_2$O]$^+$, 308 [M(^{35}Cl) + H$_2$O]$^+$, 293 [M(^{37}Cl) + H]$^+$, 291 [M(^{35}Cl) + H]$^+$. HR-MS (CI) m/z calcd for C$_{16}$H$_{16}$ClO$_3$: 291.0788 [M + H]$^+$; found: 291.0786. Anal. calcd for C$_{16}$H$_{15}$ClO$_3$: C 66.10, H 5.20; found: C 65.98, H 5.24.

1.25.13.5 Isopropyl 4′-fluoro-3-hydroxybiphenyl-2-carboxylate (**131e**)
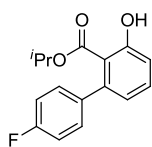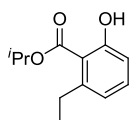
According to general procedure **D**, aromatization of enone–dioxinone **335d** (35 mg, 0.21 mmol) and chromatography (hexanes/Et$_2$O, 19:1) gave salicylate **131e** (17 mg, 51%) as a colorless solid; mp 85–87 °C (Et$_2$O/pentane). IR (cm^{-1}): 1650, 1606, 1513, 1445, 1367, 1280, 1227, 1213, 1177, 1093, 842, 815. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 11.01 (s, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.22–7.16 (m, 2 H), 7.10–7.03 (m, 2 H), 7.01 (dd, J = 8.3, 1.5 Hz, 1 H), 6.74 (dd, J = 7.6, 1.2 Hz, 1 H), 4.98 (spt, J = 6.3 Hz, 1 H), 0.91 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.3, 161.7, 143.8, 139.2 133.4, 129.8, 122.5, 116.9, 114.5, 114.3, 112.5, 69.3, 21.0. MS (CI) m/z: 275 [M + H]$^+$. HR-MS (CI) m/z calcd for C$_{16}$H$_{16}$FO$_3$: 275.1083 [M + H]$^+$; found: 275.1081. Anal. calcd for C$_{16}$H$_{15}$FO$_3$: C 70.06, H 5.51; found: C 70.00, H 5.60.

1.25.13.6 Isopropyl 3-hydroxy-4′-methoxybiphenyl-2-carboxylate (**131f**)

According to general procedure **D**, aromatization of enone–dioxinone **335e** (37 mg, 0.12 mmol) and chromatography (hexanes/Et$_2$O, 100:0 to 19:1) gave salicylate **131f** (17 mg, 48%) as a yellow solid; mp 42–45 °C (Et$_2$O). IR (cm^{-1}): 1655, 1602, 1515, 1446, 1369, 1271, 1243, 1218, 1175, 1094, 1034, 807. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.86 (s, 1 H), 7.38 (t, J = 7.8 Hz, 1 H), 7.18–7.11 (m, 2 H), 6.98 (dd, J = 8.3, 1.0 Hz, 1 H), 6.94–6.87 (m, 2 H), 6.77 (dd, J = 7.3, 1.0 Hz, 1 H), 4.97 (spt, J = 6.3 Hz, 1 H), 3.86 (s, 3 H), 0.91 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.5, 161.4, 158.7, 144.6, 135.7, 133.3, 129.4, 122.6, 116.3, 113.0, 112.8, 69.1, 55.4, 21.1. MS (CI) m/z: 304 [M + H$_2$O]$^+$, 287 [M + H]$^+$. HR-MS (CI) m/z calcd for C$_{17}$H$_{19}$O$_4$: 287.1283 [M + H]$^+$; found: 287.1275. Anal. calcd for C$_{17}$H$_{18}$O$_4$: C 71.31, H 6.34; found: C 68.02, H 6.55.

1.25.13.7 Isopropyl 2-(furan-2-yl)-6-hydroxybenzoate (**131g**)

According to general procedure **D**, aromatization of enone–dioxinone **335f** (30 mg, 0.12 mmol) and chromatography (hexanes/Et$_2$O, 100:0 to 19:1) gave salicylate **131g** (13 mg, 46%) as a colorless oil. IR (cm^{-1}): 1664, 1606, 1572, 1453, 1374, 1275, 1222, 1178, 1103. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.67 (s, 1H), 7.47 (d, J = 1.0 Hz, 1 H), 7.40 (t, J = 7.8 Hz, 1 H), 7.03 (dd, J = 8.3, 1.0 Hz, 1 H), 6.95 (dd, J = 7.3, 1.0 Hz, 1 H), 6.47 (dd, J = 3.4, 2.0 Hz, 1 H), 6.40 (d, J = 2.9 Hz, 1 H), 5.13 (spt, J = 6.3 Hz, 1 H), 1.12 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.0, 161.2, 154.2, 141.7, 133.5, 132.8, 122.3, 118.0, 112.7, 111.1, 107.1, 69.3, 21.5. MS (CI) m/z: 247 [M + H]$^+$. HR-MS (CI) m/z calcd for C$_{14}$H$_{15}$O$_4$: 247.0970 [M + H]$^+$; found: 247.0972.

1.25.13.8 Isopropyl 2-hydroxy-6-methylbenzoate (**131h**)

According to general procedure **D**, aromatization of enone–dioxinone **335g** (73 mg, 0.348 mmol) and chromatography (pentane/Et$_2$O, 100:0 to 98:2) gave salicylate **131h** (45 mg, 67%) as a colorless oil. IR (cm^{-1}): 1727, 1650, 1606, 1580, 1459, 1439, 1365, 1291, 1251, 1212, 1165, 1100, 1078, 1034, 965, 911, 863, 806, 756, 702. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 11.43 (s, 1 H), 7.27 (t, J = 7.8 Hz, 1 H), 6.84 (d, J = 8.3 Hz, 1 H), 6.71 (d, J = 7.3 Hz, 1 H), 5.34 (spt, J = 6.2 Hz, 1 H), 2.56 (s, 3 H), 1.43 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 171.2, 162.8, 141.3, 133.9, 122.9, 115.6, 112.7, 69.7, 24.2, 22.0. MS (ES) m/z: 212 [M + H$_2$O]$^+$, 195 [M + H]$^+$. Anal. calcd for C$_{11}$H$_{14}$O$_3$: C 68.02, H 7.27; found: C 67.87, H 7.21.

1.25.13.9 Isopropyl 2-hydroxy-6-ethylbenzoate (**131i**)

According to general procedure **D**, aromatization of enone-dioxinone **335h** (76 mg, 0.339 mmol) and chromatography (pentane/Et$_2$O, 100:0 to 19:1) gave salicylate **131i** (41 mg, 58%) as a colorless oil. IR (cm^{-1}): 1727, 1654, 1606, 1577, 1447, 1363, 1308, 1295, 1245, 1207, 1167, 1102, 931, 908, 816. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 11.33 (s, 1 H), 7.30

(t, J = 8.1 Hz, 1 H), 6.85 (dd, J = 8.3, 1.5 Hz, 1 H), 6.74 (d, J = 7.3 Hz, 1 H), 5.36 (spt, J = 6.3 Hz, 1 H), 2.96 (q, J = 7.3 Hz, 2 H), 1.43 (d, J = 6.4 Hz, 6 H), 1.23 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 171.0, 162.6, 147.4, 134.1, 121.7, 115.6, 112.2, 69.7, 29.6, 21.8, 16.5. MS (ES) m/z: 231 [M + Na]$^+$, 209 [M + H]$^+$. Anal. calcd for C$_{12}$H$_{16}$O$_3$: C 69.21, H 7.74; found: C 69.18, H 7.64.

1.25.13.10   Isopropyl 2-hydroxy-6-isobutylbenzoate (131j)
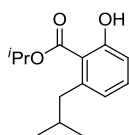
According to general procedure **D**, aromatization of enone–dioxinone **335i** (78 mg, 0.310 mmol) and chromatography (pentane/Et$_2$O, 100:0 to 19:1) gave salicylate **131j** (31 mg, 45%) as a colorless oil. IR (cm^{-1}): 1651, 1606, 1577, 1478, 1363, 1308, 1294, 1250, 1229, 1202, 1164, 1097, 1062, 911, 833, 803, 763, 709. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 11.35 (s, 1 H), 7.28 (t, J = 7.8 Hz, 1 H), 6.86 (dd, J = 8.3, 1.5 Hz, 1 H), 6.66 (dd, J = 7.6, 1.2 Hz, 1 H), 5.37 (spt, J = 6.3 Hz, 1 H), 2.82 (d, J = 7.3 Hz, 2 H), 1.76–1.91 (m, 1 H), 1.43 (d, J = 6.4 Hz, 6 H), 0.89 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 171.2, 162.8, 144.5, 133.5, 123.7, 115.8, 112.5, 69.6, 45.5, 30.0, 22.5, 21.8. MS (ES) m/z: 259 [M + Na]$^+$, 237 [M + H]$^+$. Anal. calcd for C$_{14}$H$_{20}$O$_3$: C 71.16, H 8.53; found: C 71.08, H 8.45.

1.25.13.11   Allyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate[232] (237a)
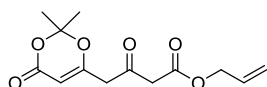
DMF (catalytic) was added to 3-(allyloxy)-3-oxopropanoic acid (2g, 13.89 mmol) and oxalyl chloride (1.33 mL, 15.28 mmol) in THF (28 mL) at 0 °C and the stirred at 25 °C for 15 min.

2,2,6-Trimethyl-4H-1,3-dioxin-4-one (5.92 g, 41.67 mmol) was added dropwise to LiHMDS (41.67 mmol) at −78 °C in THF (125 mL) and stirred for 30 min. The acid chloride from above was then added and stirred for 30 min then warmed to 25 °C over 1 h. The mixture was acidified to pH 1 with 1M aq. HCl and the layers separated. The aqueous was reextracted with ether (2 × 50 mL) and the combined organics were washed with brine (100 mL), dried (MgSO$_4$), filtered, rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 4:1 to 5:3) to give the title compound (1.17 g, 32%) as a

yellow oil. IR (cm^{-1}): 1720, 1637, 1391, 1376, 1272, 1252, 1201, 1152, 1015, 990, 932, 902, 806. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: keto: 5.75–6.03 (m, 1 H), 5.20–5.41 (m, 3 H), 4.53–4.76 (m, 2 H), 3.55 (s, 2 H), 3.50 (s, 2 H), 1.70 (s, 6 H); enol: 12.01 (s, 1H), 5.75–6.03 (m, 1 H), 5.41 (s, 1H), 5.20–5.41 (m, 2 H), 5.15 (s, 1H), 4.67–4.68 (m, 2 H), 3.13 (s, 2H), 1.70 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: keto: 195.5, 166.0, 163.4, 160.4, 131.1, 119.3, 107.3, 97.1, 66.2, 48.9, 46.9, 24.9; enol: 171.6, 170.6, 165.4, 131.6, 118.6, 107.0, 95.8, 91.8, 65.0, 39.3, 24.8. MS (CI) m/z: 286 [M+NH$_4$]$^{+}$, 269 [M+H]$^{+}$. HR-MS (CI) m/z: calcd for C$_{13}$H$_{20}$NO$_6$: 286.1291 [M+NH4]$^{+}$; found: 294.1306. In agreement with the literature.

1.25.13.12   Benzyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (237g)
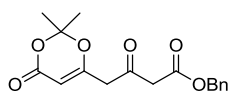
DMF (10 µL) was added to a mixture of 3-(benzyloxy)-3-oxopropanoic acid (0.97 g, 5 mmol) and oxalyl chloride (0.85 mL, 10 mmol) in CH$_2$Cl$_2$ (25 mL) at 0 °C, stirred for 1.5 h at 20 °C and then rotary evaporated to give the corresponding acid chloride used without further purification.

Dioxinone (2.13 g, 15 mmol) was added dropwise to LiN(SiMe$_3$)$_2$ (16 mmol) at −78 °C in THF and stirred for 30 min. The acid chloride from above was added dropwise over 40 min. After a further 20 min the mixture was quenched with saturated aqueous NH$_4$Cl and acidified to pH 1 with 1 M aqueous HCl. The layers were separated and the aqueous reextracted with ether (2 × 50 mL). The combined organics were washed with brine (100 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (pentane/Et$_2$O, 4:1 to 2:3) to give the title compound (666 mg, 42%) as a yellow oil. IR (cm^{-1}): 1718, 1637, 1391, 1375, 1271, 1253, 1200, 1015, 902, 806, 742, 697. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.34–7.40 (m, 5 H), 5.33 (s, 1 H), 5.20 (s, 2 H), 3.57 (s, 2 H), 3.47 (s, 2 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 195.4, 166.1, 163.4, 160.4, 134.9, 128.7, 128.6, 128.5, 107.3, 97.1, 67.5, 49.0, 47.0, 24.9. MS (CI) m/z: 336 [M+NH$_4$]$^{+}$, 319 [M+H]$^{+}$. HR-MS (CI) m/z calcd for C$_{17}$H$_{19}$O$_6$: 319.1182 [M+H]$^{+}$; found: 319.1180. Anal. calcd for C$_{17}$H$_{18}$O$_6$: C 61.14, H 5.70; found: C 61.13, H 5.80.

1.25.13.13   2,2-Dimethyl-6-(2-oxopropyl)-4H-1,3-dioxin-4-one (284a)[233]
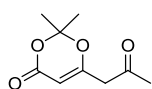
Freshly distilled 2,2,6-trimethyl-4H-1,3-dioxin-4-one (50.0 g, 352 mmol) in THF (150 mL) was added to LiN(SiMe$_3$)$_2$ (500 mmol) in THF (300 mL) over 0.5 h at −18 to −24 °C with overhead stirring. After 0.75 h, diethylzinc (500 mmol) was added dropwise over 1 h maintaining an internal temperature of −25 to −22 °C, and after a further 0.75 h the temperature was raised to −10 °C over 0.3 h. Acetyl imidazole (55.0 g, 499 mmol) was added portionwise over 0.25 h maintaining an internal temperature of −12 to −7 °C and stirred a further 2.5 h. Maintaining an internal temperature below 0 °C, H$_2$O/THF (150 mL, 1:9) was added dropwise followed by 2 M aqueous HCl (250 mL) and *tert*-butylmethyl ether (500 mL) and the mixture acidified with 25% aqueous HCl (250 mL) to pH 3. The aqueous was extracted with EtOAc (× 3) and the combined organics were rotary evaporated then allowed to stand for 24 h. The precipitated solids were removed by filtration and washed (pentane/Et$_2$O, 7:3) to give the title compound (30.0 g, 46%) as a pale yellow solid. The mother liquors were rotary evaporated and chromatographed (pentane/Et$_2$O, 3:2 to 2:3) to give a further crop (9.0 g, 14%) as a pale yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.33 (s, 1 H), 3.34 (s, 2 H), 2.23 (s, 3 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 201.0, 164.4, 160.7, 107.3, 96.8, 48.1, 30.3, 25.1. In agreement with the literature.

1.25.13.14   6-(2-(4-Methoxyphenyl)-2-oxoethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (**284c**)[234]
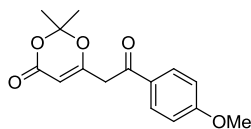
CDI (9.73g, 60 mmol) was added to *para*-anisic acid (7.6 g, 50 mmol) in THF and the mixture stirred for 15 min and then washed with water to give (1H-imidazol-1-yl)(4-methoxyphenyl)methanone (7.85 g; 78%) as a colourless solid used directly in the next step.

2,2,6-Trimethyl-4H-1,3-dioxin-4-one **xx** (4 g, 28.17 mmol) was added dropwise to LiN(SiMe$_3$)$_2$ (39.44 mol) in THF (50 mL) at −78 °C for 1 h. Diethylzinc (39.44 mmol) was added dropwise and the mixture stirred at −30 °C for 0.5 h. The mixture was warmed to −10 °C and (1H-imidazol-1-yl)(4-methoxyphenyl)methanone (6.83 g, 33.80 mmol) in THF (5 mL) was added and stirred for 2 h. The mixture was acidified with 3 M aqueous HCl and then extracted with EtOAc (× 3), washed with brine, dried (MgSO$_4$), rotary evaporated, and chromatographed (pentane/Et$_2$O, 3:2 to 0:1) to give the title compound (6.22 g, 80%) as a pale yellow solid. IR (cm^{-1}): 1722, 1679, 1634, 1596, 1571, 1508, 1466, 1418, 1404, 1390, 1376, 1332, 1314, 1256, 1218, 1202, 1190, 1162, 1114, 1013, 987, 960, 934, 868, 834, 813, 790, 753, 663, 634, 613. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.88–7.97 (m, 2H), 6.93–7.00 (m, 2H), 5.41 (s,

1H), 3.89 (s, 3H), 3.85 (s, 2H), 1.71 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 191.4, 165.5, 164.1, 160.7, 130.6, 128.8, 114.0, 107.2, 96.7, 55.5, 43.0, 24.9. MS (ES) m/z: 294 [M+H]$^+$, 277 [M+H]$^+$. HR-MS (ES) m/z: calcd for C$_{15}$H$_{17}$O$_5$: 277.1076 [M+H]$^+$; found: 277.1082. In agreement with the literature.

1.25.13.15   2,2-Dimethyl-6-(3-oxo-1-phenylbutan-2-yl)-4*H*-1,3-dioxin-4-one (±) (**284d**) and 5-Benzyl-2,2-dimethyl-6-(2-oxopropyl)-4*H*-1,3-dioxin-4-one (**284e**)
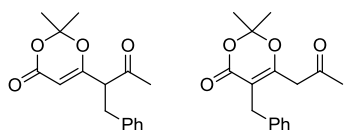
PhCH$_2$Br (711 µL, 5.98 mmol) was added with stirring to dioxinone ketone **284a** (1.00 g, 5.43 mmol) and ^{i}Pr$_2$NH (845 µL, 5.98 mmol) in THF (5.5 mL). After 14 h, the mixture was acidified to pH 1 with 1 M aqueous HCl and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$), rotary evaporated and chromatographed (pentane/Et$_2$O, 4:1 to 3:2) to give dioxinone ketone **284d** (663 mg, 45%) as a pale yellow oil and **284e** (199 mg, 13 %) as a colourless solid.

2,2-Dimethyl-6-(3-oxo-1-phenylbutan-2-yl)-4*H*-1,3-dioxin-4-one (±) (**284d**): IR (cm^{-1}): 1718, 1627, 1497, 1455, 1390, 1375, 1358, 1271, 1253, 1200, 1151, 1079, 1009, 968, 901, 854, 810, 747, 699, 612. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.12–7.34 (m, 5 H), 5.32 (s, 1 H), 3.57–3.64 (m, 1 H), 3.23 (dd, J = 14.2, 6.8 Hz, 1 H), 2.95 (dd, J = 14.2, 8.3 Hz, 1 H), 2.19 (s, 3 H), 1.61 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 202.5, 166.8, 160.4, 137.4, 128.7, 127.0, 107.0, 96.0, 59.0, 33.8, 29.5, 25.0, 24.8. MS (ES) m/z: 292 [M + NH$_4$]$^+$, 275 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{16}$H$_{19}$O$_4$: 275.1283 [M + H]$^+$; found: 275.1291. Anal. calcd for C$_{16}$H$_{18}$O$_4$: C 70.06, H 6.61; found: C 70.16, H 6.73.

5-Benzyl-2,2-dimethyl-6-(2-oxopropyl)-4H-1,3-dioxin-4-one (**284e**): IR (cm^{-1}) ν = 1713, 1686, 1620, 1585, 1515, 1497, 1455, 1430, 1391, 1375, 1256, 1201, 1161, 1101, 1045, 1023, 979, 934, 906, 889, 860, 830, 817, 753, 723, 701, 677, 637, 616. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.11–7.31 (m, 5H), 3.62 (s, 2H), 3.42 (s, 2H), 2.11 (s, 3H), 1.71 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 201.1, 162.0, 160.5, 139.1, 135.2, 128.5, 128.0, 107.4, 95.6, 45.6, 30.5, 30.1, 25.1. MS (ES) m/z: 292 [M+NH$_4$]$^+$, 275 [M+H]$^+$. HR-MS (ES) m/z: calcd for

$C_{16}H_{19}O_4$: 275.1283 [M+H]$^+$; found: 275.1292. Anal. calcd for $C_{16}H_{18}O_4$: C 70.06. H 6.61; found: C 70.15, H 6.73.

### 1.25.13.16 (*E*)-2,2-Dimethyl-6-(4-oxo-4-phenylbut-1-enyl)-4*H*-1,3-dioxin-4-one (**335a**)
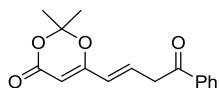
According to general procedure **C**, oxidation of dioxinone **431a** (329 mg, 1.21 mmol) for 3.5 h and chromatography (hexanes/Et$_2$O, 7:3 to 1:1) gave enone–dioxinone **335a** (255 mg, 77%) as a yellow solid; mp 58–61 °C (Et$_2$O–pentane). IR (cm^{-1}): 1714, 1687, 1655, 1597, 1392, 1369, 1278, 1204, 1019, 991, 905, 816. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.04–7.91 (m, 2 H), 7.74–7.56 (m, 1 H), 7.56–7.36 (m, 2 H), 6.85 (dt, J = 15.7, 7.1 Hz, 1 H), 6.08 (d, J = 15.6 Hz, 1 H), 5.31 (s, 1 H), 3.93 (dd, J = 7.1, 1.2 Hz, 2 H), 1.73 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 196.3, 162.4, 161.6, 136.2, 133.7, 133.7, 128.8, 128.2, 125.7, 106.6, 94.6, 41.7, 25.0. MS (ES) *m/z*: 273 [M + H]$^+$. HR-MS (EI) *m/z* calcd for $C_{16}H_{17}O_4$: 273.1127 [M + H]$^+$; found: 273.1121. Anal. calcd for $C_{16}H_{16}O_4$: C 70.58, H 5.92; found: C 70.53, H 5.85.

1.25.13.17 (*E*)-6-(4-(4-Bromophenyl)-4-oxobut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**335b**)
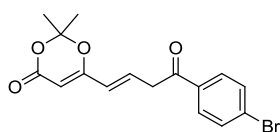
According to general procedure **C**, oxidation of dioxinone **431b** (23 mg, 0.065 mmol) for 2 h and chromatography (hexanes–Et$_2$O, 1:1) gave enone–dioxinone **335b** (19 mg, 83%) as a yellow solid; mp 68–72 °C (Et$_2$O/pentane). IR (cm^{-1}): 1713, 1693, 1659, 1586, 1391, 1374, 1273, 1199, 1011, 991, 970, 800. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.85–7.80 (m, 2 H), 7.67–7.62 (m, 2 H), 6.81 (dt, J = 15.5, 6.9 Hz, 1 H), 6.07 (d, J = 15.6 Hz, 1 H), 5.30 (s, 1 H), 3.89 (dd, J = 7.1, 1.2 Hz, 2 H), 1.72 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 187.9, 160.9, 141.9, 134.9, 133.5, 132.2, 132.0, 130.2, 129.1, 128.1, 128.0, 107.2, 100.8, 25.1. MS (CI) *m/z*: 370 [M(^{81}Br) + NH$_4$]$^+$, 368 [M (^{79}Br) + NH$_4$]$^+$. Anal. calcd for $C_{16}H_{15}BrO_4$: C 54.72, H 4.31; found: C 54.63, H 4.21.

1.25.13.18 (*E*)-6-(4-(4-Chlorophenyl)-4-oxobut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**335c**)
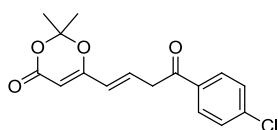
According to general procedure **C**, oxidation of dioxinone **431c** (82 mg, 0.266 mmol) for 2 h and chromatography (hexanes/Et$_2$O, 7:3 to 1:1) gave enone–dioxinone **335c** (63 mg, 77%) as an orange oil. IR (cm^{-1}): 1711, 1689, 1587, 1376, 1391, 1270, 1200, 1089, 1022, 985, 839, 784. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.93–7.88 (m, 2 H), 7.50–7.45 (m, 2 H), 6.81 (dt, J = 15.7, 7.1 Hz, 1 H), 6.07 (dt, J = 15.7, 1.5 Hz, 1 H), 5.31 (s, 1 H), 3.90 (dd, J = 6.8, 1.5 Hz, 2 H), 1.72 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 195.0, 162.3, 161.7, 140.2, 134.4, 133.2, 129.6, 129.2, 125.9, 106.6, 94.7, 41.6, 25.0. MS (ES) *m/z*: 309 [M(^{37}Cl) + H]$^+$, 307 [M(^{35}Cl) + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{16}$H$_{16}$ClO$_4$: 307.0737 [M + H]$^+$; found: 307.0732. Anal. calcd for C$_{16}$H$_{15}$ClO$_4$: C 62.65, H 4.93; found: C 62.77, H 4.84.

1.25.13.19 (*E*)-6-(4-(4-Fluorophenyl)-4-oxobut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**335d**)
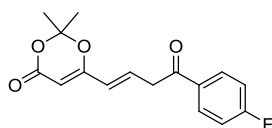
According to general procedure **C**, oxidation of dioxinone **431d** (226 mg, 0.774 mmol) for 3 h and chromatography (hexanes/Et$_2$O, 7:3 to 1:1) gave enone–dioxinone **335d** (143 mg, 67%) as an orange oil. IR (cm^{-1}): 1710, 1692, 1597, 1379, 1275, 1200, 1158, 1021, 846, 793. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.02–7.97 (m, 2 H), 7.20–7.14 (m, 2 H), 6.82 (dt, J = 15.5, 6.9 Hz, 1 H), 6.07 (d, J = 16.1 Hz, 1 H), 5.30 (s, 1 H), 3.90 (dd, J = 1.2, 7.1 Hz, 2 H), 1.72 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 194.7, 167.3, 163.5 (d, J = 239.3 Hz), 161.7, 133.4, 132.5, 130.9 (d, J = 9.6 Hz), 125.8, 116.0 (d, J = 20.9 Hz), 106.6, 94.6, 41.6, 25.0. HR-MS (CI) *m/z* calcd for C$_{16}$H$_{19}$NO$_4$F: 308.1298 [M + NH$_4$]$^+$; found: 308.1301. Anal. calcd for C$_{16}$H$_{15}$FO$_4$: C 66.20, H 5.21; found: C 66.15, H 5.14.

1.25.13.20   (*E*)-6-(4-(4-Methoxyphenyl)-4-oxobut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one
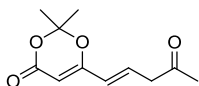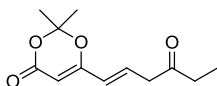(**335e**)
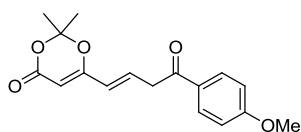
According to general procedure **C**, oxidation of dioxinone **431e** (150 mg, 0.493 mmol) for 0.75 h and chromatography (hexanes–Et$_2$O, 7:3 to 3.5:10) gave enone–dioxinone **335e** (98 mg, 66%) as a yellow solid; mp 89–92 °C (Et$_2$O/pentane). IR (cm^{-1}): 1710, 1674, 1655, 1573, 1374, 1255, 1204, 1182, 1020, 984, 967, 844, 790, 597. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.97–7.92 (m, 2 H), 6.99–6.94 (m, 2 H), 6.84 (dt, J = 15.4, 7.0 Hz, 1 H), 6.06 (d, J = 15.7 Hz, 1 H), 5.30 (s, 1 H), 3.89 (s, 3 H), 3.87 (dd, J = 7.3, 1.5 Hz, 2 H), 1.72 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 194.8, 163.9, 162.5, 161.8, 134.3, 130.6, 129.2, 125.5, 114.0, 106.5, 94.4, 55.5, 41.5, 25.0. MS (ES) *m/z*: 303 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{17}$H$_{19}$O$_5$: 303.1232 [M + H]$^+$; found: 303.1226. Anal. calcd for C$_{17}$H$_{18}$O$_5$: C 67.54, H 6.00; found: C 67.43, H 6.05.

1.25.13.21   (*E*)-6-(4-(Furan-2-yl)-4-oxobut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**335f**)
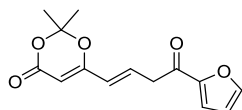
According to general procedure **C**, oxidation of dioxinone **431f** (94 mg, 0.356 mmol) for 2 h and chromatography (hexanes/Et$_2$O, 7:3 to 1:1) gave enone–dioxinone **335f** (35 mg, 38%) as a yellow oil. IR (cm^{-1}): 1721, 1675, 1655, 1466, 1392, 1376, 1275, 1204, 1019. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.63 (d, J = 1.0 Hz, 1 H), 7.28–7.25 (m, 1 H), 6.76 (dt, J = 15.6, 7.3 Hz, 1 H), 6.58 (dd, J = 3.4, 1.5 Hz, 1 H), 6.12–6.04 (m, 1 H), 5.30 (s, 1 H), 3.78 (dd, J = 7.3, 1.5 Hz, 2 H), 1.71 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 185.1, 162.4, 161.8, 152.0, 146.9, 132.9, 125.9, 117.9, 112.6, 106.6, 94.6, 41.6, 25.0. MS (ES) *m/z*: 263 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{14}$H$_{15}$O$_5$: 263.0919 [M + H]; found: 263.0912. Anal. calcd for C$_{14}$H$_{14}$O$_5$: C 64.12, H 5.38; found: C 60.65, H 5.34.

1.25.13.22   (*E*)-2,2-Dimethyl-6-(4-oxopent-1-enyl)-4*H*-1,3-dioxin-4-one (**335g**)

According to general procedure **C**, oxidation of dioxinone **431g** (145 mg, 0.684 mmol) for 1.25 h and chromatography (pentane/Et$_2$O, 1:1 to 2:3) gave enone–dioxinone **335g** (78 mg, 54%) as a yellow oil. IR (cm^{-1}): 1711, 1654, 1593, 1390, 1274, 1273, 1251, 1200, 1158, 1016, 968, 903, 859, 808.^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.67 (dt, J = 15.7, 7.3 Hz, 1 H), 6.00 (dt, J = 15.6, 1.5 Hz, 1 H), 5.32 (s, 1 H), 3.39 (dd, J = 7.3, 1.0 Hz, 2 H), 2.24 (s, 3 H), 1.74 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 204.5, 162.4, 161.8, 132.9, 125.8, 106.6, 94.7, 46.7, 30.1, 25.0. MS (ES) m/z: 233 [M + Na]$^+$, 211 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{11}$H$_{15}$O$_4$: 211.0965 [M + H]$^+$; found: 211.0966.

1.25.13.23   (*E*)-2,2-Dimethyl-6-(4-oxohex-1-enyl)-4*H*-1,3-dioxin-4-one (**335h**)

According to general procedure **C**, oxidation of dioxinone **431h** (60 mg, 0.265 mmol) for 0.75 h and chromatography (hexanes/Et$_2$O, 1:1) gave enone–dioxinone **335h** (47 mg, 79%) as a yellow oil. IR (cm^{-1}): 1711, 1630, 1586, 1460, 1391, 1376, 1276, 1252, 1200, 1096, 1017, 973, 903, 812. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.66 (dt, J = 15.6, 6.8 Hz, 1 H), 5.98 (dt, J = 15.7, 1.5 Hz, 1 H), 5.29 (s, 1 H), 3.34 (dd, J = 7.3, 1.5 Hz, 2 H), 2.50 (q, J = 7.3 Hz, 2 H), 1.71 (s, 6 H), 1.08 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 207.3, 162.4, 161.7, 133.3, 125.6, 106.5, 94.5, 45.5, 36.1, 25.0, 7.6. MS (ES) m/z: 247 [M + Na]$^+$, 225 [M + H]$^+$.

1.25.13.24   (*E*)-2,2-Dimethyl-6-(6-methyl-4-oxohept-1-enyl)-4*H*-1,3-dioxin-4-one (**335i**)
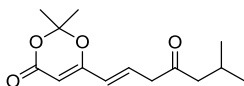
According to general procedure **C**, oxidation dioxinone **431i** (151 mg, 0.594 mmol) for 1.25 h and chromatography (pentane/Et$_2$O, 7:3 to 1:1) gave enone–dioxinone **335i** (101 mg, 67%) as a yellow oil. IR (cm^{-1}): 1707, 1655, 1594, 1451, 1392, 1373, 1277, 1204, 1105, 1019, 979, 906, 864, 849, 812. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.68 (dt, J = 15.7,

7.3 Hz, 1 H), 6.00 (dt, J = 15.7, 1.5 Hz, 1 H), 5.31 (s, 1 H), 3.34 (dd, J = 7.3, 1.0 Hz, 2 H), 2.37 (d, J = 7.3 Hz, 2 H), 2.10–2.25 (m, 1 H), 1.74 (s, 6 H), 0.96 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 206.6, 162.4, 161.8, 133.3, 125.6, 106.5, 94.5, 51.9, 46.3, 25.0, 24.5, 22.5. MS (ES) m/z: 275 [M + Na]$^+$, 253 [M + H]$^+$. Anal. calcd for C$_{14}$H$_{20}$O$_4$: C 66.65, H 7.99; found: C 66.74, H 7.90.

1.25.13.25   (*E*)-6-(4-Mesityl-4-oxobut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**335j**)
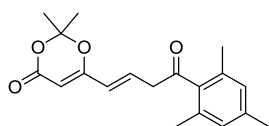
2-Iodoxybenzoic acid (842 mg, 2.94 mmol) was added with stirring to dioxinone **431j** (310 mg, 0.981 mmol) in EtOAc (7 mL) open to the air at 80 °C for 2 h. The mixture was filtered through Celite and rotary evaporated. Chromatography (hexanes/Et$_2$O, 4:1 to 1:1) of the residue gave enone–dioxinone **335j** as a 2:1 mixture of the β,δ-enone: α,β-enone (207 mg, 67%) as a yellow oil. IR (cm^{-1}): 1713, 1698, 1603, 1373, 1268, 1200, 1148, 1017, 978, 852, 802, 602. β,δ-Enone: ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.87 (s, 2 H), 6.78 (dt, J = 15.6, 7.8 Hz, 1 H), 6.04 (d, J = 15.7 Hz, 1 H), 5.31 (s, 1 H), 3.63 (dd, J = 7.1, 1.2 Hz, 2 H), 2.30 (s, 3 H), 2.21 (s, 6 H), 1.73 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 206.5, 162.4, 161.8, 138.7, 133.8, 132.8, 132.5, 128.6, 125.8, 106.6, 94.7, 47.8, 25.0, 21.1, 19.2. α,β-Enone: ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.87 (s, 2 H), 6.47–6.29 (m, 2 H), 5.22 (s, 1 H), 3.16 (d, J = 6.4 Hz, 2 H), 2.30 (s, 3 H) 2.14 (s, 6 H), 1.66 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 206.5, 162.4, 161.8, 141.6, 138.7, 136.1, 133.8, 132.5, 128.4, 106.6, 94.5, 36.3 25.0, 21.1, 19.2. MS (CI) m/z: 332 [M + H$_2$O]$^+$, 315 [M + H]$^+$. Anal. calcd for C$_{19}$H$_{22}$O$_4$: C 72.59, H 7.05; found: C 72.44, H 6.95.

### 1.25.13.26   (E)-*tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)but-3-enoate (**337a**)
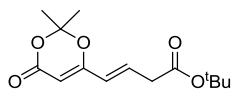
According to general procedure **F**, cross metathesis of ester **462a** (615 mg, 4.33 mmol) and dioxinone **372a** (1.00 g, 6.49 mmol) with catalyst **427a** (136 mg, 0.217 mmol) in CH_2Cl_2 (30 mL) at reflux for 2.5 h and chromatography (pentane/Et_2O, 9:1 to 4:1) gave dioxinone ester **337a** (948 mg, 82 %) as a pale yellow solid; mp 112–114 °C (CH_2Cl_2–pentane). IR (cm^{-1}): 1715, 1656, 1592, 1388, 1374, 1365, 1278, 1258, 1215, 1203, 1180, 1144, 1092, 973, 948, 935, 904, 870, 841, 796, 765, 750. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.61 (dt, J = 15.6, 7.3 Hz, 1 H), 5.99 (dt, J = 15.7, 1.5 Hz, 1 H), 5.28 (s, 1 H), 3.16 (dd, J = 7.3, 1.5 Hz, 2 H), 1.70 (s, 6 H), 1.46 (s, 9 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 169.4, 162.5, 161.7, 133.5, 125.2, 106.4, 94.4, 81.6, 38.8, 28.0, 25.0. MS (ES) m/z 269 [M + H]$^+$. HR-MS (ES) m/z calcd for $C_{14}H_{21}O_5$: 269.1389 [M + H]$^+$; found: 269.1384.

1.25.13.27 (*E*)-Ethyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)but-2-enoate (**337b**)
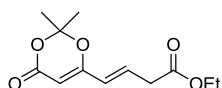
(^{i}Bu$_2$AlH)$_2$ (5.37 ml, 5.37 mmol) was added dropwise to 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-N-methoxy-N-methylacetamide (1.00g, 4.37 mmol) in THF (44 ml) at −78 ^{o}C and stirred for 15 min. Methanol (10ml) was added and stirred 5 min. This mixture was transferred to a mixture of ethyl (triphenylphosphoranylidene)acetate (1.52 g, 4.37 mmol) in THF (44 ml) at 50 ^{o}C and stirred for 45 min. The mixture was rotary evaporated and chromatographed (petroleum ether/Et_2O, 4:1 to 13:7) to give the title compound (469 mg, 45 %) as a colourless oil. IR (cm^{-1}) 1721, 1656, 1374, 1273, 1202. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.60 (dt, J = 15.2, 7.3 Hz, 1 H), 5.97–6.06 (m, 1 H), 5.29 (s, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 3.23 (dd, J = 7.3, 1.5 Hz, 2 H), 1.71 (s, 6 H), 1.27 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.3, 162.5, 161.9, 132.9, 125.7, 106.7, 94.8, 61.3, 37.9, 25.1, 14.3. HR-MS (EI) m/z calcd for $C_{12}H_{17}O_5$: 241.1067 [M+H]; found: 241.1067. Anal. calcd for $C_{12}H_{16}O_5$: C 59.99, H 6.71; found: C 59.88, H 6.60.

1.25.13.28 Phenyl but-3-enoate and (*E*)-Phenyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)but-3-enoate (**337c**)[235]
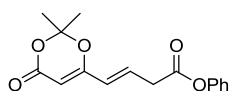
Oxalyl chloride (542 µL, 6.4 mmol) was added to vinylacetic acid (0.5 g, 5.81 mmol) in CH_2Cl_2 (2.4 mL) followed by DMF (10 µL) and the mixture stirred for 3 h. The mixture was rotary evaporated and phenol (547 mg, 5.81 mmol) in CH_2Cl_2 (1 mL) was added dropwise then stirred at 20 °C for 16 h. The mixture was rotary evaporated and chromatographed (pentane/Et_2O, 97:3 to 19:1) to give phenyl but-3-enoate (251 mg, 42%) as a colorless oil used without further purification. IR (cm^{-1}): 1754, 1492, 1328, 1237, 1192, 1162, 1133, 1071, 992, 922, 811, 774, 742, 726, 688. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.35–7.44 (m, 2 H), 7.19–7.30 (m, 1 H), 7.04–7.15 (m, 2 H), 6.08 (ddt, J = 17.1, 10.2, 7.0 Hz, 1 H), 5.23–5.36 (m, 2 H), 3.36 (dt, J = 7.0, 1.4 Hz, 2 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 169.9, 150.6, 129.6, 129.4, 125.8, 121.5, 119.2, 39.1. In agreement with the literature.

According to general procedure A, reaction of phenyl but-3-enoate (281 mg, 1.73 mmol) and dioxinone **372a** (400mg, 2.60 mmol) with catalyst **427a** (54 mg, 0.087 mmol) for 14 h and chromatography (hexanes/Et_2O, 4:1 to 1:1) gave dioxinone **337c** (577 mg, 76%) as a brown solid, mp 85–90 °C (Et_2O/pentane). IR (cm^{-1}): 1753, 1714, 1656, 1594, 1390, 1374, 1273, 1250, 1192, 1163, 1128, 1018, 968, 902, 801. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.38–7.44 (m, 2 H), 7.26–7.30 (m, 1 H), 7.09–7.13 (m, 2 H), 6.72 (dt, J = 15.5, 7.2 Hz, 1 H), 6.15 (dt, J = 15.5, 1.5 Hz, 1 H), 5.36 (s, 1 H), 3.52 (dd, J = 7.1, 1.7 Hz, 2 H), 1.74 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 168.6, 162.2, 161.6, 150.4, 131.8, 129.5, 126.2, 126.1, 121.3, 106.6, 95.0, 37.6, 25.0. MS (ES) m/z: 330 [M+MeCN +H]$^+$, 289 [M+H]$^+$. HR-MS (ES) m/z calcd for $C_{16}H_{16}O_5$: 289.1076 [M+H]$^+$; found: 289.1067.

1.25.13.29 Mixture of (E)-phenyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)but-2-enoate (**337c**) and (E)-methyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)but-3-enoate (**337d**)
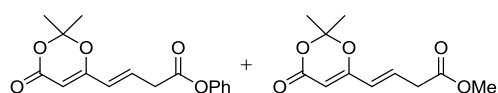
(^{i}Bu$_2$AlH)$_2$ (1M in hexanes, 3.22 mL) was added dropwise to a solution of 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-N-methoxy-N-methylacetamide (0.74g, 3.22 mmol) in THF (32 mL) at −78 ^{o}C over 10 minand stirred for a further 20 min. Methanol (6mL) was added and stirred for 5 min. The mixture was then transferred by cannula to a mixture of phenyl (triphenylphosphoranylidene)acetate (1.28 g, 3.22 mmol) in THF (32 mL) at 50 ^{o}C and stirred for 1 h. Aqueous Sodium potassium tartrate was added and the aqueous extracted with ether (× 2) and ethyl acetate (× 2). The combined organics were washed with brine, dried (MgSO$_4$),rotary evaporated and chromatographed (petroleum ether/Et_2O, 7:3) to a yellow oil (270 mg, 33%) that was a mixture of methyl and phenyl esters. Phenyl ester: ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.50–7.33 (m, 2 H), 7.33–7.17 (m, 1 H), 7.17–7.03 (m, 2 H), 6.77–6.67 (dt, J = 15.6, 7.2 Hz, 1 H), 6.13 (dt, J = 15.7, 1.5 Hz, 1 H), 5.33 (s , 1 H), 3.52 (dd, J = 7.3, 1.5 Hz, 2 H), 1.72 (s, 6 H). HR-MS (EI) m/z calcd for $C_{16}H_{17}O_5$: 289.1067 [M+H]$^+$; found: 289.1076.

Methyl ester: ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.61 (dt, J = 15.0, 7.3 Hz, 1 H), 6.02 (dt, J = 15.6, 1.5 Hz, 1 H) 5.30 (s , 1 H), 3.73 (s, 3 H), 3.25 (dd, J = 7.3, 1.5 Hz, 2 H), 1.71 (s, 6 H).

1.25.13.30 _tert_-Butyl 4-(2,2-dimethyl-4-oxo-4_H_-1,3-dioxin-6-yl)-2-methylbut-3-enoate (±) (**337e**)
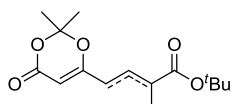
According to general procedure **F**, cross metathesis of ester **462b** (80 mg, 0.51 mmol) and dioxinone **372a** (237 mg, 1.54 mmol) with catalyst **427a** (32 mg, 0.05 mmol) in C$_6$F$_5$CF$_3$ (3 mL) at 70 °C for 2 h and chromatography (pentane/Et$_2$O, 95:5 to 17:3) gave dioxinone ester **337e** (98 mg, 68 %, 1 : 0.75 rr) as a brown oil. IR (cm^{-1}): 1724, 1653, 1637, 1595, 1458, 1390, 1369, 1271, 1252, 1202, 1149, 1125, 1065, 1015, 966, 901, 846, 804, 743. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.57–6.64 (m, 1.75 H), 5.96 (dd, J = 15.7, 1.0 Hz, 1 H), 5.30 (s, 1H), 5.27 (s, 0.75 H), 3.14–3.24 (m, 1 H), 3.08 (d, J = 7.3 Hz, 1.5 H), 1.83 (s, 2.25 H), 1.72 (s, 6 H), 1.70 (s, 4.5 H), 1.50 (s, 6.75 H), 1.46 (s, 9 H), 1.31 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 172.4, 168.5, 166.4, 162.8, 161.8, 161.0, 140.0, 133.7, 130.9, 123.1, 106.8, 106.5, 94.5, 93.9, 81.3, 80.8, 43.6, 32.8, 28.1, 28.0, 25.1, 25.0, 16.9, 12.7. MS (ES) m/z: 283 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{15}$H$_{23}$O$_5$: 283.1545 [M + H]$^+$; found: 283.1550.

1.25.13.31 _tert_-Butyl 2-benzyl-4-(2,2-dimethyl-4-oxo-4_H_-1,3-dioxin-6-yl)but-3-enoate (±) (**337f**)
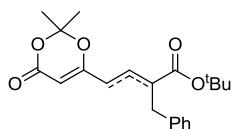
According to general procedure **F**, cross metathesis of ester **462c** (150 mg, 0.647 mmol) and dioxinone **372a** (299 mg, 1.94 mmol) with catalyst **427a** (41 mg, 0.07 mmol) in C$_6$F$_5$CF$_3$ (4 mL) at 70 °C for 2.5 h and chromatography (pentane/Et$_2$O, 19:1 to 4:1) gave dioxinone ester **337f** (142 mg, 61 %, 1 : 0.25 rr) as a brown oil. IR (cm^{-1}): 1720, 1651, 1593, 1496, 1478, 1455, 1391, 1369, 1273, 1250, 1202, 1144, 1018, 970, 902, 843, 806, 740, 699. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.12–7.32 (m, 6.25 H), 6.77 (t, J = 7.3 Hz, 0.25 H), 6.55 (dd, J =

15.7, 8.8 Hz, 1 H), 5.87 (d, J = 15.7 Hz, 1 H), 5.25 (s, 1.25 H), 3.67 (s, 0.5 H), 3.31–3.40 (m, 1 H), 3.06–3.17 (m, 1.5 H), 2.82–2.92 (m, 1 H), 1.71 (s, 6 H), 1.68 (s, 1.5 H), 1.41 (s, 9 H), 1.36 (s, 2.25 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 171.3, 168.2, 166.0, 162.5, 161.7, 160.8, 138.9, 138.1, 137.8, 136.6, 132.5, 129.1, 128.5, 128.4, 128.1, 126.7, 126.3, 124.4, 106.8, 106.5, 94.7, 94.1, 81.6, 81.1, 51.7, 38.7, 32.9, 32.6, 27.9 27.9, 25.0, 25.0. MS (ES) m/z: 376 [M + NH$_4$]$^+$, 359 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{21}$H$_{27}$O$_5$: 359.1858 [M + H]$^+$; found: 359.1865. Anal. calcd for C$_{21}$H$_{26}$O$_5$: C 70.37, H 7.31; found: C 70.26, H 7.38.

1.25.13.32 *tert*-Butyl 2-(1-(tert-butyldimethylsilyloxy)ethyl)-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)but-3-enoate (**337g**)
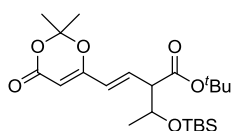
According to general procedure **F**, cross metathesis of ester **462f** (800 mg, 2.67 mmol) and dioxinone **372a** (1.232 g, 8.00 mmol) with catalyst **427a** (70 mg, 0.267 mmol) in C$_6$F$_5$CF$_3$ (16 mL) at 70 °C for 7.5 h and chromatography (pentane/Et$_2$O, 9:1 to 17:3) gave dioxinone ester **337g** (618 mg, 54%, 1:0.6 dr) as a colourless oil. IR (cm^{-1}): 1725, 1654, 1595, 1473, 1462, 1389, 1372, 1272, 1250, 1203, 1152, 1132, 1095, 1019, 979, 902, 831, 810, 775, 749, 665. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.49–6.62 (m, 1.6 H), 5.89–6.04 (m, 1.6 H), 5.30 (s, 0.6 H), 5.28 (s, 1.0 H), 4.04–4.19 (m, 1.6 H), 3.10 (dd, J = 9.5, 6.6 Hz, 0.6 H), 3.01 (dd, J = 9.3, 7.3 Hz, 1.0 H), 1.69–1.72 (m, 9.6 H), 1.45–1.47 (m, 14.4 H), 1.19 (d, J = 5.9 Hz, 3.0 H), 1.15 (d, J = 6.4 Hz, 1.8 H), 0.90 (s, 5.4 H) 0.87 (s, 9 H), 0.08 (s, 1.8 H), 0.07 (s, 1.8 H), 0.06 (s, 3 H), 0.02 (s, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.5, 170.1, 162.6, 162.5, 161.8, 161.7, 137.5, 136.3, 125.2, 125.1, 106.4 (2C), 94.6, 94.3, 81.6, 81.4, 69.8, 69.7, 58.8, 58.4, 28.1, 28.0, 25.7, 25.6, 25.1, 25.1, 24.9, 22.3, 21.4, 17.9, −4.3, −4.4, −4.9, −5.0. MS (ES) m/z: 444 [M+NH$_4$]$^+$, 427 [M+H]$^+$. HR-MS (ES) m/z: calcd for C$_{22}$H$_{38}$SiO$_6$: 427.2522 [M+H]$^+$; found: 427.2525. Anal. calcd for C$_{22}$H$_{38}$SiO$_6$: C 61.94, H 8.98, found: C 62.05, H 9.02.

1.25.13.33 *tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-methylbut-3-enoate (**337h**)
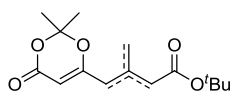
According to general procedure **I**, dehydration of β-hydroxy ester **476a** (726 mg, 2.42 mmol) for 2.5 h and chromatography (pentane/Et$_2$O, 3:1 to 7:3) gave dioxinone ester **337h** (527 mg, 77%, 1.0:0.4:0.4:0.3 rr) as a yellow oil. IR (cm^{-1}): 1721, 1649, 1584, 1458, 1389, 1368, 1322, 1272, 1250, 1202, 1139, 1014, 956, 901, 874, 851, 804, 753, 695, 657. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.79 (s, 1 H), 5.66–5.72 (m, 0.8 H), 5.25–5.30 (m, 2.1 H), 5.09 (d, J = 12.7 Hz, 0.6 H), 3.61 (s, 0.4 H), 3.37 (s, 1.2 H), 3.02–3.09 (m, 2.2 H), 2.98 (d, J = 4.4 Hz, 1 H), 2.14 (d, J = 1.5 Hz, 0.6 H), 2.08 (d, J = 1.0 Hz, 1.8 H), 1.98 (d, J = 1.0 Hz, 3 H), 1.69–1.73 (m, 8.4 H), 1.67 (s, 3.6 H), 1.48 (s, 1.8 H), 1.44–1.46 (m, 17.7 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 169.9, 169.3, 169.1, 169.0, 167.9, 164.4, 163.9, 161.9, 149.1, 148.7, 145.3, 145.0, 136.0, 121.8, 121.7, 120.7, 120.3, 118.5, 106.7, 106.5, 106.2, 106.1, 95.2, 94.9, 94.9, 94.4, 93.7, 81.4, 81.2, 81.1, 80.3, 47.9, 44.5, 42.4, 40.9, 40.1, 36.6, 28.2, 28.1, 28.0, 28.0, 26.9, 25.1, 25.0, 24.9, 19.5, 18.4. MS (ES) m/z: 305 [M + Na]$^+$, 283 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{15}$H$_{23}$O$_5$: 283.1545 [M + H]$^+$; found: 283.1547.

### 1.25.13.34 *tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-2,3-dimethylbut-3-enoate (±) (**337i**)
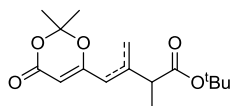
According to general procedure **I**, dehydration of β-hydroxy ester **476b** (815 mg, 2.60 mmol) for 2 h and chromatography (pentane/Et$_2$O, 4:1 to 3:1) gave dioxinone ester **337i** (590 mg, 77%, 1.0:0.6:0.6 rr) as a yellow oil. IR (cm^{-1}): 1721, 1644, 1583, 1458, 1390, 1369, 1318, 1271, 1250, 1202, 1145, 1085, 1014, 900, 875, 848, 804, 744. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.71 (s, 1.0 H), 5.69 (s, 0.6 H), 5.31 (s, 0.6 H), 5.30 (s, 0.6 H), 5.26 (s, 1.0 H), 5.13 (s, 0.6 H), 5.04 (s, 0.6 H), 3.11 (q, J = 7.2 Hz, 1.0 H), 2.96–3.06 (m, 2.4 H), 2.01–2.02 (m, 3 H), 1.86 (d, J = 1.0 Hz, 1.8 H), 1.71 (s, 9.6 H), 1.66–1.67 (m, 3.6 H), 1.43 (s, 19.8 H), 1.26 (d, J = 6.8 Hz, 3.6 H), 1.23 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 172.7, 172.1, 169.3, 164.7, 164.0, 161.9, 161.8, 161.1, 150.8, 150.4, 141.4, 119.5, 118.9, 115.7, 106.5, 106.2, 106.1, 95.2, 95.1, 94.4, 81.1, 80.9, 80.8, 50.8, 45.9, 42.9, 39.3, 28.1, 27.9, 25.1, 24.9, 24.9, 21.2, 17.3, 16.0, 15.6, 15.3. MS (ES) m/z: 314 [M + NH$_4$]$^+$, 297 [M + H]$^+$. HR-MS

(ES) *m/z* calcd for $C_{16}H_{25}O_5$: 297.1702 $[M + H]^+$; found: 297.1704. Anal. calcd for $C_{16}H_{24}O_5$: C 64.84, H 8.16; found: C 64.91, H 8.20.

1.25.13.35 *tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-methyl-2-phenylbut-3-enoate (±) (337j)
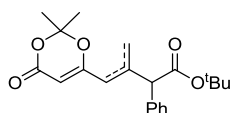
According to general procedure **I**, dehydration of β-hydroxy ester **476c** (750 mg, 1.99 mmol) for 3.5 h and chromatography (pentane/Et₂O, 17:3 to 3:1) gave dioxinone ester **337j** (532 mg, 75%, 1.0:1.0:0.7 rr) as a yellow oil. IR (cm⁻¹): 1721, 1640, 1601, 1583, 1495, 1455, 1390, 1369, 1311, 1272, 1250, 1202, 1138, 1079, 1014, 967, 901, 875, 854, 806, 754, 699, 626. ¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.10–7.34 (m, 13.5 H), 5.76 (s, 0.7 H), 5.61 (s, 1 H), 5.47 (s, 0.7 H), 5.25 (s, 0.7 H), 5.18 (s, 1 H), 5.16 (s, 1 H), 5.08–5.11 (m, 2 H), 4.24 (s, 1 H), 4.17 (s, 1 H), 2.92 (d, *J* = 15.7 Hz, 1 H), 2.80 (d, *J* = 14.7 Hz, 1 H), 1.97 (s, 3 H), 1.76 (s, 2.1 H), 1.67 (s, 2.1 H), 1.62–1.66 (m, 8.1 H), 1.57–1.61 (m, 6 H), 1.42 (s, 6.3 H), 1.37–1.40 (m, 18 H). ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 170.6, 170.2, 169.0, 164.6, 163.7, 161.8, 161.7, 161.1, 149.2, 148.9, 140.3, 137.2, 136.2, 136.0, 128.8, 128.8, 128.8, 128.7, 128.6, 128.3, 127.7, 127.6, 127.2, 120.5, 120.1, 117.4, 106.5, 106.4, 106.1, 95.6, 95.6, 94.5, 81.9, 81.7, 81.5, 77.3, 77.2, 76.7, 62.2, 57.8, 54.1, 39.5, 28.0, 27.9, 25.2, 25.1, 25.0, 24.8, 23.1, 18.9. MS (ES) *m/z*: 376 $[M + NH_4]^+$, 359 $[M + H]^+$. HR-MS (ES) *m/z* calcd for $C_{21}H_{27}O_5$: 359.1858 $[M + H]^+$; found: 359.1866. Anal. calcd for $C_{21}H_{26}O_5$: C 70.39, H 7.31; found: C 70.26, H 7.45.

1.25.13.36 *tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-2-methyl-3-methylene-5-phenylpentanoate (±) (337k)
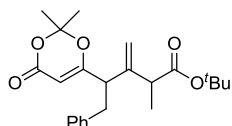
According to general procedure **I**, dehydration of β-hydroxy ester **476d** (404 mg, 1.00 mmol) for 2 h and chromatography (pentane/Et₂O, 4:1) gave dioxinone ester **337k** (317 mg, 82%) as a yellow oil. IR (cm⁻¹): 1724, 1626, 1456, 1390, 1369, 1345, 1271, 1250, 1202, 1145, 1095,

1075, 1017, 901, 847, 810, 745, 699. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.11–7.32 (m, 5 H), 5.27 (s, 2 H), 5.21 (s, 1 H), 3.34 (t, J = 7.8 Hz, 1 H), 2.95–3.06 (m, 3 H), 1.59 (s, 3 H), 1.55 (s, 3 H), 1.42 (s, 9 H), 1.21 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 172.8, 170.7, 161.1, 145.5, 138.3, 128.6, 128.4, 126.6, 114.0, 106.5, 94.5, 80.9, 50.4, 46.1, 37.2, 27.9, 25.2, 24.5, 16.3. MS (ES) m/z: 387 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{23}$H$_{31}$O$_5$: 387.2171 [M + H]$^+$; found: 387.2175. Anal. calcd for C$_{23}$H$_{30}$O$_5$: C 71.48, H 7.82; found: C 71.56, H 7.93.

1.25.13.37 *tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-(4-methoxyphenyl)but-2-enoate (**337l**)
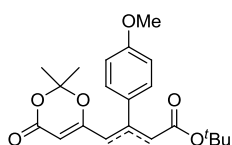
According to general procedure **I**, dehydration of β-hydroxy ester **476e** (486 mg, 1.24 mmol) for 4 h and chromatography (pentane/Et$_2$O, 4:1 to 7:3) gave dioxinone ester **337l** (376 mg, 81%, 1:0.4 rr) as a yellow oil. IR (cm^{-1}): 1725, 1702, 1624, 1602, 1513, 1390, 1369, 1274, 1250, 1203, 1180, 1139, 1029, 1012, 970, 901, 877, 832, 804, 731. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.37–7.39 (m, 2 H), 7.11–7.13 (m, 0.8 H), 6.89–6.91 (m, 2 H), 6.84–6.86 (m, 0.8 H), 6.17 (s, 1 H), 5.94 (s, 0.4 H), 5.42 (s, 1 H), 5.14 (s, 0.4 H), 3.83 (s, 5 H), 3.81 (s, 1.2 H) 3.35 (0.8 H), 1.76 (s, 6 H), 1.44 (s, 2.4 H), 1.40 (s, 9 H), 1.33 (s, 3.6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 169.6, 169.3, 165.5, 164.2, 161.8, 161.3, 160.3, 159.5, 148.7, 144.9, 133.8, 132.0, 127.9, 127.8, 120.6, 119.8, 114.1, 114.0, 106.6, 106.4, 96.1, 93.8, 81.3, 80.6, 55.3, 55.3, 39.2, 34.1, 28.2, 27.9, 25.1, 24.8. MS (ES) m/z: 392 [M + NH$_4$]$^+$, 375 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{21}$H$_{26}$O$_6$: 375.1808 [M + H]$^+$; found: 375.1820. Anal. calcd for C$_{21}$H$_{26}$O$_6$: C 67.36, H 7.00; found: C 67.21, H 7.09.

1.25.13.38 1-Ethyl 7-isopropyl 5-oxohept-2-enedioate (**338b**)
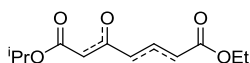
(E)-Ethyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)but-2-enoate (264 mg, 1.10 mmol) and *iso*-propanol (340 μL, 4.40 mmol) in toluene (5.00 ml) was refluxed for 4.5 h. The solution

was rotary evaporated and chromatographed (petroleum ether/ether, 4:1 to 3: 1) to give the title compound (200 mg, 75 %, 1:0.7(enol):0.5) as a colourless oil. IR (cm^{-1}) 1721, 1375, 1180, 1102, 1027. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 11.91 (d, J = 1.5 Hz, 0.7 H), 7.01 (dt, J = 15.7, 7.3 Hz, 0.5 H), 6.93 (dt, J = 16.1, 6.8 Hz, 1 H), 6.69 (dt, J = 15.7, 7.3 Hz, 0.7 H), 6.25 (dt, J = 16.1, 1.5 Hz, 1 H), 5.92 (dt, J = 15.7, 1.5 Hz, 0.5 H), 5.90 (dq, J = 15.7, 1.5 Hz, 0.7 H), 5.02 - 5.12 (m, 2.2 H), 4.99 (s, 0.7H), 4.12 - 4.24 (m, 4.4 H), 3.58 (s, 2H), 3.48 (dd, J = 7.3, 1.5 Hz, 1 H), 3.46 (s, 1 H), 3.27 (dd, J = 6.8, 1.5 Hz, 2 H), 3.21 (dd, J = 7.3, 1.5 Hz, 1.4H), 1.20 - 1.37 (m, 19.8 H). ^{13}C NMR (101 MHz, CHLOROFORM-d) δ: 198.9, 191.9, 172.4, 170.4, 169.6, 168.2, 166.7, 166.2, 165.6, 152.5, 149.4, 140.0, 138.8, 132.2, 131.2, 127.6, 125.5, 91.9, 69.4, 69.1, 67.7, 61.3, 61.0, 60.6, 49.4, 47.2, 45.4, 37.9, 37.7, 21.9, 21.7, 14.2, 14.2. MS (EI) m/z: 243 [M+H]$^+$. HR-MS (EI) m/z calcd for C$_{12}$H$_{19}$O$_5$: 243.1229 [M+H]; found: 243.1232. Anal. calcd for C$_{12}$H$_{18}$O$_5$: C 54.49, H 7.49 found: C 54.58; H 7.35.

1.25.13.39 ((2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)triphenylphosphonium bromide (343)[236]
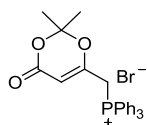
6-(Bromomethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one **xx** (500 mg, 2.26 mmol) and triphenylphosphine (593 mg, 2.26 mmol) in benzene (5 mL) was refluxed for 1.5 h, and filtered. The solids were washed with toluene, hexanes then diethyl ether to give the title compound (910 mg, 83%) as a beige solid. IR (cm^{-1}): 1657, 1525, 1480, 1433, 1355, 1254, 1200, 1184, 1154, 1101, 1019, 997, 916, 884, 839, 762, 717, 692. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.88–7.98 (m, 6 H), 7.79–7.85 (m, 3 H), 7.69-7.73 (m, 6 H), 5.82 (d, J^3 = 3.4 Hz, 1 H), 5.64 (d, J = 15.2 Hz, 2 H), 1.41 (s, 6 H). MS (EI) m/z: 403 [M−Br+H]$^+$. HR-MS (EI) m/z calcd for C$_{25}$H$_{24}$O$_3$P: 403.1463 [M−Br+H]$^+$; found: 403.1468.

1.25.13.40 *tert*-Butyl 3-oxopropanoate (344)[237]
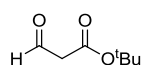
2,2-Dimethyl-4,6-dioxo-1,3-dioxane-5-carbaldehyde (3.40 g, 19.77 mmol) in benzene (40 mL) and *tert*-butanol (1.60 g, 21.74 mmol) was refluxed for 1.5 h then rotary evaporated and distilled to give

the title compound (353 mg, 12%) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: Keto form: 9.79 (t, J = 2.7 Hz, 1 H), 3.31 (d, J = 2.4 Hz, 2 H), 1.50 (s, 9 H); Enol form: 11.57 (d, J = 12.2 Hz, 1 H), 7.06 (dd, J = 12.2, 5.9 Hz, 1 H), 4.98 (d, J = 6.4 Hz, 1 H), 1.50 (s, 9 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 195.8, 166.0, 163.1, 128.3, 94.9, 82.5, 49.7, 31.2, 28.2, 28.0. in agreement with literature.
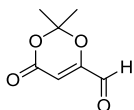
1.25.13.41   6-(Bromomethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (345)[238]
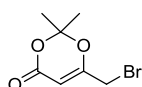
Bromine (5.13 mL, 100 mmol) in CCl$_4$ (20 mL) was added to diketene (8.4 g, 100 mmol) in CCl$_4$ (50 mL), dropwise at −20 °C over 30 min. The mixture was stirred for a further 1 h then water was added dropwise over a further 1 h maintaining an internal temperature of −20 to −30 °C. The mixture was then filtered and the solids were dissolved in boiling CCl$_4$. On cooling a precipitate formed which was recrystalized from boiling CCl$_4$ to give 4-bromo-3-oxobutanoic acid (16.35 g, 90%) as a light brown solid used without further purification. IR (cm^{-1}): 1733, 1687, 1441, 1400, 1377, 1321, 1256, 1108, 1045, 925, 709. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: (keto : enol 3.5 : 1) keto: 8.87 (br. s, 1 H), 4.06 (s, 2 H), 3.81 (s, 2 H); enol: 11.63 (br. s., 1 H), 7.53 (br. s., 1 H), 5.36 (s, 1 H), 3.88 (s, 2 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 194.3, 176.1, 173.3, 172.0, 90.9, 45.3, 33.7, 28.2.

Concentrated H$_2$SO$_4$ (160 µL, 2.93 mmol) was added to a mixture of 4-bromo-3-oxobutanoic acid (5.3 g, 29.3 mmol), acetic anhydride (5.54 mL, 58.7 mmol) and acetone (4.29 mL, 58.7 mmol) at 0 °C and stirred for 0.5 h then a further 2 h at 22 °C. The mixture was poured into cold 10 Aqueous Na$_2$CO$_3$ (150 mL) and stirred for 5 min. The aqueous was extracted with CH$_2$Cl$_2$ (3 × 200 mL) and the combined organics were dried (MgSO$_4$), rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 9:1 to 4:1) to give the title compound (4.92 g, 76 %) as a brown oil. IR (cm^{-1}): 1723, 1635, 1390, 1375, 1272, 1254, 1224, 1200, 1178, 1013, 908, 804, 697. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.54 (s, 1 H), 3.89 (s, 2 H), 1.73 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 164.3, 160.5, 107.5, 95.7, 26.9, 24.7. MS (CI) m/z: 240 [M^{81}+NH$_4$]$^+$, 238 [M^{79}+NH$_4$]$^+$, 223[M^{81}+H]$^+$, 221[M^{79}+H]$^+$. HR-MS (CI) m/z calcd for C$_7$H$_{13}$NO$_3$Br: 238.0079[M+NH$_4$]$^+$; found: 238.0085. In agreement with the literature.

### 1.25.13.42   2,2-Dimethyl-4-oxo-4H-1,3-dioxine-6-carbaldehyde (346)[239]

Manganese dioxide (1.2 g, 13.80 mmol) was added to 6-(hydroxymethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (109 mg, 0.69 mmol) in CH_2Cl_2 (2 mL) and stirred for 48 h. The mixture was filtered through celite and rotary evaporated to give the title compound (90 mg, 84 %) as a colourless oil. IR (cm^{-1}): 1707, 1643, 1627, 1392, 1378, 1279, 1248, 1199, 1159, 1012, 966, 904, 871, 815. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 9.50 (s, 1 H), 6.08 (s, 1 H), 1.77 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 185.5, 160.1, 157.7, 108.5, 104.0, 24.9. In agreement of the literature.

1.25.13.43   (2-Carboxyethyl)-triphenylphosphonium Bromide (**347**) [240]
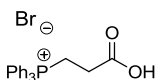
3-Bromopropionic acid (2.5 g, 16.34 mmol) and triphenylphosphine (4.29 g, 16.34 mmol) in acetonitrile (20 mL) were heated by microwave irradiation at 100 °C for 10 h. The mixture was rotary evaporated to give the title compound (6.7 g, quantitative) as a colourless solid. IR (cm^{-1}): 1728, 1436, 1184, 1110, 996, 742, 723, 687. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.95 (br. s, 1 H), 7.70–7.83 (m, 15 H), 3.75 (dt, ^2J = 12.7, ^3J = 7.6 Hz, 2 H), 3.05 (dt, ^3J = 13.2, ^2J = 7.6 Hz, 2 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 171.20 (d, ^3J = 13.87 Hz), 135.36 (d, ^4J = 3.47 Hz), 133.55 (d, ^2J = 10.40 Hz), 130.63 (d, ^3J = 12.14 Hz), 117.32 (d, ^1J = 86.70 Hz), 28.20, 18.98 (d, ^1J = 55.49 Hz). MS (EI) m/z: 335 [M−Br]$^+$. HR-MS (EI) m/z calcd for $C_{21}H_{20}O_2P$: 335.1201[M−Br]$^+$; found: 335.1204. In agreement with the literature.

1.25.13.44   6-(Hydroxymethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (**348**)[238]
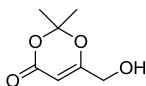
Potassium carbonate (202 mg, 1.46 mmol) in water (2.25 mL) was added to (2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl acetate (450 mg, 2.25 mmol) in methanol (9 mL) at 5 °C. The mixture was stirred for 0.5 h and then the methanol rotary evaporated. The residue was acidified with 1M aqueous HCl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried (MgSO$_4$), rotary evaporated and chromatographed (pentane/Et$_2$O, 3:2 to 1:3) to give the title compound (156 mg, 44 %) as a colourless solid. IR (cm^{-1}): 1705, 1638, 1391, 1378, 1316, 1273, 1252, 1200, 1095, 1081, 1044, 1007, 904, 869, 809, 659. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.57 (br. t, 1 H), 4.18 (br. d, 2

H), 2.93 (br. t, 1 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.8, 161.6, 107.1, 91.9, 60.7, 24.9. In agreement with the literature.

1.25.13.45 2-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetaldehyde (350)
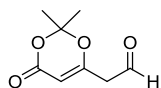
Palldium on charcoal (100% by wt. (10% Pd) and triethylsilane (250 μL, 1.57 mmol) were added sequentially to *S*-ethyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)ethanethioate (120 mg, 0.522 mmol) in CH$_2$Cl$_2$ (1 mL) and stirred for 24 h. The mixture was filtered through celite and rotary evaporated then left to stand 5 d. The title compound (40 mg) was obtained as an impure red oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 9.71 (t, *J* = 1.5 Hz, 1 H), 5.41 (s, 1 H), 3.37 (d, *J* = 1.6 Hz, 2 H), 1.69 ppm (s, 6 H). Cross peak in COSY for 9.71 and 3.37 ppm. ^{1}H NMR (400 MHz, Acetone-*d*6, ppm) δ: (keto-form) 9.69 (t, J = 1.1 Hz, 1 H), 5.46 (s, 1 H), 3.54 (d, J = 1.3 Hz, 2 H), 1.69 (s, 6 H); (enol form) 7.46 (d, J = 12.1 Hz, 1 H), 5.51 (d, J = 12.1 Hz, 1 H), 5.07 (s, 1 H), 1.65 (s, 6 H).
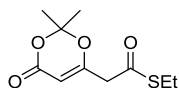
1.25.13.46 2-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-N-methoxy-N-methylacetamide (351)
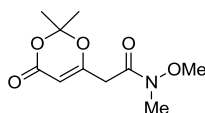
2,2,6-Trimethyl-4H-1,3-dioxin-4-one (4.50 g, 0.032 mmol) in THF (15 ml) was added dropwise to LiHMDS (7.74 ml, 0.036 mmol) in THF (90 ml) at −78 °C. After 0.5 h, 2-chloro-N-methoxy-N-methylacetamide **xx** (1.96 g, 0.016 mmol) was added and the mixture stirred for 0.5 h then stirred at 20 °C for 14 h. Saturated aqueous NH$_4$Cl (100 mL) was added and the layers separated. The aqueous was extracted with EtOAc (2 × 75 ml) and the combined organics were dried (MgSO$_4$), rotary evaporated, and chromatographed (petroleum ether/Et$_2$O, 1:3 to 0:1) to give the title compound (2.6 g, 71 %) as colourless needles. IR (cm^{-1}): 1726, 1661, 1394, 1372, 1273, 1198. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.37 (s, 1 H), 3.71 (s, 3 H), 3.39 (s, 2 H), 3.19 (s, 3 H), 1.71 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 167.6, 165.1, 160.9, 107.2, 96.4, 61.4, 37.4, 32.2, 25.0. MS (CI) *m/z*: 230 (M+H)$^+$.

HR-MS (CI) *m/z* calcd for $C_{10}H_{16}NO_5$: 230.1031 [M+H]; found: 230.1028. Anal. calcd for $C_{10}H_{15}O_5N$: C 52.40, H 6.60, N 6.11; found: C 52.56, H 6.51, N 5.99.

### 1.25.13.47 *S*-Ethyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)ethanethioate (**352**)

To 2-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetic acid (448 mg, 2.41 mmol) was added Ghosez's reagent (414 μL, 3.13 mmol) in CH_2Cl_2 (50 mL) and stirred for 5 min. Ethanethiol (178 μL, 24.2 mmol) was then added dropwise and stirred 15 min and then pyridine (388 μL, 4.82 mmol) was added and stirred for 12 h. The mixture was poured in saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (× 2), dried ($MgSO_4$), rotary evaporated and chromatographed (pentane/Et_2O, 7:3) to give the title compound (166 mg, 72%) as a pale yellow oil. IR (cm^{-1}): 1725, 1686, 1634, 1389, 1372, 1270, 1252, 1200, 1012, 961, 900, 808, 639. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.41 (s, 1 H), 3.45 (s, 2 H), 2.94 (q, *J* = 7.5 Hz, 2 H), 1.71 (s, 6 H), 1.28 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 192.1, 163.4, 160.5, 107.2, 96.8, 47.9, 24.9, 24.0, 14.5. MS (EI) *m/z*: 231 [M+H]$^{+}$. HR-MS (EI) *m/z*: calcd for $C_{10}H_{15}O_4S$: 231.0691[M+H]$^{+}$; found: 231.0697.

### 1.25.13.48 2,2-Dimethyl-4,6-dioxo-1,3-dioxane-5-carbaldehyde (**354**)[237]
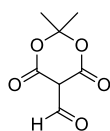
Meldrums acid (5.06 g, 35.1 mmol) in triethylformate (18.94 mL, 113.7 mmol) was heated at 85 °C for 2.5 h then rotary evaporated and a solution of 2 M aqueous HCl added and stirred a further 1 h at 25 °C. The mixture was diluted with brine (100 mL) and extracted with ether (3 × 100 mL), dried (Na$_2$SO$_4$), and rotary evaporated to give the title compound (3.40 g, 56%) as an orange solid. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.81 (br. s., 2 H), 0.48 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 177.0, 171.8, 168.0, 107.1, 95.4, 27.3. In agreement with literature.

1.25.13.49 (2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl acetate (**355**)[238]
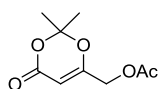
Sodium acetate (1.04 g, 12.67 mmol) was added to 6-(bromomethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (1.4 g, 6.33 mmol) in DMF (12.7mL) and heated at 70 °C for 2 h. The mixture poured into ice (100 g) and the aqueous was extracted with ether (3 × 60 mL) and the combined organics washed with brine (2 × 30 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 7:3 to 3:2) to give the title compound (563 mg, 44%) as a colourless oil used without further purification. IR (cm^{-1}): 1728, 1647, 1413, 1393, 1378, 1326, 1273, 1218, 1203, 1180, 1070, 1045, 1012, 903, 813. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.45 (t, J = 1.2 Hz, 1 H), 4.61 (d, J = 1.0 Hz, 2 H), 2.14 (s, 3 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 169.8, 165.2, 160.4, 107.3, 93.6, 60.8, 24.9, 20.5. MS (CI) m/z: 218 [M+NH$_4$]$^+$, 201 [M+H]$^+$. HR-MS (CI) m/z calcd for C$_9$H$_{16}$NO$_5$: 218.1028 [M+NH$_4$]$^+$; found: 218.1035. In agreement with the literature.
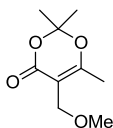
1.25.13.50   5-(Hydroxymethyl)-2,2,6-trimethyl-4H-1,3-dioxin-4-one (**358**)
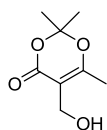
2,2,6-Trimethyl-4H-1,3-dioxin-4-one (0.50 g, 3.5 mmol) was added dropwise to LDA (3.87 mmol) in THF (2 ml) at −78 °C and stirred for 1 h in flask A. In flask B, THF (100 mL) was added to paraformaldehyde (3 g, 0.1 mol) and p-tolenesulfonic acid (0.49 g, 1.5 mmmol) and distilled. The formaldehyde/THF co-distillate (80 ml) was added dropwise to the flask A over 30 min. The mixture was allowed to warm to room temperature and stirred for 14 h. Saturated aqueous NH$_4$Cl (10 ml) and water (10 ml) were added and the mixture extracted with diethyl ether (3 × 40 ml). The combined organics were washed with brine (45 ml), dried (Na$_2$SO$_4$), filtered, rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 1:1 to 0:1) to give the title compound (54 mg, 9%) as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 4.38 (s, 2 H), 2.48 (br. s, 1 H), 2.12 (s, 3 H), 1.71 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 166.3, 162.6, 105.7, 105.2, 56.8, 25.1, 17.3.

### 1.25.13.51   5-(Methoxymethyl)-2,2,6-trimethyl-4H-1,3-dioxin-4-one (**359**)

2,2,6-Trimethyl-4H-1,3-dioxin-4-one (0.50g, 3.5 mmol) was added dropwise to LDA (3.87 mmol) in THF (5 ml) at −78 °C. After 0.5 h, chloromethyl methyl ether (1.42 g, 17.6 mmol) was added dropwise and the mixture stirred for 3 h at −78 °C. Further chloromethyl methyl ether (0.36 g, 4.4 mmol) was added and the mixture warmed to 20 °C and stirred for a further 16 h. Saturated aqueous NH$_4$Cl (10 mL) and water (10 mL) was added and the mixture extracted with diethyl ether (3 × 50 mL). The combined organics were washed with brin (50 mL), dried (Na$_2$SO$_4$), rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 1:1 to 0:1) to yield the title compound (128 mg, 28%) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 4.19 (s, 2 H) 3.37 (s, 3 H) 2.11 (s, 3 H) 1.70 (s, 6 H); ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 168.8, 161.8, 105.6, 102.7, 65.1, 58.0, 25.1, 17.6.

1.25.13.52   9H-Carbazole-9-carbaldehyde (**361**)[241]
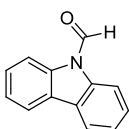
Carbazole (5.00 g, 29.9 mmol) in formic acid (37.5 mL) was refluxed for 9 h then rotary evaporated and recrystalized (EtOAc) to give the title compound (3.22 g, 55%) as a colourless solid. IR (cm^{-1}): 1699, 1482, 1446, 1420, 1361, 1324, 1301, 1225, 1215, 1155, 1079, 946, 752, 723, 686, 616. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 9.67 (s, 1 H), 8.50–8.65 (m, 1 H), 7.97 (d, J = 7.8 Hz, 2 H), 7.63–7.75 (m, 1 H), 7.37–7.57 (m, 4 H).^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: (101 MHz, CDCl$_3$, ppm) δ: 157.4, 137.7, 137.1, 127.7, 127.0, 126.1, 124.6, 124.3, 120.7, 119.8, 116.7, 109.8. MS (EI) m/z: 196 [M+H]$^+$. HR-MS (EI) m/z: calcd for C$_{13}$H$_{10}$NO: 196.0762 [M+H]$^+$; found: 196.0766. In agreement with the literature.

### 1.25.13.53   Methoxy(methyl)carbamic chloride (**364**)[242]
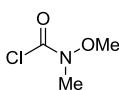
N,O-Dimethylamine hydrochloride (8.33 g, 85.4 mmol) was added portionwise over 10 min to a solution of triphosgene (10.2 g, 34.2 mmol) in CH_2Cl_2 (85 ml) maintaining the temperature below -70 °C and stirred for 0.5 h. Pyridine (13.73 mmol, 170.8 mmol) in CH_2Cl_2 (28 ml) was added dropwise over 1.5 h maintaining the temperature below -73 °C then stirred 13.5 h at 20 °C. Water (100 ml) was added dropwise, the layers were separated and aqueous further extracted with CH_2Cl_2 (3 × 50 ml). The combined organics were washed with 0.5 M HCl (2 × 100 ml), $NaHCO_3$ (75 ml), brine (75 ml), dried ($MgSO_4$), rotary evaporated (CARE: water bath at 35 °C, no more than 500 torr below atmospheric pressure) and distilled (60 °C, 1.0 torr) to give title compound (8.213 g, 78 %) as a colourless oil. IR (cm^{-1}): 1719, 1459, 1443, 1406, 1348, 1181, 1081, 980, 856, 668, 651. (^{1}H NMR 400 MHz, $CDCl_3$, ppm) δ: 3.76 (s, 3 H), 3.32 (br. s., 3 H). MS (CI) m/z: 141 $[M+NH_4]^+$. HR-MS (CI) m/z calcd for $C_3H_{10}N_2O_2Cl$: 141.0431 $[M+NH_4]$; found: 141.0431. Compound too volatile for microanalysis. In agreement with the literature.

1.25.13.54   (E)-6-(2-(Methoxy(methyl)amino)vinyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (365)
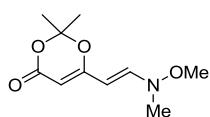
($^iBu_2AlH)_2$ (1M in hexanes, 3.22 mL) was added dropwise to a solution of 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-N-methoxy-N-methylacetamide (0.74g, 3.22 mmol) in THF (32 mL) at −78 °C over 10 min and stirred for a further 20 min. Phenol (0.41 g, 4.37 mmol) was added and stirred for 10 min. The mixture was then added to phenyl (triphenylphosphoranylidene)acetate (0.87g, 2.19 mmol) in THF (22 mL) at 50 °C and stirred for 4 h. Aqueous Sodium potassium tartrate was added and the aqueous extracted with ether (× 2) and ethyl acetate (× 2). The combined organics were washed with brine, dried ($MgSO_4$), rotary evaporated and chromatographed (petroleum ether/Et_2O, 1:1 to 0:1) to give the title compound (0.16 g, 35%) a yellow oil. IR (cm^{-1}): 1702, 1609, 1581, 1365, 1267, 1247, 1201, 1173, 1104, 1066, 1013, 944, 899, 792, 681. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 6.94 (d, J = 12.7 Hz, 1 H), 5.19 (d, J = 12.7 Hz, 1 H), 5.05 (s, 1 H), 3.67 (s, 3 H), 3.07 (s, 3 H), 1.70 (s, 6 H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ: 165.5, 162.7, 143.7, 105.4, 92.8, 88.1, 60.2, 40.3, 25.1. MS (CI) m/z: 214 $[M+H]^+$. HR-MS (EI) m/z calcd for $C_{10}H_{16}NO_4$: 214.1079 $[M+H]^+$; found: 214.1075. Anal. calcd for $C_{10}H_{15}NO_4$: C 56.33, H 7.09, N 6.57; found: C 56.44, H 6.97, N 6.45.

1.25.13.55   *tert*-Butyl (triphenylphosphoranylidene)acetate (366b)[243]
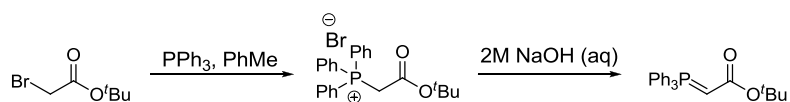
tert-Butyl bromoacetate (7.60 mL, 51.4 mmol) was added to to triphenylphosphine (12.00 g, 45.8 mmol) in toluene (20 mL) and stirred for 2h and then a further 12 h at 3 °C. The solids were collected by filtration and washed sequentially with toluene and then hexane and dried *in vacuo* to give (*tert*-butylcarbonylmethyl)triphenylphosphonium bromide (**349a**) as a colourless solid (16 g, 76%) used directly in the next step.

A cold solution of 2 M aqueous NaOH was added to (*tert*-Butylcarbonylmethyl)triphenylphosphonium bromide in cold water and stirred vigorously. The solids were collected by filtration, washed with cold water and dried in air to give the title compound. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.70–7.61 (m, 6 H), 7.58–7.51 (m, 3 H), 7.49 (td, J = 7.6, 2.7 Hz, 6 H), 2.71 (br. d, 1 H), 1.27 (br. d, 9 H). In agreement with the literature.

1.25.13.56   Phenyl (triphenylphosphoranylidene)acetate (**366c**)[244]
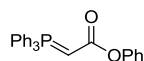
Phenylbromoacetate (2.15 g, 10 mmol) in chloroform (5 mL) was added to triphenylphosphine (2.62g, 10 mmol) in chloroform (5 mL) at 0 °C and the mixture allowed to stir at 25 °C for 40 min. The mixture was rotary evaporated, suspended in ether and the solids collected by filtration, washing with further diethyl ether (× 3) and dried *in vacuo*. The salt obtained was dissolved in CH$_2$Cl$_2$ (60 mL) and washed with 2 M aqueous NaOH (50 mL), dried (MgSO$_4$) and rotary evaporated to give the title compound (3.81 g, 96%) as a coulourless solid. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.80–7.65 (m, 7 H), 7.61–7.45 (m, 9 H), 7.28 (br. s, 1 H), 7.22–7.08 (m, 1 H), 7.05 (br. s, 1 H), 6.65 (br. s, 1 H), 3.19–2.85 (m, 1 H).

1.25.13.57   PSB160-1 1(Benzoylmethylene)triphenylphosphorane (**367a**)[245]
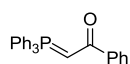
2-Bromoacetophenone (1.99 g, 10 mmol) in acetone (10 mL) was added to triphenylphosphine (2.62g, 10 mmol) in acetone (10 mL) stirred for 30 min. The solids were collected by filtration and were washed with ether. The resulting salt was dissolved in CH$_2$Cl$_2$ (60 mL) and washed with 2 M aqueous NaOH (50 mL). dried (MgSO$_4$) and rotary evaporated to give the title compound (2.67 g, 70%) as a

solourless solid. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.12–7.86 (m, 2 H), 7.86–7.62 (m, 5 H), 7.62–7.42 (m, 10 H), 7.42–7.31 (m, 3 H), 4.45 (d, J = 24.9 Hz, 1 H). In agreement with the literature.

### 1.25.13.58 [(*p*-Nitrobenzoyl)methylene]triphenylphosphorane (367b)[245]
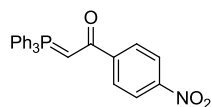
2-Bromo-4'-nitroacetophenone (2.44 g, 10 mmol) in chloroform (5 mL) was added to triphenylphosphine (2.62g, 10 mmol) in chloroform (5 mL) at 0 °C and allowed to stir at 25 °C for 40 min. The mixture was rotary evaporated, suspended in ether and the solids collected by filtration, washing with further diethyl ether (× 3) and dried *in vacuo*. The salt obtained was dissolved in CH$_2$Cl$_2$ (60 mL) and washed with 2 M aqueous NaOH (50 mL), dried (MgSO$_4$) and rotary evaporated to give the title compound (3.47 g, 82%) as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.20 (m, 2 H), 8.14–8.04 (m, 2 H), 7.76–7.65 (m, 6 H), 7.63–7.44 (m, 9 H), 4.51 (d, J = 23.0 Hz, 1 H). MS (EI) *m/z*: 426 [M+H]$^+$. HR-MS (EI) *m/z* calcd for C$_{26}$H$_{21}$NO$_3$P: 426.1259 [M+H]$^+$; found: 426.1258. In agreement with the literature.

### 1.25.13.59 2-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetic acid (368)
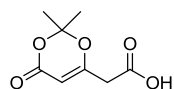
Hydrogen was bubbled through a mixture of Benzyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetate (530 mg, 1.92 mmol) and Pd/C (53 mg, 10% by wt.) in EtOAc (19 mL) for 5 min and then the mixture was stirred under a hydrogen atmosphere (balloon) for 45 min. The mixture was filtered through celite and rotary evaporated to give the title compound (332 mg, 90%) as a colourless solid. IR (cm^{-1}): 1734, 1701, 1646, 1422, 1393, 1373, 1340, 1275, 1235, 1200, 1177, 1014, 948, 917, 903, 832, 752, 735. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.75 (br. s, 1 H), 5.45 (s, 1 H), 3.32 (s, 2 H), 1.71 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 172.2, 163.4, 161.2, 107.5, 96.5, 39.1, 24.8. MS (CI) *m/z*: 204 [M+NH4]$^+$, 160 [M-CO$_2$+NH$_4$]$^+$, 143 [M-CO$_2$+H]$^+$. HR-MS (CI) *m/z* calcd for C$_8$H$_{14}$NO$_5$: 204.0872 [M+NH4]$^+$; found: 204.0880.

### 1.25.13.60 2,2-Dimethyl-6-vinyl-1,3-dioxan-4-one (372a)[246246]
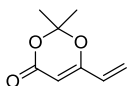
Triethylamine (28.5 mL, 204 mmol) was added dropwise to a solution of 6-(2-chloroethyl)-2,2-dimethyl-1,3-dioxan-4-one (19.5 g, 102 mmol) in CH_2Cl_2 (250 mL) at 0 °C and the mixture stirred at 25 °C for 3 h. The mixture was diluted with CH_2Cl_2 (150 mL) then washed with 1 M aqueous HCl (200 mL), brine (200 mL), dried (MgSO$_4$) rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 3:1 to 2:1) to give the title compound (11.29 g, 73% over 3 steps) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.21 (dd, J = 17.1, 10.3 Hz, 1 H), 6.02 (dd, J = 17.1, 1.0 Hz, 1 H), 5.60 (d, J = 10.3, 1.0 Hz, 1 H), 5.34 (s, 1 H), 1.71 (s, 6 H).^{13}C NMR (101 MHz, CDCl3, ppm) δ: 162.8, 161.7, 129.3, 123.8, 106.5, 95.2, 25.0. MS (CI) m/z: 155 [M+H]$^+$; HR-MS (CI) m/z calcd for C$_8$H$_{11}$O$_3$: 155.0708 [M+H]$^+$; found: 155.0708. In agreement with the literature.

### 1.25.13.61   2,2-Dimethyl-6-(prop-1-en-2-yl)-4H-1,3-dioxin-4-one (372b)
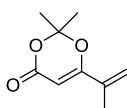
(CF$_3$CO)$_2$O (5.72 mL, 37.4 mmol), CF$_3$CO$_2$H (28.4 mL, 370 mmol) and Ac$_2$O (4.4 mL, 47 mmol) were added dropwise with stirring to *tert*-butyl 4-methyl-3-oxopent-4-enoate in Me$_2$CO at −78 °C and the mixture was allowed to warm to 25 °C. After 14 h, the mixture was poured into cold saturated aqueous NaHCO$_3$ (800 mL) and extracted with EtOAc (2 × 100 mL). The combined organic phases were dried (MgSO$_4$), filtered, rotary evaporated and chromatographed (pentane/Et$_2$O, 95:5 to 90:10) to give the title compound (353 mg, 33%) as a yellow oil. IR (cm^{-1}): 1721, 1635, 1593, 1391 1369, 1283, 1253, 1202, 1146, 1016, 998, 921, 903, 887, 820, 754, 617. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.80 (s, 1 H), 5.47 (s, 1 H), 5.37–5.40 (m, 1 H), 1.92 (s, 3 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 164.5, 162.0, 135.3, 121.1, 106.2, 92.8, 24.9, 18.1. MS (ES) m/z: 210 [M + MeCN + H]$^+$, 169 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_9$H$_{13}$O$_3$: 169.0865 [M + H]$^+$; found: 169.0869.

1.25.13.62   3,3-Dimethyl-9-phenyl-5,6-dihydro-[1,3]dioxino[5,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,8,10(9H)-trione (373)
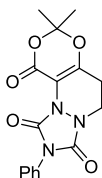
4-Phenyl-1,2,4-triazole-3,5-dione (85 mg, 0.49 mmol) was added to 2,2-dimethyl-6-vinyl-4H-1,3-dioxin-4-one (50 mg, 0.325 mmol) in CH_2Cl_2 (3 mL) and stirred for 14 h. Saturated aqueous $NaHCO_3$ was added and stirred for 0.5 h. The aqueous was extracted with CH_2Cl_2 (× 2) and the combined organics were washed with brine, dried ($MgSO_4$), rotary evaporated and chromatographed (pentane/EtOAc, 1:1 to 3:7) to give the title compound (38 mg, 36%) as a yellow solid. IR (cm^{-1}): 1773, 1744, 1703, 1642, 1495, 1456, 1424, 1393, 1322, 1300, 1280, 1195, 1162, 1143, 1126, 1093, 1069, 1029, 983, 913, 886, 856, 799, 779, 762, 749, 693, 733, 675, 650. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.58–7.50 (m, 2 H), 7.49–7.41 (m, 2 H), 7.41–7.31 (m, 1 H), 4.05 (t, J = 5.6 Hz, 2 H), 2.66 (t, J = 5.6 Hz, 2 H), 1.79 (s, 6 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 156.4, 153.5, 148.8, 148.4, 131.3, 129.2, 128.4, 125.7, 107.7, 107.0, 37.9, 26.8, 24.9. MS (ES) m/z: 330 [M+H]$^+$. HR-MS (ES) m/z calcd for $C_{16}H_{16}N_3O_5$: 330.1090 [M+H]$^+$; found: 330.1104.

1.25.13.63   6-Allyl-2,2-dimethyl-4H-1,3-dioxin-4-one (**405**)
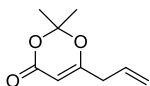
m-CPBA (32 mg, 0.185 mmol) in CH_2Cl_2 (1 mL) was added dropwise to 2,2-dimethyl-6-(3-(phenylselanyl)propyl)-4H-1,3-dioxin-4-one (50 mg, 0.154 mmol) in CH_2Cl_2 (1 mL) and stirred for 30 min. This mixture was transferred into refluxing CH_2Cl_2 (6 mL) and after a further 2.5 h, rotary evaporated and chromatographed (petroleium ether/Et$_2$O, 9 :1 to 7:3) to give the title compound (15 mg, 58%) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.87–5.70 (m, 1 H), 5.29–5.25 (m, 2 H), 5.24–5.20 (m, 1 H), 3.03–2.95 (m, 2 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 169.9, 161.3, 130.1, 119.8, 106.5, 93.5, 37.9, 25.0. MS (ES) m/z: 210 [M+MeCN+H]$^+$, 169 [M+H]$^+$. HR-MS (ES) m/z calcd for $C_9H_{12}O_3$: 169.0865 [M+H]$^+$; found: 169.0859.

1.25.13.64   1-Phenylbut-3-en-1-one (**407**)[247]
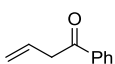
1-Phenylbut-3-en-1-ol (490 mg, 3.3 mmol) in CH_2Cl_2 (4 mL) was added dropwise to PCC (1.0 g, 4.8 mmol) in CH_2Cl_2 (6 mL) and stirred for 14 h . The mixture was filtered through celite twice, rotary evaporated and chromatographed (petroleum ether/Et_2O, 97:3) to give the title compound (308 mg, 64 %) as a pale yellow oil ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 8.14–7.84 (m, 2 H), 7.80–7.52 (m, 1 H), 7.52–7.36 (m, 2 H), 6.20–5.99 (m, 1 H), 5.31–5.13 (m, 2 H), 3.77 (dt, J = 6.8, 1.5 Hz, 2 H). HR-MS (EI) m/z calcd for $C_{10}H_{10}O$: 146.0732 $[M]^+$; found: 146.0732. In agreement with the literature.

1.25.13.65 *tert*-Butyl 2-phenylacetate (**408c**)[248]
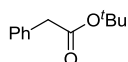
Thionyl chloride (5.47 mL, 75 mmol) was added to phenylacetic acid (6.81 g, 50 mmol) in CH_2Cl_2 (50 mL) and DMF (387 µL, 5 mmol) and stirred for 1.2 h then rotary evaporated to give phenylacetyl chloride.

tert-Butanol (4.78 mL, 50 mmol) and pyridine (6.03 mL, 75 mmol) were added to phenylacetyl chloride (from above) and stirred at reflux for 0.5 h and then at 25 °C for 2 h. Saturated aqueous NH_4Cl and CH_2Cl_2 were added and the organics washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), rotary evaporated and chromatographed (pentane/Et_2O, 99.5 to 49:1) to give the title compound (3.95 g, 41%) as a pale brown oil. IR (cm^{-1}): 1729, 1497, 1455, 1393, 1368, 1343, 1299, 1254, 1228, 1135, 1075, 1031, 954, 908, 864, 834, 742, 711, 695. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.23–7.36 (m, 5H), 3.54 (s, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 170.9, 134.7, 129.2, 128.4, 126.8, 80.8, 42.6, 28.0. MS (CI) m/z: 210 $[M+NH_4]^+$, 193 $[M+H]^+$. HR-MS (CI) m/z: calcd for $C_{12}H_{20}NO_2$: 210.1494 $[M+NH_4]^+$; found: 210.1489. In agreement with the literature.

1.25.13.66 Ethyl but-3-enoate (**409**)[249]
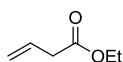

Sulfuric acid (0.2 mL) was added to vinylacetic acid (2 g, 23.3 mmol) in ethanol (40 mL) and the mixture refluxed for 4 h. Ethyl acetate (100 mL) and water (100 mL) were added and organics were washed with saturated aqueous $NaHCO_3$ (40 mL), dried ($MgSO_4$), and the solvent removed at atmospheric pressure to give the title compound (0.55 g, 21 %) as a yellow oil. ^{1}H NMR (400 MHz,

CDCl$_3$, ppm) δ: 5.93 (ddt, J = 17.2, 9.9, 7.2 Hz, 1 H), 5.39–5.14 (m, 2 H), 4.15 (q, J = 7.3 Hz, 2 H), 3.09 (dt, J = 7.2, 1.3 Hz, 2 H), 1.27 (t, J = 7.1 Hz, 3 H). In agreement with the literature.

1.25.13.67 *tert*-Butyl 3-oxohex-5-enoate (**410**)
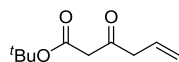
tert-Butylacetate (1.1 mL, 8.3 mmol) was added to LDA (8.0 mmol) in THF (4 mL) at −78 °C and stirred 30 min. This mixture was added to ethyl but-3-enoate (0.45 g, 4.0 mmol) in THF (8 mL) at −78 °C by cannula and stirred for 15 min. Acetic acid (4.0 mL) was added and the mixture diluted with water (20 mL) and ether (60 mL). The organic phase was washed with 20% aqueous K$_2$CO$_3$ (3 × 20 mL), brine (40 mL), dried (MgSO$_4$) rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 1:0 to 9:1) to give the title compound (191 mg, 26%) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.92 (tdd, J = 17.2, 10.1, 7.1 Hz, 1 H), 5.26–5.06 (m, 2 H), 3.38 (s, 2 H), 3.35–3.24 (m, 2 H), 1.47 (s, 9 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 201.2, 166.2, 129.8, 119.5, 82.1, 50.0, 47.6, 27.9. HR-MS (CI) *m/z* calcd for C$_{10}$H$_{20}$NO$_3$: 202.1443 [M+NH$_4$]$^+$; found: 202.1444.

1.25.13.68 (*E*)-2,2-Dimethyl-6-(prop-1-enyl)-1,3-dioxan-4-one (**414**)[250]
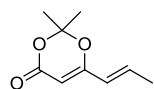
Oxalyl chloride (2.71 mL, 32 mmol) was added to vinylacetic acid (2.5 g, 29 mmol) in CH$_2$Cl$_2$ (12 mL) followed by a few drops of DMF at 0 °C and stirred for 30 min and then stirred a further 2 h at 25 °C. Distallation (97–99 °C) gave vinylacetoyl chloride a a brown oil. IR (cm^{-1}) 1792 cm^{-1}.

Pyridine (3.75 ml, 46 mmol) was added dropwise to meldrums acid (3.34 g, 23 mmol) in CH$_2$Cl$_2$ (50 mL) at 0 °C over 10 min followed by vinylacetoyl chloride prepared above and the mixture was stirred for 1 h then for 14 h at 25 °C. The mixture was washed with 1 M aqueous HCl (× 2), water (× 2), dried (MgSO$_4$) and rotary evaporated to give a brown gum. This was dissolved in toluene (25 mL) and acetone (2 mL) and refluxed vigorously for 1 h. The mixture was rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 9:1 to 4:1) to give the title compound (53 mg, 2 %) as coulourless oil.^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.61 (dq, J = 15.6, 6.9 Hz, 1H), 5.96 (dq, J = 15.4, 1.5 Hz, 1H), 5.26 (s, 1H), 1.93 (dd, J = 7.0, 1.7 Hz, 3H), 1.73 (s, 6H). HR-MS (CI) *m/z* calcd for C$_9$H$_{13}$O$_3$ 169.0865 [M+H]$^+$; found: 169.0866.

### 1.25.13.69 Mixture of 6-allylidene-2,2-dimethyl-1,3-dioxan-4-one (415) and (E)-2,2-dimethyl-6-(prop-1-enyl)-1,3-dioxan-4-one (414)
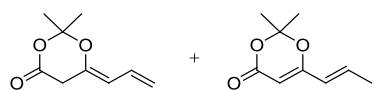
LiHMDS (0.14 mmol) was added to (E)-2,2-dimethyl-6-(prop-1-enyl)-1,3-dioxan-4-one **xx** (18 mg, 0.11 mmol) in THF (1 mL) with stirring at −78 °C. After 0.5 h acetic acid (0.1 mL) was added to the mixture to give the title compounds as a mixture (rr 1.0:0.9).

6-Allylidene-2,2-dimethyl-1,3-dioxan-4-one (415): ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.73–6.44 (m, 1 H), 5.39 (d, J = 10.8 Hz, 1 H), 5.13 (d, J = 17.1 Hz, 1 H), 5.00 (d, J = 9.9 Hz, 1 H), 3.41 (s, 2 H), 1.65 (s, 6 H).

1.25.13.70 tert-Butyl 6-chloro-3-oxohexanoate (417)[251]
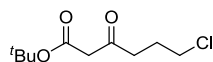
tert-Butylacetate (7.5 mL, 21.3 mmol) was added to LDA (53.0 mmol) in THF (25 mL) at −78 °C and stirred 30 min. This mixture was added to ethyl-4-chlorobutanoate (4.00 g, 27.0 mmol) in THF (50 mL) at −78 °C by cannula and stirred for 15 min. Acetic acid (25 mL) was added and the mixture diluted with water (125 mL) and ether (375 mL). The organic phase was washed with 20% aqueous K$_2$CO$_3$ (3 × 125 mL), brine (250 mL), dried (MgSO$_4$) rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 17:3 to 3:1) to give the title compound (3.95 g, 67%) as a pale yellow oil. IR (cm^{-1}): 1733, 1713, 1368, 1319, 1252, 1149. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 3.61 (t, J = 6.4 Hz, 2 H), 3.39 (s, 2 H), 2.77 (t, J = 7.1 Hz, 2 H), 2.09 (quin, J = 6.6 Hz, 2 H), 1.50 (s, 9 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 202.2, 166.2, 82.2, 50.7, 44.2, 39.5, 27.9, 26.0. MS (CI) *m/z*: 238 [M+NH$_4$]$^+$, 220 [M+H]$^+$. HR-MS (CI) *m/z* calcd for C$_{10}$H$_{21}$NO$_3$Cl: 238.1210 [M+NH$_4$]$^+$; found: 238.1211. Anal. calcd for C$_{10}$H$_{17}$ClO$_3$: C 54.42, H 7.76; found: C 52.03, H 6.77. In agreement with the literature.

1.25.13.71 6-(3-Chloropropyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (418)
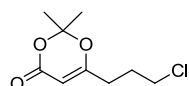
Sulfuric acid (0.483 mL, 9.1 mmol) was added dropwise to a solution of *tert*-butyl 6-chloro-3-oxohexanoate (2 g, 9.1 mmol) and acetic acnhydride (2.57 mL, 27.3 mmol) in acetone (1.33 mL, 18.1 mmol) at 0 °C and the mixture allowed to stir at 25 °C for 15 h. The mixture was diluted with water (100 mL), layers separated and aqueous reextracted with CH_2Cl_2 (2 × 100 mL). The combine organics were washed with brine, dried ($MgSO_4$), rotary evaporated and chromatographed (petroleum ether/Et_2O, 3:1 to 3:2) to give the title compound (1.25 g, 67%) as a pale yellow oil. IR (cm^{-1}): 1727, 1634, 1391, 1376, 1273, 1204, 1013, 902, 808. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.29 (s, 1 H), 3.58 (t, J = 6.4 Hz, 2 H), 2.45–2.38 (m, 2 H), 2.09–1.98 (m, 2 H), 1.69 (s, 6 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 170.1, 161.0, 106.5, 93.8, 43.6, 30.8, 28.5, 25.0. MS (CI) *m/z*: 222[M+NH$_4$]$^+$, 205 [M+H]$^+$. HR-MS (CI) *m/z* calcd for $C_9H_{17}NO_3Cl$: 222.0897 [M+NH$_4$]$^+$; found: 222.0901. Anal. calcd for $C_9H_{13}ClO_3$: C 52.82, H 6.40; found: C 53.39, H, 6.17.

1.25.13.72   *tert*-Butyl 3-cyclopropyl-3-oxopropanoate (**419**)
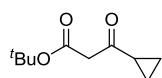
Potassium *tert*-butoxide (0.23g, 1.96 mml) was added to 6-(3-chloropropyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (0.2 g, 0.98 mmol) in THF (1 mL) and *tert*-BuOH (1 mL) and stirred for 2 h. The mixture was then heated at 85 °C for a further 14 h. 1 M aqueous HCl was added and the aqueous extracted with ether (2 x 10 mL). The combined organics were rotary evaporated and chromatographed (petroleum ether/Et_2O, 4:1) to give the title compound (30 mg, 17%) as a colourless oil. IR (cm^{-1}): 1734, 1703, 1372, 1153. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 3.47 (s, 2 H), 2.09–1.98 (m, 1 H), 1.48 (s, 9 H), 1.13–1.08 (m, 2 H), 0.98–0.91 (m, 2 H). MS (CI) *m/z*: 202 [M+NH$_4$]$^+$. HR-MS (CI) *m/z* calcd for $C_{10}H_{20}NO_3$: 202.1443 [M+NH$_4$]$^+$; found: 202.1447.

1.25.13.73   2,2-Dimethyl-6-(3-(phenylselanyl)propyl)-4H-1,3-dioxin-4-one (**420**)
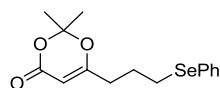
^{n}BuLi (2.5M in hexanes, 0.52 mL)was added to benzeneselenol (138 μL, 1.303 mmol) in THF (4.5 mL) at 0 °C the mixture stirred at 25 °C for 20 min. This solution was then added to 6-(3-chloropropyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (222 mg, 1.083 mmol) in THF (11mL) at -5 °C and the mixture allowed to warm to 5 °C over 4.5 h. The mixture was warmed to 25 °C and further PhSeLi (0.2 equiv) was added and stirred for a further 1 h. Saturated aqueous NH$_4$Cl (15 mL) and water (5 mL) were added and the layers separated. The aqueous was reextracted with ether (3 × 15 mL) and

then the combined organics were washed with brine (20 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 9:1 to 7:3) to give the title compound (255 mg, 72%) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.57–7.50 (m, 2 H), 7.34–7.26 (m, 3 H), 5.24 (s, 1 H), 2.93 (t, J = 7.3 Hz, 2 H), 2.39 (t, J = 7.6 Hz, 2 H), 1.95 (quin, J = 7.3 Hz, 2 H), 1.67 (s, 6 H). ^{13}C NMR (101MHz, CDCl3, ppm) δ: 170.7, 161.1, 133.1, 129.4, 129.2, 127.3, 106.4, 93.6, 33.3, 26.8, 26.2, 25.0. MS (EI) m/z: 368 [M+MeCN+H]$^+$, 327 [M+H]$^+$. HR-MS (EI) m/z calcd for C$_{15}$H$_{19}$SeO$_3$: 327.0499 [M+H]$^+$; found: 327.0487. Anal. calcd for C$_{15}$H$_{18}$SeO$_3$: C 55.39, H 5.58, N 6.57; found: C 55.48, H 5.44.

1.25.13.74 *tert*-Butyl 5-chloro-3-oxopentanoate (**425**)[251]
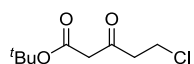
*tert*-Butylacetate (30.0 mL, 220 mmol) was added to LDA (200 mmol) in THF (200 mL) at −78 °C and stirred 30 min. This mixture was added to a solution of ethyl 3-chloropropionate (13.6 mL, 100 mmol) in THF (100 mL) at −78 °C by cannula and stirred for 15 min. Acetic acid (100 mL) was added and the mixture diluted with water (400 mL) and ether (800 mL). The organic phase was washed with 20% aqueous K$_2$CO$_3$ (3 × 450 mL), brine (400 mL), dried (MgSO$_4$) and rotary evaporated to give the title compound (23.4 g) as a pale yellow oil used without further purification. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 3.73 (t, J = 6.6 Hz, 2 H), 3.38 (s, 2 H), 3.02 (t, J = 6.6 Hz, 2 H), 1.46 (s, 9 H). In agreement with the literature.

1.25.13.75 6-(2-Chloroethyl)-2,2-dimethyl-1,3-dioxan-4-one (**426**)[246]
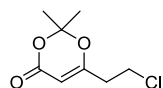
Sulfuric acid (6.02 mL, 113 mmol) was added dropwise to a solution of *tert*-butyl 5-chloro-3-oxopentanoate (23.00 g, 113 mmol) and acetic anhydride (32.0 mL, 339 mmol) in acetone (16.86 mL, 226 mmol) at 0 °C and the mixture allowed to stir at 25 °C 14 h. The mixture was poured into 20% aqueous K$_2$CO$_3$ (800 mL) and extracted with CH$_2$Cl$_2$ (3 × 400 mL). The combined organics were washed with brine, dried (MgSO$_4$), rotary evaporated to give the title compound (19.5 g) as a yellow oil used without further purification. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.36 (s, 1 H), 3.69 (t, J = 6.4 Hz, 2 H), 2.70 (t, J = 6.1 Hz, 2 H), 1.71 (s, 6 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 167.0,

160.6, 106.8, 95.6, 39.3, 36.4, 24.9. MS (CI) m/z: 208 [M+NH$_4$]$^+$. HR-MS (CI) m/z calcd for C$_8$H$_{15}$NO$_3$Cl: 208.0740 [M+NH$_4$]$^+$; found: 208.0743. In agreement with the literature.

1.25.13.76   1-Phenylbut-3-en-1-ol (**430a**)[252]
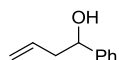
According to general procedure D, benzaldehyde (3.6 mL, 3.5 mmol) and chromatography (petroleum ether/Et$_2$O 9:1) gave alcohol **430a** (398 mg, 77%) as a colorless oil. IR (cm^{-1}): 1641, 1453, 1044, 990, 913, 756, 698. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.51–7.25 (m, 5 H), 5.94–5.75 (m, 1 H), 5.28–5.07 (m, 2 H), 4.75 (ddd, J = 7.7, 5.0, 2.9 Hz, 1 H), 2.58–2.50 (m, 2 H), 2.13 (d, J = 2.9 Hz, 1 H). HR-MS (CI) m/z calcd for C$_{10}$H$_{16}$NO: 166.1232 [M+NH$_4$]$^+$; found: 166.1229.

1.25.13.77   1-(4-Bromophenyl)but-3-en-1-ol (**430b**)[253]

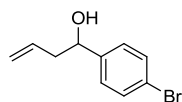According to general procedure A, p-bromobenzaldehyde (648 mg, 3.50 mmol) and Kughelrohr distillation (0.4 Torr, 102−105 $^{\circ}$C) gave the title compound (721 mg, 91%) as a colourless oil. IR (cm^{-1}) 1641, 1593, 1488, 1404, 1069, 1010, 918, 824. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.51–7.44 (m, J = 8.3 Hz, 2 H), 7.24 (d, J = 8.3 Hz, 2 H), 5.87–5.71 (m, 1 H), 5.24–5.10 (m, 2 H), 4.71 (ddd, J = 7.9, 4.8, 3.4 Hz, 1 H), 2.57–2.40 (m, 2 H), 2.11 (d, J = 2.9 Hz, 1 H). ^{13}C NMR (101MHz , CDCl$_3$, ppm) δ: 142.8, 133.9, 131.4, 127.5, 121.2, 118.9, 72.5, 43.8. MS (CI) 228 [M+H]$^+$. HR-MS (CI) m/z calcd for C$_{10}$H$_{13}$NBr: 226.0231 [M-H$_2$O+NH$_4$]; found: 226.0239. In agreement with the literature

1.25.13.78   1-(4-Chlorophenyl)but-3-en-1-ol (430c)[254]
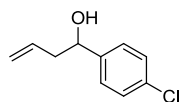
According to general procedure A, p-chlorobenzaldehyde (506 mg, 3.5mmol) and Kughelrohr distillation (0.2 Torr, 94–96 $^{\circ}$C) gave the title compound (557 mg, 85%) as a

colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.35–7.26 (m, 4 H), 5.85–5.72 (m, 1 H), 5.21–5.12 (m, 2 H), 4.72 (ddd, J = 7.8, 4.9, 3.4 Hz, 1 H), 2.57–2.38 (m, 2 H), 2.15 (d, J = 2.9 Hz, 1 H). ^{13}C NMR (101MHz , CDCl$_3$, ppm) δ: 142.2, 133.9, 133.1, 128.5, 127.2, 118.9, 72.5, 43.8. MS (CI) 200 [M-H$_2$O+NH$_4^+$]. HR-MS (CI) m/z calcd for C$_{10}$H$_{15}$NOCl: 200.0842 [M-H$_2$O+NH$_4$]; found: 200.0844. In agreement with the literature.

1.25.13.79   1-(4-Fluorophenyl)but-3-en-1-ol (**430d**)[254]

According to general procedure A, p-fluorobenzaldehyde (372 mg, 3.5mmol) and Kughelrohr distillation (0.10 Torr, 63–66 ^{o}C) gave the title compound (431 mg, 74%) as a colourless oil. IR (cm^{-1}): 1621, 1604, 1509, 1221, 917, 833. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.37–7.29 (m, 2 H), 7.09–6.99 (m, 2 H), 5.88–5.71 (m, 1 H), 5.23–5.11 (m, 2 H), 4.73 (ddd, J = 7.8, 5.1, 3.2 Hz, 1 H), 2.57–2.39 (m, 2 H), 2.13 (d, J = 2.9 Hz, 1 H). ^{13}C NMR (101MHz , CDCl$_3$, ppm) δ: 162.1, 139.5, 134.1, 127.4, 118.7, 115.2, 72.6, 43.9. MS (CI) 166 [M$^+$]. HR-MS (CI) m/z calcd for C$_{10}$H$_{13}$NF: 166.1032 [M-H$_2$O+NH$_4$]; found: :166.1035.

1.25.13.80   1-(4-Methoxyphenyl)but-3-en-1-ol (**430e**)[255]
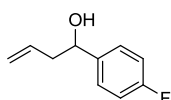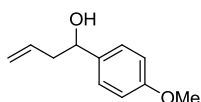

According to general procedure A, p-anisaldehyde (425 µL, 3.50 mmol) and chromatography (petroleum ether/Et$_2$O, 1:0 to 4:1) gave the title compound (541 mg, 87%) as a pale yellow oil. IR (cm^{-1}): 1611, 1511, 1243, 1173, 1033, 914, 829. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.31–7.24 (m, 2 H), 6.91–6.85 (m, 2 H), 5.86–5.74 (m, 1 H), 5.19–5.10 (m, 2 H), 4.69 (td, J = 6.5, 2.2 Hz, 1 H), 3.80 (s, 3 H), 2.52–2.43 (m, 2 H), 1.99 (d, J = 2.4 Hz, 1 H); MS (CI) 178 [M]$^+$, 161, 61. In agreement with the literature

1.25.13.81   1-(Furan-2-yl)but-3-en-1-ol (**430f**)[256]

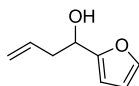According to general procedure A, furaldehyde (290 µL, 3.5 mmol) and Kughelrohr distillation (0.70 Torr, 78-80 °C) gave the title compound (400 mg, 83%) as a colourless oil. IR (cm^{-1}): 1642, 1504, 1433, 1339, 1227, 1148, 1054, 1008, 917, 733. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.39 (d, J = 1.0 Hz, 1 H), 6.34 (dd, J = 3.2, 1.7 Hz, 1 H), 6.26 (d, J = 2.9 Hz, 1 H), 5.81 (tdd, J = 17.2, 10.1, 7.1 Hz, 1 H), 5.25–5.12 (m, 2 H), 4.79–4.70 (m, 1 H), 2.70–2.55 (m, 2 H), 2.14 (d, J = 4.9 Hz, 1 H). ^{13}C NMR (101MHz , CDCl$_3$, ppm) δ: 156.0, 142.0, 133.6, 118.6, 110.1, 106.1, 66.9, 40.0. MS (CI) 138 [M-H$_2$O+NH$_4^+$]. HR-MS (CI) m/z calcd for C$_{12}$H$_{12}$NO: 138.0919 [M-H$_2$O+NH$_4$]; found: 138.0921. In agreement with the literature.

1.25.13.82   <u>Hex-5-en-3-ol (**430h**)</u>[257]
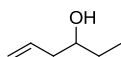
According to general procedure D acetaldehyde (252 µL, 3.5 mmol) gave the title compound (330 mg, 94%) as a colorless oil. This compound was used without further purification. IR (cm^{-1}): 1641, 1460, 1438, 1112, 1016, 995, 969, 911. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.78–5.90 (m, 1 H), 5.11– 5.18 (m, 2 H), 3.54–3.63 (m, 1 H), 2.26–2.37 (m, 1 H), 2.09–2.20 (m, 1 H), 1.63 (d, J = 4.4 Hz, 1 H), 1.44– 1.57 (m, 2 H), 0.96 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 134.9, 118.0, 72.0, 41.4, 29.5, 9.9.

1.25.13.83   <u>6-Methylhept-1-en-4-ol (**430i**)</u>[257]
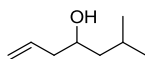
According to general procedure D iso-valeraldhyde (375 µL, 3.5 mmol) and chromatography (pentane/Et$_2$O, 17 : 1 to 4 : 1) gave the title compound (400 mg, 89%) as a colorless oil. IR (cm^{-1}): 1643, 1468, 1367, 1137, 1058, 1025, 996, 976, 912. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ : 5.80–5.90 (m, 1 H), 5.11–5.18 (m, 2 H), 3.70– 3.78 (m, 1 H), 2.26–2.34 (m, 1 H), 2.10–2.19 (m, 1 H), 1.70–1.86 (m, 1 H), 1.59 (s, 1 H), 1.36–1.47 (m, 1 H), 1.20–1.30 (m, 1 H), 0.94 (dd, J = 6.6, 5.1 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 134.9, 118.1, 68.7, 46.0, 42.5, 24.6, 23.4, 22.1.

1.25.13.84   1-Mesitylbut-3-en-1-o (**430j**)[256]
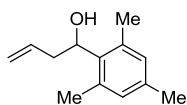
According to general procedure A, mesitaldehyde (534 mg, 3.5mmol) and Kughelrohr distillation (0.70 Torr, 95–97 $^\circ$C) gave the title compound (560 mg, 82%) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.84 (s, 2 H), 5.94–5.80 (m, 1 H), 5.24–5.11 (m, 3 H), 2.79–2.68 (m, 1 H), 2.55–2.47 (m, 1 H), 2.43 (s, 6 H), 2.27 (s, 3 H), 2.23 (s, 1 H). ^{13}C NMR (101MHz , CDCl$_3$, ppm) δ: 136.6, 136.0, 135.3, 130.1, 129.1, 117.7, 70.7, 40.3, 20.8, 15.8; MS (ES) 173 [M-H$_2$O]. HR-MS (ES) m/z calcd for C$_{13}$H$_{17}$: 173.1330 [M-H$_2$O]; found: 173.1323.

1.25.13.85   1-(Pyridin-2-yl)but-3-en-1-ol (**430k**)[258]
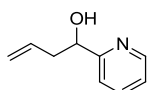
According to general procedure A, 2-pyridine carboxaldehyde (333 µL, 3.5mmol) and Kughelrohr distillation (1.60 Torr, 110 $^\circ$C) gave the title compound (434 mg, 83%) as a colourless oil. IR (cm^{-1}): 1641 1594, 1435, 1056, 996, 914, 749, 610. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.52 (d, J = 4.9 Hz, 1 H), 7.67 (m, 1 H), 7.32–7.23 (m, 1 H), 7.22–7.14 (m, 1 H), 5.82 (ddt, J = 17.1, 10.2, 6.9, Hz, 1 H), 5.15–4.94 (m, 2 H), 4.80 (dd, J = 7.3, 4.9 Hz, 1 H), 4.14 (br. s., 1 H), 2.82–2.57 (m, 1 H), 2.52–2.43 (m, 1 H). ^{13}C NMR (101MHz , CDCl$_3$, ppm) δ: 161.4, 148.2, 136.6, 134.1, 122.3, 120.4, 118.0, 72.2, 42.8. MS (ES) 150 [M+H$^+$]. HR-MS (CI) m/z calcd for C$_9$H$_{12}$NO: 150.0919 [M+H]$^+$; found: 150.0908. In agreement with the literature.

1.25.13.86   (*E*)-6-(4-Hydroxy-4-phenylbut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**431a**)
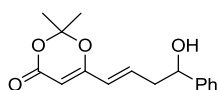
According to general procedure **B**, reaction of alcohol **430a** (210 mg, 1.42 mmol) and dioxinone **372a** (328 mg, 2.13 mmol) with catalyst **427a** (45 mg, 0.071 mmol) for 14 h and chromatography (hexanes/Et$_2$O, 7:3 to 1:1) gave dioxinone **431a** (315 mg, 81%) as a brown oil. IR (cm^{-1}): 3422, 1703, 1649, 1589, 1389, 1373, 1273, 1252, 1200, 1018, 967, 903, 757, 700. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.40–7.32 (m, 5 H), 6.64–6.55 (m, 1 H), 6.02–5.95 (m, 1 H), 5.25 (s, 1 H), 4.84 (dd, J = 7.8, 4.9 Hz, 1 H), 2.70–2.60 (m, 2 H), 2.27 (br s, 1 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 162.9, 162.0, 143.5, 137.9, 128.6, 128.0, 125.6, 125.0, 106.4, 93.9, 73.3, 42.3, 25.0. MS (EI) m/z: 275 [M + H]$^+$. HR-MS (EI) m/z calcd for C$_{16}$H$_{19}$O$_4$: 275.1283 [M + H]$^+$; found: 275.1288. Anal. calcd for C$_{16}$H$_{18}$O$_4$: C 70.06, H 6.61; found: C 70.15, H 6.71.

1.25.13.87   (*E*)-6-(4-(4-Bromophenyl)-4-hydroxybut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**431b**)
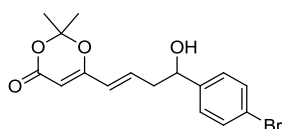
According to general procedure **B**, reaction of alcohol **430b** (491 mg, 2.16 mmol) and dioxinone **372a** (500 mg, 3.25 mmol) with catalyst **427a** (68 mg, 0.11 mmol) for 16 h and chromatography (hexanes/Et$_2$O, 7:3 to 1:3) gave dioxinone **431b** (577 mg, 76%) as a brown solid; mp 85–90 °C (Et$_2$O/pentane). IR (cm^{-1}): 3451, 1689, 1651, 1590, 1391, 1375, 1275, 1201, 1010, 971, 820, 600. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.49 (d, J = 8.3 Hz, 2 H), 7.23 (d, J = 8.3 Hz, 2 H), 6.56 (dt, J = 15.6, 7.8 Hz, 1 H), 5.97 (d, J = 15.6 Hz, 1 H), 5.24 (s, 1 H), 4.81 (t, J = 6.1 Hz, 1 H), 2.64–2.56 (m, 2 H), 2.31 (br s, 1 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 162.8, 162.0, 142.5, 137.3, 131.7, 127.4, 125.3, 121.7, 106.4, 94.0, 72.6, 42.3, 25.0. MS (ES) m/z: 355 [M(^{81}Br) + H]$^+$, 353 [M(^{79}Br) + H]$^+$. HR-MS (ES) m/z calcd for C$_{16}$H$_{18}$BrO$_4$: 353.0388 [M + H]$^+$; found: 353.0389. Anal. calcd for C$_{16}$H$_{17}$BrO$_4$: C 54.41, H 4.85; found: C 54.25, H 4.73.

1.25.13.88   (*E*)-6-(4-(4-Chlorophenyl)-4-hydroxybut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**431c**)
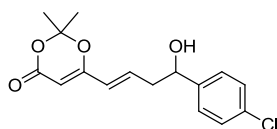
According to general procedure **B**, reaction of alcohol **430c** (183 mg, 1 mmol) and dioxinone **372a** (308 mg, 2 mmol) with catalyst **427a** (63 mg, 0.1 mmol) for 18 h and chromatography (hexanes/Et$_2$O, 3:2 to 2:3) gave dioxinone **431c** (271 mg, 88%) as a brown solid; mp 76–80 °C (Et$_2$O/pentane). IR (cm^{-1}): 3457, 1690, 1652, 1591, 1394, 1376, 1279, 1203, 1087, 1021, 971, 830. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.36–7.26 (m, 4 H), 6.55 (dt, J = 15.7, 7.8 Hz, 1 H), 5.97 (d, J = 15.6 Hz, 1 H), 5.24 (s, 1 H), 4.85–4.77 (m, 1 H), 2.66–2.56 (m, 2 H), 2.14 (d, J = 3.4 Hz, 1 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 162.7, 161.9, 141.9, 137.2, 133.6, 128.8, 127.0, 125.4, 106.4, 94.1, 72.6, 42.4, 25.0. MS (ES) m/z: 311 [M(^{37}Cl) + H]$^+$, 309 [M(^{35}Cl) + H]$^+$. HR-MS (ES) m/z calcd for C$_{16}$H$_{18}$ClO$_4$: 309.0894 [M + H]$^+$; found: 309.0887. Anal. calcd for C$_{16}$H$_{17}$ClO$_4$: C 62.24, H 5.55; found: C 62.18, H 5.43.

1.25.13.89 (*E*)-6-(4-(4-Fluorophenyl)-4-hydroxybut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (431d)
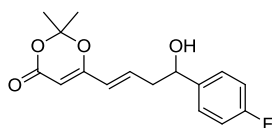
According to general procedure **B**, reaction of alcohol **430d** (166 mg, 1 mmol) and dioxinone **372a** (308 mg, 2 mmol) with catalyst **427a** (63 mg, 0.1 mmol) for 18 h and chromatography (hexanes/Et$_2$O, 3:2 to 2:3) gave dioxinone **431d** (244 mg, 84%) as a brown gum. IR (cm^{-1}): 3429, 1701, 1650, 1603, 1508, 1390, 1375, 1274, 1202, 1156, 1018, 835. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.35–7.30 (m, 2 H), 7.08–7.03 (m, 2 H), 6.56 (dt, J = 15.2, 7.8 Hz, 1 H), 5.98 (d, J = 15.6 Hz, 1 H), 5.25 (s, 1 H), 4.83 (dd, J = 7.8, 4.9 Hz, 1 H), 2.70–2.55 (m, 2 H), 2.21 (br s, 1 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 162.8, 162.0, 162.3 (d, J = 245.7 Hz), 139.3, 137.5, 127.3 (d, J = 8 Hz), 125.2, 115.4 (d, J = 22.5 Hz), 106.4, 94.0, 72.6, 42.4, 25.0. MS (ES) m/z: 293 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{16}$H$_{18}$FO$_4$: 293.1189 [M + H]$^+$; found: 293.1177. Anal. calcd for C$_{16}$H$_{17}$FO$_4$: C 65.74, H 5.86; found: C 65.90, H 5.90.

1.25.13.90 (*E*)-6-(4-Hydroxy-4-(4-methoxyphenyl)but-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**431e**)
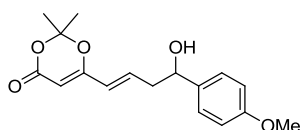
According to general procedure **B**, reaction of alcohol **430e** (120 mg, 0.67 mmol) and dioxinone **372a** (156 mg, 1.01 mmol) with catalyst **427a** (21 mg, 0.034 mmol) for 18 h and chromatography (hexanes/Et$_2$O, 3:2 to 2:3) gave dioxinone **431e** (158 mg, 78%) as a brown oil. IR (cm^{-1}): 3424, 1702, 1650, 1512, 1389, 1374, 1245, 1018, 831. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.30–7.27 (m, 2 H), 6.92–6.89 (m, 2 H), 6.59 (dt, J = 15.7, 7.8 Hz, 1 H), 5.99 (d, J = 15.6 Hz, 1 H), 5.26 (s, 1 H), 4.79 (dd, J = 7.8, 4.9 Hz, 1 H), 3.82 (s, 3 H), 2.73–2.54 (m, 2 H), 1.90 (br s, 1 H), 1.71 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 162.9, 162.0, 159.3, 138.0, 135.6, 126.9, 125.0, 114.0, 106.4, 93.9, 73.0, 55.3, 42.3, 25.0. MS (ES) *m/z*: 305 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{17}$H$_{21}$O$_5$: 305.1389 [M + H]$^+$; found: 305.1382. Anal. calcd for C$_{17}$H$_{20}$O$_5$: C 67.09, H 6.62; found: C 66.96, H 6.55.

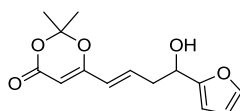### 1.25.13.91 (*E*)-6-(4-(Furan-2-yl)-4-hydroxybut-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**431f**)

According to general procedure **B**, reaction of alcohol **430f** (138 mg, 1 mmol) and dioxinone **372a** (308 mg, 2 mmol) with catalyst **427a** (63 mg, 0.1 mmol) for 18 h and chromatography (hexanes/Et$_2$O, 3:2 to 1:1) gave dioxinone **431f** (228 mg, 86%) as a brown gum. IR (cm^{-1}): 3400, 1689, 1654, 1590, 1379, 1280, 1197, 1017, 1003, 973, 728, 596. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.41–7.38 (m, 1 H), 6.58 (dt, J = 16.1, 7.8 Hz, 1 H), 6.36 (dd, J = 2.9, 2.0 Hz, 1 H), 6.27 (d, J = 3.4 Hz, 1 H), 6.02 (d, J = 15.6 Hz, 1 H), 5.27 (s, 1 H), 4.89–4.80 (m, 1 H), 2.80–2.72 (m, 2 H), 2.19 (d, J = 4.4 Hz, 1 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 162.8, 162.0, 155.5, 142.2, 137.0, 125.2, 110.3, 106.4, 106.3, 94.0, 66.6, 38.8, 25.0. MS (ES) *m/z*: 265 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{14}$H$_{17}$O$_5$: 265.1076 [M + H]$^+$; found: 265.1075. Anal. calcd for C$_{14}$H$_{16}$O$_5$: C 63.63, H 6.10; found: C 63.53, H 6.05.

1.25.13.92 (*E*)-6-(4-Hydroxypent-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**431g**)

According to general procedure **B**, reaction of alcohol **430g** (103 μL, 1.00 mmol) and dioxinone **372a** (308 mg, 2.00 mmol) with catalyst **427a** (63 mg, 0.10 mmol) for 18 h and chromatography (pentane/Et$_2$O, 55:45 to 1:3) gave dioxinone **431g** (173 mg, 82%) as a brown oil. IR (cm^{-1}): 3435, 1702, 1650, 1590, 1389, 1374, 1273, 1253, 1201, 1123, 1017, 971, 903, 816, 796, 603. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.60 (dt, J = 15.4, 7.5 Hz, 1 H), 6.01 (dt, J = 15.6, 1.0 Hz, 1 H), 5.28 (s, 1 H), 3.99 (m, 1 H), 2.35–2.42 (m, 2 H), 1.72–1.75 (m, 7 H), 1.26 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 163.0, 162.1, 138.2, 124.9, 106.4, 93.8, 67.0, 42.3, 25.1, 25.0, 23.4. MS (ES) *m/z*: 213 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{11}$H$_{17}$O$_4$: 213.1127 [M + H]$^+$; found: 213.1123. Anal. calcd for C$_{11}$H$_{16}$O$_4$: C 62.25, H 7.60; found: C 62.12, H 7.48.

1.25.13.93 (*E*)-6-(4-Hydroxyhex-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**431h**)
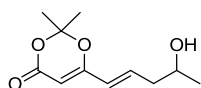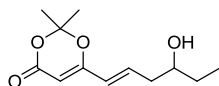

According to general procedure **B**, reaction of alcohol **430h** (300 mg, 3.00 mmol) and dioxinone **372a** (693 mg, 4.80 mmol) with catalyst **427a** (94 mg, 0.15 mmol) for 18 h and chromatography (hexanes/Et$_2$O, 1:1 to 2:3) gave dioxinone **431h** (372 mg, 55%) as a brown oil. IR (cm^{-1}): 3427, 1707, 1650, 1591, 1340, 1375, 1274, 1254, 1203, 1019, 971, 904, 801, 603. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.60 (dt, J = 15.4, 7.5 Hz, 1 H), 5.99 (dt, J = 15.7, 1.5 Hz, 1 H), 5.26 (s, 1 H), 3.63–3.74 (m, 1 H), 2.37–2.47 (m, 1 H), 2.28–2.37 (m, 1 H), 1.70 (s, 7 H), 1.45–1.57 (m, 2 H), 0.97 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 162.9, 162.0, 138.5, 124.7, 106.3, 93.7, 72.1, 40.1, 30.0, 25.0, 9.8. MS (ES) *m/z*: 227 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{12}$H$_{19}$O$_4$: 227.1283 [M + H]$^+$; found: 227.1283. Anal. calcd for C$_{12}$H$_{18}$O$_4$: C 63.70, H 8.02; found: C 63.75, H 8.13.

1.25.13.94 (*E*)-6-(4-Hydroxy-6-methylhept-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (**431i**)
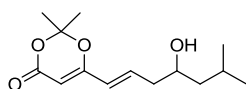
According to general procedure **B**, reaction of alcohol **430i** (128 mg, 1.00 mmol) and dioxinone **372a** (308 mg, 2.00 mmol) with catalyst **427a** (63 mg, 0.10 mmol) for 18 h and chromatography (hexanes/Et$_2$O, 55:45 to 45:55) gave dioxinone **431i** (185 mg, 73%) as a brown gum. IR (cm^{-1}): 3421, 1703,1650, 1590, 1389, 1374, 1273, 1253, 1202, 1017, 969, 903. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.63 (dt, J = 15.4, 7.5 Hz, 1 H), 6.01 (dt, J = 15.6, 1.5 Hz, 1 H), 5.28 (s, 1 H), 3.81–3.91 (m, 1 H), 2.38–2.48 (m, 1 H), 2.26–2.37 (m, 1 H), 1.77–1.84 (m, 1 H), 1.73 (s, 6 H), 1.65 (d, J = 4.4 Hz, 1 H), 1.43–1.50 (m, 1 H), 1.24–1.32 (m, 1 H), 0.93–0.97 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 163.0, 162.0, 138.5, 124.9, 106.4, 93.8, 68.8, 46.5, 41.2, 25.1, 25.0, 24.6, 23.4, 22.0. MS (ES) m/z: 277 [M + Na]$^+$, 255 [M + H]$^+$. Anal. calcd for C$_{14}$H$_{22}$O$_4$: C 66.12, H 8.72; found: C 66.10, H 8.65.

1.25.13.95   (E)-6-(4-Hydroxy-4-mesitylbut-1-enyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (431j)
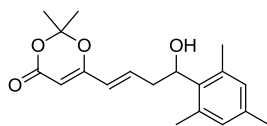

According to general procedure **B**, reaction of alcohol **430j** (350 mg, 1.84 mmol) and dioxinone **372a** (426 mg, 2.76 mmol) with catalyst **427a** (58 mg, 0.09 mmol) for 16 h and chromatography (hexanes/Et$_2$O, 4:1 to 1:1) gave dioxinone **431j** (377 mg, 65%) as a brown gum. IR (cm^{-1}): 3442, 2951, 1702, 1650, 1591, 1389, 1373, 1273, 1202, 1017, 967, 851, 801. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.84 (s, 2 H), 6.64 (dt, J = 15.7, 7.8 Hz, 1 H), 6.02 (d, J = 15.6 Hz, 1 H), 5.29–5.22 (m, 2 H), 2.97–2.85 (m, 1 H), 2.63–2.49 (m, 1 H), 2.41 (s, 6 H), 2.26 (s, 3 H), 2.00 (d, J = 2.4 Hz, 1 H), 1.71 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 163.0, 162.0, 138.8, 137.0, 135.8, 135.6, 130.3, 124.6, 106.3, 93.8, 70.5, 39.0, 25.0, 24.9, 20.7. MS (ES) m/z: 317 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{19}$H$_{25}$O$_4$: 317.1753 [M + H]$^+$; found: 317.1753. Anal. calcd for C$_{19}$H$_{24}$O$_4$: C 72.13, H 7.65; found: C 71.97, H 7.59.

1.25.13.96   (E)-4-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-1-phenylbut-3-ene-1,2-dione (433a)
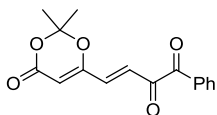
According to general procedure **L** (E)-6-(4-hydroxy-4-phenylbut-1-enyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (0.5 g, 1.82 mmol) and chromatography (pentane/Et$_2$O, 3:17 to 1:3) gave the title compound (234 mg, 45%) as a yellow amorphous solid. IR (cm^{-1}): 1719, 1671, 1580, 1394, 1377, 1275, 1253, 1199, 1115, 1016, 819, 738, 687, 635. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.04 (m, 2 H), 7.69 (m, 1 H), 7.54 (m, 2 H), 7.27 (d, J = 15.7 Hz, 1 H), 7.11 (d, J = 15.7 Hz, 1 H), 5.71 (s, 1 H), 1.76 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 191.2, 190.0, 160.4, 160.3, 137.1, 135.1, 132.0, 130.4, 129.0, 128.4, 107.4, 101.7, 25.0.

1.25.13.97 (E)-5-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)pent-4-ene-2,3-dione (**433b**)
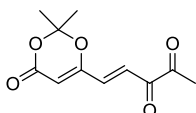
According to general procedure **L** oxidation of (*E*)-6-(4-Hydroxypent-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (191 mg, 0.90 mmol) and chromatography (pentane/Et$_2$O, 4:1 to 1:1) gave the title compound (39 mg, 19 %) as an amorphous yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.48 (d, J = 15.7 Hz, 1 H), 7.15 (d, J = 15.6 Hz, 1 H), 5.70 (s, 1 H), 2.45 (s, 3 H), 1.76 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 197.3, 185.7, 160.5 (2C), 136.9, 125.0, 107.4, 101.6, 25.0, 24.0. MS (CI) m/z:242 [M+NH$_4$]$^+$, 225 [M+H]$^+$. HR-MS (CI) m/z: calcd for C$_{11}$H$_{16}$NO$_5$: 242.1028 [M+NH$_4$]$^+$; found: 242.1035.

1.25.13.98 1-Ethyl 7-isopropyl 5-oxo-3-(phenylthio)heptanedioate (**447**)
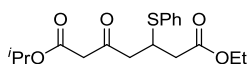
n-BuLi (2.5M in hexanes, 0.84 mL) was added to thiophenol (0.22 mL, 0.021 mmol) in THF (1.40 ml) at 0 °C. After 5 min, titanium isopropoxide (0.68 mL) was added dropwise to give an orange solution stirred for 15 min.

The complex prepared above (0.05 mL, 16 mol%) was added to 1-ethyl 7-isopropyl 5-oxohept-2-enedioate (50 mg, 0.207 mmol) in THF (0.5 mL) at −78 °C and allowed to stir for 14 h between −40 and −10 °C. Further complex (0.05 mL, 16 mol%) was added at r.t. and stirred for a further 3 h

followed by a further identical addition of complex and stirring for 12 h. The mixture was acidified by addition of cold 0.1 M aqueous HCl and extracted with CH$_2$Cl$_2$ (× 3). The combined organics were washed with 1 M aqueous KOH, dried (MgSO$_4$) rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 9:1 to 4:1) to give the title compound (32 mg, 44%) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.51–7.45 (m, 2 H), 7.36–7.28 (m, 3 H), 5.04 (quin, J = 6.4 Hz, 1 H), 4.16–4.10 (m, 2 H), 3.92 (m, 1 H), 3.41 (s, 2 H), 2.93 (dd, J = 3.7, 6.6 Hz, 2 H), 2.63 (dd, J = 5.1, 6.6 Hz, 2 H), 1.27–1.23 (m, 9 H). MS (EI) m/z: 375 [M+Na]$^+$. HR-MS (EI) m/z calcd for C$_{18}$H$_{24}$O$_5$SNa: 375.1242 [M+Na]; found: 375.1232.

1.25.13.99 Mixture of (E)-7-isopropyl1-methyl 5-oxohept-3-enedioate (**338c**) and (E)-7-isopropyl 1-phenyl 5-oxohept-2-enedioate **338d**); Isopropyl 2-(2-oxo-2H-pyran-6-yl)acetate **448**
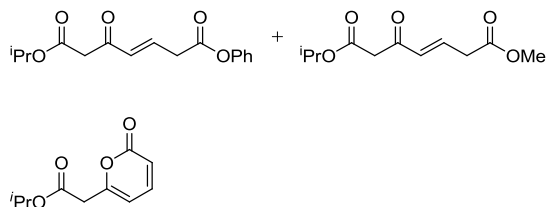
A mixture of (E)-phenyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)but-2-enoate and (E)-ethyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)but-2-enoate (200mg, 0.694 mmol) and isopropanol (0.27 mL 3.17 mmol) in toluene (3.5 mL) was heated to reflux for 15 h. The mixture was rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 3:1 to 1:1) to give a mixture of phenyl/methyl esters **338c** and **338d** as shown and isopropyl 2-(2-oxo-2H-pyran-6-yl)acetate **448** as a yellow oil, all in impure form. Peaks of Pyrone **448**: ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.31 (dd, J = 9.5, 6.5 Hz 1 H), 6.22 (d, J = 9.3 Hz, 1 H), 6.16 (d, J = 6.4 Hz, 1 H), 5.04 (hept, J = 6.3 Hz, 1 H), 3.48 (s, 2 H), 1.24 (d, J = 6.3 Hz, 6 H).

1.25.13.100 Benzyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-hydroxybutanoate (**449a**)
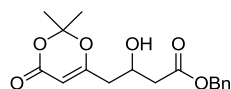
Sodium borohydride (358 mg, 9.43 mmol) was added to 3-(benzyloxy)-3-oxopropanoic acid (3 g, 9.43 mmol) in EtOH (90 mL) at 0 °C and stirred for 0.5 h. Further sodium borohydride (358 mg, 9.43 mmol) was added and stirred for 0.5 h. The mixture was quenched by addition of acetic acid and rotary evaporated. The mixture was dissolved in EtOAc (130 mL) and washed with saturated aqueous

NaHCO$_3$. The aqueous was then reexctracted with EtOAc (2 × 100 mL) and the combined organics were dried (MgSO$_4$), filtered, rotary evaporated and chromatographed (pentane/Et$_2$O, 1:1 to 1:3) to give the title compound (2.49 g, 83%) as a pale yellow oil. IR (cm^{-1}): 1727, 1635, 1391, 1275, 1204, 1014, 904, 806, 751, 699. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.31–7.42 (m, 5 H), 5.34 (s, 1 H), 5.17 (s, 2 H), 4.34 (tt, J = 8.0, 4.5 Hz, 1 H), 3.17 (br. s., 1 H), 2.51–2.65 (m, 2 H), 2.32–2.49 (m, 2 H), 1.69 (m, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 171.9, 168.0, 160.9, 135.2, 128.6, 128.5, 128.3, 106.7, 95.5, 66.8, 65.0, 40.7, 40.4, 25.4, 24.6. MS (CI) m/z: 338 [M+NH$_4$]$^+$, 321 [M+H]$^+$. HR-MS (CI) m/z calcd for C$_{17}$H$_{21}$O$_6$: 321.1338 [M+H]$^+$; found: 321.1337.

1.25.13.101   1-Benzyl 7-isopropyl 3-hydroxy-5-oxoheptanedioate (450a)
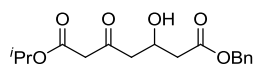
Benzyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-hydroxybutanoate (80 mg, 0.25 mol) and *iso*-PrOH (0.76 mL, 10 mmol) in EtOAc (5 mL) were microwave irradiated 120 °C for 30 min, rotary evaporated and chromatographed (pentane/Et$_2$O, 7:3 to 2:3) gave the title compound (51 mg, 63 %) as a colourless oil. IR (cm^{-1}): 1732, 1376, 1313, 1266, 1168, 1105, 968, 751, 697. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.31–7.41 (m, 5 H), 5.16 (s, 2 H), 5.02–5.09 (m, 1 H), 4.48–4.57 (m, 1 H), 3.44 (s, 2 H), 3.30 (d, J = 3.9 Hz, 1 H), 2.76–2.83 (m, 2 H), 2.56–2.61 (m, 2 H), 1.26 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 202.3, 171.6, 166.4, 135.5, 128.6, 128.4, 128.2, 69.2, 66.6, 64.2, 50.1, 48.6, 40.5, 21.8, 21.7. Anal. calcd for C$_{17}$H$_{22}$O$_6$: C 63.34, H 6.88; found: C 63.41, H 6.95.

1.25.13.102   3-(Benzyloxy)-3-oxopropanoic acid (451a)[259]
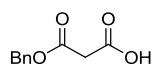
Benzyl alcohol (15 g, 139 mmol) and Meldrum's acid (20 g, 139 mmol) in toluene (15 mL) were refluxed for 3 h. The organics were extracted with NaHCO$_3$ (3 × 150 mL) and the combined aqueous layers were acidified to pH 2 with 1M aq. HCl. The aqueous was then extracted with ether (5 × 200 mL) and the combined organics were dried (MgSO$_4$), filtered and rotary evaporated to give the title compound (20.7g, 77%) as a colourless solid used without further purification. IR (cm^{-1}): 1728, 1713, 1701, 1433, 1381, 1334, 1354, 1309, 1200, 1167, 982, 951, 925, 903, 842, 756. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 11.01 (br. s, 1 H), 7.29–7.43 (m, 5 H), 5.22 (s, 2 H), 3.50 (s, 2 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 171.7, 166.4, 134.9, 128.6, 128.5, 128.3, 67.6, 40.8. MS (ES) m/z: 194 [M]$^+$.

HR-MS (ES) *m/z* calcd for $C_{10}H_{10}O_4$: 194.0579 $[M]^+$; found: 194.0593. In agreement with the literature.

1.25.13.103 Benzyl 3-(tert-butyldimethylsilyloxy)-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)butanoate (**452**)
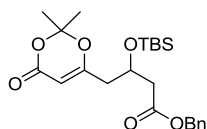
tert-Butyldimethylsilyl chloride (1.18 g, 7.830 mmol) was added to benzyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-hydroxybutanoate (1.00 g, 3.125 mmol) and imidazole (1.06 g, 15.588 mmol) in DMF (3.1 mL) and stirred at 25 °C for 15 h. The mixture was washed with saturated aqueous NH_4Cl (100 mL) and the aqueous reextracted with ether (100 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$), rotary evaporated and chromatographed (pentane/Et_2O, 1:4 to 3:7) to give the title compound (1.22 g, 90%) as a colourless oil. IR (cm^{-1}): 1730, 1636, 1389, 1376, 1272, 1252, 1203, 1152, 1087, 1013, 967, 908, 828, 809, 739, 697. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.32–7.39 (m, 5 H), 5.28 (s, 1 H), 5.06–5.17 (m, 2 H), 4.42 (quin, J = 6.0 Hz, 1 H), 2.58 (dd, J = 6.1, 4.2 Hz, 2 H), 2.45 (d, J = 6.4 Hz, 2 H), 1.69 (s, 3 H), 1.67 (s, 3 H), 0.84–0.86 (m, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 170.6, 168.2, 160.9, 135.6, 128.6, 128.4, 128.3, 106.5, 95.8, 66.5, 66.4, 42.2, 41.8, 25.7, 25.6, 24.4, 17.9, −4.8, −4.9. MS (ES) *m/z*: 457 $[M+Na]^+$, 435 $[M+H]^+$. HR-MS (ES) *m/z* calcd for $C_{23}H_{34}O_6Si$: 435.2203 $[M+H]^+$; found: 435.2217. Anal. calcd for $C_{23}H_{34}SiO_6$: C 63.56, H 7.89; found: C 63.48, H 7.99.

1.25.13.104 1-Benzyl 7-isopropyl 3-(tert-butyldimethylsilyloxy)-5-oxoheptanedioate (**453**)
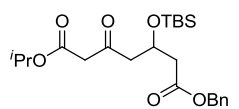
Benzyl 3-(tert-butyldimethylsilyloxy)-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)butanoate (600 mg, 1.380 mmol) and ^{i}PrOH (4.21 mL, 55.3 mmol) in toluene (14 mL) was refluxed for 7.5 h then rotary evaporated and chromatographed (pentane/Et_2O, 1:0 to 7:3) to give **xx** (540 mg, 90%) as a pale yellow oil. IR (cm^{-1}): 1736, 1375, 1310, 1250, 1167, 1146, 1081, 977, 828, 811, 777, 737, 697. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.33–7.38 (m, 5 H), 5.02–5.13 (m, 3 H), 4.60 (quin, J = 6.0 Hz, 1 H), 3.41 (s, 2 H), 2.81 (d, J = 6.4 Hz, 2 H), 2.54–2.60 (m, 2 H), 1.26 (d, J = 6.4 Hz, 6 H), 0.84 (s, 9

H), 0.05–0.08 (m, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 201.1, 170.7, 166.4, 135.7, 128.5, 128.3, 128.2, 69.0, 66.3, 65.5, 50.7, 49.8, 42.2, 25.7, 21.7, 17.9, −4.9, −5.0. MS (ES) m/z: 459 [M+Na]$^+$. HR-MS (ES) m/z calcd for C$_{23}$H$_{36}$O$_6$NaSi: 459.2179 [M+H]$^+$; found: 459.2170. Anal. calcd for C$_{23}$H$_{36}$SiO$_6$: C 63.27, H 8.31; found: C 63.37, H 8.39.

1.25.13.105   Isopropyl 2-(4-(tert-butyldimethylsilyloxy)-6-oxotetrahydro-2H-pyran-2-ylidene)acetate (455)
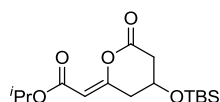
Hydrogen was bubbled through a mixture of palladium on activated charcoal (10 mg, 10% by wt.) and 1-benzyl 7-isopropyl 3-(tert-butyldimethylsilyloxy)-5-oxoheptanedioate (100 mg, 0.229 mmol) in EtOAc (2.5 mL) for 10 min, and then stirred for a further 50 min under an atmosphere of hydrogen (balloon). Filtration through celite and rotary evaporation gave 3-(tert-butyldimethylsilyloxy)-7-isopropoxy-5,7-dioxoheptanoic acid 454 as a pale yellow oil used directly without further purification. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.18 (br. s, 1 H), 5.07 (hept, J = 6.3 Hz, 1 H), 4.59 (p, J = 5.9 Hz, 1 H), 3.44 (s, 1 H), 2.83 (d, J = 6.0 Hz, 2 H), 2.56 (qd, J = 15.2, 5.9 Hz, 2 H), 1.27 (d, J = 6.3 Hz, 6 H), 0.86 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3H).

Ghosez's reagent (30 µL, 0.229 mmol) was added to the above oil in CH$_2$Cl$_2$ (5 mL) and stirred for 40 min then collidine (60 µL, 0.458 mmol) was added and stirred for 1 h.The mixture was quenched with 1M aq. HCl (5mL) and the layers separated. The aqueous was reextracted with CH$_2$Cl$_2$ (2 × 10 mL) and the combined organics were washed with water (10 mL), brine (10 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (pentane/Et$_2$O, 3:1 to 0:1) to give the title compound (34 mg, 45%) as a pale yellow solid; mp 46–48 °C (CH$_3$Cl$_3$). IR (cm^{-1}): 1779, 1706, 1650, 1254, 1192, 1081, 1057, 990, 867, 836, 824, 808, 777, 721. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.67 (d, J = 2.0 Hz, 1 H), 5.03 (spt, J = 6.3 Hz, 1 H), 4.26–4.36 (m, 1 H), 3.61–3.72 (m, 1 H), 2.84 (dt, J = 17.1, 2.4 Hz, 1 H), 2.72–2.77 (m, 2 H), 1.23–1.27 (dd, J = 6.4, 3.4 Hz, 6 H), 0.84 (s, 9 H), 0.06–0.09 (m, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 166.1, 165.5, 163.3, 104.2, 67.5, 62.5, 39.9, 32.9, 25.5, 21.8, 17.8, −5.0, −5.1. MS (CI) m/z 351 [M+Na]$^+$, 329 [M+H]$^+$. HR-MS (CI) m/z calcd for C$_{16}$H$_{28}$O$_5$NaSi: 351.1604 [M+H]$^+$; found: 351.1591. Anal. calcd for C$_{16}$H$_{30}$SiO$_6$: C 55.46, H 8.73; found: C 57.56, H 8.63.

1.25.13.106   4-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-hydroxybutanoic acid (456)
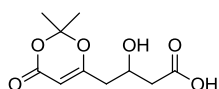
Hydrogen gas was bubbled through a vigorously stirred mixture of benzyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-hydroxybutanoate (199 mg, 0.62 mmol) and palladium on charcoal (20 mg, 10% wt.) in ethyl acetate (6.5 mL) for 5 min. The mixture was then stirred under an atmosphere of hydrogen (balloon) for 30 min. The mixture was filtered through celite and rotary evaporated to give the title compound (142 mg, quantitative) as a colourless waxy solid. IR (cm^{-1}): 1714, 1687, 1639, 1394, 1374, 1350, 1276, 1258, 1197, 1183, 1083, 1028, 1012, 812, 617. ^{1}H NMR (400 MHz, CD$_3$OD, ppm) δ: 7.37 (br. s, 1 H), 5.37 (s, 1 H), 4.22–4.34 (m, 1 H), 2.35–2.59 (m, 4 H), 1.71 (s, 6 H). ^{13}C NMR (101 MHz, CD$_3$OD, ppm) δ: 175.1, 171.7, 163.7, 108.3, 96.0, 66.5, 43.2, 42.1, 25.6, 24.9. MS (CI) *m/z*: 248 [M+NH$_4$]$^+$, 231 [M+H]$^+$. HR-MS (CI) *m/z* calcd for C$_{10}$H$_{14}$O$_6$: 231.0869 [M+H]$^+$; found: 231.0862. Anal. calcd for C$_{10}$H$_{14}$O$_6$: C 52.17, H 6.13; found: C 52.07, H 5.80.

1.25.13.107   5-Hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**457a**)[260]
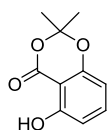
According to general procedure **K**, aromatization of acid **458a** (100 mg, 0.472 mmol) and chromatography (pentane/Et$_2$O, 95:5) gave resorcylate **457a** (70 mg, 76%) as a colorless solid; mp 63–64 °C (CH$_2$Cl$_2$–pentane). IR (cm^{-1}): 1687, 1631, 1584, 1469, 1385, 1343, 1277, 1249, 1205, 1167, 1151, 1079, 1056, 1047, 970, 920, 850, 803, 778, 688, 666, 631, 620. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.35 (s, 1 H), 7.42 (t, *J* = 8.3 Hz, 1 H), 6.64 (dd, *J* = 8.3, 1.0 Hz, 1 H), 6.45 (dd, *J* = 7.8, 1.0 Hz, 1 H), 1.76 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 165.5, 161.4, 155.6, 137.9, 110.8, 107.2, 107.1, 99.3, 25.7. MS (CI) *m/z*: 195 [M + H]$^+$. HR-MS (CI) *m/z* calcd for C$_{10}$H$_{11}$O$_4$: 195.0657 [M + H]$^+$; found: 195.0654. In agreement with the literature.

1.25.13.108   5-Hydroxy-2,2,7-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**457b**)
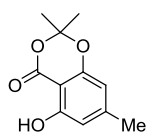
According to general procedure **K**, aromatization of acid **458e** (192 mg, 0.850 mmol) and chromatography (pentane/Et$_2$O, 49:1 to 19:1) gave resorcylate **457b** (110 mg, 62%) as a colorless solid. Alternatively, according to general procedure F, aromatization of acid **479a** (100 mg, 0.410 mmol) and chromatography (pentane–Et$_2$O, 19 : 1) gave resorcylate **457b** (36 mg, 42%) as a colorless solid; mp 97–100 °C (CH$_2$Cl$_2$–pentane). IR (cm^{-1}): 1689, 1643, 1585, 1466, 1381, 1361, 1273, 1204, 1059, 1091, 996, 964, 906, 831, 797, 707, 677, 627. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.24 (s, 1 H), 6.46 (s, 1 H), 6.28 (s, 1 H), 2.32 (s, 3 H), 1.74 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 165.4, 161.1, 155.3, 150.0, 111.2, 108.0, 107.0, 96.9, 25.6, 22.5. MS (CI) m/z: 226 [M + NH$_4$]$^+$, 209 [M + H]$^+$. HR-MS (CI) m/z calcd for C$_{11}$H$_{13}$O$_4$: 209.0814[M + H]$^+$; found: 229.0808.

1.25.13.109   5-Hydroxy-2,2,6-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**457c**)
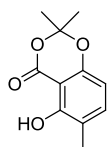
According to general procedure **K**, aromatization of acid **458b** (67 mg, 0.30 mmol) and chromatography (hexanes/Et$_2$O, 98:2 to 98:5) gave resorcylate **457c** (30 mg, 49%) as a colorless solid; mp 70–73 °C (CH$_2$Cl$_2$–pentane). IR (cm^{-1}): 1739, 1681, 1598, 1473, 1421, 1395, 1304, 1269, 1248, 1199, 1074, 992, 972, 940, 882, 798, 779, 704. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.55 (s, 1 H), 7.27 (d, J = 8.3 Hz, 1 H), 6.37 (d, J = 8.3 Hz, 1 H), 2.20 (s, 3 H), 1.74 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 165.9, 159.3, 153.4, 138.5, 119.7, 107.2, 106.3, 98.8, 25.6, 14.8. MS (CI) m/z: 226 [M + NH$_4$]$^+$, 209 [M + H]$^+$. HR-MS (CI) m/z calcd for C$_{11}$H$_{16}$NO$_4$: 226.1079 [M + NH$_4$]$^+$; found: 226.1079. Anal. calcd for C$_{11}$H$_{12}$O$_4$: C 63.45, H 5.81; found: C 63.38, H, 5.92.

1.25.13.110   6-Benzyl-5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**457d**)
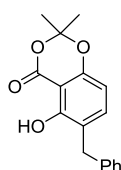
According to general procedure **K**, aromatization of acid **458c** (82 mg, 0.27 mmol) and chromatography (pentane/Et$_2$O, 90:10) gave resorcylate **457d** (45 mg, 58%) as a colorless solid; mp 100–103 °C (CH$_2$Cl$_2$–pentane). IR (cm^{-1}): 1692, 1631, 1498, 1446, 1390, 1379, 1352, 1272, 1241, 1205, 1093, 927, 809, 699, 631. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.66 (s, 1 H), 7.17–7.35 (m, 6 H), 6.39 (d, J = 8.3 Hz, 1 H), 3.95 (s, 2 H), 1.75 (s, 6 H. ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 165.8, 159.0, 153.8, 140.1, 138.4, 128.9, 128.4, 126.2, 123.1, 107.3, 106.6, 99.0, 34.7, 25.6. MS (ES) m/z: 285 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{17}$H$_{17}$O$_4$: 285.1127 [M + H]$^+$; found: 285.1130. Anal. calcd for C$_{17}$H$_{16}$O$_4$: C 71.82, H 5.67; found: C 71.92, H 5.77.

### 1.25.13.111   5-Hydroxy-2,2,6,7-tetramethyl-4H-benzo[d][1,3]dioxin-4-one (**457e**)
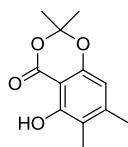
According to general procedure **K**, aromatization of acid **458f** (100 mg, 0.417 mmol) and chromatography (pentane/Et$_2$O, 90:10) gave resorcylate **457e** (40 mg, 43%) as a colorless solid; mp 94–97 °C (CH$_2$Cl$_2$–pentane). IR (cm^{-1}): 1678, 1630, 1580, 1536, 1505, 1453, 1418, 1393, 1377, 1354, 1318, 1269, 1200, 1180, 1134, 1099, 1047, 1021, 993, 966, 907, 865, 849, 816, 797, 734, 695, 651, 638, 608. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.54 (s, 1 H), 6.29 (s, 1 H), 2.27 (s, 3 H), 2.11 (s, 3 H), 1.72 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 165.9, 158.8, 152.7, 148.3, 118.1, 108.2, 106.9, 96.8, 25.6, 21.1, 10.5. MS (ES) m/z: 222 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{12}$H$_{15}$O$_4$: 223.0970 [M + H]$^+$; found: 223.0972. Anal. calcd for C$_{12}$H$_{14}$O$_4$: C 64.85, H 6.35; found: C 64.96, H 6.46.

### 1.25.13.112   5-Hydroxy-2,2,7-trimethyl-6-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**457f**)

According to general procedure **K**, aromatization of acid **458g** (137 mg, 0.454 mmol) and chromatography (pentane/Et$_2$O, 90:10) gave resorcylate **457f** (68 mg, 53%) as a colorless solid; mp 148–150 °C (CH$_2$Cl$_2$–pentane). IR (cm^{-1}): 1719, 1672, 1636, 1577, 1509, 1490,

1455, 1436, 1388, 1377, 1364, 1319, 1308, 1290, 1259, 1236, 1202, 1189, 1143, 1088, 1052, 1031, 1020, 998, 968, 910, 860, 842, 808, 798, 758, 742, 722, 703, 670, 641, 611. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.54 (s, 1 H), 7.36–7.49 (m, 3 H), 7.24–7.29 (m, 2 H), 6.43 (s, 1 H), 2.13 (s, 3 H), 1.80 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 165.6, 158.5, 154.1, 148.2, 135.3, 130.1, 128.4, 127.4, 124.3, 108.4, 107.2, 97.0, 25.7, 21.6. MS (ES) m/z: 285 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{17}$H$_{17}$O$_4$: 285.1127 [M + H]$^+$; found: 285.1138. Anal. calcd for C$_{17}$H$_{16}$O$_4$: C 71.82, H 5.67; found: C 71.73, H 5.85.

### 1.25.13.113   8-Benzyl-5-hydroxy-2,2,7-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**457h**)
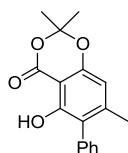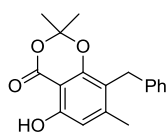

According to general procedure **K**, aromatization of acid **479b** (121 mg, 0.362 mmol) and chromatography (pentane/Et$_2$O, 9:1) gave resorcylate **457h** (50 mg, 46%) as a colorless solid; mp 80–81 °C (CH$_2$Cl$_2$–pentane). IR (cm^{-1}): 1688, 1634, 1585, 1494, 1481, 1453, 1390, 1379, 1364, 1338, 1264, 1247, 1208, 1097, 1071, 1040, 1075, 1002, 980, 903, 849, 823, 792, 727, 697, 646, 616. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.23 (s, 1 H), 7.24–7.29 (m, 2 H), 7.17–7.22 (m, 1 H), 7.08–7.12 (m, 2 H), 6.54 (s, 1 H), 3.93 (s, 2 H), 2.27 (s, 3 H), 1.64 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 165.7, 159.4, 153.2, 149.1, 140.0, 128.3, 128.0, 126.0, 118.0, 112.2, 107.1, 97.3, 30.7, 25.5, 20.9. MS (ES) m/z: 299 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{18}$H$_{19}$O$_4$: 299.1283 [M + H]$^+$; found: 299.1280.

1.25.13.114   5-Hydroxy-7-(4-methoxyphenyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (**457i**)
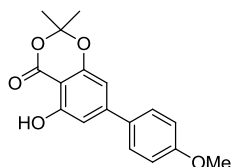
According to general procedure **K**, aromatization of acid **479c** (300 mg, 0.893 mmol) and chromatography (pentane/Et$_2$O, 7:3 to 1:1) gave resorcylate **457i** (102 mg, 38%) as a colorless solid; mp 108–110 °C (CH$_2$Cl$_2$–pentane). IR (cm^{-1}): 1676, 1634, 1604, 1583, 1563, 1518, 1499, 1489, 1459, 1444, 1389, 1375, 1341, 1312, 1289, 1272, 1256, 1207, 1183, 1117, 1094, 1060, 1046, 1028, 967, 926, 855, 841, 824, 733, 718, 698, 666, 625, 603. ^{1}H NMR

(400 MHz, CDCl$_3$, ppm) δ: 10.33 (s, 1 H), 7.52–7.57 (m, 2 H), 6.93–7.01 (m, 2 H), 6.85 (d, J = 1.5 Hz, 1 H), 6.67 (d, J = 1.5 Hz, 1 H), 3.87 (s, 3 H), 1.78 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 165.4, 161.4, 160.5, 155.7, 150.6, 131.4, 128.3, 114.3, 108.5, 107.2, 105.3, 97.5, 55.4, 25.7. MS (ES) m/z: 301 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{17}$H$_{17}$O$_5$: 301.1076 [M + H]$^+$; found: 301.1084. Anal. calcd for C$_{17}$H$_{16}$O$_5$: C 67.99, H 5.37; found: C 67.85, H 5.47.

1.25.13.115   6-(1-Chloroethyl)-5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**457j**)
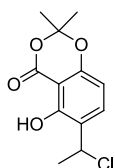
According to general procedure **K** reaction of 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-2-(1-hydroxyethyl)but-3-enoic acid (135 mg, 0.527 mmol) and chromatography (pentane/Et$_2$O, 19:1 to 9:1) gave the title compound (7 mg, 5%) as a colourless solid. IR (cm^{-1}): 1685, 1629, 1594, 1503, 1439, 1393, 1376, 1353, 1266, 1241, 1203, 1182, 1099, 1085, 1062, 976, 924, 975, 852, 826, 803, 746, 719, 698, 639, 628. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.60 (s, 1 H), 7.55 (d, J = 8.3 Hz, 1 H), 6.49 (d, J = 8.8 Hz, 1 H), 4.72 (q, J = 6.4 Hz, 1 H), 1.76 (s, 6 H), 1.41 (d, J = 6.4 Hz, 3 H). ^{13}C NMR (101, MHz, CDCl$_3$, ppm) δ: 165.8, 158.3, 154.5, 134.9, 125.1, 107.3, 107.1, 98.8, 56.6, 25.7, 25.6, 22.0. MS (CI) m/z: 221 [M−Cl]$^+$, 359. HR-MS (CI) m/z: calcd for C$_{12}$H$_{13}$O$_4$: 221.0814 [M−Cl]$^+$; found: 221.0820.

1.25.13.116   (E)-4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)but-3-enoic acid (**458a**)
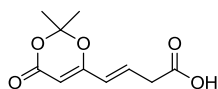
According to general procedure **G**, deprotection of ester **337a** (1.504 g, 5.61 mmol) for 2 h gave carboxylic acid **458a** (1.130 g, 95%) as an amorphous tan solid. IR (cm^{-1}): 1743, 1682, 1621, 1586, 1399, 1379, 1277, 1264, 1201, 1136, 1096, 1024, 979, 938, 909, 859, 834, 797, 752, 681. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 9.94 (br. s, 1 H), 6.61 (dt, J = 15.6, 7.3 Hz, 1 H), 6.06 (d, J = 15.6 Hz, 1 H), 5.34 (s, 1 H), 3.31 (d, J = 7.3 Hz, 2 H), 1.72 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 175.6, 162.3, 162.0, 131.8, 126.0, 106.7, 94.9, 37.2, 25.0.

MS (ES) *m/z*: 213 [M + H]⁺. HR-MS (ES) *m/z* calcd for $C_{10}H_{13}O_5$: 213.0763 [M + H]⁺; found: 213.0753. Additional HMBC spectrum provided in the additional NMR spectra section.
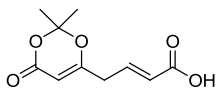
In one instance the title compound was obtained with the regioisomeric compound (E)-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)but-2-enoic acid (rr, 9:1). ¹H NMR (400 MHz, CDCl₃, ppm) *δ*: 6.99 (dt, *J* = 15.6, 7.1 Hz, 1 H), 6.82 (br.s, 1 H), 6.00 (dt, *J* = 15.6, 1.5 Hz, 1 H), 5.33 (t, *J* = 0.8 Hz, 1 H), 3.17 (ddd, *J* = 7.1, 1.5, 0.8 Hz, 2 H), 1.71 (s, 6 H).

1.25.13.117   4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-2-methylbut-3-enoic acid (±) (**458b**)
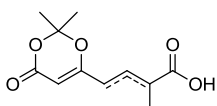
According to general procedure **G**, deprotection of ester **337e** (108 mg, 0.383 mmol) for 1.5 h gave carboxylic acid **458b** (84 mg, 97%, 1.0:0.9 rr) as a brown oil. IR (cm⁻¹): 1698, 1649, 1591, 1458, 1391, 1376, 1273, 1200, 1125, 1097, 1015, 970, 903, 857, 805, 744, 683, 614. ¹H NMR (400 MHz, CDCl₃, ppm) *δ*: 8.78 (br. s, 1.9 H), 6.86 (t, *J* = 7.3 Hz, 1 H), 6.63 (dd, *J* = 15.7, 7.8 Hz, 0.9 H), 6.04 (d, *J* = 15.6 Hz, 0.9 H), 5.36 (s, 0.9 H), 5.32 (s, 1 H), 3.34–3.38 (m, *J* = 7.1 Hz, 0.9 H), 3.16 (d, *J* = 7.3 Hz, 2 H), 1.89 (s, 3 H), 1.72 (m, 11.4 H), 1.40 (d, *J* = 6.8 Hz, 2.7 H). ¹³C NMR (101 MHz, CDCl₃, ppm) *δ*: 178.6, 172.1, 167.9, 162.5, 161.0, 140.0, 138.3, 134.9, 131.2, 123.9, 106.9, 106.6, 94.9, 94.1, 42.3, 32.9, 25.0, 24.9, 16.5, 12.3. MS (ES) *m/z*: 225 [M–H]⁻. HR-MS (ES) *m/z* calcd for $C_{11}H_{13}O_5$: 225.0763 [M–H]⁻; found: 225.0762.

1.25.13.118   2-Benzyl-4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)but-3-enoic acid (±) (**458c**)
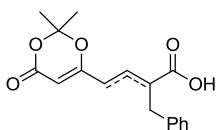
According to general procedure **G**, deprotection of ester **337f** (120 mg, 0.335 mmol) for 6 h gave carboxylic acid **458c** (97 mg, 96%, 1.0:0.8 rr) as a brown oil. IR (cm^{-1}): 1707, 1649, 1592, 1391, 1377, 1275, 1255, 1200, 1101, 1017, 968, 905, 857, 803, 738, 698. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.37 (br. s, 1.8 H), 7.12–7.36 (m, 9 H), 7.03 (t, J = 7.6 Hz, 0.8 H), 6.53 (dd, J = 15.7, 8.8 Hz, 1 H), 5.89 (d, J = 15.6 Hz, 1 H), 5.27 (s, 1 H), 5.26 (s, 0.8 H), 3.73 (s, 1.6 H), 3.40–3.57 (m, 1.8 H), 3.15–3.26 (m, 1.8 H), 2.88–2.97 (m, 1 H), 1.72 (s, 6 H), 1.69 (s, 4.8 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 177.2, 171.6, 167.6, 162.2, 161.9, 161.0, 138.1, 137.3, 136.8, 136.4, 134.2, 129.0, 128.7, 128.6, 128.1, 127.0, 126.6, 125.4, 107.0, 106.7, 95.1, 94.4, 50.5, 38.2, 33.2, 32.1, 25.0, 25.0. MS (ES) m/z: 320 [M + NH$_4$]$^+$, 303 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{17}$H$_{19}$O$_5$: 303.1232 [M + H]$^+$; found: 303.1239.

1.25.13.119   4-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-2-(1-hydroxyethyl)but-3-enoic acid (458d)
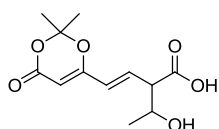
According to general procedure **G** deprotection of **337g** (300 mg, 0.704 mmol) for 1.5 h gave the carboxylic acid **458d** (164 mg, 91%, dr 1:0.6) as a colourless gum. IR (cm^{-1}): 1707, 1653, 1592, 1394, 1378, 1278, 1203, 1021, 977, 907, 805. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.96 (br. s., 3.2 H), 6.65 (dd, J = 15.6, 9.8 Hz, 1.0 H), 6.50 (dd, J = 15.6, 9.8 Hz, 0.6 H), 6.15 (d, J = 15.6 Hz, 0.6 H), 6.14 (d, J=15.7 Hz, 1 H), 5.41 (s, 1.6 H), 4.29– 4.38 (m, 1 H), 4.17–4.23 (m, 0.6 H), 3.18–3.33 (m, 1.6 H), 1.74 (s, 9.6 H), 1.30 (d, J = 6.4 Hz, 1.8 H), 1.27 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 176.0, 176.0, 162.8, 162.6, 162.5, 162.4, 134.1, 133.5, 127.5, 126.6, 107.0, 107.0, 95.2, 94.9, 68.7, 68.0, 56.6, 55.2, 25.0, 24.8, 21.0, 20.3. MS (ES) m/z: 274 [M+NH$_4$]$^+$, 256 [M+H]$^+$. HR-MS (ES) m/z: calcd for C$_{12}$H$_{17}$O$_6$: 257.1025 [M+H]$^+$; found: 257.1030.

### 1.25.13.120   4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-methylbut-3-enoic acid (458e)
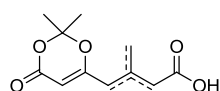
According to general procedure **G**, deprotection of ester **337h** (440 mg, 1.56 mmol) for 0.5 h gave carboxylic acid **458e** (268 mg, 76%, 1.0:0.6:0.5:0.4 rr) as a brown gum. IR (cm^{-1}): 1698, 1642, 1582, 1561, 1391, 1375, 1275, 1251, 1201, 1163, 1015, 969, 902, 856, 827, 805, 752, 694, 639, 612. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.01 (br. s, 2.5 H), 6.09 (s, 1 H), 5.83 (s, 0.4 H), 5.79 (s, 1 H), 5.34–5.36 (m, 1 H), 5.33 (s, 1 H), 5.21 (s, 0.6 H), 5.18 (s, 0.6 H), 3.56 (s, 1.2 H), 3.21 (s, 2 H), 3.17 (s, 1.2 H), 3.13 (s, 1 H), 3.08 (s, 0.8 H), 2.22 (s, 1.2 H), 2.18 (s, 1.5 H), 2.15 (s, 3 H), 1.64–1.80 (m, 15 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 176.3, 175.5, 172.6, 171.0, 169.0, 167.4, 164.4, 162.9, 162.4, 161.1, 156.3, 155.7, 154.5, 144.1, 134.7, 121.5, 119.7, 119.2, 112.1, 108.8, 107.0, 106.8, 106.4, 95.5, 95.2, 95.1, 94.3, 46.1, 44.7, 40.9, 40.1, 39.3, 38.9, 25.1, 24.9, 21.4, 19.6, 19.0. MS (ES) *m/z*: 249 [M + Na]$^+$, 227 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{11}$H$_{15}$O$_5$: 227.0919[M + H]$^+$; found: 227.0930.

### 1.25.13.121 4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-2,3-dimethylbut-3-enoic acid (±) (**458f**)
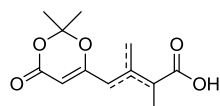
According to general procedure **G**, deprotection of ester **337i** (550 mg, 1.86 mmol) for 1 h gave carboxylic acid **458f** (433 mg, 97%, 1.0:0.5:0.5 rr) as a yellow oil. IR (cm^{-1}): 1718, 1642, 1579, 1392, 1377, 1276, 1204, 1078, 1018, 905, 810. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.61 (br. s, 2 H), 6.04 (s, 0.5 H), 5.78 (s, 1 H), 5.33 (s, 0.5 H), 5.32 (s, 1 H), 5.23 (s, 0.5 H), 5.14 (s, 0.5 H), 3.52 (s, 1 H), 3.27 (q, *J* = 6.8 Hz, 1 H), 3.20 (q, *J* = 7.2 Hz, 0.5 H), 3.02–3.11 (m, 1 H), 2.13 (s, 1.5 H), 2.07 (s, 3 H), 2.04 (s, 1.5 H), 1.73 (s, 9 H), 1.67–1.68 (m, 3 H), 1.32–1.38 (m, 4.5 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 179.1, 178.3, 173.0, 169.3, 164.6, 164.0, 162.3, 161.5, 152.0, 149.8, 149.5, 140.3, 120.1, 119.8, 117.1, 109.9, 106.7, 106.3, 95.6, 94.3, 49.6, 44.9, 39.2, 38.7, 25.2, 25.1, 25.0, 24.8, 19.5, 17.3, 15.8, 15.4, 12.2. MS (ES) *m/z*: 241 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{12}$H$_{17}$O$_5$: 241.1076 [M + H]$^+$; found: 241.1087. Anal. calcd for C$_{12}$H$_{16}$O$_5$: C 59.99, H 6.71; found: C 59.87, H 6.63.

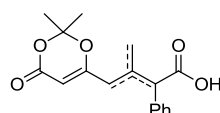### 1.25.13.122 4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-methyl-2-phenylbut-3-enoic acid (±) (**458g**)

According to general procedure **G**, deprotection of ester **337j** (470 mg, 1.31 mmol) for 2.5 h gave carboxylic acid **458g** (390 mg, 98%, 1.0:1.0:0.8 rr) as a yellow gum. IR (cm^{-1}): 1710, 1631, 1581, 1494, 1455, 1390, 1375, 1274, 1254, 1200, 1165, 1078, 1017, 984, 963, 904, 875, 807, 783, 752, 699, 640, 617. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 9.93 (br. s, 2.8 H), 7.18–7.46 (m, 14 H), 6.19 (s, 0.8 H), 5.79 (s, 1 H), 5.31 (s, 1 H), 5.24–5.29 (m, 3 H), 4.46 (s, 1 H), 4.40 (s, 1 H), 3.60 (s, 1.6 H), 3.02 (d, J = 15.7 Hz, 1 H), 2.90 (d, J = 15.7, 1 H), 2.04–2.08 (m, 5.4 H), 1.72 (s, 10.8 H), 1.66 (s, 3 H), 1.65 (s, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 176.7, 176.1, 172.7, 168.9, 164.4, 162.7, 162.1, 161.4, 153.8, 151.3, 147.9, 139.1, 135.1, 134.9, 133.4, 129.8, 128.9, 128.8 128.8, 128.4, 128.1, 124.8, 120.6, 118.3, 109.9, 106.7, 106.4, 95.9, 94.5, 61.0, 56.7, 39.4, 38.8, 25.1, 25.0, 24.9, 24.8, 20.4, 18.8. MS (ES) m/z: 320 [M + NH$_4$]$^+$, 303 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{17}$H$_{19}$O$_5$: 303.1232 [M + H]$^+$; found: 303.1235.

1.25.13.123   4-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-2-methyl-3-methylene-5-phenylpentanoic acid (±) (**458h**)
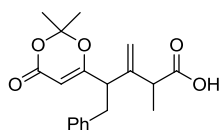
According to general procedure **G**, deprotection of ester **337k** (300 mg, 0.777 mmol) for 2 h gave carboxylic acid **458h** (217 mg, 85%) as a yellow oil. IR (cm^{-1}): 1702, 1455, 1391, 1377, 1273, 1201, 1166, 1076, 1018, 905, 854, 810, 731, 698, 647, 606. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 9.90 (br. s, 1 H), 7.05–7.33 (m, 5 H), 5.37 (s, 1 H), 5.35 (s, 1 H), 5.26 (s, 1 H), 3.36 (m, 1 H), 3.17 (q, J = 7.3 Hz, 1 H), 2.97–3.09 (m, 2 H), 1.60 (s, 3 H), 1.55 (s, 3 H), 1.24 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 179.1, 170.9, 161.7, 144.3, 138.0, 128.8, 128.4, 126.7, 115.7, 106.7, 94.1, 49.8, 45.2, 37.4, 25.0, 24.5, 15.9. MS (ES) m/z: 348 [M + NH$_4$]$^+$, 331 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{19}$H$_{23}$O$_5$: 331.1545 [M + H]$^+$; found: 331.1541. Anal. calcd for C$_{19}$H$_{22}$O$_5$: C 69.07, H 6.71; found: C 69.20, H 6.63.

1.25.13.124   3-(Tert-butyldimethylsilyloxy)-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)butanoic acid (**459**)[261]
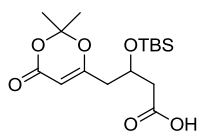
Hydrogen was bubbled through a mixture of palladium on activated charcoal (60 mg, 10% by wt.) and benzyl 3-(tert-butyldimethylsilyloxy)-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)butanoate (600 mg, 1.380 mmol) in EtOH (14 mL) for 10 min, and then stirred for a further 50 min under an atmosphere of hydrogen (balloon). The mixture was filtered through celite and rotary evaporated to give the title compound (475 mg, quantitative) as a colourless oil. IR (cm^{-1}): 1708, 1632, 1391, 1377, 1274, 1254, 1202, 1087, 1013, 829, 808, 776. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.85 (br. s, 1 H), 5.31 (s, 1 H), 4.40 (quin, J = 6.0 Hz, 1 H), 2.56 (d, J = 6.4 Hz, 2 H), 2.48 (d, J = 5.9 Hz, 2 H), 1.71 (s, 3 H), 1.69 (s, 3 H), 0.86 (s, 9 H), 0.06–0.09 (m, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 176.4, 168.1, 161.0, 106.6, 95.8, 66.3, 42.2, 41.7, 25.7, 25.6, 24.5, 17.9, −4.8, −5.0. MS (CI) m/z: 362 [M+NH$_4$]$^+$, 345 [M+H]$^+$. HR-MS (CI) m/z calcd for C$_{16}$H$_{34}$NO$_6$Si: 362.1999 [M+NH$_4$]$^+$; found: 362.2004. In agreement with the literature.

1.25.13.125   Methyl 3-(Tert-butyldimethylsilyloxy)-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)butanoylcarbamate (**460**)
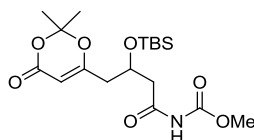
3-(*tert*-Butyldimethylsilyloxy)-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)butanoic acid (38 mg, 0.110 mmol) and Burgess reagent (58 mg, 0.243 mmol) in acetonitrile (2 mL) was heated at 70 °C for 4 h. Saturated aqueous NH$_4$Cl (5 mL) was added and the layers separated. The aqueous was reextracted with EtOAc (2 x 5 mL) and the combined organics washed with brine, dried (MgSO$_4$), filtered, rotary evaporated and Chromatographed (hexanes/Et$_2$O, 7:3 to 1:1) to give the title compound (34 mg, 77 %) as a colourless oil. IR (cm^{-1}): 1763, 1709, 1634, 1504, 1390, 1377, 1273, 1252, 1202, 1075, 1014, 951, 902, 829, 809, 775. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.01 (br. s., 1 H), 5.30 (s, 1 H), 4.47 (quin, J = 5.9 Hz, 1 H), 3.78 (s, 3 H), 2.80–3.06 (m, 2 H), 2.41–2.52 (m, 2 H), 1.70 (s, 3 H) 1.69 (s, 3 H), 0.86 (s, 9 H), 0.08 (d, J = 7.3 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 171.2, 168.1, 160.9, 151.8, 106.6, 95.8, 66.0, 53.0, 43.4, 41.6, 30.3, 25.7, 25.6, 24.4, −4.9 (2C). MS (ES) m/z: 424 [M+Na]$^+$. HR-MS (ES) m/z calcd for C$_{18}$H$_{31}$NO$_7$NaSi: 424.1768 [M+H]$^+$; found: 424.1761.

1.25.13.126   *tert*-Butyl but-3-enoate (**462a**)[262]
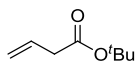
Crotonyl chloride (5.10 mL, 52.27 mmol) was added dropwise to triethylamine (7.37 mL, 52.27 mmol) in benzene (9.2 mL) over 25 min and stirred a further 1 h. The mixture was poured into saturated aqueous NH$_4$Cl and extracted with EtOAc. The aqueous was furhter extracted with ether and the combined organics dried (MgSO$_4$) and rotary evaporated to give the title compound (5.40 g, 73%) as a pale brown oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.97–5.84 (m, 1 H), 5.22–5.05 (m, 2 H), 3.00 (dt, J = 6.9, 1.5 Hz, 2 H), 1.45 (s, 9 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 170.9, 130.9, 117.9, 80.6, 40.4, 28.0. In agreement with the literature.

1.25.13.127 _tert_-Butyl 2-methylbut-3-enoate (**462b**)[263]
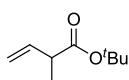
According to general procedure **E** alkylation with methyl iodide (526 µL, 8.45 mmol) and distillation (75 °C, 30 Torr) gave the title compound (692 mg, 63 %) as a colourless oil. IR (cm^{-1}): 1728, 1367, 1272, 1256, 1141, 916, 851. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.90 (ddd, J = 17.2, 10.1, 7.3 Hz, 1 H), 5.05–5.15 (m, 2 H), 2.96–3.09 (m, 1 H), 1.45 (s, 9 H), 1.23 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 173.8, 137.7, 115.3, 80.3, 44.6, 28.0, 16.7. In agreement with the literature.

1.25.13.128 _tert_-Butyl 2-benzylbut-3-enoate (**462c**)[264]
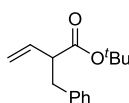
According to general procedure **E** reaction with benzyl bromide (838 µL, 7.04 mmol) and chromatography (pentane/Et$_2$O, 1:0 to 99:1) gave the title compound (1.022 g, 63%) as a colourless oil. IR (cm^{-1}): 1725, 1367, 1248, 1144, 993, 919, 846, 740, 698. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.31–7.26 (m, 2 H), 7.23–7.20 (m, 3 H), 5.93–5.81 (m, 1 H), 5.13 (m, 1 H), 5.09 (m, 1 H), 3.30–3.18 (m, 1 H), 3.13–3.02 (m, 1 H), 2.83 (dd, J = 6.8, 13.7 Hz, 1 H), 1.38 (s, 9 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 172.6, 138.9, 136.0, 129.1, 128.2, 126.2, 117.0, 80.6, 52.8, 38.5, 27.9. MS (EI) m/z: 231 [M-H]$^+$. HR-MS (EI) m/z: calcd for C$_{15}$H$_{19}$O$_2$: 231.1385 [M-H]$^+$; found: 231.1392. In agreement with the literature.

1.25.13.129   *tert*-Butyl 3-phenylbut-3-enoate (**462d**)[265]
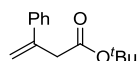
According to general procedure **E**, reaction of (E)-*tert*-Butyl 3-phenylbut-2-enoate (1.00 g, 4.59 mmol) with acetic acid and chromatography (pentane/Et$_2$O, 99.5:0.5 to 99:1) gave the title compound (516 mg, 52%) as a colourless oil. IR (cm^{-1}): 1725, 1367, 1291, 1256, 1143, 969, 900, 842, 776, 700. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.48–7.40 (m, 2 H), 7.36–7.22 (m, 3 H), 5.50 (s, 1 H), 5.23–5.19 (m, 1 H), 3.45–3.43 (m, 2 H), 1.36 (s, 9 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.6, 141.7, 140.2, 128.2, 127.6, 125.9, 115.7, 80.7, 42.7, 27.9. MS (EI) *m/z*: 217 [M-H]$^+$. HR-MS (EI) *m/z*: calcd for C$_{14}$H$_{17}$O$_2$: 217.1229 [M-H]$^+$; found: 217.1232. In agreement with the literature.

1.25.13.130   *tert*-Butyl 2-(1-hydroxyethyl)but-3-enoate (**462e**)
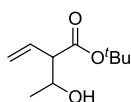
According to general procedure **E** reaction with acetaldehyde (791 μL, 14.08 mmol) and chromatography (pentane/Et$_2$O, 19:1 to 3:1) gave the title compound (829 mg, 63%) as a colourless oil. IR (cm^{-1}): 1724, 1638, 1458, 1383, 1368, 1253, 1205, 1148, 994, 920, 873, 842, 797, 744, 611. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.70–6.00 (m, 1 H), 5.17–5.32 (m, 2 H), 3.92–4.08 (m, 1 H), 2.84–2.98 (m, 1 H), 2.64–2.77 (m, 1 H), 1.46 (2 × s, 9 H), 1.18 (m, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 172.5, 172.5, 133.3, 132.3, 120.1, 118.9, 81.4, 68.6, 67.6, 58.9, 58.1, 28.0, 20.7, 19.9. MS (CI) *m/z*: 204 [M+NH$_4$]$^+$, 186 [M+H]$^+$. HR-MS (CI) *m/z*: calcd for C$_{10}$H$_{19}$O$_3$: 187.1334 [M+H]$^+$; found: 187.1327.

1.25.13.131   *tert*-Butyl 2-(1-(tert-butyldimethylsilyloxy)ethyl)but-3-enoate (**462f**)
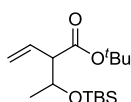
4-Dimethylaminopyridine (19 mg, 0.16 mmol) was added to a mixture of *tert*-butyl 2-(1-hydroxyethyl)but-3-enoate (590 mg, 3.17 mmol), imidazole (280 mg, 4.12 mmol) and *tert*-butyldimethylsilyl chloride (526 mg, 3.49 mmol) in DMF (2 mL) and stirred for 7 h, before

addition of water and stirring for an additional 12 h. The mixture was extracted with ether (× 3), washed with saturated aqueous NH$_4$Cl, saturated aqueous NaHCO$_3$, brine, dried (MgSO$_4$), rotary evaporated and chromatographed (pentane/Et$_2$O, 49:1) to give the title compound (894 mg, 94 %, dr 1:1) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.87 (ddd, J = 17.1, 10.3, 9.3 Hz, 0.5 H), 5.75 (ddd, J = 17.1, 10.3, 9.3 Hz, 0.5 H), 5.04–5.22 (m, 2 H), 4.03–4.15 (m, 1 H), 2.82–2.96 (m, 1 H), 1.45 (2 × s, J = 2.4 Hz, 9 H), 1.17 (2 × s, J = 5.9 Hz, 1.5 H), 1.12 (2 × s, 1.5 H), 0.87–0.88 (m, 9 H), 0.01–0.08 (m, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 171.8, 134.4, 133.9, 118.4, 118.0, 80.5, 80.3, 69.5, 69.4, 60.6, 59.9, 28.1, 28.0, 25.8, 25.8, 25.7, 25.6, 21.8, 21.3, 18.0, −3.0, −4.3, −4.7, −4.9. MS (CI) m/z: 300 [M+H]$^+$. HR-MS (CI) m/z: calcd for C$_{16}$H$_{33}$SiO$_3$: 301.2199 [M+H]$^+$; found: 301.2188.

1.25.13.132   2,2-Dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-7-yl formate (464)[266]
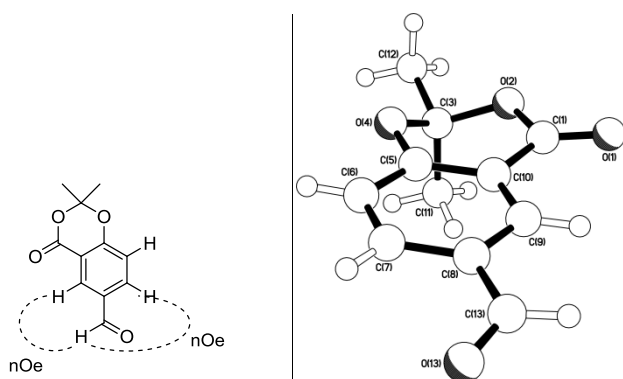
Oxalyl chloride (120 µL, 1.415 mmol) and DMF (110 µL, 1.415 mmol) were added to (E)-4-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)but-3-enoic acid (100 mg, 0.472 mmol) and stirred for 20 h. The mixture was diluted with CH$_2$Cl$_2$ and washed with 1 M aqueous HCl, brine, dried (MgSO$_4$), filtered, rotary evaporated and chromatographed (pentane/Et$_2$O, 9:1 to 0:1 to give the title compound (32 mg, 33%) as a colourless solid. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 9.91–10.07 (br. s, 1 H), 8.48 (d, J = 1.8 Hz, 1 H), 8.13 (ddd, J = 8.6, 2.1, 0.9 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1 H), 1.75–1.83 (m, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 189.6, 160.4, 159.8, 135.7, 133.4, 131.4, 118.4, 113.5, 107.3, 25.9 ppm

1.25.13.133   *tert*-Butyl 4-methyl-3-oxopent-4-enoate (465a)[267]**Error! Bookmark not defined.**
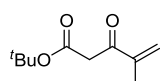
DMSO (2.86 mL, 40.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise to oxalyl chloride (1.77 mL, 20.97 mmol) in CH_2Cl_2 (140 mL) and stirred for 10 min. *tert*-Butyl 3-hydroxy-4-methylpent-4-enoate (3.00 g, 16.13 mmol) was added dropwise and stirred for 10 min. Triethylamine (22.6 mL, 161.3 mmol) was then added dropwise over 10 min and the mixture warmed to 25 °C for 30 min. $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2, dried ($MgSO_4$), rotary evaporated and chromatographed (pentane/Et_2O, 9:1 to 17:3) to give the title compound (1.321 g, 45%) as a colourless oil. IR (cm^{-1}): 1735, 1708, 1684, 1596, 1368, 1296, 1252, 1144, 1071, 1012, 984, 922, 831. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: Keto-form : 5.95(s, 1 H), 5.88(s, 1 H), 3.64 (s, 2 H), 1.90 (s, 3 H), 1.46 (s, 9 H). MS (CI) *m/z*: 202 [M+NH$_4$]$^+$. HR-MS (CI) *m/z*: calcd for $C_{10}H_{20}NO_3$: 202.1443 [M+NH$_4$]$^+$; found: 202.1452. In agreement with the literature.

1.25.13.134 (E)-*tert*-Butyl 3-phenylbut-2-enoate (**466a**)[268]
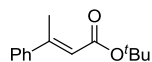
tert-Butyl 2-(diethoxyphosphoryl)acetate (5.00 g, 19.84 mmol) was added to sodium hydride (60% in mineral oil; 794 mg, 19.84 mmol) in THF (35 mL) at 0 °C and stirred for 0.5 h. Acetophenone (1.85 mL, 15.87 mmol) was added and stirring continued for 20 h at 25 °C, before addition of saturated aqueous NH$_4$Cl (40 mL). The mixture was extracted with ether (3 × 60), washed with brine (3 × 50 mL), dried (MgSO$_4$), rotary evaporated and chromatographed (pentane/Et_2O, 99:1 to 97:3) to give the title compound (2.35 g, 68%) as a colourless oil. IR (cm^{-1}): 1706, 1627, 1366, 1348, 1274, 1140, 1012, 873, 769, 759, 693. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.49–7.44 (m, 2 H), 7.41–7.33 (m, 3 H), 6.07 (q, J = 1.0 Hz, 1 H), 2.55 (d, J = 1.5 Hz, 3 H), 1.53 (s, 9 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 166.4, 154.0, 142.5, 128.7, 128.4, 126.2, 119.1, 80.0, 28.3, 17.7. MS (EI) *m/z*: 217 [M-H]$^+$. HR-MS (EI) *m/z*: calcd for $C_{14}H_{17}O_2$: 217.1229 [M+-H]$^+$; found: 217.1233.

1.25.13.135 *tert*-Butyl 2-(diethoxyphosphoryl)acetate (**467a**)[269]
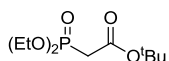
tert-Butyl bromoacetate (4.88g, 25 mmol) and triethyl phosphite (4.15g, 25 mmol) were heated at 60 °C for 6 h to give the title compound (5.85 g, 93%) as a colourless oil. IR (cm^{-1}): 1725, 1394, 1367, 1287, 1255, 1211, 1164, 1114, 1050, 1020, 956, 882, 828, 790, 769, 752, 700, 612. ^{1}H

NMR (400 MHz, CDCl$_3$, ppm) δ: 4.24–4.12 (m, 4 H), 2.91 (s, 1 H), 2.86 (s, 1 H), 1.48 (s, 9 H), 1.35 (t, J = 7.1 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 164.9 (d, J = 5.2 Hz), 82.0, 62.4 (d, J = 5.2 Hz), 35.6 (d, J = 131.8 Hz) , 27.9, 16.3 (d, J = 5.2 Hz). MS (EI) m/z: 275 [M+Na]$^+$. HR-MS (EI) m/z: calcd for C$_{10}$H$_{21}$O$_4$NaP: 275.1024 [M+Na]$^+$; found: 275.1011. In agreement with the literature.

1.25.13.136   *tert*-Butyl 2-(diethoxyphosphoryl)-2-phenylacetate (**469a**)
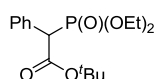
tert-Butyl 2-bromo-2-phenylacetate (1.5 g, 5.54 mmol) and triethyl phosphite (920 mg, 5.54 mmol) in acetonitrile (2 mL) were heated under microwave irradiation for 6 h at 100 °C and chromatography (pentane/Et$_2$O, 1:1 to 7:13) gave the title compound (1.183 g, 65 %) as a colourless oil. IR (cm^{-1}): 1727, 1479, 1497, 1455, 1393, 1368, 1346, 1278, 1254, 1218, 1136, 1098, 1049, 1019, 960, 887, 854, 820, 782, 743, 697, 610. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.48–7.54 (m, 2H), 7.28–7.37 (m, 3H), 4.16 (d, J = 24.0 Hz, 1H), 3.91–4.11 (m, 4H), 1.47 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: ppm) 166.6 (d, J = 3.5 Hz), 131.3 (d, J = 8.7 Hz), 129.6 (d, J = 5.2 Hz), 128.4 (d, J = 3.5 Hz), 127.7 (d, J = 3.5 Hz), 82.3, 63.1 (d, J = 6.9 Hz), 62.9 (d, J = 6.9 Hz), 53.2 (d, J = 133.5 Hz), 27.9, 16.3(2 × d, J = 6.9 Hz). ^{31}P NMR (162MHz, CDCl$_3$, ppm) δ: 19.33. MS (ES) m/z: 329 [M+H]$^+$. HR-MS (ES) m/z: calcd for C$_{16}$H$_{26}$PO$_5$: 329.1518[M+H]$^+$; found: 329.1527.

1.25.13.137   *tert*-Butyl 3-hydroxy-4-methylpent-4-enoate (**472**)[267]
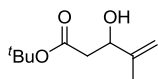
tert-Butyl acetate (3.51 mL, 26.1 mmol) was added dropwise to LDA (31.3 mmol) in THF (42 mL) at −78 °C and stirred for 1 h. Methacrolein (2.48 mL, 30 mmol) was added dropwise and stirred for 15 min followed by addition of saturated aqueous NH$_4$Cl. The mixture was partitioned between ether and water then extracted with EtOAc, dried (MgSO$_4$) and rotary evaporated to give the title compound (4.857 g, 87%) as a pale yellow oil used without further purification. IR (cm^{-1}): 1708, 1368, 1255, 1147, 1046, 1027, 954, 889, 843, 765. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.02 (s, 1 H), 4.87 (s, 1 H), 4.38–4.45 (m, 1 H), 3.15 (br. s, 1 H), 2.41–2.54 (m, 2 H), 1.75 (s, 3 H), 1.46 (s,

9 H).^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 172.0, 145.5, 111.2, 81.3, 71.6, 40.9, 28.0, 18.2.MS (CI) m/z: 204 [M+NH$_4$]$^+$, 187 [M+H]$^+$. HR-MS (CI) m/z: calcd for C$_{10}$H$_{22}$NO$_3$: 204.1600 [M+NH$_4$]$^+$; found: 204.1609. In agreement with the literature.

1.25.13.138   *tert*-Butyl 2-bromo-2-phenylacetate (**475**)[270]
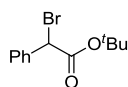
Thionyl chloride (13.5 mL, 186 mmol) was added to α-bromophenylacetic acid (10 g, 46.5 mmol) and DMF (50 μL, 0.685 mmol) and stirred for 18 then rotary evaporated to give α-bromophenylacetyl chloride (IR (cm^{-1}): 1796). This was added to *tert*-butanol (8.9 mL, 93 mol) and triethylamine (13 mL, 93 mmol) in CH$_2$Cl$_2$ (10 mL) an sitrrred for 2 h. The mixture was washed with saturated aqueous NH$_4$Cl and extracted with CH$_2$Cl$_2$, dried (MgSO$_4$), rotary evaporated and chromatographed (pentane/Et$_2$O, 19:1) to give the title compound (5.1 g, 40%) as a colourless oil. IR (cm^{-1}): 1737, 1478, 1497, 1455, 1369, 1306, 1285, 1255, 1223, 1031, 1076, 1031, 1004, 959, 916, 846, 745, 693. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.44–7.58 (m, 2H), 7.31–7.42 (m, 3H), 5.22–5.28 (m, 1H), 1.44–1.48 (m, 9H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 167.2, 136.3, 129.0, 128.7, 128.6, 127.8, 83.1 (2C), 60.0, 48.3, 27.7. MS (CI) m/z: 288 [M+NH$_4$]$^+$(Br^{79}), 290 [M+NH$_4$]$^+$(Br^{81}). HR-MS (CI) m/z: calcd for C$_{12}$H$_{19}$NO$_2$Br: 288.0599 [M+NH$_4$]$^+$; found: 288.0602. In agreement with the literature.

1.25.13.139   *tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxy-3-methylbutanoate (±) (**476a**)
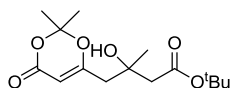
According to general procedure **H**, aldol reaction of ester **408a** (731 μL, 5.43 mmol) and dioxinone ketone **248a** (1.00 g, 5.43 mmol) gave, after chromatography (pentane/Et$_2$O, 7:3 to 3:2), dioxinone ester **476a** (775 mg, 48%) as a yellow oil. IR (cm^{-1}): 1713, 1629, 1390, 1369, 1273, 1249, 1202, 1150, 116, 1091, 1014, 963, 901, 814. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.31 (s, 1 H), 4.06 (s, 1 H), 2.40–2.53 (m, 4 H), 1.70 (s, 3 H), 1.70 (s, 3 H), 1.48 (s, 9 H), 1.30 (s, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 172.0, 168.0, 160.9, 106.5, 96.2, 82.1, 70.5, 45.4, 45.3, 28.0, 27.4, 25.2, 25.1. MS (ES) m/z: 623 [M$_2$ + Na]$^+$, 601 [M$_2$ + H]$^+$. HR-MS (ES) m/z calcd for C$_{30}$H$_{49}$O$_{12}$: 601.3224 [M$_2$ + H]$^+$; found: 601.3231.

1.25.13.140   *tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxy-2,3-dimethylbutanoate (±) (**476b**)
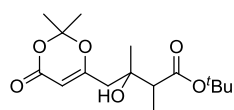
According to general procedure **H**, aldol reaction of ester **408b** (820 µL, 5.43 mmol) and dioxinone ketone **248a** (1.00 g, 5.43 mmol) gave, after chromatography (pentane/Et$_2$O, 7:3 to 1:1), dioxinone ester **476b** (845 mg, 50%, 1.0:0.6 dr) as a yellow oil. IR (cm^{-1}): 1721, 1630, 1458, 1390, 1368, 1273, 1255, 1204, 1148, 1008, 1076, 1013, 933, 901, 847, 811. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.32 (s, 1.0 H), 5.31 (s, 0.6 H), 3.91 (br. s, 0.6 H), 3.55 (br. s, 1.0 H), 2.41–2.53 (m, 3.8 H), 2.33 (d, J = 13.7, 1.0 H), 1.70 (s, 9.6 H), 1.46–1.48 (m, 14.4 H), 1.29 (s, 3 H), 1.19–1.22 (m, 6.6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 176.0, 175.3, 168.3, 168.2, 160.9, 106.5, 106.4, 96.4, 96.2, 81.9, 81.8, 72.7, 72.5, 48.7, 47.5, 45.3, 42.4, 28.0, 26.0, 25.2, 25.0, 23.9, 12.4, 12.3. MS (CI) *m/z*: 332 [M + NH$_4$]$^+$, 315 [M + H]$^+$. HR-MS (CI) *m/z* calcd for C$_{16}$H$_{30}$NO$_6$: 332.2073 [M + NH$_4$]$^+$; found: 332.2070. Anal. calcd for C$_{16}$H$_{26}$O$_6$: C 61.13, H 8.34; found: C 60.95, H 8.45.

1.25.13.141   *tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxy-3-methyl-2-phenylbutanoate (±) (**476c**)
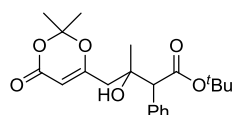
According to general procedure **H**, aldol reaction of ester **408c** (1.04 g, 5.43 mmol) and dioxinone ketone **284a** (1.00 g, 5.43 mmol) gave, after chromatography (pentane/Et$_2$O, 9:1 to 1:1), dioxinone ester **476c** (853 mg, 42 %, 1:0.8 dr) as a colorless gum. IR (cm^{-1}): 1721, 1630, 1455, 1390, 1369, 1273, 1251, 1203, 1146, 1088, 1014, 955, 900, 863, 808, 754, 701, 622. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.29–7.41 (m, 9 H), 5.34 (s, 0.8 H), 5.26 (m, 1 H), 4.42 (s, 0.8 H), 3.97 (s, 1 H), 3.57 (s, 1 H), 3.54 (s, 0.8 H), 2.62 (d, J = 13.7 Hz, 0.8 H), 2.57 (d, J = 13.7 Hz, 0.8 H), 2.36 (d, J = 14.2 Hz, 1 H), 2.13 (d, J = 13.7 Hz, 1 H), 1.75 (s, 2.4 H), 1.74 (s, 2.4H), 1.71 (s, 3 H), 1.70 (s, 3 H), 1.40–1.42 (m, 19.2 H), 1.04 (s, 2.4 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 173.6, 173.0, 168.4, 168.1, 160.9, 160.9, 134.7, 134.6, 129.7, 129.5, 128.4, 128.4, 127.8, 127.7, 106.6, 106.4, 96.6, 96.4, 82.5, 82.3, 73.4, 73.2, 60.4, 59.0, 46.1, 42.9, 27.9, 26.6, 25.3, 25.2, 25.1, 24.8. MS (CI) *m/z*: 394 [M + NH$_4$]$^+$, 376 [M]$^+$. HR-MS (CI)

m/z calcd for $C_{21}H_{32}NO_6$: 394.2230 $[M + NH_4]^+$; found: 394.2219. Anal. calcd for $C_{21}H_{28}O_6$: C 67.00, H 7.50; found: C 66.73, H 7.64.

1.25.13.142   *tert*-Butyl 4-(2,2-dimethyl-4-oxo-*4H*-1,3-dioxin-6-yl)-3-hydroxy-2,3-dimethyl-5-phenylpentanoate (±) (**476d**)
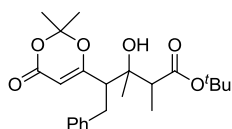
According to general procedure **H**, aldol reaction of ester **408b** (341 µL, 2.26 mmol) and dioxinone ketone **248d** (620 mg, 2.26 mmol) gave, after chromatography (pentane/Et$_2$O, 4:1 to 13:7), dioxinone ester **476d** (452 mg, 50%) as a colorless gum. IR (cm^{-1}): 1731, 1699, 1629, 1494, 1456, 1392, 1374, 1366, 1345, 1320, 1291, 1272, 1258, 1203, 1160, 1141, 1095, 1069, 1018, 972, 944, 900, 855, 845, 832, 809, 753, 736, 702, 983, 658, 615. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.22–7.29 (m, 2 H), 7.10–7.21 (m, 3 H), 5.06 (s, 1 H), 4.29 (s, 1 H), 3.30–3.42 (m, 1 H), 2.75–2.83 (m, 2 H), 2.49 (q, $J = 7.3$ Hz, 1 H), 1.55 (s, 3 H), 1.52 (s, 3 H), 1.48 (s, 9 H), 1.30 (d, $J = 7.3$ Hz, 3 H), 1.22 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 177.0, 170.0, 160.5, 139.3, 128.7, 128.4, 126.4, 106.4, 96.7, 82.2, 74.3, 55.9, 46.1, 32.7, 27.9, 25.0, 20.1, 12.9. MS (CI) m/z: 405 $[M + H]^+$. HR-MS (CI) m/z calcd for $C_{23}H_{33}O_6$: 405.2277 $[M + H]^+$; found: 405.2267. Anal. calcd for $C_{23}H_{32}O_6$: C 68.29, H 7.97; found: C 68.44, H 8.11.

1.25.13.143   *tert*-Butyl 4-(2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxy-3-(4-methoxyphenyl)butanoate (±) (**476e**)
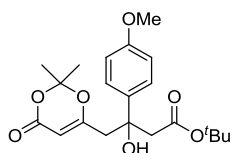
According to general procedure **H**, aldol reaction of ester **408a** (729 µL, 5.43 mmol) and dioxinone ketone **248c** (1.50 g, 5.43 mmol) gave, after chromatography (pentane/Et$_2$O, 4:1 to 3:1), dioxinone ester **476e** (1.10 g, 52%) as a yellow gum. IR (cm^{-1}): 1721, 1644, 1583, 1458, 1390, 1369, 1319, 1373, 1251, 1203, 1147, 1084, 1047, 1015, 901, 877, 848, 805, 744, 605. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.29–7.35 (m, 2 H), 6.82–6.88 (m, 2 H), 5.14 (s, 1 H), 4.61 (s, 1 H), 3.80 (s, 3 H), 2.88 (d, $J = 15.2$ Hz, 1 H), 2.79 (d, $J = 15.7$ Hz, 1 H), 2.68 (s,

2 H), 1.56 (s, 3 H), 1.51 (s, 3 H), 1.29 (s, 9 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 171.5, 167.4, 161.0, 158.8, 135.9, 126.3, 113.4, 106.4, 96.5, 82.2, 74.2, 55.3, 46.7, 46.2, 27.8, 25.0, 24.9. MS (CI) m/z: 410 [M + NH$_4$]$^+$. HR-MS (CI) m/z calcd for C$_{21}$H$_{32}$NO$_7$: 410.2179 [M + NH$_4$]$^+$; found: 410.2171. Anal. calcd for C$_{21}$H$_{28}$O$_7$: C 64.27, H 7.19; found: C 64.19, H 7.30.

1.25.13.144   2-(4-(4-Methoxyphenyl)-2-oxo-2*H*-pyran-6-yl)acetic acid (**478**)
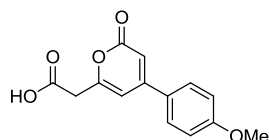
According to general procedure **G**, reaction of ester **337l** (329 mg, 0.880 mmol) for 2 h gave pyrone **478** (206 mg, 74%) as a yellow solid; decomposition (-CO$_2$) 148 °C (MeOH). IR (cm^{-1}): 1729, 1671, 1619, 1598, 1580, 1544, 1517, 1433, 1401, 1323, 1314, 1291, 1272, 1248, 1186, 1146, 1122, 1055, 1019, 1006, 895, 862, 846, 827, 802, 741, 730, 712, 694, 640, 624. ^{1}H NMR (400 MHz, CD$_3$OD, ppm) δ: 7.36–7.44 (m, 2 H), 6.69–6.78 (m, 2 H), 6.34 (d, $J =$ 1.5 Hz, 1 H), 6.07 (d, $J =$ 1.5 Hz, 1 H), 3.56 (s, 3 H), 3.27 (s, 2 H). ^{13}C NMR (101 MHz, CD$_3$OD, ppm) δ: 151.3, 144.6, 143.9, 140.9, 136.0, 110.8, 110.4, 97.0, 89.6, 86.4, 37.4, 21.5. MS (ES) m/z: 302 [M + MeCN + H]$^+$, 261 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{14}$H$_{13}$O$_5$: 261.0763 [M + H]$^+$; found: 261.0779. Anal. calcd for C$_{14}$H$_{12}$O$_5$: C 64.61, H 4.65. found: C 64.46, H 4.74.

1.25.13.145   4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxy-3-methylbutanoic   acid   (±) (**479a**)
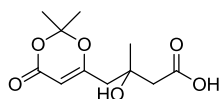
According to general procedure **J**, aldol reaction of dioxinone ketone **284a** (1.00 g, 5.43 mmol) and benzyl acetate **480a** (815 mg, 5.43 mmol) gave, after hydrogenolysis, carboxylic acid **479a** (500 mg, 38%) as a yellow gum. IR (cm^{-1}): 1714, 1658, 1624, 1501, 1463, 1435, 1419, 1390, 1378, 1326, 1289, 1258, 1205, 1188, 1159, 1116, 1098, 1052, 1021, 972, 964, 928, 905, 886, 865, 848, 821, 790, 754, 698, 677, 621. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.00 (br. s, 2 H), 5.39 (s, 1 H), 2.69 (d, $J =$ 17.1, 1 H), 2.62 (d, $J =$ 16.1, 1 H), 2.56 (s, 2 H), 1.73 (s, 3 H), 1.72 (s, 3 H), 1.39 (s, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 175.6, 167.8,

161.2, 106.8, 96.5, 70.5, 45.4, 44.2, 27.6, 25.1 (2C). MS (CI) m/z: 262 [M + NH$_4$]$^+$, 245 [M + H]$^+$. HR-MS (CI) m/z calcd for C$_{11}$H$_{20}$NO$_6$: 262.1291 [M + NH$_4$]$^+$; found: 262.1285.

1.25.13.146   4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxy-3-methyl-5-phenylpentanoic acid (±) (**479b**)
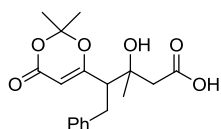
According to general procedure **J**, aldol reaction of dioxinone ketone **284d** (204 mg, 0.745 mmol) and benzyl acetate **480a** (112 mg, 0.745 mmol) gave, after hydrogenolysis, carboxylic acid **479b** (140 mg, 56%, 1.0:0.4 dr) as a colorless gum. IR (cm^{-1}): 1702, 1623, 1497, 1456, 1391, 1377, 1272, 1255, 1200, 1120, 1075, 1020, 956, 858, 811, 731, 699, 647. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.12–7.29 (m, 7.0 H), 5.23 (s, 0.4 H), 5.21 (s, 1.0 H), 3.25 (dd, J = 13.4, 3.2 Hz, 1.0 H), 3.14 (d, J = 11.7 Hz, 0.4 H), 2.60–2.93 (m, 5.6 H), 1.49–1.54 (m, 8.4 H), 1.45 (s, 1.2 H), 1.41 (s, 3.0 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 176.2, 176.1, 170.0, 161.2, 138.5, 138.2, 128.7, 128.5, 126.7, 126.6, 106.8, 97.1, 96.7, 72.2, 55.7, 55.4, 43.3, 43.0, 32.8, 32.3, 25.8, 25.2, 25.1, 24.8, 24.7, 24.5. MS (ES) m/z: 376 [M + MeCN + H]$^+$, 352 [M + NH$_4$]$^+$, 335 [M + H]$^+$. HR-MS (ES) m/z calcd for C$_{18}$H$_{23}$O$_6$: 335.1495 [M + H]$^+$; found: 335.1507.

1.25.13.147   4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxy-3-(4-methoxyphenyl)butanoic acid (±) (**479c**)
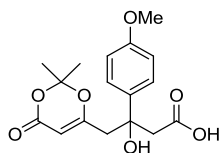
According to general procedure **J**, aldol reaction of dioxinone ketone **284c** (1.00 g, 5.43 mmol) and benzyl acetate **480a** (815 mg, 5.43 mmol) gave, after hydrogenolysis, carboxylic acid **479c** (784 mg, 43%) as a yellow gum. IR (cm^{-1}): 1712, 1680, 1621, 1586, 1515, 1461, 1430, 1393, 1375, 1332, 1288, 1257, 1200, 1168, 1122, 1101, 1046, 1022, 936, 907, 889, 846, 829, 817, 775, 754, 717, 701, 677, 637, 616. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.28–7.34 (m, 2 H), 6.83–6.90 (m, 2 H), 5.15 (s, 1 H), 3.80 (s, 3 H), 2.89–3.05 (m, 2 H), 2.69–2.80 (m, 2 H), 1.51, (s, 3 H), 1.50 (s, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 176.0, 167.3, 161.3,

159.0, 135.4, 126.1, 113.7, 106.6, 96.6, 74.0, 55.2, 46.4, 44.9, 24.9, 24.8. (ES) *m/z*: 354 [M + NH$_4$]$^+$, 336 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{17}$H$_{21}$O$_7$: 337.1287 [M + H]$^+$; found: 337.1304.

1.25.13.148 4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxy-2,3-dimethyl-5-phenylpentanoic acid (±) (479d)
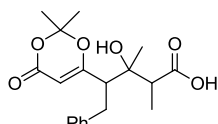
According to general procedure **J**, aldol reaction of dioxinone ketone **284d** (204 mg, 0.745 mmol) and benzyl propanoate **480b** (122 mg, 0.745 mmol) gave, after hydrogenolysis, carboxylic acid **479d** (106 mg, 41%, 1.0:0.4 dr) as a colorless gum. IR (cm^{-1}): 1702, 1622, 1497, 1456, 1391, 1377, 1273, 1255, 1200, 1101, 1074, 1019, 905, 859, 810, 730, 699, 648. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 8.46 (br. s, 0.4 H), 7.11–7.29 (m, 7.0 H), 5.20 (s, 1.0 H), 5.16 (s, 0.4 H), 3.94 (br. s, 0.4 H), 3.26–3.38 (m, 1.4 H), 2.67–2.91 (m, 5.2 H), 1.52–1.57 (m, 4.2 H), 1.46–1.49 (m, 4.2 H), 1.41 (s, 1.2 H), 1.33–1.39 (m, 5.2 H), 1.28 (s, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 180.1, 179.8, 170.2, 169.8, 161.3, 160.9, 138.7, 128.9, 128.7, 128.5, 126.6, 106.8, 106.7, 96.7, 96.6, 74.5, 73.5, 55.2, 52.7, 46.6, 45.3, 32.6, 32.4, 25.4, 25.1, 24.7, 24.5, 23.1, 20.4, 12.8, 11.9. MS (ES) *m/z*: 390 [M + MeCN + H]$^+$, 366 [M + NH$_4$]$^+$, 349 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{19}$H$_{25}$O$_6$: 349.1651 [M + H]$^+$; found: 349.1643.

1.25.13.149 4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-3-hydroxy-3-methyl-2-phenylbutanoic acid (±) (479e)
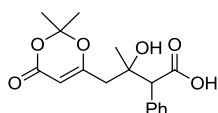
According to general procedure **J**, aldol reaction of dioxinone ketone **284a** (1.00 g, 5.43 mmol) and benzyl phenylacetate **480c** (1.23 g, 5.43 mmol) gave, after hydrogenolysis, carboxylic acid **479e** (325 mg, 19%, 1.0:0.8 dr) as a yellow oil. Alternatively, carboxylic acid **479e** was synthesized by addition of the dianion derived from PhCH$_2$CO$_2$H to dioxinone ketone **284a**. *n*-BuLi in hexanes (13.6 mL, 32.6 mmol) was added dropwise with stirring to (^{i}Pr)$_2$NH (4.61 mL, 32.6 mmol) in THF (30 mL) at 0 °C. After 15 min, PhCH$_2$CO$_2$H (2.22 g,

16.3 mmol) in THF (20 mL) was added dropwise with stirring. After 30 min, the solution was heated at 50 °C for 2 h. After cooling to −78 °C, dioxinone ketone **284a** (3.00 g, 16.3 mmol) in THF (10 mL) was added dropwise. After a further 20 min, AcOH (2.42 mL, 42.3 mmol) in THF (10 mL) was added dropwise. Water (100 mL) was added and the mixture extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine, dried (MgSO$_4$), rotary evaporated, and chromatographed (CH$_2$Cl$_2$/MeOH/AcOH, 99:0.9:0.1 to 95:4.9:0.1) to give carboxylic acid **479e** (2.00g, 38%, 1.0 : 0.8 dr) as a yellow oil. IR (cm^{-1}): 1702, 1626, 1497, 1455, 1390, 1375, 1275, 1257, 1200, 1175, 1088, 1016, 906, 810, 725, 700, 644, 624. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.32–7.44 (m, 9.0 H), 5.40 (s, 1.0 H), 5.29 (s, 0.8 H), 3.75 (s, 0.8 H), 3.72 (s, 1.0 H), 2.59 (s, 2.0 H), 2.49 (d, J = 14.2 Hz, 0.8 H), 2.16–2.22 (m, 0.8 H), 1.72 (s, 3 H), 1.71 (s, 3 H), 1.69, (s, 2.4 H) 1.68 (s, 2.4 H), 1.42 (s, 2.4 H), 1.11 (s, 3.0 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 177.3, 177.0, 168.3, 168.1, 161.6, 161.4, 133.9, 133.8, 129.8, 129.7, 128.7, 128.6, 128.3, 128.2, 106.9, 106.7, 96.6, 96.6, 73.5, 73.2, 59.9, 58.6, 45.8, 42.6, 26.5, 25.2, 25.0, 24.7. MS (ES) *m/z*: 362 [M + MeCN + H]$^+$, 338 [M + NH$_4$]$^+$, 321 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{17}$H$_{21}$O$_6$: 321.1338 [M + H]$^+$; found: 321.1365.

1.25.13.150 Benzyl acetate (**480a**)[271]

4-Dimethylaminepyridine (244 mg, 2 mmol) was added to phenylacetic acid (2.72 g, 20 mmol), benzyl alcohol (2.28 mL, 22 mol), and EDCI (4.22g, 22 mmol) at 0 °C and then stirred at 25 °C for 3 h. The mixture was diluted with CH$_2$Cl$_2$ and washed with 1 M aqueous HCl (× 2), water, brine, dried (MgSO$_4$), rotary evaporated and chromatographed (pentane/Et$_2$O, 99:1 to 97: 3) to give the title compound (4.43 g, 98%) as a pale yellow oil. In agreement with the literature. IR (cm^{-1}): 1736, 1498, 1456, 1380, 1362, 1222, 1081, 1025, 964, 921, 903, 836, 736, 696, 643, 611. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.31–7.43 (m, 5H), 5.12 (s, 2H), 2.12 (s, 3H). MS (CI) *m/z*: 168 [M+NH$_4$]$^+$. HR-MS (CI) *m/z*: calcd for C$_9$H$_{14}$NO$_2$: 168.1025 [M+NH$_4$]$^+$; found: 168.1029. In agreement with the literature.

1.25.13.151 Benzyl propionate (**480b**)[272]

Triethylamine (21.0 mL, 150 mmol) was added dropwise to a stirred solution of benzyl alcohol (5.17 mL, 50 mmol) and propionic anhydride (9.62 mL, 75 mmol) in CH_2Cl_2 (50 mL) at 0 °C. After stirring for 2 h at 25 °C, saturated ammonium chloride was added and the organics washed with water, brine, dried ($MgSO_4$), and rotary evaporated to give the title compound (8.00 g, 98%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.46–7.29 (m, 5 H), 5.15 (s, 2 H), 2.41 (q, J = 7.5 Hz, 2 H), 1.19 (t, J = 7.6 Hz, 3 H). In agreement with the literature.

1.25.13.152 Benzyl 2-phenylacetate (480c)[273]

EDCI (4.22g, 22 mmol) was added with stirring to phenylacetic acid (2.72 g, 20 mmol), benzyl alcohol (2.28 mL, 22 mmol) and DMAP (244 mg, 2.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After stirring for 3 h at 25 °C, the mixture was diluted with CH_2Cl_2, washed with 1 M aqueous HCl ($\times$ 2), water, and brine, dried ($MgSO_4$), rotary evaporated and chromatographed (pentane/Et_2O, 99:1 to 97:3) to give the title compound (4.43 g, 98%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.44–7.29 (m, 10 H), 5.18 (s, 2 H), 3.72 (s, 2 H). In agreement with the literature.

1.25.13.153 5-Hydroxy-8-isobutyryl-2,2,6-trimethyl-4H-benzo[d][1,3]dioxin-4-one (482)
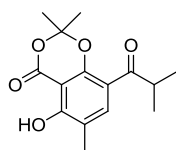
Ghosez's reagent (22 µL, 0.161 mmol) was added to 4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)-2-methylbut-3-enoic acid ($\pm$) (28 mg, 0.124 mmol) in CH_2Cl_2 (1.5 mL) and the mixture stirred for 12 h. The mixture was poured into saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), rotary evaporated and chromatographed (pentane/Et_2O, 19:1 to 9:1) to give the title compound (5 mg, 15%) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 11.19 (s, 1 H), 7.87 (s, 1 H), 3.40 (spt, J = 6.8 Hz, 1 H), 2.22 (s, 3 H), 1.82 (s, 6 H), 1.16 ppm (d, J = 6.8 Hz, 6 H).^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 202.4, 165.7, 163.4, 152.8, 139.9, 121.0,

117.2, 107.4, 98.1, 39.5, 25.7, 18.7, 14.8. MS (CI) *m/z*: 279 [M+H]$^+$. HR-MS (CI) *m/z*: calcd for $C_{15}H_{19}O_5$: 279.1232[M+H]$^+$; found: 279.1239.

1.25.13.154   6-(1-(2,3-Dimethyl-4-oxooxetan-2-yl)-2-phenylethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (±) (483a)
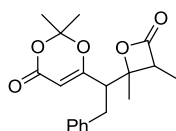
According to general procedure **K**, attempted aromatization of carboxylic acid **479d** (85 mg, 0.24 mmol) and chromatography (pentane/Et$_2$O, 7:3 to 1:1) gave β-lactone **483a** (50 mg, 62%, 1.0 : 0.15 dr) as a colorless solid; decomposition (-CO$_2$) 104 °C (CH$_2$Cl$_2$–pentane). IR (cm^{-1}): 1815, 1723, 1634, 1499, 1454, 1376, 1273, 1253, 1199, 1041, 1014, 958, 901, 809, 744, 721, 700, 649, 616. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) (data for major diastereoisomer only) *δ*: 7.19–7.32 (m, 3 H), 7.13–7.18 (m, 2 H), 5.19 (s, 1 H), 3.66 (q, *J* = 7.8 Hz, 1 H), 3.04–3.15 (m, 1 H), 2.86–2.97 (m, 2 H), 1.58 (s, 6 H), 1.58 (s, 3 H), 1.30 (d, *J* = 7.8 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) (data for major diastereoisomer only) *δ*: 170.7, 167.2, 160.0, 137.2, 128.7, 128.5, 127.0, 107.0, 97.0, 81.4, 55.4, 52.1, 32.5, 25.3, 24.6, 17.7, 9.2. MS (ES) *m/z*: 372 [M + MeCN + H]$^+$, 348 [M + NH$_4$]$^+$, 331 [M + H]$^+$. HR-MS (ES) *m/z* calcd for $C_{19}H_{23}O_5$: 331.1545 [M+H]$^+$; found: 331.1544.

1.25.13.155   2,2-Dimethyl-6-((2-methyl-4-oxo-3-phenyloxetan-2-yl)methyl)-4*H*-1,3-dioxin-4-one (±) (483b)
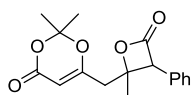
According to general procedure **K**, attempted aromatization of carboxylic acid **479e** (547 mg, 1.71 mmol) and chromatography (pentane/Et$_2$O, 1:1 to 0:1) gave β-lactone **483b** (160 mg, 31%, 1.0 : 0.25 dr) as a yellow oil. IR (cm^{-1}): 1818, 1722, 1633, 1496, 1455, 1392, 1378, 1343, 1327, 1303, 1279, 1252, 1202, 1174, 1149, 1111, 1075, 1041, 1014, 972, 948, 905, 848, 831, 802, 729, 699, 648. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) (data for major diastereoisomer only) *δ*: 7.37–7.43 (m, 3 H), 7.20–7.25 (m, 2 H), 5.45 (s, 1 H), 4.88 (s, 1 H), 2.93–2.94 (m, 2 H), 1.76 (s, 3 H), 1.73(s, 3 H), 1.28 (s, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) (data for major diastereoisomer only) *δ*: 167.9, 165.4, 160.2, 130.5, 129.1, 128.6, 128.3, 107.3, 97.1,

80.7, 63.5, 44.6, 25.4, 24.8, 21.4. MS (ES) *m/z*: 344 [M + MeCN + H]$^+$, 320 [M + NH$_4$]$^+$, 303 [M + H]$^+$. HR-MS (ES) *m/z* calcd for C$_{17}$H$_{19}$O$_5$: 303.1232 [M + H]$^+$; found: 303.1236.

1.25.13.156   Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (**484**)[274]
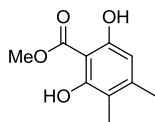
Caesium carbonate (60 mg, 0.18 mmol) was added to 5-hydroxy-2,2,6,7-tetramethyl-4H-benzo[d][1,3]dioxin-4-one (20.0 mg, 0.09 mmol) in methanol (0.2 mL) and stirred for 7 h. The mixture was rotary evaporated and partitioned between ether and saturated aqueous NH$_4$Cl. The organics were washed with brine, dried (MgSO$_4$), rotary evaporated and chromatographed (pentane/Et$_2$O, 19:1) to give the title compound (15 mg, 85%) as a colourless solid; mp 104–105 °C (CH$_2$Cl$_2$–pentane). IR (cm^{-1}): 1665, 1633, 1575, 1429, 1387, 1337, 1310, 1248, 1209, 1152, 1095, 1074, 1008, 978, 936, 860, 799, 778, 736, 632. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.17 (br. s, 1 H), 9.20 (br. s, 1 H), 6.34 (s, 1 H), 4.06 (s, 3 H), 2.23 (s, 3 H), 2.07 (s, 3 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 170.4, 158.1, 157.8, 147.1, 115.4, 109.3, 97.6, 52.8, 21.0, 11.0. MS (CI) *m/z*: 197 [M+H]$^+$. HR-MS (CI) *m/z* calcd for C$_{10}$H$_{13}$O$_4$: 197.0814 [M+H]$^+$; found: 197.0820. In agreement with the literature.

1.25.13.157   2,2,7-Trimethyl-5-(pyrrolidin-1-yl)-4H-benzo[d][1,3]dioxin-4-one (**492a**)
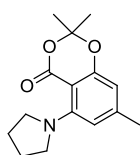
2,2-Dimethyl-6-(2-methyl-4-oxo-4-(pyrrolidin-1-yl)but-1-enyl)-4H-1,3-dioxin-4-one (30 mg, 0.108 mmol) and 2,4,6-collidine (16 µL, 0.118 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise to triflic anhydride (20 µL, 0.118 mmol) in CH$_2$Cl$_2$ (1 mL) at reflux over 1 h and heated for a further 13 h. Mixture poured into saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$, washed with brine, dried (MgSO$_4$) rotary evaporated and chromatographed (pentane/Et$_2$O, 7:3 to 1:1) to give the title compound (7 mg, 25%) as beige oil. IR (cm^{-1}): 1706, 1613, 1552, 1481, 1443, 1388, 1375, 1346, 1323, 1294, 1261, 1232, 1208, 1141, 1105, 1035, 1107, 969, 914, 881, 851, 838, 827, 809, 781, 815, 670, 633, 611. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.26 (s, 1 H), 6.12 (s, 1 H), 3.29– 3.38 (m, 4 H), 2.30 (s, 3 H), 1.93–2.03 (m, 4 H), 1.75 (s, 6

H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 159.2, 157.4, 150.7, 146.4, 107.9, 104.0, 103.6, 97.9, 51.9, 25.9, 25.3, 22.5. MS (ES) m/z: 262 [M+H]$^+$. HR-MS (ES) m/z: calcd for C$_{15}$H$_{20}$NO$_3$: 262.1443 [M+H]$^+$; found: 262.1446.

1.25.13.158   2,2-Dimethyl-6-(2-methyl-4-oxo-4-(pyrrolidin-1-yl)but-1-enyl)-4H-1,3-dioxin-4-one (498)
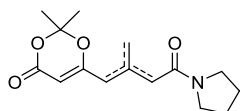
According to general procedure **I**, dehydration of β-hydroxy amide **499** (286 mg, 0.963 mmol) for 3 h and chromatography (pentane/EtOAc, 1:1 to 0:1) gave dioxinone amide **498** (138 mg, 51%, 1.0:1.0:0.7 rr) as a yellow oil. IR (cm^{-1}): 1718, 1627, 1582, 1432, 1388, 1373, 1321, 1272, 1251, 1200, 1014, 964, 901, 872, 805. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.82 (s, 0.7 H), 5.66 (s, 1.0 H), 5.29 (s, 1.0 H), 5.25 (s, 1.7 H), 5.08 (s, 1.0 H), 5.04 (s, 1.0 H), 3.34–3.51 (m, 12.2 H), 3.15 (s, 2 H), 3.10 (s, 2 H), 3.06 (s, 2 H), 2.08–2.11 (m, 3 H), 1.82–2.00 (m, 12.9 H), 1.71 (s, 6 H) 1.65–1.68 (m, 10.2 H) ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 169.3, 168.2, 167.7, 167.6, 164.5, 164.2, 162.0, 161.9, 161.1, 146.3, 146.1, 136.5, 120.3, 120.1, 117.9, 106.5, 106.1, 95.0, 94.8, 94.2, 47.2, 46.9, 46.8, 46.6, 45.9, 45.8, 42.0, 40.3, 40.2, 26.9, 26.1, 25.1, 24.9, 24.3, 19.8. MS (ES) m/z: 302 [M+Na]$^+$, 280 [M+H]$^+$. HR-MS (ES) m/z: calcd for C$_{15}$H$_{21}$NO$_4$Na: 302.1368 [M+H]$^+$; found: 302.1379. Anal. calcd for C$_{15}$H$_{21}$NO$_4$: C 64.50, H 7.58, N 5.01; found: C 64.39, H 6.70, N 5.11.

1.25.13.159   6-(2-Hydroxy-2-methyl-4-oxo-4-(pyrrolidin-1-yl)butyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (499)
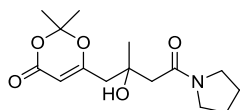
According to general procedure **H** reaction of N-acetyl pyrrolidine (614 mg, 5.43 mmol) and 2,2-dimethyl-6-(2-oxopropyl)-4H-1,3-dioxin-4-one (1.00 g, 5.43 mmol) and chromatography (pentane/EtOAc, 1:1 to 0:1) gave the title compound (413 mg, 26%) as a pale yellow oil. IR (cm^{-1}): 1721, 1613, 1451, 1389, 1373, 1273, 1252, 1202, 1118, 1090, 1014, 971, 901, 860, 911, 783, 613. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.75 (s, 1H), 5.27 (s, 1H), 3.47 (t, J = 6.8 Hz, 2H),

3.36 (t, J = 6.6 Hz, 2H), 2.44–2.60 (m, 3H), 2.35–2.44 (m, 1H), 1.82–2.01 (m, 4H), 1.69 (s, 6H), 1.31 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.7, 168.7, 161.0, 106.4, 95.9, 70.9, 46.7, 45.7, 45.5, 42.7, 27.9, 25.8, 25.2, 25.0, 24.2. MS (ES) m/z: 298 [M+H]$^+$. HR-MS (ES) m/z: calcd for C$_{15}$H$_{24}$NO$_5$: 298.1654 [M+H]$^+$; found: 298.1668. Anal. calcd for C$_{15}$H$_{23}$NO$_5$: C 60.59, H 7.80, N 4.71; found: C 60.47, H 7.89, N 4.82.

1.25.13.160   <u>N-Acetyl pyrrolidine (**500**)[275]</u>

Acetic anhydride (12.29 mL, 130 mmol) and triethylamine (28.0 mL, 200 mL) were added to pyrrolidine (8.27 mL, 100 mmol) in CH$_2$Cl$_2$ (100 mL) and stirred for12 h. The mixture was washed with saturated aqueous NH$_4$Cl (× 2), water, brine, dried (MgSO$_4$), and rotary evaporated to give the title compound (5.00 g, 44%) as a pale pink oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 3.34–3.46 (m, 4H), 2.01 (s, 3H), 1.87–1.97 (m, 2H), 1.76–1.87 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 169.0, 47.3, 45.4, 26.0, 24.5, 22.4. MS (APCI) m/z: 114 [M+H]$^+$. HR-MS (APCI) m/z: calcd for C$_{16}$H$_{12}$NO: 114.0913 [M+H]$^+$; found: 114.0914. In agreement with the literature.

1.25.13.161   <u>(E)-*tert*-Butyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)vinylcarbamate (**503**)</u>
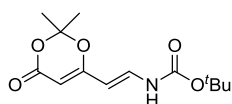
(E)-isopropyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)vinylcarbamate (158 mg, 0.709 mmol) was heated with *tert*-butanol (3.40 mL, 35.43 mmol) in toluene (7 mL) at 75 °C for 3 h. The mixture was rotary evaporated and chromatographed (pentane/ether, 4:1 to 1:1) to give the title compound (142 mg, 75%) as a colourless solid. IR (cm^{-1}): 1730, 1730, 1691, 1628, 1501, 1458, 1392, 1376, 1303, 1248, 1227, 1203, 1143, 1108, 1052, 1017, 974, 961, 908, 879, 848, 796, 759, 730, 678, 660, 609. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.48 (t, J = 12.7 Hz, 1H), 6.91 (d, J = 11.7 Hz, 1H), 5.45 (d, J = 14.2 Hz, 1H), 5.14 (s, 1H), 1.70 (s, 6H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 164.2, 162.2, 151.8, 133.6, 106.1, 100.7, 91.2, 82.5, 28.1, 25.0. MS (ES) m/z: 270 [M+H]$^+$. HR-MS(ES) m/z: calcd for C$_{13}$H$_{20}$NO$_5$: 270.1341

[M+H]$^+$; found: 270.1339. Anal. calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20; found: C, 57.85; H, 7.21; N, 5.07.

1.25.13.162   (E)-2,2-Dimethyl-6-(4-oxo-4-(pyrrolidin-1-yl)but-1-enyl)-4H-1,3-dioxin-4-one (**505**)
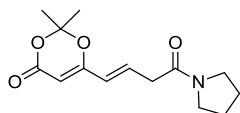
EDCI (99 mg, 0.52 mmol) was added to (E)-4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)but-3-enoic acid (100 mg, 0.47 mmol), pyrrolidine (43 µL, 0.52 mmol) and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) and stirred for 4 h. The mixture was diluted with CH_2Cl_2, washed with 1 M aqueous HCl (× 2), saturated aqueous NaHCO$_3$ and brine, dried (MgSO$_4$), rotary evaporated and chromatographed (EtOAc) to give the title compound (70 mg, 56%) as a pale yellow amorphous solid. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.73 (dt, J = 15.7, 7.0 Hz, 1 H), 5.99 (d, J = 15.7 Hz, 1 H), 5.26 (s, 1 H), 3.45 (dt, J = 19.4, 6.9 Hz, 4 H), 3.22 (d, J = 7.0 Hz, 2 H), 1.98 (p, J = 6.7 Hz, 2 H), 1.87 (p, J = 6.7 Hz, 2 H), 1.69 (s, 6 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 167.8, 162.8, 162.0, 134.8, 125.0, 106.6, 94.4, 46.9, 46.0, 38.6, 26.2, 25.1, 24.5. MS (CI) *m/z*: 266 [M+H]$^+$. HR-MS (CI) *m/z* calcd for $C_{14}H_{20}NO_4$: 266.1391 [M+H]$^+$; found: 266.1392.

1.25.13.163   (E)-6-(2-(5,5-Dichloro-4-oxo-2-(pyrrolidin-1-yl)-4,5-dihydrofuran-3-yl)vinyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (**506**)
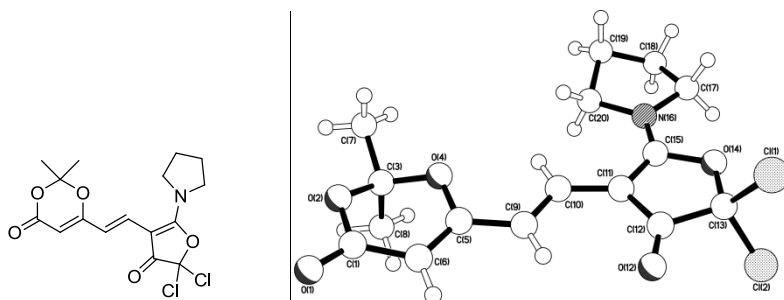
(E)-2,2-Dimethyl-6-(4-oxo-4-(pyrrolidin-1-yl)but-1-enyl)-4H-1,3-dioxin-4-one (28.0 mg, 0.106 mmol) and oxalyl chloride (18 µL, 0.21 mmol) were refluxed in CH_2Cl_2 (1 mL) for 2.5 h then rotary evaporated and chromatographed (pentane/EtOAc, 1:1 to 2:3) to give the title compound (35 mg, 89%) as a colourless solid. IR (cm^{-1}) 1709, 1598, 1450, 1380, 1372, 1353, 1267, 1250, 1201, 1169, 1083, 1020, 953, 922, 842, 814, 800, 742, 724, 712, 698, 666, 651. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 7.20 (d, J = 15.4 Hz, 1 H), 7.06 (d, J = 15.0 Hz, 1 H), 5.34 (s, 1 H), 3.86 (br. s, 4 H), 2.22 (br. s, 2 H), 2.08

(br. s, 2 H), 1.73 (s, 6 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 183.1, 168.0, 164.3, 162.3, 124.1, 117.6, 106.1, 103.5, 93.4, 87.2, 50.3, 49.4, 26.3, 25.3, 24.1.

1.25.13.164   (E)-*tert*-Butyl 3-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acrylate (**507**)
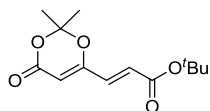
2,2-Dimethyl-6-vinyl-1,3-dioxan-4-one (300 mg, 1.95 mmol) and *tert*-butyl acrylate (856 µL, 5.84 mmol) in CH$_2$Cl$_2$ (20 mL) were refluxed in the presence of catalyst **427a** (20 mg, 0.032 mmol) for 24 h. The mixture was rotary evaporated and chromatographed (pentane/Et$_2$O, 17:3 to 4:1) to give the title compound (368 mg, 74 %) as a colourless solid. IR (cm^{-1}): 1705, 1644, 1590, 1401, 1392, 1378, 1368, 1274, 1257, 1245, 1206, 1160, 1097, 1025, 980, 909, 857, 844, 811, 785, 739. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.93 (d, J = 15.7 Hz, 1 H), 6.47 (d, J = 15.7 Hz, 1 H), 5.57 (s, 1 H), 1.73 (s, 6 H), 1.51 (s, 9 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 164.3, 160.9, 160.8, 133.9, 128.7, 107.0, 99.3, 81.8, 28.0, 25.0. MS (EI) *m/z*: 296 [M+MeCN]$^{+}$, 255 [M+H]$^{+}$. HR-MS (EI) *m/z*: calcd for C$_{13}$H$_{19}$O$_5$: 255.1232 [M+H]$^{+}$; found: 255.1229. Anal. calcd for C$_{13}$H$_{18}$O$_5$: C 61.40, H 7.14; found: C 61.28, H 7.24.

1.25.13.165   (E)-3-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acrylic acid (**508**)
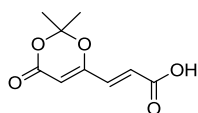
According to general procedure **G**, deprotection of ester **507** (150 mg, 0.591 mmol) for 16 h gave the title compound (111 mg, 92 %) as a colourless solid. IR (cm^{-1}): 1720, 1689, 1645, 1592, 1422, 1392, 1377, 1311, 1275, 1259, 1206, 1096, 1025, 976, 965, 944, 911, 891, 871, 855, 807, 743, 713, 643. ^{1}H NMR (400 MHz, THF-d_8, ppm) δ: 11.42 (br. s., 1 H), 7.09 (d, J = 15.6 Hz, 1 H), 6.46 (d, J = 15.7 Hz, 1 H), 5.69 (s, 1 H), 1.69 (s, 6 H). ^{13}C NMR (101 MHz THF-d_8, ppm) δ: 166.5, 161.5, 160.2, 136.1, 127.5, 107.6, 100.9, 25.1. MS (EI) *m/z*: 199 [M+H]$^{+}$. HR-MS (EI) *m/z*: calcd for C$_9$H$_{11}$O$_5$: 199.0606 [M+H]$^{+}$; found: 199.0610. Anal. calcd for C$_9$H$_{10}$O$_5$: C 54.55, H 5.09; found: C 54.03, H 5.64.

1.25.13.166   (E)-3-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acryloyl azide (**509**)
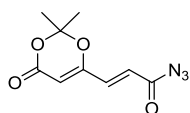
Ghosez's reagent (321 µL, 2.42 mmol) was added dropwise to (E)-3-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acrylic acid (400 mg, 2.02 mmol) in THF (5 mL) and stirred for 10 min. This mixture was then added to a vigourously stirred mixture of sodium azide in water. After 5 min, the mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ (× 7), dried ($MgSO_4$), rotary evaporated and chromatographed (pentane/Et_2O, 3:1) to give the title compound (220 mg, 49%) as a colourless solid. IR (cm^{-1}): 1722, 1675, 1637, 1586, 1393, 1375, 1288, 1270,1249, 1204, 1176, 1155, 1125, 1104, 1078, 1018, 1005, 981, 963, 905, 877, 856, 821, 784, 741, 718, 648, 605. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.09 (d, J = 15.6 Hz, 1H), 6.51 (d, J = 15.2 Hz, 1H), 5.65 (s, 1H), 1.74 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 170.7, 160.4, 159.9, 136.3, 126.9, 107.3, 101.0, 25.0. MS (CI) m/z: 256 [M+H]$^+$. HR-MS (CI) m/z: calcd for $C_{12}H_{18}NO_5$: 256.1185 [M+H]$^+$; found: 256.1190. Anal. calcd for $C_9H_9N_3O_4$: C 48.43, H 4.06, N 18.83; found: C 48.59, H 3.97, N 18.75.

1.25.13.167   (E)-Isopropyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)vinylcarbamate (510) and (Z)-Isopropyl 5-(isopropoxycarbonylamino)-3-oxopent-4-enoate (511)
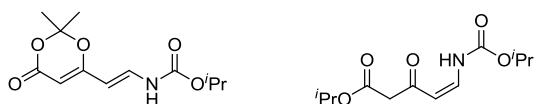
(E)-Isopropyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)vinylcarbamate (30 mg, 0.135 mmol) was heated with *iso*-propanol (584 µL, 7.65 mmol) in toluene (3 mL) at 75 °C for 12 h. The mixture was rotary evaporated and chromatographed (pentane/ether, 4:1 to 1:1) to give (E)-isopropyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)vinylcarbamate (26 mg, 76%) as a colourless solid and (Z)-isopropyl 5-(isopropoxycarbonylamino)-3-oxopent-4-enoate (3 mg, 9%).

(E)-Isopropyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)vinylcarbamate (510): IR (cm^{-1}): 1731, 1695, 1630, 1502, 1375, 1295, 1254, 1225, 1203, 1168, 1102, 1043, 1021, 966, 909, 844, 799, 735, 679, 611. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.48 (app. t, J = 12.7 Hz, 1H), 7.14 (d, J = 12.2 Hz, 1H), 5.50 (d, J = 13.7 Hz, 1H), 5.15 (s, 1H), 5.02 (spt, J = 6.3 Hz, 1H), 1.71 (s, 6H), 1.29 (d, J = 6.4 Hz, 6H), ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 164.2, 162.2, 152.6, 133.5, 106.2, 101.3, 91.4, 70.5, 25.0, 21.9. MS (ES) m/z: 241 [M+NH$_4$]$^+$, 224 [M+H]$^+$. HR-

MS (ES) m/z: calcd for $C_9H_{13}N_4O_4$: 241.0937$[M+H]^+$; found: 241.0931. Anal. calcd for $C_{12}H_{17}NO_5$: C 56.46, H 6.71, N 5.49; found: C 56.32, H 6.78, N, 5.62.

(Z)-Isopropyl 5-(isopropoxycarbonylamino)-3-oxopent-4-enoate (**511**): IR (cm^{-1}): 1734, 1662, 1591, 1470, 1387, 1376, 1311, 1257, 1223, 1196, 1180, 1146, 1094, 1046, 972, 916, 828, 773, 727. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.59 (d, J = 10.8 Hz, 1H), 7.30 (dd, J = 12.0, 8.6 Hz, 1H), 5.51 (d, J = 8.3 Hz, 1H), 4.97–5.13 (m, 2H), 3.43 (s, 2H), 1.27 (d, J = 6.4 Hz, 6H), 1.30 (2 × s, J = 6.4 Hz, 6H). MS (ES) m/z: 258 $[M+H]^+$. HR-MS (ES) m/z: calcd for $C_{12}H_{20}NO_5$: 258.1341$[M+H]^+$; found: 258.1342.

1.25.13.168 Isopropyl 3,6-dihydroxybiphenyl-2-carboxylate (514a)
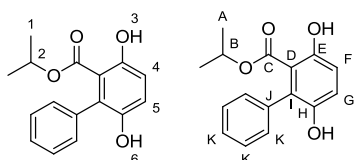
According to general procedure **D**, dione **433a** (50 mg, 0.175 mmol) gave, after chromatography (hexanes/Et$_2$O, 9:1 to 7:3) the title compound (15 mg, 32%) as a pale yellow solid. IR (cm^{-1}): 1678, 1662, 1597, 1559, 1365, 1317, 1290, 1216, 1176, 1099, 895, 826, 767, 728, 699. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.74 (s, 1 H, **3**), 7.39–7.51 (m, 3 H, **Ar-H**), 7.20–7.25 (m, 2 H, **Ar-H**), 7.13 (d, J = 8.8 Hz, 1 H, **5×**), 6.98 (d, J = 9.3 Hz, 1 H, **4**), 4.92 (spt, J = 6.3 Hz, 1 H, **2**), 4.52 (s, 1 H, **6**), 0.80 (d, J = 6.4 Hz, 6 H, **1**). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 169.9 (q, **C**), 156.0 (q, **E**), 145.8 (q, **H**), 136.5 (q, **J**), 129.5 (CH, **K**), 129.0 (CH, **K**), 127.9 (CH, **K**), 127.4 (q, **I**), 122.5 (CH, **F**), 118.3 (CH, **G**), 111.9 (q, **D**), 68.9 (CH, **B**), 20.9 (CH, **A**). MS (CI) m/z: 290 $[M+NH_4]^+$, 273 $[M+H]^+$. HR-MS (CI) m/z calcd for $C_{16}H_{16}O_4$: 273.1127 $[M+H]^+$; found: 273.1138. Anal. calcd for $C_{16}H_{16}O_4$: C 70.57, H 5.92; found: C 70.43; H 6.05. A HMBC NMR spectrum is provided in the additional NMR spectra section.

1.25.13.169 Propyl 3,6-dihydroxybiphenyl-2-carboxylate (514b)
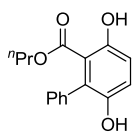
According to general procedure **D** with n-propanol, dione **433a** (50 mg, 0.175 mmol) gave, after chromatography (hexanes/Et$_2$O, 9:1 to 7:3) the title compound (15 mg, 31%) as a pale yellow solid.

IR (cm^{-1}): 1656, 1594, 1458, 1442, 1400, 1350, 1324, 1287, 1228, 1208, 1180, 1161, 1142, 133, 1088, 889, 840, 828, 806, 762, 731, 699. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.69 (s, 1 H), 7.39–7.50 (m, 3 H), 7.20–7.26 (m, 2 H), 7.14 (d, J = 8.8 Hz, 1 H), 6.99 (d, J = 8.8 Hz, 1 H), 4.53 (s, 1 H), 3.86 (t, J = 6.6 Hz, 2 H), 1.00–1.12 (m, 2 H), 0.59 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.7, 156.1, 145.8, 136.4, 129.4, 129.0, 128.0, 127.3, 122.7, 118.4, 111.6, 66.9, 21.0, 10.3. MS (CI) m/z: 290 [M+NH$_4$]$^+$., 273 [M+H]$^+$. HR-MS (CI) m/z calcd for C$_{16}$H$_{17}$O$_4$: 273.1127 [M+H]$^+$; found: 273.1117. Anal. calcd for C$_{16}$H$_{16}$O$_4$: C 70.57, H 5.92; found: C 70.53, H 6.01.

1.25.13.170 Isopropyl 3,6-dihydroxy-4'-methoxybiphenyl-2-carboxylate (514c)
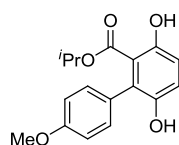
According to general procedures **L** and **D** (*E*)-6-(4-Hydroxy-4-(4-methoxyphenyl)but-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (274 mg, 0.9 mmol) gave the title compound (40 mg, 15%) as a brown oil. IR (cm^{-1}): 3512, 1655, 1611, 1514, 1455, 1361, 1321, 1289, 1248, 1197, 1168, 1135, 1102, 1086, 1024, 830, 813, 803, 791, 722. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.69 (s, 1 H), 7.10–7.16 (m, 3 H), 6.98–7.04 (m, 2 H), 6.96 (d, J = 8.8 Hz, 1 H), 4.94 (spt, J = 6.3 Hz, 1 H), 4.58 (s, 1 H), 3.88 (s, 3 H), 0.86 (d, J = 5.9 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 170.0, 159.6, 155.9, 146.1, 130.7, 128.3, 127.1, 122.2, 118.2, 114.5, 112.4, 68.8, 55.4, 21.1. MS (EI) m/z: 303 [M+H]$^+$. HR-MS (EI) m/z: calcd for C$_{17}$H$_{19}$O$_5$: 303.1232 [M+H]$^+$; found: 303.1243.

1.25.13.171 Isopropyl 4'-bromo-3,6-dihydroxybiphenyl-2-carboxylate (514d)
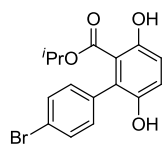
According to general procedure **L** and **D** (*E*)-6-(4-Hydroxy-4-(4-bromophenyl)but-1-enyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (318 mg, 0.9 mmol) gave the title compound (47 mg, 15%) as a brown oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 10.78 (s, 1 H), 7.60–7.65 (m, 2 H), 7.10–7.15 (m, 3 H), 6.99 (d, J = 8.8 Hz, 1 H), 4.95 (spt, J = 6.2 Hz, 1 H), 4.38 (s, 1 H), 0.87 (d, J = 6.4 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 169.7, 156.3, 145.5, 135.6, 132.1,

131.3, 126.1, 122.9, 122.1, 118.8, 111.7, 69.2, 21.0. MS (EI) *m/z*: 352 [M^{81}]$^+$, 350 [M^{79}]$^+$. HR-MS (EI) *m/z* calcd for C$_{16}$H$_{15}$BrO$_5$: 350.0154[M+H]$^+$; found: 350.0155.

1.25.13.172 (E)-6-(3-Hydroxy-3-(2-(4-methoxyphenyl)-1,3-dithian-2-yl)prop-1-enyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (516a)
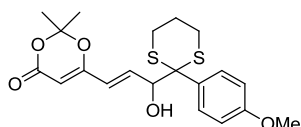
n-BuLi (76 µL, 0.181 mmol) was added to 2-(4-methoxyphenyl)-1,3-dithiane **xx** (41 mg, 0.181 mmol) at −78 °C and then stirred at −30 °C for 5 min. (E)-3-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acrylaldehyde (30 mg, 0.165 mmol) in THF (2 mL) was added at −78 °C and stirred for 10 min then poured into water. The mixture was extracted with ether (× 2), washed with brine, dried (MgSO$_4$), rotary evaporated and chromatographed (pentane/Et$_2$O, 3:1, 1:1) to give the title compound (11 mg, 16%) as a colourless impure oil. IR (cm^{-1}): 1720, 1654, 1603, 1505, 1391, 1251, 1033. ^{1}H NMR (400 MHz, CDCl$_3$, ppm)(product peaks only) *δ*: 7.85–7.80 (m, 2 H), 6.99–6.88 (m, 2 H), 6.47 (dd, *J* = 15.2, 4.9 Hz, 1 H), 6.10 (dd, *J* = 15.7, 1.7 Hz, 1 H), 5.29 (s, 1 H), 4.53 (dd, *J* = 4.9, 1.5 Hz, 1 H), 3.85 (s, 3 H), 2.82–2.66 (m, 4 H), 2.63 (d, *J* = 4.9 Hz, 1 H), 2.01–1.92 (m, 2 H), 1.69 (s, 6 H). MS (EI) *m/z*: 431 [M+Na]$^+$, 409 [M+H]$^+$. HR-MS (EI) *m/z*: calcd for C$_{20}$H$_{25}$S$_2$O$_5$: 409.1143 [M+H]$^+$; found: 409.1148.

1.25.13.173 (E)-3-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acrylaldehyde (518)
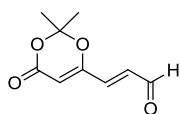
2,2-Dimethyl-6-vinyl-1,3-dioxan-4-one (100 mg, 0.649 mmol) and acrolein (128 µL, 1.948 mmol) in CH$_2$Cl$_2$ (6.5 mL) were refluxed in the presence of catalyst **427a** (20 mg, 0.032 mmol) for 16 h. The mixture was rotary evaporated and chromatographed (pentane/Et$_2$O, 4:1 to 1:1) to give the title compound (49 mg, 41%) as a pale yellow solid. IR (cm^{-1}): 1711, 1669, 1638, 1582, 1388, 1375, 1273, 1261, 1236, 1201, 1118, 1092, 1020, 985, 967, 905, 872, 860, 825. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) *δ*: 9.74 (d, *J* = 7.3 Hz, 1 H), 6.89 (d, *J* = 16.1 Hz, 1 H), 6.73 (dd, *J* = 7.3, 15.6 Hz, 1 H), 5.71 (s, 1 H), 1.76 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) *δ*: 191.8,

160.3 (2C), 140.7, 134.2, 107.4, 100.8, 25.0. MS (EI) m/z: 183 [M+H]$^+$, 182 [M]$^+$. HR-MS (EI) m/z: calcd for $C_9H_{10}O_4$: 182.0579 [M]$^+$; found: 182.0584.

1.25.13.174   1-(1,3-Dithian-2-yl)prop-2-en-1-ol (**517**)[276]
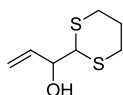
n-Buli (3.81 mL, 9.15 mmol) was added dropwise to 1,3-dithiane (1.00 g, 8.32 mmol) at −30 °C and stirred for 1 h. Acrolein (1.64 mL, 25 mmol) was added dropwise at −78 °C and stirred for 0.5 h then saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc (× 2), washed with brine, dried ($MgSO_4$), rotary evaporated and chromatographed (pentane/EtOAc, 17:3 to 4:1) to give the title compound (1.124 g, 77%) as a colourless oil. IR (cm^{-1}): 1421, 1276, 1244, 1126, 1108, 1023, 986, 826, 873, 790, 665. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.07–5.92 (m, 1 H), 5.49–5.39 (m, 1 H), 5.34–5.23 (m, 1 H), 4.43–4.30 (m, 1 H), 3.96 (d, J = 6.4 Hz, 1 H), 3.02–2.88 (m, 2 H), 2.85–2.70 (m, 2 H), 2.54 (d, J = 3.9 Hz, 1 H), 2.19–1.90 (m, 2 H). MS (ES) m/z: 176 [M-H]$^+$. HR-MS (ES) m/z: calcd for $C_7H_{11}S_2O$: 175.0251 [M-H]$^+$; found: 175.0253. In agree ment with the literature.

1.25.13.175   (E)-6-(3,3-Diethoxyprop-1-enyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (**520**)
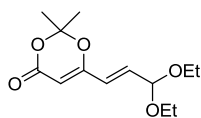
According to general procedure **F**, cross metathesis of acrolein diethylacetal (148 µL, 0.974 mmol) and dioxinone **372a** (50.0 mg, 0.325 mmol) with catalyst **427a** (20.3 mg, 0.03 mmol) in $C_6F_5CF_3$ (3.5 mL) at 70 °C for 6 h and chromatography (pentane/Et$_2$O, 9:1 to 4:1) gave the title compound (55 mg, 66%) as a pale yellow oil. IR (cm^{-1}): 1725, 1660, 1596, 1390, 1373, 1273, 1203, 1174, 1120, 1094, 1051, 1018, 961, 902, 854, 803. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 6.42 (dd, J = 15.7, 4.2 Hz, 1 H), 6.21 (dd, J = 15.8, 1.4 Hz, 1 H), 5.35 (s, 1 H), 5.03 (dd, J = 4.3, 1.3 Hz, 1 H), 3.63 (dq, J = 9.4, 7.0 Hz, 2 H), 3.50 (dq, J = 9.3, 7.0 Hz, 2 H), 1.68 (s, 6 H), 1.21 (t, J = 7.1 Hz, 6 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 162.3, 161.6, 136.8, 124.9, 106.7, 99.4, 95.9, 61.5, 25.1, 15.3. MS (CI) m/z:

274 [M+NH$_4$]$^+$, 257 [M+H]$^+$. HR-MS (CI) *m/z* calcd for C$_{13}$H$_{21}$O$_5$: 257.1389 [M+H]$^+$; found: 257.1379.

1.25.13.176 (1-(1,3-Dithian-2-yl)allyloxy)(tert-butyl)dimethylsilane (**522**)[277]
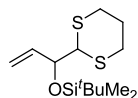
4-Dimethylaminopyridine (10 mg, 0.082 mmol) was added to a mixture of 1-(1,3-dithian-2-yl)prop-2-en-1-ol (300 mg, 1.70 mmol), imidazole (151 mg, 2.22 mmol) and *tert*-butyldimethylsilyl chloride (283 mg, 1.875 mmol) in DMF (0.6 mL) and stirred for 3 h, before addition of 1M aqueous HCl. The mixture was extracted with ether (× 3) and washed with saturated aqueous NaHCO$_3$, water, brine, dried (MgSO$_4$) , rotary evaporated and chromatographed (pentane/Et$_2$O, 19:1 to 9:1) to give the title compound (410 mg, 83%) as a colourless oil. IR (cm^{-1}): 1472, 1463, 1422, 1261, 1276, 1251, 1078, 1034, 1006, 986, 928, 909, 876, 854, 834, 775, 670, 627. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) *δ*: 5.93 (ddd, *J* = 17.0, 10.3, 6.6 Hz, 1 H), 5.34–5.18 (m, 2 H), 4.34–4.22 (m, 1 H), 4.14 (d, *J* = 6.1 Hz, 1 H), 2.97–2.73 (m, 4 H), 2.17–2.03 (m, 1 H), 1.98–1.77 (m, 1 H), 0.94 (s, 9 H), 0.14 (s, 3 H), 0.08 (s, 3 H). ^{13}C NMR (101 MHz, CDCl3, ppm) *δ*: 138.1, 117.0 ,76.7, 53.9, 30.0, 26.1, 25.9, 18.3, -4.3, -4.8.

1.25.13.177 2-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetyl chloride (**551**)
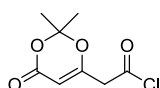
A reactIR spectrometer was used to monitor formation of the title compound. IR measurements (16 scans) were taken every 15 seconds. In a reactor cell 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetic acid (201 mg, 1.08 mmol) was added in CH$_2$Cl$_2$ (27 mL) and cooled to −14 °C. After equilibriation at this temperature, Ghosez's reagent (186 µL, 1.4 mmol) was added. The reaction was then allowed to warm to 25 °C at a rate of 2.5 °C/min and further Ghosezs reagent (186 µL, 1.4 mmol) was added at 25 °C. IR (solution cell, cm^{-1}): 1798, 1737.

1.25.13.178 Benzyl 2,2,6-trimethyl-4-oxo-4H-1,3-dioxine-5-carboxylate (**552**) and Benzyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetate (**553**)[278]
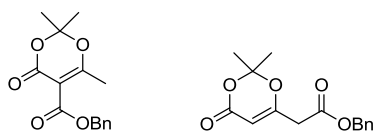
2,2,6-Trimethyl-4H-1,3-dioxin-4-one (1.00 g, 7.04 mmol) was added dropwise to LiN(SiMe₃)₂ (14.79 mmol) at −78 °C in THF (15 mL) and stirred for 30 min. Benzyl chloroformate (1.11 mL, 7.75 mmol) was added dropwise at −94 °C and the mixture allowed to warm to 20 °C over 2 h. The mixture was quenched by addition of 1 M Aqueous HCl and the layers separated. The organics were further extracted with EtOAc (2 × 50 mL) and the combined organics were washed with brine (50 mL), dried (MgSO₄), rotary evaporated and chromatographed (petroleum ether/Et₂O, 4:1 to 1:1) to give Benzyl 2,2,6-trimethyl-4-oxo-4H-1,3-dioxine-5-carboxylate (617 mg, 32%) as a colourless solid and Benzyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetate (804 mg, 42%) as a colourless oil.

Benzyl 2,2,6-trimethyl-4-oxo-4H-1,3-dioxine-5-carboxylate (**552**): IR (cm⁻¹): 1732, 1710, 1583, 1391, 1381, 1354, 1289, 1269, 1216, 1200, 1102, 1088, 1073, 1061, 1034, 1009, 982, 966, 891, 867, 794, 786, 732, 695. ¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.41–7.48 (m, 2 H), 7.29–7.41 (m, 3 H), 5.30 (s, 2 H), 2.29 (s, 3 H), 1.71 (s, 6 H). ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 175.1, 163.8, 157.4, 135.6, 128.5, 128.1, 128.0, 106.3, 101.7, 66.9, 25.1, 20.1. MS (CI) *m/z*: 294 [M+NH₄]⁺, 277 [M+H]⁺. HR-MS (CI) *m/z* calcd for C₁₅H₂₀NO₅: 294.1341 [M+NH4]⁺; found: 294.1333.

Benzyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetate (**553**): IR (cm⁻¹): 1724, 1640, 1391, 1375, 1271, 1201, 1151, 1015, 977, 902, 809, 240, 697. ¹H NMR (400 MHz, CDCl₃, ppm) δ: 7.35–7.38 (m, 5 H), 5.39 (s, 1 H), 5.17 (s, 2 H), 3.31 (s, 2 H), 1.64 (s, 6 H). ¹³C NMR (101 MHz, CDCl₃, ppm) δ: 166.9, 163.5, 160.6, 134.9, 128.7, 128.6, 128.5, 107.2, 96.4, 67.3, 39.4, 24.8, 24.6. MS (CI) *m/z*: 294 [M+NH₄]⁺, 277 [M+H]⁺. HR-MS (CI) *m/z* calcd for C₁₅H₂₀NO₅: 294.1341 [M+NH4]⁺; found: 294.1341. In agreement with the literature.

1.25.13.179   Ethyl 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetate (**554**)[278]
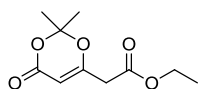
Ghosez's reagent (26 µL, 0.194 mmol) was added to 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetic acid (30 mg, 0.161 mmol) in CH₂Cl₂ (2.0 mL) at 0 °C and stirred for 10 min. EtOH (47 µL, 0.806 mmol) and pyridine (13µL, 0.161 mmol) was then added and after 5 min saturated aqueous NH₄Cl (3 mL) was added. The layers were separated and the organics dried (MgSO₄), rotary evaporated and chromatographed (petroleum ether/Et₂O, 7:3 to 3:2) to give the title compound (15 mg, 44%) as a colourless oil. IR (cm⁻¹) 1725, 1640, 1391, 1375, 1272, 1251, 1201, 1158, 1013, 902, 811. ¹H NMR

(400 MHz, CDCl$_3$, ppm) δ: 5.39 (s, 1 H), 4.20 (q, J = 7.3 Hz, 2 H), 3.26 (s, 2 H), 1.71 (s, 6 H), 1.28 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 167.1, 163.7, 160.7, 107.2, 96.4, 61.7, 39.4, 24.9, 14.1. MS (CI) m/z: 232 [M+NH$_4$]$^+$, 215 [M+H]$^+$. HR-MS (CI) m/z calcd for C$_{10}$H$_{18}$NO$_5$: 232.1185 [M+NH$_4$]$^+$; found: 232.1187. In agreement with the literature.

1.25.13.180   Allyl 2-acetyl-4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (**555**)
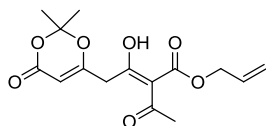
MgCl$_2$ (85 mg, 0.896 mmol) and pyridine (97 µL, 1.209 mmol) were added to allyl 4-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-3-oxobutanoate (120 mg, 0.448 mmol) in CH$_2$Cl$_2$ at 0 °C and stirred for 30 min.

Ghosez's reagent (83 µL, 0.627 mmol) was added to acetic acid in CH$_2$Cl$_2$ (4 mL) at 0 °C and stirred for 10 min. This was then added to the magnesium enolate prepared above and stirred for 10 min at 0 °C followed by addition of saturated aqueous NH$_4$Cl (5 mL). The organics were washed with brine (5 mL) dried (MgSO$_4$), rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 3:7) to give the title compound (100 mg, 79%) as a colourless oil. IR (cm^{-1}): 1721, 1666, 1635, 1391, 1375, 1271, 1251, 1202, 1161, 1064, 1015, 995, 936, 902, 807. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 17.66 (s, 1 H), 5.96 (dd, J = 17.2, 10.2 Hz, 1 H), 5.27–5.41 (m, 3 H), 4.70 (d, J = 5.7 Hz, 2 H), 3.73 (s, 2 H), 2.42 (s, 3 H), 1.68 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 196.0, 193.7, 165.8, 165.1, 160.7, 131.4, 119.6, 108.1, 107.1, 96.4, 65.8, 43.2, 25.5, 24.9. MS (EI) m/z: 310 [M]$^+$. HR-MS (EI) m/z calcd for C$_{15}$H$_{18}$O$_7$: 310.1053 [M]$^+$; found: 310.1049.

1.25.13.181   6-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-5,7-dihydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**557**)
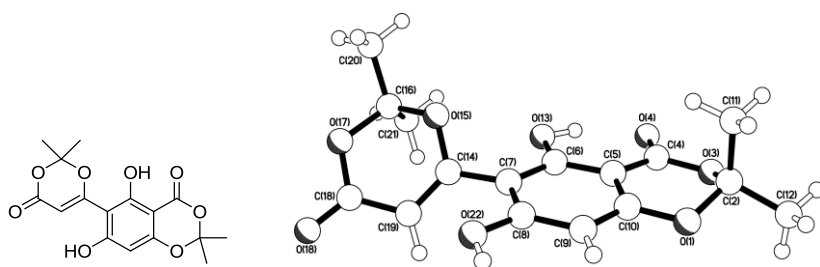
Ghosez's reagent (1.50 mL, 10.68 mmol) was added to 2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)acetic acid (903 mg, 4.85 mmol) at −78 °C and allowed to warm 25 °C over 18 h. The mixture was

rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 1:1 to 0:1) to give a yellow solid. Recrystalization from hot CHCl$_3$/pentane gave the title compound (221 mg, 27%) as a colourless solid. IR (cm^{-1}): 1728, 1682, 1607, 1389, 1316, 1274, 1257, 1194, 1122, 1098, 1017, 1003, 823, 752. ^{1}H NMR (400 MHz, CD$_3$OD, ppm) δ: 6.02 (s, 1 H), 5.54 (s, 1 H), 1.78 (s, 6 H), 1.73 (s, 6 H). ^{13}C NMR (101 MHz, CD$_3$OD, ppm) δ: 166.5, 166.3, 164.2, 163.7, 163.1, 159.8, 108.6, 108.3, 104.3, 99.5, 96.1, 92.9, 25.8, 25.1. MS (ES) m/z: 337 [M+H]$^+$. HR-MS (ES) m/z calcd for C$_{16}$H$_{17}$O$_8$: 337.0923 [M+H]$^+$; found: 337.0925.

1.25.13.182   6-(Chloromethyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (559)[279]
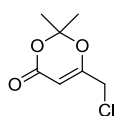
2,2,6-Trimethyl-4H-1,3-dioxin-4-one (8.00 g, 56.3 mmol) was added dropwise to LiN(^{i}Pr)$_2$ (73.2 mmol) at −78 °C in THF (50 mL) and stirred for 1 h. This mixture was then added dropwise *via* cannula to a suspension of hexachloroethane (18.67 g, 78.9 mmol) in THF (75 mL) at −50 °C over 20 min. The mixture was warmed to −20 °C over 1 h and stirred for a further 15 min. The mixture was acidified with cold 1 M aqueous HCl and extracted with Et$_2$O. The combined organics were washed with saturated aqueous NaHCO$_3$ dried (MgSO$_4$), rotary evaporated and chromatographed (petroleum ether/CH$_2$Cl$_2$, 1:1) to give the title compound (5.5 mg, 55%) as a pale yellow oil. IR (cm^{-1}): 1723, 1639, 1390, 1376, 1272, 1249, 1200, 1184, 1013, 902, 808, 740, 656. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 5.55 (s, 1 H), 4.02 (s, 2 H), 1.70 (s, 6 H). ^{13}C NMR (101 MHz, CDCl$_3$, ppm) δ: 164.4, 160.4, 107.5, 95.5, 40.9, 24.7. MS (CI) m/z: 194 [M+NH$_4$]$^+$, 177 [M+H]$^+$. HR-MS (CI) m/z calcd for C$_7$H$_{10}$O$_5$Cl: 177.0318 [M+H]$^+$; found: 177.0322. In agreement with the literature.

1.25.13.183   Methyl 3-(5,7-dihydroxy-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-6-yl)-3-oxopropanoate (561)
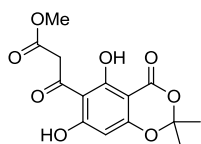
6-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-5,7-dihydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (20 mg, 0.06 mmol) in Methanol (4 mL) was microwave irradiated at 120 °C for 30 min, then rotary evaporated to give the title compound (19 mg, quantitative) as a colourless solid. ^{1}H NMR (400 MHz, THF-d_8, ppm) δ: 14.04 (s, 1 H), 12.54 (s, 1 H), 6.04 (s, 1 H), 4.04 (s, 2 H), 3.66 (s, 3 H),

1.74 (s, 6 H). ^{13}C NMR (101 MHz, THF-d_8, ppm) δ: 199.1, 173.6, 168.4, 167.4, 166.2, 162.0, 108.7, 106.6, 97.5, 92.4, 52.3, 51.0, 25.8.

1.25.13.184 6-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-5-hydroxy-7-methoxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (564)
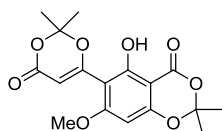
Methyl iodide (6 µL, 0.10 mmol) was added to 6-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-5,7-dihydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (20 mg, 0.06 mmol) and potassium carbonate (83 mg, 0.06 mmol) in acetone (2.4 mL) and refluxed for 6 h, then rotary evaporated to give the title compound (21 mg, quantitative) as a colourless solid. ^{1}H NMR (400 MHz, THF-d_8, ppm) δ: 10.91 (s, 1 H), 6.28 (s, 1 H), 5.39 (s, 1 H), 3.87 (s, 3 H), 1.72 (s, 12H).

1.25.13.185 1-(1-Methyl-1H-pyrrol-2-yl)butane-1,3-dione (572)
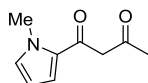
N-Methyl pyrrole (315 µL, 3.52 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (0.50 g, 3.52 mmol) in toluene (14.1 mL) were heated by microwave irradiation at 120 °C for 1.5 h and then rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 19:1) to give the the title compound (358 mg, 62%) as a beige oil. IR (cm^{-1}): 1718, 1616, 1528, 1455, 1375, 1320, 1247 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ: (keto form) 6.96 (m, 1 H), 6.87 (m, 1 H) , 6.15 (m, 1 H), 3.95 (s, 3 H), 3.88 (s, 2 H), 2.28 (s, 3 H); (enol form) 15.62 (br s, 1 H), 6.87 (m, 1 H), 6.81 (m, 1 H), 6.15 (m, 1 H), 5.91(s, 1 H), 3.98(s, 3 H), 2.05 (s, 3 H); ^{13}C NMR (101 MHz, CDCl$_3$) 202.8, 183.8, 183.4, 180.8, 132.4, 131.1, 130.4, 129.3, 121.2, 117.5, 108.7, 108.5, 96.9, 55.7, 37.9, 37.8, 30.4, 22.7; HRMS (EI) m/z calc for C$_9$H$_{12}$NO$_2$ 166.0871 [M+H], found 166.0868.

1.25.13.186 (E)-tert-Butyl 7-(1-methyl-1H-pyrrol-2-yl)-5,7-dioxohept-3-enoate (573)
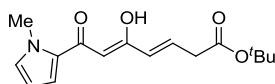
N-Methyl pyrrole (27 μL, 0.30 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (80 mg, 0.30 mmol) in EtOAc (5 mL) were heated by microwave irradiation at 120 ^{o}C for 0.5 h and then rotary evaporated and chromatographed (petroleum ether/Et$_2$O, 19:1 to 4:1) to give the the title compound (47 mg, 54%) as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$, ppm) δ: 15.04 (s, 1 H), 6.90 (dd, J=4.2, 1.7 Hz, 1 H), 6.74 - 6.84 (m, 2 H), 6.15 (dd, J=3.9, 2.4 Hz, 1 H), 5.98 (d, J=15.7 Hz, 1 H), 5.93 (s, 1 H), 3.99 (s, 3 H), 3.17 (dd, J=7.3, 1.5 Hz, 2 H), 1.47 ppm (s, 9 H). ^{13}C NMR (101 MHz, CDCl3, ppm) δ: 184.9, 171.2, 169.6, 132.4, 131.2, 130.1, 128.3, 117.9, 108.5, 98.1, 81.3, 39.2, 37.8, 28.0. MS (EI) m/z: 292 [M+H]$^+$. HR-MS (EI) m/z: calcd for C$_{16}$H$_{22}$NO$_4$: 292.1549 [M+H]$^+$; found: 292.1560.

1.25.14   X-Ray Crystallography Information[280]

1.25.14.1 2,2-Dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-7-yl formate (**464**)

Table 1. Crystal data and structure refinement for AB1313.

Identification code	AB1313
Formula	C11 H10 O4
Formula weight	206.19
Temperature	173 K
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å
Crystal system, space group	Orthorhombic, P b c a
Unit cell dimensions	a = 12.6471(4) Å α = 90°
	b = 7.9916(2) Å β = 90°
	c = 19.1936(6) Å γ = 90°
Volume, Z	1939.90(10) Å^3, 8
Density (calculated)	1.412 Mg/m^3
Absorption coefficient	0.108 mm^{-1}
F(000)	864
Crystal colour / morphology	Colourless blocky needles
Crystal size	0.56 x 0.50 x 0.36 mm^3
θ range for data collection	2.664 to 27.463°
Index ranges	-16<=h<=15, -10<=k<=6, -24<=l<=24
Reflns collected / unique	9306 / 2026 [R(int) = 0.0342]
Reflns observed [F>4σ(F)]	1752
Absorption correction	Analytical
Max. and min. transmission	0.967 and 0.954
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2026 / 0 / 139
Goodness-of-fit on F^2	1.048
Final R indices [F>4σ(F)]	R1 = 0.0352, wR2 = 0.0794
R indices (all data)	R1 = 0.0431, wR2 = 0.0839
Largest diff. peak, hole	0.248, -0.181 eÅ^{-3}
Mean and maximum shift/error	0.000 and 0.001

Table 2. Bond lengths [Å] and angles [°] for AB1313.

C(1)-O(1)	1.2022(15)
C(1)-O(2)	1.3590(15)
C(1)-C(10)	1.4723(17)
O(2)-C(3)	1.4503(15)
C(3)-O(4)	1.4392(15)
C(3)-C(12)	1.5054(18)
C(3)-C(11)	1.5093(19)
O(4)-C(5)	1.3609(15)
C(5)-C(6)	1.3909(17)
C(5)-C(10)	1.3949(17)
C(6)-C(7)	1.3765(18)
C(7)-C(8)	1.4026(18)
C(8)-C(9)	1.3858(18)
C(8)-C(13)	1.4675(18)
C(9)-C(10)	1.3851(17)
C(13)-O(13)	1.2100(17)

O(1)-C(1)-O(2)	119.04(11)
O(1)-C(1)-C(10)	125.35(12)
O(2)-C(1)-C(10)	115.48(10)
C(1)-O(2)-C(3)	118.52(9)
O(4)-C(3)-O(2)	109.62(10)
O(4)-C(3)-C(12)	106.45(11)
O(2)-C(3)-C(12)	106.05(10)
O(4)-C(3)-C(11)	110.38(10)
O(2)-C(3)-C(11)	110.04(11)
C(12)-C(3)-C(11)	114.11(12)
C(5)-O(4)-C(3)	114.71(9)
O(4)-C(5)-C(6)	118.59(11)
O(4)-C(5)-C(10)	120.05(11)
C(6)-C(5)-C(10)	121.32(11)
C(7)-C(6)-C(5)	118.89(11)
C(6)-C(7)-C(8)	120.62(11)
C(9)-C(8)-C(7)	119.73(11)
C(9)-C(8)-C(13)	118.84(12)
C(7)-C(8)-C(13)	121.42(12)
C(10)-C(9)-C(8)	120.33(11)
C(9)-C(10)-C(5)	119.08(11)
C(9)-C(10)-C(1)	121.35(11)
C(5)-C(10)-C(1)	119.42(11)
O(13)-C(13)-C(8)	125.08(13)

1.25.14.2 (E)-6-(2-(5,5-Dichloro-4-oxo-2-(pyrrolidin-1-yl)-4,5-dihydrofuran-3-yl)vinyl)-2,2-dimethyl-4H-1,3-dioxin-4-one (506)

Table 1. Crystal data and structure refinement for AB1404.

Identification code	AB1404	
Formula	C16 H17 Cl2 N O5, C H2 Cl2	
Formula weight	459.13	
Temperature	173 K	
Diffractometer, wavelength	Agilent Xcalibur 3 E, 0.71073 Å	
Crystal system, space group	Monoclinic, P 21/n	
Unit cell dimensions	a = 14.6907(8) Å	α = 90°
	b = 9.5478(5) Å	β = 99.279(5)°
	c = 14.8016(8) Å	γ = 90°
Volume, Z	2049.0(2) Å^3, 4	
Density (calculated)	1.488 Mg/m^3	
Absorption coefficient	0.605 mm^{-1}	
F(000)	944	
Crystal colour / morphology	Pale yellow blocks	
Crystal size	0.69 x 0.59 x 0.38 mm^3	
θ range for data collection	2.789 to 28.178°	
Index ranges	-18<=h<=16, -11<=k<=12, -12<=l<=19	
Reflns collected / unique	7072 / 4090 [R(int) = 0.0174]	
Reflns observed [F>4σ(F)]	3184	
Absorption correction	Analytical	
Max. and min. transmission	0.842 and 0.740	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4090 / 39 / 254	
Goodness-of-fit on F^2	1.027	
Final R indices [F>4σ(F)]	R1 = 0.0395, wR2 = 0.0810	
R indices (all data)	R1 = 0.0577, wR2 = 0.0902	
Largest diff. peak, hole	0.338, -0.393 eÅ^{-3}	
Mean and maximum shift/error	0.000 and 0.000	

Table 2. Bond lengths [Å] and angles [°] for AB1404.

O(1)-C(1)	1.208(2)
C(1)-O(2)	1.372(3)
C(1)-C(6)	1.440(3)
O(2)-C(3)	1.444(2)
C(3)-O(4)	1.437(2)
C(3)-C(7)	1.502(3)
C(3)-C(8)	1.508(3)
O(4)-C(5)	1.361(2)
C(5)-C(6)	1.348(3)
C(5)-C(9)	1.441(3)
C(9)-C(10)	1.347(3)
C(10)-C(11)	1.436(3)
C(11)-C(15)	1.410(3)
C(11)-C(12)	1.421(3)
C(12)-O(12)	1.221(2)
C(12)-C(13)	1.547(3)

C(13)-O(14)	1.399(3)
C(13)-Cl(2)	1.764(2)
C(13)-Cl(1)	1.769(2)
O(14)-C(15)	1.378(2)
C(15)-N(16)	1.301(3)
N(16)-C(20)	1.474(3)
N(16)-C(17)	1.487(3)
C(17)-C(18)	1.505(4)
C(17)-C(18')	1.536(6)
C(18)-C(19)	1.524(7)
C(19)-C(20)	1.525(5)
C(18')-C(19')	1.508(9)
C(19')-C(20)	1.542(8)
C(30)-Cl(4)	1.751(3)
C(30)-Cl(3)	1.761(2)
O(1)-C(1)-O(2)	117.66(19)
O(1)-C(1)-C(6)	126.7(2)
O(2)-C(1)-C(6)	115.50(19)
C(1)-O(2)-C(3)	118.40(16)
O(4)-C(3)-O(2)	109.75(16)
O(4)-C(3)-C(7)	106.44(17)
O(2)-C(3)-C(7)	106.09(17)
O(4)-C(3)-C(8)	110.46(17)
O(2)-C(3)-C(8)	110.34(17)
C(7)-C(3)-C(8)	113.58(19)
C(5)-O(4)-C(3)	115.59(16)
C(6)-C(5)-O(4)	120.37(18)
C(6)-C(5)-C(9)	125.1(2)
O(4)-C(5)-C(9)	114.45(17)
C(5)-C(6)-C(1)	120.8(2)
C(10)-C(9)-C(5)	122.5(2)
C(9)-C(10)-C(11)	125.63(19)
C(15)-C(11)-C(12)	107.16(17)
C(15)-C(11)-C(10)	128.52(19)
C(12)-C(11)-C(10)	124.20(18)
O(12)-C(12)-C(11)	132.49(19)
O(12)-C(12)-C(13)	122.30(19)
C(11)-C(12)-C(13)	105.20(17)
O(14)-C(13)-C(12)	106.70(16)
O(14)-C(13)-Cl(2)	109.24(14)
C(12)-C(13)-Cl(2)	111.47(15)
O(14)-C(13)-Cl(1)	108.12(15)
C(12)-C(13)-Cl(1)	111.31(15)
Cl(2)-C(13)-Cl(1)	109.88(12)
C(15)-O(14)-C(13)	108.08(15)
N(16)-C(15)-O(14)	113.06(17)
N(16)-C(15)-C(11)	134.09(19)
O(14)-C(15)-C(11)	112.86(18)
C(15)-N(16)-C(20)	125.16(17)
C(15)-N(16)-C(17)	123.19(17)
C(20)-N(16)-C(17)	111.59(17)
N(16)-C(17)-C(18)	102.9(2)
N(16)-C(17)-C(18')	102.1(3)
C(17)-C(18)-C(19)	104.8(4)
C(18)-C(19)-C(20)	102.5(4)
C(19')-C(18')-C(17)	103.0(5)
C(18')-C(19')-C(20)	104.5(5)
N(16)-C(20)-C(19)	103.0(2)
N(16)-C(20)-C(19')	103.3(3)
Cl(4)-C(30)-Cl(3)	111.45(14)

1.25.14.3 6-(2,2-Dimethyl-4-oxo-4H-1,3-dioxin-6-yl)-5,7-dihydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (557)

Table 1. Crystal data and structure refinement for AB1205b.

Identification code	AB1205b	
Formula	C16 H16 O8	
Formula weight	336.29	
Temperature	203 K	
Diffractometer, wavelength	OD Xcalibur PX Ultra, 1.54184 Å	
Crystal system, space group	Triclinic, P-1	
Unit cell dimensions	a = 7.8746(3) Å	α = 114.468(5)°
	b = 9.6386(6) Å	β = 90.215(4)°
	c = 11.0491(5) Å	γ = 91.686(4)°
Volume, Z	762.87(7) Å^3, 2	
Density (calculated)	1.464 Mg/m^3	

Absorption coefficient	1.017 mm^{-1}
F(000)	352
Crystal colour / morphology	Colourless tabular needles
Crystal size	0.22 x 0.14 x 0.07 mm^3
θ range for data collection	4.40 to 72.44°
Index ranges	-5<=h<=9, -11<=k<=11, -13<=l<=12
Reflns collected / unique	5475 / 2942 [R(int) = 0.0223]
Reflns observed [F>4σ(F)]	2541
Absorption correction	Analytical
Max. and min. transmission	0.933 and 0.854
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2942 / 2 / 225
Goodness-of-fit on F^2	1.058
Final R indices [F>4σ(F)]	R1 = 0.0399, wR2 = 0.1110
R indices (all data)	R1 = 0.0453, wR2 = 0.1177
Largest diff. peak, hole	0.221, -0.223 eÅ^{-3}
Mean and maximum shift/error	0.000 and 0.000

Table 2. Bond lengths [Å] and angles [°] for AB1205b.

O(1)-C(10)	1.3626(15)
O(1)-C(2)	1.4380(15)
C(2)-O(3)	1.4527(17)
C(2)-C(12)	1.5010(19)
C(2)-C(11)	1.507(2)
O(3)-C(4)	1.3473(16)
C(4)-O(4)	1.2214(17)
C(4)-C(5)	1.4464(18)
C(5)-C(10)	1.3952(19)
C(5)-C(6)	1.4096(18)
C(6)-O(13)	1.3414(16)
C(6)-C(7)	1.3987(18)
C(7)-C(8)	1.4082(18)
C(7)-C(14)	1.4712(17)
C(8)-O(22)	1.3417(15)
C(8)-C(9)	1.3991(17)
C(9)-C(10)	1.3789(18)
C(14)-C(19)	1.3427(18)
C(14)-O(15)	1.3495(15)
O(15)-C(16)	1.4407(15)
C(16)-O(17)	1.4483(16)
C(16)-C(20)	1.505(2)
C(16)-C(21)	1.509(2)
O(17)-C(18)	1.3495(17)
C(18)-O(18)	1.2218(16)
C(18)-C(19)	1.4410(18)

C(10)-O(1)-C(2)	115.56(10)
O(1)-C(2)-O(3)	110.06(10)
O(1)-C(2)-C(12)	106.42(11)
O(3)-C(2)-C(12)	105.85(11)
O(1)-C(2)-C(11)	110.90(11)
O(3)-C(2)-C(11)	109.58(11)
C(12)-C(2)-C(11)	113.85(12)
C(4)-O(3)-C(2)	117.78(10)
O(4)-C(4)-O(3)	118.53(11)
O(4)-C(4)-C(5)	124.76(12)
O(3)-C(4)-C(5)	116.63(11)
C(10)-C(5)-C(6)	118.92(11)
C(10)-C(5)-C(4)	120.02(12)
C(6)-C(5)-C(4)	120.78(12)
O(13)-C(6)-C(7)	118.82(11)
O(13)-C(6)-C(5)	120.47(11)
C(7)-C(6)-C(5)	120.63(11)
C(6)-C(7)-C(8)	118.24(11)
C(6)-C(7)-C(14)	120.10(11)
C(8)-C(7)-C(14)	121.61(11)
O(22)-C(8)-C(9)	120.85(11)
O(22)-C(8)-C(7)	117.31(11)
C(9)-C(8)-C(7)	121.83(11)
C(10)-C(9)-C(8)	118.37(11)
O(1)-C(10)-C(9)	118.58(11)
O(1)-C(10)-C(5)	119.37(11)
C(9)-C(10)-C(5)	121.99(12)
C(19)-C(14)-O(15)	121.01(12)
C(19)-C(14)-C(7)	125.07(11)
O(15)-C(14)-C(7)	113.91(10)
C(14)-O(15)-C(16)	116.05(10)
O(15)-C(16)-O(17)	110.00(10)
O(15)-C(16)-C(20)	106.10(11)
O(17)-C(16)-C(20)	106.36(12)
O(15)-C(16)-C(21)	110.32(11)
O(17)-C(16)-C(21)	109.70(11)

C(20)-C(16)-C(21)	114.21(12)
C(18)-O(17)-C(16)	117.89(10)
O(18)-C(18)-O(17)	117.67(12)
O(18)-C(18)-C(19)	125.41(12)
O(17)-C(18)-C(19)	116.72(11)
C(14)-C(19)-C(18)	119.79(12)

1.25.15   Selected 1D and 2D NMR spectra

1.25.15.1 (E)-4-(2,2-Dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)but-3-enoic acid (**357a**)
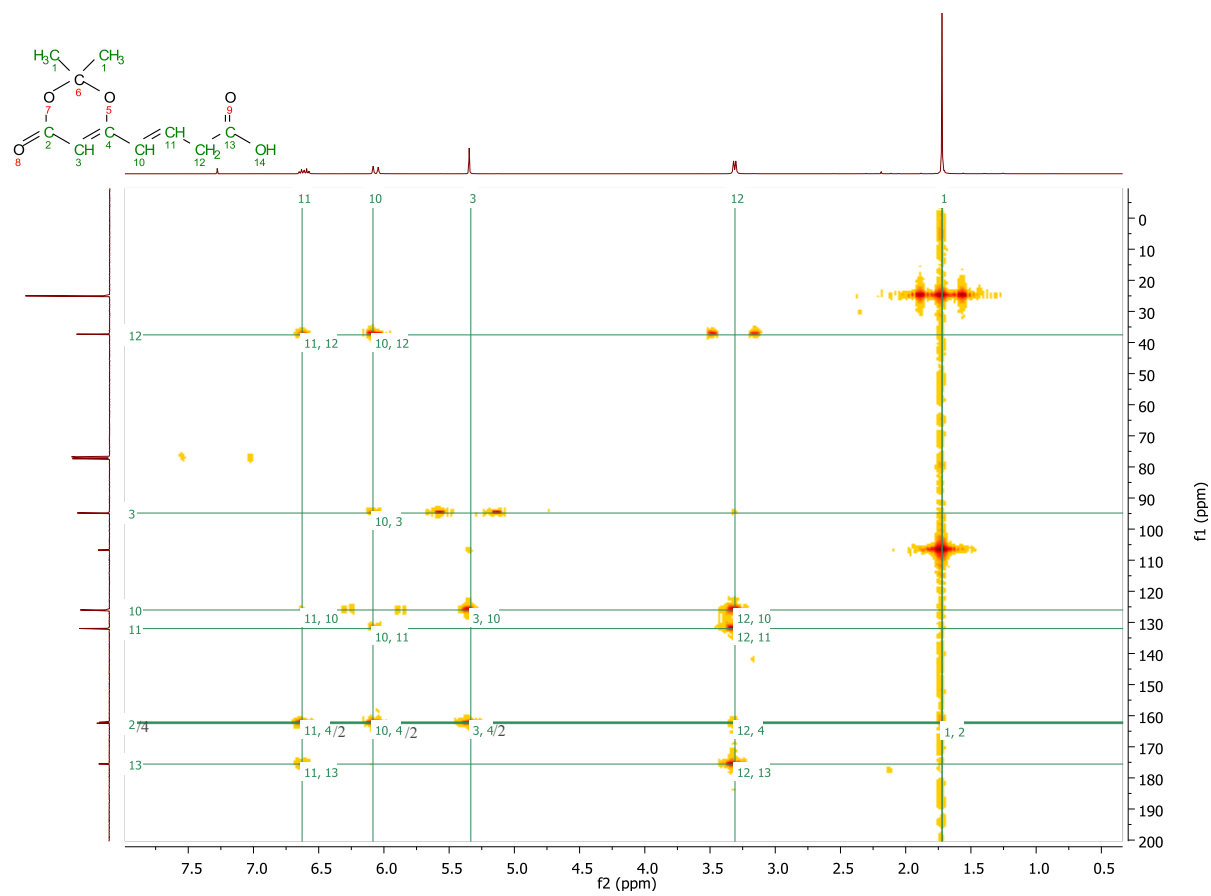
Spectrum 1. HMBC spectrum for compound **458a**.

1.25.15.2 Isopropyl 3,6-dihydroxybiphenyl-2-carboxylate (**514a**)
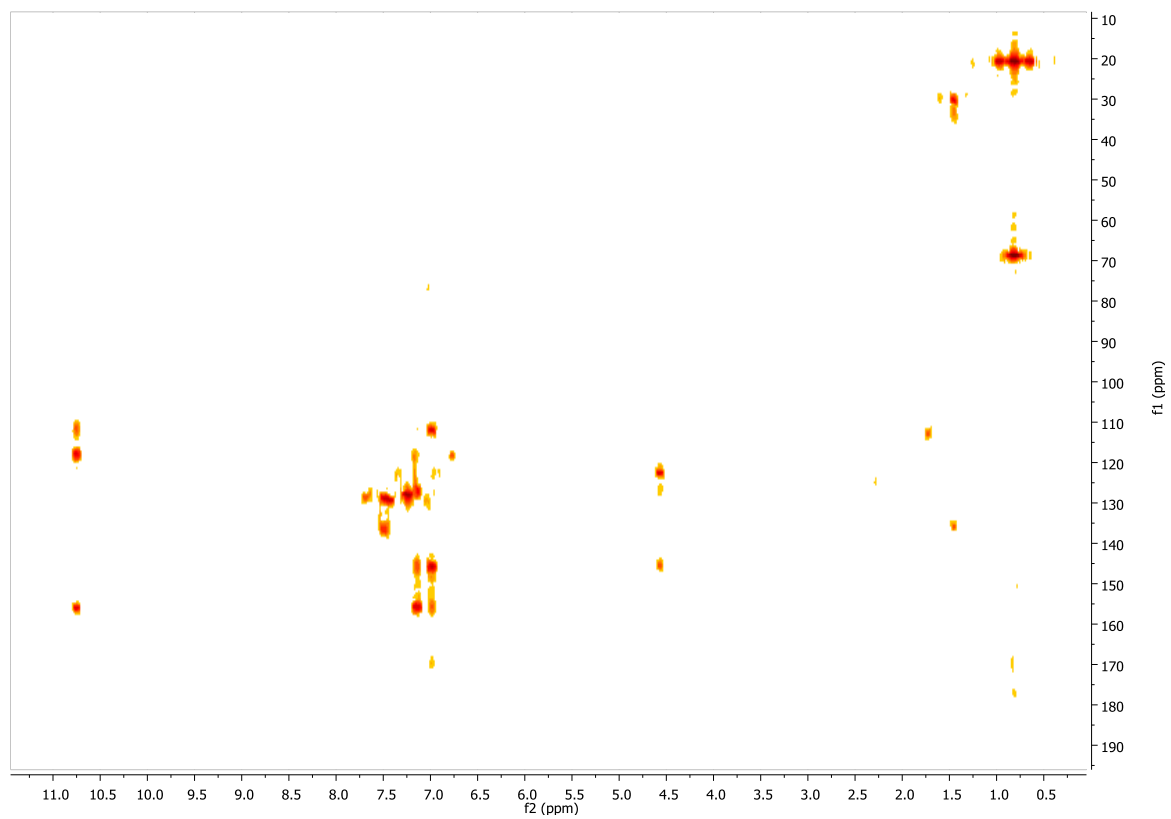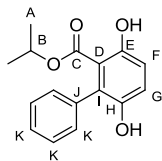
Spectrum xx. HMBC spectrum for **514a**.

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